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# Global excellence in cardiovascular medicine: Africa

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# Global excellence in cardiovascular medicine: Africa

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# Editorial: Global Excellence in Cardiovascular Medicine in Africa: challenges and opportunities

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Editorial on the Research Topic
Global Excellence in Cardiovascular Medicine in Africa: challenges and opportunities

Cardiovascular medicine in Africa has seen several advances in recent years, driven by innovative approaches, international collaborations, and a growing focus on non-communicable diseases. With the rise in the utilization of the internet-based technology, remote access telemedicine platforms have been established to provide remote consultation and diagnosis, especially in rural and underserved areas in some African countries in addition mobile health applications and SMS-based interventions are being used to monitor patients' conditions, remind them to take medications, and provide educational information about cardiovascular health (1).

Other recent advances include the increasing number of local training programs for cardiologists and other cardiovascular specialists often facilitated by the Pan African Society of Cardiology (PASCAR) and/or its affiliate national societies (2, 3). Some of these training courses are founded on partnerships with institutions in high-income countries and collaborations with international societies.

Other training opportunities have been facilitated through a growing number of successful south-south partnerships. An example is the Medtronic Foundation sponsored, PASCAR pacing training initiative which aimed to address the fact that less than a dozen African countries could offer lifesaving Pacemakers locally (4). Programs such as the Medical Education Partnership Initiative (MEPI) have been crucial in enhancing medical education and training in cardiology in many countries (5).

Conducting large-scale epidemiological studies to understand the burden and risk factors of cardiovascular disease (CVD) in African populations represent another area of recent development in the field. As can be seen from some of the published studies in this special Research Topic focusing on Africa, this area started to grow slowly, but

steadily in many parts of the continent. There is certainly a great deal of improvement in data collection and health information systems to track CVD prevalence and outcomes more accurately. This data is vital for shaping public health policies and interventions. In addition, several national and regional programs were founded to focus on screening, diagnosing, and managing emerging CVD major risk factors such as hypertension, and diabetes (6) and reduce older CVD diseases such as RHD Working in collaboration with the WHO, World Heart Federation, and learning from the experience of international societies such as ESC and ACC, PASCAR and its affiliate national societies across Africa have been important in the drive to develop national, and continental policies towards the prevention and management of heart disease and its risk factors (3, 7). For example, South Africa's Strategic Plan for the Prevention and Control of Non-Communicable Diseases outlines specific targets for reducing the burden of CVD (8–10). Countries such as Nigeria and Ghana successfully implemented hypertension awareness and control programs (11, 12) that were coupled with community health workers initiatives to educate the public about cardiovascular risk factors and promote healthy lifestyles. This approach has been effective in increasing awareness and prevention efforts.

It is also important to note the enormous efforts in improving healthcare infrastructure devoted to cardiac centers of excellence in almost all African countries. Countries of noted advances include Uganda, Senegal, Cote d'Ivoire, Kenya, South Africa, Nigeria and all countries in North Africa (13, 14).

Philanthropic endeavors and other effort at investments in modern diagnostic and therapeutic equipment, including catheterization labs, echocardiography machines, and cardiac surgery facilities, are allowing a growing number of centers such as these to provide previously unavailable much needed advanced cardiac therapies and services in many African nations (15). In Egypt, Magdi Yacoub Heart Foundation transformed a public hospital in Aswan into the Aswan Heart Centre (AHC) in 2009 to serve for underserved communities in the Upper Egypt (16). The AHC has been continuously modernized to a large-scale academic medical institution that involves comprehensive clinical services (e.g., pediatric and adult cardiovascular medicine, cardiac surgery, imaging), fellowship programs, and basic science research, now serving for not only Egyptian patients but also those referred from other African nations including Mozambique, Ethiopia, Uganda, and Gambia. These enormous efforts in Africa led to overall improvement in CVD health care in the continent and decreasing the need to seek heart treatment in European countries as done in the past (14).

Despite all the above noted advances, Africa still faces several unique challenges that impact the prevention, diagnosis, and treatment of cardiovascular diseases (CVD). The continents late epidemiological transition and the slow reduction of its high burden of infectious disease, has meant that the continent now faces a double burden of both infectious diseases and non-communicable diseases (NCDs) including CVD, stretching already limited healthcare resources Increasing urbanization and lifestyle changes in many parts of Africa are leading to higher rates of hypertension, obesity, diabetes, and smoking, which are major risk factors for CVD. Persistent poverty, overcrowding and poor access to primary care has also meant that Africa also remains one of the global epicenters of Rheumatic heart disease (RHD) (17).

Unfortunately, the increased NCD and CVD burden and related risk factors has not been met by a matching rise in awareness programs, and health educational campaigns in many parts of the continent and CVD now the leading cause of morbidity and mortality in most of Africa. Additional challenges to confronting this health problem include limited adequately equipped healthcare facilities, and a grossly inadequate number of appropriately trained health care personnel for either the continent's population or burden of disease. Inadequate emergency services to handle what are often time-dependent acute cardiovascular conditions (e.g., myocardial infarction and stroke), characterize most countries across the continent including those classified as high and middle-income. Specialized training programs for Emergency Medical Technicians (EMT) to help mitigate the problem do not exist in most countries while many healthcare professionals leave Africa for better opportunities abroad, exacerbating the shortage (18). The impact of this limited access to heart health facilities and care is most evident in rural areas where disparities in health outcomes are evident (19, 20).

Finally, what cannot be overstated is wars and political disruptions in some parts of Africa which have contributed greatly to the weakening of cardiovascular medicine services undermining the public health in such areas (21). It is worth noting the ongoing war in Sudan which resulted in a complete termination of the cardiovascular medicine services in the country affecting more than 40 million Sudanese people and increasing the burden on neighboring countries who received refuges due to the ongoing war (22).

Despite these challenges, progress towards improving cardiovascular medicine in Africa remains promising and reflects a growing recognition of the importance of addressing non-communicable diseases on the continent and the political will to do so. Overcoming these challenges will require coordinated efforts from governments, healthcare providers, researchers, and the community, and continued investment in health infrastructure, training and public health initiatives to create sustainable and effective multidirectional interventions. It will also need collaborative efforts from the developed nations, and the involvement of leading heart disease professional organizations such as the American Heart Association, The American College of Cardiology, The National Lipids Association, and the European Society of Cardiology.

This Research Topic entitled, "Global Excellence in Cardiovascular Medicine in Africa" sponsored by the Frontiers in Cardiovascular Medicine highlights the advances and challenges in cardiovascular medicine across Africa, showcasing the academic excellence in the field of CVD.

Articles accepted in this collection are diverse, covering a wide range of areas of cardiovascular diseases in Africa.

RHD impacts many children across Africa. This was covered in part by an elegant review of Dr. Magdi Yacoub and his associate who reviewed the ARGI database, a hospital-based registry in a tertiary referral national center of the AHC in which all patients with the diagnosis of RHD are being included and discussed (21).

The study showed an in-depth analysis of the severity and phenotype of the disease in Egyptian patients and its progression and provided a way to compare to other regions. The ARGI database represent a good resource for other African countries. Another paper on RHD in this issue is presented behalf of the Sudanese RHD Guideline Committee. This article outlined the Sudan's rheumatic fever and RHD guidelines providing a simplified approach for countries with endemic RHD (23). In addition, the situation of anticoagulation control after mechanical heart valve replacement in low- to middle-income countries where RHD still predominates and that in developed countries substantially differs. Based on their data from 552 consecutive cases with mechanical valve replacement for RHD, Zilla et al. presented a review that outlines some best practice and guidelines for the use of mechanical valve replacement for patients with RHD discussing the international normalized ratio control in Africa and elsewhere beyond. A general commentary article by Ntsekhe and Doubell in this issue titled "*Eradicating Rheumatic Heart Disease in Africa: Have we made progress since the Drakensberg Declaration*?" summaries the state of the progress made in RHD management in Africa.

Two studies were published in this issue from Ethiopia: the first one discussing hypertension and the second presenting the incidence and predictors of recurrent acute coronary syndrome among adult patients in West Amhara. In their cross-sectional study, Gobezie et al. reported that more than half of the hypertensive patients in Ethiopia have uncontrolled BP, and diabetes mellitus. On the other hand, a study by Alamaw et al. indicated a higher incidence rate of recurrent ACS in Ethiopia, which can be explained on the light of uncontrolled major risk factors such as BP and diabetes. On the same line, Tsabedze et al. presented data for 11,860 participants from four randomized control trials on the efficacy of beta-blockers on blood pressure control and morbidity and mortality endpoints in hypertension of African ancestry. The study reported that the third-generation beta-blockers (STGBBs) can reduce the mean arterial pressure compared to other modalities, showing that these STGBBs were not associated with increased risk of stroke. Similarly reported in this issue by Musa et al. a high prevalence of hypertension among Sudanese women who had given birth to 5 fetus or more.

Other areas that were covered extensively in this issue is a study by Giliomee et al. who discussed in their review cases relevant the role of cardiovascular MRI on contextualizing tuberculous pericardial inflammation and edema as predictors of constrictive pericarditis.

The aortic diseases received extensive coverage in this issue. Meel et al. published a study involved 139 subjects with thoracic ascending aortic (TAA) aneurysms (52.5% females). The study reported an association between TAA and hypertension and HIV with considerable morbidity and mortality Indicating that a two-dimensional echocardiography and advanced strain imaging are effective methods for detecting and risk stratifying TAA aneurysms. Mvondo et al. presented an original article that discusses the pathogenesis of aortic root enlargement (ARE) in 69 patients who underwent mitral and aortic replacement. The authors reported that the association between ARE and double valve replacement (DVR) did not significantly affect the operative mortality and that ARE can be safely used whenever indications arise to reduce the occurrence of prosthesis mismatch among young patients with growth potential.

Hugo et al. in their original research article published in this issue investigated a subgroup of patients 55 years and younger of a cohort of 169 adult patients between the ages of 18 and 60, who received permanent pacemakers between 2010 and 2020 performed a retrospective audit of these young adults in South Africa. The team presented interesting data with potential utilities.

Finally, Weich et al. published an interesting original article in this special issue reporting a study that developed and tested transcatheter heart valves (THVs) that can have a reduced calcification potential. Using a juvenile sheep THV model, the authors investigated the effects of various modalities on the development of calcification and the hemodynamic function. The authors suggested that this new approach may potentially benefit younger patients.

In conclusion, this special Research Topic in Frontiers in Cardiovascular Medicine journal entitled, "Global Excellence in Cardiovascular Medicine" provides a glimpse of the challenges and opportunities in the field of cardiovascular medicine in Africa. We hope that these efforts stimulate interest in similar endeavors by the scientific community. Supporting similar work by others will greatly impact the scientific productivity by cardiovascular scientists in Africa and will eventually contribute to improving cardiovascular health care in the continent and decreasing the burden of heart diseases in Africa.

## Author contributions

MG: Conceptualization, Writing – original draft, Writing – review & editing. MN: Writing – original draft, Writing – review & editing. AD: Writing – original draft, Writing – review & editing. MA: Conceptualization, Writing – original draft, Writing – review & editing.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Publisher's note

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# Spectrum of ascending aortic aneurysms at a peri-urban tertiary hospital: an echocardiography-based study

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**Introduction:** Thoracic ascending aortic (TAA) aneurysms are an important cause of disability and death and require early detection for effective management. Currently, there is a paucity of data from Africa pertaining to TAA aneurysms. This study describes the spectrum of TAA aneurysms at a peri-urban tertiary hospital.
**Methods:** A descriptive retrospective study based on clinical and echocardiographic imaging data of patients with TAA aneurysms from October 2017–October 2022. Advanced strain imaging was performed to measure left ventricular (LV) basal, apical, and global longitudinal strain as well as circumferential strain (CS) of the ascending aorta as a proxy measurement of aortic compliance.
**Results:** The study comprised 139 cases of TAA aneurysms (52.5% females) with a mean age of 50 ± 14.8 years with 45 age and gender matched controls. Most cases (95%) were of African ethnicity. The main etiologies were hypertension (41.7%), HIV (36.6%), connective tissue disease (10.7%), congenital (2.2%) and mixed pathologies (8.6%). Two-thirds of patients (69.7%) presented in heart failure, 10% presented with aortic dissection. Thirty percent of the patients were classified as New York Heart Association (NYHA) class I, 59.7% NYHA II, 8.6% NYHA III and two patients NYHA class IV. Echocardiography revealed enlarged aortic dimensions compared to controls ($P < 0.001$). TAA aneurysms were complicated by severe aortic regurgitation (AR) in half (50.3%) of patients, moderate AR in 25.8%, and mild AR in 14.3%. The mean LV ejection fraction (46.9 ± 12.7%) was reduced compared to controls ($P < 0.001$). Aortic CS was reduced compared to controls [4.4 (3.2–6.2) % vs. 9.0 (7.1–13.4) %, $P < 0.001$]. Aortic stiffness was higher in the aortic aneurysm group compared to controls (15.39 ± 20.65 vs. 5.04 ± 2.09, $P = 0.001$). LV longitudinal strain (–13.9 ± 3.9% vs. 18.1 ± 6.7%), basal CS (–13.9 ± 5.6% vs. –17.9 ± 5.8%) and apical CS (–8.7 ± 8.5% vs. –30.6 ± 3.8%) were reduced compared to controls ($P < 0.001$). Most patients were on diuretic and anti-remodeling therapy. Surgery was performed in 29.4% and overall mortality was 7.9%. Mortality for acute aortic dissection was 40%.
**Conclusion:** TAA aneurysms associated with hypertension and HIV are common in this predominantly African female population and are associated with considerable morbidity and mortality. Two-dimensional echocardiography and advanced strain imaging are potential tools for detecting and risk stratifying TAA aneurysms.

KEYWORDS

Africa, aneurysms, echocardiography, strain imaging, ascending aorta, aortic regurgitation 2

# 1. Introduction

Aneurysms of the ascending aorta often develop undetected due to their non-specific and late-stage clinical presentation. These aneurysms can rapidly lead to death due to aortic rupture or dissection (1) and thus are an important cause of mortality in adults. Although no specific data exists regarding the true mortality from thoracic ascending aortic (TAA) aneurysms, studies have shown a prevalence of aortic aneurysms ranging from 1.6% to 7.2% in a general population aged 60 years or older (2). Mortality due to aortic aneurysms is estimated to be between 157,357 and 18,899 (3) globally according to the global burden of disease (GBD) 2019, thus making death due to aortic aneurysms a significant public health concern.

TAA aneurysms occur more commonly in males than females with a ratio of 1.7–3:1 and with a mean age of 65 years at presentation, however this distribution may change with age. Ogeng'o et al. in their paper in Kenya showed a male-to-female ratio of 1.4:1 in patients before the age of 40 years, however a 1:1 ratio before 50 years and a 1:2, male-to-female ratio after 50 years of age (4).

In terms of the main aetiologies causing TAA aneurysms, it is well documented that atherosclerosis, hypertension, connective tissue and inflammatory disease, congenital heart disease, and infectious causes such as syphilis and human immunodeficiency virus (HIV) can cause TAA aneurysms (5). Further to this, ethnicity, geography, and burden of risk factors can also dictate the pattern of aneurysmal disease of the aorta (4). In African populations, hypertension and syphilis have been noted as frequent risk factors whereas the most frequent risk factors in people of European-origin are hypertension, ischemic heart disease (IHD) and age (6, 7).

Recent work by Høgh et al. has shown a direct association between HIV and TAA aneurysms. It was found that there was a four-fold higher odds of aortic aneurysms compared to uninfected controls likely due to the proinflammatory state associated with HIV (8, 9). Given that Southern Africa has amongst the highest rates of people living with HIV globally, HIV is thus an important cause of aortic aneurysms in this population (10, 11).

Strain imaging of the aorta using speckle tracking echocardiography (STE) has emerged as an important feasible and reproducible bedside tool to assess aortic stiffness (12). In the context of proximal TAA aneurysms use of circumferential strain may impact the prognosis of these patients by aiding risk stratification of patients that are at risk for further aortic dilatation or dissection (13, 14).

As it stands, there is a paucity of data on the clinical spectrum, screening processes and management of TAA aneurysms in Africa. As a result, this study aims to begin building information around demographics, clinical characteristics, two-dimensional echocardiography and strain imaging of TAA aneurysms, and morbidity and mortality by characterizing the spectrum of ascending aortic aneurysm in a peri-urban tertiary hospital in South Africa.

# 2. Methods

## 2.1. Study population

This was a descriptive retrospective cross-sectional study of 139 patients with confirmed TAA aneurysms seen at Chris Hani Baragwanath Academic Hospital (2017–2022). The data were extracted from an established database of patients with aortopathy as well as from pre-recorded echocardiographic images and surgical presentation reports. Results of routinely performed blood tests for clinical management of patients were also retrieved and analysed.

Data of forty-five age and gender matched healthy controls were extracted from a prior study that included normal participants (M200977). The inclusion criteria were (i) age greater than 18 years, (ii) confirmed TAA aneurysm (aorta >40 mm in size or dilation greater than 1.5 times the normal diameter of the adjacent healthy arterial segment) (15–17). The exclusion criteria were (i) suboptimal image quality of aorta (ii) isolated abdominal aortic or arch aneurysms (iii) extensive missing data. Eight patients were excluded due to extremely poor echocardiographic imaging quality, five due to extensive missing data, one due to an isolated arch aneurysm and two due to an exclusive abdominal aortic aneurysm.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) available at: https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2013-JAMA.pdf. Ethics approval for the study was obtained from the University of the Witwatersrand ethics committee (M170389).

## 2.2. Echocardiographic examination

Aortic measurements were obtained as per the 2015 American Society of Echocardiography guidelines using a Philips EPIQ 9 system (18). Circumferential Strain (CS) of the ascending aorta (AAO) was measured using Philips QLAB version 11.0 software for the left ventricle which allowed offline semi-automated analysis of speckle-based strain two-dimensional speckle-tracking software (Amsterdam, Netherlands). All echocardiographic measurements were performed by an experienced cardiologist and clinical technologist.

Transthoracic echocardiographic examinations were performed on all patients in the left lateral position. An S5-1 transducer on a Philips EPIQ 9 system was used to obtain the aortic measurements from parasternal long axis views where the aortic root and proximal aorta and the left ventricle (LV) could be visualized. Measurements at four different levels in the proximal aorta were made namely (i) the aortic annulus (AA); (ii) sinuses of Valsalva (SOV); (iii) Sino-tubular junction (STJ); and (iv) the proximal ascending aorta (AAO). From the same window, with appropriate probe rotation, two-dimensional short-axis views at the level of the aortic valve plane were acquired and the image depth and the sector width were adjusted to optimize proximal aorta visualization. Zoomed-in images of both left ventricle

outflow tract (LVOT) in the parasternal long-axis view and of the aortic valve in the parasternal short-axis view were obtained and recorded.

As recommended by the 2015 American Society of Echocardiography (ASE) Guidelines, the aortic annulus was measured at mid-systole from the inner-edge to inner-edge. All other aortic root measurements (i.e., maximal diameter of the sinuses of Valsalva (SV), the Sino-tubular junction (STJ), and the proximal ascending aorta (AAO) were made at end-diastole (QRS complex onset), in a leading-edge-to-leading-edge convention (18). The European Society of Cardiology (ESC) 2017 valvular heart disease guidelines were used to quantify the severity of valvular regurgitation (19). The measurements of LV diastolic function were performed following the standard guidelines on diastolic function by Nagueh et al. (20). Measurements relating to the right ventricle were based on the ASE guidelines (21).

Two-dimensional (2D) speckle-tracking (ST) echocardiography was used to determine the circumferential strain (CS) (22). Images of the ascending aorta were first obtained in the high parasternal long-axis view until the largest diameter of the ascending aorta was visualized. Then, akin to the measurement of CS of the left ventricle, in short axis view a loop was manually drawn along the inner edge of the aortic wall during systole and then an additional loop near the outer edge of the aortic wall was automatically generated by the software. The software then divided the aortic wall image into six equally sized segments and the global circumferential ascending aortic strain was calculated as the mean value of the peak CS of the six segments. The data was then transferred and analysed offline using the Philips X-Celera workstation.

Aortic stiffness index ($\beta_2$) was calculated as follows (23):

$$\beta_2 = \frac{\ln\left(\frac{SBP}{DBP}\right)}{Aortic\ CS}$$

***β₂***: Aortic Stiffness index
***SBP***: Systolic Blood Pressure
***DBP***: Diastolic Blood Pressure
***CS***: Circumferential strain

Two-dimensional echocardiographic images were obtained at end-expiration from LV apical long-axis 4-, 3-, and 2-chamber views with frame rates between 60 and 80 frames per second (24). Three consecutive cardiac cycles were recorded and averaged. Global LV systolic strain was calculated by averaging the three apical views as previously described.

## 2.3. Statistical analysis

All computations for this data were carried out using Statistica version 14.00.15. Continuous variables were expressed as mean and standard deviation (SD) or median (interquartile range). Student's *t*-test or Mann-Whitney *U* test were used to compare continuous variables. Categorical data were expressed as percentages. Categorical variables were evaluated by the Chi-square test. Pearson's correlation coefficient was used to measure the association between two continuous variables. A *P* value of ≤0.05 was considered statistically significant. One-way analysis of variance (ANOVA) was used to compare continuous variables and *post hoc* comparisons were performed using Scheffé test. For Non-parametric data Kruskal-wallis test was performed with *post hoc* testing using Dunn's test.

# 3. Results

The demographic and clinical characteristics of study patients are summarised in **Table 1**. Most of the patients were female and of African ethnicity (95%), six patients were of mixed race and one patient was of Indian descent. There was only one patient of European origin. This patient presented with acute aortic dissection and demised soon after admission, and so was excluded from the current study due to lack of data.

Regarding the presenting clinical symptoms, dyspnoea as a result of heart failure (70%) was the most common complaint. Fourteen (10%) patients presented with chronic aortic dissection. Five patients presented with acute aortic dissection but were excluded from the study due to a lack of data.

In terms of medical management, diuretic and angiotensin-converting enzyme inhibitor use for heart failure was common. However, Beta-blocker use was comparatively restricted likely due to fear of worsening aortic regurgitation related to prolonged

TABLE 1 Clinical characteristics of the study population and control group.

| Variable | Study patients | Controls | *P*-value |
|---|---|---|---|
| | *N* = 139 | *N* = 45 | |
| Age (years) | 50 ± 14.8 | 46.3 ± 6.7 | 0.106 |
| Gender (M/F) | 66/73 (47.4%/52.6%) | 24/21 (53.3%/47.7%) | 0.9 |
| BSA ($m^2$) | 1.73 ± 0.2 | 1.81 ± 0.2 | 0.02 |
| SBP (mmHg) | 137.2 ± 22.1 | 128.4 ± 10.5 | 0.01 |
| DBP (mmHg) | 72.7 ± 16.6 | 81.6 ± 10.2 | <0.001 |
| Heart rate (bpm) | 80.6 ± 14.7 | 73.7 ± 10.7 | 0.004 |
| NYHA class (I/II/III/IV) | (30.2%/59.7%/8.6%/1.4%) | | |
| Co-morbidities | | | |
| Hypertension | 58 (41.7%) | | |
| HIV | 51 (36.7%) | | |
| Diabetes | 4 (2.8%) | | |
| Medication | | | |
| Carvedilol | 62 (44.6%) | | |
| Enalapril | 87 (62.5%) | | |
| Coversyl | 6 (4.3%) | | |
| Furosemide | 84 (60.4%) | | |
| Hydrochlorothiazide | 15 (10.7%) | | |
| Amlodipine | 21 (15.1%) | | |
| Nifedipine XL | 10 (7.2%) | | |

BSA, body surface area; DBP, diastolic blood pressure; SBP, systolic blood pressure; NYHA, New York Heart Association.

diastole from bradycardia. All patients with HIV were on anti-retroviral medication.

## 3.1. Aetiological distribution in the study population

The main aetiologies of TAA aneurysms are depicted in Figure 1. Hypertension and HIV were the most common aetiologies. There were eight cases of Marfan syndrome, two cases of bicuspid aortic valve, two non-specified cases of connective tissue disease and one case of Ehlers-Danlos syndrome, who presented with pulmonary embolism. In terms of autoimmune aetiologies, there were two cases of Takayasu's arteritis. Regarding cases with congenital heart disease, there was a participant who had a congenital repaired ventricular septal defect (VSD) with subaortic membrane and right ventricular outflow tract obstruction, another patient with a restrictive VSD, as well as one case of Tetralogy of Fallot with a concurrent TAA aneurysm.

In 8.6% of the cases there were multiple or mixed aetiologies. There were two participants who were HIV positive and had a congenital heart lesion. One of these patients had a VSD and the other had a VSD combined with a subaortic membrane. There were also two cases of TAA aneurysms in patients who had had coronavirus disease-associated pneumonia, one of these cases had a background of Marfan syndrome and the other had a background of hypertension. One patient with HIV had a history of pulmonary tuberculosis. There were three cases that had dyslipidaemia, one patient was also HIV positive, one had hypertension and ischaemic heart disease and the third patient had hypertension with diabetes, all three were on lipid-lowering therapy.

Based on the Treponema Pallidum Haemagglutination test, syphilis was suspected in four cases. Two of which had HIV and two were hypertensive. Eleven cases of TAA aneurysms had concurrent arch or descending aorta aneurysms. Of these, seven had HIV, one had Takayasu's arteritis and three were hypertensive.

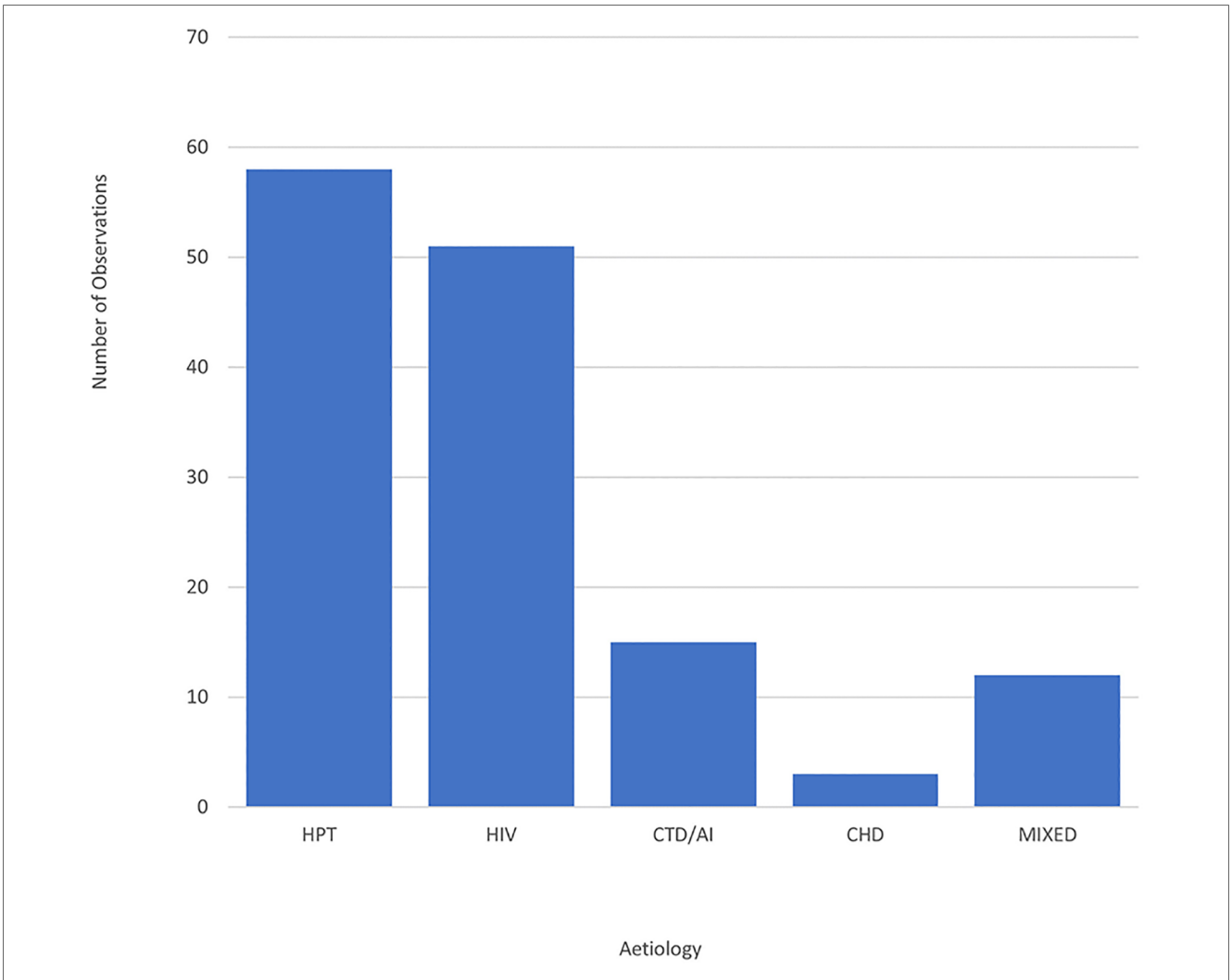


FIGURE 1
Bar graph showing the distribution of TAA aneurysm cases by aetiology. CHD, congenital heart disease; CTD/AI, connective tissue disease/autoimmune; HIV, human immunodeficiency virus; HPT, hypertension; Mixed, mixed aetiologies.

In terms of differences based on gender, there was no statistical difference between genders in terms of the main aetiologies of hypertension (27 M vs. 38 F, $P = 0.42$) and HIV (28 M vs. 35 F, $P = 0.68$).

## 3.2. Echocardiographic characteristics of the study population

The aorta was significantly enlarged from the root to the ascending aorta compared to controls. Patients that presented with aortic dissection had larger diameters compared to the group without dissection ($54.5 \pm 8.0$ mm vs. $48.2 \pm 10.3$ mm, $P = 0.02$). These results remained statistically significant when indexed to body surface area ($36.3 \pm 11.5$ mm/m$^2$ vs. $28.2 \pm 7$ mm/m$^2$, $P < 0.001$). Nine patients with dissection were hypertensive (Figure 2), four had HIV and one had connective tissue disease (Table 2).

Compared to controls, patients with aortopathy had a significantly dysfunctional LV. As most patients presented in decompensated heart failure, secondary to aortic valvular regurgitation (Figure 3), systolic function was reduced and filling pressures were high. The left ventricle was hypertrophied in the study population. The measurements of both the interventricular septum and the posterior LV wall and mass were on average greater in the study group than that of the control group.

In addition to the above, right ventricular enlargement was noted in the patients with aortopathy when compared to controls, resulting in impaired early filling, and raised pulmonary artery systolic pressures implying long-standing disease and late presentation.

Most of the patients had functional aortic regurgitation (Table 2, Figures 2–4). The mean vena contracta (VC) width was $0.5 \pm 0.2$ cm, with an effective regurgitant orifice area of 0.2 (0.14–0.37) cm$^2$ and an end-diastolic velocity of 18.2 (11.2–22.3) cm/s. In terms of the cases that had valvular structural abnormalities, there were two cases who had bicuspid valves (without aortic regurgitation or stenosis), one with degenerative aortic valve stenosis and one with mild rheumatic mitral valve stenosis. There was also a case of severe rheumatic mitral valve stenosis (Figure 5), one case with myxomatous mitral valve disease with mitral regurgitation and two patients who had mitral valve prolapse but no mitral regurgitation.

The aortic circumferential strain was markedly reduced in the aortopathy group compared to controls (Figure 6). Further to this, the aortic stiffness index was higher in the aortic aneurysm group compared to controls, suggesting reduced compliance. Finally, left ventricular longitudinal and circumferential strain parameters were significantly reduced compared to controls.

Table 3 depicts the subgroup comparisons of patients with severe aortic regurgitation (AR) compared to patients with moderate and no or mild aortic regurgitation. Patients with severe aortic regurgitation had larger aortic diameters, most significant at the ascending aorta and sino-tubular junction

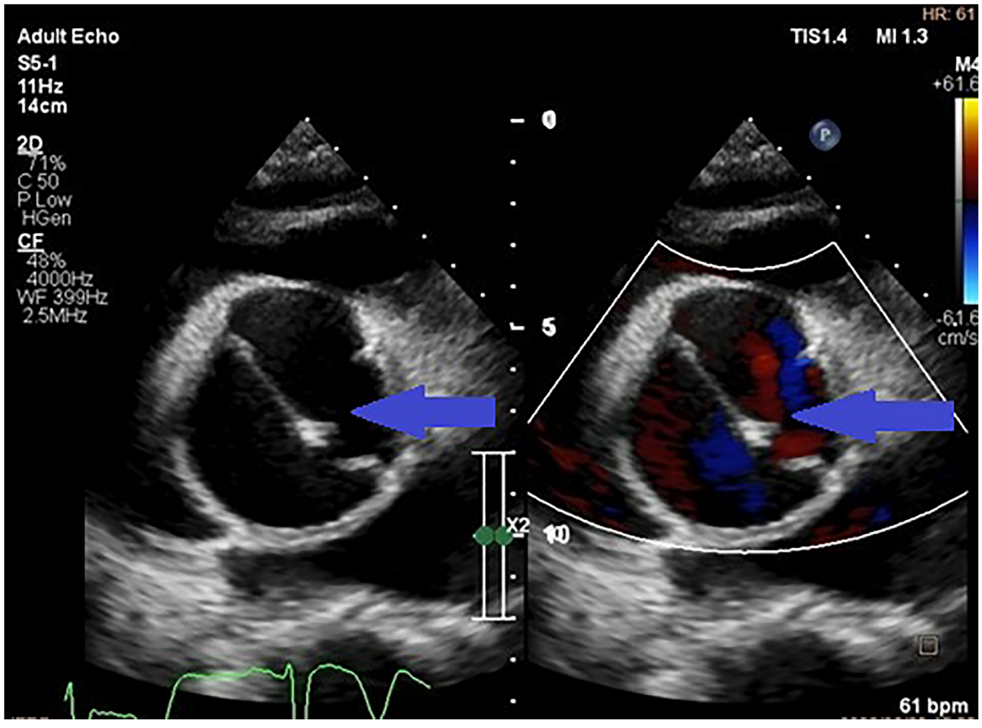


FIGURE 2
Parasternal short axis transthoracic view showing a dissection flap in an aneurysmal thoracic aorta (indicated by the blue arrows) in a patient with uncontrolled hypertension.

10.3389/fcvm.2023.1209969

TABLE 2 Echocardiographic characteristics of the study population compared to control group.

| Variable | Study patients ($n = 139$) | Controls ($n = 45$) | *P*-value |
|---|---|---|---|
| **Left ventricular function** | | | |
| LV EDD (mm) | 55.2 ± 10.1 | 42.7 ± 4.7 | <0.001 |
| LV EDD (mm/m$^2$) | 32.6 ± 7.4 | 23.6 ± 3.4 | <0.001 |
| LV ESD (mm) | 41.8 ± 11.0 | 29.1 ± 4.9 | <0.001 |
| LV ESD (mm/m$^2$) | 29.4 ± 7.4 | 16.1 ± 2.7 | <0.001 |
| IVSD (mm) | 10.32 ± 2.29 | 7.02 ± 1.52 | <0.001 |
| IVSD (mm/m$^2$) | 6.05 ± 1.53 | 4.38 ± 1.09 | <0.001 |
| LVPWD (mm) | 10.32 ± 2.29 | 7.34 ± 1.36 | <0.001 |
| LVPWD (mm/m$^2$) | 6.05 ± 1.53 | 4.59 ± 1.07 | <0.001 |
| LV mass (g) | 230.76 ± 89.62 | 96.87 ± 38.77 | <0.001 |
| LV mass (g/m$^2$) | 136.42 ± 53.90 | 60.16 ± 24.22 | <0.001 |
| EDV (ml) | 162.7 ± 73.1 | 84.4 ± 19.5 | <0.001 |
| EDV (ml/m$^2$) | 96.3 ± 44.2 | 46.3 ± 10.6 | <0.001 |
| ESV | 89.9 ± 54.8 | 33.1 ± 15.1 | <0.001 |
| ESV (ml/m$^2$) | 53.2 ± 32.8 | 17.9 ± 7.1 | <0.001 |
| LVEF (%) | 46.7 ± 12.7 | 63.3 ± 7.0 | <0.001 |
| E wave (cm/s) | 78.3 ± 30.2 | 77.7 ± 18.6 | 0.910 |
| E/A ratio | 69.7 ± 27.4 | 59.9 ± 15.8 | 0.020 |
| E' lateral (cm/s) | 8.0 ± 3.8 | 11.9 ± 2.9 | <0.001 |
| Lateral E/E' (cm/s) | 9.6 (6.6–14.2) | 6 (5.2–8.2) | 0.002 |
| S' lateral (cm/s) | 6.82 ± 2.1 | 8.3 ± 1.9 | <0.001 |
| Left atrial volume (ml) | 58.5 ± 25.6 | 41.6 ± 14.7 | <0.001 |
| Left atrial volume (ml/m$^2$) | 34.4 ± 15.2 | 23.3 ± 7.4 | <0.001 |
| **Aortic measurements** | | | |
| Annulus (mm) | 23.5 ± 4.3 | 19.6 ± 2.5 | <0.001 |
| Annulus (mm/m$^2$) | 13.8 ± 2.9 | 10.8 ± 1.4 | <0.001 |
| Sinuses (mm) | 44.1 ± 9.2 | 28.8 ± 7.9 | <0.001 |
| Sinuses (mm/m$^2$) | 26 ± 6.5 | 15.7 ± 3.5 | <0.001 |
| Sino-tubular junction (mm) | 46.2 ± 10.1 | 26.0 ± 3.2 | <0.001 |
| Sino-tubular junction (mm/m$^2$) | 27.3 ± 7.4 | 14.3 ± 1.6 | <0.001 |
| Ascending aorta (mm) | 48.9 ± 10.1 | 26.5 ± 3.0 | <0.001 |
| Ascending aorta (mm/m$^2$) | 28.9 ± 7.8 | 14.5 ± 1.6 | <0.001 |
| **Valvular pathology** | | | |
| Aortic regurgitation (none/mild/moderate/severe) (%) | 9.3/14.3/25.8/50.3 | - | |
| Mitral regurgitation (none/mild/mod/severe) (%) | 52.5/33.1/10.8/3.6 | - | |
| Tricuspid regurgitation (none/mild/mod/severe) (%) | 43.8/41.7/7.2/7.2 | - | |
| **Right ventricle function** | | | |
| Right ventricle base (mm) | 34.7 ± 8.2 | 29.5 ± 5.5 | <0.001 |
| Right ventricle base (mm/m$^2$) | 20.2 ± 5.4 | 16.3 ± 3.3 | <0.001 |
| TAPSE (mm) | 19.9 ± 11.1 | 18.6 ± 4.5 | 0.460 |
| S' (cm/s) | 11.12 ± 3.2 | 11.2 ± 2.2 | 0.840 |
| E' (cm/s) | 8.9 ± 3.6 | 10.5 ± 3.1 | 0.008 |
| A' (cm/s) | 12.6 ± 7.5 | 11.6 ± 3.0 | 0.390 |
| E'/A' ratio | 0.82 ± 0.6 | 0.97 ± 0.3 | 0.170 |
| PASP (mmHg)[a] | 30.7 ± 20.8 | 17.6 ± 5.7 | <0.001 |
| **Strain parameters** | | | |
| Left ventricle GLS (%) | −13.9 ± 3.9 | −18.1 ± 6.7 | <0.001 |
| Left ventricle basal CS strain (%) | −13.9 ± 5.6 | −17.9 ± 5.8 | <0.001 |
| Left ventricle apical CS strain (%) | −19 (−23 to −12.7) | −24.6 (−32.7 to −20.6) | 0.002 |
| Aortic CS (%)[b] | 4.4 (3.2–6.2) | 9.0 (7.1–13.4) | <0.001 |
| Aortic stiffness index ($\beta_2$) | 15.39 ± 20.65 | 5.04 ± 2.09 | 0.001 |

Data are presented as mean ± SD, median (IQR) or %. CS, circumferential strain; EDV, end-diastolic volume indexed; ESV, end-systolic volume indexed; GLS, global longitudinal strain; IVSD, interventricular septum diameter; LV, left ventricle; LV EDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVPWD, left ventricular posterior wall diameter; PASP, pulmonary artery systolic pressure; TAPSE, tricuspid annular plane systolic excursion.

[a]PASP measurement was feasible in 32 controls and 108 study patients.

[b]Aortic CS and $\beta_2$ was not feasible in 14 patients that presented with aortic dissection of the ascending aortic aneurysm due to intimal disruption **IVSD in diastole.

level. There was no difference in CS between the three groups, however, the aortic stiffness index was higher in the severe aortic regurgitation group compared to mild or no AR group. There was no difference in the LV strain parameters between the three groups. Most of the patients with severe AR had HIV (57.9%) or hypertension (24.6%). Those with severe AR and connective tissue disease comprised 15.9% of the cases.

## 3.3. Correlations between aortic regurgitation severity and aortic diameter

There was a positive correlation between AR severity parameters of vena contracta (VC) and end-diastolic velocity and aortic diameters. The most significant correlation was between VC and STJ diameter ($r = 0.32$, $P = 0.003$), and VC and AAO diameter ($r = 0.34$, $P = 0.002$). A significant correlation was also noted between AR end-diastolic velocity and STJ diameter ($r = 0.29$, $P = 0.001$), and AR end-diastolic velocity and AAO ($r = 0.30$, $P < 0.001$). Further to this, there was a positive correlation between sinus diameters and VC ($r = 0.30$, $P = 0.004$) and sinus diameter and end-diastolic velocity ($r = 0.13$, $P = 0.03$). However, there was no significant correlation noted between AR severity parameters and aortic annulus diameter ($P > 0.05$).

## 3.4. Blood biochemistry of the study patients

In terms of the blood biochemistry most (115) of the patients had borderline anaemia with a mean haemoglobin of 12.5 ± 2.6 g/dl. All of which had normal kidney function with urea of 6.5 ± 5.0 μmol/L and creatinine of 84 (68–107) μmol/L. The mean total cholesterol (56) was 3.9 (3.0–4.6) mmol/L. In group of HIV positive patients, the median CD4 count was (357–593 cells/μl). Nine had lower than detectable viral loads, while 27 patients had a median viral load of 1,020,000 (2,000,000–2,660,000) copies/ml.

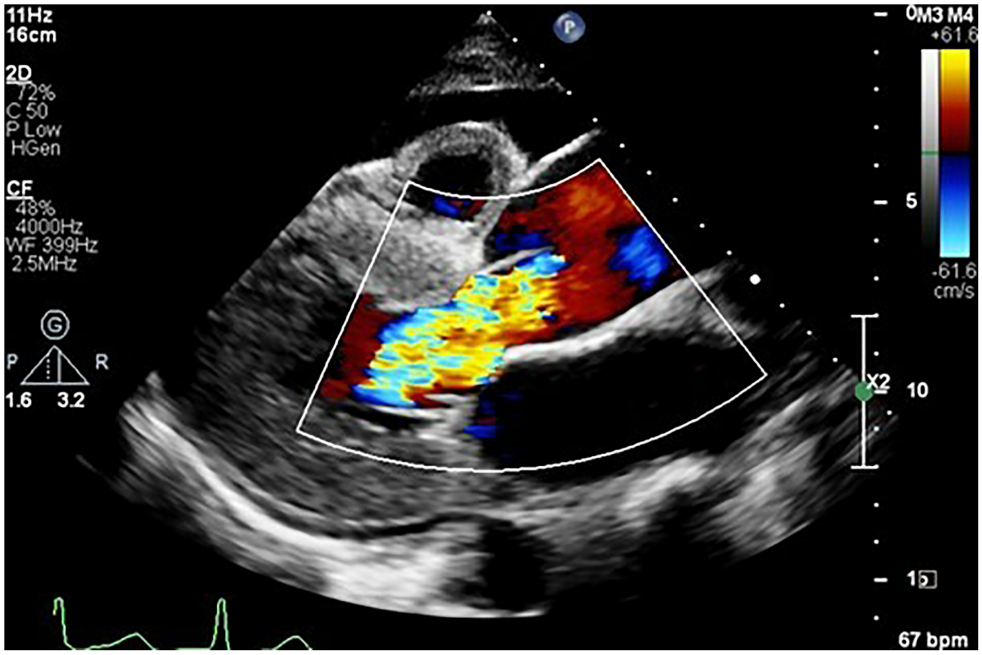


FIGURE 3
Parasternal long axis view showing an aortic aneurysm secondary to hypertension complicated by heart failure, as evidenced by the anterior pericardial effusion secondary to severe aortic regurgitation.

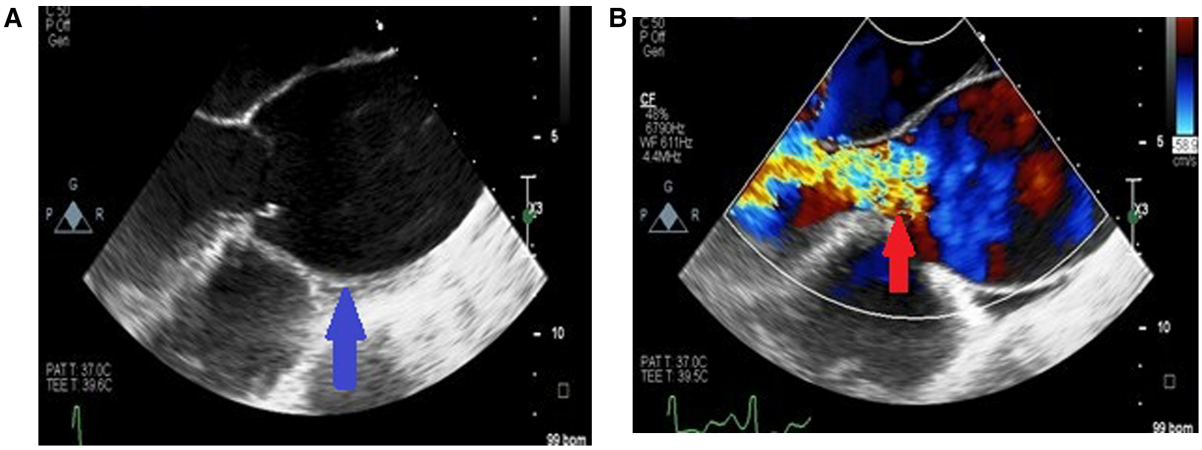


FIGURE 4
Long axis view of the aortic aneurysm in a patient with HIV showing enlargement from the root to the ascending aorta with effacement of sino tubular junction (blue arrow) (A) and malcoaptation of the leaflets with severe aortic regurgitation (red arrow) (B).

## 3.5. Morbidity and mortality of the study patients

The morbidity due to heart failure and chronic aortic dissection was high in this study. All 14 patients in the chronic dissection group had uncontrolled hypertension with SBP $\geq$ 145 mmHg.

All patients were presented for surgery, except for 12 patients who either refused surgery or were considered too high of an intraoperative risk. Four patients demised while awaiting surgery, two patients refused surgery and then subsequently demised. A total of 41 patients (29.4%) ultimately underwent surgery. Five patients demised post operatively and one patient developed severe post-operative aortic regurgitation. The overall mortality was 7.9% (11/139). This is likely a significant underestimate as there was follow up of only 54% of the patients due to difficulties with contacting the patients. Of note, five patients with acute aortic dissection were excluded due to lack of data, three of these patients demised and two underwent successful surgery. The mortality for this subgroup was 40%.

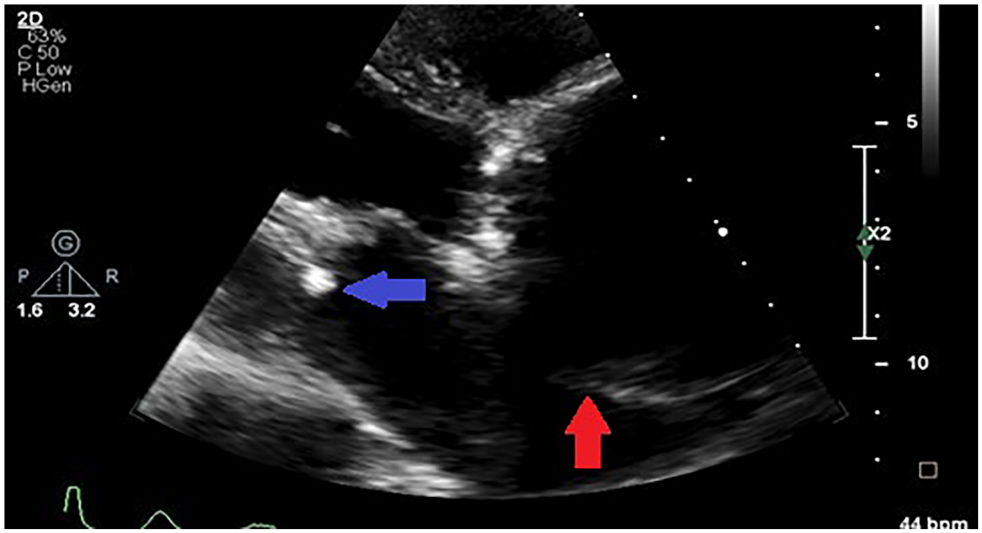


FIGURE 5
Parasternal off-axis view of the aorta in a hypertensive patient showing a markedly aneurysmal aorta compressing the left atrium (red arrow) and concurrent rheumatic mitral valve stenosis (blue arrow).

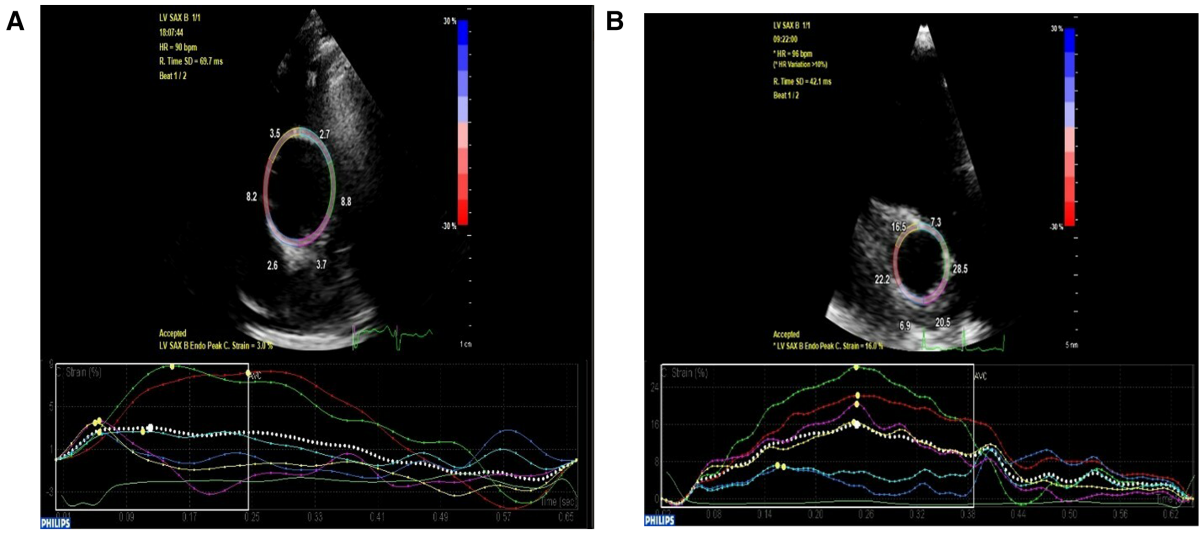


FIGURE 6
High parasternal short axis view of the ascending aorta depicting decreased circumferential strain at 3% in a patient with ascending aortic aneurysm (A) compared to age and gender-matched normal control with preserved circumferential strain at 16% (B).

# 4. Discussion

## 4.1. Distribution of TAA aneurysms by aetiology

Hypertension and HIV were the most common aetiologies in this study. In some cases, participants were noted to have multiple comorbidities making it challenging to discern the true aetiology of TAA aneurysm. In comparison to similar studies performed in African populations, Kitchen's 1980 study in Zimbabwe noted syphilis was the most common aetiology at the time, while syphilis was a suspected aetiology for TAA in only 4 of 139 patients in this study. In Kitchen's paper, hypertension was found to be less prevalent cause of TAAs. However, it was predicted that hypertension would become a predominant cause for TAAs due to a shift towards a westernized lifestyle and diet in African populations (7). This forecast has proved true in the results from the current study as well as the studies by Ogeng'o et al. in Kenya (4) and Mvondo et al. (25) and Antunes et al. in South Africa (26) wherein hypertension were found to be the predominant aetiology of TAAs.

TABLE 3 Comparison of aortic parameters between severe and non-severe aortic regurgitation groups.

| Parameter | Severe AR ($n = 70$) | Moderate AR ($n = 36$) | Mild and No AR ($n = 33$) | $P$ value (ANOVA) |
|---|---|---|---|---|
| Age (years) | 51.611 ± 14.89 | 52.47 ± 15.35 | 54.81 ± 16.42 | 0.610 |
| Gender (M/F) | 34/36 | 17/19 | 15/18 | 0.594 |
| Body surface area ($m^2$) | 1.68 ± 0.21 | 1.76 ± 0.22 | 1.79 ± 0.26 | 0.057 |
| Systolic blood pressure (mmHg) | 135.34 ± 19.85 | 134.89 ± 20.27 | 143.59 ± 27.63 | 0.170 |
| Diastolic blood pressure (mmHg) | 66.39 ± 14.56 | 72.46 ± 13.46 | 86.81 ± 15.88[a,c] | <0.001 |
| Aortic annulus (mm) | 24.45 ± 5.22 | 23.29 ± 4.58 | 22.55 ± 4.12 | 0.152 |
| Aortic annulus ($mm/m^2$) | 14.67 ± 3.14[c] | 13.43 ± 2.89 | 12.87 ± 3.21 | 0.016 |
| Aortic sinus (mm) | 46.33 ± 9.35[c] | 42.52 ± 8.33 | 41.00 ± 9.21 | 0.012 |
| Aortic sinus ($mm/m^2$) | 27.89 ± 6.37[c] | 24.37 ± 4.47[b] | 23.39 ± 7.67 | 0.001 |
| Sino-tubular junction (mm) | 49.94 ± 10.38[c] | 44.30 ± 7.39[b] | 40.30 ± 9.74 | <0.001 |
| Sino-tubular junction ($mm/m^2$) | 30.08 ± 7.20[c] | 25.32 ± 4.31[b] | 23.18 ± 8.53 | <0.001 |
| Ascending aorta (mm) | 24.45 ± 5.22[c] | 23.29 ± 4.58 | 22.55 ± 4.12 | <0.001 |
| Ascending aorta ($mm/m^2$) | 14.67 ± 3.14[c] | 13.43 ± 2.89[b] | 12.87 ± 3.21 | <0.001 |
| LV Ejection fraction (%) | 48.50 ± 13.36 | 48.00 ± 10.89 | 53.94 ± 12.19 | 0.087 |
| LV Basal strain (%) | −14.42 ± 5.33 | −14.31 ± 6.14 | −12.34 ± 5.98 | 0.24 |
| LV Apex strain (%) | −18.36 ± 8.47 | −18.35 ± 7.00 | −18.68 ± 11.17 | 0.985 |
| LV Global longitudinal strain (%) | −13.78 ± 6.01 | −13.70 ± 3.56 | −13.77 ± 3.66 | 0.997 |
| Circumferential strain of AAO (%) | 4.82 ± 4.67 | 4.34 ± 2.46 | 3.78 ± 3.73 | 0.503 |
| Aortic stiffness index ($\beta_2$) | 19.30 ± 25.40[c] | 12.95 ± 12.82 | 8.75 ± 10.31[a] | <0.001 |

Data are presented as mean ± SD, median (IQR) or %. AAO, ascending aorta; AR, aortic regurgitation; LV, left ventricle.
Aortic CS and $\beta_2$ was not feasible in 14 patients that presented with aortic dissection of the ascending aortic aneurysm due to intimal disruption.
[a]Mild or no AR vs. moderate AR.
[b]Moderate vs. severe AR.
[c]Severe vs. mild or no AR.

To our knowledge this is the first study performed in an African population to attribute HIV as a cause for TAAs. In all four similar studies performed on the continent, HIV has not been specifically mentioned as a cause for TAAs. This is likely due to studies being done in the pre-HIV era and due to the higher rate of HIV in South Africa contributing to the higher burden of TAA aneurysms when compared to other African countries.

## 4.2. Clinical characteristics of patients with TAA aneurysms

Regarding sex and age, in this study the predominant sex was female and the mean age of patients with TAA aneurysms is 50 years old, which correlates with findings by Kitchen and Antunes et al. By contrast the study by Ogeng'o et al. had an older (56 years on average) female predominant population, while Mvondo et al., had a younger mean age of 43 years who were predominantly male.

Dyspnoea due to heart failure as well as aortic dissection were a frequent causes of index presentation in this study. Ten percent of patients presented with aortic dissection and 70% presented in heart failure. This is fewer compared to the study by Mvondo et al., where 30% of patients presented with dissection and 90% of patients who presented with dyspnoea. The overall mortality in this study was lower compared to other centers in Africa (4, 25). However, it is likely to be underestimated as only a third of the patients ultimately received surgery. This was due to limited expertise, selection bias, poor follow-up data and scarcity of resources. High mortality of acute aortic dissection was consistent with the literature (27).

A high prevalence of hypertension (67.3%–76.6%) has been reported in patients with aortic dissection (28, 29). This was true for the patients in this study where, majority of the patients were hypertensive suggesting that this is a major risk factor for aortic dissection in this study population. In this study, the patients with aortic dissection also had larger aortic diameters. This is likely due to hypertension playing a role in increasing wall stress, predisposing the aortic wall to dilatation and ultimately dissection.

A meta-analysis showed that the risk of aortic dissection increased at a systolic blood pressure >132 mmHg and diastolic blood pressure >75 mmHg, highlighting the importance of stringent blood pressure control. Therefore, it is suggested that to reduce risk of aortic dissection, the mean blood pressure goals should be even lower than the threshold for hypertension (30).

## 4.3. Impact of aortic regurgitation on aorta size, aortic stiffness index and LV mechanics in TAA aneurysms

In the current study, half of the patients with aortic aneurysms had severe AR. AR has been shown to have a negative impact on the aortic wall secondary to increased shear wall stress (31). This is caused by the remodeling of the medial layer and apoptosis of the cells in the media due to marked medial remodeling and medial cell apoptosis, possibly related to dysregulated endothelial nitric oxide synthase (eNOS) signaling in the endothelium. Thus, a vicious cycle may be created whereby aneurysmal dilation

results in severe aortic regurgitation which in turn results in further enlargement of the aorta.

A subgroup analyses of aortic aneurysm patients with severe AR, moderate AR and mild AR was performed. Despite no difference in systolic blood pressure and ejection fraction compared to non-severe AR group and a lower diastolic blood pressure, patients with severe AR had larger aortic diameters, with the most significant difference noted at the level of the sino-tubular junction (STJ) and ascending aorta. Furthermore, there was a statistically significant positive correlation between the parameters of AR severity and aortic diameters of the root and ascending aorta. Therefore, there is a complex interaction between AR severity and aorta dilation. From our findings it seems that all components of the aortic root likely contribute to aortic regurgitation, but the STJ and ascending aorta play a more dominant role. This correlates with the study by Wenzel et al. who also concluded that the STJ diameter had the greatest association with aortic regurgitation severity in an aging population (32). Hypertension is associated with dilation of STJ due to disease of the media (33) and this is a likely mechanism of AR in hypertensive patients with normal leaflet morphology but mal-coaptation. However, in this study it was noted that most patients with severe AR were HIV reactive and we speculate that HIV valvulitis, as an extension of aortitis (34), also contributed to valvular regurgitation in this subgroup of patients.

Advanced imaging of the aortic circumferential strain (CS) and calculation of the aortic stiffness index revealed stiffer aortas in the patients with aortic aneurysms, portending an increased risk of further dilation and dissection (13). Further, we noted that compared to non-severe AR groups in this study, severe AR was also associated with greater aortic stiffness, further adding to the risk of dissection and likely signaling a poorer prognosis for this subgroup of patients with aortic aneurysms. Poor distensibility of the aorta has been correlated with faster hemodynamic deterioration and rapid progression of disease in patients with aortic regurgitation (35).

All left ventricular longitudinal and circumferential strain parameters were significantly reduced compared to controls. Except for the LV mass which was greater in study patients, likely secondary to hypertension and/or severe aortic regurgitation causing an increased LV preload and afterload (35). No difference was noted between LVEF and strain parameters according to AR severity and this could be partly explained by the influence of co-morbidities on reduced LV function in all three groups independent of AR.

Initially, as the LV longitudinal function declines the circumferential function increases to maintain ventricular contractility and cardiac output (36). As the disease progresses the circumferential compensation likely declines and the ventricle fails. The decline in both longitudinal and circumferential function of the patients' ventricles in this study implies long-standing disease secondary to delayed diagnosis. The former statement is also supported by the markedly increased left ventricle end-diastolic and end systolic volumes, LV mass, as well as the impaired diastolic relaxation and increased left atrial volumes of the study patients.

### 4.4. Role of echocardiography in TAA aneurysms

Echocardiography, especially Speckle-Tracking analysis, has been shown to be an accessible and useful tool for the detection of TAA aneurysms and measurement of circumferential vascular mechanics (12) in a resource-limited setting where cardiac computed tomography (CT) services are overburdened with resultant delayed diagnosis (37). Guideline recommendations for screening of thoracic ascending aortic aneurysms are scarce compared to those for abdominal aortic aneurysms. Currently, guidelines suggest screening older patients and those with risk factors for aneurysm formation (38). Several countries have attempted to implement surveillance programs for aortic aneurysm detection; however, resource limitations have made these programs difficult to replicate (39). However, this retrospective data is hypothesis generating and future studies would be needed to define the role of echocardiography in screening TAA.

