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REVIEW

Screening for rheumatic heart disease: is a paradigm shift required?

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Abstract

This focused review presents a critical appraisal of the World Heart Federation criteria for the echocardiographic diagnosis of rheumatic heart disease (RHD) and its performance in African RHD screening programmes. It identifies various logistical and methodological problems that negatively influence the current guideline's performance. The authors explore novel RHD screening methodology that could address some of these shortcomings and if proven to be of merit, would require a paradigm shift in the approach to the echocardiographic diagnosis of subclinical RHD.

Key Words
- 2D echocardiography
- rheumatic heart disease
- screening

Background

Rheumatic heart disease (RHD) remains one of the leading causes of cardiovascular morbidity and mortality in developing countries (1). Sub-Saharan Africa has been identified as an endemic RHD region with extrapolated figures estimating the disease burden of latent RHD to be anywhere from 1.1 to 13.2 million (2). To address the burden of RHD on the continent, the African Union adopted the Addis Ababa Communique (3) at the 25th African Union Heads of State and Government Summit held in Johannesburg, 2015.

The communique is a seminal position statement devised by RHD clinicians and researchers affiliated with the Pan-African Society of Cardiology (PASCAR) and outlies seven priority areas of action for the eradication of RHD in Africa. The fourth recommendation of the communique recognises the pivotal role that cardiac ultrasound will fulfil to assist in '*the early detection, diagnosis, secondary prevention and treatment of RHD*' (3).

However, an incomplete understanding of the natural history of latent RHD, coupled with various deficiencies in the current RHD echocardiographic diagnostic guideline, has precluded its endorsement for use in large-scale echocardiographic screening programmes.

This article will review the 2012 World Heart Federation (WHF) echocardiographic criteria for the diagnosis of RHD and its performance in African RHD screening programmes. It hopes to outline the various deficiencies inherent to the current guideline and highlight novel alternative methods of echocardiographic RHD identification that may improve the performance of screening criteria.

The role of echocardiography in RHD screening

The efficacy of secondary prevention in acute rheumatic fever (ARF) is well documented and originates from current understanding that individuals with a previous history of ARF are predisposed to recurrent attacks, which can be prevented by the administration of regular prophylactic antibiotics (4, 5, 6). However, the

accurate identification of those with an increased risk is fraught with complexities as it is estimated that up to 40% of individuals with established RHD have no recollection of having symptoms compatible with an ARF episode (7).

This provides an ideal opportunity for disease control programmes to institute targeted screening to identify those individuals at risk for further progression to symptomatic disease. Prior to the advent of echocardiography and its utility in RHD diagnosis, RHD screening programmes relied on cardiac auscultation to identify potential cases of RHD. Most of the published prevalence rates of antecedent RHD screening programmes in Africa ranged from 1.0 to 10.2/1000 (8, 9, 10, 11, 12). However, echocardiography has since proven to be a more sensitive screening tool with detection rates of RHD considerably higher than those of its auscultation-based counterpart with prevalence rates in Africa as high as 30.4/1000 (13). The prospect of early detection of subclinical disease (asymptomatic individuals with no previous history of ARF) coupled with the presumed efficacy of secondary prophylaxis to avert progression to severe symptomatic disease led to a reinvigoration of African RHD research (14, 15, 16, 17, 18, 19, 20).

The 2012 World Heart Federation criteria

Due to the systematic differences in the diagnostic approach and reporting of screening echocardiograms in subclinical RHD, the World Heart Federation (WHF) developed a set of consensus-based criteria – the 2012 WHF criteria for echocardiographic diagnosis of RHD (21) (Table 1).

The criteria have been widely adopted and have resulted in the publication of a wealth of standardised data that document a latent RHD disease burden of epidemic proportions amongst African school-going children (22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32). This provides an impetus for African countries to endorse the recommendations of the Addis Ababa Communique and amend health policy accordingly to include routine RHD screening. However, the screening experience whilst utilising the WHF criteria has also raised sufficient concern to limit its implementation in resource-restricted areas (33, 34, 35). This is due to various methodological and performance-related issues that will require further scrutiny and possible amendment should large-scale RHD screening be endorsed in the future.

