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STATE OF THE ART REVIEW
Valvular heart disease

Unmet needs in valvular heart disease

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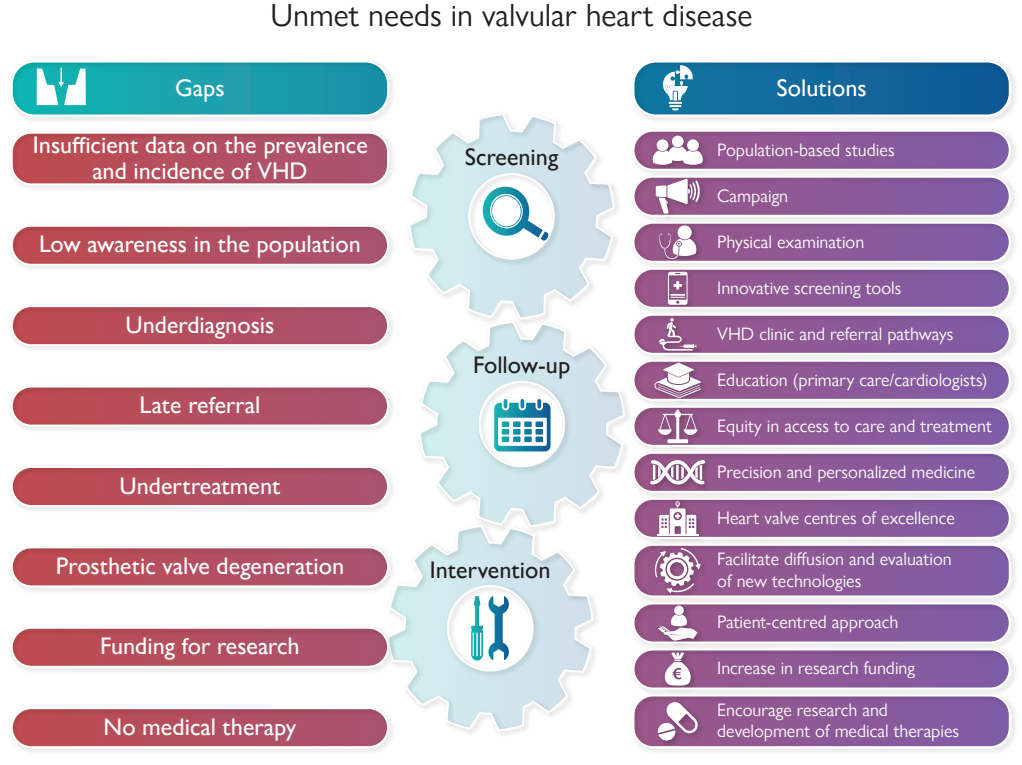
Graphical Abstract



Gaps/challenges and potential solutions in valvular heart disease (VHD).

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Abstract

Valvular heart disease (VHD) is the next epidemic in the cardiovascular field, affecting millions of people worldwide and having a major impact on health care systems. With aging of the population, the incidence and prevalence of VHD will continue to increase. However, VHD has not received the attention it deserves from both the public and policymakers. Despite important advances in the pathophysiology, natural history, management, and treatment of VHD including the development of transcatheter therapies, VHD remains underdiagnosed, identified late, and often undertreated with inequality in access to care and treatment options, and there is no medication that can prevent disease progression. The present review article discusses these gaps in the management of VHD and potential actions to undertake to improve the outcome of patients with VHD.

Keywords Valvular heart disease • Outcome • Intervention • Epidemiology • Public health

Introduction

The epidemiology and management of patients with valvular heart disease (VHD) has markedly changed in the last few decades with a marked decrease in the prevalence of rheumatic disease, advances in cardiovascular imaging, improvements in surgical techniques and postoperative care, an evolution to earlier rather than later interventions, and the rapid development and expansion of transcatheter therapies. Rheumatic valve disease is now rare in western countries and is predominantly observed in migrant and indigenous populations but remains highly prevalent in low- and medium-income countries and is associated with poor socio-economic status. The management of rheumatic heart disease and the system issues observed in low- and medium-income countries are different than those faced by high-income countries. The present review article focuses on western and high-income countries, highlights the burden of VHD, identifies gaps and area for improvement in the diagnosis and management of patients with VHD, and finally suggests actions to undertake to improve the outcome of patients with VHD. Infective endocarditis will not be discussed.

