Isolated mechanical aortic valve replacement in rheumatic patients in a low- to middle-income country

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ABSTRACT

Objective: Although the results of aortic valve replacement are well documented for industrialized countries, the outcome in patients with rheumatic aortic valve disease in low- to middle-income countries is less well explored. The aim of this study was to determine the long-term survival and clinical outcomes after isolated aortic valve replacement in patients with rheumatic heart disease in a Sub-Saharan country where follow-up of indigent patients is often challenging.

Methods: A retrospective review of 969 aortic valve replacements performed between 2003 and 2013 was conducted at Cape Town's Groote Schuur Hospital. Patients who underwent concomitant procedures ($n = 664$) or had nonrheumatic valve pathology ($n = 185$) were excluded. The mean age of the rheumatic cohort ($n = 121$) was 43.1 ± 11.6 years with a mean follow-up period of 6.14 ± 3.44 years. The primary end points were survival and valve-related complications.

Results: A 15% cardiac- or valve-related 10-year mortality after receiving a mechanical prosthesis corresponded with a significantly higher mortality rate than that of a matched population. Overall cumulative survival at 1, 5, and 10 years was 93.5% (87.0-96.9), 86.4% (78.4-91.8), and 78.1% (67.5-86.0), respectively, and the corresponding cumulative freedom from combined thromboembolism and bleeding was 94.4% (88.2-97.5), 87.4% (79.4-92.5), and 86.1% (77.9-91.6), respectively.

Conclusions: In low- to middle-income countries, with their unique mix of indigent and "First World" patients, rheumatic heart disease still accounts for a significant proportion of patients requiring isolated aortic valve replacement. Although mechanical prostheses are often selected in these young adults, survival remains suboptimal. Major bleeding and thromboembolic events account for the majority (77%) of the reported valve-related complications. (*J Thorac Cardiovasc Surg* 2019;157:886-93)

Freedom from major adverse valve-related events after mechanical AVR.

Central Message

In low- to middle-income countries, up to 1 of every 4 young rheumatic patients receiving a mechanical AVR have a major valve-related event within the first decade after valve replacement.

Perspective

None of the current heart valve prostheses offer a true lifelong solution. In young patients with RHD, compelling evidence is lacking to balance the risk of thromboembolic/bleeding events with mechanical valves against reoperative risk inherent to bioprostheses. Technological developments and evolving transcatheter solutions may together favor more liberal use of bioprostheses in these patients.

See Commentary on page 894.

In low- to middle-income countries, rheumatic heart disease (RHD) still accounts for the majority of patients in need of cardiac surgery. It is estimated that in Africa alone, there are

15 million patients living with RHD, of whom 100,000 per year may need valve surgery during some stage of their lives,¹ provided cardiac surgery is available. Because of the nature of the underlying disease, aortic valve repair options are limited, and as such, surgical aortic valve replacement (AVR) remains the treatment of choice for the majority of patients with symptomatic rheumatic aortic valve disease. Apart from access to open surgery, the choice of valve prosthesis presents a particular challenge given the socioeconomic circumstances of these patients. Yet, in the absence of local evidence-based recommendations, low- to middle-income countries largely apply First World guidelines when it comes to valve selection.²⁻⁴ As such, the majority of patients still receive mechanical valves at

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Abbreviations and Acronyms

AVR = aortic valve replacement

INR = international normalized ratio

RHD = rheumatic heart disease

VIV = valve-in-valve

a time when the collective experience of industrialized countries had long swung toward tissue valves because of their significantly older patient population. The de facto paradigm of this decision continues to be that the anticipation of premature tissue valve degeneration in young patients outweighs poverty-, culture-, and access-related adverse events associated with mechanical heart valves. Given this prevailing assumption, prospective comparative studies between the 2 valve types would be considered unethical, although the true outcome of mechanical valve replacements remains unknown. A first step toward evidence-based decision-making would be to determine the long-term fate of mechanical valve replacements in the largely young patients with rheumatic disease of a low- to middle-income country with reasonable access to cardiac surgery.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board (Human Research Ethics Committee: Approval Ref 344/2014; Faculty of Health Sciences, University of Cape Town. Institutional Review Board: IRB00001938).

