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Poorly suited heart valve prostheses heighten the plight of patients with rheumatic heart disease

Jacques Scherman, Peter Zilla *

Christiaan Barnard Department of Cardiothoracic Surgery, University of Cape Town, South Africa

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A B S T R A C T

Rheumatic heart disease (RHD) still affects more patients globally than degenerative valve disease. The vast majority of these patients live in low- to middle-income countries. Once symptomatic, they will need heart valve surgery. Unfortunately, prosthetic valves perform poorly in these patients given their young age, the high incidence of multi-valve disease, late diagnoses and often challenging socio-economic circumstances.
Notwithstanding the fact that better valve designs would ideally be available, ill-informed decision making processes between bioprosthetic and mechanical valves are contributing to the poor results. In the absence of multicentred, randomised clinical trials, comparing the current generations of bioprostheses with mechanical valves across all age groups Western guidelines tend to be uncritically applied. As a consequence, mechanical valves are being implanted into patients who are often not able to deal with anticoagulation while bioprosthetic valves may be overly shunned for fear of reoperations.
Almost sixty years after the advent of cardiac surgery heart valve prostheses have eventually undergone improvements and several potentially disruptive developments are on the horizon. Until they materialise, however, choices between contemporary valve prostheses need to be made on the basis of individual risk and life-expectancy rather than an uncritical implementation of guidelines that were derived for very different patients and under distinctly different conditions.
Given the fast expansion of cardiac surgery in middle-income countries and a growing number of independently operating centres in low-income countries a critical appraisal of facts underlying the choice of heart valve prostheses for patients with RHD seems opportune.

1. Introduction

Contemporary replacement heart valves were developed for the patients of industrialised countries with their advanced medical systems. To keep complication rates within an acceptable range mechanical valves need reliable anti-coagulation monitoring and bioprosthetic valves should preferentially go into older patients. Both these preconditions are insufficiently met in low- to middle-income countries (LMICs) where the dominant valve pathology is rheumatic rather than degenerative [1–13] *(*Fig. 1*)*. Typically, these patients are young, poor, uneducated, and often have difficulty in accessing medical care [11,14,15]. Unsurprisingly, even if they have access to cardiac surgery, clinical results are disappointing. Low anticoagulation compliance due to socioeconomic and cultural circumstances leads to a high incidence of lethal or debilitating thromboembolic complications in patients with mechanical valves [16–21]. Alternatively, many patients have no choice but receiving a bioprosthetic valve at a relatively young age notwithstanding the possibility of needing several re-operations over their life span [22] *(*Fig. 2*)*.

2. Heart valve surgery for RHD

Rheumatic heart disease (RHD) is not limited to developing countries. Contrary to perceptions, RHD still claims a large proportion of its global burden of deaths in middle-income countries (MICs) [23]. While these countries increasingly have access to open heart surgery, they share many of the specific challenges associated with RHD in low-income countries (LICs) foremost the poor suitability of replacement heart valves for a significant proportion of patients.

Locally produced valves continue to be cheaper clones rather than alternatives that address the specific needs of MICs [24,25]. Moreover, as long as the perception prevails that RHD is a condition of the past, efforts to develop own alternatives will be hampered by a lack of economic incentive. Aggravating the situation is the fact that chronic RHD seems to be increasingly decoupled from a history of acute rheumatic

* Corresponding author.
E-mail address: peter.zilla@uct.ac.za (P. Zilla).

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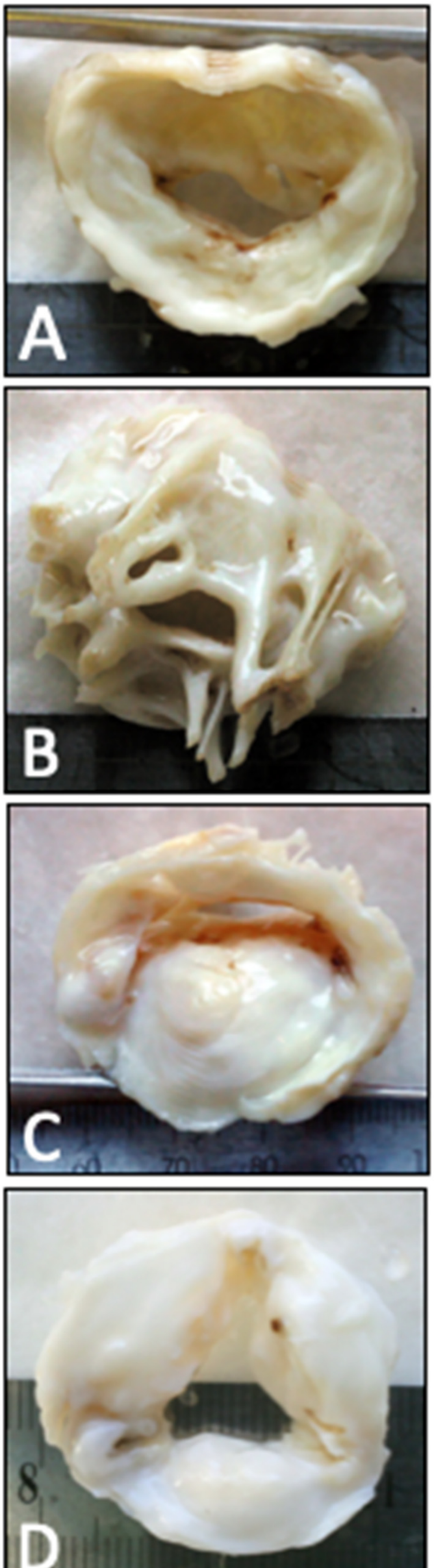

Fig. 1. Typical rheumatic heart valves needing replacement. (A) MS in 26 year old female; (B) MS in 30 year old female; (C) Mixed MV-disease 52 year old female and (D) mixed AV disease in 57 year old male.

fever (ARF) the prevailing benchmark for the disease. Predictably, governments interpreted the low incidences of ARF [26] as a sign of near eradication of RHD. Yet, the actual number of cases requiring surgery remains high [27,28]. This decoupling is still poorly understood and cannot only be explained with a clinical lag-phase. In a recent Brazilian national survey, for instance, decades of declining incidence of acute rheumatic fever [26] were opposed by a continually large proportion of patients needing heart valve surgery for chronic RHD [5,28].

