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Tertiary prevention and treatment of rheumatic heart disease: a National Heart, Lung, and Blood Institute working group summary

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ABSTRACT

Although entirely preventable, rheumatic heart disease (RHD), a disease of poverty and social disadvantage resulting in high morbidity and mortality, remains an ever-present burden in low-income and middle-income countries (LMICs) and rural, remote, marginalised and disenfranchised populations within high-income countries. In late 2021, the National Heart, Lung, and Blood Institute convened a workshop to explore the current state of science, to identify basic science and clinical research priorities to support RHD eradication efforts worldwide. This was done through the inclusion of multidisciplinary global experts, including cardiovascular and non-cardiovascular specialists as well as health policy and health economics experts, many of whom also represented or closely worked with patient-family organisations and local governments. This report summarises findings from one of the four working groups, the Tertiary Prevention Working Group, that was charged with assessing the management of late complications of RHD, including surgical interventions for patients with RHD. Due to the high prevalence of RHD in LMICs, particular emphasis was made on gaining a better understanding of needs in the field from the perspectives of the patient, community, provider, health system and policy-maker. We outline priorities to support the development, and implementation of accessible, affordable and sustainable interventions in low-resource settings to manage RHD and related complications. These priorities and other interventions need to be adapted to and driven by local contexts and integrated into health systems to best meet the needs of local communities.

SUMMARY BOX

- ⇒ At patient, health system and policy levels, there are gaps in tertiary care that lead to long-term morbidity and premature mortality for those living with rheumatic heart disease (RHD).
- ⇒ Evidence-based guidelines recommend surgical and catheter-based intervention for severe or symptomatic valvular heart disease, as there is little evidence that pharmacological management changes outcomes.
- ⇒ There is an unmet need for surgical correction of severe valvular diseases due to dearth of cardiac surgical care in most parts of low-income and middle-income countries (LMICs) where RHD is prevalent. Current evidence shows an estimated need for valvular surgery for patients with RHD in LMIC is far greater than 100 000 per year worldwide.
- ⇒ Development of lower-cost valves, valve rings and open-heart surgery disposables is needed to close a large gap between those who need surgery and those who receive it.
- ⇒ Increased research around and access to lower cost procedures, both closed surgical and catheter-based need to be prioritised to bring down costs and increase access.
- ⇒ Robust research and development are needed to improve comprehensive tertiary care and implementation of evidence-based interventions while developing new innovations, technologies and interventions.
- ⇒ Health systems strengthening efforts are necessary to support the continuity of primordial, primary, secondary, and tertiary prevention and care for RHD, especially in or closer to local communities where RHD is endemic.

INTRODUCTION

Rheumatic heart disease (RHD) is a neglected chronic disease preceded by untreated, uncontrolled and/or repetitive group A Streptococcal (GAS) infections and the consequent episodes of acute rheumatic fever (ARF). RHD cases have significantly declined in high-income countries (HICs). However, the same cannot be said for low-income and middle-income countries

(LMICs). In select HICs, RHD remains prevalent in populations living in rural or remote areas or who have poorer access to healthcare services. As a result, while absolute and relative burdens have improved over time, Indigenous Peoples, immigrant communities and disenfranchised populations (eg, homeless people) remain at risk for ARF and RHD, as has been observed in Australia, Canada, the USA and some island states.[1 2] The disease is endemic in the world's poorest billion, with its highest burden seen among children, adolescents, young adults, females and pregnant women in LMICs. According to the Global Burden of Disease (GBD) study in 2019, more than 40 million people worldwide are affected, and there are >350 000 new cases every year.[3] Among patients with RHD, >300 000 deaths and >630 000 cases of severe heart failure (HF) occur annually.[4] The most common causes of death are haemodynamic decompensation secondary to HF and arrythmias, sudden cardiac arrest and thromboembolic events.

Preventative interventions are an essential component of effective healthcare models, deployed during distinct stages of disease acquisition and progression to improve outcomes. These strategies are implemented during the symptomatic phase, to reduce the severity of the disease, as well as of any associated sequelae. Tertiary care, in the form of HF management and rehabilitation, is currently the primary treatment option available for the majority of the patients with RHD. While HF treatment has been shown to improve outcomes for patients with mild to moderate valvular disease, patients with severe valvular disease, especially mitral stenosis, usually require valvular replacement or valvuloplasty to improve quality of life.[5 6] Women of childbearing age living in RHD endemic regions are especially vulnerable to complications of RHD[7] leading to significant maternal and perinatal morbidity and mortality.[8] Moreover, as a result of different cultures, traditions and associated potential gender roles, women may have poorer access to preventive and healthcare services, thereby increasing the risk of developing RHD and related complications.