Patients

All patients who underwent an AVR at Cape Town's Groote Schuur Hospital between January 2003 and December 2013 were followed up retrospectively. A total of 969 patients were identified. Patients who underwent concomitant procedures, aortic root replacements, aortic valve repairs, transcatheter, or redo procedures were excluded ($n = 664$ patients). We further excluded all patients who had underlying calcific degenerative disease, endocarditis, congenital aortic valve disease, or any other nonrheumatic heart valve pathology ($n = 184$ patients), leaving 121 patients who underwent an isolated first-time AVR for RHD. The majority of these patients (89%, $n = 108$) received a mechanical prosthesis. The subgroup of patients who received a bioprosthesis was small (11%, $n = 13$) and significantly older (mean age of 58.6 ± 11.6 years) than the mechanical group and therefore not included in the subsequent analysis. The preoperative baseline characteristics are summarized in Table 1. The mean age of this rheumatic cohort was 43.1 ± 11.6 years at the time of surgery, with 63.8% ($n = 69$) of the cohort being male. Pure aortic regurgitation occurred in 61% of patients ($n = 66$), pure aortic stenosis occurred in 8% of patients ($n = 9$), and 31% of patients ($n = 33$) had a mixed (predominantly regurgitant) aortic valve lesion. Atrial fibrillation was present in 8% of patients ($n = 9$) preoperatively. The majority of patients (90%) presented in New York Heart Association class II or III at the time of surgery. The mean calculated Society of Thoracic Surgeons score (risk of mortality) of this rheumatic cohort was $0.7\% \pm 0.2\%$.

TABLE 1. Preoperative demographic characteristics of 108 rheumatic patients who underwent an isolated first-time mechanical aortic valve replacement

Baseline characteristics	N (%)
Age, mean (SD), y	43.1 (11.6)
Men	69 (63.8%)
Race/ethnicity	
Mixed race	62 (57.4%)
Black	41 (34.2%)
White	4 (3.7%)
Indian	3 (2.8%)
Asian	2 (1.9%)
Cardiovascular risk factors/comorbidities	
Hypertension	25 (23.1%)
Diabetes	7 (6.5%)
Dyslipidemia	7 (6.5%)
Smoker	14 (12.9%)
Atrial fibrillation	9 (8.3%)
Immunocompromised (HIV positive)	4 (3.7%)
New York Heart Association class	
I	7 (6.5%)
II	59 (54.6%)
III	38 (35.2%)
IV	4 (3.7%)
Left ventricular ejection fraction	
<35%	11 (10.2%)
35%-49%	30 (27.8%)
≥50%	67 (62.0%)
Aortic valve pathology	
Regurgitation	66 (61.1%)
Stenosis	9 (8.3%)
Mixed disease	33 (30.6%)
STS score (mortality), mean (SD)	0.7 (0.2)
Level of education	
Did not complete secondary school education	91 (84.3%)
Completed secondary school education	14 (12.9%)
Tertiary education	3 (2.8%)
Employment status	
Unemployed	77 (71.3%)
Employed (temporary or permanent)	28 (25.9%)
Social grant/retired	3 (2.8%)

SD, Standard deviation; HIV, human immunodeficiency virus; STS, Society of Thoracic Surgeons.

Operative Data and Prosthesis Selection

The mean cardiopulmonary bypass time was 114 ± 26 minutes with a crossclamp time of 78 ± 21 minutes. All procedures were performed under moderate hypothermia using St Thomas crystalloid cardioplegic solution. The distribution of mechanical prostheses was as follows: St Jude Medical (Saint Paul, Minn) in 32 patients (26%), On-X (CryoLife Inc, Kennesaw, Ga) in 30 patients (25%), Edwards MIRA (Edwards Lifesciences Inc, Irvine, Calif) in 23 patients (19%), Medtronic Advantage (Medtronic Inc, Minneapolis, Minn) in 19 patients (16%), and Medtronic ATS (Medtronic Inc) in 4 patients (3%).

FIGURE 1. Survival in a rheumatic cohort of patients who underwent isolated mechanical AVR, compared with a sex- and age-matched population in the Western Cape, South Africa. AVR, Aortic valve replacement.

Anticoagulation and Postoperative Management

Anticoagulation therapy with warfarin was routinely commenced on the first postoperative day in all patients who received a mechanical prosthesis. A low-molecular-weight heparin was concomitantly used until a target international normalized ratio (INR) between 2 and 3 was reached. After discharge from the hospital, all patients were referred to their closest medical clinic or facility where further INR testing and follow-up could be performed.