Epidemiology of valvular heart disease

As the population ages, VHD becomes an increasingly important cause of morbidity and mortality with a gross estimated prevalence of 5%–10% in patients 65–74 years and 10%–20% in those older than 75 years.[1–3] However, VHD prevalence is likely underestimated. Physical examination underestimates the prevalence of VHD, and large population-based studies relying on echocardiography to precisely assess VHD prevalence are scarce. The two most common VHD observed in western countries are 'degenerative' aortic stenosis (AS) (also referred to as non-rheumatic calcific aortic valve disease) and mitral regurgitation (MR). Based on the Global Burden of Disease Study (GBD) report, there were more than 9 million of people with moderate or severe AS in 2019.[4] With aging of the population, AS prevalence has almost tripled between 1990 and 2019 (from 45.5 cases per 100 000 people to 116.3 cases per 100 000) with a prevalence >1000 cases per 100 000 people beyond the age of 75 years (*Figure 1*). The European Society of Cardiology Atlas reported a sevenfold increase in the prevalence of calcific aortic valve disease during the last 30 years.[7] Patients with bicuspid aortic valve (BAV) present an early and accelerated disease course, and it is estimated that bicuspid valve accounts for up to 50% of AS at the time of intervention.[8] The estimated burden of degenerative mitral valve disease in 2019 according to the GBD report was 24.2 million. In the OxVALVE study, which screened 2500 individuals aged 65 or older, with no known VHD attending a visit to their general practitioner (GP) using transthoracic echocardiography, the prevalence of moderate or greater MR was 3.5% and up to 7.7% after 75 years.[9,10] Secondary MR (SMR) can be caused by left ventricular dysfunction/remodelling as a result of ischaemic or dilated cardiomyopathy (i.e. ventricular SMR), but also by left atrial/mitral annulus enlargement [atrial secondary (MSR)].[11] Atrial SMR has recently attracted significant interest and has been reported to account for up to one-third of MR mechanisms (one-third primary MR, one-third ventricular SMR, and one-third atrial SMR).[12] Calcific mitral valve disease (CMVD), which is caused by mitral annular calcification (MAC) extending into the leaflets, can present as mitral stenosis, MR, or a combination of both. Calcific mitral valve disease mostly affects elderly females with multiple comorbidities and is observed in 0.5%–1% of all echocardiograms performed.[13] Patients with CMVD are often left untreated even when symptomatic.[13,14] Surgery is high risk and transcatheter mitral valve interventions are emerging as an alternative treatment strategy, but remain associated with high mortality and morbidity.[15] Tricuspid regurgitation (TR) has been long overlooked, but its rising prevalence, strong and consistent association with increased mortality, improvements in imaging and in our understanding of the tricuspid valve anatomy, and the development of transcatheter therapies have shed new lights on this disease.[16–21] The main aetiology of TR is functional, and population-based studies have suggested a TR prevalence of 0.55% in the total population, increasing with age as with other VHD (2.6% in adults ≥65 years and up to 6.6% after 75 years) (*Figure 1*).[6,10] It is estimated that the prevalence of TR is similar to that of AS. Both functional TR and atrial SMR are strongly linked to atrial fibrillation, highly prevalent in western countries, especially in the elderly population, and are therefore expected to further increase in the near future. Aortic regurgitation (AR) is the third most common cause of VHD. Aortic regurgitation aetiologies are dominated by BAV, aortopathy, degenerative aetiologies, and infective endocarditis. Global estimates of AR prevalence are not available, but AR prevalence was 1.6% in the OxVALVE study, and an incidence of 19.7 in men and 10.8 in women per 100 000 person-years was reported in a Swedish registry.[1] Multivalvular diseases are encountered in ∼30% of patients. This population experiences high mortality rates and lower rates of intervention than single VHD.[22] Finally, following the growing epidemics of VHD, the number of patients who underwent a surgical or transcatheter valve intervention has markedly increased. This population is exposed to the risk of infective endocarditis and mechanical complications including prosthetic valve degeneration requiring subsequent interventions.[23]

