2019

Abouzeid M, Wyber R, La Vincente S, Sliwa K, Zuhlke L, Mayosi B, et al. Time to tackle rheumatic heart disease: Data needed to drive global policy dialogues. Glob Public Health. 2019;14(3):456–468. doi: 10.1080/17441692.2018.1515970. **Full text not freely available**.

Rheumatic heart disease (RHD) is an avoidable disease of poverty that persists predominantly in low resource settings and among Indigenous and other high-risk populations in some high-income nations. Following a period of relative global policy inertia on RHD, recent years have seen a resurgence of research, policy and civil society activity to tackle RHD; this has culminated in growing momentum at the highest levels of global health diplomacy to definitively address this disease of disadvantage. RHD is inextricably entangled with the global development agenda, and effective RHD action requires concerted efforts both within and beyond the health policy sphere. This report provides an update on the contemporary global and regional policy landscapes relevant to RHD, and highlights the fundamental importance of good data to inform these policy dialogues, monitor systems responses and ensure that no one is left behind.

Chasseuil E, McGrath JA, Seo A, Balguerie X, Bodak N, Chasseuil H, et al. Dermatological manifestations of hereditary fibrosing poikiloderma with tendon contractures, myopathy and pulmonary fibrosis (POIKTMP): A case series of 28 patients. Br J of Dermatol. 2019. doi: 10.1111/bjd.17996. **Full text not freely available.**

Hereditary Fibrosing Poikiloderma with Tendon Contractures, Myopathy and Pulmonary Fibrosis (POIKTMP [MIM 615704]) is a recently described autosomal dominant disorder due to missense mutations in the FAM111B gene. Key features are early-onset poikiloderma, muscle contractures in particular of the triceps surae, diffuse progressive fatty myopathy, pulmonary fibrosis in adulthood and exocrine pancreatic insufficiency. Dermatological manifestations seem to be constant and early however, a precise description is lacking.

Karthikeyan G, Devasenapathy N, Zuhlke L, Engel ME, Rangarajan S, Teo KK, et al. Digoxin and clinical outcomes in the Global Rheumatic Heart Disease Registry. Heart. 2019;105(5):363–369. doi: 10.1136/heartjnl-2018-313614. **Full text available here.**

Objective: Digoxin is widely used in patients with rheumatic heart disease (RHD) despite a lack of data on its

impact on clinical outcomes. We aimed to determine the association of digoxin use on clinical outcomes in patients with RHD.
Methods: We performed a retrospective analysis of the association of digoxin use with mortality at 2 years in a large RHD registry. Secondary outcomes were recurrent heart failure (HF) and hospitalisation for any cause. We assessed associations using multivariable logistic regression in the entire cohort and in subgroups of patients with atrial fibrillation (AF) and HF. We also estimated average treatment effects from propensity-adjusted analyses using inverse probability treatment weighting.
Results: Information on digoxin use at baseline was available for 98.7% (3298/3343) of patients. In the overall population, digoxin was significantly associated with mortality (OR 1.63, 95% CI 1.30 to 2.04, p<0.0001) and recurrent HF (OR 1.48, 95% CI 1.07 to 2.04, p=0.019). On propensity-weighted analyses, this effect was markedly attenuated (OR 1.05, 95% CI 1.01 to 1.09, p=0.005). Patients in sinus rhythm without HF had a higher propensity-adjusted odds of death with digoxin use (OR 1.06, 95% CI 1.01 to 1.12, p=0.015), but those with both AF and HF had lower mortality (OR 0.88, 95% CI 0.80 to 0.98, p=0.019).
Conclusion: Digoxin use is associated with higher mortality in patients with RHD, but this is greatly attenuated on propensity adjustment, indicating the presence of substantial treatment bias. The adjusted estimates may therefore not be reliable, and large randomised trials are needed to determine the true effect of digoxin in patients with RHD.

Mweemba O, Musuku J, Mayosi BM, Parker M, Rutakumwa R, Seeley J, et al. Use of broad consent and related procedures in genomics research: Perspectives from research participants in the Genetics of Rheumatic Heart Disease (RHDGen) study in a university teaching hospital in Zambia. Glob Bioeth. 2019. doi: 10.1080/11287462.2019.1592868. **Full text available here**.

The use of broad consent for genomics research raises important ethical questions for the conduct of genomics research, including relating to its acceptability to research participants and comprehension of difficult scientific concepts. To explore these and other challenges, we conducted a study using qualitative methods with participants enrolled in an H3Africa Rheumatic Heart Disease genomics study (the RHDGen network) in Zambia to explore their views on broad consent, sample and data sharing and secondary use. In-depth interviews were conducted with RHDGen participants (n = 18), study staff (n = 5) and with individuals who refused to participate (n = 3). In general, broad consent was seen to be reasonable if reasons for storing the samples for future research use were disclosed. Some felt that broad consent should be restricted by specifying planned future studies and that secondary research should ideally relate to original disease for which samples were collected. A few participants felt that broad consent would delay the return of research results to participants. This study echoes findings in other similar studies in other parts of the continent that suggested that broad consent could be an acceptable consent model in Africa if careful thought is given to restrictions on re-use.

Ojji DB, Mayosi B, Francis V, Badri M, Cornelius V, Smythe W, et al. Comparison of dual therapies for lowering blood pressure in black Africans. N Engl J Med. 2019;380(25):2429–2439. doi: 10.1056/NEJMoa1901113. **Full text not freely available**.

Background: The prevalence of hypertension among black African patients is high, and these patients usually need two or more medications for blood-pressure control. However, the most effective two-drug combination that is currently available for blood-pressure control in these patients has not been established.

Methods: In this randomized, single-blind, three-group trial conducted in six countries in sub-Saharan Africa, we randomly assigned 728 black patients with uncontrolled hypertension (≥140/90 mm Hg while the patient was not being treated or taking only one antihypertensive drug) to receive a daily regimen of 5 mg of amlodipine plus 12.5 mg of hydrochlorothiazide, 5 mg of amlodipine plus 4 mg of perindopril, or 4 mg of perindopril plus 12.5 mg of hydrochlorothiazide for 2 months. Doses were then doubled (10 and 25 mg, 10 and 8 mg, and 8 and 25 mg, respectively) for an additional 4 months. The primary end point was the change in the 24-hour ambulatory systolic blood pressure between baseline and 6 months.

Results: The mean age of the patients was 51 years, and 63% were women. Among the 621 patients who underwent 24-hour blood-pressure monitoring at baseline and at 6 months, those receiving amlodipine plus hydrochlorothiazide and those receiving amlodipine plus perindopril had a lower 24-hour ambulatory systolic blood pressure than those receiving perindopril plus hydrochlorothiazide (between-group difference in the change from baseline, −3.14 mm Hg; 95% confidence interval [CI], −5.90 to −0.38; P=0.03; and −3.00 mm Hg; 95% CI, −5.8 to −0.20; P=0.04, respectively). The difference between the group receiving amlodipine plus hydrochlorothiazide and the group receiving amlodipine plus perindopril was −0.14 mm Hg (95% CI, −2.90 to 2.61; P=0.92). Similar differential effects on office and ambulatory diastolic blood pressures, along with blood-pressure control and response rates, were apparent among the three groups.

Conclusions: These findings suggest that in black patients in sub-Saharan Africa, amlodipine plus either hydrochlorothiazide or perindopril was more effective than perindopril plus hydrochlorothiazide at lowering blood pressure at 6 months. (CREOLE ClinicalTrials.gov number, NCT02742467).

Owolabi MO, Akpa OM, Made F, Adebamowo SN, Ojo A, Adu D, et al. Data resource profile: Cardiovascular H3Africa Innovation Resource (CHAIR). Int J Epidemiol. 2019;48(2):366–367g. doi: 10.1093/ije/dyy261. F**ull text available here**.

No abstract available.

Shenje J, Gumbo T, Wiesner L, Ntsekhe M, Mayosi B, Ross I. Detectable prednisolone is delayed in pericardial fluid, compared with plasma of patients with tuberculous pericarditis: A pilot study. Int J Cardiol Heart Vasc. 2019;22:105–110. doi: 10.1016/j.ijcha.2018.12.008. **Full text available here.**

Background: In patients with tuberculous pericarditis [TBP] adjunctive prednisolone reduces the incidence of constrictive pericarditis. It is unknown whether prednisolone permeates adequately into pericardial fluid. Drug measurements in pericardial fluid require invasive procedures, and thus less invasive methods are needed to perform full pharmacokinetic characterization of prednisolone in large numbers of patients. We sought to evaluate the relationship between prednisolone concentrations in pericardial fluid, plasma, and saliva.

Methods: Plasma, pericardial fluid, and saliva samples were collected at 7 timepoints from TBP patients randomized to 120mg prednisolone or placebo. Compartmental pharmacokinetic parameters, peak concentration [C_{max}], and 0–24 h area under the concentration-time curve [AUC_{0-24}] were identified in plasma, saliva and pericardial fluid.

Results: There were five patients each in the prednisolone and placebo groups. Prednisolone concentrations were best described using a one compartment model. The absorption half-life into plasma was 1 h, while that into pericardial fluid was 9.4 h, which led to a median time-to-maximum concentration in plasma of 2.0 h versus 5.0 h in pericardial fluid [p = 0.048]. The concentration-time profiles in pericardial fluid versus plasma exhibited system hysteresis. The pericardial fluid-to-plasma C_{max} peak concentration ratio was 0.28 (p = 0.032), while the AUC_{0-24} ratio was 0.793. The concentration-time profiles in saliva had a similar shape to those in plasma, but the salivato-plasma C_{max} was 0.59 [p = 0.032].

Conclusion: The prednisolone AUC_{0-24} achieved in pericardial fluid approximates that in plasma, but the C_{max} is low due to delayed absorption. Saliva can be used as surrogate sampling site for pericardial fluid prednisolone.

2018

Barth D, Mayosi BM, Badri M, Whitelaw A, Engel ME. Invasive and non-invasive group A β-haemolytic streptococcal infections in patients attending public sector facilities in South Africa: 2003–2015. S Afr J Infect Dis. 2018;33(1):12–17. doi: 10.1080/23120053.2017.1376546. **Full text available here.**

Background: The burden of disease caused by group A streptococcus (GAS) in Africa is largely unknown. The aim of this study was to determine the incidence of invasive (iGAS) and non-invasive GAS (non-iGAS) infections in patients attending the public health sector of South Africa.

Methods: iGAS and non-iGAS infection was defined as GAS isolated in culture from sterile and non-sterile sites respectively. Using annual census data, we calculated incidence rates (IR) of iGAS and non-iGAS infection by reviewing cases from the National Health Laboratory Service (NHLS) database derived from the 9 provinces of South Africa between 2003 and 2015.

Results: About 50% of the samples were collected in the Eastern Cape province which had data for all the years under observation; missing data from the other eight provinces precluded analysis of annual incidence. A multi-modal distribution of 5 256 GAS cases was observed in the Eastern Cape province. iGAS cases (n = 428) showed an annual mean IR of 0.48 (Range: 0.15–1.12) cases per 10^5 per year (py) with a marginal decrease from 2003 to 2015 (Rate Difference (RD), 0.23/10^5 py; 95% CI: 0.02–0.44/10^5 py). The mean annual IR for non-iGAS infection (n = 4828) was 5.48 (Range: 0.19–11.55) cases/10^5py; IR showed a decrease (RD, 11.36/10^5 py; 95% CI: 10.53–12.19/10^5 py). The Mann–Kendall test and the Theil–Sen estimator showed a decreasing trend in the incidence of non-iGAS infection (p = 0.002) over the study period.

Conclusions: The incidence of non-iGAS infection in the Eastern Cape province of South Africa declined from 2003 to 2015. The trends from the Eastern Cape and incomplete data from other provinces indicate the need for a detailed prospective evaluation of GAS infection in South Africa to verify this trend and provide information for planning appropriate interventions.

Bonny A, Ngantcha M, Jeilan M, Okello E, Kaviraj B, Talle MA, et al. Statistics on the use of cardiac electronic devices and interventional electrophysiological procedures in Africa from 2011 to 2016: Report of the Pan African Society of Cardiology (PASCAR) Cardiac Arrhythmias and Pacing Task Forces. Europace. 2018;20(9):1513–1526. doi: 10.1093/europace/eux353. **Full text available here.**

Aims: To provide comprehensive information on the access and use of cardiac implantable electronic devices (CIED) and catheter ablation procedures in Africa.

Methods and results: The Pan-African Society of Cardiology (PASCAR) collected data on invasive management of cardiac arrhythmias from 2011 to 2016 from 31 African countries. A specific template was completed by physicians, and additional information obtained from industry. Information on health care systems, demographics, economics, procedure rates, and specific training programs was collected. Considerable heterogeneity in the access to arrhythmia care was observed across Africa. Eight of the 31 countries surveyed (26%) did not perform pacemaker implantations. The median pacemaker implantation rate was 2.66 per million population per country (range: 0.14–233 per million population). Implantable cardioverter-defibrillator and cardiac resynchronization therapy were performed in 12/31 (39%) and 15/31 (48%) countries respectively, mostly by visiting teams. Electrophysiological studies, including complex catheter ablations were performed in all countries from Maghreb, but only one sub-Saharan African country (South Africa). Marked variation in cost (up to 1000-fold) was observed across countries with an inverse correlation between implant rates and the procedure fees standardized to the gross domestic product per capita. Lack of economic resources and facilities, high cost of procedures, deficiency of trained physicians, and non-existent fellowship programs were the main drivers of under-utilization of interventional cardiac arrhythmia care.

Conclusion: There is limited access to CIED and ablation procedures in Africa. A quarter of countries did not have pacemaker implantation services, and catheter ablations were only available in one country in sub-Saharan Africa.

Coetzee E, Biccard BM, Dyer RA, Meyersfeld ND, Chishala C, Mayosi BM. Incidence of myocardial injury after non-cardiac surgery: Experience at Groote Schuur Hospital, Cape Town, South Africa. S Afr Med J. 2018;108(5):408–412. doi: 10.7196/SAMJ.2018.v108i5.12784. **Full text available here**.

Background: Myocardial injury after non-cardiac surgery (MINS) is a newly recognised entity identified as an independent risk factor associated with increased 30-day all-cause mortality. MINS increases the risk of death in the perioperative period by ~10-fold. More than 80% of patients with MINS are asymptomatic, so the majority of diagnoses are missed. Awareness of MINS is therefore important for perioperative physicians.

Objectives: To investigate the incidence of MINS after elective elevated-risk non-cardiac surgery at Groote Schuur Hospital, Cape Town, South Africa (SA).

Methods: Patients aged ≥45 years undergoing elective elevated-risk non-cardiac surgery were enrolled via convenience sampling. The new fifth-generation high-sensitivity cardiac troponin T blood test was used postoperatively to identify MINS. Preoperative troponin levels were not measured.

Results: Among 244 patients included in the study, the incidence of MINS was 4.9% (95% confidence interval (CI) 2.8 – 8.5), which was not significantly different from that in a major international prospective observational study (VISION) (8.0% (95% CI 7.5 – 8.4)); p=0.080.

Conclusions: Our SA cohort had a lower cardiovascular risk profile but a similar incidence of MINS to that described in international literature. The impact of MINS on morbidity and mortality is therefore likely to be proportionally higher in SA than in published international studies. The limited sample size and lower event rate

weaken our conclusions. Larger studies are required to establish patient and surgical risk factors for MINS, allowing for revision of cardiovascular risk prediction models in SA.

Deffur A, Wilkinson RJ, Mayosi BM, Mulder NM. ANIMA: Association network integration for multiscale analysis. Wellcome Open Res. 2018;3:27. doi: 10.12688/wellcomeopenres.14073.3. **Full text available here.**

Contextual functional interpretation of -omics data derived from clinical samples is a classical and difficult problem in computational systems biology. The measurement of thousands of data points on single samples has become routine but relating 'big data' datasets to the complexities of human pathobiology is an area of ongoing research. Complicating this is the fact that many publicly available datasets use bulk transcriptomics data from complex tissues like blood. The most prevalent analytic approaches derive molecular 'signatures' of disease states or apply modular analysis frameworks to the data. Here we describe ANIMA (association network integration for multiscale analysis), a network-based data integration method using clinical phenotype and microarray data as inputs. ANIMA is implemented in R and Neo4j and runs in Docker containers. In short, the build algorithm iterates over one or more transcriptomics datasets to generate a large, multipartite association network by executing multiple independent analytic steps (differential expression, deconvolution, modular analysis based on co-expression, pathway analysis) and integrating the results. Once the network is built, it can be queried directly using Cypher (a graph query language), or by custom functions that communicate with the graph database via language-specific APIs. We developed a web application using Shiny, which provides fully interactive, multiscale views of the data. Using our approach, we show that we can reconstruct multiple features of disease states at various scales of organization, from transcript abundance patterns of individual genes through co-expression patterns of groups of genes to patterns of cellular behaviour in whole blood samples, both in single experiments as well in meta-analyses of multiple datasets.

Devereaux PJ, Duceppe E, Guyatt G, Tandon V, Rodseth R, Biccard BM, et al. Dabigatran in patients with myocardial injury after non-cardiac surgery (MANAGE): An international, randomised, placebo-controlled trial. Lancet. 2018;391(10137):2325–2334. doi: 10.1016/s0140-6736(18)30832-8. **Full text not freely available.**

Background: Myocardial injury after non-cardiac surgery (MINS) increases the risk of cardiovascular events and deaths, which anticoagulation therapy could prevent. Dabigatran prevents perioperative venous thromboembolism, but whether this drug can prevent a broader range of vascular complications in patients with MINS is unknown. The MANAGE trial assessed the potential of dabigatran to prevent major vascular complications among such patients.

Methods: In this international, randomised, placebo-controlled trial, we recruited patients from 84 hospitals in 19 countries. Eligible patients were aged at least 45 years, had undergone non-cardiac surgery, and were within 35

days of MINS. Patients were randomly assigned (1:1) to receive dabigatran 110 mg orally twice daily or matched placebo for a maximum of 2 years or until termination of the trial and, using a partial 2-by-2 factorial design, patients not taking a proton-pump inhibitor were also randomly assigned (1:1) to omeprazole 20 mg once daily, for which results will be reported elsewhere, or matched placebo to measure its effect on major upper gastrointestinal complications. Research personnel randomised patients through a central 24 h computerised randomisation system using block randomisation, stratified by centre. Patients, health-care providers, data collectors, and outcome adjudicators were masked to treatment allocation. The primary efficacy outcome was the occurrence of a major vascular complication, a composite of vascular mortality and non-fatal myocardial infarction, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation, and symptomatic venous thromboembolism. The primary safety outcome was a composite of life-threatening, major, and critical organ bleeding. Analyses were done according to the intention-to-treat principle. This trial is registered with ClinicalTrials.gov, number NCT01661101.

Findings: Between Jan 10, 2013, and July 17, 2017, we randomly assigned 1754 patients to receive dabigatran (n=877) or placebo (n=877); 556 patients were also randomised in the omeprazole partial factorial component. Study drug was permanently discontinued in 401 (46%) of 877 patients allocated to dabigatran and 380 (43%) of 877 patients allocated to placebo. The composite primary efficacy outcome occurred in fewer patients randomised to dabigatran than placebo (97 [11%] of 877 patients assigned to dabigatran *vs* 133 [15%] of 877 patients assigned to placebo; hazard ratio [HR] 0.72, 95% CI 0.55–0.93; p=0.0115). The primary safety composite outcome occurred in 29 patients (3%) randomised to dabigatran and 31 patients (4%) randomised to placebo (HR 0.92, 95% CI 0.55–1.53; p=0.76).

Interpretation: Among patients who had MINS, dabigatran 110 mg twice daily lowered the risk of major vascular complications, with no significant increase in major bleeding. Patients with MINS have a poor prognosis; dabigatran 110 mg twice daily has the potential to help many of the 8 million adults globally who have MINS to reduce their risk of a major vascular complication.

Duceppe E, Yusuf S, Tandon V, Rodseth R, Biccard BM, Xavier D, et al. Design of a randomized placebo-controlled trial to assess Dabigatran and Omeprazole in patients with myocardial injury after noncardiac surgery (MANAGE). Can J Cardiol. 2018;34(3):295–302. doi: 10.1016/j.cjca.2018.01.020. **Full text not freely available.**

Background: Worldwide approximately 200 million adults undergo major surgery annually, of whom 8 million are estimated to suffer a myocardial injury after noncardiac surgery (MINS). There is currently no trial data informing the management of MINS. Antithrombotic agents such as direct oral anticoagulants might prevent major vascular complications in patients with MINS.

Methods: The Management of Myocardial Injury After Noncardiac Surgery (MANAGE) trial is a large international blinded randomized controlled trial of dabigatran *vs* placebo in patients who suffered MINS. We

used a partial factorial design to also determine the effect of omeprazole *vs* placebo in reducing upper gastrointestinal bleeding and complications. Both study drugs were initiated in eligible patients within 35 days of suffering MINS and continued for a maximum of 2 years. The primary outcome is a composite of major vascular complications for the dabigatran trial and a composite of upper gastrointestinal complications for the omeprazole trial. We present the rationale and design of the trial and baseline characteristics of enrolled patients.
Results: The trial randomized 1754 patients between January 2013 and July 2017. Patients' mean age was 69.9 years, 51.1% were male, 14.3% had a history of peripheral artery disease, 6.6% had a history of stroke or transient ischemic attack, 12.9% had a previous myocardial infarction, and 26.0% had diabetes. The diagnosis of MINS was on the basis of an isolated ischemic troponin elevation in 80.4% of participants.
Conclusion: MANAGE is the first randomized controlled trial to evaluate a potential treatment of patients who suffered MINS.

Dzudie A, Ojji D, Damasceno A, Sani MU, Kramoh E, Kacou JB, et al. Development of the certificate course in the management of hypertension in Africa (CCMH–Africa): Proceedings of the first continental faculty meeting, Nairobi, Kenya, 25–26 February 2018. Cardiovasc J Afr. 2018;29(5):331–334. doi: 10.5830/cvja-2018-055. **Full text not freely available.**

Background: In response to the call by the World Health Organisation to reduce premature deaths from non-communicable diseases by 25% by the year 2025 (25×25), the Pan-African Society of Cardiology (PASCAR), in partnership with several organisations, including the World Heart Federation, have developed an urgent 10-point action plan to improve detection, treatment and control of hypertension in Africa. Priority six of this action plan is to promote a task-shifting/task-sharing approach in the management of hypertension.
Aim: This capacity-building initiative aims to enhance the knowledge, skills and core competences of primary healthcare physicians in the management of hypertension and related complications.
Methods: In a collaborative approach with the International Society of Hypertension, the British and Irish Hypertension Society, the Public Health Foundation of India and the Centre for Chronic Disease Control, the PASCAR hypertension taskforce held a continental faculty meeting in Kenya on 25 and 26 February 2018 to review and discuss a process of effective contextualisation and implementation of the Indian hypertension management course on the African continent.
Results: A tailored African course in terms of evidence-based learning, up-to-date curriculum and on-the-job training was developed with a robust monitoring and evaluation strategy. The course will be offered on a modular basis with a judicious mix of case studies, group discussions and contact sessions, with great flexibility to accommodate participants' queries.
Conclusions: Hypertension affects millions of people in Africa and if left untreated is a major cause of heart disease, kidney disease and stroke. CCMH–Africa will train in the next 10 years, 25 000 certified general physicians and 50 000 nurses, capable of adequately managing uncomplicated hypertension, thereby freeing the

few available specialists to focus on severe or complicated cases.

Gcelu A, Deshpande G, Shaboodien G, Spracklen TF, Kalla A, Tikly M, et al. Mutations of *FAM111B* gene are not associated with systemic sclerosis. Sci Rep. 2018;8(1):15988. doi: 10.1038/s41598-018-34341-7. **Full text available here**.

Systemic sclerosis (SSc) is a prototypic systemic fibrotic disease with unclearly characterized genetic basis. We have discovered that mutations in family with sequence similarity 111, member B (*FAM111B*) gene cause hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis, a multisystem fibrotic condition with clinical similarities to SSc. This observation has established *FAM111B* as a candidate gene for SSc.

Patients and Methods: Demographic and clinical characteristics of consenting adults with definite SSc were recorded. Blood DNA analysis was performed using the High-Resolution Melt technique, and samples with abnormal electropherograms were selected for Sanger sequencing to identify mutations. Ethnically-matched controls from the general South African population were used to verify the frequency of variants in *FAM111B*. Public databases such as 1000 Genomes and ExAC were also used to verify the frequency of variants in *FAM111B*.

Results: Of 131 patients, 118 (90.1%) were female, and 78 (59.5%) were black Africans. Genetic analysis revealed two *FAM111B* genetic variants. The c.917 A>G variant (rs200497516) was found in one SSc patients, and one control, and was classified as a missense variant of unknown significance. The c.988 C>T variant (rs35732637) occurred in three SSc patients and 42/243 (17.3%) of healthy controls, and is a known polymorphism.

Conclusion: One rare variant was found in a patient with SSc but has no functional or structural impact on the *FAM111B* gene. In this cohort, *FAM111B* gene mutations are not associated with SSc.

Isiguzo G, Mayosi B, Thabane L. Quality of abstracts of pilot trials in heart failure: A systematic review. J Hypertens. 2018;36:E207–E208. doi: 10.1097/01.hjh.0000548847.31664.ef. **Full text available here**.

Objectives: In this systematic survey, we analyzed the quality measured as the completeness of the reporting of pilot trial abstracts in heart failure based on the CONSORT extension for reporting abstracts of the pilot trial. We also identified factors that are associated with reporting quality.

Methods: We searched Medline (PUBMED), Cochrane Controlled Trials Register, Scopus and African-wide information databases for abstracts from heart failure pilot trials in humans published from 1 January 1990 to 30 November 2016. These were assessed to determine the extent of adherence to CONSORT extension checklist for reporting of abstracts of pilot trials. Identified studies were screened for inclusion based on title and abstract. Data were independently extracted by two reviewers in duplicate using the checklist.

Results: Two hundred and twenty-eight (228) articles were retrieved, out of which, 92 met the inclusion criteria. The mean CONSORT extension score was 8.3/16 (Standard Deviation 1.7), the least reported items were the

source of funding (1% [1/92]), trial registration (13% [12/92]), randomization sequence (13% [12/92]), number randomized to each arm (16% [15/92]), and number analyzed in each arm (16% [15/92]). Multivariable regression analysis showed that pharmacological intervention pilot trials [Incidence rate ratio (IRR) = 0.83; 95% confidence interval (CI), 0.81–0.97], structured abstract (IRR = 1.10; 95% CI, 0.99–1.23), and CONSORT endorsement (IRR = 1.10; 955 CI, 1.09–1.23) were significantly associated with slightly better reporting quality.

Conclusion: The quality of reporting of abstracts of heart failure pilot trials from was suboptimal and influenced by use of structured abstract, journal endorsement of CONSORT statement and type of intervention. These findings are consistent with previous researches.

Isiguzo GC, Zunza M, Chirehwa M, Mayosi BM, Thabane L. Quality of pilot trial abstracts in heart failure is suboptimal: A systematic survey. Pilot Feasibility Stud. 2018;4:107. doi: 10.1186/s40814-018-0302-8. **Full text available here**.

Background: Pilot trials are miniature researches carried out with the sole aim of acting as the precursor for larger more definitive studies. Abstracts are used to summarize and introduce the findings to the reading audience. There is substantive empirical evidence showing that abstracts, despite their important roles, are not informative enough, lacking the necessary details. This systematic survey was designed to assess the quality of reporting of heart failure pilot trial abstracts. The quality of reporting was defined as the completeness of reporting based on adherence to the CONSORT extension for reporting of pilot trial abstracts. We also identified factors associated with reporting quality.

Methods: We searched MEDLINE (PubMed), Cochrane Controlled Trials Register, Scopus, and African-wide information databases for abstracts from heart failure pilot trials in humans published from 1 January 1990 to 30 November 2016. These were assessed to determine the extent of adherence to CONSORT extension checklist for reporting of abstracts of pilot trials. We screened identified studies for inclusion based on title and abstract. Data were independently extracted by two reviewers using the checklist. We used regression analysis to assess the association between completeness of reporting (measured as the number of items in the CONSORT extension checklist for reporting of abstracts in pilot trials contained in each abstract) and factors influencing the quality of the reports.

Results: Two hundred and twenty-eight (228) articles were retrieved, of which 92 met the inclusion criteria. The mean CONSORT extension score was 8.3/16 (standard deviation 1.7); the least reported items were the source of funding (1% [1/92]), trial registration (13% [12/92]), randomization sequence (13% [12/92]), number randomized to each arm (16% [15/92]), and number analyzed in each arm (16% [15/92]). Multivariable regression analysis showed that pharmacological intervention pilot trials [incidence rate ratio (IRR) = 0.88; 95% confidence interval (CI), 0.81–0.97] were significantly associated with better reporting. Other factors such as structured abstract (IRR = 1.10; 95% CI, 0.99–1.23) and CONSORT endorsement (IRR = 1.10; 95% CI, 0.99–1.23) only showed minimal relationship with better reporting quality.

Conclusion: The quality of reporting of abstracts of heart failure pilot trials was suboptimal. Pharmacological intervention was significantly associated with better reporting. These findings are consistent with previous research on reporting of trials.

Kengne AP, Mayosi BM. Modifiable stroke risk factors in Africa: Lessons from SIREN. Lancet Glob Health. 2018;6(4):e363–e364. doi: 10.1016/s2214-109x(18)30030-5. **Full text available here.**

No abstract available.

Langhorne P, O'Donnell MJ, Chin SL, Zhang H, Xavier D, Avezum A, et al. Practice patterns and outcomes after stroke across countries at different economic levels (INTERSTROKE): An international observational study. Lancet. 2018;391(10134):2019–2027. doi: https://doi.org/10.1016/S0140-6736(18)30802-X. **Full text not freely available**.

Background: Stroke disproportionately affects people in low-income and middle-income countries. Although improvements in stroke care and outcomes have been reported in high-income countries, little is known about practice and outcomes in low and middle-income countries. We aimed to compare patterns of care available and their association with patient outcomes across countries at different economic levels.

Methods: We studied the patterns and effect of practice variations (i.e., treatments used and access to services) among participants in the INTERSTROKE study, an international observational study that enrolled 13 447 stroke patients from 142 clinical sites in 32 countries between Jan 11, 2007, and Aug 8, 2015. We supplemented patient data with a questionnaire about health-care and stroke service facilities at all participating hospitals. Using univariate and multivariate regression analyses to account for patient case mix and service clustering, we estimated the association between services available, treatments given, and patient outcomes (death or dependency) at 1 month.

Findings: We obtained full information for 12 342 (92%) of 13 447 INTERSTROKE patients, from 108 hospitals in 28 countries; 2576 from 38 hospitals in ten high-income countries and 9766 from 70 hospitals in 18 low and middle income countries. Patients in low-income and middle-income countries more often had severe strokes, intracerebral haemorrhage, poorer access to services, and used fewer investigations and treatments (p<0·0001) than those in high income countries, although only differences in patient characteristics explained the poorer clinical outcomes in low and middle-income countries. However across all countries, irrespective of economic level, access to a stroke unit was associated with improved use of investigations and treatments, access to other rehabilitation services, and improved survival without severe dependency (odds ratio [OR] 1·29; 95% CI 1·14–1·44; all p<0·0001), which was independent of patient casemix characteristics and other measures of care. Use of acute antiplatelet treatment was associated with improved survival (1·39; 1·12–1·72) irrespective of other patient and service characteristics.

Interpretation: Evidence-based treatments, diagnostics, and stroke units were less commonly available or used in

low and middle-income countries. Access to stroke units and appropriate use of antiplatelet treatment were associated with improved recovery. Improved care and facilities in low-income and middle-income countries are essential to improve outcomes.

Munung NS, Mayosi BM, de Vries J. Genomics research in Africa and its impact on global health: Insights from African researchers. Glob Health Epidemiol Genom. 2018;3:e12. doi: 10.1017/gheg.2018.3. **Full text available here.**

Africa may be heading for an era of genomics medicine. There are also expectations that genomics may play a role in reducing global health inequities. However, the near lack of genomics studies on African populations has led to concerns that genomics may widen, rather than close, the global health inequity gap. To prevent a possible genomics divide, the genomics 'revolution' has been extended to Africa. This is motivated, in part, by Africa's rich genetic diversity and high disease burden. What remains unclear, however, are the prospects of using genomics technology for healthcare in Africa. In this qualitative study, we explored the views of 17 genomics researchers in Africa on the prospects and challenges of genomics medicine in Africa. Interviewees were researchers in Africa who were involved in genomics research projects in Africa. Analysis of in-depth interviews suggest that genomics medicine may have an impact on disease surveillance, diagnosis, treatment and prevention. However, Africa's capacity for genomics medicine, current research priorities in genomics and the translation of research findings will be key defining factors impacting on the ability of genomics medicine to improve healthcare in Africa.

Musuku J, Engel ME, Musonda P, Lungu JC, Machila E, Schwaninger S, et al. Prevalence of rheumatic heart disease in Zambian school children. BMC Cardiovasc Disord. 2018;18(1):135. doi: 10.1186/s12872-018-0871-8. **Full text available here**.

Background: The large global burden of rheumatic heart disease (RHD) has come to light in recent years following robust epidemiologic studies. As an operational research component of a broad program aimed at primary and secondary prevention of RHD, we sought to determine the current prevalence of RHD in the country's capital, Lusaka, using a modern imaging-based screening methodology.

In addition, we wished to evaluate the practicality of training local radiographers in echocardiography screening methods.

Methods: Echocardiography was conducted on a random sample of students in 15 schools utilizing a previously validated, abbreviated screening protocol. Through a task-shifting scheme, and in the spirit of capacity-building to enhance local diagnostic and research skills, general radiographers based at Lusaka University Teaching Hospital (UTH) were newly trained to use portable echocardiography devices. Students deemed as screen-positive were referred for comprehensive echocardiography and clinical examination at UTH. Cardiac abnormalities were classified according to standard World Heart Federation criteria.

Results: Of 1102 students that were consented and screened, 53 students were referred for confirmatory echo-cardiography. Three students had definite RHD, 10 had borderline RHD, 29 were normal, and 11 students were lost to follow-up. The rates of definite, borderline, and total RHD were 2.7 per 1000, 9.1 per 1000, and 11.8 per 1000, respectively. Anterior mitral valve leaflet thickening and chordal thickening were the most common morphological defects. The pairwise kappa test showed fair agreement between the local radiographers and an echocardiographer quality assurance specialist.
Conclusion: The prevalence of asymptomatic RHD in urban communities in Zambia is within the range of results reported in other sub-Saharan African countries using the WHF criteria. Task-shifting local radiographers to conduct echocardiography was feasible. The results of this study will be used to inform ongoing efforts in Zambia to control and eventually eliminate RHD.
Trial registration: The study was registered on clinicaltrials.gov (#NCT02661763).

Ojji DB, Poulter N, Damasceno A, Sliwa K, Smythe W, Kramer N, et al. Rationale and design of the comparison of 3 combination therapies in lowering blood pressure in black Africans (CREOLE study): 2 × 3 factorial randomized single-blind multicenter trial. Am Heart J. 2018;202:5–12. doi: 10.1016/j.ahj.2018.03.023. **Full text not freely available**.

Background: Current hypertension guidelines recommend the use of combination therapy as first-line treatment or early in the management of hypertensive patients. Although there are many possible combinations of blood pressure (BP)-lowering therapies, the best combination for the black population is still a subject of debate because no large randomized controlled trials have been conducted in this group to compare the efficacy of different combination therapies to address this issue.
Methods: The comparison of 3 combination therapies in lowering BP in the black Africans (CREOLE) study is a randomized single-blind trial that will compare the efficacy of amlodipine plus hydrochlorothiazide versus amlodipine plus perindopril and versus perindopril plus hydrochlorothiazide in blacks residing in sub-Saharan Africa (SSA). Seven hundred two patients aged 30–79 years with a sitting systolic BP of 140 mm Hg and above, and less than 160mm Hg on antihypertensive monotherapy, or sitting systolic BP of 150mm Hg and above, and less than 180mm Hg on no treatment, will be centrally randomized into any of the 3 arms (234 into each arm). The CREOLE study is taking place in 10 sites in SSA, and the primary outcome measure is change in ambulatory systolic BP from baseline to 6 months. The first patient was randomized in June 2017, and the trial will be concluded by 2019.
Conclusions: The CREOLE trial will provide unique information as to the most efficacious 2-drug combination in blacks residing in SSA and thereby inform the development of clinical guidelines for the treatment of hypertension in this subregion.

Prabhakaran D, Anand S, Watkins D, Gaziano T, Wu Y, Mbanya JC, et al. Cardiovascular, respiratory, and

related disorders: Key messages from Disease Control Priorities, 3rd edition. Lancet. 2018; 391(10126):1224–1236. doi: 10.1016/S0140-6736(17)32471-6. **Full text not freely available**.

Cardiovascular, respiratory, and related disorders (CVRDs) are the leading causes of adult death worldwide, and substantial inequalities in care of patients with CVRDs exist between countries of high income and countries of low and middle income. Based on current trends, the UN Sustainable Development Goal to reduce premature mortality due to CVRDs by a third by 2030 will be challenging for many countries of low and middle income. We did systematic literature reviews of effectiveness and cost-effectiveness to identify priority interventions. We summarise the key findings and present a costed essential package of interventions to reduce risk of and manage CVRDs. On a population level, we recommend tobacco taxation, bans on trans fats, and compulsory reduction of salt in manufactured food products. We suggest primary health services be strengthened through the establishment of locally endorsed guidelines and ensured availability of essential medications. The policy interventions and health service delivery package we suggest could serve as the cornerstone for the management of CVRDs, and afford substantial financial risk protection for vulnerable households. We estimate that full implementation of the essential package would cost an additional US$21 per person in the average low-income country and $24 in the average lower-middle-income country. The essential package we describe could be a starting place for low-income and middle-income countries developing universal health coverage packages. Interventions could be rolled out as disease burden demands and budgets allow. Our outlined interventions provide a pathway for countries attempting to convert the UN Sustainable Development Goal commitments into tangible action.

Prendergast EA, Perkins S, Engel ME, Cupido B, Francis V, Joachim A, et al. Participation in research improves overall patient management: Insights from the Global Rheumatic Heart Disease registry (REMEDY). Cardiovasc J Afr. 2018;29(2):98–105. doi: 10.5830/cvja-2017-054. **Full text not freely available**.

Background: Rheumatic heart disease (RHD) is a major public health problem in low- and middle-income countries (LIMCs), with a paucity of high-quality trial data to improve patient outcomes. Investigators felt that involvement in a recent large, observational RHD study impacted positively on their practice, but this was poorly defined. Aim: The purpose of this study was to document the experience of investigators and research team members from LMICs who participated in a prospective, multi-centre study, the global Rheumatic Heart Disease Registry (REMEDY), conducted in 25 centres in 14 countries from 2010 to 2012.

Method: We conducted an online survey of site personnel to identify and quantify their experiences. Telephone interviews were conducted with a subset of respondents to gather additional qualitative data. We asked about their experiences, positive and negative, and about any changes in RHD management practices resulting from their participation in REMEDY as a registry site.

Results: The majority of respondents in both the survey and telephone interviews indicated that participation as a registry site improved their management of RHD patients. Administrative changes included increased attention to follow-up appointments and details in patient records. Clinical changes included increased use of penicillin

prophylaxis, and more frequent INR monitoring and contraceptive counselling.
Conclusion: Our study demonstrates that participation in clinical research on RHD can have a positive impact on patient management. Furthermore, REMEDY has led to increased patient awareness and improved healthcare workers' knowledge and efficiency in caring for RHD patients.

Ramasamy V, Mayosi BM, Sturrock ED, Ntsekhe M. Established and novel pathophysiological mechanisms of pericardial injury and constrictive pericarditis. World J Cardiol. 2018;10(9):87–96. doi: 10.4330/wjc.v10.i9.87.

This review article aims to: (1) discern from the literature the immune and inflammatory processes occurring in the pericardium following injury; and (2) to delve into the molecular mechanisms which may play a role in the progression to constrictive pericarditis. Pericarditis arises as a result of a wide spectrum of pathologies of both infectious and non-infectious aetiology, which lead to various degrees of fibrogenesis. Current understanding of the sequence of molecular events leading to pathological manifestations of constrictive pericarditis is poor. The identification of key mechanisms and pathways common to most fibrotic events in the pericardium can aid in the design and development of novel interventions for the prevention and management of constriction. We have identified through this review various cellular events and signalling cascades which are likely to contribute to the pathological fibrotic phenotype. An initial classical pattern of inflammation arises as a result of insult to the pericardium and can exacerbate into an exaggerated or prolonged inflammatory state. Whilst the implication of major drivers of inflammation and fibrosis such as tumour necrosis factor and transforming growth factor beta were foreseeable, the identification of pericardial deregulation of other mediators (basic fibroblast growth factor, galectin-3 and the tetrapeptide Ac-SDKP) provides important avenues for further research.

Sani MU, Davison BA, Cotter G, Mayosi BM, Edwards C, Ogah OS, et al. Prevalence, clinical characteristics and outcomes of valvular atrial fibrillation in a cohort of African patients with acute heart failure: Insights from the THESUS-HF registry. Cardiovasc J Afr. 2018;29(3):139–145. doi: 10.5830/cvja-2017-051. **Full text not freely available**.

Introduction: Rheumatic heart disease (RHD) is the commonest cause of valvular heart disease and a common cause of heart failure in sub-Saharan Africa (SSA). Atrial fibrillation (AF) complicates RHD, precipitates and worsens heart failure and cause unfavourable outcomes. We set out to describe the prevalence, clinical characteristics and outcomes of valvular atrial fibrillation in a cohort of African patients with acute heart failure (AHF).
Methods: The sub-Saharan Africa Survey of Heart Failure (THESUS-HF) was a prospective, observational survey of AHF in nine countries. We collected demographic data, medical history and signs and symptoms of HF. Electrocardiograms (ECGs) were done in a standard fashion. AF was defined as either a history of AF or AF on the admission ECG. Using Cox regression models, we examined the associations of AF with all-cause death over

180 days and a composite endpoint of all-cause death or readmission over 60 days.
Results: There were 1 006 patients in the registry. The mean age was 52.3 years and 50.8% were women. AF was present in 209 (20.8%) cases. Those with AF were older (57.1 *vs* 51.1 years), more likely to be female (57.4 *vs* 49.1%), had significantly lower systolic (125 *vs* 132 mmHg) and diastolic (81 *vs* 85 mmHg) blood pressure (BP), and higher heart rates (109 *vs* 102 bpm). Ninety-two (44%) AF patients had valvular heart disease. The presence of AF was not associated with the primary endpoints, but having valvular AF predicted death within 180 days.
Conclusions: AF was present in one-fifth of African patients with AHF. Almost half of the AF patients had valvular disease (RHD) and were significantly younger and at risk of dying within six months. It is important to identify these high-risk patients and prioritise their management, especially in SSA where resources are limited.

Shenje J, Lai RP, Ross IL, Mayosi BM, Wilkinson RJ, Ntsekhe M, et al. Effect of prednisolone on inflammatory markers in pericardial tuberculosis: A pilot study. Int J Cardiol Heart Vasc. 2018; 18:104–108. doi: 10.1016/j.ijcha.2017.10.002. **Full text available here**.

Background: Pericardial disorders are a common cause of heart disease, and the most common cause of pericarditis in developing countries is tuberculous (TB) pericarditis. It has been shown that prednisolone added to standard anti-TB therapy leads to a lower rate of constrictive pericarditis. We conducted a pilot study to evaluate the effect of adjunctive prednisolone treatment on the concentration of inflammatory markers in pericardial tuberculosis, in order to inform immunological mechanisms at the disease site.
Methods: Pericardial fluid, plasma and saliva samples were collected from fourteen patients with pericardial tuberculosis, at multiple time points. Inflammatory markers were measured using multiplex luminex analysis and ELISA.
Results: In samples from 14 patients we confirmed a strongly compartmentalized immune response at the disease site and found that prednisolone significantly reduced IL-6 concentrations in plasma by 8 hours of treatment, IL-1beta concentrations in saliva, as well as IL-8 concentrations in both pericardial fluid and saliva by 24 hours.
Conclusion: Monitoring the early effect of adjunctive immunotherapy in plasma or saliva is a possibility in pericarditis.

Szymanski PZ, Badri M, Mayosi BM. Clinical characteristics and causes of heart failure, adherence to treatment guidelines, and mortality of patients with acute heart failure: Experience at Groote Schuur Hospital, Cape Town, South Africa. S Afr Med J. 2018;108(2):94–98. doi: 10.7196/SAMJ.2017.v108i2.12519. **Full text available here**.

Background: There is limited information on acute heart failure (AHF) and its treatment in sub-Saharan Africa.
Objective: To describe the clinical characteristics and causes of heart failure (HF), adherence to HF treatment guidelines, and mortality of patients with AHF presenting to Groote Schuur Hospital (GSH), Cape Town, South

Africa.
Methods: This sub-study of The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF) was a prospective and observational survey that focused on the enrolment and follow-up of additional patients with AHF presenting to GSH and entered into the existing registry after publication of the primary THESUS-HF article in 2012. The patients were classified into prevalent (existing) or incident (new) cases of HF.
Results: Of the 119 patients included, 69 (58.0%) were female and the mean (standard deviation) age was 49.9 (16.3) years. The majority of prevalent cases were patients of mixed ancestry (63.3%), and prevalent cases had more hypertension (70.0%), diabetes mellitus (36.7%), hyperlipidaemia (33.3%) and ischaemic heart disease (IHD) (36.7%) than incident cases. The top five causes of HF were cardiomyopathy (20.2%), IHD (19.3%), rheumatic valvular heart disease (RHD) (18.5%), cor pulmonale (11.8%) and hypertension (10.1%), with the remaining 20.1% consisting of miscellaneous causes including pericarditis, toxins and congenital heart disease. Most patients received renin-angiotensin system blockers and loop diuretics on discharge. There was a low rate of beta-blocker, aldosterone antagonist and digoxin use. Rehospitalisation within 180 days occurred in 25.2% of cases. In-hospital mortality was 8.4% and the case fatality rate at 6 months was 26.1%.
Conclusion: In Cape Town, the main causes of AHF are cardiomyopathy, IHD and RHD. AHF affects a young population and is associated with a high rate of rehospitalisation and mortality. There is serious under-use of beta-blockers, aldosterone antagonists and digoxin. Emphasis on the rigorous application of treatment guidelines is needed to reduce readmission and mortality.

Talle MA, Bonny A, Scholtz W, Chin A, Nel G, Karaye KM, et al. Status of cardiac arrhythmia services in Africa in 2018: a PASCAR Sudden Cardiac Death Task Force report. Cardiovasc J Afr. 2018; 29(2):115–121. doi: 10.5830/cvja-2018-027. **Full text not freely available**.

Background: There is limited information on the availability of health services to treat cardiac arrhythmias in Africa.
Methods: The Pan-African Society of Cardiology (PASCAR) Sudden Cardiac Death Task Force conducted a survey of the burden of cardiac arrhythmias and related services over two months (15 October to 15 December) in 2017. An electronic questionnaire was completed by general cardiologists and electrophysiologists working in African countries. The questionnaire focused on availability of human resources, diagnostic tools and treatment modalities in each country.
Results: We received responses from physicians in 33 out of 55 (60%) African countries. Limited use of basic cardiovascular drugs such as anti-arrhythmics and anticoagulants prevails. Non-vitamin K-dependent oral anticoagulants (NOACs) are not widely used on the continent, even in North Africa. Six (18%) of the sub-Saharan African (SSA) countries do not have a registered cardiologist and about one-third do not have pacemaker services. The median pacemaker implantation rate was 2.66 per million population per country, which is 200-fold lower than in Europe. The density of pacemaker facilities and operators in Africa is quite low, with a median of 0.14 (0.03–6.36) centres and 0.10 (0.05–9.49) operators per million population. Less than half of the African countries

have a functional catheter laboratory with only South Africa providing the full complement of services for cardiac arrhythmia in SSA. Overall, countries in North Africa have better coverage, leaving more than 110 million people in SSA without access to effective basic treatment for cardiac conduction disturbances.
Conclusion: The lack of diagnostic and treatment services for cardiac arrhythmias is a common scenario in the majority of SSA countries, resulting in sub-optimal care and a subsequent high burden of premature cardiac death. There is a need to improve the standard of care by providing essential services such as cardiac pacemaker implantation.

Thomas V, Schulein S, Millar RN, Mayosi BM. Clinical characteristics and outcome of lone atrial fibrillation at a tertiary referral centre: The Groote Schuur Hospital experience. Cardiovasc J Afr. 2018; 29(5):268–272. doi: 10.5830/cvja-2018-005. **Full text not freely available**.

Introduction: Atrial fibrillation (AF) is a relatively common arrhythmia. When AF represents an electrophysiological phenomenon in structurally normal hearts, it is termed lone AF. This study was a retrospective, case-based analysis of patients attending the Cardiac Clinic at Groote Schuur Hospital (GSH) and describes the clinical characteristics and outcomes of patients classified as having lone atrial fibrillation. To the best of our knowledge there are no such studies reported from Africa.
Methods: This was a retrospective, descriptive study in which 289 medical records of patients with AF at the GSH Cardiac Clinic were reviewed from 1992 to 2006. The clinical data were interrogated to exclude identifiable causes of AF. Information on clinical characteristics and outcomes were entered into a data-entry form. Baseline descriptive statistics were expressed as means and range for continuous variables, and counts with percentages for categorical variables.
Results: Fifteen per cent (n = 42) of patients were identified as having lone AF, with a mean follow-up time of 5.8 years. Males comprised 57% (n = 24) and females 43% (n = 18). Fifty per cent (n = 21) of the patients had paroxysmal AF, 29% (n = 12) had persistent AF, and 12% (n = 5) progressed from paroxysmal to permanent AF. Subsets of lone AF included concomitant atrial flutter (17%) (n = 7) and sick sinus syndrome (21%) (n = 9). Complications were stroke (10%) (n = 4), tachycardia-related cardiomyopathy (17%) (n = 7) and bleeding complications on warfarin (11%) (n = 3).
Conclusions: Lone AF is not an uncommon arrhythmia, with a preponderance in thin, middle-aged males. The symptoms of lone AF can be debilitating. It has associated morbidity, including tachycardia-related cardiomyopathy and thromboembolism. Rate control and appropriate anticoagulation are the cornerstones of patient management.

Watkins DA, Beaton AZ, Carapetis JR, Karthikeyan G, Mayosi BM, Wyber R, et al. Rheumatic heart disease

worldwide: JACC Scientific Expert Panel. J Am Coll Cardiol. 2018;72(12):1397–1416. doi: 10.1016/j.jacc.2018.06.063. **Full text not freely available**.

Rheumatic heart disease (RHD) is a preventable heart condition that remains endemic among vulnerable groups in many countries. After a period of relative neglect, there has been a resurging interest in RHD worldwide over the past decade. In this Scientific Expert Panel, the authors summarize recent advances in the science of RHD and sketch out priorities for current action and future research. Key questions for laboratory research into disease pathogenesis and epidemiological research on the burden of disease are identified. The authors present a variety of pressing clinical research questions on optimal RHD prevention and advanced care. In addition, they propose a policy and implementation research agenda that can help translate current evidence into tangible action. The authors maintain that, despite knowledge gaps, there is sufficient evidence for national and global action on RHD, and they argue that RHD is a model for strengthening health systems to address other cardiovascular diseases in limited-resource countries.

Wiyeh AB, Ochodo EA, Wiysonge CS, Kakia A, Awotedu AA, Ristic A, et al. A systematic review of the efficacy and safety of intrapericardial fibrinolysis in patients with pericardial effusion. Int J Cardiol. 2018;250:223–228. doi: 10.1016/j.ijcard.2017.10.049. **Full text available here**.

Pericardial effusion is the abnormal accumulation of fluid in the pericardial space. The complications of pericardial effusion can either be acute (e.g., cardiac tamponade) or chronic (e.g., constrictive pericarditis). We have conducted a systematic review of the scientific literature to evaluate the efficacy and safety of intrapericardial fibrinolysis in preventing complications of pericardial effusion. We searched for both published and unpublished studies. 29 studies, with a total of 109 patients were included in this review; 17 case reports, 11 case series, and one randomised controlled trial (RCT). All included studies had a high risk of bias. The most common causes of pericardial effusion were *Staphylococcus aureus* (12 studies with 23 cases) and *Mycobacterium tuberculosis* (2 studies with 19 cases). The most common fibrinolytic agents used were streptokinase (15 studies) and urokinase (5 studies). Intrapericardial fibrinolysis prevented complications in 94 (86.2%) patients. Non-fatal procedure-related complications were reported 21 (19.2%) patients. No patient died following intrapericardial fibrinolysis. There is very low certainty of the efficiency and safety of intrapericardial fibrinolysis in preventing the complications of pericardial effusion. High quality RCTs are required to address this question.

Wiysonge CS, Bradley HA, Volmink J, Mayosi BM. Cochrane corner: Beta-blockers for hypertension. Heart. 2018;104(4):282–283. doi: 10.1136/heartjnl-2017-311585. **Full text available here**.

No abstract available.

Wunderly K, Yousef Z, Bonny A, Weatherwax KJ, Lavan B, Allmendinger C, et al. Using reconditioned

pacemakers to treat bradycardia in Africa. Nat Rev Cardiol. 2018;15(12):725–726. doi: 10.1038/s41569-018-0076-y. **Full text not freely available**.

No abstract available.

Zilla P, Bolman RM, Yacoub MH, Beyersdorf F, Sliwa K, Zuhlke L, et al. The Cape Town declaration on access to cardiac surgery in the developing world. S Afr Med J. 2018;108(9):702–704. doi: 10.7196/SAMJ.2018.v108i9.13102. **Full text available here**.

Twelve years after cardiologists and cardiac surgeons from all over the world issued the 'Drakensberg Declaration on the Control of Rheumatic Fever and Rheumatic Heart Disease in Africa', calling on the world community to address the prevention and treatment of rheumatic heart disease (RHD) through improving living conditions, to develop pilot programmes at selected sites for control of rheumatic fever and RHD, and to periodically review progress made and challenges that remain, RHD still accounts for a major proportion of cardiovascular diseases in children and young adults in low- and middle-income countries, where more than 80% of the world population live. Globally equal in prevalence to human immunodeficiency virus infection, RHD affects 33 million people worldwide. Prevention efforts have been important but have failed to eradicate the disease. At the present time, the only effective treatment for symptomatic RHD is open heart surgery, yet that life-saving cardiac surgery is woefully absent in many endemic regions. In this declaration, we propose a framework structure to create a co-ordinated and transparent international alliance to address this inequality.

Zilla P, Yacoub M, Zuhlke L, Beyersdorf F, Sliwa K, Khubulava G, et al. Global unmet needs in cardiac surgery. Glob Heart. 2018;13(4):293–303. doi: 10.1016/j.gheart.2018.08.002. **Full text available here**.

More than 6 billion people live outside industrialized countries and have insufficient access to cardiac surgery. Given the recently confirmed high prevailing mortality for rheumatic heart disease in many of these countries together with increasing numbers of patients needing interventions for lifestyle diseases due to an accelerating epidemiological transition, a significant need for cardiac surgery could be assumed. Yet, need estimates were largely based on extrapolated screening studies while true service levels remained unknown. A multi-author effort representing 16 high-, middle-, and low-income countries was undertaken to narrow the need assessment for cardiac surgery including rheumatic and lifestyle cardiac diseases as well as congenital heart disease on the basis of existing data deduction. Actual levels of cardiac surgery were determined in each of these countries on the basis of questionnaires, national databases, or annual reports of national societies. Need estimates range from 200 operations per million in low-income countries that are nonendemic for rheumatic heart disease to >1,000 operations per million in high-income countries representing the end of the epidemiological transition. Actually provided levels of cardiac surgery range from 0.5 per million in the assessed low- and lower-middle income countries (average 107 ± 113 per million; representing a population of 1.6 billion) to 500 in the upper-middle-

income countries (average 270 ± 163 per million representing a population of 1.9 billion). By combining need estimates with the assessment of de facto provided levels of cardiac surgery, it emerged that a significant degree of underdelivery of often lifesaving open heart surgery does not only prevail in low-income countries but is also disturbingly high in middle-income countries.

2017

Agyepong IA, Sewankambo N, Binagwaho A, Coll-Seck AM, Corrah T, Ezeh A, et al. The path to longer and healthier lives for all Africans by 2030: The Lancet Commission on the future of health in sub-Saharan Africa. Lancet. 2017;390(10114):2803–2859. doi: 10.1016/S0140-6736(17)31509-X. **Full text not freely available**.

> Sub-Saharan Africa's health challenges are numerous and wide-ranging. Most sub-Saharan African countries face a double burden of traditional, persisting health challenges, such as infectious diseases, malnutrition, and child and maternal mortality, and emerging challenges from an increasing prevalence of chronic conditions, mental health disorders, injuries, and health problems related to climate change and environmental degradation. Although there has been real progress on many health indicators, life expectancy and most population health indicators remain behind most low-income and middle-income countries in other parts of the world.
>
> Our Commission was prompted by sub-Saharan Africa's potential to improve health on its own terms, and largely with its own resources. The spirit of this Commission is one of evidence-based optimism, with caution. We recognise that major health inequities exist and that health outcomes are worst in fragile countries, rural areas, urban slums, and conflict zones, and among the poor, disabled, and marginalised. Moreover, sub- Saharan Africa is facing the challenges and opportunities of the largest cohort of young people in history, with the youth population aged under 25 years predicted to almost double from 230 million to 450 million by 2050. The future of health in Africa is bright, but only if no one is left behind.

Attaei MW, Khatib R, McKee M, Lear S, Dagenais G, Igumbor EU, et al. Availability and affordability of blood pressure-lowering medicines and the effect on blood pressure control in high-income, middle-income, and low-income countries: An analysis of the PURE study data. Lancet Public Health. 2017;2(9):e411–e419. doi: 10.1016/S2468-2667(17)30141-X. **Full text available here**.

> Background: Hypertension is considered the most important risk factor for cardiovascular diseases, but its control is poor worldwide. We aimed to assess the availability and affordability of blood pressure-lowering medicines, and the association with use of these medicines and blood pressure control in countries at varying levels of economic development.
>
> Methods: We analysed the availability, costs, and affordability of blood pressure-lowering medicines with data recorded from 626 communities in 20 countries participating in the Prospective Urban Rural Epidemiological

(PURE) study. Medicines were considered available if they were present in the local pharmacy when surveyed, and affordable if their combined cost was less than 20% of the households' capacity to pay. We related information about availability and affordability to use of these medicines and blood pressure control with multilevel mixed-effects logistic regression models, and compared results for high-income, upper-middle-income, lower-middle-income, and low-income countries. Data for India are presented separately because it has a large generic pharmaceutical industry and a higher availability of medicines than other countries at the same economic level.

Findings: The availability of two or more classes of blood pressure-lowering drugs was lower in low-income and middle-income countries (except for India) than in high-income countries. The proportion of communities with four drug classes available was 94% in high-income countries (108 of 115 communities), 76% in India (68 of 90), 71% in upper-middle-income countries (90 of 126), 47% in lower-middle-income countries (107 of 227), and 13% in low-income countries (nine of 68). The proportion of households unable to afford two blood pressure-lowering medicines was 31% in low-income countries (1069 of 3479 households), 9% in middle-income countries (5602 of 65 471), and less than 1% in high-income countries (44 of 10 880). Participants with known hypertension in communities that had all four drug classes available were more likely to use at least one blood pressure-lowering medicine (adjusted odds ratio [OR] 2·23, 95% CI 1·59–3·12); p<0·0001), combination therapy (1·53, 1·13–2·07; p=0·054), and have their blood pressure controlled (2·06, 1·69–2·50; p<0·0001) than were those in communities where blood pressure-lowering medicines were not available. Participants with known hypertension from households able to afford four blood pressure-lowering drug classes were more likely to use at least one blood pressure-lowering medicine (adjusted OR 1·42, 95% CI 1·25–1·62; p<0·0001), combination therapy (1·26, 1·08–1·47; p=0·0038), and have their blood pressure controlled (1·13, 1·00–1·28; p=0·0562) than were those unable to afford the medicines.

Interpretation: A large proportion of communities in low-income and middle-income countries do not have access to more than one blood pressure-lowering medicine and, when available, they are often not affordable. These factors are associated with poor blood pressure control. Ensuring access to affordable blood pressure-lowering medicines is essential for control of hypertension in low-income and middle-income countries.

Calligaro GL, Zijenah LS, Peter JG, Theron G, Buser V, McNerney R, et al. Effect of new tuberculosis diagnostic technologies on community-based intensified case finding: A multicentre randomised controlled trial. Lancet Infect Dis. 2017;17(4):441–450. doi: 10.1016/s1473-3099(16)30384-x. **Full text not freely available**.

Background: Inadequate case detection results in high levels of undiagnosed tuberculosis in sub-Saharan Africa. Data for the effect of new diagnostic tools when used for community-based intensified case finding are not available, so we investigated whether the use of sputum Xpert-MTB/RIF and the Determine TB LAM urine test in two African communities could be effective.

Methods: In a pragmatic, randomised, parallel-group trial with individual randomisation stratified by country, we compared sputum Xpert-MTB/RIF, and if HIV-infected, the Determine TB LAM urine test (novel diagnostic group), with laboratory-based sputum smear microscopy (routine diagnostic group) for intensified case finding in communities with high tuberculosis and HIV prevalence in Cape Town, South Africa, and Harare, Zimbabwe. Participants were randomly assigned (1:1) to these groups with computer-generated allocation lists, using culture as the reference standard. In Cape Town, participants were randomised and tested at an Xpert-equipped mobile van, while in Harare, participants were driven to a local clinic where the same diagnostic tests were done. The primary endpoint was the proportion of culture-positive tuberculosis cases initiating tuberculosis treatment in each study group at 60 days. This trial is registered at ClinicalTrials.gov, number NCT01990274.
Findings: Between Oct 18, 2013, and March 31, 2015, 2261 individuals were screened and 875 (39%) of these met the criteria for diagnostic testing. 439 participants were randomly assigned to the novel group and 436 to the routine group. 74 (9%) of 875 participants had confirmed tuberculosis. If late culture-based treatment initiation was excluded, more patients with culture-positive tuberculosis were initiated on treatment in the novel group at 60 days (36 [86%] of 42 in the novel group *vs* 18 [56%] of 32 in the routine group). Thus the difference in the proportion initiating treatment between groups was 29% (95% CI 9–50, p=0.0047) and 53% more patients initiated therapy in the novel diagnostic group than in the routine diagnostic group. One culture-positive patient was treated based only on a positive LAM test.
Interpretation: Compared with traditional tools, Xpert-MTB/RIF for community-based intensified case finding in HIV and tuberculosis-endemic settings increased the proportion of patients initiating treatment. By contrast, urine LAM testing was not found to be useful for intensive case finding in this setting.

Dehghan M, Mente A, Zhang X, Swaminathan S, Li W, Mohan V, et al. Associations of fats and carbo-hydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): a prospective cohort study. Lancet. 2017;390(10107):2050–2062. doi: 10.1016/S0140-6736(17)32252-3. **Full text not freely available**.

Background: The relationship between macronutrients and cardiovascular disease and mortality is controversial. Most available data are from European and North American populations where nutrition excess is more likely, so their applicability to other populations is unclear.
Methods: The Prospective Urban Rural Epidemiology (PURE) study is a large, epidemiological cohort study of individuals aged 35–70 years (enrolled between Jan 1, 2003, and March 31, 2013) in 18 countries with a median follow-up of 7·4 years (IQR 5·3–9·3). Dietary intake of 135 335 individuals was recorded using validated food frequency questionnaires. The primary outcomes were total mortality and major cardiovascular events (fatal cardiovascular disease, non-fatal myocardial infarction, stroke, and heart failure). Secondary outcomes were all myocardial infarctions, stroke, cardiovascular disease mortality, and non-cardiovascular disease mortality. Participants were categorised into quintiles of nutrient intake (carbohydrate, fats, and protein) based on

percentage of energy provided by nutrients. We assessed the associations between consumption of carbohydrate, total fat, and each type of fat with cardiovascular disease and total mortality. We calculated hazard ratios (HRs) using a multivariable Cox frailty model with random intercepts to account for centre clustering.
Findings: During follow-up, we documented 5796 deaths and 4784 major cardiovascular disease events. Higher carbohydrate intake was associated with an increased risk of total mortality (highest [quintile 5] *vs* lowest quintile [quintile 1] category, HR 1·28 [95% CI 1·12–1·46], p_{trend}=0·0001) but not with the risk of cardiovascular disease or cardiovascular disease mortality. Intake of total fat and each type of fat was associated with lower risk of total mortality (quintile 5 *vs* quintile 1, total fat: HR 0·77 [95% CI 0·67–0·87], p_{trend}<0·0001; saturated fat, HR 0·86 [0·76–0·99], p_{trend}=0·0088; monounsaturated fat: HR 0·81 [0·71–0·92], p_{trend}<0·0001; and polyunsaturated fat: HR 0·80 [0·71–0·89], p_{trend}<0·0001). Higher saturated fat intake was associated with lower risk of stroke (quintile 5 *vs* quintile 1, HR 0·79 [95% CI 0·64–0·98], p_{trend}=0·0498). Total fat and saturated and unsaturated fats were not significantly associated with risk of myocardial infarction or cardiovascular disease mortality.
Interpretation: High carbohydrate intake was associated with higher risk of total mortality, whereas total fat and individual types of fat were related to lower total mortality. Total fat and types of fat were not associated with cardiovascular disease, myocardial infarction, or cardiovascular disease mortality, whereas saturated fat had an inverse association with stroke. Global dietary guidelines should be reconsidered in light of these findings.

Dzudie A, Rayner B, Ojji D, Schutte AE, Twagirumukiza M, Damasceno A, et al. Roadmap to achieve 25% hypertension control in Africa by 2025. Cardiovasc J Afr. 2017;28(4):262–273. doi: 10.5830/CVJA-2017-040. **Full text not freely available**.

Background and aim: The Pan-African Society of Cardiology (PASCAR) has identified hypertension as the highest area of priority for action to reduce heart disease and stroke on the continent. The aim of this PASCAR roadmap on hypertension was to develop practical guidance on how to implement strategies that translate existing knowledge into effective action and improve detection, treatment and control of hypertension and cardiovascular health in sub-Saharan Africa (SSA) by the year 2025.
Methods: Development of this roadmap started with the creation of a consortium of experts with leadership skills in hypertension. In 2014, experts in different fields, including physicians and non-physicians, were invited to join. Via face-to-face meetings and teleconferences, the consortium made a situation analysis, set a goal, identified roadblocks and solutions to the management of hypertension and customised the World Heart Federation roadmap to Africa.
Results: Hypertension is a major crisis on the continent but very few randomised, controlled trials have been conducted on its management. Also, only 25.8% of the countries have developed or adopted guidelines for the management of hypertension. Other major roadblocks are either government and health-system related or healthcare professional or patient related. The PASCAR hypertension task force identified a 10-point action plan to be implemented by African ministries of health to achieve 25% control of hypertension in Africa by 2025.

Conclusions: Hypertension affects millions of people in SSA and if left untreated, is a major cause of heart disease and stroke. Very few SSA countries have a clear hypertension policy. This PASCAR roadmap identifies practical and effective solutions that would improve detection, treatment and control of hypertension on the continent and could be implemented as is or adapted to specific national settings.

Engel ME, Cohen K, Gounden R, Kengne AP, Barth DD, Whitelaw AC, et al. The Cape Town clinical decision rule for streptococcal pharyngitis in children. Pediatr Infect Dis J. 2017;36(3):250–255. doi: 10.1097/inf.0000000000001413. **Full text not freely available**.

Background: Existing clinical decision rules (CDRs) to diagnose group A streptococcal (GAS) pharyngitis have not been validated in sub-Saharan Africa. We developed a locally applicable CDR while evaluating existing CDRs for diagnosing GAS pharyngitis in South African children.

Methods: We conducted a prospective cohort study and enrolled 997 children 3–15 years of age presenting to primary care clinics with a complaint of sore throat, and whose parents provided consent. Main outcome measures were signs and symptoms of pharyngitis and a positive GAS culture from a throat swab. Bivariate and multivariate analyses were used to develop the CDR. In addition, the diagnostic effectiveness of 6 existing rules for predicting a positive culture in our cohort was assessed.

Results: A total of 206 of 982 children (21%) had a positive GAS culture. Tonsillar swelling, tonsillar exudates, tender or enlarged anterior cervical lymph nodes, absence of cough and absence of rhinorrhea were associated with positive cultures in bivariate and multivariate analyses. Four variables (tonsillar swelling and one of tonsillar exudate, no rhinorrhea, no cough), when used in a cumulative score, showed 83.7% sensitivity and 32.2% specificity for GAS pharyngitis. Of existing rules tested, the rule by McIsaac et al had the highest positive predictive value (28%), but missed 49% of the culture-positive children who should have been treated.

Conclusion: The new 4-variable CDR for GAS pharyngitis (ie, tonsillar swelling and one of tonsillar exudate, no rhinorrhea, no cough) outperformed existing rules for GAS pharyngitis diagnosis in children with symptomatic sore throat in Cape Town.

Essop MR, Mayosi BM. Echocardiographic detection of latent rheumatic heart disease: A Pandora's box? Circulation. 2017;136(23):2245–2247. doi: 10.1161/circulationaha.117.030642. **Full text not freely available**.

No abstract available.

Gcelu A, Deshpande G, Kalla AA, Tikly M, Mayosi B, Hodkinson B. Prevelance of *FAM111B* gene mutations in systemic sclerosis. Ann Rheum Dis. 2017;76:631. doi: 10.1136/annrheumdis-2017-eular.6719. **Full text not freely available**.

Background: Systemic sclerosis (SSc) is a prototypic systemic fibrotic disease with unclearly characterized genetic

basis. Implicated genes have been associated with autoimmune dysregulation with relatively few variants associated with fibrosis. We have discovered that mutations in *FAM111B* gene cause hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis (POIKTMP), a multisystem fibrotic condition with clinical aspects of SSc. This observation has established *FAM111B* as a candidate gene for SSc.

Objectives: The objective is to investigate whether *FAM111B* gene mutations are present in SSc patients and further explore relationships between *FAM111B* mutations and clinical expression of SSc.

Methods: Patients with a definite diagnosis of SSc attending the Rheumatology outpatient departments at Groote Schuur Hospital, Cape Town, and Chris Hani Baragwanath Hospital, Johannesburg, were enrolled into the study. Physical examination assessing the extent of disease was done in all patients and the modified Rodnan skin score (mRSS) was used to determine the extent of the skin involvement. Blood samples were collected for DNA extraction and mutation screening using the high-resolution melt technique. Samples with abnormal electropherograms were selected for Sanger sequencing to identify mutations. Public databases were used to verify the frequency of variants in *FAM111B*.

Results: 131 patients were genotyped, 13 men and 118 women, with a mean age of 26.6 years and mean age of symptom onset at 25.3 years. The majority of patients were black (59.5%). 72% of patients had diffuse systemic sclerosis (DSSc) with a median mRSS of 11. Genetic analysis revealed seven rare genetic variants (C832G>A; C855G>T; C917A>G; C937G>A; C988C>T; C995A>C and C1006G>C) in eight patients (five patients from Johannesburg and three patients from Cape Town). These variants were missense mutations of unknown significance with a minor allele frequency <0.01. No *FAM111B* mutations that cause POIKMT were found in patients with SSc.

Conclusions: Rare genetic variants of unknown significance (GVUS) in *FAM111B* gene were found in patients with SSc. It is possible that the GVUS may modify the function of *FAM111B*, and influence the pathogenesis of SSc or are rare polymorphisms with no functional impact.

Hyle EP, Mayosi BM, Middelkoop K, Mosepele M, Martey EB, Walensky RP, et al. The association between HIV and atherosclerotic cardiovascular disease in sub-Saharan Africa: A systematic review. BMC Public Health. 2017;17(1):954. doi: 10.1186/s12889-017-4940-1. **Full text available here**.

Background: Sub-Saharan Africa (SSA) has confronted decades of the HIV epidemic with substantial improvements in access to life-saving antiretroviral therapy (ART). Now, with improved survival, people living with HIV (PLWH) are at increased risk for non-communicable diseases (NCDs), including atherosclerotic cardiovascular disease (CVD). We assessed the existing literature regarding the association of CVD outcomes and HIV in SSA.

Methods: We used the PRISMA guidelines to perform a systematic review of the published literature regarding the association of CVD and HIV in SSA with a focus on CVD surrogate and clinical outcomes in PLWH.

Results: From January 2000 until March 2017, 31 articles were published regarding CVD outcomes among PLWH in SSA. Data from surrogate CVD outcomes (n = 13) suggest an increased risk of CVD events among PLWH in SSA. Although acute coronary syndrome is reported infrequently in SSA among PLWH, limited data from five studies suggest extensive thrombus and hypercoagulability as contributing factors. Additional studies suggest an increased risk of stroke among PLWH (n = 13); however, most data are from immunosuppressed ART-naive PLWH and thus are potentially confounded by the possibility of central nervous system infections.
Conclusions: Given ongoing gaps in our current understanding of CVD and other NCDs in PLWH in SSA, it is imperative to ascertain the burden of CVD outcomes, and to examine strategies for intervention and best practices to enhance the health of this vulnerable population.

Isiguzo G, Zunza M, Chirehwa M, Mayosi BM, Thabane L. Quality of abstracts of pilot trials in heart failure: A protocol for a systematic survey. Contemp Clin Trials Commun. 2017;8:258–263. doi: 10.1016/j.conctc.2017.11.004. **Full text available here**.

Introduction: Pilot trials are initial small-scale studies done to inform the design of larger trials. Their findings like other studies are usually disseminated as peer-reviewed journal articles. Abstracts are used to introduce the contents to readers, and give a general idea about the full reports and sometimes are the only source of information available to readers. Despite their importance, the contents of abstracts of trial reports are usually not informative enough and lack the essential details.
Methods and Analysis: This is a protocol for a planned systematic survey with a primary aim of analyzing the reporting quality measured as the completeness of the reporting of pilot trial abstracts in heart failure. The secondary aim will be to explore factors associated with better reporting quality. Abstracts of heart failure pilot trials in humans (journal and conference abstracts) published in the English language from 1 January 1990 to 30 November 2016 will be assessed to determine the reporting quality, based on the CONSORT 2010 statement extension to randomized pilot and feasibility trials. All non-pilot/feasibility trials and non-human pilot trials will be excluded. We will search Medline (PUBMED), Cochrane controlled trials register, Scopus and African wide information databases for pilot trials in heart failure. Title and abstracts of identified studies will be screened for inclusion and data extracted independently by two reviewers in duplicate without using the full text. Reported and unreported items on the abstracts will be presented as frequencies and percentages, a descriptive analysis will be used to interpret the reporting quality and regression analysis used for characteristics associated with greater statistical reporting at 95% confidence interval.
Review registration number: PROSPERO CRD42016049911.