This increasingly diverse manifestation of RHD is also reflected in the time the inflammatory process needs to cause clinically symptomatic heart valve disease requiring surgery. As a consequence, the patient age at surgery – one of the main determinants of prosthetic performance - varies widely.

Differences to the typical patients of high-income countries (HICs) do not only apply to the suitability of valve prostheses but also to operative techniques from ‘peeling’ of excess fibrous leaflet tissue in mitral repairs [29] to the preservation of the sub-valvular apparatus (PSVA) in mitral valve replacements (MVRs) [30]. Similarly, predicted mortalities as reflected in the scoring system of large supra-continental databases like STS or EuroSCORE poorly apply. Inherently, they represent mean values of vast numbers of the largely elderly patients of HICs with predominantly degenerative or secondary valve disease. These calculated risk scores also reflect the advanced medical systems of these countries. As such, in the absence of own comparable databases, multicentre comparisons or even sufficiently available cardiac surgical services in the regions rife with RHD, decision making processes largely rely on sub-compatible North American and European prostheses and guidelines, often reluctantly carried over to LMICs in the absence of alternatives. Few will dispute the inadequacy of this compromise. The example of a HIC like Australia where the indigenous population had twice as high a mortality after valve replacement for RHD than predicted by EuroSCORE II [31] is a similar case in point as surgery for infective endocarditis in South Africa where actual results deviated significantly from EuroSCORE predictions [32].

Another fundamental difference between these two worlds is the predominance of single valve disease – often together with the need for revascularisation procedures - in the non-rheumatic patients of HICs as opposed to a high percentage of double- or even triple-valve disease in LMICs patients with RHD [10,22,28,33–35]. This further complicates the choice of valve prosthesis as the different flow and stress conditions associated with the particular anatomical location of one valve may affect the valve choice for the other.

2.1. Patient characteristics

Even if future valve prostheses resolve key issues of prostheses-inherent failure modes, patient specific circumstances will still modulate their performance. The underlying pathology, socioeconomic embedding, or patient age create fundamentally different conditions for the longevity and performance of replacement valves. By being in average 30 years younger than Western patients with degenerative diseases, rheumatic patients are largely deemed to not qualify for contemporary tissue valves due to their accelerated degeneration in this age group. On the other hand, socioeconomic circumstances prevailing in areas endemic for RHD concur with poor anticoagulation compliance in patients with mechanical heart valves. Furthermore, co-morbidities like atrial fibrillation affecting a significant proportion of young patients with RHD aggravate the consequences of unreliable compliance with anticoagulation. Last not least, both mechanical and tissue valves are exposed to distinctly different haemodynamic conditions in the aortic than in the mitral position making them more prone to fail in the latter. While bioprostheses degenerate there faster because of greater loading forces [36,37]} mechanical prostheses also thrombose 2–3 times more frequently in the mitral (Fig. 3B) than in the aortic position [38] due to more pro-thrombogenic fluid-dynamics. Even under the conditions of a high-income country like Canada, their 10 year cumulative stroke