Table 1

Echocardiographic criteria for RHD in individuals ≤20 years
For definite RHD (either A, B, C or D)
A: Pathological MR and ≥2 morphological features of RHD of the MV
B: MS (mean gradient ≥4 mmHg)
C: Pathological AR and ≥2 morphological features of RHD of the AV
D: Borderline disease of both the MV and AV
For borderline RHD (either A, B or C)
A: ≥2 morphological features of RHD of the MV without pathological MR or MS
B: Pathological MR
C: Pathological AR
Echocardiographic criteria for pathological regurgitation
Doppler echocardiographic criteria for MR (all four must be met)
1. Seen in two views
2. In at least one view, jet length ≥2 cm
3. Velocity ≥3 m/s for one complete envelope
4. Pansystolic jet in at least one envelope
Doppler echocardiographic criteria for AR (all four must be met)
1. Seen in two views
2. In at least one view, jet length ≥1 cm
3. Velocity ≥3 m/s for one complete envelope
4. Pan-diastolic jet in at least one envelope
Echocardiographic criteria for morphological features of RHD
Features in the MV
• AMVL thickening ≥3 mm
• Chordal thickening
• Restricted leaflet motion
• Excessive leaflet tip motion during systole
Features in the AV
• Irregular or focal thickening
• Coaptation defect
• Restricted leaflet motion
• Prolapse

AMVL, anterior mitral valve leaflet; AR, aortic regurgitation; AV, aortic valve; MR, mitral regurgitation; MS, mitral stenosis; MV, mitral valve; RHD, rheumatic heart disease.

These concerns are broadly summarised and discussed as follows:

1. The state of African health care systems.
2. The logistical requirements of the WHF criteria.
3. Simplification of the WHF criteria.
4. Methodological deficiencies in the WHF criteria.
5. The natural history of subclinical RHD.

The state of African health care systems

The Addis Ababa Communique identifies the importance of decentralising the diagnostic services for RHD to district and primary health care hospitals in Africa. This involves the training of designated health care workers in echocardiography and the provision of adequate

ultrasound equipment, technical support and basic infrastructural requirements to create a sustainable service. However, this poses a massive challenge to African countries whose overextended health systems are limited by budgetary constraints, excessive disease burden and dire shortages of skilled staff (36). Furthermore, an important limitation that has been described in African RHD literature is the frequency of enrolled participants who are subsequently 'lost to follow-up'. This is attributed to various factors, which include a high 'drop-out rate' amongst school children, a '*migratory culture*' amongst certain communities and poor access to mobile phone technology (23, 32, 37). Although these difficulties are inherent in any study, they are nonetheless obstacles that can impact significantly on the success of a programme.

The minutiae detailing presents health care constraints and the reform that is required to successfully implement effective RHD screening in African countries lies outside the scope of this article. These challenges however must be borne in mind as they arguably represent the most significant obstacle to the institution of a successful screening programme in resource-poor settings.

The logistical requirements of the WHF criteria

To provide an evidence-based guideline for the detection of RHD, a screened case with either mitral or aortic valve regurgitation is evaluated according to specific Doppler-based measurements (Table 1). These include various spectral Doppler parameters that effectively limit the 'gold standard' technology with which to effectively screen for RHD to echocardiographic machines that are equipped with this functionality.

These units are expensive and are dependent on a reliable supply of wired electricity making them unattractive options for use in a resource-limited setting (29, 31).

The advent of the hand-held echocardiographic device has heralded an attractive solution for large-scale screening programmes as they are portable, battery powered and marketed at a fraction of the cost of the conventional machines. The advantages of portability and cost of the units are however somewhat offset by various technological issues that require further elucidation.

Firstly, the most notable disadvantage of the current hand-held devices is the absence of spectral Doppler functionality, which as previously indicated is mandatory for the successful utilisation of the current criteria. Secondly, the unit scans with obligatory tissue harmonic imaging (THI) that could explain the observation made by Beaton and coworkers (29) of thicker cardiac structures and increased false-positive diagnoses of chordal thickening and leaflet restriction in their studied cohort. In addition, the WHF guideline recommends that anterior mitral valve leaflet thickness measurements obtained using THI should be cautiously interpreted and a thickness of up to 4 mm should be considered normal in individuals ≤20 years of age (21). Thirdly, the potential discrepancies in the leaflet assessment are further exacerbated by a basic 'point-of-care' measurement tool that is limited to one millimetre increments and has been recognised to overestimate leaflet thickness (29). Lastly, the units require regular recharging due to a limited battery lifespan and overheat during prolonged scanning with the added risk of a reduction in scanning frame rate. (30, 31, 38).