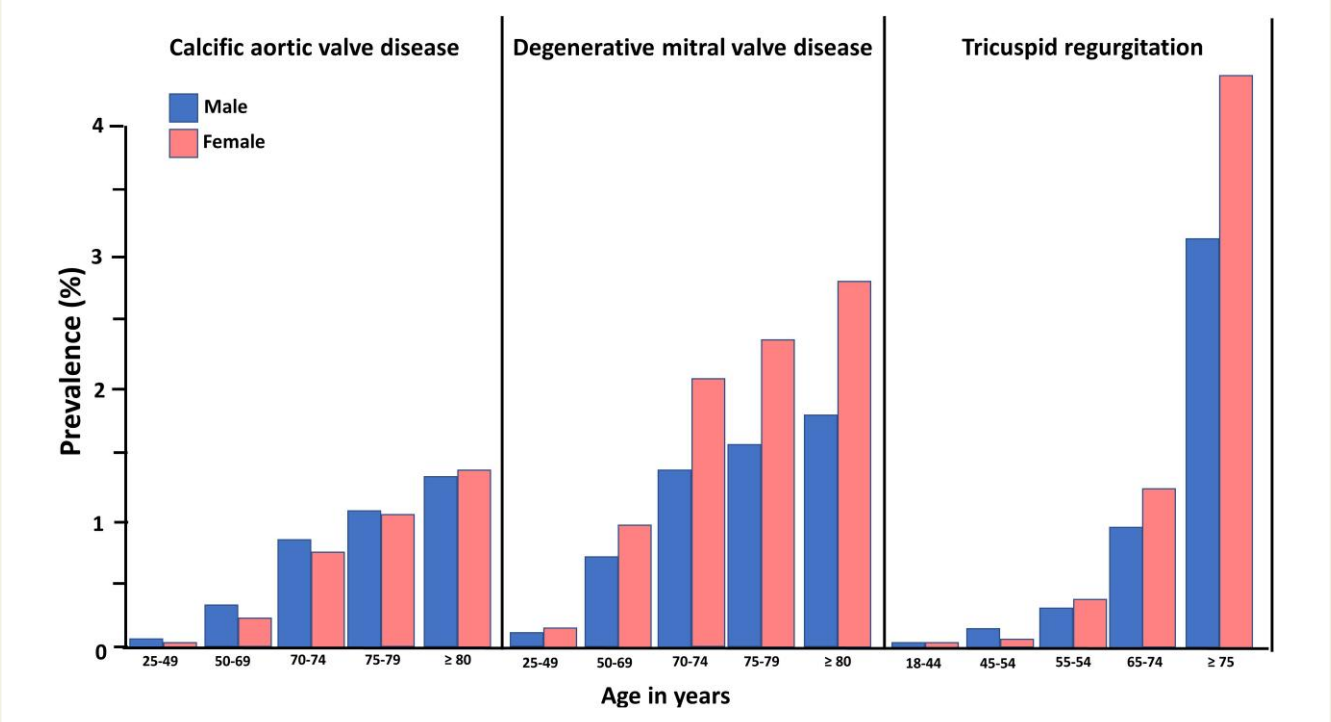

Figure 1 Age-specific and sex-specific prevalence of calcific aortic valve disease, degenerative mitral valve disease and tricuspid regurgitation. From Coffey et al. and Topilsky et al.[5,6]

Valvular heart disease is a major contributor of death and loss in disability-adjusted life years. With aging of the population, the prevalence of VHD in western countries is expected to at best double by 2050.[9] These patients, frequently elderly and with inherent associated co-morbidities, will challenge health care systems with increasing deaths, hospital admissions, VHD-related complications, disability-adjusted life years loss, and consequently health care expenditures. Valvular heart disease is therefore a major threat to public health and health care systems.