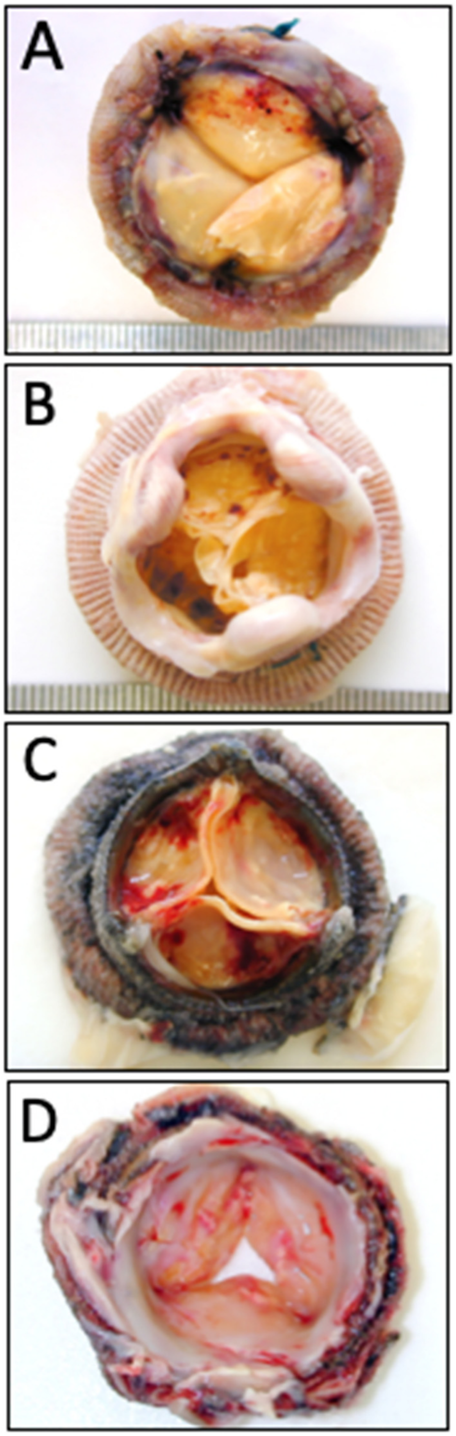

Fig. 2. Failed early-generation bioprosthetic heart valves implanted into patients with RHD in the 1990s. Most long-term studies are based on this second generation of tissue valves. (A) MVR with CE Porcine Valve implanted in a 39 yr old patient deemed non-compliant for anticoagulation. Prosthetic endocarditis (Infected sewing ring) and ruptured leaflet at age 45; (B) AVR with Hancock I Porcine Valve at age 33 failed (calcified, ruptured) after 19 years at age 52; (C) MVR with St.Jude Pericardial valve in 36 yr old woman after 2 blocked mechanical valves. Explant after 9 yrs. (stenosed, MV gradient 34 mm); (D) Pericardial prosthesis of unknown make failing after 9 yrs. (primarily stenosed) at age 45 after 2 previous mechanical valves clotted.

rate was twice as high after mitral valve replacements (MVRs) than after aortic valve replacement (AVR) [39]. As such - independent of prostheses related challenges - patients needing surgery for RHD have a significantly higher risk of prosthetic valve failure than those with degenerative or congenital valve disease.

2.2. Underlying pathology and influence of gender

In exaggerated terms, symptomatic RHD preferentially affects the mitral valve of young to middle-aged females [18,21,22,31,40] while degenerative disease affects the aortic valve of elderly males [41–43]. In countries like Sweden where RHD affects <1% of valve patients the aortic valve accounted for 69% of all valve procedures. With the advent of TAVIs, this percentage increased to 79% in Germany in 2017 [43], the country with the highest TAVI rate globally [41,42]. In contrast, the mitral valve was replaced or repaired in 71% of rheumatic patients in an urban South African study [33] and was in need of surgery in >96% of patients in the 'REMEDY' study, analysing symptomatic patients with RHD from 14 LMICs in Africa and Asia [35]. Coinciding with the high prevalence of the mitral valve in RHD is an overall female gender bias of between two thirds [18,21,40] and three quarters [22,44]. Thus, as a natural consequence of a female predominance and their prevailing need for mitral valve surgery, one can conclude that female patients have a higher likelihood of experiencing early structural valve degeneration or thromboembolic events than males. As such, a significant baseline bias against female patients already exists even before one takes the conundrum into account that pregnancy presents for heart valve surgery.

To make things worse, women also have a higher incidence of rheumatic mitral valve stenosis [45–47] due to a more prominent and aggressive inflammatory process [48]. One possible implication of this may be a higher recurrence rate after mitral repairs [48]. A more aggressive inflammatory process may also augment intimal hyperplasia and as such pannus overgrowth [49]. Pannus overgrowth can either lead to a narrowing of the orifice of mechanical valves (Fig. 3A or to bioprosthetic leaflet immobilization and is estimated to be behind obstructive valve failure in between 31% [50] and 53% [51] of cases.

Notwithstanding the fact that mitral valve disease remains the major indication for surgery in RHD [6,10,18,21,22,28,33,40] the aortic valve becomes increasingly affected as patients get older in the course of the epidemiologic transition [5,11]. Our own most recent 10-year cohort (2008–2018) at Groote Schuur Hospital/University of Cape Town (mean age 45 $\pm$ 14 years) confirms this trend: mitral valve surgery was still required in 78% of all patients with RHD but aortic valve replacement (AVR)/AV-repair occurred in 50% (more than half of them needing double valve replacement). In contrast to degenerative disease, aortic regurgitation (AR) by far outweighs stenosis (AS) in RHD. AR poses both a diastolic as well as a systolic volume overload, thereby causing early irremediable damage [52]. The timing of surgery is challenging as the morbidity and mortality associated with aortic valve replacement in a LMIC needs to be weighed against the disease progressing to the point from which onwards a recovery of LV function and improved survival can no longer be achieved [53]. Cut-off points for prognostically meaningful surgery have been >55 mm for end-systolic left ventricular diameter and 25–35% for ejection fraction [53,54].

2.3. Patient age and pregnancy

Patient age at the time of surgery – which is a crucial determinant for both bioprosthetic valve degeneration and compliance with anticoagulation [55,56]– varies widely. A majority of the often rural patients of low-income countries (LICs) need surgery when they are still in their early twenties [18]. It is unfortunately in those regions where patients are youngest that socioeconomic conditions result in the lowest compliance with anticoagulation. The problem often starts with the regular availability of warfarin itself [18]. In an Indian study, only 44% of patients were in the therapeutic range and as few as 8% fully compliant [20]. Results from Turkey [57], Ethiopia [18], Kenya [58] and Cameroon [6]all reported similar anticoagulation-related bleeding events. Thomson-Mangnall et all found young age to be a risk factor for non-compliance [55] and Koshy et al. found it significantly more often in males [56]. Yet, as much as maleness and being young are co-