Long A, Lungu JC, Machila E, Schwaninger S, Spector J, Tadmor B, et al. A programme to increase appropriate usage of benzathine penicillin for management of streptococcal pharyngitis and rheumatic heart disease in Zambia. Cardiovasc J Afr. 2017;28(4):242–247. doi: 10.5830/cvja-2017-002. **Full text not freely available**.

Rheumatic heart disease is highly prevalent and associated with substantial morbidity and mortality in many resource-poor areas of the world, including sub-Saharan Africa. Primary and secondary prophylaxis with penicillin has been shown to significantly improve outcomes and is recognised to be the standard of care, with intra-muscular benzathine penicillin G recommended as the preferred agent by many technical experts. However, ensuring compliance with therapy has proven to be challenging. As part of a public-private partnership initiative in Zambia, we conducted an educational and access-to-medicine programme aimed at increasing appropriate use of benzathine penicillin for the prevention and management of rheumatic heart disease, according to national guidelines. The programme was informed early on by identification of potential barriers to the administration of injectable penicillin, which included concern by health workers about allergic events. We describe this programme and report initial signs of success, as indicated by increased use of benzathine penicillin. We propose that a similar approach may have benefits in rheumatic heart disease programmes in other endemic regions.

Masiye F, Mayosi B, de Vries J. "I passed the test!" Evidence of diagnostic misconception in the recruitment of population controls for an H3Africa genomic study in Cape Town, South Africa. BMC Med Ethics. 2017;18(1):12. doi: 10.1186/s12910-017-0175-z. **Full text available here.**

Background: Advances in genetic and genomic research have introduced challenges in obtaining informed consent for research in low and middle-income settings. However, there are only few studies that have explored challenges in obtaining informed consent in genetic and genomic research in Africa and none in South Africa. To start filling this gap, we conducted an empirical study to investigate the efficacy of informed consent procedures for an H3Africa genomic study on Rheumatic Heart Disease (RHDGen) at the University of Cape Town in South Africa. The main aim of the study was to understand ethical challenges in obtaining informed consent in the RHDGen study.

Methods: We used a qualitative study methodology involving in-depth interviews and participant observations. Our study participants were RHDGen cases (patients), healthy controls and research staff involved in the recruitment of RHDGen cases and controls. In total, we conducted 32 in-depth interviews with RHDGen cases and controls, 2 in-depth interviews with research staff and 57 direct observations of the consent procedures of RHDGen cases and controls. The interviews were conducted in English, audio-recorded and transcribed verbatim. Data were analyzed using thematic content analysis. The study was conducted in 3 sites within Cape Town, South Africa.

Results: Most healthy controls joined the RHDGen study in order to be screened for rheumatic heart disease

(diagnostic misconception). A majority of RHDGen cases decided to join the RHDGen study because of therapeutic misconception.
Conclusion: The ethical challenges that impacted on obtaining informed consent in the RHDGen study were complex. In this study, the main challenges were diagnostic misconception among RHDGen controls and therapeutic misconception among RHDGen cases.

Mayosi BM, Fish M, Shaboodien G, Mastantuono E, Kraus S, Wieland T, et al. Identification of Cadherin 2 (CDH2) mutations in arrhythmogenic right ventricular cardiomyopathy. Circ Cardiovasc Genet. 2017;10(2):e001605. doi: 10.1161/CIRCGENETICS.116.001605. **Full text not freely available**.

Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetically heterogeneous condition caused by mutations in genes encoding desmosomal proteins in up to 60% of cases. The 40% of genotype-negative cases point to the need of identifying novel genetic substrates by studying genotype-negative ARVC families.
Methods and Results: Whole exome sequencing was performed on 2 cousins with ARVC. Validation of 13 heterozygous variants that survived internal quality and frequency filters was performed by Sanger sequencing. These variants were also genotyped in all family members to establish genotype–phenotype cosegregation. High-resolution melting analysis followed by Sanger sequencing was used to screen for mutations in cadherin 2 (CDH2) gene in unrelated genotypenegative patients with ARVC. In a 3-generation family, we identified by whole exome sequencing a novel mutation in CDH2 (c.686A>C, p.Gln229Pro) that cosegregated with ARVC in affected family members. The CDH2 c.686A>C variant was not present in >200 000 chromosomes available through public databases, which changes a conserved amino acid of cadherin 2 protein and is supported as the causal mutation by parametric linkage analysis. We subsequently screened 73 genotype-negative ARVC probands tested previously for mutations in known ARVC genes and found an additional likely pathogenic variant in CDH2 (c.1219G>A, p.Asp407Asn). CDH2 encodes cadherin 2 (also known as N-cadherin), a protein that plays a vital role in cell adhesion, making it a biologically plausible candidate gene in ARVC pathogenesis.
Conclusions: These data implicate CDH2 mutations as novel genetic causes of ARVC and contribute to a more complete identification of disease genes involved in cardiomyopathy.

Mente A, Dehghan M, Rangarajan S, McQueen M, Dagenais G, Wielgosz A, et al. Association of dietary nutrients with blood lipids and blood pressure in 18 countries: A cross-sectional analysis from the PURE study. Lancet Diabetes and Endocrinol. 2017;5(10):774–787. doi: 10.1016/S2213-8587(17)30283-8. **Full text not freely available**.

Background: The relation between dietary nutrients and cardiovascular disease risk markers in many regions worldwide is unknown. In this study, we investigated the effect of dietary nutrients on blood lipids and blood pressure, two of the most important risk factors for cardiovascular disease, in low-income, middle-income, and

high-income countries.
Methods: We studied 125287 participants from 18 countries in North America, South America, Europe, Africa, and Asia in the Prospective Urban Rural Epidemiology (PURE) study. Habitual food intake was measured with validated food frequency questionnaires. We assessed the associations between nutrients (total fats, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, carbohydrates, protein, and dietary cholesterol) and cardiovascular disease risk markers using multilevel modelling. The effect of isocaloric replacement of saturated fatty acids with other fats and carbohydrates was determined overall and by levels of intakes by use of nutrient density models. We did simulation modelling in which we assumed that the effects of saturated fatty acids on cardiovascular disease events was solely related to their association through an individual risk marker, and then compared these simulated risk marker based estimates with directly observed associations of saturated fatty acids with cardiovascular disease events. Findings: Participants were enrolled into the study from Jan 1, 2003, to March 31, 2013. Intake of total fat and each type of fat was associated with higher concentrations of total cholesterol and LDL cholesterol, but also with higher HDL cholesterol and apolipoprotein A1 (ApoA1), and lower triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and ratio of apolipoprotein B (ApoB) to ApoA1 (all p_{trend}<0·0001). Higher carbohydrate intake was associated with lower total cholesterol, LDL cholesterol, and ApoB, but also with lower HDL cholesterol and ApoA1, and higher triglycerides, ratio of total cholesterol to HDL cholesterol, ratio of triglycerides to HDL cholesterol, and ApoB-to-ApoA1 ratio (all p_{trend}<0·0001, apart from ApoB [p_{trend}=0·0014]). Higher intakes of total fat, saturated fatty acids, and carbohydrates were associated with higher blood pressure, whereas higher protein intake was associated with lower blood pressure. Replacement of saturated fatty acids with carbohydrates was associated with the most adverse effects on lipids, whereas replacement of saturated fatty acids with unsaturated fats improved some risk markers (LDL cholesterol and blood pressure), but seemed to worsen others (HDL cholesterol and triglycerides). The observed associations between saturated fatty acids and cardiovascular disease events were approximated by the simulated associations mediated through the effects on the ApoB-to-ApoA1 ratio, but not with other lipid markers including LDL cholesterol.
Interpretation: Our data are at odds with current recommendations to reduce total fat and saturated fats. Reducing saturated fatty acid intake and replacing it with carbohydrate has an adverse effect on blood lipids. Substituting saturated fatty acids with unsaturated fats might improve some risk markers, but might worsen others. Simulations suggest that ApoB-to-ApoA1 ratio probably provides the best overall indication of the effect of saturated fatty acids on cardiovascular disease risk among the markers tested. Focusing on a single lipid marker such as LDL cholesterol alone does not capture the net clinical effects of nutrients on cardiovascular risk.

Miller V, Mente A, Dehghan M, Rangarajan S, Zhang X, Swaminathan S, et al. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): A prospective cohort study. Lancet. 2017;390(10107):2037–2049. doi: 10.1016/S0140-6736(17)32253-5. **Full text not freely available**.

Background: The association between intake of fruits, vegetables, and legumes with cardiovascular disease and deaths has been investigated extensively in Europe, the USA, Japan, and China, but little or no data are available from the Middle East, South America, Africa, or south Asia.
Methods: We did a prospective cohort study (Prospective Urban Rural Epidemiology [PURE] in 135 335 individuals aged 35 to 70 years without cardiovascular disease from 613 communities in 18 low-income, middle-income, and high income countries in seven geographical regions: North America and Europe, South America, the Middle East, south Asia, China, southeast Asia, and Africa. We documented their diet using country-specific food frequency questionnaires at baseline. Standardised questionnaires were used to collect information about demographic factors, socioeconomic status (education, income, and employment), lifestyle (smoking, physical activity, and alcohol intake), health history and medication use, and family history of cardiovascular disease. The follow-up period varied based on the date when recruitment began at each site or country. The main clinical outcomes were major cardiovascular disease (defined as death from cardiovascular causes and non-fatal myocardial infarction, stroke, and heart failure), fatal and non-fatal myocardial infarction, fatal and non-fatal strokes, cardiovascular mortality, non-cardiovascular mortality, and total mortality. Cox frailty models with random effects were used to assess associations between fruit, vegetable, and legume consumption with risk of cardiovascular disease events and mortality.
Findings: Participants were enrolled into the study between Jan 1, 2003, and March 31, 2013. For the current analysis, we included all unrefuted outcome events in the PURE study database through March 31, 2017. Overall, combined mean fruit, vegetable and legume intake was 3·91 (SD 2·77) servings per day. During a median 7·4 years (5·5–9·3) of followup, 4784 major cardiovascular disease events, 1649 cardiovascular deaths, and 5796 total deaths were documented. Higher total fruit, vegetable, and legume intake was inversely associated with major cardiovascular disease, myocardial infarction, cardiovascular mortality, non-cardiovascular mortality, and total mortality in the models adjusted for age, sex, and centre (random effect). The estimates were substantially attenuated in the multivariable adjusted models for major cardiovascular disease (hazard ratio [HR] 0·90, 95% CI 0·74–1·10, p_{trend} =0·131), myocardial infarction (0·99, 0·74–1·31; p_{trend}=0·2033), stroke (0·92, 0·67–1·25; p_{trend}=0·7092), cardiovascular mortality (0·73, 0·53–1·02; p_{trend}=0·0568), non-cardiovascular mortality (0·84, 0·68–1·04; p_{trend}=0·0038), and total mortality (0·81, 0·68–0·96; p_{trend}<0·0001). The HR for total mortality was lowest for three to four servings per day (0·78, 95% CI 0·69–0·88) compared with the reference group, with no further apparent decrease in HR with higher consumption. When examined separately, fruit intake was associated with lower risk of cardiovascular, non-cardiovascular, and total mortality, while legume intake was inversely associated with non-cardiovascular death and total mortality (in fully adjusted models). For vegetables, raw vegetable intake was strongly associated with a lower risk of total mortality, whereas cooked vegetable intake showed a modest benefit against mortality.
Interpretation: Higher fruit, vegetable, and legume consumption was associated with a lower risk of non-cardiovascular, and total mortality. Benefits appear to be maximum for both non-cardiovascular mortality and total mortality at three to four servings per day (equivalent to 375–500 g/day).

Munung NS, Mayosi BM, de Vries J. Equity in international health research collaborations in Africa: Perceptions and expectations of African researchers. PLoS One. 2017;12(10):e0186237. doi: 10.1371/journal.pone.0186237. **Full text available here**.

Introduction and Method: Africa is currently host to a number of international genomics research and biobanking consortia, each with a mandate to advance genomics research and biobanking in Africa. Whilst most of these consortia promise to transform the way international health research is done in Africa, few have articulated exactly how they propose to go about this. In this paper, we report on a qualitative interviewing study in which we involved 17 genomics researchers in Africa. We describe their perceptions and expectations of international genomics research and biobanking initiatives in Africa.

Results: All interviewees were of the view that externally funded genomics research and biobanking initiatives in Africa, have played a critical role in building capacity for genomics research and biobanking in Africa and in providing an opportunity for researchers in Africa to collaborate and network with other researchers. Whilst the opportunity to collaborate was seen as a benefit, some interviewees stressed the importance of recognizing that these collaborations carry mutual benefits for all partners, including their collaborators in HICs. They also voiced two major concerns of being part of these collaborative initiatives: the possibility of exploitation of African researchers and the non-sustainability of research capacity building efforts. As a way of minimising exploitation, researchers in Africa recommended that genuine efforts be made to create transparent and equitable international health research partnerships. They suggested that this could be achieved through: having rules of engagement, enabling African researchers to contribute to the design and conduct of international health projects in Africa, and mutual and respectful exchange of experience and capacity between research collaborators. These were identified as hallmarks to equitable international health research collaborations in Africa.

Conclusion: Genomics research and biobanking initiatives in Africa such as H3Africa have gone some way in defining aspects of fair and equitable research collaborations in Africa. However, they will need to strive at achieving equitable health research collaborations if they truly aim at setting a gold standard for how international health research should be conducted in Africa.

Sani MU, Mayosi BM. The pacemaker and ICD reuse programme of the Pan-African Society of Cardiology. Heart. 2017;103(23):1844–1845. doi: 10.1136/heartjnl-2017-311462. **Full text available here**.

No abstract available.

Sani MU, Cotter G, Davison BA, Mayosi BM, Damasceno A, Edwards C, et al. Symptoms and signs of heart failure at admission and discharge and outcomes in the Sub-Saharan Acute Heart Failure (THESUS-HF) Registry. J Card Fail. 2017;23(10):739–742. doi: 10.1016/j.cardfail.2016.09.016. **Full text not freely available**.

Background: Symptoms and signs of heart failure (HF) are the most common reasons for admission to hospital

for acute HF (AHF) and are used routinely throughout admission to assess the severity of disease and response to therapy.

Methods and Results: The data were collected in The Sub-Saharan Africa Survey on Heart Failure (THESUS-HF) study, a prospective, multicenter, observational survey of AHF from 9 countries in sub-Saharan Africa. A total of 1006 patients, ≥12 years of age, hospitalized for AHF were recruited. Symptoms and signs of HF and changes in dyspnea and well-being, relative to admission, were assessed at entry and on days 1, 2, and 7 (or on discharge if earlier) and included oxygen saturation, degree of edema and rales, body weight, and level of orthopnea. The patient determined dyspnea and general well-being, whereas the physician determined symptoms and signs of HF, as well as improvements in vital sign measurement, throughout the admission. After multivariable adjustment, baseline rales and changes to day 7 or discharge in general well-being predicted death or HF hospitalization through day 60, and baseline orthopnea, edema, rales, oxygen saturation, and changes to day 7 or on discharge in respiratory rate and general well-being were predictive of death through day 180.

Conclusions: In AHF patients in sub-Saharan Africa, symptoms and signs of HF improve throughout admission, and simple assessments, including edema, rales, oxygen saturation, respiratory rate, and asking the patient about general well-being, are valuable tools in patients' clinical assessment.

Sani MU, Davison BA, Cotter G, Damasceno A, Mayosi BM, Ogah OS, et al. Echocardiographic predictors of outcome in acute heart failure patients in sub-Saharan Africa: Insights from THESUS-HF. Cardiovasc J Afr. 2017;28(1):60–67. doi: 10.5830/cvja-2016-070. **Full text not freely available**.

Background: The role of echocardiography in the risk stratification of acute heart failure (HF) is unknown. Some small studies and retrospective analyses have found little change in echocardiographic variables during admission for acute HF and some echocardiographic parameters were not found to be associated with outcomes. It is unknown which echocardiographic variables will predict outcomes in sub-Saharan African patients admitted with acute HF. Using echocardiograms, this study aimed to determine the predictors of death and re-admissions within 60 days and deaths up to 180 days in patients with acute heart failure.

Methods: Out of the 1 006 patients in the THESUS-HF registry, 954 had had an echocardiogram performed within a few weeks of admission. Echocardiographic measurements were performed according to the American Society of Echocardiography guidelines. We examined the associations between each echocardiographic predictor and outcome using regression models.

Results: Heart rate and left atrial size predicted death within 60 days or re-admission. Heart rate, left ventricular posterior wall thickness in diastole (PWTd), and presence of aortic stenosis were associated with the risk of death within 180 days. PTWd added to clinical variables in predicting 180-day mortality rates.

Conclusions: Echocardiographic variables, especially those of left ventricular size and function, were not found to have additional predictive value in patients admitted for acute HF. Left atrial size, aortic stenosis, heart rate and measures of hypertrophy (LV PWTd) had some predictive value, suggesting the importance of early treatment of

hypertension and severe valvular heart disease.

Smedema JP, Van Geuns RJ, Truter R, Mayosi BM, Crijns HJGM. Contrast-enhanced cardiac magnetic resonance: Distinction between cardiac sarcoidosis and infarction scar. Sarcoidosis Vasc Diffuse Lung Dis. 2017;34(4):307–314. **Full text not freely available**.

Objectives: To review the value of delayed contrast-enhanced cardiac magnetic resonance (CECMR) in differentiating patients with cardiac sarcoidosis (CS) from those with coronary artery disease and recent myocardial infarctions.

Background: Late gadolinium enhancement (LGE) accurately delineates myocardial necrosis or fibrosis. The pattern of LGE in ischemic and non-ischemic myocardial disease is different, and might be helpful in distinguishing CS from ischemic disease.

Methods: The CECMR studies of 30 patients with CS were compared to those performed in 30 consecutive infarct patients, who had been managed with primary coronary interventions, and 10 healthy controls. Two experienced blinded observers classified patients by assessing the distribution of LGE.

Results: LV LGE was present in 29/30 CS (mean 3.8 segments, range 0–12), all infarct (mean 4.3 segments, range 0–9), and none of the patients in the control group. The amount of LV LGE did not differ significantly between CS and infarct patients (19 ± 11% and 19 ± 12%, P= 0.8). The CS group exhibited a predominantly patchy, 3 layer LGE (P = 0.01), whereas confluent transmural LGE (P = 0.04) with a vascular distribution (P < 0.001) was prevalent in the infarct group. Significantly more RV LGE (P = 0.01) and dilation (P = 0.02) were found in the CS group. The two observers classified patients correctly as CS in 72% and 83% of cases, as ischemic in nature in 77% and 80% of cases, and as normal in 90% and 100% respectively.

Conclusions: Gadolinium CMR was helpful in differentiating patients with CS from patients with ischemic heart disease and previous myocardial infarctions. In a subgroup of ischemic patients the pattern of LGE was atypical, and suggestive of non-ischemic etiology.

Wang H, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national under-5 mortality, adult mortality, age-specific mortality, and life expectancy, 1970–2016: A systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1084–1150. doi: 10.1016/S0140-6736(17)31833-0. **Full text not freely available**.

Background: Detailed assessments of mortality patterns, particularly age-specific mortality, represent a crucial input that enables health systems to target interventions to specific populations. Understanding how all-cause mortality has changed with respect to development status can identify exemplars for best practice. To accomplish this, the Global Burden of Diseases, Injuries, and Risk Factors Study 2016 (GBD 2016) estimated age-specific and sex-specific all-cause mortality between 1970 and 2016 for 195 countries and territories and at the subnational

level for the five countries with a population greater than 200 million in 2016.
Methods: We have evaluated how well civil registration systems captured deaths using a set of demographic methods called death distribution methods for adults and from consideration of survey and census data for children younger than 5 years. We generated an overall assessment of completeness of registration of deaths by dividing registered deaths in each location-year by our estimate of all-age deaths generated from our overall estimation process. For 163 locations, including subnational units in countries with a population greater than 200 million with complete vital registration (VR) systems, our estimates were largely driven by the observed data, with corrections for small fluctuations in numbers and estimation for recent years where there were lags in data reporting (lags were variable by location, generally between 1 year and 6 years). For other locations, we took advantage of different data sources available to measure under-5 mortality rates (U5MR) using complete birth histories, summary birth histories, and incomplete VR with adjustments; we measured adult mortality rate (the probability of death in individuals aged 15–60 years) using adjusted incomplete VR, sibling histories, and household death recall. We used the U5MR and adult mortality rate, together with crude death rate due to HIV in the GBD model life table system, to estimate age-specific and sex-specific death rates for each location-year. Using various international databases, we identified fatal discontinuities, which we defined as increases in the death rate of more than one death per million, resulting from conflict and terrorism, natural disasters, major transport or technological accidents, and a subset of epidemic infectious diseases; these were added to estimates in the relevant years. In 47 countries with an identified peak adult prevalence for HIV/AIDS of more than 0·5% and where VR systems were less than 65% complete, we informed our estimates of age–sex-specific mortality using the Estimation and Projection Package (EPP)-Spectrum model fitted to national HIV/AIDS prevalence surveys and antenatal clinic sero surveillance systems. We estimated stillbirths, early neonatal, late neonatal, and childhood mortality using both survey and VR data in spatiotemporal Gaussian process regression models. We estimated abridged life tables for all location-years using age-specific death rates. We grouped locations into development quintiles based on the Sociodemographic Index (SDI) and analysed mortality trends by quintile. Using spline regression, we estimated the expected mortality rate for each age–sex group as a function of SDI. We identified countries with higher life expectancy than expected by comparing observed life expectancy to anticipated life expectancy on the basis of development status alone.
Findings: Completeness in the registration of deaths increased from 28% in 1970 to a peak of 45% in 2013; completeness was lower after 2013 because of lags in reporting. Total deaths in children younger than 5 years decreased from 1970 to 2016, and slower decreases occurred at ages 5–24 years. By contrast, numbers of adult deaths increased in each 5-year age bracket above the age of 25 years. The distribution of annualised rates of change in age-specific mortality rate differed over the period 2000 to 2016 compared with earlier decades: increasing annualised rates of change were less frequent, although rising annualised rates of change still occurred in some locations, particularly for adolescent and younger adult age groups. Rates of stillbirths and under-5 mortality both decreased globally from 1970. Evidence for global convergence of death rates was mixed; although

the absolute difference between age-standardised death rates narrowed between countries at the lowest and highest levels of SDI, the ratio of these death rates – a measure of relative inequality – increased slightly. There was a strong shift between 1970 and 2016 toward higher life expectancy, most noticeably at higher levels of SDI. Among countries with populations greater than 1 million in 2016, life expectancy at birth was highest for women in Japan, at 86·9 years (95% UI 86·7–87·2), and for men in Singapore, at 81·3 years (78·8–83·7) in 2016. Male life expectancy was generally lower than female life expectancy between 1970 and 2016, and the gap between male and female life expectancy increased with progression to higher levels of SDI. Some countries with exceptional health performance in 1990 in terms of the difference in observed to expected life expectancy at birth had slower progress on the same measure in 2016.

Interpretation: Globally, mortality rates have decreased across all age groups over the past five decades, with the largest improvements occurring among children younger than 5 years. However, at the national level, considerable heterogeneity remains in terms of both level and rate of changes in age-specific mortality; increases in mortality for certain age groups occurred in some locations. We found evidence that the absolute gap between countries in age-specific death rates has declined, although the relative gap for some age–sex groups increased. Countries that now lead in terms of having higher observed life expectancy than that expected on the basis of development alone, or locations that have either increased this advantage or rapidly decreased the deficit from expected levels, could provide insight into the means to accelerate progress in nations where progress has stalled.

Watkins DA, Hasan B, Mayosi B, Bukhman G, Marin-Neto JA, Rassi Jr A, et al. Structural heart diseases. In: Prabhakaran D, Anand S, Gaziano TA, Mbanya JC, Wu Y, Nugent R, editors. Cardiovascular, respiratory, and related disorders 3rd ed. Volume 5. Washington (DC): World Bank; 2017. p. 191–208. https://www.ncbi.nlm.nih.gov/books/NBK525139/. **Full text available here**

Structural heart diseases constitute a large proportion of the burden of cardiovascular disease in low- and middle-income countries (LMICs). Some conditions, such as rheumatic heart disease (RHD) and Chagas disease (CD), are associated with poverty and are preventable. Congenital heart disease (CHD), in contrast, is prevalent in all regions, but treatment is more readily available in higher-income countries. All structural heart diseases have a progressive course in the absence of prevention or surgical treatment. This chapter summarizes the key clinical and public health issues around three key groups of structural heart disease: major congenital heart defects, RHD, and CD. Although advanced surgical care for these conditions is a rapidly evolving topic, this chapter emphasizes the importance of primary prevention and early detection, which are the missing links in many programs. These activities have particular relevance in resource-constrained settings, where access to advanced surgical and interventional care is not feasible.

Watkins DA, Johnson CO, Colquhoun SM, Karthikeyan G, Beaton A, Bukhman G, et al. Global, regional, and national burden of rheumatic heart disease, 1990–2015. N Engl J Med. 2017;377(8):713–722. doi: 10.1056/NEJMoa1603693. **Full text not freely available**.

Background: Rheumatic heart disease remains an important preventable cause of cardiovascular death and disability, particularly in low-income and middle-income countries. We estimated global, regional, and national trends in the prevalence of and mortality due to rheumatic heart disease as part of the 2015 Global Burden of Disease study.

Methods: We systematically reviewed data on fatal and nonfatal rheumatic heart disease for the period from 1990 through 2015. Two Global Burden of Disease analytic tools, the Cause of Death Ensemble model and DisMod-MR 2.1, were used to produce estimates of mortality and prevalence, including estimates of uncertainty.

Results: We estimated that there were 319,400 (95% uncertainty interval, 297,300 to 337,300) deaths due to rheumatic heart disease in 2015. Global age-standardized mortality due to rheumatic heart disease decreased by 47.8% (95% uncertainty interval, 44.7 to 50.9) from 1990 to 2015, but large differences were observed across regions. In 2015, the highest age-standardized mortality due to and prevalence of rheumatic heart disease were observed in Oceania, South Asia, and central sub-Saharan Africa. We estimated that in 2015 there were 33.4 million (95% uncertainty interval, 29.7 million to 43.1 million) cases of rheumatic heart disease and 10.5 million (95% uncertainty interval, 9.6 million to 11.5 million) disability-adjusted life-years due to rheumatic heart disease globally.

Conclusions: We estimated the global disease prevalence of and mortality due to rheumatic heart disease over a 25-year period. The health-related burden of rheumatic heart disease has declined worldwide, but high rates of disease persist in some of the poorest regions in the world.

Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Opie LH. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2017;1:Cd002003. doi: 10.1002/14651858.CD002003.pub5. **Full text not freely available**.

Background: Beta-blockers refer to a mixed group of drugs with diverse pharmacodynamic and pharmacokinetic properties. They have shown long-term beneficial effects on mortality and cardiovascular disease (CVD) when used in people with heart failure or acute myocardial infarction. Beta-blockers were thought to have similar beneficial effects when used as first-line therapy for hypertension. However, the benefit of beta-blockers as first-line therapy for hypertension without compelling indications is controversial. This review is an update of a Cochrane Review initially published in 2007 and updated in 2012.

Objectives: To assess the effects of beta-blockers on morbidity and mortality endpoints in adults with hypertension.

Search methods: The Cochrane Hypertension Information Specialist searched the following databases for randomized controlled trials up to June 2016: the Cochrane Hypertension Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL) (2016, Issue 6), MEDLINE (from 1946), Embase (from 1974),

and ClinicalTrials.gov. We checked reference lists of relevant reviews, and reference lists of studies potentially eligible for inclusion in this review, and also searched the the World Health Organization International Clinical Trials Registry Platform on 06 July 2015.
Selection criteria: Randomised controlled trials (RCTs) of at least one year of duration, which assessed the effects of beta-blockers compared to placebo or other drugs, as first-line therapy for hypertension, on mortality and morbidity in adults.
Data collection and analysis: We selected studies and extracted data in duplicate, resolving discrepancies by consensus. We expressed study results as risk ratios (RR) with 95% confidence intervals (CI) and conducted fixed-effect or random-effects meta-analyses, as appropriate. We also used GRADE to assess the certainty of the evidence. GRADE classifies the certainty of evidence as high (if we are confident that the true effect lies close to that of the estimate of effect), moderate (if the true effect is likely to be close to the estimate of effect), low (if the true effect may be substantially different from the estimate of effect), and very low (if we are very uncertain about the estimate of effect).
Main Results: Thirteen RCTs met inclusion criteria. They compared beta-blockers to placebo (4 RCTs, 23,613 partici-pants), diuretics (5 RCTs, 18,241 participants), calcium-channel blockers (CCBs: 4 RCTs, 44,825 participants), and renin-angiotensin system (RAS) inhibitors (3 RCTs, 10,828 participants). These RCTs were conducted between the 1970s and 2000s and most of them had a high risk of bias resulting from limitations in study design, conduct, and data analysis. There were 40,245 participants taking beta-blockers, three-quarters of them taking atenolol. We found no outcome trials involving the newer vasodilating beta-blockers (e.g. nebivolol).There was no difference in all-cause mortality between beta-blockers and placebo (RR 0.99, 95% CI 0.88 to 1.11), diuretics or RAS inhibitors, but it was higher for beta-blockers compared to CCBs (RR 1.07, 95% CI 1.00 to 1.14). The evidence on mortality was of moderate-certainty for all comparisons.Total CVD was lower for beta-blockers compared to placebo (RR 0.88, 95% CI 0.79 to 0.97; low-certainty evidence), a reflection of the decrease in stroke (RR 0.80, 95% CI 0.66 to 0.96; low-certainty evidence) since there was no difference in coronary heart disease (CHD: RR 0.93, 95% CI 0.81 to 1.07; moderate-certainty evidence). The effect of beta-blockers on CVD was worse than that of CCBs (RR 1.18, 95% CI 1.08 to 1.29; moderate-certainty evidence), but was not different from that of diuretics (moderate-certainty) or RAS inhibitors (low-certainty). In addition, there was an increase in stroke in beta-blockers compared to CCBs (RR 1.24, 95% CI 1.11 to 1.40; moderate-certainty evidence) and RAS inhibitors (RR 1.30, 95% CI 1.11 to 1.53; moderate-certainty evidence). However, there was little or no difference in CHD between beta-blockers and diuretics (low-certainty evidence), CCBs (moderate-certainty evidence) or RAS inhibitors (low-certainty evidence). In the single trial involving participants aged 65 years and older, atenolol was associated with an increased CHD incidence compared to diuretics (RR 1.63, 95% CI 1.15 to 2.32). Participants taking beta-blockers were more likely to discontinue treatment due to adverse events than participants taking RAS inhibitors (RR 1.41, 95% CI 1.29 to 1.54; moderate-certainty evidence), but there was little or no difference with placebo, diuretics or CCBs (low-certainty evidence).

Authors' conclusions: Most outcome RCTs on beta-blockers as initial therapy for hypertension have high risk of bias. Atenolol was the beta-blocker most used. Current evidence suggests that initiating treatment of hypertension with beta-blockers leads to modest CVD reductions and little or no effects on mortality. These beta-blocker effects are inferior to those of other antihypertensive drugs. Further research should be of high quality and should explore whether there are differences between different subtypes of beta-blockers or whether beta-blockers have differential effects on younger and older people.

Wiysonge CS, Ntsekhe M, Thabane L, Volmink J, Majombozi D, Gumedze F, et al. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2017;9:Cd000526. doi: 10.1002/14651858.CD000526.pub2. **Full text not freely available**.

Background: Tuberculous pericarditis can impair the heart's function and cause death; long term, it can cause the membrane to fibrose and constrict causing heart failure. In addition to antituberculous chemotherapy, treatments include corticosteroids, drainage, and surgery.

Objectives: To assess the effects of treatments for tuberculous pericarditis.

Search methods: We searched the Cochrane Infectious Diseases Group Specialized Register (27 March 2017); the Cochrane Central Register of Controlled Trials (CENTRAL), published in the Cochrane Library (2017, Issue 2); MEDLINE (1966 to 27 March 2017); Embase (1974 to 27 March 2017); and LILACS (1982 to 27 March 2017). In addition we searched the metaRegister of Controlled Trials (mRCT) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal using 'tuberculosis' and 'pericard*' as search terms on 27 March 2017. We searched ClinicalTrials.gov and contacted researchers in the field of tuberculous pericarditis. This is a new version of the original 2002 review.

Selection criteria: We included randomized controlled trials (RCTs) and quasi-RCTs.

Data collection and analysis: Two review authors independently screened search outputs, evaluated study eligibility, assessed risk of bias, and extracted data; and we resolved any discrepancies by discussion and consensus. One trial assessed the effects of both corticosteroid and *Mycobacterium indicus pranii* treatment in a two-by-two factorial design; we excluded data from the group that received both interventions. We conducted fixed-effect meta-analysis and assessed the certainty of the evidence using the GRADE approach.

Main results: Seven trials met the inclusion criteria; all were from sub-Saharan Africa and included 1959 participants, with 1051/1959 (54%) HIV-positive. All trials evaluated corticosteroids and one each evaluated colchicine*, M. indicus pranii* immunotherapy, and open surgical drainage. Four trials (1841 participants) were at low risk of bias, and three trials (118 participants) were at high risk of bias.In people who are not infected with HIV, corticosteroids may reduce deaths from all causes (risk ratio (RR) 0.80, 95% confidence interval (CI) 0.59 to 1.09; 660 participants, 4 trials, low certainty evidence) and the need for repeat pericardiocentesis (RR 0.85, 95% CI 0.70 to 1.04; 492 participants, 2 trials, low certainty evidence). Corticosteroids probably reduce deaths from pericarditis (RR 0.39, 95% CI 0.19 to 0.80; 660 participants, 4 trials, moderate certainty evidence). However, we do

not know whether or not corticosteroids have an effect on constriction or cancer among HIV-negative people (very low certainty evidence). In people living with HIV, only 19.9% (203/1959) were on antiretroviral drugs. Corticosteroids may reduce constriction (RR 0.55, 0.26 to 1.16; 575 participants, 3 trials, low certainty evidence). It is uncertain whether corticosteroids have an effect on all-cause death or cancer (very low certainty evidence); and may have little or no effect on repeat pericardiocentesis (RR 1.02, 0.89 to 1.18; 517 participants, 2 trials, low certainty evidence). For colchicine among people living with HIV, we found one small trial (33 participants) which had insufficient data to make any conclusions about any effects on death or constrictive pericarditis. Irrespective of HIV status, due to very low certainty evidence from one trial, it is uncertain whether adding *M. indicus pranii* immunotherapy to antituberculous drugs has an effect on any outcome. Open surgical drainage for effusion may reduce repeat pericardiocentesis In HIV-negative people (RR 0.23, 95% CI 0.07 to 0.76; 122 participants, 1 trial, low certainty evidence) but may make little or no difference to other outcomes. We did not find an eligible trial that assessed the effects of open surgical drainage in people living with HIV. The review authors found no eligible trials that examined the length of antituberculous treatment needed nor the effects of other adjunctive treatments for tuberculous pericarditis.

Authors' conclusions: For HIV-negative patients, corticosteroids may reduce death. For HIV-positive patients not on antiretroviral drugs, corticosteroids may reduce constriction. For HIV-positive patients with good antiretroviral drug viral suppression, clinicians may consider the results from HIV-negative patients more relevant. Further research may help evaluate percutaneous drainage of the pericardium under local anaesthesia, the timing of pericardiectomy in tuberculous constrictive pericarditis, and new antibiotic regimens.

Yacoub M, Mayosi B, ElGuindy A, Carpentier A, Yusuf S. Eliminating acute rheumatic fever and rheumatic heart disease. Lancet. 2017;390(10091):212–213. doi: 10.1016/s0140-6736(17)31608-2. **Full text not freely available**.

No abstract available.

Zuhlke L, Mayosi BM. The life and the legacy of Hamilton Naki: Experimental heart transplant surgeon and teacher. J Heart Lung Transplant. 2017;36(12):1309–1310. doi: 10.1016/j.healun.2017.10.006. **Full text not freely available**.

In 1991, Hamilton Naki retired from his position as a surgical laboratory assistant after 37 years of service to the profession of transplant surgery at the University of Cape Town. He was a consummate animal surgeon, a dedicated and patient teacher, and a pioneer in transplant techniques. His talent, innate surgical skill, and his outstanding contribution to the training of heads of department of future transplant and surgical programs resulted in him being honored with a Master of Science in Medicine degree by the University of Cape Town in 2003. This despite his humble beginnings and the oppressive apartheid regime under which he lived for most of

his life.

2016

Barth DD, Engel ME, Whitelaw A, Alemseged A, Sadoh WE, Ali SKM, et al. Rationale and design of the African Group A Streptococcal infection registry: The AFROStrep study. BMJ Open. 2016; 6(2):e010248. doi: 10.1136/bmjopen-2015-010248. **Full text not freely available.**

Introduction: Group A β-haemolytic Streptococcus (GAS), a Gram-positive bacterium, also known as Streptococcus pyogenes, causes pyoderma, pharyngitis and invasive disease. Repeated GAS infections may lead to autoimmune diseases such as acute post-streptococcal glomerulonephritis, acute rheumatic fever (ARF) and rheumatic heart disease (RHD). Invasive GAS (iGAS) disease is an important cause of mortality and morbidity worldwide. The burden of GAS infections is, however, unknown in Africa because of lack of surveillance systems.

Methods and analysis: The African group A streptococcal infection registry (the AFROStrep study) is a collaborative multicentre study of clinical, microbiological, epidemiological and molecular characteristics for GAS infection in Africa. The AFROStrep registry comprises two components: (1) active surveillance of GAS pharyngitis cases from sentinel primary care centres (non-iGAS) and (2) passive surveillance of iGAS disease from microbiology laboratories. Isolates will also be subjected to DNA isolation to allow for characterisation by molecular methods and cryopreservation for long-term storage. The AFROStrep study seeks to collect comprehensive data on GAS isolates in Africa. The biorepository will serve as a platform for vaccine development in Africa.

Ethics and dissemination: Ethics approval for the AFROStrep registry has been obtained from the Human Research Ethics Committee at the University of Cape Town (HREC/REF: R006/2015). Each recruiting site will seek ethics approval from their local ethics' committee. All participants will be required to provide consent for inclusion into the registry as well as for the storage of isolates and molecular investigations to be conducted thereon. Strict confidentiality will be applied throughout. Findings and updates will be disseminated to collaborators, researchers, health planners and colleagues through peer-reviewed journal articles, conference publications and proceedings.

Bonny A, Karaye K, Dzudie A, Okello E, Chin A, Tibazarwa K, et al. Statistics on the use of cardiac electronic devices and electrophysiological procedures from 2011 to 2014 in 27 African countries: First report from the Pan African Society of Cardiology (PASCAR) arrhythmia study group. Eur Heart J. 2016;37(Issue Supplement 1):1302..

Background: Lack of data on cardiac electronic devices and electrophysiological (EP) procedures in Africa is impeding the formulation of appropriate health policies on the managing cardiac arrhythmias. We conducted a survey on pacing and EP activities throughout Africa.
Material and method: A questionnaire regarding activities from 2011 to 2014 was sent to EP physicians. Additional information was obtained through manufacturers or local distributors.
Results: 27 countries were surveyed, out of which 6 (22%) did not report their data, and 5 (19%) did not have any cardiac electrophysiology services. Twentyfour centers were included, of which 20 (83%) were from public sector. No country had a centralized national registry. Among the 16 countries (76%) with facilities for implanting cardiac devices, cardiac resynchronization therapy (CRT) was performed in 9 (56%), implantable cardioverter-defibrillator (ICD) in 11 (68.7%), and EP procedures in 6 (37.5%) countries. Only 4 (25%) countries offered the full complements of EP services (pacemaker, CRT, ICD and simple/complex ablations), with none from West, Central and East Africa. Per million inhabitants, median number of centers was 3 (1 to 60) and implanting physicians was 9 (2 to 173). The implant rates per million habitants was 36.7 (0.2 to 218). Reused devices were implanted in 6 (37.5%) countries; accounting for up to 11% of all procedures (median rate of 4%). The patient charges for dual-chamber (DDD) pacemaker implantation ranged from $0,00 (in countries with reimbursement policies) to $5,556 (in private clinics) with the median cost of $2570. Wide variation cost was observed across the countries, with a high inter-center variability. An inverse correlation between implant rates per million inhabitants and the procedure fees standardizes to the Gross Domestic Product per habitants (Correlation Coefficient r^2=−0.17) was found.
Conclusion: Although increasing in most countries, pacemaker implantations are still suboptimal in Africa, mainly in sub-Saharan Africa, and EP procedures are in their embryonic stages.

Bright PD, Mayosi BM, Martin WJ. An immunological perspective on rheumatic heart disease pathogenesis: More questions than answers. Heart. 2016;102(19):1527–1532. doi: 10.1136/heartjnl-2015-309188. **Full text not freely available.**

Acute rheumatic fever (ARF) and the related rheumatic heart disease (RHD) are autoimmune diseases thought to be triggered by group A streptococcal (GAS) pharyngitis. RHD is a leading cause of mortality in the developing world. The strong epidemiological association between GAS throat infection and ARF is highly suggestive of causation, but does not exclude other infections as contributory. There is good evidence of both humoral and cellular autoreactivity and GAS/self cross-reactivity in established RHD. RHD pathogenesis could feasibly be triggered and driven by humoral and/or cellular molecular cross-reactivity between GAS and host cardiac tissues (molecular mimicry). However, good evidence of humoral pathogenicity is lacking and the specific triggering event for RHD remains unknown. It is likely that the critical immunological events leading to ARF/RHD occur at the point of contact between GAS and the immune system in the throat, strongly implicating the mucosal

immune system in RHD pathogenesis. Additionally, there is circumstantial evidence that continued live GAS may play a role in ARF/RHD pathogenesis. We suggest that future avenues for study should include the exclusion of GAS components directly contributing to RHD pathogenesis; large genome-wide association studies of patients with RHD looking for candidate genes involved in RHD pathogenesis; genome-wide association studies of GAS from patients with ARF taken at diagnosis to look for characteristics of rheumatogenic strains; and performing case/control studies of GAS pharyngitis/ARF/patients with RHD, and controls to identify microbiological, immunological and environmental differences to elucidate RHD pathogenesis.

Carapetis JR, Beaton A, Cunningham MW, Guilherme L, Karthikeyan G, Mayosi BM, et al. Acute rheumatic fever and rheumatic heart disease. Nat Rev Dis Primers. 2016;2:15084. doi: 10.1038/nrdp.2015.84. **Full text not freely available.**

Acute rheumatic fever (ARF) is the result of an autoimmune response to pharyngitis caused by infection with group A Streptococcus. The long-term damage to cardiac valves caused by ARF, which can result from a single severe episode or from multiple recurrent episodes of the illness, is known as rheumatic heart disease (RHD) and is a notable cause of morbidity and mortality in resource-poor settings around the world. Although our understanding of disease pathogenesis has advanced in recent years, this has not led to dramatic improvements in diagnostic approaches, which are still reliant on clinical features using the Jones Criteria, or treatment practices. Indeed, penicillin has been the mainstay of treatment for decades and there is no other treatment that has been proven to alter the likelihood or the severity of RHD after an episode of ARF. Recent advances – including the use of echocardiographic diagnosis in those with ARF and in screening for early detection of RHD, progress in developing group A streptococcal vaccines and an increased focus on the lived experience of those with RHD and the need to improve quality of life – give cause for optimism that progress will be made in coming years against this neglected disease that affects populations around the world, but is a particular issue for those living in poverty.

Fish M, Shaboodien G, Kraus S, Sliwa K, Seidman CE, Burke MA, et al. Mutation analysis of the phospholamban gene in 315 South Africans with dilated, hypertrophic, peripartum and arrhythmogenic right ventricular cardiomyopathies. Sci Rep. 2016;6:22235. doi: 10.1038/srep22235. Corrigendum in: Sci Rep. 2016;6:25863. doi: 10.1038/srep25863. **Full text available here.**

Cardiomyopathy is an important cause of heart failure in Sub-Saharan Africa, accounting for up to 30% of adult heart failure hospitalisations. This high prevalence poses a challenge in societies without access to resources and interventions essential for disease management. Over 80 genes have been implicated as a cause of cardiomyopathy. Mutations in the phospholamban (PLN) gene are associated with dilated cardiomyopathy (DCM) and severe heart failure. In Africa, the prevalence of PLN mutations in cardiomyopathy patients is unknown. Our aim was to screen 315 patients with arrhythmogenic right ventricular cardiomyopathy (n = 111),

DCM (n = 95), hypertrophic cardiomyopathy (n = 40) and peripartum cardiomyopathy (n = 69) for disease-causing PLN mutations by high resolution melt analysis and DNA sequencing. We detected the previously reported PLN c.25C > T (p.R9C) mutation in a South African family with severe autosomal dominant DCM. Haplotype analysis revealed that this mutation occurred against a different haplotype background to that of the original North American family and was therefore unlikely to have been inherited from a common ancestor. No other mutations in PLN were detected (mutation prevalence = 0.2%). We conclude that PLN is a rare cause of cardiomyopathy in African patients. The PLN p.R9C mutation is not well-tolerated, emphasising the importance of this gene in cardiac function.

Fish M, Shaboodien G, Kraus S, Sliwa K, Seidman CE, Burke MA, et al. Mutation analysis of the phospholamban gene in 315 South Africans with dilated, hypertrophic, peripartum and arrhythmogenic right ventricular cardiomyopathies. Sci Rep. 2016;6:25863. doi: 10.1038/srep25863. Corrigendum for: Sci Rep. 2016;6:22235. doi: 10.1038/srep22235. **Full text available here**.

No abstract available.

Kakia A, Wiysonge CS, Ochodo EA, Awotedu AA, Ristic AD, Mayosi BM. The efficacy and safety of complete pericardial drainage by means of intrapericardial fibrinolysis for the prevention of complications of pericardial effusion: A systematic review protocol. BMJ Open. 2016;6(1):e007842. doi: 10.1136/bmjopen-2015-007842. . **Full text available here.**

Introduction: Intrapericardial fibrinolysis has been proposed as a means of preventing complications of pericardial effusion such as cardiac tamponade, persistent and recurrent pericardial effusion, and pericardial constriction. There is a need to understand the efficacy and safety of this procedure because it shows promise.

Methods and Analysis: We aim to assess the effects of intrapericardial fibrinolysis in the treatment of pericardial effusion. We will search PubMed, the Cochrane Library, African Journals online, Cumulative Index to Nursing and Allied Health Literature, Trip database, Clinical trials.gov and the WHO International Clinical Trials Registry Platform for studies that evaluate the efficacy and/or safety of complete pericardial fluid drainage by intrapericardial fibrinolysis irrespective of study design, geographical location, language, age of participants, aetiology of pericarditis or types of fibrinolytics. Two authors will do the search independently, screen the search outputs for potentially eligible studies and assess whether the studies meet the inclusion criteria. Discrepancies between the two authors will be resolved through discussion and arbitration by a third author. Data from the selected studies shall be extracted using a standardised data collection form which will be piloted before use. The methodological quality of studies will be assessed using the Cochrane Collaboration's tools for assessing risk of bias for experimental studies and non-randomised studies, respectively. The primary meta-analysis will use random effects models due to expected interstudy heterogeneity. Dichotomous data will be analysed using relative

risk and continuous with data mean differences, both with 95% CIs.
Ethics and dissemination: Approval by an ethics committee is not required for this study as it is a protocol for a systematic review of published studies. The results will be disseminated through a conference presentation and peer-reviewed publication.
Review Registration Number: PROSPERO, CRD42014015238.

Kassebaum NJ, Arora M, Barber RM, Brown J, Carter A, Casey DC, et al. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016; 388(10053):1603–1658. doi: 10.1016/S0140-6736(16)31460-X. **Full text available here**.

Background: Healthy life expectancy (HALE) and disability-adjusted life-years (DALYs) provide summary measures of health across geographies and time that can inform assessments of epidemiological patterns and health system performance, help to prioritise investments in research and development, and monitor progress toward the Sustainable Development Goals (SDGs). We aimed to provide updated HALE and DALYs for geographies worldwide and evaluate how disease burden changes with development.
Methods: We used results from the Global Burden of Diseases, Injuries, and Risk Factors Study 2015 (GBD 2015) for all-cause mortality, cause-specific mortality, and non-fatal disease burden to derive HALE and DALYs by sex for 195 countries and territories from 1990 to 2015. We calculated DALYs by summing years of life lost (YLLs) and years of life lived with disability (YLDs) for each geography, age group, sex, and year. We estimated HALE using the Sullivan method, which draws from age-specific death rates and YLDs per capita. We then assessed how observed levels of DALYs and HALE diff ered from expected trends calculated with the Socio-demographic Index (SDI), a composite indicator constructed from measures of income per capita, average years of schooling, and total fertility rate.
Findings: Total global DALYs remained largely unchanged from 1990 to 2015, with decreases in communicable, neonatal, maternal, and nutritional (Group 1) disease DALYs off set by increased DALYs due to non-communicable diseases (NCDs). Much of this epidemiological transition was caused by changes in population growth and ageing, but it was accelerated by widespread improvements in SDI that also correlated strongly with the increasing importance of NCDs. Both total DALYs and age-standardised DALY rates due to most Group 1 causes significantly decreased by 2015, and although total burden climbed for the majority of NCDs, age-standardised DALY rates due to NCDs declined. Nonetheless, age-standardised DALY rates due to several high-burden NCDs (including osteoarthritis, drug use disorders, depression, diabetes, congenital birth defects, and skin, oral, and sense organ diseases) either increased or remained unchanged, leading to increases in their relative ranking in many geographies. From 2005 to 2015, HALE at birth increased by an average of 2·9 years (95% uncertainty interval 2·9–3·0) for men and 3·5 years (3·4–3·7) for women, while HALE at age 65 years improved by 0·85 years (0·78–0·92) and 1·2 years (1·1–1·3), respectively. Rising SDI was associated with consistently higher

HALE and a somewhat smaller proportion of life spent with functional health loss; however, rising SDI was related to increases in total disability. Many countries and territories in central America and eastern sub-Saharan Africa had increasingly lower rates of disease burden than expected given their SDI. At the same time, a subset of geographies recorded a growing gap between observed and expected levels of DALYs, a trend driven mainly by rising burden due to war, interpersonal violence, and various NCDs.

Interpretation: Health is improving globally, but this means more populations are spending more time with functional health loss, an absolute expansion of morbidity. The proportion of life spent in ill health decreases somewhat with increasing SDI, a relative compression of morbidity, which supports continued efforts to elevate personal income, improve education, and limit fertility. Our analysis of DALYs and HALE and their relationship to SDI represents a robust framework on which to benchmark geography-specific health performance and SDG progress. Country specific drivers of disease burden, particularly for causes with higher-than-expected DALYs, should inform financial and research investments, prevention efforts, health policies, and health system improvement initiatives for all countries along the development continuum.

Kirigia JM, Ota MO, Senkubuge F, Wiysonge CS, Mayosi BM. Developing the African national health research systems barometer. Health Res Policy Syst. 2016;14(1):53. doi: 10.1186/s12961-016-0121-4. **Full text available here**.

Background: A functional national health research system (NHRS) is crucial in strengthening a country's health system to promote, restore and maintain the health status of its population. Progress towards the goal of universal health coverage in the post-2015 sustainable development agenda will be difficult for African countries without strengthening of their NHRS to yield the required evidence for decision-making. This study aims to develop a barometer to facilitate monitoring of the development and performance of NHRSs in the African Region of WHO.

Methods: The African national health research systems barometer algorithm was developed in response to a recommendation of the African Advisory Committee for Health Research and Development of WHO. Survey data collected from all the 47 Member States in the WHO African Region using a questionnaire were entered into an Excel spreadsheet and analysed. The barometer scores for each country were calculated and the performance interpreted according to a set of values ranging from 0% to 100%.

Results: The overall NHRS barometer score for the African Region was 42%, which is below the average of 50%. Among the 47 countries, the average NHRS performance was less than 20% in 10 countries, 20–40% in 11 countries, 41–60% in 16 countries, 61–80% in nine countries, and over 80% in one country. The performance of NHRSs in 30 (64%) countries was below 50%.

Conclusion: An African NHRS barometer with four functions and 17 sub-functions was developed to identify the gaps in and facilitate monitoring of NHRS development and performance. The NHRS scores for the individual sub-functions can guide policymakers to locate sources of poor performance and to design interventions to

address them.

Küry S, Mercier S, Shaboodien G, Besnard T, Barbarot S, Khumalo NP, et al. CUGC for hereditary fibrosing poikiloderma with tendon contractures, myopathy, and pulmonary fibrosis (POIKTMP). Eur J Hum Genet. 2016;24(5):e1–e4. doi: 10.1038/ejhg.2015.205. **Full text not freely available.**

No abstract available.

Kwan GF, Mayosi BM, Mocumbi AO, Miranda JJ, Ezzati M, Jain Y, et al. Endemic cardiovascular diseases of the poorest billion. Circulation. 2016;133(24):2561–2575. doi: 10.1161/circulationaha.116.008731. **Full text not freely available.**

The poorest billion people are distributed throughout the world, though most are concentrated in rural sub-Saharan Africa and South Asia. Cardiovascular disease (CVD) data can be sparse in low- and middle-income countries beyond urban centers. Despite this urban bias, CVD registries from the poorest countries have long revealed a predominance of nonatherosclerotic stroke, hypertensive heart disease, nonischemic and Chagas cardiomyopathies, rheumatic heart disease, and congenital heart anomalies, among others. Ischemic heart disease has been relatively uncommon. Here, we summarize what is known about the epidemiology of CVDs among the world's poorest people and evaluate the relevance of global targets for CVD control in this population. We assessed both primary data sources, and the 2013 Global Burden of Disease Study modeled estimates in the world's 16 poorest countries where 62% of the population are among the poorest billion. We found that ischemic heart disease accounted for only 12% of the combined CVD and congenital heart anomaly disability-adjusted life years (DALYs) in the poorest countries, compared with 51% of DALYs in high-income countries. We found that as little as 53% of the combined CVD and congenital heart anomaly burden (1629/3049 DALYs per 100 000) was attributed to behavioral or metabolic risk factors in the poorest countries (eg, in Niger, 82% of the population among the poorest billion) compared with 85% of the combined CVD and congenital heart anomaly burden (4439/5199 DALYs) in high-income countries. Further, of the combined CVD and congenital heart anomaly burden, 34% was accrued in people under age 30 years in the poorest countries, while only 3% is accrued under age 30 years in high-income countries. We conclude although the current global targets for noncommunicable disease and CVD control will help diminish premature CVD death in the poorest populations, they are not sufficient. Specifically, the current framework (1) excludes deaths of people <30 years of age and deaths attributable to congenital heart anomalies, and (2) emphasizes interventions to prevent and treat conditions attributed to behavioral and metabolic risks factors. We recommend a complementary strategy for the poorest populations that targets premature death at younger ages, addresses environmental and infectious risks, and introduces broader integrated health system interventions, including cardiac surgery for congenital and rheumatic heart disease.

Kyriakakis CG, Mayosi BM, de Vries E, Isaacs A, Doubell AF. An approach to the patient with suspected pericardial disease. S Afr Med J. 2016;106(2):151–155. **Full text available here**.

Diseases of the pericardium commonly manifest in one of three ways: acute pericarditis, pericardial effusion and constrictive pericarditis. In the developed world, the most common cause of acute pericarditis is viral or idiopathic disease, while in the developing world tuberculous aetiology, particularly in sub-Saharan Africa, is commonplace owing to the high prevalence of HIV. This article provides an approach to the diagnosis, investigation and management of these patients.

Lim SS, Allen K, Dandona L, Forouzanfar MH, Fullman N, Goldberg EM, et al. Measuring the health-related Sustainable Development Goals in 188 countries: A baseline analysis from the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1813–1850. doi: 10.1016/S0140-6736(16)31467-2. F**ull text available here**.

Background: In September, 2015, the UN General Assembly established the Sustainable Development Goals (SDGs). The SDGs specify 17 universal goals, 169 targets, and 230 indicators leading up to 2030. We provide an analysis of 33 health-related SDG indicators based on the Global Burden of Diseases, Injuries, and Risk Factors Study 2015 (GBD 2015).

Methods: We applied statistical methods to systematically compiled data to estimate the performance of 33 health-related SDG indicators for 188 countries from 1990 to 2015. We rescaled each indicator on a scale from 0 (worst observed value between 1990 and 2015) to 100 (best observed). Indices representing all 33 health-related SDG indicators (health-related SDG index), health-related SDG indicators included in the Millennium Development Goals (MDG index), and health-related indicators not included in the MDGs (non-MDG index) were computed as the geometric mean of the rescaled indicators by SDG target. We used spline regressions to examine the relations between the Socio-demographic Index (SDI, a summary measure based on average income per person, educational attainment, and total fertility rate) and each of the health-related SDG indicators and indices.

Findings: In 2015, the median health-related SDG index was 59·3 (95% uncertainty interval 56·8–61·8) and varied widely by country, ranging from 85·5 (84·2–86·5) in Iceland to 20·4 (15·4–24·9) in Central African Republic. SDI was a good predictor of the health-related SDG index (r^2=0·88) and the MDG index (r^2=0·92), whereas the non-MDG index had a weaker relation with SDI (r^2=0·79). Between 2000 and 2015, the health-related SDG index improved by a median of 7·9 (IQR 5·0–10·4), and gains on the MDG index (a median change of 10·0 [6·7–13·1]) exceeded that of the nonMDG index (a median change of 5·5 [2·1–8·9]). Since 2000, pronounced progress occurred for indicators such as met need with modern contraception, under-5 mortality, and neonatal mortality, as well as the indicator for universal health coverage tracer interventions. Moderate improvements were found for indicators such as HIV and tuberculosis incidence, minimal changes for hepatitis B incidence took place, and

childhood overweight considerably worsened.
Interpretation: GBD provides an independent, comparable avenue for monitoring progress towards the health-related SDGs. Our analysis not only highlights the importance of income, education, and fertility as drivers of health improvement but also emphasises that investments in these areas alone will not be sufficient. Although considerable progress on the health-related MDG indicators has been made, these gains will need to be sustained and, in many cases, accelerated to achieve the ambitious SDG targets. The minimal improvement in or worsening of health-related indicators beyond the MDGs highlight the need for additional resources to effectively address the expanded scope of the health-related SDGs.

Madeira G, Mocumbi AO, Mayosi BM. Advice to health professionals: Use of lignocaine as a diluent to reduce the pain associated with the administration of benzathine penicillin G. S Afr Med J. 2016; 106(8):742. doi: 10.7196/SAMJ.2016.v106i8.10864. **Full text available here**.

No abstract available.

Mayosi BM. Foreword. In: Stewart S, Sliwa K, Mocumbi A, Damasceno A, Ntsekhe M, editors. Heart of Africa: Clinical profile of an evolving burden of heart disease in Africa. Chichester, West Sussex: John Wiley & Sons; 2016. p. x–xi. doi: 10.1002/9781119097136.fmatter **Full text not freely available.**.

No abstract available.

Mayosi BM. Screening for rheumatic heart disease in eastern Nepal. JAMA Cardiol. 2016;1(1):96–97. doi: 10.1001/jamacardio.2015.0303. **Full text available here**.

No abstract available.

Mayosi BM. 2016 National rheumatic fever week: The status of rheumatic heart disease in South Africa. S Afr Med J. 2016;106(8):740–741. doi: 10.7196/SAMJ.2016.v106i8.11253. **Full text available here**

There is evidence of early progress in the efforts to eliminate acute rheumatic fever (ARF) and control rheumatic heart disease (RHD) in South Africa. The caseload of ARF and RHD in paediatric units appears to be falling in some provinces such as Gauteng, and the mortality attributed to rheumatic heart disease at a population level has fallen from 1.3/100 000 in 2001 to 0.7/100 000 in 2012. However, the incidence of congestive heart failure due to RHD in adults remains high (~25/100 000/year) in Gauteng Province, and is associated with a high case fatality rate of up to 35% in 6 months. There is a need to intensify the application of comprehensive interventions to enhance the primary and secondary prevention and treatment of ARF/RHD in a registry-based national programme.

Ntusi NA, Shaboodien G, Badri M, Gumedze F, Mayosi BM. Clinical features, spectrum of causal genetic mutations and outcome of hypertrophic cardiomyopathy in South Africans. Cardiovasc J Afr. 2016;27(3):152–158. doi: 10.5830/cvja-2015-075. **Full text not freely available.**

Background: Little is known about the clinical characteristics, spectrum of causal genetic mutations and outcome of hypertrophic cardiomyopathy (HCM) in Africans. The objective of this study was to delineate the clinical and genetic features and outcome of HCM in African patients.

Methods: Information on clinical presentation, electrocardiographic and echocardiographic findings, and outcome of cases with HCM was collected from the Cardiac Clinic at Groote Schuur Hospital over a mean duration of follow up of 9.1 ±3.4 years. Genomic DNA was screened for mutations in 15 genes that cause HCM, i.e. cardiac myosin-binding protein C (*MYBPC3*), cardiac beta-myosin heavy chain (*MYH7*), cardiac troponin T2 (*TNNT2*), cardiac troponin I (*TNNI3*), regulatory light chain of myosin (*MYL2*), essential light chain of myosin (*MYL3*), tropomyosin 1 (*TPM1*), phospholamban (*PLN*), α-actin (*ACTC1*), cysteine and glycine-rich protein 3 (*CSRP3*), AMP-activated protein kinase (*PRKAG2*), α-galactosidase *(GLA*), four-and-a-half LIM domains 1 (*FHL1*), lamin A/C (*LMNA*) and lysosome-associated membrane protein 2 (*LAMP2*). Survival and its predictors were analysed using the Kaplan–Meier and Cox proportional hazards regression methods, respectively.

Results: Forty-three consecutive patients [mean age 38.5 ± 14.3 years; 25 (58.1%) male; and 13 (30.2%) black African] were prospectively enrolled in the study from January 1996 to December 2012. Clinical presentation was similar to that reported in other studies. The South African founder mutations that cause HCM were not found in the 42 probands. Ten of 35 index cases (28.6%) tested for mutations in 15 genes had disease–causing mutations in *MYH7* (six cases or 60%) and *MYBPC3* (four cases or 40%). No disease–causing mutation was found in the other 13 genes screened. The annual mortality rate was 2.9% per annum and overall survival was 74% at 10 years, which was similar to the general South African population. Cox's proportional hazards regression showed that survival was predicted by New York Heart Association (NYHA) functional class at last visit ($p = 0.026$), but not by the presence of a disease–causing mutation ($p = 0.474$).

Conclusions: Comprehensive genetic screening was associated with a 29% yield of causal genetic mutations in South African HCM cases, all in *MYH7* and *MBPC3* genes. A quarter of the patients had died after a decade of follow up, with NYHA functional class serving as a predictor of survival.

Oni T, Mayosi BM. Mortality trends in South Africa: progress in the shadow of HIV/AIDS and apartheid. Lancet Glob Health. 2016;4(9):e588–589. doi: 10.1016/s2214-109x(16)30178-4. **Full text available here.**

No abstract available.

Pandie S, Peter JG, Kerbelker ZS, Meldau R, Theron G, Govender U, et al. The diagnostic accuracy of pericardial and urinary lipoarabinomannan (LAM) assays in patients with suspected tuberculous pericarditis. Sci Rep. 2016;6:32924. doi: 10.1038/srep32924. **Full text available here**.

We evaluated the diagnostic accuracy of urinary and pericardial fluid (PF) lipoarabinomannan (LAM) assays in tuberculous pericarditis (TBP). From October 2009 through September 2012, 151 patients with TBP were enrolled. *Mycobacterium tuberculosis* culture and/or pericardial histology were the reference standard for definite TBP. 49% (74/151), 33.1% (50/151) and 17.9% (27/151) of patients had definite-, probable-, and non-TB respectively; 69.5% (105/151) were HIV positive. LAM ELISA had the following sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value and negative predictive values (95% confidence interval): urinary −17.4% (9.1–30.7), 93.8% (71.7–98.9), 2.8 (0.1–63.3), 0.9 (0.8–0.9), 88.9% (56.5–98.0), and 28.3% (17.9–41.6); PF −11.6% (6.0–21.3), 88% (70.0–95.8), 0.9 (0.08–12.0), 1.0 (0.9–1.1), 72.7% (43.4–90.1), and 26.6% (18.2–36.9). Sensitivity increased with a CD4≤100 cells/mm^3 from 3.5% to 50% ($p<0.001$) for urinary LAM ELISA; for urinary LAM strip test, grade 1 and 2 cut-points performed similarly, irrespective of HIV status or CD4 count. For PF LAM strip tests, switching cut-points from grade 1 to 2 significantly reduced test sensitivity (54.5% versus 19.7%; $p<0.001$). Urinary and PF LAM assays have low sensitivity but high specificity for diagnosis of TBP. The sensitivity of urinary LAM is increased in HIV-infected patients with a CD4≤100 cells/mm^3.

Peprah E, Wiley K, Troyer J, Adebamowo SN, Adu D, Mayosi BM, et al. Building a platform to enable NCD research to address population health in Africa: CVD Working Group discussion at the Sixth H3Africa Consortium meeting in Zambia. Glob Heart. 2016;11(1):165–170. doi: 10.1016/j.gheart.2015.11.002. **Full text not freely available.**

No abstract available.

Sacco RL, Roth GA, Reddy KS, Arnett DK, Bonita R, Gaziano TA, et al. The heart of 25 by 25: Achieving the goal of reducing global and regional premature deaths from cardiovascular diseases and stroke: A modeling study from the American Heart Association and World Heart Federation. Glob Heart. 2016;11(2):251–264. doi: 10.1016/j.gheart.2016.04.002. **Full text not freely available.**

In 2011, the United Nations set key targets to reach by 2025 to reduce the risk of premature noncommunicable disease death by 25% by 2025. With cardiovascular disease being the largest contributor to global mortality, accounting for nearly half of the 36 million annual noncommunicable disease deaths, achieving the 2025 goal requires that cardiovascular disease and its risk factors be aggressively addressed. The Global Cardiovascular Disease Taskforce, comprising the World Heart Federation, American Heart Association, American College of Cardiology Foundation, European Heart Network, and European Society of Cardiology, with expanded representation from Asia, Africa, and Latin America, along with global cardiovascular disease experts,

disseminates information and approaches to reach the United Nations 2025 targets. The writing committee, which reflects Global Cardiovascular Disease Taskforce membership, engaged the Institute for Health Metrics and Evaluation, University of Washington, to develop region-specific estimates of premature cardiovascular mortality in 2025 based on various scenarios.

Results show that >5 million premature CVD deaths among men and 2.8 million among women are projected worldwide by 2025, which can be reduced to 3.5 million and 2.2 million, respectively, if risk factor targets for blood pressure, tobacco use, diabetes mellitus, and obesity are achieved. However, global risk factor targets have various effects, depending on region. For most regions, United Nations targets for reducing systolic blood pressure and tobacco use have more substantial effects on future scenarios compared with maintaining current levels of body mass index and fasting plasma glucose. However, preventing increases in body mass index has the largest effect in some high-income countries. An approach achieving reductions in multiple risk factors has the largest impact for almost all regions. Achieving these goals can be accomplished only if countries set priorities, implement cost-effective population wide strategies, and collaborate in public–private partnerships across multiple sectors.

Shung-King M, Zuhlke L, Engel ME, Mayosi BM. Asymptomatic rheumatic heart disease in South African schoolchildren: Implications for addressing chronic health conditions through a school health service. S Afr Med J. 2016;106(8):761–762. doi: 10.7196/SAMJ.2016.v106i8.10756. **Full text available here**.

When new evidence comes to light, it compels us to contemplate the implications of such evidence for health policy and practice. This article examines recent research evidence on the prevalence of asymptomatic rheumatic heart disease (RHD) in South Africa and considers the implications for the Integrated School Health Programme (ISHP). RHD is still a major burden of disease in developing countries, and elimination of this preventable condition ranks high among World Heart Federation goals. If left untreated, it becomes a chronic health condition that individuals have to cope with into their adult lives. The ISHP regards the health needs of children with chronic health conditions, which include conditions such as RHD, as a key service component. However, the chronic health component of the ISHP is still poorly developed and can benefit from good evidence to guide implementation. A recent study to ascertain the prevalence of RHD in asymptomatic schoolchildren through mass screening affords an opportunity to reflect on whether, and how, asymptomatic chronic health conditions in schoolchildren could be addressed, and what the implications would be if this were done through a school-based programme such as the ISHP.

Sliwa K, Damasceno A, Davison BA, Mayosi BM, Sani MU, Ogah O, et al. Bi treatment with hydralazine/nitrates *vs*. placebo in Africans admitted with acute HEart Failure (BA-HEF). Eur J Heart Fail. 2016;18(10):1248–1258. doi: 10.1002/ejhf.581. **Full text not freely available.**

Aims: Patients with acute heart failure (HF) in Africa are rarely being treated with a hydralazine/nitrates combination. Therefore the effect of this treatment was studied here.
Methods and Results: The study was planned to enrol 500 patients during an acute HF admission, from nine sub-Saharan African countries. Patients were randomized in a double-blind manner to receive 50 mg hydralazine/ 20 mg isosorbide dinitrate (HYIS) t.i.d. or matching placebo for 24 weeks followed by open label HYIS for all patients. The study was terminated after 147 patients were enrolled due mostly to issues with recruitment into a prospective, placebo-controlled study. Most patients were recruited from Mozambique, South Africa, Kenya, and Uganda. The primary endpoint of death or HF readmission through 24 weeks was neutral [hazard ratio (HR) 1.05, 95% confidence interval (CI) 0.48–2.27, P = 0.90] in the 133 randomized patients included in the analyses. There were non-signficant effects in favour of HYIS in secondary endpoints including change in dyspnoea severity at day 7 or discharge, decrease in systolic blood pressure, greater decrease in weight, and increase in 6-min walk test distance at week 24. There were also small changes in echocardiographic indices of cardiac size and function in favour or HYIS, but none was significant.
Conclusion: The BA-HEF trial demonstrated challenges in recruiting the expected number of patients with acute HF in a number of African countries, which highlights the need for strategic logistic support.
Trial Registration: NCT01822808.

Springer DB, Brennan T, Ntusi N, Abdelrahman HY, Zuhlke LJ, Mayosi BM, et al. Automated signal quality assessment of mobile phone-recorded heart sound signals. J Med Eng Technol. 2016; 40(7–8):342–355. doi: 10.1080/03091902.2016.1213902. **Full text not freely available.**

Mobile phones, due to their audio processing capabilities, have the potential to facilitate the diagnosis of heart disease through automated auscultation. However, such a platform is likely to be used by non-experts, and hence, it is essential that such a device is able to automatically differentiate poor quality from diagnostically useful recordings since non-experts are more likely to make poor-quality recordings. This paper investigates the automated signal quality assessment of heart sound recordings performed using both mobile phone-based and commercial medical-grade electronic stethoscopes. The recordings, each 60 s long, were taken from 151 random adult individuals with varying diagnoses referred to a cardiac clinic and were professionally annotated by five experts. A mean voting procedure was used to compute a final quality label for each recording. Nine signal quality indices were defined and calculated for each recording. A logistic regression model for classifying binary quality was then trained and tested. The inter-rater agreement level for the stethoscope and mobile phone recordings was measured using Conger's kappa for multiclass sets and found to be 0.24 and 0.54, respectively. One-third of all the mobile phone-recorded phonocardiogram (PCG) signals were found to be of sufficient quality for analysis. The classifier was able to distinguish good- and poor-quality mobile phone recordings with 82.2% accuracy, and those made with the electronic stethoscope with an accuracy of 86.5%. We conclude that our classification approach provides a mechanism for substantially improving auscultation recordings by non-experts. This work is the first

systematic evaluation of a PCG signal quality classification algorithm (using a separate test dataset) and assessment of the quality of PCG recordings captured by non-experts, using both a medical-grade digital stethoscope and a mobile phone.

Wang H, Naghavi M, Allen C, Barber RM, Carter A, Casey DC, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: A systematic analysis for the Global Burden of Disease Study 2015. Lancet. 2016;388(10053):1459–1544. doi: 10.1016/S0140-6736(16)31012-1. **Full text available here.**

Background: Improving survival and extending the longevity of life for all populations requires timely, robust evidence on local mortality levels and trends. The Global Burden of Disease 2015 Study (GBD 2015) provides a comprehensive assessment of all-cause and cause-specific mortality for 249 causes in 195 countries and territories from 1980 to 2015. These results informed an in-depth investigation of observed and expected mortality patterns based on sociodemographic measures.

Methods: We estimated all-cause mortality by age, sex, geography, and year using an improved analytical approach originally developed for GBD 2013 and GBD 2010. Improvements included refinements to the estimation of child and adult mortality and corresponding uncertainty, parameter selection for under-5 mortality synthesis by spatiotemporal Gaussian process regression, and sibling history data processing. We also expanded the database of vital registration, survey, and census data to 14 294 geography–year datapoints. For GBD 2015, eight causes, including Ebola virus disease, were added to the previous GBD cause list for mortality. We used six modelling approaches to assess cause-specific mortality, with the Cause of Death Ensemble Model (CODEm) generating estimates for most causes. We used a series of novel analyses to systematically quantify the drivers of trends in mortality across geographies. First, we assessed observed and expected levels and trends of cause-specific mortality as they relate to the Socio-demographic Index (SDI), a summary indicator derived from measures of income per capita, educational attainment, and fertility. Second, we examined factors affecting total mortality patterns through a series of counterfactual scenarios, testing the magnitude by which population growth, population age structures, and epidemiological changes contributed to shifts in mortality. Finally, we attributed changes in life expectancy to changes in cause of death. We documented each step of the GBD 2015 estimation processes, as well as data sources, in accordance with Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER).