Once chronic disease sets in, an RHD patient suffers irreversible heart valve damage and has no option but to depend on biomedical interventions such as surgical valve replacement or repair, and palliative medication and rehabilitation schedules. Like many other chronic diseases, RHD also has severe effects on the economic landscape, including the individual, family and community levels, which has implications for the structural integrity of a society.[9 10]

In 2021, the National Heart, Lung, and Blood Institute solicited the input of global experts to assess the current state of research and potential priorities within the RHD field. Findings were presented during the 'Eradication of Rheumatic Heart Disease: Assessing Research Challenges and Opportunities' Workshop. The continuum of primordial, primary and secondary prevention and care of ARF and RHD is essential in sustainably addressing the global burden of RHD. This includes investment in GAS vaccine development, the timely detection and antibiotic treatment of GAS infections and ARF, as well as early screening programmes for RHD and the management of postoperative recurrence and complications. These issues are discussed in greater detail in parallel manuscripts by the other expert working groups that participated in the workshop. Tertiary prevention of RHD is defined as the prevention of exacerbation, progression and development of complications due to RHD. This includes but is not limited to cardiac rehabilitation, appropriate anticoagulation regimens, and cardiac follow-up. Tertiary care for RHD is defined as the management of RHD at tertiary care hospitals, which includes but is not limited to valvular surgery, valvuloplasty and valvulotomy. The narrative review presented here is representative of the Tertiary Prevention Working Group's (TPWG) discussions. It focuses on gaps at the patient, health system and policy levels. Specific areas of research and development focus are provided in the table below (table 1).

CURRENT STATUS OF TERTIARY CARE

A fundamental hindrance to advancement within the field is that there is an unmet need for surgical correction of severe valvular diseases due to dearth of cardiac surgical care in most parts of LMICs where RHD is prevalent. Current evidence shows an estimated need for valvular surgery for patients with RHD in LMIC is far greater than 100 000 per year worldwide.[11] While surgical management limits disability by improving cardiac function, it often comes with the chronic need for warfarin therapy, with its lifetime requirement for international normalised ratio (INR) measurement in the majority of patients as a result of the mechanical prosthesis inserted to replace the damaged heart valve. In addition, there is a need for community-based services, including rehabilitation and follow-up, to ensure that patients can safely return to their normal lives and the incidence of complications and the need for reinterventions can be timely detected and addressed.

RHD morbidity and mortality

The morbidity associated with RHD is substantial, with 10.7 million disability-adjusted life-years per annum in a recent GBD assessment, especially in those with advanced disease living in LMICs in need of tertiary care.[3] One-fifth of those enrolled in a prospective RHD registry (REMEDY) experienced a major cardiovascular event during a 24-month follow-up period.[5] Clinical RHD was associated with high mortality at a median age of 28.7 years. Mortality was higher in low-income and low-middle-income in comparison with upper-middle-income countries.[5] Complications such as stroke, HF and atrial fibrillation (AF) are occurring in young (median age 26 years) patients with significant impact on lives and livelihoods. A recent Ugandan paediatric RHD registry study found that the 5-year survival of children with clinical RHD who did not have surgery was under 60% with a median time

Table 1 Areas of focus and priorities for research and development at the patient, health systems and policy levels

Levels	Areas of focus	Research and development priorities
Patient	Heart failure	Novel point of care diagnostics
		Handheld ultrasound devices
		Telemedicine
		Digital registries with mobile app capabilities
		Artificial intelligence
	Arrhythmias	Point of care anticoagulation management
		Genomics and pharmacogenetics of drug response
		New antiarrhythmic medications
		Novel anticoagulants
	Pregnancy	Tools for risk stratification
		Qualitative research
		Community-based screening
		Defining outcomes
	Surgery and catheterisation	Development of lower cost surgical valves, valve rings and open-heart surgery disposables
		Transcatheter aortic and mitral valves focused on RHD
		Sutureless heart valve design
		New methods of decellularisation including polymer-based heart valve leaflet
		Mechanical prosthesis that do not need anticoagulation
Health system	Facility capacity development	Low-cost operating rooms, catheterisation labs, hybrid suites
		Equipment and consumables: availability, development and maintenance
		North-South partnerships
	Training	Webinars, scholarships and training grants
		Focus on nurses, technicians and physician extenders
		Low fidelity simulators and virtual reality tools
	Funding and costing	Models for health system and patient costs of living with advanced RHD
		Treatment costs for advanced RHD
		Cost-effectiveness of alternative financing models
		Supply side/procurement
	Disease burden	Identify and improve tools (cohorts, GBD modelling) that quantify the burden of advanced RHD
Policy	Stakeholders	Identify current and potential roles of stakeholders
		Explore private/public collaboration including industry
	Programme implementation	Establishment of regional centres of excellence and training supported by governmental and non-governmental organisations
		Integration into existing chronic care programmes
		North/South and South/South collaboration
		Pathways connecting prevention, primary care and tertiary care
	Policy	Integration of RHD care into national policy
		NCD-specific response
		Partnerships with global organisations advocating for RHD policy