Data Collection and Outcomes

During the past decade, the widespread use of prepaid mobile phones, as well as institutional and national laboratory databases, introduced improved means for follow-up, thus far unavailable, for a patient population with a significant rural component.

Data were retrospectively collected using the cardiac surgical database of the Chris Barnard Division of Cardiothoracic Surgery, University of Cape Town, as well as from hospital medical records, the metropolitan hospital-link database, the National Health Laboratory Service's database, and telephone interviews.

The follow-up period ended in October 2014. The mean follow-up period was 6.1 ± 3.4 years and 100% complete. The primary outcomes were valve-related mortality and valve-related morbidity, which included prosthetic valve dysfunction, bleeding and embolic events, prosthetic valve endocarditis, and the need for reintervention. The outcomes were reported as per guidelines for reporting mortality and morbidity after cardiac valve interventions.⁵

Statistical Analysis

Statistical analysis was performed using the JMP statistical software package (version 10.0.2, SAS Institute Inc, Cary, NC). All continuous numeric data were expressed as means $\pm$ standard deviation. Kaplan-Meier survival estimates were expressed as percentages and 95% confidence intervals. For comparison of mortality rates with that of the standard population, the method described by Finkelstein and colleagues,⁶ using age- and sex-matched vital data, obtained for the Western Cape Province

from Statistics South Africa, was used.⁶ Statistical comparison between standard population and cohort patient survival was performed using the 1-sample log-rank test. For visual comparison, 95% pointwise confidence intervals were included.

RESULTS

The main finding of this retrospective analysis was a significantly inferior long-term survival of the study group compared with an age- and sex-matched comparable South African subpopulation (Figure 1) with 39% ($n = 7$) of late deaths being valve related. Major bleeding and thromboembolic events ($n = 17$ events) accounted for the majority (77%) of the reported valve-related complications. One of every 4 of these young rheumatic patients had a major adverse valve-related event (mortality or major morbidity) during the first decade after having received a mechanical aortic valve prosthesis.

Early Mortality and Complications

The in-hospital/30-day mortality for the rheumatic mechanical AVR cohort was 1.9% ($n = 2$). The causes of early death were multiorgan failure ($n = 1$) and a thromboembolic neurologic event ($n = 1$). New-onset atrial fibrillation/flutter occurred in 4.6% ($n = 5$) of patients. New-onset atrioventricular block requiring a permanent pacemaker occurred in 1.9% ($n = 2$). Bleeding requiring reoperation (<48 hours) occurred in 2.8% ($n = 3$), late drainage of a pericardial effusion (<30 days) occurred in 1.9% ($n = 2$), renal failure occurred in 0.9% ($n = 1$), and early stroke occurred in 0.9% ($n = 1$) of patients.

TABLE 2. Late mortalities

	Mechanical AVR prosthesis (n = 106 patients)
Total all-cause late mortalities	N = 18 (17.0%)
Valve related	n = 7 (38.9%)
Endocarditis	1
Thromboembolism	1
Bleeding event	1
Reoperation	2
Sudden unexplained	2
Other cardiac related	n = 9 (50.0%)
Congestive cardiac failure	9
Acute myocardial infarction	0
Arrhythmias	0
Noncardiac	n = 2 (11.1%)

AVR, Aortic valve replacement.

Late Mortality

Late mortality (all cause) occurred in 18 of 106 patients (17%) at a mean of 43 ± 37 months after surgery. The majority of the late deaths were cardiac or valve related (89%, $n = 16$). Table 2 summarizes the causes of late deaths. Cumulative survival at 1, 5, and 10 years after mechanical AVR was 93.5% (87.0-96.9), 86.4% (78.4-91.8), and 78.1% (67.5-86.0), respectively. This was considerably lower than that of the age- and sex-matched population in the Western Cape Province, South Africa, where this study was conducted, whose expected survival was 97.7% (97.0-98.4), 91.8% (90.2-93.4), and 86.6% (79.6-93.7), respectively ($P < .001$) (Figure 1).

Valve-Related Morbidity

Overall, 9 major bleeding and 8 thromboembolic events occurred in 14 patients. Of the thromboembolic events, 7 were strokes and 1 was a transient ischemic event. The cumulative freedom from the composite of thromboembolism and bleeding after mechanical AVR was 94.4% (88.2-97.5), 87.4% (79.4-92.5), and 86.1% (77.9-91.6) at 1, 5, and 10 years, respectively (Figure 2).