Current management of patients with valvular heart disease

Optimal management of the patient with VHD relies on three main pillars: (i) early disease detection, (ii) regular follow-up by physicians with knowledge of VHD, specifically the natural history of the disease, how to evaluate VHD, and the indications for intervention, and (iii) timely intervention in a centre with expertise in VHD, offering the full range of therapeutic options and the ability to achieve excellent outcome results (*Figure 2*). These same concepts apply to the follow-up of patients after an intervention. Early detection is key to enable appropriate follow-up and avoid late presentation of the disease with associated worse outcomes. Follow-up and timely intervention are critical to avoid irreversible adverse consequences such as atrial fibrillation or left ventricular dysfunction. This is even more critical as evidence regarding the survival benefit of an early intervention in selected patients with asymptomatic severe AS or degenerative MR (in experienced hands) is accumulating.[24–26] Importantly, severe VHD is lethal if left untreated, but in many cases curable if an intervention is performed early enough in the disease course. In contrast, late presentation is associated with an increased risk of morbidity and mortality, which is not restored by a successful intervention.[18,26–29] Unfortunately, real-life evidence from different geographical zones as discussed below has shown that patients with VHD are often underdiagnosed, undertreated, and frequently referred (too) late in the course of their disease.

Underdetection and underdiagnosis

Despite the high prevalence of VHD, and the undisputable negative impact of VHD on mortality and quality of life, there is little awareness of VHD among the population. In a survey conducted to evaluate the awareness of AS, only a tiny percentage (2%) of the 8800 respondents across Europe was concerned or aware of AS, far less than for cancer (28%), Alzheimer's disease (25%), stroke (12%), or heart attack (9%).[30] This low awareness obviously contrasts with the burden caused by VHD.

The simplest and probably most cost-effective way to diagnose VHD is cardiac auscultation. Although the sensitivity and specificity of auscultation are imperfect, its availability, accessibility, and portability are unequalled and cardiac auscultation should be considered as the first-line tool for the diagnosis of VHD. Unfortunately, no cardiac auscultation was performed in close to 50% of the visits carried out at the GPs' level.[30] In a survey performed among physicians, including GPs, to assess their perceived needs in knowledge, skills, and confidence and their actual practice according to case scenarios, a similar underuse of auscultation was highlighted.[31] With the COVID-19 pandemic and marked decrease of in-person visits, underdiagnosis has, in all likelihood, increased. In the OxVALVE study, half of the patients with moderate/severe VHD were not detected/diagnosed, showing the magnitude of VHD underdiagnosis at the population level.[9,10]

Undertreatment and late referral

Undertreatment and late referral were confirmed in the EORP Valvular Heart Disease II survey which collected 5219 patients with severe native VHD across 28 countries.[32,33] In symptomatic patients, concordance between guidelines and intervention (Class I recommendation) was only acceptable for AS (79%) and suboptimal for primary MR (71%). Late referral was also observed, with half of the patients referred for an intervention having NYHA Class III/IV symptoms and one in six presenting with congestive heart failure. Concerningly, when an intervention was scheduled, it was performed within 6 months in only one-half of the patients, despite the well-demonstrated relationship between prolonged waiting times and mortality.[34]

The IMPULSE registry, a large multicentre prospective registry from 23 centres across 9 European countries, gathered 2171 patients with severe AS and also showed that patients were still referred late in the course of the disease with severe symptoms and/or left ventricular dysfunction, and that despite the availability of transcatheter aortic valve implantation (TAVI), more than 20% of the symptomatic patients were denied an intervention.[35] Other investigators have shown a similar undertreatment of the AS population.[36,37]