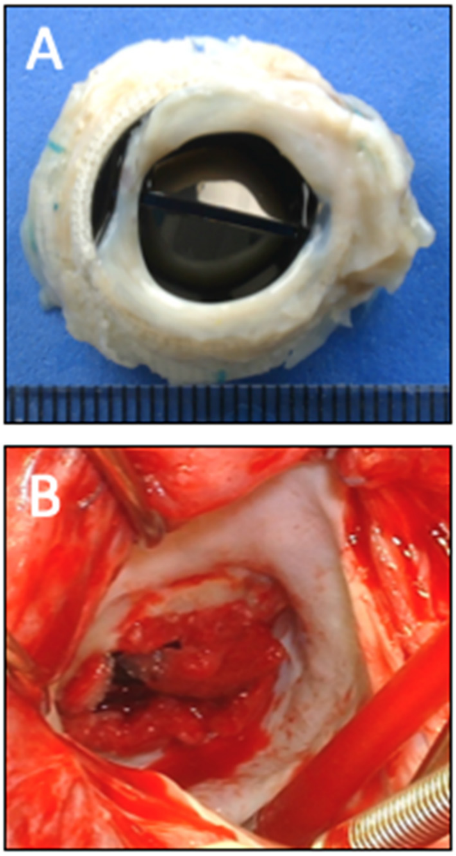

Fig. 3. The two primary failure modes of mechanical heart valves in the young patients of low- to middle-income countries with RHD: (A) vigorous infra-valvular pannus ingrowth seven years after AVR with Mira (Edwards) at age 25 and (B) clotted and sub-totally obstructed mitral valve (Reproduced from [179] with permission).

factors towards poor INR control, the female bias of RHD in this age group [22,40] makes women in child bearing age particularly endangered by inadequate replacement valves [21,59]. For them, inadequate anticoagulation control [6,18,20] (frequently aggravated by anti-retroviral medication) coincides with high birth rates and therefore with a higher probability of not being on contraception after heart valve replacement or even experiencing more than one pregnancy with a prosthetic valve [60]. <5% of women with RHD of childbearing age in Uganda, for instance, are on contraceptions [61]. The fact that pregnancies happen 11 years earlier and fertility rates are >4 times higher even in countries where cardiac surgery has been established [9,62,63] seriously impacts the outcome of heart valve replacements. In a Bangladeshi comparative study 12% of patients showed thrombus formation on mechanical valves during pregnancy and 3% had warfarin embryopathies. Normal pregnancy-outcome was only achieved in 2 out of 3 women in the mechanical group versus almost all in the bioprosthetic group [64]. Together with other reasons for poor results such as high rates of infective endocarditis [32,33] this age group is left with a particularly dire choice of heart valve prostheses [21,65].

In MICs the mean age of these patients at the time of surgery has gradually increased as a consequence of urbanisation and affluence [in South Africa from 22 in the early 1980s [66] and 31 in the 1990s [67] to 41 in the late 2000s [33]; in Brazil to 44 [28] and in Korea to 52 years [68]]. As such, today's largely urban patients of MICs are well into their fourties when they need heart valve replacements for `RHD [28,33]. Although they are 10–20 years older than in LICs [18,22,40] these patients would still be 20 years too young to qualify for tissue valves under European and North American guidelines [69,70] As older patients not only mean a slower degeneration of tissue valves but in the case of mitral valve disease, for instance, also a higher incidence of chronic atrial fibrillation, this dynamic shift of patient characteristics needs to be taken into account when it comes to valve choices and eventually guidelines.

2.4. Atrial fibrillation (AF)

The incidence of new onset AF in RHD is 3.5% per year overall and 6.0% per year in patients with an enlarged left atrium (≥47 mm) [71]. Its prevalence is particularly high in patients with advanced valvular disease [72] with 40% of RHD patients undergoing valve surgery having AF and another one-third of the remaining 60% developing AF after surgery [73]. It is also valvular AF that is associated with the highest risk of stroke [57] particularly in rheumatic patients [74]. It is estimated that at least 3–7.5% of new strokes each year worldwide are directly due to RHD, representing 144,000–360,000 strokes and 108,000–269,000 stroke deaths per year and 640,000–1.6 million stroke survivors in less developed countries [75]. A hospital-based stroke registry in Iran found RHD in almost 45% of patients admitted with cardioembolic stroke [75] and 29% of cardioembolic strokes in India [76] were due to RHD.

Again, the highest risk group are females post MVR who are in chronic AF. In a 2014 study from Turkey initially screening >2000 patients, 74% of all patients with a prosthetic heart valve who were in AF had an MVR and 72% were female [57]. It were these patients – already at higher risk of thromboembolic incidences due to the specific mitral valve heamodynamics – who also had the poorest INR control (only 36% showed therapeutic levels) [57].

The key question in this context is whether a mechanical valve is less forgiving regarding INR fluctuations than AF. Non-warfarin anticoagulants (NOACs) for post-surgical anticoagulation won't be available for mechanical valve replacements in rheumatic patients and fixed-dose warfarin regimens were shown to lead to an increase in thromboembolic events [77]. Yet, in the clear absence of anticoagulation requirements for the replacement valve itself - as is the case in patients with tissue valves - NOACs may still affect the choice of prosthesis. One of the warfarin-controlled pivotal non-vitamin K oral anticoagulants trials in AF comprising >21,000 participants included patients with bioprosthetic valves [78]. A subgroup analysis showed that patients with low dose edoxaban had similar rates of stroke/SEE but lower rates of major bleeding compared with warfarin suggesting that edoxaban is a reasonable alternative to warfarin in patients with AF and a bioprosthetic valve [79]. In some young patients with RHD and AF whose life expectancy would make them potential candidates for a bioprosthetic valve a significantly lower bleeding risk may give further support to this option. Furthermore, even in Western patients with their largely degenerative valve diseases, AF is known to adversely influence ventricular function and survival [80,81] - particularly after MVR [82]. In patients with RHD in LMICs this already reduced baseline survival often coincides with typical late presentation and an associated poor ventricular function. As the presence of NYHA functional class III/IV and AF at surgery was shown to further increase the ten-year mortality by 32% and 40%, respectively [83], the presence of chronic AF in patients needing valve replacement highlights more than any other co-morbidity how different and multifactorial the decision making process is when it comes to the choice between mechanical and bioprosthetic replacement valves in rheumatic patients of LMIC as opposed to the typical patients needing valve surgery in HICs.