Simplification of the WHF criteria – a solution for large-scale screening?

Marijon and coworkers (1) describe a two-step screening process whereby health care workers (nurses/technicians) identify potential RHD cases using a hand-held device with a basic on-site screening protocol. Positive cases are then referred to a medical centre equipped with a comprehensive echocardiographic machine for a second confirmatory scan.

Recent RHD research has thus focused on simplifying the current WHF criteria to enable its incorporation into hand-held screening protocols (25, 29, 30, 31, 39, 40). The use of a single mitral regurgitation (MR) jet length measurement to denote RHD has been put forward (41) and remains an attractive option, but may contrive to cause undesirable consequences.

Firstly, validation of the 'focused' protocol becomes problematic as the same parameter remains at the crux of the comprehensive WHF functional assessment and risks confirmation bias (42). Secondly, it risks missing true rheumatic disease cases with either isolated morphological features or a functional assessment measurement just below the cut-off value (reducing sensitivity of the criteria) (7). Thirdly, an additional case-load of alternative causes of 'pathological MR' could be included in this subset (reducing specificity), which may overburden the tertiary referral-care services and swamp the '*already stretched paediatric cardiology services*' (7). Fourthly, it overlooks the finding of Marijon and coworkers who noted that their 'combined criteria' (requiring features of chronic morphological RHD and any degree of regurgitation) led to a markedly improved detection rate of RHD as compared to a functional Doppler assessment alone (43). Lastly, the

impact of a false-positive result on an individual patient level cannot be discounted and would undoubtedly result in unnecessary anxiety and the inappropriate prescription of long-term secondary prophylaxis (7, 44).

Methodological deficiencies in the WHF criteria

Lack of a RHD-specific scanning protocol A challenging aspect of RHD screening remains the identification of subtle structural changes that are recognised to only affect specific leaflet segments. The WHF guideline recognises this and cautions that some children with pathology will be missed if only '*standard, adult-style echocardiographic views are assessed*' (21).

The current guideline however, does not define a standardised screening protocol that will successfully identify subtle RHD pathology. The validation and subsequent introduction of a tailored screening protocol for RHD identification could improve the overall standard of screening and potentially reduce the amount of missed RHD cases.

The Doppler criteria and alternative causes of pathological MR The Doppler criteria stem from early Doppler-work that identified its potential to effectively differentiate between physiological and pathological regurgitant jets (45, 46, 47, 48). This body of research was incorporated into echocardiographic criteria used to identify subclinical ARF carditis (49, 50) and later RHD (51). The Doppler criteria were amalgamated into the current 2012 WHF criteria largely based on data suggesting that pathological MR was more likely to be observed in children in high-risk RHD areas than low-risk RHD areas (52) (Table 1).

The criteria however have been identified as a shortcoming of the current WHF guideline for two principal reasons. Firstly, they comprise a set of somewhat arbitrary and redundant parameters, which include a non-physiological regurgitant jet velocity cut-off (42, 53), a requirement to identify the jet in two views (testing only the screener's ability) (42), the requirement of a pansystolic/pan-diastolic jet, which provides no additional information regarding the mechanism of regurgitation (42) and a jet-length measurement that is subject to interobserver variability and whose specificity in identifying disease progression has been questioned (25). Use of the current Doppler criteria could risk labelling screened cases of arguably true RHD (with specific morphological features of RHD) as 'borderline RHD' because they are deficient in any one of the measured Doppler parameters (Figs 1, 2 and Videos 1, 2).

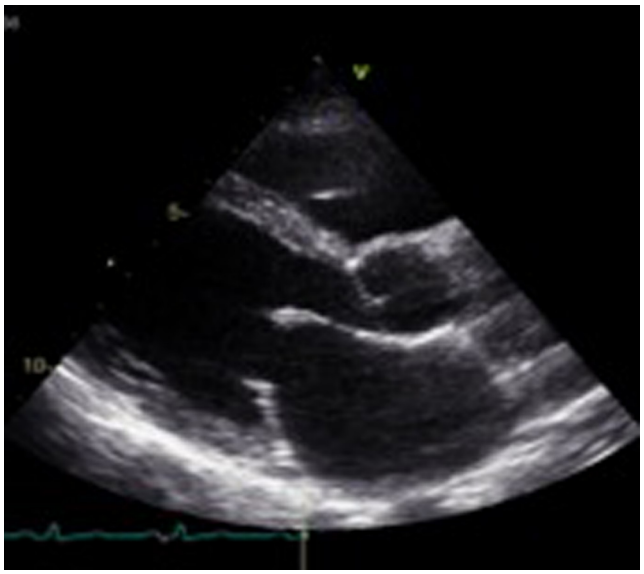

Figure 1
Still image taken from a screening 2D echocardiogram in a parasternal long axis view. There are morphological features of RHD of the mitral valve (diastolic restriction of both leaflets with thickening of the leaflet tips. See also Video 1.