## 5. Conclusion

This is the first study from Africa detailing the differences in clinical and echocardiographic characteristics in those with thoracic ascending aortic aneurysms compared to controls. Thoracic ascending aortic aneurysms were mostly present in young black African females and the main aetiologies were hypertension and HIV. This study reveals a high burden of ascending aortic aneurysms in the study population, which largely develop undetected and ultimately present late with advanced heart failure or aortic dissection. Delayed presentation of TAA aneurysms results in considerable morbidity and mortality and highlights the need for (i) prevention and control of modifiable risk factors for aortic aneurysms such as hypertension and HIV and (ii) screening programs and establishment of centers of excellence for effective management of aortic aneurysms in Africa. Echocardiography has been presented as a useful low-cost tool for the detection of aneurysms and potential risk stratification using advanced strain imaging, however further studies are needed to define its role in screening in this population.

## 6. Limitations

In terms of the limitations of this study, the study comprised a predominantly African population and therefore limiting the applicability to other populations. Morbidity and mortality data could not be fully accessed due to poor patient follow-up. Furthermore, interobserver variability may have affected the measurement of echocardiographic parameters, however, standard deviations of measurements were small and like those reported in other studies and so interobserver variability

influence was negligible. The absolute values of aorta CS are subject to inter-vendor differences.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving human participants were reviewed and approved by Ethics approval for the study was obtained from the University of the Witwatersrand ethics committee (M170389). The patients/participants provided their written informed consent to participate in this study.

## Author contributions

RM and RG contributed to conception and design of the study. RM and SM collected the data and RM performed the statistical analysis. RM, MH, RG wrote the first draft of the manuscript. SM wrote sections of the manuscript. KB contributed to revision, reading and formatting document and RM, MH, RG, SM contributed to approving the submitted version. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Transcatheter heart valve interventions for patients with rheumatic heart disease

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Rheumatic heart disease [RHD] is the most prevalent cause of valvular heart disease in the world, outstripping degenerative aortic stenosis numbers fourfold. Despite this, global resources are firmly aimed at improving the management of degenerative disease. Reasons remain complex and include lack of resources, expertise, and overall access to valve interventions in developing nations, where RHD is most prevalent. Is it time to consider less invasive alternatives to conventional valve surgery? Several anatomical and pathological differences exist between degenerative and rheumatic valves, including percutaneous valve landing zones. These are poorly documented and may require dedicated solutions when considering percutaneous intervention. Percutaneous balloon mitral valvuloplasty (PBMV) is the treatment of choice for severe mitral stenosis (MS) but is reserved for patients with suitable valve anatomy without significant mitral regurgitation (MR), the commonest lesion in RHD. Valvuloplasty also rarely offers a durable solution for patients with rheumatic aortic stenosis (AS) or aortic regurgitation (AR). MR and AR pose unique challenges to successful transcatheter valve implantation as landing zone calcification, so central in docking transcatheter aortic valves in degenerative AS, is often lacking. Surgery in young RHD patients requires mechanical prostheses for durability but morbidity and mortality from both thrombotic complications and bleeding on Warfarin remains excessively high. Also, redo surgery rates are high for progression of aortic valve disease in patients with prior mitral valve replacement (MVR). Transcatheter treatments may offer a solution to anticoagulation problems and address reoperation in patients with prior MVR or failing ventricles, but would have to be tailored to the rheumatic environment. The high prevalence of MR and AR, lack of calcification and other unique anatomical challenges remain. Improvements in tissue durability, the development of novel synthetic valve leaflet materials, dedicated delivery systems and docking stations or anchoring systems to securely land the transcatheter devices, would all require attention. We review the epidemiology of RHD and discuss anatomical differences between rheumatic valves and other pathologies with a view to transcatheter solutions. The shortcomings of current RHD management, including current transcatheter treatments, will be discussed and finally we look at future developments in the field.

KEYWORDS
rheumatic heart disease, transcatheter intervention, mitral, aortic stenosis, regurgitation

## Introduction

Transcatheter aortic valve implantation [TAVI] has signaled a new chapter in the management of valvular heart disease. Resources have mostly been focused on treating senile degenerative disease in mostly affluent populations with rheumatic heart disease [RHD] remaining an orphan disease. However, RHD remains the most common cause of

death from valvular heart disease in the world at almost double the rate of non-RHD valve lesions (1).

RHD has been virtually abolished from many developed countries (2) and the preferred approach to management is prevention rather than treating complications (3, 4). However, in countries where RHD has the highest prevalence and mortality, there is inadequate use of proven treatments such as antibiotic prophylaxis (5). Although prophylaxis should be the cornerstone of management, it cannot be ignored that the burden of established valvular disease and complications of RHD are likely to remain with us for decades to come.

Management of patients with significant valvular lesions require surgery that is not freely available in areas where RHD is common and post operative anticoagulation is often poorly administered in such areas (6).

Transcatheter treatments in isolation or combined with surgery hold significant promise as a solution. Most of the current transcatheter treatments are however inappropriate for RHD patients. Rather than waiting for first world solutions to become more applicable, we believe that dedicated solutions should be sought.

This review will evaluate how the anatomy of rheumatic valves differ from other pathologies with a specific view to transcatheter solutions. This will be contextualized against a focused epidemiological discussion of RHD, providing a rationale for considering such interventions. The many shortcomings in current RHD management, interventional management and current transcatheter treatments will be discussed and finally we will look at future developments in the field.

## Scope of the problem

Acute rheumatic fever disproportionately affects children and young adults, with a peak incidence reached between 5 and 15 years of age (7). Recurrent inflammatory damage to heart valves leads to progressive valve dysfunction with established rheumatic valvular involvement peaking between the ages of 20 and 29, and only declining again after the age of 40 (1). The prevalence has not declined much over a 25year period from 1990 to 2015 in many regions where it is most prevalent (>70% of the world's cases occur in sub-Saharan Africa, South Asia, and Oceania) and mortality remains high in South Asia and sub-Saharan Africa (7).

The World Health Organization (WHO) and the Global Burden of Disease study respectively estimate that RHD affects 33 and 40.5 million persons globally, eclipsing the degenerative aortic valve stenosis [AS] burden 4-fold, and with annual death rates exceeding 300,000 cases. Although mortality related to RHD had appeared to decline between 1990 and 2012, a worrying trend has seen mortality rising sharply since 2017 (1, 8).

Involvement of the mitral valve is the hallmark of RHD with >95% of cases in epidemiological studies exhibiting mitral valve involvement (9, 10). Chronic RHD of the mitral valve progresses over years and causes mitral regurgitation [MR] early in the disease process and mitral stenosis [MS] later on (11). Aortic valve involvement occurs in 20%–30% of cases, although rarely in isolation, but typically with associated mitral valve involvement (12). The REMEDY study evaluated 3,343 patients with RHD from 14 low- and middle-income countries and found mixed valvular involvement in the majority of cases with the most valve lesions being moderate or severe (5) (**Figure 1**). Multivalve involvement often leads to difficult management decisions because not all lesions are severe at the time of first surgery and the disease is progressive [will be discussed later].

Epidemiological studies have documented that approximately two thirds of RHD patients are female (13). Stenotic left heart valve lesions are poorly tolerated during pregnancy (14), and it is therefore not surprising that many patients present for the first time with RHD during pregnancy (13). The mortality of untreated severe MS in pregnancy is as high as 34% in countries with limited access to surgery (15) or percutaneous balloon mitral valvuloplasty [PBMV], despite good results with this procedure in pregnancy (16, 17). Management decisions in such woman are often complex and with the high fetal mortality of conventional surgery (18), access to a wider scope of less invasive alternatives [even if used as a temporizing measure] may provide a better outcome.

## The anatomical challenges for transcatheter treatments

The anatomy of rheumatic valves differs significantly from that of degenerative valves which limits the applicability of current transcatheter devices in most RHD populations. The landing zone in the degenerated calcified AS valve provides good anchoring for a TAVI prosthesis and represented relatively low hanging fruit for designers. In the aortic valve, the process of degenerative valve calcification starts with fibrocalcific changes on the aortic aspect of the valves, near the hinge points. From here it progresses through the coalescence of microcalcifications into larger nodules mostly on the aortic leaflet surface (19). In a small study of 39 explanted valves, the calcification of rheumatic valves was more diffuse than in non-rheumatic valves (20). The hallmark of rheumatic AS is fibrotic fusion of the commissures which leads to a potentially different anchor for a transcatheter valve compared to the large nodules of calcium in degenerative valves. In a study of aortic valves, researchers found good correlation between CT scan calcium scores and AS severity in older patients, but not in those <51 yrs of age [where calcification was generally less] (21). This study however did not include any confirmed rheumatic valves and the younger patients generally had bicuspid valves where the pathology is not comparable to RHD in terms of simulating commissural fusion and its progression. This lack of detailed descriptions of calcium distribution in rheumatic valves is a significant obstacle in the development of transcatheter valves for this indication.

The dominant indication for aortic valve replacement in emerging economies remains aortic regurgitation (6, 22, 23) which is ill suited to treatment with current generations of TAVI prostheses. Fibrosis predominates in these valves with less significant calcification to anchor the TAVI prosthesis (24).

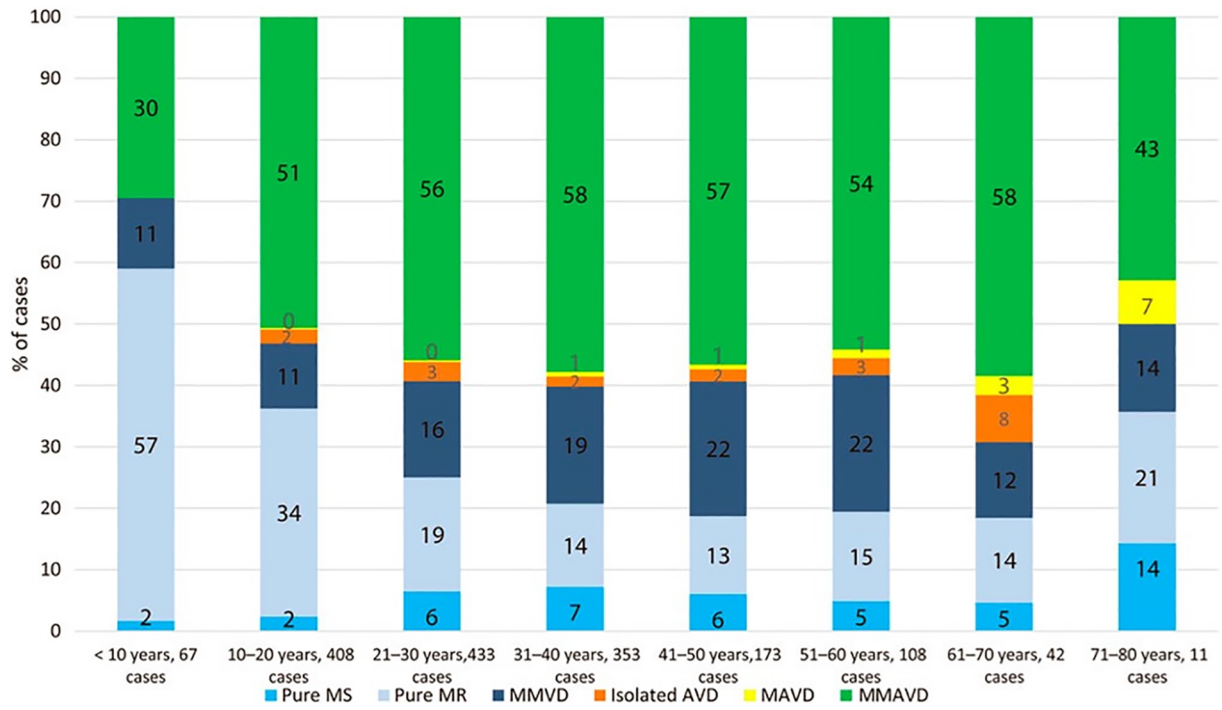


FIGURE 1
The pattern of native rheumatic valve disease in 2,475 children and adults with no percutaneous or surgical interventions. AVD, aortic valve disease; MAVD, mixed aortic valve disease; MMAVD, mixed mitral and aortic valve disease; MMVD, mixed mitral valve disease; MR, mitral regurgitation; MS, mitral stenosis from (5). Used with permission.

The mitral valve structure and function in health is far more complex than that of the aortic valve and diseased mitral valves pose an even bigger obstacle to transcatheter solutions. Morphologic features of rheumatic MS include commissural fusion, thickening of the leaflets and thickening and shortening of the subvalvular apparatus (25). In the earlier stages of the disease, the leaflets are minimally fibrosed in the majority of patients under the age of 30, while in patients over 40 the majority have significant valvular scarring (26). Calcification of the mitral valve in degenerative MS is usually concentrated in the annulus which creates a potential anchor for transcatheter valves (27). In rheumatic MS however, calcification can be limited early in the disease process but accumulates progressively and can be present in any part of the valve, often very asymmetrically (28). Heavy calcification, particularly involving the commissures, decreases the success rate of balloon valvuloplasty and becomes a potential indication for valve replacement (29). From **Figure 1** it can be seen that the vast majority of patients present with mixed valve disease which further complicates the evaluation of the anatomy and the design of studies to delineate it with a view to designing transcatheter devices to treat it. See **Table 1**.

TABLE 1 A summary of the challenges in the application of transcatheter treatments for RHD with potential solutions.

| Challenge | Solution |
|---|---|
| **Anatomical challenges** | |
| Lack of data on calcification patterns | Studies utilizing cardiac CT to delineate better |
| Dominant aortic lesion is AR | Dedicated TAVI anchoring mechanisms |
| Limited MAC | Dedicated TMVR anchoring mechanisms |
| Mitral commissural fusion | TMVR that anchors at commissural level |
| Accurate deployment of balloon expandable TAVI in non-calcified anatomy | NOB to deploy balloon expandable TAVI |
| **Other** | |
| Progressive disease requiring different valve surgeries at different times | Hybrid approach with surgical MVR as first operation and TAVI later |
| No dedicated TMVR device currently available | Surgical valve dedicated as docking station for transcatheter re-intervention in future |
| Patients present late with decompensated LV function | NOB to deploy balloon expandable TAVI |
| Poor durability of bioprosthetic leaflets in young patients | • Improved bioprosthetic tissue treatments<br>  • Decellularization<br>  • Improved tissue fixation techniques<br>• Polymer leaflets |

AR, aortic valve regurgitation; TAVI, transcatheter aortic valve implant; MAC, mitral annular calcification; TMVR, transcatheter mitral valve replacement; NOB, non-occlusive balloon catheter; MVR, mitral valve replacement.

## Established management

Medical management is appropriate for the earlier stages of RHD and the management of concomitant atrial fibrillation [AF]. However, once symptoms and signs of decompensation develop, there is little evidence that medical management alters outcome and exploring interventional treatments become warranted (30). In a large study of low- and middle-income

countries, 16,9% of patients died at an average age of 28 within 2 years of being diagnosed. Mortality was significantly higher in lower income countries where access to surgery or percutaneous treatment options were limited (13). This illustrates the scope of the problem and lends important justification for actively exploring alternative treatment strategies.

## Mitral valve disease

The pathology in rheumatic MS is complex and typically represents advanced valvular fibrosis, calcification and commissural fusion. Despite this, commissural fusion without superimposed calcification is very amenable to being cleaved effectively. Initially this was achieved by surgical techniques (31). Subsequently PBMV was established and this is now the preferred option for intervention (25, 32). PBMV has been shown to be at least as effective as the initial surgical techniques but is significantly less invasive (33, 34). For this reason, patients are evaluated for PBMV as an initial strategy and surgery is offered when this is deemed unlikely to succeed (35). The valve morphology is evaluated with echocardiography [and sometimes fluoroscopy to assess calcification] and a variety of scoring systems exist to aid evaluation (36, 37). Medium term results are very good but after 5yrs there is a steady rise in event rates particularly in less suitable valves. In a large study comparing patients with a Wilkins score <8 with those >8, survival (82% vs. 57%) and event-free survival (38% vs. 22%) at 12-year follow-up was better when the score was low (36). A number of clinical and valve related factors that predicted adverse outcomes included a Wilkens echo score >8, age, prior surgical commissurotomy, NYHA functional class IV, pre-BMV mitral regurgitation ≥2+, post-BMV mitral regurgitation ≥3+ and higher post-BMV pulmonary artery pressure (38). The combination of MS and MR is present in 20%–30% of cases (9, 10) and when the MR is moderate, this is an indicator of adverse outcome with PBMV and mitral valve replacement may then be required.

When MR is the predominant lesion, and the patient develops an indication for intervention, surgical repair or valve replacement are currently the only options. Valve repair is only possible in non-calcified valves and requires significant expertise. The results with repair in children and young adults are acceptable (39–41) but is performed in only a small proportion of cases (42). Valve replacement is performed more often but outcomes are limited by the durability of bioprosthetic valves, particularly in younger individuals and complications of anticoagulation when mechanical valves are used. Because of the relatively young RHD population, mechanical valves are favored [65%–85% of cases in adult populations] (43, 44) and when compared to repair cohorts, patients who receive mechanical valves tend to be older patients and have more mixed valvular pathology and AF (45). Heart valves in the mitral position are less durable because they are subjected to different hemodynamic loads than the aortic position. While mitral bioprostheses degenerate faster because of greater loading forces (46), mechanical prostheses are two to three times more likely to thrombose (47).

The RHD population often include patients from poorly serviced areas and problems with anticoagulation have led some authors to recommend the use of tissue valves in certain populations, particularly young females who have not completed their families (48). Such patients are then very likely to require redo surgery, which is more complex and carries up to double the mortality of first operations (49). Transcatheter valve-in-valve procedures may have a role in these patients.

## Aortic valve disease

Although true isolated aortic valve disease is rare in RHD, approximately one third of RHD patients have aortic valve involvement in combination with mitral valve disease (13, 50). In these patients, AR is much more common than AS. Most patients however require mitral valve surgery in isolation as a first operation (51) and the place for transcatheter aortic valve interventions may lie with the group of patients who present with aortic valve disease after an initial mitral valve intervention. One would unfortunately have to speculate on the true requirement for this as current literature simply does not provide answers. In one of the very few studies that provides some insight, Russell et al. looked at a large Australian database of 17,000 heart valve surgeries, including 1,384 cases of RHD. Compared to non-RHD patients, it was found that patients undergoing RHD surgery were significantly younger and more likely to be female, of indigenous ethnicity and have had prior PMBV or surgery. Indigenous Australians were 15 times more likely to come from remote areas [with problematic anti-coagulation], partly explaining why they were more likely to receive valve repairs or bioprosthetic valves. Although 16% of all RHD operations were redo operations, we do not know how many were redo operations for a different valve. Twenty three percent of patients underwent isolated aortic valve operations and 20% combined aortic and mitral valve operations (51). One might therefore speculate that there is likely to be a moderate sized group of patients that may benefit from transcatheter aortic valve interventions after previously receiving either PMBV or mitral valve replacement.

# Challenges of current interventional management

Once valve lesions become severe and symptoms develop, intervention is generally indicated but even this well-established approach is hampered by a number of factors in the RHD population.

One of the biggest challenges in the management of RHD is the limited access to open-heart surgery in the areas where RHD is still rife. The vast majority of new, less invasive developments are aimed at treating patients from affluent countries where 85% of the world's open-heart surgeries are performed on 11% of the world's population (52). A number of studies have now shown an alarming lack of access to surgery in the countries with the

highest burden of disease requiring such surgeries. In Sub-Saharan Africa, there is one cardiac surgeon per 14.3million population compared to one per 1.1 million in North Africa and one per 0.1 million in Brazil (53). The number of surgical procedures is similarly lacking in Sub-Saharan Africa (6, 53). See **Figure 2**. In another study, only 11% of patients from low-income countries received a valve repair or replacement, compared to 60,8% of patients in upper-middle-income countries. Approximately 90% of patients received mechanical valves and although most were prescribed oral anti-coagulants, 12% had no INR monitoring and 34% had three or less INR measurements in the preceding 6 months (13). Apart from poor monitoring, the complication rates of these valves are high and even in an upper-middle income country, up to 1 in 4 young patients with RHD receiving a mechanical AVR have a major valve-related event within the first decade after the procedure (6, 53). Ineffective anti-coagulation has been associated with poverty, low levels of education and larger distances to monitoring clinics (54). This problem is likely to remain as only +/- 10% of Western patients are still receiving mechanical valves (55), which explains why the most commonly used mechanical valve has remained largely unchanged for more than 40 years (56). Improvements in anti-coagulation have included home INR monitoring which is not available to most patients in low-income countries, and non-vitamin K oral anticoagulants [NOACs] which has disappointingly been found to be suboptimal for these patients and are therefore not recommended by major guidelines for use in valve prostheses (35, 57). These inadequacies in access to surgical management raise the question of whether access to catheter-based interventions will be any better. There are however countries in sub-Saharan Africa [such as Zimbabwe, Zambia, and the Democratic Republic of the Congo] where interventional cardiology services have recently been established for the first time. This growth in catheterization laboratories may hold the answer, provided that procedures and devices can be developed that are applicable for RHD patients.

PBMV is probably the most cost effective and least invasive intervention for RHD valve pathology and should be considered a priority to provide. Unfortunately, the opposite is true with only 1.1% of RHD cases in low-income countries receiving it, compared to 8% in upper middle income [African] countries. One reason for this is that many patients do not have access to a catheterization laboratory. Unfortunately, patients present late in the disease course and PBMV is often not suitable, as evidenced by the 7-fold higher rates of surgery [compared to PBMV] reported in the REMEDY study (5, 13).

Another significant problem is that RHD is a progressive disease, and one is often confronted with a patient who has had one valve replaced previously and now presents with significant dysfunction of another valve. This requires high risk re-do surgery and often very difficult decision making. The alternative approach of operating on mild aortic valve disease at the time of the mitral valve replacement has been found to yield no benefit and the current recommendation is to leave other mild valve

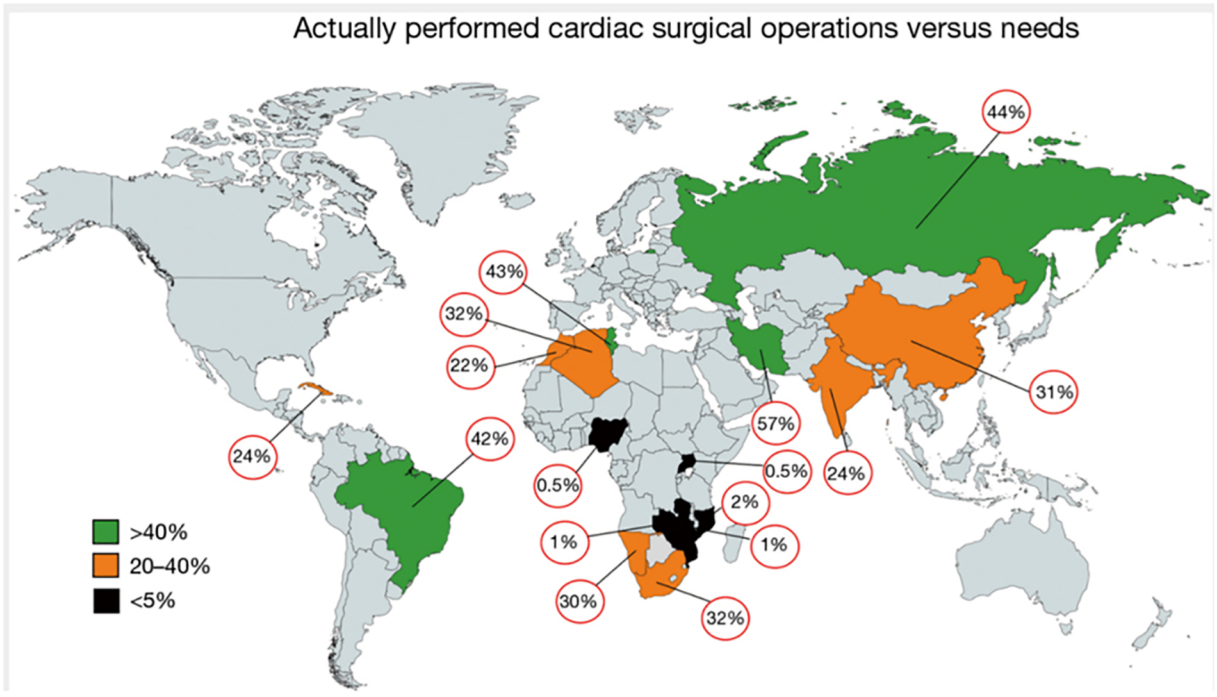


FIGURE 2
Level of actually performed cardiac surgery as a percentage of the needs for surgery in the individual country. This data was generated from a study investigating the current state of cardiac surgery in a variety of low- and middle-income countries. It clearly illustrates the dire shortage of access to surgery in Sub-Saharan Africa. The percentages depicted represent mean values thereby masking country-specific social, geographic or political diversities. From (22). Used with permission.

disease at the time of the initial operation (58). Re-do mitral valve surgery in one South African study was performed a mean of only 4 years after the initial surgery and in 73% of these cases the surgery was performed as an emergency. The majority of these [80%] were due to valve thrombosis, in fact, 25 of the 26 patients with multiple redo surgeries had valve thrombosis with reportedly high rates of post-operative complications (59).

# Challenges of current transcatheter therapies

## Aortic valve

Transcatheter balloon aortic valvuloplasty for rheumatic AS is performed relatively infrequently with significantly less case selection guidance from literature than for MS. When the anatomy is deemed suitable, the results are however acceptable with 85% of patients obtaining a >50% reduction in gradients of the valve in one large study (60). These results were sustained at 5 years and only 2% developed severe regurgitation.

Although the use of transcatheter valves for AS due to RHD has been described in the literature, it is limited to case reports and small series (61, 62). In the largest cohort described to date >1,000 TAVI patients with rheumatic aortic valve involvement were obtained from the Medicare database (63). The diagnosis of RHD in this study was dependent on correct ICD-10 codes and therefore is open to criticism. Although the results did not differ significantly between rheumatic and non-rheumatic valves, the patients in both groups were elderly [79 and 81 years old] and the behavior of a TAVI prostheses at this stage in the disease course is likely to be similar. The applicability of these results to younger populations is therefore questionable. Unfortunately, this study did not report on other valve involvement which would have added to the diagnostic accuracy of RHD and could provide information on the real-world dilemma of multiple valve involvement and previous valve surgery in TAVI candidates. The lack of anatomical and clinical data in the RHD population raises a number of questions when we consider the applicability of current TAVI prostheses to the RHD population.

Anchoring of the TAVI prosthesis in the heavily calcified landing zone in senile degenerative AS is now well established. It is however not known whether the performance of the valves will be the same in a rheumatic landing zone with commissural fusion and potentially different patterns of calcification. Published case series included older patients with mean ages between 79 and 83, when calcification is likely extensive (61, 63, 64) and the dominant lesion is AS. The predominant aortic valve lesion in low- and middle-income countries is however AR (6) and most current prostheses are either not approved or have shown inferior results in AR patients as compared to AS. In a systematic review by Yousef et al, a total of 175 cases of TAVI implantation for AR from 31 studies were included and demonstrated valve malposition [3,4%], second valve required [11.3%], residual AR grade ≥2+ [17.7%] and conversion to SAVR [2.3%] (65). These rates do not compare well with contemporary practice in AS patients (66, 67). The only valve currently approved for use in isolated aortic regurgitation [AR], is the JenaValve [Irvine, CA] (68) which has anchoring arms that grip the native aortic valve leaflets. It may therefore be applicable to the anatomy of some RHD patients but more research exploring novel approaches to anchoring TAVI valves is required.

The durability of current bioprosthetic valves [aortic and mitral] in younger patients is unacceptable for most clinical scenarios (69). Numerous approaches to overcome this problem are being investigated: new tissue fixation techniques have been tested in animal models (70–75) but translating these very early developments into a functional valve approved for human implantation is time consuming and has not realized.

The cost of all current TAVI prostheses is prohibitive in most settings where RHD is prevalent. Studies comparing the cost of SAVR with TAVI have found comparable total hospitalization cost in first world elderly populations (76). The higher TAVI prosthesis expense is offset by shorter hospital stay and is used, at least in part, as justification for the extremely high cost of all current TAVI systems. This argument does not hold for younger, lower risk RHD patients where one would expect lower total hospitalization costs for surgery (70, 77). Although there are no robust cost analyses for the cost of cardiac surgery in Africa compared to the first world, there is some data to indicate that it could be performed at a relatively affordable cost (78) and the price of TAVI devices aimed at RHD patients would therefore have to be more affordable.

Transcatheter heart valves require large bore arterial access [typically 18Fr]. The management of this access requires skill and potentially expensive bailout equipment such as covered stents, balloons, snares, and vascular closure devices. This is not widely available in low-income settings.

## Mitral valve

Since the advent of PBMV, a large body of evidence in support of it has accumulated. Although the results are very good in appropriate candidates, access to the procedure and expertise is limited—as discussed above. Attempts at improving on the original Inoue technique (32) have included double balloon (79), using lithotripsy to fracture calcification (80), over-the-wire techniques (81) and the use of intracardiac echocardiography to guide the procedure (82). The Inoue technique remains the most used and because it works so well, is unlikely to change too drastically. The shortcoming of this technique is more one of logistics: improved access to it and detecting disease earlier when PMBV is still possible.

Other transcatheter treatments techniques to intervene on non-rheumatic mitral valves [such as transcatheter edge-to-edge repair and transcatheter annuloplasty] is not applicable to RHD because of anatomical limitations (83) and cost. The solution would therefore more likely be the development of applicable transcatheter mitral valve replacement [TMVR] devices. No current TMVR design is intended for treatment of rheumatic mitral valve disease and all the valves with human implant data

are primarily intended for degenerative mitral regurgitation (84–87). Despite this, the impressive engineering that has gone into their development should offer important lessons that may aid in the design of dedicated RHD mitral valve devices. One such feature is the double stent design where an outer, flexible stent anchors the valve in the annulus and isolates the inner valved stent from systolic compression by the ventricle. See **Figure 3**. Another important design feature is different anchoring mechanisms such as either sharp hooks that penetrates into the annulus or a nitinol self-expanding frame with ventricular anchors that engage the leaflets and subvalvular anatomies to secure placement of the EVOQUE valve [Edwards Lifesciences LLC, Irvine, CA] -see **Figure 4**. How this type of design will interact with a diseased subvalvular apparatus remains unclear. Although these designs are a step in the right direction, their general applicability to the RHD population is doubtful for a number of reasons. Annular calcification that might aid anchoring of a transcatheter valve is less prevalent. In fact, significant annular calcification is uncommon. In a pathology study, only 23% of excised rheumatic mitral valves had significant annular calcification. If the dominant lesion was however MS, 80% had significant calcification (28). Studies evaluating calcification on CT-scans include very few RHD cases but indicated that some calcification is visible in the leaflets of MS patients and with older age and more severe MS, the presence of annular calcification increases (88).

Commissural fusion is the hallmark of rheumatic MS and is likely to be a prominent factor in most candidates for TMVR. Because of the complex three-dimensional shape of the mitral valve, commissural fusion is likely to grip the prosthesis at the level of the native leaflet tips, rather than the annulus and designs may have to incorporate this to ensure secure anchoring. Although implantation of a TAVI device has been described in a rheumatic mitral valve with very little annular calcification, this was in an 80 yr old patient and therefore represents a unique case with limited generalizability (89).

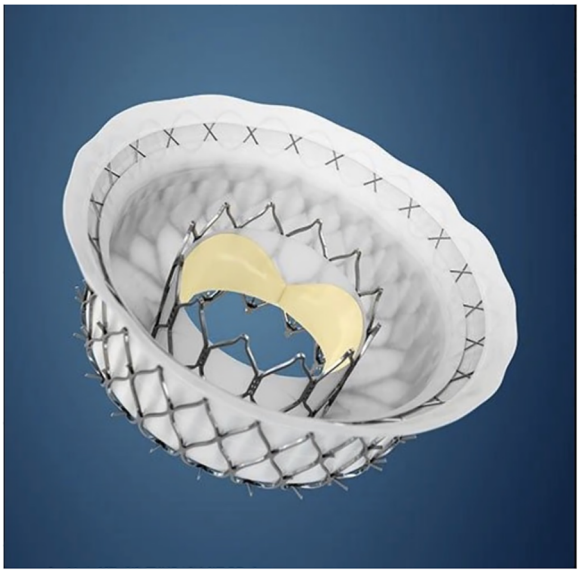

FIGURE 3
The intrepid transcatheter mitral valve [Medtronic, MN]. Note the double stent design with the outer flexible anchor stent [with small hooks on outside] which isolates the inner valved stent from ventricular compression and therefore may improve durability. Image supplied by Medtronic.

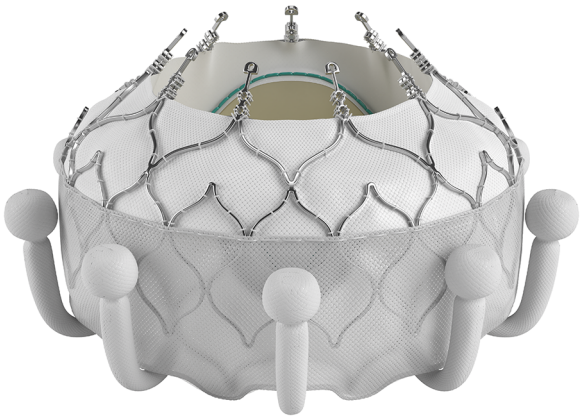

FIGURE 4
The EVOQUE transcatheter mitral valve [Edwards Lifesciences LLC, Irvine, CA]. Note the anchors that engage the leaflets and subvalvular anatomy to secure placement. This system is designed to treat non-rheumatic mitral valve regurgitation and is not indicated for rheumatic heart disease. Image supplied by Edwards Lifesciences.

One of the major drivers of mortality post TMVR is LVOT obstruction which is partially due to systolic anterior motion of the anterior mitral valve leaflet (90). Attempts to predict this complication may have improved outcomes but it remains a major limitation in the development of this field (90). It is not known how significant rheumatic subvalvular apparatus involvement will influence this complication but theoretically, it may be protective if the anterior mitral valve leaflet is retracted and immobile and therefore pulled out of the LVOT.

## Future developments

There appears to be a large potential for transcatheter developments directed at patients with RHD.

Although the list of challenges is extensive, a few teams have made some progress to address two of them: deliverability/anchoring and durability. What is encouraging is that many of these developments originate in countries where RHD is prevalent (72, 73, 75, 91–96).

If we consider that since the greatest need is for mitral valve prostheses and that we are probably furthest away from a viable transcatheter valve for this indication, a hybrid approach may be the first step. A surgically implanted bioprostheses designed specifically as a docking station for future transcatheter re-intervention should be investigated. Implanting a transcatheter valve inside a degenerated bioprosthetic valve is less challenging because the landing zone is radio-dense, and anchorage should be simpler. Furthermore, the native mitral valve apparatus is less

likely to interfere with the LVOT. This surgical valve would however still require improvements in durability. The transcatheter alternative to this hybrid approach is unfortunately a field with the least progress and to our knowledge, there are no published reports of transcatheter mitral valves designed specifically for RHD. This is hardly surprising, given the complexity of the mitral anatomy and initial attempts have therefore focused on the aortic valve. The team of Zilla et al. in Cape Town has the only reported TAVI device with animal implant data designed specifically for RHD. This device addresses the issue of deliverability and anchoring with several unique features [see **Figure 5**]: to enable positioning in a non-calcified landing zone and align the cusps with those of the native aortic valve, three locator trunks are first deployed, and the valve is then inflated with a lumen-preserving, non-occlusive balloon that does not require rapid pacing. During expansion, three sets of arms protrude from the valve to anchor it in the sinuses in the absence of calcification. Although this device requires transapical access and is still in the preclinical phase, it represents a significant first step in the right direction (91). The utility of a non-occlusive balloon is based on the belief that many of the patients with RHD present at the stage of inoperability because of ventricular decompensation. A balloon expandable valve that does not require rapid ventricular pacing may therefore be of benefit (92). It is not known whether this will eventually be a significant benefit, but similar balloons have been tested (96) and may be utilized in pre- or post-dilatation of valves. See **Figure 6**.

The need for anti-coagulation with all its problems and the need to crimp valves, disqualify mechanical valves from utility in the field of transcatheter heart valves. The durability problems with flexible leaflets have been the subject of a lot of research, which has focused on improving pericardial tissue and non-biological alternatives. Pericardium harvested from animals needs to be fixed with glutaraldehyde [GA] which provides mechanical stability to the tissues and reduces antigenicity, but at the cost of increasing susceptibility to calcification and impairment of growth potential (97). Cellular toxicity is associated with the free aldehyde groups of GA, which contributes to preventing the repopulation of tissue with host cells (98). De-toxification of GA fixed pericardium through binding these aldehyde groups have been shown to reduce calcification of tissue (99). Another area of research is decellularization of tissue which involves the removal of host cells and nuclear material while keeping the extracellular matrix intact and thereby reducing antigenicity and potentially improving durability (72, 75, 100).These efforts are valuable in our search for alternative bioprosthetic materials but the development/testing process that starts with subcutaneous rat implants and progresses through arterial patches to valves in animals and fatigue testers and then to elderly humans and eventually the wider population. This progresses over decades and then requires outcome studies requiring more decades to fully assess its utility.

Although the first synthetic flexible leaflet heart valve was implanted as far back as 1960 (101) and despite countless efforts to improve on the poor early results (102), development in this field has been fraught with problems such as mechanical deterioration and calcification of leaflets. The potential for a valve with a long shelf life, no anticoagulation requirement and excellent durability keeps research in the field active. There are many valves in the development phase but only the siloxane-

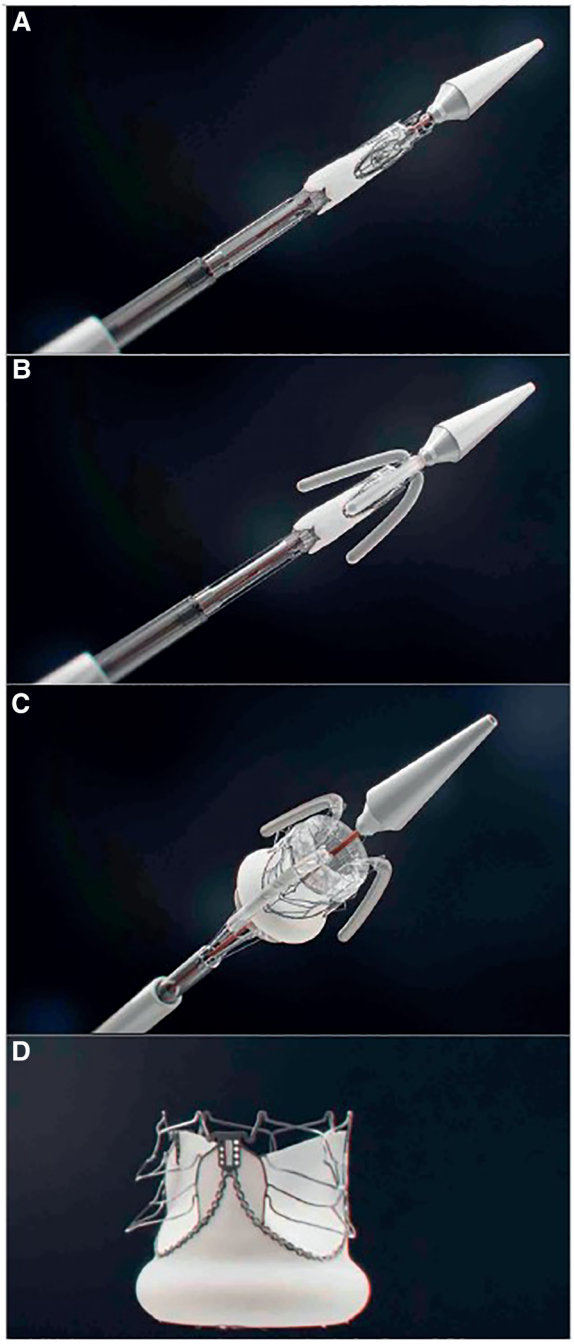


FIGURE 5
Key stages of the deployment of the self-homing, nonocclusive SAT-TAVI valve. Crimped SAT-TAVI system pushed out of the deployment sheath (A), with the locator and stabilizer trunks deployed (B) followed by the full expansion of the scalloped, self-anchoring stent (C) The cobalt-chromium stent is designed to lift up six arms through plastic deformation (D) All arms are seated supra-annularly creating sinus-like outward bulges of the leaflets that firmly anchor the stent in the absence of leaflet calcification. From (91). Used with permission.

FIGURE 6
The outflow non-occlusive balloon catheter [DISA Medinotec, South Africa]. On the left is a photograph of the device from the side and on the right is an end on view showing 8 smaller balloons arranged in a circular fashion to allow blood flow down the central channel during expansion. This may be more stable during valve deployment without the need for rapid ventricular pacing (96). Pictures supplied by DISA Medinotec.

based polyurethane-urea TRIA LifePolymer (Foldax USA) surgical aortic valve has human implant data with 15 implants and good outcomes at 1year (103). This group have also developed a TAVI prosthesis with some animal data based on the same LifePolymer (104). To expand polymer leaflet technology to transcatheter valves requires additionally that the leaflets be thinner and resistant to the crimping process requirement—ideally for prolonged periods to simplify pre-procedural preparation. Recent reports indicate that crimping has an influence on the structure of bioprosthetic tissue (105) but there is only one study with extensive data on the effect of crimping on a polymeric valve [the PolyNova TAVI valve] where the leaflet structure remained stable despite being in the crimped state for up to 8 days (106). A number of polymer valves have shown durability *in vitro* fatigue testers for longer than the required 200 million cycles [as per ISO 5840 requirements] (107) and have also undergone animal implants (91). These valves probably hold the most likely solution to the RHD transcatheter treatment conundrum although history have taught us that we remain further away from an answer than our optimism would want us to believe.

## Conclusion

RHD and its consequences represent a very large clinical and social burden which are likely to be with us for a long time to come. Current treatment modalities fall far short in a number of areas. Major stumbling blocks in the development and implementation of transcatheter solutions for RHD include:

- a paucity of data on the unique anatomy of rheumatic valves
- the high cost of developing new prostheses.
- a perceived lack of financial gain in finding solutions.
- the lack of infrastructure and skills to implant these valves/devices.
- anchoring transcatheter prostheses in a non-calcified environment.
- a critical problem to solve will be the development of foldable valve leaflets that have sufficient durability to be utilized in young patients. Improvements in pericardial tissue fixation is likely the first step but the most likely answer may be the development of synthetic leaflet materials.

## Author contributions

HW contributed by conceptualizing and writing the first draft of the manuscript PH, FS, AD contributed to the manuscript by providing critical review and improving the intellectual content. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# The Aswan Rheumatic heart disease reGIstry: rationale and preliminary results of the ARGI database

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**Background:** Rheumatic Heart Disease (RHD) remains a major cause of valvular heart disease related mortality and morbidity in low- and middle-income countries, with significant variation in characteristics and course of the disease across different regions. However, despite the high disease burden, there is sparse region-specific data on demographics, disease characteristics and course in treated and untreated patients to guide policy.
**Methods:** The ARGI database is a hospital-based registry in a tertiary referral national centre (Aswan Heart Centre, AHC) in which all patients with the diagnosis of RHD are being included. The mode of presentation, including baseline clinical and echocardiographic characteristics (as well as other imaging modalities), biomarkers and genetics are being documented. Treatment modalities and adherence to treatment is being recorded and patients are followed up regularly every 6 and/or 12 months, or more frequently if needed.
**Discussion:** This study shows for the first time an in-depth analysis of the severity and phenotype of disease in Egyptian patients presenting with RHD as well as the progression with time and provides a platform for further comparisons of regional differences in these details as well as their causes. The ARGI database will be of help in achieving the objectives of the Cairo Accord aiming at eradication of RF and RHD.

KEYWORDS

Rheumatic heart disease, Egypt, Aswan, database, registry

## 1. Introduction and rationale for the study

Rheumatic heart disease (RHD) is the most common cause of acquired heart disease in children and young adults globally (1, 2) and remains a major health care problem causing significant morbidity and mortality at all ages. On global scale, RHD caused 305,651 deaths in 2019 and led to nearly 10.7 million (9.2–12.1) DALYs lost (3). In 2019, there were 2.8 million new cases and 40.5 million prevalent cases of RHD, representing 49.7% and 70.5% increases since 1990, respectively.

The characteristics and course of the disease vary across different regions (4–9). However, there is sparse data on RHD demographics, disease characteristics, age distribution, course of the disease, adverse events, the need and timing of medical interventions, long term outcomes, and mortality (4, 10, 11). To date, there is no similar data from Egypt (12, 13).

Development of databases for accurate data on epidemiology and natural disease history is vital for the prevention and control of RHD, as recommended in the Cairo Accord aiming at disease eradication (15). Comparing the results of different regional registries and the main causative factors, including the influence of genetics and epigenetics should help the global efforts to eradicate RHD (16, 17).

The Aswan Heart Centre (AHC) is a high volume tertiary referral centre with over 45,000 patients seen in outpatient clinics yearly, in which around one-quarter of the workload is related to RHD. The number of patients requiring interventions for RHD is increasing at AHC, and

while there are other centres dealing with the disease, there is a pressing need to increase access to surgery for a population of 105 million individuals.

Furthermore, in spite of current medical and surgical treatment, adverse events remain significant (4, 14). Of particular interest remains the thrombosis of prosthetic valves which has been highlighted in a previous publication from AHC (14) but requires continuous efforts.

Our objective is to establish a RHD registry (Aswan Rheumatic heart disease registry, ARGI) to provide disease and regional specific data which could enhance the understanding of the global and regional epidemiology of RHD.

# 2. Methods

## 2.1. Study design

The ARGI database is a hospital-based registry in which all patients from all over Egypt with the diagnosis of RHD are being included.

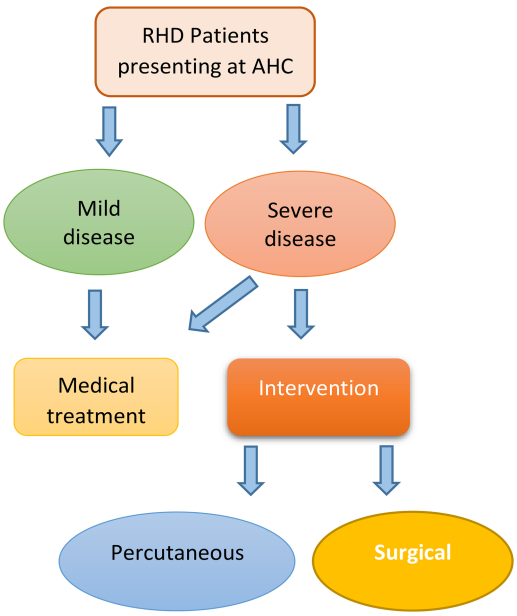
### 2.1.1. Objectives

The ARGI database was designed to address the following aims:

(1) Mode of presentation
(2) Type of treatment (and adherence, including penicillin prophylaxis)
(3) The outcome over time

### 2.1.2. Patient cohort and study eligibility

All consecutive patients with a primary diagnosis of RHD (clinical or echocardiographic) seen at the out-patient clinics (OPD) and inpatient facilities at AHC are eligible to participate (**Algorithm 1**).




ALGORITHM 1
Patient flow chart.

### 2.1.3. Plan of investigation

(1) Mode of presentation
  (a) Demographic characteristics (age and gender, etc), history of ARF
  (b) Valves affected (the pattern and severity of valvular involvement)
  (c) Previous interventions
(2) Type of treatment at the AHC and patient adherence
  (a) Pharmacologic treatments, antibiotic prophylaxis, oral anticoagulation
  (b) Intervention (percutaneous, surgical)
(3) Monitoring Rheumatic activity
  (a) BioBank (blood samples taken at regular intervals from all patients (6-months))
  (b) Collection of all surgically explanted tissues from repaired or replaced valves
(4) Monitoring outcome over time
  (a) Adverse events
  (b) Progression of cardiac disease (progression valvular disease, heart failure, etc)

## 2.2. Data collection

### 2.2.1. Mode of presentation

Demographic information (age, gender, social class, geographic distribution, familial incidence, history of ARF) and clinical data (BP, heart rate, height, weight, medical history, co-morbidities, and previous interventions) are being collected at intervals of 6 months.

Echocardiography is performed for the analysis of the pattern and severity of valvular involvement at presentation and at each follow-up visit, classified using the current World Heart Federation (WHF) criteria (**Supplementary Table S1**) (18). Cardiac echocardiographic studies are stored online on a specialized platform. All images are reviewed by experienced cardiologists and the heart team.

MRI, CT and cardiac catheterization are performed when indicated.

### 2.2.2 . Genetics and biomarkers

Blood samples are being taken for biomarkers and DNA extraction. Following separation of the blood into serum and cell components as well as extraction of DNA, the samples are stored in the biobank for future analysis.

### 2.2.3. Treatment modalities

(A) Pharmacologic treatments and adherence are being documented, particularly secondary antibiotic prophylaxis, oral anticoagulation and anti-arrhythmic therapy
(B) Percutaneous (Balloon mitral valvuloplasty)
(C) Surgical interventions

### 2.2.4. Follow-up

Quality of life, adverse events (**Supplementary Table S2**), exercise capacity, LV and RV function, pulmonary hypertension

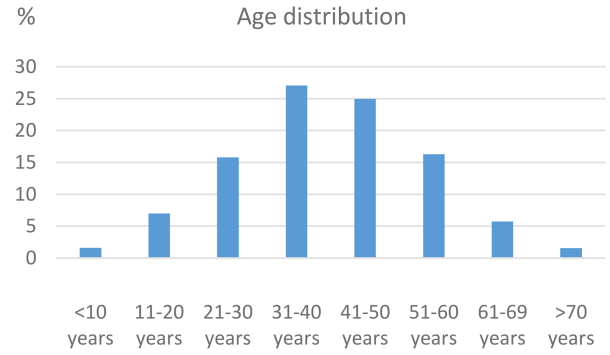



FIGURE 1
Age distribution at presentation (baseline).

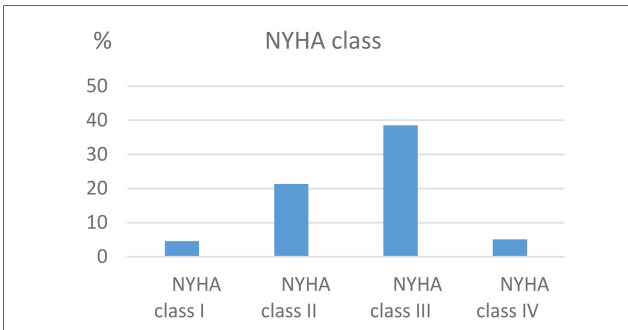



FIGURE 2
Distribution of NYHA class at presentation.

TABLE 1 Dominant valve pathology.

| Dominant valve pathology | *n*= | % |
|---|---|---|
| Mitral stenosis | 1,034 | 41.195 |
| Mitral regurgitation | 903 | 35.976 |
| Aortic stenosis | 146 | 5.817 |
| Aortic regurgitation | 423 | 16.853 |
| Tricuspid regurgitation | 4 | 0.159 |

and progression of valve disease are being assessed during 6 monthly follow-up visits. All-cause mortality is being monitored.

## 2.3. Study management

Management of the database is based at the AHC. The principal investigators (PI's) are responsible for the management of the registry, overseeing data collection and quality assurance. The PI's have been responsible for the development of the CRFs, consent forms, patient information sheets, and management algorithms, in addition to the development and maintenance of the web-based database.

### 2.3.1. Ethics

The study has been approved by the Magdi Yacoub Foundation-AHC Research Ethics Committee (AHC-REC) in accordance with current practices, a consent form is obtained for specimen collection, storage and analysis. Detailed information sheets have been developed and are provided to each participant. All invasive investigations performed are according to prevailing standard of care guidelines.

## 2.4. Status of the study

A total of 2,510 consecutive patients with clinical and echocardiographic RHD have been enrolled in the ARGI database since March 2009. The age at the time of the first visit ranged from 3 to 86 years (40.11 ± 13.86) (Figure 1). The majority was female ($n$ = 1,695, 67.5%). Only 123 patients (4.9%) had history of RF of which 23 (0.92%) were on secondary penicillin prophylaxis. Symptoms were present in 75.8% ($n$ = 1,902) of the patients, with dyspnea present in 69.6% ($n$ = 1,746) (Figure 2).

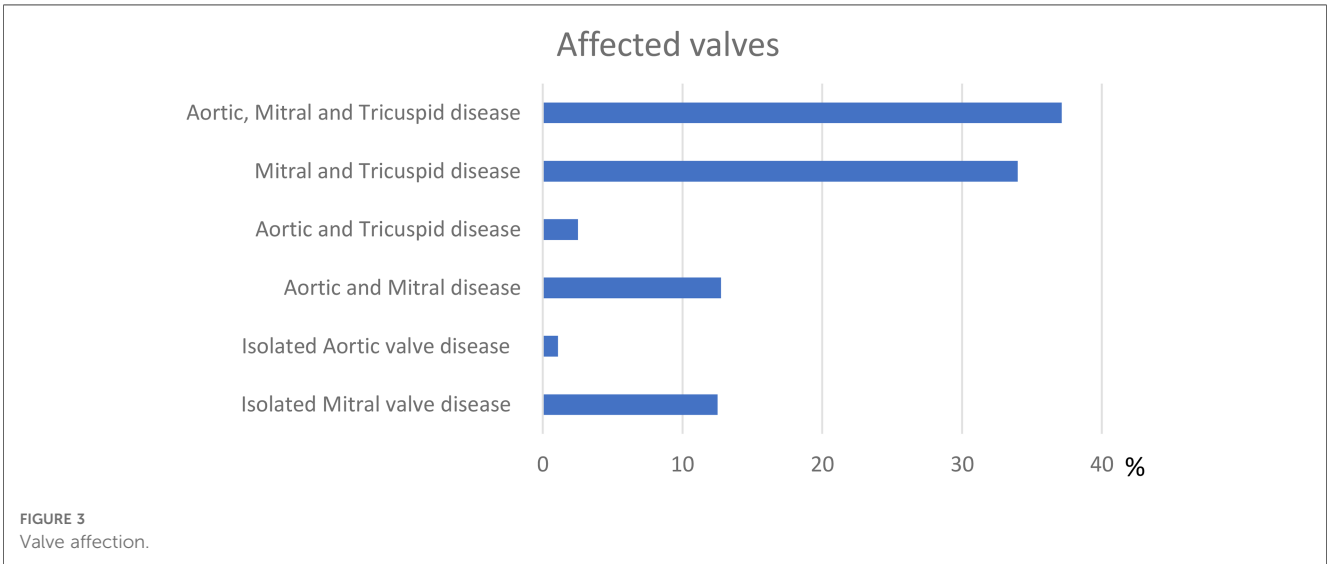



FIGURE 3
Valve affection.

At enrolment, the majority ($n = 2,287$, 91.1%) of patients had moderate-to-severe valvular disease (Table 1 and Figure 3) complicated by atrial fibrillation (AF) ($n = 723$, 28.8%), cerebrovascular events ($n = 146$, 5.8%), infective endocarditis ($n = 16$, 0.63%) and thrombosis of valve prosthesis ($n = 12$, 0.47%). Previous cardiac intervention prior to the first visit to our centre was reported in 19.4% of the patients ($n = 487$). The age at the time of the first intervention ranged from 4 to 68 (28.21 ± 11.47). The most common first intervention reported was percutaneous balloon mitral valvoplasty (BMV) ($n = 232$, 47.6%).

TABLE 2 Patient characteristics at the time of last follow-up.

| Patient characteristics at the time of last follow-up | $n = 1,795$ (range) | % |
|---|---|---|
| Follow-up time (months) | 6–142 | 39.46 ± 34.18 |
| Gender (female) % | 1,202 | 67.0 |
| Age (years) | 5–90 | 44.15 ± 15.7 |
| Symptoms | 1,136 | 63.3 |
| NYHA class | | |
| NYHA class I | 523 | 29.1 |
| NYHA class II | 294 | 16.4 |
| NYHA class III | 153 | 8.5 |
| NYHA class IV | 16 | 0.9 |

TABLE 3 Interventions.

| Type of intervention | $n$ | % |
|---|---|---|
| BMV | 286 | 21.95 |
| MV repair | 317 | 24.33 |
| AV repair | 12 | 0.92 |
| AV + MV repair | 19 | 1.46 |
| Ross procedure | 22 | 1.69 |
| +MV repair | 11 | 0.84 |
| Valve replacement-AV | | |
| Prosthetic | 39 | 2.99 |
| +MV repair | 14 | 1.07 |
| +MVR | 40 | 3.07 |
| +TVR bio-prosthesis | 1 | 0.08 |
| +MVR + TVR | 1 | 0.08 |
| +MVR + TVR (bio) | 2 | 0.15 |
| Bio-prosthesis | 87 | 6.68 |
| +MV repair | 62 | 4.76 |
| +MVR | 21 | 1.61 |
| +MVR bio-prosthesis | 2 | 0.15 |
| +MVR (bio) +TVR (bio) | 1 | 0.08 |
| Valve replacement-MV | | 0.00 |
| Prosthetic | 258 | 19.80 |
| +AV repair | 7 | 0.54 |
| +CABG | 3 | 0.23 |
| +TVR | 6 | 0.46 |
| +TVR bio-prosthesis | 6 | 0.46 |
| Bio-prosthesis | 69 | 5.30 |
| +TVR bio-prosthesis | 1 | 0.08 |
| Valve replacement-TV | 2 | 0.15 |
| Other | 14 | 1.07 |

During regular 6 monthly follow-up at our centre ($n = 1,795$) for periods ranging from 6 to 142 months (39.46 ± 34.18) (Table 2) a total of 1,303 (72.6%) patients underwent cardiac procedures (Table 3). The age at the time of the intervention ranged from 5 to 79 years (35.64 ± 12.63) at an average of 49.4 months since first presentation (range: 0–140 months, SD: 37.3 months).

Cerebrovascular events ($n = 83$, 4.6%), LA thrombus ($n = 20$, 1.1%), infective endocarditis ($n = 13$, 0.7%) and thrombosis of valve prosthesis ($n = 18$, 1%) occurred during follow-up. Patient mortality was 16% ($n = 287$) during the study period (39.46 ± 34.18 months), of which 162 (56.4%) patients had history of intervention.

Penicillin prophylaxis rate was 34.7% ($n = 623$), however, only 12.9% of these patients followed a correct penicillin prophylaxis schedule.

## 2.5. Limitations

The ARGI database deals with late chronic disease and initiatives to diagnose earlier phases of disease including ARF (15, 19, 20) as well as population studies (21) are essential.

# 3. Discussion

The preliminary results show for the first time an in-depth analysis of the severity and phenotype of disease in Egyptian patients presenting with RHD as well as the progression with time. The ARGI database provides a platform for further comparisons of regional differences in these details as well as their causes.

In addition, with the increasing numbers of patients recruited, the ARGI study will be combined and compared to similar studies from Egypt (13, 22, 23).

It is hoped that the ARGI study will be of help in achieving the objectives of the Cairo Accord aiming at eradication of RF and RHD.

# Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) are: https://redcap.ahc-research.com/redcap/ with accession number: PID 117. Further enquiries can be directed to the corresponding author(s).

# Author contributions

The authors confirm contribution to the paper as follows: study conception and design: MY, SK; data collection: SK; analysis and interpretation of results: MY, SK; draft manuscript preparation: MY, SK. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1230965/full#supplementary-material

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# A retrospective audit of young adults who received permanent pacemakers at a teaching hospital in the Western Cape, South Africa

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**Introduction:** While most pacemaker implantations occur in older individuals, younger patients also receive pacemakers. In these, degenerative conduction system disease is less likely to be the cause of atrioventricular block (AVB), with other diseases being more common. There is, however, a paucity of data on this group as well as on younger pacemaker recipients that have undergone pacemaker implantation for reasons other than AVB. The aim of this study was to perform an audit of young adult permanent pacemaker recipients.

**Method:** This was a retrospective record review, conducted in the Division of Cardiology at Tygerberg Hospital, Cape Town, South Africa. We included 169 adult patients between the ages of 18 and 60, who received permanent pacemakers between 2010 and 2020. A subgroup analysis of patients 55 years and younger was also performed.

**Results:** Third degree AVB was the most common indication for pacemaker implantation ($n = 115$; 68%), followed by high degree AVB ($n = 23$; 13.6%) and sick sinus syndrome (SSS; $n = 14$; 8.3%). A specific underlying cause for conduction system abnormalities was found in only 25.4% of patients ($n = 43$), with most of them being 55 years or younger ($n = 32$; 30.8% of patients $\leq 55$ years). Specific causes that were identified included prosthetic valve implantation and/or valve repair ($n = 14$; 8.3%), myocardial infarction ($n = 6$; 3.6%), cardiac sarcoidosis ($n = 5$; 3.0%), coronary artery bypass grafting ($n = 3$; 1.8%), cardiomyopathy ($n = 2$; 1.2%), muscular dystrophy ($n = 2$; 1.2%), congenital heart disease (ventricular septal defect; atrioventricular septal defect; Tetralogy of Fallot; bicuspid aortic valve; $n = 6$; 3.6%), acute myocarditis ($n = 1$; 0.6%), atrial myxoma removal ($n = 1$; 0.6%), planned AV node ablation ($n = 2$; 1.2%), and following a previous stab in the chest ($n = 1$; 0.6%).

**Conclusion:** Given that the mean age of our study population was high, the low number of identified underlying causes in the whole cohort (≤60 years) may reflect some AVB due to age related degeneration of the conductions system in the patients 56 to 60 years age, but also raises the possibility that these patients may be less likely to be extensively investigated for an underlying cause than those ≤55 years, where diseases such as sarcoidosis were more readily confirmed. As access to advanced diagnostic tools improves, the percentage of young pacemaker recipients with an underlying cause identified may increase.