Findings: Globally, life expectancy from birth increased from 61·7 years (95% uncertainty interval 61·4–61·9) in 1980 to 71·8 years (71·5–72·2) in 2015. Several countries in sub-Saharan Africa had very large gains in life expectancy from 2005 to 2015, rebounding from an era of exceedingly high loss of life due to HIV/AIDS. At the same time, many geographies saw life expectancy stagnate or decline, particularly for men and in countries with rising mortality from war or interpersonal violence. From 2005 to 2015, male life expectancy in Syria dropped by 11·3 years (3·7–17·4), to 62·6 years (56·5–70·2). Total deaths increased by 4·1% (2·6–5·6) from 2005 to 2015, rising

to 55·8 million (54·9 million to 56·6 million) in 2015, but age-standardised death rates fell by 17·0% (15·8–18·1) during this time, underscoring changes in population growth and shifts in global age structures. The result was similar for non-communicable diseases (NCDs), with total deaths from these causes increasing by 14·1% (12·6–16·0) to 39·8 million (39·2 million to 40·5 million) in 2015, whereas age-standardised rates decreased by 13·1% (11·9–14·3). Globally, this mortality pattern emerged for several NCDs, including several types of cancer, ischaemic heart disease, cirrhosis, and Alzheimer's disease and other dementias. By contrast, both total deaths and age-standardised death rates due to communicable, maternal, neonatal, and nutritional conditions significantly declined from 2005 to 2015, gains largely attributable to decreases in mortality rates due to HIV/AIDS (42·1%, 39·1–44·6), malaria (43·1%, 34·7–51·8), neonatal preterm birth complications (29·8%, 24·8–34·9), and maternal disorders (29·1%, 19·3–37·1). Progress was slower for several causes, such as lower respiratory infections and nutritional deficiencies, whereas deaths increased for others, including dengue and drug use disorders. Age-standardised death rates due to injuries significantly declined from 2005 to 2015, yet interpersonal violence and war claimed increasingly more lives in some regions, particularly in the Middle East. In 2015, rotaviral enteritis (rotavirus) was the leading cause of under-5 deaths due to diarrhoea (146 000 deaths, 118 000–183 000) and pneumococcal pneumonia was the leading cause of under-5 deaths due to lower respiratory infections (393 000 deaths, 228 000–532 000), although pathogen-specific mortality varied by region. Globally, the effects of population growth, ageing, and changes in age-standardised death rates substantially differed by cause. Our analyses on the expected associations between cause-specific mortality and SDI show the regular shifts in cause of death composition and population age structure with rising SDI. Country patterns of premature mortality (measured as years of life lost [YLLs]) and how they differ from the level expected on the basis of SDI alone revealed distinct but highly heterogeneous patterns by region and country or territory. Ischaemic heart disease, stroke, and diabetes were among the leading causes of YLLs in most regions, but in many cases, intraregional results sharply diverged for ratios of observed and expected YLLs based on SDI. Communicable, maternal, neonatal, and nutritional diseases caused the most YLLs throughout sub-Saharan Africa, with observed YLLs far exceeding expected YLLs for countries in which malaria or HIV/AIDS remained the leading causes of early death. Interpretation At the global scale, age-specific mortality has steadily improved over the past 35 years; this pattern of general progress continued in the past decade. Progress has been faster in most countries than expected on the basis of development measured by the SDI. Against this background of progress, some countries have seen falls in life expectancy, and age-standardised death rates for some causes are increasing. Despite progress in reducing age-standardised death rates, population growth and ageing mean that the number of deaths from most non-communicable causes are increasing in most countries, putting increased demands on health systems.

Wang H, Wolock TM, Carter A, Nguyen G, Kyu HH, Gakidou E, et al. Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2015: the Global Burden of Disease Study 2015. Lancet HIV. 2016;3(8):e361–e387. doi: 10.1016/S2352-3018(16)30087-X. Erratum in: Lancet HIV. 2016;3(9):e408. doi: 10.1016/S2352-3018(16)30125-4. **Full text available here**.

Background: Timely assessment of the burden of HIV/AIDS is essential for policy setting and programme evaluation. In this report from the Global Burden of Disease Study 2015 (GBD 2015), we provide national estimates of levels and trends of HIV/AIDS incidence, prevalence, coverage of antiretroviral therapy (ART), and mortality for 195 countries and territories from 1980 to 2015.

Methods: For countries without high-quality vital registration data, we estimated prevalence and incidence with data from antenatal care clinics and population-based seroprevalence surveys, and with assumptions by age and sex on initial CD4 distribution at infection, CD4 progression rates (probability of progression from higher to lower CD4 cell-count category), on and off antiretroviral therapy (ART) mortality, and mortality from all other causes. Our estimation strategy links the GBD 2015 assessment of all-cause mortality and estimation of incidence and prevalence so that for each draw from the uncertainty distribution all assumptions used in each step are internally consistent. We estimated incidence, prevalence, and death with GBD versions of the Estimation and Projection Package (EPP) and Spectrum software originally developed by the Joint United Nations Programme on HIV/AIDS (UNAIDS). We used an open-source version of EPP and recoded Spectrum for speed, and used updated assumptions from systematic reviews of the literature and GBD demographic data. For countries with high-quality vital registration data, we developed the cohort incidence bias adjustment model to estimate HIV incidence and prevalence largely from the number of deaths caused by HIV recorded in cause-of-death statistics. We corrected these statistics for garbage coding and HIV misclassification.

Findings: Global HIV incidence reached its peak in 1997, at 3·3 million new infections (95% uncertainty interval [UI] 3·1–3·4 million). Annual incidence has stayed relatively constant at about 2·6 million per year (range 2·5–2·8 million) since 2005, after a period of fast decline between 1997 and 2005. The number of people living with HIV/AIDS has been steadily increasing and reached 38·8 million (95% UI 37·6–40·4 million) in 2015. At the same time, HIV/AIDS mortality has been declining at a steady pace, from a peak of 1·8 million deaths (95% UI 1·7–1·9 million) in 2005, to 1·2 million deaths (1·1–1·3 million) in 2015. We recorded substantial heterogeneity in the levels and trends of HIV/AIDS across countries. Although many countries have experienced decreases in HIV/AIDS mortality and in annual new infections, other countries have had slowdowns or increases in rates of change in annual new infections.

Interpretation: Scale-up of ART and prevention of mother-to-child transmission has been one of the great successes of global health in the past two decades. However, in the past decade, progress in reducing new infections has been slow, development assistance for health devoted to HIV has stagnated, and resources for health in low-income countries have grown slowly. Achievement of the new ambitious goals for HIV enshrined in Sustainable Development Goal 3 and the 90–90–90 UNAIDS targets will be challenging, and will need continued

efforts from governments and international agencies in the next 15 years to end AIDS by 2030.

Wang H, Wolock TM, Carter A, Nguyen G, Kyu HH, Gakidou E, et al. Erratum: Estimates of global, regional, and national incidence, prevalence, and mortality of HIV, 1980–2015: The Global Burden of Disease Study 2015. Lancet HIV. 2006:3(9);e408. doi: 10.1016/S2352-3018(16)30125-4. Erratum for: Lancet HIV. 2016:3(8):e361–387. **Full text available here.**

No abstract available.

Watkins D, Lubinga SJ, Mayosi B, Babigumira JB. A cost-effectiveness tool to guide the prioritization of interventions for rheumatic fever and rheumatic heart disease control in African nations. PLoS Negl Trop Dis. 2016;10(8):e0004860. doi: 10.1371/journal.pntd.0004860. **Full text available here.**

Background: Rheumatic heart disease (RHD) prevalence and mortality rates remain especially high in many parts of Africa. While effective prevention and treatment exist, coverage rates of the various interventions are low. Little is known about the comparative cost-effectiveness of different RHD interventions in limited resource settings. We developed an economic evaluation tool to assist ministries of health in allocating resources and planning RHD control programs.

Methodology/Principal Findings: We constructed a Markov model of the natural history of acute rheumatic fever (ARF) and RHD, taking transition probabilities and intervention effectiveness data from previously published studies and expert opinion. Our model estimates the incremental cost-effectiveness of scaling up coverage of primary prevention (PP), secondary prevention (SP) and heart valve surgery (VS) interventions for RHD. We take a healthcare system perspective on costs and measure outcomes as disability-adjusted life-years (DALYs), discounting both at 3%. Univariate and probabilistic sensitivity analyses are also built into the modeling tool. We illustrate the use of this model in a hypothetical low-income African country, drawing on available disease burden and cost data. We found that, in our hypothetical country, PP would be cost saving and SP would be very cost-effective. International referral for VS (e.g., to a country like India that has existing surgical capacity) would be cost-effective, but building in-country VS services would not be cost-effective at typical low-income country thresholds.

Conclusions/Significance: Our cost-effectiveness analysis tool is designed to inform priorities for ARF/RHD control programs in Africa at the national or subnational level. In contrast to previous literature, our preliminary findings suggest PP could be the most efficient and cheapest approach in poor countries. We provide our model for public use in the form of a Supplementary File. Our research has immediate policy relevance and calls for renewed efforts to scale up RHD prevention.

Watkins D, Zuhlke L, Engel M, Daniels R, Francis V, Shaboodien G, et al. Seven key actions to eradicate rheumatic heart disease in Africa: The Addis Ababa communique. Cardiovasc J Afr. 2016; 27(3):184–187. doi: 10.5830/cvja-2015-090. **Full text not freely available.**

Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) remain major causes of heart failure, stroke and death among African women and children, despite being preventable and imminently treatable. From 21 to 22 February 2015, the Social Cluster of the Africa Union Commission (AUC) hosted a consultation with RHD experts convened by the Pan-African Society of Cardiology (PASCAR) in Addis Ababa, Ethiopia, to develop a 'roadmap' of key actions that need to be taken by governments to eliminate ARF and eradicate RHD in Africa. Seven priority areas for action were adopted: (1) create prospective disease registers at sentinel sites in affected countries to measure disease burden and track progress towards the reduction of mortality by 25% by the year 2025, (2) ensure an adequate supply of high-quality benzathine penicillin for the primary and secondary prevention of ARF/RHD, (3) improve access to reproductive health services for women with RHD and other non-communicable diseases (NCD), (4) decentralise technical expertise and technology for diagnosing and managing ARF and RHD (including ultrasound of the heart), (5) establish national and regional centres of excellence for essential cardiac surgery for the treatment of affected patients and training of cardiovascular practitioners of the future, (6) initiate national multi-sectoral RHD programmes within NCD control programmes of affected countries, and (7) foster international partnerships with multinational organisations for resource mobilisation, monitoring and evaluation of the programme to end RHD in Africa. This Addis Ababa communique has since been endorsed by African Union heads of state, and plans are underway to implement the roadmap in order to end ARF and RHD in Africa in our lifetime.

Zuhlke L, Engel ME, Lemmer CE, van de Wall M, Nkepu S, Meiring A, et al. The natural history of latent rheumatic heart disease in a 5 year follow-up study: A prospective observational study. BMC Cardiovasc Disord. 2016;16(1):46. doi: 10.1186/s12872-016-0225-3. **Full text available here**.

Background: Latent rheumatic heart disease (RHD) occurs in asymptomatic individuals with echocardiographic evidence of RHD and no history of acute rheumatic fever. The natural history of latent RHD is unclear but has important clinical and economic implications about whether these children should receive penicillin prophylaxis or not. We performed a 5-year prospective study of this question.

Methods: In August 2013 through September 2014, we conducted a follow-up study of latent RHD among school pupils using the World Heart Federation (WHF) echocardiographic criteria. Contingency tables were used to assess progression, persistence or regression of latent RHD.

Results: Forty two borderline and 13 definite cases of RHD (n = 55) were identified, 44 (80%; mean age 13.8 ± 4.0 years; 29 (65.9%) female) of whom were available for echocardiographic examination at a median follow-up of 60.8 months (interquartile range 51.3–63.5). Over the follow-up period, half the participants (n = 23; 52.3%)

improved to normal or better WHF category (regressors), a third (n = 14, 31.8%) remained in the same category (persistors), while seven others (15.9%) progressed from borderline to definite RHD (progressors). In total, 21 subjects (47.7%) reverted to a normal status, nine (20.4%) either improved from definite to borderline or remained in the borderline category, and 14 (31.8%) either remained definite or progressed from borderline to a definite status. Two cases (20%) progressed to symptomatic disease.
Conclusions: ccLatent RHD has a variable natural history that ranges from regression to normal in nearly half of cases, to persistence, progression or development of symptoms in the remainder of subjects.

Zuhlke LJ, Engel ME, Nkepu S, Mayosi BM. Evaluation of a focussed protocol for hand-held echocardiography and computer-assisted auscultation in detecting latent rheumatic heart disease in scholars. Cardiol Young. 2016;26(6):1097–1106. doi: 10.1017/S1047951115001857. **Full text not freely available.**

No abstract available.

Zuhlke L, Karthikeyan G, Engel ME, Rangarajan S, Mackie P, Cupido-Katya Mauff B, et al. Clinical outcomes in 3343 children and adults with rheumatic heart disease from 14 low- and middle-income countries: Two-year follow-up of the Global Rheumatic Heart Disease Registry (the REMEDY Study). Circulation. 2016;134(19):1456–1466. doi: 10.1161/circulationaha.116.024769. **Full text not freely available.**

Background: There are few contemporary data on the mortality and morbidity associated with rheumatic heart disease or information on their predictors. We report the 2-year follow-up of individuals with rheumatic heart disease from 14 low- and middle-income countries in Africa and Asia.
Methods: Between January 2010 and November 2012, we enrolled 3343 patients from 25 centers in 14 countries and followed them for 2 years to assess mortality, congestive heart failure, stroke or transient ischemic attack, recurrent acute rheumatic fever, and infective endocarditis.
Results: Vital status at 24 months was known for 2960 (88.5%) patients. Two-thirds were female. Although patients were young (median age, 28 years; interquartile range, 18–40), the 2-year case fatality rate was high (500 deaths, 16.9%). Mortality rate was 116.3/1000 patient–years in the first year and 65.4/1000 patient–years in the second year. Median age at death was 28.7 years. Independent predictors of death were severe valve disease (hazard ratio [HR], 2.36; 95% confidence interval [CI], 1.80–3.11), congestive heart failure (HR, 2.16; 95% CI, 1.70–2.72), New York Heart Association functional class III/IV (HR, 1.67; 95% CI, 1.32–2.10), atrial fibrillation (HR, 1.40; 95% CI, 1.10–1.78), and older age (HR, 1.02; 95% CI, 1.01–1.02 per year increase) at enrollment. Postprimary education (HR, 0.67; 95% CI, 0.54–0.85) and female sex (HR, 0.65; 95% CI, 0.52–0.80) were associated with lower risk of death. Two hundred and four (6.9%) patients had new congestive heart failure (incidence, 38.42/1000 patient–years), 46 (1.6%) had a stroke or transient ischemic attack (8.45/1000 patient–

years), 19 (0.6%) had recurrent acute rheumatic fever (3.49/1000 patient–years), and 20 (0.7%) had infective endocarditis (3.65/1000 patient–years). Previous stroke and older age were independent predictors of stroke/transient ischemic attack or systemic embolism. Patients from low- and lower-middle-income countries had significantly higher age- and sex-adjusted mortality than patients from upper-middle-income countries. Valve surgery was significantly more common in upper-middle-income than in lower-middle- or low-income countries.

Conclusions: Patients with clinical rheumatic heart disease have high mortality and morbidity despite being young; those from low- and lower-middle-income countries had a poorer prognosis associated with advanced disease and low education. Programs focused on early detection and the treatment of clinical rheumatic heart disease are required to improve outcomes.

2015

Adler Y, Charron P, Imazio M, Badano L, Baron-Esquivias G, Bogaert J, et al. 2015. ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36(42):2921–2964. doi: https://doi.org/10.1093/eurheartj/ehv318. **Full text not freely available.**

No abstract available.

Barth DD, Mayosi BM, Jabar A, Engel ME. Prevalence of group A streptococcal disease in North and Sub-Saharan Africa: a systematic review protocol. BMJ Open. 2015;5(8):e008646. doi: 10.1136/bmjopen-2015-008646. **Full text available here.**

Introduction: The true burden of group A streptococcal (GAS) disease in Africa is not known. GAS is a significant cause of mortality and morbidity on the global scale and in developing countries. According to Carapetis et al, the prevalence of severe GAS disease is at least 18.1 million cases with an incidence of at least 1.78 million cases per year.

Methods and analyses: We aim to provide a systematic review of studies measuring the prevalence of GAS infection among people in North and Sub-Saharan African countries. A comprehensive literature search of a number of databases will be undertaken, using an African search filter, to identify GAS prevalence studies that have been published. Full copies of articles will be identified by a defined search strategy and will be considered for inclusion against predefined criteria. Statistical analysis will include two steps: (1) identification of data sources and documenting of estimates, and (2) the application of the random-effects and fixed-effects meta-analysis model to aggregate prevalence estimates, and to account for between study variability in calculating the overall pooled estimates and 95% CI for GAS prevalence. Heterogeneity will be evaluated using the I^2 statistic to determine the extent of variation in effect estimates that is due to heterogeneity rather than chance. This systematic review protocol was prepared according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) 2015 Statement. This review will provide updated evidence of a review published in 2009. Our data will have implications for the development of a GAS vaccine. Ethics and dissemination: Ethics approval is not required for this study given that this is a protocol for a systematic review of published studies. The results of this study will be disseminated through a peer-reviewed publication and conference presentation.

Systematic review registration number: PROSPERO CRD42014012900.

Barth DD, Zuhlke LJ, Joachim A, Hoegger T, Mayosi BM, Engel ME. Effect of distance to health facility on the maintenance of INR therapeutic ranges in rheumatic heart disease patients from Cape Town: No evidence for an association. BMC Health Serv Res. 2015;15:219. doi: 10.1186/s12913-015-0890-4. **Full text available here.**

Background: Lack of adherence to international normalised ratio (INR) monitoring in rheumatic heart disease (RHD) patients is a contributor to cardio-embolic complications. This population-based observational study investigated whether the distance between home and an INR clinic affects the maintenance of therapeutic INR in RHD patients on warfarin.

Methods: Residential addresses, INR clinics, and INR results of patients with RHD were extracted from the Cape Town component of the Global Rheumatic Heart Disease Registry (REMEDY) database. Addresses of homes and INR clinics were converted to geographical coordinates and verified in ArcGIS 10®. ArcGIS 10® and Google Maps® were used for spatial mapping and obtaining shortest road distances respectively. The travel distance between the home and INR clinic was correlated with time within therapeutic range (TTR) using the Rosendaal linear interpolation method, and with the fraction of INR within range, based on an average of three INR readings of patients and compared with recommended therapeutic ranges.

Results: RHD patients (n = 133) resided between 0.2 km and 50.8 km (median distance, 3.60 km) from one of 33 INR clinics. There was no significant difference in the achievement of the therapeutic INR between patients who travelled a shorter distance compared to those who travelled a longer distance (in range = 3.50 km versus out of range = 3.75 km, p = 0.78). This finding was the same for patients with mechanical valve replacement (n = 105) (3.50 km versus 3.90 km, p = 0.81), and native valves (3.45 km versus 2.75 km, p = 0.84).

Conclusions: There is no association between the maintenance of INR within therapeutic range amongst RHD patients in Cape Town and distance from patients' residence to the INR clinic.

Benatar SR, Mayosi BM. Health and health care in South Africa. N Engl J Med. 2015;372(1):95. doi: 10.1056/NEJMc1413160. **Full text not freely available.**

No abstract available.

Bloomfield GS, Alenezi F, Barasa FA, Lumsden R, Mayosi BM, Velazquez EJ. Human Immuno-deficiency Virus and heart failure in low- and middle-income countries. JACC Heart Fail. 2015; 3(8):579–590. doi: 10.1016/j.jchf.2015.05.003. **Full text not freely available.**

Successful combination therapy for human immunodeficiency virus (HIV) has transformed this disease from a short-lived infection with high mortality to a chronic disease associated with increasing life expectancy. This is

true for high- as well as low- and middle-income countries. As a result of this increased life expectancy, people living with HIV are now at risk of developing other chronic diseases associated with aging. Heart failure has been common among people living with HIV in the eras of pre- and post- availability of antiretroviral therapy; however, our current understanding of the pathogenesis and approaches to management have not been systematically addressed. HIV may cause heart failure through direct (e.g., viral replication, mitochondrial dysfunction, cardiac autoimmunity, autonomic dysfunction) and indirect (e.g., opportunistic infections, antiretroviral therapy, alcohol abuse, micronutrient deficiency, tobacco use) pathways. In low- and middle-income countries, 2 large observational studies have recently reported clinical characteristics and outcomes in these patients. HIV-associated heart failure remains a common cardiac diagnosis in people living with heart failure, yet a unifying set of diagnostic criteria is lacking. Treatment patterns for heart failure fall short of society guidelines. Although there may be promise in cardiac glycosides for treating heart failure in people living with HIV, clinical studies are needed to validate in vitro findings. Owing to the burden of HIV in low- and middle-income countries and the concurrent rise of traditional cardiovascular risk factors, strategic and concerted efforts in this area are likely to impact the care of people living with HIV around the globe.

de Vries J, Tindana P, Littler K, Ramsay M, Rotimi C, Abayomi A, et al. The H3Africa policy framework: Negotiating fairness in genomics. Trends Genet. 2015;31(3):117–119. doi: 10.1016/j.tig.2014.11.004. **Full text available here.**

Human Heredity and Health in Africa (H3Africa) research seeks to promote fair collaboration between scientists in Africa and those from elsewhere. Here, we outline how concerns over inequality and exploitation led to a policy framework that places a firm focus on African leadership and capacity building as guiding principles for African genomics research.

Dzudie A, Ojji D, Anisiuba BC, Abdou BA, Cornick R, Damasceno A, et al. Development of the roadmap and guidelines for the prevention and management of high blood pressure in Africa: Proceedings of the PASCAR Hypertension Task Force meeting: Nairobi, Kenya, 27 October 2014. Cardiovasc J Afr. 2015;26(2):82–85. **Full text not freely available.**

Africa has one of the fastest growing economies in the world. The economic changes are associated with a health transition characterised by a rise in cardiovascular risk factors and complications, which tend to affect the African population at their age of maximum productivity. Recent data from Africa have highlighted the increasing importance of high blood pressure in this region of the world. This condition is largely underdiagnosed and poorly treated, and therefore leads to stroke, renal and heart failure, and death. Henceforth, African countries are taking steps to develop relevant policies and programmes to address the issue of blood pressure and other cardiovascular risk factors in response to a call by the World Health Organisation (WHO) to reduce premature

deaths from non-communicable diseases (NCDs) by 25% by the year 2025 (25 × 25). The World Heart Federation (WHF) has developed a roadmap for global implementation of the prevention and management of raised blood pressure using a health system approach to help realise the 25 × 25 goal set by the WHO. As the leading continental organisation of cardiovascular professionals, the Pan-African Society of Cardiology (PASCAR) aims to contextualise the roadmap framework of the WHF to the African continent through the PASCAR Taskforce on Hypertension. The Taskforce held a workshop in Kenya on 27 October 2014 to discuss a process by which effective prevention and control of hypertension in Africa may be achieved. It was agreed that a set of clinical guidelines for the management of hypertension are needed in Africa. The ultimate goal of this work is to develop a roadmap for implementation of the prevention and management of hypertension in Africa under the auspices of the WHF.

Engel ME, Haileamlak A, Zuhlke L, Lemmer CE, Nkepu S, Van De Wall M, et al. Prevalence of rheumatic heart disease in 4720 asymptomatic scholars from South Africa and Ethiopia. Heart. 2015; 101(17):1389–1394. doi: 10.1136/heartjnl-2015-307444. **Full text not freely available.**

Background: In Africa, screening for asymptomatic rheumatic heart disease (RHD) has been conducted in single communities using non-standardised echocardiographic criteria. The use of different diagnostic criteria has led to widely variable estimates of the prevalence of RHD in the same communities.

Methods: Randomly selected school pupils, from 4 to 24 years of age in Bonteheuwel and Langa communities of Cape Town, South Africa, and Jimma, Ethiopia, respectively, were screened for RHD according to standardised evidence-based echocardiographic diagnostic criteria of the World Heart Federation (WHF).

Results: We screened 4720 scholars. In South Africa (n=2720), 1604 (58.9%) were female and the mean age was 12.2±4.2 years. In Ethiopia (n=2000), 1012 (50.6%) were female and the mean age was 10.7 ±2.5 years. Echocardiographic screening revealed 55 cases of definite and borderline RHD by WHF criteria in South Africa and 61 cases in Ethiopia, corresponding to a prevalence of 20.2 cases per 1000 (95% CI 15.3 to 26.2) and 31 cases per 1000 (95% CI 23.4 to 39.0), respectively. The odds of detecting a scholar with RHD in Ethiopia were 1.5 times higher than in South Africa (OR 1.5; 95% CI 1.04 to 2.2, p=0.02). The prevalence of RHD was 27 cases per 1000 (95% CI 19.3 to 36.8) in Langa, and 12.5 cases per 1000 (95% CI 7.1 to 20.2) in Bonteheuwel. The odds of detecting a schoolchild with RHD in Langa compared with Bonteheuwel were 2.2 (OR 2.2; 95% CI 1.2 to 4.2, p=0.0071).

Interpretation: There were significant differences in detecting asymptomatic RHD in school pupils of different countries and in different communities within a country in sub-Saharan Africa. The variation in the prevalence of RHD between countries and communities has important implications for the modelling of the global burden of RHD.

Ezzati M, Obermeyer Z, Tzoulaki I, Mayosi BM, Elliott P, Leon DA. Contributions of risk factors and

medical care to cardiovascular mortality trends. Nat Rev Cardiol. 2015;12(9):508–530. doi: 10.1038/nrcardio.2015.82. **Full text not freely available.**

Ischaemic heart disease, stroke, and other cardiovascular diseases (CVDs) lead to 17.5 million deaths worldwide per year. Taking into account population ageing, CVD death rates are decreasing steadily both in regions with reliable trend data and globally. The declines in high-income countries and some Latin American countries have been ongoing for decades without slowing. These positive trends have broadly coincided with, and benefited from, declines in smoking and physiological risk factors, such as blood pressure and serum cholesterol levels. These declines have also coincided with, and benefited from, improvements in medical care, including primary prevention, diagnosis, and treatment of acute CVDs, as well as post-hospital care, especially in the past 40 years. These variables, however, explain neither why the decline began when it did, nor the similarities and differences in the start time and rate of the decline between countries and sexes. In Russia and some other former Soviet countries, changes in volume and patterns of alcohol consumption have caused sharp rises in CVD mortality since the early 1990s. An important challenge in reaching firm conclusions about the drivers of these remarkable international trends is the paucity of time-trend data on CVD incidence, risk factors throughout the life-course, and clinical care.

Forouzanfar MH, Alexander L, Anderson HR, Bachman VF, Biryukov S, Brauer M, et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks in 188 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(10010):2287–2323. doi: 10.1016/s0140-6736(15)00128-2. **Full text not freely available.**

Background: The Global Burden of Disease, Injuries, and Risk Factor study 2013 (GBD 2013) is the first of a series of annual updates of the GBD. Risk factor quantification, particularly of modifiable risk factors, can help to identify emerging threats to population health and opportunities for prevention. The GBD 2013 provides a timely opportunity to update the comparative risk assessment with new data for exposure, relative risks, and evidence on the appropriate counterfactual risk distribution.

Methods: Attributable deaths, years of life lost, years lived with disability, and disability-adjusted life-years (DALYs) have been estimated for 79 risks or clusters of risks using the GBD 2010 methods. Risk-outcome pairs meeting explicit evidence criteria were assessed for 188 countries for the period 1990–2013 by age and sex using three inputs: risk exposure, relative risks, and the theoretical minimum risk exposure level (TMREL). Risks are organised into a hierarchy with blocks of behavioural, environmental and occupational, and metabolic risks at the first level of the hierarchy. The next level in the hierarchy includes nine clusters of related risks and two individual

risks, with more detail provided at levels 3 and 4 of the hierarchy. Compared with GBD 2010, six new risk factors have been added: handwashing practices, occupational exposure to trichloroethylene, childhood wasting, childhood stunting, unsafe sex, and low glomerular filtration rate. For most risks, data for exposure were synthesised with a Bayesian meta-regression method, DisMod-MR 2.0, or spatial–temporal Gaussian process regression. Relative risks were based on meta-regressions of published cohort and intervention studies. Attributable burden for clusters of risks and all risks combined took into account evidence on the mediation of some risks such as high body-mass index (BMI) through other risks such as high systolic blood pressure and high cholesterol.

Findings: All risks combined account for 57.2% (95% uncertainty interval [UI] 55.8–58.5) of deaths and 41.6% (40.1–43.0) of DALYs. Risks quantified account for 87.9% (86.5–89.3) of cardiovascular disease DALYs, ranging to a low of 0% for neonatal disorders and neglected tropical diseases and malaria. In terms of global DALYs in 2013, six risks or clusters of risks each caused more than 5% of DALYs: dietary risks accounting for 11.3 million deaths and 241.4 million DALYs, high systolic blood pressure for 10.4 million deaths and 208.1 million DALYs, child and maternal malnutrition for 1.7 million deaths and 176.9 million DALYs, tobacco smoke for 6.1 million deaths and 143.5 million DALYs, air pollution for 5.5 million deaths and 141.5 million DALYs, and high BMI for 4.4 million deaths and 134.0 million DALYs. Risk factor patterns vary across regions and countries and with time. In sub-Saharan Africa, the leading risk factors are child and maternal malnutrition, unsafe sex, and unsafe water, sanitation, and handwashing. In women, in nearly all countries in the Americas, north Africa, and the Middle East, and in many other high-income countries, high BMI is the leading risk factor, with high systolic blood pressure as the leading risk in most of Central and Eastern Europe and south and east Asia. For men, high systolic blood pressure or tobacco use are the leading risks in nearly all high-income countries, in north Africa and the Middle East, Europe, and Asia. For men and women, unsafe sex is the leading risk in a corridor from Kenya to South Africa.

Interpretation: Behavioural, environmental and occupational, and metabolic risks can explain half of global mortality and more than one-third of global DALYs providing many opportunities for prevention. Of the larger risks, the attributable burden of high BMI has increased in the past 23 years. In view of the prominence of behavioural risk factors, behavioural and social science research on interventions for these risks should be strengthened. Many prevention and primary care policy options are available now to act on key risks.

Gewitz MH, Baltimore RS, Tani LY, Sable CA, Shulman ST, Carapetis J, et al. Revision of the Jones Criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: A scientific statement from the American Heart Association. Circulation. 2015;131(20):1806–1818. doi: 10.1161/cir.0000000000000205. **Full text not freely available.**

Background: Acute rheumatic fever remains a serious healthcare concern for the majority of the world's population despite its decline in incidence in Europe and North America. The goal of this statement was to

review the historic Jones criteria used to diagnose acute rheumatic fever in the context of the current epidemiology of the disease and to update those criteria to also take into account recent evidence supporting the use of Doppler echocardiography in the diagnosis of carditis as a major manifestation of acute rheumatic fever.

Methods and results: To achieve this goal, the American Heart Association's Council on Cardiovascular Disease in the Young and its Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee organized a writing group to comprehensively review and evaluate the impact of population-specific differences in acute rheumatic fever presentation and changes in presentation that can result from the now worldwide availability of nonsteroidal anti-inflammatory drugs. In addition, a methodological assessment of the numerous published studies that support the use of Doppler echocardiography as a means to diagnose cardiac involvement in acute rheumatic fever, even when overt clinical findings are not apparent, was undertaken to determine the evidence basis for defining subclinical carditis and including it as a major criterion of the Jones criteria. This effort has resulted in the first substantial revision to the Jones criteria by the American Heart Association since 1992 and the first application of the Classification of Recommendations and Levels of Evidence categories developed by the American College of Cardiology/American Heart Association to the Jones criteria.

Conclusions: This revision of the Jones criteria now brings them into closer alignment with other international guidelines for the diagnosis of acute rheumatic fever by defining high-risk populations, recognizing variability in clinical presentation in these high-risk populations, and including Doppler echocardiography as a tool to diagnose cardiac involvement.

Jama ZV, Chin A, Badri M, Mayosi BM. Performance of re-used pacemakers and implantable cardioverter defibrillators compared with new devices at Groote Schuur Hospital in Cape Town, South Africa. Cardiovasc J Afr. 2015;26(4):181–187. doi: 10.5830/cvja-2015-048. **Full text not freely available.**

Objectives: Little is known about the performance of re-used pacemakers and implantable cardioverter defibrillators (ICDs) in Africa. We sought to compare the risk of infection and the rate of malfunction of re-used pacemakers and ICDs with new devices implanted at Groote Schuur Hospital in Cape Town, South Africa.

Methods: This was a retrospective case comparison study of the performance of re-used pacemakers and ICDs in comparison with new devices implanted at Groote Schuur Hospital over a 10-year period. The outcomes were incidence of device infection, device malfunction, early battery depletion, and device removal due to infection, malfunction, or early battery depletion.

Results: Data for 126 devices implanted in 126 patients between 2003 and 2013 were analysed, of which 102 (81%) were pacemakers (51 re-used and 51 new) and 24 (19%) were ICDs (12 re-used and 12 new). There was no device infection, malfunction, early battery depletion or device removal in either the re-used or new pacemaker groups over the median follow up of 15.1 months [interquartile range (IQR), 1.3–36.24 months] for the re-used pacemakers, and 55.8 months (IQR, 20.3–77.8 months) for the new pacemakers. In the ICD group, no device

infection occurred over a median follow up of 35.9 months (IQR, 17.0–70.9 months) for the re-used ICDs and 45.7 months (IQR, 37.6–53.7 months) for the new ICDs. One device delivered inappropriate shocks, which resolved without intervention and with no harm to the patient. This re-used ICD subsequently needed generator replacement 14 months later. In both the pacemaker and ICD groups, there were no procedure-non-related infections documented for the respective follow-up periods.

Conclusion: No significant differences were found in performance between re-used and new pacemakers and ICDs with regard to infection rates, device malfunction, battery life and device removal for complications. Pacemaker and ICD re-use is feasible and safe and is a viable option for patients with bradyarrhythmias and tachyarrthythmias.

Johnson TD, Grainger Gasser A, Boardman C, Remenyi B, Wyber R, Mayosi BM. The 5 × 5 path toward rheumatic heart disease control: Outcomes from the third rheumatic heart disease forum. Global Heart. 2015;10(1):75–78. doi: 10.1016/j.gheart.2014.12.005. **Full text not freely available.**

No abstract available.

London GM, Mayosi BM, Khati M. Isolation and characterization of 2'-F-RNA aptamers against whole HIV-1 subtype C envelope pseudovirus. Biochem Biophys Res Commun. 2015;456(1):428–433. doi: https://doi.org/10.1016/j.bbrc.2014.11.101. **Full text not freely available.**

Aptamers, which are artificial nucleic acid ligands akin to antibodies in function, represent a new class of molecules that can prevent HIV infection. In this study, we isolated RNA aptamers against whole HV-1_{CAP45} enveloped pseudotyped virus, with a view to target surface molecules that facilitate infection, such as the envelope protein, in their native form. HIV-1_{CAP45} belongs to subtype C viruses endemic in Sub-Saharan Africa and responsible for the majority of the global HIV-1 infections. After nine rounds of the systematic evolution of ligands by exponential enrichment (SELEX) method, we isolated twenty-three aptamer clones that inhibited infection of target cells by HIV-1_{CAP45} with 50% inhibitory concentration (IC_{50}) values of 0.1–50 nM. Four of these aptamers called CSIR1.1, CSIR1.4, CSIR1.5 and CSIR1.6 bound to gp120 with affinity constant (K_D) values between 16.9 and 195 nM and one aptamer called CSIR1.2 bound gp41. Interestingly, one aptamer called CSIR1.3 that did not bind gp120 or gp41 also inhibited infection of the target cells by HIV-1_{CAP45} with IC_{50} of less than 5 nM. Taken together, these data show that the aptamers inhibit infection of HIV-1_{CAP45} by binding to gp120 or gp41, or other viral surface molecules necessary for infection. The results argue in favour of using these aptamers as analytical tools to further probe HIV-1 entry, and their future development as HIV-1 entry inhibitors.

Matthews K, Deffur A, Ntsekhe M, Syed F, Russell JB, Tibazarwa K, et al. A compartmentalized profibrotic immune response characterizes pericardial tuberculosis, irrespective of HIV-1 infection. Am J Respir Crit

Care Med. 2015;192(12):1518–1521. doi: 10.1164/rccm.201504-0683LE. **Full text not freely available.**

No abstract available.

Mayosi BM. Pericarditis-associated atrial fibrillation. Heart. 2015;101(18):1439–1440. doi: 10.1136/heartjnl-2015-307917. **Full text not freely available.**

No abstract available.

Mayosi BM. Medical history. The first black doctors and their influence in South Africa. S Afr Med J. 2015;105(8):635–636. doi: 10.7196/SAMJnew.7821. **Full text available here.**

The early black doctors who qualified from foreign medical schools between 1883 and 1940 were pioneers in the history of South Africa. They made seminal contributions to the struggle against colonialism and apartheid, established the principle of fighting against racism in healthcare through the courts, and were trailblazers in academic medicine. They have bequeathed a remarkable legacy to the new South Africa.

Mercier S, Kury S, Salort-Campana E, Magot A, Agbim U, Besnard T, et al. Expanding the clinical spectrum of hereditary fibrosing poikiloderma with tendon contractures, myopathy and pulmonary fibrosis due to *FAM111B* mutations. Orphanet J Rare Dis. 2015;10:135. doi: 10.1186/s13023-015-0352-4. **Full text available here.**

Background: Hereditary Fibrosing Poikiloderma (HFP) with tendon contractures, myopathy and pulmonary fibrosis (POIKTMP [MIM 615704]) is a very recently described entity of syndromic inherited poikiloderma. Previously by using whole exome sequencing in five families, we identified the causative gene, *FAM111B* (NM_198947.3), the function of which is still unknown. Our objective in this study was to better define the specific features of POIKTMP through a larger series of patients.

Methods: Clinical and molecular data of two families and eight independent sporadic cases, including six new cases, were collected.

Results: Key features consist of: (i) early-onset poikiloderma, hypotrichosis and hypohidrosis; (ii) multiple contractures, in particular triceps surae muscle contractures; (iii) diffuse progressive muscular weakness; (iv) pulmonary fibrosis in adulthood and (v) other features including exocrine pancreatic insufficiency, liver impairment and growth retardation. Muscle magnetic resonance imaging was informative and showed muscle atrophy and fatty infiltration. Histological examination of skeletal muscle revealed extensive fibroadipose tissue infiltration. Microscopy of the skin showed a scleroderma-like aspect with fibrosis and alterations of the elastic network. *FAM111B* gene analysis identified five different missense variants (two recurrent mutations were found respectively in three and four independent families). All the mutations were predicted to localize in the trypsin-like cysteine/serine peptidase domain of the protein. We suggest gain-of-function or dominant-negative

mutations resulting in *FAM111B* enzymatic activity changes.
Conclusions: HFP with tendon contractures, myopathy and pulmonary fibrosis, is a multisystemic disorder due to autosomal dominant *FAM111B* mutations. Future functional studies will help in understanding the specific pathological process of this fibrosing disorder.

Mnguni AT, Engel ME, Borkum MS, Mayosi BM. The effects of angiotensin converting enzyme inhibitors (ACE-I) on human N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) levels: A systematic review and meta-analysis. PLoS One. 2015;10(12):e0143338. doi: 10.1371/journal.pone.0143338. **Full text available here.**

Background: Tuberculous pericardial effusion is a pro-fibrotic condition that is complicated by constrictive pericarditis in 4% to 8% of cases. N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is a ubiquitous tetrapeptide with anti-fibrotic properties that is low in tuberculous pericardial effusion, thus providing a potential mechanism for the heightened fibrotic state. Angiotensin-converting enzyme inhibitors (ACE-I), which increase Ac-SDKP levels with anti-fibrotic effects in animal models, are candidate drugs for preventing constrictive pericarditis if they can be shown to have similar effects on Ac-SDKP and fibrosis in human tissues.
Objective: To systematically review the effects of ACE-Is on Ac-SDKP levels in human tissues.
Methods: We searched five electronic databases (1996 to 2014) and conference abstracts with no language restrictions. Two reviewers independently selected studies, extracted data and assessed methodological quality. The protocol was registered in PROSPERO.
Results: Four studies with a total of 206 participants met the inclusion criteria. Three studies (106 participants) assessed the change in plasma levels of Ac-SDKP following ACE-I administration in healthy humans. The administration of an ACE-I was associated with an increase in Ac-SDKP levels (mean difference (MD) 5.07 pmol/ml (95% confidence intervals (CI) 0.64 pmol/ml to 9.51 pmol/ml)). Two studies with 100 participants further assessed the change in Ac-SDKP level in humans with renal failure using ACE-I. The administration of an ACE-I was associated with a significant increase in Ac-SDKP levels (MD 8.94 pmol/ml; 95% CI 2.55 to 15.33; I2 = 44%).
Conclusion: ACE-I increased Ac-SDKP levels in human plasma. These findings provide the rationale for testing the impact of ACE-I on Ac-SDKP levels and fibrosis in tuberculous pericarditis.

Murray CJ, Barber RM, Foreman KJ, Abbasoglu Ozgoren A, Abd-Allah F, Abera SF, et al. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: Quantifying the epidemiological transition. Lancet. 2015;386(10009):2145–2191. doi: 10.1016/s0140-6736(15)61340-x. **Full text not freely available.**

Background: The Global Burden of Disease Study 2013 (GBD 2013) aims to bring together all available epidemiological data using a coherent measurement framework, standardised estimation methods, and

transparent data sources to enable comparisons of health loss over time and across causes, age–sex groups, and countries. The GBD can be used to generate summary measures such as disability-adjusted life-years (DALYs) and healthy life expectancy (HALE) that make possible comparative assessments of broad epidemiological patterns across countries and time. These summary measures can also be used to quantify the component of variation in epidemiology that is related to sociodemographic development.

Methods: We used the published GBD 2013 data for age-specific mortality, years of life lost due to premature mortality (YLLs), and years lived with disability (YLDs) to calculate DALYs and HALE for 1990, 1995, 2000, 2005, 2010, and 2013 for 188 countries. We calculated HALE using the Sullivan method; 95% uncertainty intervals (UIs) represent uncertainty in age-specific death rates and YLDs per person for each country, age, sex, and year. We estimated DALYs for 306 causes for each country as the sum of YLLs and YLDs; 95% UIs represent uncertainty in YLL and YLD rates. We quantified patterns of the epidemiological transition with a composite indicator of sociodemographic status, which we constructed from income per person, average years of schooling after age 15 years, and the total fertility rate and mean age of the population. We applied hierarchical regression to DALY rates by cause across countries to decompose variance related to the sociodemographic status variable, country, and time.

Findings: Worldwide, from 1990 to 2013, life expectancy at birth rose by 6.2 years (95% UI 5.6–6.6), from 65.3 years (65.0–65.6) in 1990 to 71.5 years (71.0–71.9) in 2013, HALE at birth rose by 5.4 years (4.9–5.8), from 56.9 years (54.5–59.1) to 62.3 years (59.7–64.8), total DALYs fell by 3.6% (0.3–7.4), and age-standardised DALY rates per 100 000 people fell by 26.7% (24.6–29.1). For communicable, maternal, neonatal, and nutritional disorders, global DALY numbers, crude rates, and age-standardised rates have all declined between 1990 and 2013, whereas for non-communicable diseases, global DALYs have been increasing, DALY rates have remained nearly constant, and age-standardised DALY rates declined during the same period. From 2005 to 2013, the number of DALYs increased for most specific non-communicable diseases, including cardiovascular diseases and neoplasms, in addition to dengue, food-borne trematodes, and leishmaniasis; DALYs decreased for nearly all other causes. By 2013, the five leading causes of DALYs were ischaemic heart disease, lower respiratory infections, cerebrovascular disease, low back and neck pain, and road injuries. Sociodemographic status explained more than 50% of the variance between countries and over time for diarrhoea, lower respiratory infections, and other common infectious diseases; maternal disorders; neonatal disorders; nutritional deficiencies; other communicable, maternal, neonatal, and nutritional diseases; musculoskeletal disorders; and other non-communicable diseases. However, sociodemographic status explained less than 10% of the variance in DALY rates for cardiovascular diseases; chronic respiratory diseases; cirrhosis; diabetes, urogenital, blood, and endocrine diseases; unintentional injuries; and self-harm and interpersonal violence. Predictably, increased sociodemographic status was associated with a shift in burden from YLLs to YLDs, driven by declines in YLLs and increases in YLDs from musculoskeletal disorders, neurological disorders, and mental and substance use disorders. In most country-specific estimates, the increase in life expectancy was greater than that in HALE. Leading causes of DALYs are

highly variable across countries.
Interpretation: Global health is improving. Population growth and ageing have driven up numbers of DALYs, but crude rates have remained relatively constant, showing that progress in health does not mean fewer demands on health systems. The notion of an epidemiological transition – in which increasing sociodemographic status brings structured change in disease burden – is useful, but there is tremendous variation in burden of disease that is not associated with sociodemographic status. This further underscores the need for country-specific assessments of DALYs and HALE to appropriately inform health policy decisions and attendant actions.

Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M, et al. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117–171. doi: 10.1016/S0140-6736(14)61682-2. **Full text not freely available.**

Background: Up-to-date evidence on levels and trends for age-sex-specific all-cause and cause-specific mortality is essential for the formation of global, regional, and national health policies. In the Global Burden of Disease Study 2013 (GBD 2013) we estimated yearly deaths for 188 countries between 1990, and 2013. We used the results to assess whether there is epidemiological convergence across countries.
Methods: We estimated age-sex-specific all-cause mortality using the GBD 2010 methods with some refinements to improve accuracy applied to an updated database of vital registration, survey, and census data. We generally estimated cause of death as in the GBD 2010. Key improvements included the addition of more recent vital registration data for 72 countries, an updated verbal autopsy literature review, two new and detailed data systems for China, and more detail for Mexico, UK, Turkey, and Russia. We improved statistical models for garbage code redistribution. We used six different modelling strategies across the 240 causes; cause of death ensemble modelling (CODEm) was the dominant strategy for causes with sufficient information. Trends for Alzheimer's disease and other dementias were informed by meta-regression of prevalence studies. For pathogen-specific causes of diarrhoea and lower respiratory infections we used a counterfactual approach. We computed two measures of convergence (inequality) across countries: the average relative difference across all pairs of countries (Gini coefficient) and the average absolute difference across countries. To summarise broad findings, we used multiple decrement life-tables to decompose probabilities of death from birth to exact age 15 years, from exact age 15 years to exact age 50 years, and from exact age 50 years to exact age 75 years, and life expectancy at birth into major causes. For all quantities reported, we computed 95% uncertainty intervals (UIs). We constrained cause-specific fractions within each age-sex-country-year group to sum to all-cause mortality based on draws from the uncertainty distributions.
Findings: Global life expectancy for both sexes increased from 65·3 years (UI 65·0–65·6) in 1990, to 71·5 years (UI 71·0–71·9) in 2013, while the number of deaths increased from 47·5 million (UI 46·8–48·2) to 54·9 million (UI

53·6–56·3) over the same interval. Global progress masked variation by age and sex: for children, average absolute differences between countries decreased but relative differences increased. For women aged 25–39 years and older than 75 years and for men aged 20–49 years and 65 years and older, both absolute and relative differences increased. Decomposition of global and regional life expectancy showed the prominent role of reductions in age-standardised death rates for cardiovascular diseases and cancers in high-income regions, and reductions in child deaths from diarrhoea, lower respiratory infections, and neonatal causes in low-income regions. HIV/AIDS reduced life expectancy in southern sub-Saharan Africa. For most communicable causes of death both numbers of deaths and age-standardised death rates fell whereas for most non-communicable causes, demographic shifts have increased numbers of deaths but decreased age standardised death rates. Global deaths from injury increased by 10·7%, from 4·3 million deaths in 1990 to 4·8 million in 2013; but age-standardised rates declined over the same period by 21%. For some causes of more than 100 000 deaths per year in 2013, age-standardised death rates increased between 1990 and 2013, including HIV/AIDS, pancreatic cancer, atrial fibrillation and flutter, drug use disorders, diabetes, chronic kidney disease, and sickle-cell anaemias. Diarrhoeal diseases, lower respiratory infections, neonatal causes, and malaria are still in the top five causes of death in children younger than 5 years. The most important pathogens are rotavirus for diarrhoea and pneumococcus for lower respiratory infections. Country-specific probabilities of death over three phases of life were substantially varied between and within regions.

Interpretation: For most countries, the general pattern of reductions in age-sex specific mortality has been associated with a progressive shift towards a larger share of the remaining deaths caused by non-communicable disease and injuries. Assessing epidemiological convergence across countries depends on whether an absolute or relative measure of inequality is used. Nevertheless, age-standardised death rates for seven substantial causes are increasing, suggesting the potential for reversals in some countries. Important gaps exist in the empirical data for cause of death estimates for some countries; for example, no national data for India are available for the past decade.

Ntusi NB, Badri M, Gumedze F, Sliwa K, Mayosi BM. Pregnancy-associated heart failure: A comparison of clinical presentation and outcome between hypertensive heart failure of pregnancy and idiopathic peripartum cardiomyopathy. PLoS One. 2015;10(8):e0133466. doi: 10.1371/journal.pone.0133466. **Full text available here.**

Aims: There is controversy regarding the inclusion of patients with hypertension among cases of peripartum cardiomyopathy (PPCM), as the practice has contributed significantly to the discrepancy in reported characteristics of PPCM. We sought to determine whether hypertensive heart failure of pregnancy (HHFP) (i.e., peripartum cardiac failure associated with any form of hypertension) and PPCM have similar or different clinical features and outcome.

Methods and results: We compared the time of onset of symptoms, clinical profile (including

electrocardiographic [ECG] and echocardiographic features) and outcome of patients with HHFP (n = 53; age 29.6 ± 6.6 years) and PPCM (n = 30; age 31.5 ± 7.5 years). The onset of symptoms was postpartum in all PPCM patients, whereas it was antepartum in 85% of HHFP cases ($p<0.001$). PPCM was more significantly associated with the following features than HHFP ($p<0.05$): twin pregnancy, smoking, cardiomegaly with lower left ventricular ejection fraction on echocardiography, and longer QRS duration, QRS abnormalities, left atrial hypertrophy, left bundle branch block, T wave inversion and atrial fibrillation on ECG. By contrast, HHFP patients were significantly more likely ($p<0.05$) to have a family history of hypertension, hypertension and pre-eclampsia in a previous pregnancy, tachycardia at presentation on ECG, and left ventricular hypertrophy on echocardiography. Chronic heart failure, intra-cardiac thrombus and pulmonary hypertension were found significantly more commonly in PPCM than in HHFP ($p<0.05$). There were 5 deaths in the PPCM group compared to none among HHFP cases ($p = 0.005$) during follow-up.

Conclusion: There are significant differences in the time of onset of heart failure, clinical, ECG and echocardiographic features, and outcome of HHFP compared to PPCM, indicating that the presence of hypertension in pregnancy-associated heart failure may not fit the case definition of idiopathic PPCM.

Ogah OS, Davison BA, Sliwa K, Mayosi BM, Damasceno A, Sani MU, et al. Gender differences in clinical characteristics and outcome of acute heart failure in sub-Saharan Africa: Results of the THESUS-HF study. Clin Res Cardiol. 2015;104(6):481–490. doi: 10.1007/s00392-015-0810-y. **Full text not freely available.**

Background: The impact of gender on the clinical characteristics, risk factors, co-morbidities, etiology, treatment and outcome of acute heart failure in sub-Saharan Africa has not been described before. The aim of this study was to evaluate the sex differences in acute heart failure in sub-Saharan Africa using the data from the sub-Saharan Africa Survey of Heart Failure (THESUS-HF).

Methods and Results: 1,006 subjects were recruited into this prospective multicenter, international observational heart failure survey. The mean age of total population was 52.4 years (54.0 years for men and 50.7 years for women). The men were significantly older ($p = 0.0045$). Men also presented in poorer NYHA functional class (III and IV), $p = 0.0364$). Cigarette smoking and high blood pressure were significantly commoner in men (17.3 *vs.* 2.6% and 60.0 *vs.* 51.0% respectively). On the other hand, atrial fibrillation and valvular heart disease were significantly more frequent in women. The mean hemoglobin concentration was lower in women compared to men (11.7 *vs.* 12.6 g/dl, $p \leq 0.0001$), while the blood urea and creatinine levels were higher in men ($p < 0.0001$). LV systolic dysfunctional was also seen more in men. Men also had higher E/A ratio indicating higher LV filling pressure. Outcomes were similar in both sexes.

Conclusions: Although the outcome of patients admitted for AHF in sub-Saharan regions is similar in men and women, some gender differences are apparent suggesting that in men more emphasis should be put on modifiable life risk factors, while in women prevention of rheumatic heart diseases and improved nutrition should be addressed vigorously.

Pasipanodya JG, Mubanga M, Ntsekhe M, Pandie S, Magazi BT, Gumedze F, et al. Tuberculous pericarditis is multibacillary and bacterial burden drives high mortality. EBioMedicine. 2015; 2(11):1634–1639. doi: 10.1016/j.ebiom.2015.09.034. **Full text available here.**

Background: Tuberculous pericarditis is considered to be a paucibacillary process; the large pericardial fluid accumulation is attributed to an inflammatory response to tuberculoproteins. Mortality rates are high. We investigated the role of clinical and microbial factors predictive of tuberculous pericarditis mortality using the artificial intelligence algorithm termed classification and regression tree (CART) analysis.

Methods: Patients were prospectively enrolled and followed in the Investigation of the Management of Pericarditis (IMPI) registry. Clinical and laboratory data of 70 patients with confirmed tuberculous pericarditis, including time-to-positive (TTP) cultures from pericardial fluid, were extracted and analyzed for mortality outcomes using CART. TTP was translated to log10 colony forming units (CFUs) per mL, and compared to that obtained from sputum in some of our patients.

Findings: Seventy patients with proven tuberculous pericarditis were enrolled. The median patient age was 35 (range: 20–71) years. The median, follow up was for 11.97 (range: 0.03–74.73) months. The median TTP for pericardial fluid cultures was 22 (range: 4–58) days or 3.91(range: 0.5–8.96) log10CFU/mL, which overlapped with the range of 3.24–7.42 log10CFU/mL encountered in sputum, a multi-bacillary disease. The overall mortality rate was 1.43 per 100 person-months. CART identified follow-up duration of 5.23 months on directly observed therapy, a CD4 + count of ≤199.5/mL, and TTP ≤14 days (bacillary load ≥5.53 log10 CFU/mL) as predictive of mortality. TTP interacted with follow-up duration in a non-linear fashion.

Interpretation: Patients with culture confirmed tuberculous pericarditis have a high bacillary burden, and this bacterial burden drives mortality. Thus proven tuberculosis pericarditis is not a paucibacillary disease. Moreover, the severe immunosuppression suggests limited inflammation. There is a need for the design of a highly bactericidal regimen for this condition.

Shaboodien G, Watkins DA, Pillay K, Beighton P, Heckmann JM, Mayosi BM. Limb-girdle weakness in a marfanoid man: Distinguishing calpainopathy from Becker's muscular dystrophy. Pract Neurol. 2015;15(2):152–154. doi: 10.1136/practneurol-2014-000992. **Full text not freely available.**

No abstract available.

Shenje J, Ifeoma Adimora-Nweke F, Ross IL, Ntsekhe M, Wiesner L, Deffur A, et al. Poor penetration of antibiotics into pericardium in pericardial tuberculosis. EBioMedicine. 2015;2(11):1640–1649. doi: 10.1016/j.ebiom.2015.09.025. **Full text available here.**

Pericardial tuberculosis (TB) is associated with high therapy failure and high mortality rates. Antibiotics have to penetrate to site of infection at sufficient non-protein bound concentrations, and then enter bacteria to inhibit

intracellular biochemical processes. The antibiotic concentrations achieved in pericardial fluid in TB pericarditis have never been measured before. We recruited two cohorts of patients with TB pericarditis, and left a pigtail catheter in-situ for serial drug concentration measurements over 24 h. Altogether, 704 drug concentrations were comodeled for pharmacokinetic analyses. The drug concentrations achieved in pericardial fluid were compared to the minimum inhibitory concentrations (MICs) of clinical *Mycobacterium tuberculosis* isolates. The total rifampicin concentration pericardial-to-serum ratios in 16 paired samples were 0.19 ± 0.33. The protein concentrations of the pericardial fluid in TB pericarditis were observed to be as high as in plasma. The non-protein bound rifampicin concentrations in pericardial fluid were 4-fold lower than rifampicin MICs in the pilot study, and the peak concentration was 0.125 versus 0.208 mg/L in the second ($p = 0.001$). The rifampicin clearance from pericardial fluid was 9.45 L/h versus 7.82 L/h in plasma ($p = 0.002$). Ethambutol peak concentrations had a pericardial-to-plasma ratio of 0.55 ± 0.22; free ethambutol peak concentrations were 2.30-lower than MICs ($p < 0.001$). The pericardial fluid pH was 7.34. The median pyrazinamide peak concentrations were 42.93 mg/L versus a median MIC of 800 mg/L at pH 7.34 ($p < 0.0001$). There was no significant difference between isoniazid pericardial fluid and plasma concentrations, and isoniazid peak concentrations were above MIC. This is the first study to measure anti-TB drug concentrations, pH and protein in the pericardial TB fluid. Pericardial concentrations of the key sterilizing drugs for TB were below MIC, which could contribute to poor outcomes. A new regimen that overcomes these limitations might need to be crafted.

Uthman OA, Wiysonge CS, Ota MO, Nicol M, Hussey GD, Ndumbe PM, et al. Increasing the value of health research in the WHO African Region beyond 2015 – reflecting on the past, celebrating the present and building the future: A bibliometric analysis. BMJ Open. 2015;5(3):e006340. doi: 10.1136/bmjopen-2014-006340. **Full text available here.**

Objective: To assess the profile and determinants of health research productivity in Africa since the onset of the new millennium.

Design: Bibliometric analysis.

Data collection and synthesis: In November 2014, we searched PubMed for articles published between 2000 and 2014 from the WHO African Region, and obtained country-level indicators from World Bank data. We used Poisson regression to examine time trends in research publications and negative binomial regression to explore determinants of research publications.

Results: We identified 107,662 publications, with a median of 727 per country (range 25–31,757). Three countries (South Africa, Nigeria and Kenya) contributed 52% of the publications. The number of publications increased from 3623 in 2000 to 12,709 in 2014 (relative growth 251%). Similarly, the per cent share of worldwide research publications per year increased from 0.7% in 2000 to 1.3% in 2014. The trend analysis was also significant to confirm a continuous increase in health research publications from Africa, with productivity increasing by 10.3% per year (95% CIs +10.1% to +10.5%). The only independent predictor of publication outputs was national gross

domestic product. For every one log US$ billion increase in gross domestic product, research publications rose by 105%: incidence rate ratio (IRR=2.05, 95% CI 1.39 to 3.04). The association of private health expenditure with publications was only marginally significant (IRR=1.86, 95% CI 1.00 to 3.47).
Conclusions: There has been a significant improvement in health research in the WHO African Region since 2000, with some individual countries already having strong research profiles. Countries of the region should implement the WHO Strategy on Research for Health: reinforcing the research culture (organisation); focusing research on key health challenges (priorities); strengthening national health research systems (capacity); encouraging good research practice (standards); and consolidating linkages between health research and action (translation).

van Dam J, Musuku J, Zuhlke LJ, Engel ME, Nestle N, Tadmor B, et al. An open-access mobile compatible electronic patient register for rheumatic heart disease ('eRegister') based on the World Heart Federation's framework for patient registers. Cardiovasc J Afr. 2015;26(6):227–233. doi: 10.5830/cvja-2015-058. **Full text not freely available**.

Background: Rheumatic heart disease (RHD) remains a major disease burden in low-resource settings globally. Patient registers have long been recognised to be an essential instrument in RHD control and elimination programmes, yet to date rely heavily on paper-based data collection and non-networked data-management systems, which limit their functionality.
Objectives: To assess the feasibility and potential benefits of producing an electronic RHD patient register.
Methods: We developed an eRegister based on the World Heart Federation's framework for RHD patient registers using CommCare, an open-source, cloud-based software for health programmes that supports the development of customised data capture using mobile devices.
Results: The resulting eRegistry application allows for simultaneous data collection and entry by field workers using mobile devices, and by providers using computer terminals in clinics and hospitals. Data are extracted from CommCare and are securely uploaded into a cloud-based database that matches the criteria established by the WHF framework. The application can easily be tailored to local needs by modifying existing variables or adding new ones. Compared with traditional paper-based data-collection systems, the eRegister reduces the risk of data error, synchronises in real-time, improves clinical operations and supports management of field team operations.
Conclusions: The user-friendly eRegister is a low-cost, mobile, compatible platform for RHD treatment and prevention programmes based on materials sanctioned by the World Heart Federation. Readily adaptable to local needs, this paperless RHD patient register program presents many practical benefits.

Vos T, Barber RM, Bell B, Bertozzi-Villa A, Biryukov S, Bolliger I, et al. Global, regional, and national

incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;386(9995):743–800. doi: 10.1016/S0140-6736(15)60692-4. **Full text not freely available**.

Background: Up-to-date evidence about levels and trends in disease and injury incidence, prevalence, and years lived with disability (YLDs) is an essential input into global, regional, and national health policies. In the Global Burden of Disease Study 2013 (GBD 2013), we estimated these quantities for acute and chronic diseases and injuries for 188 countries between 1990 and 2013.

Methods: Estimates were calculated for disease and injury incidence, prevalence, and YLDs using GBD 2010 methods with some important refinements.

Results for incidence of acute disorders and prevalence of chronic disorders are new additions to the analysis. Key improvements include expansion to the cause and sequelae list, updated systematic reviews, use of detailed injury codes, improvements to the Bayesian meta-regression method (DisMod-MR), and use of severity splits for various causes. An index of data representativeness, showing data availability, was calculated for each cause and impairment during three periods globally and at the country level for 2013. In total, 35 620 distinct sources of data were used and documented to calculated estimates for 301 diseases and injuries and 2337 sequelae. The comorbidity simulation provides estimates for the number of sequelae, concurrently, by individuals by country, year, age, and sex. Disability weights were updated with the addition of new population-based survey data from four countries.

Findings: Disease and injury were highly prevalent; only a small fraction of individuals had no sequelae. Comorbidity rose substantially with age and in absolute terms from 1990 to 2013. Incidence of acute sequelae were predominantly infectious diseases and short-term injuries, with over 2 billion cases of upper respiratory infections and diarrhoeal disease episodes in 2013, with the notable exception of tooth pain due to permanent caries with more than 200 million incident cases in 2013. Conversely, leading chronic sequelae were largely attributable to non-communicable diseases, with prevalence estimates for asymptomatic permanent caries and tension-type headache of 2·4 billion and 1·6 billion, respectively. The distribution of the number of sequelae in populations varied widely across regions, with an expected relation between age and disease prevalence. YLDs for both sexes increased from 537·6 million in 1990 to 764·8 million in 2013 due to population growth and ageing, whereas the age-standardised rate decreased little from 114·87 per 1000 people to 110·31 per 1000 people between 1990 and 2013. Leading causes of YLDs included low back pain and major depressive disorder among the top ten causes of YLDs in every country. YLD rates per person, by major cause groups, indicated the main drivers of increases were due to musculoskeletal, mental, and substance use disorders, neurological disorders, and chronic respiratory diseases; however HIV/AIDS was a notable driver of increasing YLDs in sub-Saharan Africa. Also, the proportion of disability-adjusted life years due to YLDs increased globally from 21·1% in 1990 to 31·2% in 2013.

Interpretation: Ageing of the world's population is leading to a substantial increase in the numbers of individuals with sequelae of diseases and injuries. Rates of YLDs are declining much more slowly than mortality rates. The

non-fatal dimensions of disease and injury will require more and more attention from health systems. The transition to non-fatal outcomes as the dominant source of burden of disease is occurring rapidly outside of sub-Saharan Africa. Our results can guide future health initiatives through examination of epidemiological trends and a better understanding of variation across countries.

Watkins DA, Mvundura M, Nordet P, Mayosi BM. A cost-effectiveness analysis of a program to control rheumatic fever and rheumatic heart disease in Pinar del Rio, Cuba. PLoS One. 2015;10(3):e0121363. doi: 10.1371/journal.pone.0121363. **Full text available here.**

Background: Acute rheumatic fever (ARF) and rheumatic heart disease (RHD) persist in many low- and middle-income countries. To date, the cost-effectiveness of population-based, combined primary and secondary prevention strategies has not been assessed. In the Pinar del Rio province of Cuba, a comprehensive ARF/RHD control program was undertaken over 1986–1996. The present study analyzes the cost-effectiveness of this Cuban program.

Methods and findings: We developed a decision tree model based on the natural history of ARF/RHD, comparing the costs and effectiveness of the 10-year Cuban program to a "do nothing" approach. Our population of interest was the cohort of children aged 5–24 years resident in Pinar del Rio in 1986. We assessed costs and health outcomes over a lifetime horizon, and we took the healthcare system perspective on costs but did not apply a discount rate. We used epidemiologic, clinical, and direct medical cost inputs that were previously collected for publications on the Cuban program. We estimated health gains as disability-adjusted life years (DALYs) averted using standard approaches developed for the Global Burden of Disease studies. Cost-effectiveness acceptability thresholds were defined by one and three times per capita gross domestic product per DALY averted. We also conducted an uncertainty analysis using Monte Carlo simulations and several scenario analyses exploring the impact of alternative assumptions about the program's effects and costs. We found that, compared to doing nothing, the Cuban program averted 5051 DALYs (1844 per 100,000 school-aged children) and saved $7,848,590 (2010 USD) despite a total program cost of $202,890 over 10 years. In the scenario analyses, the program remained cost saving when a lower level of effectiveness and a reduction in averted years of life lost were assumed. In a worst-case scenario including 20-fold higher costs, the program still had a 100% of being cost-effective and an 85% chance of being cost saving.

Conclusions: A 10-year program to control ARF/RHD in Pinar del Rio, Cuba dramatically reduced morbidity and premature mortality in children and young adults and was cost saving. The results of our analysis were robust to higher program costs and more conservative assumptions about the program's effectiveness. It is possible that the program's effectiveness resulted from synergies between primary and secondary prevention strategies. The findings of this study have implications for non-communicable disease policymaking in other resource-limited settings.

Zuhlke L, Engel ME, Karthikeyan G, Rangarajan S, Mackie P, Cupido B, et al. Characteristics, complications,

and gaps in evidence-based interventions in rheumatic heart disease: The Global Rheumatic Heart Disease Registry (the REMEDY study). Eur Heart J. 2015;36(18):1115–1122a. doi: 10.1093/eurheartj/ehu449. **Full text available here.**

Aims: Rheumatic heart disease (RHD) accounts for over a million premature deaths annually; however, there is little contemporary information on presentation, complications, and treatment.

Methods and results: This prospective registry enrolled 3343 patients (median age 28 years, 66.2% female) presenting with RHD at 25 hospitals in 12 African countries, India, and Yemen between January 2010 and November 2012. The majority (63.9%) had moderate-to-severe multivalvular disease complicated by congestive heart failure (33.4%), pulmonary hypertension (28.8%), atrial fibrillation (AF) (21.8%), stroke (7.1%), infective endocarditis (4%), and major bleeding (2.7%). One-quarter of adults and 5.3% of children had decreased left ventricular (LV) systolic function; 23% of adults and 14.1% of children had dilated LVs. Fifty-five percent (n = 1761) of patients were on secondary antibiotic prophylaxis. Oral anti-coagulants were prescribed in 69.5% (n = 946) of patients with mechanical valves (n = 501), AF (n = 397), and high-risk mitral stenosis in sinus rhythm (n = 48). However, only 28.3% (n = 269) had a therapeutic international normalized ratio. Among 1825 women of childbearing age (12–51 years), only 3.6% (n = 65) were on contraception. The utilization of valvuloplasty and valve surgery was higher in upper-middle compared with lower-income countries.

Conclusion: Rheumatic heart disease patients were young, predominantly female, and had high prevalence of major cardiovascular complications. There is suboptimal utilization of secondary antibiotic prophylaxis, oral anti-coagulation, and contraception, and variations in the use of percutaneous and surgical interventions by country income level.

Zuhlke LJ, Engel ME, Watkins D, Mayosi BM. Incidence, prevalence and outcome of rheumatic heart disease in South Africa: A systematic review of contemporary studies. Int J Cardiol. 2015;199:375–383. doi: 10.1016/j.ijcard.2015.06.145. **Full text not freely available.**

Background: Twenty years after its first democratic election, South Africa is experiencing a health transition. The impact of change on the incidence, prevalence and outcome of rheumatic heart disease (RHD) is unknown.

Methods: We conducted a systematic overview of the incidence, prevalence and outcomes of RHD in South Africa over the past two decades according to a published protocol.

Results: The overall crude incidence of symptomatic RHD was 24.7 per 100,000 (95% confidence interval (CI) 22.1 to 27.4) population per annum among adults (>13years) in Soweto, while the prevalence of asymptomatic echocardiographic RHD in schoolchildren was 20.2 cases per 1000 children (95% CI 15.3 to 26.2) in Cape Town. The 60-day mortality after admission with acute heart failure due to RHD was 24.8% (95% CI 13.6% to 42.5%) and 180-day mortality was 35.4% (95% CI 21.6% to 54.4%). Postoperative mortality at 30 days was 2% (95% CI 0.0% to 4%). Post-surgical survival was over 75% at 5years, and over 70% at 10years. Cause-specific mortality rate

per 100,000 population decreased from 1.27 (95% CI 1.17 to 1.39) in 1997 to 0.7 (95% CI 0.63 to 0.78) in 2012. Conclusions: The incidence of symptomatic RHD in adults and prevalence of asymptomatic RHD in schoolchildren are high in South Africa. Mortality was high in patients with RHD-related heart failure, although post-surgical morbidity and mortality were low. Mortality attributed to RHD may be falling at a population level.

Zumla A, Maeurer M. Host-directed therapies for tackling multi-drug resistant tuberculosis: Learning from the Pasteur–Bechamp debates. Clin Infect Dis. 2015;61(9):1432–1438. doi: 10.1093/cid/civ631. **Full text not freely available. Full text available here.**

No abstract available.

Zumla A, Maeurer M, Chakaya J, Hoelscher M, Ntoumi F, Rustomjee R, et al. Towards host-directed therapies for tuberculosis. Nat Rev Drug Discov. 2015;14(8):511–512. doi: 10.1038/nrd4696. **Full text not freely available.**

The treatment of tuberculosis is based on combinations of drugs that directly target *Mycobacterium tuberculosis*. A new global initiative is now focusing on a complementary approach of developing adjunct host-directed therapies.

Zumla A, Maeurer M, Moll G, Mayosi BM. Host-directed therapies for tuberculous pericarditis. Int J Infect Dis. 2015;32:30–31. doi: 10.1016/j.ijid.2014.11.017. **Full text available here.**

TB pericarditis is associated with significant inflammatory and immune responses which can paradoxically cause injury to the pericardium and myocardium. Management with anti-TB therapy alone does not prevent complications or reduce mortality. Thus the prevailing view is that adjunct host-directed therapies such as use of glucocorticoid treatment could attenuate destructive inflammatory responses and improve morbidity and mortality rates. A recent trial showed no advantage of using adjunct corticosteroid treatment on the combined endpoint of death, cardiac tamponade or constriction. The current lack of effective medical treatment for reducing the significant morbidity and mortality associated with TB pericarditis, highlights the urgent need for newer approaches to treating the disease. Newer treatment options for pericarditis using adjunct host-directed therapies, including autologous bone-marrow-derived Mesenchymal Stromal Cells (MSCs) therapy, now require evaluation in randomized placebo-controlled controlled trials.

2014

Alfieri O, Mayosi BM, Park SJ, Sarrafzadegan N, Virmani R. Exploring unknowns in cardiology. Nat Rev Cardiol. 2014;11(11):664–670. doi: 10.1038/nrcardio.2014.123. **Full text not freely available.**

To mark the 10th anniversary of Nature Reviews Cardiology in November 2014, five of our Advisory Board members were invited to consider a topic within cardiology about which we know too little. A diverse range of subjects are highlighted in this Perspectives article, including preoperative assessment of right ventricular function, the burden of cardiomyopathies in Africa, the measurement of fractional flow reserve to guide coronary intervention, the interaction between genes and environment in cardiovascular disease, and the difficulty of predicting atherosclerotic plaque rupture. The five key opinion leaders from around the globe also suggest ways in which future research could be targeted to address the deficits in our understanding, with the aim of preventing cardiovascular disease, improving patient care, and reducing morbidity and mortality.

Dzudie A, Milo O, Edwards C, Cotter G, Davison BA, Damasceno A, et al. Prognostic significance of ECG abnormalities for mortality risk in acute heart failure: Insight from the Sub-Saharan Africa Survey of Heart Failure (THESUS-HF). J Card Fail. 2014;20(1):45–52. doi: 10.1016/j.cardfail.2013.11.005. **Full text not freely available.**

Objective: The aim of this study was to assess the predictive utility of 12-lead electrocardiogram (ECG) abnormalities among Africans with acute heart failure (HF).

Methods and results: We used the Sub-Saharan Africa Survey of Heart Failure, a multicenter prospective cohort study of 1,006 acute HF patients, and regression models to relate baseline ECG findings to all-cause mortality and readmission during a 6-month follow-up period. Of 814 ECGs available, 523 (49.0% male) were obtained within 15 days of admission, among which 97.7% showed abnormalities. Mean age was 52.0 years and median follow-up was 180 days, with 77 deaths (Kaplan-Meier 17.5%) through day 180 and 63 patients with death or readmission to day 60. QRS width, QT duration, bundle branch block, and ischemic changes were not associated with outcomes. Increasing ventricular rate was associated with increasing risk of both outcomes (hazard ratio [HR] 1.07 per 5 beats/min increase for 60-day death or readmission, 95% confidence interval [CI] 1.02–1.12; P = .0047), and the presence of sinus rhythm was associated with lower risk (HR 0.58, 95% CI 0.34–0.97; P = .0385). There was a strong association between survival and heart rate in patients in sinus rhythm, with heart rate >119 beats/min conveying the worst mortality risk.