GBD, Global Burden of Disease; NCD, non-communicable disease.

from diagnosis to death of under 1 year.[12] Patients who do not receive surgery or valvuloplasty are at a high risk of deterioration of their RHD, especially if symptomatic. For example, in Uganda, approximately half of patients with RHD present with either HF (46.9%), pulmonary arterial hypertension (32.7%), AF (13.9%) or ARF recurrence (11.4%), requiring urgent management of the underlying cause and the complication.[6]

Surgery and valvuloplasty are associated with good short-term outcomes, but access is confined to only a few low-income and lower-middle-income countries.[11] The risks of complications are highest in the first year after surgery, especially for HF, AF and infective endocarditis.[13] Outcomes can also markedly differ depending on the time of presentation (ie, extent of valvular calcification and destruction) and the presence of comorbidities Patients with RHD and preoperative comorbidities have a higher risk of operative mortality, especially when suffering from chronic kidney disease, coronary artery disease and pulmonary artery disease. In the long term, the presence of comorbidities may also negate the survival benefits associated with surgical care for RHD.[14]

Implementation of evidence-based interventions is suboptimal

An observational cohort study of patients with RHD in LMICs found that about a fifth of patients presenting to hospital had AF and that the presence of AF conferred a twofold increased risk of stroke in these young patients.[5] Oral anticoagulation may mitigate this risk substantially. Lifelong anticoagulation for the prevention of thromboembolism is also recommended for patients with RHD after mechanical heart valve implantation. However, the prescription and use of anticoagulation interventions are limited in LMICs. As an example, among patients with AF, only two-thirds of patients were on vitamin K antagonists.[5] Further, the frequency of INR testing among patients with AF and the time spent in therapeutic range are low. In a large international registry, just over a third had 1–3 INR tests done over a 6-month period, and even among these patients, just over a fifth were in therapeutic range.[5] More recent data from an ongoing randomised controlled trial of over 4500 patients with rheumatic AF showed that only 53% were on anticoagulation at the time of enrolment, and just one-third of the INR values were in therapeutic range.[15] Poor anticoagulation quality is associated with increased risk of thromboembolic and bleeding events. Among patients with mechanical heart valves, poor anticoagulation can result in valve thrombosis, which carries high morbidity and mortality.[16]

There is a need for community-based services, including rehabilitation and follow-up, to ensure that patients can safely return to their normal lives and the incidence of complications and the need for reinterventions can be timely detected and addressed. Additionally, there is a need to consider patients' oral hygiene and health due to the increased risk of infective endocarditis in patients with RHD who received a valve replacement and undergo invasive dental procedures. In LMICs, infective endocarditis most commonly occurs after RHD.[17] In many LMICs and remote communities, access to oral health services is limited and awareness surrounding oral hygiene and infective endocarditis may be poor. Comprehensive prevention and care models for RHD must also embed culturally sensitive and gender-appropriate social and emotional well-being services. There remains stigma associated with having RHD, which may lead to marginalisation within communities. Moreover, after receiving specialty care for RHD, individuals may face challenges associated with rehabilitation and reintegration within their work and society. As such, contextual supportive services may greatly benefit patients with RHD; however, such services are insufficiently available in regions where RHD is endemic.