3. Valve failures

As much as valve sparing operations even in the presence of severe fibrosis [84] have significantly expanded the spectrum of mitral repairs [6,44,85–88] and aortic valve repairs [89] including the Ross operation

[90] are beginning to be applied to patients with RHD [91] a significant proportion of patients will continue to rely on valve replacements. The lack of repair skills in frontline low-volume centres [11] and the high incidences of endocarditis [32] are only two of the reasons.

3.1. Lack of guidelines

Roughly generalising the caveat that needs to be observed when trying to employ Western guidelines to the rheumatic patients of LMICS: mechanical valve-failures are potentially catastrophic whereas tissue valve degeneration occurs over time. In a study from Turkey involving rheumatic patients with failing valve prostheses the re-operative mortality was 3 times higher in the mechanical group, not even taking those patients with clotted mechanical valves into consideration who died before reaching the hospital [92]. Yet, while the likelihood of a patient reaching hospital for re-intervention is significantly higher in bioprosthetic valves, one needs to weigh this survival advantage against the rising mortality coming with each re-operation caused by a degenerated tissue valve. There is also an ethical predicament in offering multiple operations to one patient in a resource constrained environment. Normally, guidelines help in complex clinical decision-making processes. In HICs, extensive data underlie the guidelines for valve choices. Current North American and European guidelines recommend mechanical valves for patients younger than 60 with a grey-zone of either mechanical or tissue valves between age 60 to 65 and clear recommendations for tissue valves beyond 65 [93]. No such clear recommendations emerge from the often scanty data collected in LMICs with their predominantly rheumatic burden of valve disease.

3.2. Mechanical valves

In LICs like the Fijiis the ten year mortality for mechanical heart valves (mean age 26 yrs) was 24% with death occurring 3.2 years after surgery [21]. Similarly, in Cameroon (mean age 28 yrs) the 6-year mortality with mechanical valves was 21% [6]. Maori and Pacific island women (mean age 25 yrs) had a seven- to eight-fold relative risk of death after heart valve replacement, compared with European women [65]. Although rapid tissue valve degeneration in this age group led to an almost 3 times higher re-operation rate after bioprosthetic valve replacement at 10 years compared to mechanical valves the relative risk of death in the same time period was 2.2 times higher after mechanical valve replacement [65]. A similar trend was seen in children in Saudi Arabia where the 15 year survival with bioprosthetic valves was 92% as opposed to 76% with mechanical valves [94]. In a Pakistani study, 18% of children with mechanical valves had serious thromboembolic or haemorrhagic incidences within 10 years [95].

Similarly, the 10-year mortality for MVRs in a MIC like South Africa (mean age at implantation 41 yrs) [96] was 20% and the 10-year mortality for rheumatic AVR (mean age 43 yrs) was 15% [16]. Differently looked at these results, every one in four relatively young patient post mechanical AVR was either dead or had a major thromboembolic/haemorrhagic incident after 10 years [16]. In India, the actuarial 10-year death-rate in patients operated at a mean age of 16 years was 41% after mechanical MVR and 28% after mechanical AVR [97].

3.3. Bioprosthetic ('tissue') valves

Given the disappointing results with mechanical valves in LMICs, it is remarkable that only one contemporary study offers data on bioprosthetic valves in the young rheumatic patients of these countries [98]. To the contrary, high re-operation rates in young patients in HICs [99–105] are being used to justify the near-complete avoidance of tissue valves in the rheumatic patients of LMICs [6,16,18,21,22,86,95,106]. Ironically, a reverse trend emerged over the years: while LMICs increasingly followed the North American and European recommendation of mechanical valves for patients younger than sixty, the age-boundaries for tissue valves have continuously been downward-eroded in HICs [99–102,104,105,107–112]. Between 1997 and 2014, for instance, the proportion of patients in California and New York State who received a tissue valve increased from 14% to 47% [109]. In a propensity matched study analysing such patients a mean age of 43 years was associated with a 2.6 times higher re-operation rate than mechanical valves at 15 years. Therefore, long-term data on tissue valves in young patients do exist, albeit from patient with degenerative disease in HICs and from 2nd rather than 4th generation prostheses. For early implants, mean-times to reoperations were 7.7 years in patients younger than 40, 12.9 years for age 40 to 60 [113], 16.6 years for age 60–70 [114] and 19.4 for patients older than 70 years [114]. Studies of the intervening period concluded for the 30-50 yr age group that reinterventions reached 25–35% between 10 and 20 years of implantation [99] and 55–86% after 20 years [100,102,105,108,115]. In the middle-age group of 50-60 years, reintervention rates were not too different with 37% at 10 years [102] and 45–81% at 20 years [105,115]. However, arguments why one should not uncritically extrapolate these data to today's young rheumatic patients in LMICs are manifold. For one, patients, circumstances and prostheses have changed over time. Although all key studies were published between 2005 and 2018 their actual implants go back to the 1970s and 1980s [108,112,115]. Furthermore, although most of the recommendations coming out of the research of recent years have not been implemented in contemporary valves [49,116–120] some of them have [121]. This is partially reflected in performance differences between different makes: a 3 year freedom from valve related failure of 18% in Mitroflow valves, for instance, was opposed by 100% in Edwards Perimount Magna valves [122] most likely on the grounds of alcohol-based lipid extraction in the Edwards valves not used in early Mitroflow models. Similarly, the long outstanding verdict on pericardial versus porcine valves seems to have come closer to a conclusion as pericardial valves saw a longer freedom from valve related failure than porcine prostheses (10.2 versus 5.7 years) [103] and a higher rate of freedom from reoperation in a most recent study [123].