KEYWORDS

pacemaker, atrioventricular block, heart block, mobitz type 1, aetiology, young pacemaker recipients

# Introduction

Atrioventricular block (AVB) is the most common indication for permanent pacemaker implantation (1–4). Individuals requiring permanent pacemakers are generally older (3, 5, 6) with a mean age between 64 and 77 (5). This is attributed to the fact that ageing is associated with cardiac conduction system fibrosis (1, 4).

In younger individuals and/or healthy athletes, some degree of heart block may reflect mainly high vagal tone rather than a disease process in the conduction system (7, 8). In other younger patients, a conduction defect may reflect disease processes other than fibrosis, e.g., sarcoidosis (1, 4). There is, however, little data on the progression of disease in this specific patient group, raising the possibility that some younger patients with conduction system disease may not suffer the same risk as older patients with degenerative conduction disease. This may be particularly relevant in young patients with Mobitz 1 AVB, where the current recommendation to consider permanent pacing in individuals as young as 45 years, is largely based on a single study performed in the United Kingdom (9). More data is needed on this subgroup in general, but also specifically for the local population.

The aim of this study was to perform an audit of first time adult permanent pacemaker recipients that were 60 years or younger at first implant with a subgroup analysis of those ≤55 year of age. The objectives were to determine their clinical profile, the indication for permanent pacemaker implantation, the underlying pathology if known, and the pacing need/frequency for those who did not have complete AVB. We set out to better the understanding of which underlying conditions are common in our patient population to inform an appropriate work-up for younger adults presenting with conduction system disease. We also hoped to better understand the disease progression of the young patient with Mobitz 1 AVB.

# Methods

## Study location and population

This was a retrospective record review conducted in the Division of Cardiology at Tygerberg Hospital, Cape Town, South Africa. Ethics approval for the study, which included a waiver of written informed consent, was provided by the Health Research Ethics Committee of the University of Stellenbosch (HREC U21/09/138).

Our study population comprised of permanent pacemaker recipients aged 18 to 60 years, implanted from 2010 to 2020. To be included in the study, patients must have had at least a 6 month follow up and the indication for permanent pacemaker implantation must have been available. Patients that only received a temporary pacemaker and patients with a non-bradycardia indication for device implantation (cardiac resynchronization therapy and implantable cardioverter defibrillators) were excluded from the study. To align with publications utilizing an age cut-off of <55 for young pacemaker recipients we also performed a pre-specified subgroup analysis of this age group.

Data was collected by reviewing the files of adult permanent pacemaker patients, including the Tygerberg Hospital electronic patient records (ECM) and electronic electrocardiogram (ECG) database.

For each patient, their age at first implant, sex, comorbidities, the type of bradyarrhythmia they presented with, the indication for permanent pacemaker implantation, the type of permanent pacemaker implanted, the duration post implant (follow-up period), the pacing need of these patients (expressed as a percentage pacing) at follow-up, the diagnostic imaging modalities utilised and the underlying cause of the conduction system defect, if known, were recorded. The investigations done, type of pacemaker implanted as well as their follow-up were all at the discretion of the attending cardiologist, in accordance with the established guidelines that were available at the time (10–13).

## Statistical analysis

For descriptive purposes frequencies and percentages were reported for categorical variables. Means, standard deviations and medians were reported for continuous measurements. Categorical variables were compared using the Fishers' exact test. Cross tabulation with the Chi-square test was used to test the relationship between age groups and whether a specific underlying cause was identified. Statistical significance was noted if the *p*-value was less than 0.05.

# Results

After reviewing the patient information and applying our in- and exclusion criteria, 169 patients were included in the study. Thirty patients were excluded; 6 with no recorded indication for pacemaker implant and 24 that did not attend their six months follow up (**Figure 1**).

The mean age of our study population was 50.72 (±8.93) years. Fifty three percent of patients ($n = 90$) were female. More than half of our study population ($n = 104$; 61.5%) received their pacemaker at, or before, the age of 55. In the subgroup of 55 years and younger, the mean age was 46.07 (±8.49) years.

Third degree AVB was the most common indication for pacemaker implantation ($n = 115$; 68%), followed by high degree AVB ($n = 23$; 13.6%) and sick sinus syndrome (SSS; $n = 14$; 8.3%). A summary of all the indications for permanent pacemaker implantation can be seen in **Table 1**.

Amongst the patients who presented with third degree AVB, 49 patients (42.6%) had a narrow complex escape, 45 patients (39.1%) had a broad complex escape, 1 patient had a junctional escape with underlying right bundle branch block (RBBB), 2 patients had a junctional escape with underlying bifascicular block and 2 patients had no escape post cardiac surgery, requiring permanent pacing.

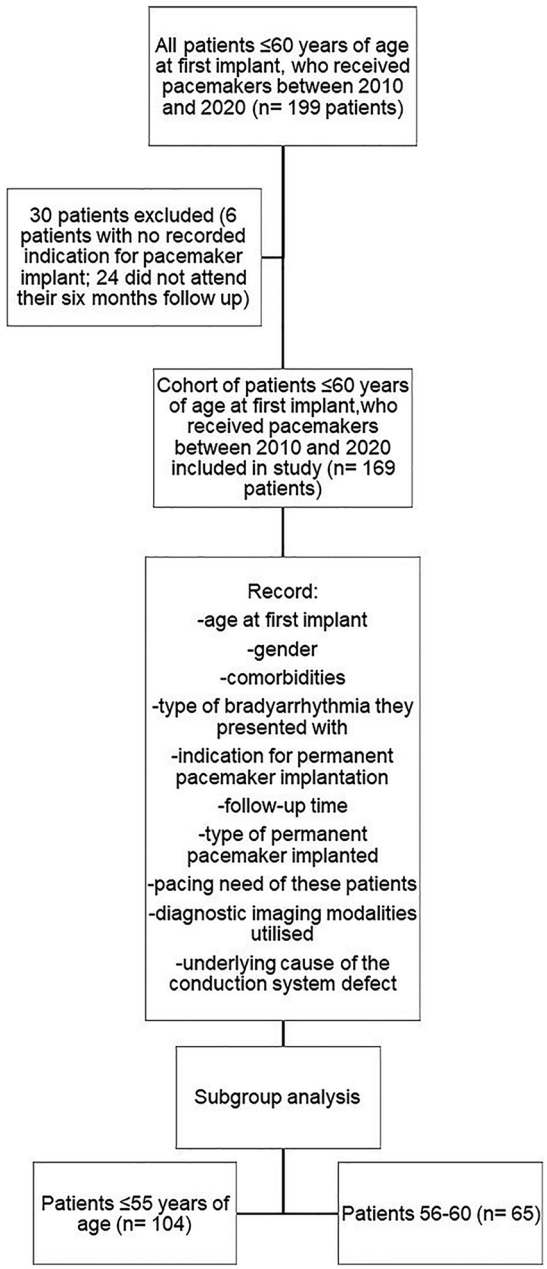


FIGURE 1
Study layout.

Fourteen patients presented with SSS (8.3% of the cohort). Amongst the patients who had SSS, 6 (42.9%) presented with sinus pauses and 3 (21.4%) with tachycardia-bradycardia syndrome. No underlying causes for SSS were identified in this cohort.

Two patients (1.2% of the cohort) presented with atrial fibrillation with a rapid ventricular response and received a pacemaker in view of planned AV nodal ablation.

The subgroup analysis of patients 55 years or younger at the time of implant produced similar results. The most common indication was also third degree AVB ($n = 72$; 69.2% of the subgroup). The other indications for permanent pacemaker implantation in this subgroup included high degree AVB ($n = 13$; 12.5% of the subgroup), second degree AVB Mobitz type 2 ($n = 2$; 1.9% of the subgroup), second degree AVB Mobitz type 1 ($n = 6$; 5.8% of the subgroup), trifascicular block ($n = 1$; 1% of the subgroup) and SSS ($n = 10$; 9.6% of the subgroup).

TABLE 1 Indications for permanent pacemaker implant.

| Indication | *n* (%) |
|---|---|
| Third degree AVB | 115 (68%) |
| High degree AVB (intermittent third degree AVB/2:1 AVB) | 23 (13.6%) |
| SSS | 14 (8.3%) |
| Mobitz type 1 | 6 (3.6%) |
| Mobitz type 2 | 6 (3.6%) |
| Atrial fibrillation in view of AV nodal ablation | 2 (1.2%) |
| Other[a] | 3 (1.8%) |
| **Total** | **169** |

AVB, atrioventricular block; SSS, sick sinus syndrome; AV, atrioventricular; BBB, bundle branch block.
[a]First degree AVB with alternating left and right BBB ($n = 1$; 0.6%); bifascicular block, second degree AVB (Mobitz type 1) when exercising ($n = 1$; 0.6%), trifascicular block ($n = 1$; 0.6%).

The majority of patients received a dual chamber pacemaker ($n = 113$; 66.9%) with the most common pacing mode being DDD ($n = 84$; 49.7%).

The mean follow-up time amongst the study population was 4.71 years (±2.88) and the median follow-up time amongst the study population 4.31 years (±2.88). The longest follow-up was 12 years. The overall spread of follow-up times amongst our study population can be seen in **Figure 2**. Data reported on pacing mode and percentage were taken from the last follow-up visit for each patient.

Overall, 44.4% of patients ($n = 75$) were 100% ventricular paced, the mean ventricular pacing percentage was 75.5% and the median ventricular pacing percentage was 99.0% The mean ventricular pacing percentages were 87.3% for patients with third degree heart block, 64.5% with high degree AVB, 64.7% with second degree AVB Mobitz type 2, 45.4% with second degree AVB Mobitz type 1, and 19.6% with SSS. The patient who had first degree AVB with alternating left and right BBB had a ventricular pacing percentage of 19%, the patient with a bifascicular block and second degree AVB Mobitz type 1 when exercising had a ventricular pacing percentage of 99.9% and the patient with trifascicular block had a ventricular pacing percentage of 98%. The mean atrial pacing percentage for those with SSS was 33.4%.

In the subgroup of patients 55 years and younger, the right ventricular pacing percentages were 84.8% for patients with third degree AVB, 75.2% with high degree AVB, 48.5% with second degree AVB Mobitz type 2, 45.4% with second degree AVB Mobitz type 1 and 14.5% with SSS. In the subgroup of patients between the age 56 and 60, the right ventricular pacing percentages were 91.5% for patients with third degree AVB, 50.5% with high degree AVB, 72.8% with second degree AVB Mobitz type 2, 32.3% with SSS and 52% with atrial fibrillation in view of AV nodal ablation. The patient who had first degree AVB with alternating left and right BBB and the patient with a bifascicular block and second degree AVB Mobitz type 1 when exercising were both older than 55 years of age.

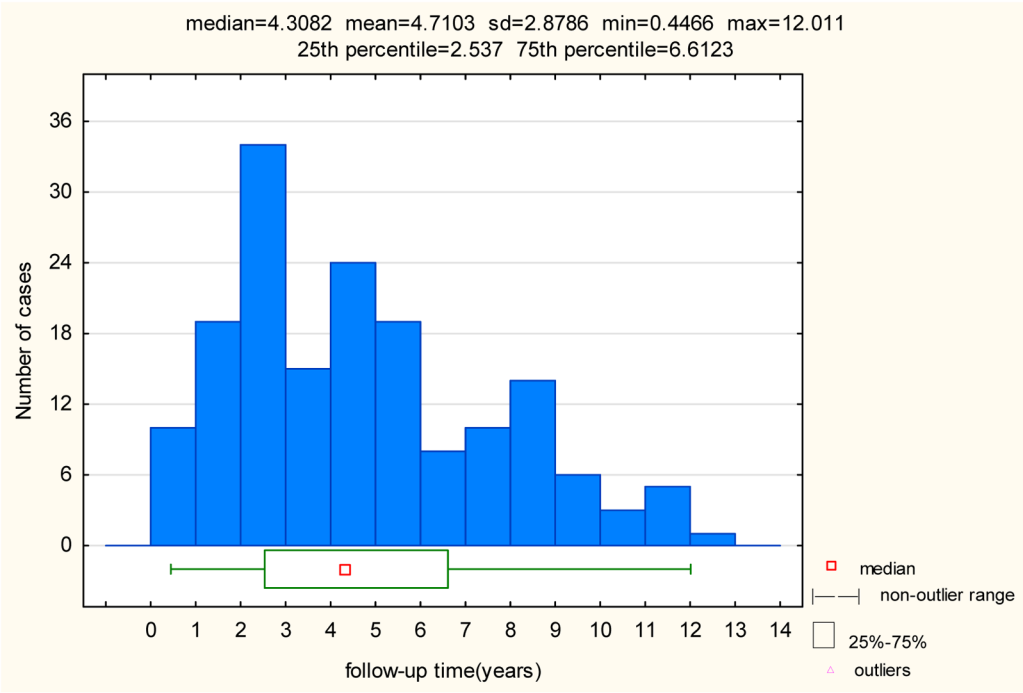


FIGURE 2
Follow-up time post pacemaker implant.

Overall, 23 patients (13.6%) required less than 5% ventricular pacing as indicated by the diagnostic pacemaker parameters at their last follow-up, amongst which 14 patients (8.3%) were 55 years and younger. Amongst the patients 55 years and younger requiring less than 5% right ventricular pacing, 4 patients received their pacemaker for third degree AVB, 1 for high degree AVB, 1 patient for second degree Mobitz type 2, 1 patient for second degree AVB Mobitz type 1 and 7 for SSS.

All of the patients who received their permanent pacemaker for second degree AVB Mobitz type 1 were ≤55 of age at first implant. Half of these patients were male ($n = 3$). The mean right ventricular pacing percentage of 45.4% mentioned above therefore only refers to patients ≤ 55 of age. Only one patient with Mobitz type 1 had a pacing percentage of more than 95% at their last follow-up and only one patient had a right ventricular pacing percentage of less than 5%. All the other patients had some degree of pacing. For 4 out of the 6 patients (66.7% of those with Mobitz type 1), no underlying cause for conduction system abnormalities were identified. Identifiable causes for patients with Mobitz type 1 included valve replacement and/or valve repair ($n = 1$; 16.7%) and Tetralogy of Fallot ($n = 1$; 16.7%).

The majority of patients received a transthoracic echocardiogram (TTE; $n = 125$; 74%) during their hospital stay. Seventy four patients (43.8%) also received a diagnostic chest x-ray, 24 patients (14.2%) a cardiac magnetic resonance (CMR) imaging scan and 7 patients (4.1%) a positron emission tomography (PET) scan during their clinical work-up. A specific cause for the conduction disease was identified in eleven patients in whom CMR imaging was performed (45.8% of patients undergoing CMR imaging) and 4 patients who had a PET scan (57.1% of patients undergoing PET scans).

A specific underlying cause was identified in 25.4% of patients ($n = 43$). This was more likely in the younger subgroup with 32 out of the 43 patients (74.4%) in which an underlying cause was identified, being 55 years and younger and the other 11 (25.6%) being between the age of 56 and 60 ($p = 0.04$).

Specific causes that were identified included prosthetic valve implantation and/or valve repair ($n = 14$; 8.3%), myocardial infarction ($n = 6$; 3.6%), cardiac sarcoidosis ($n = 5$; 3.0%), coronary artery bypass grafting ($n = 3$; 1.8%), cardiomyopathy ($n = 2$; 1.2%), muscular dystrophy ($n = 2$; 1.2%), congenital heart disease ($n = 6$; 3.6%), acute myocarditis ($n = 1$; 0.6%), atrial myxoma removal ($n = 1$; 0.6%), planned AV node ablation ($n = 2$; 1.2%), and following a previous stab in the chest ($n = 1$; 0.6%). Of the 6 patients with congenital heart disease, 3 occurred late post-operative [ventricular septal defect (VSD); atrioventricular septal defect (AVSD); Tetralogy of Fallot (TOF)] and 3 occurred early post-operative (bicuspid aortic valve; AVSD with mitral valve abnormality; TOF). A summary of underlying causes of conduction system defects identified in patients 55 years and younger and those between 56 and 60 can be seen in **Table 2**.

## Discussion

Globally, pacemaker recipients are generally older, reflecting the fact that ageing is associated with fibrosis of the cardiac

TABLE 2 Underlying causes of conduction system defects identified in patients ≤ 55 vs. 56–60.

| Underlying cause identified | Total cohort ($n = 169$) | Patients ≤ 55 years of age ($n = 104$) | Patients 56–60 years of age ($n = 65$) | *p*-value |
|---|---|---|---|---|
| Valve replacement and/or repair | 14 (8.3%) | 12 (11.5%) | 2 (3.1%) | 0.08 |
| Myocardial infarction | 6 (3.6%) | 2 (1.9%) | 4 (6.2%) | 0.21 |
| Sarcoidosis | 5 (3.0%) | 5 (4.8%) | 0 (0%) | 0.16 |
| CABG | 3 (1.8%) | 3 (2.9%) | 0 (0%) | 0.29 |
| Cardiomyopathy | 2 (1.2%) | 1 (1.0%) | 1 (1.5%) | 1.0 |
| Muscular dystrophy | 2 (1.2%) | 1 (1.0%) | 1 (1.5%) | 1.0 |
| Congenital heart disease | 6 (3.6%) | 5 (4.8%) | 1 (1.5%) | 0.41 |
| Acute myocarditis | 1 (0.6%) | 1 (1.0%) | 0 (0%) | 1.0 |
| Atrial myxoma removal | 1 (0.6%) | 1 (1.0%) | 0 (0%) | 1.0 |
| Following a previous stab in the chest | 1 (0.6%) | 1 (1.0%) | 0 (0%) | 1.0 |
| Planned AV node ablation | 2 (1.2%) | 0 (0%) | 2 (3.1%) | 0.15 |
| **Total** | **43** | **32** | **11** | |

CABG, coronary artery bypass grafting; AV, atrioventricular.

conduction system. Assuming similar pathology in younger patients, especially from demographic areas where there is little published data, may result in the search for an underlying cause in young people with conduction disease (e.g., sarcoidosis) being incomplete or inadequate. Underlying causes identified in our study population were not dissimilar from cohorts reported from high income countries. A notable difference is the number of patients receiving pacemakers following valve replacements for rheumatic heart disease.

Some investigations required, such as CMR imaging or PET scans are costly with limited availability in our resource limited environment, and this study emphasizes the value of performing comprehensive investigations for an underlying cause in younger patients requiring pacemaker implantation, particularly in patients ≤ 55 years. The varying pacing requirements in younger individuals with Mobitz 1 AVB in our cohort suggests that in some of these patients, pacemaker implantation may not be required, but this group will require further study to improve the selection of patients with Mobitz 1 AVB that can be managed conservatively.

Given that the mean age of our cohort was 50.72 (±8.93) years, there were some similarities with cohorts not limited by an age cut-off of 60 years. Almost 40% of our cohort was in the 56 to 60 year range, possibly explaining these similarities. In the subgroup of 55 years and younger, the mean age was 46.07 (±8.49). Other studies conducted on young pacemaker recipients who received permanent pacemakers for AVB had a lower mean age, i.e., between 38 and 41 years (1, 2, 4). Women accounted for 54.1% of our study population which is in keeping with a study conducted on cardiac pacing in a referral service in sub-Saharan Africa (14). The relatively high age of our cohort of "young pacemaker recipients" must be taken into account when reflecting on the relatively low number of patients in whom a specific underlying cardiac pathology requiring pacing was identified.. It is likely that a number of patients, even in our age-defined cohort, received pacemakers for AVB due to degenerative changes in the conduction system.

In our study, the majority of patients receiving pacemakers presented with third degree AVB, including those patients ≤ 55 years. This has been shown to be the case for patients across the age spectrum (6, 14–18) and in young cohorts presenting with AVB (1, 4).

The median ventricular pacing percentage of our study population was 99%. The fact that some patients required only 0%–5% ventricular pacing, raises the possibility that some of these younger patients might not have required permanent pacing. Patients with SSS had low ventricular pacing percentages, as expected, since these patients would mainly require atrial pacing. Although the mean right ventricular pacing percentage of those with Mobitz type 1 was not high, the majority of patients required some degree of pacing, with one patient being more than 95% paced. This may support the need to pace younger patients with Mobitz type 1, as found by Shaw et al. (9), but may also reflect pacemaker settings promoting rather than limiting RV pacing, and suggests the need for a further investigation of young patients with Mobitz 1 AVB in order to better the understanding of disease progression.

In our study, a specific cause for the conduction abnormality was found in 25.4% of patients. This was slightly higher in the subgroup ≤ 55 years ($n = 32$; 30.8% of the subgroup). From literature, it is however apparent that this low yield may not be unique to our study population (1, 2, 4). It is important to note that the usual practice in our hospital was to exclude all reversible causes. This includes stopping beta-blocker therapy in patients presenting with heart block and re-evaluating prior to pacemaker implantation.

The most common cause identified in our study was prior cardiac surgery. This was mainly following prosthetic valve implantation and/or valve repair. Other disease states identified were myocardial infarction, cardiac sarcoidosis, muscular dystrophy, congenital heart disease and acute myocarditis. Although the studies conducted by Rudbeck-Resdal et al. (1) and Mkoko et al. (4) included a slightly younger population receiving pacemakers due to AVB, their findings were similar to ours. The most common underlying cause of the AVB in their studies was also following cardiac surgery (1, 4). Similar to our findings, surgical valve replacement was also the main cause of AVB in one of these studies (4). Other underlying causes that have been previously described included congenital heart disease, radiofrequency ablation, cardiomyopathy, muscular dystrophy, ischemic heart disease, sarcoidosis and myocarditis (1). We identified similar causes in our cohort. In our cohort the majority of patients in whom an underlying cause was identified were 55 years and younger. This raises the question whether the patient group between 56 and 60 were not

scrutinized sufficiently, or whether these patients had age related degeneration of their conduction system. The most common identified underlying cause in the patients between 56 and 60 years of age was myocardial infarction whereas all the cases caused by sarcoidosis were in the subgroup ≤ 55 years. These findings support the notion that the underlying causes of conduction system defects differ between these age groups of patients. Post-operative heart block following the surgical correction or repair of congenital heart disease has been well described (19–22). In our study population, three patients with congenital heart disease had immediate post-operative heart block which did not revert back to their pre-operative rhythm requiring permanent pacemaker implantation during their time of admission. Three other patients had a delayed presentation of heart block, also requiring permanent pacemaker implantation. Although AVB usually develops at the time or shortly after corrective surgeries, late-onset AVB, as seen in our cohort, also occurs (20, 23).

In our cohort, no patients were recorded to have congenital AVB. This is in contrast to the findings of other studies done on young pacemaker recipients (1, 4). This might be attributed to incomplete record keeping or due to the fact that some patients with congenital heart block might have received permanent pacemakers before the age of 18 and were therefore excluded from our study population.

It is important to note that cardiac imaging modalities such as CMR and PET scans were not readily available at the onset of the study period which may have had an effect on the number of patients in which a specific underlying cause were identified. Cardiac PET scans became available in June 2014 while CMR scans only became available in March 2017. CMR and PET scans are recommended for most patients younger than 60 years of age presenting with AVB to increase the likelihood of identifying the underlying cause (4). Mkoko et al. indicated that CMR imaging has especially been shown to be important diagnostic tool in identifying cardiac sarcoidosis (4). In our study, 45% of those who received CMR imaging and 57% of patients who received a PET scan had an underlying cause identified, suggesting that these are helpful investigations in young patient with conduction disease. As access to these advanced diagnostic tools improves, it will become important to utilize them in the most cost-effective way to improve the diagnostic capabilities in young patients with conduction system disease.

## Limitations

Retrospective studies have inherent limitations. These may include incomplete and/or missing patient data and the inability to collect additional information from patients. An additional limitation was that advanced imaging modalities such as CMR and PET scans were not readily available from the start of the study period, which may have affected the number of patients in which a specific underlying cause was identified.

## Conclusion

In this retrospective cohort, the most common indication for pacemaker implantation was third degree AVB, followed by high degree AVB and SSS. A specific underlying cause was found in 25.4% of patients of which prosthetic valve implantation and/or valve repair was the most common.

Since the mean age of our study populations was high at 50.95 (±8.72) years, we cannot exclude the possibility that some of these patients, especially those between the ages of 55 and 60, might have developed conduction defects as a result of degeneration of their conduction system. The low number of underlying causes identified in patients between the ages of 56 and 60 also raises the possibility that patients in this age bracket are less likely to be extensively investigated for an underlying cause in comparison to those 55 years or younger. As access to advanced diagnostic tools improves, the percentage of young pacemaker recipients with an underlying cause identified may however increase.

Although the mean right ventricular pacing percentage of those with Mobitz type 1 was not high, the majority of patients required some degree of pacing. The reason for this is unclear from this study as it could be due to disease progression or due to pacemaker programming. Further investigation of young patients with Mobitz 1 AVB is needed in order to better the understanding on the predictors of disease progression.

In young patients requiring permanent pacemaker implantation, particularly if they are ≤55 years, we should have a low threshold to recommend augmenting standard echocardiographic imaging with advanced imaging such as CMR/PET scans to identify specific underlying causes. Further prospective studies that include adolescents and young adults are needed to provide more comprehensive and robust data and to improve on our ability to detect underlying causes and risk factors for disease progression in patient with second degree block.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

This study involving humans was approved by die Health Research Ethics Committee of the University of Stellenbosch. It was conducted in accordance with the local legislation and institutional requirements. The Ethics Committee/institutional review board waived the requirement of written consent for participation from the participants or the participants' legal guardians/next of kin because this was a retrospective

study with minimal risk to the patients, patients' rights and/or welfare.

## Author contributions

AD, JS, and JM: contributed to the study concept and design. EH: wrote the first draft of the article. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Incidence and predictors of recurrent acute coronary syndrome among adult patients with acute coronary syndrome in West Amhara, Ethiopia: a multicenter retrospective follow-up study

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**Introduction:** Acute coronary syndrome (ACS) is the most common cause of morbidity and mortality in patients with coronary heart disease. Furthermore, the recurrence of this problem has significant adverse outcomes. However, there is insufficient information pertaining to this problem in Ethiopia; hence, this study aims to assess the incidence rate and identify the predictors of ACS recurrence in the West Amhara region.

**Methods:** A retrospective follow-up study was conducted among 469 patients diagnosed with primary ACS. Data from the patient chart were collected using a pre-tested structured data extraction tool. The study employed the Weibull regression analysis model, and the effect size was measured using an adjusted hazard ratio (HR) with a 95% confidence interval (CI). The statistical significance of the findings was established based on a $p$-value <0.05.

**Result:** A total of 429 patients were included in the final analysis [average age, $60 \pm 13.9$ years; and 245 (57.1%) men]. A total of 53 patients (12.35%; 95% CI: 9.55%–15.83%) experienced recurrent ACS. The overall risk time was found to be 93,914 days (3,130.47 months), and the recurrence rate was 17/1,000 patients/month. The identified predictors were the typical symptoms of ACS such as syncope (HR: 3.54, $p = 0.013$), fatigue (HR: 5.23, $p < 0.001$), history of chronic kidney disease (HR: 8.22, $p < 0.001$), left ventricular ejection fraction of <40% (HR: 2.34, $p = 0.009$), not taking in-hospital treatments [aspirin (HR: 9.22, $p < 0.001$), clopidogrel (HR: 4.11, $p = 0.001$), statins (HR: 2.74, $p = 0.012$)], and medication at discharge [statins (HR: 4.56, $p < 0.001$)].

Abbreviations

ACS, acute coronary syndrome; AHA, American Heart Association; AMI, acute myocardial infarction; NSTEMI, non-ST segment elevated myocardial infarction; Re-ACS, recurrent acute coronary syndrome; STEMI, ST segment elevated myocardial infarction; UA, unstable angina; WHO, World Health Organization.

**Conclusion:** This study found a higher incidence rate of recurrent ACS. Hence, the implementation of guideline-recommended anti-ischemic treatment should be strengthened.

KEYWORDS

parametric model, recurrent acute coronary syndrome, survival analysis, Weibull regression model, incidence rate

## Introduction

Acute coronary syndrome (ACS) is a general term used to describe a spectrum of conditions that are consistent with acute ischemia or infarction, which is characterized by an abrupt decrease in coronary blood flow (1). The resulting undersupply of blood and oxygen to the heart itself can lead to a range of heart conditions, ranging from chest pain to a heart attack/myocardial infarction (MI), during which the heart is damaged (2–4).

According to a report by the British Heart Foundation, Africa had a total of 58 million cases of heart and circulatory diseases, resulting in 1.7 million deaths attributable to these diseases (5). Despite the decline in mortality rates due to ischemic heart disease (IHD) in high-income countries, its trend is increasing in low-income countries from 243,000 in 2000 to 304,000 in 2010, and further increased to 379,000 in 2019. Furthermore, over three-fourth of the global fatalities resulting from cardiovascular diseases (CVDs) occurred in developing countries (4, 6, 7). The economic burden of coronary heart disease (CHD) is also drastically increasing. According to a report conducted in the United States, it is estimated that the indirect costs associated with CVD are projected to increase by 52% (from $202.5 billion to $308.2 billion) from 2013 to 2030. Approximately 43% of the total indirect cost is predicted to be attributed to CHD, making it the condition with the highest indirect expenses (8).

Recurrent ischemia following the initial presentation of an ACS is indicative of an adverse outcome and has major implications for the allocation of healthcare resources. The prevalence of recurrent ACS in developed countries nowadays has become a major concern due to its increasing incidence rate, and it was associated with high adverse outcomes, including stroke, congestive heart failure, CHF), cardiogenic shock, and death (9–15). Recurrent ACS was found to be associated with an increase in mortality rates immediately after the adverse event. Specifically, the hazard ratio for mortality during the first day following a recurrent MI was observed to exceed 14 times. Subsequently, the risk of mortality was reduced but still remained significantly higher (five times) between 1 day and 1 year following a recurrent MI (12). There was a significant difference in death for recurrent ACS compared with death among patients without recurrent ACS (5.2% vs. 2.2% at $p < 0.01$) (16). Pooled data indicate that the patients aged 45 years or older had a mortality rate of 19% for men and 26% for women within the first year. After a period of 5 years following the initial occurrence of MI, the mortality rates for men and women were recorded at 36% and 47%, respectively (17).

Studies from developed nations reveal that the readmission rate due to recurrent ACS has increased from time to time. The study findings show that the readmission rate increased as the time interval between the first ACS discharge and readmission time increased, ranging from 11.7% to 61.7% within the first 30 days and the first year following discharge (10, 13, 15, 18). Furthermore, the median time for readmission was found to be 0.8 months (18).

The prevalence of ACS in Africa has also become increasingly high, as evidenced by available data. In addition, there has been a concurrent rise in the rates of re-infarction and recurrence associated with ACS. According to a study on treatment outcomes of ACS in different sub-Saharan African countries, the re-infarction rate in Kenya was found to be 6.6% (19).

A study conducted in Ethiopia examined the prevalence of CVD among adults at six university referral hospitals. The findings revealed that IHD ranked among the top three types of CVD, accounting for 11.5% (20). In addition, re-infarction ACS was observed in 14.6% of the patients in Mekelle, Ethiopia (21).

In general, the available data show that recurrent ACS has become a challenging problem worldwide. In recent decades, various organizations such as the American College of Cardiology Foundation/American Heart Association (AHA), British Heart Foundation, and other national cardiac associations have actively engaged in addressing this issue by implementing treatment guidelines and secondary prevention measures.

Despite the efforts of national and international organizations to develop prevention and treatment guidelines for ACS, this problem remains a prominent issue worldwide. Despite the existence of established guidelines developed for ACS in developed nations, which have been adopted and implemented in many countries worldwide, ACS has also become a significant concern in developing nations, including in African countries. However, the issue of recurrent ACS in developing nations has not been thoroughly examined in terms of the magnitude of the problem and effective management strategies. Furthermore, the recurrence of this problem has been observed to result in high adverse outcomes, as evidenced by various studies conducted worldwide. However, the extent of this problem in Ethiopia remains mostly unexplored.

This study includes the majority of studies conducted on myocardial infarction, either ST segment elevated myocardial infarction (STEMI) or non-ST segment elevated myocardial infarction (NSTEMI). Furthermore, we incorporated typical symptoms of ACS as individual and independent predictors in this study, which were previously referred to generally as “having typical symptoms” in prior research. Therefore, it is important to

study the incidence rate of recurrent ACS and its predictors within the specific context of developing nations. This approach may help in implementing measures at the source of the problem.

Because there is insufficient information regarding this problem in Ethiopia, understanding its incidence and predictors is crucial in order to take secondary preventative measures against its adverse outcomes. Furthermore, it will serve as baseline data for future research.

# Material and methods

## Study design and period

An institutional-based retrospective follow-up study with a record review of patients admitted with the diagnosis of acute coronary syndrome from 1 January 2017 to 31 December 2021 was conducted.

## Study area

The study was conducted in the Comprehensive Specialized Hospitals located in West Amhara, specifically Debre Markos Comprehensive Specialized Hospital, Tibebe Ghion Comprehensive Hospital, Felege Hiwot Comprehensive Specialized Hospital, Debre Tabor Comprehensive Specialized Hospital, and University of Gondar Comprehensive Specialized Hospital (UoGCSH). These hospitals are among the eight comprehensive specialized hospitals found in the region and serve more than 3.5 million people from each town and adjacent catchment areas. The hospitals provide multidimensional aspects of care for clients, including outpatient, inpatient, emergency, intensive care unit, and other services. Most patients with the diagnosis of ACS are admitted to the medical intensive care unit (MICU). However, due to the limited number of beds, a significant number of patients receive treatment either in the emergency department or in the general wards.

## Population

### Source population

The source population of this study includes all ACS patients receiving care at the comprehensive specialized hospitals in West Amhara. The study population comprises all patients diagnosed with primary ACS who were registered in the admission registration book at the Comprehensive Specialized Hospitals in West Amhara from 1 January 2017 to 31 December 2021.

### Eligibility criteria

The study included all individuals diagnosed with either STEMI or NTEMI who were admitted to the hospital as primary ACS patients. The inclusion criteria required that these individuals had fully recovered and were discharged alive between 1 January 2017 and 31 December 2021. Patients with incomplete medical records, missing time variables, those who were transferred in, those without at least one follow-up, and those who developed re-infarction were excluded from the study.

### Sample size determination

Given the absence of any existing research conducted in Ethiopia on this topic, we have undertaken a pilot study. The pilot study was conducted at UoGCSH, serving as an internal pilot study with a sample size of 80 charts of ACS patients. The study revealed that the incidence recurrence rate was 11.25%. Subsequently, the minimum sample size required was calculated using a formula for a single population proportion by considering the following statistical assumptions: $p = 0.1125$, $Z\alpha/2$ = corresponding $Z$ score of 95% CI and $d$ = margin of error (3%).

$$n = z\left(\frac{a}{2}\right)^2 \frac{p(1-p)}{d^2}$$

Single population proportion formula $n = (1.96)^2 \times 0.1125 \times 0.8875/(0.03)^2 = 426$. After assuming a 10% margin of error to account for the incomplete chart, the determined minimum sample size required was 469.

### Sampling procedure and sampling technique

The study was conducted in all five comprehensive specialized hospitals located in the West Amhara district. The method for proportional allocation was utilized for each hospital. The study samples were obtained by identifying the chart numbers of all patients diagnosed with ACS who were admitted to the emergency department, MICU, and medical ward at the selected hospitals. Only patients who were discharged alive after recovering from ACS between 1 January 2017 and 31 December 2021 were included; the chart numbers were retrieved from the registry book. Then, by compiling a list of the index chart numbers of the ACS patients, systematic random sampling methods were used to select a sample of 469 charts. The k interval for each hospital was determined by dividing the total study population of each hospital by the sample population in those hospitals. The selected ACS patient was retrospectively monitored for a maximum of 1 year.

## Operational and standard definition

**Acute coronary syndrome**: For this study, ACS encompasses both myocardial infarction (STEMI and NSTEMI). **STEMI** is characterized by new ST elevation at the J point in two contiguous leads with the cutoff points of ≥0.1 mV in all leads other than the V2–V3 leads. In the V2–V3 leads, the following cutoff points apply: ≥0.2 mV in men aged ≥40 years, ≥0.25 mV in men aged <40 years, or ≥0.15 mV in women (22). **NSTEMI** is characterized by the presence of new horizontal or down-sloping ST depression of ≥0.05 mV in two contiguous leads and/or T-wave inversion of ≥0.1 mV in two contiguous leads with prominent R wave or an R/S ratio of >1 (22). **Chronic kidney disease (CKD)** is defined as a condition of decreased kidney

function as indicated by a glomerular filtration rate (GFR) of less than 60 ml/min per 1.73 $m^2$, or the presence of markers indicating kidney damage, or both, for a duration of at least 3 months, regardless of the underlying cause (23). **Renal dysfunction** is defined as having blood urea nitrogen levels exceeding 40 mg/dl or creatinine levels exceeding 2.5 mg/dl (9). **Recurrent myocardial infarction (re-MI)** is specifically characterized as MI events occurring beyond a period of 28 days following the initial index MI event. However, MI that occurs within 28 days of the initial MI event is classified as a case of re-infarction (24). In this study, **recurrent ACS** refers to any acute coronary event that occurs after 28 days following the initial incident of ACS (25). **Primary ACS** is used to describe ACS that is diagnosed for the first time during the study period. The **left ventricular ejection fraction (LVEF)** is categorized as either ≥40% and <40% (26). The term **Recovery** is used to refer to patients who were declared recovered during their admission. The term **Censored Cases** refers to cases where ACS patients died after discharge, opted out of follow-up, were transferred out, or did not develop any outcomes. **Event** refers to recurrent acute coronary syndrome that occurs after 28 days of recovery and successful discharge. **Follow-up time** was determined by measuring the time from baseline to the earliest date at which a patient experienced an outcome.

## Data collection tools and procedure

A structured data abstraction tool was adapted from different studies and used to obtain information from the chart (21, 27–29). The data were obtained by a group of six BSc nurses who underwent training and conducted the collection process from 12 May 2022 to 6 June 2022. The investigator facilitated the process and was designated as the supervisor of the data collectors. The accuracy of the data was verified daily.

## Data quality control

To maintain the quality of the data, a pretest was conducted at UoGCSH, which involved a random selection of 15 charts to assess the data abstraction checklist, as well as the quality of the instrument and the completeness of the variables. The pretest results were utilized to inform and implement necessary corrections and modifications.

## Data processing and analysis

Data were coded and entered into Epi info version 7 statistical software and exported to STATA version 14 software for data cleaning, checking, and analysis. The descriptive statistics for various variables were presented by text, frequency, cross-tabulations, pie charts, and bar charts. The parametric survival analysis model (Weibull regression) was implemented to assess the statistical significance of the bivariable analysis. The multivariable analysis included variables with a $p$-value ≤ 0.25 from the bivariable analysis. Kaplan–Meier curves were used to estimate the recurrence-free survival rate and statistical log rank. The proportional hazard assumptions were evaluated using global testing. The multivariable analysis employing Weibull regression was utilized to determine the adjusted hazard ratio (AHR) with a 95% confidence interval (CI) and a significance level of $p < 0.05$ to identify statistically significant predictors of the outcome variable.

# Result

## Socio-demographic characteristics of ACS patients

Out of the 469 patient records of acute coronary syndrome that were reviewed, a total of 429 records were included in the final analysis. Among the participants, more than half (57.1%) of the study participants were male, and the majority (65%) were from urban areas. The mean age of the participants at the time of follow-up initiation was 60 ± 13.9 years. The mean age of patients without recurrent ACS was 58.98 ± 13.47 years, while the mean age of patients who experienced recurrent AMI was 67.25 ± 14.81% years (**Table 1**).

## Baseline clinical characteristics and diagnostic tests

### Baseline vital sign and presentation symptoms

Among the 429 patients diagnosed with ACS, 346 (80.7%) of them experienced chest pain as their initial symptom upon presentation. Subsequently, 46 (13.3%) of those with chest pain developed recurrent ACS. Other frequently observed symptoms were shortness of breath, cough, diaphoresis, and vomiting with a proportion of 54.1%, 42.2%, 27%, and 24.7%, respectively. The baseline vital sign results included a median systolic blood pressure of 120 mmHg (IQR: 110–140), pulse rate 87 beats/min (IQR: 78–100), and random blood sugar of 159.6 mg/dl (95% CI: 151.5–167.6 mg/dl) (**Table 2**).

TABLE 1 Baseline socio-demographic characteristics of acute coronary syndrome patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

| Variables | Category | Total $N = 429$ | Outcomes | |
|---|---|---|---|---|
| | | | Censored | Recurrent |
| Age (years) | Mean, SD | 60 ± 13.89 | 58.98 ± 13.47 | 67.25 ± 14.81 |
| Age categorized (years) | 18–44 | 58 (13.5%) | 53 (91.4) | 5 (8.6) |
| | 45–64 | 204 (47.6%) | 191 (93.6) | 13 (6.4) |
| | 65–74 | 86 (20.7) | 74 (86.0) | 12 (14.0) |
| | ≥75 | 81 (18.9%) | 58 (71.6) | 23 (28.4) |
| Sex | Male | 245 (57.1%) | 215 (87.8) | 30 (12.2) |
| | Female | 184 (42.9%) | 161 (87.5) | 23 (12.5) |
| Residence | Urban | 279 (65%) | 243 (87.1) | 36 (12.9) |
| | Rural | 150 (35%) | 133 (88.7) | 17 (11.3) |

TABLE 2 Baseline clinical characteristics of ACS patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

| Variables | Category | Total | Outcomes | |
|---|---|---|---|---|
| | | | Censored | Recurrent |
| Systolic blood pressure (mmHg) | Median (IQR) | 120 (110–140) | 120 (110–140) | 120 (100–150) |
| Diastolic blood pressure (mmHg) | Median (IQR) | 78 (70–86) | 79 (70–85) | 70 (70–90) |
| Pulse rate (beats/min) | Median (IQR) | 87 (78–100) | 87 (78–100) | 84 (79–95) |
| Chest pain | No | 82 (19.1%) | 75 (91.5%) | 7 (8.5%) |
| | Yes | 347 (80.9%) | 301 (86.7%) | 46 (13.3%) |
| Shortness of breathing | No | 195 (45.5%) | 178 (91.3%) | 17 (8.7%) |
| | Yes | 234 (54.5%) | 198 (84.6%) | 34 (15.4%) |
| Cough | No | 248 (57.8%) | 219 (88.3%) | 29 (11.7%) |
| | Yes | 181 (42.2%) | 157 (86.7%) | 24 (13.3%) |
| Nausea | No | 372 (86.7%) | 326 (87.6%) | 46 (12.4%) |
| | Yes | 57 (13.3%) | 50 (87.7%) | 7 (12.3%) |
| Vomiting | No | 323 (75.3%) | 280 (86.7%) | 43 (13.3%) |
| | Yes | 106 (24.7%) | 96 (90.6%) | 10 (9.4%) |
| Diaphoresis | No | 313 (72.9%) | 280 (89.5%) | 33 (10.5%) |
| | Yes | 116 (27.1%) | 96 (82.1%) | 21 (17.9%) |
| Syncope | No | 403 (93.9%) | 357 (88.6%) | 46 (11.4%) |
| | Yes | 26 (6.1%) | 19 (73.1%) | 7 (16.9%) |
| Fatigue | No | 390 (90.9%) | 346 (88.7%) | 44 (11.3%) |
| | Yes | 39 (9.1%) | 30 (76.9%) | 9 (23.1%) |
| Others symptoms | | 6 (1.4%) | 5 (83.3%) | 1 (16.7%) |

## Baseline history of comorbidities

The most prevalent comorbidities upon admission were hypertension, diabetes mellitus (DM), pneumonia, and CHF accounting for 175 (40.8%), 92 (21.4%), 74 (17.2%), and 71 (16.6%) cases, respectively. Major comorbidities were observed among patients with recurrent ACS, with DM affecting 19.1% and hypertension affecting 15.4% of the patients (Figure 1).

## Diagnostic tests and diagnosis

Among the 429 ACS cases that were studied, 114 (26.6%) cases exhibited a LVEF of less than 40%. Among these cases, 21.1% experienced recurrent ACS events. A total of 294 (68.5%) patients had left ventricular dysfunction, and 46 (15.6%) patients among this subgroup experienced recurrent ACS. In relation to the lipid profile, it was shown that half (50.3%) of the ACS patients exhibited hyperlipidemia during their initial admission. Among the total follow-up cases, 65.5% were diagnosed with STEMI, whereas the other cases were classified as NSTEMI (Table 3).

## In-hospital treatment provided at the primary admission

Regarding the treatment at primary admission, it was observed that aspirin, clopidogrel, statins, beta-blockers, and anticoagulants were not administered for 4.7%, 9.8%, 7.9%, 13.5%, and 17.7% of

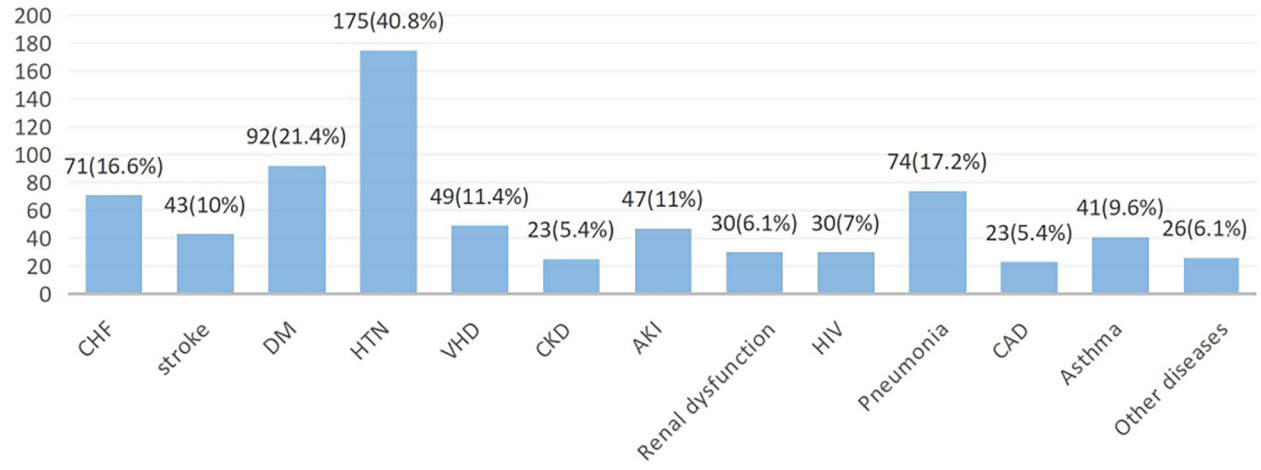


FIGURE 1
Patterns of comorbidities at primary admission among ACS patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022. CHF, congestive heart failure; DM, diabetes mellitus; HTN, hypertension; VHD, ventricular heart disease; AKI, acute kidney injury; HIV, human immunodeficiency virus; CAD, coronary artery disease.

TABLE 3 Baseline diagnostic tests and diagnosis of acute coronary syndrome patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

| Variables | Category | Total, *n* (%) | Outcome | |
|---|---|---|---|---|
| | | | Censored, *n* (%) | Recurrent, *n* (%) |
| Troponin (ng/ml) | Median, IQR | 2.9 (0.19–9.32) | 2.81 (0.19–9.32) | 6.4 (0.172–14.74) |
| Echocardiography LVEF (%) | <40 | 114 (26.6) | 90 (78.9) | 24 (21.1) |
| | ≥40 | 315 (73.4) | 286 (90.8) | 29 (9.2) |
| LV dysfunction | Yes | 294 (68.5) | 248 (84.4) | 46 (15.6) |
| | No | 135 (31.5) | 128 (94.80 | 7 (5.2) |
| Hyperlipidemia | Yes | 216 (50.3) | 189 (87.5) | 27 (12.5) |
| | No | 213 (49.7) | 187 (87.8) | 26 (12.2) |
| Type of MI | STEMI | 281 (65.5) | 242 (86.1) | 39 (13.9) |
| | NSTEMI | 148 (34.5) | 134 (90.5) | 14 (9.5) |

ACS patients, respectively. Those who did not receive these medications exhibited a higher incidence of recurrent ACS with 55%, 34.5%, 29.4%, 15.5%, and 21.1%, respectively (Table 4).

### Treatment administered upon discharge

Among the 429 ACS patients included in this study, the percentage of patients who have not received evidence-based anti-ischemic medication were aspirin (6.8%), statins (8.6%), clopidogrel (11.9%), beta-blockers (15.2%), and angiotensin converting enzyme inhibitors (ACEIs) (51%). Among those who did not receive those medications (aspirin, statins, and clopidogrel), a higher incidence of recurrent ACS was observed, with 41.4%, 40.5%, and 35.3%, respectively (Table 5).

## Incidence and survival pattern of ACS patients

With the a minimum follow-up period of 30 days and a maximum follow-up of 365 days, a total of 53 (12.35%, 95% CI: 9.55%–15.83%) individuals experienced recurrent ACS, while 7.22% of the participants were dead, 6.75% withdrew from follow-up, and 6.52% transferred out. The remaining two-third (67.1%) did not develop any outcome (Figure 2). The total duration at risk for 429 ACS patients was 3,130.467 months (93,914 days). The incidence rate of recurrent ACS was 0.01693 (95% CI: 0.0129–0.0222) per person-month [16.93 Re-ACS/1,000 person-month] or 5.6 (95% CI: 4.3–7.4) per 10,000 person-day observation among follow-up ACS patients. The incidence rates observed at 60, 90,180, and 365 days were 4.02, 9.53, 6.55, and 4.98 per 10,000 person-day observation, respectively. The probability of survival without recurrence at 60, 90, 180, and 365 days following discharge were 0.978, 0.950, 0.893, and 0.817, respectively.

TABLE 4 In-hospital treatments of acute coronary syndrome patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

| Treatments | Category | Total, *n* (%) | Outcome | |
|---|---|---|---|---|
| | | | Censored, *n* (%) | Recurrent, *n* (%) |
| Aspirin | Yes | 408 (95.4) | 367 (90.0) | 41 (10.0) |
| | No | 21 (4.7) | 9 (42.9) | 12 (57.1) |
| Clopidogrel | Yes | 387 (90.2) | 351 (90.7) | 43 (9.3) |
| | No | 42 (9.8) | 25 (76.2) | 17 (23.8) |
| Statins | Yes | 393 (92.1) | 350 (89.1) | 43 (10.9) |
| | No | 36 (7.9) | 26 (72.2) | 10 (27.8) |
| ACEIs | Yes | 285 (66.4) | 248 (87) | 37 (13) |
| | No | 144 (35.6) | 128 (88.9) | 16 (11.1) |
| Beta-blockers | Yes | 371 (86.5) | 335 (90.3) | 40 (9.7) |
| | No | 58 (13.5) | 49 (84.5) | 9 (15.5) |
| Anticoagulant | Yes | 353 (82.3) | 316 (89.5) | 37 (10.5) |
| | No | 76 (17.7) | 60 (78.9) | 16 (21.1) |
| Diuretics | Yes | 178 (41.5) | 154 (86.5) | 24 (13.5) |
| | No | 251 (58.5) | 222 (88.4) | 29 (11.6) |

## Failure function

The restricted mean survival time was 328.8 days with 95% CI (319.3–338.3 days). The cumulative probability of failure at 60, 90, 180, and 365 days was 0.022, 0.0499, 0.107, and 0.182, respectively (Figure 3).

## Survival functions of predictors

The survival curves of different predictor variables were tested for equality using the log-rank test. The statistics and the survival

TABLE 5 Medication prescribed at discharge of ACS patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

| Variables | Category | Total, *n* (%) | Outcomes | |
|---|---|---|---|---|
| | | | Censored, *n* (%) | Recurrent, *n* (%) |
| Aspirin | Yes | 400 (93.2) | 359 (89.8) | 41 (10.3) |
| | No | 29 (6.8) | 17 (58.6) | 12 (41.4) |
| Clopidogrel | Yes | 378 (88.1) | 343 (90.7) | 35 (9.3) |
| | No | 51 (11.9) | 33 (64.7) | 18 (35.3) |
| Statins | Yes | 392 (92.4) | 354 (90.3) | 38 (9.7) |
| | No | 37 (8.6%) | 22 (59.5) | 15 (40.5) |
| ACEIs | Yes | 219 (51.0) | 189 (86.3) | 30 (13.7) |
| | No | 210 (49.0) | 187 (89.0) | 23 (11.0) |
| Beta-blockers | Yes | 364 (84.8) | 321 (88.2) | 43 (11.8) |
| | No | 65 (15.2) | 55 (84.6) | 10 (15.4) |
| Diuretics | Yes | 111 (25.9) | 97 (87.4) | 14 (12.6) |
| | No | 318 (74.1) | 279 (87.7) | 39 (12.3) |

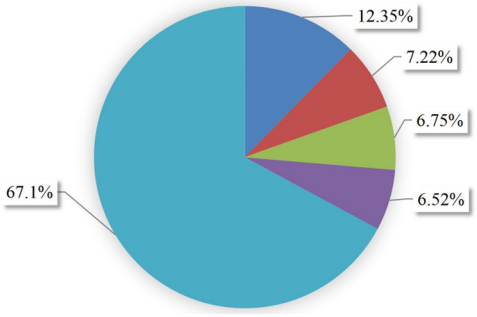


FIGURE 2
Outcomes proportion of follow-up patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

curve showed that there were significant differences in the survival functions of different categorical variables. These variables were syncope, fatigue, history of CKD, LVEF, administering aspirin, clopidogrel, and statins during hospitalization, and administering statins at discharge.

In this study, we found that typical clinical symptom complaints during primary admission highly predicted the recurrence rate of ACS. The recurrence-free survival rate at the end of the follow-up period was higher among patients who had not complained of syncope during their initial admission compared with those who had complained of it (83.2% and 63.6%, respectively) (Figure 4A).

Another significant predictor was baseline fatigue symptoms. At the end of the follow-up, 83.3% of patients without complaints of fatigue survived, while only 65.2% of patients who experienced fatigue survived (Figure 4B).

Patients who had a history or comorbidity of chronic kidney disease also had a significant difference, as shown in the figure below. ACS patients with a history of CKD had a considerably lower survival rate than those without CKD history, with rates of

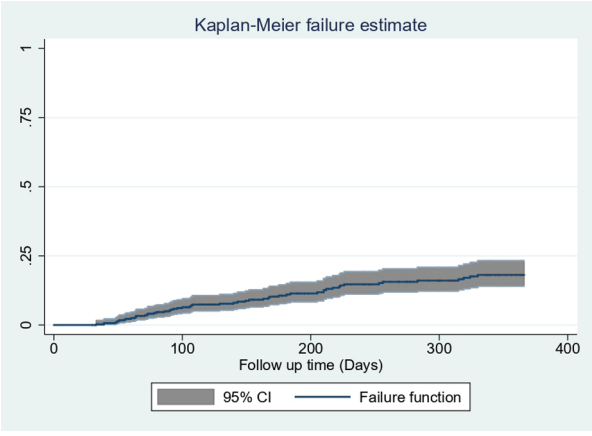


FIGURE 3
Overall Kaplan–Meier estimation of failure function with 95% confidence intervals of follow-up patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

40% and 84.7%, respectively (Figure 4C). Patients with ACS who exhibited a reduced level of LVEF (<40%) also experienced a lower recurrence-free survival rate (69.8%) compared with those with an LVEF level of >40% (86.2%) (Figure 4D).

Anti-ischemic treatments during primary admission also exhibited a significant difference in the recurrence-free survival rates. The survival rate of ACS patients without aspirin was significantly lower (33.8%) compared with those who received aspirin (84.5%). Another anti-ischemic drug is clopidogrel with a recurrence-free survival rate of 45% among prescribed patients and 85.8% among non-clopidogrel-prescribed ACS patients. Statins also had a significant difference as evidenced by a lower recurrence-free survival rate of 57.4% among the statins group compared with a rate of 84% among the non-statins group (Figure 5).

Another very important treatment provided upon discharge (medication taken home) was statins, which have been shown to effectively reduce lipid levels, as evidenced by the recurrence-free survival rates of 85.4% and 48.2% observed among those who were prescribed statins and those who were not, respectively (Figure 6).

## The goodness of fit of the final model

The goodness of fit of the final regression model was evaluated using the Schoenfeld residuals test and the estimate of Cox–Snell residuals drawn against the Nelson–Aalen cumulative hazard function. The global test of the proportional hazard assumption was conducted, revealing a lack of significance (the $p$-value for each variable ranges from 0.0811 to 0.9980, and the global test $p$-value of 0.5092). The Cox–Snell residual plot also indicated that the goodness of fit of the model was satisfied, as the hazard function follows the 45° line very closely. Therefore, we would conclude that the final model well aligns with the data. Unobserved heterogeneity in hospitals was also assessed using the gamma shared frailty model, and it was found that the theta value was approximately 0 (0.1344). Furthermore, the probability of the chi-square test was determined to be statistically insignificant ($p = 0.236$). Therefore, we concluded that the null hypothesis was not rejected, indicating that fixed effect models are suitable for analyzing the data.

## Model comparison

The log likelihood ratio, Akaike's information criterion (AIC), and Bayesian information criterion (BIC) were used to analyze the goodness of fit of the final model among semi-parametric and parametric models. Based on the available data, the Weibull PH regression model with the highest log likelihood, least AIC, and BIC was chosen as the final fitted analysis model (Table 6).

Figures 7A–D present a comparison between the Nelson–Aalen cumulative hazard function and Cox–Snell residual multivariable regressions, and the Weibull PH regression model was found to be the best-fit model.

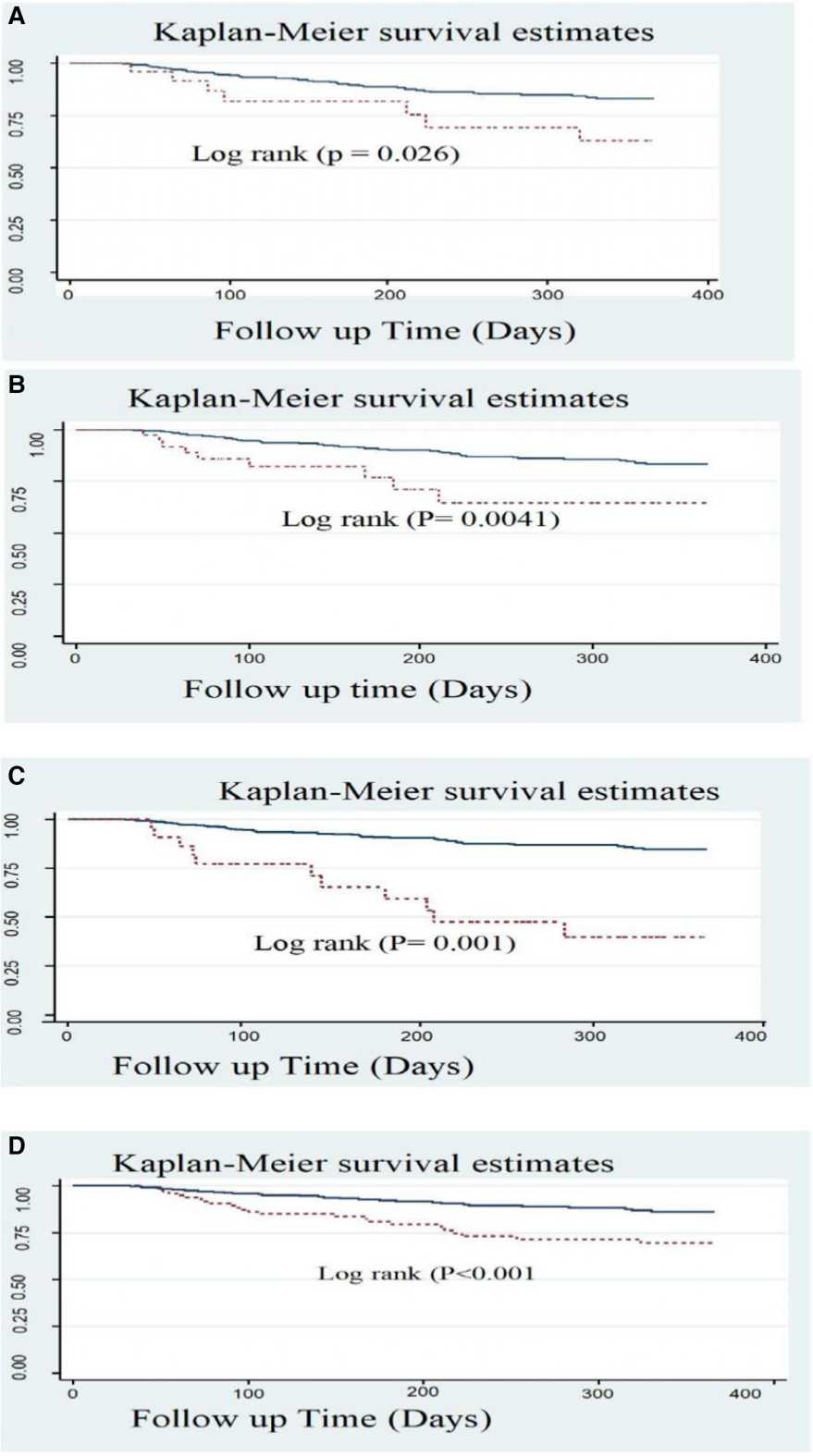


FIGURE 4
Kaplan Meier survival estimate of ACS patients with typical symptoms; (A) Syncope, (B) Fatigue; (C) CKD, and (D) LVEF <40% in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

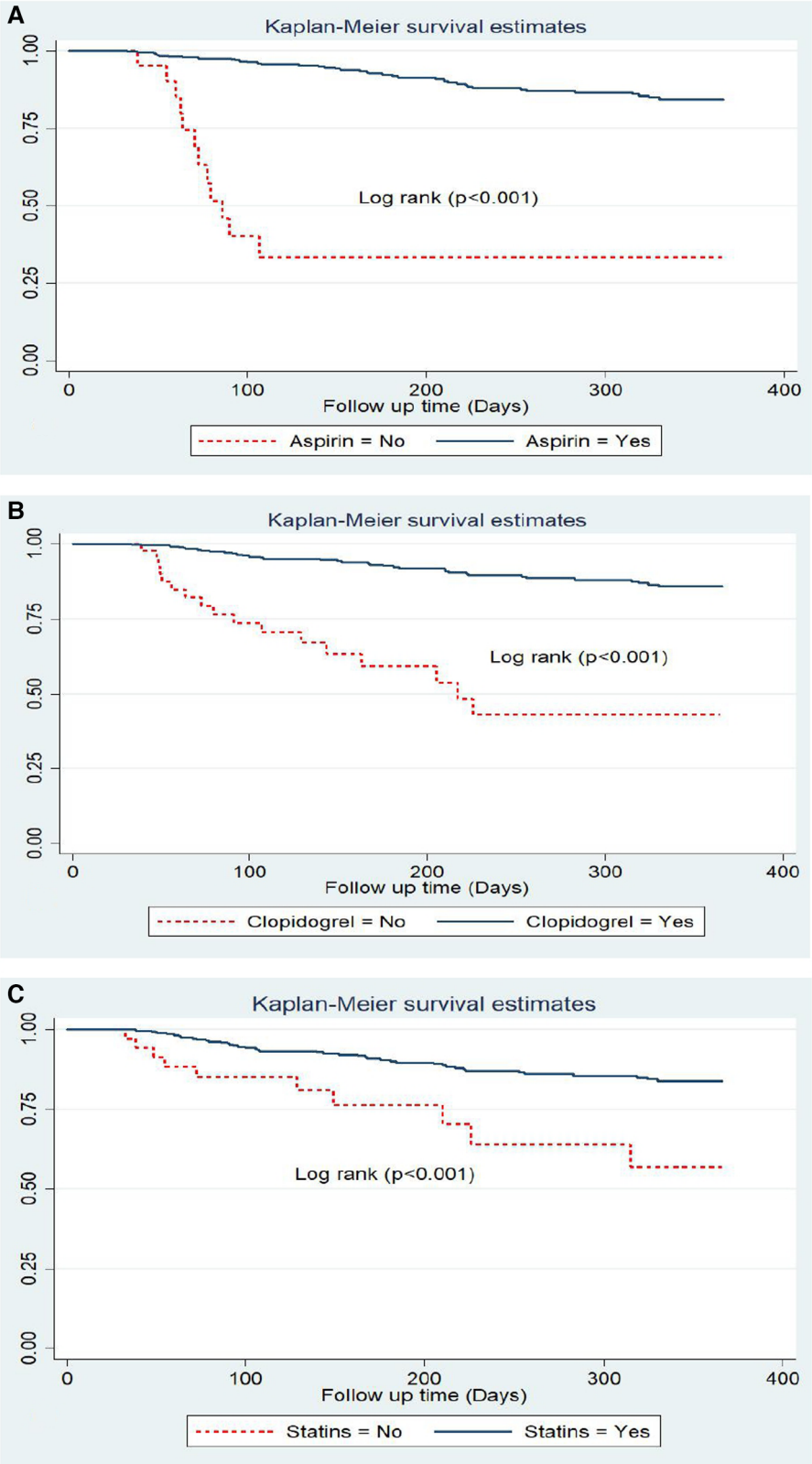


FIGURE 5
Kaplan Meier survival estimate by in hospital treatments; (A) aspirin, (B) clopidogrel and (C) statins among follow-up patients in West Amhara comprehensive specialized hospitals, amhara, Ethiopia, 2022.