Only 2 reoperations were performed during the follow-up period (6.14 ± 3.44 years). The indications for reintervention were valve thrombosis ($n = 1$) and prosthetic valve endocarditis ($n = 1$). As such, freedom from reoperation at 1, 5, and 10 years was 100%, 99.0% (93.0-99.9), and 96.9% (87.4-99.3), respectively.

Freedom from any valve-related event (ie, prosthetic valve dysfunction, bleeding/thromboembolic events, prosthetic valve endocarditis, and the need for reintervention) at 1, 5, and 10 years was 94.4% (88.2-97.5), 87.4% (79.4-92.5), and 82.9% (73.5-89.4), respectively (Figure 3).

Major Adverse Valve-Related Events

Freedom from major adverse valve-related events (ie, valve-related mortality, valve-related morbidity, and the

need for a new pacemaker) at 1, 5, and 10 years was 92.6% (85.9-96.3), 82.6% (74.0-88.8), and 78.1% (68.4-85.5), respectively (Figure 4). A further subanalysis comparing the different types of mechanical prosthesis used did not show any significant difference in terms of major adverse valve-related events ($P = .23$).

DISCUSSION

With the often remarkable growth of cardiac surgery in emerging economies in which RHD still prevails, the reliance on First World guidelines for the choice of replacement valves that do not take the specific pathology, patient age, and socioeconomic circumstances of the affected patients into account may result in unintended poor outcomes.

Our cohort analysis of single mechanical AVRs in rheumatic patients showed a significantly higher 10-year mortality than their matched population counterparts. This sobering outcome was aggravated by the fact that the mean age of these patients was less than 45 years. Together with low mortality rates for reoperations for degenerated tissue valves,⁷⁻⁹ a 15% ten-year cardiac- or valve-related mortality after receiving a mechanical valve prosthesis justifies a critical appraisal of our current practice of prosthesis selection.

Recent renewed interest in RHD and the increasing volumes of cardiac operations performed in the affected countries have led to a shift in focus from merely emulating First World standards toward recognition of the need to respond to a distinctly different pathology, resource, and patient baseline.^{1,10} Epidemiologic assessments of disease burdens countering the widely held belief that RHD has been largely contained need to form the backbone of such a reorientation. Validating this quest, Sliwa and colleagues¹¹ found the incidence of RHD in South African patients aged 14 years or more as high as 24 per 100,000 per year, a stark contrast to the less than 1 of 100,000 in developed countries.¹² More important, within 30 months of diagnosis, 22% of these newly diagnosed patients needed heart valve surgery.¹¹

Challenges in Dealing With Patients With Rheumatic Heart Disease

In the relatively young patients with RHD, compelling evidence is still lacking to balance the risk of anticoagulation-related bleeding and thromboembolism associated with a mechanical valve with the risk of structural valve deterioration and potential reoperation inherent to bioprostheses.¹³ Yet, observational studies have shown that major bleeding and thromboembolic complications in patients with mechanical valves are generally higher in low- to middle-income countries than in high-income countries.¹⁴ In the present study, the majority of patients did not complete secondary school education (84%) and 71% were

FIGURE 2. Freedom from major bleeding and thromboembolic events in a rheumatic cohort of patients who underwent isolated mechanical AVR.

unemployed. Infrastructure such as transportation and access to health facilities in low- to middle-income countries is often suboptimal for ensuring therapeutic anticoagulation.¹⁵ In the current series, major bleeding and thromboembolic events accounted for the majority (77%, $n = 17$) of the reported valve-related complications.