Secondly, the incorporation of a 'borderline RHD' category to improve the sensitivity of the WHF criteria has illuminated the Doppler criteria's lack of specificity. This is

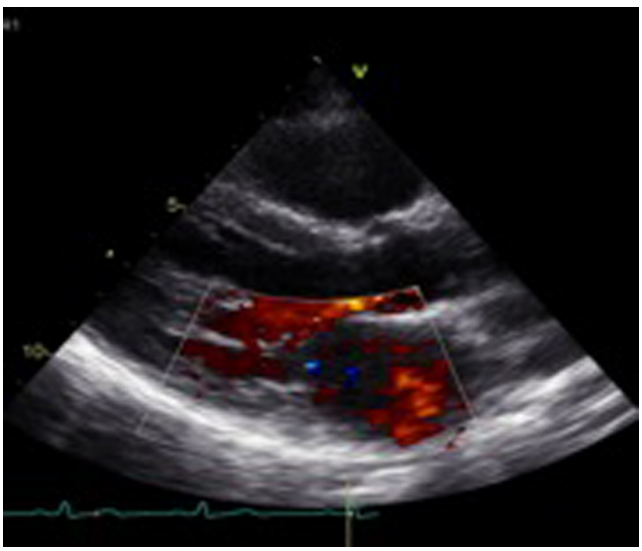

Figure 2
Still image of corresponding case with colour Doppler interrogation of the mitral valve. There is pixel mitral regurgitation during ventricular systole. The regurgitant jet measured <2 cm and therefore case designated as 'borderline RHD'. See also Video 2.

Video 1
Screening 2D echocardiogram in a parasternal long axis view. There are morphological features of RHD of the mitral valve (diastolic restriction of both leaflets with thickening of the leaflet tips). View Video 1 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0037/video-1.

Video 2
Colour Doppler interrogation of the mitral valve. There is pixel mitral regurgitation during ventricular systole. The regurgitant jet measured <2 cm and therefore case designated as 'borderline RHD'. View Video 2 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0037/video-2.

exemplified by the finding of 'pathological MR' that was attributable to congenital mitral valve (MV) variants in screened cases from both high- and low-risk populations (24, 52, 53, 54, 55) (Figs 3, 4, 5, 6 and Videos 3, 4, 5).

The WHF guideline made provision for this contingency by adding a pre-requisite that '*congenital, acquired and degenerative heart disease of the MV and AV*' are excluded before presuming rheumatic origin (21). The guideline further adds that '*congenital cardiac defects are easily differentiated from RHD, as they have unique identifying features (for example, bicuspid AV or MV cleft)*' (21). Whilst this may be true for entities such as the bicuspid AV, MV cleft and MV prolapse that have been well described

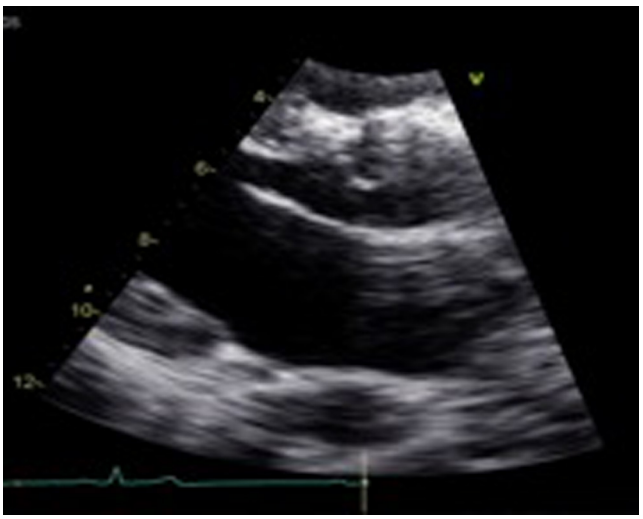

Figure 3
Still image taken from a screening 2D echocardiogram in a parasternal long axis view with mitral valve leaflets at maximal diastolic excursion. There are no morphological features of RHD of the mitral valve (both leaflets are thin and demonstrate no diastolic restriction). See also Video 3.