Impact of socioeconomic status

Low socioeconomic status (SES)—characterised by poverty, low education, illiteracy, overcrowding, rural dwelling, healthcare barriers and maternal unemployment—is a critical social determinant of health (SDOH) associated with RHD incidence, prevalence, mortality and access to tertiary intervention. Although a direct linkage between socioeconomic factors and RHD is unconfirmed, these factors contribute to conditions that promote endemic RHD and offer valuable insights into the priorities and barriers to dissemination of preventive services.[18–21] Estimates of relative risk suggest that RHD incidence in Ugandan patients is 1.7 times higher for unemployment status and 1.3 times higher for overcrowding—an effect that is strengthened with longer distance from the nearest healthcare centre.[22] Similar results have been found in studies conducted in other LMICs, such as Bangladesh[23] and Fiji,[24] and in disadvantaged populations in HICs (eg, Indigenous Peoples in the Northern Territory of Australia displaying an exceptionally high prevalence of disease (11.8 per 1000, all ages)).[19]

Barriers to cardiac surgery/interventional cardiology

With delayed diagnosis and limited access to secondary prevention, progression of the valvulopathy associated with RHD to the point where surgery or catheter-based intervention is required, occurs in many patients. Perhaps not surprisingly, more than 90% of people in LMICs, or about 6 billion people, lack access to safe, timely and affordable cardiac surgery.[25] This is often viewed as (merely) an economic problem; clearly more financial resources are needed in many places, but other obstacles that hamper progress. There are severe shortages of trained cardiologists, cardiac surgeons and nurses in much of the world, but particularly in areas where RHD is prevalent, such as sub-Saharan Africa and Southeast Asia. Furthermore, practising cardiac surgery requires a team working together in a centre where there is not only reliable electricity and water, but also oxygen, blood banking, imaging and laboratory services. These are lacking in many LMICs. While North America has one cardiac surgical centre per 100 000 people, the ratio in sub-Saharan Africa is one per 33 million.[25] A native surgeon or cardiologist who goes outside to train, then, has limited ability to practice effectively in their home country. Cardiac surgery is expensive, but there is a growing recognition that, particularly in the young, it is reasonably cost-effective.[26]

MAJOR GAPS IN TERTIARY CARE

Patient level

At multiple levels, there are gaps in tertiary care that lead to long-term morbidity and premature mortality for those living with RHD. Opportunities exists to assess the factors contributing to these rifts, to form solutions in order to bridge the chasm. To begin, factors at the patient-level should be evaluated and to identify patients viewed as high risk and in need of tertiary care. Efforts should be made the recognise SDOH contributing to gaps in care. Such determinants may include a lack of education to understand disease processes, lack of transportation to appointments, no employment disallowing ability to pay for medications, and other such incapacitating factors that limit the care of patients with RHD. Studies have shown the positive correlation of SDOH factors such as crowding and SES with acquisition and progression of RHD as well as limitations in access to tertiary care.[5] Though the connection has been made, there is minimal research on interventions to address these factors.[27]

Once patients with RHD have been identified as high risk, it is incumbent on their providers to educate them on the severity of their condition and the need for close follow-up care. The REMEDY study showed that low education was associated with poor outcomes in LMICs.[5] Teach-back methods, whereby patients are asked to repeat, in their own words, what they have to know about their illness and care, have been shown to be effective means of improving patient understanding of disease and quality of life with chronic illness.[28 29] Such a method can be implemented to improve RHD education and self-efficacy, and empower those living with severe RHD. However, it is important for the community to also bear the onus of educating its members on the disease and continual need for care. For example, innovative strategies can be used to teach the masses. In Brazil, tablets have been used to disseminate RHD educational materials among school children, showing significant improvement in their understanding of RHD.[30]

Clinical level

Correlated with the shortage of surgical centres mentioned above, low-income countries have only 0.04 cardiac surgeons per million population, compared with 7.15 in HICs.[31] RHD predominantly affects the mitral and the aortic valves. Valve surgery remains the lifesaving treatment of choice when available. When possible, mitral valve repair is desirable for the treatment of mitral regurgitation.[32] Despite the established benefits of mitral valve repair over replacement in terms of early and late mortality, morbidity, valve related complications, quality of life and life expectancy,[33 34] the majority of surgeons in LMICs choose replacement over repair, in part due to being more comfortable with replacement and in part due to late presentations of patients with RHD, whereby the valve is too calcified to be adequately repaired.[35] Present-day prosthetic heart valves suffer from complications and require several considerations. Mechanical heart valves require lifelong anticoagulation therapy, while bioprosthetic heart valves based on fixed tissue are plagued with durability, immunogenic and calcification issues, which are a particularly worrisome problem in young patients. Transcatheter aortic valve replacement technology has emerged as an effective therapy for patients with severe degenerative calcific aortic stenosis but its application presents significant challenges in RHD as devices are not approved and indicated for RHD-related valve pathology and calcification. The ideal valve prosthesis for the young patient with RHD would be a low-cost non-tissue-based biocompatible tri-leaflet heart valve that has the promise of the best of mechanical valves and bioprosthetic heart valves. Furthermore, it would be ideal to consider the development of durable implanted prosthetics and efforts to reduce the risk of reoperation throughout the patients' lifetimes, without the need for lifelong anticoagulation. Polymer-based heart valve leaflets have shown early promise in these areas.[36 37]