3.4. Considerations for valve selection

Fear of reoperations has deadlocked discussions around valve choices on the level of evidence rooted in the 1980s and 1990s. Overall cardiac surgical mortalities are different in today's era. As such, contemporary operative mortality rates of 4–5% for first time re-operations [124–127] may make re-interventions a costly inconvenience rather than a deterrent. In modern series analysing redo AVRs and MVRs separately, the operative mortality of the first re-operation lay in the 3–4% range for AVRs [128–130] and 4–8% for MVRs [131,132]. For redo-AVRs, Turina et al. [133] have even shown that mortalities can be brought down to 1.4% if only elective cases were considered. Less invasive operative techniques also had an impact in recent years. Schneider et al. reported a decrease of the mortality of redo-AVRs from 9.3% to zero over the last decade [134]. Similarly, no mortality was also observed in redo-MVRs both using minimally invasive [135] and beating heart techniques [136].

In order for bioprosthetic valves to be considered for young patients, however, the morbidity and mortality associated with mechanical valves would need to outweigh the accumulated mortality and inconvenience of re-interventions for bioprosthetic valves. Several Western studies did conclude that there was no difference in long-term mortality between mechanical and tissue valves [109,110,137–142] In patients with RHD in LMICs, the high rate of thromboembolic and haemorrhagic incidences in mechanical valves needs to be additionally taken into account. Importantly, the limited capacity of the health care systems to deal with acutely failing valves [16,96] must also be considered. In a study from Turkey reporting on the re-operation of 700 patients who had a valve replacement mainly for RHD at a relatively young age, the mortality was three times higher in urgent (mostly mechanical valves) than in elective (mostly bioprosthetic) re-operations [92].

Against this background, the individual life expectancy of a patient needs to be the final determinant in the choice of the least detrimental valve prosthesis. In developing countries, patients from rural backgrounds and low socioeconomic status very often present with advanced disease. Hence, despite being young in age, the life expectancy of these patients is much lower than that of Western populations. As such, the assessment of life expectancy, based solely upon chronological age, is erroneous and age-related Western cut-offs are not valid [143]. Besides age, the cardiac condition of the patient, systemic illnesses and the socioeconomic status, life expectancy is also affected by the patient's gender and location (urban vs rural). In India, for instance, the life expectancy of a rural male (60.2 years) is much less than that of urban female (69.0 years) [143]. Life expectancy is also a direct reflection of an individual's socioeconomic and educational status [143]. Thus, the 11.9 years life expectancy of a 60-year-old patient receiving a bioprosthesis in India [144] is much shorter than the life expectancy of 22.6 years for 60-year-olds reported by the US National Centre for Health Statistics [143,145]. On top of this, valve patients live shorter, even in HICs. Lindblom and colleagues [146] have shown that the relative life expectancy was only 78% post AVR and 65% post MVR [146] and less in younger patients [146]. As patients with RHD often have advanced disease their life expectancy is even shorter as symptoms of heart failure and/or AF further reduce the expected survival [143]. The presence of aortic regurgitation and mitral regurgitation further contribute to excess mortality [83,143,146]. Therefore, it can be assumed that in a significant proportion of patients life expectancy will lie below the implant duration of the first tissue valve.

Overall, other considerations also need to come in like the potentially game-changing effect transcatheter therapies may have on valve choices. Ample evidence exists that by now valve-in-valve (VIV)-TAVI/TMVR is an established procedure that allows redo-AVRs [147–149] and MVRs [150] without re-opening of the chest. At its extreme it includes the possibility of insertion into a failing tissue valve during pregnancy [148]. Yet, there are limitations. In VIV-TMVRs, a known complication in every 50th ‘Western’ patient is left ventricular outflow tract (LVOT) obstruction [150]. Given the small ventricular cavity of patients with rheumatic mitral valve stenosis and as such of patients with stenosed bioprosthetic valves, the higher incidence of LVOT obstruction may be a limiting factor for this indication. Furthermore, costs are a prohibitive obstacle for valve-in-valve transcatheter solutions in LMICs but more affordable local makes have begun to emerge [151,152]. Whether transcatheter VIV-procedures will further significantly lower reoperative mortality will need to be shown. In a 2019 meta-analysis a zero operative mortality in the VIV-TAVI group increased to 4% when the 30 day mortality was assessed, matching that of surgical reoperations by the time of discharge.

4. In summary

In the absence of large, multicentred, randomised clinical trials, using the current generations of bioprostheses and mechanical valves across all age groups [143] valve choices will be least harmful if sensible and appropriate criteria rather than Western guidelines are being uncritically applied.

At the outset of such an approach must be an assessment of a patient's life expectancy taking his/her geographic, socioeconomic and medical background into consideration. Assessment criteria must be continually adjusted: overall life expectancies have increased (in India eg from 54 in 1980 to 70 in 2019 [153]); pericardial valves have emerged as more durable [98,103,123] and scientific insights into mechanisms of tissue degeneration or thrombus formation are beginning to be reflected in contemporary prostheses [121]. Other aspects such as whether a prosthesis is for the aortic or the mitral position should also be taken into account. As much as surgeons in LMICs have somehow considered these criteria in the past, the supremacy of the ‘chronological age’ of patients enshrined in the guidelines of HICs still dominates the decision making process in LMICs.