Although the rate of structural valve degeneration of bioprostheses is inversely proportional to a patient's age,¹⁶ prosthesis durability, a patient's life expectancy, operative risk of a redo procedure, and the socioeconomic circumstances of typical rheumatic populations must be interpreted together. Even in industrialized countries, the life expectancy of patients who underwent an AVR is substantially lower than that of the general population.^{17,18} In a large contemporary First World series, Bouhout and colleagues¹⁹ also reported suboptimal survival in young patients receiving mechanical prostheses. Of note is their higher cumulative survival at 1, 5, and 10 years of $98\% \pm 1\%$, $95\% \pm 1\%$, and $87\% \pm 1\%$, respectively, despite an older mean age of 53 ± 9 years compared with 43.1 ± 11.6 years in our series.¹⁹ Therefore, weighing the risk of anticoagulation-related events versus prosthesis longevity needs to be interpreted in the context of the even lower life expectancy of AVR recipients in low- to middle-income countries. Thus, when several large series reported the operative mortality risk for reoperative AVR cases to be 5% to 7%,⁷⁻⁹ this relatively low risk must be compared with the lifetime risk of anticoagulation-related events in the poorly anticoagulated communities of developing countries. During the follow-up in a Kenyan series, for instance, only 7% of mechanical valve recipients had

adequate anticoagulation for more than 50% of the 5-year observation period.²⁰

Cardiac disease in pregnancy is associated with high morbidity and mortality rates.^{1,21} RHD is the most common underlying cardiac lesion in pregnant patients presenting at referral hospitals in South Africa, and as such the incidence of AVRs in this age group is also higher than in developed countries.²² Although the patient's young age would qualify them for a mechanical valve, the detrimental effects of warfarin during the first and last trimesters of pregnancy have been well described. Our study underlined the magnitude of this most distinctive difference in patient populations: More than one third (36.2%) of our rheumatic patients with mechanical AVR were female (mean age, 44.3 ± 11.5 years), and a significant proportion presented during their childbearing years or even during pregnancy.

Alternative Solutions for Low- to Middle-Income Countries

The use of new anticoagulants, such as direct thrombin inhibitors, is particularly attractive and shown to be an effective alternative to warfarin in patients with atrial fibrillation. However, its use in patients with mechanical heart valves has been associated with increased rates of thromboembolic and bleeding complications.²³ In view of this excess risk, warfarin remains the drug of choice in patients with mechanical prostheses, until new evidence becomes available.

Genotype-based warfarin dosing has shown some promise during the initiation phase of warfarin therapy.²⁴

FIGURE 3. Freedom from any valve-related complication (including prosthetic valve dysfunction, bleeding and thromboembolic events, prosthetic valve endocarditis, and the need for reintervention) in a rheumatic cohort of patients who underwent isolated mechanical AVR.

However, these trials have been limited to patients with European ethnic and socioeconomic backgrounds and provide no guidance on long-term anticoagulation management in our environment.

The recent results from the PROACT trial are encouraging in that INR levels after mechanical AVR with the On-X prosthesis can be safely maintained at lower levels (1.5 to 2.0), without increased risk of anticoagulation-

related events.²⁵ However, this strategy still requires the use of warfarin with careful monitoring (including home-based monitoring) and is better suited for selected patients only. Furthermore, the results from this study only demonstrated a reduction in the rate of major bleeding events, but a higher number of thromboembolic events.

Transcatheter valve-in-valve (VIV) procedures are also of potential interest in this setting.²⁶ Results of

FIGURE 4. Freedom from major adverse valve-related events in a rheumatic cohort of patients who underwent isolated mechanical AVR.

perioperative outcomes from global VIV registries are encouraging, but the paucity of information about the long-term durability of aortic VIV procedures warrants further investigations.²⁷

Study Limitations

This study is observational, and data were collected retrospectively.

CONCLUSIONS

In low- to middle-income countries, RHD still accounts for the major burden of disease in patients needing heart valve interventions. None of the current heart valve prostheses offer a lifelong solution. Given that, (1) the life expectancy after an AVR (with either prosthesis), particularly in younger patients with RHD, is substantially lower than the life expectancy of the general population; (2) warfarin compliance and INR control are suboptimal in developing countries; (3) the incidence of major bleeding and thromboembolic complications is significantly higher in developing countries; and (4) a significant part of rheumatic patients present during their childbearing years; thus, a substantial number of young rheumatic patients living in low- to middle-income countries may be exposed to a lower lifetime risk of experiencing a valve-related event by selecting a bioprosthetic heart valve from the outset. Despite the relative increased mortality risk associated with reoperations for degenerated bioprostheses, new technological developments that may increase the longevity of soft-leaflet prostheses^{28,29} and evolving transcatheter solutions for low-income countries that may broaden the access of patients to heart valve replacements³⁰ may together favor a more liberal use of bioprosthetic valves in young patients with RHD.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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