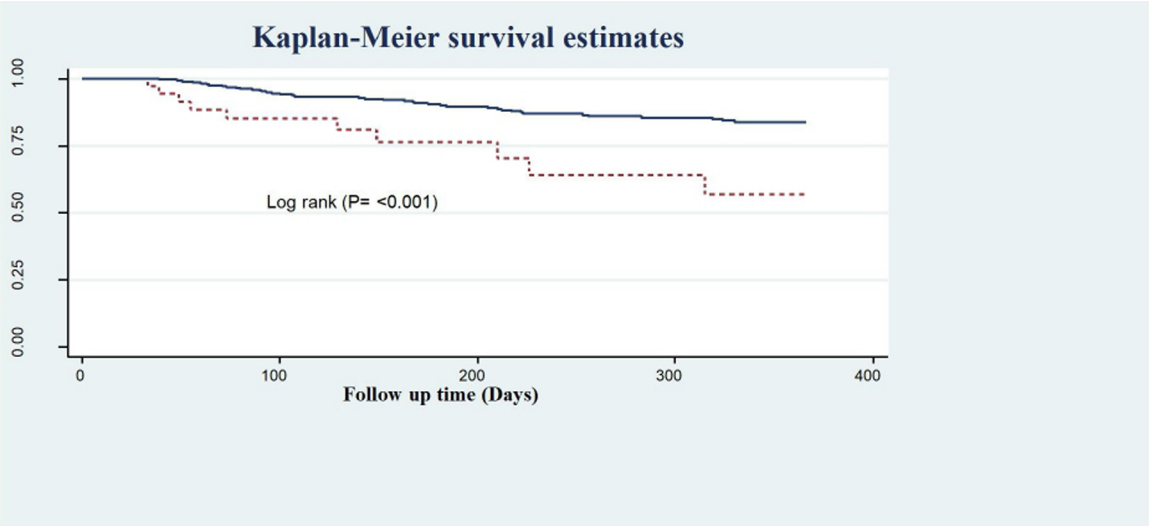


FIGURE 6
Kaplan–Meier survival estimate of LVEF of follow-up patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

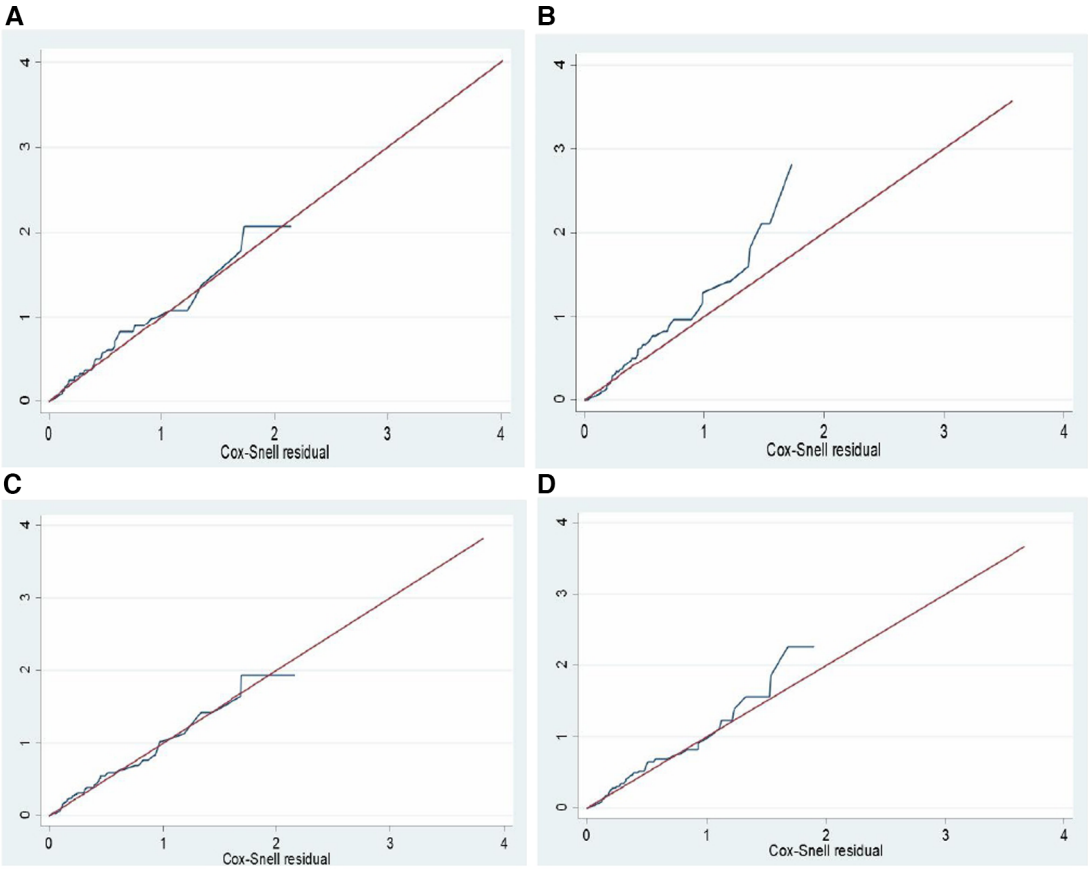


FIGURE 7
Nelson Aalen cumulative hazard function against Cox Snell residual multiple regression by; (A) cox regression, (B): exponential, (C): weibull, and (D): gompertz regression models for a survival study on ACS patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

TABLE 6 Survival model selection with model fitness tests for a survival study on ACS patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

| Model fitness tests | Survival proportional hazard models | | | |
|---|---|---|---|---|
| | Cox | Exponential | Weibull | Gompertz |
| Log likely hood ratio | −222.83993 | −127.04174 | −116.91283 | −123.2621 |
| AIC | 487.6799 | 298.0835 | 279.8257 | 292.5242 |
| BIC | 572.9704 | 387.4355 | 373.2392 | 385.9377 |

## Predictors of recurrent acute coronary syndrome

Based on bivariable Weibull regression analysis, 19 variables were significant at $p$-value ≤ 0.25. Age, having symptoms of SOB, diaphoresis, syncope, and fatigue, history of comorbidities [stroke, DM, hypertension (HTN), CKD, HIV], altered level of LVEF, LV dysfunction, in-hospital treatments (aspirin, clopidogrel, statins, anticoagulant), and discharge medications (aspirin, clopidogrel, statins) were found to be significant predictors of recurrent ACS (**Table 7**). However, only eight variables were found to be predictors of recurrent ACS in a multivariable Weibull regression analysis, including syncope, fatigue, history of CKD, altered level of LVEF, in-hospital treatments (aspirin, statins, and anticoagulants), and discharge treatment (statins).

In this study, we found that typical clinical symptoms of ACS complaints during primary admission highly predict the recurrence rate of ACS. These symptoms were syncope and fatigue. Patients who had syncope complaints during primary admission were shown to have a 3.5-fold increased likelihood of experiencing recurrent ACS (AHR: 3.54, 95% CI: 1.31–9.55). ACS patients who presented with symptoms of fatigue also had more than five times higher hazard of developing recurrent ACS than those who had not (AHR: 5.23, 95% CI: 2.27–12.07).

Patients who had a history or comorbidity of chronic kidney disease had more than eight times the higher hazard of recurrent ACS compared with those who had not (AHR: 8.22, 95% CI: 3.03–22.27). ACS patients who had a decreased level of left ventricular ejection fraction (<40%) were also at a higher risk of developing recurrent ACS at a hazard of 2.34 times (AHR: 2.34, 95% CI: 1.24–4.43) when compared with those with LVEF of ≥40%.

Moreover, anti-ischemic treatments during primary admission were crucial to prevent secondary events such as recurrent ACS. ACS patients who did not take aspirin exhibited a higher hazard of developing recurrent ACS, which was 9.22 times compared with those who took aspirin (AHR: 9.22, 95% CI: 3.58–23.90).

Statins also had a significant difference as evidenced by a hazard ratio of 2.74 (AHR: 2.74, 95% CI: 1.24–6.04), which suggests a higher risk of recurrent ACS among those who were not prescribed with statins compared with those who had it. Another very important treatment at discharge (medication taken to home) was anticoagulants, which were found to have a strong association with a 4.56-fold increase (AHR: 4.56, 95% CI: 2.14–9.72) in the risk of developing recurrent ACS among those who did not take anticoagulants compared with those who did.

# Discussion

In this study, the rate of ACS recurrence 1 year after discharge was 12.35%. This finding is consistent with the previous reports conducted in developed nations such as the United States (9.6%) (30), Thailand (11.4%) (31), Australia (12.2%) (16), and Italy (10.1%) (32). One potential explanation could be due to the age similarity of the study population, which consisted of adults older than18 years. Another possible explanation could be the inclusion of all patients with ACS (STEMI and NSTEMI). In addition, the duration of follow-up in these studies was 1 year or longer.

However, the recurrent rate observed in this study is higher compared with a prior study conducted in Saudi Arabia (2.1%) (10), China (2.5%) (9), Japan (4.5%) (26), United States [(1.34%) (33), 4.7% (34), 8.47% (35)], Netherlands (8.0%) (12), and Brazil (9.14%) (13). The increased incidence of recurrent ACS may be attributed to the difference in the demographic characteristics of the study population. The study conducted in Saudi Arabia only included the recurrent ACS events that occurred during the in-hospital stay. Consequently, it may be associated with in-hospital intensive management that could reduce the recurrence rate. On the other hand, their duration of follow-up or time at risk was short, which may have decreased the incidence rate of recurrent ACS (10), whereas our study was conducted with a maximum follow-up period of 1 year, which may be the reason for the increased rate of ACS recurrence. Comparing our level of economic development level to that of these countries may also be a factor; in particular, it impedes our access to potent anti-ischemic and lipid-lowering drugs.

However, our results were lower than the 30% Re-ACS found in the French study (25). This previous study was conducted on an adult population aged 35–74 years, excluding individuals between the ages of 18 and 35 years. According to different literatures, this age group was at a lower risk of recurrent ACS. Therefore, neglecting this age group may result in a larger difference in the rate of recurrent ACS. Another reason could be that the French study included all events that occurred after discharge and during in-hospital treatments. Our study adopted a universal definition of recurrent myocardial infarction as recurrent ACS after 28 days of discharge, and incidents that occurred prior to this period were excluded. This could be the reason for the greater incidence rate in that study (25).

Second, we identified predictors of recurrent ACS, which is essential for a comprehensive understanding of patients with recurrent ACS and for taking secondary preventative measures. ACS recurrence was predicted by typical symptoms, such as altered levels of LVEF, CKD, and in-hospital and discharge medications, according to previous studies. Our multivariable Weibull regression analysis confirms these predictors.

Syncope and fatigue were found to be significant predictors of the recurrence rate of ACS in our study. These findings were supported by a French study in which typical symptoms of ACS at presentation were identified as predictors of Re-ACS (25).

TABLE 7 Bivariable and multivariable Weibull regression analysis of predictors of recurrence among adult acute coronary syndrome patients in West Amhara comprehensive specialized hospitals, Amhara, Ethiopia, 2022.

| Variables | Category | Outcome | | CHR (95% CI) | *p*-value | AHR (95% CI) | *p*-value |
|---|---|---|---|---|---|---|---|
| | | Censored, *n* (%) | Recurrent, *n* (%) | | | | |
| Age (year) | 18–44 | 53 (91.4) | 5 (8.6) | 1 | | 1 | |
| | 45–64 | 191 (93.6) | 13 (6.4) | 0.63 (0.22–1.76) | 0.376 | 0.33 (0.11–1.01) | 0.053 |
| | 65–74 | 74 (86.0) | 12 (14) | 1.41 (0.50–4.01) | 0.516 | 0.90 (0.28–2.84) | 0.852 |
| | ≥75 | 58 (71.6) | 23 (28.4) | 2.92 (1.11–7.68) | 0.030 | 1.42 (0.49–4.10) | 0.518 |
| Shortness of breathing | No | 178 (91.3) | 17 (8.7) | 1 | | 1 | |
| | Yes | 198 (84.6) | 34 (15.4) | 2.0 (1.12–3.57) | 0.019 | 1.31 (0.67–2.60) | 0.433 |
| Diaphoresis | No | 280 (86.7) | 33 (10.5) | 1 | | 1 | |
| | Yes | 96 (82.1) | 21 (17.9) | 1.91 (1.09–3.33) | 0.023 | 1.45 (0.72–2.920 | 0.301 |
| Syncope | No | 357 (88.6) | 46 (11.4) | 1 | | 1 | |
| | Yes | 19 (73.1) | 7 (16.9) | 2.40 (1.08–5.32) | 0.031 | 3.54 (1.31–9.55) | 0.013* |
| Fatigue | No | 346 (88.7) | 44 (11.3) | 1 | | 1 | |
| | Yes | 30 (76.9) | 9 (23.1) | 2.83 (1.38–5.81) | 0.005 | 5.23 (2.27–12.07) | <0.001** |
| History of stroke | No | 347 (89.9) | 39 (10.1) | 1 | | 1 | |
| | Yes | 29 (67.4) | 14 (32.6) | 3.96 (2.15–7.30) | 0.000 | 1.12 (0.48–2.56) | 0.815 |
| History of DM | No | 304 (89.4) | 36 (10.6) | 1 | | 1 | |
| | Yes | 72 (80.9) | 17 (19.1) | 1.91 (1.07–3.40) | 0.028 | 1.43 (0.72–2.81) | 0.306 |
| History of HTN | No | 228 (89.8) | 26 (10.1) | 1 | | 1 | |
| | Yes | 148 (84.6) | 27 (15.4) | 1.54 (0.897–2.63) | 0.118 | 1.84 (0.93–3.65) | 0.081 |
| History of CKD | No | 364 (89.7) | 42 (10.3) | 1 | | 1 | |
| | Yes | 12 (52.2) | 11 (47.8) | 5.92 (3.04–11.51) | 0.000 | 8.22 (3.03–22.27) | <0.001** |
| History of HIV | No | 357 (89.5) | 42 (10.5) | 1 | | 1 | |
| | Yes | 19 (63.3) | 11 (36.7) | 3.83 (1.97–7.44) | 0.000 | 0.66 (0.24–1.80) | 0.413 |
| LVEF (%) | ≥40 | 286 (90.8) | 29 (9.2) | 1 | | 1 | |
| | <40 | 90 (78.9) | 24 (21.1) | 2.58 (1.5–4.43) | 0.001 | 2.34 (1.24–4.43) | 0.009* |
| LV dysfunction | No | 128 (94.8) | 7 (5.2) | 1 | | 1 | |
| | Yes | 248 (84.4) | 46 (15.6) | 3.09 (1.4–6.84) | 0.005 | 1.88 (0.69–5.11) | 0.215 |
| Aspirin | Yes | 367 (90.0) | 41 (10.0) | 1 | | 1 | |
| | No | 9 (42.9) | 12 (57.1) | 12.9 (6.68–24.99) | 0.000 | 9.22 (3.56–23.90) | <0.001** |
| Clopidogrel | Yes | 351 (90.7) | 43 (9.3) | 1 | | 1 | |
| | No | 25 (76.2) | 17 (23.8) | 6.95 (3.88–12.46) | 0.000 | 4.11 (1.75–9.63) | 0.001* |
| Statins | Yes | 350 (89.1) | 43 (10.9) | 1 | | 1 | |
| | No | 26 (72.2) | 10 (27.8) | 3.29 (1.65–6.55) | 0.001 | 2.74 (1.24–6.04) | 0.012* |
| Anticoagulant | Yes | 316 (89.5) | 16 (11.1) | 1 | | 1 | |
| | No | 60 (78.9) | 16 (21.1) | 2.29 (1.27–4.12) | 0.006 | 1.66 (0.85–3.24) | 0.136 |
| Aspirin at discharge | Yes | 359 (89.8) | 41 (10.3) | 1 | | 1 | |
| | No | 17 (58.6) | 12 (41.4) | 5.74 (3.0–10.94) | 0.000 | 1.79 (0.72–4.43) | 0.207 |
| Clopidogrel at discharge | Yes | 343 (90.7) | 35 (9.3) | 1 | | 1 | |
| | No | 33 (64.7) | 18 (35.3) | 4.37 (2.48–7.72) | 0.000 | 1.15 (0.48–2.73) | 0.753 |
| Statins at discharge | Yes | 354 (90.3) | 38 (9.7) | 1 | | 1 | |
| | No | 22 (59.5) | 15 (40.5) | 4.98 (2.74–9.06) | 0.000 | 4.56 (2.14–9.72) | <0.001** |

CHR, crude hazard ratio.
*Statistically significant at *p*-value < 0.05.
**Highly statistically significant at *p*-value < 0.001.

As indicated by previous studies, the altered level of LVEF was an independent predictor of recurrent ACS. Our study also revealed that ACS patients with LVEF levels below 40% at their initial admission had a risk of recurrent ACS that was more than twice as high. This finding is consistent with a study conducted in Australia, which demonstrated that individuals with reduced LVEF had an increased risk of having recurrent ACS. On the contrary, studies conducted in China and Japan has indicated that a reduced level of LVEF was not significantly associated with recurrent ACS (9, 26).

Another predictor that was identified was the comorbidity of CKD, which was found to substantially predict the recurrence of ACS. A report from previous studies showed that patients who had a history of comorbidities were at higher risk of recurrent ACS (9, 10, 25, 31, 36). This finding is also consistent with previously published literature on the effect of CKD on patients with acute myocardial conditions. The reduction in GFR increases the risk of serious cardiovascular complications by approximately 20% (compared with subjects with normal renal function) (37). Our findings contribute to the existing knowledge by further supporting the association between chronic kidney disease and recurrent cardiovascular events.

This study found that evidence-based dual antiplatelet therapies (DAPT) were the major predictors of recurrent ACS. As reported in

present and previous studies, in-hospital treatment with aspirin has demonstrated to reduce the risk of recurrent ACS. Individuals who did not take aspirin were at higher risk of developing Re-ACS. This was supported by previous studies in the United States and Saudi Arabia (10, 30). In contrast, a Chinese study showed that aspirin was not significantly associated with recurrent ACS (9). The pathophysiology of ACS was explained as the formation of a thrombus by platelet activation and aggregation. Guidelines recommended aspirin for such cases, and it works mainly by inhibiting the thromboxane A2 pathway and has additive anti-inflammatory effects. Non-enteric-coated, oral aspirin (162–325 mg) should be administered to all patients with ACS without contraindications as soon as possible after the presentation, and a maintenance dose of 81 mg (75–150 mg) aspirin per day should be continued indefinitely (38, 39).

The other guideline-recommended component of DAPT is clopidogrel, which is a P2Y12 receptor inhibitor broadly prescribed in our setup. Previous literature found that this medication was significantly associated with reducing the recurrence rate of ACS (9). Our study also agreed with the previous studies and found that patients who did not take clopidogrel were at higher risk of recurrent ACS. Individuals presenting with an ACS are recommended to be treated with a P2Y12 inhibitor in addition to aspirin, which is indicated as DAPT. Evidence shows that clopidogrel with or without aspirin is directed at limiting platelet adhesion and aggregation, which prevents additional thrombus formation. ACS patients are typically prescribed aspirin with clopidogrel (300 mg loading dose and 75 mg/day maintenance dose) for 3–12 months to improve their health (40).

Another predictor found in our study was statins. Statins are the main component of ACS treatment, which plays a crucial role in reducing cholesterol levels. Our study revealed that patients who were not prescribed statins during their hospital stay were at higher risk of Re-ACS compared with those who took statins. Other reports remarkably supported that statins were highly associated with reducing Re-ACS (9, 10, 30). However, a study conducted in Japan did not find a significant association between statins and the recurrent rate of ACS (26). In this study, we also found that statins prescription at discharge was highly associated with the recurrent rate of ACS.

The evidence showed that the long-term use of statins was beneficial for patients with ACS. Using these agents in combination with other anti-ischemic agents has a significant beneficial effect and should be administered concurrently to ACS patients. Statin therapy should be initiated early and continued long-term in all ACS patients irrespective of baseline LDL levels. In addition to lowering LDL levels, the potential benefits of statin therapy include plaque stabilization, improvement of endothelial function, reduced thrombogenicity, and reduced inflammation (41).

## Limitations and strengths of the study

The present study constitutes a secondary data review, wherein our focus was solely on only documented variables such as socio-demographics, typical symptoms of ACS, vital signs, diagnostic tests, comorbidities, and prescription of guideline-based medications. However, the exclusion of socio-demographic, behavioral, and nutritional status as key predictors of recurrence in earlier research was due to their insufficient data. These factors might be effectively examined through a prospective study. Furthermore, there is a need to evaluate whether the use of thrombolysis or revascularization, as well as coronary angiography procedures, have influenced the subsequent rates of recurrent infarction.

Despite the above potential limitations, the strength of this study is that it was conducted for an optimal period. This may increase the period of observation, which helps for better estimation of the post-discharge ACS recurrence rate. This study may also be used as a baseline for researchers in the context of resource-limited countries such as Ethiopia, since this is the first research specifically with this title as per the researcher's level of search.

## Conclusion

This study found a higher rate of ACS recurrence compared with almost all studies reviewed. The main factors for this increased rate of Re-ACS were having a history of typical symptoms of ACS (syncope and fatigue), LVEF of <40%, history of comorbidity (CKD), and not taking in-hospital and discharge medications such as anti-ischemic and lipid-lowering treatments. Long-term intensive statin therapy may also be a reasonable therapeutic approach for those patients, and strengthening antiplatelet and lipid-lowering treatments are crucial.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by the institution review committee of the School of Nursing on behalf of the institutional review board of the University of Gondar. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this study was conducted with secondary data/patient chart review.

## Author contributions

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and

interpretation of data; took part in drafting the research and revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. Specifically, the corresponding author contributed to the conception and design, acquisition of data, data analysis, interpretation of data, and discussion. TA and BL contributed to revising and editing the manuscript, and GA and AZ had a role in the conception and analysis of the result.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# The association between parity and hypertension: a cross-sectional, community-based study

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**Background:** The available data on the association between parity and hypertension are inconclusive. This study was conducted to investigate the prevalence of hypertension and its association with parity among adult Sudanese women.

**Methods:** A multi-stage sampling survey was conducted in four villages in the River Nile State in Sudan between July and September 2022. The World Health Organization's three-level stepwise questionnaire was used to gather the participants' sociodemographic characteristics (age, sex, marital status, parity, educational level, occupation, obstetric history, family history of hypertension, weight and height). Regression analyses were performed.

**Results:** A total of 408 women were recruited. The median [measured in terms of interquartile range (IQR)] age was 45.0 years (33.0–55.7 years). A linear regression analysis revealed a significant association between parity and diastolic blood pressure (coefficient, 0.60; $P = 0.011$). The prevalence of hypertension (55.9%) increased with parity and ranged from 43.7% to 74.9%. In the multivariate analyses, increasing age (adjusted odds ratio [AOR], 1.03; 95% confidence interval [CI], 1.02–1.05), increasing parity (AOR, 1.09; 95% CI, 1.01–1.19), family history of hypertension (AOR, 1.79; 95% CI, 1.15–2.77), and increasing body mass index (AOR, 1.09; 95% CI, 1.05–1.13) were associated with hypertension. In women of ages ≥ 50 years, increasing parity was significantly associated with hypertension (AOR, 1.15; 95% CI, 1.2–1.29). Para > 5 (AOR, 2.73; 95% CI, 1.11–6.73) was associated with hypertension.

**Conclusion:** A high prevalence of hypertension was found among Sudanese women, and that parity at 5 or more is linked to hypertension.

KEYWORDS

parity, age, hypertension, associated factor, Sudan, body mass index

## 1. Introduction

Hypertension is one of the major non-communicable diseases (1). Around one-third (31.1%) of the global adult population (1.39 billion people) have hypertension (1, 2). Low- and middle-income countries (31.5%) and African countries (46.0%) (3) have higher prevalence rates of hypertension than high-income countries (28.5%) (1, 2). Sociodemographic, environmental, behavioural factors, high sodium intake, low potassium intake, obesity, alcohol consumption, smoking, lack of physical activity, and nutrition are the identified risk factors for developing hypertension (1, 2). Hypertension is the leading preventable risk factor of cardiovascular diseases and all-cause mortality across the globe (4). Several factors such as lack of awareness of health status, delayed diagnosis, poorly controlled hypertension, and a weak health system expose patients with hypertension in

Africa to the highest risk of stroke and heart and renal diseases (3). Ethnicity and race can influence the management of hypertension and its related complications (5). In the global initiatives of the International Society of Hypertension for the screening and management of hypertension, early diagnosis and treatment of hypertension are recommended (6, 7).

The effect of parity on blood pressure levels or hypertension has been reported in several studies (8–13). This may be explained by increased blood volume, increased heart rate, altered myocardial contractility, and reduced afterload and preload, which lead to expanded cardiac output during pregnancy (14). While some studies have shown that parity is associated with an increased risk of developing hypertension (11, 12, 15), others have reported no such association (16). Most of these studies were conducted outside of sub-Saharan African countries. A higher prevalence of parity among women in sub-Saharan Africa was recently reported (17). In studies on the global epidemiology of hypertension, Sudan was identified as one of the countries with a hypertension prevalence rate >34% (1, 2). This is consistent with the findings of some recently published studies on the prevalence of hypertension among the general Sudanese population (35.2%–41.0%) (18, 19). A higher prevalence of hypertension among females was reported in Eastern Sudan (41.0%) (19). Sudanese women have high parity, with most of them having five deliveries (grand multiparity) at a younger age, before 35 years old (20). Given the importance of the two clinical entities, their potential coexistence, and the meagre published clinical data on this issue in Sudan and in the region, the present study aimed to investigate the prevalence of hypertension among Sudanese women and the influence of parity, especially high parity, and other factors on the development of hypertension among Sudanese women.

# 2. Materials and methods

## 2.1. Study design

This study was conducted in accordance with the principles stipulated in the Declaration of Helsinki. Ethical approval was obtained from the health authority of Almatamah, Sudan (reference No. 03/2021). Signed written informed consent forms were collected from all participants. A multi-stage sampling study was conducted in the River Nile State, northern Sudan, between July and September 2022. River Nile State is one of the 18 states of Sudan and has a total population of 1,120,441 (21). Almatamah is one of the seven localities (the smallest administrative unit in Sudan) in River Nile State and was initially selected by simple random sampling. Adult women in the households of four villages (Hajer Alteer, Athawra Kabota, Alkoumer, and Wadi Alshohda) were selected randomly from the Almatamah locality on the basis of the population size of all sectors. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) standard checklists were followed (22). Only Sudanese women (>18 years of age) from the selected households who agreed to participate in the study were selected. Two trained medical officers interviewed the participants during the study period.

## 2.2. Participants

After signing an informed consent form, the participants completed a questionnaire that collected their sociodemographic information, clinical and physical measurements, blood pressures, and weights and heights. Pregnant women; those with known causes of secondary hypertension, renal diseases, medication use (steroid therapy), substance abuse, mental illness, disabilities, or congenital deformities; and those who refused to participate in the study were excluded. The World Health Organization's (WHO) three-level stepwise approach questionnaire was used to collect data (23) on the participants' sociodemographic characteristics, including age; marital status, categorised as married, widow, or divorced; educational level (≤secondary level or >secondary level); and past medical history of hypertension and drug history (steroid therapy). Moreover, a detailed history was obtained regarding the women's menopausal status, history of miscarriage, and live birth/parity. According to the Sudanese tradition, smoking and alcohol consumption are not female habits; hence, we did not include these in the questionnaire to avoid a loss of cooperation among the participants.

An OMRON 3 (with an appropriate cuff size) automated blood measuring device was used to obtain two blood pressure readings after the participant had rested for at least 10 min. The measurement was performed with the participant's arm placed at the level of the heart. The mean of two blood pressure readings (at an interval of 1–2 min) was computed and registered. When the difference between the two readings was significant, that is, >5 mmHg, new measurements were taken until a stable reading was obtained. The method adopted for measuring blood pressure was based on recent recommendations and requirements (24). Women were considered hypertensive on the basis of a reading of ≥140 mmHg for systolic blood pressure and ≥90 mmHg for diastolic blood pressure or both of them. Both criteria were recorded in repeated measurements or reported as having previous hypertension and receiving anti-hypertensive medications (1). The body mass index (BMI) was calculated from the patient's weight and height and grouped according to the WHO's classification for females as follows: underweight (<18.5 kg/m$^2$), normal weight (18.5–24.9 kg/m$^2$), overweight (25.0–29.9 kg/m$^2$), or obese (≥30.0 kg/m$^2$) (25).

Parity is defined as the number of times a woman had given birth to a foetus with a gestational age of ≥24 weeks, irrespective of whether the baby was born alive or stillborn (26). Nulliparity is considered as para 0, or no previous delivery, and multipara is defined as a woman who has given birth 2 or more times (26).

### 2.2.1. Sample size

A sample size of 408 women was calculated using the Open Epi Menu (27), with an assumption of a type I error of 5% and an adequate power of 80% ($\beta = 0.2$). The estimated sample size ($n = 408$) was calculated on the basis of the assumed

hypertension prevalence rate (41.0%) among women. This assumption was based on our previous observations in eastern Sudan (19). Thus, the ratio of women with hypertension to women without hypertension was expected to be 2:3. We assumed that 27.0% of women with hypertension and 15.0% of women without hypertension would have a para ≥5. This assumption was based on our recent work on reproductive health in Sudan (28).

## 2.3. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) for Windows (IBM SPSS v.25) was used to analyse the data. The chi-square test was used to compare the proportions between the women with and those without hypertension. Continuous data were assessed for normality using the Shapiro-Wilk test. A *t*-test and the Mann-Whitney test were used to compare the normally distributed and non-normally distributed data, respectively, between the two groups of women (hypertensive and non-hypertensive). Spearman correlations were performed between continuous variables (age, parity and BMI). Multiple linear regression analysis was conducted for parity with systolic and diastolic blood pressures to assess the risk factors. Logistic regression analyses were performed by entering the dependent (hypertension) and independent variables (age, BMI, educational level, occupation, past medical history of hypertension, and live birth/parity number). Variance inflation factor (<4) and the presence of high correlations ($r = 0.9$) were used to assess the presence of multi-collinearity and there was no multi-collinearity between the independent variables including age, parity and BMI. The independent variables with a univariate $P$ value < 0.20 were entered into the model. The adjusted odds ratio (AORs) and 95% confidence intervals (Cis) were calculated, with $P$ values < 0.05 considered statistically significant. Backward likelihood ratio adjustments were then performed in the different models.

# 3. Results

Four hundred and eight women were enrolled in this study. Their median [interquartile range (IQR)] age was 45.0 years (33.0–55.7 years). Their parity ranged from 0 to 10, with a median of 2. A total of 158 women (38.7%) were nulliparous, whereas 95 (23.3%), 73 (17.9%), and 82 (20.1%) had para 1 to 3, 4 or 5, and more than 5, respectively. Of the 408 women, 276 (67.6%) had an educational level ≥ secondary education, and 223 (54.7%) were housewives. Age increased with parity, and women who had para >5 had the highest median (IQR) age [53.0 years (42.0–60.0), years]. Of 408 enrolled women, 131(32.1%), 39 (9.6%), 123(30.1%) and 115 (28.2%) were normal weight, underweight, overweight and obese, respectively. The women who had para 4 or 5 had the highest BMI [27.6 kg/m$^2$ (23.7–32.9 kg/m$^2$)]. There was a borderline correlation between age ($r = 0.294$), parity ($r = 0.139$) and BMI. No significant difference in educational level was found between the women in the different parity groups. A significantly higher number of women with para >5 were housewives (see **Table 1**). While no significant difference in median (IQR) systolic blood pressure was found, diastolic blood pressure was significantly higher in the women with para 4 or 5 [85.0 mmHg (80.0–95.0 mmHg); see **Table 1**].

In the multiple linear regression analysis, parity was not associated with systolic blood pressure, however there was a significant association between parity and diastolic blood pressure (coefficient, 0.60; $P = 0.011$; see **Table 2**).

A total of 228 women (55.9%) had hypertension, 71 women (17.4%) had known hypertension, and 157 women (38.5%) had newly discovered hypertension. The prevalence of hypertension increased with parity and ranged from 43.7% to 74.9%. Women who had para >5 had the highest prevalence of hypertension (74.9%; see **Table 1** and **Figure 1**). In the univariate analysis, increasing age, increasing parity, family history of hypertension, and increasing BMI were associated with hypertension. Educational level and occupation were not associated with hypertension (see **Table 3**). When these variables were adjusted in the multivariate analysis, increasing age (AOR, 1.03; 95% CI, 1.02–1.05), increasing parity (AOR, 1.09; 95% CI, 1.01–1.19), family history of hypertension (AOR, 1.79; 95% CI, 1.15–2.77), and increasing BMI (AOR, 1.09; 95% CI, 1.05–1.13) were associated with hypertension. Next, we removed parity as a continuous variable and entered the parity groups into the model. In this case, compared with the nulliparity (reference), para 1 to 3 (AOR, 1.35; 95% CI, 0.77–2.38), para 4 or 5 (AOR, 1.37; 95% CI, 0.73–2.55) was not associated with hypertension. Women with para >5 (AOR, 2.40; 95% CI, 1.26–4.58) were at higher risk of hypertension (see **Table 4**).

We then divided the women into two age groups (≥50 and <50 years). In the women aged ≥50 years, increasing parity was associated with hypertension (AOR, 1.15; 95% CI, 1.2–1.29). Compared with the nulliparous women (reference), para 1 to 3 (AOR, 1.31; 95% CI, 0.48–3.55) and para 4 or 5 (AOR, 2.33; 95% CI, 0.84–6.45) were not associated with hypertension. Para >5 (AOR, 2.73; 95% CI, 1.11–6.73) was associated with hypertension (see **Table 4**). In the women aged <50 years, parity and parity groups were not associated with hypertension (see **Table 4**).

# 4. Discussion

The main findings of this study were a higher hypertension prevalence rate, and after adjusting for age and BMI, parity and increasing parity became significant risk factors for developing hypertension among Sudanese women. The hypertension prevalence rate among the Sudanese women (55.9%) in our study was comparatively higher than that obtained in eastern Sudan (40.8%) (19) and in some African countries such as Ethiopia (19.1%) (29) and Ghana (16%) (11). The differences in hypertension prevalence rate could be explained by the differences in sodium intake, potassium intake, alcohol consumption, obesity, nutrition, and physical activity across the regions (1, 2). The main findings of this study indicate that after adjusting for age and BMI, increasing parity was associated with

TABLE 1 Comparison of the factors between the parity groups in women in Sudan, 2022.

| Characteristics | | Total (number = 408) | Nulliparity (number = 158) | Para 1–3 (number = 95) | Para 4 and 5 (number = 73) | Para > 5 (number = 82) | *P* |
|---|---|---|---|---|---|---|---|
| Age | | 45.0 (33.0–55.7) | 41.0 (26.0–55.0) | 40.0 (32.0–50.0) | 50.0 (35.0–57.0) | 53.0 (42.0–60.0) | <0.001 |
| Body mass index, kg/m$^2$ | | 26.4 (22.5–30.5) | 24.5 (19.9–28.6) | 27.1 (23.5–30.8) | 27.6 (23.7–32.9) | 27.0 (23.7–31.3) | <0.001 |
| Systolic blood pressure, mmHg | | 128.6 (119.0–140.0) | 126.5 (119.7–135.0) | 124.0 (115.0–140.0) | 128.6 (120.0–140.0) | 130.0 (118.0–146.2) | 0.160 |
| Diastolic blood pressure, mmHg | | 85.0 (80.0–92.7) | 82.5 (75.8–90.0) | 85.0 (80–90.0) | 85.0 (80.0–95.0) | 81.7 (90–103.1) | <0.001 |
| Education level | ≥Secondary | 276 (67.6) | 106 (67.1) | 60 (63.2) | 51 (69.9) | 59 (72.0) | 0.625 |
| | <Secondary | 132 (32.4) | 52 (32.9) | 35 (36.8) | 22 (30.1) | 23 (28.0) | |
| Occupation | Housewives | 223 (54.7) | 70 (44.3) | 57 (60.0) | 44 (60.3) | 52 (63.4) | 0.010 |
| | Employed | 185 (45.7) | 88 (55.7) | 38 (40.0) | 29 (39.7) | 30 (36.6) | |
| Hypertension | No | 180 (44.1) | 89 (56.3) | 42 (44.2) | 28 (38.4) | 21 (25.6) | |
| | Yes | 228 (55.9) | 69(43.7) | 53(55.8) | 45(61.6) | 61(74.9) | <0.001 |

hypertension (in terms of diastolic blood pressure) and women aged ≥50 years. Parity was not associated with systolic blood pressure or hypertension in the women aged <50 years.

The present study indicates that compared with nulliparity (reference), para 1 to 3 and para 4 or 5 are not at higher risk of hypertension. Para > 5 are 2.40 times more likely to have hypertension. This is in concordance with the results obtained in Mali, in which women with para ≥5 had significantly higher blood pressures (in terms of increased systolic blood pressure) than those with para 1 to 3 (30). In Ghana, women (ages 45–49 years) with para 2 or 3 had a higher likelihood of being hypertensive than younger and nulliparous women (11). A similar finding was observed in our study among Chinese post-menopausal women with para ≥5 had higher blood pressures than women with para 0 or 1; however, parity was not associated with hypertension in pre-menopausal women (15). Similarly, Turkish women with para ≥4 were at a higher risk of having hypertension than those who had para less than 4 (31). Likewise, in rural Bangladesh, high parity was positively associated with a risk of hypertension among women with obesity who had ≥4 pregnancies compared with those aged 15–75 years who only had one pregnancy (32). A previous study showed that in Iran, compared with para 2, para ≥3 was significantly associated with hypertension; however, these findings were mainly among younger women, that is, <50 years of age (12).

By comparison, Khalid (2006) reported no association between parity and hypertension among 441 women aged between 15 and 60 years in Abha, Saudi Arabia (16). A Swiss study recruited 2,837 women aged 30–73 years and demonstrated that parity had a significant adverse effect on the development of hypertension in women at 60 years; however, parity had a protective effect against hypertension in women aged <40 years (9). Giubertoni et al. reported that in Italy, while parity is associated with early hypertension during the transition to menopause, parity is not associated with hypertension in the post-menopausal period (13). In Bangladesh, women with para 1 as the reference, diastolic blood pressure was higher in nulliparous women and in para ≥3. The association between increased diastolic blood pressure and nulliparity was mainly observed in women aged >45 years, and the same association was observed among women in Bangladesh (8). Likewise, a global epidemiological study in sub-Saharan Africa demonstrated higher diastolic blood pressures (6). Our study showed that a family history of hypertension was not associated with hypertension among women with increased parity, which may reflect the heterogeneity of essential hypertension.

The results of these studies must be compared with caution. The discrepancies and modelling differences in the methods used in these studies were obvious: some studies compared women with high parity (≥5 children) with those with low-to-moderate parity, and some studies did not include nulliparous women in their analyses. Differences in lifestyle, cultural factors, genetic influence, and hypertension prevalence rate might have contributed to the differences in the results of these studies and hypertension prevalence rates among different populations (33, 34).

TABLE 2 Multiple linear regression analysis of the adjusted factors associated with systolic and diastolic blood pressure among women in Sudan, 2022.

| | | Systolic blood pressure | | Diastolic blood pressure | |
|---|---|---|---|---|---|
| | | Coefficient (standard error) | *P* | Coefficient (standard error) | *P* |
| Age, years | | 0.34 (0.05) | <0.001 | 0.14 (0.04) | 0.001 |
| Parity | | 0.39 (0.32) | 0.222 | 0.60 (0.23) | 0.011 |
| Body mass index, kg/m$^2$ | | 0.133 (0.14) | 0.359 | 0.40 (0.10) | <0.001 |
| Family history of hypertension | No | Reference | | Reference | 0.001 |
| | Yes | 2.38 (1.78) | 0.182 | 2.01 (1.35–2.99) | |
| Para | Nulli | Reference | | Reference | |
| | 1–3 | 0.20 (2.36) | 0.932 | 0.75 (1.71) | 0.660 |
| | 4 and 5 | −0.97 (2.59) | 0.707 | 1.57 (1.87) | 0.402 |
| | >5 | 3.04 (2.53) | 0.229 | 6.61 (1.82) | <0.001 |

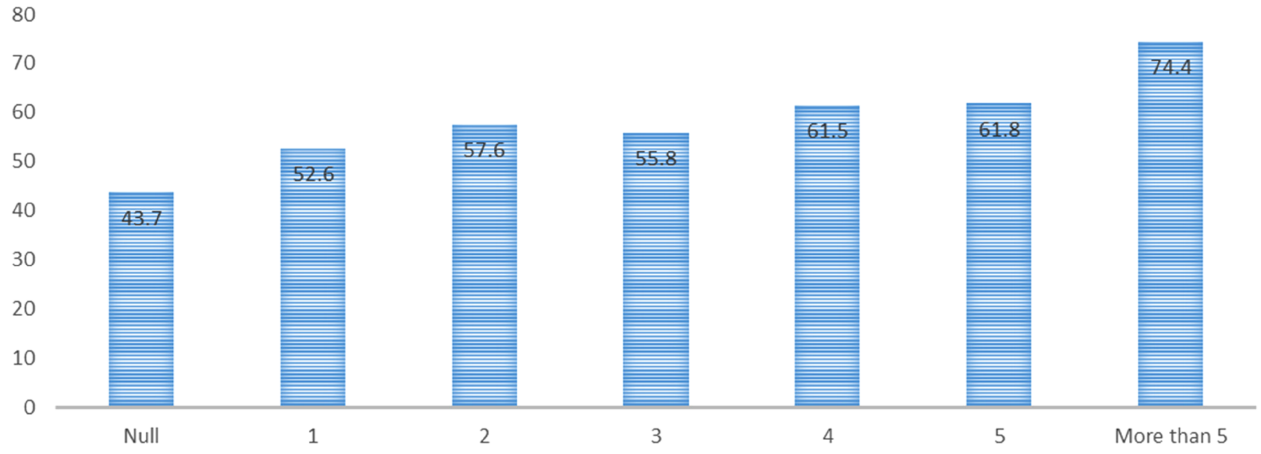


FIGURE 1
The prevalence of hypertension by parity among Sudanese women in 2022.

Parity exposes women to the risk of clinical placental syndrome (pregnancy loss, foetal growth restriction, and pre-eclampsia) as a result of altered uterine and intervillous blood flow, which is linked to inflammatory processes that lead to maternal vascular endothelial dysfunction and permanent vascular damage, thereby accelerating the development of atherosclerosis, hypertension, and cardiovascular diseases (35). Higher parity has been associated with increases in some inflammatory markers (fibrinogen, D-dimer, GlycA, high-sensitivity C-reactive protein, and interleukin-6 levels), which reflect increased risks of cardiovascular diseases and metabolic syndrome (36). In addition, the loss of the protective effect of oestrogen in postmenopausal women might lead to endothelial dysfunction and increased BMI, which are the main negative indicators of hypertension, particularly among women aged >50 years (37). The renin-angiotensin-aldosterone system in females is influenced significantly (38). Our study and several previous studies have documented significant associations between parity, BMI, and hypertension (4, 24, 28, 32). The prevalence 28.2% of obesity in the current study was slightly lower than the prevalence (33.5%) of obesity reported in eastern Sudan (19).

Several studies have reported a significant association between increasing parity and metabolic syndrome (obesity, diabetes mellitus, and dyslipidaemia), which is associated with oxidative stress and inflammation that induces endothelial dysfunction, vascular stiffening, atherosclerosis, and hypertension (39, 40). Furthermore, the physiologic cardiometabolic changes associated with pregnancy, such as insulin resistance, increased plasma glucose, weight gain, dyslipidaemia, and cardiovascular complications, increase the potential risk for developing hypertension (12, 41, 42). However, the previous studies have found positive correlations in women with a much lower number of children than what the current study is reporting. Perhaps, some other possible contributors to hypertension such as geographic location and high levels of

TABLE 3 Univariate analysis of the factors (unadjusted) associated with hypertension among women in Sudan, 2022.

| | | Women with hypertension (number = 228) | Women without hypertension (number = 180) | OR (95% CI) | *P* |
|---|---|---|---|---|---|
| | | Median (interquartile range) | | | |
| Age, years | | 50.0 (38.0-60.0) | 38.0 (28.0-50.0) | 1.04 (1.02-1.05) | <0.001 |
| Para | | 3 (0-6) | 1 (0-4) | 1.17 (1.09-1.26) | <0.001 |
| Body mass index, kg/m$^2$ | | 27.6 (24.0-31.3) | 24.3 (19.5-28.3) | 1.10 (1.06-1.14) | <0.001 |
| | | Frequency (proportion) | | | |
| Education level | ≥Secondary | 154 (67.5) | 122 (67.8) | Reference | 0.960 |
| | <Secondary | 74 (32.5) | 58 (32.2) | 1.01 (0.66-1.53) | |
| Occupation | Housewives | 132 (57.9) | 91 (50.6) | Reference | 0.140 |
| | Employed | 96 (42.1) | 89 (49.4) | 1.34 (0.90-1.99) | |
| Family history of hypertension | No | 100 (43.9) | 110 (61.1) | Reference | 0.001 |
| | Yes | 128 (56.1) | 70 (38.9) | 2.01 (1.35-2.99) | |
| Para | Null | 69 (30.3) | 89 (49.4) | Reference | |
| | 1-3 | 53 (23.2) | 42 (23.3) | 1.62 (0.97-2.71) | 0.063 |
| | 4 and 5 | 45 (19.7) | 28 (15.6) | 2.07 (1.17-3.65) | 0.012 |
| | More than 5 | 61 (26.8) | 21 (11.7) | 3.74 (2.08-6.74) | <0.001 |

TABLE 4 Multivariate analysis of the adjusted factors associated with hypertension among women in Sudan, 2022.

| | | All women (408) | | Women with age ≥ 50 years | | Women with age <50 years | |
|---|---|---|---|---|---|---|---|
| | | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Age, years | | 1.03 (1.02–1.05) | <0.001 | - | | - | |
| Parity | | 1.09 (1.01–1.19) | 0.025 | 1.15 (1.2 –1.29) | 0.018 | 1.07 (0.95–1.20) | 0.242 |
| Body mass index | | 1.09 (1.05–1.13) | <0.001 | 1.05 (0.99–1.11) | 0.091 | 1.13 (1.07–1.19) | <0.001 |
| Family history of hypertension | No | Reference | 0.009 | Reference | | Reference | 0.156 |
| | Yes | 1.79 (1.15–2.77) | | 2.73 (1.34–5.53) | 0.005 | 1.49 (0.85–2.59) | |
| Para | Nulli | Reference | | Reference | | Reference | |
| | 1–3 | 1.35 (0.77–2.38) | 0.287 | 1.31 (0.48–3.55) | 0.592 | 1.41 (0.72–2.77) | 0.313 |
| | 4 and 5 | 1.37 (0.73–2.55) | 0.321 | 2.33 (0. 84–6.45) | 0.103 | 1.02 (0.44–2.36) | 0950 |
| | >5 | 2.40 (1.26–4.58) | <0.001 | 2.73 (1.11–6.73) | 0.028 | 2.44 (0.99–5.99) | 0.052 |

stress among these women who raised 5 or more children and were homemakers.

## 5. Conclusion

The hypertension prevalence rate in the Sudanese women in this study was significantly high, and that parity at 5 or more is linked to hypertension.

## 6. Limitation

This study has certain limitations that should be considered. The study was a questionnaire-based survey conducted over a 3-month period. The participants' reproductive histories were self-reported, which might have increased the possibility of misclassification of parity and gravidity, particularly among the older women. Similarly, the self-reporting of menopausal status might have resulted in some misclassification. In addition, other risk factors such as history of gestational hypertension or preeclampsia, salt intake, physical exercise, oral contraceptive use, smoking, alcohol consumption, lipid profile, and blood sugar status were not assessed. Moreover, all the data obtained (apart from the blood pressure measurements) were declarative, so descriptive elements regarding the causes of secondary hypertension and other factors were lacking.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by Ethical approval was obtained from the health authority of Almatamah, Sudan (reference No. 03/2021). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

## Author contributions

IRM and OEO conceived the study; OEO and IA supervised the work, guided the analysis and critically reviewed the manuscript; IRM and IA prepared the analysis plan, performed the data analysis and wrote the first draft of the paper; IRM and OEO supervised data collection All authors reviewed and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Aortic root enlargement in patients undergoing mitral and aortic replacement: early outcomes in a sub-Saharan population

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**Introduction:** Aortic root enlargement (ARE) is often required to avoid patient–prosthesis mismatch (PPM) in young patients undergoing aortic surgery, including those undergoing combined mitral and aortic valve replacement (double valve replacement, DVR). Adding ARE to DVR may increase the operative risk by extending the surgical time. Herein, we review our experience with ARE in patients who underwent DVR.
**Materials and methods:** The medical records of 69 patients who underwent DVR at our institution between February 2008 and November 2021 were retrospectively reviewed. The patients were divided into two groups according to the ARE procedure (ARE-DVR: 25 patients; DVR: 44 patients). Descriptive and comparative analyses of demographic, clinical, and surgical data were performed.
**Results:** Among the 69 patients who underwent DVR, 35 were women (sex ratio, 0.97). The mean age at surgery was 26.7 ± 13.9 years (range: 7–62 years). Among the 47 patients aged ≤30 years, 40.4% (19/47) were aged between 10 and 20 years, and 6.3% (3/47) were aged <10 years. Patients in the ARE-DVR group were younger (23.3 ± 12.9 years vs. 28.5 ± 14.2 years, $p < 0.05$). The New York Heart Association Class ≥III dyspnea was the most common symptom (89.9%), with no differences between the two groups. Of all the patients, 84.1% had sinus rhythm. Rheumatic disease was the most common etiology in the entire cohort (91.3%). The mean aortic annulus diameter was 20.54 mm, with smaller sizes found in the ARE-DVR group (18.00 ± 1.47 mm vs. 22.50 ± 2.35 mm, $p < 0.05$). The aortic cross-clamping duration was greater in the ARE-DVR group (177.6 ± 37.9 min vs. 148.3 ± 66.3 min, $p = 0.047$). The operative mortality rate was 5.6% for the entire cohort (ARE-DVR: 8% vs. DVR: 4.5%, $p = 0.46$). Among the patients who underwent echocardiographic control at follow-up, the mean aortic gradient was 19.6 ± 7.2 mmHg (range: 6.14–33 mmHg), with no differences among the groups.

**Conclusion:** The association between ARE and DVR did not significantly affect operative mortality. ARE can be safely used whenever indications arise to reduce the occurrence of PPM, especially in young patients with growth potential.

KEYWORDS

aortic root enlargement, valve replacement, patient–prosthesis mismatch, sub-Saharan Africa, rheumatic disease

# 1. Introduction

Aortic root enlargement (ARE) is a surgical technique that allows the implantation of a larger prosthesis during aortic valve replacement (AVR). Posterior ARE includes a patch enlargement of the aortic annulus through an incision extended to the anterior mitral leaflet, as first reported by Nicks et al. (1) and Manoughian and Seybold-Epting (2) more than four decades ago. These techniques are mainly recommended for children and young adults with small aortic annuli to limit the risk of patient–prosthesis mismatch (PPM), which has been associated with poor ventricular mass regression, increased risk of heart failure, and mortality (3–5). Although ARE has been shown to be a safe technique (6, 7), its association with concomitant procedures such as double valve replacement (DVR) might result in increased operative length and perioperative morbidity (8). This is particularly challenging in children and young adults with rheumatic valvular disease living in developing countries, where countless people present with multivalvular lesions (9).

This study reports our experiences with ARE in a sub-Saharan population that underwent DVR by reviewing early surgical outcomes.

# 2. Materials and methods

The clinical records of 69 patients who underwent DVR at our institution between February 2008 and November 2021 were retrospectively reviewed. A total of 44 patients ($n = 44$) underwent combined DVR and ARE, whereas 25 ($n = 25$) underwent DVR alone. Among the patients with ARE, Nick's procedure was the most common. Rheumatic heart disease was the predominant etiology in both groups. **Table 1** presents the patient demographic characteristics.

## 2.1. Preoperative evaluation and indication of ARE

The expected minimal effective orifice area (eEOA) required to avoid PPM was calculated preoperatively for all patients [eEOA = body surface area (BSA) × 0.85]. Following the analysis of the hemodynamic profiles provided by the manufacturers, prosthetic valves that provided similar or greater eEOA values were selected. ARE was performed in cases where the native aortic annulus diameter was smaller than that of the selected prosthetic valve.

## 2.2. Operative technique

Following aortic cross-clamping, a cardioplegic solution was administered to the aortic root or selectively to the coronary ostia. A "hockey stick" aortotomy and complete resection of the aortic leaflets were performed, followed by annular sizing, to assess the adequacy of the selected prosthetic valve. When indicated, ARE was performed first. Our preferred technique was Nick's technique (NT) (10), using a heterologous pericardial patch through an incision in the non-coronary cusp, extending to approximately 1.5 cm into the anterior mitral leaflet (**Figure 1**). The annular diameter was measured after ARE to ensure proper enlargement prior to prosthetic replacement. The mitral valve was then accessed through a standard left atriotomy and replaced using single interrupted sutures reinforced with pledgets. Particular attention was paid to maintaining the annulo-ventricular continuity by preserving the posterior leaflet or implanting artificial polytetrafluoroethylene (PTFE) chords. The aortic valve was successively implanted in a supra-annular position using single interrupted sutures reinforced with pledgets.

## 2.3. Statistical analysis

Statistical analysis was conducted using SPSS version 26.0 and Microsoft Excel 2016. The variables for descriptive analysis were expressed as proportions and mean ± standard deviation, while comparative analyses were performed using the chi-squared test. The correlation between variables was established by determining the $p$-value, which was considered statistically significant at $p < 0.05$.

# 3. Results

Among the 69 patients who underwent DVR, 35 were women (sex ratio, 0.97). The mean age at surgery was 26.7 ± 13.9 years (range: 7–62 years). Among the 47 patients aged ≤30 years, 40.4% (19/47) were aged between 10 and 20 years, and 6.3% (3/47) were aged <10 years. Patients in the ARE-DVR group were younger (23.3 ± 12.9 years vs. 28.5 ± 14.2 years, $p < 0.05$). The most common symptom was New York Heart Association Class ≥III dyspnea (89.9%), with no differences between the two groups. Sinus rhythm was present in 84.1% of the patients. A left ventricular ejection fraction ≥50% was found in 77.8% of the cases. Rheumatic disease was the most common etiology in the entire cohort (91.3%). The mean aortic annulus diameter was

TABLE 1 Patients' demographics and preoperative characteristics.

| Variables | ARE-DVR ($n = 25$) | DVR ($n = 44$) | Total | $p$-value |
|---|---|---|---|---|
| Age (years), mean ± SD | 23.3 ± 12.9 | 28.5 ± 14.2 | 26.7 ± 13.9 | <0.05 |
| Female sex, $n$ (%) | 14 (56%) | 21 (47.7) | 35 (50.7) | <0.27 |
| BSA (kg/m$^2$), mean ± SD | 1.48 ± 0.39 | 1.59 ± 0.28 | 1.55 ± 0.32 | 0.187 |
| NYHA ≥III, $n$ (%) | 23 (92%) | 39 (88.6%) | 62 (89.8%) | 0.68 |
| LVEF ≤50%, $n$ (%) | 19 (76%) | 36 (82%) | 55 (79.7%) | 0.28 |
| PAPs >35 mmHg, $n$ (%) | 71.4% | 86.1% | | 0.15 |
| Aortic annulus (mm), mean ± SD | 18.00 ± 1.47 | 22.50 ± 2.35 | 20.54 | 0.05 |
| Aortic dysfunction, $n$ (%) | | | | |
| Pure regurgitation | 21 (84%) | 38 (86.3%) | 59 (85.5%) | |
| Pure stenosis | 1 (4%) | 1 (2.2%) | 2 (2.8%) | |
| Mixed | 3 (12%) | 5 (11.3%) | 8 (11.5%) | |
| Mitral dysfunction, $n$ (%) | | | | |
| Pure regurgitation | 16 (64%) | 28 (63.6%) | 44 (63.7%) | |
| Pure stenosis | 4 (16%) | 8 (18.1%) | 12 (17.3%) | |
| Mixed | 5 (2%) | 8 (18.1%) | 13 (18.8%) | |
| Associated TV lesions, $n$ (%) | 16 (64%) | 23 (52.2%) | 39 (56.5%) | |
| Atrial fibrillation, $n$ (%) | 2 (8%) | 9 (20.4%) | 11 (15.9%) | |
| Rheumatic etiology, $n$ (%) | 24 (96%) | 39 (88.6%) | 63 (91.3%) | |

NYHA, New York Heart Association; BSA, body surface area; LVEF, left ventricle ejection fraction; PAPs, systolic pulmonary artery pressure; SD, standard deviation.

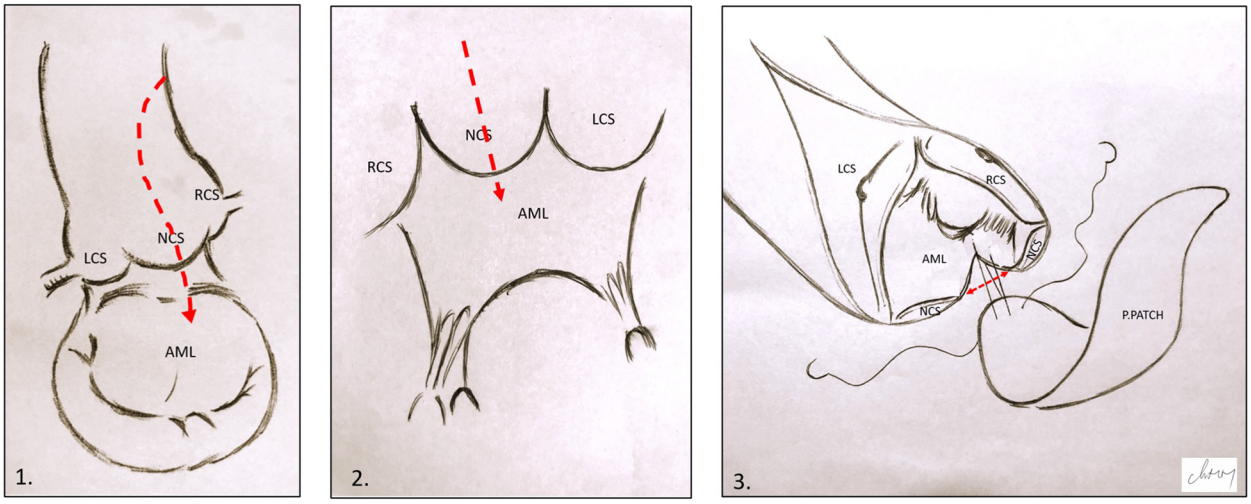


FIGURE 1
Illustration of Nick's technique. (1) and (2) Hockey stick aortotomy extended in the middle of the NCS and the anterior mitral leaflet. (3) Pericardial patch suturing; the red arrow shows the opening in the aortic annulus and AML. LCS, left coronary sinus; RCS, right coronary sinus; NCS, non-coronary sinus; AML, anterior mitral leaflet; P.PATCH, pericardial patch.