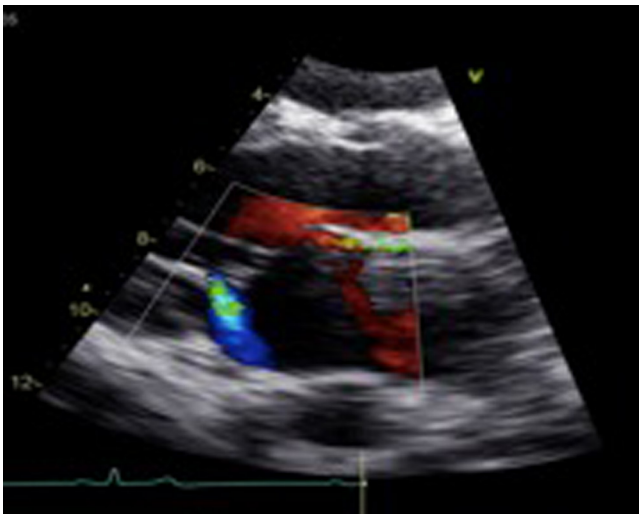

Figure 4
Still image of corresponding case during ventricular systole with colour Doppler interrogation of the mitral valve. The white arrow shows WHF pathological mitral regurgitation during ventricular systole. The regurgitant jet measured >2 cm and met all additional Doppler criteria. The screened case is therefore case designated 'borderline RHD'. See also Video 4.

in both anatomical pathology and echocardiographic literature and have pathognomonic echocardiographic features that identify them as such. The premise however does not hold true for all cases that are identified as 'borderline' RHD based on an isolated pathological MR jet. A subset of these cases has been alluded to in current RHD literature as being on the 'upper *limit of physiological mitral valve regurgitation*' (56) or screened cases with '*minor congenital MV anomalies*' (53). However, the exact

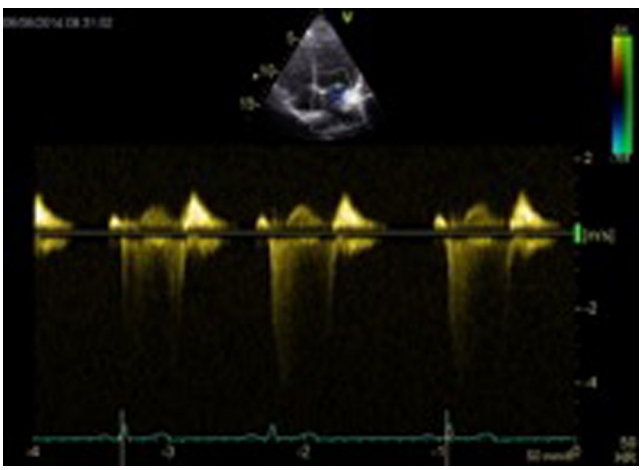

Figure 5
Still image of corresponding case with continuous-wave Doppler trace through the mitral valve. The trace confirms a pansystolic jet with a complete envelope and a peak velocity > 3m/s.

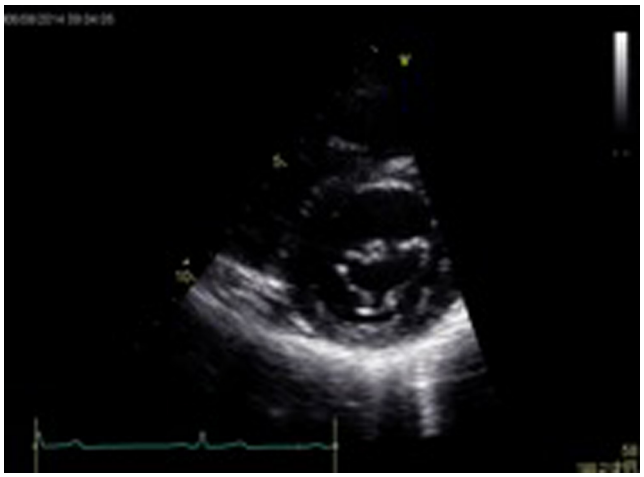

Figure 6
Still image of corresponding case in parasternal short axis view. There is a prominent interscallop separation of the posterior leaflet. Colour Doppler interrogation subsequently demonstrated the interscallop separation to be the cause of the incompetence. See also Video 5.

mechanism of valvular incompetence in these cases has not been identified.