Conclusions: ECG abnormalities are almost universal among Africans with acute HF, which may add to the

immediate diagnosis of patients presenting with dyspnea. Although some ECG findings have prognostic value for risk of adverse outcomes, most of them are nonspecific and add little to the risk stratification of these patients.

Engel ME, Muhamed B, Whitelaw AC, Musvosvi M, Mayosi BM, Dale JB. Group A streptococcal *emm* type prevalence among symptomatic children in Cape Town and potential vaccine coverage. Pediatr Infect Dis J. 2014;33(2):208–210. doi: 10.1097/INF.0b013e3182a5c32a. **Full text not freely available.**

The molecular epidemiology of group A streptococcal pharyngeal infections in children in the Vanguard Community of Cape Town revealed 26 *emm* types among 157 isolates from 742 subjects. Coverage of a 30-valent vaccine is predicted to be 95% of pharyngitis cases in this population at high risk of rheumatic fever.

Irlam JH, Mayosi BM, Engel ME, Gaziano TA, Whitelaw AC. Primary prevention of rheumatic fever in children: Key factors to consider. S Afr Med J. 2014;104(3):157. doi: 10.7196/SAMJ.7880. **Full text available here.**

No abstract available.

Karthikeyan G, Mayosi BM. Letter by Karthikeyan et al regarding article, "Acute rheumatic fever and rheumatic heart disease: Incidence and progression in the Northern Territory of Australia, 1997 to 2010". Circulation. 2014;129(11):e396. doi: 10.1161/circulationaha.113.005651. **Full text not freely available.**

No abstract available.

Katz AA, Futter M, Mayosi BM. The intercalated BSc (Med) Honours/MB ChB and integrated MB ChB/PhD tracks at the University of Cape Town: Models for a national medical student research training programme. S Afr Med J. 2014;104(2):111–113. **Full text available here.**

The Faculty of Health Sciences at the University of Cape Town is addressing the shortage of clinician-scientists in South Africa by introducing two research training tracks in parallel with the professional MB ChB programme, namely the intercalated BSc (Med) Hons/MB ChB track and the integrated MB ChB/PhD track. The BSc (Med) Hons/MB ChB track is available to MB ChB students who have completed the first two years of study. The track comprises a course in Molecular Medicine given concurrently with the MB ChB third-year curriculum, followed by a BSc (Med) Hons as a 'year out' of MB ChB. Subsequently students may enroll into the integrated MB ChB/PhD track that enables them to undertake a PhD concurrently with MB ChB studies, which will be spread over additional years, or alternatively to undertake a PhD after completion of the MB ChB. These tracks, which were launched in 2011, represent an opportunity to train a new cadre of young African clinician-scientists at the undergraduate level.

Kengne AP, Mayosi BM. Readiness of the primary care system for non-communicable diseases in sub-Saharan Africa. Lancet Glob Health. 2014;2(5):e247–248. doi: 10.1016/s2214-109x(14)70212-8. **Full text available here.**

No abstract available.

Lemmer CE, Engel ME, Stanfliet JC, Mayosi BM. Reference intervals for the echocardiographic measurements of the right heart in children and adolescents: A systematic review. Cardiovasc Ultrasound. 2014;12:3. doi: https://doi.org/10.1186/1476-7120-12-3. **Full text available here.**

Background: Transthoracic echocardiography is the primary imaging modality for the diagnosis of right ventricular (RV) involvement in congenital and acquired heart diseases. There is increasing recognition of the contribution of RV dysfunction in heart diseases affecting children and adolescents, but there is insufficient information on reference intervals for the echocardiographic measurements of the right heart in children and adolescents that represent all the continental populations of the world.

Objective: The aim of this systematic review was to collate, from published studies, normative data for echocardiographic evaluation of the right heart in children and adolescents, and to identify gaps in knowledge in this field especially with respect to sub-Saharan Africans.

Methods: We performed a systematic literature search to identify studies of reference intervals for right heart measurements as determined by transthoracic echocardiography in healthy children and adolescents of school-going age. Articles were retrieved from electronic databases with a combination of search terms from the earliest date available until May 2013.

Results: Reference data were available for a broad range of variables. Fifty one studies out of 3096 publications were included. The sample sizes of the reference populations ranged from 13 to 2036 with ages varying from 5 to 21 years. We identified areas lacking sufficient reference data. These included reference data for determining right atrial size, tricuspid valve area, RV dimensions and areas, the RV % fractional area change, pulmonary artery pressure gradients and the right-sided haemodynamics, including the inferior vena cava dimensions and collapsibility. There were no data for sub-Saharan African children and adolescents.

Conclusion: Reliable reference data are lacking for important echocardiographic measurements of the RV in children and adolescents, especially for sub-Saharan Africans.

London GM, Khati M, Mayosi B. Potential of RNA Aptamers in the prevention of HIV-1 subtype C infections. AIDS Res Hum Retroviruses. 2014;30(S1):A146. **Full text not freely available.**

Background: Compounds that have been used to prevent human immunodeficiency virus type-I (HIV-1)

infections include synthetic chemicals, plant extras and monoclonal antibodies. Although most of these compounds have potent antiviral activity, they often fail to progress to later stages of clinical trials due to high toxicity and lack of specificity. Therefore, as an alternative to circumvent the above mentioned limitations we used aptamers, which are small nucleic acid ligands that recognize their target with high specificity and have no toxicity in clinical applications.

Methods: In this study, we evaluated efficacy of four gp120aptamers against Env pseudovirus panel derived from HIV-1 subtype C, using virus inhibition assay in TZM-bl cells, as well as toxicity. Binding specificity of one potent aptamer (CSIR1.1) to gp120 was determined by Enzyme-Linked-Immunosorbent Assay. Subsequently, a virus inhibition assay was performed to test whether CSIR1.1 can inhibit HIV-1 pseudotyped with vesicular stomatitis virus envelope glycoprotein (HIV-VSVG.)

Results: All four aptamers inhibited infectivity of 81–84 % of the tested viruses with mean inhibition concentration (IC_{50}) of 6.4–9 nM. The specificity results showed that CSIR1.1 only bound to gp120 and did not bind other tested proteins (HIV-1 gp41, mycobacterium tuberculosis virulent protein (CFP10), human interferon gamma (IFN-γ) and BSA). CSIR1.1 also failed to inhibit HIV-1 pseudotyped with VSV-G protein and showed no toxicity in vitro, even at concentration (500 nM), which was 5 × higher than one used for virus inhibition assays.

Conclusions: Aptamers showed significant efficacy against HIV-1 subtype C isolates and specificity to gp120 without causing cytoxicity effects. These properties make aptamers attractive candidates for prevention of HIV-1.

Lopes de Campos WR, Chirwa N, London G, Rotherham LS, Morris L, Mayosi BM, et al. HIV-1 subtype C unproductively infects human cardiomyocytes in vitro and induces apoptosis mitigated by an anti-Gp120 aptamer. PLoS One. 2014;9(10):e110930. doi: 10.1371/journal.pone.0110930. **Full text available here**.

HIV-associated cardiomyopathy (HIVCM) is of clinical concern in developing countries because of a high HIV-1 prevalence, especially subtype C, and limited access to highly active antiretroviral therapy (HAART). For these reasons, we investigated the direct and indirect effects of HIV-1 subtype C infection of cultured human cardiomyocytes and the mechanisms leading to cardiomyocytes damage; as well as a way to mitigate the damage. We evaluated a novel approach to mitigate HIVCM using a previously reported gp120 binding and HIV-1 neutralizing aptamer called UCLA1. We established a cell-based model of HIVCM by infecting human cardiomyocytes with cell-free HIV-1 or co-culturing human cardiomyocytes with HIV-infected monocyte derived macrophages (MDM). We discovered that HIV-1 subtype C unproductively (i.e. its life cycle is arrested after reverse transcription) infects cardiomyocytes. Furthermore, we found that HIV-1 initiates apoptosis of cardiomyocytes through caspase-9 activation, preferentially via the intrinsic or mitochondrial initiated pathway. CXCR4 receptor-using viruses were stronger inducers of apoptosis than CCR5 utilizing variants. Importantly, we discovered that HIV-1 induced apoptosis of cardiomyocytes was mitigated by UCLA1. However, UCLA1 had no protective effective on cardiomyocytes when apoptosis was triggered by HIV-infected MDM. When HIV-1 was treated with UCLA1 prior to infection of MDM, it failed to induce apoptosis of cardiomyocytes. These data

suggest that HIV-1 causes a mitochondrial initiated apoptotic cascade, which signal through caspase-9, whereas HIV-1 infected MDM causes apoptosis predominantly via the death-receptor pathway, mediated by caspase-8. Furthermore, the data suggest that UCLA1 protects cardiomyocytes from caspase-mediated apoptosis, directly by binding to HIV-1 and indirectly by preventing infection of MDM.

Magula NP, Madala ND, Kriel Y, Bayi V, Duze NP, Manzini TC, et al. Prevalence of drug resistant tuberculosis in patients presenting with a large pericardial effusion at King Edward VIII Hospital. Int J Infect Dis. 2014;21:87. doi: 10.1016/j.ijid.2014.03.611. **Full text not freely available.**

Background: Tuberculosis (TB) accounts for 70% of pericardial effusions in sub-Saharan Africa. There is a high burden of drug resistant TB in South Africa, with an estimated 4600 new cases identified in 2012, but its frequency in patients with pericardial TB is unknown. The aim ofthis study was to determine the prevalence of drug resistant tuberculosis in patients admitted to King Edward VIII hospital with a pericardial effusion.

Methods and Materials: This was a cross sectional study of participants enrolled in the Investigation of the Management of Pericarditis (IMPI) study from October 2009 to August 2013. Enrolled participants were adults with a clinical diagnosis of TB pericarditis. Diagnostic and therapeutic pericardiocentesis was preformed where suitable. Biochemistry, microscopy, liquid culture (MGIT 960), line probe assay, direct sensitivity testing and cytology were performed.

Results: A total of 163 participants were enrolled, 129 (79.6%) of whom were HIV infected. Pericardiocentesis was performed in 100 (64%) participants and diagnostic tests for tuberculosis were performed in 78 of these. Acid fast bacilli were observed in 10/75 (13.3%) using Auramine stain and 23/78 (29.5%) were culture positive (3/78 samples were not suitable for Auramine stain). Where acid fast bacilli were observed, either by smear microscopy or culture, line probeassay identified *Mycobacterium tuberculosis complex* in 21/24 (87.5%); 2/21 (9.5%) isolates were resistant to isoniazid and rifampicin (MDR-TB) with 1 of the 2 also resistant to streptomycin, ofloxacin and kanamycin (XDR-TB). No patients were found to have co-infections or malignancy.

Conclusion: Drug resistant TB was present in nearly 10% of patients with culture positive TB pericarditis. The finding of resistant TB, isolated only from the pericardial space, underscores the importance of diagnostic pericardiocentesis in patients with a presumed diagnosis of TB pericarditis.

Martin RI, Owens WA, Cunnington MS, Mayosi BM, Koref MS, Keavney BD. Chromosome 16q22 variants in a region associated with cardiovascular phenotypes correlate with ZFHX3 expression in a transcript-specific manner. BMC Genet. 2014;15:136. doi: 10.1186/s12863-014-0136-1. **Full text available here.**

Background: The ZFHX3 gene, located in Chromosome 16q22.3, codes for a transcription factor which is widely expressed in human tissues. Genome-wide studies have identified associations between variants within the gene and Kawasaki disease and atrial fibrillation. ZFHX3 has two main transcripts that utilise different transcription

start sites. We examined the association between genetic variants in the 16q22.3 region and expression of ZFHX3 to identify variants that regulate gene expression.
Results: We genotyped 65 single-nucleotide polymorphisms to tag genetic variation at the ZFHX3 locus in two cohorts, 451 British individuals recruited in the North East of England and 310 mixed-ancestry individuals recruited in South Africa. Allelic expression analysis revealed that the minor (A) allele of rs8060701, a variant in the first intron of ZFHX3, was associated with a 1.16-fold decrease in allelic expression of both transcripts together, (p = 4.87e-06). The minor (C) allele of a transcribed variant, rs10852515, in the second exon of ZFHX3 isoform A was independently associated with a 1.36-fold decrease in allelic expression of ZFHX3 A (p = 7.06e-31), but not overall ZFHX3 expression. However, analysis of total gene expression of ZFHX3 failed to detect an association with genotype at any variant. Differences in linkage disequilibrium between the two populations allowed fine-mapping of the locus to a 7 kb region overlapping exon 2 of ZFHX3 A. We did not find any association between ZFHX3 expression and any of the variants identified by genome wide association studies.
Conclusions: ZFHX3 transcription is regulated in a transcript-specific fashion by independent cis-acting transcribed polymorphisms. Our results demonstrate the power of allelic expression analysis and trans-ethnic fine mapping to identify transcript-specific cis-acting regulatory elements.

Mayosi BM. The challenge of silent rheumatic heart disease. Lancet Glob Health. 2014;2(12):e677–678. doi: 10.1016/s2214-109x(14)70331-6. **Full text available here.**

No abstract available.

Mayosi BM. Cardiomyopathies: MOGE(S): A standardized classification of cardiomyopathies? Nat Rev Cardiol. 2014;11(3):134–135. doi: 10.1038/nrcardio.2013.219. **Full text not freely available.**

Cardiomyopathy classification has been subject to revisions for >60 years. The new MOGE(S) classification system, which incorporates information on structural and functional abnormalities, organ involvement, genetics, aetiology, and disease severity, is a step towards a globally accepted nomenclature, but needs to be applicable in all health-care systems around the world.

Mayosi BM, Benatar SR. Health and health care in South Africa – 20 years after Mandela. N Engl J Med. 2014;371(14):1344–1353. doi: 10.1056/NEJMsr1405012. **Full text not freely available.**

No abstract available.

Mayosi BM, Gamra H, Dangou JM, Kasonde J, Abul-Fadl A, Adeoye MA, et al. Rheumatic heart disease in Africa: The Mosi-o-Tunya call to action. Lancet Glob Health. 2014;2(8):e438-e439. doi: 10.1016/S2214-109X(14)70234-7. **Full text available here.**

No abstract available.

Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F, et al. Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. N Engl J Med. 2014;371(12):1121–1130. doi: 10.1056/NEJMoa1407380. **Full text not freely available.**

Background: Tuberculous pericarditis is associated with high morbidity and mortality even if antituberculosis therapy is administered. We evaluated the effects of adjunctive glucocorticoid therapy and *Mycobacterium indicus pranii* immunotherapy in patients with tuberculous pericarditis.

Methods: Using a 2-by-2 factorial design, we randomly assigned 1400 adults with definite or probable tuberculous pericarditis to either prednisolone or placebo for 6 weeks and to either *M. indicus pranii* or placebo, administered in five injections over the course of 3 months. Two thirds of the participants had concomitant human immunodeficiency virus (HIV) infection. The primary efficacy outcome was a composite of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis.

Results: There was no significant difference in the primary outcome between patients who received prednisolone and those who received placebo (23.8% and 24.5%, respectively; hazard ratio, 0.95; 95% confidence interval [CI], 0.77 to 1.18; P=0.66) or between those who received *M. indicus pranii* immunotherapy and those who received placebo (25.0% and 24.3%, respectively; hazard ratio, 1.03; 95% CI, 0.82 to 1.29; P=0.81). Prednisolone therapy, as compared with placebo, was associated with significant reductions in the incidence of constrictive pericarditis (4.4% *vs*. 7.8%; hazard ratio, 0.56; 95% CI, 0.36 to 0.87; P=0.009) and hospitalization (20.7% *vs.* 25.2%; hazard ratio, 0.79; 95% CI, 0.63 to 0.99; P=0.04). Both prednisolone and *M. indicus pranii*, each as compared with placebo, were associated with a significant increase in the incidence of cancer (1.8% *vs.* 0.6%; hazard ratio, 3.27; 95% CI, 1.07 to 10.03; P=0.03, and 1.8% *vs.* 0.5%; hazard ratio, 3.69; 95% CI, 1.03 to 13.24; P=0.03, respectively), owing mainly to an increase in HIV-associated cancer.

Conclusions: In patients with tuberculous pericarditis, neither prednisolone nor *M. indicus pranii* had a significant effect on the composite of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis.

Mayosi BM, Ntsekhe M, Smieja M. [Immunotherapy for tuberculous pericarditis] The authors reply. N Engl J Med. 2014;371(26):2534. doi: 10.1056/NEJMc1413185. **Full text not freely available.**

No abstract available.

Murray CJL, Ortblad KF, Guinovart C, Lim SS, Wolock TM, Roberts DA, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9947):1005–1070. doi:

10.1016/S0140-6736(14)60844-8. **Full text not freely available.**

Background: The Millennium Declaration in 2000 brought special global attention to HIV, tuberculosis, and malaria through the formulation of Millennium Development Goal (MDG) 6. The Global Burden of Disease 2013 study provides a consistent and comprehensive approach to disease estimation for between 1990 and 2013, and an opportunity to assess whether accelerated progress has occured since the Millennium Declaration.

Methods: To estimate incidence and mortality for HIV, we used the UNAIDS Spectrum model appropriately modified based on a systematic review of available studies of mortality with and without antiretroviral therapy (ART). For concentrated epidemics, we calibrated Spectrum models to fit vital registration data corrected for misclassification of HIV deaths. In generalised epidemics, we minimised a loss function to select epidemic curves most consistent with prevalence data and demographic data for all-cause mortality. We analysed counterfactual scenarios for HIV to assess years of life saved through prevention of mother-to-child transmission (PMTCT) and ART. For tuberculosis, we analysed vital registration and verbal autopsy data to estimate mortality using cause of death ensemble modelling. We analysed data for corrected case-notifications, expert opinions on the case-detection rate, prevalence surveys, and estimated cause-specific mortality using Bayesian meta-regression to generate consistent trends in all parameters. We analysed malaria mortality and incidence using an updated cause of death database, a systematic analysis of verbal autopsy validation studies for malaria, and recent studies (2010–13) of incidence, drug resistance, and coverage of insecticide-treated bednets.

Findings: Globally in 2013, there were 1·8 million new HIV infections (95% uncertainty interval 1·7 million to 2·1 million), 29·2 million prevalent HIV cases (28·1 to 31·7), and 1·3 million HIV deaths (1·3 to 1·5). At the peak of the epidemic in 2005, HIV caused 1·7 million deaths (1·6 million to 1·9 million). Concentrated epidemics in Latin America and eastern Europe are substantially smaller than previously estimated. Through interventions including PMTCT and ART, 19·1 million life-years (16·6 million to 21·5 million) have been saved, 70·3% (65·4 to 76·1) in developing countries. From 2000 to 2011, the ratio of development assistance for health for HIV to years of life saved through intervention was US$4498 in developing countries. Including in HIV-positive individuals, all-form tuberculosis incidence was 7·5 million (7·4 million to 7·7 million), prevalence was 11·9 million (11·6 million to 12·2 million), and number of deaths was 1·4 million (1·3 million to 1·5 million) in 2013. In the same year and in only individuals who were HIV-negative, all-form tuberculosis incidence was 7·1 million (6·9 million to 7·3 million), prevalence was 11·2 million (10·8 million to 11·6 million), and number of deaths was 1·3 million (1·2 million to 1·4 million). Annualised rates of change (ARC) for incidence, prevalence, and death became negative after 2000. Tuberculosis in HIV-negative individuals disproportionately occurs in men and boys (versus women and girls); 64·0% of cases (63·6 to 64·3) and 64·7% of deaths (60·8 to 70·3). Globally, malaria cases and deaths grew rapidly from 1990 reaching a peak of 232 million cases (143 million to 387 million) in 2003 and 1·2 million deaths (1·1 million to 1·4 million) in 2004. Since 2004, child deaths from malaria in sub-Saharan Africa have decreased by 31·5% (15·7 to 44·1). Outside of Africa, malaria mortality has been steadily decreasing since 1990.

Interpretation: Our estimates of the number of people living with HIV are 18·7% smaller than UNAIDS's

estimates in 2012. The number of people living with malaria is larger than estimated by WHO. Incidence rates for HIV, tuberculosis, and malaria have all decreased since 2000. At the global level, upward trends for malaria and HIV deaths have been reversed and declines in tuberculosis deaths have accelerated. 101 countries (74 of which are developing) still have increasing HIV incidence. Substantial progress since the Millennium Declaration is an encouraging sign of the effect of global action.

Mutyaba AK, Balkaran S, Cloete R, du Plessis N, Badri M, Brink J, et al. Constrictive pericarditis requiring pericardiectomy at Groote Schuur Hospital, Cape Town, South Africa: Causes and peri-operative outcomes in the HIV era (1990–2012). J Thorac Cardiovasc Surg. 2014; 148(6):3058–3065.e3051. doi: 10.1016/j.jtcvs.2014.07.065. **Full text not freely available.**

Objective: The causes of constrictive pericarditis and predictors of perioperative outcome after pericardiectomy have not been clearly elucidated, especially in Africa, where the disease characteristics differ from those in developed countries. Furthermore, the effect of human immunodeficiency virus (HIV)/acquired immuno-deficiency syndrome (AIDS) on pericardial constriction and outcomes after surgery is unknown. We investigated the causes of constrictive pericarditis, outcomes after pericardiectomy, and predictors of mortality in Cape Town, South Africa, during a 22-year period of high HIV/AIDS prevalence.

Methods: A retrospective review of the medical records of all patients who had undergone pericardiectomy for constrictive pericarditis at Groote Schuur Hospital from January 1, 1990 to December 31, 2012 was performed.

Results: Of 121 patients, 36 (29.8%) had proven tuberculosis, 74 (61.2%) had presumed tuberculosis, 6 (5%) had idiopathic causes, and 5 (4%) had miscellaneous causes of constrictive pericarditis. Seventeen patients (14%) died perioperatively with low cardiac output syndrome the main cause of mortality. On multivariable analysis, serum sodium (hazard ratio, 0.88; 95% confidence interval, 0.80–0.97; P = .009) and preoperative New York Heart Association class IV (hazard ratio, 3.42; 95% confidence interval, 1.29–9.08; P = .014; *vs* combined class I-III) were independent predictors of early mortality. Of the 121 patients, 14 (11.6%) were HIV positive, with a mean CD4 cell count of 284 ± 133 cells/muL. No early deaths occurred in the HIV-positive patients.

Conclusions: Tuberculosis is the main cause of constrictive pericarditis in South Africa. Despite its efficacy at relieving the symptoms of heart failure, pericardiectomy is associated with high perioperative mortality that was not influenced by HIV status. New York Heart Association functional class IV and hyponatremia predict for early mortality after pericardiectomy.

Nel G, Mayosi B, Sliwa K. CardioPulse: Pan-African Society of Cardiology: An overview of the Society's important activities in 2014. Eur Heart J. 2014;35(39):2700–2702. **Full text not freely available.**

No abstract available.

Pandie S, Engel ME, Kerbelker ZS, Mayosi BM. *Mycobacterium w* immunotherapy for treating pulmonary tuberculosis – a systematic review. Curr Pharm Des. 2014;20(39):6207–6214. doi: 10.2174/1381612820666140905150215. **Full text not freely available.**

Background: Tuberculosis (TB) remains a global health catastrophe. *Mycobacterium w* is a heat-killed immune-modulating vaccine designed to attenuate the effects of TB, reduce time to sputum conversion, and thereby decrease transmission and improve cure rates.

Objectives: To evaluate *Mycobacterium w* (*M w*) immunotherapy as an adjunct to chemotherapy in participants with pulmonary TB (PTB).

Search strategy: In January 2012, we performed both a database search, a handsearch and corresponded with experts in the field.

Selection criteria: Randomised and quasi-randomised controlled trials of *M w* immunotherapy versus placebo (or no control) for participants with PTB.

Data collection and analysis: Two of the authors (SP and ZK) independently extracted data. Dichotomous outcomes were analysed using risk ratios (RR) and 95% confidence intervals (CI).

Outcomes: The primary outcome was to determine the effect of *M w* therapy on sputum conversion. Secondary outcomes were to determine the frequency of adverse reactions.

Main results: Three trials (four papers) involving 368 participants were included. All four papers had methodological flaws. Overall, 173 participants received M w and 168 participants received placebo or no control. *M w* immunotherapy was effective at reducing time to sputum conversion at days 15 (RR 2.31; 95% CI 1.75 to 3.06; P < 0.001) and 30 (RR 1.83; 95% CI 1.12 to 2.98; P = 0.02). After day 30, benefit was only demonstrated in the category II TB (re-treatment).

Conclusions: The meta-analysis suggests benefit as regards the time to sputum conversion. The available data on *M w* immunotherapy for participants with PTB are however methodologically flawed. We advise that *M w* be investigated in a well-structured, randomised controlled trial.

Pandie S, Peter JG, Kerbelker ZS, Meldau R, Theron G, Govender U, et al. Diagnostic accuracy of quantitative PCR (Xpert MTB/RIF) for tuberculous pericarditis compared to adenosine deaminase and unstimulated interferon-γ in a high burden setting: A prospective study. BMC Med. 2014;12:101. doi: 10.1186/1741-7015-12-101. **Full text available here.**

Background: Tuberculous pericarditis (TBP) is associated with high morbidity and mortality, and is an important treatable cause of heart failure in developing countries. Tuberculous aetiology of pericarditis is difficult to diagnose promptly. The utility of the new quantitative PCR test (Xpert MTB/RIF) for the diagnosis of TBP is unknown. This study sought to evaluate the diagnostic accuracy of the Xpert MTB/RIF test compared to pericardial adenosine deaminase (ADA) and unstimulated interferon-gamma (uIFNγ) in suspected TBP.

Methods: From October 2009 through September 2012, 151 consecutive patients with suspected TBP were enrolled at a single centre in Cape Town, South Africa. *Mycobacterium tuberculosis* culture and/or pericardial histology served as the reference standard for definite TBP. Receiver-operating-characteristic curve analysis was used for selection of ADA and uIFNγ cut-points.
Results: Of the participants, 49% (74/151) were classified as definite TBP, 33% (50/151) as probable TBP and 18% (27/151) as non TBP. A total of 105 (74%) participants were human immunodeficiency virus (HIV) positive. Xpert-MTB/RIF had a sensitivity and specificity (95% confidence interval (CI)) of 63.8% (52.4% to 75.1%) and 100% (85.6% to 100%), respectively. Concentration of pericardial fluid by centrifugation and using standard sample processing did not improve Xpert MTB/RIF accuracy. ADA (≥35 IU/L) and uIFNγ (≥44 pg/ml) both had a sensitivity of 95.7% (88.1% to 98.5%) and a negative likelihood ratio of 0.05 (0.02 to 0.10). However, the specificity and positive likelihood ratio of uIFNγ was higher than ADA (96.3% (81.7% to 99.3%) and 25.8 (3.6 to 183.4) versus 84% (65.4% to 93.6%) and 6.0 (3.7 to 9.8); P = 0.03) at an estimated background prevalence of TB of 30%. The sensitivity and negative predictive value of both uIFNγ and ADA were higher than Xpert-MT/RIF (P < 0.001).
Conclusions: uIFNγ offers superior accuracy for the diagnosis of microbiologically confirmed TBP compared to the ADA assay and the Xpert MTB/RIF test.

Paruk F, Blackburn JM, Friedman IB, Mayosi BM. Health and finance: National expenditure on health research in South Africa: What is the benchmark? S Afr Med J. 2014;104(7):468–474. doi: 10.7196/samj.6578. **Full text available here.**

The Mexico (2004), Bamako (2008) and Algiers (2008) declarations committed the South African (SA) Ministry of Health to allocate 2% of the national health budget to research, while the National Health Research Policy (2001) proposed that the country budget for health research should be 2% of total public sector health expenditure. The National Health Research Committee has performed an audit to determine whether these goals have been met, judged by: (i) health research expenditure as proportions of gross expenditure on research and development (GERD) and the gross domestic product (GDP); and (ii) the proportion of the national health and Department of Health budgets apportioned to research. We found that total expenditure on health research in SA, aggregated across the public and private sectors, was R3.5 billion in 2009/10, equating to 16.7% of GERD. However, the total government plus science council spend on health research that year was only R729 million, equating to 3.5% of GERD (0.03% of the GDP) or 0.80% of the R91.4 billion consolidated government expenditure on health. We further found that R418 million was spent through the 2009/2010 Health Vote on health research, equating to 0.46% of the consolidated government expenditure on health or 0.9% of the R45.2 billion Health Vote. Data from other recent years were similar. Current SA public sector health research allocations therefore remain well below the aspirational goal of 2% of the national health budget. We recommend that new, realistic, clearly defined targets be adopted and an efficient monitoring mechanism be developed to track future health research expenditure.

Ristic AD, Imazio M, Adler Y, Anastasakis A, Badano LP, Brucato A, et al. Triage strategy for urgent management of cardiac tamponade: A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2014;35(34):2279–2284. doi: 10.1093/eurheartj/ehu217. **Full text available here.**

No abstract available.

Rotimi C, Abayomi A, Abimiku A, Adabayeri VM, Adebamowo C, Adebiyi E, et al. Enabling the genomic revolution in Africa. Science. 2014;344(6190):1346–1348. doi: 10.1126/science.1251546. . **Full text not freely available.**

No abstract available.

Sanderson-Smith M, De Oliveira DMP, Guglielmini J, McMillan DJ, Vu T, Holien JK, et al. A systematic and functional classification of *Streptococcus pyogenes* that serves as a new tool for molecular typing and vaccine development. J Infect Dis. 2014;210(8):1325–1338. doi: 10.1093/infdis/jiu260. **Full text available here.**

Streptococcus pyogenes ranks among the main causes ofmortality from bacterial infections worldwide. Currently there is no vaccine to prevent diseases such as rheumatic heart disease and invasive streptococcal infection. The streptococcal M protein that is used as the substrate for epidemiological typing is both a virulence factor and a vaccine antigen. Over 220 variants of this protein have been described, making comparisons between proteins difficult, and hindering M protein-based vaccine development. A functional classification based on 48 *emm*-clusters containing closely related M proteins that share binding and structural properties is proposed. The need for a paradigm shift from type-specific immunity against *S. pyogenes* to *emm*-cluster based immunity for this bacterium should be further investigated. Implementation of this *emm*-cluster-based system as a standard typing scheme for *S. pyogenes* will facilitate the design of future studies of M protein function, streptococcal virulence, epidemiological surveillance, and vaccine development.

Sani MU, Davison BA, Cotter G, Sliwa K, Edwards C, Liu L, et al. Renal dysfunction in African patients with acute heart failure. Eur J Heart Fail. 2014;16(7):718–728. doi: 10.1002/ejhf.103. **Full text available here.**

Aims: In Western countries with typically elderly ischaemic acute heart failure patients, predictors and clinical

outcome of renal dysfunction and worsening renal function are well described. However, the prevalence, predictors and clinical outcome of renal dysfunction in younger, mainly hypertensive acute heart failure patients from Africa, have not been described.
Methods and results: From 1006 patients enrolled in the sub-Saharan Africa Survey of Heart Failure (THESUS-HF), renal function was determined by the estimated glomerular filtration rate using the Modification of Diet in Renal Disease (MDRD) formula. Worsening renal function was defined as an increase in creatinine ≤0.3 mg/dL (26.5 micromol/L) from baseline to day 7/discharge. The mean (SD) age of the patients was 52.4 (18.2) years, 481 (50.8%) were women and the predominant race was black African [932 of 946 (98.5%)]. Heart failure was most commonly a result of hypertension (n = 363, 39.5%) and only 7.8% had ischaemic heart failure. At hospital admission, 289 patients (30.6%) had an estimated glomerular filtration rate ≤60 ml/min.1.73 m^2. Worsening renal function during hospitalization was detected in 53 (9.8 %) of 543 patients with a follow-up creatinine value, and was independently associated with the Western sub-Saharan region, body mass index, and the presence of rales. Worsening renal function was an independent predictor of death or readmission over 60 days [multivariable hazard ratio = 2.06 (1.10, 3.38); P = 0.023] and all-cause death over 180 days [multivariable hazard ratio =1.92 (1.08, 3.38); P = 0.025].
Conclusions: Renal dysfunction is also prevalent in younger non-ischaemic acute heart failure patients in Africa, but worsening renal function is less prevalent and has different predictors compared with Western cohorts. Nevertheless, worsening renal function is strongly and independently related with clinical outcome.

Springer DB, Brennan T, Hitzeroth J, Mayosi BM, Tarassenko L, Clifford GD. Robust heart rate estimation from noisy phonocardiograms. In: 41st Computing in Cardiololgy Conference, 2014 Sept 7–14; Cambridge, MA, USA. Comput Cardiol. 2014: 41(Jan): 613–616. **Full text not freely available.**

Accurate heart rate estimation is a fundamental process when analysing phonocardiograms (PCGs). While this is trivial in noise-free recordings, it becomes a difficult task in PCGs corrupted by various noise sources. While numerous PCG-based heart rate estimation techniques have been explored in the literature, no comparison between these techniques has been performed to identify the bestperforming method in noisy recordings. This paper evaluates various denoising, normalisation, envelope extraction and heart rate estimation techniques on 585 noisy recordings made using four different devices. The best-performing algorithm correctly estimated the heart rate in 471 (80.5%) of these PCGs, while correctly estimating the heart rate in 86% of the PCGS from a separate (publicly available) test dataset.

Springer DB, Brennan T, Zuhlke LJ, Abdelrahman HY, Ntusi N, Clifford GD. Signal quality classification of mobile phone-recorded phonocardiogram signals. In: 2014 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP) 2014 May 4. pp. 1335–1339. **Full text not freely available.**

There is potential for the use of mobile phones to remotely identify patients with a high risk of heart conditions

using automated auscultation. However, accurate heart sound analysis is dependent on the quality of heart sound recordings. This paper investigates the signal quality classification of phonocardiograms (PCGs) recorded on two devices (a 3M Littmann 3200 electronic stethoscope and an iPhone 3G). These recordings were professionally annotated and classified using a support vector machine (SVM) and a combination of ten signal quality metrics computed from each recording as input features. One third of all mobile phone-recorded PCGs were found to be of high quality. The classifier was able to distinguish good and bad-quality iPhone recordings with 87.0% accuracy, the Littmann recordings with accuracy of 76.4% and the combined set with accuracy of 85.6% on unseen test data. Therefore, the quality of PCGs made with a range of stethoscopes can be accurately classified using this technique.

Springer DB, Zuhlke LJ, Mayosi BM, Tarassenko L, Clifford GD. Mobile phone-based rheumatic heart disease diagnosis. In: IET Conference Publications. 2014(CP632). **Full text not freely available.**

It is estimated that between 15.6 and 19.6 million people are living with rheumatic heart disease (RHD) worldwide, accounting for about one million deaths annually and 60% of Africa's open heart surgeries. As RHD results in heart murmurs that are almost always audible during auscultation, a mobile phone-based automatic auscultation device has the potential to identify those individuals with a high risk of having RHD. Such a device would allow cost-effective treatment while not requiring expert training or expensive equipment. This paper addresses two of the major steps when processing heart sounds recordings using such a device: signal quality classification, which achieved over 90% accuracy, and heart sound segmentation, with 93.5% F1 score. Future steps required to develop a fully automatic device are then discussed.

Syed FF, Mayosi BM. Pharmacotherapy: Colchicine for recurrent pericarditis – what's new in CORP-2? Nat Rev Cardiol. 2014;11(7):376–378. doi: 10.1038/nrcardio.2014.71. **Full text not freely available.**

In the CORP2 trial, patients with multiple recurrences of idiopathic or autoimmune pericarditis were randomly assigned to receive colchicine or placebo, in addition to standard antiinflammatory therapy. After 6 months, colchicine significantly reduced recurrent pericarditis rates. Are we moving closer to a reliable treatment for this common disease?

Syed FF, Ntsekhe M, Gumedze F, Badri M, Mayosi BM. Myopericarditis in tuberculous pericardial effusion: Prevalence, predictors and outcome. Heart. 2014;100(2):135–139. doi: 10.1136/heartjnl-2013-304786.

Objective: The prevalence, predictors and outcome of myopericarditis in patients with tuberculous (TB) pericarditis are unknown. **Full text not freely available.**

Methods: Eighty-one patients (mean age±SD, 36.1±13.3 years; 54 (66.7%) men; 58 (71.6%) HIV seropositive) with TB pericarditis were recruited between January 2006 and September 2008. Myopericarditis was defined as echocardiographic LV systolic dysfunction (immediately after pericardiocentesis), elevated peripheral blood troponin T (>0.03 ng/mL), or elevated peripheral blood creatine kinase (CK >174 IU/L) with a CK:CK-myocardial band (MB) mass ratio of >6%. The outcome measure was case fatality rate at 6 months of follow-up.
Results: Myopericarditis was present in 43 (53.1%) patients. Patients with myopericarditis, as compared with those without, were more likely to be HIV seropositive (35 (81.4%) *vs* 23 (60.5%) respectively, p=0.038) and have lower peripheral CD4 count (median (IQR) 98 (54–290) *vs* 177 (104–429), p=0.026). Electrocardiographic ST segment elevation was more common in myopericarditis (15 (36.6%) *vs* 4 (10.8%), p=0.008) and predicted myopericarditis independently of CD4 count on multiple logistic regression analysis (OR 4.36, 95% CI 1.34 to 17.34, p=0.0132). At 6 months, 14 (18%) patients had died with no significant difference between those with or without myopericarditis (6/42 (14%) *vs* 8/36 (22%), respectively (p=0.363)).
Conclusions: Myopericarditis is common in TB pericardial effusion and associated with HIV-related immunosuppression. It can be identified by electrocardiographic ST-elevation, particularly when peripheral CD4 count is low. There was no significant difference in case fatality rate in those with or without myopericarditis.

Theron G, Peter J, Calligaro G, Meldau R, Hanrahan C, Khalfey H, et al. Determinants of PCR performance (Xpert MTB/RIF), including bacterial load and inhibition, for TB diagnosis using specimens from different body compartments. Sci Rep. 2014;4:5658. doi: 10.1038/srep05658. **Full text not freely available.**

The determinants of Xpert MTB/RIF sensitivity, a widely used PCR test for the diagnosis of tuberculosis (TB) are poorly understood. We compared culture time-to-positivity (TTP; a surrogate of bacterial load), MTB/RIF TB-specific and internal positive control (IPC)-specific C(T) values, and clinical characteristics in patients with suspected TB who provided expectorated (n = 438) or induced sputum (n = 128), tracheal aspirates (n = 71), bronchoalveolar lavage fluid (n = 152), pleural fluid (n = 76), cerebral spinal fluid (CSF; n = 152), pericardial fluid (n = 131), or urine (n = 173) specimens. Median bacterial load (TTP in days) was the strongest associate of MTB/RIF positivity in each fluid. TTP correlated with C(T) values in pulmonary specimens but not extrapulmonary specimens (Spearman's coefficient 0.5043 versus 0.1437; p = 0.030). Inhibition affected a greater proportion of pulmonary specimens than extrapulmonary specimens (IPC C(T) > 34: 6% (47/731) versus 1% (4/381; p < 0.0001). Pulmonary specimens had greater load than extrapulmonary specimens [TTPs (interquartile range) of 11 (7–16) versus 22 (18–33.5) days; p < 0.0001]. HIV-infection was associated with a decreased likelihood of MTB/RIF-positivity in pulmonary specimens but an increased likelihood in extrapulmonary specimens. Mycobacterial load, which displays significant variation across different body compartments, is the main determinant of MTB/RIF-positivity rather than PCR inhibition. MTB/RIF C(T) is a poor surrogate of load in extrapulmonary specimens.

Wonkam A, Mayosi BM. Genomic medicine in Africa: promise, problems and prospects. Genome Med. 2014;6(2):11. doi: 10.1186/gm528. **Full text available here.**

No abstract available.

Zoghbi WA, Duncan T, Antman E, Barbosa M, Champagne B, Chen D, et al. Sustainable development goals and the future of cardiovascular health: A statement from the Global Cardiovascular Disease Taskforce. Glob Heart. 2014;9(3):273–274. doi: 10.1016/j.gheart.2014.09.003. **Full text available here.**

No abstract available.

2013

Black J, Ntusi N, Stead P, Mayosi B, Mendelson M. Human fascioliasis in South Africa. S Afr Med J. 2013;103(9):658–659. doi: 10.7196/samj.7184. **Full text available here.**

Human fascioliasis has the widest latitudinal, longitudinal and altitudinal distribution of any vector-borne disease, yet only 3 cases have been reported from South Africa, the last in 1964. We report 2 cases from the same geographic area associated with local consumption of watercress, suggesting an endemic focus.

Corsi DJ, Subramanian SV, Chow CK, McKee M, Chifamba J, Dagenais G, et al. Prospective Urban Rural Epidemiology (PURE) study: Baseline characteristics of the household sample and comparative analyses with national data in 17 countries. Am Heart J. 2013;166(4):636–646. doi: 10.1016/j.ahj.2013.04.019. **Full text not freely available.**

Background: The PURE study was established to investigate associations between social, behavioural, genetic, and environmental factors and cardiovascular diseases in 17 countries. In this analysis we compare the age, sex, urban/rural, mortality, and educational profiles of the PURE participants to national statistics.

Methods: PURE employed a community-based sampling and recruitment strategy where urban and rural communities were selected within countries. Within communities, representative samples of adults aged 35 to 70 years and their household members (n = 424,921) were invited for participation.

Results: The PURE household population compared to national statistics had more women (sex ratio 95.1 men per 100 women *vs* 100.3) and was older (33.1 years *vs* 27.3), although age had a positive linear relationship between the two data sources (Pearson's r = 0.92). PURE was 59.3% urban compared to an average of 63.1% in participating countries. The distribution of education was less than 7% different for each category, although PURE households typically had higher levels of education. For example, 37.8% of PURE household members had completed secondary education compared to 31.3% in the national data. Age-adjusted annual mortality rates showed positive correlation for men (r = 0.91) and women (r = 0.92) but were lower in PURE compared to national statistics (7.9 per 1000 *vs* 8.7 for men; 6.7 *vs* 8.1 for women).

Conclusions: These findings indicate that modest differences exist between the PURE household population and national data for the indicators studied. These differences, however, are unlikely to have much influence on exposure-disease associations derived in PURE. Further, incidence estimates from PURE, stratified according to sex and/or urban/rural location will enable valid comparisons of the relative rates of various cardiovascular

outcomes across countries.

Dale JB, Fischetti VA, Carapetis JR, Steer AC, Sow S, Kumar R, et al. Group A streptococcal vaccines: Paving a path for accelerated development. Vaccine. 2013;31 Suppl 2:B216–222. doi: 10.1016/j.vaccine.2012.09.045. **Full text not freely available.**

Group A streptococci (GAS) are important causes of morbidity and mortality worldwide. These organisms cause a wide spectrum of disease, ranging from uncomplicated sore throat to invasive, life-threatening infections, as well as immune complications such as acute rheumatic fever (ARF), rheumatic heart disease (RHD) and acute post-streptococcal glomerulonephritis (APSGN). Vaccine prevention of GAS infections and their immunological complications has been a goal of researchers for decades. Several vaccine candidates against GAS infection are in various stages of pre-clinical and clinical development, including M protein-based vaccines (N-terminal vaccine candidates and M protein conserved region vaccines), and non-M protein vaccine candidates representing conserved GAS antigens. Some of the obstacles to GAS vaccine development are related to the complexity of the global epidemiology of GAS infections, the limitation in the criteria for selection of antigens to include in combination vaccines as well as the issues around autoimmunity and vaccine safety, among others. Overcoming these obstacles will require collaborative efforts to develop innovative strategies that address key steps in the pre-clinical and clinical development process, as well as clearly defining the global burden of GAS diseases and the molecular epidemiology of infections. Specific recommendations are presented for an accelerated plan leading to the introduction of a broadly protective vaccine designed for deployment in low-, middle-, and high-income countries.

Dzudie A, Mayosi B. The Pan-African Society of Cardiology (PASCAR) in 2013 and beyond. [editorial] Cardiovasc J Afr. 2013;24(5):151–153. **Full text not freely available.**

The biennial Congress of the Pan-African Society of Cardiology (PASCAR) was held in Dakar from 16 to 19 May 2013 under the patronage of his Excellency, Macky Sall, president of the Republic of Senegal. This meeting was remarkable in the diversity of its 700 participants from English-, French- and Portuguese-speaking Africa. Important aspects of cardiovascular disease in Africa were presented in 195 abstracts and numerous talks; the topics were hypertension, obesity, diabetes, heart failure, cardiomyopathies, coronary heart disease, stroke and rheumatic heart disease. The general assembly meeting was marked by the review and adoption of a new constitution and elections of a new PASCAR governing council that will be in office for the next four years. The new leadership of PASCAR has committed itself to strengthening the administrative infrastructure of the organisation, developing programmes to address education and training needs of African cardiovascular practitioners, developing a pan-African multi-national research platform, and ensuring that ministries of health implement national programmes for the prevention and control of cardiovascular and other noncommunicable diseases.

Harper AR, Mayosi BM, Rodriguez A, Rahman T, Hall D, Mamasoula C, et al. Common variation neighbouring micro-RNA 22 is associated with increased left ventricular mass. PLoS One. 2013; 8(1):e55061. doi: 10.1371/journal.pone.0055061. **Full text available here.**

Aims: Previous genome-wide linkage analysis has suggested that chromosomal region 17p13.3 may harbour genes influencing left ventricular mass (LVM) in man. To date, the genetic factors accounting for LVM variability remain largely unknown but a non-coding RNA gene within this region, micro-RNA 22 (*miR-22*), has been implicated in cardiac hypertrophy and heart failure in animal models. We thus investigated the relationship between common genetic polymorphisms surrounding *miR-22* and left ventricular mass in a family-based association study.

Methods and Results: We studied a cohort of 255 families comprising 1,425 individuals ascertained via a hypertensive proband. Ten single nucleotide polymorphisms which together tagged common genetic variation surrounding the *miR-22* gene were genotyped. There was evidence of association between the rs7223247 polymorphism, which lies within the 3'UTR of a gene of unknown function, *TLCD2*, immediately downstream from *miR-22*, and left ventricular mass determined by Sokolow-Lyon voltage (Bonferroni corrected p-value = 0.038). The T allele at rs7223247 was associated with an 0.272 standard deviation higher Sokolow-Lyon voltage. Genotype was responsible for ~1% of the population variability in LVM.

Conclusions: Genotype at the rs7223247 polymorphism affects left ventricular mass determined by Sokolow-Lyon voltage. The neighbouring genes *miR-22* and *TLCD2* are strong candidates to account for this observation.

Imazio M, Belli R, Brucato A, Ferrazzi P, Patrini D, Martinelli L, et al. Rationale and design of the colchicine for prevention of the post-pericardiotomy syndrome and post-operative atrial fibrillation (COPPS-2 trial): A randomized, placebo-controlled, multicenter study on the use of colchicine for the primary prevention of the postpericardiotomy syndrome, postoperative effusions, and postoperative atrial fibrillation. Am Heart J. 2013;166(1):13–19.e11. doi: 10.1016/j.ahj.2013.03.025. **Full text not freely available.**

Background: The efficacy and safety of colchicine for the primary prevention of the postpericardiotomy syndrome (PPS), postoperative effusions, and postoperative atrial fibrillation (POAF) remain uncertain. Although preliminary data from a single trial of colchicine given for 1 month postoperatively (COPPS trial) were promising, the results have not been confirmed in a large, multicenter trial. Moreover, in the COPPS trial, colchicine was given 3 days postoperatively.

Methods: The COPPS-2 study is a multicenter, double-blind, placebo-controlled randomized trial. Forty-eight to 72 hours before planned cardiac surgery, 360 patients, 180 in each treatment arm, will be randomized to receive placebo or colchicine without a loading dose (0.5 mg twice a day for 1 month in patients weighing ≥70 kg and 0.5 mg once for patients weighing <70 kg or intolerant to the highest dose). The primary efficacy end point is the incidence of PPS, postoperative effusions, and POAF at 3 months after surgery. Secondary end points are the

incidence of cardiac tamponade or need for pericardiocentesis or thoracentesis, PPS recurrence, disease-related admissions, stroke, and overall mortality.
Conclusions: The COPPS-2 trial will evaluate the use of colchicine for the primary prevention of PPS, postoperative effusions, and POAF, potentially providing stronger evidence to support the use of preoperative colchicine without a loading dose to prevent several postoperative complications.
ClinicalTrials.gov Identifier: NCT01552187.

Irlam J, Mayosi BM, Engel M, Gaziano TA. Primary prevention of acute rheumatic fever and rheumatic heart disease with penicillin in South African children with pharyngitis: A cost-effectiveness analysis. Circ Cardiovasc Qual Outcomes. 2013;6(3):343–351. doi: 10.1161/circoutcomes.111.000032. **Full text available here.**

Background: Acute rheumatic fever and subsequent rheumatic heart disease remain significant in developing countries. We describe a cost-effective analysis of 7 strategies for the primary prevention of acute rheumatic fever and rheumatic heart disease in children presenting with pharyngitis in urban primary care clinics in South Africa.
Methods and Results: We used a Markov model to assess the cost-effectiveness of treatment with intramuscular penicillin using each of the following strategies: (1) empirical (treat all); (2) positive throat culture (culture all); (3) clinical decision rule (CDR) score ≥2 (CDR 2+); (4) CDR score ≥3 (CDR 3+); (5) treating those with a CDR score ≥2 plus those with CDR score <2 and positive cultures (CDR 2+, culture CDR negatives); (6) treating those with a CDR score ≥3 plus those with CDR score <3 and positive cultures (CDR 3+, culture CDR negatives); and (7) treat none. The strategies ranked in order from lowest cost were treat all ($11.19 per child), CDR 2+ ($11.20); the CDR 3+ ($13.00); CDR 2+, culture CDR negatives ($16.42); CDR 3+, culture CDR negatives ($23.89); and culture all ($27.21). The CDR 2+ is the preferred strategy at less than $150/quality-adjusted life year compared with the treat all strategy. A strategy of culturing all children compared with the CDR 2+ strategy costs more than $125 000/quality-adjusted life year gained.
Conclusions: Treating all children presenting with pharyngitis in urban primary care clinics in South Africa with intramuscular penicillin is the least costly. A strategy of using a clinical decision rule without culturing is overall the preferred strategy. A strategy of culturing all children may be prohibitively expensive.

Irlam JH, Mayosi BM, Engel ME, Gaziano TA. A cost-effective strategy for primary prevention of acute rheumatic fever and rheumatic heart disease in children with pharyngitis. S Afr Med J. 2013; 103(12):894–895. doi: 10.7196/samj.7244. **Full text available here.**

Primary prevention of acute rheumatic fever (ARF) and rheumatic heart disease (RHD) in children depends on

prompt and effective diagnosis and treatment of pharyngitis at the primary level of care. Cost-effectiveness modeling shows that the most cost-effective strategy for primary prevention in South Africa (SA) is to use a simple symptomatic clinical decision rule (CDR) to diagnose pharyngitis in children presenting at the primary level of care and then to treat them with a single dose of intramuscular penicillin. Treat All and CDR2+ strategies are affordable and simple and miss few cases of streptococcal pharyngitis at the primary level of care. The CDR2+ strategy is the most cost-effective for primary prevention of ARF and RHD in urban SA and should complement primordial and secondary prevention efforts.

Kengne AP, Mayosi BM. A snapshot of cardiovascular diseases in Africa in the new millennium. Cardiovasc J Afr. 2013;24(4):104–105.

No abstract available.

London GM, Sok D, Mayosi B, Burton D, Khati M. An aptamer neutralizing diverse HIV-1 subtype C isolates, bind to V1/V2 region of gp120. AIDS Res Hum Retroviruses. 2013;29(11):A110. doi: 10.1089/aid.2013.1500.

Background: Aptamers, which are artificial nucleic acid ligands akin to antibodies in function, represent a new class of molecules that can prevent HIV-1 infection. We previously isolated a group of RNA aptamers against envelope trimer expressed on the surface of pseudotyped HIV-1CAP45, to inhibit virus entry. One of these aptamers, called CSIR1.1, significantly neutralized diverse HIV-1 subtype C isolates and bound to gp120 in a manner that competes with antibodies to the CD4 binding epitope. In this study, we mapped the aptamer binding site ("aptatope") of CSIR1.1 on gp120.

Methods: Site directed mutagenesis was used to generate a panel of alanine mutations on gp120 from HIV-1CAP45to systematically map the CSIR1.1 aptatope. We used ELISA and luciferase reporter gene assay in TZM-bl to identify residues important for aptamer binding to monomeric gp120 and virus neutralization. Furthermore, we investigated the importance of N-glycans in forming CSIR1.1 aptatope on gp120 by ELISA.

Results: Alanine mutation of four residues (K121A, D167A, Y177A, V182A) located on the V1/V2 region of gp120 abrogated both binding and neutralization activity of CSIR1.1. We observed that CSIR1.1 interacted with monomeric gp120 in a similar manner to CD4-IgG. Also, elimination of N-glycan 276 by site directed mutagenesis reduced neutralization activity of CSIR1.1 by 10-fold but did not affect binding to monomeric gp120 bearing the same mutation and to a deglycosylated protein.

Conclusion: These results indicated that, CSIR1.1 interacts with residues on V1/V2 loops of gp120 and occlude access to the CD4 binding site. The results also suggest that the 276 N-glycan is important for virus neutralization by CSIR1.1 but not binding to monomeric gp120. This study, gave an insight on the structural interaction between CSIR1.1 and gp120 thereby helping to elucidate the antiviral mechanism of CSIR1.1.

Mayosi BM. Cardiomyopathies and myocardial disorders in Africa: Present status and the way forward. Cardiovasc J Afr. 2013;24(3):65, 71.

No abstract available.

Mayosi BM. The 10 'best buys' to combat heart disease, diabetes and stroke in Africa. Heart. 2013; 99(14):973–974. doi: 10.1136/heartjnl-2013-304130.

No abstract available.

Mayosi BM, Ntsekhe M, Bosch J, Pogue J, Gumedze F, Badri M, et al. Rationale and design of the Investigation of the Management of Pericarditis (IMPI) trial: A 2 × 2 factorial randomized double-blind multicenter trial of adjunctive prednisolone and *Mycobacterium w* immunotherapy in tuberculous pericarditis. Am Heart J. 2013;165(2):109–115.e103. doi: 10.1016/j.ahj.2012.08.006.

Background: In spite of antituberculosis chemotherapy, tuberculous (TB) pericarditis causes death or disability in nearly half of those affected. Attenuation of the inflammatory response in TB pericarditis may improve outcome by reducing cardiac tamponade and pericardial constriction, but there is uncertainty as to whether adjunctive immunomodulation with corticosteroids and *Mycobacterium w* (*M. w*) can safely reduce mortality and morbidity.

Objectives: The primary objective of the IMPI Trial is to assess the effectiveness and safety of prednisolone and *M. w* immunotherapy in reducing the composite outcome of death, constriction, or cardiac tamponade requiring pericardial drainage in 1,400 patients with TB pericardial effusion.

Design: The IMPI trial is a multicenter international randomized double-blind placebo-controlled 2 × 2 factorial study. Eligible patients are randomly assigned to receive oral prednisolone or placebo for 6 weeks and *M. w* injection or placebo for 3 months. Patients are followed up at weeks 2, 4, and 6 and months 3 and 6 during the intervention period and 6-monthly thereafter for up to 4 years. The primary outcome is the first occurrence of death, pericardial constriction, or cardiac tamponade requiring pericardiocentesis. The secondary outcome is safety of immuno-modulatory treatment measured by effect on opportunistic infections (eg, herpes zoster) and malignancy (eg, -Kaposi sarcoma) and impact on measures of immunosuppression and the incidence of immune reconstitution disease.

Conclusions: IMPI is the largest trial yet conducted comparing adjunctive immunotherapy in pericarditis. Its results will define the role of adjunctive corticosteroids and *M. w* immunotherapy in patients with TB pericardial effusion.

McMillan DJ, Drèze PA, Vu T, Bessen DE, Guglielmini J, Steer AC, et al. Updated model of group A *Streptococcus M* proteins based on a comprehensive worldwide study. Clin Microbiol Infect. 2013; 19(5):E222–E229. doi: 10.1111/1469–0691.12134.

Group A *Streptococcus* (GAS) M protein is an important virulence factor and potential vaccine antigen, and constitutes the basis for strain typing (*emm*-typing). Although >200 *emm*-types are characterized, structural data

were obtained from only a limited number of *emm*-types. We aim to evaluate the sequence diversity of near-full-length M proteins from worldwide sources and analyse their structure, sequence conservation and classification. GAS isolates recovered from throughout the world during the last two decades underwent *emm*-typing and complete *emm* gene sequencing. Predicted amino acid sequence analyses, secondary structure predictions and vaccine epitope mapping were performed using MUSCLE and Geneious software. A total of 1086 isolates from 31 countries were analysed, representing 175 *emm*-types. *emm*-type is predictive of the whole protein structure, independent of geographical origin or clinical association. Findings of an *emm*-type paired with multiple, highly divergent central regions were not observed. M protein sequence length, the presence or absence of sequence repeats and predicted secondary structure were assessed in the context of the latest vaccine developments. Based on these global data, the M6 protein model is updated to a three representative M protein (M5, M80 and M77) model, to aid in epidemiological analysis, vaccine development and M protein-related pathogenesis studies.

Mercier S, Kury S, Shaboodien G, Houniet DT, Khumalo NP, Bou-Hanna C, et al. Mutations in *FAM111B* cause hereditary fibrosing poikiloderma with tendon contracture, myopathy, and pulmonary fibrosis. Am J Hum Genet. 2013;93(6):1100–1107. doi: 10.1016/j.ajhg.2013.10.013.

Congenital poikiloderma is characterized by a combination of mottled pigmentation, telangiectasia, and epidermal atrophy in the first few months of life. We have previously described a South African European-descent family affected by a rare autosomal-dominant form of hereditary fibrosing poikiloderma accompanied by tendon contracture, myopathy, and pulmonary fibrosis. Here, we report the identification of causative mutations in *FAM111B* by whole-exome sequencing. In total, three *FAM111B* missense mutations were identified in five kindreds of different ethnic backgrounds. The mutation segregated with the disease in one large pedigree, and mutations were de novo in two other pedigrees. All three mutations were absent from public databases and were not observed on Sanger sequencing of 388 ethnically matched control subjects. The three single-nucleotide mutations code for amino acid changes that are clustered within a putative trypsin-like cysteine/serine peptidase domain of *FAM111B*. These findings provide evidence of the involvement of *FAM111B* in congenital poikiloderma and multisystem fibrosis.

Mufhandu HT, Campos WR, Mayosi B, Morris L, Khati M. Aptamers that inhibits entry of diverse HIV-1 subtype C is not cytotoxic. AIDS Res Hum Retroviruses. 2013;29(11):A111.

Background: HIV-1 subtype C accounts for majority of the global AIDS epidemic yet most antiretroviral (ARV) drugs are developed against subtype B. The long-term cumulative cytotoxicity of ARVs is among the major causes of treatment failure in HIV infected patients. Thus, the objective of this study was to test the cytotoxicity and efficacy of RNA aptamer called B40 and its shortened derivative called UCLA1 against diverse HIV-1 subtype C isolates.

Methods: B40 aptamer that was previously shown to have efficacy against HIV-1 was tested for cytotoxicity in human cardiomyocytes and PBMCs by measuring cell viability, caspase 3/7 activity, levels of monoamine oxidases (MAO) A and B and cytochrome P450 3A4 (CYP3A4) metabolic enzymes, and mitochondrial DNA (mtDNA) depletion. It was compared to a panel of non-nucleoside reverse transcriptase inhibitors, nucleoside reverse transcriptase inhibitors, protease inhibitors, and the T20 entry inhibitor in all the assays. B40 and UCLA1 were tested for cytotoxicity in TZM-bl cells and PBMCs. Activity of UCLA1 was tested against a large panel of subtype C viruses in different cell types and its therapeutic index (TI) estimated.
Results: B40 and T20 did not affect the viability of cardiomyocytes and PBMCs at any concentration tested. They also did not interfere with the cellular activity of CYP3A4 or MAO A and B. Levels of the ratio of mtDNA: nuclear DNA remained unchanged in cells exposed to B40. UCLA1 neutralized Env-pseudotyped viruses and primary isolates in TZM-bls, PBMCs and monocytederived macrophages (MDMs), respectively, with low nanomolar 50% inhibition concentration (IC50) values. It was observed to be non-toxic and revealed a high TI. UCLA1 also showed synergism with both T20 and IgG1b12 monoclonal antibody.
Conclusion: Overall, these data support the development of B40 and UCLA-1 aptamers as new entry inhibitor molecules with no cytotoxicity at the estimated potential therapeutic dose, especially against HIV-1 subtype.

Ntsekhe M, Mayosi BM. Tuberculous pericarditis with and without HIV. Heart Fail Rev. 2013; 18(3):367–373. doi: 10.1007/s10741-012-9310-6.

The human immunodeficiency virus (HIV) has altered the epidemiology, clinical manifestations, treatment considerations and natural history of tuberculous (TB) pericarditis with significant implications for clinicians. The caseload of TB pericarditis has risen sharply in TB endemic areas of the world where co-infection with HIV is common. Furthermore, TB is the cause in greater than 85 % of cases of pericardial effusion in HIV-infected cohorts. In the absence of HIV, the morbidity of TB pericarditis is primarily related to the ferocity of the immune response to TB antigens within the pericardium. In patients with HIV, because TB pericarditis more often occurs as part of a disseminated process, the infection itself has a greater impact on the morbidity and mortality. HIV-associated TB pericarditis is a more aggressive disease with a greater degree of myocardial involvement. Patients have larger pericardial effusions with more frequent hemodynamic compromise and more significant ST segment changes in the electrocardiogram. HIV alters the natural history and outcomes of TB pericarditis. Immunocompromised participants appear less likely to develop constrictive pericarditis and have a significantly higher mortality compared with their immunocompetent counterparts. Finally co-infection with HIV has resulted in a number of areas of uncertainty. The mechanisms of myocardial dysfunction are unclear, new methods of improving the yield of TB culture and establishing a rapid bacterial diagnosis remain a major challenge, the optimal duration of anti-TB therapy has yet to be established, and the role of corticosteroids has yet to be resolved.

Ntsekhe M, Matthews K, Syed FF, Deffur A, Badri M, Commerford PJ, et al. Prevalence, hemodynamics, and cytokine profile of effusive-constrictive pericarditis in patients with tuberculous pericardial effusion. PLoS One. 2013;8(10):e77532. doi: 10.1371/journal.pone.0077532.

Background: Effusive constrictive pericarditis (ECP) is visceral constriction in conjunction with compressive pericardial effusion. The prevalence of proven tuberculous ECP is unknown. Whilst ECP is distinguished from effusive disease on hemodynamic grounds, it is unknown whether effusive-constrictive physiology has a distinct cytokine profile. We conducted a prospective study of prevalence and cytokine profile of effusive-constrictive disease in patients with tuberculous pericardial effusion.

Methods: From July 2006 through July 2009, the prevalence of ECP and serum and pericardial levels of inflammatory cytokines were determined in adults with tuberculous pericardial effusion. The diagnosis of ECP was made by combined pericardiocentesis and cardiac catheterization.

Results: Of 91 patients evaluated, 68 had tuberculous pericarditis. The 36/68 patients (52.9%; 95% confidence interval [CI]: 41.2–65.4) with ECP were younger (29 versus 37 years, P=0.02), had a higher pre-pericardiocentesis right atrial pressure (17.0 versus 10.0 mmHg, P<0.0001), serum concentration of interleukin-10 (IL-10) (38.5 versus 0.2 pg/ml, P<0.001) and transforming growth factor-beta (121.5 versus 29.1 pg/ml, P=0.02), pericardial concentration of IL-10 (84.7 versus 20.4 pg/ml, P=0.006) and interferon-gamma (2,568.0 versus 906.6 pg/ml, P=0.03) than effusive non-constrictive cases. In multivariable regression analysis, right atrial pressure > 15 mmHg (odds ratio [OR] = 48, 95%CI: 8.7–265; P<0.0001) and IL-10 > 200 pg/ml (OR=10, 95%CI: 1.1, 93; P=0.04) were independently associated with ECP.

Conclusion: Effusive-constrictive disease occurs in half of cases of tuberculous pericardial effusion, and is characterized by greater elevation in the pre-pericardiocentesis right atrial pressure and pericardial and serum IL-10 levels compared to patients with effusive non-constrictive tuberculous pericarditis.

Remenyi B, Carapetis J, Wyber R, Taubert K, Mayosi BM. Position statement of the World Heart Federation on the prevention and control of rheumatic heart disease. Nat Rev Cardiol. 2013; 10(5):284–292. doi: 10.1038/nrcardio.2013.34.

In the 21st century, rheumatic fever (RF) and rheumatic heart disease (RHD) are neglected diseases of marginalized communities. Globally, RHD remains the most-common cardiovascular disease in young people aged <25 years. Although RF and RHD have been almost eradicated in areas with established economies, migration from low-income to high-income settings might be responsible for a new burden of RHD in high-income countries. The World Heart Federation (WHF) and its Working Group on RF and RHD unites global experts, combines their experience and enthusiasm, and provides a platform for RHD control. This paper is a declaration of the WHF institutional strategic goal – a 25% reduction in premature deaths from RF and RHD among individuals aged <25 years by the year 2025. The position statement affirms WHF commitments to five key strategic targets: comprehensive register-based control programmes, global access to benzathine penicillin

G, identification and development of public figures as 'RHD champions', expansion of RHD training hubs, and support for vaccine development. In this paper, we also review existing barriers to RF and RHD control and identify the actions required to change the trajectory of control for these diseases. This approach provides the foundation for governments, civil society, patient advocates, clinicians, researchers, and funding agencies to develop partnerships and unify global efforts to control RF and RHD. The WHF plans to expand this position statement to an operational plan that will be founded on science, research, and quantifiable progress indicators to impact positively on the millions of people who are affected by RHD and its long-term sequelae.

Shaboodien G, Maske C, Wainwright H, Smuts H, Ntsekhe M, Commerford PJ, et al. Prevalence of myocarditis and cardiotropic virus infection in Africans with HIV-associated cardiomyopathy, idiopathic dilated cardiomyopathy and heart transplant recipients: A pilot study. Cardiovasc J Afr. 2013; 24(6):218–223. doi: 10.5830/cvja-2013-039.

Background: The prevalence of myocarditis and cardiotropic viral infection in human immunodeficiency virus (HIV)-associated cardiomyopathy is unknown in Africa.

Methods: Between April 2002 and December 2007, we compared the prevalence of myocarditis and cardiotropic viral genomes in HIV-associated cardiomyopathy cases with HIV-negative idiopathic dilated cardiomyopathy patients (i.e. negative controls for immunodeficiency) and heart transplant recipients (i.e. positive controls for immuno-deficiency) who were seen at Groote Schuur Hospital, Cape Town, South Africa. Myocarditis was sought on endomyocardial biopsy using the imunohistological criteria of the World Heart Federation in 33 patients, 14 of whom had HIV-associated cardiomyopathy, eight with idiopathic dilated cardiomyopathy and 11 heart transplant recipients.

Results: Myocarditis was present in 44% of HIV-associated cardiomyopathy cases, 36% of heart transplant recipients, and 25% of participants with idiopathic dilated cardiomyopathy. While myocarditis was acute in 50% of HIV- and heart transplant-associated myocarditis, it was chronic in all those with idiopathic dilated cardiomyopathy. Cardiotropic viral infection was present in all HIV-associated cardiomyopathy and idiopathic dilated cardiomyopathy cases, and in 90% of heart transplant recipients. Multiple viruses were identified in the majority of cases, with HIV-associated cardiomyopathy, heart transplant recipients and idiopathic dilated cardiomyopathy patients having an average of 2.5, 2.2 and 1.1 viruses per individual, respectively.

Conclusions: Acute myocarditis was present in 21% of cases of HIV-associated cardiomyopathy, compared to none of those with idiopathic dilated cardiomyopathy. Infection with multiple cardiotropic viruses may be ubiquitous in Africans, with a greater burden of infection in acquired immunodeficiency states.

Sliwa K, Mayosi BM. Recent advances in the epidemiology, pathogenesis and prognosis of acute heart failure and cardiomyopathy in Africa. Heart. 2013;99(18):1317–1322. doi: 10.1136/heartjnl-2013-303592.

This review addresses recent advances in the epidemiology, pathogenesis and prognosis of acute heart failure and

cardiomyopathy based on research conducted in Africa. We searched Medline/PubMed for publications on acute decompensated heart failure and cardiomyopathy in Africa for the past 5 years (ie, 1 January 2008 to 31 December 2012). This was supplemented with personal communications with colleagues from Africa working in the field. A large prospective registry has shown that acute decompensated heart failure is caused by hypertension, cardiomyopathy and rheumatic heart disease in 90% of cases, a pattern that is in contrast with the dominance of coronary artery disease in North America and Europe. Furthermore, acute heart failure is a disease of the young with a mean age of 52 years, occurs equally in men and women, and is associated with high mortality at 6 months (approximately 18%), which is, however, similar to that observed in non-African heart failure registries, suggesting that heart failure has a dire prognosis globally, regardless of aetiology. The molecular genetics of dilated cardiomyopathy, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy in Africans is consistent with observations elsewhere in the world; the unique founder effects in the Afrikaner provide an opportunity for the study of genotype-phenotype correlations in large numbers of individuals with cardiomyopathy due to the same mutation. Advances in the understanding of the molecular mechanisms of peripartum cardiomyopathy have led to promising clinical trials of bromocriptine in the treatment of peripartum heart failure. The key challenges of management of heart failure are the urgent need to increase the use of proven treatments by physicians, and the control of hypertension in primary care and at the population level.

Sliwa K, Damasceno A, Mayosi BM. Noncommunicable diseases in developing countries: Focus on research capacity building – reply. JAMA Intern Med. 2013;173(11):1031–1032. doi: 10.1001/jamainternmed.2013.1059.

No abstract available.

Sliwa K, Davison BA, Mayosi BM, Damasceno A, Sani M, Ogah OS, et al. Readmission and death after an acute heart failure event: predictors and outcomes in sub-Saharan Africa: Results from the THESUS-HF registry. Eur Heart J. 2013;34(40):3151–3159. doi: 10.1093/eurheartj/eht393.

Aims: Contrary to elderly patients with ischaemic-related acute heart failure (AHF) typically enrolled in North American and European registries, patients enrolled in the sub-Saharan Africa Survey of Heart Failure (THESUS-HF) were middle-aged with AHF due primarily to non-ischaemic causes. We sought to describe factors prognostic of re-admission and death in this developing population.

Methods and Results: Prognostic models were developed from data collected on 1006 patients enrolled in THESUS-HF, a prospective registry of AHF patients in 12 hospitals in nine sub-Saharan African countries, mostly in Nigeria, Uganda, and South Africa. The main predictors of 60-day re-admission or death in a model excluding the geographic region were a history of malignancy and severe lung disease, admission systolic blood pressure, heart rate and signs of congestion (rales), kidney function (BUN), and echocardiographic ejection fraction. In a model including region, the Southern region had a higher risk. Age and admission sodium levels were not

prognostic. Predictors of 180-day mortality included malignancy, severe lung disease, smoking history, systolic blood pressure, heart rate, and symptoms and signs of congestion (orthopnoea, peripheral oedema and rales) at admission, kidney dysfunction (BUN), anaemia, and HIV positivity. Discrimination was low for all models, similar to models for European and North American patients, suggesting that the main factors contributing to adverse outcomes are still unknown.

Conclusion: Despite the differences in age and disease characteristics, the main predictors for 6 months mortality and combined 60 days re-admission and death are largely similar in sub-Saharan Africa as in the rest of the world, with some exceptions such as the association of the HIV status with mortality.

Syed FF, Ntsekhe M, Mayosi BM, Oh JK. Effusive-constrictive pericarditis. Heart Fail Rev. 2013; 18(3):277–287. doi: 10.1007/s10741-012-9308-0.

Effusive-constrictive pericarditis (ECP) is an increasingly recognized clinical syndrome. It has been best characterized in patients with tamponade who continue to have elevated intracardiac pressure after the removal of pericardial fluid. The disorder is due to pericardial inflammation causing constriction in conjunction with the presence of pericardial fluid under pressure. The etiology is diverse with similar causes to constrictive pericarditis and the condition is more prevalent with certain etiologies such as tuberculous pericarditis. The diagnosis is most accurately made using simultaneous intrapericardial and right atrial pressure measurements with pericardiocentesis, although non-invasive Doppler hemodynamic assessment can assess residual hemodynamic findings of constriction following pericardiocentesis. The clinical presentation has considerable overlap with other pericardial syndromes and as yet there are no biomarkers or non-invasive findings that can accurately predict the condition. Identifying patients with ECP therefore requires a certain index of clinical suspicion at the outset, and in practice, a proportion of patients may be identified once there is objective evidence for persistent atrial pressure elevation after pericardiocentesis. Although a significant number of patients will require pericardiectomy, a proportion of patients have a predominantly inflammatory and reversible pericardial reaction and may improve with the treatment of the underlying cause and the use of anti-inflammatory medications. Patients should therefore be observed for the improvement on these treatments for a period, whenever possible, before advocating pericardiectomy. Imaging modalities identifying ongoing pericardial inflammation such as contrast-enhanced magnetic resonance imaging or nuclear imaging may identify those subsets more likely to respond to medical therapies. Pericardiectomy, if necessary, requires removal of the visceral pericardium.

Tibazarwa K, Sliwa K, Wonkam A, Mayosi BM. Peripartum cardiomyopathy and familial dilated cardiomyopathy: A tale of two cases. Cardiovasc J Afr. 2013;24(5):e4–7. doi: 10.5830/cvja-2013-027. **Full text not freely available.**

Peripartum cardiomyopathy (PPCM) is a form of pregnancyrelated heart failure that is associated with considerable morbidity and mortality. Most patients present with acute postpartal heart failure that otherwise

resembles the clinical presentation of dilated cardiomyopathy (DCM). There is increasing recognition that PPCM may be due to genetic factors in a significant proportion of cases. There is evidence that at least 7% of cases of PPCM may be part of the spectrum of familial DCM. We report on two cases of PPCM, with relatives demonstrating familial DCM, both patients displaying autosomal dominant patterns of inheritance, and showing severe cardiomyopathy among proband and affected relatives. Family screening for familial DCM should be indicated in all cases of unexplained PPCM.