In a community-based study collecting all consecutive patients diagnosed with moderate or severe MR based on echocardiography, only 15% were referred to surgery despite a clear indication for intervention.[38] Similar results were observed in France using an administrative database in which among more than 107 000 patients admitted with a diagnosis of MR, only 8% were referred for an intervention within a year.[39] The prognosis of patients conservatively managed was poor with a 14% 1-year mortality, and one-third of patients were either dead or readmitted for heart failure at 1 year irrespective of the primary or secondary aetiology for the regurgitation. Mitral regurgitation represented an estimated annual cost between 350 and 550 million euros (390 to 615 million US dollars). Interestingly, the mean age of the conservatively managed population was 77 years, 50% were 80 years or older, and multiple comorbidities were frequent, significantly different than the usual baseline characteristics of patients reported in surgical series. These marked differences illustrate that outcomes reported in highly selected series[40–42] are not representative of the overall MR population in real-life practice.

Undertreatment is also observed in the TR population. In a nationwide study of patients admitted with TR during a 2-year period, only 10% were referred for an intervention within 1 year, mainly at the time of a mitral surgery.[19] Among those referred for a mitral valve intervention, TR was neglected in one-third of the cases. While it should be acknowledged that formal proof supporting that correcting TR improves outcome is still lacking, TR has been consistently associated with an increased risk of mortality and morbidity in all settings.[16,19–21] In contrast with the prevalence of TR, the number of isolated tricuspid valve surgeries performed either in Europe or in the USA is remarkably low.[17,18,28,43]

It is important to highlight that because of advanced age and comorbidities, a conservative management might have been appropriate in a subset of patients avoiding potentially futile interventions, but the magnitude of undertreatment as shown in *Table 1* and the literature are clearly showing that for most patients, conservative management was inappropriate.

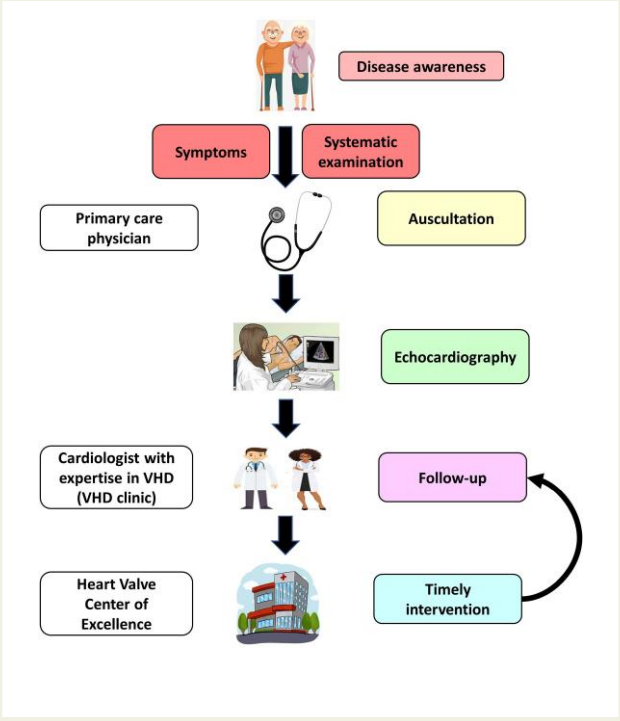

Figure 2 The optimal journey of a patient with valvular heart disease. Optimal management of patients with valvular heart disease relies on early detection (diagnosis), careful evaluation and follow-up (monitoring), and timely intervention performed in a valvular heart disease centre of excellence offering all treatment modalities and excellent outcomes. VHD, valvular heart disease.