An additional cause for concern is the description of an entity identified in South African high-risk children that may be mistakenly identified as potential RHD. These have been described as normal spectrum MVs with WHF pathological regurgitation identified through '*prominent posterior leaflet interscallop separations*' (42). Currently, it remains unclear as to whether these '*interscallop separations*' are related to similar entities described in the literature as posterior MVs with '*isolated clefts*' (57), '*subclefts*' (58), '*interscallop malcoaptations*' (57) and '*slits*' (59). It is evident that more work is required to investigate and describe the aetiology, common echocardiographic characteristics and clinical course of non-rheumatic MVs, which display WHF pathological MR.

The natural history of subclinical RHD An early echocardiographic diagnosis of subclinical RHD has particular bearing for screened cases in resource-poor African countries. In these communities, the management options for individuals with symptomatic severe RHD become extremely limited due to constrained cardiothoracic/interventional cardiology services (60). Individuals identified with subclinical disease in these instances would intuitively benefit the most from the early institution of an appropriate secondary prophylaxis regimen to avert progression to symptomatic disease.

However, the efficacy of secondary prophylaxis to prevent further ARF recurrences and progression of clinically detectable RHD cannot be automatically extrapolated to include screened cases with subclinical RHD (56). This is in part related to the paucity of long-term echocardiographic follow-up studies utilising standardised diagnostic and reporting methodology (21). Furthermore, the establishment of a randomised control trial (RCT) evaluating prophylaxis vs no prophylaxis in subclinical RHD is controversial as it is considered that withholding prophylaxis to an individual with WHF-identified 'definite RHD' is unethical (56).

The diagnostic confidence that a 'borderline RHD' diagnosis conveys however is not as robust. The borderline group was introduced to improve the sensitivity of the guideline at the expense of the specificity and has resulted in the identification of a large, diverse indeterminate group of cases with unknown clinical significance. Accordingly, the WHF guideline does not advocate that patients with 'borderline RHD' disease receive penicillin prophylaxis. This has become the subject of much debate amongst members of the RHD research community with the suggestion that the use of screening echocardiography in subclinical RHD should for now, be viewed as a research tool, pending more definite studies of impact on prognosis (7, 33, 52, 53, 54, 55, 61, 62).

Video 3
Screening 2D echocardiogram in a parasternal long axis view with mitral valve leaflets at maximal diastolic excursion. There are no morphological features of RHD of the mitral valve (both leaflets are thin and demonstrate no diastolic restriction). View Video 3 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0037/video-3.

Video 4
Ventricular systole with colour Doppler interrogation of the mitral valve. There is WHF pathological mitral regurgitation during ventricular systole. The regurgitant jet measured >2 cm and met all additional Doppler criteria. View Video 4 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0037/video-4.

Video 5
Inparasternal short axis view. There is a prominent interscallop separation of the posterior leaflet. Colour Doppler interrogation subsequently demonstrated the interscallop separation to be the cause of the incompetence. View Video 5 at http://movie-usa.glencoesoftware.com/video/10.1530/ERP-17-0037/video-5.