20.54 mm, with smaller sizes found in the ARE-DVR group (18.00 ± 1.47 mm vs. 22.50 ± 2.35 mm, $p < 0.05$). The mean EOA values of the implanted aortic valve were 1.59 ± 0.25 cm$^2$ and 1.64 ± 0.19 cm$^2$ for ARE-DVR and DVR, respectively ($p = 0.47$). Table 2 summarizes the data on the prosthetic valves.

## 3.1. Operative and late outcomes

The aortic cross-clamping duration was greater in the ARE-DVR group (177.6 ± 37.9 min vs. 148.3 ± 66.3 min, $p = 0.047$). The operative mortality rate was 5.6% for the entire cohort, and no statistically significant difference was found between the groups (ARE-DVR: 8% vs. DVR: 4.5%, $p = 0.46$) (Table 3). Table 4 summarizes the clinical data of the deceased patients. The postoperative mean aortic gradient was 19.68 ± 7.20 mmHg (range: 6.14–24 mmHg), with no statistically significant differences between the groups (ARE-DVR: 16.2 ± 9.9 mmHg vs. DVR: 17.3 ± 6.6 mmHg, $p = 0.62$). Table 5 reports the post-operative events according to age. At a mean follow-up of 6.9 ± 3.9 years, the estimated 5-year survival rates for ARE-DVR and DVR were 86.5 ± 7.2% and 89.9 ± 4.8%, respectively ($p = 0.52$) (Figure 2). Only one patient in the ARE-DVR group had undergone reoperation at follow-up for prosthetic valve endocarditis ($n = 1/22$, 4.5%).

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TABLE 2 Prosthetic valve models and characteristics.

| Prosthetic valve size (mm) | Models | EOA ($cm^2$) | ARE-DVR *n* (%) | DVR *n* (%) | Total *n* (%) |
|---|---|---|---|---|---|
| Aortic | | | | | |
| 17 | SJM HP | 1.1 ± 0.3 | 2 (8) | 4 (9) | 6 (8.6) |
| 18 | Medtronic AP | 1.5 ± 0.3 | 5 (20) | 4 (9) | 9 (13.0) |
| 19 | On-X | 1.5 ± 0.2 | 8 (32) | 11 (25) | 19 (27.5) |
| 19 | SJM Regent | 1.7 ± 0.2 | 1 (4) | 0 | 1 (1.4) |
| 20 | Medtronic AP | 1.7 ± 0.2 | 5 (20) | 3 (6.8) | 8 (11.5) |
| 20* | Aspire | — | 1 (4) | 1 (2.2) | 2 (2.8) |
| 21 | On-X | 1.7 ± 0.4 | 1 (4) | 14 (31) | 15 (21.7) |
| 21* | Slimline | — | 1 (4) | 0 | 1 (1.4) |
| 21 | SJM HP | 1.4 ± 0.2 | 0 | 2 (4.5) | 2 (2.8) |
| 21 | CE Magna Ease | 1.7 ± 0.3 | 0 | 1 (2.2) | 1 (1.4) |
| 23 | On-X | 2.0 ± 0.6 | 0 | 3 (6.8) | 3 (4.3) |
| 25 | On-X | 2.4 ± 0.8 | 1 (0) | 1 (2.2) | 2 (2.8) |
| Mitral | | | | | |
| 23 | On-X | 2.0 ± 0.6 | 1 | 1 | 2 (2.8) |
| 25 | On-X | 2.2 ± 0.9 | 20 | 36 | 56 (81.1) |
| 27 | On-X | 2.2 ± 0.9 | 2 | 4 | 6 (8.6) |
| 27 | CE-Perimount | 1.8 ± 0.4 | 0 | 1 | 1 (1.4) |
| 29* | Aspire | — | 1 | 2 | 3 (4.3) |
| 31 | On-X | 2.2 ± 0.9 | 1 | 1 | 2 (2.8) |

EOA, effective orifice area; SJM, St. Jude Medical Hemodynamic Plus; AP, advance performance; CE, Carpentier Edwards.
*EOA not available.

TABLE 3 Operative data and early clinical outcomes.

| Variables | ARE-DVR (*n* = 25) | DVR (*n* = 44) | Total | *p*-value |
|---|---|---|---|---|
| Mechanical prostheses, *n* (%) | | | | |
| Aortic | 24 (96.0) | 42 (95.4) | 66 (95.6) | |
| Mitral | 24 (96.0) | 42 (95.4) | 66 (95.6) | |
| Associated procedures, *n* (%) | 12 (48.0) | 18 (40.9) | 30 (43.4) | 0.34 |
| Tricuspid surgery | 10 (40.0) | 17 (38.6) | 27 (39.1) | |
| Myectomy for HOCM | 1 (4.0) | 0 (0.0) | 1 (1.4) | |
| AV fistula repair | 1 (4.0) | 1 (2.2) | 2 (2.9) | |
| Nick's technique, *n* (%) | 24 (96.0) | — | | |
| Nunes | 1 (4.0) | — | — | |
| CPB time (min), mean ± SD | 221.2 ± 57.9 | 195.6 ± 75.8 | | 0.148 |
| X-clamp time (min), mean ± SD | 177.6 ± 37.9 | 148.3 ± 66.3 | | 0.047 |
| Postoperative events, *n* (%) | | | | |
| Bleeding | 4 (16.0) | 4 (9.0) | 8 (11.5) | 0.36 |
| Arrhythmias | 3 (12.0) | 6 (13.6) | 9 (13.0) | 0.84 |
| Tamponade | 1 (4.0) | 0 (0.0) | 1 (1.4) | |
| LCO | 2 (8.0) | 3 (4.3) | 5 (7.2) | 0.85 |
| >24 h intubation | 1 (4.0) | 1 (2.2) | 2 (2.9) | |
| ICU stay >96 h | 7 (28.0) | 17 (38.6) | 24 (34.7) | 0.37 |
| Operative mortality | 2 (8%) | 2 (4.5) | 4 (5.7) | 0.46 |

CPB, cardiopulmonary bypass; X-clamp, cross-clamping; ICU, intensive care unit; LCO, low cardiac output; HOCM, hypertrophic obstructive cardiomyopathy; AV, aortoventricular; SD, standard deviation.

TABLE 4 Data of the four patients who died during the admission.

| | ARE-DVR | | DVR | |
|---|---|---|---|---|
| | Patient 1 | Patient 2 | Patient 3 | Patient 4 |
| Age | 24 years | 32 years | 45 years | 24 years |
| Gender | F | M | M | F |
| Preop NYHA class | IV | IV | IV | IV |
| Cardiac rhythm | Sinus | Sinus | Sinus | Sinus |
| LVEF | 30% | 40% | 66% | 55% |
| Mitral lesions | SMR | Mixed | SMR | SMR |
| Aortic lesions | SAR | SAR | SAR | SAR |
| Tricuspid lesions | STR | None | MTR | MTR |
| Cardioplegia | Custodiol | Custodiol | Custodiol | Custodiol |
| ECC time (min) | 250 | 246 | 208 | 128 |
| Mech ventilation (h) | 22 | 30 | | 74 |
| ICU length of stay (h) | 114 | 121 | 184 | 76 |
| Cause of death | LCO | LCO, tamponade | PE | LCO |

NYHA, New York Heart Association; LVEF, left ventricle ejection fraction; ECC, extracorporeal circulation; ICU, intensive care unit; SMR, severe mitral regurgitation; SAR, severe aortic regurgitation; STR, severe tricuspid regurgitation; MTR, moderate tricuspid regurgitation; LCO, low cardiac output; PE, pulmonary embolism.

## 3.2. Discussion

PPM is caused by an inadequacy between the prosthesis orifice area and the body size of the patient. When severe, PPM is associated with increased cardiac events such as poor regression of the left ventricular mass and reduced survival (3). Although PPM occurs in all cardiac valves, it is more common after AVR, with a reported prevalence rate between 20% and 70% (3). Smaller aortic annular size, increased BSA, and younger age at surgery were found to be associated with a major risk of PPM (11, 12).

Although other preventive measures, such as the use of aortic sutureless valves, have progressively gained interest, ARE techniques have historically been advocated to avoid PPM. Castro et al. (13) reported a reduction in the incidence rate of PPM to 2.5% (compared with 17%) in 657 patients who underwent combined ARE and AVR, with no increase in operative mortality. In the largest comparative study by Rocha et al. (14), ARE-AVR and AVR patients had similar postoperative mortality outcomes despite the longer cardiopulmonary bypass (CPB) and X-clamping times in the ARE-AVR group. However, higher in-hospital mortality was found in patients who underwent ARE-AVR when other procedures (coronary bypass or other valve surgeries) were performed. This was corroborated by a recent meta-analysis that reported increased mortality in patients who underwent ARE-AVR in combination with other cardiac procedures (8, 15). In a cohort of 13,174 patients, Sà et al. (8) reported an increase in perioperative mortality in patients who underwent ARE-AVR associated with other procedures compared with those who underwent AVR and associated procedures alone. A successive meta-analysis of 40,447 AVR cases by the same authors confirmed previous findings, with a higher mortality rate in the ARE-AVR and concomitant procedures groups ($p < 0.001$) (15). Although this increased mortality is potentially related to patient factors rather than to ARE, the reluctance to associate ARE techniques with complex surgeries is understandable. Although

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TABLE 5 Postoperative events according to age.

| Variables | ARE-DVR | | | DVR | | |
|---|---|---|---|---|---|---|
| | <20 | 20–29 | >30 | <20 | 20–29 | >30 |
| Patients, *n* (%) | 11 (44.0) | 7 (28.0) | 7 (28.0) | 14 (31.8) | 16 (36.3) | 15 (34.0) |
| Prosthesis EOA, mean ± SD | 1.42 ± 0.22 | 1.58 ± 0.10 | 1.73 ± 0.28 | 1.54 ± 0.19 | 1.63 ± 0.16 | 1.68 ± 0.16 |
| Operative mortality | 0 | 1 | 1 | 0 | 1 | 1 |
| Complications[a] | 3 | 4 | 1 | 4 | 5 | 4 |

[a]Bleeding, LCO, arrhythmias, and tamponade.

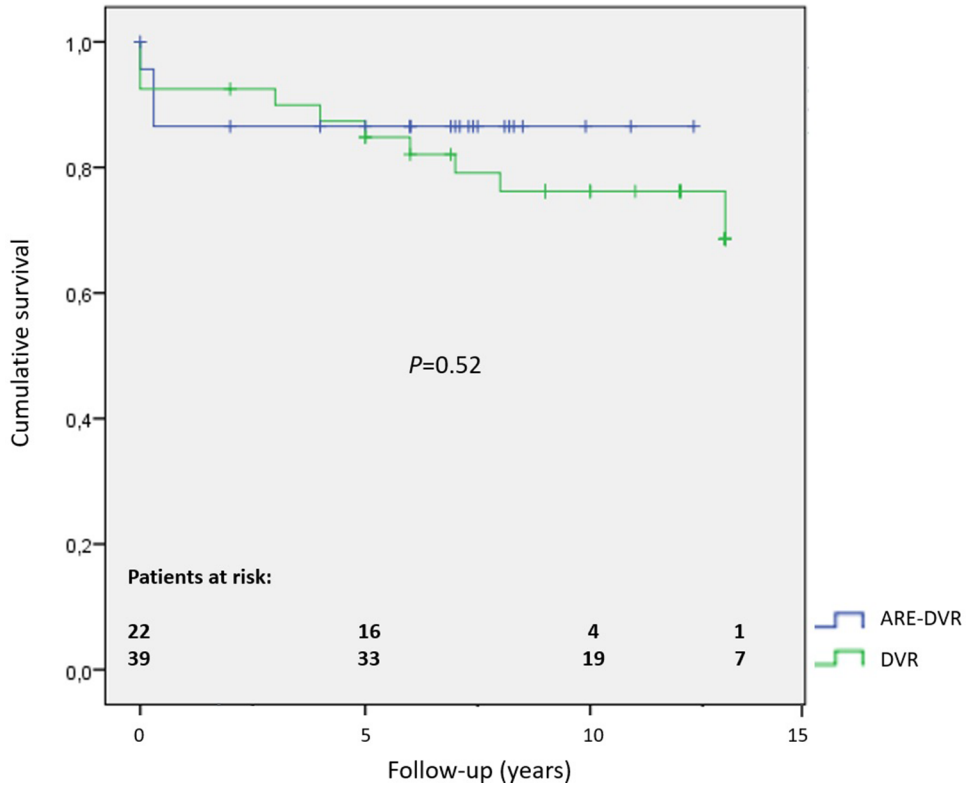


FIGURE 2
Kaplan–Meier estimates of survival at follow-up.

ARE has been used for more than four decades, experience with such techniques remains poor globally and has been potentially associated with adverse procedural events such as bleeding, patch rupture, and death. Indeed, ARE has been reported in only 5.7%–26.3% of patients undergoing AVR in meta-analyses (8). Moreover, the controversial benefits of ARE in some groups and the growing interest in other techniques, such as transcatheter aortic valve replacement (TAVI) and sutureless valves, have contributed to limiting the need for ARE. In fact, TAVI and sutureless prostheses might be preferable in elderly patients with comorbidities undergoing concomitant procedures rather than a more time-consuming ARE-AVR (16, 17). This re-emphasizes the need to tailor PPM preventive strategies to specific cases, considering the physician's skills, device availability, patient clinical characteristics, and local context.

ARE is commonly indicated in sub-Saharan African (SSA) patients undergoing AVR (36.2% in our series). In fact, a large number of patients, including those with multiple valve diseases, present at surgery with a hypoplastic annulus due to their younger age and small BSA. In this subgroup, biological options, such as stentless or sutureless valves, are limited by early structural deterioration and prohibitive costs. Although technically challenging, the Ross procedure remains a valuable tool because it allows for the growth potential of the neo-aortic valve. However, it is less suitable for cases with multiple valvular lesions, and a high long-term failure rate has been reported in patients with rheumatic diseases (18–20).

To our knowledge, this is the first study to report ARE and double DVR in SSA. We routinely perform aggressive ARE in young patients requiring AVR or DVR by implanting adult-sized

prostheses whenever possible, as the potential for growth in these patients remains a determining factor for the late recurrence of PPM. In addition to ARE, high hemodynamic profile prostheses (21) (Medtronic Advance Performance, SJM Hemodynamic Plus, or Regent) were preferred in our aortic patients, representing 42% of the implanted valves. NT has been our preferred ARE technique. When used with the appropriate technique, NT is associated with excellent root stability in the long term, even with an autologous pericardial patch (22). All patients received a larger aortic prosthesis, and no technical difficulties regarding prosthesis implantation were reported despite concomitant adult-size mitral prostheses. We believe that NT is less time-consuming than Manougian's technique. The latter might require a deeper extension in the anterior mitral leaflet and dome of the left atrium, with extensive patch reconstruction time. Despite the higher procedural duration in ARE-DVR patients, no significant differences were found in operative mortality between the two groups. Similar findings were reported by Okuyama et al. (23) and Zhong et al. (24), suggesting that ARE is not an independent factor for mortality in DVR despite the increased operative time. This contrasts with some meta-analyses that reported increased perioperative mortality in patients undergoing ARE-AVR and associated cardiac procedures (15, 15). It is possible that differences in patient demographics and clinics between the current and previous studies led to the observed heterogeneous outcomes. While our study was performed in an SSA environment with younger patients with Rheumatic Heart Diseases (RHD), the patients in the meta-analyses were from Western countries, were older, and presented with degenerative etiologies, including coronary diseases, and high comorbidity rates. As stated earlier, the strategy for PPM prevention, including the indication for ARE, should be tailored to the specific case following an exhaustive assessment of patient characteristics, disease patterns, and team expertise.

The small number of cohorts that have potentially impacted the statistical power of our analysis is a limitation of this study.

In conclusion, the association of the ARE technique with DVR does not significantly affect operative mortality in young SSA with RHD. ARE can be safely used whenever indications arise to reduce the occurrence of PPM and the risk of reoperation, especially in patients with growth potential.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

## Ethics statement

The studies involving humans were approved by the Cardiac Center Shisong Scientific Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

## Author contributions

CM performed the conceptualization, formal analysis, and methodology. CM and CD performed the data collection and curation and writing—original draft. CM, CD, LN, and others performed the writing—review and final approval of the article. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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# Development and testing of a transcatheter heart valve with reduced calcification potential

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**Introduction:** Patients from developing countries who require heart valve surgery are younger and have less access to open heart surgery than those from developed countries. Transcatheter heart valves (THVs) may be an alternative but are currently unsuitable for young patients because of their inadequate durability. We developed and tested a THV utilizing two new types of decellularized bovine pericardial leaflets in an ovine model.

**Methods:** The two decellularized tissues [one with a very low dose (0.05%) of monomeric glutaraldehyde (GA) fixation and detoxification (DF) and the other without glutaraldehyde (DE)] were compared to an industry standard [Glycar—fixed with the standard dose (0.625%) of glutaraldehyde]. THVs were manufactured with the three tissue types and implanted in the pulmonary position of nine juvenile sheep for 180 days. Baseline and post-explantation evaluations were performed to determine the hemodynamic performance of the valves and their dynamic strength, structure, biological interaction, and calcification.

**Results:** Heart failure occurred in one animal due to incompetence of its Glycar valve, and the animal was euthanized at 158 days. The gradients over the Glycar valves were higher at the explant than at the implant, but the DE and DF valves maintained normal hemodynamic performance throughout the study. The DF and DE tissues performed well during the mechanical testing of explanted leaflets. Glycar tissue developed thick pannus and calcification. Compared to Glycar, the DF tissue exhibited reduced pannus overgrowth and calcification and the DE tissue exhibited no pannus formation and calcification. All tissues were endothelialized adequately. There was a striking absence of host ingrowth in the DE tissue leaflets, yet these leaflets maintained integrity and mechanical function.

**Conclusion:** In the juvenile sheep THV model, Glycar tissue developed significant pannus, calcification, and hemodynamic deterioration. Using a very low dose of monomeric GA to fix the decellularized bovine pericardium yielded less pannus formation, less calcification, and better hemodynamic function. We postulate that the limited pannus formation in the DF group results from GA. Bovine pericardium decellularized with our proprietary method resulted in inert tissue, which is a unique finding. These results justify further development and evaluation of the two decellularized tissue types in THVs for use in younger patients.

KEYWORDS

TAVI, transcatheter heart valve, decellularized pericardium, low-dose glutaraldehyde, calcification, ovine model

# Introduction

Transcatheter aortic valve implants (TAVIs) have revolutionized the management of elderly patients with severe aortic stenosis (AS) and have now surpassed surgical aortic valve replacement (SAVR) as the preferred treatment modality in First World countries (1). They provide a less invasive and more durable alternative for patients who may well otherwise have struggled to cope with the trauma of SAVR. TAVI, as an alternative procedure to SAVR, has proven to be safe and efficient for the whole risk spectrum of patients, including patients deemed to be inoperable (2), high risk (3, 4), intermediate risk (5, 6), or even low risk (7, 8). All TAVIs and other transcatheter heart valves (THVs) are biological valves of either porcine or bovine origin. These materials have been shown to deteriorate and calcify in younger patients in large surgical series (9–11). Hence, a crucial caveat in all these randomized TAVI trials was that the participants were elderly, with mean age ranging from 74 to 83 years. In view of this, the European Society of Cardiology (ESC) guidelines recommend that TAVIs be reserved for patients ≥75 years or with high surgical risk and mechanical valves should be used in patients younger than 60 years when SAVR is performed (12). In the United States, only 18% of SAVR procedures and 30% of mitral valve replacements utilize mechanical valves, as the mean age of surgical valve recipients is 67 years (13, 14). This is in stark contrast to studies from Africa, where the average age of heart valve surgery candidates was 19 years in Ethiopia (15) and Uganda (16), 26 years in the Côte d'Ivoire (17), 27 years in Nigeria (18), and 42 years in South Africa (19). In these age groups, the recommendation is that all patients receive mechanical prostheses, but the problems associated with lifelong anticoagulation treatment are well documented (20–22). If one adds to this the fact that rheumatic heart disease (RHD) remains the most prevalent cause of significant heart valve disease in the world (23) and that there is a huge unmet need for surgery for these patients (24), there is a lot of potential for improved THVs to address these needs (23, 24). In this context, a durable bioprosthetic transcatheter valve with reliable and reproducible deployment is an attractive future alternative. Although transcatheter valve implantation in younger patients faces design, deployment, and structural challenges, the durability of bioprosthetic or tissue-engineered leaflet alternatives remains the Achilles' heel of this concept. The durability of bioprosthetic valves in patients under 40 years is poor (25–27) and therefore makes this type of valve inappropriate for the largest group of potential recipients of heart valves in the world (23). Improved durability of bioprosthetic material is therefore imperative. Since the very first valve replacements (28, 29), the only landmark improvement in bioprosthetic tissue fixation has been the switch from formaldehyde to glutaraldehyde (GA) (30). However, GA fixation has been plagued with valve deterioration and calcification, both as a result of ongoing immune processes and toxicity associated with the aldehydes. Various anti-calcification techniques have been investigated (31–33), but an ideal process for producing durable biological valves remains elusive. The process of biological valve deterioration is complex and includes remnant tissue immunogenicity, inflammatory cell infiltration, toxicity of GA fixation, mechanical damage, calcification, lack of repair, and pannus overgrowth (34). Therefore, the development of tissue-engineered alternatives and biological or artificial scaffolds has become a major research focus (35).

The Robert W M Frater Cardiovascular Research Centre (Frater Centre) at the University of the Free State (UFS) has been involved in the development of a biological tissue scaffold with reduced immune response from the host while maintaining sufficient dynamic strength to survive in the harsh mechanical stress environment to which heart valves are exposed. These processes can be broadly divided into decellularization, fixation, and detoxification. After evaluating the contributions of various decellularization steps and combinations, we have developed a unique method to decellularize bovine pericardium (BP) without significantly altering its strength and collagen structure (36, 37). This decellularized (DE) tissue performed well in 6-month implants in ovine aortas and pulmonary arteries, with less pannus formation, limited calcification, and adequate strength (38). Despite these results, it is not known whether the DE tissue would be strong enough to function in a high mechanical stress environment such as a THV. Therefore, additional cross-linking with GA may be required, and we have developed an additional decellularized, fixed, and detoxified (DF) tissue. The hypothesis is that GA has detrimental effects on tissue and should be limited as much as possible. This tissue was therefore fixed with a very low dose of GA, which was combined with a proprietary amino acid detoxification process, which in turn indicated no toxicity, excellent cross-linking, resistance to calcification, and porosity, allowing host cell recellularization in a subcutaneous rat model (39). To improve cross-linking, we utilized monomeric GA, which has been shown to produce less calcification (40).

We have developed a balloon expandable THV designed to be manufactured with bovine pericardial leaflets (41–45). This THV provided the platform on which we tested the different pericardial leaflets.

This study aimed to test DE, DF, and an industry standard bovine pericardium (Glycar, Glycar Pty Ltd, Irene, South Africa) in THVs implanted in the right ventricular outflow tract (RVOT) of juvenile sheep for 180 days. We compared the hemodynamic performance, structural degeneration and tissue strength, host tissue repopulation, inflammatory response, and calcification.

# Materials and methods

## Study design

The study was conducted as a prospective analytical cohort experimental study. Baseline and post-explantation tissue data were documented and compared between groups. Three THVs per group were constructed from bovine pericardium: either decellularized (DE) according to our proprietary method ($n = 3$) (37, 38) or decellularized, fixed, and detoxified (DF) ($n = 3$) or an industry standard (Glycar) ($n = 3$). The valves were then

implanted as interposition grafts in the main pulmonary artery (MPA) of juvenile Merino sheep ($n = 3$ per group) for 180 days. Echocardiography was performed at implantation and after 3 and 6 months to monitor valve function. Valve leaflet tissue at the explant was evaluated macroscopically and radiographically. Dynamic strength testing was performed using tensile strength (TS) and flexibility [Young's modulus (YM)] analyses, and morphological evaluation included hematoxylin and eosin (H&E) staining, von Kossa staining, Verhoeff–Van Gieson elastic staining (EVG), scanning electron microscopy (SEM), and transmission electron microscopy (TEM). A schematic representation of the study design is presented in **Figure 1**.

The Animal Ethics Committees of the University of the Free State (UFS-AED2016/0008/2020/21) and the University of Stellenbosch (SU-ACUD15-00120) approved the project.

## Experimental animals

The juvenile ovine model was selected for testing the valve *in vivo* because of the similarity of the animal's anatomy and hemodynamics to humans (46, 47) and because the model is approved by both the FDA and CE Mark (48). The exact definition of what constitutes a juvenile sheep is lacking, and in line with others (49–51), we elected to use animals that were 6 months of age. This negates the excessive growth of younger animals while still providing an accelerated calcification model for the valves. Furthermore, they are considered the ideal valve calcification model (52). Nine juvenile Merino sheep of 6 months of age and weighing between 40 and 45 kg were used to achieve a satisfactory match between valve size and pulmonary artery size. All animals were vaccinated, treated against ecto- and endoparasites, and subjected to a complete blood count prior acceptance for surgery. All animal experiments and surgical procedures were performed in compliance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (53) and guided by the South African National Standard 10386:2021 for the care and use of animals for scientific purposes.

## Tissue processing

Three groups of bovine pericardial leaflet constructs were used in the study:

(i) Glycar bovine pericardial tissue: Using EnCap technology, Glycar bovine pericardial tissue was selected as the industry standard since it has an established track record in the field (54, 55). Furthermore, we have used Glycar as a comparator in our previous work (37, 38) and deemed it the most suitable tissue available for use as a control. This tissue was GA-tanned (0.625%), formaldehyde (4%)-sterilized, detoxified with propylene glycol (100%), and stored in propylene oxide (2%).

(ii) Decellularized (DE) tissue: A decellularized bovine pericardial scaffold was prepared by decellularizing fresh bovine pericardium using a proprietary process developed by our group. This process combines the use of osmotic shock, a multi-detergent solution, delipidation with ethanol, and sterilization in an antibiotic and anti-mycotic solution according to a patented method (Patent: 16702008.0-1455, EU, 2017) (38).

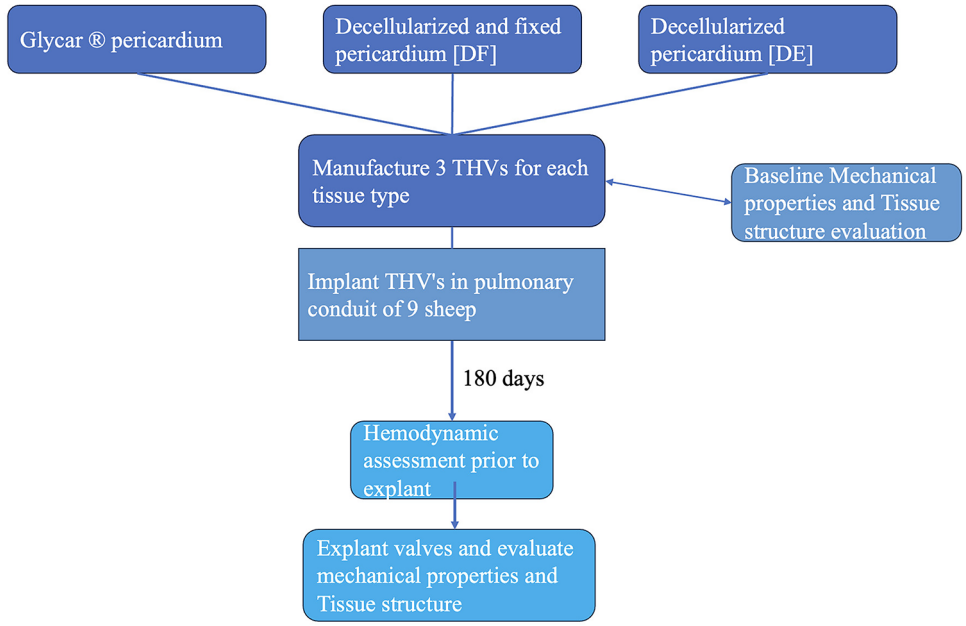


FIGURE 1
Schematic representation of the study design.

(iii) Decellularized-fixed (DF) tissue: Bovine pericardium decellularized as in (ii), then fixed with 0.05% monomeric GA (Polysciences, Inc., USA), and detoxified with an amino acid solution containing 0.1 M glycine (39).

Decellularization was evaluated by measuring the DNA content and inspecting H&E staining to confirm acellularity. DNA was extracted from the tissue using a Quick-DNATM Miniprep Plus Kit (Zymo Research, USA), and the complete decellularization of the tissue was confirmed by measuring the DNA content (ng DNA/mg tissue) using a BioDrop spectrophotometer (Biochrom Ltd., Cambridge, UK). After processing, the tissue was confirmed to be culture-negative (anaerobic and aerobic bacteria, fungi, and yeast) by a registered pathology laboratory (PathCare Veterinary Laboratory Bloemfontein, South Africa).

## Valve construction

A stainless-steel stent platform for the THV prosthesis was developed and tested *in vitro* and virtually to optimize the design and geometry of the leaflets (41–45). The valves were constructed in an ISO 14385-compliant clean room (Next Biosciences, Johannesburg, South Africa). A hemostatic cuff made from braided PTFE (Bard, Tempe, AZ, USA) was sutured onto the inside of the stent with individual self-locking sutures using CV-7 monofilament Gore-Tex (W.L. Gore & Associates, DE, USA). Three sets of valves were prepared for comparison using leaflet tissue supplied by Glycar and DE and DF pericardium scaffolds supplied by the Frater Centre. A leaflet template was manufactured to cut three identical-sized leaflets from a single sheet of pericardium, and the leaflets were then sutured with CV-7 Gore-Tex sutures onto the stent frame. A 22-mm THV valve was constructed according to the design parameters developed by our group (**Figure 2**).

Swabs for microbiology testing were taken from the covered stent and the completed valve before final storage in 2% propylene oxide (Glycar leaflets) or an 85% glycerol/15% ethanol solution (decellularized leaflets), as well as a tissue sample from the pericardial tissue used for the construction of the valve leaflets.

## Surgical implantation of transcatheter heart valves

The THV prosthesis was aseptically removed from the storage solution in the theater and rinsed in sterile 0.9% saline solution for 3–5 min. To expose the tissue to the mechanical forces of a transcatheter implant, it was crimped onto a 23-mm Z-Med balloon (Numed, NY, USA) using a commercially available crimping tool. The crimped diameter was confirmed to be small enough to fit through an 18-French sheath by inserting it into a dedicated Perspex tube with a 6 mm inner diameter. The crimped valve was then fully deployed with balloon inflation within a 22-mm Jotec FlowWeave Bioseal woven polyester vascular graft (JOTEC GmbH, Germany), secured with three polypropylene sutures at each end to prevent migration. The vascular graft was 3 mm longer than the THV on either side (total length ± 24 mm) to enable suturing and was then implanted as an RVOT conduit.

Recipient sheep were sedated (morphine sulfate 1 mg/ml, 0.2–0.5 mg/kg IM; ketamine hydrochloride 100 mg/ml, 5–15 mg/kg IM; Robinul 4 mg/2 ml, 0.005–0.01 mg/kg IM), anesthetized (Propofol 10 mg/ml, 2–6 mg/kg IV, Esmeron 50 mg/5 ml, 0.5 mg/kg IV), intubated, and ventilated (Isofor 2.5%, 1%–3% inhalation). A central venous line (CVP) was inserted in the left jugular vein, an arterial line was placed in the left carotid artery for hemodynamic monitoring, and the left carotid artery was cannulated for bypass. A left thoracotomy was performed, and the fourth rib was removed. Removal of the rib allows for a wider field of view during surgery and better echo windows at the follow-up. The right atrium was cannulated to achieve cardiopulmonary bypass (CPB), allowing the surgical procedure to be performed on a beating heart. The main pulmonary artery was clamped and transected, native pulmonary valve leaflets were removed, and the THV conduit was implanted as an interposition graft using continuous 4/0 prolene sutures in the pulmonary artery. The animal was weaned off CPB, hemostasis was secured, and an intrathoracic sonar was performed to confirm adequate valve functioning. The pressure gradient across the conduit was measured through needle insertion on either side of the conduit. A single chest drain was inserted on the left side, and all incisions were closed. The animal was extubated

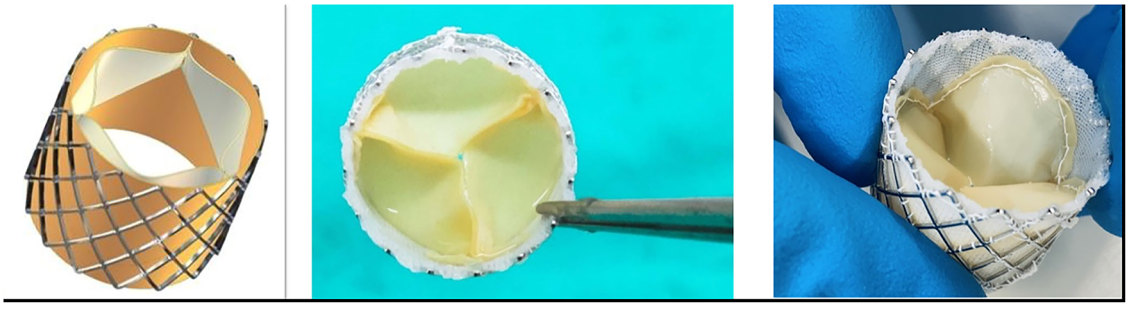

FIGURE 2
THV. On the left is a computer design of the valve that was developed using finite-element analysis (41–44). Note the balloon expandable stent frame with pericardial leaflets and a braided PTFE hemostatic cuff on the inside of the stent. On the right are two photographs of a manufactured valve.

when awake and breathing on its own, and the chest drain and monitoring lines were removed soon after. The sheep were moved back to the indoor holding pens with companion sheep in adjacent pens. Precisely, 5 ml of Depomycin (MSD Intervet) as a broad-spectrum antibiotic and 0.1–0.2 mg/kg morphine sulfate (Fresenius Medical Care, South Africa) as pain medication were administered intramuscularly twice daily for 5 days after surgery, and the animals were followed up and monitored daily for 6 months until they were killed; the valves were explanted for further analysis of the leaflet tissue. A piece of the adjacent pulmonary artery was excised and sent for microscopy and culture to exclude infection (negative in all cases).

## Clinical performance of implanted valves

Echocardiography was performed just after implanting the conduit, at days 30 and 90 post-surgery, and just before killing them using a GE Vivid-Q portable sonar machine. Over the study period, implanted valves were evaluated for transvalvular gradients, valve regurgitation, calcification, and possible aneurysm formation.

At the end of the study period, the animals were again anesthetized as described above and analgesia was administered (morphine sulfate 0.1–0.2 mg/kg); the chest was opened, hemodynamic pressures were measured over the valve by needle insertion, and intrathoracic echocardiography was performed. Animals were then killed by injecting a bolus of 10 ml of 15% hyperosmolar potassium chloride directly into the right atrium to cause cardiac arrest and then exsanguinated, and the valves were removed for further analyses.

## Tissue analysis

Mechanical properties, tissue histology, and ultrastructure of a representative piece of pericardium used to manufacture each valve were analyzed (baseline analysis) and compared to results of similar analyses on the tissue leaflets after 180 days in the sheep (explant analysis).

### Mechanical properties

Pericardial thickness was measured prior to surgical implantation and repeated after explantation using an ElectroPhysik MiniTest thickness gauge (Cologne, Germany). Samples were cut into 5-mm-wide strips, three to five thickness measurements were taken over the central section of the test strip, and then the average was calculated.

The dynamic strength test (tensile strength and Young's modulus analyses) of the bovine pericardium tissue was uniaxially performed at room temperature by an automated and computerized TS testing apparatus (Lloyds LS100 Plus, IMP, South Africa). Preimplantation tissue (5 cm × 5 mm) and tissue at the explant (5 mm wide) were cut. The average thickness was then measured, and the tissue sample was gradually stretched between two grips until the breaking point was achieved. Force was calculated using a 500-N load cell. The tensile strength (MPa) and Young's modulus (MPa) were calculated from the stress–strain curve using Nexygen Plus 3 software (Lloyd Instruments, IMP, Johannesburg, South Africa).

### Histology

A tissue sample from each pericardial patch used for leaflet construction was collected in 4% buffered formalin, dehydrated in graded alcohol steps, cleared in xylene, embedded in a paraffin wax block, sectioned, and stained according to standard protocols for H&E, von Kossa, and Verhoeff–Van Gieson staining for histological evaluation (56). The H&E-stained samples were evaluated for pannus formation, which was classified into three categories: none, non-confluent, and confluent pannus (covering the whole segment evaluated and both sides of the leaflet).

Pericardial tissue samples for electron microscopy evaluation were collected in 3% buffered GA and processed according to standard protocols for SEM and TEM evaluations (57).

## Statistical analysis

Due to the limited sample size, non-parametric analysis was used. Statistical analyses were performed using GraphPad Prism version 9.3.1. Continuous values were subjected to a Kruskal–Wallis (KW) multiple comparison analysis with Dunn's *post-hoc test* to compare individual groups. For two group comparisons, the Mann–Whitney *U*-test was used to measure differences between independent groups, and the Wilcoxon singed-rank test was used to measure differences between dependent groups.

# Results

Adequate decellularization was confirmed for both DE and DF tissues prior to implantation (**Figure 3**).

Valves were successfully implanted into 10 animals. One animal developed acute respiratory decompensation immediately post-operatively and was sacrificed. The other nine animals (three per tissue type) survived the procedure. All animals survived for 180 days except for one sheep with the Glycar valve, which developed heart failure and was euthanized at 158 days. The heart failure was due to a calcified prosthetic pulmonary valve with one of its leaflets overgrown by pannus and fixed in the open position (**Figure 4**). Endocarditis was excluded with blood cultures, c-reactive protein (CRP), and histology of this valve. The other valves were found to function adequately and competently, as observed by echocardiography (**Supplementary Video S1**). Obtaining accurate transvalvular gradients on echocardiography proved unreliable, and this parameter was obtained with direct invasive measurement prior to euthanasia. As can be observed in **Figure 5**, the gradients remained unchanged from implantation to explantation except for the Glycar valves, where the gradient increased numerically from a mean of 12 to 37 mmHg, although this was not statistically significant.

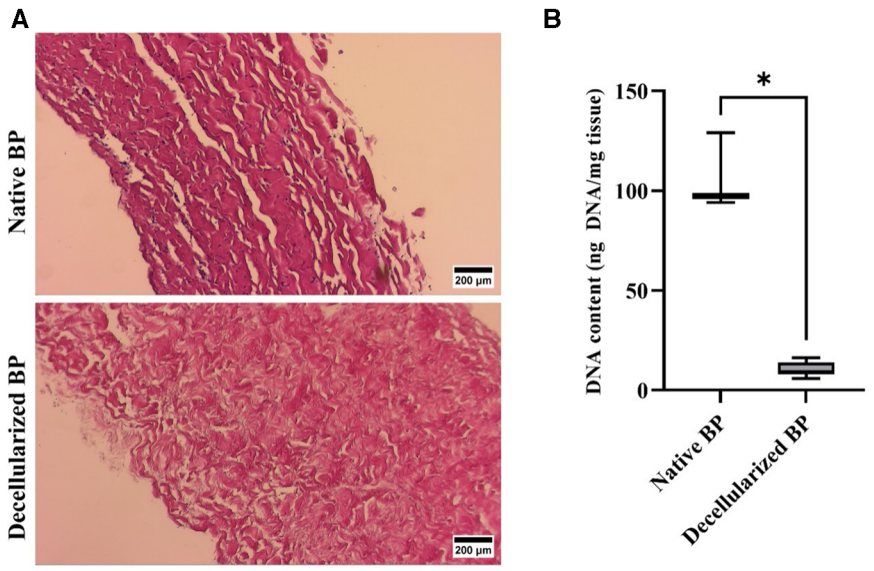


FIGURE 3
Confirmation of decellularization of bovine pericardium. (**A**) Representative light microscope images for H&E-stained tissue, indicating the presence of cells in the native BP and the complete removal of cells following decellularization (magnification 100×, scale 200 µM). (**B**) DNA content of the native and decellularized bovine pericardium ($n = 6$). * $p < 0.05$. The DNA content was well below the required 50 ng/mg tissue (71).

Macroscopic evaluation of the valves indicated that the stents remained structurally unchanged from implantation. Glycar leaflets were rigid with nodules of calcifications and thickened by pannus overgrowth. DE leaflets were soft, pliable, and non-calcified. DF leaflets were pliable, non-calcified, and of the same thickness as at implantation. An X-ray of the explanted valves showed calcification of the Glycar leaflets. The DE and DF leaflets were generally free from calcification,

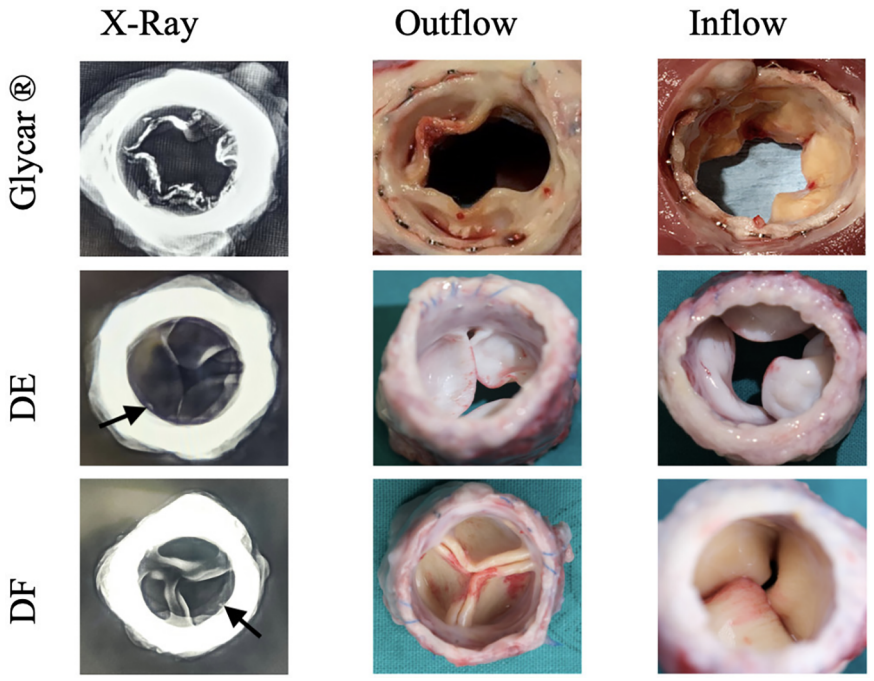


FIGURE 4
Representative X-ray images and photographs of the three differently processed valves at explantation. Note the calcification visible on the X-ray in the Glycar valve. The outflow view of this valve shows extensive pannus overgrowth, which has fixed one leaflet in the open position. Calcified nodules are visible on the inferior leaflet in the image. The decellularized (DE) and decellularized, low-dose glutaraldehyde-fixed, and detoxified (DF) bovine pericardium leaflets show no overt calcification, although there are possibly punctuated calcium spicules near the sewing margin (arrows), which may represent suture trauma. Glycar is the commercially available Glycar bovine pericardium fixed with conventional high-dose GA.

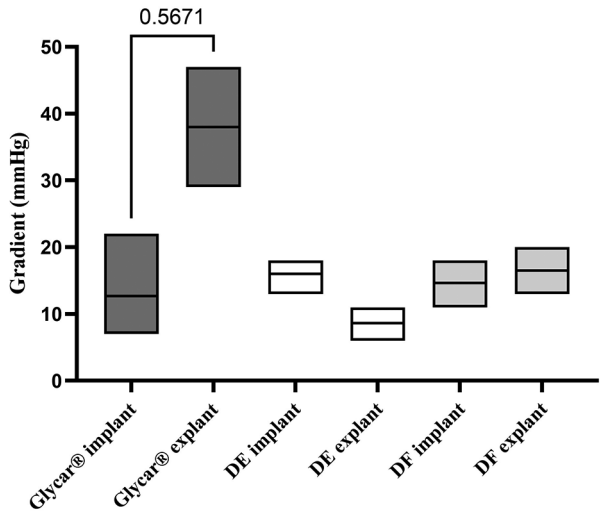


FIGURE 5
Invasively measured gradients (means and ranges) across the valves at the time of implantation compared to just prior to explantation. Note the unchanged gradients in DF and DE tissue valves. The change in gradients over the Glycar tissue valves was not statistically significant ($p = 0.5671$). DE denotes decellularized bovine pericardium; DF denotes decellularized, low-dose glutaraldehyde-fixed, and detoxified bovine pericardium; Glycar is the commercially available Glycar bovine pericardium fixed with conventional high-dose GA.

although there were a few spots next to the stent frame that could represent calcification due to suture trauma (Figure 4).

There was no difference in thickness, tensile strength, and Young's modulus from baseline to explantation in either of the two decellularized tissues (DE and DF). The Glycar tissue presented a significant reduction in tensile strength. This was caused by one of the tissues of the Glycar valve that fractured at low traction forces (Figure 6).

H&E staining demonstrated pronounced pannus overgrowth of the Glycar leaflet tissue. Of seven sections evaluated, six (86%) had confluent pannus and one (14%) had non-confluent pannus. No pannus was observed in the DE group and the DF group; of four sections, three (75%) had non-confluent pannus and one (25%) had none. In DE explants, no inflammatory process could be identified. There were no inflammatory infiltrates in DF explants, apart from the pannus mentioned previously. In fact, apart from the endothelium and the non-confluent pannus in the DF tissue, these explants were acellular. All tissues had good endothelial coverage, although the endothelium covered the pannus in the Glycar leaflets (Figures 7, 8) and in some portions of the DF leaflets. Scanning electron microscopy confirmed good reendothelialization of all three tissue types at the explant (Figure 8).

Evaluation of the elastin content of the tissues with Verhoeff–Van Gieson staining revealed a dense presence in the Glycar tissue pre-implant while limited presence in the DE and DF tissues. All tissues showed little or no elastin upon explantation (Figure 9). Transmission electron microscopy demonstrated a well-preserved collagen framework in all tissues, closely resembling preimplantation (Figure 10).

The Von Kossa staining results demonstrated marked calcification in the Glycar tissue and none in the DE and DF groups (Figure 11).

## Discussion

We aimed to develop bioprosthetic THV leaflets with improved durability and potential use in younger patients. Both the decellularized tissues (DE and DF) showed promising results when implanted for 180 days in juvenile sheep. The structure of the DE tissue remained intact, elicited no detectable

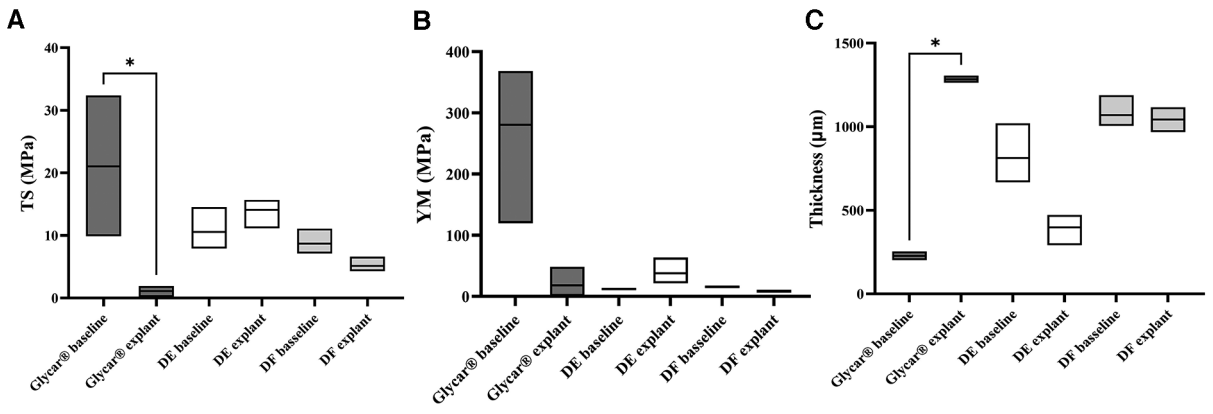


FIGURE 6
Physical properties of the tissue expressed as medians and ranges. (A) TS. Note the significant (*$p = 0.033$) difference between the Glycar baseline and at explantation. This is due to a single Glycar sample that was severely calcified and fractured with minimal traction. The other tissues all had non-significant differences from baseline to explantation. (B) YM analysis with no differences between baseline and explantation. (C) Tissue thickness, with only the Glycar tissue showing a significant (*$p = 0.0249$) change from baseline to explantation. As detailed in the Materials and Methods section, the thickness was measured (physically with calipers) in four places on the leaflet; therefore, a more representative of actual thickness than the single histology slices is shown in Figures 7, 9, and 11. DE denotes decellularized bovine pericardium; DF denotes decellularized, low-dose glutaraldehyde-fixed, and detoxified bovine pericardium; Glycar is the commercially available Glycar bovine pericardium fixed with conventional high-dose GA.

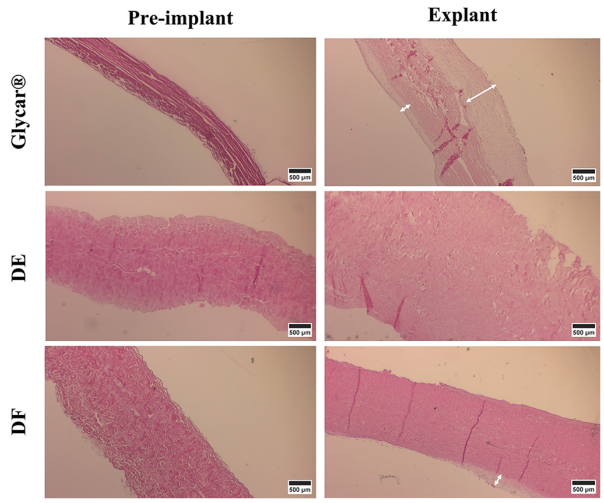


FIGURE 7
Results of H&E staining of the pericardial tissue at baseline (left) and explantation (right). At the explant, the Glycar tissue has a thick layer of pannus (white arrows), the DF has minimal pannus, and the DE tissue has no pannus. DE denotes decellularized bovine pericardium; DF denotes decellularized, low-dose glutaraldehyde-fixed, and detoxified bovine pericardium; Glycar is the commercially available Glycar bovine pericardium fixed with conventional high-dose GA.

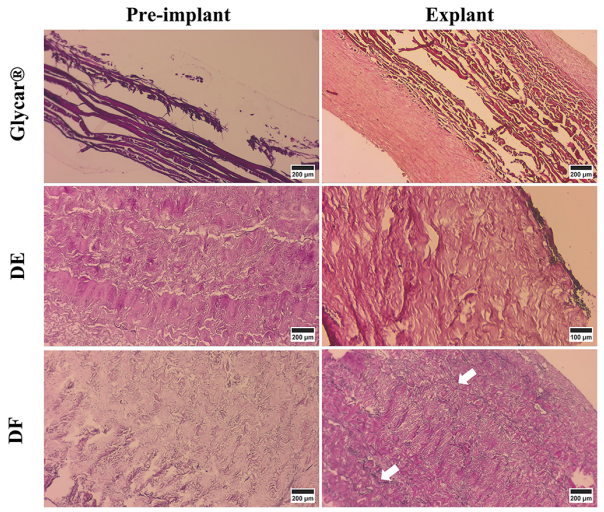


FIGURE 9
Results of EVG (highlighting elastin) of pericardial tissue at baseline (left) and explantation (right). All tissues had elastin at baseline, but at the explant, DE and Glycar had none and DF had minimal elastin (white arrows). DE denotes decellularized bovine pericardium; DF denotes decellularized, low-dose glutaraldehyde-fixed, and detoxified bovine pericardium; Glycar is the commercially available Glycar bovine pericardium fixed with conventional high-dose GA.

inflammatory response, and showed no calcification. When a very low dose of GA was added, the DF tissue developed small non-confluent areas of pannus. No calcification was seen during histological examination of the DF valve, and the small spots of calcification seen on an X-ray were near the stent frame and interpreted as a consequence of suture trauma. Elastin, as expected from previous work by others (58), was largely absent from all tissues at the explant.

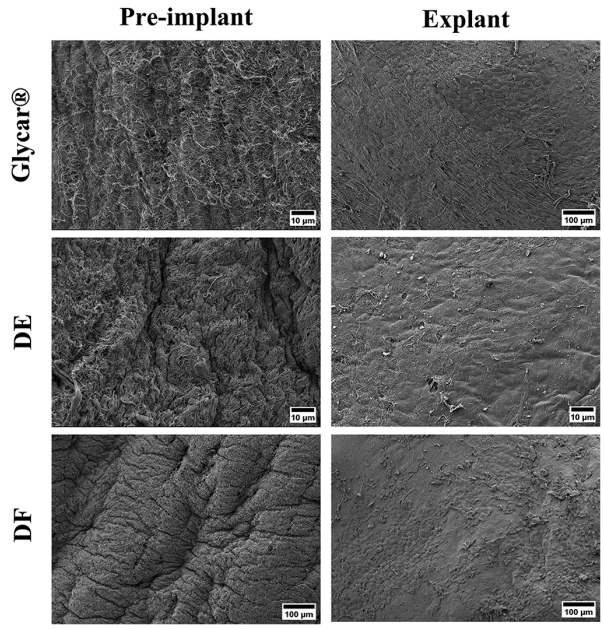


FIGURE 8
Results of scanning electron microscopy of the pericardial tissue at baseline (left) and explantation (right). All three tissue types were well covered with endothelium at the explant. DE denotes decellularized bovine pericardium; DF denotes decellularized, low-dose glutaraldehyde-fixed, and detoxified bovine pericardium; Glycar is the commercially available Glycar bovine pericardium fixed with conventional high-dose GA.

During preparation of bovine pericardial leaflets, we focused on three aspects that are deemed important in the search for more durable tissues for bioprosthetic THVs in younger patients, namely, lower-dose GA exposure, detoxification, and decellularization.

GA has been used in the fixation of pericardium for bioprosthetic heart valves since the 1970s (59) and has remained a crucial step in the preparation of tissues for heart valves. Currently, bovine pericardium is fixed with GA to provide greater mechanical stability, improve tissue handling, and reduce antigenicity, with a standard concentration of 0.625% used (60). Despite the beneficial effects of GA fixation, it is also implicated in various detrimental effects on the durability of the tissue, including reduced endothelial coverage (61), increased calcium influx into cells (62), inflammatory cell infiltration into tissues (61), and pannus formation (38). We hypothesized that a reduced concentration and the use of monomeric GA will at least partially mitigate some of these effects while providing adequate cross-linking. During the development of our proprietary fixation technique, it was found that the degree of cross-linking reduced with reducing doses of GA. Cross-linking was calculated as the ratio of the bound amino groups in the cross-linked (fixed) samples to the free amino groups from unfixed tissues and was determined using the ninhydrin assay (63). However, when the tissue was exposed to $H_2O_2$, the cross-linking with a very low dose of monomeric GA (0.05%) was similar to that with

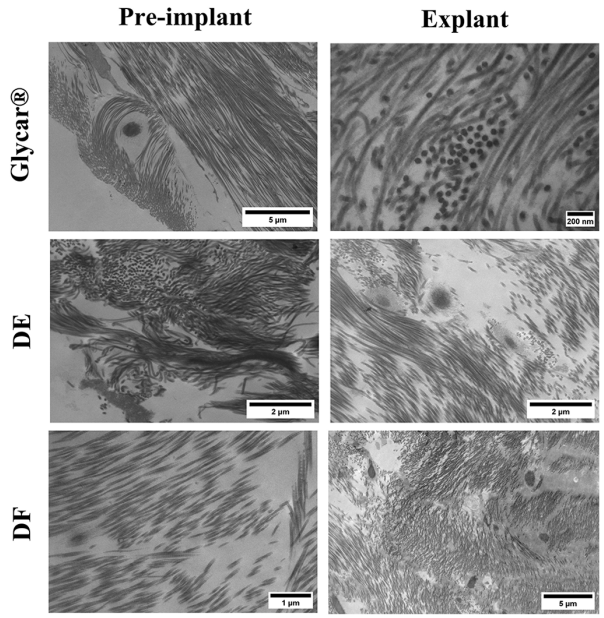


FIGURE 10
Results of transmission electron microscopy of pericardial tissue at baseline (left) and explantation (right). Note the preservation of collagen structure in all tissues at explantation. DE denotes decellularized bovine pericardium; DF denotes decellularized, low-dose glutaraldehyde-fixed, and detoxified bovine pericardium; Glycar is the commercially available Glycar bovine pericardium fixed with conventional high-dose GA.

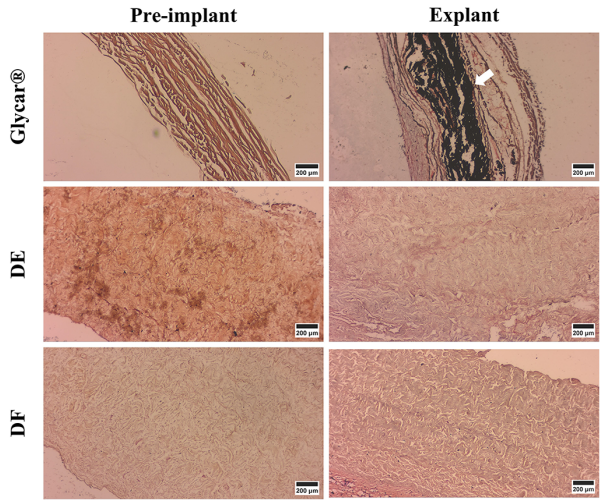


FIGURE 11
Representative von Kossa-stained samples (indicating calcification in black) of pericardial tissue at baseline (left) and explantation (right). Note the dense calcification in the Glycar tissue (white arrow) at the explant and none in the decellularized tissues. DE denotes decellularized bovine pericardium; DF denotes decellularized, low-dose glutaraldehyde-fixed, and detoxified bovine pericardium; Glycar is the commercially available Glycar bovine pericardium fixed with conventional high-dose GA.

standard 0.625% GA fixation. Further support that our cross-linking process was adequate can be deducted from the fact that the tensile strength of the DF tissue remained unchanged from baseline to explantation. We have previously shown that Glycar tissue developed pannus in the ovine aorta and ovine pulmonary artery, but in these vascular locations, the Glycar tissue did not calcify excessively (38). Although Glycar tissue is suitable for use in vascular and valvular repair and congenital repair, the current study suggests that it is not suitable for constructing leaflets for a THV. The major differences that the tissues are exposed to in the two locations include the initial potential injury caused by the crimping and balloon expansion of the THV and the repetitive motion and associated mechanical strain experienced by the valvular leaflets, forces that do not occur in vascular grafts. Furthermore, the pannus observed in the Glycar tissue may also have reduced the flexibility of the leaflets, thereby placing more mechanical stress on them, leading to calcification. The lack of calcification in the DF and DE tissues, where minimal or no pannus developed, is in keeping with this interpretation. Although the exact mechanism of calcification in the Glycar tissue remains speculative, this study supports the notion that reducing the exposure to GA limits calcification, particularly when the tissue is exposed to high mechanical stresses such as crimping and expansion of a THV and functioning as a valve leaflet *in vivo*.

Inflammation is widely viewed as an important contributor to bioprosthetic heart valve degeneration (64–67). Pannus tissue contains a variety of chronic inflammatory cells (lymphocytes, plasma cells, macrophages, and foreign body giant cells) and represents a host reaction against a foreign material (67). We did not see an acute inflammatory response to any of the tissues, but the extent of pannus formation was significant in Glycar (with high-dose GA exposure), very little in DF tissue (with a very low dose of GA exposure), and absent in DE (with no GA exposure). Since there were other differences in tissue preparation, we cannot conclude that GA exposure was the sole explanation for this finding. The results would however suggest that any use of GA might have to be avoided, or alternatively, the fixation technique requires further refinement to avoid pannus formation, which could alter hemodynamics and ultimately lead to valve degeneration and calcification. Another factor that has been shown to contribute to the immunogenic response to implanted bioprosthetic leaflets is cellular remnants of bacteria on the tissue (65). However, we did not test for this prior to implantation.