5. Glimmers of hope

The quest for longer lasting tissue valves and anticoagulation-free mechanical valves of young patients of HICs who are eager to live an active life may add weight to the efforts of middle-income countries addressing the needs of their patients with RHD.

Low-thrombogenicity designs of mechanical valves have been a holy grail for decades but with tri-leaflet concepts [154] they may eventually be within reach. A novel design that placed the hinges of a tri-leaflet valve distinctly into the central systolic blood-flow, thereby eluding the adverse flow areas near the housing of the valve, showed very promising in-vitro results [155] and most recently also an in-vivo breakthrough (personal communication)(Fig. 4).

Calcific bioprosthetic degeneration of tissue valves was shown to hinge on remnant immunogenicity [156]. Better immune-suppression through alternative crosslinking approaches [49,157] and/or decellularization [118,120] were shown to mitigate calcification. Alternatively, alpha-gal receptor-depleted trans-genic pigs were suggested

Fig. 4. Novel tri-leaflet mechanical heart valve: Main characteristics are zero back flow during diastole, pivoting completely in systolic flow, no contact of the leaflets with the valve ring in systole, antithrombotic material (titanium and PEEK), aerodynamically optimized leaflet configuration (similar to one wing aircraft) and ring design preventing suture pledgets from protruding into the blood-flow (Courtesy of H.Sievers with permission from [155].

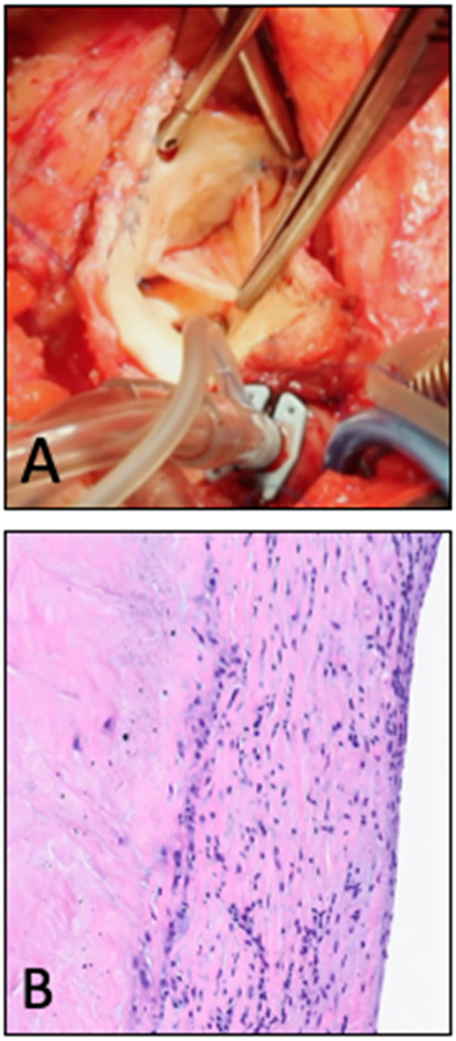

Fig. 5. Decellularized xeno-pericardium as a promise for bioprosthetic longevity: (A)"Auto Tissue Berlin" Matrix Patch (decellularized, non-crosslinked equine pericardium) [166] 5 years after replacing one cusp during aortic valve repair in a 7-year old child. The patch is still thin and pliable. Redo surgery was necessary because of the retraction of the two shaved native cusps. (Courtesy of Boulos Asfour, St. Augustin, Germany) (B) Hematoxylin & Eosin stain of the explanted patch. Pseudointima formation (right half of the image) covering the decellularized equine surgical patch (left half of the image) demonstrating sparse cell infiltration and no significant cellular inflammatory reaction. (Courtesy of Matthias Sigler, University of Göttingen, Germany).

as tissue source [158]. As a first step towards clinical implementation, cell membrane extraction through alcohol-based lipid wash-out [116,117,119] was partially introduced to commercial valves [121]. Complete decellularization with the goal of extracting the main antigen carriers from the tissue was clinically successfully demonstrated in allografts [159]. Decellularization of xenografts tissue [118] was a logical next step. Non-crosslinked in order to allow tissue regeneration, such tissue was clinically tried with poor outcome [160] suggesting that unmasked/non-crosslinked extracellular matrix may still be sufficiently immunogenic to trigger an inflammatory xenograft response. While gentler decellularization may allow for non-crosslinked decellularization [161] (Fig. 5) either mildly [162] or conventionally crosslinked decell-pericardium [163] have been clinically successfully used for valve reconstruction patches [164]. Following two decades of conclusive research, decellularized tissue valves potentially combined with engineered crosslinking [165] will undoubtedly introduce a quantum leap into bioprosthetic heart valve developments. In its wake, one can expect a dramatic downward-shift of the age limit for tissue valves. Unsurprisingly, MICs like Brazil and South Africa [166] and HICs with a significant burden of RHD like Australia [162] are currently pioneering such prostheses.

Polymeric leaflet materials are immune-quiescent but had previously experienced calcific degeneration due to polymer degradation and imperfect production [167]. Daebritz and Jansen had shown the potential of polymer valves in the challenging calf model [168,169]. Momentum has built up in recent years [170] culminating in first-in-man implants in 2019 [171].

Given the often very young age of patients with RHD, replacing diseased heart valves with living prostheses has been the ultimate goal of generations of researchers. Over the past decade, the focus of tissue engineering has shifted from in-vitro bio-reactor-based concepts [172,173] to self-regenerating polymer-based approaches [174]. The recent failure of clinically implanted 'Xeltis' valves [175], after promising pre-clinical trials [176], however, demonstrated the complexity of the balance between degradation and regeneration.