Health system level

Guidelines for diagnosis, management and prophylaxis of ARF/RHD have been evolving, but still are fewer than needed and usually not evidence based. For the prevention of recurrence of ARF, the WHO recommends 3–4 weekly intramuscular BPG, the duration depending on age, time since the last episode of ARF, perceived risk of streptococcal infection and presence of RHD.[38] In practice, monthly injections have been used to simplify the regimen and promote better adherence in patients with low health literacy and socioeconomic constraints, despite lack of strong evidence to support this approach. Patients should be divided into low-risk and elevated-risk groups, based on symptoms and the severity of underlying heart disease, and those with elevated risk (severe mitral stenosis, aortic stenosis and aortic insufficiency), decreased left ventricular systolic dysfunction, and no symptoms, should be considered for oral prophylaxis.[39] In addition, multifaceted strategies for vasovagal risk reduction during BPG injections have been suggested, but no consensus guidelines have been widely adopted.

Managing RHD requires continuous linkage to the health system; this constitutes a major burden to already poor families and under-resourced health systems in most endemic areas. To do so, increased emphasis on health systems strengthening efforts, which are horizontal programmes across the health system, are needed as opposed to conventional vertical disease silos, which may undermine existing or much-needed community-led efforts. These efforts may be adapted to specifically address RHD by adopting a diagonal approach, whereby both vertical (RHD) and horizontal (health systems) needs are addressed, and community-level efforts are respected. These health systems usually lack the needed trained workforce, technology and infrastructure for the diagnosis and management, as well as to deal with primary, secondary and tertiary prevention.[40] The health systems in endemic areas are equally ill prepared to integrate care

across the lifespan for those affected, as they are typically based on vertical child and maternal health programmes. Moreover, health sector priorities and interventions to prevent and manage non-communicable diseases (NCDs) and injuries in low-income and lower-middle-income countries have primarily adopted elements of the WHO Global Action Plan for NCDs 2013–2020–which are more easily externally funded– but do not include RF/RHD prevention and control.

Health financing level

RHD remains one of the most underfunded diseases relative to its disease burden.[41] Whereas malaria, HIV/AIDS and tuberculosis receive approximately half of all global health funding, NCDs, including all cardiovascular diseases, receive less than 2%.[42] Funding is largely driven by HIC actors, such as countries' development assistance for health agencies and large international organisations, commonly resulting in earmarked funding for prespecified disease silos. The near-complete eradication of RHD in HICs and lack of policy prioritisation of RHD across the globe has perpetuated the existing underfunding of RHD.[43] Yet, state-of-the-art modelling suggests that investments in RHD care can greatly benefit countries at macro-economic and societal levels: if secondary prevention and secondary and tertiary care interventions for RHD were to be scaled up, the African Union would observe a net benefit of US$2.8 billion through 2030.[9] Although the costs of setting up and maintaining cardiac surgical centres are high, the experiences of relatively low-cost cardiac centres, such as Narayana Health in India and more recently Cayman Islands, the Shisong Cardiac Centre in Cameroon, and the National Cardiothoracic Centre in Ghana, suggest that costs can be greatly reduced through higher volumes, economies of scale, shorter surgical supply chains, and environmentally optimised infrastructure.[44 45]

At the patient-family level, the costs of RHD care, as well as the socioeconomic impact of lack of care, are equally considerable. Although the exact risk of catastrophic and impoverishing expenditure due to RHD care is unknown, it may be expected to be large. Over 80 million people[46] are pushed (further) into poverty due to requiring some type of surgical care and, considering the costs of cardiac surgery, a considerable portion of this population includes patients with cardiac surgical disease, including RHD.