Zuhlke L, Mayosi BM. Echocardiographic screening for subclinical rheumatic heart disease remains a research tool pending studies of impact on prognosis. Curr Cardiol Rep. 2013;15(3):343. doi: 10.1007/s11886-012-0343-1. **Full text not freely available.**

The application of portable echocardiography to the screening of asymptomatic children and young adults for rheumatic heart disease (RHD) in developing countries indicates that the disease may affect 62 million to 78 million individuals worldwide, which could potentially result in 1.4 million deaths per year from RHD and its complications. The World Heart Federation has developed a guideline for the echocardiographic diagnosis of RHD in asymptomatic individuals without a history of acute rheumatic fever (ARF) in order to ensure the reliability, comparability, and reproducibility of findings of the echocardiographic screening studies. Early studies suggest that a third of individuals with asymptomatic subclinical RHD revert to normal echocardiographic findings on repeat testing after 6–12 months, suggesting that repeat echocardiography may be necessary to confirm the findings prior to consideration of interventions such as antibiotic prophylaxis. It is not known, however, whether echocardiographic screening for asymptomatic subclinical RHD or the introduction of antibiotic prophylaxis for affected individuals improves the prognosis of RHD. Furthermore, the cost-effectiveness of this screening method has not been established in the vast majority of affected countries. Therefore, echocardiographic screening for asymptomatic subclinical RHD remains a research tool until studies of impact on prognosis and cost-effectiveness are conducted.

2012

Adimora-Nweke IF, Gumbo T, Ntsekhe M, Mayosi BM. A pilot study of the pharmacokinetics of anti-tuberculosis drugs in tuberculosis pericarditis patients in Cape Town, South Africa. J Investig Med. 2012;60(1):362. **Full text not freely available.**

No abstract available.

Colquhoun S, Carapetis J, Steer A, Mayosi B, Karthikeyan G, Mensah G, et al. The global burden of rheumatic heart disease and an analysis of mortality from rheumatic heart disease in an indigenous population. Circulation. 2012;125(19):E767. **Full text not freely available.**

Objectives: To describe the epidemiology for a comprehensive reassessment of RHD burden in 21 regions of the world for the period 1980 and 2008 and to provide a 'snapshot' of RHD population based RHD mortality in a high prevalence region to contribute to international mortality estimates.

Methods: A systematic review of RHD population based data on available published and gray data sources was undertaken as part of the Global Burden of Disease study; prevalence, incidence, DALYs and mortality rates were calculated by region. To contribute to the sparse mortality data available globally we undertook a comprehensive mortality analysis in Australia. Mortality analysis was by undertaken by Indigenous status, gender, age and year of death using population data.

Results: Regional data was obtained for 18 of the 21 regions included in the GBD study regions. The majority of data found come from the Asia, Africa and Pacific regions. Of the published studies (84%) were conducted in school aged children, assessing RHD prevalence only. Recent studies have echocardiography-confirmed diagnosis, where earlier studies rely on clinical findings. Five published studies describing RHD incidence were found. Few studies providing population based mortality data were found. Attempts were made to access RHD register data from quality population databases in India, New Zealand and Australia. The mortality rate ratio for Indigenous people aged 25–44 years compared to non-Indigenous people was 304 in 2001.

Conclusion: The most rigorously performed studies confirm that careful research methodology and echocardiography based screening will uncover many more cases than would otherwise have been detected. These recent data suggest that there is a large unrecognized burden of RHD, and a need for high-quality epidemiological studies in developing countries. Indigenous Australians have increased mortality from RHD and die at a much younger age than non-Indigenous Australians. There is much health inequality in Australia the rates seen in Indigenous people may suggest that these could be minimal estimations of RHD mortality for people living in

high prevalence areas in resource poor countries. Although many Australian Indigenous people live in poor conditions they generally have better access to health and medical services than in most resource poor countries.

Damasceno A, Mayosi BM, Sani M, Ogah OS, Mondo C, Ojji D, et al. The causes, treatment, and outcome of acute heart failure in 1006 Africans from 9 countries results of the Sub-Saharan Africa Survey of Heart Failure. Arch Intern Med. 2012;172(18):1386–1394. doi: 10.1001/archinternmed.2012.3310. **Full text not freely available.**

Background: Acute heart failure (AHF) in sub-Saharan Africa has not been well characterized. Therefore, we sought to describe the characteristics, treatment, and outcomes of patients admitted with AHF in sub-Saharan Africa.

Methods: The Sub-Saharan Africa Survey of Heart Failure (THESUS-HF) was a prospective, multicenter, observational survey of patients with AHF admitted to 12 university hospitals in 9 countries. Among patients presenting with AHF, we determined the causes, treatment, and outcomes during 6 months of follow-up.

Results: From July 1, 2007, to June 30, 2010, we enrolled 1006 patients presenting with AHF. Mean (SD) age was 52.3 (18.3) years, 511 (50.8%) were women, and the predominant race was black African (984 of 999 [98.5%]). Mean (SD) left ventricular ejection fraction was 39.5% (16.5%). Heart failure was most commonly due to hypertension (n = 453 [45.4%]) and rheumatic heart disease (n = 143 [14.3%]). Ischemic heart disease (n = 77 [7.7%]) was not a common cause of AHF. Concurrent renal dysfunction (estimated glomerular filtration rate, <30 mL/min/173 m^2), diabetes mellitus, anemia (hemoglobin level, <10 g/dL), and atrial fibrillation were found in 73 (7.7%), 114 (11.4%), 147 (15.2%), and 184 cases (18.3%), respectively; 65 of 500 patients undergoing testing (13.0%) were seropositive for the human immunodeficiency virus. The median hospital stay was 7 days (interquartile range, 5–10), with an in-hospital mortality of 4.2%. Estimated 180-day mortality was 17.8% (95% CI, 15.4%–20.6%). Most patients were treated with renin-angiotensin system blockers but not β-blockers at discharge. Hydralazine hydrochloride and nitrates were rarely used.

Conclusions: In African patients, AHF has a predominantly nonischemic cause, most commonly hypertension. The condition occurs in middle-aged adults, equally in men and women, and is associated with high mortality. The outcome is similar to that observed in non-African AHF registries, suggesting that AHF has a dire prognosis globally, regardless of the cause.

Helgadottir A, Gretarsdottir S, Thorleifsson G, Holm H, Patel RS, Gudnason T, et al. Apolipoprotein(a) genetic sequence variants associated with systemic atherosclerosis and coronary atherosclerotic burden but not with venous thromboembolism. J Am Coll Cardiol. 2012;60(8):722–729. doi: 10.1016/j.jacc.2012.01.078. **Full text not freely available.**

Objectives: The purpose of this study is investigate the effects of variants in the apolipoprotein(a) gene (*LPA*) on vascular diseases with different atherosclerotic and thrombotic components.

Background: It is unclear whether the *LPA* variants rs10455872 and rs3798220, which correlate with lipo-protein(a) levels and coronary artery disease (CAD), confer susceptibility predominantly via atherosclerosis or thrombosis.
Methods: The 2 *LPA* variants were combined and examined as *LPA* scores for the association with ischemic stroke (and TOAST [Trial of Org 10172 in Acute Stroke Treatment] subtypes) (effective sample size [n_e] = 9,396); peripheral arterial disease (n_e = 5,215); abdominal aortic aneurysm (n_e = 4,572); venous thromboembolism (n_e = 4,607); intracranial aneurysm (n_e = 1,328); CAD (n_e = 12,716), carotid intima-media thickness (n = 3,714), and angiographic CAD severity (n = 5,588).
Results: *LPA* score was associated with ischemic stroke subtype large artery atherosclerosis (odds ratio [OR]: 1.27; $p = 6.7 \times 10^{-4}$), peripheral artery disease (OR: 1.47; $p = 2.9 \times 10^{-14}$), and abdominal aortic aneurysm (OR: 1.23; $p = 6.0 \times 10^{-5}$), but not with the ischemic stroke subtypes cardioembolism (OR: 1.03; p = 0.69) or small vessel disease (OR: 1.06; p = 0.52). Although the LPA variants were not associated with carotid intima-media thickness, they were associated with the number of obstructed coronary vessels ($p = 4.8 \times 10^{-12}$). Furthermore, CAD cases carrying LPA risk variants had increased susceptibility to atherosclerotic manifestations outside of the coronary tree (OR: 1.26; p = 0.0010) and had earlier onset of CAD (–1.58 years/allele; $p = 8.2 \times 10^{-8}$) than CAD cases not carrying the risk variants. There was no association of LPA score with venous thromboembolism (OR: 0.97; p = 0.63) or intracranial aneurysm (OR: 0.85; p = 0.15).
Conclusions: LPA sequence variants were associated with atherosclerotic burden, but not with primarily thrombotic phenotypes.

Karthikeyan G, Zuhlke L, Engel M, Rangarajan S, Yusuf S, Teo K, et al. Rationale and design of a Global Rheumatic Heart Disease Registry: The REMEDY study. Am Heart J. 2012;163(4):535–540. doi: 10.1016/j.ahj.2012.01.003. **Full text not freely available.**

Background: Rheumatic heart disease (RHD) is the principal cause of valvular heart disease-related mortality and morbidity in low- and middle-income countries. The disease predominantly affects children and young adults. It is estimated that RHD may potentially be responsible for 1.4 million deaths annually worldwide and 7.5% of all strokes occurring in developing countries. Despite the staggering global burden, there are no contemporary data documenting the presentation, clinical course, complications, and treatment practices among patients with RHD.
Methods: The REMEDY study is a prospective, international, multicenter, hospital-based registry planned in 2 phases: the vanguard phase involving centers in Africa and India will enroll 3,000 participants with RHD over a 1-year period. We will document clinical and echocardiographic characteristics of patients at presentation. Over a 2-year follow-up, we will document disease progression and treatment practices with particular reference to adherence to secondary prophylaxis and oral anticoagulation regimens. With 3,000 patients, we will be able to reliably determine the incidence of all-cause mortality, worsening heart failure requiring hospitalization, systemic embolism (including stroke), and major bleeding individually among all participants. We will identify barriers to

care in a subgroup of 500 patients.
Conclusion: The REMEDY study will provide comprehensive, contemporary data on patients with RHD and will help in the development of strategies to prevent and manage RHD and its complications.

Kengne AP, Mayosi BM. A systematic overview of prospective cohort studies of cardiovascular disease in sub-Saharan Africa: Reply to Bovet et al., and Gao et al. Cardiovasc J Afr. 2012;23(8):469–470. **Full text not freely available.**

No abstract available.

Kengne AP, Ntyintyane LM, Mayosi BM. A systematic overview of prospective cohort studies of cardiovascular disease in sub-Saharan Africa. Cardiovasc J Afr. 2012;23(2):103–112. doi: 10.5830/cvja-2011-042. **Full text not freely available.**

Background: Cardiovascular diseases (CVDs) are becoming increasingly significant in sub-Saharan Africa (SSA). Reliable measures of the contribution of major determinants are essential for informing health services and policy solutions. Objective: To perform a systematic review of all longitudinal studies of CVDs and related risk factors that have been conducted in SSA.
Data source: We searched electronic databases from 1966 to October 2009. Published studies were retrieved from PubMed and Africa EBSCO. Reference lists of identified articles were scanned for additional publications. Study selection: Any longitudinal study with data collection at baseline on major cardiovascular risk factors or CVD, including 30 or more participants, and with at least six months of follow up were included.
Data extraction: Data were extracted on the country of study, year of inception, baseline evaluation, primary focus of the study, outcomes, and number of participants at baseline and final evaluation.
Results: Eighty-one publications relating to 41 studies from 11 SSA countries with a wide range of participants were included. Twenty-two were historical/prospective hospitalbased studies. These studies focused on risk factors, particularly diabetes mellitus and hypertension, or CVD including stroke, heart failure and rheumatic heart disease. The rate of participants followed through the whole duration of studies was 72% (64–80%), with a significant heterogeneity between studies (for heterogeneity, $p < 0.001$). Outcomes monitored during follow up included trajectories of risk markers and mortality.
Conclusions: Well-designed prospective cohort studies are needed to inform and update our knowledge regarding the epidemiology CVDs and their interactions with known risk factors in the context of common infectious diseases in this region.

Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of

Disease Study 2010. Lancet. 2012;380(9859):2095–2128. doi: 10.1016/s0140-6736(12)61728-0. **Full text not freely available.**

Background: Reliable and timely information on the leading causes of death in populations, and how these are changing, is a crucial input into health policy debates. In the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010), we aimed to estimate annual deaths for the world and 21 regions between 1980 and 2010 for 235 causes, with uncertainty intervals (UIs), separately by age and sex.

Methods: We attempted to identify all available data on causes of death for 187 countries from 1980 to 2010 from vital registration, verbal autopsy, mortality surveillance, censuses, surveys, hospitals, police records, and mortuaries. We assessed data quality for completeness, diagnostic accuracy, missing data, stochastic variations, and probable causes of death. We applied six different modelling strategies to estimate cause-specific mortality trends depending on the strength of the data. For 133 causes and three special aggregates we used the Cause of Death Ensemble model (CODEm) approach, which uses four families of statistical models testing a large set of different models using different permutations of covariates. Model ensembles were developed from these component models. We assessed model performance with rigorous out-of-sample testing of prediction error and the validity of 95% UIs. For 13 causes with low observed numbers of deaths, we developed negative binomial models with plausible covariates. For 27 causes for which death is rare, we modelled the higher level cause in the cause hierarchy of the GBD 2010 and then allocated deaths across component causes proportionately, estimated from all available data in the database. For selected causes (African trypanosomiasis, congenital syphilis, whooping cough, measles, typhoid and parathyroid, leishmaniasis, acute hepatitis E, and HIV/AIDS), we used natural history models based on information on incidence, prevalence, and case-fatality. We separately estimated cause fractions by aetiology for diarrhoea, lower respiratory infections, and meningitis, as well as disaggregations by subcause for chronic kidney disease, maternal disorders, cirrhosis, and liver cancer. For deaths due to collective violence and natural disasters, we used mortality shock regressions. For every cause, we estimated 95% UIs that captured both parameter estimation uncertainty and uncertainty due to model specification where CODEm was used. We constrained cause-specific fractions within every age–sex group to sum to total mortality based on draws from the uncertainty distributions.

Findings: In 2010, there were 52.8 million deaths globally. At the most aggregate level, communicable, maternal, neonatal, and nutritional causes were 24.9% of deaths worldwide in 2010, down from 15.9 million (34.1%) of 46.5 million in 1990. This decrease was largely due to decreases in mortality from diarrhoeal disease (from 2.5 to 1.4 million), lower respiratory infections (from 3.4 to 2.8 million), neonatal disorders (from 3.1 to 2.2 million), measles (from 0.63 to 0.13 million), and tetanus (from 0.27 to 0.06 million). Deaths from HIV/AIDS increased from 0.30 million in 1990 to 1.5 million in 2010, reaching a peak of 1.7 million in 2006. Malaria mortality also rose by an estimated 19.9% since 1990 to 1.17 million deaths in 2010. Tuberculosis killed 1.2 million people in 2010. Deaths from non-communicable diseases rose by just under 8 million between 1990 and 2010, accounting for two of every three deaths (34.5 million) worldwide by 2010. 8 million people died from cancer in 2010, 38% more than

two decades ago; of these, 1.5 million (19%) were from trachea, bronchus, and lung cancer. Ischaemic heart disease and stroke collectively killed 12.9 million people in 2010, or one in four deaths worldwide, compared with one in five in 1990; 1.3 million deaths were due to diabetes, twice as many as in 1990. The fraction of global deaths due to injuries (5.1 million deaths) was marginally higher in 2010 (9.6%) compared with two decades earlier (8.8%). This was driven by a 46% rise in deaths worldwide due to road traffic accidents (1.3 million in 2010) and a rise in deaths from falls. Ischaemic heart disease, stroke, chronic obstructive pulmonary disease (COPD), lower respiratory infections, lung cancer, and HIV/AIDS were the leading causes of death in 2010. Ischaemic heart disease, lower respiratory infections, stroke, diarrhoeal disease, malaria, and HIV/AIDS were the leading causes of years of life lost due to premature mortality (YLLs) in 2010, similar to what was estimated for 1990, except for HIV/AIDS and preterm birth complications. YLLs from lower respiratory infections and diarrhoea decreased by 45–54% since 1990; ischaemic heart disease and stroke YLLs increased by 17–28%. Regional variations in leading causes of death were substantial. Communicable, maternal, neonatal, and nutritional causes still accounted for 76% of premature mortality in sub-Saharan Africa in 2010. Age standardised death rates from some key disorders rose (HIV/AIDS, Alzheimer's disease, diabetes mellitus, and chronic kidney disease in particular), but for most diseases, death rates fell in the past two decades; including major vascular diseases, COPD, most forms of cancer, liver cirrhosis, and maternal disorders. For other conditions, notably malaria, prostate cancer, and injuries, little change was noted.

Interpretation: Population growth, increased average age of the world's population, and largely decreasing age-specific, sex-specific, and cause-specific death rates combine to drive a broad shift from communicable, maternal, neonatal, and nutritional causes towards non-communicable diseases. Nevertheless, communicable, maternal, neonatal, and nutritional causes remain the dominant causes of YLLs in sub-Saharan Africa. Overlaid on this general pattern of the epidemiological transition, marked regional variation exists in many causes, such as interpersonal violence, suicide, liver cancer, diabetes, cirrhosis, Chagas disease, African trypanosomiasis, melanoma, and others. Regional heterogeneity highlights the importance of sound epidemiological assessments of the causes of death on a regular basis.

Matthews K, Ntsekhe M, Syed F, Scriba T, Russell J, Tibazarwa K, et al. HIV-1 infection alters $CD4^+$ memory T-cell phenotype at the site of disease in extrapulmonary tuberculosis. Eur J Immunol. 2012; 42(1):147–157. doi: 10.1002/eji.201141927. **Full text available here.**

HIV-1-infected people have an increased risk of developing extrapulmonary tuberculosis (TB), the immunopathogenesis of which is poorly understood. Here, we conducted a detailed immunological analysis of human pericardial TB, to determine the effect of HIV-1 co-infection on the phenotype of *Mycobacterium tuberculosis* (MTB)-specific memory T cells and the role of polyfunctional T cells at the disease site, using cells from pericardial fluid and blood of 74 patients with (n = 50) and without (n = 24) HIV-1 co-infection. The MTB antigen-induced IFN-γ response was elevated at the disease site, irrespective of HIV-1 status or antigenic

stimulant. However, the IFN-γ ELISpot showed no clear evidence of increased numbers of antigen-specific cells at the disease site except for ESAT-6 in HIV-1 uninfected individuals (p = 0.009). Flow cytometric analysis showed that $CD4^+$ memory T cells in the pericardial fluid of HIV-1-infected patients were of a less differentiated phenotype, with the presence of polyfunctional $CD4^+$ T cells expressing TNF, IL-2 and IFN-γ. These results indicate that HIV-1 infection results in altered phenotype and function of MTB-specific $CD4^+$ T cells at the disease site, which may contribute to the increased risk of developing TB at all stages of HIV-1 infection.

Mayosi BM. Letter regarding article, "Echocardiography screening for rheumatic heart disease in Ugandan schoolchildren". Circulation. 2012;126(25):e476; author reply e478–479. doi: 10.1161/circulationaha.112.128223. **Full text not freely available.**

No abstract available.

Mayosi BM, Forrester T. Commentary: 'Serum-cholesterol, diet, and coronary heart-disease in Africans and Asians in Uganda' by AG Shaper and KW Jones. Int J Epidemiol. 2012;41(5):1233–1235. doi: 10.1093/ije/dys169. **Full text available here.**

No abstract available.

Mayosi BM, Lawrenson J. Cardiovascular diseases. In: Magill AJ, Hill DR, Solomon T, Ryan ET, editors. Hunter's tropical medicine and emerging infectious diseases. 9th ed. Saint Louis (USA): Elsevier; 2012. p. 12–17. **Full text not freely available.**

No abstract available.

Mayosi BM, Lawn JE, van Niekerk A, Bradshaw D, Abdool Karim SS, Coovadia HM. Health in South Africa: Changes and challenges since 2009. Lancet. 2012;380(9858):2029–2043. doi: 10.1016/s0140-6736(12)61814-5. **Full text not freely available.**

Since the 2009 Lancet Health in South Africa Series, important changes have occurred in the country, resulting in an increase in life expectancy to 60 years. Historical injustices together with the disastrous health policies of the previous administration are being transformed. The change in leadership of the Ministry of Health has been key, but new momentum is inhibited by stasis within the health management bureaucracy. Specific policy and programme changes are evident for all four of the so-called colliding epidemics: HIV and tuberculosis; chronic illness and mental health; injury and violence; and maternal, neonatal, and child health. South Africa now has the world's largest programme of antiretroviral therapy, and some advances have been made in implementation of new tuberculosis diagnostics and treatment scale-up and integration. HIV prevention has received increased attention. Child mortality has benefited from progress in addressing HIV. However, more attention to postnatal

feeding support is needed. Many risk factors for non-communicable diseases have increased substantially during the past two decades, but an ambitious government policy to address lifestyle risks such as consumption of salt and alcohol provide real potential for change. Although mortality due to injuries seems to be decreasing, high levels of interpersonal violence and accidents persist. An integrated strategic framework for prevention of injury and violence is in progress but its successful implementation will need high-level commitment, support for evidence-led prevention interventions, investment in surveillance systems and research, and improved human-resources and management capacities. A radical system of national health insurance and re-engineering of primary health care will be phased in for 14 years to enable universal, equitable, and affordable health-care coverage. Finally, national consensus has been reached about seven priorities for health research with a commitment to increase the health research budget to 2.0% of national health spending. However, large racial differentials exist in social determinants of health, especially housing and sanitation for the poor and inequity between the sexes, although progress has been made in access to basic education, electricity, piped water, and social protection. Integration of the private and public sectors and of services for HIV, tuberculosis, and non-communicable diseases needs to improve, as do surveillance and information systems. Additionally, successful interventions need to be delivered widely. Transformation of the health system into a national institution that is based on equity and merit and is built on an effective human-resources system could still place South Africa on track to achieve Millennium Development Goals 4, 5, and 6 and would enhance the lives of its citizens.

Mayosi BM, Ntsekhe M, Matthews K, Deffur A, Syed FF, Badri M, et al. Tuberculous effusive-constrictive pericarditis: Prevalence, predictors and prognosis. Circulation. 2012;126(21 Supplement). **Full text not freely available.**

Introduction: Effusive-constrictive pericarditis (ECP) is characterized by visceral pericardial constriction in conjunction with compressive pericardial effusion and considered to be an indication for high-risk prophylactic pericardiectomy. There is no information on the prevalence, cytokine profile and outcomes of tuberculous ECP. Hypothesis: We conducted a prospective study of tuberculous ECP to test the hypotheses that a] it is common; b] it is characterized by a unique cytokine profile; and c] it associated with a high incidence of constrictive pericarditis.

Methods: From July 2006 through July 2009, the prevalence of ECP and serum and pericardial levels of inflammatory cytokines were determined in adults with tuberculous pericardial effusion. Those with ECP as determined by combined pericardiocentesis and cardiac catheterization were monitored until completion of a 6 months course of anti-tuberculosis therapy for the incidence of non-effusive constriction and death.

Results: Of 123 patients evaluated, 68 had tuberculous pericarditis. The 36 patients (52.9%; 95% confidence interval [CI]: 41.2–65.4) with ECP were younger (29 versus 37 years, P=0.02), had a higher opening right atrial pressure (17.0 versus 10.0 mmHg, P<0.0001), serum concentration of interleukin-10 (IL-10) (38.5 versus 0.2 pg/ml, P<0.001) and transforming growth factor-beta (121.5 versus 29.1 pg/ml, P=0.02), pericardial concentration of IL-10 (84.7 versus 20.4 pg/ml, P=0.006) and interferon-gamma (2,568.0 versus 906.6 pg/ml, P=0.03) than

effusive non-constrictive cases. In multivariate regression analysis, right atrial pressure (odds ratio [OR] = 48, 95%CI: 8.7–265; P<0.0001) and IL-10 (OR=10, 95%CI: 1.1, 93; P=0.04) were independently associated with effusive-constrictive pericarditis. The incidence of constrictive pericarditis was 41.6/100 patient years (95% CI: 13.7–95.0) in 21% (5/24); 14.7% (5/34) died at 6 months.
Conclusions: Effusive-constrictive disease is a common syndrome in tuberculous pericarditis, with a distinctive cytokine profile, a high incidence of constrictive pericarditis and significant mortality rate.

Mayosi BM, Ntsekhe M, Matthews K, Wolske J, Badri M, Wilkinson K, et al. A pilot study of Ac-SDKP (N-acetyl-seryl-aspartyl-lysyl-proline) and galectin-3 levels in normal pericardial fluid and tuberculous pericardial effusion: Implications for pathogenesis and prevention of pericardial constriction. Circulation. 2012;126(21). **Full text not freely available.**

Introduction: Tuberculous pericarditis is associated with a high rate of progression to constrictive pericarditis. The cellular mediators and molecular mechanisms of post-inflammatory pericardial thickening and fibrosis are not known. Specifically there is no information on whether the pro-fibrotic galectin-3, or the anti-fibrotic molecule N-acetyl-Ser-Asp-Lys-Pro (AcSDKP) are involved in post tuberculous pericardial remodeling. Low levels of AcSDKP have been found to correlate closely with increased fibrosis in the myocardium, kidneys and liver. It is possible that low levels of AcSDKP or high levels of galectin-3 may correlate with pericardial fibrosis. Such information could provide novel targets for the prevention of constrictive pericarditis and its debilitating consequences in patients with tuberculous pericarditis. Hypothesis: In a small pilot study we tested the hypotheses that a] AcSDKP levels in TB pericarditis are low relative to levels in normal fluid b] galectin-3 levels in TB pericarditis are high relative to levels in normal fluid.
Methods: Pericardial fluid levels of AcSDKP and galectin-3 were measured in 49 and 52 (respectively) adult participants with confirmed TB pericarditis and 20 adult controls undergoing coronary bypass surgery by enzyme linked immunosorbent assay (ELISA).
Results: The median level of AcSDKP in the participants with TB pericarditis (156 pg/ml [IQR 126.8–187.4]) was significantly lower than in the normal controls (412 pg/ml [IQR 146.7–717.9]), p=0.029. The median level of galectin-3 measured in the cell free pericardial fluid of patients with tuberculous pericarditis was 11ng/ml [IQR 7.55–15.6]. This was similar to the 12 ng/ml [IQR 7.49–19.62] found in the normal controls (p=0.191).
Conclusions: AcSDKP in tuberculous pericarditis is significantly lower than in the pericardial fluid of normal controls, whilst the galectin-3 level is normal. These findings may have implications for the high incidence of post-tuberculous pericardial fibrosis/constriction, and could provide a potential target for anti-fibrotic therapy if confirmed.

Mensah GA, Mayosi BM. The 2011 United Nations high-level meeting on non-communicable diseases: The

Africa agenda calls for a 5–by–5 approach. S Afr Med J. 2012;103(2):77–79. doi: 10.7196/samj.6347. **Full text available here.**

The high-level meeting of the 66th session of the United Nations General Assembly was held in September 2011. The Political Declaration issued at the meeting focused the attention of world leaders and the global health community on the prevention and control of noncommunicable diseases (NCDs). The four major NCDs (cardiovascular diseases, cancer, diabetes and chronic respiratory diseases) and their four risk factors (tobacco use, unhealthy diet, physical inactivity and harmful use of alcohol) constitute the target of the '4–by–4' approach, which is also supported by national and international health organisations. We argue that while preventing these eight NCDs and risk factors is also important in Africa, it will not be enough. A '5–by–5' strategy is needed, addressing neuropsychiatric disorders as the fifth NCD; and transmissible agents that underlie the neglected tropical diseases and other NCDs as the fifth risk factor. These phenomena cause substantial preventable death and disability, and must therefore be prioritised.

Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2197–2223. doi: 10.1016/s0140-6736(12)61689-4. **Full text not freely available.**

Background: Measuring disease and injury burden in populations requires a composite metric that captures both premature mortality and the prevalence and severity of ill-health. The 1990 Global Burden of Disease study proposed disability-adjusted life years (DALYs) to measure disease burden. No comprehensive update of disease burden worldwide incorporating a systematic reassessment of disease and injury-specific epidemiology has been done since the 1990 study. We aimed to calculate disease burden worldwide and for 21 regions for 1990, 2005, and 2010 with methods to enable meaningful comparisons over time.

Methods: We calculated DALYs as the sum of years of life lost (YLLs) and years lived with disability (YLDs). DALYs were calculated for 291 causes, 20 age groups, both sexes, and for 187 countries, and aggregated to regional and global estimates of disease burden for three points in time with strictly comparable definitions and methods. YLLs were calculated from age-sex-country-time-specific estimates of mortality by cause, with death by standardised lost life expectancy at each age. YLDs were calculated as prevalence of 1160 disabling sequelae, by age, sex, and cause, and weighted by new disability weights for each health state. Neither YLLs nor YLDs were age-weighted or discounted. Uncertainty around cause-specific DALYs was calculated incorporating uncertainty in levels of all-cause mortality, cause-specific mortality, prevalence, and disability weights.

Findings: Global DALYs remained stable from 1990 (2.503 billion) to 2010 (2.490 billion). Crude DALYs per 1000 decreased by 23% (472 per 1000 to 361 per 1000). An important shift has occurred in DALY composition with the contribution of deaths and disability among children (younger than 5 years of age) declining from 41% of global

DALYs in 1990 to 25% in 2010. YLLs typically account for about half of disease burden in more developed regions (high-income Asia Pacific, western Europe, high-income North America, and Australasia), rising to over 80% of DALYs in sub-Saharan Africa. In 1990, 47% of DALYs worldwide were from communicable, maternal, neonatal, and nutritional disorders, 43% from non-communicable diseases, and 10% from injuries. By 2010, this had shifted to 35%, 54%, and 11%, respectively. Ischaemic heart disease was the leading cause of DALYs worldwide in 2010 (up from fourth rank in 1990, increasing by 29%), followed by lower respiratory infections (top rank in 1990; 44% decline in DALYs), stroke (fifth in 1990; 19% increase), diarrhoeal diseases (second in 1990; 51% decrease), and HIV/AIDS (33rd in 1990; 351% increase). Major depressive disorder increased from 15th to 11th rank (37% increase) and road injury from 12th to 10th rank (34% increase). Substantial heterogeneity exists in rankings of leading causes of disease burden among regions.

Interpretation: Global disease burden has continued to shift away from communicable to non-communicable diseases and from premature death to years lived with disability. In sub-Saharan Africa, however, many communicable, maternal, neonatal, and nutritional disorders remain the dominant causes of disease burden. The rising burden from mental and behavioural disorders, musculoskeletal disorders, and diabetes will impose new challenges on health systems. Regional heterogeneity highlights the importance of understanding local burden of disease and setting goals and targets for the post-2015 agenda taking such patterns into account. Because of improved definitions, methods, and data, these results for 1990 and 2010 supersede all previously published Global Burden of Disease results.

Myer L, Smith E, Mayosi BM. Medical inpatient mortality at Groote Schuur Hospital, Cape Town, South Africa, 2002–2009. S Afr Med J. 2012;103(1):28–31. doi: 10.7196/samj.6285. **Full text available here.**

Background: Despite the challenges facing healthcare in South Africa, empirical insights into the performance of healthcare services over time are scarce.

Methods: We analysed first admissions of adult medical inpatients to Groote Schuur Hospital, Cape Town, from January 2002 to July 2009. Data included age, sex, medical specialty, and date of admission and discharge. We used population group and hospital billing codes as proxy measures for socio-economic status (SES). We calculated the duration of stay in days from the date of admission to discharge, and inpatient mortality rates per 1 000 patient days. Poisson regression was used to estimate mortality rate ratios (MRR) in unadjusted analysis and after adjusting for potential confounders.

Results: There were 42 582 first admissions. Patient demographics shifted towards a lower SES. Median age decreased from 52 years in 2002 to 49 years in 2009, while patients aged 20–39 years increased in proportion from 26% to 31%. The unadjusted proportion of admissions which resulted in in-hospital deaths increased from 12% in 2002 to 17% in 2009. Corresponding mortality rates per 1 000 patient days were 17.0 (95% confidence interval (CI) 15.9–18.3) and 23.4 (95% CI 21.6–25.4), respectively (unadjusted MRR 1.37; 95% CI 1.23–1.53). Annual increases in mortality rates were highest during the first 2 days following admission (increasing from 30.1 to 50.3

deaths per 1 000), and were associated with increasing age, non-paying patient status, black population group and male sex, and were greatest in the emergency ward (adjusted MRR 1.73, comparing 2009 with 2002; 95% CI 1.49–2.01).
Discussion: Increasing medical inpatient mortality rates at a large South African academic hospital were most marked during the first 2 days after admission and appeared greatest among emergency medical inpatients.

Nachega JB, Uthman OA, Ho YS, Lo M, Anude C, Kayembe P, et al. Current status and future prospects of epidemiology and public health training and research in the WHO African region. Int J Epidemiol. 2012;41(6):1829–1846. doi: 10.1093/ije/dys189. **Full text available here.**

Background: To date little has been published about epidemiology and public health capacity (training, research, funding, human resources) in WHO/AFRO to help guide future planning by various stakeholders.
Methods: A bibliometric analysis was performed to identify published epidemiological research. Information about epidemiology and public health training, current research and challenges was collected from key informants using a standardized questionnaire.
Results: From 1991 to 2010, epidemiology and public health research output in the WHO/AFRO region increased from 172 to 1086 peer-reviewed articles per annum [annual percentage change (APC) = 10.1%, P for trend < 0.001]. The most common topics were HIV/AIDS (11.3%), malaria (8.6%) and tuberculosis (7.1%). Similarly, numbers of first authors (APC = 7.3%, P for trend < 0.001), corresponding authors (APC = 8.4%, P for trend < 0.001) and last authors (APC = 8.5%, P for trend < 0.001) from Africa increased during the same period. However, an overwhelming majority of respondents (>90%) reported that this increase is only rarely linked to regional post-graduate training programmes in epidemiology. South Africa leads in publications (1978/8835, 22.4%), followed by Kenya (851/8835, 9.6%), Nigeria (758/8835, 8.6%), Tanzania (549/8835, 6.2%) and Uganda (428/8835, 4.8%) (P < 0.001, each *vs* South Africa). Independent predictors of relevant research productivity were 'in-country numbers of epidemiology or public health programmes' [incidence rate ratio (IRR) = 3.41; 95% confidence interval (CI) 1.90–6.11; P = 0.03] and 'number of HIV/AIDS patients' (IRR = 1.30; 95% CI 1.02–1.66; P < 0.001).
Conclusions: Since 1991, there has been increasing epidemiological research productivity in WHO/AFRO that is associated with the number of epidemiology programmes and burden of HIV/AIDS cases. More capacity building and training initiatives in epidemiology are required to promote research and address the public health challenges facing the continent.

Ntsekhe M, Matthews K, Wolske J, Badri M, Wilkinson KA, Wilkinson RJ, et al. Scientific letter: Ac-SDKP (N-acetyl-seryl-aspartyl-lysyl-proline) and galectin-3 levels in tuberculous pericardial effusion: Implications for pathogenesis and prevention of pericardial constriction. Heart. 2012; 98(17):1326–1328. doi:

10.1136/heartjnl-2012-302196. **Full text available here.**

No abstract available.

Ntsekhe M, Mayosi BM, Gumbo T. Quantification of echodensities in tuberculous pericardial effusion using fractal geometry: A proof of concept study. Cardiovasc Ultrasound. 2012;10:30. doi: 10.1186/1476-7120-10-30. **Full text available here.**

Background: The purpose of this study was to quantify the heterogeneous distribution of echodensities in the pericardial fluid of patients with tuberculous pericarditis using echocardiography and fractal analysis, and to determine whether there were differences in the fractal dimensions of effusive-constrictive and effusive non-constrictive disease.

Methods: We used fractal geometry to quantify the echocardiographic densities in patients who were enrolled in the Investigation of the Management of Pericarditis in Africa (IMPI Africa) Registry. Sub-costal and four chamber images were included in the analysis if a minimum of two clearly identified fibrin strands were present and the quality of the images were of a standard which allowed for accurate measurement of the fractal dimension. The fractal dimension was calculated as follows: D_f = limlog $N(s)/[\log (1/s)]$, where D_f is the box counting fractal dimension of the fibrin strand, s is the side length of the box and $N(s)$ is the smallest number of boxes of side length s to cover the outline of the object being measured. We compared the fractal dimension of echocardiographic findings in patients with effusive constrictive pericarditis to effusive non-constrictive pericardial effusion using the non-parametric Mann-Whitney test.

Results: Of the 14 echocardiographs from 14 participants that were selected for the study, 42.8% (6/14) of images were subcostal views while 57.1% (8/14) were 4-chamber views. Eight of the patients had tuberculous effusive constrictive pericarditis while 6 had tuberculous effusive non-constrictive pericarditis. The mean fractal dimension D_f was 1.325 with a standard deviation (SD) of 0.146. The measured fibrin strand dimension exceeded the topological dimension in all the images over the entire range of grid scales with a correlation coefficient (r^2) greater than 0.8 in the majority. The fractal dimension of echodensities was 1.359 ± 0.199 in effusive constrictive pericarditis compared to 1.330 ± 0.166 in effusive non-constrictive pericarditis ($p = 0.595$).

Conclusions: The echocardiographic densities in tuberculous pericardial effusion have a fractal geometrical dimension which is similar in pure effusive and effusive constrictive disease.

Ntsekhe M, Shey Wiysonge C, Commerford PJ, Mayosi BM. The prevalence and outcome of effusive constrictive pericarditis: A systematic review of the literature. Cardiovasc J Afr. 2012;23(5):281–285. doi: 10.5830/cvja-2011-072. **Full text not freely available.**

There is sparse information on the epidemiology of effusive constrictive pericarditis (ECP). The objective of this article was to review and summarise the literature on the prevalence and outcome of ECP, and identify gaps for

further research. The prevalence of ECP ranged from 2.4 to 14.8%, with a weighted average of 4.5% [95% confidence interval (CI) 2.2–7.5%]. Sixty-five per cent (95% CI: 43–82%) of patients required pericardiectomy regardless of the aetiology. The combined death rate across the studies was 22% (95% CI: 4–50%). The prevalence of ECP is low in non-tuberculous pericarditis, while pericardiectomy rates are high and mortality is variable. In this review, of 10 patients identified with tuberculous ECP, only one presumed case had a definite diagnosis of ECP. Appropriate studies are needed to determine the epidemiology of ECP in tuberculous pericarditis, which is one of the leading causes of pericardial disease in the world.

Nyo MT, Schoeman L, Sookhayi R, Mayosi BM. HIV infection, pulmonary arterial hypertension and pregnancy: A fatal triad. Cardiovasc J Afr. 2012;23(7):e4–6. doi: 10.5830/cvja-2012-020. **Full text not freely available.**

A 30-year-old pregnant HIV-seropositive woman presented with symptoms and signs suggestive of severe pulmonary arterial hypertension, with a fatal outcome. Histological features of pulmonary arterial hypertension were present at post mortem. This is the first report of histologically confirmed HIV-associated pulmonary arterial hypertension associated with pregnancy in Africa.

Rottingen JA, Chamas CI, Correa CM, Durongkaveroj P, Berrada R, Goyal LC, et al. Research and development to meet health needs in developing countries: Strengthening global financing and coordination. Report of the Consultative Expert Working Group on Research and Development: Financing and Coordination. Geneva: World Health Organization; 2012. **Full text available here.**

The Consultative Expert Working Group on Research and Development: Financing and Coordination (CEWG) was established by the World Health Assembly (WHA) in 2010 by resolution WHA63.28 with the principal task of deepening the analysis and taking forward the work done by the previous Expert Working Group on Research and Development: Coordination and Financing (EWG) which reported in 2010. Underlying both expert groups was the objective set out in the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI): “to examine current financing and coordination of research and development, as well as proposals for new and innovative sources of financing to stimulate research and development related to Type II and Type III diseases and the specific research and development needs of developing countries in relation to Type I diseases.”In undertaking our work we were mindful of the request that we “observe scientific integrity and be free from conflict of interest” in our work and we also decided to be as open and transparent as possible by providing an open forum during our first meeting, calling for submissions, providing open briefings after each of our meetings, and publishing as much as possible on our web site.

Rottingen JA, Chamas C, Goyal LC, Harb H, Lagrada L, Mayosi BM. Securing the public good of health

research and development for developing countries. Bull World Health Organ. 2012; 90(5):398–400. doi: 10.2471/blt.12.105460. **Full text available here.**

No abstract available.

Syed FF, Ntsekhe M, Wiysonge CS, Badri M, Oh JK, Mayosi BM. Atrial fibrillation as a consequence of tuberculous pericardial effusion. Int J Cardiol. 2012;158(1):152–154. doi: 10.1016/j.ijcard.2012.04.075. **Full text not freely available.**

No abstract available.

Tibazarwa K, Lee G, Mayosi B, Carrington M, Stewart S, Sliwa K. The 12-lead ECG in peripartum cardiomyopathy. Cardiovasc J Afr. 2012;23(6):322–329. doi: 10.5830/cvja-2012-006. **Full text not freely available.**

Background: The value of the 12-lead electrocardiogram (ECG) to provide prognostic information in the deadly and disabling syndrome peripartum cardiomyopathy (PPCM) is unknown.

Aims: To determine the prevalence of major and minor ECG abnormalities in PPCM patients at the time of diagnosis, and to establish whether there are ECG correlates of persistent left ventricular dysfunction and/or clinical stability at six months of follow up, where available.

Methods: Twelve-lead ECGs were performed at the point of diagnosis on 78 consecutive women presenting with PPCM to two tertiary centres in South Africa and 44 cases (56%) at the six-month follow up. Blinded Minnesota coding identified major ECG abnormalities and minor ECG changes.

Results: The cohort mainly comprised young women of black African ancestry (90%) [mean age 29 ± 7 years and median body mass index 24.3 (IQR: 22.7–27.5) kg/m^2]. The majority of cases (n = 70; 90%) presented in sinus rhythm (mean heart rate 100 ± 21 beats/min). At baseline, at least one ECG Abnormality/variant was detected in 96% of cases. Major ECG abnormalities and minor changes were detected in 49% (95% CI: 37–60%) and 62% (95% CI: 51–74%) of cases, respectively; the most common being T-wave changes (59%), p-wave abnormality (29%) and QRS-axis deviation (25%). Of the 44 cases (56%) reviewed at six months, normalisation of the 12-lead ECG occurred in 25%; the most labile ECG features being heart rate (mean reduction of 27 beats/min; $p < 0.001$) and abnormal QRS axis (36 *vs* 14%; $p = 0.014$). On an adjusted basis, major T-wave abnormalities on the baseline 12-lead ECG were associated with lower left ventricular ejection fraction (LVEF) at baseline (average of –9%, 95% CI: –1 to –16; $p = 0.03$) and at six months (–12%; 95% CI: –4 to –24; $p = 0.006$). Similarly, baseline ST-segment elevation was also associated with lower LVEF at six months (–25%; 95% CI: –0.7 to –50; $p = 0.04$).

Conclusions: In this unique study, we found that almost all women suffering from PPCM had an 'abnormal' 12-lead ECG. Pending more definitive studies, the ECG appears to be a useful adjunctive tool in both screening and prognostication in resource-poor settings.

Tibazarwa K, Sliwa K, Wonkam A, Stevens J, Boulle A, Mayosi B. Familial aggregation of dilated cardiomyopathy in patients with peripartum cardiomyopathy. Circulation. 2012;125(19):E770. **Full text not freely available.**

Introduction: Peripartum cardiomyopathy (PPCM) is a form of unexplained pregnancy-associated heart failure that is associated with considerable morbidity and mortality. Most patients present with acute postpartal heart failure that otherwise resembles the clinical presentation of dilated cardiomyopathy (DCM). Insufficient data exists to formally evaluate any genetic contribution; most being case reports of PPCM cases whose mothers or sisters had the same diagnosis. Two recent Western studies and one local study favour theories that some cases of PPCM may be part of the spectrum of familial DCM (FDCM). Objectives: We hereby report on a study of the familial aggregation of DCM in patients with PPCM.

Methods: Of prevalent and incident PPCM patients seen at two tertiary hospitals across South Africa, 51 were approached for consent to screen their first degree relatives. Consenting relatives underwent screening for DCM that included interview, clinical examination, ECG, 2D-transthoracic echocardiography, and, only in relatives thought to bear signs of DCM, the necessary additional investigations to exclude other causes of heart failure. For the sake of comparison, a subset of 9 patients manifesting hypertensive heart failure of pregnancy (HHFP; ie. pregnancy-associated heart failure with current or prior history of hypertension) also underwent family screening.

Results: A total of 18 index patients with PPCM had at least one first-degree relative who was screened for DCM. Of these, 4 index cases (22%) had confirmed familial disease (i.e., DCM on echocardiography), whilst an additional 3 (17%) had possible familial disease, (i.e., early echocardiographic signs of DCM). Of these, autosomal dominant patterns of inheritance were observed in 4 families, while 3 families displayed autosomal recessive inheritance. None of the HHFP cases had confirmed familial DCM, but one (11%) had possible familial disease; and displayed autosomal dominance.

Conclusion: Our findings support the notion that over a third of PPCM cases bear familial DCM, thus confirming the notion that PPCM is part of the spectrum of familial DCM. Our study also suggests that while HHFP are at far lower risk of familial disease, larger studies will still be needed to better quantify this risk. Detailed family history and routine family screening may be as much merited in PPCM as it is in DCM.

Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: A systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2163–2196. doi: 10.1016/S0140-6736(12)61729-2. **Full text not freely available.**

Background: Non-fatal health outcomes from diseases and injuries are a crucial consideration in the promotion and monitoring of individual and population health. The Global Burden of Disease (GBD) studies done in 1990 and 2000 have been the only studies to quantify non-fatal health outcomes across an exhaustive set of disorders at

the global and regional level. Neither eff ort quantified uncertainty in prevalence or years lived with disability (YLDs).

Methods: Of the 291 diseases and injuries in the GBD cause list, 289 cause disability. For 1160 sequelae of the 289 diseases and injuries, we undertook a systematic analysis of prevalence, incidence, remission, duration, and excess mortality. Sources included published studies, case notification, population-based cancer registries, other disease registries, antenatal clinic serosurveillance, hospital discharge data, ambulatory care data, household surveys, other surveys, and cohort studies. For most sequelae, we used a Bayesian meta-regression method, DisMod-MR, designed to address key limitations in descriptive epidemiological data, including missing data, inconsistency, and large methodological variation between data sources. For some disorders, we used natural history models, geospatial models, back-calculation models (models calculating incidence from population mortality rates and case fatality), or registration completeness models (models adjusting for incomplete registration with health-system access and other covariates). Disability weights for 220 unique health states were used to capture the severity of health loss. YLDs by cause at age, sex, country, and year levels were adjusted for comorbidity with simulation methods. We included uncertainty estimates at all stages of the analysis.

Findings: Global prevalence for all ages combined in 2010 across the 1160 sequelae ranged from fewer than one case per 1 million people to 350 000 cases per 1 million people. Prevalence and severity of health loss were weakly correlated (correlation coefficient –0·37). In 2010, there were 777 million YLDs from all causes, up from 583 million in 1990. The main contributors to global YLDs were mental and behavioural disorders, musculoskeletal disorders, and diabetes or endocrine diseases. The leading specific causes of YLDs were much the same in 2010 as they were in 1990: low back pain, major depressive disorder, iron-deficiency anaemia, neck pain, chronic obstructive pulmonary disease, anxiety disorders, migraine, diabetes, and falls. Age-specific prevalence of YLDs increased with age in all regions and has decreased slightly from 1990 to 2010. Regional patterns of the leading causes of YLDs were more similar compared with years of life lost due to premature mortality. Neglected tropical diseases, HIV/AIDS, tuberculosis, malaria, and anaemia were important causes of YLDs in sub-Saharan Africa.

Interpretation: Rates of YLDs per 100 000 people have remained largely constant over time but rise steadily with age. Population growth and ageing have increased YLD numbers and crude rates over the past two decades. Prevalences of the most common causes of YLDs, such as mental and behavioural disorders and musculoskeletal disorders, have not decreased. Health systems will need to address the needs of the rising numbers of individuals with a range of disorders that largely cause disability but not mortality. Quantification of the burden of non-fatal health outcomes will be crucial to understand how well health systems are responding to these challenges. Effective and affordable strategies to deal with this rising burden are an urgent priority for health systems in most parts of the world.

Watkins DA, Sebitloane M, Engel ME, Mayosi BM. The burden of antenatal heart disease in South Africa: a systematic review. BMC Cardiovasc Disord. 2012;12:23. doi: 10.1186/1471-2261-12-23. **Full text available here.**

Background: Maternal mortality in South Africa is rising, and heart conditions currently account for 41 per cent of indirect causes of deaths. Little is known about the burden of heart disease in pregnant South Africans.
Methods: We systematically reviewed the contemporary epidemiology and peripartum outcomes of heart disease in South African women attending antenatal care. Searches were performed in PubMed, ISI Web of Science, the EBSCO Africa-Wide database, the South African Union Catalogue, and the Current and Completed Research database (South Africa). References of included articles were also hand-searched. Studies reporting epidemiologic data on antenatal heart disease in South Africa were included. Data on morbidity and mortality were also collected.
Results: Seven studies were included in the systematic review. The prevalence of heart disease ranged from 123 to 943 per 100,000 deliveries, with a median prevalence of 616 per 100,000. Rheumatic valvular lesions were the commonest abnormalities, although cardiomyopathies were disproportionately high in comparison with other developing countries. Peripartum case-fatality rates were as high as 9.5 per cent in areas with limited access to care. The most frequent complications were pulmonary oedema, thromboembolism, and major bleeding with warfarin use. Perinatal mortality ranged from 8.9 to 23.8 per cent, whilst mitral lesions were associated with low birth weight. Meta-analysis could not be performed due to clinical and statistical heterogeneity of the included studies.
Conclusion: Approximately 0.6 per cent of pregnant South Africans have pre-existing cardiac abnormalities, with rheumatic lesions being the commonest. Maternal and perinatal morbidity and mortality continue to be very high. We conclude this review by summarising limitations of the current literature and recommending standard reporting criteria for future reports.

Wiysonge CS, Bradley HA, Volmink J, Mayosi BM, Mbewu A, Opie LH. Beta-blockers for hypertension. Cochrane Database Syst Rev. 2012;11:Cd002003. doi: 10.1002/14651858.CD002003.pub4. **Full text not freely available.**

Background: This review is an update of the Cochrane Review published in 2007, which assessed the role of beta-blockade as first-line therapy for hypertension.
Objectives: To quantify the effectiveness and safety of beta-blockers on morbidity and mortality endpoints in adults with hypertension.
Search methods: In December 2011 we searched the Cochrane Central Register of Controlled Trials, Medline, Embase, and reference lists of previous reviews; for eligible studies published since the previous search we conducted in May 2006.

Selection criteria: Randomised controlled trials (RCTs) of at least one year duration, which assessed the effects of beta-blockers compared to placebo or other drugs, as first-line therapy for hypertension, on mortality and morbidity in adults.
Data collection and analysis: We selected studies and extracted data in duplicate. We expressed study Results as risk ratios (RR) with 95% confidence intervals (CI) and combined them using the fixed-effects or random-effects method, as appropriate.
Main results: We included 13 RCTs which compared beta-blockers to placebo (4 trials, N=23,613), diuretics (5 trials, N=18,241), calcium-channel blockers (CCBs: 4 trials, N=44,825), and renin-angiotensin system (RAS) inhibitors (3 trials, N=10,828). Three-quarters of the 40,245 participants on beta-blockers used atenolol. Most studies had a high risk of bias; resulting from various limitations in study design, conduct, and data analysis. Total mortality was not significantly different between beta-blockers and placebo (RR 0.99, 95%CI 0.88 to 1.11; I^2=0%), diuretics or RAS inhibitors, but was higher for beta-blockers compared to CCBs (RR 1.07, 95%CI 1.00 to 1.14; I^2=2%). Total cardiovascular disease (CVD) was lower for beta-blockers compared to placebo (RR 0.88, 95%CI 0.79 to 0.97; I^2=21%). This is primarily a reflection of the significant decrease in stroke (RR 0.80, 95%CI 0.66 to 0.96; I^2=0%), since there was no significant difference in coronary heart disease (CHD) between beta-blockers and placebo. There was no significant difference in withdrawals from assigned treatment due to adverse events between beta-blockers and placebo (RR 1.12, 95%CI 0.82 to 1.54; I^2=66%).The effect of beta-blockers on CVD was significantly worse than that of CCBs (RR 1.18, 95%CI 1.08–1.29; I^2=0%), but was not different from that of diuretics or RAS inhibitors. In addition, there was an increase in stroke in beta-blockers compared to CCBs (RR 1.24, 95%CI 1.11–1.40; I^2=0%) and RAS inhibitors (RR 1.30, 95% CI 1.11 to 1.53; I^2=29%). However, CHD was not significantly different between beta-blockers and diuretics, CCBs or RAS inhibitors. Participants on beta-blockers were more likely to discontinue treatment due to adverse events than those on RAS inhibitors (RR 1.41, 95% CI 1.29 to 1.54; I^2=12%), but there was no significant difference with diuretics or CCBs.
Authors' conclusions: Initiating treatment of hypertension with beta-blockers leads to modest reductions in cardiovascular disease and no significant effects on mortality. These effects of beta-blockers are inferior to those of other antihypertensive drugs. The GRADE quality of this evidence is low, implying that the true effect of beta-blockers may be substantially different from the estimate of effects found in this review. Further research should be of high quality and should explore whether there are differences between different sub-types of beta-blockers or whether beta-blockers have differential effects on younger and elderly patients.

Zuhlke LJ, Karthikeyan G, Engel M, Cupido B, Joachim A, Daniels R, et al. The Rheumatic Heart Disease Global Registry (REMEDY) study: Preliminary report. Circulation. 2012;125(19):E723. **Full text not freely available.**

No abstract available.

Zuhlke L, Myer L, Mayosi BM. The promise of computer-assisted auscultation in screening for structural heart disease and clinical teaching. Cardiovasc J Afr. 2012;23(7):405–408. doi: 10.5830/cvja-2012-007. **Full text not freely available.**

Cardiac auscultation has been the central clinical tool for the diagnosis of valvular and other structural heart diseases for over a century. Physicians acquire competence in this technique through considerable training and experience. In Africa, however, we face a shortage of physicians and have the lowest health personnel-to-population ratio in the world. One of the proposed solutions for tackling this crisis is the adoption of health technologies and product innovations to support different cadres of health workers as part of task shifting. Computer-assisted auscultation (CAA) uses a digital stethoscope combined with acoustic neural networking to provide a visual display of heart sounds and murmurs, and analyses the recordings to distinguish between innocent and pathological murmurs. In so doing, CAA may serve as an objective tool for the screening of structural heart disease and facilitate the teaching of cardiac auscultation. This article reviews potential clinical applications of CAA.

2011

Bousquet J, Anto JM, Sterk PJ, Adcock IM, Chung KF, Roca J, et al. Systems medicine and integrated care to combat chronic noncommunicable diseases. Genome Med. 2011;3(7):43. doi: 10.1186/gm259. **Full text not freely available.**

We propose an innovative, integrated, cost-effective health system to combat major non-communicable diseases (NCDs), including cardiovascular, chronic respiratory, metabolic, rheumatologic and neurologic disorders and cancers, which together are the predominant health problem of the 21st century. This proposed holistic strategy involves comprehensive patient-centered integrated care and multi-scale, multi-modal and multi-level systems approaches to tackle NCDs as a common group of diseases. Rather than studying each disease individually, it will take into account their intertwined gene-environment, socio-economic interactions and co-morbidities that lead to individual-specific complex phenotypes. It will implement a road map for predictive, preventive, personalized and participatory (P4) medicine based on a robust and extensive knowledge management infrastructure that contains individual patient information. It will be supported by strategic partnerships involving all stakeholders, including general practitioners associated with patient-centered care. This systems medicine strategy, which will take a holistic approach to disease, is designed to allow the results to be used globally, taking into account the needs and specificities of local economies and health systems.

Bryer A, Mayosi B, Jacobs M, Madhari A. Bryan Kies *in memoriam*. S Afr Med J. 2011;101(11):802. **Full text not freely available.**

No abstract available.

Coltart C, Anderson I, Barh B, Dewhurst N, Donohoe J, Dukat A, et al. An international consensus for medical leadership on alcohol. Lancet. 2011;378(9798):1215. doi: 10.1016/s0140-6736(11)61461-x. **Full text not freely available.**

No abstract available.

Engel ME, Stander R, Vogel J, Adeyemo AA, Mayosi BM. Genetic susceptibility to acute rheumatic fever: A systematic review and meta-analysis of twin studies. PLoS One. 2011;6(9):e25326. doi: 10.1371/journal.pone.0025326. **Full text available here**.

Background: Acute rheumatic fever is considered to be a heritable condition, but the magnitude of the genetic effect is unknown. The objective of this study was to conduct a systematic review and meta-analysis of twin studies of concordance of acute rheumatic fever in order to derive quantitative estimates of the size of the genetic effect.

Methods: We searched PubMed/MEDLINE, ISI Web of Science, EMBASE, and Google Scholar from their inception to 31 January 2011, and bibliographies of retrieved articles, for twin studies of the concordance for acute rheumatic fever or rheumatic heart disease in monozygotic versus dizygotic twins that used accepted diagnostic criteria for acute rheumatic fever and zygosity without age, gender or language restrictions. Twin similarity was measured by probandwise concordance rate and odds ratio (OR), and aggregate probandwise concordance risk was calculated by combining raw data from each study. ORs from separate studies were combined by random-effects meta-analysis to evaluate association between zygosity status and concordance. Heritability was estimated by fitting a variance components model to the data.

Results: 435 twin pairs from six independent studies met the inclusion criteria. The pooled probandwise concordance risk for acute rheumatic fever was 44% in monozygotic twins and 12% in dizygotic twins, and the association between zygosity and concordance was strong (OR 6.39; 95% confidence interval, 3.39 to 12.06; $P<0.001$), with no significant study heterogeneity ($P = 0.768$). The estimated heritability across all the studies was 60%.

Conclusions: Acute rheumatic fever is an autoimmune disorder with a high heritability. The discovery of all genetic susceptibility loci through whole genome scanning may provide a clinically useful genetic risk prediction tool for acute rheumatic fever and its sequel, rheumatic heart disease.

Hall D, Mayosi BM, Rahman TJ, Avery PJ, Watkins HC, Keavney B. Common variation in the CD36 (fatty acid translocase) gene is associated with left-ventricular mass. J Hypertens. 2011;29(4):690–695. doi: 10.1097/HJH.0b013e3283440115. **Full text not freely available.**

Aims: Genetic variation in the fatty acid translocase (CD36) gene has been shown in animal models to affect several risk factors for the development of left-ventricular hypertrophy, but this phenotype has not, thus far, been investigated in humans. We examined the relationship between common genetic polymorphisms in the CD36 gene and left-ventricular mass.

Methods and results: We studied a cohort of 255 families comprising 1425 individuals ascertained via a hypertensive proband. Seven single-nucleotide polymorphisms which together tagged common genetic variation in the CD36 gene were genotyped using a SEQUENOM MALDI-TOF instrument. There was evidence of association between the rs1761663 polymorphism in intron 1 of the CD36 gene and left-ventricular mass determined either by echocardiography ($P=0.003$, $N=780$) or electrocardiography ($P=0.001$, $N=814$). There was also association between rs1761663 genotype and body mass index ($P<0.001$, $N=1354$). Genotype was associated with between 2 and 8% differences in these phenotypes per allele. After adjustment for the effect of body mass

index, there remained significant associations between genotype and left ventricular mass measured either by echo (P=0.017) or ECG (P=0.007).
Conclusions: Genotype at the rs1761663 polymorphism has independent effects both on body mass index and left-ventricular mass. Genes with such pleiotropic effects may be particularly attractive therapeutic targets for interventions to modify multiple risk factors for cardiovascular events.

Lemmer CE, Badri M, Visser M, Mayosi BM. A lower body mass index is associated with cardio-myopathy in people with HIV infection: Evidence from a case comparison study. S Afr Med J. 2011; 101(2):119–121. **Full text available here.**

The cause of cardiomyopathy in patients infected with the human immunodeficiency virus (HIV) remains largely unknown, although a number of predisposing factors have been identified. Malnutrition has been postulated to be a contributory factor, but the association of anthropometric measures of nutritional status with HIV-associated cardiomyopathy has not been established.
Method: We investigated the association between anthropometric measures of nutritional status and cardiomyopathy in HIV-positive individuals in a cross-sectional case comparison study.
Results: Seventeen cases of HIV-associated cardiomyopathy and a comparison group of 18 HIV-positive individuals without cardiomyopathy were studied. There was no significant difference between the two groups in age, gender, CD4 cell count, HIV RNA viral load or World Health Organization (WHO) clinical stage of HIV disease. Patients with HIV-associated cardiomyopathy had evidence of undernutrition compared with HIV-infected people without cardiomyopathy, as evidenced by a significantly lower body mass index (BMI) (20.9 kg/m^2 v. 27.0 kg/m^2, p = 0.02), mid-upper arm circumference (26.2 cm v. 27.3 cm, p = 0.02), and bone-free arm muscle area (26.7 cm^2 v. 32.8 cm^2, p = 0.02). However, in a multivariate stepwise logistic regression model, a lower BMI was the only independent anthropometric risk factor for cardiomyopathy (odds ratio 0.76, 95% confidence interval 0.64 - 0.97, p = 0.02).
Conclusion: A lower BMI is associated with cardiomyopathy in people who are living with HIV.

Madiba TE, Awotedu AA, du Plessis D, Nchabeleng M, Sathekge MM, Velaphi SC, et al. The Hamilton Naki scholarship, 2007–2011. S Afr Med J. 2011;102(1):20. **Full text available here.**

No abstract available.

Matthews K, Wilkinson KA, Kalsdorf B, Roberts T, Diacon A, Walzl G, et al. Predominance of interleukin-22 over interleukin-17 at the site of disease in human tuberculosis. Tuberculosis (Edinb). 2011;91(6):587–593. doi: 10.1016/j.tube.2011.06.009. **Full text available here.**

The inflammatory response to *Mycobacterium tuberculosis* (*M.tb*) at the site of disease is Th1 driven. Whether the

Th17 cytokines, IL-17 and IL-22, contribute to this response in humans is unknown. We hypothesized that IL-17 and IL-22 contribute to the inflammatory response in pleural and pericardial disease sites of human tuberculosis (TB). We studied pleural and pericardial effusions, established TB disease sites, from HIV-uninfected TB patients. Levels of soluble cytokines were measured by ELISA and MMP-9 by luminex. Bronchoalveolar lavage or pericardial mycobacteria-specific T cell cytokine expression was analyzed by intracellular cytokine staining. IL-17 was not abundant in pleural or pericardial fluid. IL-17 expression by mycobacteria-specific disease site T cells was not detected in healthy, *M.tb*-infected persons, or patients with TB pericarditis. These data do not support a major role for IL-17 at established TB disease sites in humans. IL-22 was readily detected in fluid from both disease sites. These IL-22 levels exceeded matching peripheral blood levels. Further, IL-22 levels in pericardial fluid correlated positively with MMP-9, an enzyme known to degrade the pulmonary extracellular matrix. We propose that our findings support a role for IL-22 in TB-induced pathology or the resulting repair process.

Ntusi NB, Badri M, Gumedze F, Wonkam A, Mayosi BM. Clinical characteristics and outcomes of familial and idiopathic dilated cardiomyopathy in Cape Town: A comparative study of 120 cases followed up over 14 years. S Afr Med J. 2011;101(6):399–404. **Full text available here.**

Background: It is not known whether there are differences in clinical characteristics and outcomes of patients with familial and idiopathic dilated cardiomyopathy (DCM) in an African setting.
Purpose: To compare the clinical characteristics and outcomes of familial and idiopathic DCM.
Methods: We performed a retrospective study of familial and idiopathic DCM at Groote Schuur Hospital, Cape Town, between 1 February 1996 and 31 December 2009. Clinical, electrocardiographic (ECG) and imaging characteristics were compared, in addition to treatment and survival.
Results: Eighty patients with idiopathic DCM and 40 familial cases were studied. ECG T-wave inversion was significantly more frequent in familial DCM (87.5%) than in idiopathic cases (68.8%) (p=0.014), whereas idiopathic patients had a higher prevalence of pathological Q waves (32.5%) than familial cases (12.5%) (p=0.028). Cardiac chambers were significantly more dilated with poorer systolic function in idiopathic than familial cases. A mortality rate of 40% after a median follow-up of 5 years was, however, similar in both groups. The presence of New York Heart Association functional class III and IV symptoms was an independent predictor of mortality (odds ratio (OR) 3.85, 95% confidence interval (CI) 1.30 – 48.47, p<0.001), while heart transplantation was an independent predictor of survival (OR 4.72, 95% CI 1.31 – 72.60, p=0.026) in both groups. Digoxin use without serum monitoring was a significant predictor of mortality in idiopathic DCM (OR 1.62, 95% CI 1.04 - 3.98, p=0.037).
Conclusion: Patients with idiopathic DCM have greater cardiac dysfunction than those with familiar disease, but mortality is similarly high in both groups. Digoxin use without drug level monitoring may be associated with increased mortality in idiopathic DCM.

Ntusi NB, Wonkam A, Shaboodien G, Badri M, Mayosi BM. Frequency and clinical genetics of familial

dilated cardiomyopathy in Cape Town: Implications for the evaluation of patients with unexplained cardiomyopathy. S Afr Med J. 2011;101(6):394–398. **Full text available here.**

Background: Studies from Europe and North America suggest that 20–50% of patients with dilated cardio-myopathy (DCM) may have familial disease. There is little information on the frequency and clinical genetics of familial DCM in Africa.

Purpose: To determine the frequency and probable mode of inheritance of familial DCM in patients referred for investigation of the cause of DCM at a tertiary centre in Cape Town.

Methods: We conducted a retrospective analysis of consecutive patients diagnosed with DCM between 1 February 1996 and 31 December 2009 to determine the frequency of familial disease.

Results: Of 109 unrelated patients with DCM, 29 (26.6%) had familial disease. Their mean age of onset of cardiomyopathy (28.01 (standard deviation (SD) 15.33) years) was significantly younger than that for non-familial cases (39.1 (SD 12.6) years) (p=0.001). Male predominance (N=21, 72.4%) and racial distribution (15 (48.3%) coloured patients, 10 (34.5%) black Africans, 4 (13.8%) white individuals, and 1 (3.4%) of Indian descent) of familial DCM probands were similar to the non-familial cases. Of the 29 patients with familial DCM, 2 (7%) had at least one relative diagnosed with peripartum cardiomyopathy. Pedigree analysis of the 29 families was consistent with autosomal dominant inheritance in 72.4%, autosomal recessive inheritance in 17.2% and X-linked recessive inheritance in 10.4%.

Conclusions: Familial DCM affects at least a quarter of African patients with DCM, presents at a young age, is associated with peripartum cardiomyopathy, and follows an autosomal dominant pattern of inheritance in the majority of families. Family screening for familial DCM is indicated in all cases of unexplained DCM, including patients with peripartum cardiomyopathy.

Rahman TJ, Mayosi BM, Hall D, Avery PJ, Stewart PM, Connell JM, et al. Common variation at the 11-β hydroxysteroid dehydrogenase type 1 gene is associated with left ventricular mass. Circ Cardiovasc Genet. 2011;4(2):156–162. doi: 10.1161/circgenetics.110.958496. **Full text not freely available.**

Background: Polymorphisms in 11-β hydroxysteroid dehydrogenase type 1 (11β-HSD1, encoded by *HSD11B1*) have been reported to be associated with obesity-related cardiovascular risk factors, such as type II diabetes and hypertension. Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular death associated with these factors but has significant additional heritability, the cause of which is undetermined. The 11β-HSD1 is believed to maintain tonic inhibition of the mineralocorticoid receptor in cardiomyocytes, and mineralocorticoid receptor activation is involved in the pathophysiology of LVH. We assessed the association between polymorphisms in the *HSD11B1* gene and left ventricular mass (LVM) in 248 families ascertained through a proband with hypertension.

Methods and results: LVM was measured by electrocardiography and echocardiography in 868 and 829

participants, respectively. Single-nucleotide polymorphisms (SNPs) tagging common variation in the *HSD11B1* gene were genotyped by mass spectrometry. The rs846910 SNP, which lies in the flanking region 5' to exon 1B of *HSD11B1*, was associated with LVM both by electrocardiography (approximately 5% lower LVM per copy of the rare allele, P=0.02) and by echocardiography (approximately 10% lower LVM per copy of the rare allele, P=0.003). Genotype explained 1% to 2% of the population variability in LVM, or approximately 5% of the heritable fraction. There were no significant associations between any *HSD11B1* SNP and blood pressure or body mass index that could have confounded the association with LVM.

Conclusions: Genotype at *HSD11B1* has a small, but significant effect on LVM, apparently independently of any effect on obesity-related traits. These findings suggest a novel action of 11β-HSD1 in the human cardiomyocyte, which may be of therapeutic importance.

Rahman TJ, Walker EA, Mayosi BM, Hall DH, Avery PJ, Connell JM, et al. Genotype at the P554L variant of the hexose-6 phosphate dehydrogenase gene is associated with carotid intima-medial thickness. PLoS One. 2011;6(8):e23248. doi: 10.1371/journal.pone.0023248. **Full text available here**.

Objective: The combined thickness of the intima and media of the carotid artery (carotid intima-medial thickness, CIMT) is associated with cardiovascular disease and stroke. Previous studies indicate that carotid intima-medial thickness is a significantly heritable phenotype, but the responsible genes are largely unknown. Hexose-6 phosphate dehydrogenase (H6PDH) is a microsomal enzyme whose activity regulates corticosteroid metabolism in the liver and adipose tissue; variability in measures of corticosteroid metabolism within the normal range have been associated with risk factors for cardiovascular disease. We performed a genetic association study in 854 members of 224 families to assess the relationship between polymorphisms in the gene coding for hexose-6 phosphate dehydrogenase (H6PD) and carotid intima-medial thickness.

Methods: Families were ascertained via a hypertensive proband. CIMT was measured using B-mode ultrasound. Single nucleotide polymorphisms (SNPs) tagging common variation in the H6PD gene were genotyped. Association was assessed following adjustment for significant covariates including "classical" cardiovascular risk factors. Functional studies to determine the effect of particular SNPs on H6PDH were performed.

Results: There was evidence of association between the single nucleotide polymorphism rs17368528 in exon five of the H6PD gene, which encodes an amino-acid change from proline to leucine in the H6PDH protein, and mean carotid intima-medial thickness (p = 0.00065). Genotype was associated with a 5% (or 0.04 mm) higher mean carotid intima-medial thickness measurement per allele, and determined 2% of the population variability in the phenotype.

Conclusions: Our results suggest a novel role for the H6PD gene in atherosclerosis susceptibility.

Shah S, Nelson CP, Gaunt TR, van der Harst P, Barnes T, Braund PS, et al. Four genetic loci influencing

electrocardiographic indices of left ventricular hypertrophy. Circ Cardiovasc Genet. 2011; 4(6):626–635. doi: 10.1161/circgenetics.111.960203. **Full text not freely available.**

Background: Presence of left ventricular hypertrophy on an ECG (ECG-LVH) is widely assessed clinically and provides prognostic information in some settings. There is evidence for significant heritability of ECG-LVH. We conducted a large-scale gene-centric association analysis of 4 commonly measured indices of ECG-LVH.

Methods and results: We calculated the Sokolow-Lyon index, Cornell product, 12-lead QRS voltage sum, and 12-lead QRS voltage product in 10 256 individuals from 3 population-based cohorts and typed their DNA using a customized gene array (the Illumina HumanCVD BeadChip 50K array), containing 49 094 genetic variants in approximately 2100 genes of cardiovascular relevance. We followed-up promising associations in 11 777 additional individuals. We identified and replicated 4 loci associated with ECG-LVH indices: 3p22.2 (*SCN5A*, rs6797133, $P=1.22 \times 10^{-7}$) with Cornell product and 12q13.3 (*PTGES3*, rs2290893, $P=3.74 \times 10^{-8}$), 15q25.2 (*NMB*, rs2292462, $P=3.23 \times 10^{-9}$), and 15q26.3 (*IGF1R*, rs4966014, $P=1.26 \times 10^{-7}$) with the 12-lead QRS voltage sum. The odds ratio of being in the top decile for the 12-lead QRS voltage sum for those carrying 6 trait-raising alleles at the 12q13.3, 15q25.2, and 15q26.3 loci versus those carrying 0 to 1 alleles was 1.60 (95% CI: 1.20 to 2.29). Lead single-nucleotide polymorphisms at the 12q13.3 and 15q25.2 loci showed significant expression quantitative trait loci effects in monocytes.

Conclusions: These findings provide novel insights into the genetic determination of ECG-LVH. The findings could help to improve our understanding of the mechanisms determining this prognostically important trait.

Watkins D, Omokhodion SI, Mayosi BM. The history of the Pan-African Society of Cardiology (PASCAR): the first 30 years, 1981–2011. Cardiovasc J Afr. 2011;22(3):122–123. **Full text not freely available.**

The year 2011 marks the 30th anniversary of the founding of the Pan-African Society of Cardiology (PASCAR). Throughout its brief history, PASCAR has been integral to improving the cardiovascular health of the people of Africa. During the past three decades, many African countries have been vulnerable to political and social turmoil, and PASCAR itself has been repeatedly challenged to press on with its mission, in spite of innumerable practical obstacles. This article celebrates the hard work and dedication of PASCAR's founders and subsequent leaders, and challenges the present and future generations to carry on the charge of furthering the health of Africans.

2010

Colquhoun S, Steer A, Mayosi B, Karthikeyan G, Mensah G, Carapetis J. The global burden of rheumatic heart disease. Circulation. 2010;122(2):E236. **Full text not freely available.**

Background: Rheumatic heart disease (RHD) remains the most common cardiovascular disease affecting children and young people globally. Up to 15 million people live with RHD. The annual mortality from RHD has previously been estimated to be in excess of 300,000, while approximately 460,000 new cases are diagnosed annually. The burden of RHD lies almost exclusively in developing countries. In 1990 the Global Burden of Disease study published population based data showing estimates of RHD prevalence, incidence and mortality. Since that time a number of important population based studies have been published. Although the number of new studies are relatively few, most of them have used echocardiography as the primary diagnostic tool, resulting in much more accurate estimates of disease burden than previously published.