Last not least, lack of cardiac surgical capacity is not only a big challenge for LICs but also for MICs outside the urban reach [5,11,177]. A combination of easy-to-place trans-catheter technologies tailor-made for non-sophisticated medical facilities (Fig. 6) and suitable for the often compliant, non-calcified valves of patients with RHD with long-lasting leaflet material (Fig. 7) may introduce replacement valves that eventually address the "needs of the many" [166,178].

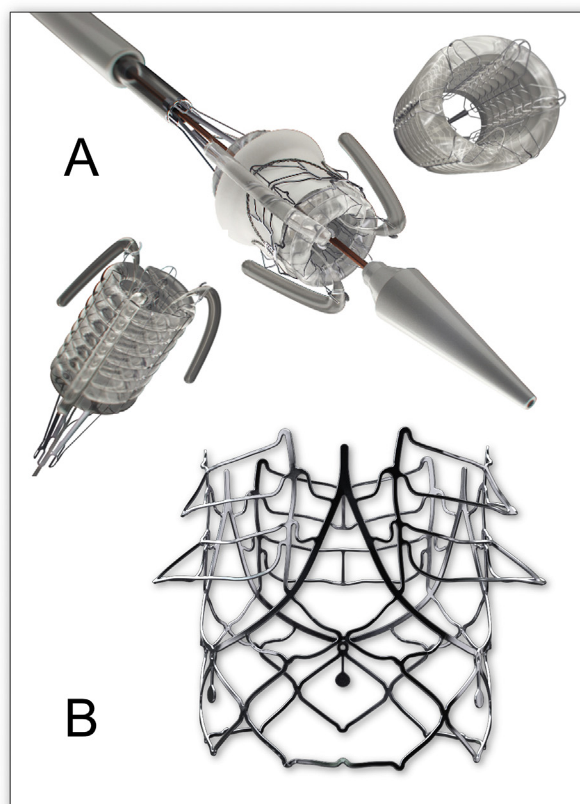

Fig. 6. Transcatheter system enabling the implantation of replacement valves under basic conditions. (A) Self-homing, non-occlusive delivery system for the deployment of balloon expandable TAVI s (reproduced with permission from [166] (B) TAVI-stent developed for the largely non-calcified, compliant aortic roots of patients with AR in low- to middle-income countries with RHD (with permission of Strait Access Technologies (SAT) / University of Cape Town).

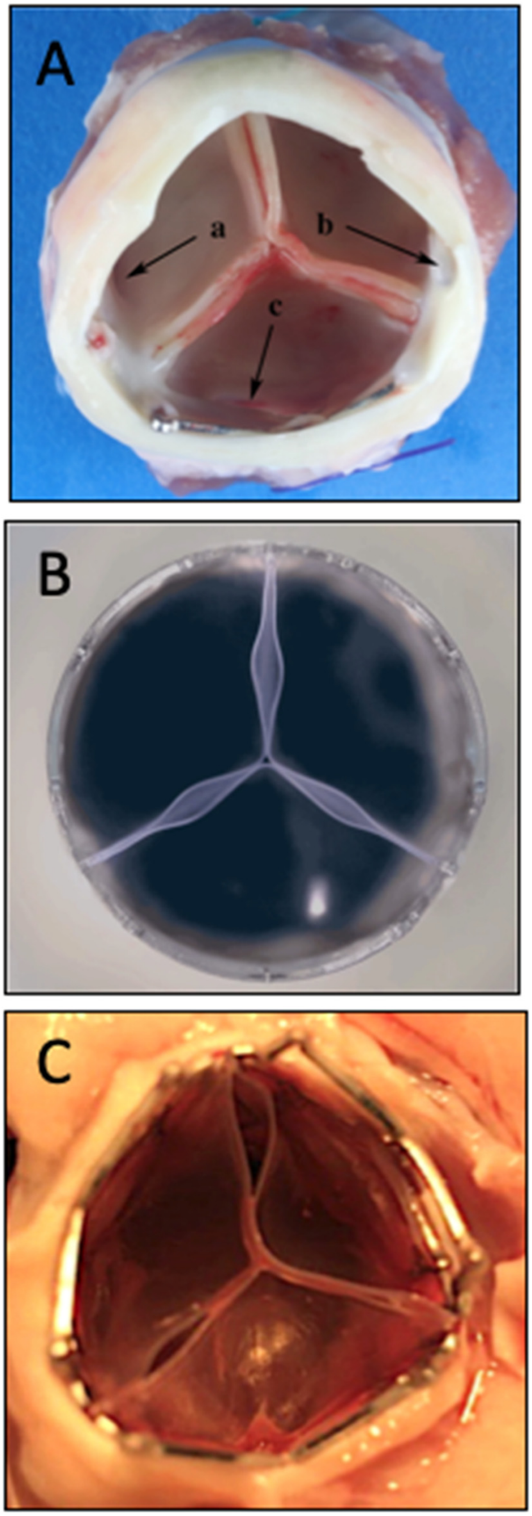

Fig. 7. SAT TAVIs (A) with decellularized bovine pericardial leaflets (reproduced from [166] with permission) after 4 5 months in sheep orthotopic position (B) with polymer leaflets in vitro and (C) polymer leaflets after 5 months in the sheep [166]. At explantation, both leaflet types (A,C) had no traces of calcification and were soft and pliable.

Declaration of Competing Interest

PZ is a shareholder in the University of Cape Town start-up company 'Strait Access technologies'

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