Maternal health

Pre-existing cardiac disease is an important contributor to maternal mortality; however, many patients present de novo with previously undiagnosed heart disease during pregnancy.[47 48] Prospective and ongoing registries from vulnerable populations provide repositories of data that assist in understanding the epidemiology of the disease.[48] This type of evidence would assist in informing policy and clinical guidelines to fill the major gaps in tertiary care. Pregnancy provides a unique opportunity for the detection and risk stratification for RHD. Prior to pregnancy, there is a need for new and unique tools for risk stratification, and predictors of poor outcomes. The knowledge about biomarkers, immunological markers and genetic mutations for RHD risk is rapidly expanding, even though there are no new clinical strategies for detection.[49] Early detection and novel screening tools during the antenatal period would assist in identifying women who require district or secondary care. Collaborative drug trials have the potential to alter clinical course and treatment outcomes of pregnant women with RHD.[15] There is a need for exploratory interventional and surgical care studies during pregnancy and the peripartum period.

Heart failure

Evidence-based guidelines recommend surgical and catheter-based intervention for severe or symptomatic valvular heart disease, as there is little evidence that pharmacological management changes outcomes.[50] This is mainly because, there have been no large randomised controlled trials evaluating potential treatments which may ameliorate symptoms of HF, delay surgery or improve outcomes. Drug therapy is particularly important in patients with RHD and HF, due to the long waiting times to definitive surgery or intervention, in countries where these are available.[11] Large trials are needed to test the utility of rate control medications (such as beta-blockers and digoxin) in patients with AF and HF,[51] and ACE-I and ARBs in those with dominant regurgitant lesions. A large, ongoing, multicentre trial in India may help understand the role of digoxin in patients with RHD.[52]

Unfortunately, the vast majority of people with symptomatic RHD reside in locations where there is not ready access to surgical or catheter-based management.[4 53] The REMEDY study and a single country report from Uganda highlight the large gap between patients in need of surgery and those who actually receive it in LMICs.[6 54] In this population, medical management is often the only option for symptomatic improvement.[55] The management of cardiovascular disease in LMICs requires access to specialists for accurate diagnosis and timely initiation of therapy.[56 57] While cardiologists trained in echocardiography provide care in capital cities throughout sub-Saharan Africa and other LMICs, 80% of the population lives in rural settings.[58 59] Specialists in rural areas are rare, resulting in long waiting times, substantial transportation costs, and high out-of-pocket payments, further limiting universal access to care.[60–62] Decentralisation of care through task-sharing has demonstrated promise for improving access in this setting.[63 64] Task-sharing can improve care by increasing access, decreasing cost and freeing higher-level providers to engage in more complex tasks.[65]

Arrhythmias

AF is associated with a poor prognosis in patients with RHD, causing HF, stroke, peripheral thromboembolism and premature death[5 66] and is most common in

patients with a combination of mixed mitral valve disease and tricuspid regurgitation.[67] Electrical (cardioversion or catheter ablation) or pharmacological (usually amiodarone)[68] rhythm control is superior to rate control for treatment of symptomatic AF. The role for percutaneous left atrial appendage occlusion in patients with RHD and AF is unknown and left atrial clots in RHD are not limited to the left atrial appendage.[69] Ablation, appendage occlusion and other catheter-based valvular interventions may not be readily available or affordable in LMICs. Anticoagulation with vitamin K oral antagonists, or direct thrombin or factor Xa inhibitors is recommended for stroke prevention when AF/flutter is present.[69] The investigation of rheumatic Atrial Fibrillation Treatment Using Vitamin K Antagonists, Rivaroxaban or Aspirin Studies, Non-Inferiority (INVICTUS-VKA non-inferiority trial) is enrolling patients to evaluate non-inferiority of rivaroxaban vs standard vitamin K antagonists in patients with RHD with AF/flutter.[15]

PRIORITIES AND STRATEGIES

Integrated chronic care/PEN-Plus

Development of culturally safe and community-driven comprehensive RHD prevention and control programmes is needed in order to ensure a continuum of care for people living with RF/RHD, including through integrated high-quality care. This involves promoting changes in the model of care to overcome barriers in most endemic areas of the world, particularly in Africa, where the RHD Global Registry (63.9% from Africa) has shown low usage of interventions such as percutaneous valve dilatation, cardiac surgery, secondary antibiotic prophylaxis and anticoagulation in patients with severe multivalvular disease.[54]