Decellularization in bioprosthetic tissues has been utilized and evaluated with the potential benefit of removal of immunogenic components and reducing stimulus for calcium influx into the tissue (68–72). Decellularized allografts (without GA fixation) have been evaluated in humans (73) with good midterm results. In this cohort of younger patients, one patient required a reoperation after 18 months for another indication and a small portion of the allograft tissue was removed at the time. Histology revealed well-preserved collagen fibers in the media and intimal hyperplasia of moderate intensity. There were a limited number of fibroblasts in the media and minimal inflammatory cells. The concept of utilizing decellularization without fixation is therefore not new, but its utility for xenografts is less well established, with some discouraging results described (74). Our two decellularized

tissues showed very encouraging results, but because of the proprietary preparation process, these results should not be generalized to other decellularization protocols or other implantation techniques and animal models. Decellularization can be obtained through various methods (physical, enzymatic, or chemical) but needs to be tailored for each tissue type depending on cellularity, density, lipid content, and thickness (75). Each step of the process has different effects on the outcome (36), and related techniques may yield different results depending on small variations in the technique. Our decellularization methodology has been developed over various iterations, and the results reported here are from tissues with encouraging performance in the subcutaneous rat model and aortic and pulmonary artery ovine implants (38). However, the durability of the unfixed DE tissue after 6 months in the high mechanical stress environment of a THV in sheep is somewhat surprising. No host fibroblast ingrowth was seen in this tissue, which implies that the collagen structure from the implant was still sufficiently stable, as seen from the TEM images, and remained functional, as demonstrated by the tensile strength and Young's modulus evaluation. This is contrary to the current view that regenerative tissue engineering supplies a scaffold for the host tissue to infiltrate, produce new structural elements, and eventually take over the functioning of the original xenograft (76). Although recellularization is an accepted endpoint in most tissue-engineered scaffolds, no one has been able to stimulate pericardial tissue to regenerate into the complex and specialized three-layered structure of native aortic valve leaflets. Although researchers have been able to populate scaffolds with the appropriate cells (*in vivo* and *in vitro*), they have been unable to stimulate them to produce a new extracellular matrix with mature composition, distribution, and conformation (76). Our decellularized tissue, conversely, was essentially inert despite 6 months of exposure to an accelerated calcification model (juvenile sheep). This finding is unique and challenges conventional dogma. Further research is required to fully understand this finding and its potential impact on future transcatheter valves. Each tissue was tested on three animals only, which makes the data preliminary and exploratory at best. However, because of the encouraging results, they justify expanding it to a larger cohort. The results were obtained in the lower-pressure environment and must be validated with aortic implants. The encouraging results in the RVOT, however, raise the question of whether the tissue is suitable for pulmonary THVs in younger patients. To evaluate long-term mechanical integrity of the tissue, our valves are currently being fatigue-tested to 200 million cycles per ISO 5840 standards. Longer-term implants will be required to prove durability, especially for the unfixed DE tissue. Finally, the response of the tissue to anti-Gal antibodies was not tested, and primate implants or *in vitro* exposure to human tissue must be performed.

Another feature of our work that is relatively unique is that valves were implanted in a synthetic tube and therefore (although exposed to host blood) not in direct contact with host tissue. This may be part of the explanation for the lack of host cell infiltration in the decellularized tissues, although it did not protect the Glycar tissue from pannus formation nor the DF group from limited non-confluent pannus formation. Applying this concept of limiting host tissue contact to aortic valves will be difficult because of the coronary ostia, but it may have utility in pulmonary valve implants where the recipients also tend to be younger.

## Conclusions

In the juvenile sheep THV model, Glycar tissue (with high-dose GA fixation) developed significant pannus, calcification, and hemodynamic deterioration. Using a very low dose of monomeric GA to fix decellularized bovine pericardium yielded less pannus formation, less calcification, and better hemodynamic functioning. We postulate that the limited pannus formation in the DF group results from GA, as no cellular response or pannus formation was demonstrated when GA was omitted in the similarly decellularized DE tissue. Bovine pericardium decellularized with our proprietary method resulted in essentially inert tissue, which is a unique finding. These results justify further development and evaluation of the two decellularized tissue types in THVs for use in younger patients.

## Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

## Ethics statement

The Animal Ethics Committees of the University of the Free State (UFS-AED2016/0008/2020/21) as well as the University of Stellenbosch (SU-ACUD15-00120) approved the project.

## Author contributions

HW: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. LB: Data curation, Investigation, Writing – review & editing. AD: Methodology, Writing – review & editing. JJ: Investigation, Methodology. AL: Conceptualization, Data curation, Investigation, Methodology, Software, Writing – review & editing. PM: Investigation, Methodology, Data curation. JH: Conceptualization, Data curation, Investigation, Methodology, Writing – review & editing. FS: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1270496/full#supplementary-material

SUPPLEMENTARY VIDEO S1
Representative echocardiogram [in a view comparable to a parasternal short axis view] showing color Doppler over the right ventricular outflow and pulmonary artery with no regurgitation of the valve in situ.

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# Efficacy of beta-blockers on blood pressure control and morbidity and mortality endpoints in hypertensives of African ancestry: an individual patient data meta-analysis

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**Introduction:** Compared with first-line antihypertensives, beta-blockers (BB) have been reported to lower the central aortic blood pressure suboptimally and are associated with increased stroke risk. This observation has not been investigated in hypertensives of African ancestry. We hypothesised that an individual patient data meta-analysis (IPD-MA) on the efficacy of second- or third-generation beta-blockers (STGBBs) in hypertensives of African descent may provide new insights.

**Methods:** A single-stage IPD-MA analysed the efficacy of STGBB in lowering the mean arterial blood pressure and reducing the composite outcomes: cardiovascular death, stroke, and myocardial infarction.

**Results:** A total of 11,860 participants from four randomised control trials were included in the analysis. Second- or third-generation beta-blockers reduced the mean arterial pressure by 1.75 mmHg [95% confidence interval (CI):1.16–2.33; $P < 0.001$] in all participants included in the analysis, and by 1.93 mmHg (95% CI: 0.86–3.00; $P < 0.001$) in hypertensive Africans. In patients with established cardiovascular disease, where the benefits of BB therapy are well established, STGBBs were associated with an adjusted odds ratio of 1.33 (95% CI: 1.06–1.65; $P = 0.015$) of the composite outcome, most likely due to confounding. Similarly, the risk of total myocardial infarction was 1.76 times higher (95% CI: 1.15–2.68; $P = 0.008$) in hypertensives of African ancestry on STGBBs.

**Conclusion:** The STGBBs reduced the mean arterial pressure comparably to other antihypertensives, and they were not associated with an increased risk of stroke.

KEYWORDS

hypertension, beta-blocker, antihypertensive, individual patient data meta-analysis, cardiovascular outcomes, Africa, blood pressure (BP)

Abbreviations

STGBB, second- or third-generation beta-blocker; SNS, sympathetic nervous system; LIFE, Losartan Intervention For Endpoint reduction in hypertension; ASCOT, Anglo-Scandinavian Cardiac Outcomes Trial; IPD, individual patient-level data; BioLINCC, Biologic Specimen and Data Repository Information Coordinating Center; IPD-MA, individual patient data meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RoB, risk of bias; GoF, goodness of fit; GLMM, generalised linear mixed effects models [also known as mixed models (MM), hierarchical or multi-level models, or random effects models].

# 1 Introduction

Beta-blockers are classified by generation as follows: first-generation beta-blockers refer to non-selective beta-blockers without any additional vasodilatory effects; second-generation beta-blockers generally refer to $\beta_1$-selective beta-blockers; and third-generation beta-blockers refer to beta-blockers that possess additional vasodilatory action, often mediated by the release of nitric oxide.

Beta-blockers (BBs) are a pharmacologically heterogeneous class of drugs widely used over the past five decades (1). The ability of BBs to modulate the sympathetic nervous system (SNS) through the adrenergic blockade of $\beta_1$ and $\beta_2$ receptors, and variable vasodilatory properties, position these agents as efficacious first-line antihypertensives. However, several clinical guidelines for the management of hypertension have recently withdrawn BBs as a first-line therapy (2–5), citing that, compared with other classes of antihypertensives, BBs reduce central aortic pressure suboptimally and offer less protection against fatal and non-fatal strokes (6).

This contentious decision to withdraw BB as a first-line therapy has been found to be controversial and met with some opposition. No prospective randomised control trials (RCTs) have investigated the efficacy of, specifically, second or third-generation beta-blockers (STGBBs) in reducing morbidity and mortality in hypertensives. Furthermore, individuals of African ancestry are usually underrepresented in RCTs (7). Yet, they have a higher prevalence of hypertension and are more likely to experience target organ damage caused by poorly controlled hypertension (8–11). This increase in hypertension-related morbidity and mortality may be because of the interplay between biological factors and myriad social drivers (12–15). We conducted an individual patient data meta-analysis (IPD-MA) of RCTs evaluating the efficacy of STGBBs in hypertensives of African ancestry in lowering blood pressure and the risk of cardiovascular death, fatal and non-fatal myocardial infarction (MI), and strokes.

# 2 Materials and methods

The study protocol was registered on the International Prospective Register for systematic reviews (PROSPERO ID = CRD42022344733). This IPD-MA adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for individual patient data systematic reviews (PRISMA-IPD) statement (16).

## 2.1 Selection of randomised control trials and participants included in the individual patient data meta-analysis

Following a prespecified search strategy, we performed a comprehensive systematic literature search in multiple clinical trial registries, search engines, and dataset repositories. (Supplementary material 1). All published and unpublished RCTs that assessed the efficacy of BBs, or antihypertensives, including STGBBs, compared with placebo, standard-of-care (SoC), or other antihypertensives (including first-generation BBs) in hypertensive participants were eligible for inclusion. Eligible RCTs were required to report the efficacy of BBs in lowering blood pressure and outcomes such as cardiovascular death, MI, and strokes in hypertensive individuals. Furthermore, RCTs required a proportion of the study participants to be of African descent. We excluded RCTs with a follow-up duration shorter than 1 year, participants younger than 18 years of age, studies conducted on healthy volunteers, and those without participants of African descent.

The risk of confounding was minimised by excluding participants with a history of previous major cardiovascular events. Participants were excluded from the analysis if they had a prior history of MI, congestive heart failure (CHF), arrhythmia, history of coronary revascularisation, and transient ischaemic attacks (TIAs) or stroke. Two reviewers independently examined the eligibility of all potential RCTs and assessed the risk of bias (RoB). Differences were resolved through discussion and consensus, and, where required, a third clinical expert arbitrator was consulted.

## 2.2 Individual patient data collection and assessment

The individuals listed as corresponding authors were contacted via email for each RCT study that met the inclusion criteria (Supplementary material 2). The integrity of the obtained datasets was checked for consistency and completeness (17). Also, summary statistics of received datasets were matched with published results, and internal summary statistics were generated as part of the IPD-MA to identify discrepancies. The variables of interest were extracted, standardised, and merged into a single dataset, ensuring that standard scales and definitions were used (Supplementary material 3). The study participants self-identified their ethnicity. The RoB 2 tool adapted for IPD-MA was used to assess the RoB in each study included in the meta-analysis (18, 19) (Supplementary material 4). All datasets included in this study were obtained from repositories within the National Institute of Health umbrella or Vivli.org. No IPD integrity or RoB 2 concerns were identified (Supplementary material 4). The internal and external summary statistics of the individual datasets matched, verifying the accuracy of the datasets employed in the final analysis.

## 2.3 Outcomes and treatment group allocation

The efficacy of BBs was assessed by evaluating the rate of cardiovascular mortality, myocardial infarction, and non-fatal and fatal strokes in hypertensives included in the IPD-MA prescribed STGBB compared with those on a placebo or first-generation BB therapy. To estimate the risk of composite events, odds ratios (OR) were extracted from each study, and the reduction in blood pressure (BP) was calculated by measuring the difference between the baseline and exit mean arterial blood pressure (MAP).

The treatment arm consisted of the whole BB class, which was partitioned into a newer second- and third-generation BB (STGBB group), defined by the $\beta_1$ adrenergic receptor affinity (second generation) and/or vasodilatory properties mediated by the release of Nitric oxide (third generation) (20), and their respective individual components of non-selective, selective β-receptor properties and vasodilatory properties. For studies that did not have a BB treatment arm, we reviewed the documented concomitant medication to allocate participants to their respective treatment groups. Participants were included in the STGBB group if they were on a BB for at least 18 months.

## 2.4 Statistical analysis

The respective RCT data were combined, creating a standardised IPD dataset. Exploratory and descriptive analysis preceded the one-stage IPD-MA. Categorical variables were summarised with frequencies and percentages. The mean and standard deviation and the median with minimum and maximum values were used to summarise numerical variables. The intraclass coefficient (ICC) was calculated by quantifying the degree to which participants within RCTs were alike, based on proportional variance. The generalised linear mixed effects model (GLMM) building process, evaluating both the fit of random intercept and/or random slopes in the modelling process was used. Known confounders (age, gender, ethnicity, diabetes, and smoking) for cardiovascular death were included in the analysis if they were statistically significant, clinically relevant, or the inclusion improved the model's goodness of fit (GoF) statistics. The iterative process assessed each covariate in this manner. Assumptions of GLMMs were robustly evaluated to curb any violations that may negatively influence the validity of the results (Supplementary material 5). Univariate logistic regression analysis was conducted and the odds ratios were adjusted for confounding by including covariates traditionally regarded as predictors of cardiovascular outcomes. Confidence intervals (CIs) were set at 95% and a *P*-value <0.05 was set as a threshold for statistical significance. Sensitivity analysis quantifying study heterogeneity and trends were performed as part of the statistical analysis. All data manipulation and analyses were done in R (version 4.2.1) (21) using the *Tidyverse* (22) and *lme4* (23) packages.

## 2.5 Role of the funding

The funder of this research (Merck) had no role in data collection, statistical analysis, data wrangling, data interpretation, and manuscript writing. The funders gave their consent towards the publication of the manuscript.

## 2.6 Ethics

Permission to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical), ethics clearance certificate number: W-CBP-211102-01.

# 3 Results

## 3.1 Study cohort selection and baseline characteristics

The search strategy resulted in 30 eligible RCTs (Figure 1). All authors listed in the respective trials were contacted, of which 23 authors responded. Of the 30 RCT datasets requested, access was granted to seven datasets. We excluded 19,494 participants with established severe CVD. The final study cohort in the IPD-MA comprised 11,860 hypertensives from four RCTs (Table 1). The STGBB arm had 3,864 (32.6%) hypertensives with a mean age of 66.4 ± 9.2 years, of which 1,339 (34.7%) hypertensives were of African ancestry. Similarly, the non-STGBB arm had 2,541 (31.8%) hypertensives of African ancestry. The STGBB arm had more individuals who had been prescribed concomitant antihypertensive medication; with diuretics prescribed to 3,131 (81.1%) vs. 3,781 (47.3%) in the non-STGBB arm. Of note, 2,075 (53.7%) participants in the STGBB arm were prescribed calcium channel blockers (CCB), compared with the 2,827 (35.4%) in the non-STGBB arm. The baseline mean systolic and diastolic blood pressures were comparable in both arms of the study. Table 2 depicts the type of BBs prescribed in each RCT.

## 3.2 Study outcomes

Hypertensives included in the IPD-MA had a mean follow-up duration of 4.13 years. The STGBB arm recorded 217 (5.6%) primary events compared with 374 (4.7%) events in the non-STGBB arm (Table 3). Myocardial infarction occurred in 134 (3.5%) and 178 (2.2%) hypertensives in the STGBB and non-STGBB arms, respectively. In the included RCTs, strokes were more likely to be non-fatal, occurring in 81 (2.1%) hypertensives in the STGBB arm, compared with 140 (1.7%) in the non-STGBB arm.

Hypertensives on STGBB were 1.2 times more likely to experience composite primary outcomes (95% CI: 1.02–1.44; *P*-value = 0.028) compared with those in the non-STGBB arm (Table 4). Myocardial infarctions were 1.8 times (95% CI: 1.15–2.68; *P*-value = 0.008) more likely to occur in hypertensives of African ancestry compared to the entire population (95% CI: 1.24–1.96; *P*-value < 0.001) on STGBB. After adjusting the odds ratios for confounders such as age, gender, and smoking (Table 5), there were no statistically significant differences in the risk of composite primary outcomes in the STGBB arm when comparing hypertensives of African ancestry and other racial groups.

## 3.3 Efficacy of second- and third-generation beta-blockers in lowering the mean arterial pressure

Second- and third-generation BBs reduced the MAP in the whole population by 1.75 mmHg (95% CI: 1.16–2.33; $P < 0.001$) compared with 1.93 mmHg (95% CI: 0.86–3.00; $P < 0.001$) in

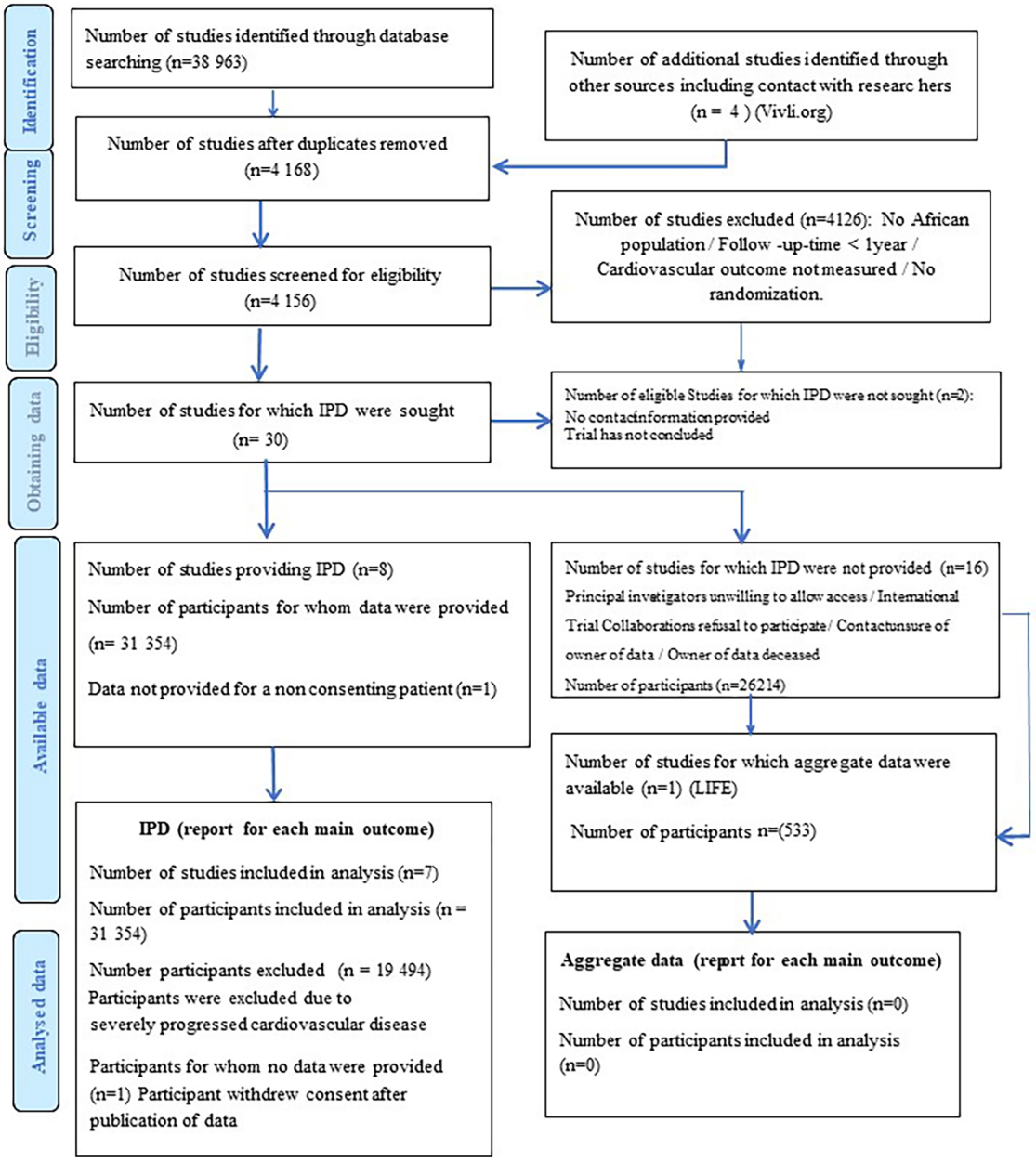


FIGURE 1
PRISMA flow chart showing the selection of studies and participants included in the meta-analysis.

hypertensives of African ancestry (Table 6). The multivariable generalised mixed effects model also demonstrated a statistically significant reduction in the MAP in hypertensives prescribed angiotensin-converting enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARB), calcium channel blockers, and diuretics. The highest reduction in the MAP was 3.88 mmHg (95% CI: 3.23–4.54; $P < 0.001$) and was associated with diuretic use. In hypertensives of African ancestry, diuretics decreased the MAP by 4.17 mmHg (95% CI: 2.78–5.50; $P < 0.001$). Despite a relatively smaller sample size in the African population, diuretics, ARBs, and STGBBs reduced the MAP more effectively in the African population than in the whole study population.

# 4 Discussion

In this IPD-MA, we evaluated the efficacy of STGBBs in reducing the risk of cardiovascular death, strokes, and MI in hypertensives of African ancestry compared with other racial groups on non-STGBBs. The composite primary outcome was higher in the STGBB arm (5.6%), compared with the 4.7% in the non-STGBB arm. In the entire hypertensive study population, including hypertensives of African ancestry, STGBBs were efficacious in reducing the risk of cardiovascular death. Although the trend was evident in African hypertensive, the estimate was not statistically

TABLE 1 Standardised demographic and clinical characteristics of patients included in the meta-analysis stratified by the trial providing the patient data.

| Study name | Systolic hypertension in the elderly program (24) | | Action to control cardiovascular risk in diabetes (25) | | Systolic blood pressure intervention trial (26) | | African-American study of kidney disease and hypertension (27) | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| Acronym | SHEP ($n = 1,497$) | | ACCORD ($n = 3,053$) | | SPRINT ($n = 6,802$) | | AASK ($n = 508$) | | $N = 11,860$ | |
| | STGBB | No STGBB | STGBB | No STGBB | STGBB | No STGBB | STGBB | No STGBB | STGBB | No STGBB |
| Number randomised | 389 | 1,108 | 660 | 2,393 | 2,609 | 4,193 | 206 | 302 | 3,864 | 7,996 |
| Age | | | | | | | | | | |
| Mean (SD) | 71.4 (6.37) | 71.8 (6.42) | 63.3 (5.854) | 62.8 (5.89) | 67.3 (2.93 | 66.7 (9.29) | 55.1 [10.3] | 54.6 (10.7) | 66.4 (9.20) | 65.8 (8.86) |
| Median (min, max) | 71.0 (60.0, 90.0) | 71.0 (60.0, 91.0) | 62.3 (55.0, 78.5) | 61.9 (55.0, 79.3) | 66.0 (50.0, 90.0) | 65.0 (46.0, 90.0) | 56.5 (24.0, 70.0) | 56.0 (21.0, 70.0) | 65.5 (24.0, 90.0) | 65.0 (21.0, 91.30) |
| Gender | | | | | | | | | | |
| Male | 179 (46.0%) | 488 (44.0%) | 333 (50.5%) | 1,092 (45.6%) | 1,512 (58.0%) | 2,675 (63.8%) | 117 (56.8%) | 166 (55.0%) | 2,141 (55.4%) | 4,421 (55.3%) |
| Female | 210 (54.0%) | 620 (54.0%) | 327 (49.5%) | 1,301 (54.4%) | 1,097 (42.0%) | 1,518 (36.2%) | 89 (43.2%) | 136 (45.0%) | 1,723 (44.6%) | 3,575 (44.7%) |
| Race | | | | | | | | | | |
| White | 298 (76.6%) | 871 (78.6%) | 379 (57.4%) | 1,357 (56.7%) | 1,607 (61.6%) | 2,580 (61.5%) | 0 (0%) | 0 (0%) | 2,284 (59.1%) | 4,808 (60.2%) |
| African | 56 (14.4%) | 162 (14.6%) | 169 (25.6%) | 612 (25.6%) | 908 (34.9%) | 1,465 (34.9%) | 206 (100.0%) | 302 (100.0%) | 1,339 (34.7%) | 2,541 (31.8%) |
| Other | 35 (9.0%) | 75 (6.8%) | 112 (17.0%) | 424 (17.7%) | 94 (3.6%) | 148 (3.5%) | 0 (0%) | 0 (0%) | 241 (6.3%) | 647 (8.1%) |
| Average follow-up time (years) | 4.58 (0.798) | 4.53 (0.800) | 5.06 (1.18) | 4.68 (1.48) | 3.95 (0.703) | 3.71 (1.03) | 4.51 (1.23) | 4.51 (1.23) | 4.24 (0.950) | 4.15 (1.25) |
| History of diabetes | | | | | | | | | | |
| No | 339 (87.1%) | 1,017 (91.8%) | 0 (0%) | 0 (0%) | 2,565 (98.7%) | 4,144 (98.6%) | 206 (100%) | 302 (100%) | 3,120 (80.7%) | 5,453 (68.2%) |
| Yes | 50 (12.9%) | 91 (8.2%) | 660 (100%) | 2,393 (100%) | 34 (1.3%) | 59 (1.4%) | 0 (0%) | 0 (0%) | 744 (19.3%) | 2,543 (31.8%) |
| Current smoking | | | | | | | | | | |
| No | 355 (91.3%) | 966 (87.2%) | 77 (11.7%) | 298 (12.5%) | 2,253 (86.7%) | 3,623 (86.2%) | 155 (75.2%) | 235 (77.8%) | 2,850 (73.8%) | 5,122 (63.9%) |
| Yes | 34 (8.7%) | 142 (12.8%) | 583 (88.3%) | 2,095 (87.5%) | 346 (13.3%) | 580 (13.8%) | 51 (24.8%) | 51 (24.8%) | 1,014 (26.2%) | 2,884 (36.2%) |
| Concomitant antihypertensive medication | | | | | | | | | | |
| Diuretic use | | | | | | | | | | |
| No | 0 (0%) | 1,108 (100%) | 94 (14.2%) | 1,529 (63.9%) | 433 (16.7%) | 1,276 (30.4%) | 206 (100%) | 302 (100%) | 733 (19.0%) | 4,215 (52.6%) |
| Yes | 389 (100%) | 0 (0%) | 566 (85.8%) | 864 (36.1%) | 2,176 (83.4%) | 2,917 (69.6%) | 0 (0%) | 0 (0%) | 3,131 (81.0%) | 3,781 (47.3%) |
| ACE-inhibitor use | | | | | | | | | | |
| No | 389 (100%) | 1,108 (100%) | 285 (43.2%) | 1,502 (62.8%) | 1,297 (49.7%) | 2,064 (49.2%) | 206 (100%) | 95 (31.5%) | 2,177 (56.4%) | 4,769 (59.6%) |
| Yes | 0 (0%) | 0 (0%) | 375 (56.6%) | 891 (37.2%) | 1,312 (50.3%) | 2,129 (50.8%) | 0 (0%) | 207 (68.5%) | 1,687 (43.7%) | 3,227 (40.4%) |
| Calcium channel blocker use | | | | | | | | | | |
| No | 389 (100%) | 1,108 (100%) | 405 (61.4%) | 2,065 (86.3%) | 789 (30.2%) | 1,789 (42.7%) | 206 (100%) | 207 (68.5%) | 1,789 (46.3%) | 5,169 (64.6%) |
| Yes | 0 (0%) | 0 (0%) | 255 (38.6%) | 328 (13.7%) | 1,820 (69.8%) | 2,404 (57.3%) | 0 (0%) | 95 (31.5%) | 2,075 (53.7%) | 2,827 (35.4%) |
| Angiotensin II receptor blocker | | | | | | | | | | |
| No | 389 (100%) | 1,108 (100%) | 396 (60.0%) | 1,968 (86.3%) | 1,470 (56.3%) | 2,673 (63.8%) | 206 (100%) | 302 (100%) | 2,461 (63.7%) | 6,051 (75.7%) |
| Yes | 0 (0%) | 0 (0%) | 264 (40.0%) | 425 (13.7%) | 1,139 (43.7%) | 1,520 (36.2%) | 0 (0%) | 0 (0%) | 1,401 (36.3%) | 1,945 (24.3%) |

(*Continued*)

TABLE 1 Continued

| Study name | Systolic hypertension in the elderly program (24) | | Action to control cardiovascular risk in diabetes (25) | | Systolic blood pressure intervention trial (26) | | African-American study of kidney disease and hypertension (27) | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| Acronym | SHEP ($n = 1,497$) | | ACCORD ($n = 3,053$) | | SPRINT ($n = 6,802$) | | AASK ($n = 508$) | | $N = 11,860$ | |
| | STGBB | No STGBB | STGBB | No STGBB | STGBB | No STGBB | STGBB | No STGBB | STGBB | No STGBB |
| Blood pressure (mmHg) | | | | | | | | | | |
| Baseline systolic | | | | | | | | | | |
| Mean (SD) | 173 (13.2) | 171 (13.4) | 143 (16.2) | 139 (15.1) | 141 (16.3) | 139 (15.0) | 146 (21.7) | 146 (20.8) | 145 (18.8) | 144 (18.8) |
| Median (min, max) | 171 (134, 217) | 171 (130, 217) | 143 (98.0, 228) | 137 (96.0, 202) | 140 (87.0, 231) | 138 (93.0, 214) | 145 (99.0, 206) | 143 (98.0, 228) | 142 (87.0, 231) | 141 (93.0, 228) |
| Baseline diastolic | | | | | | | | | | |
| Mean (SD) | 76.5 (9.75) | 80.7 (10.0) | 94.3 (13.1) | 76.5 (9.75) | 79.2 (12.3) | 79.3 (11.4) | 93.6 (12.7) | 94.3 (13.1) | 80.0 (12.2) | 79.2 (11.2) |
| Median (min, max) | 76.0 (20.00, 99.0) | 81.0 (0, 99.0) | 96.0 (44.0, 146) | 76 (45.0, 113) | 79.0 (42.0, 134) | 79.0 (42.0, 126) | 96.0 (62.0, 134) | 96.0 (44.0, 146) | 80 (42.0, 134) | 79.0 (20.0, 146) |

The studies are stratified by the use of STGBBs. Hypertension is often treated with combination/multiple agents. Both the STGBB and non-STGBB groups could be on multiple antihypertensives. The only difference is the fact that the STGBB group were on STGBB.

TABLE 2 Beta-blocker prescription in each randomised control trial.

| | Randomised control trial | | | |
|---|---|---|---|---|
| | AASK ($n = 206$) | ACCORD ($n = 681$) | SHEP ($n = 389$) | SPRINT ($n = 2,878$) |
| Propranolol (first-generation BB) | | | | 29 (1.0%) |
| Nadolol (first-generation BB) | | | | 3 (0.1%) |
| Metoprolol (first-generation BB) | 206 (100%) | 556 (81.6%) | | 1 446 (50.2%) |
| Acebutolol (second-generation BB) | | | | 0 (0%) |
| Atenolol (second-generation BB) | | | 389 (100%) | 1 188 (41.3%) |
| Bisoprolol (second-generation BB) | | | | 13 (0.5%) |
| Carvedilol (third-generation BB) | | 105 (15.4%) | | 153 (5.3%) |
| Labetalol (third-generation BB) | | | | 43 (1.5%) |
| Nebivolol (third-generation BB) | | | | 3 (0.1%) |
| Other beta-blockers | | 20 (3.0%) | | |

This table reports on the BB used per trial and not what was finally analysed in the IPD-MA.

significant. Furthermore, STGBBs had a greater MAP reduction in the African population.

Data supporting the recommendation to withdraw BBs as first-line therapy suggested that BBs failed to reduce the central aortic pressure and were associated with a greater risk of cardiovascular death or stroke (28–31). In this IPD-MA, we found that STGBBs reduced the MAP as efficiently as other antihypertensives in the African population and other racial groups included in the analysis. The findings from our meta-analysis indicate a need for prospective outcomes-driven RCTs to definitively examine the role of STGBBs in treating uncomplicated hypertension.

Beta-blockers prevent complications in patients with hypertension by lowering blood pressure and reducing cardiovascular events with an efficacy similar to other antihypertensives (30, 32–40). In this IPD-MA, we found that STGBBs significantly reduced the MAP in participants of African ancestry. However, the risk of MI was higher in hypertensives of African ancestry who were prescribed STGBB. A meta-analysis by Lindholm et al. published in 2005 evaluating whether BBs should remain first-line agents in the treatment of hypertension found that the relative risk of stroke was 26% higher in participants prescribed atenolol vs. other antihypertensive treatment (41). However, in this study, atenolol was not associated with an increased risk of stroke.

Hypertension is common in individuals of African ancestry and tends to follow a severe course associated with a higher rate of morbidity and mortality (14). The higher prevalence of hypertension in the African population compared with their counterparts has been attributed to biological factors, increased psychological stress, poor socioeconomic status, disparities in salt retention, and a higher rate of obesity among individuals of African ancestry (42, 43). Recent evidence suggests that there may be no racial disparities in the response to antihypertensive treatment (44).

Some of the trials that demonstrated higher adverse events in hypertensives treated with BBs include the Cardiovascular Morbidity and Mortality in the Losartan Intervention For Endpoint (LIFE) Reduction in Hypertension Trial and the

TABLE 3 Primary and secondary outcomes stratified by randomised control trial.

| Study name | Systolic hypertension in the elderly program | | Action to control cardiovascular risk in diabetes | | Systolic blood pressure intervention trial | | African-American study of kidney disease and hypertension | | Total | |
|---|---|---|---|---|---|---|---|---|---|---|
| Acronym | SHEP ($n = 1,497$) | | ACCORD ($n = 3\ 053$) | | SPRINT ($n = 6,802$) | | AASK (n = 508) | | | |
| | STGBB | No STGBB | STGBB | No STGBB | STGBB | No STGBB | STGBB | No STGBB | STGBB | No STGBB |
| Total cardiovascular mortality | 4 (1.0%) | 11 (1.0%) | 1 (0.2%) | 46 (1.9%) | 9 (0.3%) | 23 (0.5%) | 5 (2.4%) | 3 (1.0%) | 19 (0.5%) | 83 (1.0%) |
| Total stroke | 14 (3.6%) | 53 (4.8%) | 14 (2.1%) | 40 (1.7%) | 51 (2.0%) | 51 (1.2%) | 8 (3.9%) | 10 (3.3%) | 87 (2.3%) | 154 (1.9%) |
| Total myocardial infarction | 5 (1.3%) | 22 (2.0%) | 29 (4.4%) | 88 (3.7%) | 96 (3.7%) | 62 (1.5%) | 4 (1.9%) | 8 (2.6%) | 134 (3.5%) | 178 (2.2%) |
| Primary outcome | | | | | | | | | | |
| No | 369 (94.9%) | 1,028 (92.8%) | 617 (93.5%) | 2,234 (93.4%) | 2,460 (94.7%) | 4,087 (97.2%) | 191 (92.7%) | 283 (93.7%) | 3,637 (94.4%) | 7,632 (95.3%) |
| Yes | 20 (5.1%)[a] | 80 (7.2%) | 43 (6.5%) | 159 (6.6%) | 139 (5.3%) | 116 (2.8%) | 15 (7.3%) | 19 (6.3%) | 217 (5.6%) | 374 (4.7%) |
| Total cardiovascular events | | | | | | | | | | |
| No | 348 (89.5%) | 935 (84.4%) | 617 (93.5%) | 2,234 (93.4%) | 2,408 (92.3%) | 4,053 (96.7%) | 190 (92.2%) | 281 (93.0%) | 3,563 (92.2%) | 7,503 (93.8%) |
| Yes | 41 (10.5%) | 173 (15.6%) | 43 (6.5%) | 159 (6.6%) | 201 (7.7%) | 140 (3.3%) | 16 (7.6%) | 21 (7.0%) | 301 (7.8%) | 493 (6.2%) |
| Stroke | | | | | | | | | | |
| Non-fatal | 13 (3.3%) | 52 (4.7%) | 14 (2.1%) | 34 (1.4%) | 48 (1.8%) | 44 (1.0%) | 6 (2.9%) | 10 (3.3%) | 81 (2.1%) | 140 (1.7%) |
| Fatal | 2 (0.5%) | 1 (0.1%) | 0 (0.0%) | 9 (0.4%) | 3 (0.1%) | 7 (0.2%) | 2 (1.0%) | 0 (0%) | 7 (0.2%) | 17 (0.2%) |
| Total | 14 (3.6%)[a] | 53 (4.8%) | 14 (2.1%) | 40 (1.7%) | 51 (2.0%) | 51 (1.2%) | 8 (3.9%) | 10 (3.3%) | 87 (2.3%) | 154 (1.9%) |
| Myocardial infarction | | | | | | | | | | |
| Non-fatal | 5 (1.3%) | 18 (1.6%) | 29 (4.4%) | 88 (3.7%) | 93 (3.6%) | 50 (1.2%) | 4 (1.9%) | 7 (2.3%) | 131 (3.4%) | 163 (2.0%) |
| Fatal | 0 (0%) | 4 (0.4%) | 0 (0%) | 4 (0.2%) | 3 (0.1%) | 12 (0.3%) | 0 (0%) | 1 (0.3%) | 3 (0.1%) | 21 (0.3%) |
| Total | 5 (1.3%) | 22 (2.0%) | 29 (4.4%) | 88 (3.7%) | 96 (3.7%) | 62 (1.5%) | 4 (1.9%) | 8 (2.6%) | 134 (3.5%) | 178 (2.2%) |
| Congestive heart failure | | | | | | | | | | |
| Non-fatal | 7 (1.8%) | 33 (3.0%) | 14 (2.1%) | 39 (1.6%) | 79 (3.0%) | 41 (1.0%) | 6 (2.9%) | 3 (1.0%) | 106 (2.7%) | 116 (1.5%) |
| Fatal | 1 (0.3%) | 2 (0.2%) | 0 (0%) | 13 (0.5%) | 3 (0.1%) | 4 (0.1%) | 0 (0%) | 0 (0%) | 4 (0.1%) | 19 (0.2%) |
| Total | 8 (2.1%) | 34 (3.1%)[a] | 14 (2.1%) | 52 (2.2%) | 82 (3.1%) | 45 (1.1%) | 6 (2.9%) | 3 (1.0%) | 110 (2.8%) | 134 (1.5%) |
| Blood pressure (mmHg) | | | | | | | | | | |
| Exit systolic | | | | | | | | | | |
| Mean (SD) | 147 (18.7%) | 155 (18.2) | 124 (16.2) | 129 (16.1) | 131 (16.3) | 131 (15.1) | 136 (13.0) | 135 (13.6) | 131 (17.5) | 134 (18.3) |
| Median (min, max) | 143 (100, 214) | 154 (87.0, 218) | 121 (86.0, 206) | 128 (79.0, 217) | 130 (74.0, 189) | 130 (77, 206) | 135 (102, 168) | 133 (93.3, 177) | 130 (74.0, 214) | 130 (77.0, 214) |
| Exit diastolic | | | | | | | | | | |
| Mean (SD) | 81.2 (8.63) | 81.0 (8.98) | 78.0 (10.5) | 76.7 (9.72) | 79.3 (12.2) | 79.3 (11.1) | 93.7 (12.7) | 94.3 (13.1) | 80.1 (12.1) | 79.5 (11.1) |
| Median (min, max) | 82.0 (57.0, 99.0) | 81.0 (20.0, 99.0) | 78.0 (50.0, 108) | 76.0 (45.0, 113) | 79.0 (43.0, 123) | 79.0 (43.0, 123) | 96.0 (62.0, 134) | 96.0 (44.0, 146) | 80.0 (42.0, 134) | 79.0 (20.0, 146) |

[a]The events are not mutually exclusive. For example, participants may have a non-fatal major cardiovascular event followed by a fatal cardiovascular event resulting in the respective sum of events not equalling the totals displayed. The studies are stratified by the use of STGBB. Hypertension is often treated with combination/multiple agents. Both the STGBB and non-STGBB groups could be on multiple antihypertensives. The defining difference is that the STGBB group were on STGBB.

Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm (ASCOT-BPLA). The LIFE trial randomised 9,222 hypertensives to atenolol or losartan. After a follow-up duration of 4.8 years, the rate of cardiovascular mortality was 10.6 per 1,000 patient-years of follow-up in the atenolol arm vs. 9.2 per 1,000 patient-years in the losartan arm (28). The stroke rate was also higher in the atenolol arm (14.5 vs. 10.8 per 1,000 patient-years of follow-up). In the ASCOT-BPLA, participants were randomly assigned to either atenolol plus a thiazide diuretic or amlodipine and perindopril. Strokes, cardiovascular events, and all-cause mortality rates were higher in participants randomised to atenolol and a thiazide diuretic (29). Although these studies highlight a higher risk of stroke in patients prescribed BBs, both RCTs had suboptimal dosing of atenolol.

In this IPD-MA, confounding was partially controlled for by excluding participants with previous cardiovascular events and adjusting the odds ratio in the multivariable regression model. For example, we relied on documented baseline clinical history and examination findings to identify high-risk hypertensives with previous MI, strokes, or CHF, requiring exclusion from the study. As such, the significant increase in the risk of MI in hypertensives could be accounted for by including

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TABLE 4 Univariate analysis looking at the STGBB arm compared with the non-use of STGBB.

| | Whole population | | | | African population | | | |
|---|---|---|---|---|---|---|---|---|
| | | 95% confidence interval | | | | 95% confidence interval | | |
| Outcome | Odds ratio | Lower | Upper | *P*-value | Odds ratio | Lower | Upper | *P*-value |
| Cardiovascular mortality | | | | | | | | |
| STGBB | 0.47 | 0.28 | 0.76 | 0.003 | 0.69 | 0.29 | 1.49 | 0.370 |
| Total stroke | | | | | | | | |
| STGBB | 1.17 | 0.9 | 1.53 | 0.239 | 1.13 | 0.72 | 1.74 | 0.595 |
| Total myocardial infarction | | | | | | | | |
| STGBB | 1.56 | 1.24 | 1.96 | <0.001 | 1.76 | 1.15 | 2.68 | 0.008 |
| Primary outcome | | | | | | | | |
| STGBB | 1.22 | 1.02 | 1.44 | 0.028 | 1.26 | 0.93 | 1.7 | 0.136 |
| Non-fatal stroke | | | | | | | | |
| STGBB | 1.20 | 0.91 | 1.58 | 0.193 | 1.17 | 0.73 | 1.84 | 0.513 |
| Non-fatal myocardial infarction | | | | | | | | |
| STGBB | 1.69 | 1.33 | 2.13 | <0.001 | 1.80 | 1.17 | 2.75 | 0.007 |
| Total cardiovascular disease | | | | | | | | |
| STGBB | 1.29 | 1.11 | 1.49 | <0.001 | 1.28 | 0.98 | 1.66 | 0.073 |
| Change in blood pressure (exit-baseline) | Change in blood pressure (mmHg) | | | | Change in blood pressure (mmHg) | | | |
| Systolic (mmHg) (ICC = 34%) | | | | | | | | |
| STGBB | −2.4 | −3.25 | −1.54 | <0.001 | −3.05 | −4.61 | −1.49 | <0.001 |
| Diastolic (mmHg) (ICC = 41%) | | | | | | | | |
| STGBB | −1.33 | −1.83 | −0.84 | <0.001 | −1.71 | −2.61 | −0.81 | <0.001 |

TABLE 5 Multivariable logistic regression model predicting the primary outcome: total cardiovascular mortality, total stroke, and total myocardial infarction in 11,860 patients included in the meta-analysis.

| | | 95% confidence interval | | |
|---|---|---|---|---|
| | aOR | Lower | Upper | *P*-value |
| STGBB | 1.33 | 1.06 | 1.65 | 0.015 |
| Race | | | | |
| White | 1 | | | |
| African | 1.09 | 0.85 | 1.39 | 0.497 |
| Other | 0.68 | 0.44 | 1.05 | 0.080 |
| Age | 1.05 | 1.04 | 1.06 | <0.001 |
| Gender | | | | |
| Male | 1 | | | |
| Female | 0.80 | 0.67 | 0.95 | 0.010 |
| Current smoker | | | | |
| No | 1 | | | |
| Yes | 1.47 | 1.14 | 1.89 | 0.003 |
| STGBB × African race | 1.00 | 0.69 | 1.46 | 0.989 |
| STGBB × Other race | 1.12 | 0.53 | 2.36 | 0.765 |

History of diabetes was neither statistically significant nor did it improve the model fit statistics [likelihood ratio test (LRT)], and therefore it was omitted from this model. The adjusted odds ratio (aOR) was controlled for age, gender, and current smoker status.
*N* = 11,860 participants included in this analysis.

undocumented high-risk hypertensives in the IPD-MA. Although reasonable attempts were made to minimise confounding, the STGBB group was still a higher risk group than the non-STGBB group. The patients in the STGBB group were on more antihypertensive medication than those in the non-STGBB group. This may explain the increased risk of cardiovascular outcomes associated with the STGBB group found in this study.

Individual patient data meta-analysis is considered the most reliable and robust method for obtaining evidence (45). Despite this, most authors prefer conducting systematic reviews and meta-analyses based on aggregated data from various research studies instead of requesting individual participant data from the data custodians. The major drawback of conducting IPD-MA is the unpredictable access to data. Despite receiving a response from 77% of the authors contacted, we could only access data from seven RCTs and eventually only analysed four. Some reasons cited in the literature restricting access to data include a lack of response from the authors or data custodians contacted, operational constraints, staff relocation, and lack of communication (46). Data-sharing policies vary with each country, and authors requesting access to data may be expected to apply for ethical clearance in multiple institutions prior to accessing data. The median time from the first request to accessing data to fully receiving the data can also be excessively long and may take up to 242 days (46). Realising that obtaining data for IPD-MA comes with many challenges, Ventresca et al. recommend requesting data through personal contact, offering incentives such as coauthorship and setting up a data-sharing agreement (47). Furthermore, consenting authors could also deposit de-identified data in a common data repository site. Data

TABLE 6 Multivariable generalised mixed effects model with the respective RCT as a random effect (random intercept).

| | Whole population ($n = 10,210$) | | | | African population ($n = 3,276$) | | | |
|---|---|---|---|---|---|---|---|---|
| | | 95% confidence interval | | | | 95% confidence interval | | |
| | mmHg | Lower | Upper | *P*-value | mmHg | Lower | Upper | *P*-value |
| (Intercept) | −6.70 | −11.80 | −1.61 | 0.01 | −6.52 | −12.56 | −0.48 | 0.034 |
| STGBB | −1.75 | −2.33 | −1.16 | <0.001 | −1.93 | −3.00 | −0.86 | <0.001 |
| ACE-I | −1.67 | −2.33 | −1.05 | <0.001 | −1.57 | −2.67 | −0.48 | 0.005 |
| Angiotensin II receptor blockers | −2.22 | −2.89 | −1.54 | <0.001 | −3.17 | −4.44 | −1.90 | <0.001 |
| Diuretic use | −3.88 | −4.54 | −3.23 | <0.001 | −4.17 | −5.5 | −2.78 | <0.001 |
| Calcium channel blockers | −2.61 | −3.25 | −1.97 | <0.001 | −1.86 | −3.07 | −0.66 | <0.001 |

confidentiality breach and leakage are some of the key areas that need to be addressed before implementing such data repositories.

## 5 Limitations

This IPD-MA's chief limitation is the incomplete acquisition of IPD from previously conducted RCTs, leading to a smaller sample size. Although generalisability is improved, severe confounding was introduced through the surrogacy BB treatment, since BBs are traditionally prescribed in individuals with established or advanced cardiovascular risk factors. A higher proportion of ACE-I, CCB, ARB, and diuretics use in participants in the STGBB arm demonstrated this BB surrogacy phenomenon. Including the daily cumulative dose of each BB used in the analysis may have provided more insights into the added benefit of STGBBs compared to other BBs in reducing the MAP.

## 6 Conclusions

Second- and third-generation BBs effectively reduced the MAP in hypertensives of African ancestry as well as in other racial groups. Compared with other racial groups, the risk of stroke was not increased in hypertensives of African descent who were prescribed STGBBs. However, the risk of myocardial infarction was higher in hypertensives of African descent on STGBBs. This IPD-MA suggests that the cardiovascular outcomes associated with STGBB use in managing essential hypertension may differ according to ethnicity and generation of BB therapy.

## Data availability statement

Data was obtained from the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC), and requests to access the data should be directed towards the data repository. Further enquiries can be directed to the corresponding author.

## Ethics statement

The studies involving humans were approved by The University of the Witwatersrand Human Research Ethics Committee (Medical), ethics clearance certificate number: W-CBP-211102-01. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because the study analysed pre-existing datasets from various trials.

## Author contributions

NT: Conceptualization, Methodology, Supervision, Validation, Writing – review & editing. RDN: Conceptualization, Supervision, Writing – review & editing, Methodology. SM: Conceptualization, Supervision, Writing – review & editing, Methodology.

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## Conflict of interest

RDN and SM are Merck employees. NT has received consulting & speaker fees from Merck, Acino Health Care Group, Boehringer-Ingelheim, Boston Scientific, Eli Lilly, Novartis Pharmaceuticals, NovoNordisk, Pfizer, Phillips, Servier, and Takeda. NT has also received educational grants from Biotronik, Boston Scientific, Medtronic, and Vertice Health Care Group.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1280953/full#supplementary-material

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# Mechanical valve replacement for patients with rheumatic heart disease: the reality of INR control in Africa and beyond

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The majority of patients requiring heart valve replacement in low- to middle-income countries (LMICs) need it for rheumatic heart disease (RHD). While the young age of such patients largely prescribes replacement with mechanical prostheses, reliable anticoagulation management is often unattainable under the prevailing socioeconomic circumstances. Cases of patients with clotted valves presenting for emergency surgery as a consequence of poor adherence to anticoagulation control are frequent. The operative mortality rates of reoperations for thrombosed mechanical valves are several times higher than those for tissue valves, and long-term results are also disappointing. Under-anticoagulation prevails in these regions that has clearly been linked to poor international normalised ratio (INR) monitoring. In industrialised countries, safe anticoagulation is defined as >60%–70% of the time in the therapeutic range (TTR). In LMICs, the TTR has been found to be in the range of twenty to forty percent. In this study, we analysed >20,000 INR test results of 552 consecutive patients receiving a mechanical valve for RHD. Only 27% of these test results were in the therapeutic range, with the vast majority (61%) being sub-therapeutic. Interestingly, the post-operative frequency of INR tests of one every 3–4 weeks in year 1 had dropped to less than 1 per year by year 7. LMICs need to use clinical judgement and assess the probability of insufficient INR monitoring prior to uncritically applying Western guidelines predominantly based on chronological age. The process of identification of high-risk subgroups in terms of non-adherence to anticoagulation control should take into account both the adherence history of >50% of patients with RHD who were in chronic atrial fibrillation prior to surgery as well as geographic and socioeconomic circumstances.

KEYWORDS

rheumatic heart disease, international normalised ratio (INR), mechanical heart valve (MHV), low- to middle-income countries (LMICs), anticoagulation (AC)

## Introduction

In industrialised countries with predominantly degenerative heart valve pathologies, the proportion of patients receiving a mechanical prosthesis has steadily decreased to just 10% of all valve replacements (1). The situation is distinctly different in low- to middle-income countries (LMICs), where RHD still prevails. Contrary to general perceptions, the rate of prevalence of RHD has been increasing steadily, reaching 41 million in 2019 (2, 3). Since 2017, the number of deaths from RHD has also been increasing (2). In a global context, RHD remains the most common cause of death

from valvular heart disease, with an incidence rate almost double that of non-rheumatic valve lesions (2, 4).

As patients with RHD are on average 30 years younger than their Western counterparts with degenerative valve diseases (5), mechanical prostheses are favoured whenever a minimum level of anticoagulation compliance can be expected and when valves cannot be repaired (6, 7).

Unfortunately, for the vast majority of patients, their socio-economic circumstances are not conducive for availing anticoagulation therapy. Yet, in a resource-deprived environment where cardiac surgical capacity is insufficient (8, 9), the fear of re-operations often leads to an inordinate preference for mechanical valves. Hence, LMICs tend to adhere more rigidly to Western age guidelines (5, 10) than industrialised countries, where the age bracket for tissue valves has continuously been downward-adjusted in spite of their superior monitoring abilities (11, 12). This strict choice of mechanical valves over tissue valves results in a situation where the vast majority of redo valve surgeries in LMICs are done for valve thrombosis of mechanical prostheses (13) and not for the degeneration of tissue valves.

The fact that these clotted valves are not a rare phenomenon but occur disturbingly often, is not only an observation of clinicians on the ground (13), but also reflected in the poor survival results of these patients (14–18) and often directly related to poor anticoagulation compliance (16, 19–24). Nonetheless, unwavering optimism often prevails in clinicians, with the belief that patients will somehow manage their anticoagulation. Underlying this firm position is the belief that the need for a re-operation of a failed tissue valve represents the worst of all outcomes. Nothing confirms this immutable optimism that the vast majority of patients will cope with anticoagulation better than the fact that patients with thrombosed valves often receive mechanical valves again, although they keep returning for redo valve surgeries (13). Indeed, 19% of patients needing redo surgeries for clotted mechanical valves were shown to have at least another re-operation when the second mechanical valve clotted again (13).

Therefore, when it comes to heart valve choices in LMICs, we tend to follow a clinical decision-making process that is based on Western assumptions rather than the critical consideration of local realities. In a major study across Africa, it was found that approximately 90% of patients received mechanical valves and, although every 10th patient stopped warfarin, 12% had no international normalised ratio (INR) monitoring at all, while 34% had only sporadic INR measurements (25).

## Outcomes after mechanical valve replacement in patients with RHD in LMICS

Valve thrombosis is the predominant major valve-related event (13) in regions with poor INR control, often requiring emergency redo valve surgeries within less than 4 years after the initial surgery (13). As a consequence of the clinical emergency presentation, the re-operative mortality rate is high (14). Since a significant proportion of valve thromboses events are likely to occur in remote areas, deaths may often not be recognised as "valve-related."

As such, long-term results may, in reality, be worse than some local studies with selected patients may suggest. For instance, a third of all late deaths fell into this category in a recent study from Uganda (26). In a previous follow-up study at our institution, only 21% of remote deaths could be clearly assigned to "valve thrombosis"; however, if one added other categories of "sudden death" or "congestive cardiac failure with pulmonary edema," that result rose to 57%. In an Ethiopian study with a 27% 6-year mortality rate for single mechanical MVR, 22% of deaths were "sudden" or "unknown," 7% were lost to follow-up, and 44% died of "heart failure" without excluding underlying valve thrombosis (16). As such, the 6-year mortality rate after mechanical valve replacement of 21% in Cameroon (16) may also have been too optimistic. Confirming this, the 10-year death rate in young patients in India was 41% after mechanical MVR and 28% after mechanical AVR (18). However, for RHD, mechanical valve replacement showed poor results even if the patients underwent surgery in an industrialised country. In Australia's aboriginal population, the 10-year mortality rate after mechanical valve replacement was 38% (27). Similarly, Maori and Pacific Island women returning from mechanical heart valve replacement in New Zealand had a 7–8-fold higher relative risk of death compared with their European counterparts operated at the same institution (17) and more than double the risk of dying compared with those with tissue valves in spite of a 2.8-fold higher risk of re-operation in the latter group. In young adults in Saudi Arabia who underwent double valve replacement for RHD, the 15-year survival rate for those with bioprosthetic valves was 92% compared with 76% for those with mechanical valves (28), and, in a locally operated series in the Fijis, the 10-year mortality rate for mechanical heart valves for those with RHD was 24%, with death occurring on average 3.2 years after surgery (15).

## Insufficient compliance with anticoagulation

Without trivialising the seriousness of bleeding complications associated with over-anticoagulation, under-anticoagulation in LMICs by far exceeds the former (20, 29–34). Catastrophic clinical emergencies due to clotted valves have been linked to sub-therapeutic INR ranges falling below the recommended 2.5–3.5 (20, 35). In two African studies involving patients with RHD who had undergone mechanical valve replacement, most thromboembolic complications (20), including clotting of the valves (35), occurred at an INR <2.

Furthermore, under-anticoagulation has been linked to poor INR monitoring. For each 10% of missed INR tests, the odds of under-coagulation increase by 14% (36). Since LMIC patients require surgery predominantly for RHD (8, 9, 37), under-adherence is aggravated by the fact that 40% of patients with RHD undergoing valve surgery are already in atrial fibrillation (AF) pre-operatively and one-third of the remaining 60% develop AF after surgery (38).

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While anticoagulation control is also often suboptimal in industrialised countries (36, 39), poor adherence is a hallmark of LMICs. In an Ethiopian cross-sectional study, it was found that patients spent 52% of their time in sub-therapeutic INR ranges (30). In the Fijis, 39% of patients with mechanical valves either had no or poor adherence (21), and in an Indian study, it was found that only 8% were fully compliant (33) compared with 25% in South Africa (40).

The degree of non-compliance becomes particularly evident when non-adherence is expressed as the percentage of time within the therapeutic INR range (%TTR). In industrialised countries, "safe anticoagulation" is defined as a TTR ≥60%–70% (39, 41), *de facto* lying between 59% and 67% according to a meta-analysis of 38 studies (32). Time below range and thromboembolism exhibits a significant correlation (32). Reflecting a dangerously low compliance level, the TTR has been found to be notoriously low in LMICs, e.g., 43% in China (29), 42% in Thailand (31), 49% in South Africa (20), 28% in Ethiopia (30), and 44% in India (33), and <40% in a multi-country LMIC study (34). Most of the time, INRs were sub-therapeutic (30). Our own data obtained at the University of Cape Town confirm this trend, in spite of the fact that the drainage area is one of the best-administered provinces in sub-Saharan Africa, with two-thirds of the population living in a metropolis with access to three teaching hospitals offering open heart surgery. Of 21,826 tests conducted over 8 years in 552 consecutive mechanical heart valve recipients, the results revealed that only 27% of therapeutic time fell within the therapeutic range overall (Figure 1B). Over a period of 7 years, the frequency of post-operative tests decreased from 1 every 3–4 weeks to less than 1 per year (Figure 1C).

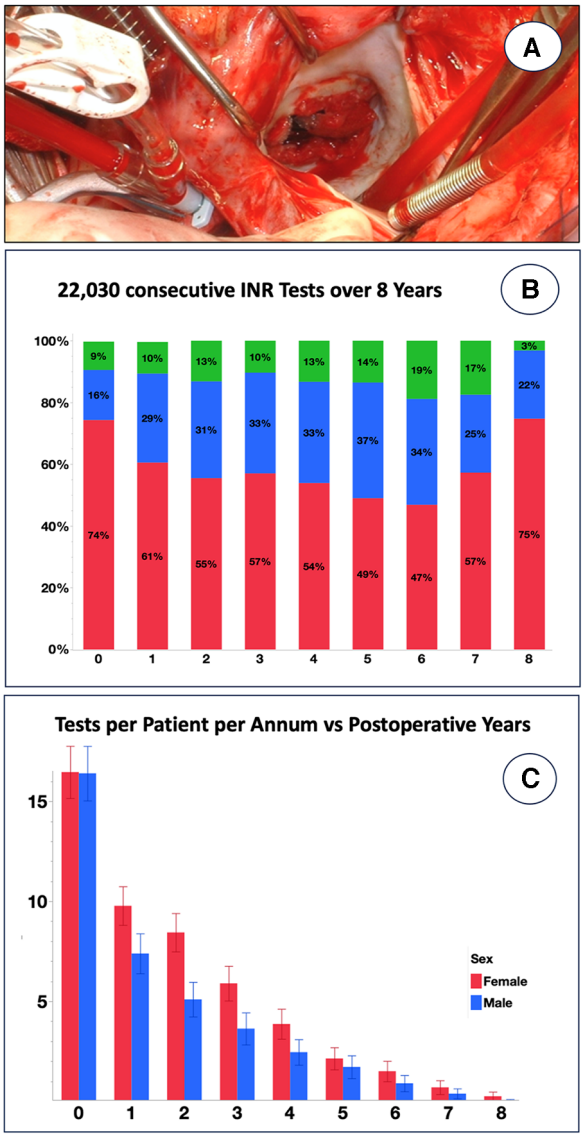


FIGURE 1
Eight-year INR follow-up of 552 consecutive patients receiving a mechanical prosthesis for rheumatic heart disease at Groote Schuur Hospital, University of Cape Town between 2015 and 2023. (**A**) Emergency re-replacement of clotted mechanical mitral valve <4 years after primary operation in a patient with notoriously low INR results [from (5) with permission]. (**B**) A total of 21,826 INR tests were recorded on the National Health Laboratory Database regardless of where the test was done. Although fluctuating over the years, INRs were below range most of the time [the percentage of INR time in range (TTR%) was 27.2% ± 24.1% (blue); below range was 61.4% ± 30.5% (red), and above range was 11.4% ± 17.3% (green)]. (**C**) Frequency of INR tests per patient, shown separately for men and women, was one every 3–4 weeks on average in the first post-operative year, but it fell progressively to 6–7/year at year 2 and eventually had fallen below 1 year by year 7.

## Risk-factors for poor compliance

Risk factors for under-adherence are young patient age (21, 40, 42, 43), lack of formal education (42), which is indirectly also associated with unemployment (21),and female gender (5, 21, 44). Unfortunately, some of these patient characteristics are, at the same time, the hallmark features of RHD, for which a significant association with low socio-economic circumstances exists (25, 37). Accordingly, a South African anticoagulation study in patients with RHD found those patients who completely defaulted on their INR controls to be significantly younger than those in the compliant group (35 vs. 43 years) (5). The observation that young patient age generally leads to lower adherence was highlighted by the fact that it also applied to patients who did follow-up with their INR testing but did so irregularly (40, 42).

Gender-wise, an overall prevalence of the female gender was continually shown (5, 44), confirming the findings of Thomson–Mangnall's key study from the South Pacific (21). However, apart from young age and female gender being associated with non-adherence to warfarin therapy, other independent predictors of discontinuation of warfarin therapy were related to those who did not understand why warfarin was needed in the first place, had a history of forgetting to take warfarin and had a travel time to a heart clinic exceeding 1 h (21). The last-mentioned predictor can be assumed for a majority of patients in low-income countries. There also seems to be an individual metabolic component. Counterintuitively, patients with a lower percentage of time in the therapeutic range typically had more INR tests

done per year than those with good INR control, indicating an individual preponderance to wider INR fluctuations (40).

Our analysis during the initial 30 post-operative days confirmed this observation: Applying partition modelling of the INR test intervals (INR gaps) against therapeutic INR ranges showed that the percentage of time in the therapeutic range was the highest when the INR gap was ≥17 days, less so when the interval fell between 4 and 17 days, and worse when it fell below 4 days. While this provisional criterion for fewer INR tests may allow a narrowing of the focus group, the low overall number of tests "in therapeutic range" shows that, in a majority of patients, sub-optimal anticoagulation coincides with dismal surveillance. To what extent poor surveillance overlaps with poor medication compliance remains speculative—a topic in which anticoagulation and anti-retroviral therapy share some ground. Yet, cultural contributors also play a strong role. Although the time in therapeutic range was indistinct between South African black, white, and mixed-race women in our cohort, it was distinctly lower in black men vs. white ($p = 0.015$) and mixed-race ($p = 0.016$) men.