Objective: Describe the epidemiology for a comprehensive reassessment of RHD burden in 21 regions of the world for the period 1980 and 2008.

Methods: A systematic review of RHD population based data is currently underway. A Medline search of peer reviewed publications found 126 studies that fit the inclusion criteria for review. These papers are currently being reviewed by a panel of experts. As the number of published population based studies is limited the RHD writing group is currently seeking more comprehensive information by requesting grey data from regional and national registers, reports and theses to attempt to provide a more accurate estimate of the true burden of disease.

Results: Data for all regions has not been collated at the time of abstract submission; however comprehensive data for all 21 regions will be presented. A recent review of the global disease burden showed that although the regional estimates for prevalence in school-aged children may not be as high as previously published studies in sub-Saharan Africa, the total burden of cases (between 10.8 and 15.9 million cases in all ages) and deaths (356 000 to 524 000 each year) is higher than seen in the 1990 review. The two most rigorously performed studies in Asia, from Pakistan and Cambodia, confirm that careful research methodology will uncover many more cases than would otherwise have been detected. These recent data suggest that there is an immense unrecognized burden of RHD, and a need for high-quality epidemiological studies in developing countries. Mortality data is particularly difficult to qualify as there are only two studies (from Ethiopia and Fiji) that calculate population based mortality rates.

Conclusion: Estimations of RHD burden are hampered by the fact that this disease is largely restricted to low and middle income countries, where accurate epidemiological data are often lacking. School surveys and registers suggest that sub-Saharan Africa, South Asia and the Pacific have particularly high prevalence rates and mortality.

Cunnington M, Koref MS, Mayosi B, Burn J, Keavney B. Modulation of anril expression may mediate the association of chromosome 9p21 variants with coronary artery disease and stroke. Atherosclerosis Supplements. 2010;11(2):22. doi: 10.1016/s1567-5688(10)70093-3. **Full text not freely available.**

Introduction: Single nucleotide polymorphisms (SNPs) on chromosome 9p21 are associated with coronary artery disease and stroke. The mechanisms mediating the association are unknown, but risk SNPs are mainly non-coding and may influence gene expression.

Aim: To investigate whether 9p21 SNPs are associated with expression of the three nearest genes; the cell-cycle inhibitors CDKN2A/2B and a non-coding RNA of unknown function, ANRIL.

Methods: We examined association between 56 SNPs in the region and peripheral blood expression of CDKN2A/B and ANRIL in 495 healthy volunteers, using allelic and total expression. Association between SNPs and expression was assessed using likelihood ratio tests.

Results: Total expression of the three genes was correlated ($P < 0.05$), suggesting they are co-regulated. Allelic expression was also correlated ($P < 0.05$), suggesting shared cis-acting elements. SNP effects mapped by allelic and total expression were similar ($r = 0.96$, $P = 2\times10^{-92}$), but the power to detect effects was greater for allelic expression. The proportion of expression variance attributable to cis-acting effects was 8% for CDKN2A, 5% for CDKN2B, and 20% for ANRIL. Multiple SNPs were independently associated with expression of each gene ($P < 0.01$), suggesting that several sites may modulate disease susceptibility. Risk SNPs were all highly associated ($P < 1\times10^{-7}$) with up to 1.9-fold reduction in ANRIL expression, whilst association with the other two genes was only detectable for some. SNPs had an inverse effect on ANRIL and CDKN2B expression, suggesting a possible role of ANRIL in CDKN2B regulation.

Conclusions: Modulation of ANRIL expression may mediate susceptibility to atherosclerosis.

Cunnington MS, Koref MS, Mayosi B, Burn J, Keavney B. Modulation of anril expression may mediate the association between chromosome 9p21 variants and coronary atherosclerosis risk. Heart. 2010;96:A2. doi: 10.1136/hrt.2010.196113.16. **Full text not freely available.**

Introduction: Single nucleotide polymorphisms (SNPs) on chromosome 9p21 are associated with coronary artery disease, stroke, diabetes and several cancers. The mechanisms mediating these associations are unknown, but risk variants are mainly non-coding and may act through regulation of gene expression in cis. We investigated whether 9p21 SNPs were associated with total and allelic expression of the three nearest genes; the cell-cycle inhibitors CDKN2A/CDKN2B, and a non-coding RNA of unknown function, ANRIL.

Methods: We genotyped 56 SNPs, selected to tag the common variation in the region and include SNPs with reported functional effects. We studied peripheral blood expression in two populations of healthy volunteers: 177 British Caucasians and 310 mixed-ancestry South Africans. Total expression was measured using TaqMan real-time PCR. Allelic expression was quantified by mass spectrometry (Sequenom) and analysed by novel methodology using data from two transcribed SNPs per gene. Association between mapping SNPs and expression

was assessed using likelihood ratio tests.
Results: Total expression of CDKN2A, CDKN2B and ANRIL was correlated ($p<0.05$), suggesting that they are co-regulated. Allelic expression was also correlated ($p<0.05$), suggesting that transcription is influenced by shared cis acting elements. SNP associations mapped by total and allelic expression were similar ($r=0.96$, $p=2\times10^{-92}$), but the power to detect effects was greater for allelic expression, indicating the presence of substantial trans-acting effects on expression. The proportion of expression variance attributable to cis-acting effects was 8% for CDKN2A, 5% for CDKN2B, and 20% for ANRIL. SNP associations were similar in the two populations ($r=0.94$, $p=1\times10^{-72}$) which permitted analysis of the combined dataset (Abstract C figure 1). Multiple SNPs were independently associated with expression of each gene ($p<0.01$), suggesting that several sites may modulate disease susceptibility. Risk SNPs for coronary disease and stroke were all highly associated with allelic expression of ANRIL (all $p<1\times10^{-7}$), whilst association with the other two genes was only detectable for some. Risk alleles all correlated with ANRIL under-expression (up to 1.9-fold). Individual SNPs were associated with opposite effects on ANRIL and CDKN2B expression, suggesting a possible role of ANRIL in CDKN2B regulation.

Cunnington MS, Santibanez Koref M, Mayosi BM, Burn J, Keavney B. Chromosome 9p21 SNPs associated with multiple disease phenotypes correlate with *ANRIL* expression. PLoS Genet. 2010; 6(4):e1000899. doi: 10.1371/journal.pgen.1000899. **Full text available here**.

Single nucleotide polymorphisms (SNPs) on chromosome 9p21 are associated with coronary artery disease, diabetes, and multiple cancers. Risk SNPs are mainly non-coding, suggesting that they influence expression and may act in *cis*. We examined the association between 56 SNPs in this region and peripheral blood expression of the three nearest genes *CDKN2A, CDKN2B*, and *ANRIL* using total and allelic expression in two populations of healthy volunteers: 177 British Caucasians and 310 mixed-ancestry South Africans. Total expression of the three genes was correlated ($P<0.05$), suggesting that they are co-regulated. SNP associations mapped by allelic and total expression were similar ($r = 0.97$, $P = 4.8\times10^{-99}$), but the power to detect effects was greater for allelic expression. The proportion of expression variance attributable to cis-acting effects was 8% for *CDKN2A*, 5% for *CDKN2B*, and 20% for *ANRIL*. SNP associations were similar in the two populations ($r = 0.94$, $P = 10^{-72}$). Multiple SNPs were independently associated with expression of each gene ($P<0.05$ after correction for multiple testing), suggesting that several sites may modulate disease susceptibility. Individual SNPs correlated with changes in expression up to 1.4-fold for *CDKN2A*, 1.3-fold for *CDKN2B*, and 2-fold for *ANRIL*. Risk SNPs for coronary disease, stroke, diabetes, melanoma, and glioma were all associated with allelic expression of *ANRIL* (all $P<0.05$ after correction for multiple testing), while association with the other two genes was only detectable for some risk SNPs. SNPs had an inverse effect on *ANRIL* and *CDKN2B* expression, supporting a role of antisense transcription in *CDKN2B* regulation. Our study suggests that modulation of *ANRIL* expression mediates susceptibility to several important human diseases.

Gersh BJ, Sliwa K, Mayosi BM, Yusuf S. Novel therapeutic concepts: the epidemic of cardiovascular disease in the developing world: global implications. Eur Heart J. 2010;31(6):642–648. doi: 10.1093/eurheartj/ehq030. **Full text available here.**

The epidemic of cardiovascular disease (CVD) is a global phenomenon, and the magnitude of its increase in incidence and prevalence in low- and middle-income countries (LIMIC) has potentially major implications for those high-income countries that characterize much of the developed world. Cardiovascular disease remains the leading cause of death in the world and approximately 80% of all cardiovascular-related deaths occur in LIMIC and at a younger age in comparison to high-income countries. The economic impact in regard to loss of productive years of life and the need to divert scarce resources to tertiary care is substantial. The 'epidemiologic transition' provides a useful framework for understanding changes in the patterns of disease as a result of societal and socioeconomic developments in different countries and regions of the world. A burning but as yet unanswered question is whether gains made over the last four decades in reducing cardiovascular mortality in high-income countries will be offset by changes in risk factor profiles, and in particular obesity and diabetes. Much of the population attributable risk of myocardial infarction is accountable on the basis of nine modifiable traditional risk factors, irrespective of geography. Developing societies are faced with a hostile cardiovascular environment, characterized by changes in diet, exercise, the effects of tobacco, socioeconomic stressors, and economic constraints at both the national and personal level in addition to exposure to potential novel risk factors and perhaps a genetic or programmed foetal vulnerability to CVD in later life. There are major challenges for primary and secondary prevention including lack of data, limited national resources, and the lack of prediction models in certain populations. There are two major approaches to prevention: public health/community-based strategies and clinic-based with a targeted approach to high-risk patients and combinations of these. There are concerns that in comparison with communicable diseases, cardiovascular and chronic diseases have a relatively low priority in the global health agenda and that this requires additional emphasis.

The human race has had long experience and a fine tradition in surviving adversity, but we now face a task for which we have little experience, the task of surviving prosperity. Alan Gregg 1890–1957, Rockefeller Foundation.

Hendricks N, Watkins DA, Mayosi BM. Lessons from the first report of the Arrhythmogenic Right Ventricular Cardiomyopathy Registry of South Africa. Cardiovasc J Afr. 2010;21(3):129–130. **Full text not freely available.**

No abstract available.

Imazio M, Brucato A, Mayosi BM, Derosa FG, Lestuzzi C, Macor A, et al. Medical therapy of pericardial diseases: Part I: Idiopathic and infectious pericarditis. J Cardiovasc Med (Hagerstown). 2010;11(10):712–722. doi: 10.2459/JCM.0b013e3283340b97. **Full text not freely available.**

The treatment of pericardial diseases is largely empirical because of the relative lack of randomized trials compared with other cardiovascular diseases. The main forms of pericardial diseases that can be encountered in the clinical setting include acute and recurrent pericarditis, pericardial effusion with or without cardiac tamponade, and constrictive pericarditis. Medical treatment should be targeted at the cause of the disease as much as possible. However, the cause of pericardial diseases may be varied and depends on the prevalence of specific diseases (especially tuberculosis). The search for an etiology is often inconclusive, and most cases are classified as idiopathic in developed countries where tuberculosis is relatively rare, whereas a tuberculous etiology is often presumed in developing countries where tuberculosis is endemic. The aim of the present article is to review current medical therapy for pericardial diseases, highlighting recent significant advances in clinical research, ongoing challenges and unmet needs. Following a probabilistic approach, the most common causes are considered (idiopathic, viral, tuberculous, purulent, connective tissue diseases and neoplastic pericardial disease). In this article, the therapy of idiopathic and more common forms of infectious pericarditis (viral and bacterial) is reviewed.

Imazio M, Brucato A, Mayosi BM, Derosa FG, Lestuzzi C, Macor A, et al. Medical therapy of pericardial diseases: Part II: Noninfectious pericarditis, pericardial effusion and constrictive pericarditis. J Cardiovasc Med (Hagerstown). 2010;11(11):785–794. **Full text not freely available.**

The treatment of pericardial diseases is largely empirical because of the relative lack of randomized trials compared with other cardiovascular diseases. The main forms of pericardial diseases that can be encountered in the clinical setting include acute and recurrent pericarditis, pericardial effusion with or without cardiac tamponade, and constrictive pericarditis. Medical treatment should be targeted at the cause as much as possible. In this article, the therapy of more common forms of noninfectious pericarditis (pericarditis in systemic autoimmune diseases and neoplastic pericardial disease), pericardial effusion, and constrictive pericarditis is reviewed.

Imazio M, Mayosi BM, Brucato A, Adler Y. Pericardial effusion triage. Int J Cardiol. 2010; 145(2):403–404. doi: 10.1016/j.ijcard.2010.04.031. **Full text not freely available.**

Isolated pericardial effusion is a common finding in clinical practice, and may be detected by chance during echocardiography in a patient otherwise asymptomatic or following a diagnostic imaging study in a patient with correlated symptoms (e.g. dyspnea, asthenia, chest pain, and palpitations).

Imazio M, Mayosi BM, Brucato A, Markel G, Trinchero R, Spodick DH, et al. Triage and management of pericardial effusion. J Cardiovasc Med (Hagerstown). 2010;11(12):928–935. doi: 10.2459/JCM.0b013e32833e5788. **Full text not freely available.**

Pericardial effusion may be detected as an incidental finding during echocardiography or following a diagnostic imaging study for a symptomatic patient. When a pericardial effusion is detected the first step is to assess its size, hemodynamic importance, and possible associated diseases. The more common causes of pericardial effusions include infections (viral, bacterial, especially tuberculosis), cancer, connective tissue diseases, pericardial injury syndromes, metabolic causes (i.e. hypothyroidism), myopericardial and aortic diseases. The relative frequency of different causes depends on the local epidemiology, the hospital setting and the diagnostic protocol that has been adopted. Many cases still remain idiopathic in developed countries, whereas tuberculosis is the dominant cause in developing countries. Specific testing should be performed according to clinical suspicion. The presence of elevated inflammatory markers and other criteria (chest pain, pericardial rubs, ECG changes) suggest pericarditis and management should be directed accordingly. Treatment should be targeted at the etiology as much as possible. Nevertheless, when diagnosis is still unclear, or idiopathic and inflammatory markers are elevated, empiric anti-inflammatory therapy may be worthwhile. A true isolated effusion may not require a specific treatment if the patient is asymptomatic, but large ones have a theoretical risk of progression to cardiac tamponade (up to one-third) if subacute with signs of right-sided collapse, and especially chronic (>3 months). Pericardiocentesis alone may be curative for large effusions but recurrences are also common and pericardiectomy or less invasive options (i.e. pericardial window) should be considered whenever fluid re-accumulates (especially with tamponade), becomes loculated, or biopsy material is required.

Karthikeyan G, Mayosi BM. Response to Letter regarding Article, "Is primary prevention of rheumatic fever the missing link in the control of rheumatic heart disease in Africa?". Circulation. 2010; 121(15):e385. doi: 10.1161/CIR.0b013e3181dbdf0b. **Full text not freely available.**

No abstract available.

Kiechl S, Laxton RC, Xiao Q, Hernesniemi JA, Raitakari OT, Kahonen M, et al. Coronary artery disease-related genetic variant on chromosome 10q11 is associated with carotid intima-media thickness and atherosclerosis. Arterioscler Thromb Vasc Biol. 2010;30(12):2678–2683. doi: 10.1161/atvbaha.110.213785. **Full text not freely available.**

Objective: To investigate whether chromosome 10q11.21 influences common carotid intima-media thickness (IMT) and atherosclerosis and whether it is associated with stromal cell-derived factor-1α (SDF-1α) plasma levels. Methods and results: Variation on chromosome 10q11.21 has been consistently associated with coronary artery disease. The genetic variant lies upstream of the gene encoding SDF-1 α. We genotyped 3 population cohorts (Bruneck [age range, 45 to 94 years; 50.0% men; n=738], Health2000 [age range, 46 to 76 years; 55.4% men; n=1237], and essential hypertension in families collected in the region of Oxford [HTO] [age range, 19 to 88 years; 47.9% men; n=770]) for single-nucleotide polymorphism *rs501120* at the 10q11.21 locus and conducted a

meta-analysis in these cohorts to ascertain a relationship between the polymorphism and carotid IMT. The analysis showed that individuals with the *T/T* genotype had a significantly higher carotid IMT than individuals with the *C/T* or *C/C* genotype (pooled weighted mean difference, 23 μm [95% CI, 9 to 37 μm], P=0.0014 under a fixed-effects model; and 23 μm [95% CI, 6 to 41 μm], P=0.009 under a random-effects model). In the Bruneck cohort, in which data for carotid atherosclerosis and plasma SDF-1 α levels were available, we observed an association of the *T/T* genotype with a higher burden of atherosclerosis and increased susceptibility to the development of atherosclerosis during a 5-year follow-up (multivariable odds ratio, 1.73 [95% CI, 1.18 to 2.52]; P=0.005 for the recessive model) and an association between the *T/T* genotype and lower SDF-1α levels (2.62 ng/mL for *T/T* versus 2.74 ng/mL for *C/C* or *C/T*; P=0.023).

Conclusions: The coronary heart disease-related variant at the 10q11.21 locus is associated with carotid IMT and atherosclerosis.

Lemmer C, Mayosi B. HIV Cardiomyopathy is associated with a low body mass index: evidence from a case-comparison study. Circulation. 2010;122(2):E130. **Full text not freely available.**

Introduction: The cause of cardiomyopathy patients infected with human immunodeficiency virus (HIV) remains largely unknown, although a number of predisposing factors have been identified. Malnutrition has been postulated as a contributory factor but the association of malnutrition with HIV-associated cardiomyopathy has not been established in prospective studies.

Method: We prospectively investigated the association between nutritional state measured by anthropometric measures of lean body mass and HIV positive individuals with and without cardiomyopathy.

Results: 17 cases of HIV-associated cardiomyopathy (HIVAC) and a comparison group of 18 HIV positive patients without heart disease were recruited. There were no significant differences in age, CD4 cell count, HIV RNA viral load and WHO clinical stage of HIV disease between the two groups. HIVAC cases had evidence of malnutrition compared to those without cardiomyopathy: a significantly lower Body Mass Index (cases: 20.9kg/m^2; controls: 27.0kg/m^2; P=0.02), Mid-Upper Arm Circumference (cases: 26.2cm; controls: 27.3cm; P=0.02), and Bone Free Arm Muscle Area (cases: 26.7cm^2; controls: 32.8cm^2; P=0.02). However, in a multi-variate step-wise logistic regression model, body mass index (BMI) was the only independent anthropometric risk factor for cardiomyopathy (odds ratio=0.73 95%CI 0.64–0.97, p=0.02).

Conclusion: Cardiomyopathy is associated with a lower BMI in people who are living with HIV.

Mayosi B. The four pillars of rheumatic heart disease control. S Afr Med J. 2010;100(8):506. **Full text available here.**

No abstract available.

Mayosi BM. The UCT Department of Medicine at 90 years – continuity and change. S Afr Med J. 2010;100(9):548, 550. **Full text available here.**

No abstract available.

Mayosi BM, Commerford PJ. Rheumatic heart disease: Prevention and acute treatment. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, editors. Evidence-based cardiology. 3rd ed. Chichester, West Sussex (UK): Wiley; 2010. p. 859–868. **Full text not freely available.**

No abstract available.

Ntusi NBA, Mayosi BM. Risk factors for disease development and predictors of outcome in peripartum cardiomyopathy. Eur Heart J. 2010;31:27. **Full text not freely available.**

Background: Risk factors for development of peripartum cardiomyopathy (PPCM) are poorly understood. Reports on outcome of PPCM are conflicting, with variable mortality rates reported by different authors.

Purpose: To define the risk factors for development of PPCM and the predictors of survival outcome in PPCM.

Methods: Retrospective analysis of the medical records of patients diagnosed with PPCM at the Groote Schuur Hospital Cardiac Clinic, South Africa, between February 1 1996 and December 31 2009. Diagnosis of PPCM was based on development of heart failure between the last month of pregnancy and fifth postpartum month in women without pre-existing heart disease, or any other identifiable cause of heart failure, including pregnancy-induced hypertension. Patients also needed to fulfill established echocardiographic criteria for diagnosis. Measurements from clinical assessment, chest radiography, electrocardiography, twodimensional and Doppler colour-flow echocardiography and cardiac catheterisation (where available) were reviewed.

Results: There were 30 PPCM patients studied, with a mean age of 31.45±7.48 years. Ethnicity, gravidity, parity, and unemployment were not associated with increased risk of developing PPCM in this study. However, twin pregnancy emerged as a significant risk factor for disease development in PPCM ($p<0.001$). The median follow-up was 4.33 years (range 0.16 – 13.8). During the study period 5 (16.6%) subjects died and 24 (80%) patients remained in chronic heart failure. Complications included intra-cardiac thrombus formation (16.7%), atrial fibrillation (10.0%), stroke (6.7%), and pulmonary hypertension (13.3%). One patient had cardiac resynchronisation therapy and another patient had orthotopic heart transplantation. Predictors of increased mortality in the time-to-event analysis included twin pregnancy ($p<0.001$), heart rate greater than 120 bpm at first clinic visit ($p=0.017$), presence of atrial fibrillation ($p=0.023$), use of warfarin ($p=0.019$), and NYHA functional class III and IV symptoms at last visit ($p=0.005$). On multivariate logistic regression analysis only NYHA functional class III/IV status at last visit was a significant predictor of mortality (OR 3.107 [1.329 – 11.981], $p=0.047$).

Conclusions: PPCM affects young women, with significant morbidity and mortality. Mortality in this study is

lower than in many other previously reported studies. Twin pregnancy is a risk factor for development of PPCM. The NYHA functional class emerges as a powerful predictor of mortality in this study.

Okpechi IG, Rayner BL, van der Merwe L, Mayosi BM, Adeyemo A, Tiffin N, et al. Genetic variation at selected SNPs in the leptin gene and association of alleles with markers of kidney disease in a Xhosa population of South Africa. PLoS One. 2010;5(2):e9086. doi: 10.1371/journal.pone.0009086. **Full text available here**.

Background: Chronic kidney disease (CKD) is a significant public health problem that leads to end-stage renal disease (ESRD) with as many as 2 million people predicted to need therapy worldwide by 2010. Obesity is a risk factor for CKD and leptin, the obesity hormone, correlates with body fat mass and markers of renal function. A number of clinical and experimental studies have suggested a link between serum leptin and kidney disease. We hypothesised that variants in the *leptin* gene (*LEP*) may be associated with markers of CKD in indigenous black Africans.

Methodology/principal findings: Black South Africans of Xhosa (distinct cultural Bantu-speaking population) descent were recruited for the study and four common polymorphisms of the *LEP* (rs7799039, rs791620, rs2167270 and STS-U43653 [ENSSNP5824596]) were analysed for genotype and haplotype association with urine albumin-to-creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), Serum creatinine (Scr) and serum leptin level. In one of the four single nucleotide polymorphisms (SNPs) we examined, an association with the renal phenotypes was observed. Hypertensive subjects with the T allele (CT genotype) of the ENSSNP5824596 SNP had a significantly higher eGFR ($p = 0.0141$), and significantly lower Scr ($p = 0.0137$). This was confirmed by haplotype analysis. Also, the haplotype GAAC had a modest effect on urine albumin-to-creatinine ratio in normotensive subjects ($p = 0.0482$).

Conclusions/significance: These results suggest that genetic variations of the *LEP* may be associated with phenotypes that are markers of CKD in black Africans.

Sliwa K, Carrington M, Mayosi BM, Zigiriadis E, Mvungi R, Stewart S. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: Insights from the heart of Soweto study. Eur Heart J. 2010;31(6):719–727. doi: 10.1093/eurheartj/ehp530. **Full text available here.**

Aims: Little is known on the incidence and clinical characteristics of newly diagnosed rheumatic heart disease (RHD) in adulthood from urban African communities in epidemiologic transition.

Methods and Results: Chris Hani Baragwanath Hospital services the black African community of 1.1 million people in Soweto, South Africa. A prospective, clinical registry captured data from all de novo cases of structural

and functional valvular heart disease (VHD) presenting to the Cardiology Unit during 2006/07. We describe in detail all cases with newly diagnosed RHD. There were 4005 de novo presentations in 2006/07 and 960 (24%) had a valvular abnormality. Of these, 344 cases (36%) were diagnosed with RHD. Estimated incidence of new cases of RHD for those aged >14 years in the region was 23.5 cases/100 000 per annum. Most were black African females (n = 234 -68%) with a similar age profile to males [median 41 (interquartile range 30–55) years *vs.* 42 (interquartile range 31–55) years]. The predominant valvular lesion (n = 204, 59%) was mitral regurgitation (MR), with 48 (14%) and 43 (13%) cases, respectively, having combination lesions of aortic plus MR and mixed mitral VHD. Impaired systolic function was found in 28/204 cases (14%) of predominant MR and in 23/126 cases (18%) with predominant aortic regurgitation. Elevated right ventricular systolic pressure >35 mmHg (62 cases), atrial fibrillation (34 cases), and anaemia (27 cases) were found in 18, 10, and 8% of 344 RHD cases, respectively. Subsequent valve replacement/repair was performed in 75 patients (22%). A total of 90 cases (26%) were admitted within 30 months of initial diagnosis for suspected bacterial endocarditis.
Conclusion: These data reveal a high incidence of newly diagnosed RHD within an adult urban African community. These data argue strongly for the first episode of RHD to be made a notifiable condition in high burden countries in order to ensure control of the disease through register-based secondary prophylaxis programmes.

Syed FF, Mayosi BM. Pericardial disease: An evidence-based approach to clinical management. In: Yusuf S, Cairns JA, Camm AJ, Fallen EL, Gersh BJ, editors. Evidence-based cardiology. 3rd ed. Chichester, West Sussex (UK): Wiley; 2010. p. 843–858. **Full text not freely available.**

No abstract available.

Syed FF, Ntsekhe M, Mayosi BM. Tailoring diagnosis and management of pericardial disease to the epidemiological setting. Mayo Clin Proc. 2010;85(9):866. doi: 10.4065/mcp.2010.0377. **Full text not freely available.**

No abstract available.

Watkins D, Hendricks N, Vezi B, Little F, Badri M, Okreglicki A, et al. Survival of patients with arrhythmogenic right ventricular cardiomyopathy is similar to a population with a large burden of HIV/AIDS: Evidence from the ARVC Registry of South Africa. Circulation. 2010;122(2):E38. **Full text not freely available.**

No abstract available.

2009

Alvarez-Madrazo S, Padmanabhan S, Mayosi BM, Watkins H, Avery P, Wallace AM, et al. Familial and phenotypic associations of the aldosterone Renin ratio. J Clin Endocrinol Metab. 2009; 94(11):4324–4333. doi: 10.1210/jc.2009-1406. **Full text not freely available.**

Context: The aldosterone to renin ratio (ARR) is a marker of aldosterone excess, widely used to screen for primary aldosteronism (PA). The significance of a raised ARR in normotensive and hypertensive subjects and the phenotypic and familial factors affecting it are unclear.
Objective: We estimated the distribution and heritability of the ARR and tested for associations between ARR and blood pressure (BP) with 11 polymorphisms at the *CYP11B1/CYP11B2* locus.
Design and setting: A total of 1172 individuals from 248 Caucasian families ascertained via a hypertensive proband were evaluated.
Main outcome measure: Plasma aldosterone was measured by RIA, and plasma renin concentration was measured by the LIAISON Direct Renin chemiluminescent immunoassay.
Results: Unadjusted and adjusted ARR were continuously distributed in normotensives and hypertensives, with no evidence of a cutoff that would identify a separate population with PA. Median ARR was 4.19 ng/liter per mIU/liter (range, 0.04–253.16). ARR levels were higher in females and associated with age, body mass index, and potassium. Antihypertensive agents had significant predictable effects on the ARR. Renin was negatively associated, and ARR was positively associated with ambulatory BP readings ($P<0.001$) in subjects not taking antihypertensives. The heritability of the ARR was 38.1% ($P<10^{-8}$). Plasma aldosterone, but not ARR, was influenced by the intron 2 conversion variation in the *CYP11B2* gene ($\beta = -0.07$; $P = 0.04$).
Conclusions: The ARR is continuously distributed, is influenced by genetic and environmental factors, and is not a marker of a distinct pathological abnormality but possibly reflects the long-term influence of aldosterone on cardiovascular homeostasis.

Chopra M, Lawn JE, Sanders D, Barron P, Karim SSA, Bradshaw D, et al. Achieving the health Millennium Development Goals for South Africa: Challenges and priorities. Lancet. 2009; 374(9694):1023–1031. doi: 10.1016/s0140-6736(09)61122-3. **Full text not freely available.**

15 years after liberation from apartheid, South Africans are facing new challenges for which the highest calibre of leadership, vision, and commitment is needed. The effect of the unprecedented HIV/AIDS epidemic has been immense. Substantial increases in mortality and morbidity are threatening to overwhelm the health system and undermine the potential of South Africa to attain the Millennium Development Goals (MDGs). However The Lancet's Series on South Africa has identified several examples of leadership and innovation that point towards a different future scenario. We discuss the type of vision, leadership, and priority actions needed to achieve such a change. We still have time to change the health trajectory of the country, and even meet the MDGs. The South African Government, installed in April, 2009, has the mandate and potential to address the public health emergencies facing the country – will they do so or will another opportunity and many more lives be lost?

Cunnington MS, Kay C, Avery PJ, Mayosi BM, Koref MS, Keavney B. *STK39* polymorphisms and blood pressure: an association study in British Caucasians and assessment of *cis*-acting influences on gene expression. BMC Med Genet. 2009;10:135. doi: 10.1186/1471-2350-10-135. **Full text available here.**

Background: Blood pressure (BP) has significant heritability, but the genes responsible remain largely unknown. Single nucleotide polymorphisms (SNPs) at the *STK39* locus were recently associated with hypertension by genome-wide association in an Amish population; *in vitro* data from transient transfection experiments using reporter constructs suggested that altered *STK39* expression might mediate the effect. However, other large studies have not implicated *STK39* in hypertension. We determined whether reported SNPs influenced *STK39* expression *in vivo*, or were associated with BP in a large British Caucasian cohort.

Methods: 1372 members of 247 Caucasian families ascertained through a hypertensive proband were genotyped for reported risk variants in *STK39* (rs6749447, rs3754777, rs35929607) using Sequenom technology. MERLIN software was used for family-based association testing. *Cis*-acting influences on expression were assessed in *vivo* using allelic expression ratios in cDNA from peripheral blood cells in 35 South African individuals heterozygous for a transcribed SNP in *STK39* (rs1061471) and quantified by mass spectrometry (Sequenom).

Results: No significant association was seen between the SNPs tested and systolic or diastolic BP in clinic or ambulatory measurements (all $p > 0.05$). The tested SNPs were all associated with allelic expression differences in peripheral blood cells ($p < 0.05$), with the most significant association for the intronic SNP rs6749447 ($P = 9.9 \times 10^{-4}$). In individuals who were heterozygous for this SNP, on average the G allele showed 13% overexpression compared to the T allele.

Conclusions: *STK39* expression is modified by polymorphisms acting in *cis* and the typed SNPs are associated with allelic expression of this gene, but there is no evidence for an association with BP in a British Caucasian cohort.

Cunnington MS, Koref MS, Mayosi BM, Burn J, Keavney B. Modulation of anril expression is a possible mechanism mediating the association between chromosome 9p21 polymorphisms and coronary

atheresclerosis risk. Circulation. 2009;120(18(Supplement)):S564. **Full text not freely available**

Background: Several recent studies have shown an association between single nucleotide polymorphisms (SNPs) on chromosome 9p21 and coronary artery disease (CAD) risk. These SNPs are outside any known coding region and the mechanisms mediating the association are still unknown. One possibility is that it reflects polymorphisms in factors affecting expression of adjacent genes in *cis*. We therefore investigate whether 9p21 SNPs are associated with allelic expression in *cis* of genes in this region, namely the two cell-cycle inhibitors (CDKN2A and 2B) and an antisense non-coding RNA of unknown function (ANRIL).

Methods: We genotyped 54 SNPs in a 270kb region in two cohorts of healthy volunteers (178 Caucasians and 309 mixed ancestry South Africans). *Cis*-acting effects were assessed by allelic expression ratios in cDNA from peripheral blood in individuals heterozygous for at least one of two transcribed SNPs tested for each gene. Allelic ratios were quantified by mass spectrometry and the association between the SNPs and allelic expression assessed using novel methods that allow combining data from several transcribed SNPs. 192, 185 and 202 individuals were informative for CDKN2A, 2B and ANRIL respectively.

Results: Allelic expression of CDKN2A, 2B and ANRIL is correlated ($p<0.05$) and influenced by *cis*-acting factors. Patterns in the two cohorts were similar. For each gene several SNPs were associated with expression ($p<10^{-6}$ in the combined data set); some of the functional SNPs are shared whilst others are specific for particular genes. For example, CDKN2A promoter SNPs are independently associated with CDKN2A and 2B expression ($p<10^{-4}$) but not with ANRIL expression. Lead CAD SNPs (rs1333049, rs10757278 and rs2383206) are associated with ANRIL expression ($p<10^{-9}$), but not with CDKN2A/2B. Other SNPs within the CAD risk haplotype (rs496892 and rs7044859) are associated with allelic expression of all three genes ($p<10^{-3}$). CAD risk SNPs correlate with ANRIL under-expression.

Conclusions: CDKN2A, 2B and ANRIL expression is influenced by multiple *cis*-acting SNPs. CAD risk SNPs are highly associated with expression of ANRIL, but less consistently with CDKN2A/2B. ANRIL down-regulation is a potential mechanism by which these SNPs confer disease susceptibility.

Cunnington MS, Mayosi BM, Hall DH, Avery PJ, Farrall M, Vickers MA, et al. Novel genetic variants linked to coronary artery disease by genome-wide association are not associated with carotid artery intima-media thickness or intermediate risk phenotypes. Atherosclerosis. 2009;203(1):41–44. doi: 10.1016/j.atherosclerosis.2008.06.025. **Full text available here.**

Background: It is uncertain whether the novel single nucleotide polymorphisms (SNPs) that have recently been associated with coronary artery disease (CAD) in genome-wide studies also influence carotid atheroma and stroke risk. The mechanisms of their association with CAD are unknown; relationships to other cardiovascular phenotypes may give mechanistic clues. Carotid artery intima-media thickness (CIMT) is a subclinical marker of atherosclerosis associated with stroke. We investigated association of reported CAD risk variants with CIMT, and

with other intermediate phenotypes that may implicate causative pathways.
Methods: We studied 1425 members of 248 British Caucasian families ascertained through a hypertensive proband. We genotyped CAD risk SNPs on chromosomes 9 (rs1333049, rs7044859, rs496892, rs7865618), 6 (rs6922269) and 2 (rs2943634) using TaqMan. Merlin software was used for family-based association testing.
Results: No significant association was found between genotype at any SNP and CIMT in 846 individuals with acceptable measurements. Nor were SNPs significantly associated with blood pressure, obesity, cholesterol, CRP, interleukin-6, TNF-α, or leptin.
Conclusions: These novel CAD variants are not associated with CIMT and do not appear to mediate the risk of atherothrombosis through known risk factors.

Cunnington MS, Mayosi BM, Hall DH, Avery PJ, Farrall M, Vickers MA, et al. Genetic polymorphisms linked to coronary artery disease are not associated with carotid artery intima-media thickness, left ventricular size, or intermediate risk phenotypes. Heart. 2009;95:A83. **Full text not freely available**

Background: A number of single nucleotide polymorphisms (SNP) hasbeen robustly associated with coronary artery disease (CAD) in genome-wide studies, but the mechanisms of these associations are unknown. A relationship of these SNP to other cardiovascular phenotypes may give mechanistic clues. Carotid artery intimamedia thickness (CIMT) is a subclinical marker of atherosclerosis associated with stroke. We investigated the association of reported CAD risk variants with CIMT, and with other intermediate risk factors and cardiovascular phenotypes that may implicate causative pathways.
Methods: We studied 1425 members of 248 white British families ascertained through a hypertensive proband. We genotyped CAD risk SNP on chromosomes 9p21 (rs1333049, rs7044859, rs496892, rs7865618), 6q25 (rs6922269) and 2q36 (rs2943634) using TaqMan. Adjustments were made for significant covariates (determined by linear regression) and Merlin software was used for family-based association testing.
Results: Despite the documented heritability of CIMT in this population, no significant association was found between genotype at any SNP and CIMT in 846 individuals with acceptable measurements. Nor were SNP significantly associated with intermediate phenotypes including clinic blood pressure (n = 1171), mean ambulatory blood pressure (n = 958), body mass index (n = 1402), waist–hip ratio (n = 1357), serum total cholesterol (n = 1319), C-reactive protein (n = 1300), IL-6 (n = 1182), tumour necrosis factor alpha (n = 1179), leptin (n = 1319), urine aldosterone (n = 636), or echocardiographic measures of left ventricular mass and left ventricular cavity size (n = 794; all $p>0.05$ after adjustment for multiple testing). The maximum plausible genetic effect (based on the 95% CI) associated with each SNP was estimated using linear regression models and was found to be low (<2%) in all cases, suggesting that the observed lack of association was unlikely to be due to inadequate statistical power.
Conclusions: Novel variants associated with CAD are not associated with CIMT, left ventricular hypertrophy or left ventricular cavity size and do not appear to mediate the risk of atherothrombosis through the known risk factors studied.

Heradien M, Revera M, van der Merwe L, Goosen A, Corfield VA, Brink PA, et al. Abnormal blood pressure response to exercise occurs more frequently in hypertrophic cardiomyopathy patients with the R92W troponin T mutation than in those with myosin mutations. Heart Rhythm. 2009;6(11 Suppl):S18–24. doi: 10.1016/j.hrthm.2009.07.020. **Full text not freely available**

Abnormal blood pressure response to exercise is reported to occur in up to a third of hypertrophic cardiomyopathy (HCM) cases and is associated with an increased risk of death, particularly in the young, but it is not known whether the HCM-causing mutation influences blood pressure response to exercise. The purpose of this article is to ascertain whether the blood pressure response to exercise differs among carriers of the R92W mutation in the cardiac troponin T gene (TNNT2), which has been associated with an increased risk of sudden cardiac death in young males; carriers of mutations in the cardiac beta-myosin heavy chain gene (*MYH7*); and their noncarrier relatives. Thirty $R92W_{TNNT2}$ carriers, 51 MYH7 mutation carriers, and 68 of their noncarrier relatives were subjected to bicycle ergonometric exercise testing to assess blood pressure response to, as well as heart rate recovery after, exercise. Additional echocardiographic and demographic details were documented for all participants. $R92W_{TNNT2}$ carriers demonstrated significantly more abnormal blood pressure responses to exercise (P = .021; odds ratio 3.03; confidence interval 1.13–8.12) and smaller increases in systolic blood pressure than MYH7 mutation carriers or related noncarrier control individuals. Although abnormal blood pressure response occurred at similar frequencies in males in all groups (23%–26%), the percentage of $R92W_{TNNT2}$ females with abnormal blood pressure response was 64%, compared with 25% for *MYH7* and 22% for noncarriers. Therefore, these results show that blood pressure response to exercise is influenced by genotype and gender in patients with HCM.

Karthikeyan G, Mayosi BM. Is primary prevention of rheumatic fever the missing link in the control of rheumatic heart disease in Africa? Circulation. 2009;120(8):709–713. doi: 10.1161/circulationaha.108.836510. **Full text not freely available**

Rheumatic fever and rheumatic heart disease continue to be major public health problems in the developing world, particularly in the countries of sub-Saharan Africa. Because of its cost effectiveness, secondary prophylaxis is advocated as the principal means of disease prevention and control. However, in developing countries, valvular damage, due to earlier, unrecognized episodes of rheumatic fever, has already occurred by the time secondary prophylaxis is instituted. Secondary prophylaxis cannot reduce the incidence of new cases of rheumatic fever and has not been shown to alter the natural history of rheumatic valvular disease. Experience from several regions of

the world suggests that incorporation of a strategy of primary antibiotic prophylaxis into a comprehensive program for disease control can reduce the incidence of rheumatic fever and rheumatic heart disease. In this article, we argue that a strategy of primary antibiotic prophylaxis, with appropriate modifications, can be successfully implemented in resource-poor settings across the world and should be a key component of any rheumatic heart disease control program. This, we believe, is essential for reducing the global burden of rheumatic heart disease.

Kuper H, Nicholson A, Kivimaki M, Aitsi-Selmi A, Cavalleri G, Deanfield JE, et al. Evaluating the causal relevance of diverse risk markers: horizontal systematic review. BMJ. 2009;339(7732):1240. doi: https://doi.org/10.1136/bmj.b4265. **Full text not freely available**

Objectives: To develop a new methodology to systematically compare evidence across diverse risk markers for coronary heart disease and to compare this evidence with guideline recommendations.

Design: "Horizontal" systematic review incorporating different sources of evidence.

Data sources: Electronic search of Medline and hand search of guidelines.

Study selection: Two reviewers independently determined eligibility of studies across three sources of evidence (observational studies, genetic association studies, and randomised controlled trials) related to four risk markers: depression, exercise, C reactive protein, and type 2 diabetes. Data extraction for each risk marker, the largest metaanalyses of observational studies and genetic association studies, and meta-analyses or individual randomised controlled trials were analysed.

Results: Meta-analyses of observational studies reported adjusted relative risks of coronary heart disease for depression of1.9 (95% confidence interval 1.5 to 2.4), for top compared with bottom fourths of exercise 0.7 (0.5 to 1.0), for top compared with bottom thirds of C reactive protein 1.6 (1.5 to 1.7), and for diabetes in women 3.0 (2.4 to 3.7) and in men 2.0 (1.8 to 2.3). Prespecified study limitations were more common for depression and exercise. Meta-analyses of studies that allowed formal Mendelian randomisation were identified for C reactive protein (and did not support a causal effect), and were lacking for exercise, diabetes, and depression. Randomised controlled trials were not available for depression, exercise, or C reactive protein in relation to incidence of coronary heart disease, but trials in patients with diabetes showed some preventive effect of glucose control on risk of coronary heart disease. None of the four randomised controlled trials of treating depression in patients with coronary heart disease reduced the risk of further coronary events. Comparisons of this horizontal evidence review with two guidelines published in 2007 showed inconsistencies, with depression prioritised more in the guidelines than in our review.

Conclusions: This horizontal systematic review pinpoints deficiencies and strengths in the evidence for depression, exercise, C reactive protein, and diabetes as unconfounded and unbiased causes of coronary heart disease. This new method could be used to develop a field synopsis and prioritise future development of guidelines and research.

Lim V, Stubbs JW, Nahar N, Amarasena N, Chaudry ZU, Weng SCK, et al. Politicians must heed health effects of climate change. Lancet. 2009;374(9694):973. doi: 10.1016/s0140-6736(09)61641-x. **Full text not freely available**

No abstract available.

Lopes de Campos WR, Coopusamy D, Morris L, Mayosi BM, Khati M. Cytotoxicological analysis of a gp120 binding aptamer with cross-clade human immunodeficiency virus type 1 entry inhibition properties: Comparison to conventional antiretrovirals. Antimicrob Agents Chemother. 2009; 53(7):3056–3064. doi: 10.1128/aac.01502-08. **Full text not freely available**

The long-term cumulative cytotoxicity of antiretrovirals (ARVs) is among the major causes of treatment failure in patients infected with human immunodeficiency virus (HIV) and patients with AIDS. This calls for the development of novel ARVs with less or no cytotoxicity. In the present study, we compared the cytotoxic effects of a cross-clade HIV type 1-neutralizing aptamer called B40 with those of a panel of nonnucleoside reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), and the entry inhibitor (EI) T20 in human cardiomyocytes and peripheral blood mononuclear cells. An initial screen in which cell death was used as the end-point measurement revealed that the B40 aptamer and T20 were the only test molecules that had insignificant ($0.61 < P < 0.92$) effects on the viability of both cell types at the maximum concentration used. PIs were the most toxic class ($0.001 < P < 0.00001$), followed by NNRTIs and NRTIs ($0.1 < P < 0.00001$). Further studies revealed that B40 and T20 did not interfere with the cellular activity of the cytochrome P450 3A4 enzyme ($0.78 < P < 0.24$) or monoamine oxidases A and B ($0.83 < P < 0.56$) when the activities of the enzymes were compared to those in untreated controls of both cell types. Mitochondrion-initiated cellular toxicity is closely associated with the use of ARVs. Therefore, we used real-time PCR to quantify the relative ratio of mitochondrial DNA to nuclear DNA as a marker of toxicity. The levels of mitochondrial DNA remained unchanged in cells exposed to the B40 aptamer compared to the levels in untreated control cells ($0.5 > P > 0.06$). These data support the development of B40 and related EI aptamers as new ARVs with no cytotoxicity at the estimated potential therapeutic dose.

Mayosi BM, Dhai A, Folb P, Gevers W, Hussey G, Kirkman M, et al. Consensus report on revitalising clinical research in South Africa. Pretoria: Academy of Science of South Africa (ASSAf); 2009. **Full text not freely available**

Clinical research in a developing country like South Africa contributes to health care at all levels by identifying the causes of problems, facilitating diagnosis, improving the efficiency and effectiveness of care, and promoting good policy-making. It also supports the training of competent health professionals of all kinds, and contributes to global knowledge about locally, as well as generally, prevalent diseases in terms of prevention and treatment. The key

narrative of clinical research in South Africa over the last two decades has been that of a largely unplanned, but cumulative, disinvestment in publicly funded programmes, resulting from the withdrawal of the health departments of provincial governments from this sector (academic hospitals are now funded for service functions only), the absence of discounts for research tests from the business model of the National Health Laboratory Service (NHLS), chronic underfunding of the Medical Research Council (MRC) despite its obviously important mandate for maintaining and developing medical/clinical research capacity in the country, and the lack of funding streams to universities that might in principle have been applied to meet the overall shortfall in support.
These intersecting developments are a kind of 'elephant in the room', well known to all participants, but very poorly documented. Tertiary service units struggle to remain active in research, and to translate their expertise into improved health service. As a result, many clinical researchers have been left with no option but to turn to the pharmaceutical industry for the funding of those clinical trials in which the companies concerned have an interest, or to international donors who conduct large-scale, short- to medium-term, projects in South Africa, with local researchers drawn into international teams, often led by outsiders. The pharmaceutical investment is directed predominantly at the profitable areas of chronic diseases of lifestyle, mental illness and allergy, while most of the external donor funding is directed at the serious local HIV and TB pandemics. Local and international clinical conference activity has accordingly begun to reflect the agendas of donors and industry. There is little likelihood that continuation of the present situation is compatible with rebuilding and sustaining solid research capacity in the clinical domain, nor can the ideal of well-coordinated state support for a health system, built on the 'intelligence' of good clinical research, ever be realised. The serious decline in clinical research activity and capacity has prompted this study by ASSAf (http://www.assaf.org.za) in order to make recommendations on the overall revitalisation of clinical research in the country within the broad paradigm of essential national health research. An additional stimulus is the emphasis of government in its ten-year science and technology plan on the development of new medicines and other biologically useful agents ('farmer to pharma').

Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. The burden of non-communicable diseases in South Africa. Lancet. 2009;374(9693):934–947. doi: 10.1016/s0140-6736(09)61087-4. **Full text not freely available**

15 years after its first democratic election, South Africa is in the midst of a profound health transition that is characterised by a quadruple burden of communicable, non-communicable, perinatal and maternal, and injury-related disorders. Non-communicable diseases are emerging in both rural and urban areas, most prominently in poor people living in urban settings, and are resulting in increasing pressure on acute and chronic health-care services. Major factors include demographic change leading to a rise in the proportion of people older than 60 years, despite the negative effect of HIV/AIDS on life expectancy. The burden of these diseases will probably increase as the roll-out of antiretroviral therapy takes effect and reduces mortality from HIV/AIDS. The scale of the challenge posed by the combined and growing burden of HIV/AIDS and non-communicable diseases

demands an extraordinary response that South Africa is well able to provide. Concerted action is needed to strengthen the district-based primary health-care system, to integrate the care of chronic diseases and management of risk factors, to develop a national surveillance system, and to apply interventions of proven cost-effectiveness in the primary and secondary prevention of such diseases within populations and health services. We urge the launching of a national initiative to establish sites of service excellence in urban and rural settings throughout South Africa to trial, assess, and implement integrated care interventions for chronic infectious and non-communicable diseases.

Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D. Transmissible cancer in Africa – Authors' reply. Lancet. 2009;374(9707):2052–2053. doi: 10.1016/S0140-6736(09)62149-8. **Full text not freely available**

No abstract available.

Mayosi BM, van Veen K, Syed F, Russell J, Tibazarwa K, Usim O, et al. Immunological correlates of tuberculous effusive constrictive pericarditis. J Am Coll Cardiol. 2009;53(10):A172. **Full text not freely available**

Background: Effusive constrictive pericarditis is present when there is evidence of clinical and haemodynamic constriction following pericardiocentesis in a patient with a pericardial effusion. It is not known whether effusive constrictive physiology is associated with specific immunological changes compared to pure effusive disease in tuberculous pericarditis.

Methods: The expression of inflammatory, anti-inflammatory, and fibrotic response genes were analysed using quantitative RT-PCR of RNA extracted from pericardial fluid and blood of 23 patients with tuberculous pericardial effusion. Gene expression was normalized to human beta-actin in the same sample. Blood and pericardial fluid was compared in all patients, after which patients were stratified according to disease outcomes of either pure effusive or effusive-constrictive pericarditis according to invasive haemodynamic monitoring of the pericardium and right side of the heart.

Results: There was abundant expression of the profibrotic TGF-beta, inflammatory IL-1 beta, SPARC (a fibrotic response gene with a regulatory role) and Timp1 (the natural inhibitor of matrix metalloproteinase 2 and 9) in both blood and pericardial fluid. There was clear evidence of compartmentalized gene expression as RNA levels of genes associated with fibrosis Col1a1, Col1a2, Col4a1 and Col4a2 (encoding procollagen molecules) and regulatory FOXP3 were significantly upregulated in the pericardial fluid compared to the blood. We next stratified the data according to disease status and found that TGF-beta (p=0.016) and IFN-gamma (p=0.014) were significantly down regulated in the pericardial fluid of patients with effusive constrictive pericarditis compared to those with purely effusive pericardial disease.

Conclusion: We show for the first time that effusive constrictive pericarditis is associated with a specific pattern of cytokine expression in tuberculosis. These findings may assist in the development of predictive biomarkers for fibrosis in pericardial tuberculosis.

Ntsekhe M, Mayosi BM. Cardiac manifestations of HIV infection: an African perspective. Nat Clin Pract Cardiovasc Med. 2009;6(2):120–127. doi: 10.1038/ncpcardio1437. **Full text not freely available**

The pericardium, myocardium, coronary arteries and pulmonary arteries are the main targets for cardiac disease in people who are infected with HIV. Geography and access to highly active anti-retroviral therapy (HAART) have a major influence on which of these targets is affected. In sub-Saharan Africa, where tuberculosis is endemic and access to HAART is limited, the dominant forms of HIV-associated heart disease are pericardial tuberculosis and cardiomyopathy. However, in industrialized countries, where tuberculosis is rare and HAART is widely available, coronary artery disease is the main cause of death and disability in these patients. Observational data suggest that HAART, by preserving immune function, reduces the incidence of myopericardial disease and pulmonary hypertension. The result has been that, although optimal strategies to reduce vascular disease in this population continue to be sought and debated in industrialized nations, the focus of prevention and treatment strategies for HIV-related heart disease in developing countries has been to support the active campaigns to get universal access to HAART in the first place. Herein, we review the cardiac manifestations of HIV in sub-Saharan Africa.

Ntsekhe M, Syed FS, Russell J, Usim P, Mayosi BM. The prevalence of effusive constrictive pericarditis in patients with confirmed tuberculous pericarditis. J Am Coll Cardiol. 2009;53(10):A169. **Full text available here**.

Background: Effusive constrictive pericarditis (ECP) occurs when pericardial effusion and visceral pericardial constriction coexist and is thought to be a precursor to constrictive pericarditis. In the largest study reported to date <10% of the 190 patients undergoing pericardiocentesis had evidence of ECP. A small minority in the study had tuberculosis pericarditis where ECP may be more common. Using the Initiative for the Investigation and Management of Pericarditis In Africa (IMPI Africa) registry we set out to determine the prevalence of ECP in patients with TB pericarditis.

Methods: Between Jan '06 and May '08 consecutive patients with symptomatic pericardial effusions referred for therapeutic or diagnostic pericardiocentesis were recruited. Simultaneous right atrial and intra-pericardial pressures were measured pre and post pericardiocentesis in all who met entry criteria. Tuberculosis was confirmed by pericardial fluid microbiology and or chemistry. ECP was defined as failure of the right atrial pressure to fall by 50% or to a new level of ≤12mmHg after the intra-pericardial pressure was normalized. Tamponade was defined as equalization of the intra-pericardial and mean right atrial pressure.

Results: In the period under review, of 148 consecutive patients referred with symptomatic pericardial effusions, 60 had a tuberculous etiology confirmed and had complete hemodynamic data for analysis. 38% met criteria for

ECP. 52% met criteria for cardiac tamponade. By univariate analysis the hemodynamic predictors of ECP were RAP ≥ 20mmHg OR 24.08 [p=,006]) and pericardial pressure ≥ 20mmHg OR 10.93[p=.004]). Cardiac tamponade was not associated with ECP (OR 0.87) [p=.673] By multivariate analysis only RAP ≥ 20mmHg remained significantly [.001] associated with ECP (OR 18 [p=.001])

Conclusions: We show, in this first and largest study of its kind anywhere, that effusive constrictive pericarditis is relatively common (38% prevalence) in tuberculous pericardial effusions.

Ntusi NB, Mayosi BM. Epidemiology of heart failure in sub-Saharan Africa. Expert Rev Cardiovasc Ther. 2009;7(2):169–180. doi: 10.1586/14779072.7.2.169.

Heart failure has emerged as a dominant form of cardiovascular disease in Africa, and has great social and economic relevance owing to its high prevalence, mortality and impact on young, economically active individuals. The causes of heart failure in Africans remain largely nonischemic. Hypertension, cardiomyopathy, rheumatic heart disease, chronic lung disease and pericardial disease are the main contributors to the etiology of cardiac failure in sub-Saharan Africa, accounting for over 90% of cases. Hypertensive heart disease complications occur more frequently in Africans and the majority of affected patients are younger. Endemic cardiomyopathies include dilated cardiomyopathy, peripartum cardiomyopathy and endomyocardial fibrosis. Nonendemic cardio-myopathies apparently occur with the same frequency as in other parts of the world, and include hypertrophic cardiomyopathy and arrhythmogenic right ventricular dysplasia/cardiomyopathy. Coronary artery disease and its complications remain uncommon in Africa, but the situation is changing due to modifications in lifestyle, risk-prone behavior, diet, cultural attitudes and other consequences of rapid urbanization. As the prevalence of heart failure is expected to rise substantially in sub-Saharan Africa, the authors call for population-based studies and registries of the epidemiology of heart failure in Africans and the urgent study of interventions that will decrease morbidity and mortality from the causes of heart failure, with a focus both on nonischemic and ischemic risk factors.

Ntusi NB, Mayosi BM. Aetiology and risk factors of peripartum cardiomyopathy: a systematic review. Int J Cardiol. 2009;131(2):168–179. doi: 10.1016/j.ijcard.2008.06.054. **Full text not freely available.**

Background: Peripartum cardiomyopathy (PPCM) is a disorder of unknown aetiology in which heart failure due to left ventricular dysfunction occurs between the last month of pregnancy and first five months post-partum. Theories abound concerning the specific cause and risk factors for PPCM, but none have been accepted universally. The primary objective of this review was to summarize the state of knowledge on the pathogenesis of PPCM, especially in light of recent studies.

Methods: We searched MEDLINE (January 1966-September 2007), OVID, and reference lists of articles for studies containing information on the aetiology and risk factors for PPCM, and published in English.

Results: The literature reveals a wealth of articles proposing various mechanisms for aetiology and risk factors of PPCM. There is conflicting evidence on the pathogenetic role of viral myocarditis, abnormal immune response to

pregnancy, abnormal response to the haemodynamic stress of pregnancy, accelerated myocyte apoptosis, cytokine-induced inflammation, malnutrition, genetic factors, excessive prolactin production, abnormal hormonal function, increased adrenergic tone, and myocardial ischaemia. A number of factors are postulated to increase the risk of the development of PPCM. These include non-Caucasian ethnicity, advanced maternal age, multiparity, poor socioeconomic status, multiple pregnancy and prolonged tocolytic use. The authors call for a strict definition of PPCM that excludes known causes of heart failure, such as the pregnancy-induced hypertensive spectrum of disorders.

Conclusion: The aetiology and risk factors for PPCM are poorly defined. There is a need for large-scale multi-centre epidemiological studies and registries to delineate the aetiology and pathogenesis of PPCM.

Parker M, Kinnear C, Keavney B, Watkins H, Mayosi BM, Moolman-Smook J. The growth hormone inducible transmembrane gene is a novel genetic modifier of left ventricular hypertrophy in families with hypertrophic cardiomyopathy. Eur Heart J. 2009;30 Supplement 1:542. **Full text not freely available.**

Purpose: To test positional candidate genes for association with quantitative variation in left ventricular hypertrophy. These positional candidate genes were identified by genome-wide mapping in a collection of families with hypertension from Oxford, United Kingdom in a previous study. In this study, South African families with hypertrophic cardiomyopathy were used as a model for studying genetic modifiers of left ventricular hypertrophy. The most promising candidate gene, from a region on chromosome 10 with a LOD score >2, was selected for investigation. This gene, GHITM, encoding a growth hormone inducible transmembrane protein, is highly expressed in the heart and is likely to be involved in growth hormone signalling and energy metabolism.

Methods: We performed the quantitative genetic association analysis in a unique panel of South African families with hypertrophic cardiomyopathy due to known founder gene mutations. All 267 affected and non-affected members of these families were studied. SNaPshot was employed for single nucleotide polymorphism (SNP) genotyping of 8 haplotype tagging SNPs across the GHITM gene. Family based tests of genetic association were implemented in the Quantitative Transmission Disequilibrium Test.

Results: Despite a modest size of the cohort, our results show significant association between the rs2306321 SNP in GHITM and a range of measures of echocardiographic left ventricular hypertrophy, including the cumulative wall thickness score and interventricular septum ($p<0.005$). The rs7096124 SNP in GHITM was associated with ECG QRS duration ($p=0.028$)

Conclusion: Our data suggest that the GHITM gene is a novel genetic modifier of echocardiographic and electrocardiographic LVH in families with hypertrophic cardiomyopathy.

Rahman T, Avery PJ, Mayosi BM, Watkins H, Keavney B. Association between *HSD11B1* polymorphism

and left ventricular mass in families with hypertension. Heart. 2009;95:A60-A61. **Full text not freely available.**

Background: The 11β-hydroxysteroid dehydrogenase type 1 (*HSD11B1*) gene plays an important role in glucocorticoid metabolism. *HSD11B1* is a bidirectional enzyme, but it displays oxoreductase activity in intact cells, converting inactive cortisone to cortisol. The reductase activity of *HSD11B1* plays an important role in the growth and differentiation of adipose tissue via the activation of glucocorticoids. Increased *HSD11B1* activity has been proposed as a mechanism underlying the association between multiple cardiovascular risk factors, whereas inhibition of *HSD11B1* has been proposed for the treatment of diabetes and central obesity. Left ventricular mass (LVM) is a significantly heritable trait that is associated with cardiovascular morbidity and mortality independent of hypertension. The genetic factors responsible for differences in LVM within the general population are, as yet, largely unknown. We investigated the contribution of common genetic variants in the *HSD11B1* to LVM in a family-based study.

Methods: 1425 individuals from 248 white families were analysed. Families were ascertained through a proband with essential hypertension. The proband was required to have had an ambulatory blood pressure monitor (>140 mm Hg mean daytime systolic blood pressure (SBP) and >90 mm Hg mean daytime diastolic blood pressure (DBP)/multiple office SBP >160 mm Hg and DBP >95 mm Hg). Ambulatory blood pressure was recorded in all family members using the A&D TM2421 monitor for 24 h. LVM was measured using both electrocardiography and echocardiography. We genotyped 13 Tag single nucleotide polymorphisms (SNP) on a Sequenom MassArray MALDI-TOF platform that together captured the common genetic variability in the *HSD11B1* gene (fig). The LVM was adjusted for covariates including drug treatment, age and gender, by linear regression, and a family-based association analysis was conducted using MERLIN. Results were corrected for multiple comparisons specifying a false discovery rate of 5%.

Results: Out of 13 Tag SNP analysed in *HSD11B1*, one SNP was associated with a difference in LVM measured either by echocardiography or electrocardiography (rs846910: p=0.003 for echo LVM; p=0.03 for ECG LVM; see table). The rarer A allele of rs846910 (frequency 0.052) was associated with lower LVM both in analyses of linear trend and under a dominant model.

Conclusion: The *HSD11B1* SNP rs846910 was significantly associated with both echocardiographic and electrocardiographic LVM in these families, although the size of the effect was small. This SNP has been associated with hypertension in one previous study, although there was no significant association with blood pressure phenotypes in the present study. rs846910 is located in the first intron of *HSD11B1*, and its function is as yet unclear. This is the first study to demonstrate an association between the *HSD11B1* gene and LVM; future studies will be necessary to determine the mechanism of the effect.

Schmied C, Zerguini Y, Junge A, Tscholl P, Pelliccia A, Mayosi BM, et al. Cardiac findings in the

precompetition medical assessment of football players participating in the 2009 African Under-17 Championships in Algeria. Br J Sports Med. 2009;43(9):716–721. doi: 10.1136/bjsm.2009.064196. **Full text not freely available.**

Objectives: To screen all players registered for the 8th CAF African Under-17 Championship for risk factors of sudden cardiac death.

Design: Standardised cardiac evaluation prior to the start of the competition.

Study population: 155 male football players from all eight qualified teams; mean age 16.4 (SD 0.68) years (range 14 to 17).

Methods: The cardiac evaluation consisted of a medical history, clinical examination, 12-lead resting electro-cardiogram (ECG) and echocardiography, and was performed by three experienced cardiologists using established guidelines.

Results: Nine (5.8%) players reported cardiac symptoms, and the clinical examination was abnormal in only two players with elevated blood pressure. A total of 40 players (25.8%) showed abnormal ECG patterns. None of the players with a positive ECG showed correlating echocardiographic findings. The echocardiogram of one player appeared highly suspicious for early-stage hypertrophic cardiomyopathy, and in another player the myocardium was suspicious for non-compaction cardiomyopathy, but both had normal ECGs. Thirteen (8.4%) players showed echocardiographic findings that needed further follow-up. The percentage of players with pathological ECG patterns and some abnormal echocardiographic measurements varied substantially between different ethnic groups.

Conclusion: Cardiological screening for risk factors of sudden cardiac death of football players prior to an international competition proved feasible, and conduction by independent experts allowed high-quality standards and a consistent protocol for the examinations. Differences observed between ethnic groups indicate that guidelines for the analysis of ECGs and echocardiography might be adjusted to the target population.

Schwartz PJ, Mayosi B, Opie LH. Foreword. In: Cardiac Arrhythmias and Sudden Death: From Genes to Prevention Symposium. 2008 Aug 15–16; Cape Town, South Africa. Heart Rhythm. 2009;6(11):S1. doi: 10.1016/j.hrthm.2009.10.020. **Full text not freely available.**

No abstract available.

Shaboodien G, Engel ME, Syed FF, Poulton J, Badri M, Mayosi BM. The mitochondrial DNA T16189C polymorphism and HIV-associated cardiomyopathy: a genotype–phenotype association study. BMC Med Genet. 2009;10:37. doi: 10.1186/1471-2350-10-37. **Full text available here.**

Background: The mitochondrial DNA (mtDNA) T16189C polymorphism, with a homopolymeric C-tract of 10–12 cytosines, is a putative genetic risk factor for idiopathic dilated cardiomyopathy in the African and British

populations. We hypothesized that this variant may predispose to dilated cardiomyopathy in people who are infected with the human immunodeficiency virus (HIV).
Methods: A case-control study of 30 HIV-positive cases with dilated cardiomyopathy and 37 HIV-positive controls without dilated cardiomyopathy was conducted. The study was confined to persons of black African ancestry to minimize confounding of results by population admixture. HIV-positive patients with an echocardiographically confirmed diagnosis of dilated cardiomyopathy and HIV-positive controls with echocardiographically normal hearts were studied. Patients with secondary causes of cardiomyopathy (such as hypertension, diabetes, pregnancy, alcoholism, valvular heart disease, and opportunistic infection) were excluded from the study. DNA samples were sequenced for the mtDNA T16189C polymorphism with a homopolymeric C-tract in the forward and reverse directions on an ABI3100 sequencer.
Results: The cases and controls were well matched for age (median 35 years versus 34 years, P = 0.93), gender (males 60% *vs* 53%, P = 0.54), and stage of HIV disease (mean CD4 T cell count 260.7/μL *vs*. 176/μL, P = 0.21). The mtDNA T16189C variant with a homopolymeric C-tract was detected at a frequency of 26.7% (8/30) in the HIV-associated cardiomyopathy cases and 13.5% (5/37) in the HIV-positive controls. There was no significant difference between cases and controls (Odds Ratio 2.33, 95% Confidence Interval 0.67–8.06, p = 0.11).
Conclusion: The mtDNA T16189C variant with a homopolymeric C-tract is not associated with dilated cardiomyopathy in black African people infected with HIV.

Sliwa K, Carrington M, Mayosi B, Zigriades E, Mvungi R, Stewart S, et al. Burden and characteristics of newly diagnosed rheumatic heart disease in urban African adults: Insights from the Heart of Soweto Study. Eur Heart J. 2009;30:606–606. **Full text not freely available.**

Background: There is a paucity of data to describe the burden and clinical characteristics of newly diagnosed rheumatic heart disease (RHD) in adulthood from urban African communities in epidemiologic transition.
Methods: The Hospital services the black African community of 1.1 million people in Soweto, South Africa. A prospective, clinical registry captured data from all de novo cases of structural and functional valve disease (determined via systematic echocardiographic screening) presenting to the Cardiology Unit during 2006/2007. We describe in detail all cases with newly diagnosed RHD.
Results: There were 4005 de novo presentations in 2006/07 and 960 (24%) had a valvular abnormality. Of these, 344 (36%) were diagnosed with RHD. The majority were black African females (n = 234 –68%) with a mean age of 43±22 years (41% aged 19–49 years) compared to 44±27 years in men. The most common predominant valvular lesion (n = 204–59%) was mitral regurgitation with 48 (14%) and 43 (13%) cases, respectively, having combination lesions of aortic and mitral regurgitation and mixed mitral valve disease. Impaired systolic function was common affecting 53/204 cases (26%) with predominant mitral regurgitation and 35/126 cases (28%) with predominant aortic regurgitation. Overall, elevated right ventricular systolic pressure >35 mmHg was found in 88 cases (26%) with concurrent anemia and atrial fibrillation found in 27 (8%) and 34 (10%) cases respectively. Subsequent valve

replacement/repair was performed in 75 patients (22%). Based on these presentations alone, the estimated incidence of new cases of RHD for the population of Soweto aged >14 years was 23.5 cases/100,000 per annum.
Conclusion: These contemporary data highlight a high incidence of newly diagnosed RHD within an adult urban African community. With the majority of cases presenting in middle age and above it appears that the burden of RHD extends well beyond childhood.

Spottiswoode BS, Zhong X, Lorenz CH, Mayosi BM, Meintjes EM, Epstein FH. Motion-guided segmentation for cine DENSE MRI. Med Image Anal. 2009;13(1):105–115. doi: 10.1016/j.media.2008.06.016. **Full text not freely available.**

Defining myocardial contours is often the most time-consuming portion of dynamic cardiac MRI image analysis. Displacement encoding with stimulated echoes (DENSE) is a quantitative MRI technique that encodes tissue displacement into the phase of the complex MRI images. Cine DENSE provides a time series of these images, thus facilitating the non-invasive study of myocardial kinematics. Epicardial and endocardial contours need to be defined at each frame on cine DENSE images for the quantification of regional displacement and strain as a function of time. This work presents a reliable and effective two-dimensional semi-automated segmentation technique that uses the encoded motion to project a manually-defined region of interest through time. Contours can then easily be extracted for each cardiac phase. This method boasts several advantages, including, (1) parameters are based on practical physiological limits, (2) contours are calculated for the first few cardiac phases, where it is difficult to visually distinguish blood from myocardium, and (3) the method is independent of the shape of the tissue delineated and can be applied to short- or long-axis views, and on arbitrary regions of interest. Motion-guided contours were compared to manual contours for six conventional and six slice-followed mid-ventricular short-axis cine DENSE datasets. Using an area measure of segmentation error, the accuracy of the segmentation algorithm was shown to be similar to inter-observer variability. In addition, a radial segmentation error metric was introduced for short-axis data. The average radial epicardial segmentation error was 0.36±0.08 and 0.40±0.10 pixels for slice-followed and conventional cine DENSE, respectively, and the average radial endocardial segmentation error was 0.46±0.12 and 0.46±0.16 pixels for slice following and conventional cine DENSE, respectively. Motion-guided segmentation employs the displacement-encoded phase shifts intrinsic to DENSE MRI to accurately propagate a single set of pre-defined contours throughout the remaining cardiac phases.

Syed FF, Wilkinson KA, Wilkinson RJ, Ntsekhe M, Mayosi BM. The prevalence, correlates and outcome of atrial fibrillation in tuberculous pericarditis. Eur Heart J. 2009;30:1000. **Full text not freely available.**

Purpose: There is no prospective information on the prevalence, correlates and outcome of atrial fibrillation (AF) in tuberculous (TB) pericarditis. We determined the prevalence, correlates, and outcome of AF in TB pericarditis in the Cape Town component of the multi-national Investigation of the Managament of Pericarditis (IMPI)

Registry.

Methods: All patients presenting with a diagnosis of TB pericardial effusion were enrolled over a three year period. AF was diagnosed on 12-lead electrocardiography taken at presentation and repeated at follow-up intervals of 2 weeks, 2 months, 6 months, and 1 year. Correlation was sought between the presence of AF at presentation and the following potential determinants: age, HIV status, CD4 cell count in HIV positive individuals, serum CKMB levels, echocardiographic left ventricular systolic dysfunction (LVSD) (EF <50% andd/or dilated left ventricle), and serum and pericardial fluid levels of the following cytokines, measured by ELISA: IL-1β, IL-6, IL-10, IL-17, IL-22, TNF, IFN-γ, and TGF-β.

Results: Eighty-five consecutive patients (age 36±13 years, M:F 1.9:1) who were treated for TB pericardial effusion were enrolled. The prevalence of AF was 27% (23/85). There was no significant association with age (mean±SD age: AF 40.1±15.8 *vs* SR 35.1±12.1 years, p=0.123), nor was there an association with HIV status (p=0.33). However, in HIV positive individuals the CD4 cell count was lower in patients with AF (133±163 *vs* SR 277±220, p=0.05). Serum levels of CKMB were higher in patients in AF (30.2±33.8 *vs* SR 17.4±9.9 U/l, p=0.011), and there was a higher proportion of patients in AF who had LVSD (10/20 [50%] *vs* SR 12/60 [20%], p=0.018). There were significantly lower levels of the proinflammatory cytokines IL-6 (p=0.0003) and IL-17 (p=0.017) in serum and IL1β (p=0.033) and IL-17 (p=0.029) in pericardial fluid in patients in AF. Over the follow-up period, there was a progressive reduction in the prevalence of AF, with most cases resolving in the first 2 weeks and no new cases being observed by 6 months of follow-up (2 weeks: 4/63 [6.3%], 2 months: 2/53 [3.8%], 6 months: 0/38 [0%], 1 year: 0/15 [0%]).

Conclusions: There is a high prevalence of AF in patients with suspected pericardial tuberculosis, which remits spontaneously over two months of antituberculosis treatment. The correlates of AF in TB pericarditis are myocarditis (high CKMB with LVSD), low CD4 cell count in HIV infected individuals, and lower levels of proinflammatory cytokines. These data suggest a central role of myocardial inflammation in the pathogenesis of atrial fibrillation in TB pericarditis.

Tibazarwa K, Lee G, Carrington M, Stewart SS, Mayosi BM, Sliwa K. ECG characteristics in peripartum cardiomyopathy. Eur Heart J. 2009;30(Suppl 1):827. **Full text not freely available.**

Purpose: Despite the incidence of peripartum cardiomyopathy (PPCM) being high in Africa, diagnosis is often made late or missed. The ECG is a simple and accessible screening test for heart disease. However, the nature, frequency and evolution of ECG abnormalities in PPCM is not well defined. We assessed the prevalence of ECG abnormalities in newly diagnosed PPCM patients at baseline and at 6 months of follow-up.

Methods: 12-Lead ECGs were conducted on 83 consecutive patients presenting with PPCM to two tertiary centres in South Africa on diagnosis and at six-month follow-up. ECG analysis was standardised by use of the Minnesota code.

Results: Almost all patients included were black African women, of mean age 29±7 years and median body mass

index of 24.3 (IQR22.7–27.5) kg/m^2. At baseline, mean systolic and diastolic blood pressures were 116±20mmHg and 76±14mmHg, respectively. 86% of ECGs were in sinus rhythm, with mean heart rate 100±21 beats per minute. On first diagnosis, ECG abnormalities included the following:[1]abnormal frontal plane QRS axis in 25% (95% CI16–36), with left and right axis deviation evident in 11% (95% CI5–21) and 10% (95% CI4–19), respectively, and 4% with indeterminate axis (95% CI0.8–11); [2] bundle-branch block in 11% (95% CI 5–21); [3] atrial abnormality was detected in 29% (95% CI 19–40), specific to left and right atria in 10% and 14%, respectively;[4] T-wave abnormalities occurred in 59% (95% CI48–70). Major and minor T-wave changes were evident in 38% (95% CI27–50) and 32% (95% CI22–43) of ECGs, respectively. Six-month follow-up ECGs were available for 43 patients; for whom only 65% of ECGs remained in sinus rhythm (95% CI49–79; p=0.04). Mean heart rate was lower than at baseline (mean 76±14 beats per minute p<0.001). At six months, QRS-axis and T-wave abnormalities decreased to 12% and 40%, respectively. Bundle-branch block occurred at similar prevalence than at baseline; as did left ventricular hypertrophy. Atrial abnormalities appeared in 9% of ECGs at followup; only 2% and 7% showing left and right atrial abnormalities, respectively. No patients demonstrated atrial fibrillation or ventricular tachy-arrhythmias.