The cascade of care for RHD highlights the need to invest in decentralisation to ensure retention in care and achieve disease prevention and control.[70] These efforts should be complementary to existing programmes such as those in maternal and child health as well as NCDs, to increase access to early diagnostics and effective interventions and to improve policies for good quality continuum of care. Only integrated approaches to strengthening health systems and true commitment to provide universal healthcare will guarantee a continuum of care for RHD in the most endemic areas. Hence this was prioritised by The Lancet Commission on Reframing NCDs and Injuries for the Poorest Billion, and its National Commissions.[71 72]

A decentralised integrated nurse-led model to provide longitudinal care for patients with advanced RHD at district hospitals in rural Rwanda showed that nurses and clinical officers who are trained and periodically supervised were able to monitor patients' clinical status, support adherence to penicillin prophylaxis, and manage anticoagulation by using tailored standardised algorithms.[73] This model is currently being disseminated in other low-income and lower-middle-income countries in sub-Saharan Africa under the Package of Essential NCD Interventions-Plus (PEN-Plus),[74] aimed at expanding cardiac care for the poor, by increasing case finding and assuring good outcomes.

PEN-Plus is an integrated strategy that builds on the WHO's PEN focused on increasing the quality of services for severe chronic NCDs at primary referral facilities (particularly district hospitals) and accelerating decentralisation of services for common NCDs at primary care facilities. It ensures technical assistance to organise integrated services for RHD in such countries, by strengthening infrastructure and supply chains, by training non-specialist staff (nurses and clinical officers) in the skills needed to detect and manage patients with RHD, and by building monitoring and evaluation systems for efficient implementation, with the support of the NCDs and Injuries Poverty Network.[75] The goal is to create scalable models of care for RHD and other severe and difficult to manage NCDs in LMICs.

Diagnostics

There are multiple points in which current technological advancements can improve clinical care. The combination of task shifting and innovative telemedicine (that can overcome challenges from limited bandwidth), primarily tele-echocardiography, can provide remote populations in LMICs expanded access to medical services.[8 63] Pilot experiences with e-learning modules and workshops to facilitate task-sharing of focused echocardiography from cardiovascular care specialists to community health workers appear feasible.[76] Task shifting of focused echocardiography to non-physician workers with limited training using highly portable hand-held ultrasound devices is feasible for diagnosis of RHD in LMICs.[76–78] Telemedicine (most commonly asynchronous), complemented by task shifting, can allow cardiologists in tertiary care centres around the world to consult directly with providers caring for patients with RHD and other cardiovascular diseases in LMICs.[79] Sharing of images via cloud-based technology can advance research and clinical collaboration.[8 77] More rapid, portable and innovative uses of tele-echocardiography can provide remote populations in LMICs expanded access to medical services. These include enhanced data compression technology,[80] novel training methods for international support[81] and the use smartphones for near-instantaneous image review.[82] Artificial intelligence focused on both image acquisition guidance[83] and automatic diagnoses[84] can further increase the power of telemedicine for detection of RHD and other CVD. A recent publication from Uganda showed that transmission and interpretation of echocardiograms from a remote clinic in northern Uganda is feasible, serves a population with a high burden of heart disease, has a significant impact on patient care, is favourably received by patients and can be delivered at low cost.[85]

Surgery/interventional cardiology

The TPWG stressed that simulation-based training is accessible to surgeons and cardiologists to achieve proficiency

in basic skills within shorter training time periods, whereas practicing clinicians can be more swiftly trained in novel techniques.[86] Three-dimensional (3D) printing has steadily gained traction as a clinical tool in cardiac surgery.[87] The next frontier in 3D printed patient specific models is the simulation of the biomechanical properties of human tissue, which could be used to effectively model patient-specific geometry, for use as task trainers for surgical simulation required to advance surgical interventions. Other training opportunities for development of standardised international surgical certification as part of South–South and North-South collaborations through introduction of virtual simulation models and centralised (eg, at conferences) skills workshops, physical mentorship, and adoption of models embedding experienced cardiac surgeons—ranging from sabbatical years and academic collaborations to retired surgeons—in nascent or growing international cardiac centres could accelerate the institutional learning curve for training of cardiac surgical teams in LMICs.[25 88]

Polymer-based heart valve leaflets have shown early promise to combine the best of mechanical and bioprosthetic heart valves. An early clinical feasibility study showed that a surgical polymer aortic valve had met all of its primary endpoints at 1 year, including improvement in valve effective orifice area, clinically significant increase in New York Heart Association class and safety.[37] Decellularised homologous tissue engineered heart valves have shown encouraging long-term performance in the clinic, with cell repopulation and adaptive growth. [89 90] Bioresorbable polymer-based tissue engineered matrices, including supramolecular polymers, have shown promise in other cardiac applications[91] and may be translated to the clinic following preclinical functionality testing.