## Balancing harm

Most importantly, the risks in the use of mechanical valves in regions dominated by RHD are acute, and often catastrophic, events. In an LMIC such as South Africa, 74% of redo valve operations were for clotted valves less than 4 years after the original operation, with 73% presenting as clinical emergencies (44). However, because of the acute nature of the event, re-operations for mechanical valves are associated with significantly high mortality rates. In a study from Turkey, it was found that redo surgery for mechanical valves exhibited a three times higher operative mortality rate than that for tissue valves (14), and 16% of South African patients experienced critical post-operative complications following the re-operation of a mechanical valve (13). In a cohort of the 1990s involving Maori and Pacific Island women, it was found that serious thromboembolic events occurred in 57% of women with mechanical valves within 10 years. Although these first-generation tissue valves used in these studies experienced a 3-fold higher re-operation rate than mechanical valves, the relative risk of death was 2.2 times higher after mechanical valve replacement (17). In a most recent study of pregnant women among Bangladeshi patients with mechanical valves, it was found that 12% had thrombus formation on the leaflets and 3% had warfarin embryopathies, with 35% requiring termination of pregnancy in the first trimester (45).

When considering tissue valves in young patients with RHD, circumstances have to be taken into account that hold different levels of significance in Western countries. A delayed re-intervention, or even the lack of it, with the associated ventricular damage and increased mortality (46), is predominantly seen in regions where even primary operations are provided to only a fraction of those in need (8, 9, 47).

At the same time, mortality of tissue valve re-operations has continually decreased over time. While it was over 40% in the 1960s/1970s (48), the operative mortality rate of a first re-operation in a modern series is 3%–4% for AVRs (49–51) and 4%–8% for MVRs (52, 53).

As much as valve-in-valve TAVRs are seen as a remedy to further lower the bar towards tissue valves in industrialised countries, they will remain a distant dream until costs have significantly decreased and delivery has been simplified to reflect the largely unsophisticated infrastructure of LMICs outside metropolitan centres where the majority of patients with RHD reside (8, 9).

## Unmet needs

The dilemmas faced by those who need heart valve replacements for RHD in LMICs are 2-fold: first, contemporary heart valves are catering for the elderly patients of industrialised countries, where mechanical prostheses were nearly abandoned in favour of tissue valves. As such, there is minimal commercial incentive to produce less thrombogenic valve designs. At the same time, the increasing number of older patients receiving tissue valves contributed to the limited translation of the exciting scientific breakthroughs of new tissue treatments over the past decades. The slower bioprosthetic degeneration processes observed in older patients allowed commercial valve manufacturers to stall implementing the often radically different tissue treatments (54, 55), thus avoiding the costly regulatory processes of non-incremental changes. Yet, there may be hope on the horizon for the hitherto neglected millions of young heart valve recipients for RHD, as their plight is shared with those patients of industrialised countries who are too young for contemporary TAVR and are therefore excluded from transcatheter solutions.

With the hopes for more reliable anticoagulation options dashed in LMICs, when direct oral anticoagulants (DOACs) were not approved for mechanical heart valves, the only alternatives are either significantly less thrombogenic mechanical prostheses or radically different materials for soft-leaflet valves that make them as durable as well-anticoagulated mechanical valves.

As most mechanical heart valves represent designs of the 1970s, little progress has been made towards improved fluid dynamics with better mitigation of platelet activation and clot formation. Yet, some significant innovations have recently emerged. The discovery that high-amplitude flow velocities of short duration close to valve closure cause substantial shear stress with subsequent initiation of the blood coagulation pathways (56) makes disruptive tri-leaflet designs a promising alternative (Figure 2). For tissue valves, on the other hand, the late acknowledgement that remnant immunogenicity plays a crucial role in accelerated bioprosthetic mineralisation (60–62) has validated the use of decellularisation in tissue treatment (54, 63). Yet, clinical trials are scarce, either limited to decellularised homografts (64, 65) or non-cross-linked xenografts (66, 67), with the vast majority of publications failing to assess calcification. However, the fact that the remaining extracellular matrix still exhibited xenogenic antigens (68, 69) further contributed to the revival of the concept of polymer leaflets (70). The first one to pioneer the concept in patients was Foldax®. Soon after

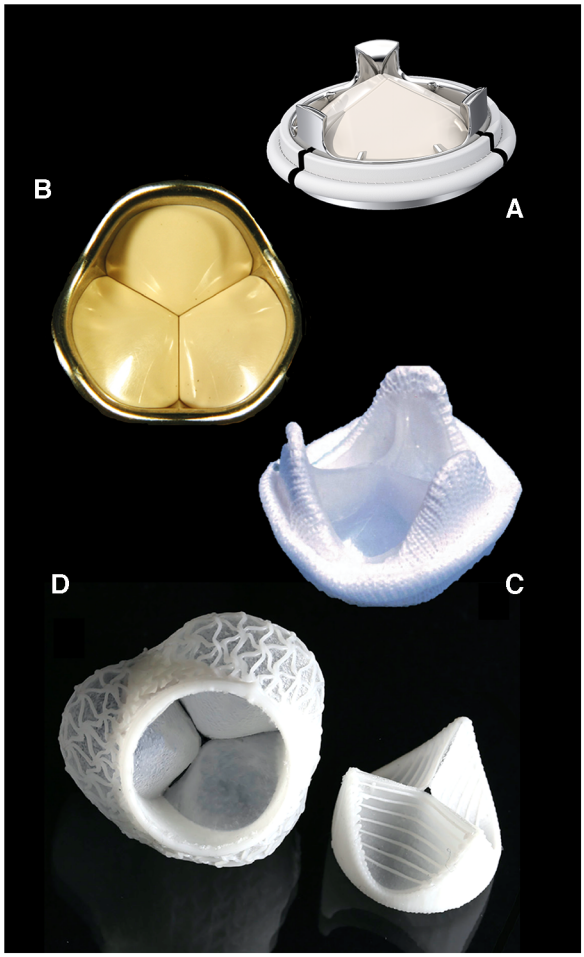


FIGURE 2
Contemporary valve prostheses catering to elderly patients and optimal anticoagulation controls of industrialised countries are poorly suited for LMICs. Valve designs promising to comply with the high demands of young patients with RHD on leaflet durability and thrombogenicity will rapidly materialise if young patients and poor INR control become the benchmark of valve design. Typical disruptive technologies in-waiting include tri-leaflet mechanical valves: (**A**) Triflo, Novostia, Switzerland (with permission); (**B**) Sievers valve, [from (57) with permission] and polymeric valves; (**C**) Reul–Ghista valve [from (58) with permission]; and (**D**) ETH Zurich valve [from (59) with permission].

successful "first-in-man" implants in aortic valves (70), it was recognised that young patients with RHD present an ideal opportunity for introducing a disruptive technology that could potentially create non-calcifying soft-leaflet valves for life. Should polymer valves prove successful, it will also remove the age barrier for TAVR in patients younger than 60 years in high-income countries.

## Discussion

The reality of anticoagulation control after mechanical heart valve replacement in regions where RHD predominates is not comparable to that in developed countries. Factors such as lower life expectancy due to different underlying pathologies, delayed surgery, and inadequate "compliance" with anticoagulation do not justify the direct uncritical application of Western guidelines. Nonetheless, before radically different heart valve prostheses become available, the choice will continue to be between mechanical and tissue valves.

Our data obtained from 552 consecutive patients who had a mechanical valve replacement for RHD confirm key findings from studies conducted in other LMICs. First, the patients were notoriously under-anticoagulated, although they had carefully been educated by social workers before being discharged into local care regarding the importance of ongoing tests and not falling below a defined INR limit. The rapid decrease in the number of INR tests from $16.1 \pm 10.0$ to $1.0 \pm 3.4$ per patient per annum over as short a period as 6 years cannot only be explained by a stabilisation of INR levels over time, as this trend was observed across the board.

Going forward, Thomson–Mangnall's principles (21) provide a starting point for identifying patients at risk for poor adherence: With a significant proportion of patients being on anticoagulation for chronic atrial fibrillation at the time of surgery, an assessment of their compliance history should be possible. If a patient's test records fall outside an acceptable frequency and INR range, tissue valves in combination with non-vitamin K oral anticoagulants have been recommended (71) as a more stable form of anticoagulation, eventually leading to better survival. The rationale behind this is the higher efficacy of anticoagulation in atrial fibrillation than in mechanical heart valves, where higher stroke rates were seen even in industrialised countries despite reasonably good anticoagulation (72, 73).

A travel time of more than an hour to the next INR clinic was highlighted as the second risk factor for safe anticoagulation. This may again pose a challenge since, although rural patients often move to a metropolitan area to increase their likelihood of undergoing valve surgery, a sizeable proportion eventually return to their rural home, particularly male patients at the peak of their productivity who have dependants at their point of origin.

Most importantly, one must individually weigh the risks of poor INR control against a patient's life expectancy. To name a few life-shortening contributors, patients from rural backgrounds and low socio-economic status often present with advanced disease. Similarly, the presence of aortic regurgitation and/or mitral regurgitation also contributes to excess mortality rates.

Crucially, a surgeon working in an LMIC needs to have the self-confidence to be assertive, even if a decision is at variance with what one would normally make under the circumstances prevailing in a developed country. This critical re-assessment may begin at the collective clinical decision level, where differentiated clinical intuition tends to get overruled by chronological age as the primary determinant for valve choice.

On their part, valve companies need to recognise the fact that neither can septua- and octogenarian patients serve as the point of reference for bioprosthetic degeneration, nor are sophisticated self-tests for controlling anticoagulation available. Once young patients from LMICs have been accepted as the challenging new benchmark for valve replacement, exciting new concepts will emerge, leading

to better prostheses for all (Figure 2), thus justifying the rollout of such technologies to poor regions with a high burden of RHD in spite of low-profit margins.

## Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

## Ethics statement

The studies involving humans were approved by the University of Cape Town Human Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

## Author contributions

PZ: Conceptualisation, Supervision, Writing – original draft, Writing – review & editing. PH: Data curation, Formal Analysis, Writing – review & editing. TP: Resources, Supervision, Writing – review & editing.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The reviewer TF declared a past co-authorship with the authors PH, PZ to the handling editor and confirmed the absence of any ongoing collaboration during the review.

## Publisher's note



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# Novel role of cardiovascular MRI to contextualise tuberculous pericardial inflammation and oedema as predictors of constrictive pericarditis

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Tuberculosis (TB) and human immunodeficiency virus/acquired immunodeficiency syndrome have reached epidemic proportions, particularly affecting vulnerable populations in low- and middle-income countries of sub-Saharan Africa. TB pericarditis is the commonest cardiac manifestation of TB and is the leading cause of constrictive pericarditis, a reversible (by surgical pericardiectomy) cause of diastolic heart failure in endemic areas. Unpacking the complex mechanisms underpinning constrictive haemodynamics in TB pericarditis has proven challenging, leaving various basic and clinical research questions unanswered. Subsequently, risk stratification strategies for constrictive outcomes have remained unsatisfactory. Unique pericardial tissue characteristics, as identified on cardiovascular magnetic resonance imaging, enable us to stage and quantify pericardial inflammation and may assist in identifying patients at higher risk of tissue remodelling and pericardial constriction, as well as predict the degree of disease reversibility, tailor medical therapy, and determine the ideal timing for surgical pericardiectomy.

KEYWORDS

TB pericarditis, constrictive pericarditis, pericardial inflammation, pericardial oedema, CMR, pericardial effusion, risk stratification, diastolic cardiac dysfunction

## Introduction

The pericardial sac surrounds the heart in a unique double-layered manner, containing a small amount of fluid between these layers, and it serves to both stabilise the heart and provide a favourable environment to ensure minimal friction during each cardiac cycle (1). Tuberculosis (TB), the most common cause of pericardial constriction in endemic areas (2–5), can however disrupt this favourable environment, leading to a state of severe inflammation dominated by maladaptive tissue remodelling, fibrosis, and calcification (6–8). As a result, the heart becomes encased with impaired diastolic cardiac filling, characterising constrictive pericarditis (CP) (9, 10).

Chronic CP represents an irreversible state of haemodynamic compromise and is an indication for pericardiectomy, as untreated cases exhibit poor outcomes (9). While potentially curative, pericardiectomy carries high surgical risk, with significant peri- and post-operative morbidity and mortality (9–12). Early diagnosis and treatment, particularly when pericardial constriction is less advanced and associated with less

fibro-calcification, lead to better surgical outcomes (13). On the other hand, premature intervention carries the risk of exposure to unnecessary surgery, as the dynamic inflammatory component seen in effusive-constrictive pericarditis (ECP) is typically reversible (14, 15). Therefore, optimal surgical timing is crucial to ensure favourable patient outcomes, but it remains challenging and often elusive in clinical practice.

This case-based review aims to illustrate the potential of new cardiovascular magnetic resonance (CMR) imaging data, which enables the staging and quantification of pericardial inflammation (16), in offering significant improvements in prognostication by identifying patients at higher risk for developing pericardial constriction. It may also guide clinical decision-making to optimise medical and surgical interventions and assist in determining the optimal timing for pericardiectomy.

## Case 1

A 36-year-old human immunodeficiency virus (HIV)-uninfected man presented with a 2-week history of dyspnoea, constitutional symptoms, and clinical findings suggestive of a pericardial effusion.

The diagnosis of a large circumferential pericardial effusion was confirmed via transthoracic echocardiogram (TTE), and a pericardiocentesis was performed, which confirmed a definitive diagnosis of rifampicin-sensitive TB pericarditis (17). Despite maximal drainage of the pericardial effusion (>1,000 ml), constrictive physiology (18) persisted, further classifying this case as ECP (19).

He was subsequently initiated on the local first-line anti-tuberculous chemotherapy regimen (20) without adjunctive anti-inflammatory therapy and was scheduled for review at 3-month intervals.

At the 3-month follow-up, he exhibited clinical features of predominantly right heart failure despite being compliant with his anti-tuberculous chemotherapy, and a diagnosis of constrictive pericarditis was confirmed via TTE (18, 19, 21).

A CMR study was performed, which demonstrated severe residual pericardial inflammation, as evidenced by diffuse, circumferential hyperenhancement of the thickened pericardium observed on late gadolinium enhancement (LGE) imaging (see Figure 1A). Areas of residual pericardial oedema were also identified, as demonstrated by the focal areas of increased T2 short tau inversion recovery (STIR) and T2 mapping signal (see arrows in Figures 1B,C), without any re-accumulation of the pericardial effusion. In addition, CMR confirmed constrictive physiology on free-breathing real-time cine sequences (22–24).

Based on the presence of constrictive physiology 3 months after the initiation of anti-tuberculous chemotherapy and in accordance with expert consensus recommending optimal surgical timing to be 6–8 weeks after the initiation of anti-tuberculous chemotherapy, the patient was referred for surgical pericardiectomy (25).

However, the patient declined surgical intervention at this time, and the best medical therapy was continued (anti-tuberculous chemotherapy and diuretics) in addition to planning further clinical follow-up.

After 4 months of anti-tuberculous chemotherapy, the patient was found to be asymptomatic with complete resolution of symptoms and free from all signs of constrictive physiology on repeat TTE, despite the patient having stopped his diuretic therapy in the weeks preceding this follow-up.

Repeat CMR confirmed the complete resolution of pericardial oedema on T2-STIR imaging and T2 mapping (see Figures 2B, C), with minimal residual pericardial inflammatory signal seen on LGE sequences (see Figure 2A).

### Case 1: discussion

ECP is an umbrella term used to describe the presence of constrictive physiology after drainage of a large pericardial effusion (19). Increased pericardial stiffness in this setting results from a

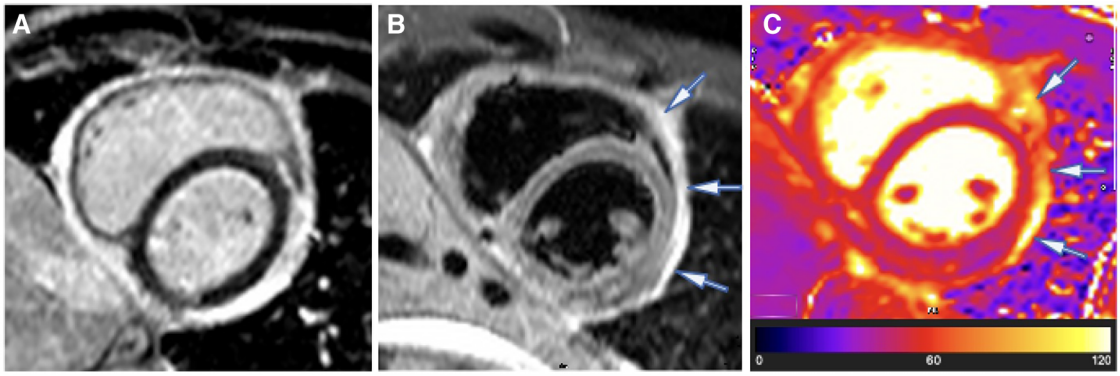


FIGURE 1
Case 1: 3-month CMR findings—sub-acute TB pericarditis with marked residual pericardial inflammation. (A) LGE image showing an intense circumferential pericardial signal indicative of marked circumferential pericardial inflammation. (B) T2-STIR and (C) T2 mapping images showing a high pericardial signal of segments overlying the LV lateral and anterior walls and anterior to the right ventricular (RV) free wall (indicated by arrows), with normal pericardial signal intensity of the other pericardial segments. Marked pericardial inflammation (A) demonstrates a risk of continued tissue remodelling and pericardial fibrosis; however, oedematous segments with acute pericarditis (arrows in B,C) represent reversible constrictive haemodynamics.

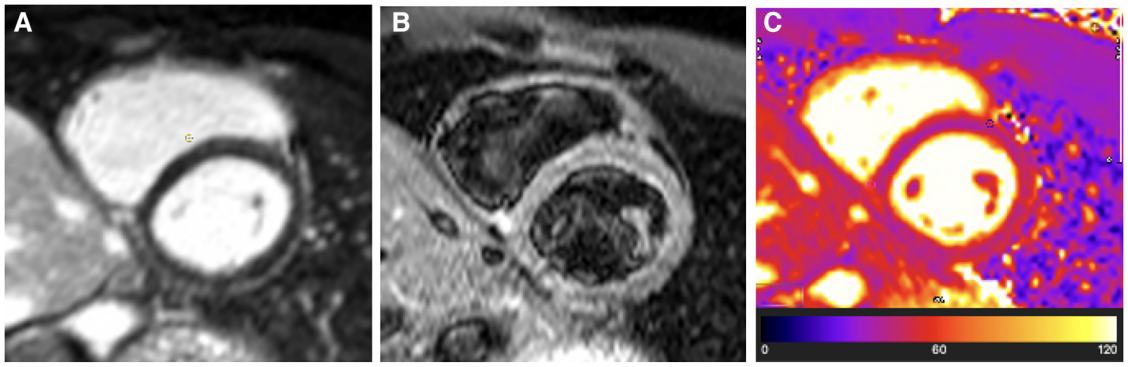


FIGURE 2
Case 1: 4-month CMR findings—burnt-out TB pericarditis. (**A**) LGE image showing normal pericardial signal intensity indicative of complete resolution of pericardial inflammation. (**B**) T2-STIR and (**C**) T2 mapping images showing normal pericardial signal intensities indicative of absent pericardial oedema. A burnt-out (resolved pericardial inflammation and oedema) CMR picture of TB pericarditis in the setting of non-constrictive haemodynamics is an indication that medical therapy can be stopped (or can be stopped as soon as the patient has completed the standard 6-month anti-tuberculous chemotherapy course) and that a pericardiectomy is not indicated.

variable contribution of (1) acute pericardial inflammation and oedema and (2) established pericardial scarring, which cumulatively result in physiologically significant constrictive haemodynamics, persisting despite the drainage of pericardial fluid (16, 26, 27).

Constrictive haemodynamics is a term used to describe a specific form of physiologically significant haemodynamic compromise seen in pericardial constriction due to severe restriction of diastolic cardiac filling by the thickened and adhered pericardium (27). This is characterised by two important physiological principles: (1) dissociation of intrathoracic and intracardiac pressures, which drives respirophasic and reciprocal filling rates of the left and right ventricles, and (2) enhanced ventricular interaction due to respirophasic septal shift, which causes reciprocal ventricular filling of the left and right heart (27). These features are evident in pressure-volume haemodynamics and imaging modalities in patients with pericardial constriction (19). However, as seen in this case of ECP, the term "constrictive haemodynamics" does not specifically address the underlying pathophysiologic mechanism responsible for the increased pericardial stiffness leading to this impairment.

Echocardiography is widely regarded as the first-line investigation for the assessment of constrictive haemodynamics (25, 28, 29) and effectively demonstrates the principles of haemodynamic impairment through a combination of three echocardiographic measurements—also commonly known as the Mayo Clinic Criteria. (1) Respirophasic ventricular septal shift is used as a sensitive inclusion marker (87%) of constriction, whereafter a combination with either (2) medial e prime (e′) ≥9 cm/s (indicating normal intrinsic myocardial relaxation ability) or (3) hepatic vein early expiratory diastolic wave flow reversal ratio ≥0.79 is used to increase specificity to 91% (18).

Also, strain evaluation using 2D speckle tracking has yielded promising results (30). It illustrates that pericardial tethering (pericardial attachment to the epicardial cardiac surface pulling on the myocardium) causes decreased peak systolic strain in free cardiac walls (adjacent to the adherent pericardium), while septal peak systolic strain is maintained—the strain equivalent of annulus reversus seen on tissue Doppler. A left ventricular (LV) lateral wall to LV septal wall strain ratio of <0.96 was shown to diagnose constrictive haemodynamics with a sensitivity of 89% and a specificity of 96% (30).

Although effective in demonstrating the constrictive haemodynamics seen in ECP, its inability to differentiate between the underlying mechanisms responsible for constrictive haemodynamics remains a significant limitation. Therefore, whether the constriction is related to a transient, reversible process or whether it is chronic and irreversible cannot be judged by looking at the presence or absence of constrictive haemodynamics alone.

CMR is currently described as a second-line investigation for evaluating pericardial disease (25, 28). Apart from its ability to demonstrate constrictive haemodynamics with high sensitivity and specificity (22–24), CMR can delineate potential surgical dissection planes pre-operatively (seen as epicardial and pericardial separation by epicardial fat of variable thickness) and contribute to the risk assessment plan prior to pericardiectomy (28, 31). CMR's unique ability to quantify and stage pericarditis, based on the presence of the distinct processes of pericardial inflammation and oedema, sets it apart from other imaging modalities and enables us to unravel the complex mechanisms underpinning constrictive haemodynamics (16).

Pericardial inflammation results in neovascularisation, fibroblast proliferation, and expansion of the pericardial extravascular space, causing the otherwise relatively avascular pericardium to accumulate and retain gadolinium-based contrast agents, leading to increased signal on LGE imaging (32, 33). Positron emission tomography (PET) data have shown this local pericardial inflammatory response to be especially intense in the case of TB pericarditis, where a pericardial inflammatory intensity [often quantified using the maximum standardised uptake value (SUVmax) on PET imaging] above a particular threshold was independently associated with a tuberculous aetiology (34).

Studies have also previously looked at the cytokine profile of this intense pericardial inflammatory response on a biochemical level,

which demonstrated a pro-fibrotic inflammatory character dominated by high amounts of pro-inflammatory cytokines and low levels of anti-fibrotic N-acetyl-seryl-aspartyl-proline (Ac-SDKP) (35–37). Specifically, interleukin-1 beta (IL-1B), tumour necrosis factor-alpha (TNF-α), and transforming growth factor-beta (TGF-β) are detectable in high quantities within TB pericardial effusions, and these have been closely associated with fibrosis in the setting of chronic inflammatory diseases, including TB (36, 37).

Ac-SDKP is a naturally occurring immunomodulatory peptide hydrolysed from thymosin β4 by prolyl-oligopeptidase (POP) and is converted to its inactive peptides by angiotensin-converting enzyme (ACE) (7, 35). It is hypothesised that Ac-SDKP serves a housekeeping function within the pericardium by inhibiting various major drivers of inflammation and fibrosis (see Figure 3). These include the inhibition of the galectin-3-induced TGF-β/Smad2 signalling pathway, a direct inhibitory effect on TGF-β, and a direct blocking effect on collagen synthesis. Ac-SDKP is also thought to inhibit TNF-α, resulting in a subsequent reduction of macrophage and T-cell activation and lower levels of pro-inflammatory cytokines (see Figure 3) (6–8, 35).

Furthermore, routinely available angiotensin-converting enzyme inhibitor (ACE-inhibitor) therapy was subsequently investigated and has proven effective in upregulating both local pericardial and systemic Ac-SDKP levels (7, 8), with the potential to play a pivotal role in promoting anti-fibrotic activity to reduce pericardial inflammation, fibrosis, and eventual pericardial constriction. This clinical application is still unexplored in current TB pericarditis literature.

It remains unclear whether this pro-fibrotic nature of the inflammatory response itself, the high intensity of the pericardial inflammation seen in TB pericarditis, the prolonged duration of the pericardial inflammation (due to the chronicity of TB), or another feature of the TB pathology *per se* causally drives the high incidence of pericardial constriction following TB pericarditis (38).

Although CMR does not specifically capture the pro-fibrotic nature of the inflammatory response, the intensity of pericardial inflammation can be accurately detected and quantified by evaluating the pericardial signal intensity on LGE imaging, making this CMR sequence an important modality capable of demonstrating this substitute marker of pericardial inflammation (39). Using a greater intensity of pericardial inflammation (in isolation) as a prognostic marker for developing pericardial constriction has however yielded conflicting results. While it has effectively demonstrated a more favourable prognosis by expressing the contribution of active pericardial inflammation in constrictive haemodynamics, often associated with the acute reversible phase of pericarditis (14, 15), it has also been associated with an increased risk of developing recurrent, chronic, and constrictive pericarditis (15, 16, 40–42).

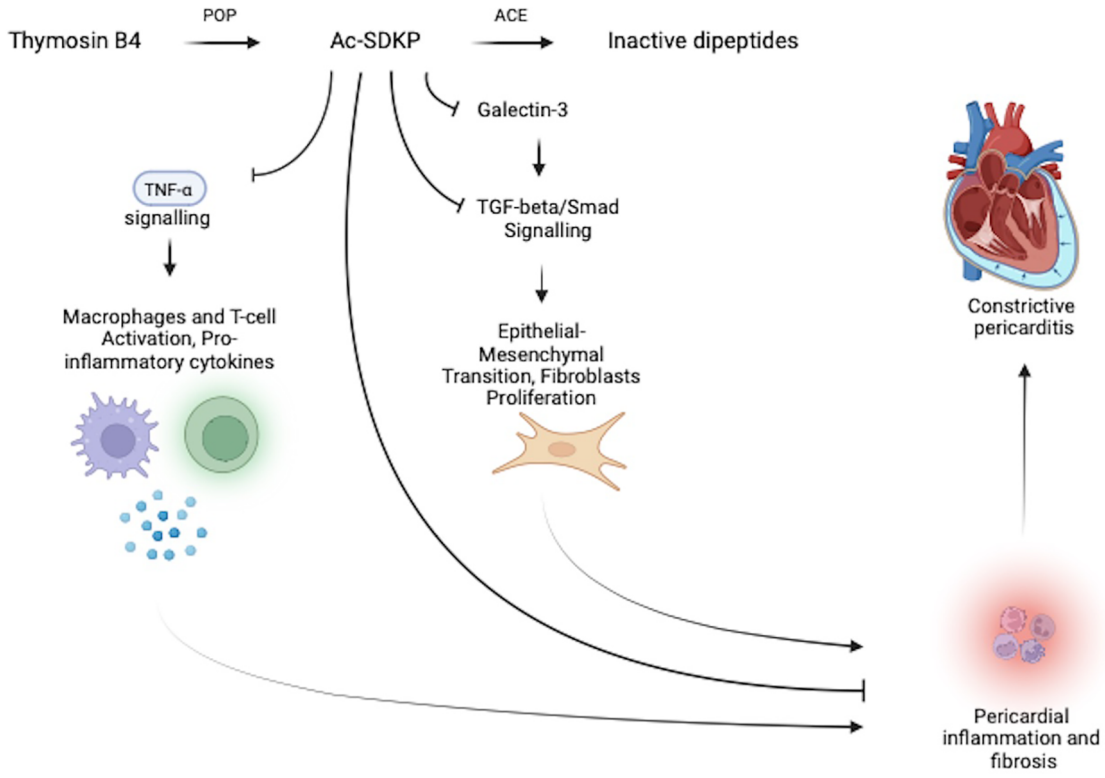


FIGURE 3
Pericardial housekeeping function of Ac-SDKP regulates pericardial inflammation and fibrosis. The anti-inflammatory peptide Ac-SDKP downregulates pericardial inflammation and fibrosis through its inhibitory effects on: (1) the galectin-3 induced TGF-β/Smad2 signalling pathway and (2) downstream and direct inhibitory effects on TGF-β, collagen synthesis, and TNF-α. Ac-SDKP is converted to its inactive peptide by ACE, which may allow for a convenient therapeutic target to upregulate both local (pericardial) and systemic Ac-SDKP levels through ACE-inhibitor therapy.

Based on a study correlating CMR signals with histology, it has recently been suggested that a combination of pericardial inflammation and oedema signifies CMR evidence of acute pericarditis (16). In contrast, the absence of these two features defines a state of inert, burnt-out pericarditis (16). Between these extremes lie sub-acute and chronic pericarditis. Although both sub-acute and chronic pericarditis are associated with variable quantities of pericardial inflammation, sub-acute pericarditis is characterised by patchy areas of residual pericardial oedema, whereas chronic pericarditis is distinguished by the absence of residual pericardial oedema (16). Therefore, CMR can be used not only to quantify pericardial inflammation but also to stage the chronicity of disease by combining an analysis of inflammation (LGE) with that of oedema (T2-STIR and T2 mapping) (16). T2-STIR sequences, as well as T2-weighted mapping, are highly specific for detecting increased water content in tissues and can therefore identify pericardial oedema, a marker of acuteness and reversibility of pericarditis and potentially its complications, particularly when seen in the setting of residual pericardial inflammation (16).

In contrast with idiopathic pericarditis (39), TB pericarditis may display a prominent chronic pericarditis phase (absent pericardial oedema), combined with high-intensity residual pericardial inflammation, as illustrated in the following case.

## Case 2

A 26-year-old HIV-uninfected man presented with constitutional symptoms, exertional dyspnoea, and a clinical examination suggestive of a pericardial effusion. TTE confirmed a large, circumferential pericardial effusion conducive to pericardiocentesis, which was subsequently performed and confirmed a diagnosis of rifampicin-sensitive, definite TB pericarditis (17). This case was classified as ECP, as evidenced by the persistence of constrictive haemodynamics following successful pericardiocentesis (19).

A CMR was performed 6 days after the initial pericardiocentesis (baseline study), which revealed a large re-accumulated circumferential pericardial effusion. The CMR further illustrated intense residual pericardial inflammation on LGE sequences (see Figure 4A) but no associated acute pericardial oedema on T2-weighted STIR or T2 mapping sequences (see Figures 4B,C).

The patient was initiated on the local first-line anti-tuberculous chemotherapy regime (20) without adjunctive anti-inflammatory medication and was followed up at a primary healthcare facility. Around the time of completing his anti-tuberculous chemotherapy (6 months after treatment initiation), the patient was noted to have developed progressive signs of predominantly right-sided cardiac failure. Due to poor access to transport and a congested medical service in a resource-limited setting, specialist follow-up was delayed, and the patient was only seen at a cardiology service 3 months later. At this stage, the TTE confirmed constrictive haemodynamics, and a repeat CMR study demonstrated complete resolution of the prior intense pericardial inflammation observed on LGE imaging (see Figure 5A). No associated pericardial oedema was present on either T2-STIR or T2 mapping sequences (see Figures 5B,C), suggesting that a burnt-out pericardial constriction phase was entered with little to no expectation of spontaneous resolution of the pericardial constriction.

The patient was subsequently referred for early pericardiectomy, which confirmed constrictive pericarditis with organised fibrosis of the pericardium demonstrated on histology.

## Case 2: discussion

Employing CMR to stage and quantify pericardial inflammation could potentially assist not only in prognosticating

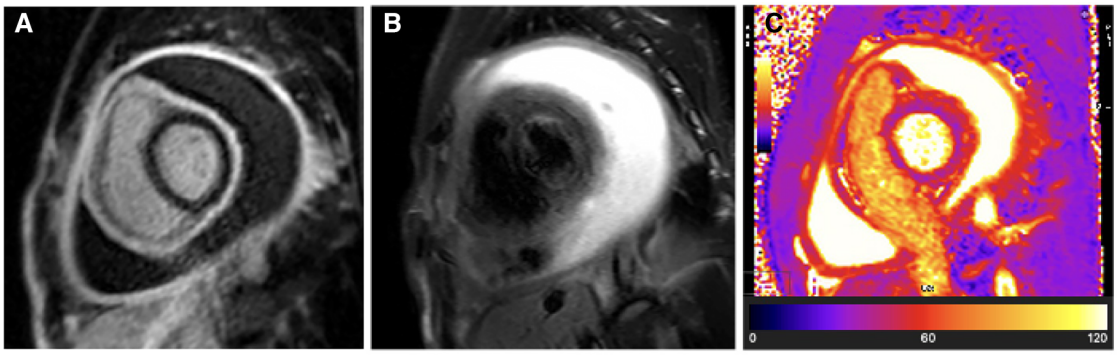


FIGURE 4
Case 2: Baseline CMR findings—chronic TB pericarditis with intense residual pericardial inflammation and a large recurrent pericardial effusion. (A) LGE image showing hyperintense circumferential pericardial signal indicative of intense circumferential pericardial inflammation. (B) T2-STIR and (C) T2 mapping images showing normal pericardial signal intensities indicative of absent pericardial oedema. The combination of (1) intense pericardial inflammation in the setting of (2) chronic pericarditis (absent pericardial oedema) likely represents the highest cumulative risk of developing constrictive pericarditis. Despite the visceral and parietal pericardium being separated by a large pericardial effusion, the pro-fibrotic "sticky" visceral and parietal pericardium is in the process of tissue remodelling and has a high risk of becoming adherent as the residual pericardial effusion resorbs. Compressive effects from the residual pericardial effusion still contribute to reversible constrictive haemodynamics; therefore, medical therapy needs to be continued until the pericardial fluid has completely resorbed.

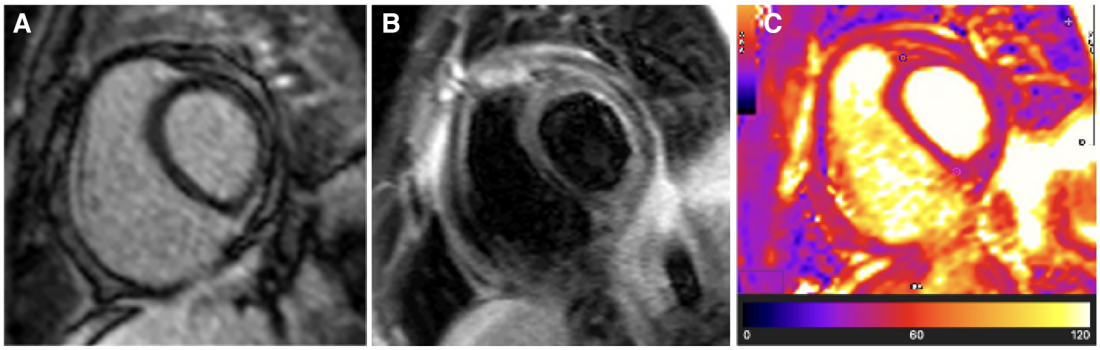


FIGURE 5
Case 2: 9-month follow-up CMR findings—burnt-out TB pericarditis. (A) LGE image showing the absence of a pericardial signal, demonstrating complete resolution of pericardial inflammation. (B) T2-STIR and (C) T2 mapping images showing normal pericardial signal intensities, demonstrating the absence of pericardial oedema. A burnt-out (resolved pericardial inflammation and oedema) CMR picture of TB pericarditis in the setting of constrictive haemodynamics is an indication for pericardiectomy.

patients at higher risk of tissue remodelling and pericardial constriction but also in predicting the degree of disease reversibility, tailoring medical therapy, and determining the ideal timing for surgical pericardiectomy (9–16).

When choosing the most appropriate therapy, the stage of pericardial inflammation (as indicated by the presence of residual pericardial oedema on T2-STIR and T2 mapping) could be used to predict the reversibility of constrictive haemodynamics, while the intensity of pericardial inflammation (as quantified on LGE sequences) could be used to predict risk for continued pericardial tissue remodelling and fibrosis (see Figure 6) (14–16).

Staging pericarditis offers a potentially elegant solution to the previously mentioned discrepant findings seen in the CMR-derived pericardial inflammatory signal to predict constriction risk. Based on this staging model, oedema (T2-STIR and T2 signal) tracks acuteness, whereas inflammation (LGE signal), although typically present in the acute phase, can also extend into the sub-acute and chronic phases (16). Therefore, an analysis of the stage of pericarditis may be required in conjunction with the inflammatory intensity to contextualise the inflammation and subsequent constriction risk (see Figure 6).

The current best evidence suggests that, in acute pericarditis, an acute inflammatory response combined with pericardial oedema causes the pericardium to stiffen and become less compliant (16). Depending on the intensity and distribution of inflammation and oedema, this initial inflammatory response can result in decreased pericardial compliance and transient constrictive haemodynamics (16). However, even though the acute stage is transient and typically reversible, the intensity of inflammation seen in this stage may predict the future risk of dysfunctional, fibrotic healing and persistent constrictive haemodynamics, i.e., chronic CP (15).

In sub-acute pericarditis, oedema is seen to have resolved in some, but not all, pericardial segments, leaving patchy areas of the T2 signal where oedema persists and actively contribute to constrictive haemodynamics (16). Areas with residual inflammation but resolved oedema are thought to represent a stage in the process of healing, which can occur either with or without the formation of visceral–parietal adhesion—once again, the risk of healing with fibrosis is likely dependent on the intensity of the initial inflammatory response during the acute stage of the disease (15, 16).

Finally, in chronic pericarditis, inflammation of varying intensity may persist, along with the potential for ongoing tissue remodelling and fibrosis. Oedema is observed to have completely resolved; therefore, areas with established pericardial fibrosis are permanent and irreversible (16). In this chronic stage of the disease, if constrictive haemodynamics is present, it is likely to be irreversible, and pericardiectomy is indicated.

## Constrictive haemodynamics—an added prognostic opportunity?

The permanence of constrictive haemodynamics needs to be assessed within the context of its associated pericardial inflammation (on LGE imaging) and oedema (T2-STIR or T2 mapping), i.e., stage of the pericarditis (16). While constrictive haemodynamics might be transient and reversible in acute pericarditis, the presence of constrictive haemodynamics in sub-acute and chronic pericarditis represents two points on the spectrum of ECP, where the relative contribution from acute (and subsequently reversible) constrictive haemodynamics becomes sequentially smaller, while the contribution from established pericardial scarring (and subsequently non-reversible constrictive haemodynamics) becomes progressively larger (16). Therefore, the presence of constrictive physiology at any stage of the disease, particularly in later stages, is likely a sign of increased pericardial fibrosis burden and represents a state of impaired physiological diastolic reserve brought about by established pericardial scarring, even in the absence of a final constrictive outcome. However, the sooner a patient transitions from constrictive to non-constrictive haemodynamics, i.e., transitions in the acute rather than the sub-acute stage, the less significant the limitation of their final physiological diastolic reserve is likely to be.

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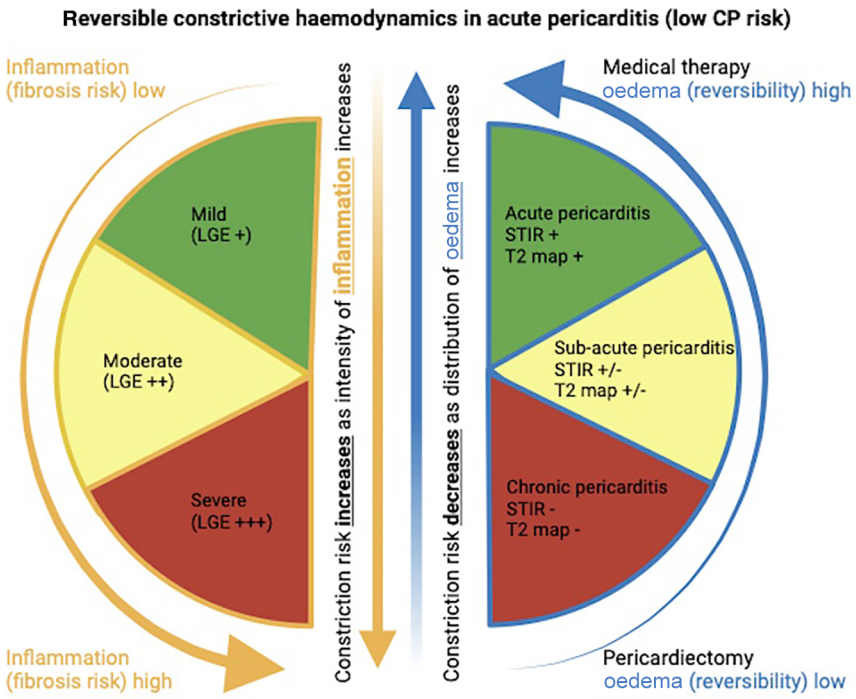


The above figure demonstrates two parallel but mechanistically different pericardial processes namely pericardial inflammation (increasing intensity illustrated by the orange arrows) and pericardial oedema (increasing intensity illustrated by the blue arrows). These processes can be assessed individually on cardiovascular magnetic resonance (CMR) imaging to inform constrictive pericarditis (CP) risk. High-risk features are expressed in red, medium-risk features are expressed in yellow, and low-risk features are expressed in green, for pericardial inflammation and oedema respectively.

Pericardial oedema is a marker of acuteness (reversibility) and is used to stage pericarditis. In acute pericarditis (green), increased tissue water content (oedema) on CMR is expressed by increased signal on T2 short tau inversion recovery (STIR +) and T2 mapping (T2 map +) sequences. In sub-acute pericarditis (yellow), patchy areas of residual oedema are present in some, but have resolved (STIR +/- and T2 map +/-) in other areas. In chronic pericarditis (red), all pericardial oedema has resolved (STIR - and T2 map -).

The intensity of pericardial inflammation (orange arrow) can be quantified on CMR late gadolinium enhancement (LGE) sequences, where increasing intensities of pericardial inflammation (LGE + (green), LGE ++ (yellow) and LGE +++ (red)) represent an increasing risk for pericardial tissue remodeling and fibrosis.

The interaction between the intensity of pericardial inflammation and oedema/disease stage, subsequently informs constrictive pericarditis (CP) risk.

The figure illustrates that high levels of oedema, demonstrating acute pericarditis (green), typically reduces the risk of CP significantly as the majority of patients, irrespective of inflammatory intensity in the acute phase, recover, without permanent constriction. However, as oedema intensity reduces (yellow and red), the residual intensity of pericardial inflammation becomes an important marker of constriction risk. Individuals with low levels of pericardial oedema (sub-acute pericarditis (yellow)) or an absence of pericardial oedema (chronic pericarditis (red)), associated with a high residual inflammatory burden (red), represent the highest risk of chronic CP.

Acute pericarditis (reversible) is an indication for medical therapy whereas chronic pericarditis (non-reversible), in the presence of constrictive haemodynamics, is an indication for pericardiectomy.

FIGURE 6
CMR-based model to predict constrictive pericarditis risk—a product of pericardial inflammation and oedema.

## T2-weighted STIR—an indicator of reversibility or merely a marker of chronicity?

The reversibility of constrictive haemodynamics, as assessed by both (1) the intensity of pericardial inflammation (LGE imaging) and (2) pericardial oedema (on T2-STIR and T2 mapping), remains poorly explored. Prior studies that evaluated the contribution of active pericardial inflammation in constrictive physiology were conducted in the "pre-staging" era of pericarditis (14, 15). Notably, these studies only evaluated the contribution of LGE, a significant methodological limitation that may now be overcome in the era of multi-parametric CMR that includes oedema imaging and T2 mapping. Although one would expect a relatively linear relationship between an intensely inflamed pericardium and pericardial oedema and that oedema would resolve as the intensity of inflammation subsides, a clear disconnect between inflammatory and oedema signals is commonly observed in the context of TB pericarditis. This then begs the question of whether residual pericardial inflammation, in the absence of associated oedema (chronic pericarditis), represents residual reversible haemodynamics. Further research utilising multi-modal CMR in regions with a high burden of TB is clearly required.

## Conclusion

Although there remains uncertainty regarding the relative contribution of isolated pericardial inflammation (the absence of oedema) to reversible constrictive haemodynamics, there is no doubt that CMR may add significant diagnostic value in complex clinical cases of pericarditis. This becomes especially relevant in low- to middle-income settings like sub-Saharan Africa, where TB pericarditis is prevalent and carries a high inherent risk of progression to pericardial constriction. Further studies are required to explore the relative contributions of pericardial inflammation and oedema as mutually non-exclusive entities (may co-exist without clear linearity), contributing to the final constrictive risk. The apparent disconnect between marked residual pericardial inflammation in the setting of chronic TB pericarditis (in the absence of pericardial oedema) needs to be further researched to determine its role as a potential catalyst underpinning the disproportionately high risk of constrictive pericarditis observed in individuals with TB pericarditis.

## Author contributions

LG: Writing – original draft, Writing – review & editing. AD: Supervision, Writing – review & editing. PR: Writing – review & editing. TJ: Writing – review & editing. PH: Supervision, Writing – review & editing.

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# Prevalence of uncontrolled hypertension and contributing factors in Ethiopia: a systematic review and meta-analysis

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**Background:** Uncontrolled hypertension (HTN) is a major risk factor for cardiovascular and cerebrovascular disease. The prevalence of HTN in the Ethiopian adult population is almost 20%.This study aimed to determine the prevalence of uncontrolled HTN and its contributing factors among patients with HTN in Ethiopia undergoing treatment.

**Methods:** Electronic bibliographic databases such as PubMed, Google Scholar, Hinari (Research4Life), Embase, and Scopus were searched for original records in the English language that assessed HTN control in Ethiopia and were available before 29 June 2023. The data were extracted using a format prepared in Microsoft Excel and exported to the software STATA 17.0 for analysis. The study protocol was registered at PROSPERO with the reference number CRD42023440121.

**Results:** A total of 26 studies with 9,046 patients with HTN were included in the systematic review and meta-analysis, of which 11 studies were used to assess factors contributing to uncontrolled blood pressure (BP) in patients in Ethiopia. The estimated prevalence of uncontrolled HTN in the population of Ethiopia is 51% [95% confidence interval (CI), 42%–60%]. The subgroup analysis, based on the assessment tools, region, and follow-up period, revealed that the prevalence of uncontrolled BP was highest following the guidelines of the American Heart Association/American College of Cardiology (AHA/ACC) (89%; 95% CI: 87%–91%) and in Addis Ababa (58%; 95% CI: 40%–76%), and the lowest proportion of uncontrolled BP was in the 3-month follow-up period (34%; 95% CI: 29%–39%). The presence of diabetes mellitus showed the highest impact (pooled odds ratio: 5.19; CI: 1.41–19.11) for uncontrolled HTN. The univariate meta-regression method confirmed that the sample size, year of publication, and subgroups were not sources of heterogeneity in the pooled estimates. Egger's regression test did not indicate the presence of publication bias.

Abbreviations
ACC, American College of Cardiology; AHA, American Heart Association; BP, blood pressure; HTN, hypertension; CS, cross-sectional; CVD, cardiovascular disease; DM, diabetes mellitus; JNC, Joint National Committee; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; WHO, World Health Organization; SSA, sub-Saharan Africa.

**Conclusion:** More than half of the hypertensive patients in Ethiopia have uncontrolled BP. Diabetes mellitus, advanced age, male sex, and the presence of comorbidities are among the factors contributing to uncontrolled HTN in Ethiopia. The concerned bodies working in this area should implement interventional strategies and recommendations that might be helpful in achieving optimal BP in hypertensive patients.

**Systematic Review Registration:** https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023440121, PROSPERO (CRD42023440121).

KEYWORDS

hypertension, cardiovascular disease, systematic review, meta-analysis, Ethiopia

# Introduction

Hypertension (HTN) is a common disease characterized by a persistently elevated arterial blood pressure (BP). According to the 2017 American Heart Association/American College of Cardiology (AHA/ACC) Blood Pressure Guideline, HTN is defined as a BP of ≥140/90 to ≥130/80 mmHg based on an average of ≥2 readings taken at ≥2 visits. Thus, awareness and treatment in adults are based on the systolic BP (SBP)/diastolic BP (DBP) cutoff points of 130/80 mmHg, and control is based on an SBP/DBP <130/80 mmHg (1).

According to the 2014 reports of the World Health Organization (WHO), the global prevalence of raised BP in adults is approximately 22% (2). In sub-Saharan Africa (SSA), an estimated 74.7 million individuals are hypertensive, and by the year 2025, the number of hypertensive individuals is projected to increase by 68% to 125.5 million individuals (3). A recent meta-analysis study in Ethiopia revealed that the prevalence of HTN among the Ethiopian adult population is almost 20% (4). This finding indicates that HTN is a public health concern in Ethiopia.

Although elevated BP was perceived to be "essential" for adequate perfusion of vital organs during the early 1900s, it has been identified for decades as one of the most significant risk factors for cardiovascular disease (CVD). In a meta-analysis of 61 prospective studies, the risk of CVD increased in a log-linear fashion from SBP levels <115 to >180 mmHg and DBP levels <75 to >105 mmHg, in which the risk of death from stroke, heart disease, or other vascular disease doubles with every 20/10 mmHg increase (1, 5). A report from developing countries also implied that the burden of 47% of mortality secondary to CVDs and 44% of CVDs is attributable to high BP (6). Also the reports of the Federal Ministry of Health of Ethiopia declare that 3% of all deaths between 2005 and 2006 were the result of HTN, which accounts for the sixth top cause of death in the country (7).

Although evidence from clinical trials definitively demonstrates that antihypertensive drug therapy substantially reduces the risk of CV events and deaths in patients with high BP (8–10), the control of BP and the quality of clinical care remain generally subpar. This deficiency exacerbates the health burden on the affected populations and presents an opportunity for clinicians to enhance HTN management and care (11). The fact that uncontrolled HTN is worse in the least developed nations may indicate that there is poor hypertensive management practice and little awareness among the population about the disease. Even though the control of HTN has become a primary goal for the Federal Ministry of Health of the country in the last 10 years, it has not been implemented to its full potential (12).

Poor medication adherence, old age, obesity, high body mass index, high waist-to-hip ratio, tobacco smoking, excessive alcohol consumption, physical inactivity, and low fruit and vegetable intake were identified as factors that caused poor BP control in different clinical trials and systematic review studies (11, 13–15) but these were inconsistent across studies in Ethiopia. Therefore, this review aimed to assess BP control and the determinant factors among patients on antihypertensive medications in different regions of Ethiopia.

# Methods

## Study protocol

Identification of records, screening of titles and abstracts, and evaluation of full-text eligibility for final analysis were performed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) algorithm (16). The study protocol was registered in PROSPERO (Ref. No.: CRD42023440121).

## Data sources and search strategy

An inclusive literature search was conducted to retrieve studies that reported the prevalence of uncontrolled BP and its contributing factors in Ethiopia. We used different electronic bibliographic databases such as PubMed, Google Scholar, Hinari (Research4Life), Embase, and Scopus. Our search included studies published in English. In addition, the proceedings of professional associations and university repositories were screened. Direct Google searches and reference tracing were conducted using the bibliographies of the identified studies to include additional relevant studies omitted during the electronic database searches.

The search was conducted using the key terms from the review question. All potentially eligible studies were assessed using the following combinations of keys: prevalence, epidemiology,

uncontrolled BP, HTN, uncontrolled HTN, BP, factors, determinant factors, associated factors, predisposing factors and Ethiopia. The Boolean operator terms "OR" and "AND" were used as necessary. The software Endnote 20.5 (17) was used to manage the references and remove duplicates. The search was conducted from 1 June to 29 June 2023, and all articles available online on the days of data collection were considered.

## Inclusion and exclusion criteria

Observational studies that fulfilled the following criteria were included in the final analysis: original articles published in peer-reviewed journals; articles published in English; studies that reported the prevalence of uncontrolled BP and contributing factors in any region of Ethiopia; and studies that involved hypertensive patients of any age in any healthcare setting. Qualitative studies, review articles, case reports, narrative reviews, conference abstracts with no full information, or if the authors did not respond to our inquiry on the full text, editorials, commentaries, letters to the editor, author replies, and studies that did not include quantitative data on the prevalence and contributing factors of uncontrolled BP were excluded.

## Screening and eligibility of studies

Related papers from the aforementioned databases were imported into EndNote 20.5 (17) to remove duplicates. Two independent reviewers (TK and MG), based on predefined eligibility criteria, carefully screened the selected papers based on the title, abstract, and full-text quality of each article. Deviations between the two reviewers were resolved by discussion, with the involvement of a third reviewer in selecting articles for the final review.

## Data extraction

Microsoft Excel was used for the data extraction. Two authors independently extracted data related to the study characteristics (first author, year of publication, region, study design, study population, study settings, sample size, follow-up period, and the number of patients with uncontrolled HTN).

## Quality assessment of studies

The Joanna Briggs Institute (JBI) Critical Appraisal Tool, adapted for cross-sectional (CS) studies, was used to assess the quality of the included studies. Overall, the tool has nine questions to rate the quality of the articles. The following aspects were considered to appraise the selected studies: (1) the appropriateness of the sampling frame to address the target population; (2) the appropriateness of the sampling technique for selecting the study participants and adequacy of sample size; (3) detailed description of the study subjects and settings; (4) sufficient analysis of the data and the validity and reliability of the methods used for the measurement of BP and the tools used for the classification of HTN as "controlled" and "uncontrolled"; (5) the appropriateness of the statistical analysis used; and (6) the adequacy of the response rate. Disagreements were resolved through consensus. Studies that scored five and more out of nine were considered low risk (Supplementary File S1).

## Statistical analysis

The extracted data were exported to the software STATA (version 17.0) for analysis (21). A weighted inverse variance random-effects model (18) was used to estimate the prevalence of uncontrolled HTN using the guidelines of the Seventh Joint National Committee (JNC)-7, JNC-8, and AHA/ACC as assessment tools. The variation in the pooled estimates of prevalence was adjusted through subgroup analysis according to the tools used, the regions where the studies were conducted, and the follow-up periods. Heterogeneity across the studies was assessed using the symmetry of forest plot and $I^2$ statistics, where 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively (19). Funnel plots and Egger regression tests were used to check for publication bias (20). A sensitivity analysis was conducted to check the stability of the summary estimate after omitting the individual studies.

# Results

## Characteristics of included studies

A total of 1,543 potential studies were identified: 838 articles from PubMed, 210 from Hinari (Research4Life), 215 from EMBASE, 232 from Scopus, and 48 from other sources. Figure 1 shows the results of the search and the reasons for the exclusion during the study selection process. A total of 26 articles published between 2014 and 2023 were included to assess the prevalence of uncontrolled HTN, of which 11 studies (22–32) were used to assess factors contributing to uncontrolled HTN in Ethiopia. A cross-sectional, cohort, and retrospective follow-up study design were used for all the included studies. The AHA/ACC guidelines (33, 34), JNC-8 (22, 24, 25, 28, 30–32, 35–45), and JNC-7 (23, 27, 29, 46, 47) were used as assessment tools for 2, 19, and 5 studies, respectively. Eight studies were conducted in the Amhara region (22, 26, 32, 33, 35, 36, 45, 46), nine in Oromia (24, 25, 28–31, 37, 43, 47), one in the Southern Nations, Nationalities, and Peoples' Region (SNNPR) (34), four in Addis Ababa (39, 40, 42, 44), and four in Tigray (23, 27, 38, 41). In this meta-analysis 9,046 study participants were involved and 4,415 of them were found to have uncontrolled HTN. Assessment with the Joanna Briggs Institute (JBI) quality appraisal checklists indicated that none of the included studies were poor in quality and those that were poor were excluded from the meta-analysis. Table 1 presents the characteristics of the studies included.

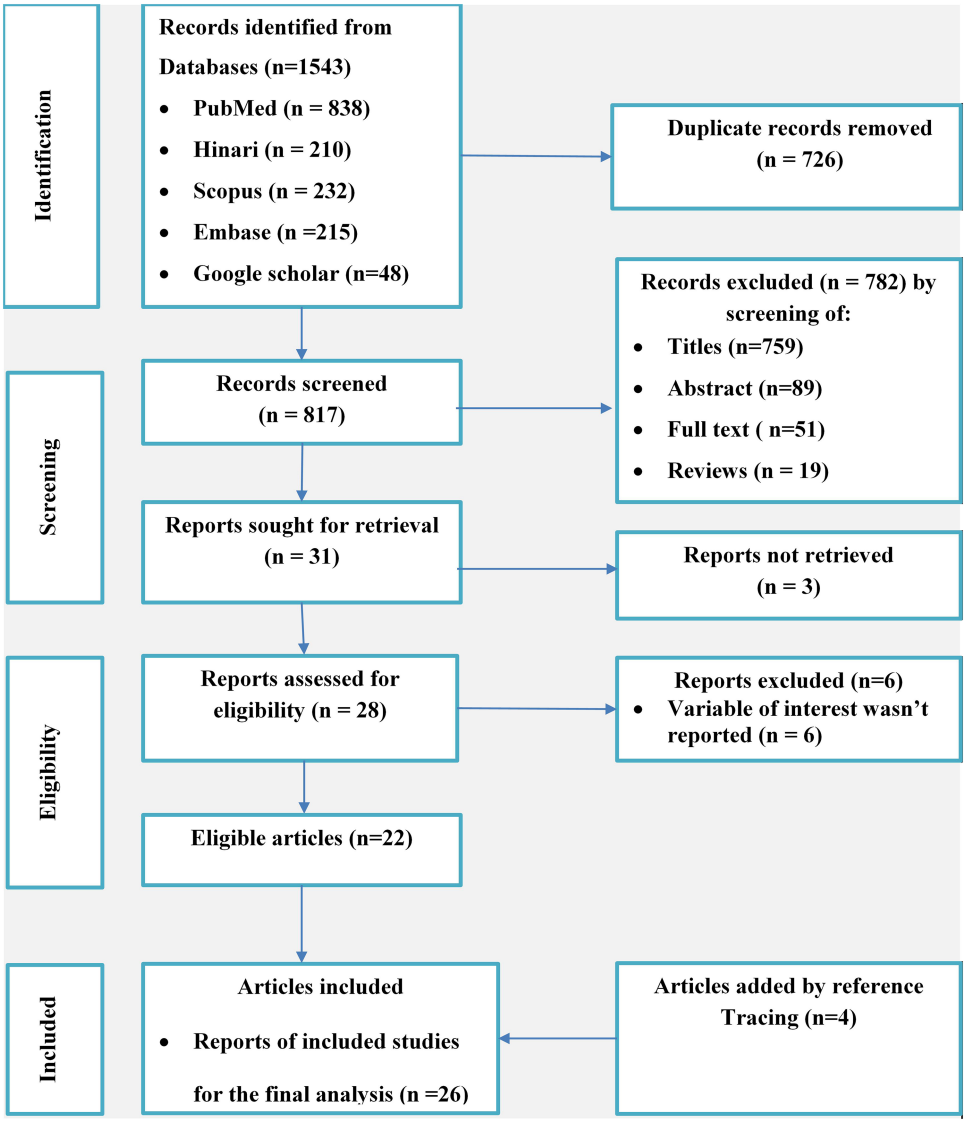


FIGURE 1
PRISMA flow diagram for the inclusion of studies in the systematic review and meta-analysis of the prevalence of uncontrolled hypertension in Ethiopia, with reasons for exclusion documented at each stage of the selection process.

## Meta-analysis

### Prevalence of uncontrolled HTN in Ethiopia

The estimated proportion of uncontrolled HTN in Ethiopia from the included 26 studies was 51% [95% confidence interval (CI), 42%–60%]. A weighted inverse variance random-effects model was used, and high degree of heterogeneity was identified between studies, as verified by the $I^2$ statistics ($I^2 = 98.9\%$, $P < 0.001$) (Figure 2).

## Heterogeneity analysis

Studies included in the analysis showed significant heterogeneity ($I^2 = 98.9\%$; $P$-value $< 0.001$), which was not sufficiently treated using a weighted inverse variance random-effects model. To further analyze the source of this heterogeneity, we used a forest plot (Figure 2) as a subjective assessment and conducted subgroup analysis, sensitivity analysis, and univariate meta-regression to objectively assess the causes of heterogeneity (Table 2, Figures 3, 4).