Conclusions: This is the first known systematic analysis of serial ECG data on PPCM women in South Africa. Most newly diagnosed PPCM patients were in sinus tachycardia, almost two-thirds having T-wave abnormalities, and a third with atrial abnormalities. These three parameters improved at six months. We note that the ECG in PPCM is abnormal in over 95% of patients and may serve as a screening tool for women presenting with non-specific peripartal symptoms of heart failure.

Watkins DA, Mayosi BM. The contribution of South Africans to the subject of dilated cardiomyopathy. Cardiovasc J Afr. 2009;20(1):11–16. **Full text not freely available.**

No abstract available.

Watkins DA, Hendricks N, Shaboodien G, Mbele M, Parker M, Vezi BZ, et al. Clinical features, survival experience, and profile of plakophylin-2 gene mutations in participants of the Arrhythmogenic Right Ventricular Cardiomyopathy Registry of South Africa. Heart Rhythm. 2009;6(11 Suppl):S10–17. doi: 10.1016/j.hrthm.2009.08.018. **Full text not freely available.**

Little is known about arrhythmogenic right ventricular cardiomyopathy (ARVC) in Africa. The objective of this study was to delineate the clinical characteristics, survival, and genetics of ARVC in South Africa. Information on clinical presentation, electrocardiographic and cardiac imaging findings, histology, and outcome of cases with suspected ARVC was collected using the standardised form of the ARVC Registry of South Africa. Genomic DNA was screened for mutations in plakophylin-2 (PKP2) gene. Survival and its predictors were analyzed using the Kaplan-Meier and Cox proportional hazards regression methods, respectively. Fifty unrelated cases who met the diagnostic criteria for ARVC were enrolled between January 2004 and April 2009. Clinical presentation was

similar to that reported in other studies. Annual mortality rate was 2.82%, five-year cumulative mortality rate 10%, and mean age at death 36.9 ± 14.7 years. Overall survival was similar to the general South African population (P = 0.25). Independent risk factors for death were syncope (Hazard Ratio [HR] 10.73, 95% Confidence Interval [CI] 1.88–61.18, P = 0.008) and sustained ventricular tachycardia (HR = 22.97, 95% CI 2.33–226.18, P = 0.007). Seven PKP2 gene mutations were found in 9/36 (25%) unrelated participants, five being novel. The novel C1162T mutation occurred in four white South Africans sharing a common haplotype, suggesting a founder effect. Compound heterozygotes exhibited a severe phenotype signifying an allele dose effect. ARVC is associated with early mortality that is no different to the general South Africa population whose lifespan is shortened by HIV/AIDS. PKP2 gene mutations are common, have an allele dose effect, and a novel founder effect in white South Africans.

Watkins DA, Zuhlke LJ, Engel ME, Mayosi BM. Rheumatic fever: Neglected again. Science. 2009; 324(5923):37. doi: 10.1126/science.324.5923.37b. **Full text not freely available.**

No abstract available.

2008

Damasceno A, Cotter G, Dzudie A, Sliwa K, Mayosi BM. Early detection of rheumatic heart disease and prevention of heart failure in Sub-Saharan-Africa. J Am Coll Cardiol. 2008;51(11):1126. doi: 10.1016/j.jacc.2007.12.008. **Full text not freely available.**

No abstract available.

Du Preez J, Matolweni LO, Greenberg J, Mntla P, Adeyemo AA, Mayosi BM. The α_{2C} Del322-325 adrenergic receptor polymorphism is not associated with heart failure due to idiopathic dilated cardiomyopathy in black Africans. Cardiovasc J Afr. 2008;19(1):15–16. **Full text not freely available.**

Background: A four-amino acid deletion was identified within the α_{2C}-adrenergic receptor (α_{2C}Del322-325) that, when homozygous, increases the risk of heart failure in African-Americans nearly six-fold. We hypothesised that homozygosity for the α_{2C}Del322-325 polymorphism may be a risk factor for heart failure due to idiopathic dilated cardiomyopathy (DCM) in black South Africans.

Methods: The α_{2C} Del322-325 polymorphism was genotyped in 37 patients with heart failure and 34 controls, all of black African ancestry. Genotyping was performed by a size-fractionation assay.

Results: The patients studied ranged in age from 21 to 79 years with a mean age of 50 years, and 62% were male. No significant difference was observed in homozygosity for the α_{2C}Del322-325 polymorphism or in allele and genotype frequencies between patients and controls. The frequency of the allele containing the deletion was 0.54 in cases and 0.53 in controls. The genotype frequencies in the patients were consistent with those of the controls ($p = 0.56$).

Conclusions: Homozygosity for the α_{2C}Del322-325 polymorphism is not associated with an increased risk for heart failure due to idiopathic DCM in black South Africans.

Irlam J, Mayosi BM, Gaziano TA. [Letter to the Editor] Rheumatic fever and rheumatic heart disease: Primary prevention is the cost effective option. Indian J Pediatr. 2008;75(1):86. **Full text not freely available.**

No abstract available.

Mayosi BM. Mortality in patients treated for tuberculous pericarditis in sub-Saharan Africa. S Afr Med J. 2008;98(1):36–40. **Full text available here**.

Objective: To determine the mortality rate and its predictors in patients with a presumptive diagnosis of tuberculous pericarditis in sub-Saharan Africa. Design. Between 1 March 2004 and 31 October 2004, we enrolled 185 consecutive patients with presumed tuberculous pericarditis from 15 referral hospitals in Cameroon, Nigeria and South Africa, and observed them during the 6-month course of antituberculosis treatment for the major outcome of mortality. This was an observational study, with the diagnosis and management of each patient left at the discretion of the attending physician. Using Cox regression, we have assessed the effect of clinical and therapeutic characteristics (recorded at baseline) on mortality during follow-up.

Results: We obtained the vital status of 174 (94%) patients (median age 33; range 14–87 years). The overall mortality rate was 26%. Mortality was higher in patients who had clinical features of HIV infection than in those who did not (40% v.17%, p=0.001). Independent predictors of death during followup were: (i) a proven non-tuberculosis final diagnosis (hazard ratio (HR) 5.35, 95% confidence interval (CI) 1.76–16.25), (ii) the presence of clinical signs of HIV infection (HR 2.28, CI 1.14–4.56), (iii) coexistent pulmonary tuberculosis (HR 2.33, CI 1.20–4.54), and (iv) older age (HR 1.02, CI 1.01–1.05). There was also a trend towards an increase in death rate in patients with haemodynamic instability (HR 1.80, CI 0.90–3.58) and a decrease in those who underwent pericardiocentesis (HR 0.34, CI 0.10–1.19).

Conclusion: A presumptive diagnosis of tuberculous pericarditis is associated with a high mortality in sub-Saharan Africa. Attention to rapid aetiological diagnosis of pericardial effusion and treatment of concomitant HIV infection may reduce the high mortality associated with the disease.

Mayosi BM, Avery PJ, Farrall M, Keavney B, Watkins H. Genome-wide linkage analysis of electro-cardiographic and echocardiographic left ventricular hypertrophy in families with hypertension. Eur Heart J. 2008;29(4):525–530. doi: 10.1093/eurheartj/ehn028. **Full text available here**.

Aims: To localize chromosomal regions (or quantitative trait loci) that harbour genetic variants influencing the variability of electrocardiographic (ECG) and echocardiographic left ventricular hypertrophy (LVH).

Methods and results: We evaluated genetic linkage to ECG Sokolow-Lyon voltage, ECG Cornell voltage product, ECG left ventricular (LV) mass, and to echocardiographic septal wall thickness, LV cavity size, and LV mass in 868 members of 224 white British families. A genome-wide scan was performed with microsatellite markers that covered the genome at 10-cM intervals and linkage was assessed by variance components analysis. We identified chromosomal regions suggestive of linkage for Sokolow-Lyon voltage on chromosome 10q23.1 [$\log_{10}$ of the odds (LOD = 2.21, P = 0.0007)], for ECG Cornell voltage product on chromosome 17p13.3 (LOD = 2.67; P = 0.0002), and for ECG LV mass on chromosome 12q14.1 (LOD = 2.19; P = 0.0007). There was a single region of possible linkage for echocardiographic LV mass on chromosome 5p14.1 (LOD = 1.6; P = 0.003).

Conclusion: Stronger genetic signals for LVH were found using electrocardiographic than echocardiographic

measurements, and the genetic determinants of each of these appear to be distinct. Chromosomes 10, 12, and 17 are likely to harbour genetic loci that exert a major influence on electrocardiographic LVH.

Mayosi BM, Wiysonge CS, Ntsekhe M, Gumedze F, Volmink JA, Maartens G, et al. Mortality in patients treated for tuberculous pericarditis in sub-Saharan Africa. S Afr Med J. 2008;98(1):36–40. **Full text available here**.

Objective: To determine the mortality rate and its predictors in patients with a presumptive diagnosis of tuberculous pericarditis in sub-Saharan Africa.

Design: Between 1 March 2004 and 31 October 2004, we enrolled 185 consecutive patients with presumed tuberculous pericarditis from 15 referral hospitals in Cameroon, Nigeria and South Africa, and observed them during the 6-month course of antituberculosis treatment for the major outcome of mortality. This was an observational study, with the diagnosis and management of each patient left at the discretion of the attending physician. Using Cox regression, we have assessed the effect of clinical and therapeutic characteristics (recorded at baseline) on mortality during follow-up.

Results: We obtained the vital status of 174 (94%) patients (median age 33; range 14–87 years). The overall mortality rate was 26%. Mortality was higher in patients who had clinical features of HIV infection than in those who did not (40% v. 17%, p=0.001). Independent predictors of death during followup were: (i) a proven non-tuberculosis final diagnosis (hazard ratio (HR) 5.35, 95% confidence interval (CI) 1.76–16.25), (ii) the presence of clinical signs of HIV infection (HR 2.28, CI 1.14–4.56), (iii) coexistent pulmonary tuberculosis (HR 2.33, CI 1.20–4.54), and (iv) older age (HR 1.02, CI 1.01–1.05). There was also a trend towards an increase in death rate in patients with haemodynamic instability (HR 1.80, CI 0.90–3.58) and a decrease in those who underwent pericardiocentesis (HR 0.34, CI 0.10–1.19).

Conclusion: A presumptive diagnosis of tuberculous pericarditis is associated with a high mortality in sub-Saharan Africa. Attention to rapid aetiological diagnosis of pericardial effusion and treatment of concomitant HIV infection may reduce the high mortality associated with the disease.

Michael KA, Paisey JR, Mayosi BM, Robinson S, Allen S, Sunni NS, et al. A hybrid form of cardiac resynchronisation therapy in patients with failing systemic right ventricles. J Interv Card Electrophysiol. 2008;23(3):229–233. doi: 10.1007/s10840-008-9296-0. **Full text not freely available.**

Introduction: Late systemic right ventricular (RV) dysfunction after atrial redirection surgery is common. Patients may require cardiac transplantation in early adulthood.

Methods: We undertook cardiac resynchronisation (CRT)/defibrillator therapy in two patients as a bridge to transplantation.

Results: Two males (aged 24, 110 kg and 26 years, 106 kg); having undergone a Mustard procedure for dextro-

transposition of the great arteries at 7 and 6 months of age respectively, presented with impaired systemic RV function and New York Heart Association III symptoms. Both patients had dual chamber pacemakers in-situ for sinus bradycardia. Upgrade to CRT was performed by conserving the existing endocardial leads and placement of epicardial electrodes. One demonstrated sustained improvement over a 24 month follow-up period.

Conclusion: A hybrid CRT strategy is feasible in patients with failing systemic RVs and pre-existent endocardial dual chamber pacemakers. Appropriate patient selection criteria and optimum lead placement, however, still needs further evaluation in this population.

Ntsekhe M, Syed F, Mayosi B, Russel J, Usim OE on behalf of IMPI Study Group. The prevalence of effusive constrictive physiology and cardiac tamponade in patients with suspected tuberculous pericardial effusion. Eur Heart J. 2008;29:434. **Full text not freely available.**

Purpose: Effusive constrictive pericarditis occurs when pericardial fluid and visceral conscriction coexist to cause pericardial tamponade and constrictive physiology. The hall mark of the syndrome is the finding of persistantly elevated right atrial pressures despite the normalization of intra-pericardial pressures following pericardiocentesis. Effusive constrictive pericarditis is thought to be a precursor to constrictive pericarditis. Because of the difficulty in establishing a definitive diagnosis, the prevalence of the syndrome in tuberculous pericardial effusions is unknown. Some have speculated that due to the inflammatory, exudative nature of tuberculous effusions, effusive constrictive pericarditis may be very common but under recognized.

Objectives: 1) To determine the prevalence of effusive constrictive pericarditis in patients with large effusions suspected to be tuberculous in aetiolgy. 2) To determine the prevalence of cardiac tamponade in patients with large effusions suspected to be TB in aetiolgy. 3) To determine the frequency of effusive constrictive pericarditis in those with cardiac tamponade prior to evacuation of the pericardium.

Methods: Consecutive patients with large effusions suspected to be TB in origin were enrolled. Right atrial and intra-pericardial pressures were obtained before and after pericardiocentesis. Effusive constrictive pericarditis was defined as failure of the right atrial pressure to fall by 50% or to a new level of ≤10mmHg after the intra-pericardial pressure was lowered to near 0 mmHg. Tamponade was defined as measured intrapericardial pressures that exceeded the upper limit of normal right atrial pressure (12mmHg).

Results: 69 patients underwent pericardiocentesis. 55 had intra-pericardial and right atrial pressure measurements that were of acceptable quality for analysis. 36.5% (20/55) met the haemodynamic criteria for effusive constrictive pericarditis. 51% (28/55) had cardiac tamponade at presentation. Of the patients with cardiac tamponade, 60.1% (17/28) had evidence of effusive constrictive disease after evacuation of the pericardium. This compared with only 9% (1/11) of the patients without features of cardiac tamponade.

Conclusion: In this first and largest study of its kind in the world, effusive constrictive pericarditis occured in 37% of patients with a suspected tuberculous pericardial effusion. Approximately half of patients with suspected

tuberculous pericardial effusion have hemodynamic evidence of cardiac tamponade at presentation and the majority of those patients with tamponade have hemodynamic evidence of co-existing visceral constriction.

Ntsekhe M, Wiysonge CS, Gumedze F, Maartens G, Commerford PJ, Volmink JA, et al. HIV infection is associated with a lower incidence of constriction in presumed tuberculous pericarditis: A prospective observational study. PLoS One. 2008;3(6):e2253. doi: 10.1371/journal.pone.0002253. **Full text available here**.

Background: Pericardial constriction is a serious complication of tuberculous pericardial effusion that occurs in up to a quarter of patients despite anti-tuberculosis chemotherapy. The impact of human immunodeficiency virus (HIV) infection on the incidence of constrictive pericarditis following tuberculous pericardial effusion is unknown.
Methods and results: We conducted a prospective observational study to determine the association between HIV infection and the incidence of constrictive pericarditis among 185 patients (median age 33 years) with suspected tuberculous pericardial effusion. These patients were recruited consecutively between March and October 2004 on commencement of anti-tuberculosis treatment, from 15 hospitals in Cameroon, Nigeria and South Africa. Surviving patients (N = 119) were assessed for clinical evidence of constrictive pericarditis at 3 and 6 months of follow-up. Clinical features of HIV infection were present in 42 (35.2%) of the 119 patients at enrolment into the study. 66 of the 119 (56.9%) patients consented to HIV testing at enrolment. During the 6 months of follow-up, a clinical diagnosis of constrictive pericarditis was made in 13 of the 119 patients (10.9%, 95% confidence interval [CI] 5.9–18%). Patients with clinical features of HIV infection appear less likely to develop constriction than those without (4.8% versus 14.3%; P = 0.08). None of the 33 HIV seropositive patients developed constriction, but 8 (24.2%, 95%CI 11.1–42.3%) of the 33 HIV seronegative patients did (P = 0.005). In a multivariate logistic regression model adjusting simultaneously for several baseline characteristics, only clinical signs of HIV infection were significantly associated with a lower risk of constriction (odd ratio 0.14, 95% CI 0.02–0.87, P = 0.035).
Conclusions: These data suggest that HIV infection is associated with a lower incidence of pericardial constriction in patients with presumed tuberculous pericarditis.

Palomino-Doza J, Rahman TJ, Avery PJ, Mayosi BM, Farrall M, Watkins H, et al. Ambulatory blood pressure is associated with polymorphic variation in P2X receptor genes. Hypertension. 2008; 52(5):980–985. doi: 10.1161/hypertensionaha.108.113282. **Full text not freely available.**

The P2X receptor gene family encodes a series of proteins that function as ATP-gated nonselective ion channels. P2X receptor channels are involved in transducing aldosterone-mediated signaling in the distal renal tubule and are potential candidate genes for blood pressure regulation. We performed a family based quantitative genetic

association study in 248 families ascertained through a proband with hypertension to investigate the relationship between common genetic variation in the P2X4, P2X6, and P2X7 genes and ambulatory blood pressure. We genotyped 28 single nucleotide polymorphisms, which together captured the common genetic variability in the 3 genes. We corrected our results for multiple comparisons specifying a false discovery rate of 5%. We found significant evidence of association between the single nucleotide polymorphism rs591874 in the first intron of the P2X7 gene and blood pressure. The strongest association was found for nighttime diastolic blood pressure (P=0.0032), although association was present for both systolic and diastolic blood pressures measured by an observer during the day and at night. Genotypes were associated with a 0.2 SD (approximately 2.5 mm Hg) difference in night diastolic blood pressure per allele and accounted for approximately 1% of the total variability in this measurement. Other suggestive associations were found, but these were nonsignificant after correction for multiple testing. These genetic data suggest that drugs affecting P2X receptor signaling may have promise as clinical antihypertensive agents.

Robertson KA, Mayosi BM. Rheumatic heart disease: Social and economic dimensions. S Afr Med J. 2008;98(10):780–781. **Full text available here**.

No abstract available.

Russell JB, Syed FF, Ntsekhe M, Mayosi BM, Moosa S, Tshifularo M, et al. Tuberculous effusive-constrictive pericarditis. Cardiovasc J Afr. 2008;19(4):200–201. **Full text not freely available.**

Infection with *Mycobacterium tuberculosis* and the human immunodeficiency virus has reached epidemic proportions in South Africa. Cardiac involvement occurs in approximately one per cent of patients suffering from active tuberculosis. This concerns predominantly pericardial involvement, resulting in chronic pericardial effusions, cardiac tamponade and constrictive pericarditis. Effusive-constrictive pericarditis is a clinical haemodynamic syndrome in which constriction by the visceral pericardium occurs in the presence of a tense effusion in a free pericardial space. We present a patient who was diagnosed with this condition, and highlight the value of contrast-enhanced magnetic resonance imaging in demonstrating the underlying structural and functional abnormalities.

Spottiswoode B, Russell JB, Moosa S, Meintjes EM, Epstein FH, Mayosi BM. Abnormal diastolic and systolic septal motion following pericardiectomy demonstrated by cine DENSE MRI. Cardiovasc J Afr. 2008;19(4):208–209. **Full text not freely available.**

Constrictive pericarditis can lead to paradoxical interventricular septal motion. Displacement encoding with stimulated echoes (DENSE) magnetic resonance imaging (MRI) provides a method for quantifying myocardial motion and strain. A case of constrictive pericarditis is presented and the diastolic 'septal bounce' is clearly

evident in both anatomical and DENSE cine MRI images. (See video link to full-text electronic article). The postoperative systolic septal wall-motion abnormality of cardiac surgery is portrayed with greater precision by DENSE than anatomical cine MRI images.

Spottiswoode BS, Zhong X, Lorenz CH, Mayosi BM, Meintjes EM, Epstein FH. 3D myocardial tissue tracking with slice followed cine DENSE MRI. J Magn Reson Imaging. 2008;27(5):1019–1027. doi: 10.1002/jmri.21317. **Full text not freely available.**

Purpose: To track three-dimensional (3D) myocardial tissue motion using slice followed cine displacement encoded imaging with stimulated echoes (DENSE).

Materials and Methods: Slice following (SF) has previously been developed for 2D myocardial tagging to compensate for the effect of through-plane motion on 2D tissue tracking. By incorporating SF into a cine DENSE sequence, and applying displacement encoding in three orthogonal directions, we demonstrate the ability to track discrete elements of a slice of myocardium in 3D as the heart moves through the cardiac cycle. The SF cine DENSE tracking algorithm was validated on a moving phantom, and the effects of through-plane motion on 2D cardiac strain were investigated in six healthy subjects.

Results: A through-plane tracking accuracy of 0.46 ± 0.32 mm was measured for a typical range of myocardial motion using a rotating phantom. In vivo 3D measurements of cardiac motion were consistent with prior myocardial tagging results. Through-plane rotation in a mid-ventricularshort-axis view was shown to decrease the magnitude of the 2D end-systolic circumferential strain by 3.91 ± 0.43% and increase the corresponding radial strain by 6.01 ± 1.07%.

Conclusion: Slice followed cine DENSE provides an accurate method for 3D tissue tracking.

Syed FF, Aje A, Ntsekhe M, Mayosi BM, Moosa S, Tshifularo M, et al. Resolution of nodular myocardial tuberculosis demonstrated by contrast-enhanced magnetic resonance imaging. Cardiovasc J Afr. 2008; 19(4):198–199. **Full text not freely available.**

In sub-Saharan Africa, pericardial tuberculosis is frequently diagnosed in HIV sero-positive patients. Myocardial involvement has only rarely been reported. We present an HIV sero-positive patient in whom both pericardial and myocardial tuberculosis were diagnosed, and highlight the value of cardiac magnetic resonance imaging in the diagnosis and management of this condition.

Westwood T, Swingler G, Ross M, Patel B, Mayosi BM. Time for adolescent medicine units in South Africa? S Afr Med J. 2008;98(11):818, 820. **Full text not freely available.**

No abstract available.

Wiysonge CS, Ntsekhe M, Gumedze F, Sliwa K, Blackett KN, Commerford PJ, et al. Contemporary use of adjunctive corticosteroids in tuberculous pericarditis. Int J Cardiol. 2008;124(3):388–390. doi: 10.1016/j.ijcard.2006.12.060. **Full text not freely available.**

There is controversy concerning the effectiveness of adjunctive corticosteroids in reducing mortality in tuberculous pericarditis. To assess the impact of this controversy on contemporary clinical practice, we studied the use of adjunctive corticosteroid in 185 consecutive patients with suspected pericardial tuberculosis from 15 hospitals in Cameroon, Nigeria, and South Africa. 109 (58.9%) patients received steroids with significant variation in corticosteroid use ranging from 0% to 93.5% per centre (P<0.0001). The presence of clinical features of HIV infection was the independent predictor of the non-use of adjunctive corticosteroids (OR 0.39, 95% CI 0.20–0.75, P=0.005). We have demonstrated marked variation in the use of corticosteroids by practitioners, with nearly half of all patients not receiving this intervention. Taken together with the statistical uncertainty regarding the effectiveness of adjunctive steroids in tuberculous pericarditis, these observations probably reflect a state of genuine uncertainty or clinical equipoise among practitioners who care for patients with tuberculous pericarditis in sub-Saharan Africa. These data provide a justification for the establishment of adequately powered randomised clinical trials to assess the effectiveness of adjunctive corticosteroids in patients with tuberculous pericarditis.

2007

Baker M, Rahman T, Hall D, Avery PJ, Mayosi BM, Connell JM, et al. The C-532T polymorphism of the angiotensinogen gene is associated with pulse pressure: A possible explanation for heterogeneity in genetic association studies of AGT and hypertension. Int J Epidemiol. 2007;36(6):1356–1362. doi: 10.1093/ije/dym213. **Full text not freely available.**

Background: Many previous studies have investigated whether there is an association between genotypes at the angiotensinogen (AGT) gene and hypertensive status, but few have incorporated quantitative data. Although meta-analyses support a possible effect of AGT variants on blood pressure (BP), substantial unexplained between-study heterogeneity has been observed. We hypothesized that a primary effect of AGT variants on arterial stiffness (and thus pulse pressure) might explain such heterogeneity, and tested for such an effect in a family study.

Methods: We studied 1425 individuals from 248 families ascertained through a proband with essential hypertension. BP was measured using 24 h ambulatory monitoring, and polymorphisms of the AGT gene that had been previously associated with hypertension and/or plasma angiotensinogen levels were typed. Pulse pressure was used as a measurement of arterial stiffness.

Results: We observed a highly significant association between genotypes at the AGT C-532T polymorphism and pulse pressure ($p = 0.00006$). Each T allele was associated with a 5% lower pulse pressure (that is, an additive effect). This resulted from opposing genotypic effects to (slightly) lower systolic BP and (slightly) elevate DBP.

Conclusions: These results suggest that genetic variation at the angiotensinogen locus may primarily affect arterial stiffness, and therefore pulse pressure. The heterogeneity between previous genetic studies of AGT and hypertension status could in part be explained by this finding, since case selection criteria based on systolic BP, diastolic BP, or both would result in different levels of selection for the -532T allele.

Dahya V, Mayosi BM. Assessing scimitar syndrome – use of MRI and MRA. S Afr Med J. 2007; 97(4):248–249. **Full text available here.**

No abstract available.

Damasceno A, Cotter G, Dzudie A, Sliwa K, Mayosi BM. Heart failure in sub-saharan Africa: Time for action. J Am Coll Cardiol. 2007;50(17):1688–1693. doi: 10.1016/j.jacc.2007.07.030. **Full text not freely available.**

No abstract available.

Engel ME, Shaboodien G, Mayosi BM. No evidence for an association between the mitochondrial variant T16189C and dilated cardiomyopathy: A systematic review and meta-analysis. S Afr Med J. 2007;97(11):1094. **Full text not freely available.**

Background: Mitochondrial (mt) point mutations are associated with maternally inherited and sporadic cases of hypertrophic and dilated cardiomyopathy (DCM). Objective: This systematic review examined the association of mt T16189C variant with DCM, a disease characterised by dilatation and impaired contraction of the heart.

Methods: The authors searched all reports from original papers published in a number of databases up to August 2007, with no restriction on language. Predefined criteria were used to identify case-control studies examining the variant's association with DCM. Two observers (ME, GS) working independently evaluated the search outputs and two studies, supplemented by one unpublished report, met the inclusion criteria. Reviews and studies with an outcome other than DCM, other polymorphisms, or those not examining gene-association, were excluded. From each study, year of publication, origin and demographics of participants, matching procedures, diagnostic criteria, and information on variants were recorded. In the study which included subjects from differing ethnic backgrounds/geographical locations, data were extracted separately. The third reviewer served as arbitrator where necessary.

Results: Four populations conducted in European and African groups, contributed a total of 1002 subjects for analysis. Control groups comprised mainly hospital inpatients. Random-effects meta-analysis revealed a per-variant odds ratio of 1.68 (confidence interval: 0.89; 3.14 p=0.107) for T16189C. There was no statistically significant between-study heterogeneity for any of the comparison groups (χ^2-based Q statistic, p>0.1).

Conclusion: Thus, in this first systematic review on the effect of mt T16189C variant on DCM risk, the authors found no evidence for an association between the variant and DCM in case-control studies. This variant is not likely to be a significant risk factor for DCM.

Imrie H, Freel M, Mayosi B, Davies E, Fraser R, Ingram M, et al. Association between aldosterone production and variation in the gene encoding 11-beta hydroxylase (CYP11B1). Heart. 2007; 93:A80–A81. **Full text not freely available.**

Context: Variation in the region of chromosome 8 including the genes steroid 11-beta hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) influences mineralocorticoid and glucocorticoid metabolism. However, the relative importance of polymorphisms in CYP11B1 and CYP11B2 in determining these phenotypes is unknown.

Objective: To investigate genetic influences of the CYP11B1 and CYP11B2 genes on mineralocorticoid metabolism.
Design: We measured 24-h urinary excretion of the key metabolites of the principal mineralocortoids, gluco-corticoids and androgens secreted by the adrenal cortex. We genotyped polymorphisms spanning the CYP11B1 and CYP11B2 genes which together capture all common variation at the locus.
Participants: 573 members of 105 British white families ascertained on a hypertensive proband.
Main Outcome Measures: Heritability of urinary tetrahydroaldosterone (THAldo) excretion; association of THAldo excretion with genotype.
Results: The heritability of THAldo excretion was 52% ($p<10–6$). There was significant association between THAldo and genotype at several of the CYP11B1/B2 polymorphisms. The strongest association was observed at the rs6387 (2803A/G) polymorphism in intron 3 of CYP11B1 ($p = 0.0004$). Association followed a codominant model with a 21% higher THAldo excretion per G allele. Genotype at rs6387 accounted for 2.1% of the total population variability of THAldo. We found significant association between THAldo excretion and urinary total androgen excretion, urinary tetrahydrodeoxycortisol level, and urinary cortisol metabolites (all $p<0.001$).
Conclusions: Aldosterone synthesis is highly heritable, and is affected by genotype at CYP11B1. Our findings support the hypothesis that genetically determined differences in 11-hydroxylation efficiency can have downstream effects on mineralocorticoid synthesis. Such effects may be of relevance to the development of low renin essential hypertension.

Mayosi BM. Contemporary trends in the epidemiology and management of cardiomyopathy and pericarditis in sub-Saharan Africa. Heart. 2007;93(10):1176–1183. doi: 10.1136/hrt.2007.127746. **Full text not freely available.**

Heart failure in sub-Saharan Africans is mainly due to non-ischaemic causes, such as hypertension, rheumatic heart disease, cardiomyopathy and pericarditis. The two endemic diseases that are major contributors to the clinical syndrome of heart failure in Africa are cardiomyopathy and pericarditis. The major forms of endemic cardiomyopathy are idiopathic dilated cardiomyopathy, peripartum cardiomyopathy and endomyocardial fibrosis. Endomyocardial fibrosis, which affects children, has the worst prognosis. Other cardiomyopathies have similar epidemiological characteristics to those of other populations in the world. HIV infection is associated with occurrence of HIV-associated cardiomyopathy in patients with advanced immunosuppression, and the rise in the incidence of tuberculous pericarditis. HIV-associated tuberculous pericarditis is characterised by larger pericardial effusion, a greater frequency of myopericarditis, and a higher mortality than in people without AIDS. Population-based studies on the epidemiology of heart failure, cardiomyopathy and pericarditis in Africans, and studies of new interventions to reduce mortality, particularly in endomyocardial fibrosis and tuberculous pericarditis, are needed.

Mayosi BM, Somers K. Cardiomyopathy in Africa: heredity versus environment. Cardiovasc J Afr. 2007; 18(3):175–179. **Full text not freely available.**

Unlike other parts of the world in which cardiomyopathy is rare, heart muscle disease is endemic in Africa. The major forms of cardiomyopathy in Africa are dilated cardiomyopathy (DCM) and endomyocardial fibrosis (EMF). Whereas DCM is a major cause of heart failure throughout the continent, EMF is restricted to the tropical regions of East, Central, and West Africa. Although epidemiological studies are lacking, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy seem to have characteristics similar to those of other populations elsewhere in the world. Recent advances in the genetic analysis of DCM in other parts of the world indicate that it is a genetically heterogeneous disorder in which some cases have a Mendelian cause and others have a non-genetic or multifactorial cause. This heterogeneous pattern of inheritance has been confirmed in small studies that have been conducted so far in Africa. The advent of human immunodeficiency virus infection and its association with cardiomyopathy has emphasised the role of inflammatory agents in the pathogenesis of DCM. By contrast with DCM in which some cases have major genetic contributions, there is scanty evidence for the role of genetic factors in the aetiology of EMF. Although the pathogenesis of EMF is not fully understood, it appears that the conditioning factor may be geography (in its widest sense, to include climate and socio-economic status), the triggering factor may be an as yet unidentified infective agent, and the perpetuating factor may be eosinophilia. There is a need for renewed effort to identify genetic and non-genetic factors in EMF and other forms of heart muscle disease that are prevalent on the continent of Africa.

Mayosi B, Bryer A, Lambert V, Levitt N, Noakes T, Ntsekhe M, et al. A statement of intent on the formation of the NCRP on Cardiovascular and Metabolic Disease: A new initiative to fight heart disease, stroke, diabetes and obesity in South Africa. Cardiovasc J S Afr. 2007;18(1):4–6. **Full text not freely available.**

No abstract available.

Nkgudi B, Engel ME, Mayosi BM. Acute rheumatic fever surveillance in South Africa: An evaluation tool based on the CDC guidelines for evaluating public health surveillance systems. S Afr Med J. 2007; 97(11):1102. **Full text not freely available.**

Background: The primary objectives of disease surveillance are to monitor and control disease trends. In South Africa (SA), the system is based on law, coupled with guidelines by the department of health. An earlier study revealed a breakdown in the reporting of acute rheumatic fever (ARF) at local, provincial and national levels of the SA Health System. The CDC has published a generic set of guidelines for evaluating surveillance systems that can be adapted to different environments. We present an evaluation tool, based on these guidelines with contextual adaptations, for conducting an evaluation of the ARF surveillance system within the Cape Metro region of SA.

Methods: Five steps are incorporated; some of those outlined by the CDC guidelines will be forgone as they will

not be directly applicable. The first step will be engagement of the relevant stakeholders to ensure that the evaluation of the ARF notification system addresses appropriate questions and that it assesses the pertinent attributes of the system. Step two will be to describe the system as regards purpose, flow of information, and the resources required in maintaining the system. The third step involves a more focused structuring of the evaluation within our developing country context. Step four focuses on evidence for performance in adhering to the national ARF guidelines. This will involve engaging the daily users of the system. Thereafter, drawing conclusions and justified recommendations, to be communicated to the relevant stakeholders by way of a written or oral presentations, constitute steps five and six, respectively.
Result and conclusion: The CDC's guidelines, together with our modifications, appear to provide a practical framework on which to base a systematic yet tailored evaluation of the ARF surveillance system in South Africa. The CDC's guidelines are largely comprehensive and amendable to the contextual issues of ARF surveillance in SA.

Rahman T, Baker M, Hall D, Avery P, Mayosi B, Connell J, et al. The C-532T polymorphism of the angiotensinogen (AGT) gene is associated with arterial stiffness: A possible explanation for heterogeneity in genetic association studies of AGT and hypertension. Heart. 2007;93:A80. **Full text not freely available.**

Background: Many previous studies have investigated whether there is an association between genotypes at the angiotensinogen (AGT) gene and hypertensive status, but few have incorporated quantitative data. Although meta-analyses have suggested a possible effect of angiotensinogen variants on blood pressure, substantial unexplained between-study heterogeneity has been observed. We hypothesised that a primary effect of angiotensinogen variants on arterial stiffness (and thus pulse pressure) might explain such heterogeneity, and tested for such an effect in a family study.
Methods and Results: We studied 1425 individuals from 248 families ascertained via a hypertensive proband. Blood pressure was measured using 24-h ambulatory monitoring, and polymorphisms of the angiotensinogen gene that had been previously associated with hypertension and/or plasma angiotensinogen levels were typed. Pulse pressure was used as a measurement of arterial stiffness. We observed a highly significant association between genotypes at the AGT C-532T polymorphism and pulse pressure ($p<0.0001$). The -532T allele was associated with a 5% lower pulse pressure, in a co-dominant fashion. This resulted from genotypic effects in opposite directions both on systolic BP (slightly lower) and DBP (slightly higher) which individually were not significant even in this large study.
Interpretation: These results suggest that genetic variation at the angiotensinogen locus principally affects arterial stiffness and therefore pulse pressure. The heterogeneity observed in previous genetic studies of
AGT and hypertension status could in part be explained by this finding, since case selection criteria based on systolic BP, diastolic BP, or both would result in different levels of selection for the -532T allele.

Robson SC, Voigt M, Zent R, Bass T, Meissner P, Hift R, et al. Eric Lemmer – In memoriam. S Afr Med J. 2007;97(9):838–839. **Full text not freely available.**

No abstract available.

Sanderson JE, Mayosi B, Yusuf S, Reddy S, Hu S, Chen Z, et al. Global burden of cardiovascular disease. Heart. 2007;93(10):1175. doi: 10.1136/hrt.2007.131060.

No abstract available.

Shaboodien G, Badri M, Mayosi BM. Is mitochonrial variant T16189C associated with an increased risk of dilated cardiomyopathy in HIV positive patients? S Afr Med J. 2007;97(11):1105. **Full text not freely available.**

Background: Mitochondrial variant T16189C has been reported to be associated with an increased risk of dilated cardiomyopathy. It generates an uninterrupted homopolymeric C-tract (approximately 10 cytosines), which causes heteroplasmic length variation of the mtDNA, possibly as a result of replication slippage. We hypothesize that this variant predisposes to HIV associated cardiomyopathy.

Objective: To determine the frequency of the T16189C variant in HIV associated cardiomyopathy (HIVAC) patients.

Method: A detailed four year case-control study (2002–2006) was designed and three South African black cohorts recruited: 30 HIV positive black patients with dilated cardiomyopathy, 38 HIV positive black controls without dilated cardiomyopathy and 117 HIV negative controls without dilated cardiomyoapthy (background population). Where possible, cases and controls were matched for age and gender. All 185 DNA samples were sequenced in the forward and reverse directions on an ABI3100 sequencer.

Results: The T16189C variant was detected at a frequency of 70% (21/30) in the HIVACs, 66% in the HIV positive controls (25/38) and 76% in the South African background population (89/117). There was no significant difference in the frequency distribution of the variant between the three groups (p=0.43). The presence of a substitution, other than the T16189C variant, appeared to stabilize the homopolymeric C-track. Numerous other variants were also found in this hypervariable region. Base substitutions were found to occur more at positions C16187 and T16189 compared with the other bases. Also observed was that more changes were prevalent in the HIV positive groups (HIVAC and HIV positive control group) compared to the background population (without HIV).

Conclusion: This study found that the T16189C variant is not a risk factor for HIV associated cardiomyopathy.

Spottiswoode BS, Zhong X, Hess AT, Kramer CM, Meintjes EM, Mayosi BM, et al. Tracking myocardial motion from cine DENSE images using spatiotemporal phase unwrapping and temporal fitting. IEEE Trans Med Imaging. 2007;26(1):15–30. doi: 10.1109/tmi.2006.884215. **Full text not freely available.**

Displacement encoding with stimulated echoes (DENSE) encodes myocardial tissue displacement into the phase of the MR image. Cine DENSE allows for rapid quantification of myocardial displacement at multiple cardiac phases through the majority of the cardiac cycle. For practical sensitivities to motion, relatively high displacement encoding frequencies are used and phase wrapping typically occurs. In order to obtain absolute measures of displacement, a two-dimensional (2-D) quality-guided phase unwrapping algorithm was adapted to unwrap both spatially and temporally. Both a fully automated algorithm and a faster semi-automated algorithm are proposed. A method for computing the 2-D trajectories of discrete points in the myocardium as they move through the cardiac cycle is introduced. The error in individual displacement measurements is reduced by fitting a time series to sequential displacement measurements along each trajectory. This improvement is in turn reflected in strain maps, which are derived directly from the trajectories. These methods were validated both in vivo and on a rotating phantom. Further measurements were made to optimize the displacement encoding frequency and to estimate the baseline strain noise both on the phantom and in vivo. The fully automated phase unwrapping algorithm was successful for 767 out of 800 images (95.9%), and the semi-automated algorithm was successful for 786 out of 800 images (98.3%). The accuracy of the tracking algorithm for typical cardiac displacements on a rotating phantom is 0.24 ± 0.15 mm. The optimal displacement encoding frequency is in the region of 0.1 cycles/mm, and, for 2 scans of 17-s duration, the strain noise after temporal fitting was estimated to be 2.5 ± 3.0% at end-diastole, 3.1 ± 3.1% at end-systole, and 5.3 ± 5.0% in mid-diastole. The improvement in intra-myocardial strain measurements due to temporal fitting is apparent in strain histograms, and also in identifying regions of dysfunctional myocardium in studies of patients with infarcts.

Syed FF, Mayosi BM. A modern approach to tuberculous pericarditis. Prog Cardiovasc Dis. 2007; 50(3):218–236. doi: 10.1016/j.pcad.2007.03.002. **Full text not freely available.**

The human immunodeficiency virus (HIV) epidemic has been associated with an increase in all forms of extrapulmonary tuberculosis including tuberculous pericarditis. Tuberculosis is responsible for approximately 70% of cases of large pericardial effusion and most cases of constrictive pericarditis in developing countries, where most of the world's population live. However, in industrialized countries, tuberculosis accounts for only 4% of cases of pericardial effusion and an even smaller proportion of instances of constrictive pericarditis. Tuberculous pericarditis is a dangerous disease with a mortality of 17% to 40%; constriction occurs in a similar proportion of cases after tuberculous pericardial effusion. Early diagnosis and institution of appropriate therapy are critical to prevent mortality. A definite or proven diagnosis is based on demonstration of tubercle bacilli in pericardial fluid or on histologic section of the pericardium. A probable or presumed diagnosis is based on proof of tuberculosis elsewhere in a patient with otherwise unexplained pericarditis, a lymphocytic pericardial exudate with elevated biomarkers of tuberculous infection, and/or appropriate response to a trial of antituberculosis chemotherapy. Treatment consists of 4-drug therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol) for 2 months followed by 2 drugs (isoniazid and rifampicin) for 4 months regardless of HIV status. It is uncertain whether

adjunctive corticosteroids are effective in reducing mortality or pericardial constriction, and their safety in HIV-infected patients has not been established conclusively. Surgical resection of the pericardium is indicated for those with calcific constrictive pericarditis or with persistent signs of constriction after a 6 to 8 week trial of antituberculosis treatment in patients with noncalcific constrictive pericarditis.

Tibazarwa K, Volmink J, Mayosi BM. The incidence of acute rheumatic fever in the world: A systematic review of population-based studies. S Afr Med J. 2007;97(11):1107. **Full text not freely available.**

Background: Acute rheumatic fever is a multi-organ disease resulting from an autoimmune response of the body to infection with Lancefield GroupA β haemolytic streptococci (GAS). Overall, industrialized countries have experienced a declining incidence of acute rheumatic fever over the past 100 years. However, despite evidence of the effectiveness of antibiotic treatment of GAS pharyngitis in reducing the incidence of ARF, developing countries continue to experience a high burden of the disease and its chronic sequel, rheumatic heart disease.

Aim: To summarise data from population-based studies on the magnitude of, and temporal trends in, the incidence of acute rheumatic fever.

Method: We conducted a comprehensive search of MEDLINE, EMBASE, and other health-related databases identifying all published prospective population-based studies of the incidence of acute rheumatic fever that fulfilled pre-specified inclusion and exclusion criteria. We critically reviewed each study assessing both mean incidence rate of first attack of acute rheumatic fever per year (calculated over the entire study period for each study), and annum specific incidence rate (for those studies documenting incident cases specific to each year of study).

Results: Our review included 10 eligible studies conducted in 10 different countries (none in Africa) The overall mean incidence rate of first attack of acute rheumatic fever per year for each study ranged from 5 to 51 per 100 000 population (mean 19 per 100 000; 95% CI 9 - 30 per 100 000). A low incidence of acute rheumatic fever of ≤10 per 100 000 per year was found in North and South America, and in Northern Europe. There was a high incidence of >10 per 100 000 in Eastern Europe, Middle East, Asia, and Australasia. Annum-specific incidence rates were higher in the Middle East than in other regions. There was a fall in the incidence of acute rheumatic fever over time in all countries with longitudinal data [Figure 1].

Conclusions: There has been a modest decline in the incidence of acute rheumatic fever over time globally, however, the disease still occurs relatively frequently in Eastern Europe, the Middle East, and Australasia. There are no population-based incidence studies of acute rheumatic fever in Africa, a continent that bears the highest number of cases of rheumatic heart disease in the world.

Vaughan CL, Mayosi BM. Origins of computed tomography. Lancet. 2007;369(9568):1168. doi: 10.1016/s0140-6736(07)60562-5. **Full text not freely available.**

No abstract available.

Wiysonge CS, Bradley H, Mayosi BM, Maroney R, Mbewu A, Opie LH, et al. Beta-blockers for hyper-tension. Cochrane Database Syst Rev. 2007(1):Cd002003. doi: 10.1002/14651858.CD002003.pub2.

Full text not freely available.

Background: Two recent systematic reviews found first-line beta-blockers to be less effective in reducing the incidence of stroke and the combined endpoint of stroke, myocardial infarction, and death compared to all other antihypertensive drugs taken together. However, beta-blockers might be better or worse than a specific class of drugs for a particular outcome measure so that comparing beta-blockers with all other classes taken together could be misleading. In addition, these systematic reviews did not assess the tolerability of beta-blockers relative to other antihypertensive medications. We thus undertook this review to re-assess the place of beta-blockade as first-line therapy for hypertension relative to each of the other major classes of antihypertensive drugs.

Objectives: To quantify the effectiveness and safety of beta-blockers on morbidity and mortality endpoints in adults with hypertension.

Search strategy: We searched eligible studies up to June 2006 in the Cochrane Controlled Trials Register, Medline, Embase, and reference lists of previous reviews, and by contacting hypertension experts.

Selection criteria: We selected randomised controlled trials which assessed the effectiveness of beta-blockers compared to placebo, no therapy or other drug classes, as monotherapy or first-line therapy for hypertension, on mortality and morbidity endpoints in men and non-pregnant women aged 18 years or older.

Data collection and analysis: At least two authors independently applied study selection criteria, assessed study quality, and extracted data; with differences resolved by consensus. We expressed study results as relative risks (RR) with 95% confidence intervals (CI) and conducted quantitative analyses with trial participants in groups to which they were randomly allocated, regardless of which or how much treatment they actually received. In the absence of significant heterogeneity between studies ($p>0.1$), we performed meta-analysis using a fixed effects method. Otherwise, we used the random effects method and investigated the cause of heterogeneity by stratified analysis. In addition, we used the Higgins statistic (I^2) to quantify the amount of between-study variability in effect attributable to true heterogeneity rather than chance.

Main results: Thirteen randomised controlled trials (N=91,561 participants), which met our inclusion criteria, compared beta-blockers to placebo or no treatment (4 trials with 23,613 participants), diuretics (5 trials with 18,241 participants), calcium-channel blockers (CCBs: 4 trials with 44,825 participants), and renin-angiotensin system (RAS) inhibitors (3 trials with 10,828 participants). The risk of all-cause mortality was not different between first-line beta-blockers and placebo (RR 0.99, 95%CI 0.88 to 1.11, I^2=0%), diuretics or RAS inhibitors, but was higher for beta-blockers compared to CCBs (RR 1.07, 95%CI 1.00 to 1.14, I^2=2.2%; ARI=0.5%, NNH=200). The risk of total cardiovascular disease (CVD) was lower for first-line beta-blockers compared to placebo (RR 0.88, 95%CI 0.79 to 0.97, I^2=21.4%, ARR=0.7%, NNT=140). This is primarily a reflection of the significant decrease in stroke (RR 0.80, 95%CI 0.66 to 0.96; I^2=0%; ARR=0.5%, NNT=200); coronary heart disease (CHD) risk was not significantly different between beta-blockers and placebo. The effect of beta-blockers on CVD was

significantly worse than that of CCBs (RR 1.18, 95%CI 1.08 to 1.29, I^2=0%; ARI=1.3%, NNH=80), but was not significantly different from that of diuretics or RAS inhibitors. Increased total CVD was due to an increase in stroke compared to CCBs (RR 1.24, 95%CI 1.11 to 1.40, I^2=0%; ARI=0.6%, NNH=180). There was also an increase in stroke with beta-blockers as compared to RAS inhibitors (RR 1.30, 95%CI 1.11 to 1.53, I^2=29.1%; ARI=1.5%, NNH=65). CHD was not significantly different between beta-blockers and diuretics or CCBs or RAS inhibitors. In addition, patients on beta-blockers were more likely to discontinue treatment due to side effects than those on diuretics (RR 1.86, 95%CI 1.39 to 2.50, I^2=78.2%, ARI=6.4% NNH=16) and RAS inhibitors (RR 1.41, 95%CI 1.29 to 1.54, I^2=12.1%; ARI=5.5%, NNH=18), but there was no significant difference with CCBs.
Authors' conclusions: The available evidence does not support the use of beta-blockers as first-line drugs in the treatment of hypertension. This conclusion is based on the relatively weak effect of beta-blockers to reduce stroke and the absence of an effect on coronary heart disease when compared to placebo or no treatment. More importantly, it is based on the trend towards worse outcomes in comparison with calcium-channel blockers, renin-angiotensin system inhibitors, and thiazide diuretics. Most of the evidence for these conclusions comes from trials where atenolol was the beta-blocker used (75% of beta-blocker participants in this review). However, it is not known at present whether beta-blockers have differential effects on younger and elderly patients or whether there are differences between the different sub-types of beta-blockers.

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Bradley HA, Wiysonge CS, Volmink JA, Mayosi BM, Opie LH. How strong is the evidence for use of beta-blockers as first-line therapy for hypertension? Systematic review and meta-analysis. J Hypertens. 2006; 24(11):2131–2141. doi: 10.1097/01.hjh.0000249685.58370.28. **Full text not freely available.**

Objective: To quantify the effect of first-line antihypertensive treatment with beta-blockers on mortality, morbidity and withdrawal rates, compared with the other main classes of antihypertensive agents.

Methods: We identified eligible trials by searching the Cochrane Controlled Trials Register, Medline, Embase, reference lists of previous reviews, and contacting researchers. We extracted data independently in duplicate and conducted meta-analysis by analysing trial participants in groups to which they were randomized, regardless of subsequent treatment actually received.

Results: Thirteen trials with 91,561 participants, meeting inclusion criteria, compared beta-blockers to placebo (four trials; n = 23,613), diuretics (five trials; n = 18,241), calcium-channel blockers (CCBs) (four trials; n = 44,825), and renin-angiotensin system (RAS) inhibitors, namely angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (three trials; n = 10,828). Compared to placebo, beta-blockers reduced the risk of stroke (relative risk 0.80; 95% confidence interval 0.66–0.96) with a marginal fall in total cardiovascular events (0.88, 0.79–0.97), but did not affect all-cause mortality (0.99, 0.88–1.11), coronary heart disease (0.93, 0.81–1.07) or cardiovascular mortality (0.93, 0.80–1.09). The effect on stroke was less than that of CCBs (1.24, 1.11–1.40) and RAS inhibitors (1.30, 1.11–1.53), and that on total cardiovascular events less than that of CCBs (1.18, 1.08–1.29). In addition, patients on beta-blockers were more likely to discontinue treatment than those on diuretics (1.80; 1.33–2.42) or RAS inhibitors (1.41; 1.29–1.54).

Conclusion: Beta-blockers are inferior to CCBs and to RAS inhibitors for reducing several important hard end points. Compared with diuretics, they had similar outcomes, but were less well tolerated. Hence beta-blockers are generally suboptimal first-line antihypertensive drugs.

Carapetis JR, Mayosi BM, Kaplan EL. Controlling rheumatic heart disease in developing countries. Cardiovasc J S Afr. 2006;17(4):164–165. **Full text not freely available.**

No abstract available.

Commerford P, Mayosi B. An appropriate research agenda for heart disease in Africa. Lancet. 2006; 367(9526):1884–1886. doi: 10.1016/s0140-6736(06)68822-3. **Full text not freely available.**

No abstract available.

Commerford PJ, Mayosi BM. Acute rheumatic fever. Medicine. 2006;34(6):239–243. doi: https://doi.org/10.1383/medc.2006.34.6.239. **Full text not freely available.**

Aetiology: Acute rheumatic fever (ARF) is a systemic inflammatory disease that occurs 2–3 weeks after a group A streptococcal infection. ARF is mediated by an autoimmune response to antigenic components of the organism that cross-react with similar epitopes in the heart, joints, brain and skin.

Presentation: ARF is characterized by major and minor manifestations. Major manifestations are arthritis (migratory polyarthritis), cardiac abnormalities (pericarditis, myocarditis, and valvulitis), neurological changes (Sydenham's chorea), and cutaneous involvement (erythema marginatum, subcutaneous nodules). Minor manifestations of ARF are fever, arthralgia, a prolonged PR interval, and elevated acute phase reactants (ESR, C-reactive protein).

Diagnosis: The diagnosis of the initial episode of ARF requires the presence of two major manifestations or one major and two minor manifestations, plus evidence of preceding group A streptococcal infection (e.g. elevated or rising streptococcal antibody titre). A recurrence may be diagnosed on the basis of a single major or several minor manifestations in a patient with a history of ARF or established rheumatic heart disease.

Management: the aims of treatment of ARF are to suppress the inflammatory response so as to minimize cardiac damage, to provide symptomatic relief and eradicate streptococcal infection. All patients with ARF require long-term secondary antibiotic prophylaxis to prevent recurrent attacks.

Prognosis: Carditis is the most serious manifestation of ARF as it may lead to severe life-threatening heart failure. If antibiotic prophylaxis is not used, repeated attacks of ARF lead to chronic rheumatic heart valve disease, heart failure, and a shortened life span.

Freel M, Keavney B, Avery P, Mayosi B, Gaukrodger N, Imrie H, et al. Genetic variation at the CYP11B locus accounts for heritabilities of aldosterone metabolite (THAIdo) excretion and 11beta-hydroxylase activity. Hypertension. 2006;48(4):e36–e37. **Full text not freely available.**

Aldosterone is a key cardiovascular hormone: 15 % of hypertensives have altered aldosterone regulation, defined by a raised ratio of aldosterone to renin. However, the causes of aldosterone excess are not understood. Polymorphic variation in the gene encoding aldosterone synthase (CYP11B2) is associated with hypertension, but the best characterised intermediate phenotype is a relative reduction in efficiency of 11β-hydroxylation (conversion of deoxycortisol to cortisol), which reflects function of the enzyme,11β-hydroxylase, encoded by the adjacent gene (CYP11B1). This is expressed in zona fasciculata, and is not involved in aldosterone synthesis. To

characterise better the genetic regulation of aldosterone synthesis we have used a family study to define heritability of steroid phenotypes and identify key genetic determinants. We genotyped 6 polymorphisms in CYP11B2 and 3 in CYP11B1 in 248 nuclear families and measured urinary excretion rates of the major metabolites of aldosterone (THAldo), deoxycortisol (THS) total cortisol (F) and androgens in 573 subjects from 105 families. The efficiency of 11β-hydroxylation, previously noted to be associated with CYP11B2, was assessed by the THS/F ratio. THAldo and THS/F were highly heritable ($p<0.0001$). THAldo excretion and THS/F associated most strongly with polymorphisms in CYP11B1 (exon 1 and intron 3) (<0.001). THAldo excretion was closely correlated with F, androgens and THS/F (all $p<0.001$). We have shown, for the first time, that aldosterone production is heritable, reflecting genetic regulation, and confirmed the heritability of THS/F, the index of 11β-hydroxylation. The same polymorphisms in CYP11B1 account for variability in THAldo excretion and reduced efficiency of 11β-hydroxylation, consistent with the hypothesis that a genetically determined change in 11βhydroxylase efficiency leads to an increase in adrenal ACTH drive that, over years, amplifies aldosterone production. This proposal is strongly supported by the correlations demonstrated between THAldo and ACTH-dependent steroids (cortisol and androgens) and between THAldo and the index of 11βhydroxylase efficiency. These data provide novel insights into the possible origins of aldosterone-associated hypertension.

Imrie H, Freel M, Mayosi BM, Davies E, Fraser R, Ingram M, et al. Association between aldosterone production and variation in the 11β-hydroxylase (CYP11B1) gene. J Clin Endocrinol Metab. 2006; 91(12):5051–5056. doi: 10.1210/jc.2006-1481. **Full text not freely available.**

Context: Variation in the region of chromosome 8 including the genes steroid 11β-hydroxylase (CYP11B1) and aldosterone synthase (CYP11B2) influences mineralocorticoid and glucocorticoid metabolism. However, the relative importance of polymorphisms in CYP11B1 and CYP11B2 in determining these phenotypes is unknown.

Objective: Our objective was to investigate genetic influences of the CYP11B1 and CYP11B2 genes on mineralocorticoid metabolism.

Design: We measured 24-h urinary excretion of the key metabolites of the principal mineralocorticoids, glucocorticoids and androgens secreted by the adrenal cortex. We genotyped polymorphisms spanning the CYP11B1 and CYP11B2 genes, which together capture all common variations at the locus.

Participants: Participants included 573 members of 105 British Caucasian families ascertained on a hypertensive proband.

Main Outcome Measures: We assessed heritability of urinary tetrahydroaldosterone (THAldo) excretion and association of THAldo excretion with genotype.

Results: The heritability of THAldo excretion was 52% ($P < 10^{-6}$). There was significant association between THAldo and genotype at several of the CYP11B1/B2 polymorphisms. The strongest association was observed at the rs6387 (2803A/G) polymorphism in intron 3 of CYP11B1 ($P = 0.0004$). Association followed a codominant model with a 21% higher THAldo excretion per G allele. Genotype at rs6387 accounted for 2.1% of the total

population variability of THAldo. We found significant association between THAldo excretion and urinary total androgen excretion, urinary tetrahydrodeoxycortisol level, and urinary cortisol metabolites (all $P < 0.001$).
Conclusions: Aldosterone synthesis is highly heritable and is affected by genotype at CYP11B1. Our findings support the hypothesis that genetically determined differences in 11-hydroxylation efficiency can have downstream effects on mineralocorticoid synthesis. Such effects may be of relevance to the development of low-renin essential hypertension.

Khumalo NP, Pillay K, Beighton P, Wainwright H, Walker B, Saxe N, et al. Poikiloderma, tendon contracture and pulmonary fibrosis: A new autosomal dominant syndrome? Br J Dermatol. 2006; 155(5):1057–1061. doi: 10.1111/j.1365-2133.2006.07473.x. **Full text not freely available.**

Members of two generations of a South African family have a unique syndrome comprising poikiloderma, tendon contractures and progressive pulmonary fibrosis. The condition is clinically important as the skin changes, which involve the face, have considerable cosmetic impact, while lung involvement is potentially lethal in adulthood. Skin manifestations which facilitate diagnosis include facial telangiectasia, mottled hypo- and hyperpigmentation, papules and epidermal atrophy. The scalp, facial and body hair are fine and scanty. The tendon contractures lead to progressive digital flexion deformities and abnormalities of the ankles and feet, with disturbance of gait. Pulmonary involvement manifests as progressive dyspnoea. Pedigree data are compatible with an autosomal dominant mode of transmission. Poikiloderma of Weary is characterized by linear sclerotic and fibrous bands and not tendon contractures and is not associated with potentially lethal pulmonary fibrosis. Rather than name this disorder a variant of Weary syndrome, it might be prudent to use as an umbrella title one composed by Weary himself: 'hereditary sclerosing poikiloderma' (HSP), under which variants such as HSP Weary type, HSP with cardiac involvement (aortic stenosis described as inconsistently associated with Weary syndrome) and HSP with tendon/pulmonary involvement (current family) may be classified. The manifestations in this family differ from other poikilodermata and, to the best of our knowledge, have not been previously documented.

Matolweni LO, Bardien S, Rebello G, Oppon E, Munclinger M, Ramesar R, et al. Arrhythmogenic right ventricular cardiomyopathy type 6 (ARVC6): Support for the locus assignment, narrowing of the critical region and mutation screening of three candidate genes. BMC Med Genet. 2006;7:29. doi: 10.1186/1471-2350-7-29. **Full text available here.**

Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heritable disorder characterized by progressive degeneration of right ventricular myocardium, arrhythmias and an increased risk of sudden death at a young age. By linkage analysis, ARVC type 6 was previously mapped to a 10.6 cM region on chromosome 10p12-p14 in a large North American kindred. To date, the genetic defect that causes ARVC6 has not been identified.
Methods: We identified a South African family of 13 members with ARVC segregating as an autosomal dominant

disorder. The diagnosis of ARVC was based on international diagnostic criteria. All available family members were genotyped with microsatellite markers at six known ARVC loci, and positional candidate gene screening was performed.
Results: Genetic linkage and haplotype analysis provided lod scores that are highly suggestive of linkage to the ARVC6 locus on chromosome 10p12-p14, and the narrowing of the critical region to approximately 2.9 Mb. Two positional candidate genes (*ITG8* and *FRMD4A*) were screened in which defects could possibly disrupt cell-cell adhesion. A non-positional candidate gene with apoptosis inducing properties, *LAMR1P6* (laminin receptor 1 pseudogene 6) was also screened. Direct sequencing of DNA from affected individuals failed to detect disease-causing mutations in the exonic sequences of the three genes investigated.
Conclusion: The narrowing of the ARVC6 critical region may facilitate progress towards the identification of the gene that is involved in ARVC. Identification of the causative genes for ARVC will contribute to the understanding of the pathogenesis and management of this poorly understood condition.

Mayosi BM. A proposal for the eradication of rheumatic fever in our lifetime. S Afr Med J. 2006; 96(3):229–230. **Full text available here**.

No abstract available.

Mayosi BM. Protocols for antibiotic use in primary and secondary prevention of rheumatic fever. S Afr Med J. 2006;96(3 Pt 2):240. **Full text available here**.

No abstract available.

Mayosi BM, Kardos A, Davies CH, Gumedze F, Hovnanian A, Burge S, et al. Heterozygous disruption of SERCA2a is not associated with impairment of cardiac performance in humans: Implications for SERCA2a as a therapeutic target in heart failure. Heart. 2006;92(1):105–109. doi: 10.1136/hrt.2004.051037. **Full text not freely available.**

Objective: To verify whether a deficiency in the cardiac sarcoplasmic reticulum pump SERCA2a causes cardiac dysfunction in humans.
Design: Cardiac performance was measured in a serendipitous human model of primary SERCA2a deficiency, Darier's disease, an autosomal dominant skin disorder caused by mutations inactivating one copy of the ATP2A2 gene, which encodes SERCA2a.
Methods: Systolic and diastolic function and contractility were assessed by echocardiography at rest and during exercise in patients with Darier's disease with known mutations. Fourteen patients with Darier's disease were compared with 14 normal controls and six patients with dilated cardiomyopathy with stable heart failure.
Results: Resting systolic and diastolic function was normal in patients with Darier's disease and in controls. The

increase in systolic function during exercise was not different between patients with Darier's disease and normal controls; neither was there a difference in contractility. As expected, patients with dilated cardiomyopathy had impaired diastolic and systolic function with depressed contractility at rest and during exercise.
Conclusion: Contrary to expectations, heterozygous disruption of SERCA2a is not associated with the impairment of cardiac performance in humans. Attempts to increase SERCA2a levels in heart failure, although showing promise in rodent studies, may not be addressing a critical causal pathway in humans.

Mayosi B, Robertson K, Volmink J, Adebo W, Akinyore K, Amoah A, et al. The Drakensberg Declaration on the control of rheumatic fever and rheumatic heart disease in Africa. S Afr Med J. 2006; 96(3 Pt 2):246. **Full text available here.**

No abstract available.

Mayosi BM, Wiysonge CS, Ntsekhe M, Volmink JA, Gumedze F, Maartens G, et al. Clinical characteristics and initial management of patients with tuberculous pericarditis in the HIV era: The Investigation of the Management of Pericarditis in Africa (IMPI Africa) registry. BMC Infect Dis. 2006; 6:2. doi: 10.1186/1471-2334-6-2. **Full text available here.**

Background: The incidence of tuberculous pericarditis has increased in Africa as a result of the human immuno-deficiency virus (HIV) epidemic. However, the effect of HIV co-infection on clinical features and prognosis in tuberculous pericarditis is not well characterised. We have used baseline data of the Investigation of the Management of Pericarditis in Africa (IMPI Africa) registry to assess the impact of HIV co-infection on clinical presentation, diagnostic evaluation, and treatment of patients with suspected tuberculous pericarditis in sub-Saharan Africa.
Methods: Consecutive adult patients in 15 hospitals in three countries in sub-Saharan Africa were recruited on commencement of treatment for tuberculous pericarditis, following informed consent. We recorded demographic, clinical, diagnostic and therapeutic information at baseline, and have used the chi-square test and analysis of variance to assess probabilities of significant differences (in these variables) between groups defined by HIV status.
Results: A total of 185 patients were enrolled from 01 March 2004 to 31 October 2004, 147 (79.5%) of whom had effusive, 28 (15.1%) effusive-constrictive, and 10 (5.4%) constrictive or acute dry pericarditis. Seventy-four (40%) had clinical features of HIV infection. Patients with clinical HIV disease were more likely to present with dyspnoea (odds ratio [OR] 3.2, 95% confidence interval [CI] 1.4 to 7.4, P = 0.005) and electrocardiographic features of myopericarditis (OR 2.8, 95% CI 1.1 to 6.9, P = 0.03). In addition to electrocardiographic features of myopericarditis, a positive HIV serological status was associated with greater cardiomegaly (OR 3.89, 95% CI 1.34 to 11.32, P = 0.01) and haemodynamic instability (OR 9.68, 95% CI 2.09 to 44.80, P = 0.0008). However, stage of

pericardial disease at diagnosis and use of diagnostic tests were not related to clinical HIV status. Similar results were obtained for serological HIV status. Most patients were treated on clinical grounds, with microbiological evidence of tuberculosis obtained in only 13 (7.0%) patients. Adjunctive corticosteroids were used in 109 (58.9%) patients, with patients having clinical HIV disease less likely to be put on them (OR 0.37, 95% CI 0.20 to 0.68). Seven patients were on antiretroviral drugs.

Conclusion: Patients with suspected tuberculous pericarditis and HIV infection in Africa have greater evidence of myopericarditis, dyspnoea, and haemodynamic instability. These findings, if confirmed in other studies, may suggest more intensive management of the cardiac disease is warranted in patients with HIV-associated pericardial disease.

Nkgudi B, Robertson KA, Volmink J, Mayosi BM. Notification of rheumatic fever in South Africa – evidence for underreporting by health care professionals and administrators. S Afr Med J. 2006; 96(3):206–208. **Full text available here**.

Objective: To determine whether under-reporting of rheumatic fever occurs at hospital, municipal, provincial and national levels of the South African health system.

Background: Information on the incidence of rheumatic fever (RF) and the prevalence of rheumatic heart disease (RHD) is required for the prevention of valvular heart disease in developing countries. In South Africa, RF was made a notifiable condition in 1989. It has recently been suggested that the reporting of RF cases may be incomplete, possibly because of underreporting by health care professionals and deficient administration of the disease notification system in South Africa.

Method and results: We assessed whether underreporting of RF cases occurs by comparing the numbers of RF cases reported per year at hospital, municipal, provincial and national levels from 1990 to 2004. There was a fall in the number of RF cases reported per year at national and provincial level over the 15 years of observation. A detailed analysis of the number of RF cases reported at hospital, municipal and provincial level for a 5-year period showed that more cases were diagnosed in one hospital (serving a smaller population) than were captured at municipal and provincial level (serving a larger population), suggesting underreporting by health care professionals. There were discrepancies in the number of cases reported at municipal, provincial and national level, suggesting poor administration of the notification system.

Conclusion: There appears to be underreporting of RF cases by health care professionals, and poor administration of the RF notification system. Health care professionals need to be educated about the statutory requirement to notify all RF cases in South Africa. An effective national disease notification system is required.

Ntsekhe M, Mayosi B. Infectious disease of the heart. CME. 2006;24(4):189–193. **Full text not freely available.**

No abstract available.

Robertson KA, Volmink JA, Mayosi BM. Towards a uniform plan for the control of rheumatic fever and rheumatic heart disease in Africa – The Awareness Surveillance Advocacy Prevention (A.S.A.P.) programme. S Afr Med J. 2006;96(3 II):241–245. **Full text available here**

No abstract available.

Segal A, Van Helden P, Quesniaux V, Brown G, Speert DP, Mantovani A, et al. Discussion. In Novartis Foundation Symposium. 2006;279:31–41. **Full text not freely available.**

No abstract available.

Smedema E, Mayosi BM, Smedema JP. Hydatid disease – the 'water lily' sign. S Afr Med J. 2006; 96(10):1042. **Full text available here**.

No abstract available.

Wiysonge CS, Ntsekhe M, Gumedze F, Maartens G, Volmink JA, Commerford PJ, et al. Excess mortality in presumed tuberculous pericarditis. Eur Heart J. 2006;27:958. doi: https://doi.org/10.1093/eurheartj/ehl215. **Full text not freely available.**

No abstract available.

2005

Baker M, Gaukrodger N, Mayosi BM, Imrie H, Farrall M, Watkins H, et al. Association between common polymorphisms of the proopiomelanocortin gene and body fat distribution: A family study. Diabetes. 2005;54(8):2492–2496. doi: 10.2337/diabetes.54.8.2492. **Full text not freely available.**

Rare mutations in the proopiomelanocortin (*POMC*) gene cause severe early-onset childhood obesity. However, it is unknown whether common variants in *POMC* are responsible for variation in body weight or fat distribution within the commonly observed range in the population. We tested for association between three polymorphisms spanning the *POMC* gene and obesity phenotypes in 1,428 members of248 families. There was significant association between genotypes at the C8246T ($P < 0.0001$) and C1032G ($P = 0.003$) polymorphisms and waist-to-hip ratio (WHR) corrected for age, sex, smoking, exercise, and alcohol consumption. Each T allele at C8246T (or G allele at C1032G) was associated with a 0.2-SD–higher WHR in a codominant fashion. When WHR was additionally corrected for BMI, thus providing a measure ofbody fat distribution throughout the range of BMI, there remained significant evidence for association with both markers that was of similar magnitude and statistical significance. There was no association between genotype at any polymorphism and BMI or plasma leptin level. These data show that genetic variants at the *POMC* locus influence body fat distribution within the normal range, suggesting a novel role for *POMC* in metabolic regulation.

Batchelder K, Mayosi BM. Pentoxifylline for heart failure: A systematic review. S Afr Med J. 2005; 95(3):171–175. **Full text available here.**

Background: Recent trials have indicated a beneficial effect of pentoxifylline on measures of inflammation and markers of cardiac dysfunction in people with heart failure. However, it is uncertain whether pentoxifylline should be used routinely in the management of heart failure.

Objective: To determine the effectiveness of pentoxifylline in heart failure.

Design: Systematic review of randomised controlled trials.

Methods: We searched MEDLINE (1 January 1966–20 November 2004), the Cochrane Controlled Trials Register (issue 4, 2004), and reference lists of related papers, for randomised controlled trials of pentoxifylline in the treatment of heart failure. Prospective, randomised, double-blind controlled trials were sought for inclusion in the study. The two reviewers independently assessed trial quality and extracted data, which were analysed using RevMan statistical software. The following outcome measures were evaluated: (i) New York Heart Association

(NYHA) functional class; (ii) left ventricular ejection fraction (LVEF); (iii) frequency of hospitalisation; and (iv) death from all causes.

Results: Four studies with a total of 144 participants met the inclusion criteria. Statistical pooling (or meta-analysis) was not performed owing to the significant clinical heterogeneity and differences in reporting of the outcomes in the included studies; instead, the trials were analysed separately for the outcomes of interest. The four studies tested the use of pentoxifylline versus placebo in patients with heart failure of varying aetiology (idiopathic dilated cardiomyopathy, 3 studies; ischaemic cardiomyopathy, 1 study). In 2 of the idiopathic dilated cardiomyopathy studies, patients were classified as NYHA class II or III, while the study population in another idiopathic cardiomyopathy study was in NYHA class IV. The trial of patients with ischaemic cardiomyopathy included patients in NYHA functional classes I–IV. The use of pentoxifylline was associated with significant improvement in symptoms (i.e. NYHA functional class) and cardiac function (i.e. LVEF) in 3 out of 4 studies. The beneficial effect on symptoms of heart failure and cardiac function was seen in all grades of severity of heart failure and in patients with ischaemic and idiopathic dilated cardiomyopathy. All 4 studies showed a trend towards reduction of mortality, but this effect was not statistically significant. The effect of pentoxifylline on the frequency of hospitalisation has not been tested in randomised controlled trials.

Interpretation: Pentoxifylline may have a beneficial effect on NYHA functional class, ejection fraction and mortality in heart failure, but published trials are too small to provide conclusive evidence. There is a need for large, placebo-controlled trials of pentoxifylline in heart failure, involving a diverse group of patients with regard to cause and severity of heart failure.

Fincham JE, Markus MB, Ngobeni JT, Mayosi BN, Adams VJ, Kwitshana ZL, et al. Synchronized and regular deworming of children and women in South Africa: policy and practice. S Afr J Sci. 2005; 101(1–2):13–17. **Full text available here.**

South Africa is a signatory to World Health Assembly (WHA) resolution 54.19 (May 2001), which calls for regular, synchronized treatment of helminthiasis in developing countries, particularly where the prevalence of worm infestation exceeds 50%. Helminthic infection is usually a hallmark of poverty and reasons why it should be controlled in disadvantaged communities are compelling. However, existing South African legislation regulating the procurement and use of anthelmintic medicines effectively renders group-based deworming as agreed to by WHA member states, and endorsed by the South African minister of health, non-implementable in practice. In order to make deworming sustainable, low-cost, unregistered anthelmintics must be imported from international procurement agencies. At present, this is not permitted. Another problem is that both medical and non-medical personnel are confused by out-of-date information in package-inserts regarding safety for young children and pregnant women. Albendazole and praziquantel should be de-scheduled and ivermectin, levamisole and possibly nitazoxanide should be registered in a way that permits treatment by non-medical personnel. Rational alternation of medication is important because reliance on mebendazole will lead to resistance. All batches of anthelmintics

ought to comply with pharmacological quality specifications and testing should be routine. Facilities for doing this are available in South Africa.

Gaukrodger N, Mayosi BM, Imrie H, Avery P, Baker M, Connell JM, et al. A rare variant of the leptin gene has large effects on blood pressure and carotid intima-medial thickness: A study of 1428 individuals in 248 families. J Med Genet. 2005;42(6):474–478. doi: 10.1136/jmg.2004.027631. **Full text available here**

Background: Rare mutations in the leptin (*LEP*) gene cause severe obesity. Common polymorphisms of *LEP* have been associated with obesity, but their association with cardiovascular disease has been little studied. We have examined the impact of both common and rare polymorphisms of the LEP gene on blood pressure (BP), subclinical atherosclerosis as measured by carotid intima-medial thickness (CIMT), and body mass index (BMI) in a large family study.