Research into funding and costing

The greatest burden of RHD is concentrated in the poorest populations, many of whom live in rural areas. Conversely, tertiary RHD services in LMICs are most accessible to those with higher incomes and are only available in urban centres. These centres often have inefficient care delivery and high per-procedure costs that result from shortages of trained personnel, equipment and disposable supplies and weak referral systems.[11 92] Open-heart surgery is notoriously expensive, and competing priorities outside and within the healthcare sector, including primary and secondary prophylaxis of RHD, mean that it is often not prioritised,[93] yet it is both effective and economical in many settings. Support for the development of lower cost valves, valve rings, and open heart surgery disposables is imperative to help resolve this discord. Additionally, increased research to lower the cost of procedures (both closed surgical and catheter based) ought to be prioritised so as to increase access. A model for cost reduction of open heart surgery in other LMICs is Narayana Health in India,[94] which has 31 centres in 19 Indian cities as well as a programme in the Cayman Islands. Through this initiative, the total cost of open-heart surgery has been greatly reduced to under US$2000/case. The innovations that supported this include (1) reliable and low-cost supply chains; (2) leveraging economies of scale; (3) using assembly line concepts for surgery; (4) reducing the average length of stay; (5) re-engineering the design, materials and use of medical equipment to reduce the cost of ownership and (6) information technology, data, a centralised cloud environment and telehealth network connecting over 800 centres that promote efficiency and standardisation throughout Narayana Health.

Establishment of regional centres of excellence supported by governmental and non-governmental organisations that would serve as referral centres for advanced care and training across borders is also a priority.[95] Along these lines, The Cape Town Declaration on Access to Cardiac Surgery in the Developing World,[96] signed in 2018, proposes ‘a framework structure to create a coordinated and transparent international alliance to address this inequality’.

Role of professional societies

The role of cardiac and cardiac surgery societies in raising the profile of RHD has grown substantially in the past two decades, led by stalwart clinicians and activists.[97] In Africa, this was heralded by the Awareness Surveillance Advocacy Prevention Programme of the Pan-African Society of Cardiology, Important research outputs were aligned with global agency advocacy campaigns which raised the level of engagement at political levels.[98] This led to important position statements from agencies such as the World Heart Federation.[99] The findings of the REMEDY study[54] helped to inform the African Union Communique about the status of RHD in endemic settings[53] leading to the landmark WHO Resolution advocating for the eradication of RF and RHD in 2018. Against this backdrop, the 2017 celebration of the first heart transplant in South Africa also marked the launch of Cardiac Surgery Intersociety Alliance to address the global need of access to cardiac surgery in Africa, particularly for RHD. In recent years, several cardiology and cardiac surgical societies had/will have sessions focusing on the global needs for cardiac surgery and interventional cardiology, stressing the importance on united action to ensure equitable access in the future. Other regional societies, such as the African Association of Thoracic and Cardio-Vascular Surgeons, the African Academy for Pediatric and Congenital Heart Surgery, the African Society for Pediatric and Congenital Heart Surgery, and the Latin American Association of Cardiac and Endovascular Surgeons are further contributing to national and regional developments in cardiac surgical capacity within their respective regions. As RHD is a condition influenced by and affecting all health system layers of prevention and care, and its political prioritisation and eradication are sensitive to health policy and systemic factors, non-cardiovascular societies must be engaged in future societal efforts. The working groups of the workshop

represent a multidisciplinary and multisectoral group of cardiovascular and non-cardiovascular health specialists as well as experts in health policy, health economics and community engagement. This provides a first and more comprehensive, although not exhaustive, effort to sustainably address ARF and RHD across the lifespan. In the future, such efforts are needed across and between professional societies beyond cardiovascular medicine.

CONCLUSIONS

Tertiary care for people living with RHD is inadequate, underfunded and poorly integrated with a resultant lack of much-needed data, resulting in over 300 000 deaths per year. Global vision and leadership to enact and implement available policies are needed to close large research gaps in all aspects at patient, health system and policy levels. Robust research and development are urgently needed to improve comprehensive tertiary care and ensure implementation of evidence-based interventions, while developing new innovations, technologies and interventions. The specific areas of focus identified in this review provide a unique opportunity for charting the future of social, behavioural, and biomedical research and development to advance quality healthcare for patients with RHD, especially in low-resource settings.

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