## Subgroup analysis

Due to differences in target levels set by various tools for defining controlled and uncontrolled hypertension, along with considerations of the treatment duration before categorizing hypertension as uncontrolled, and the potential prodigious impact of cultural and lifestyle disparities among the diverse ethnic groups residing in the country, the subgroup analysis was performed based on the tools used for the classification of uncontrolled HTN, regions where studies were conducted in different parts of the country, and follow-up periods, as

TABLE 1 Characteristics of studies included for the systematic review and meta-analysis of the prevalence of uncontrolled HTN in Ethiopia.

| Authors | Year | Region | Study design | Study population | Study setting | Sample size | NUHTN | Tool |
|---|---|---|---|---|---|---|---|---|
| Woldu et al. | 2014 | Oromia | CS | HTN patients | Hospital | 288 | 56 | JNC-7 |
| Asgedom et al. | 2016 | Oromia | CS | HTN patients | Hospital | 286 | 142 | JNC-8 |
| Abdu et al. | 2017 | Amhara | CS | HTN patients | Hospital | 310 | 115 | JNC-8 |
| Berhe et al. | 2017 | Addis Ababa | Cohort | HTN patients | Hospitals | 897 | 332 | JNC-8 |
| Muleta et al. | 2017 | Oromia | CS | HTN + DM patients | Hospital | 131 | 74 | JNC-8 |
| Abegaz et al. | 2017 | Amhara | CS | HTN patients | Hospital | 561 | 167 | JNC-8 |
| Animut et al. | 2018 | Amhara | Retrospective follow-up | HTN patients | Hospital | 395 | 196 | JNC-8 |
| Yazie et al. | 2018 | Addis Ababa | CS | HTN patients | Hospital | 356 | 249 | JNC-8 |
| Kebede et al. | 2018 | Oromia | Cohort | HTN patients | Hospitals | 416 | 238 | JNC-8 |
| Gebremichael et al. | 2018 | Tigray | CS | HTN patients | Hospital | 320 | 168 | JNC-7 |
| Abegaz et al. | 2018 | Amhara | CS | HTN patients | Hospital | 543 | 62 | JNC-7 |
| Bayray et al. | 2018 | Tigray | CS | HTN patients | Public Offices | 243 | 167 | JNC-8 |
| Teshome et al. | 2018 | Amhara | CS | HTN patients | Hospital | 392 | 224 | JNC-8 |
| Dedefo et al. | 2019 | Oromia | CS | HTN + DM patients | Hospital | 186 | 82 | JNC-8 |
| Horsa et al. | 2019 | Addis Ababa | CS | HTN patients | Hospital | 225 | 166 | JNC-8 |
| Aberhe et al. | 2020 | Tigray | CS | HTN patients | Hospitals | 391 | 190 | JNC-7 |
| Melaku et al. | 2020 | Oromia | Cohort | HTN patients | Hospital | 103 | 62 | JNC-7 |
| Kinfe et al. | 2020 | Tigray | CS | HTN patients | Hospital | 223 | 70 | JNC-8 |
| Fekadu et al. | 2020 | Oromia | CS | HTN patients | Hospital | 297 | 108 | JNC-8 |
| Bogale et al. | 2021 | Amhara | CS | HTN patients | Hospital | 203 | 178 | AHA/ACC |
| Fentaw et al. | 2022 | Amhara | CS | HTN patients | Community | 360 | 201 | JNC-8 |
| Sheleme et al. | 2022 | Oromia | CS | HTN patients | Hospital | 219 | 123 | JNC-8 |
| Sisay et al. | 2022 | Addis Ababa | CS | HTN patients | Hospital | 474 | 247 | JNC-8 |
| Yazie et al. | 2022 | Amhara | CS | HTN patients | Hospitals | 423 | 202 | JNC-8 |
| Sorato et al. | 2022 | SNNPR | CS | HTN patients | Hospitals | 406 | 362 | AHA/ACC |
| Solomon et al. | 2023 | Oromia | CS | HTN patients | Hospitals and HC | 398 | 234 | JNC-8 |

SNNPR, Southern Nations, Nationalities, and Peoples region; HC, health center; NUHTN, number of uncontrolled hypertension.

previously mentioned (Table 2). The highest proportion of uncontrolled HTN was observed when the AHA/ACC guidelines were used as an assessment tool (89%; 95% CI, 86%–91%), but the lowest was observed following the guidelines of the JNC7 Group 38 (95% CI, 19–58). The results of subgroup analysis based on regions where studies were conducted revealed the highest proportion of uncontrolled HTN in Addis Ababa (58%; 95% CI, 40%–76%), followed by the Tigray region (50%; 95% CI, 36%–64%). The results of subgroup analysis based on the follow-up period showed greater difference in prevalence of uncontrolled HTN in which the lowest (34%; 95% CI, 29%–39%) and highest (55%; 95% CI, 46%–64%) prevalence was found in the 3- and 6-month follow-up periods, respectively.

## Sensitivity analysis

We performed a sensitivity analysis of the prevalence of uncontrolled HTN by applying a random-effects model. Each excluded study showed a slight difference in pooled estimate of prevalence of uncontrolled HTN, the highest and lowest estimates being 53.1% (95% CI, 45.3%–60.8%) (35) and 49.99% (95% CI, 41.9%–57.9%) (34) when the respective studies were omitted.

## Meta-regression

Univariate meta-regression was used to assess sample size and publication year as the source of heterogeneity, and it revealed a slightly higher source of variation in sample size distribution when compared with the publication year ($\tau^2$ 0.03, $P < 001$) and ($\tau^2$ 0.027, $P = 024$), respectively (Figures 3, 4).

## Publication bias analysis

Publication bias was subjectively analyzed using a funnel plot (Figure 5), which was symmetrical, and we further conducted Egger's regression test, which resulted in a $P$-value of 0.274 and did not show the presence of publication bias.

## Contributing factors for uncontrolled hypertension in Ethiopia

In this meta-analysis, data regarding the effects of non-modifiable risk factors on uncontrolled HTN were estimated. The highest effect on uncontrolled HTN was observed in diabetes, followed by when the duration of the illness was longer than 5 years (Table 3).

# Discussion

This meta-analysis found that the estimated prevalence of patients with uncontrolled hypertension in Ethiopia was 51% (95% CI: 42%–60%). This eye-opening figure carries significant clinical implications, which underscores a substantial public

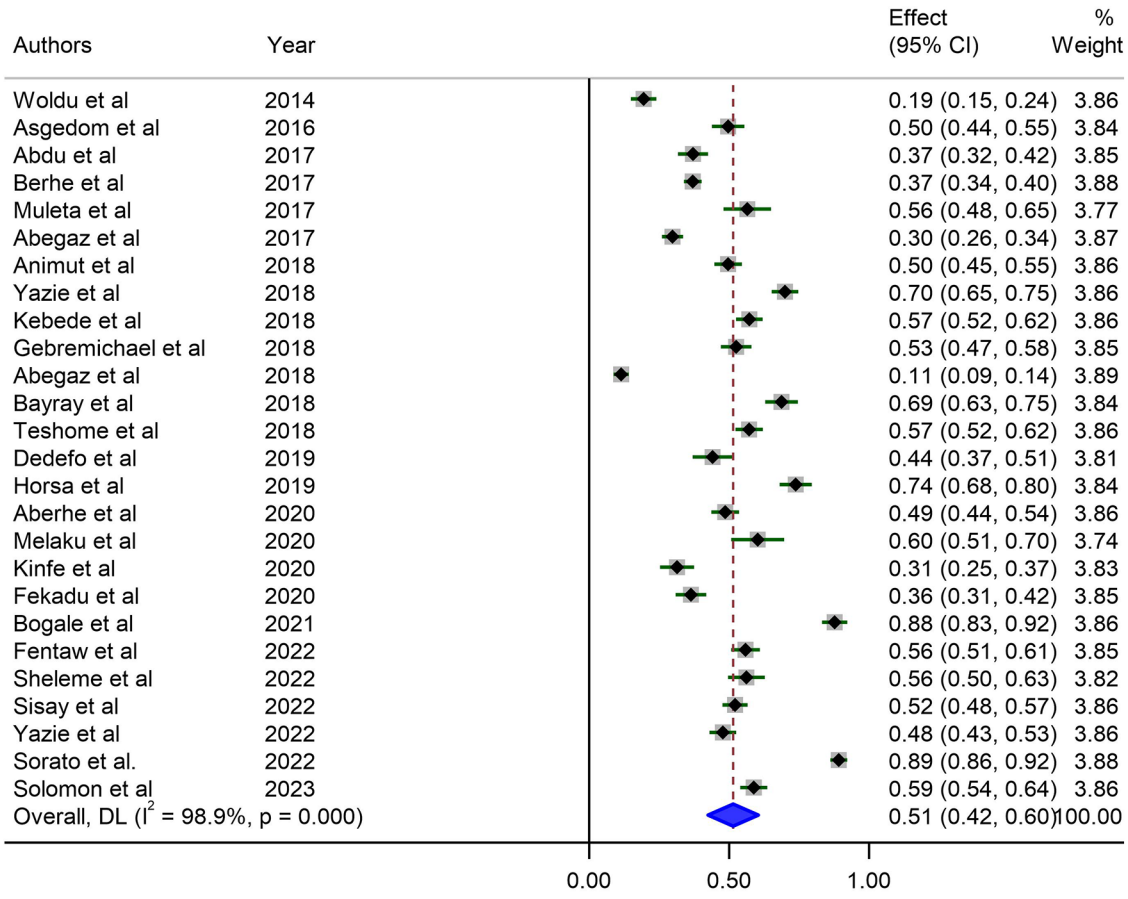


FIGURE 2
Forest plot illustrating the pooled prevalence of uncontrolled hypertension in Ethiopia from 26 observational studies. Each study's effect size (prevalence) is represented by a small solid vertical line, with its 95% CI shown by a solid horizontal line. The dashed vertical line indicates the pooled prevalence, and its 95% CI is represented by a diamond. The sizes of the shaded squares correspond to the weight assigned to each study in the pooling.

health concern and burden, emphasizing the need for targeted interventions and improved hypertension management strategies to decrease the risk of cardiovascular diseases and associated complications, such as stroke.

TABLE 2 Subgroup analysis of prevalence of uncontrolled HTN in Ethiopia based on the assessment tools, regions where studies were conducted, and follow-up periods.

| Groups | Subgroups | Pooled estimates (95% CI) | $I^2$ (%) | *P*-values |
|---|---|---|---|---|
| Assessment tools | JNC-7 | **38** (19–58) | 98.8 | <001 |
| | JNC-8 | **51** (45–57) | 96.2 | <001 |
| | AHA/ACC | **89** (86–91) | 0.0 | 0.594 |
| Regions | Addis Ababa | **58** (40–76) | 98.5 | <001 |
| | Amhara | **47** (29–65) | 99.3 | <001 |
| | Oromia | **49** (38–59) | 96.3 | <001 |
| | Tigray | **50** (36–64) | 96.1 | <001 |
| Follow-up periods (months) | 3 | **34** (29–39) | 29.5 | 0.234 |
| | 6 | **55** (46–64) | 98.5 | <001 |
| | 12 | **54** (44–64) | 71.2 | 0.062 |

Bold values represent the pooled prevalence of uncontrolled hypertension across different subgroups.

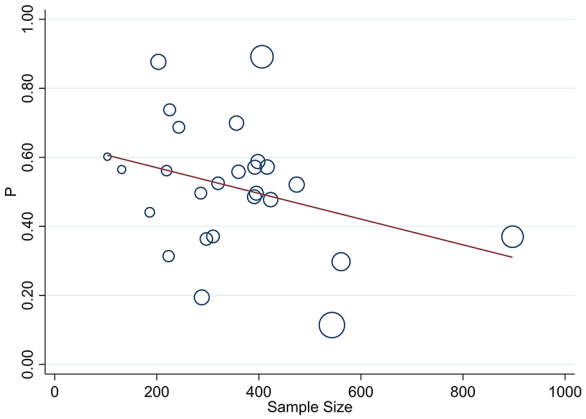


FIGURE 3
Univariate meta-regression of the prevalence of uncontrolled hypertension and sample size for analyzing heterogeneity between studies. Each circle represents a study, with the area of each circle proportional to that study's weight in the analysis. The meta-regression line is overlaid on the scatterplot, with its slope indicating the magnitude and direction of the association.

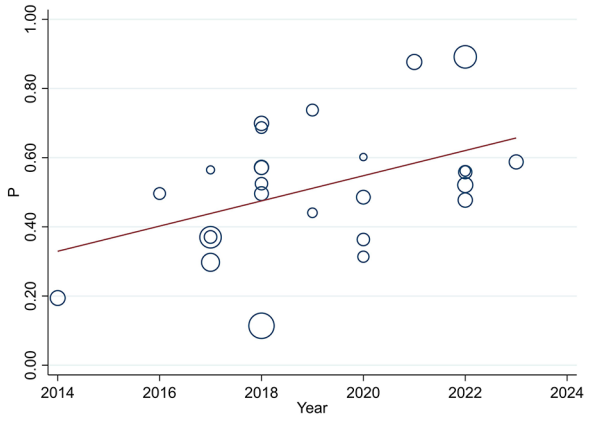


FIGURE 4
Univariate meta-regression of the prevalence of uncontrolled hypertension and year of publication for analyzing heterogeneity between studies. Each circle represents a study, with the area of each circle proportional to that study's weight in the analysis. The meta-regression line is overlaid on the scatterplot, with its slope indicating the magnitude and direction of the association.

This finding is in line with another meta-analysis conducted in 2020 (48); however, the analysis included an additional 13 articles and also conducted a factor analysis for the major determinants of uncontrolled HTN. The BP control rate was low and little improvement was observed in several SSA countries. In SSA, the percentage of people with controlled BP has remained low, and little progress has been made in improving BP control (49). Similarly, according to the national survey in Kenya, Ghana, and Lebanon, the prevalence of uncontrolled HTN was found to be 48.3%, 58%, and 51.1%, respectively (50–52). Global disparities in HTN control have also been reported, as there has been less improvement in low- and middle-income countries (53). However, this meta-analysis result is lower than a study conducted in Africa, which reported 79.3% of people with HTN who were receiving treatment had uncontrolled HTN (54). In addition, this result is lower than that of studies in Benin, Ghana, and Afghanistan, which reported the prevalence of uncontrolled HTN as 65.5%, 87.6%, and 77.3%, respectively. The difference could be explained by the differences in the study periods, as well as the sociodemographic and economic differences between the study populations. Moreover, this finding is lower than that of a study on the prevalence of uncontrolled HTN among people with comorbidities in SSA (55). Many patients with comorbidities may experience management with multiple medications, which could make it difficult to adhere strictly to HTN drug-taking behavior. Moreover, this problem could also be related to lifestyle modifications such as the management of HTN and drug-to-drug interactions among patients with comorbidities.

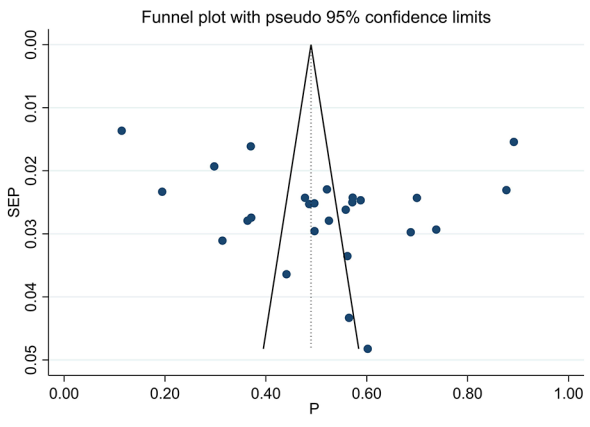


FIGURE 5
Funnel plot illustrating the prevalence of uncontrolled hypertension in Ethiopia for subjective assessment of publication bias. Each dot in the plot represents an individual study. The x-axis represents the effect size (prevalence), while the y-axis represents study precision. The vertical dotted line serves as the reference line, and the 95% confidence intervals are denoted by the distance between the two solid lines.

Conversely, this meta-analysis result is higher than that of a study conducted in Thailand (24.6%) (56). Our finding is substantially lower than the prevalence observed in low- and middle-income countries, India, and China, where it stands at 92.3%, 79.8%, and 91.9%, respectively (53, 57, 58). This divergence in prevalence rates underscores potential variations in hypertension control strategies, healthcare infrastructure, economic capabilities, implementations of lifestyle modifications, and patient adherence to treatment regimens across different regions. Understanding these variations is crucial for tailoring effective interventions that address the specific challenges faced by the different populations in the pursuit of optimal hypertension management across the global.

As indicated in previous studies, uncontrolled HTN increases the risk of all-cause and CVD-related morbidity and mortality (59–61). This finding also indicates that uncontrolled HTN is a major public health concern in Ethiopia. Moreover, a study showed that suboptimal BP control is responsible for a large and increasing economic and health burden in developing countries (62), and this high proportion of uncontrolled HTN could be linked with such problems.

This study revealed a significant association between patient age and uncontrolled HTN as the odds of uncontrolled HTN increased with advancing age. The findings of this study are in line with those of other studies conducted in Africa (63, 64) and elsewhere (65–69). This could be due to BP increasing as the arteries become less elastic with increasing age. This analysis further reported that sex was significantly associated with uncontrolled HTN, as men had significantly higher odds of uncontrolled HTN than women (56, 68, 70–72). This might be due to differences in health-seeking behavior, as women are better at having contact with health services than men (73). In addition, the difference could also be justified, as men are more likely to have unhealthy lifestyle practices, such as smoking, alcohol consumption, and poor dietary habits. Different studies have also revealed that the prevalence of uncontrolled HTN increases with the number of unhealthy lifestyle factors found in

TABLE 3 The effects of non-modifiable risk factors on uncontrolled HTN in Ethiopia.

| Factors | Studies | Number of study participants | POR (95% CI) | $I^2$ (%) | *P*-value |
|---|---|---|---|---|---|
| Age > 50 years | Aberhe et al.<br>Muleta et al. | 522 | **2.47** (1.57–3.90) | 0.00 | 0.782 |
| Age > 60 years | Kebede et al.<br>Sheleme et al.<br>Dedefo et al. | 821 | **2.04** (0.39–10.72) | 90 | <0.01 |
| Presence of comorbidity | Sheleme et al.<br>Gebremichael et al.<br>Melaku et al. | 642 | **2.51** (1.73–3.63) | 14.1 | 0.312 |
| DM | Abdu et al.<br>Dedefo et al.<br>Muleta et al. | 627 | **5.19** (1.41–19.11) | 89.5 | <0.01 |
| Duration of illness >5 years | Dedefo et al.<br>Muleta et al.<br>Fekadu et al. | 614 | **2.82** (1.47–5.41) | 0.00 | 0.830 |
| Male | Fentaw et al.<br>Fekadu et al. | 657 | **1.38** (1.14–1.67) | 0.00 | 0.392 |

Bold values indicate the pooled effects of each contributing factor for uncontrolled hypertension.

men (74), and adherence to recommended lifestyle modifications is common among women (75, 76).

Higher odds of uncontrolled HTN were reported in patients with diabetes mellitus (DM) and other diseases (56, 63, 65, 66, 71, 77, 78). A review of studies in SSA indicated a high burden of uncontrolled HTN among individuals with comorbidities (55). This could be explained by the fact that patients with comorbidities often require multiple medications, which could increase the risk of side effects and medication non-adherence. Previous studies have revealed that poor adherence among patients with HTN is significantly associated with uncontrolled HTN (51, 77, 79, 80). Moreover, limited access to quality healthcare services in developing countries can affect BP monitoring (55). Despite the challenges of optimal BP in patients with comorbidities, different studies have reported that patients with comorbidities are more likely to have their BP under control than those without comorbidities (81, 82). A possible explanation might be that patients with comorbidities may have increased adherence to antihypertensive medications due to fear of complications and death. Patients with comorbidities could have better awareness of the importance of controlling their BP by adhering to their medication, which could be a result of the close monitoring and improved counseling services they obtained from their healthcare providers. Although existing findings report contradictions, it is essential to prepare public health strategies to reduce the burden of uncontrolled HTN in SSA, and WHO also recommends the need for integrated care programs for the management of HTN and comorbidities (55).

Patients diagnosed with HTN for a longer duration are more likely to develop uncontrolled HTN. This finding is in line with that of other studies (51, 83, 84). This could be explained by the longer duration of HTN and greater likelihood of developing complications such as heart disease, stroke, and kidney disease. This may lead to polypharmacy, decreased adherence to therapy, and compromised lifestyle changes, leading to poor BP control.

High heterogeneity ($I^2 = 98.9\%$, $P < 0.001$) was found in this meta-analysis using a weighted inverse variance random-effects model. Univariate meta-regression identified significant negative coefficients for sample size, indicating a slight decrease in uncontrolled hypertension prevalence with larger studies, suggesting enhanced stability; and a positive one for "year of study," suggesting a rise over time. Larger studies contribute to more reliable estimates, while the increase over time may be influenced by evolving international guidelines favoring stringent blood pressure targets for improved cardiovascular risk management. In the subgroup analysis based on assessment tools, the prevalence rates for uncontrolled HTN were found to be 38% by following the guidelines of JNC7, 51% by JNC8, and 89% by AHA/ACC. These variations could be attributed to the evolving definitions of optimal blood pressure levels in the newer international guidelines, reflecting a more conservative approach aimed at enhancing cardiovascular risk management.

## Conclusion

More than half of the patients with hypertension in Ethiopia have uncontrolled BP. Prevalent uncontrolled HTN increases the risk of cardiac, neurological, and renal complications, which may double the burden of the healthcare system in developing countries, such as Ethiopia, in addition to communicable diseases. Diabetes mellitus, advanced age, male sex, and comorbidities are among the factors that might contribute to uncontrolled HTN in Ethiopia. In light of this evidence, policymakers and healthcare professionals working in this area should implement interventional strategies and recommendations, which might be helpful in achieving optimal BP in patients with hypertension.

## Strength and limitations of the study

A comprehensive assessment was conducted to include all relevant data concerning hypertension control in patients with HTN. However, there are some limitations. The studies incorporated for the final analysis applied different standards and follow-up periods to declare uncontrolled BP. In addition to this,

there is a significant heterogeneity among included studies, stemming from diverse study populations, assessment tools, and study designs.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

## Author contributions

MG: Conceptualization, Formal Analysis, Methodology, Writing – original draft. MH: Conceptualization, Investigation, Methodology, Supervision, Writing – original draft. NT: Conceptualization, Investigation, Methodology, Writing – original draft. TS: Conceptualization, Investigation, Methodology, Writing – original draft. MD: Conceptualization, Investigation, Methodology, Writing – original draft. TF: Conceptualization, Investigation, Methodology, Writing – original draft. GT: Formal Analysis, Methodology, Writing – original draft. TK: Conceptualization, Methodology, Writing – original draft. FB: Conceptualization, Formal Analysis, Methodology, Writing – original draft.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2024.1335823/full#supplementary-material

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# Sudan's rheumatic fever and rheumatic heart disease guidelines: a simplified approach in an endemic country

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**Background:** Rheumatic heart disease (RHD) is a preventable sequelae of group A beta hemolytic streptococcal infection leading to an immune reaction: acute rheumatic fever (ARF) and progressive heart valve dysfunction. RHD is the leading cause of acquired heart disease in children and young adults in Sudan and many low/middle-income countries. In 2018, the World Health Organization (WHO) issued a resolution for RHD mandating that each country adopt updated guidelines for ARF and RHD management. These current guidelines are mainly directed to primary healthcare workers.

**Methods:** Sudan's Federal Ministry of Health (FMOH) in collaboration with the WHO East Mediterranean Regional Office (EMRO) assembled a committee for updating RHD guidelines. We conducted a systematic literature search from 2000 to 2022 in National Institute of Health Database (PubMed) under the following titles: streptococcal pharyngitis, acute rheumatic fever, rheumatic heart disease, benzathine penicillin. Best available, evidence-based practices for diagnosis and management of ARF/RHD were selected and adapted to Sudan's situation. The guidelines were critically appraised by the committee then endorsed to the FMOH and WHO EMRO Noncommunicable Disease Departments in January 2023. This paper describes the updated guidelines.

**Results:** Simplified algorithms are provided for diagnosis of bacterial pharyngitis including two clinical criteria: sore throat and the absence of viral symptoms in the target age group. A simplified algorithm for diagnosis and management of ARF is adopted using two levels of diagnosis: suspected case at primary level where penicillin prophylaxis is started and secondary/tertiary care where echocardiography is performed and diagnosis confirmed or excluded. Echocardiography screening is recognized as the standard method for early diagnosis of RHD; however, due to the anticipated limitations, its implementation was not adopted at this time. Streptococcal skin infection is included as a precursor of ARF and a detailed protocol for benzathine penicillin administration is described.

**Conclusion:** The Sudan guidelines for ARF/RHD management were updated. Endorsement of these guidelines to FMOH and WHO EMRO is expected to improve control of RHD in the region.

KEYWORDS

Sudan, rheumatic fever, rheumatic heart disease, guidelines, updated

## Introduction

Rheumatic heart disease (RHD) is a completely preventable, most common cause of acquired cardiac mortality and morbidity in young people in Sudan and other low/middle-income countries affecting over 38 million individuals worldwide (1).

Efforts to control RHD and its precursors streptococcal group A betahemolytic streptococcal (GAS) pharyngitis and acute rheumatic fever (ARF) need to be maximized to reduce the huge health and economic burdens of this disease. A World Health Organization (WHO)-based RHD control program was implemented in Sudan from 1986 to 1990. The program implemented clinical screening and early referral of school children in Khartoum State. The program reached its deadline in 2000 but was continued by voluntary efforts from the National Cardiac Center in Khartoum and continued to follow the WHO 2002 guidelines for RF/RHD until 2009 (2). A non-governmental program for RHD control was then established in 2012, and guidelines were produced for different levels of health workers with implementation projects in nine of Sudanese states (3, 4). The areas of high RHD burden were identified through a hospital registry and echocardiography (echo) screening (Figure 1). In referral hospitals, most patients were found to have established severe RHD and only 45% were compliant with benzathine penicillin G (BPG) prophylaxis (5).

In the current era, echo screening has been the standard method for early detection of RHD as its prevalence was found to be several folds higher than that detected by clinical auscultation (6). BPG was shown to stop the progression of echo-detected RHD, and this is expected to have important implications for RHD control as echo screening can potentially be incorporated into secondary prevention policies (7). Important modifications have been introduced to the methods of BPG administration, which have the potential to improve its uptake and decrease drug-related complications (8).

In 2018, WHO issued an RHD resolution that mandated that each country establish a control program for RHD (9). Consequently, a committee was assembled by the Sudanese Ministry of Health and the WHO East Mediterranean Regional Office in July 2022, aiming to update the Sudan ARF/RHD guidelines.

## Methodology

The guidelines were based on the previous 2017 published recommendations (4). We conducted a systematic literature search from January 2000 to July 2022 in National Institute of Health Database (PubMed) as well as published guidelines from recognized international organizations (Australia, New Zealand) under the following titles: streptococcal pharyngitis, acute rheumatic fever, rheumatic heart disease, and benzathine penicillin. Table 1 shows the classes and levels of evidence. The draft was written by first author and discussions and critical reviews were conducted by face-to-face and online discussions with the guideline committee members. The final version was endorsed in January 2023. The guidelines are directed to primary healthcare workers.

### Guidelines actionable recommendations

The main features of the updated guidelines are shown in Table 2.

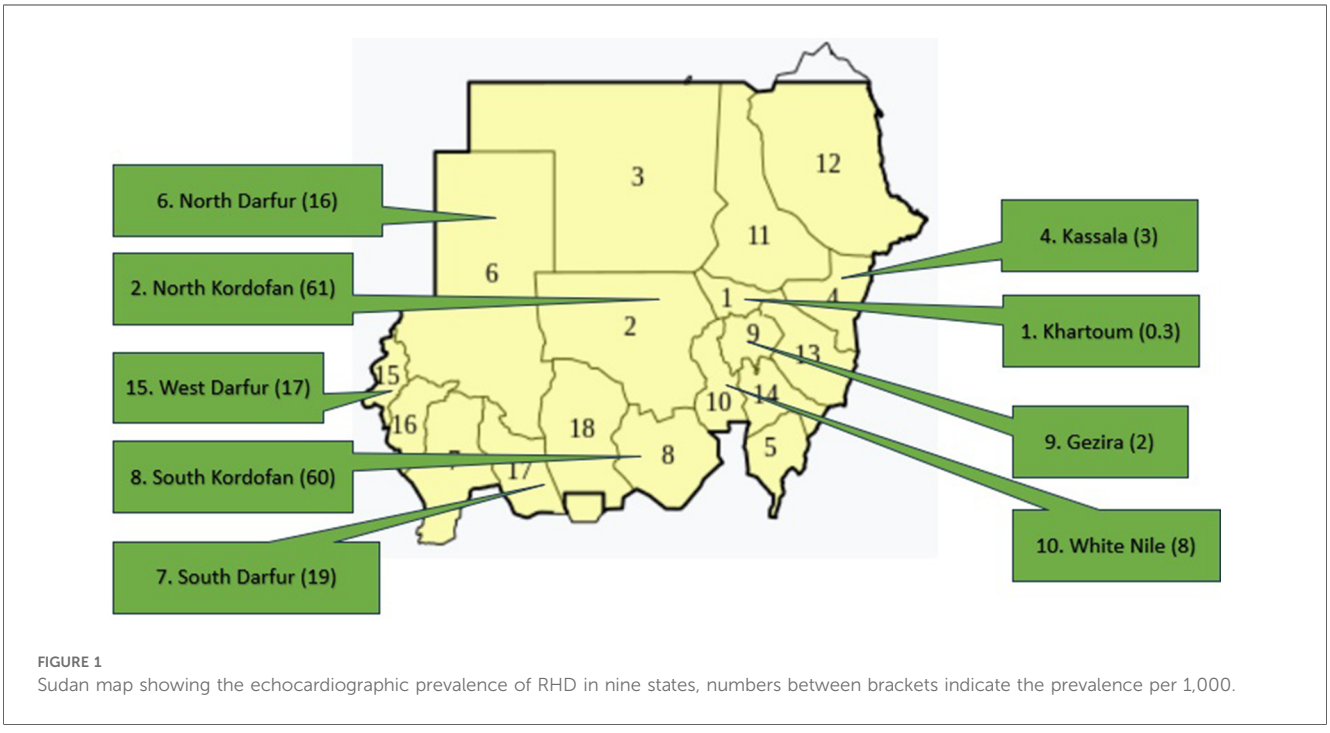


FIGURE 1
Sudan map showing the echocardiographic prevalence of RHD in nine states, numbers between brackets indicate the prevalence per 1,000.

TABLE 1 Classes and levels of evidence.

| Class | Definition |
|---|---|
| Class I | Evidence or general agreement that a treatment or procedure is beneficial, useful, effective |
| Class II | Conflicting evidence or divergence of opinions about usefulness |
| Class II-A | Weight of evidence in favor of usefulness |
| Class II-B | Usefulness not well established |
| Class III | Evidence or agreement that a treatment or procedure is not useful or may be harmful |
| Level of evidence A | Data derived from multiple randomized studies or meta-analyses |
| Level of evidence B | Data derived from a single randomized trial or large non-randomized studies |
| Level of evidence C | Consensus expert opinion or small studies |

Color, Level of evidence; Green: Class I, Yellow, Class II-A, Orange: Class II-B, Red, Class III.

## 1. Diagnosis and management of bacterial pharyngitis (BP)

In children aged 3–18 years living in RHD endemic areas, a clinical algorithm with high sensitivity is recommended for diagnosis of BP at primary healthcare settings (10–12). The diagnostic algorithm is shown in Figure 2. The first-line treatment is one injection of BPG (13–15). (For the dose and injection methods refer to the section on BPG administration). The second-line treatment is amoxicillin 40 mg/kg/day for every 12 h (max = 1,000 mg, same dose for adults) for 10 days. (For allergic patients, see the section on BPG allergy).

Patients and families need to be counseled about the importance of early treatment of pharyngitis as well as prevention by improving house ventilation and avoiding overcrowding and co-sleeping.

## 2. Diagnosis and treatment of ARF

The algorithm for diagnosis and management of ARF is shown in Figure 3. This algorithm is simplified and modified from Jones' Criteria, which has nine items (five major and four minor) and requires laboratory tests that might not be available in primary healthcare settings (16). All children with unexplained joint symptoms and heart murmurs indicating mitral and/or aortic valve disease need to be categorized as "suspected ARF." In addition, those with chorea need to be classified as ARF unless there is an obvious alternative cause for this symptom. Standard ARF management including BPG prophylaxis should be started and referral to a higher center should be arranged. This simplified approach is expected to detect more cases of ARF in primary care settings and thus potentially improve prevention, early diagnosis, and treatment of RHD. (For the dose and injection methods, refer to the section on BPG administration). BPG should be continued every 3 weeks (for children below 18 years) and every 4 weeks for adults as secondary prophylaxis.

At the secondary/tertiary center, echo should be performed and the history reviewed to confirm or rule out ARF. If the patient presented to the secondary or tertiary care unit at the time of acute symptoms, then the standard Jones Criteria can be applied.

The duration of prophylaxis is up to 25 years of age if there is healed or no carditis and lifelong if there is persistent valve disease. If there is a contraindication for BPG, alternatives include oral penicillin V; the dose for those <27 kg is 250 mg twice/day and for those >27 kg is 500 mg twice/day for the duration of prophylaxis. (For allergic patients, see the section on BPG allergy).

Patients with ARF need to receive anti-inflammatory medications. The first-line treatment is ibuprofen 10 mg/kg/day every 8 h for 2 weeks. The second-line treatment is aspirin (60 mg/kg/day) every 8 h for 2 weeks. There is no evidence supporting the use of steroids; however, it can be used if non-steroidal anti-inflammatory medications are poorly tolerated. Prednisolone 2 mg/kg/day up to 80 mg/day for can be used for 2 weeks and then tapered and discontinued. Treatment of rheumatic chorea includes carbamazepine 5–10 mg/kg per dose twice daily or sodium valproate 5–10/kg per dose twice daily.

TABLE 2 The main features of the updated guidelines.

| Item | Previous Sudan guidelines (2017) | Updated guidelines (2022) | Rationale/evidence |
|---|---|---|---|
| ARF diagnosis | Modified Jones Criteria | Simplified criteria (arthritis, carditis, chorea) | - ARF could be transient<br>- Evidence of high prevalence of subclinical carditis<br>- Need to have a low threshold in highly endemic areas<br>- Complexity of Jones Criteria<br>Class I-B |
| ARF treatment | - BPG prophylaxis only after confirmation of diagnosis by Jones Criteria<br>- Aspirin as anti-inflammatory | - BPG to all patients with arthritis, carditis, or chorea at primary care level<br>- Ibuprofen as first-line treatment | - BPG can prevent progression of subclinical carditis<br>- Ibuprofen is as effective and safer than aspirin<br>Class I-B |
| Skin infection | Not included | Diagnosis and treatment of streptococcal skin infection is included as primary prevention of ARF | Evidence that skin infection can contribute to ARF<br>Class II-B |
| Benzathine penicillin administration | No special precautions for patients with severe valve disease<br>No sensitivity testing | - Not to be given for patients with severe uncontrolled heart failure<br>- To give oral fluid before BPG injection<br>- Graded oral challenge for patients with suspected mild allergy | Evidence that there are fatal non-allergic reactions to BPG in patients with severe heart failure<br>Class II-A |

Green: Class I, Yellow, Class II-A.
Orange: Class II-B.

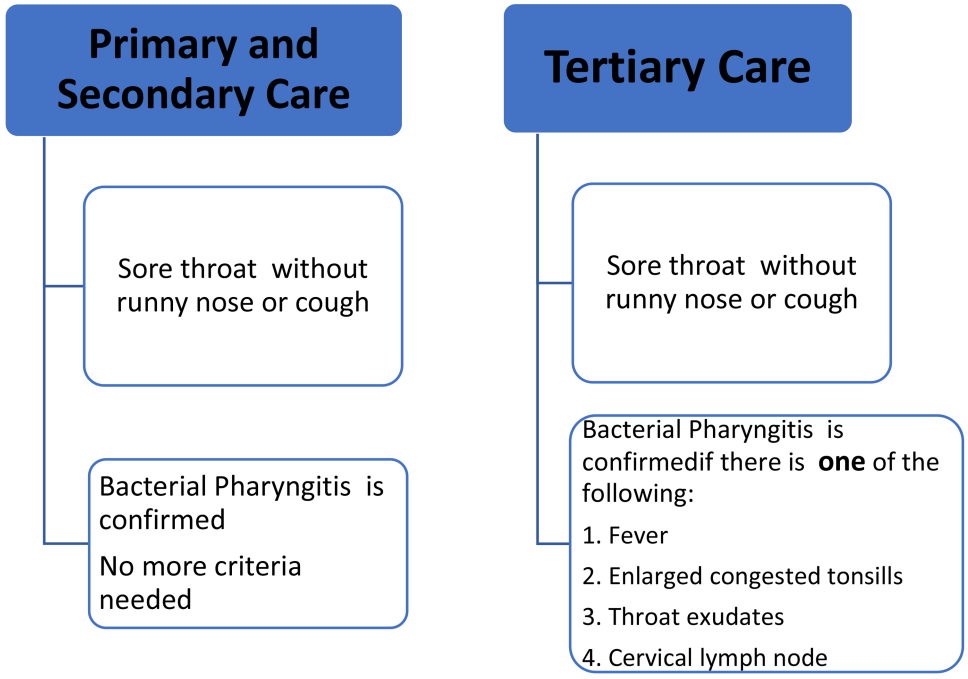


FIGURE 2
Diagnosis of bacterial pharyngitis.

After resolution of chorea, drugs can be gradually discontinued (15). Consultation with a neurologist might be needed in refractory cases. Patients with heart failure should be started on diuretics: furosemide in oral or intravenous route in a dose of 1–3 mg/kg/day (children) and 40 mg every 8–12 h (adults) with spironolactone 1 mg/kg/day (children) and 25 mg orally every 12 h (adults). Consultation with a physician or cardiologist is advised for further management.

## 3. Diagnosis and management of rheumatic heart disease

Echo was shown to detect RHD at an early (subclinical) stage in many countries including Sudan (17–19).

The World Heart Federation (WHF) recently updated echo criteria for RHD (20). The main updates include screening criteria for non-experts and then confirmatory criteria for experts. RHD was classified into five stages based on the risk of progression to more advanced disease. WHF recommended starting BPG prophylaxis for the earliest stage of subclinical disease.

Implementation of echo screening as a policy is not recommended in the current guidelines due to local country limitations; however, it can be used for studying the disease epidemiology and burden. Health workers need to be trained on the clinical diagnosis and management of RHD and its complications. Management and follow-up of patients with RHD are shown in Table 3.

Endocarditis prophylaxis should be considered for patients with RHD. Amoxicillin 50 mg/kg per dose for children and 2 g for adults can be used 1 h before procedures that lead to bacteremia. Patients need to be educated about the need to improve dental hygiene.

### *Post-intervention management*

Patients with prosthetic valves need to continue anticoagulation (warfarin) for life. Warfarin dose needs to be adjusted according to the international normalized ratio (INR) as in Table 4 (21).

## 4. Group A streptococcal skin infection

There is evidence that group A streptococcal skin infections (impetigo) alone or in combination with GAS pharyngitis may lead to ARF (22). Impetigo manifests as skin ulcers with honey-colored crusts on the face and extremities, which could be primary or secondarily infected insect bites or eczema. Treatment includes one injection of BPG (see the section on BPG administration) or cotrimoxazole (syrup 40 mg/5 ml, tablets 80/400 mg) twice daily for 3 days (15).

## 5. Benzathine penicillin administration

BPG is the main drug used for primary and secondary prevention. BPG administration needs special training of health workers to improve both their uptake as well as and the compliance of patients (2). Important considerations when giving BPG are shown in Table 5.

### *Five-step protocol for BPG administration*

**Step 1: Ask about allergy:**

- If there is no allergy: go to step 2.
- If there is a history of allergy, give an alternative medication: cefalexin 1 g (child: 25 mg/kg up to 1 g) orally every 12 h for 10 days for pharyngitis and erythromycin 250 mg twice per day for the duration of secondary prophylaxis.

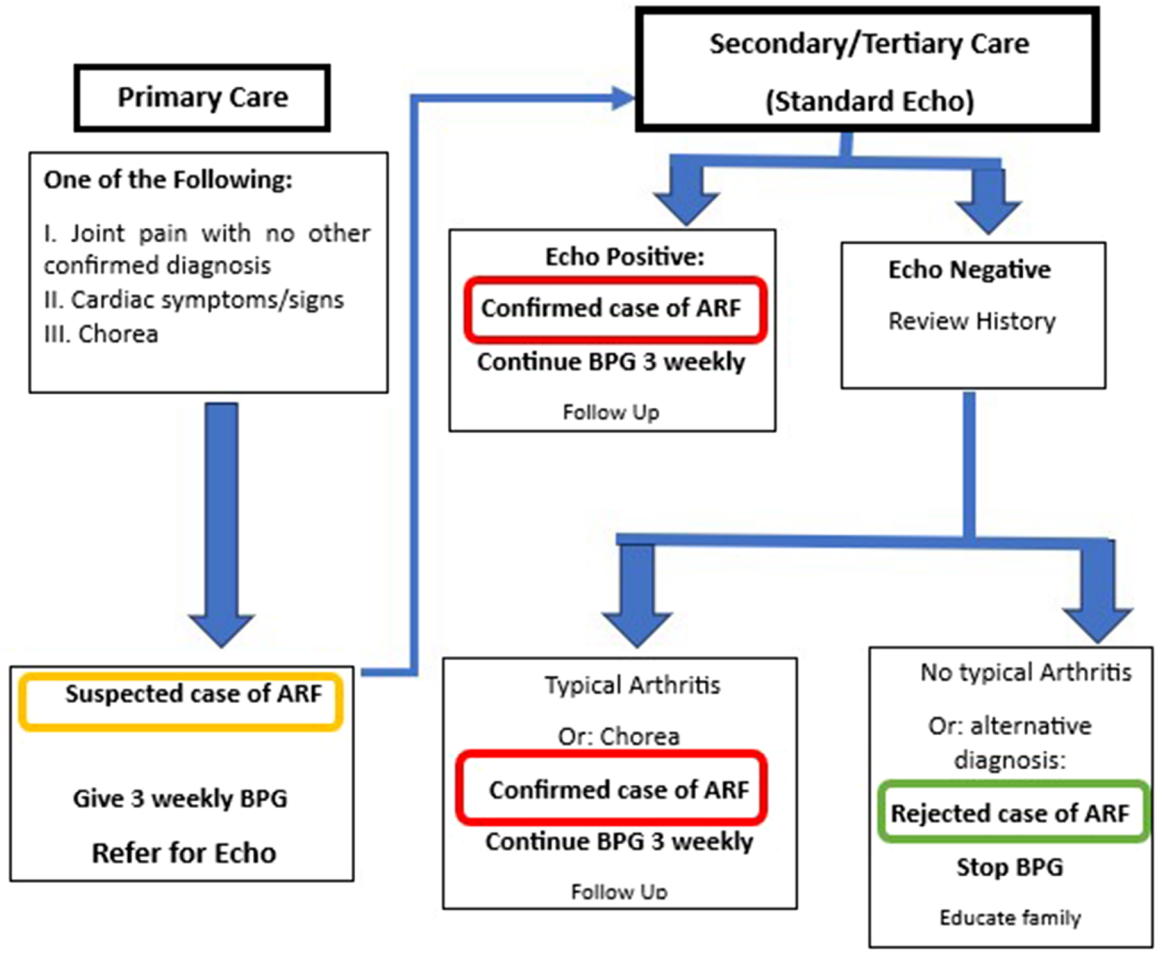


FIGURE 3
Diagnosis and management of acute rheumatic fever.

TABLE 3 Management of patients with RHD.

| Asymptomatic (clinical or sub clinical) | Symptomatic | Post-intervention |
|---|---|---|
| - Follow-up in tertiary care units<br>- Ensure compliance with BPG<br>- Dental hygiene and endocarditis prophylaxis<br>- Pregnancy planning<br>- Register and notify | - Treat heart failure<br>- Follow-up in tertiary care unit<br>- Ensure compliance with BPG for life<br>- Comply with medications<br>- Dental hygiene and endocarditis prophylaxis<br>- Interventional treatment is planned by the cardiologist<br>- Pregnancy planning<br>- Register and notify | - Follow-up in tertiary care unit<br>- Ensure compliance with anticoagulation medications and investigations<br>- Ensure compliance with BPG for life<br>- Dental hygiene and endocarditis prophylaxis<br>- Pregnancy planning<br>- Register and notify |

- Refer the patient for confirmation of allergy if BPG is given for secondary prophylaxis (see management of allergy below).

**Step 2: Prepare the items needed: shown in Figure 4.**

**Step 3: Aspirate lidocaine as a diluent and inject into the BPG vial.**

Using the 5 ml syringe needle, aspirate the volume of lidocaine denoted on the vial and inject into the BPG vial, shake till dissolved. Aspirate into the syringe.

**Warning for this step:**

IMPORTANT: TO INJECT BPG, CHANGE THE NEEDLE WITH A LARGE BORE (16 to 18 GAUGE) ONE (THE ONE PROVIDED WITH THE 10 ML SYRINGE)

BPG dose:

- For patients weighing 27 kg (about 9 years of age) or more: 1.2 million international units.
- For patients weighing <27 kg: 600,000 international units.

TABLE 4 Target INR for patients with prosthetic valves.

| Prosthetic valve thrombogenicity | INR if *No* patient-related risk factors[a] | INR if more than 1 patient-related risk factors |
|---|---|---|
| Low[b] | 2.5 | 3.0 |
| Medium[c] | 3.0 | 3.5 |
| High[d] | 3.5 | 4.0 |

[a]Patient-related risk factors: mitral or tricuspid valve replacement; previous thromboembolism; atrial fibrillation; mitral stenosis of any degree; low left ventricular ejection fraction.
[b]Carbomedics, Medtronic Hall, ATS, Medtronic Open-Pivot, St Jude Medical, On X, Sorin Bicarbon.
[c]Other bileaflet valves with insufficient data.
[d]Lillehei-Kaster, Omniscience, Starr-Edwards.

TABLE 5 Important considerations when administering BPG.

| Things that should be done | Things that should be avoided |
|---|---|
| Always ask about history of penicillin allergy | **Do not** give BPG to patients with history of **severe** allergy |
| Give 500 oral fluid before injection | **Do not** perform skin testing with dilute BPG |
| Let the patient lie for 5 min before injection | **Do not** give BPG to patients with uncontrolled heart failure or dehydration (23) |
| Use lidocaine 2% as diluent (24) | **Never** give BPG intravenous |

**Step 4: Prepare the patient and give the injection.**

- Ask the patient to take 500 ml of **oral fluid** as dehydration could precipitate vasovagal syncope.
- Let the patient **lie prone** for 5 min.
- **Using the large bore (16–18 gauge) needle**: insert the needle into the upper lateral quadrant of gluteus muscle. **Aspirate first** to ensure that you are not injecting into the vein. If **no blood** is aspirated: inject slowly.
- Document on patient records.

**Step 5: Observe for 15 min.**

- If the patient is well, discharge and **advise strict adherence** to doctor instructions.
- In case of mild allergy (itching), give antihistamine injection. In case of sever allergy/anaphylaxis follow the steps below.

Penicillin allergy:

Defined as a reaction to penicillin that appears shortly after the injection. There are two types of allergy:

i. Mild allergy, which consists of skin rash, hives, itching, fever, and mild swelling.
Management of mild (skin only) allergy:
   - If the reaction is seen, give oral or injectable antihistamine.
   - In patients with ARF who experience mild allergy with a previous injection, an **oral graded challenge** can be given to test for allergy as follows (8):
     1. Give the patient 50 mg of oral amoxicillin syrup or one-tenth of a 500 mg crushed capsule.
     2. Wait for 30 min, if no symptoms give 450 mg of oral amoxicillin.
     3. Wait for another 30 min, if no symptoms proceed for the BPG injection.

ii. Severe allergy: manifests as airway tightness or anaphylaxis reaction characterized by:
   - tightening of the airways and throat, causing difficulty of breathing,
   - nausea or abdominal cramps,
   - vomiting or diarrhea,
   - dizziness or lightheadedness, and
   - low blood pressure leading to syncope and death.

**Warning for this step:**

DO NOT GIVE BPG TO PATIENTS WITH HISTORY OF THESE SEVERE SYMPTOMS

***Management***

- Maintain airway, Breathing and Circulation
- Call for help and act promptly to do the following steps:

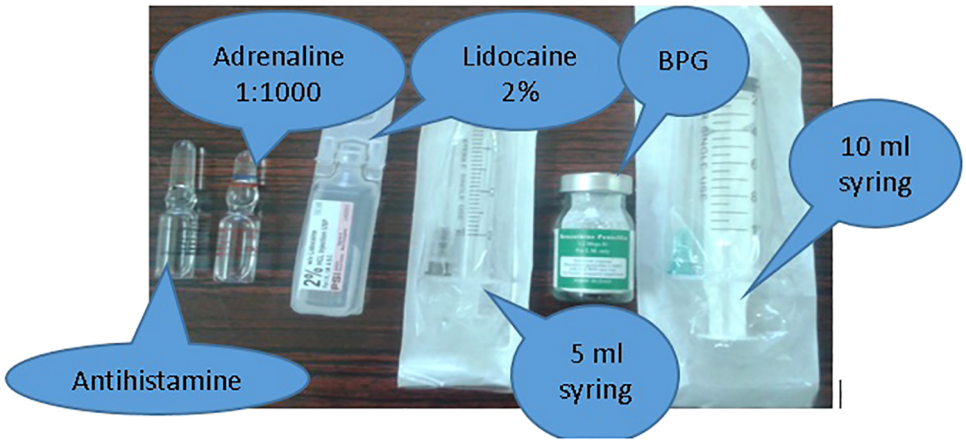


FIGURE 4
Items needed for BPG administration.

TABLE 6 Risk stratification of RHD in pregnancy (22).

| Low risk (level I) | Elevated risk (level II) | High risk (level III) | Extremely high risk (level IV): pregnancy is contraindicated and termination considered |
|---|---|---|---|
| - History of ARF but no RHD<br>- Mild asymptomatic RHD<br>- Antenatal visit <20 weeks. | - Mild asymptomatic RHD with antenatal visit >20 weeks<br>- Mild to moderate mitral or aortic regurgitation<br>- Mild mitral stenosis<br>- Bioprosthetic valve or previous mitral balloon commissurotomy<br>- Mildly reduced ejection fraction (>45%)<br>- Not level 3 or 4 | - Mechanical valve<br>- Moderate mitral stenosis: mitral valve are 1.5 cm–2 $cm^2$<br>- Severe asymptomatic aortic stenosis<br>- Severe asymptomatic mitral or aortic regurgitation<br>- Moderately decreased ejection fraction (30%–45%) | - Severe symptomatic mitral stenosis: valve area <1 $cm^2$<br>- Severe valve lesion with Pulmonary hypertension<br>- Severe symptomatic aortic stenosis<br>- Ejection fraction <30%<br>- NYHA class III/IV |

- Intramuscular adrenalin 0.3 ml (<7 years) of 1:1,000 solution and 0.5 ml (>7 years), can be repeated in 15 min.
- Lie the patient with legs up
- O2 if the patient is distressed
- Intravenous normal saline and adrenalin infusion (25)

## 6. Rheumatic heart disease and reproductive healthcare:

### *Risk stratification*

Table 6 shows risk stratification of heart disease in pregnancy (26).

### *Preconception counseling*

All adolescent girls should receive counseling about pregnancy and contraception according to their risk category including the following:

- Risk of pregnancy with RHD.
- Importance of planning pregnancy.
- Family planning options.
- Importance of visiting the specialist before getting pregnant.
- Patients need to have complete cardiac assessment (history, examination, and echo) for risk categorization before pregnancy.
- Patients who are considered high risk should be advised to take contraceptives **avoiding estrogens**. Intra-uterine contraceptive device and etonogestrel implant should be strongly encouraged (27).

### *Management during pregnancy and delivery*

- Patients need to be evaluated by a **joint team** including obstetrics and cardiology. In high-risk patients, anesthetists and intensive care physicians need to be involved.
- Termination of pregnancy may be indicated if Level III or IV RHD severity is present.
- Secondary prophylaxis (BPG injections, oral penicillin, and erythromycin) are **safe** during pregnancy and breastfeeding, and should be continued.
- Angiotensin converting enzyme inhibitors, angiotensin receptor blockers, atenolol, and spironolactone should be avoided.
- Vaginal birth is associated with less blood loss, lower risk of infection, less venous thromboembolic complications, and is advised for most women with RHD.
- Post-delivery counseling includes the need to have cardiac evaluation, advice on contraception, cardiac medication, and secondary prophylaxis by specialist.
- Delivery: hemodynamic monitoring with supervision of anesthesia/critical care specialist, correction of anemia, and a short second stage are advised (26).

### *Anticoagulation*

- Warfarin is the drug of choice for patients with prosthetic valves but it can lead to fetal embryopathy.
- Direct oral anticoagulants such as rivaroxaban **cannot be used** for patients with prosthetic valves.

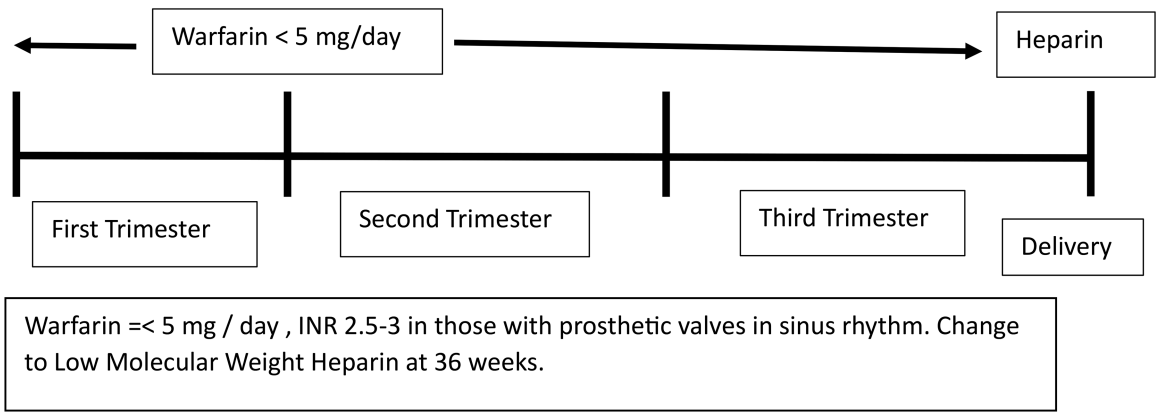


FIGURE 5
Management of anticoagulation during pregnancy.

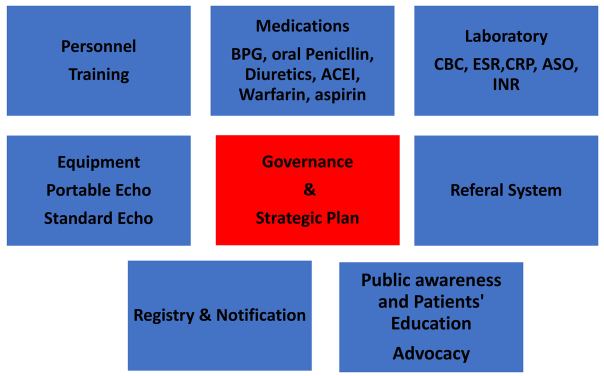


FIGURE 6
Health system requirements for implementing rheumatic heart disease guidelines.

- Balancing maternal and fetal risks and individualizing the method of anticoagulation is best done by an **expert team**.
- The regimen of warfarin during pregnancy is depicted in Figure 5.

### 7. Health system requirements for implementation of guidelines:

Strengthening the health system especially at the primary and secondary levels is mandatory to control RHD. Patients with advanced RHD need tertiary care including surgery and cardiac catheterization, which poses a significant technical and financial burden on the health system. Figure 6 shows the items needed to implement the ARF/RHD guidelines at the primary and secondary care levels.

## Conclusion

Updated ARF/RHD guidelines were produced aiming to improve diagnosis and management of the disease at primary and secondary care levels. The guidelines were adapted to suit Sudan's health system facilities by utilizing simplified diagnostic and treatment methods. Implementation of these guidelines needs strengthening of the health system as well as establishing a governing body.

## Author contributions

KA: Writing – review & editing, Writing – original draft, Investigation, Conceptualization. ZK: Writing – review & editing, Project administration, Conceptualization. NE: Writing – review & editing. NI: Writing – review & editing, Project administration.

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# Eradicating rheumatic heart disease in Africa: have we made progress since the Drakensberg declaration?

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KEYWORDS

**rheumatic heart disease, Africa, health system barriers, challenges and progress, pragmatic solutions**

In 2006 the Drakensberg Declaration on the Control of Rheumatic Fever and Rheumatic Heart Disease in Africa (1) was published, launching the Awareness Surveillance Advocacy Prevention (A.S.A.P.) program to control rheumatic fever (RF) and rheumatic heart disease (RHD) in Africa. It is almost 20 years later and a good time to take stock of our progress in dealing with this scourge on the African continent. Two articles appearing in this issue of the Journal, a] serve as a reminder of the major knowledge and treatment gaps that remain in what is the most important preventable cause of valvular heart disease on the continent of Africa; and b] shed some light on areas of progress that are being made in the field to address them.

If the enormous morbidity and mortality that is still being caused by RHD in low- and middle-income countries is to be addressed, there is reasonable consensus that a multi-pronged attack (2–4) is required, including:

- Improvement in living conditions and health care programs in these communities
- Early detection and treatment of the precursors of RHD:
  - Group A beta-hemolytic streptococcal (GAS) pharyngitis
  - Acute rheumatic fever (ARF)
- Developing a protective vaccine to prevent GAS infection
- Early detection of RHD through screening programs
- Adherence to effective programs of prophylactic treatment
- Managing patients with advanced valve lesions requiring tertiary care and access to valve replacement intervention.
- Continuing research to fill the gaps in our knowledge regarding ARF and RHD

The poverty, poor housing and overcrowding present in most African countries, accompanied by a shortage of health care resources, are a reality that is likely to remain a challenge for some time to come. This reality has prevented many health programs across the continents from being able to diagnose and treat GAS and ARF, improve the detection of latent or early RHD, and administer prophylactic treatment effectively in order to prevent progression to symptomatic severe valve lesions and the debilitating complications such as heart failure that follow.

An important aspect of the RHD focused articles in this issue of the journal is that they remind us not to become overwhelmed by the enormity of the challenges preventing us from putting in place ideal solutions. The article by Sulafa et al, whose work focusses on developing reasonable strategies that may not be perfect solutions but are practical and implementable in disadvantaged communities is an example. In it the authors provide a

simplified approach to manage GAS and ARF which may be particularly useful at primary and secondary care level where access to echocardiography and laboratory tests required for diagnosis is limited. Although developed specifically in and for Sudan, the algorithm for ARF management, is accompanied by detailed text on the administration of benzatine penicillin G (BPG) and can be put to use in many other resource-limited African countries with a similar ARF burden and health care limitation.

At the other end of the spectrum, the article from Egypt by Kotit and Jacoub in this issue provides insight into what is possible in Africa, with regard to management of advanced RHD at a tertiary centre with appropriate funding, infrastructure and expertise. Many of their patients presented with multivalvular or mitral valve disease requiring balloon valvuloplasty or surgical intervention and received their much needed percutaneous and surgical interventions with excellent results. However, the realization that very few countries on the African continent can provide these services (5) to those that need it serves to stress the need to identify latent or early RHD and prevent progression by administering prophylactic treatment.

The World Heart Federation (WHF) guidelines for the echocardiographic diagnosis of RHD, published in 2009 and updated in 2023 (6) are used by most workers in the field who are screening high risk populations in order to identify RHD early in order to initiate prophylactic treatment. Whilst these guidelines serve to drive a standardized approach to early case detection, there are significant limitations in this approach, including the complexity of the criteria and the expertise and equipment needed to assess these criteria. Efforts have been made to simplify these criteria such as the single parasternal-long-axis-view-sweep of the heart (SPLASH) in two dimensional (2D) and colour Doppler imaging proposed by Remenyi et al. (7). The WHF guidelines have largely developed from epidemiological data, expert opinion and end-user feedback and efforts to improve the performance of the diagnostic criteria have been hampered by the lack of a gold standard to diagnose RHD. A study by Hunter et al. published in 2023 addressed this limitation by developing a composite reference standard RHD-positive cohort ensuring the highest possible likelihood of RHD and a cohort with a very low risk RHD profile. They then developed morpho-mechanistic screening criteria that outperformed the WHF criteria to detect or rule out RHD in these two cohorts. More importantly they developed a simple two-step screening algorithm that will enable non-expert screeners to effectively screen for RHD in the field (8).

It is probably fair to say that, at the present time, we have not made enormous strides in Africa to eliminate RHD, a preventable cause of heart disease that has been all but eliminated in many high-income countries. It is likely that this will only be achieved against a backdrop of decreasing poverty, improving living conditions, improving education and developing well-funded, well-functioning health care programs. However, there is no need, until these objectives have been met, to not develop novel solutions and local solutions that may not be perfect but are feasible and practical in particular communities.

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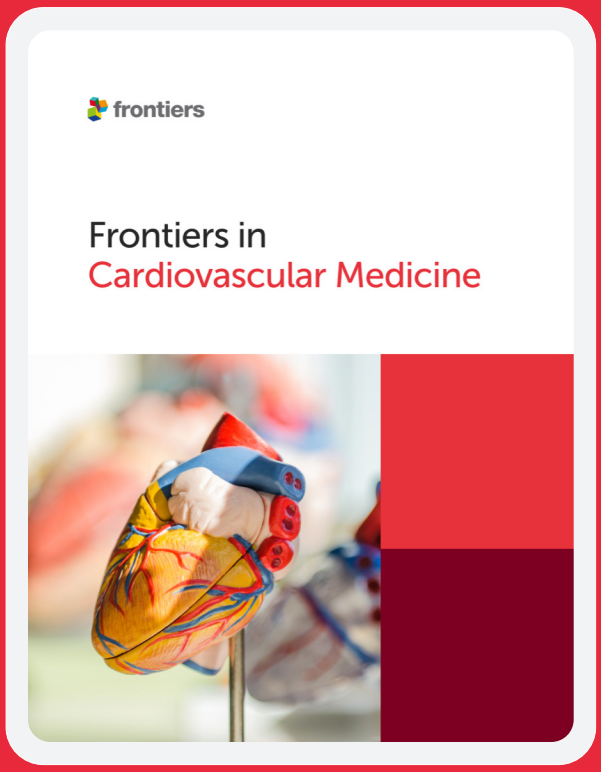


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