Methods: Five polymorphisms spanning *LEP* were typed in 1428 individuals from 248 nuclear families. BP, CIMT, BMI, and plasma leptin were measured.

Results: The polymorphisms typed captured all common haplotypes present at LEP. There was strong association between a rare polymorphism in the 3' untranslated region of *LEP* (C538T) and both pulse pressure ($p = 0.0001$) and CIMT ($p = 0.008$). C/T heterozygotes had a 22% lower pulse pressure and a 17% lower CIMT than C/C homozygotes. The polymorphism accounted for 3–5% of the population variation in pulse pressure and CIMT. There was no association between any *LEP* polymorphism and either BMI or plasma leptin level.

Conclusions: This large family study shows that the rare T allele at the C538T polymorphism of *LEP* substantially influences pulse pressure and CIMT, but does not appear to exert this effect through actions on plasma leptin level or BMI. This suggests that autocrine or paracrine effects in vascular tissue may be important physiological functions of leptin. This study also provides evidence that rare polymorphisms of particular genes may have substantial effects within the normal range of certain quantitative traits.

Keavney B, Mayosi B, Gaukrodger N, Imrie H, Baker M, Fraser R, et al. Genetic variation at the locus encompassing 11-β hydroxylase and aldosterone synthase accounts for heritability in cortisol precursor (11-deoxycortisol) urinary metabolite excretion. J Clin Endocrinol Metab. 2005;90(2):1072–1077. doi: 10.1210/jc.2004-0870. **Full text not freely available.**

Genetic variation in the gene encoding aldosterone synthase (CYP11B2) has previously been shown to be associated with hypertension and left ventricular hypertrophy. The intermediate phenotype most consistently associated with variation at this locus is that of elevated plasma 11-deoxycortisol (S). However, in normal subjects, aldosterone synthase does not metabolize S, which is converted to cortisol (F) by the enzyme 11β hydroxylase, encoded by the gene CYP11B1, which lies adjacent to CYP11B2 on chromosome 8. It is possible that the quantitative trait locus for the phenotype is within CYP11B1 and that linkage disequilibrium across the extended

locus could account for these observations. However, variation across the whole CYP11B1/B2 locus had not been extensively characterized with respect to these phenotypes. We genotyped six polymorphisms in the CYP11B2 gene and three polymorphisms in the CYP11B1 gene in 248 Caucasian nuclear families comprising 1428 individuals. We measured plasma levels of S and F in 460 individuals from 86 families and urinary excretion rates of tetrahydrodeoxycortisol (THS) and tetrahydrodeoxycorticosterone in 573 individuals from 105 families. We examined heritability of the phenotypes and their association with genotypes and haplotypes at this locus. All steroid phenotypes except urinary tetrahydrodeoxycorticosterone were highly heritable ($P < 0.00001$). There was strong linkage disequilibrium across the CYP11B1/B2 locus. There was modest evidence for association between polymorphisms of CYP11B2 and plasma levels of S ($P = 0.02$ for T4986C polymorphism) and the plasma S to F ratio, reflecting the activity of 11-beta hydroxylase ($P = 0.01$ for T4986C polymorphism). There was strong evidence for association between polymorphisms of both CYP11B1 and CYP11B2 and urinary THS, which was strongest for the CYP11B1 exon 1 polymorphism ($P = 0.00002$). Addition of other marker data to CYP11B1 exon 1 did not improve the fit of a log-linear model. Genotype at CYP11B1 explained approximately 5% of the variance in urinary THS excretion in the population. Thus, it is likely that linkage disequilibrium between causative CYP11B1 variants and CYP11B2 polymorphisms account for the previous observations. Further fine-mapping studies across the CYP11B1 locus are required to localize the causative variant(s) for the biochemical phenotype; this may also identify susceptibility alleles for hypertension and left ventricular hypertrophy.

Khumalo NP, Mayosi BM. Autosomal dominant poikiloderma, tendon contracture and pulmonary fibrosis: A new variant of hereditary sclerosing poikiloderma of Weary? Br J Dermatol. 2005; 153(Suppl 1):72. **Full text not freely available.**

A 26-year-old woman presented with a history of heat stroke, spider naevi and freckling on the cheeks from early childhood. She had stopped participation in ballet at the age of 9 years because of Achilles tendon contractures, which were treated by bilateral tendon lengthening at the age of 14 years. She had telangiectasiae on the cheeks, and mottled hyperpigmentation, papules and epidermal atrophy on the cheeks, face and extensor aspects of the arms. She was unable to extend her fingers fully because of sclerodactyly, but had no Raynaud's phenomena. Her teeth, nails and scalp hair were normal. She had fine, thin eyebrows (and used a tattoo to improve appearance) and virtually no hair on her arms and legs. Two attempts by experienced chemistry laboratory staff to collect sweat revealed insufficient amounts for analysis, confirming hypohydrosis, which, taken together with sparse hair, suggested ectodermal dysplasia. Her father, who had similar skin abnormalities, had died of pulmonary fibrosis at the age of 56 years. Her eldest brother presented with similar skin lesions and heat intolerance, and had needed tendon-lengthening surgery in both feet by the age of 5 years. He died of fibrosing alveolitis at the age of 30 years. At postmortem he was found to have tendon contractures, finger clubbing, extensive fibrosis of the lung, oesophagus and mediastinal lymph nodes. The histology showed scleroderma-like change of the skin with replacement of adnexal structures by fibrosis. The patient's surviving brother, who is 5 years older, has similar

skin changes and heat intolerance, but has not presented with features of tendon or pulmonary involvement. According to hearsay, a half-sister from her father's previous marriage has similar skin changes, although no further details are available. This kindred presents with autosomal dominant poikiloderma, tendon contracture and pulmonary fibrosis with variable penetrance. The heat intolerance, reduced sweating and sparse hair, which are reminiscent of hypohydrotic ectodermal dysplasia, are probably secondary to adnexal fibrosis. The clinical features of this family may be a variant of hereditary sclerosing poikiloderma, although pulmonary fibrosis has not been described previously. The combination of fibrotic changes with telangiectasiae suggests that transforming growth factor β-1 is an important candidate gene for this disorder.

Mayosi BM. Genetics and molecular diagnosis of cardiomyopathy: What every doctor should know. CME. 2005;23(1):22–25. **Full text not freely available.**

This article reviews the impact of new genetic information on the clinical management of patients and families with hypertrophic cardiomyopathy (HCM) and familial dilated cardiomyopathy (DCM).

Mayosi BM. SAMJ – Africa's top open access medical journal. S Afr Med J. 2005;95(11):809. **Full text available here.**

No abstract available.

Mayosi B, Avery P, Baker M, Gaukrodger N, Imrie H, Farrall M, et al. Association between the -174G/C polymorphism of the interleukin-6 gene and carotid atherosclerosis: Family study and meta-analysis. Heart. 2005;91:A15. **Full text not freely available.**

Background: Previous studies have produced conflicting results concerning the putative association between the interleukin 6 (IL-6) -174 G/C polymorphism and carotid intima-media thickness (IMT), a measure of subclinical atherosclerosis. We have used a family based genetic association design to assess the heritability of carotid IMT and investigate the hypothesised association. To place our results in context, we conducted a meta-analysis of all published studies, including a total of 3095 individuals.

Methods: 854 members of 224 white families were studied. The heritability of carotid IMT was determined using MERLIN. Genetic association analyses between carotid IMT and the IL-6 –174 G/C polymorphism were carried out using analysis of variance and family based tests of association implemented in the QTDT program.

Results: The heritability of carotid IMT was 24% ($p<0.00001$). Under a recessive model (GG and GC v CC), there was significant evidence of association between genotype and adjusted log maximal carotid IMT ($F = 5.469$, $p= 0.02$). The CC genotype was associated with a 4.3% greater adjusted log maximal carotid IMT. Genotype at the IL-6 –174 G/C polymorphism accounted for 0.6% of the observed variation in the phenotype. Ameta-analysis including the present and four previous studies yielded significant evidence of association between the IL-6 –174

C/C genotype and higher carotid IMT (p=0.0028), There was significant heterogeneity in genotype frequencies between the contributing studies (χ^2 70.21, p<0.001) which was largely accounted for by two studies with less than 100 participants. When just the three larger studies were combined, there was stronger evidence for association between the C/C genotype and CIMT (p=0.0014).

Conclusion: We observed a small but significant association between IL-6 (–174) C/C genotype and higher carotid IMT, which was confirmed in the meta-analysis. These findings support the notion that genetically determined differences in cytokine gene expression are causally related to the development of atherosclerosis, though the magnitude of such effects may be of marginal clinical relevance.

Mayosi BM, Avery PJ, Baker M, Gaukrodger N, Imrie H, Green FR, et al. Genotype at the −174G/C polymorphism of the interleukin-6 gene is associated with common carotid artery intimal-medial thickness: Family study and meta-analysis. Stroke. 2005;36(10):2215–2219. doi: 10.1161/01.Str.0000182254.47941.96. **Full text not freely available.**

Background and Purpose: Studies in unrelated individuals have produced conflicting findings concerning the putative association between the interleukin-6 (IL-6) −174G/C polymorphism and carotid intimal-medial thickness (IMT). We have used a family-based genetic association design to assess the heritability of carotid IMT and to investigate the hypothesized association of carotid IMT with the IL-6 to −174G/C polymorphism.

Methods: We studied 854 members of 224 white British families. The heritability of carotid IMT was determined using Multipoint Engine for Rapid Likelihood Inference. Genetic association analyses were carried out using ANOVA and family-based tests of association implemented in Quantitative Transmission Disequilibrium Test. A meta-analysis of previous studies of the association was conducted to place our result in context.

Results: The heritability of carotid IMT was 24%. Under a recessive model (GG+GC versus CC), there was significant evidence of association between IL-6 to the −174G/C genotype and adjusted $\log_e$ maximal carotid IMT (F=5.469; P=0.02). Family-based analyses using Quantitative Transmission Disequilibrium Test showed no evidence of population stratification as a cause of the observed association (χ^2_1=0.469; P=0.4934). The CC genotype was associated with a 4.8% increase in maximal carotid IMT and accounted for 0.6% of the observed variation in the trait, which is equivalent to 2.5% of the heritable component. A meta-analysis of the present and 2 previous large studies, which enrolled a total of 2930 subjects, confirmed the recessive effect of the C allele on carotid IMT (P=0.0014).

Conclusions: The genotype at the IL-6 to −174G/C polymorphism is associated with common carotid artery IMT, although the size of the genetic effect is small.

Mayosi BM, Burgess LJ, Doubell AF. Tuberculous pericarditis. Circulation. 2005;112(23):3608–3616. doi: 10.1161/circulationaha.105.543066. **Full text not freely available.**

Background: The incidence of tuberculous pericarditis is increasing in Africa as a result of the human immunodeficiency virus (HIV) epidemic. The primary objective of this article was to review and summarize the literature on the pathogenesis, diagnosis, and management of tuberculous pericarditis.
Methods and results: We searched MEDLINE (January 1966 to May 2005) and the Cochrane Library (Issue 1, 2005) for information on relevant references. A "definite" diagnosis of tuberculous pericarditis is based on the demonstration of tubercle bacilli in pericardial fluid or on a histological section of the pericardium; "probable" tuberculous pericarditis is based on the proof of tuberculosis elsewhere in a patient with otherwise unexplained pericarditis, a lymphocytic pericardial exudate with elevated adenosine deaminase levels, and/or appropriate response to a trial of antituberculosis chemotherapy. Treatment consists of the standard 4-drug antituberculosis regimen for 6 months. It is uncertain whether adjunctive corticosteroids are effective in reducing mortality or progression to constriction. Surgical resection of the pericardium remains the appropriate treatment for constrictive pericarditis. The timing of surgical intervention is controversial, but many experts recommend a trial of medical therapy for noncalcific pericardial constriction, and pericardiectomy in nonresponders after 4 to 8 weeks of antituberculosis chemotherapy.
Conclusions: Research is needed to improve the diagnosis, assess the effectiveness of adjunctive steroids, and determine the impact of HIV infection on the outcome of tuberculous pericarditis.

Mayosi BM, Keavney B, Watkins H, Farrall M. Corrigendum: Measured haplotype analysis of the aldosterone synthase gene and heart size. Eur J Hum Genet. 2005;13(8):992. doi: 10.1038/sj.ejhg.5201427. Corrigendum for Eur J Hum Genet. 2003;11:395–401. doi: 10.1038/sj.ejhg.5200967. **Full text not freely available.**

No abstract available.

Monya-Tambi I, Robertson KR, Volmink JA, Mayosi BM. Acute rheumatic fever. Lancet. 2005; 366(9494):1355; author reply 1355–1356. doi: 10.1016/s0140-6736(05)67559-9. **Full text not freely available.**

No abstract available.

Opie LH, Mayosi BM. Cardiovascular disease in sub-Saharan Africa. Circulation. 2005; 112(23):3536–3540. doi: 10.1161/circulationaha.105.597765. **Full text not freely available.**

No abstract available.

Robertson KA, Volmink JA, Mayosi BM. Evidence from a meta-analysis of randomised controlled trials shows that primary prevention of acute rheumatic fever with antibiotics is cost effective in developing

countries. J Am Coll Cardiol. 2005;45(3):355A.

Objective: To use the tools of systematic review and meta-analysis to quantify the effectiveness of antibiotic treatment for sore throat, with symptoms suggestive of group A streptococcal (GAS) infection, for the primary prevention of acute rheumatic fever.

Methods: Trials were identified through a systematic search of titles and abstracts found in the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 4, 2003), MEDLINE (1966-2003), EMBASE (1966–2003), and the reference lists of identified studies. The selection criteria included randomised or quasi-randomised controlled trials comparing the effectiveness of antibiotics versus no antibiotics for the prevention of rheumatic fever in patients presenting with a sore throat, with or without confirmation of GAS infection, and no history of rheumatic fever.

Results: Ten trials (n=7665) were eligible for inclusion in this review. All of the included trials were conducted during the period of 1950 and 1961 and in 8 of the 10 trials the study population consisted of young adult males living on United States military bases. Fixed effects, meta-analysis revealed an overall protective effect for the use of antibiotics against acute rheumatic fever of 70% (RR=0.32; 95% CI = 0.21–0.48). The absolute risk reduction was 1.67% with an NNT of 53. When meta-analysis was restricted to include only trials evaluating penicillin, a protective effect of 80% was found (Fixed effect RR=0.20, 95% CI=0.11–0.36) with an NNT of 60. The marginal cost of preventing one case of rheumatic fever by a single intramuscular injection of penicillin is approximately US$46.

Conclusion: Antibiotics appear to be effective in reducing the incidence of acute rheumatic fever following an episode of suspected GAS pharyngitis. This effect may be achieved at relatively low cost if a single intramuscular penicillin injection is administered.

Robertson KA, Volmink JA, Mayosi BM. Lack of adherence to the national guidelines on the prevention of rheumatic fever. S Afr Med J. 2005;95(1):52–56. **Full text available here**.

Objectives: To explore the extent to which current practices for the secondary prevention of rheumatic fever (RF) in Cape Town adhere to those outlined in the national guidelines on the primary prevention and prophylaxis of RF and rheumatic heart disease (RHD) for health professionals at primary level.

Methods: A combination of qualitative tools was used to evaluate the four priority issues identified in the guidelines as fundamental elements of a comprehensive programme for the secondary prophylaxis of RF/RHD: (i) health education and promotion; (ii) case detection of RF and RHD; (iii) secondary prophylaxis every 3–4 weeks at primary level; and (iv) notification of acute rheumatic fever (ARF). The qualitative tools included parent/child interviews of cases diagnosed with ARF in the Cape metropole area during the period 1999–2003; a physician questionnaire focused on awareness and adherence to the national guidelines; and a review of the records on acute rheumatic fever notification in the Cape metropole area from 1999 to 2003.

Results: The evaluation revealed four key findings. First, patient knowledge on the disease was almost non-

existent. Despite this lack of knowledge, adherence to secondary prophylactic treatment was good. Second, the physicians most likely to encounter a case of rheumatic fever were least likely to be aware of and to comply with the national guideline. Third, the guidelines do not clearly state how increased detection of ARF will be achieved. Finally, the RF notification system is dysfunctional, with discrepancies in the reporting of cases at hospital, city and provincial levels.

Conclusions: Since the publication of the national guidelines in 1997, little progress has been made towards achieving the implementation of a comprehensive programme for the secondary prevention of RF/RHD.

Sliwa K, Damasceno A, Mayosi BM. Epidemiology and etiology of cardiomyopathy in Africa. Circulation. 2005;112(23):3577–3583. doi: 10.1161/circulationaha.105.542894. **Full text not freely available.**

Background: Cardiomyopathy, an often irreversible form of heart muscle disease that is associated with a dismal outcome, is endemic in Africa. The primary objective of this review was to summarize the current state of knowledge on the epidemiology and etiology of cardiomyopathy in people living in Africa and to identify new avenues for research.

Methods and Results: We searched MEDLINE (January 1, 1966, through February 12, 2005) and reference lists of articles for relevant references. Unlike other parts of the world in which cardiomyopathy is rare, dilated cardiomyopathy is a major cause of heart failure throughout Africa. Similarly, peripartum cardiomyopathy is ubiquitous on the continent, with an incidence ranging from 1 in 100 to 1 in 1000 deliveries. There is an apparent marked regional variation in the pathogenesis of dilated cardiomyopathy and peripartum cardiomyopathy, underlining the heterogeneity of causative factors in these conditions. By contrast, endomyocardial fibrosis is restricted to the tropical regions of East, Central, and West Africa. Although the pathogenesis of endomyocardial fibrosis is not fully understood, it seems that the conditioning factors are geography and diet, the triggering factor may be an as yet unidentified infective agent, and the perpetuating factor is eosinophilia. Although epidemiological studies are lacking, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy seem to have characteristics similar to those of other populations elsewhere in the world.

Conclusions: There is a need for large-scale epidemiological studies of the incidence, prevalence, determinants, and outcome of cardiomyopathy in Africa to inform strategies for the treatment and prevention of heart muscle disease on the continent.

Walker K, Wilmshurst J, Monya-Tambi I, Robertson KR, Volmink JA, Mayosi BM, et al. Acute rheumatic fever [2] (multiple letters). Lancet. 2005;366(9494):1354–1355. doi: 10.1016/S0140-6736(05)67558-7. **Full text not freely available.**

No abstract available.

Wiysonge CS, Ntsekhe M, Mayosi BM. Initial report of the initiative to investigate the optimal management of tuberculous pericarditis in Africa (IMPI) registry. J Am Coll Cardiol. 2005; 45(3):141A–142A. **Full text not freely available.**

No abstract available.

2004

Robertson KA, Volmink JA, Mayosi BM. Antibiotics for the primary prevention of acute rheumatic fever: A meta-analysis. Eur Heart J. 2004;25(Suppl 1):527. **Full text available here.**

Context: Rheumatic fever continues to put a significant burden on the health of low socio-economic populations in low and middle-income countries despite the near disappearance of the disease in the developed world over the past century. Antibiotics have long been thought of as an effective method for preventing the onset of acute rheumatic fever following a Group-A streptococcal (GAS) throat infection; however, their use has not been widely adopted in developing countries for the treatment of sore throats.

Objectives: To quantify the effectiveness of antibiotic treatment for sore throat or pharyngitis on the primary prevention of acute rheumatic fever.

Data sources: Trials were identified through a systematic search of titles and abstracts found in the Cochrane Central Register of Controlled Trials (Cochrane Library Issue 4, 2003), MEDLINE (1966–2003), EMBASE (1966–2003), and the reference lists of identified studies.

Review methods: The selection criteria included randomised or quasi-randomised controlled trials comparing the effectiveness of antibiotics versus no antibiotics for the prevention of rheumatic fever in patients presenting with a sore throat, with or without confirmation of GAS infection, and no history of rheumatic fever. Two reviewers independently selected relevant studies, assessed their quality, and extracted the data. Statistical analysis was done using RevMan 4.1.

Results: Ten trials (8 using quasi-randomised methods) with a total of 7665 participants were eligible for inclusion in this review. Twenty-nine of 3996 (0.73%) patients receiving antibiotics, and 89 of 3669 (2.4%) controls not receiving antibiotics developed acute rheumatic fever 1–2 months following a suspected streptococcal throat infection. Fixed effects, meta-analysis revealed an overall protective effect (RR=0.32; 95% CI = 0.21–0.48). The absolute risk reduction with the use of antibiotics was 1.67% suggesting that 53 patients need to be treated with antibiotics to prevent 1 case of acute rheumatic fever (NNT=53). When meta-analysis was restricted to include only trials evaluating penicillin, a protective effect of 80% was found (Fixed effect RR=0.20, 95% CI=0.11–0.36) with an NNT of 60.

Conclusions: Antibiotics appear to be effective in reducing the incidence of acute rheumatic fever following an episode of suspected GAS pharyngitis in high-risk communities. This effect may be achieved at relatively low cost if a single intramuscular penicillin injection is administered.

Stern R, Mokgatle MJ, Mayosi B. The acceptibility of dry sanitation: a preliminary study in two informal settlements in Khayelitsha, Cape Town. School of Public Health, University of the Western Cape (ZA); 2004. **Full text not freely available.**

The link between health, sanitation and poverty is well known. It is estimated that diarrhoeal diseases are responsible for over a quarter of the deaths of children in the world (WHO 1996). Yet the availabilty and sustainability of sanitation in developing countries remains grossly inadequate. However, in recent years, there has been a move to remedy this situation globally. Khayelitsha, just outside of Cape Town, is part of this trend.

2003

Cocciante AG, Mayosi BM, Stevens JE. Dextrocardia with anterior myocardial infarction. Cardiovasc J S Afr. 2003;14(4):204–205. **Full text not freely available.**

A 56-year-old female smoker presented to hospital with the sudden onset of chest tightness and dyspnoea, lasting for 4 hours. Clinical and radiological examination revealed dextrocardia and situs inversus. The admission ECG, performed with the electrodes in the conventional position, showed features of dextrocardia (rS complexes and poor QRS amplitude progression from lead V1 to V6, the tall R wave in lead aVR, and P wave and QRS axes directed at +120°) and widespread changes suggestive of myocardial ischaemia/injury (ST segment elevation of 1–2 mm in aVR, ST segment depression inferiorly, and Q waves in aVR, aVL, V1 and V2).

Magula NP, Mayosi BM. Cardiac involvement in HIV-infected people living in Africa: A review. Cardiovasc J S Afr. 2003;14(5):231–237. **Full text not freely available.**

The primary objective of this study was to review and summarise the literature on the spectrum and management of cardiac disease in HIV-infected people living in Africa. We searched MEDLINE (January 1980 to February 2003), reference lists of papers, and reviews on the subject, and contacted experts working in the field for information on relevant references. The review was limited to papers that were published in peer-reviewed journals and indexed on MEDLINE. Seventeen of the 21 studies identified met the inclusion criteria for analysis. The studies confirmed that cardiac abnormalities are more common in HIV-infected people, compare to normal controls, and that about half of hospitalized patients and a significant proportion of patients followed up over several years develop cardiac abnormalities. The commonest HIV-related cardiac abnormalities were cardiomyopathy and pericardial disease. Tuberculosis was the major cause of large pericardial effusion in Africa. Myocarditis was the commonest pathological abnormality in HIV-associated cardiomyopathy, and non-viral opportunistic infections such as toxoplasmosis and cryptococcosis may account for up to 50% of cases of HIV-associated cardiomyopathy in Africa. Echocardiography is indicated in HIV-positive patients with cardiac symptoms or signs. If cardiomyopathy or pericardial disease is identified, further investigation must be considered to exclude potentially treatable opportunistic infections. Further research in large numbers of patients is needed to determine the value of endomyocardial biopsy in the management of patients with HIV-associated cardiomyopathy, and to establish the place of adjuvant steroids in the treatment of HIV-associated tuberculous pericarditis.

Manyemba J, Mayosi BM. Intramuscular penicillin is more effective than oral penicillin in secondary prevention of rheumatic fever – a systematic review. S Afr Med J. 2003;93(3):212–218. **Full text available here**.

Background: People with a history of rheumatic fever (RF) are at high risk of recurrent attacks and of developing rheumatic heart disease following a streptococcal throat infection. Giving penicillin to these people can prevent recurrent attacks of RF and subsequent rheumatic heart disease. However, there is no agreement on the most effective method of giving penicillin.

Objectives: To assess the effects of different penicillin regimens and formulations for preventing streptococcal infection and RF recurrence.

Search strategy: We searched the Controlled Trials Register (Cochrane Library Issue 2, 2001), Medline (January 1966–July 2000), Embase (January 1985–July 2000), reference lists of articles, and contacted experts in the field.

Selection criteria: Randomised and quasi-randomised studies comparing: (i) oral with intramuscular penicillin; and (ii) 2- or 3-weekly with 4-weekly intramuscular penicillin in patients with previous RF.

Data collection and Analysis: Two reviewers independently assessed trial quality and extracted data.

Main results: Six studies were included (1,707 patients). Data were not pooled because of clinical and methodological heterogeneity of the trials. Four trials (1,098 patients) compared intramuscular with oral penicillin and all showed that intramuscular penicillin was more effective in reducing RF recurrence and streptococcal throat infections than oral penicillin. One trial (360 patients) compared 2-weekly with 4-weekly intramuscular penicillin. Penicillin given every 2 weeks was better at reducing RF recurrence (relative risk (RR) 0.52, 95% confidence interval (CI): 0.33–0.83) and streptococcal throat infections (RR 0.60, 95% CI: 0.42–0.85). One trial (249 patients) showed that 3-weekly intramuscular penicillin injections reduced streptococcal throat infections (RR 0.67, 95% CI: 0.48–0.92) compared with 4-weekly intramuscular penicillin.

Conclusions: Intramuscular penicillin seemed to be more effective than oral penicillin in preventing RF recurrence and streptococcal throat infections. Two-weekly or 3-weekly injections appeared to be more effective than 4-weekly injections. However, the evidence is based on poor-quality trials and the use of outdated formulations of oral penicillin.

Mayosi BM, Keavney B, Watkins H, Farrall M. Measured haplotype analysis of the aldosterone synthase gene and heart size. Eur J Hum Genet. 2003;11(5):395–401. doi: 10.1038/sj.ejhg.5200967. Corrigendum in: Eur J Hum Genet. 2005;13(8):992. doi: 10/1038/sj.ejhg.5201427. **Full text not freely available.**

Gene-association studies of heart size and the aldosterone synthase (CYP11B2) gene have produced inconsistent results, possibly because of limitations in the sample size and/or the number and location of the polymorphisms. An analysis of six polymorphisms spanning 6 kb of the CYP11B2 gene in Caucasian British families revealed a limited number of haplotypes because of strong linkage disequilibrium over this small region. The genotype and

haplotype information was used in an association study involving 955 members of 229 families phenotyped for echocardiographic measures of heart size. In a mixed effects linear modelling analysis, the G5937C polymorphism was associated with cardiac wall thickness (P=0.02), and the intron conversion and A4550C polymorphisms were associated with left ventricular cavity size (P=0.02 and 0.002, respectively). Measured haplotype analyses confirmed the association of alleles at the intron conversion and G5937C polymorphisms with cardiac wall thickness (P=0.02), and alleles at the intron conversion polymorphism with left ventricular cavity size (P=0.04). The polymorphisms contributed to 2.0–3.4% of the variability in these traits. In summary, genetic polymorphisms at the CYP11B2 gene make a small contribution to quantitative variation in echocardiographic measures of heart size. These results point to the importance of analysing the full extent of genetic variation that captures the haplotype structure of a locus in gene association studies.

Millar RN, Mayosi BM. Utilization of implantable defibrillators in Africa. Card Electrophysiol Rev. 2003;7(1):14–16. **Full text not freely available.**

Sub-Saharan Africa is dominated by diseases of poverty. HIV/AIDS affects 28.5 out of a total of 600 million in the region. South Africa is the only country in sub-Saharan Africa in which implantable cardiovertor defibrillators (ICDs) are implanted (0.8/million in 2001). Only 3 of the 35 new ICDs were implanted in state-funded public hospitals. The pacemaker implantation rate for South Africa was 41/million in 2001. Approximately 20% of the population consume 56% of the health care expenditure, mainly funded by Medical Insurance. A tax-funded state health care system serves the rest of the population, but is concentrated on improving sanitation and primary health care. Diversion of funds from academic tertiary hospitals has reduced specialised services, particularly cardiology and cardiac surgery, and has resulted in an exodus of skilled personnel to the private sector. In the rest of sub-Saharan Africa, tertiary health care is mainly privately funded. Cardiology and cardiac surgery is not widely available. Many countries are crippled by debt and chronic local conflicts. Only one state hospital (Groote Schuur, Cape Town) provides an electrophysiology (EP) service including catheter ablation and ICD implantation, and training in EP, by two electrophysiologists. EP services are available privately in 3 centres. No EP service exists in the rest of sub-Saharan Africa.

Moolman-Smook JC, Mayosi BM, Brink PA, Corfield VA. Molecular genetics of cardiomyopathy: Changing times, shifting paradigms. Cardiovasc J S Afr. 2003;14(3):145–155. **Full text not freely available.**

Congestive heart failure is a major problem in developed and developing countries alike. Primary dysfunction of the heart muscle accounts for a significant proportion of patients with a non-ischaemic cause of heart failure. Application of genetic techniques has facilitated identification of some molecular causes of the inherited form of these diseases, dramatically increasing our understanding of the pathogenesis of these primary, previously termed ‘idiopathic’, cardiomyopathies over the last few decades. Knowledge of the different causes is beginning to coalesce into aetiological principles underlying the clinically distinguished cardiomyopathies. Hypertrophic

cardiomyopathy (HCM) now appears to be a disease caused by a dysfunctional sarcomere, dilated cardiomyopathy (DCM), a disease of myocytic structural instability, and arrhythmogenic right ventricular cardiomyopathy, a disease of accelerated myocyte death. The aetiology of both HCM and DCM probably also involves cardiac energy imbalances, while additional factors modify the clinical expression in all cardiomyopathies. Even though our knowledge of the genetic aetiology of the cardiomyopathies is still incomplete, it already has relevant clinical significance. Elucidation of the full genetic contribution to the development and progression of the cardiomyopathies represents a new challenge in the study of these diseases, and will undoubtedly lead to new therapeutic approaches in the not-too-distant future.

Ntsekhe M, Wiysonge C, Volmink JA, Commerford PJ, Mayosi BM. Adjuvant corticosteroids for tuberculous pericarditis: Promising, but not proven. QJM. 2003;96(8):593–599. **Full text available here.**

Background: There is controversy regarding the effectiveness of corticosteroids in tuberculous pericarditis, particularly in patients who are immunocompromised by HIV.

Aim: To determine the effectiveness of adjuvant corticosteroids in tuberculous pericarditis.

Design: Systematic review of randomized controlled trials.

Methods: We searched the Cochrane Infectious Diseases Group trials register (June 2002), the Cochrane Controlled Trials Register (Issue 2, 2002), MEDLINE (January 1966 to March 2003), EMBASE (1980 to May 2002), and the reference lists of existing reviews, for randomized and quasi-randomized controlled trials of adjuvant corticosteroids in the treatment of suspected tuberculous pericarditis. We also contacted organizations and individuals working in the field. Two reviewers independently assessed trial quality and extracted data. We used meta-analysis with a fixed effects model to calculate the summary statistics, provided there was no statistically significant heterogeneity, and expressed results as relative risk.

Results: Four trials with a total of 469 participants met our criteria. Three (total n = 411) tested adjuvant steroids in participants with suspected tuberculous pericarditis in the pre-HIV era. Fewer participants died in the intervention group, but the potentially large reduction in mortality was not statistically significant (relative risk RR 0.65, 95% CI 0.36–1.16, n = 350; p = 0.14). One trial with 58 patients that enrolled HIV-positive individuals also showed a promising but non-significant trend on mortality (RR 0.50, 95% CI 0.19–1.28; p = 0.15). There was no significant beneficial effect of steroids on re-accumulation of pericardial effusion or progression to constrictive pericarditis. Patients with pericardial effusion were significantly more likely to be alive with no functional impairment at 2 years following treatment. However, the effect was not sustained in a sensitivity analysis that included patients who were lost to follow-up.

Discussion: Steroids could have large beneficial effects on mortality and morbidity in tuberculous pericarditis, but published trials are too small to be conclusive. Large placebo-controlled trials are required, and should include sufficient numbers of HIV-positive and HIV-negative participants, and an adequate adjuvant steroid dose.

2002

Fincham JE, Cloete K, Mayosi B, Mtshiselwa L, Mwamba J, Chopra M, et al. Deworming by teachers in Khayelitsha, near Cape Town, South Africa. J S Afr Vet Assoc. 2002;73(3):148–149. **Full text not freely available.**

The World Health Organisation (WHO) has identified the control of geohelminth infestation as a high priority for developing countries. The reasons include public, community and environmental health, as well as the morbidity and disease these worms can cause (Montresor *et al*., 1999, WHO/CDS/CPC/SIP/99.3). When most of the children in a community are infected by the geohelminths *Ascaris lumbricoides* and *Trichuris trichiur*a, it means that human faeces are polluting the environment. Amongst others, this indicates a lack of effective sanitation and high risk of epidemic enteric diseases caused by bacteria, viruses and protozoa. Sporadic deworming of individual children contributes nothing to overall control. Deworming at clinics cannot achieve synchronised treatment and children who do not need medical attention, should not be directed into clinics crowded by sick people. To initiate control of geohelminths by means of chemotherapy, pending more holistic measures, requires regular, synchronised deworming with effective, broad-spectrum anthelmintics. Since most of the burden of helminthiasis is in school-age children, pupils are optimal for implementing a treatment programme. The main obstacle is to obtain the human resource capacity to treat regularly and keep records. Health service personnel are too heavily committed elsewhere. In several developing countries, teachers deworm the children and appropriate health education is included in the curricula. This is in accordance with advocacy of health-promoting schools by the WHO. In South Africa, no generally acceptable and effective method of applying mass-deworming in schools has been achieved. At 12 primary schools in Sites B and C of Khayelitsha, where most of the people live in shacks, the communities and the educators have authorised and support a deworming programme. About 12 000 children have been treated regularly since 1999. Generic mebendazole (D-Worm SD®, 500 mg tablets, Triomed) has been effective against *Ascaris lumbricoides* and *Trichuris trichiura*. All batches of tablets used, are polymorph C mebendazole. The programme is cost-effective and sustainable.

Johnson B, Chopra M, Alexander W, Lake L, Mayosi B, Cloete K, et al. An evaluation of a school-based programme for the prevention of helminthiasis in children. J S Afr Vet Assoc. 2002;73(3):149. **Full text not freely available.**

This descriptive study investigated the implementation of a primary school programme designed to prevent

parasitic infestation of children. The programme was piloted in 12 schools in Khayelitsha, Western Cape. Phase 1 involved the evaluation and monitoring of the training of master trainers (key educators whose task it was to train other educators). Phase 2 involved the evaluation and monitoring of the materials in the classroom. Interviews were conducted with educators from 6 of the 12 pilot schools in order to determine the factors that facilitated or hampered the success of the programme and to elicit ideas for the improvement. A semi-structured questionnaire aimed at supplementing the information gained from the interviews. It was completed either by key personnel or coordinators, at the 6 schools. Lessons were also observed in the classroom in order to determine the effectiveness and appropriateness of the materials. Factors that facilitated success, included active participation and involvement in the design of the programme, training by curriculum services, participation and involvement in a health-promoting schools group, the active involvement of the principal and support from colleagues. Factors that hampered success included competing curriculum priorities, lack of support from principal and colleagues, lack of basic facilities to monitor hygienic practices by children and conflicting messages from the community. Suggestions for the improvement of the programme included ideas around durability of materials, visual appeal of materials, ideas for improved learner interaction, classroom participation and involvement of parents and the community. This study therefore highlights the development of a school-based programme as part of an effective and sustainable prevention strategy in dealing with helminths or worms.

Manyemba J, Mayosi BM. Penicillin for secondary prevention of rheumatic fever. Cochrane Database Syst Rev. 2002(3):Cd002227. doi: 10.1002/14651858.Cd002227. **Full text available here**

Background: People with a history of rheumatic fever are at high risk of recurrent attacks of rheumatic fever and developing rheumatic heart disease following a streptococcal throat infection. Giving penicillin to these people can prevent recurrent attacks of rheumatic fever and subsequent rheumatic heart disease. However, there is no agreement on the most effective method of giving penicillin.

Objectives: To assess the effects of penicillin compared to placebo and the effects of different penicillin regimens and formulations for preventing streptococcal infection and rheumatic fever recurrence.

Search strategy: We searched the Controlled Trials Register (Cochrane Library Issue 2, 2001), MEDLINE (1997 to July 2000), EMBASE (1998 to July 2000), reference lists of articles and we contacted experts in the field.

Selection criteria: Randomised and quasi-randomised studies comparing (i) penicillin with control, (ii) oral with intramuscular penicillin (iii) 2- or 3-weekly with 4-weekly intramuscular penicillin in patients with previous rheumatic fever.

Data collection and analysis: Two reviewers independently assessed trial quality and extracted data.

Main results: Nine studies were included (n=3008). Data were not pooled because of heterogeneity. Overall, the methodological quality of included studies was poor. Three trials (n= 1301) compared penicillin with control. Only one of three studies showed that penicillin reduced rheumatic fever recurrence (RR 0.45, 95% CI 0.22 to 0.92) and streptococcal throat infection (RR 0.84, 95% CI 0.72 to 0.97). Four trials (n=1098) compared

intramuscular with oral penicillin and all showed that intramuscular penicillin reduced rheumatic fever recurrence and streptococcal throat infections compared to oral penicillin. One trial (n= 360) compared 2-weekly with 4-weekly intramuscular penicillin. Penicillin given every two-weeks was better at reducing rheumatic fever recurrence (RR 0.52, 95% CI 0.33 to 0.83) and streptococcal throat infections (RR 0.60, 95% CI 0.42 to 0.85). One trial (n= 249) showed 3-weekly intramuscular penicillin injections reduced streptococcal throat infections (RR 0.67, 95% CI 0.48 to 0.92) compared to 4-weekly intramuscular penicillin.
Reviewer's conclusions: Intramuscular penicillin seemed to be more effective than oral penicillin in preventing rheumatic fever recurrence and streptococcal throat infections. Two-weekly or 3-weekly injections appeared to be more effective than 4-weekly injections. However, the evidence is based on poor quality of trials.

Mayosi BM. SAMJ to co-publish Cochrane Reviews. S Afr Med J. 2002;92(1). **Full text not freely available.**
No abstract available.

Mayosi BM, Kardos A, Davies CH, Hovnanian A, Burge S, Watkins H. Heterozygous disruption of SERCA2a is not sufficient to impair cardiac performance in man. Circulation. 2002;106(19):570. **Full text not freely available.**
No abstract available.

Mayosi BM, Keavney B, Kardos A, Davies CH, Ratcliffe PJ, Farrall M, et al. Electrocardiographic measures of left ventricular hypertrophy show greater heritability than echocardiographic left ventricular mass: A family study. Eur Heart J. 2002;23(24):1963–1971. doi: 10.1053/euhj.2002.3288. **Full text available here.**
Aims: To assess the heritability (i.e. relative contribution of genetic factors to the variability) of continuous measures of left ventricular hypertrophy determined by electrocardiography and echocardiography.
Methods and results: We studied 955 members of 229 Caucasian families, ascertained through a hypertensive proband. Electrocardiographic measurements were performed manually on resting 12–lead electrocardiograms, and echocardiographic measurements were made on M-mode images. Sex-specific residuals for the left ventricular phenotypes were calculated, adjusted for age, systolic blood pressure, weight, height, waist–hip ratio, and presence of diabetes. Heritability was estimated in two ways: firstly, from familial correlations with adjustment for spouse resemblance; and secondly by using variance components methods with ascertainment correction for proband status. The heritability estimates (given as a range derived from the two methods) were higher for Sokolow–Lyon voltage (39–41%) than for echocardiographic left ventricular mass (23–29%). Electrocardiographic left ventricular mass, Cornell voltage, and Cornell product had heritability estimates of 12–18%, 19–25%, and 28–32%, respectively.
Conclusions: Genetic factors may explain a substantial proportion of variability in quantitative

electrocardiographic and echocardiographic measures of left ventricular hypertrophy. The greater heritability of Sokolow–Lyon voltage suggests that electrocardiographic phenotypes may be particularly important for the molecular investigation of the genetic susceptibility to cardiac hypertrophy.

Mayosi BM, Keavney B, Kardos A, Davies CH, Ratcliffe PJ, Farrell M, et al. Electrocardiographic markers of cardiac hypertrophy show greater heritability than echocardiographic left ventricular mass: A family study. J Am Coll Cardiol. 2002;39(5):237A. **Full text not freely available.**

Background: Electrocardiographic and echocardiographic measures of cardiac hypertrophy are independent predictors of cardiovascular morbidity and mortality. There is increasing evidence to show that echocardiographic left ventricular mass is genetically determined, but little is known about the magnitude of genetic determination of electrocardiographic measures of cardiac hypertrophy. We set out to assess the hedtability of continuous measures of left ventricular hypertrophy determined by electrocardiography and echocerdiography.

Methods: We studied 955 members of 229 Caucasian extended families, ascertained through a hypertensive proband. Electrocardiographic measurements were performed manually on normal resting 12-lead electro-cardiograms, and echocardiographic parameters were determined on M-mode images. Sex-specific residuals for left venthcular phenotypes were calculated, adjusted for age, systolic blood pressure, weight, height, waist-hip ratio, and presence of diabetes. Heritability was estimated from familial correlations with adjustment for spouse resemblance, and by using vadance components methods with ascertainment correction for proband status.

Results: The heritability estimates (range) were higher for Sokolow-Lyon voltage (39–41%) and RaVL voltage (30–31%) than for echocardiographic left ventricular mass (23–29%). Cornell voltage, Cornell product, and electrocardiographic left ventricular mass had heritability estimates of 19–25%, 28–32%, and 12–18%, respectively.

Conclusions: The greater heritability of Sokotow Lyon voltage and RaVL voltage suggests that electrocardiographic phenotypes may be particularly important for the molecular investigation of the genetic susceptibility to cardiac hypertrophy. Finding genes that influence the electrocardiographic markers could help unravel the pathophysiology of cardiac hypertrophy and lead to improvements in prevention, diagnosis, and treatment of at risk populations.

Mayosi BM, Keavney B, Watkins H, Farrall M. Measured haplotype analysis of the aldosterone synthase gene and cardiac hypertrophy. Circulation. 2002;106(19):733. **Full text not freely available.**

No abstract available.

Mayosi BM, Ntsekhe M, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2002(4):Cd000526. doi: 10.1002/14651858.Cd000526. **Full text available here.**

Background: Tuberculous pericarditis – tuberculosis infection of the pericardial membrane (pericardium) covering the heart – is becoming more common. The infection can result in fluid around the heart or fibrosis of the pericardium, which can be fatal.

Objectives: In people with tuberculous pericarditis, to evaluate the effects on death, life-threatening conditions, and persistent disability of: (1) 6-month antituberculous drug regimens compared with regimens of 9 months or more; (2) corticosteroids; (3) pericardial drainage; and (4) pericardiectomy.

Search strategy: We searched the Cochrane Infectious Diseases Group trials register (June 2002), the Cochrane Controlled Trials Register (Issue 2, 2002), MEDLINE (1966 to June 2002), EMBASE (1980 to May 2002), and checked the reference lists of existing reviews. We also contacted organizations and individuals working in the field.

Selection criteria: Randomized and quasi-randomized controlled trials of treatments for tuberculous pericarditis.

Data collection and analysis: Two reviewers independently assessed trial quality and extracted data. Meta-analysis using fixed effects models calculated summary statistics, provided there was no statistically significant heterogeneity, and expressed results as relative risk. Study authors were contacted for additional information.

Main results: Four trials met the inclusion criteria, with a total of 469 participants. Treatments tested were adjuvant steroids and surgical drainage. Two trials with a total of 383 participants tested adjuvant steroids in participants with suspected tuberculous pericarditis in the pre-HIV era. Fewer participants died in the intervention group, but numbers were small (relative risk [RR] 0.65; 95% confidence interval [CI] 0.36 to 1.16, n = 350). One small trial tested steroids in HIV positive participants with effusion showed a similar pattern (RR 0.50; 95% CI 0.19 to 1.28, n = 58). One trial examined open surgical drainage compared with conservative management, and showed surgery relieved cardiac tamponade.

Reviewer's conclusions: Steroids could have important clinical benefits, but the trials published to date are too small to demonstrate an effect. This requires large placebo controlled trials. Subgroup analysis could explore whether effusion or fibrosis modify the effects. Therapeutic pericardiocentesis under local anaesthesia and pericardiectomy also require further evaluation.

Vickers MA, Green FR, Terry C, Mayosi BM, Julier C, Lathrop M, et al. Genotype at a promoter polymorphism of the interleukin-6 gene is associated with baseline levels of plasma C-reactive protein. Cardiovasc Res. 2002;53(4):1029–1034. **Full text available here**

Objective: Baseline concentrations of plasma C-reactive protein (CRP) are associated with coronary heart disease. Interleukin-6 (IL-6) regulates CRP gene expression; a promoter polymorphism (–174G/C) of the IL-6 gene has been shown to influence IL-6 transcription but the relationship between genotype at this polymorphism and circulating levels of inflammatory markers remains unclear. We hypothesised that plasma CRP would be a

heritable phenotype that would be influenced by genotype at this polymorphism.
Methods: We measured baseline plasma CRP and determined genotypes at the −174G/C polymorphism of the IL-6 gene in 588 members of 98 nuclear families. The heritability of plasma CRP and the association of plasma CRP with genotype were determined using variance components methods.
Results: Baseline CRP levels were highly heritable (h^2=0.39, P<0.0000001). Presence of the −174C allele was associated with higher baseline CRP levels, both in the whole population (P=0.01), and in the founders only (n=128, P=0.001). Family-based analyses confirmed the association (P=0.02) suggesting that it arises from chromosomal proximity or identity of the typed polymorphism with a genetic variant influencing baseline CRP levels.
Conclusions: Baseline plasma CRP is a significantly heritable cardiovascular risk factor. Levels are associated with genotype at the −174G/C polymorphism of the IL-6 gene.

2001

Khogali SS, Mayosi BM, Beattie JM, McKenna WJ, Watkins H, Poulton J. A common mitochondrial DNA variant associated with susceptibility to dilated cardiomyopathy in two different populations. Lancet. 2001;357(9264):1265–1267. doi: 10.1016/s0140-6736(00)04422-6. **Full text not freely available.**

Idiopathic dilated cardiomyopathy is a recognised manifestation of mitochondrial disease due to specific mitochondrial (mt) DNA mutations. However, whether mtDNA polymorphisms predispose to sporadic dilated cardiomyopathy is not known. We analysed two populations with this disorder for a general mtDNA variant (T16189C), previously implicated in susceptibility to type 2 diabetes. We noted an increased frequency of the polymorphism in both populations compared with controls (p=0.002). The polymorphism occurred on different mtDNA backgrounds, suggesting that it might be a functional variant. This association of an mtDNA variant with increased susceptibility to dilated cardiomyopathy provides evidence for a mitochondrial cause in sporadic disease.

Pakenham-Walsh N, Mayosi BM. Where to practise evidence-based medicine? Lancet. 2001; 357(9257):723–724. **Full text not freely available.**

No abstract available.

Poulton J, Macaulay V, Livesey K, Wareham N, Parker E, Phillips D, et al. A common mtDNA variant may be a susceptibility factor in 3 multifactorial diseases. Am J Hum Genet. 2001;69(4):579. **Full text not freely available.**

No abstract available.

Yusuf S, Pogue J, Anand S, Tognoni G, Fox K, Díaz R, et al. Effects of long-term, moderate-intensity oral anticoagulation in addition to aspirin in unstable angina. J Am Coll Cardiol. 2001;37(2):475–484. doi: 10.1016/S0735-1097(00)01118-9. **Full text not freely available.**

Objectives: We sought to evaluate whether oral anticoagulant (AC) therapy given for five months was superior to standard (control) therapy in patients with unstable angina receiving aspirin.

Background: The long-term risk of myocardial infarction (MI) or death remains high in patients with unstable angina, despite the use of aspirin. Therefore, additional treatments are necessary.

Methods: Of the 10,141 patients entering the main trial, 3,712 were randomized 12 to 48 h later to receive oral AC therapy (n = 1,848) or standard therapy (n = 1,864).
Results: One-hundred forty patients (7.6%) suffered from cardiovascular death, MI or stroke while receiving oral AC, compared with 155 patients (8.3%) on standard therapy (relative risk [RR] 0.90, 95% confidence interval [CI] 0.72 to 1.14; p = 0.40). The rates of the primary outcomes plus refractory angina were 16.7% (n = 308) versus 17.5% (n = 327) (RR 0.95, 95% CI 0.81 to 1.11; p = 0.53). Countries were divided into good or poor compliers (based on the use of oral AC above or below 70% at 35 days), without knowledge of results by country. In good-complier countries, oral AC was discontinued in only 10.4% of patients at seven days and in 23.6% by five months, compared with 27.6% and 44.9%, respectively, in poor complier countries. There were significant reductions in the risks of both the primary (6.1% *vs.* 8.9%; RR 0.68, 95% CI 0.48 to 0.95; p = 0.02) and secondary outcomes (11.9% *vs.* 16.5%; RR 0.70, 95% CI 0.55 to 0.90; p = 0.005) with oral AC in the good-complier countries. There was little difference in the poor-complier countries (9.0% *vs.* 7.8% for the primary and 21.3% *vs.* 18.5% for the secondary outcomes, tests for interactions comparing the RRs for the primary and secondary outcomes were p < 0.02 and p = 0.002, respectively, between the two sets of countries). In the overall study, there was an excess of major bleeding (2.7% *vs.* 1.3%; p = 0.004), which was larger in the good-complier countries (RR 2.71) compared with the poor-complier countries (RR 1.58). There were also reductions in cardiac catheterization (RR 0.80; p = 0.004) and coronary revascularization procedures (RR 0.82; p = 0.06) in the good-complier countries, but not in the poor-complier countries (RR 0.98 and 1.06, respectively, p for interaction of 0.06 and 0.04, respectively).
Conclusions: Overall, oral AC led to a small, nonsignificant reduction in the risk of the primary and secondary outcomes. Stratifying the countries or centers by their rates of compliance to oral AC suggested that good compliance to oral AC could potentially lead to clinically important reductions in major ischemic cardiovascular events.

2000

Arendse V, Fincham J, Cloete K, Chopra M, Carolissen E, Haffejee F, et al. Khayelitsha: environment, education intestinal parasites and therapy. Medical Research Council, P.O. Box 19070, Tygerberg (ZA). 2000. **Full text not freely available.**

No abstract available.

Arendse V, Fincham J, Cloete K, Chopra M, Mnyaka A, Carolissen E, et al. Khayelitsha: Ubume bendawa (environment), Imfundo yezidleleli zamathumbu (intestinal parasites) kwakunye nonyango. Medical Research Council, P.O. Box 19070, Tygerberg (ZA). 2000. **Full text not freely available.**

No abstract available.

Fincham J, Arendse A, Mayosi B. The environment, education and community empowerment: Interim report primarily for funders. Medical Research Council, P.O. Box 19070, Tygerberg (ZA). 2000. **Full text not freely available.**

No abstract available.

Fincham J, Mayosi B, Arendse V. Khayelitsha task team: preliminary report on successful dry sanitation in the Northern Cape and the possibility of adopting it to Khayelitsha. Medical Research Council, P.O. Box 19070, Tygerberg (ZA). 2000. **Full text not freely available.**

No abstract available.

Keavney BD, Terry C, Mayosi BM, Watkins HC, Green FR, Vickers MA. Plasma C-reactive protein (CRP), a novel cardiovascular risk factor, shows high heritability but no association with the -174 G/C polymorphism of the interleukin-6 (IL-6) gene in human families. Circulation. 2000; 102(18 Supplement II):329. **Full text not freely available.**

No abstract available.

Khogali S, Mayosi B, Beattie J, McKenna W, Watkins H, Poulton J. Association of a common mitochondrial DNA D-loop variant with idiopathic dilated cardiomyopathy in two different populations. Eur Heart J. 2000;21(Abstract Supplement):24. **Full text not freely available.**

No abstract available.

Mayosi B, Blair E, Watkins H. To the Editor: Dilated cardiomyopathy and the desmin gene. Circulation. 2000;102(13):E100. **Full text not freely available.**

No abstract available.

Mayosi BM, Green FR, Vickers MA, Watkins H, Keavney B. Genetic basis of variation in fibrinogen and CRP. Heart. 2000;83(Suppl. 1). **Full text not freely available.**

Elevated plasma fibrinogen is a risk factor for coronary artery disease. There is uncertainty about the size of the genetic contribution to plasma fibrinogen, and although an association has been reported between fibrinogen gene polymorphisms and plasma fibrinogen level in population-based studies, this finding has been inconsistent. There is strong evidence for association between C-reactive protein (CRP) and vascular disease, but the genetic contribution to the variance of CRP level is unknown. Using a family-based study design, we sought to: (1) determine the heritability of plasma fibrinogen and CRP, and (2) to elucidate whether variants in the fibrinogen gene are involved in the control of plasma fibrinogen and CRP levels by linkage analysis of plasma levels using using polymorphisms at the fibrinogen locus as genetic markers. 561 members of 98 Caucasian extended families were studied. Haplotypes of two β-fibrinogen promoter variants (β-455 G/A, β-854 G/A) and genotypes of an intragenic microsatellite marker in the α-fibrinogen gene were determined by PCR. Genetic linkage between the fibrinogen gene variants and plasma fibrinogen and CRP levels were evaluated with the SOLAR variance-component linkage method. The estimated heritability of plasma fibrinogen was low at 0.22 ± 0.08, $p = 0.0007$, although the heritability of CRP was higher, 0.38 ± 0.08, $p < 0.0000001$. The proportion of variance in plasma fibrinogen and CRP explained by age, sex, cigarette smoking, and body mass index was 0.24 and 0.42 respectively. There was no evidence of genetic linkage between the fibrinogen gene and levels of plasma fibrinogen or CRP. These results, in the largest such quantitative linkage study of these questions performed to date, show that the contribution of the fibrinogen locus to the variance of fibrinogen and CRP levels is likely to be small, and thus family-based association approaches will be required to define the genetic variant(s) responsible for the observed population associations. The high heritability of CRP suggests its suitability as a phenotype for quantitative genome-wide linkage studies of cardiovascular risk.

Mayosi BM, Green FR, Vickers MA, Watkins H, Keavney B. The genetic basis of variation in plasma fibrinogen and C-reactive protein levels. Eur Heart J. 2000;21(Abstract Supplement):280. **Full text not**

freely available.

Introduction: Elevated plasma fibrinogen is a risk factor for coronary artery disease and stroke. There is uncertainty about the size of the genetic contribution to plasma fibrinogen, and although an association has been reported between fibrinogen gene polymorphisms and plasma fibrinogen level in population-based studies, this finding has been inconsistent. There is strong evidence for association between C-reactive protein (CRP) and vascular disease, but the genetic contribution to the variance of CRP level is unknown. Using a family-based study design, we sought to: (1) determine the heritability of plasma fibrinogen and CRP, and (2) to elucidate whether variants in the fibrinogen gene are involved in the control of plasma fibrinogen and CRP levels by linkage analysis of plasma levels using polymorphisms at the fibrinogen locus as genetic markers.

Method: 561 members of 98 Caucasian extended families were studied. Haplotypes of two beta-fibrinogen gene promoter variants (-455 G/A, -854 G/A) and genotypes of an intragenic microsatellite marker in the alpha-fibrinogen gene were determined by PCR. Genetic linkage between the fibrinogen gene variants and plasma fibrinogen and CRP levels was evaluated with the SOLAR variance-component linkage method.

Results: The estimated heritability of plasma fibrinogen was low at 0.22 ± 0.08, $p = 0.0007$; although the heritability of CRP was higher, 0.38 ± 0.08, $p < 0.0000001$. The proportion of variance in plasma fibrinogen and CRP explained by age, sex, cigarette smoking, and body mass index was 0.24 and 0.42 respectively. There was no evidence of genetic linkage between the fibrinogen gene and levels of plasma fibrinogen or CRP.

Conclusion: These results, in the largest such quantitative linkage study of these questions performed to date, show that the contribution of the fibrinogen locus to the variance of fibrinogen and CRP levels is likely to be small, and thus family-based association approaches will be required to define the genetic variant(s) responsible for the observed population associations. The high heritability of CRP suggests its suitability as a phenotype for quantitative genome-wide linkage studies of cardiovascular risk.

Mayosi BM, Keavney BD, Watkins HC, Vickers MA, Green FR. Quantitative genetic study of plasma fibrinogen level and the -455 G/A polymorphism of the beta-fibrinogen gene using novel family-based association methods. Circulation. 2000;102(18 Supplement II):104. **Full text not freely available.**

No abstract available.

Mayosi BM, Lombard C, Mbewu AD. The impact of lp(a) level and apo(a) isoform on left ventricular function following acute myocardial infarction. Eur Heart J. 2000;21(Abstract Supplement):601. **Full text not freely available.**

Introduction: Lipoprotein(a) [Lp(a)] concentration rises following acute myocardial infarction (AMI), and the magnitude of this rise may be dependent upon apoliporotein (a) [apo(a)] phenotype. The promoter region of apo(a) gene has the receptor sites for interleukin-6 (IL-6). Binding of IL-6 to the receptor sites and subsequent increased

rate of transcription of apo(a) may account for the rise in Lp(a) that occurs following AMI. Thirdly, the elevated levels of Lp(a) post AMI may be associated with a reduction in the degree of myocardial injury during AMI.
Method: To test these 3 hypotheses, we took blood samples from 30 patients on day 0, 1, 2, 3, 10, and 15 following AMI. Lp(a), apo(a) phenotype, IL-6 and C-reactive protein concentrations were measured in all the samples and the degree of left ventricular damage was assessed by nuclear scintigraphy 10 days following AMI.
Results: Lp(a) levels rose significantly following AMI ($p = 0.001$), reaching a peak at day 10 while CRP and IL-6 reached their peak concentrations at 24–48 hours post AMI. There was a significant correlation between the magnitude of the rise in IL-6 level and CRP, but no correlation with the rise in Lp(a) level. Patients with apo(a) phenotype for low molecular weight isoforms of apo(a) had significantly higher basal concentrations of Lp(a), and smaller increases in Lp(a) following AMI. Patients with smaller isoforms of apo(a) had significantly less left ventricular damage ($p < 0.05$).
Conclusion: (1) The magnitude of the rise in Lp(a) levels following AMI appeared to be dependent upon apo(a) phenotype, and as such may be genetically determined. (2) Patients with small isoforms of apo(a)and higher basal levels of Lp(a) had sigificantly less left ventricular damage following AMI, suggesting a role for some phenotypes of apo(a) in ameliorating myocardial damage. (3) The magnitude of the rise in Lp(a) levels following AMI was not correlated with the increase in IL-6 levels.

Mayosi BM, Lombard CJ, Mbewu AD. A prospective study of the effect of lipoprotein(a) level and apolipoprotein(a) isoform on left ventricular damage following acute myocardial function. Circulation. 2000;102(18 Supplement II):283. **Full text not freely available.**

No abstract available.

Mayosi BM, Scott Millar RN. Permanent cardiac pacing in South Africa. East Afr Med J. 2000;77(6):339. **Full text not freely available**

No abstract available.

Mayosi BM, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2000(2):Cd000526. doi: 10.1002/14651858.Cd000526. **Full text available here.**

Background: Tuberculous (TB) pericarditis is becoming more common. The infection can result in fluid around the heart, which can be fatal.
Objectives: To evaluate evidence from trials about the effects of medical and surgical treatments for TB pericarditis on death and life-threatening conditions.
Search strategy: The Cochrane Infectious Diseases Group trials register, the Cochrane controlled trials register, Medline, Embase and reference lists of articles; contact with experts in the field. Selection criteria: Randomised

and quasi-randomised trials of treatments for TB pericarditis.
Data collection and analysis: Two reviewers independently assessed trial quality and extracted data. Meta-analysis using fixed effects models calculated summary statistics, provided there was no significant heterogeneity, and expressed results as relative risk.
Main results: Three trials met the inclusion criteria, with a total of 411 participants. Treatments were adjuvant steroids and surgical drainage. Two small trials tested steroids. There were fewer deaths (all causes) in the intervention group, but the numbers were small and the result could have occurred by chance (relative risk [RR] 0.65, 95% confidence interval [CI] 0.36 to 1.16, n = 350). In one trial studying patients with effusion, "cure" was higher in the steroid group (alive and free of disability at 2 years (RR 0.69, 95% CI 0.29 to 0.80, n = 221). One trial examined open surgical drainage compared with conservative management, and showed no impact of surgery on death, but a protective effective against cadiac tamponade (RR 0.04, 95% CI 0.00 to 0.64).
Reviewer's conclusions: Steroids have potentially large impacts on survival, but trials are too small to test this. We believe further placebo controlled trials of steroids are warranted, exploring whether the presence of effusion or fibrosis modifies effects. Surgical options also require further evaluation.

Yusuf S, Mehta S, Anand S, Avezum A, Awan N, Bertrand M, et al. The clopidogrel in unstable angina to prevent recurrent events (CURE) trial programme: Rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. Eur Heart J. 2000; 21(24):2033–2041. doi: 10.1053/euhj.2000.2474. **Full text available here.**

Background: Other than aspirin, there are few oral antithrombotic treatments with proven efficacy in patients with acute coronary syndrome. In this report, we present the rationale, design and baseline characteristics of the Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events (CURE) trial, which includes a meta-analysis of the effects of thienopyridines in patients with vascular disease.
Methods and Results: Combined data from randomized trials of thienopyrindines in patients with atherosclerotic disease demonstrated a 29% reduction in vascular events when compared with placebo/control (n=2392) (OR 0·71, 95% CI 0·58–0·86, P=0·0006) and a 10% reduction in vascular events when compared with aspirin (n=22254) (OR 0·91, 95% Cl 0·84–0·99, P=0·039). Similarly, randomized trials of aspirin plus thienopyridines in patients undergoing intracoronary stenting, demonstrated a marked benefit of aspirin plus ticlopidine in reducing death or myocardial infarction compared with aspirin alone (OR 0·23, 95% CI 0·11–0·49, P=0·0001) or aspirin plus warfarin (OR 0·51, 95% CI 0·33–0·78, P=0·002). Whether these benefits extend to the much larger population of patients with acute coronary syndrome is unknown. CURE is an international, randomized, double-blind trial, in which patients with acute coronary syndrome will be randomized to receive either a bolus dose of clopidogrel (300mg) followed by 75mg per day for 3–12 months, or matching placebo. Both groups will receive aspirin. The co-primary efficacy end-points of CURE are: (1) the composite of cardiovascular death, myocardial infarction or stroke; and (2) the composite of cardiovascular death, myocardial infarction, stroke or refractory ischaemia.

CURE will recruit approximately 12500 patients with acute coronary syndrome (from 28 countries) and its power to detect moderate treatment benefits will be in the region of 80–90%, while maintaining an overall type I error (α) of 0·05. The baseline characteristics of the study population are consistent with at least a moderate risk group of patients with acute coronary syndrome.

Conclusions: Randomized trials of thienopyridines in patients with vascular disease demonstrate that thienopyridines are effective in reducing vascular events when compared with placebo/control or aspirin, as well as when used in combination with aspirin in patients undergoing intracoronary stent implantation. The CURE trial is a large international study to determine if acute and long-term treatment with the combination of clopidogrel and aspirin is superior to aspirin alone in patients with acute coronary syndrome.

1999

Mayosi BM, Watkins H. Impact of molecular genetics on clinical cardiology. J R Coll Physicians Lond. 1999;33(2):124–131. **Full text not freely available**

No abstract available.

Mayosi BM, Khogali S, Zhang B, Watkins H. Letter to the Editor: Cardiac and skeletal actin gene mutations are not a common cause of dilated cardiomyopathy. J Med Genet. 1999;36(10):796–797. doi: 10.1136/jmg.36.10.796.

No abstract available. **Full text available here.**

Mayosi BM, Little F, Scott Millar RN. Long-term survival after permanent pacemaker implantation in young adults: 30 year experience. Pacing Clin Electrophysiol. 1999;22(3):407–412. doi: 10.1111/j.1540-8159.1999.tb00468.x. **Full text not freely available.**

The goal of the present study was to determine the etiology of conduction disease and long-term outcome for young adults who undergo permanent pacemaker implantation. Permanent pacing was performed in 232 patients aged 21–50 years, 135 males and 97 females, from 1965 through 1995. One hundred and twenty-six subjects (54%) had evidence of structural heart disease, while idiopathic conduction disease accounted for 46%. About half (54%) of 106 patients with structural heart disease had surgically induced heart block. Pacing mode at primary implantation was single chamber in 65% and dual chamber in 35%. Follow-up ranged from 12–387 months, with a mean of 104-months. At the last follow-up, 133 of 232 patients (57%) were alive, 40 (17%) had died, 30 (13%) were lost to follow-up, 26 (11%) were transferred elsewhere, and 3 (1%) explanted. Patients with sick sinus syndrome had similar outcomes to those with AV block. There was a sharp decline in survival during the first six months; 7.5% of the sample died within the first year following their first pacemaker operation. After the first year, the decline in survival slowed and 70% of the patients could be expected to survive beyond 20 years. The overall survival of young patients without structural heart disease who received a permanent pacemaker was comparable to an age- and sex-matched control population, while patients with structural heart disease performed significantly worse than the control population.

Moolman-Smook JC, De Lange T, Brouwer E, Mayosi B, Ngumbela K, Watkins H, et al. Hypertrophic cardiomyopathy in South Africa – lessons learned and tenets changed. Cardiovasc J S Afr. 1999; 89(SAMJ Supplement 5):C273. **Full text not freely available.**

Hypertrophic cardiomyopathy (HCM), an autosomal dominantly inherited primary cardiac disease with risk of sudden death, is clinically characterised by unexplained hypertrophy of the myocardium, usually involving a non-dilated left ventricle. The disease is caused by mutations in various sarcomeric protein-encoding genes; furthennore, there is a correlation between the risk of sudden death and the specific mutation. Our aim was to identify the spectrum of HCM-causing mutations in South Africa, to assess associated clinical features in a family setting, and to detennine whether these causes and features were similar to or different from those reported internationally. Genomic DNA of 96 apparently unrelated HCM-probands from the Western and Eastern Cape was screened by accepted molecular genetic methods to detect novel and previously described mutations in the β cardiac myosin heavy chain (β MHC), TropomyosinTM, troponin T (TnT), troponin I (TnI), myosin binding protein C (MyBPC), myosin regulatory (MRLC) and essential chain (MELC) genes. Five mutations were found in β MHC in 15 probands, 1 in TnT in 6 probands, and 3 in MyBPC in 3 probands. Clinical evaluations were perfonned in 7 families with βMHC mutations, 5 families with the TnT mutation and 1 with a MyBPC mutation to establish genotype: phenotype correlations. The SA HCM population very infrequently shared mutations with the international HCM population, but demonstrated some unique national founder effects. Clinical nonpenetrance was a feature of all mutations studied. Genotype: phenotype correlation studies indicated that hypertrophy and the risk of sudden death are independent features of the disease and that, in the population studied, only the TnT mutation was associated with a poor prognosis, resulting in early sudden death, especially among males. These data emphasise the need for molecular diagnosis to support clinical diagnosis and serve as a guide to improved and focused patient management and counselling, while also aiding elucidation of the molecular basis of HCM.

1998

Khogali SS, Mayosi BM, Beattie JM, Watkins HC, Poulton J. Mitochondrial DNA point mutations in idiopathic dilated cardiomyopathy. Circulation. 1998;98(17):245. **Full text not freely available.**

No abstract available.

Mayosi B, Watkins H. The diagnosis of familial hypertrophic cardiomyopathy in children. Eur Heart J. 1998;19(9):1276–1278. doi: 10.1053/euhj.1998.1131. **Full text not freely available.**

No abstract available.

Mayosi BM, Latouf SE, Commerford PJ. The use of abciximab during percutaneous coronary angioplasty reduces ischaemic events, but the cost is prohibitive. S Afr Med J. 1998;88(2):130–131. **Full text not freely available.**

No abstract available.

Mayosi BM, Millar RS. The 1995 survey of cardiac pacing in South Africa. Cardiovasc J S Afr. 1998; 88(4):C207–C211. **Full text available here.**

A survey of implanters of permanent cardiac, pacemakers during 1995 was conducted to determine pacemaker implantation rates and identify present and changing patterns in pacing practice in South Africa. The five major pacemaker manufacturers/distributors provided estimates of the numbers of implanters, implanting institutions, and pacemakers implanted in South Africa in 1995.

In 1995, pacemaker implantations were performed by 75 doctors working in 30 hospitals. Since the last survey, which addressed pacing practices in 1986, the primary permanent pacemaker implantation rate increased from 16 to 31 devices per million population per year. There were, however, very large disparities in implant rates between Asians (219/million/year), whites (150/million/year), coloureds (16/million/year) and blacks (7/million/year). Over this period the number of implanting centres doubled, although more than half (53%) were located in one province. Atrioventricular block remains the main indication for permanent pacing (63% of implants), sinus node disorders accounted for 28%, bundle-branch block for 4%, atrioventricular node ablation for tachyarrhythmias for 3%, cardiomyopathy for 1%, and other causes for 1%. Single-chamber units were implanted in 62% of patients, dual-chamber units in 22.5%, and single-pass atrioventricular leads (VDD) in 15%. Twenty-four per cent of

single-chamber devices had rate modulation, and 83% of dual-chamber pacemakers had rate-adaptive features. Bipolar electrodes were used in 82% of atrial and ventricular leads; 55% used only bipolar leads, and only 10% used unipolar leads exclusively. The subclavian introducer technique was used in 80% of lead insertions; Major complications were reported in less than 1% of implants, and no deaths were documented peri-operatively. The survey has highlighted the changing trends in pacemaker use, the low pacemaker implantation rate, particularly in blacks, and the centralised nature of pacing in the country. While the situation has improved over the years, access to treatment of proven benefit remains poor. Furthermore; it is proposed that the process of pacemaker audit would be greatly simplified by the adoption of a prospective registry such as that used in Europe.

Moolman-Smook JC, Mayosi B, Brink P, Corfield VA. Identification of a new missense mutation in MyBP-C associated with hypertrophic cardiomyopathy. J Med Genet. 1998;35(3):253–254. **Full text not freely available.**

Hypertrophic cardiomyopathy is a primary cardiac disease, characterised by idiopathic myocardial hypertrophy, and is caused by defects in sarcomeric protein encoding genes. One of these genes is cardiac myosin binding protein C (MyBP-C), in which a number of splice site and duplication mutations causing HCM have been described. During mutation screening of a South African HCM population by PCR-SSCP, a missense mutation, Arg654His, was detected in one proband. Although the mutation was present in his three adult children, only the proband himself was markedly affected. This is the first report of a disease associated missense mutation in MyBP-C which does not affect the myosin or titin binding domains.

1989–1996

Mayosi BM, Commerford PJ. Pulmonary edema following electrical cardioversion of atrial fibrillation. Chest. 1996;109(1):278–280. **Full text not freely available.**

A 61-year-old man with hypertrophic cardiomyopathy developed acute pulmonary edema 29 h following cardioversion of chronic atrial fibrillation to sinus rhythm. Doppler echocardiographic evaluation of atrial function showed return of right atrial contraction but absent left atrial systole. This has not been reported previously in a case of postcardioversion pulmonary edema.

Mayosi BM, Commerford PJ, Levetan BN. Anticoagulation for prosthetic valves during pregnancy. Clin Cardiol. 1996;19(12):921. **Full text not freely available.**

No abstract available.

Khumalo N, Mayosi B. In memoriam: George Timketson Sikumbuzo Mayosi. S Afr Med J. 1993; 83(12):925. **Full text available here.**

No abstract available.

Mayosi B, Botha J, McFadyen L, Miller R. The effect of carbenoxolone on rat uterine contractility. S Afr J Sci. 1990;86(5):270–271. **Full text not freely available.**

This investigation has shown that in vitro addition of carbenoxolone has the ability to inhibit contraction of stilboestrol-pretreated rat uteri. Inhibition of spontaneous as well as oxytocin-induced contractions was found to be dose-dependent and reversible.

Coovadia YM, Mayosi B, Adhikari M, Solwa Z, van den Ende J. Hospital-acquired neonatal bacterial meningitis: The impacts of cefotaxime usage on mortality and of amikacin usage on incidence. Ann Trop Paediatr. 1989;9(4):233–239. **Full text not freely available.**

All cases of bacterial meningitis in the neonatal unit at King Edward VIII Hospital, Durban for the period 1 January 1981 to 31 December 1987 were reviewed. In particular, we looked at the impact of cefotaxime on mortality rates and amikacin on the incidence of hospital-acquired Gram-negative bacillary (GNB) meningitis. *Klebsiella* was found to be the commonest cause of neonatal meningitis, followed by *Escherichia coli* and

Streptococcus agalactiae. Eighty-four per cent of all cases of GNB meningitis presented more than 3 days after birth, with the vast majority being caused by gentamicin-resistant *Klebsiella*. A decline in the incidence of meningitis from 1.27/1000 live births in 1981 and 0.95/1000 for the period 1981–1986 to 0.22/1000 live births in 1987, with no cases of *Klebsiella* meningitis being seen in that year, coincided with the exclusive use of amikacin as the parenteral aminoglycoside in place of gentamicin in the unit after August 1986. The initial decline in the incidence of meningitis from 0.93/1000 in 1985 to 0.46/1000 in 1986 was attributed to the introduction in 1985 of strict hand disinfection measures to prevent cross-infection in the unit. The case mortality rate (CMR) fell from 0.65 for the period 1981–1984 to 0.42 for the period 1985–1987, and we believe this was largely a result of the introduction of cefotaxime in 1984 as first-line therapy for GNB meningitis, together with better patient care facilities. Our findings therefore highlight the importance of gentamicin-resistant *Klebsiella* as a cause of nosocomial neonatal meningitis and the apparent impacts of amikacin, together with strict hand disinfection measures, on the incidence rate and that of cefotaxime, albeit to a lesser extent, on the CMR of neonatal meningitis. However, our findings need to be confirmed by similar studies in other neonatal units which experience a high incidence of infections caused by gentamicin-resistant GNB.