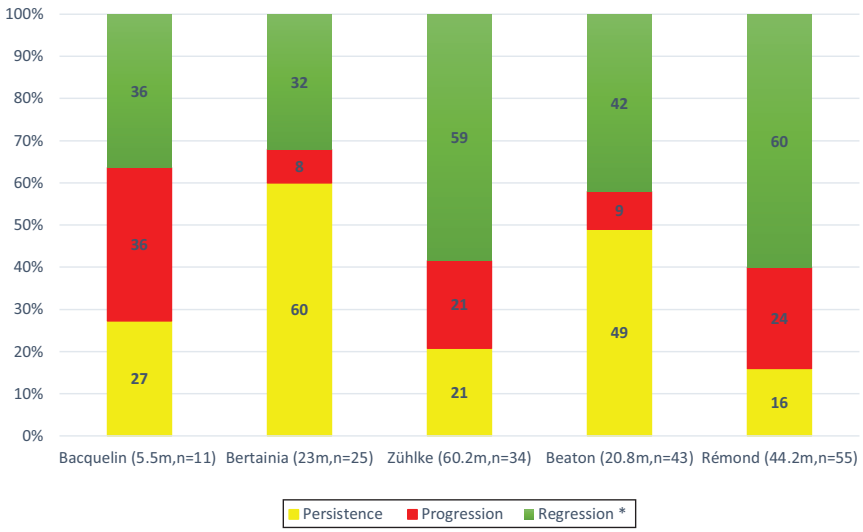

Figure 7
A comparison of the natural history of borderline rheumatic heart disease in five studies with increasing number of studied participants (m, mean duration of follow-up in months; n, sample size of borderline cases). *Rémond and coworkers' publication only presented persistence and progression data from their cohort (62). The presented regression data are thus inferred considering the total number of borderline cases that were followed up.

Five research groups who have followed cohorts of screened WHF subclinical RHD cases have subsequently published their findings (25, 33, 37, 62, 63) (Fig. 7). Despite various limitations, which include small cohorts and relatively short-term follow-up, the studies do provide a preliminary insight into the natural history of WHF subclinical disease and may highlight important principles that are deficient in the current guideline.

All five publications identify that the natural history of a screened borderline RHD case is not necessarily benign (Fig. 7). There is a variable, yet, significant proportion of borderline cases that have been demonstrated to persist at follow-up and a smaller population displaying progression to 'definite RHD'. Despite the documented risk of disease persistence and progression, the hallmark of 'borderline RHD' was its predilection to revert back to normal with so-called 'disease regression' demonstrated in the majority of these longitudinal studies (Fig. 7). Various reasons have been offered to account for these findings that include issues with interobserver variability (37, 63), the administration of secondary prophylaxis (25), the inability of the WHF criteria to classify screened individuals >20 years of age into a borderline group (37) or even that subclinical RHD represents a disease process that can resolve back to normal in a large majority of cases (37).

The notion of disease regression and improvement of 'pathological' lesions whether they be morphological or functional raises some important issues that beg further investigation. All else being equal, one would expect that chronic RHD morphological abnormalities such as thickening and restriction of the valvular and subvalvular apparatus will persist and are unlikely to improve over time. The identification of these morphological features could therefore represent the most specific predictor for true RHD (25, 62, 63).

If this hypothesis is demonstrated to be true, could the finding of subclinical RHD disease regression be a false representation of the natural history of true RHD and could the current WHF screening methodology be responsible for perpetuating this anomaly?

An alternative RHD screening methodology

A recent commentary of the WHF criteria (42) has proposed an alternative RHD screening methodology that deviates from the precepts incorporated in the current guideline.

The commentary argues that the pattern of '*diastolic leaflet restriction*' remains a principal finding in RHD and advocates that a comprehensive leaflet assessment be assimilated into a screening protocol to identify subtle focal RHD involvement. It further recognises that the current morphological and functional assessment comprises inherent technical and methodological pitfalls that necessitate further scrutiny and potential amendment as they may impede on the guideline's performance. The most notable amendment proposed in this manuscript is that the presence of regurgitation (of any degree) in a screened valve should prompt an active search for the mechanism of dysfunction. This so-called 'mechanistic evaluation' would be incorporated in lieu of the current Doppler assessment and could potentially discriminate between subtle cases of true RHD and the extraneous mimics of RHD identified in the 'borderline RHD' category.

It must be noted that the skill level required to complete such an evaluation will undoubtedly limit its applicability in 'on-site screening' and will realistically (3) only be incorporated for use by experienced echocardiographers during the confirmatory scan.

Nonetheless, the mechanistic evaluation, although untested in RHD identification may prove to be of merit as it echoes the general principles expounded in current echocardiographic recommendations for the evaluation of native valvular regurgitation (64).

Conclusion

The establishment of the WHF criteria for the echocardiographic diagnosis of RHD represents a significant endeavour to combat the scourge of RHD across the globe. The guideline has undoubtedly standardised the process of disease identification, kindled further RHD research ventures across the African continent and deepened our understanding of subclinical disease progression. Above all, the criteria have highlighted the excessive burden of disease across the continent and with it prompted African leaders to implement large-scale health policy reform. However, various logistical and methodological shortcomings have prevented its endorsement in large-scale screening programmes and cast doubt on the findings of long-term cohort studies of subclinical disease. At the heart of some of these shortcomings lies the difficulty of accurate RHD case detection using echocardiography. Our pursuit to improve this accuracy may necessitate a paradigm shift in the echocardiographic approach we use.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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