Inequity in access and treatment

There are also important disparities and inequity in the management of patients with VHD based on race, age, sex, and geographical areas.[45–47] Although prevalence of VHD may vary according to race, racial disparities in the diagnosis and treatment have been documented.[37,48–51] It is critical to highlight that the definition of underserved populations should not be restricted to minorities, but should encompass a broader spectrum based on socio-economic and socio-demographic status and geographical environment. Important geographical disparities have indeed been reported. Availability of TAVI is markedly different between and within countries.[7,52,53] The Valve for Life initiative has shown that the number of TAVI per head of population in the UK is among the lowest in Europe with major regional disparities.[54] Valve repair rates are highly variable, and the less than 1% in-hospital mortality and repair failure rate reported by expert centres are far from being achieved in all cardiac surgery centres. Repair rates in the USA and in Europe have been shown to be suboptimal even in the ideal subset of patients 60 years old or younger and without comorbidities.[55–57] A valve replacement is also often unduly performed in the older patients despite the consistent proof of benefit of repair vs. replacement in the elderly population.[58–60] Female sex has also been associated with lower repair rates irrespective of age and comorbidity index.[56] Women present later in the course of the disease and experienced higher operative mortality rates and lower long-term survival.[61] A small study has suggested that women were less likely to receive appropriate transthoracic echocardiography surveillance for VHD, similar to elderly and black patients.[62] In AS, the prognosis of women appears worse than men.[63,64] This worse outcome may be due to the different phenotypes with more concentric remodelling, myocardial fibrosis, and low-gradient

Table 1 Main studies showing the magnitude of undertreatment in patients with valvular heart disease (VHD)

First author	Type of study	Type of VHD	Patients conservatively managed despite a guideline-based recommended intervention
Iung[32]	Prospective multicentre international cohort (EORP Valvular Heart Disease II survey)	AS MR TR associated with AS or MR	21% 29% 22%
Frey[35]	Prospective multicentre international cohort (IMPULSE)	AS	20%
Li[36]	Retrospective multicentre cohort	AS	52%
Brennan[37]	Electronic health record database	AS	63%
Dziadzko[38]	Retrospective single-centre cohort	MR	85%
Messika-Zeitoun[19]	Administrative database	MR + TR	33%
Essayagh[44]	Retrospective single-centre cohort	MR + TR	70%

AS, aortic stenosis; MR, mitral regurgitation; TR, tricuspid regurgitation.

AS in women compared with men, but also to lower referral rates for intervention.[65] Addressing inequality in access and quality of care and understanding the underlying barriers are critical issues to improve VHD outcome at the population level.

A shift in paradigm

However, 'mismanagement' of patients with VHD needs to be contextualized. Studies published in the 1970s–80s have ill-informed the medical community suggesting that VHD condition was mostly benign. At that time, risk of surgery was much higher than nowadays and has only progressively and relatively recently decreased. Surgery was thus only offered in selected cases, and elderly patients were mostly conservatively managed. Hence, undertreatment was not for long a mistake but a legitimate concern. In the last decades, natural history of VHD has been better defined and risk of the disease/impact on outcome better recognized. In parallel, surgical techniques have significantly improved including development of minimally invasive interventions and valve repair, as well as peri- and post-operative care. Our armamentarium to treat patients with VHD has also considerably expanded with the development of transcatheter therapies which offer a less invasive alternative to surgery to treat patients previously denied an intervention for both AS with TAVI[23,50,66–68] and edge-to-edge repair for MR including those with SMR.[69,70] All these advances and progresses have justified the change of perspective from 'selection of the best case' to 'treat all those in need'.

How to improve detection and screening?

One important goal is to raise awareness in the public, physicians, and other stakeholders about the burden and consequences of VHD, and the importance of screening for early detection. Large campaigns dedicated to the public are clearly needed. Similar to awareness campaigns related to cancer or stroke, the public should be informed that VHD is a main cause of mortality and morbidity that could be markedly reduced with early detection of the disease. Medical societies in collaboration with patient organizations should lead these initiatives. The testimony of patients with VHD can draw public attention, and champions from politics, arts, or business sectors should be recruited, as occurs with other disease awareness campaigns. When patients are aware and convinced of the importance of VHD, they will prompt health care providers to be screened for VHD.

Auscultation is the simplest way to identify patients with possible VHD, however, as noted previously, is underperformed especially at the primary care level. Limited time allocated for the clinical visit, lack of expertise, and lack of confidence of the health care practitioner are some of the reasons. Computer-aided auscultation and artificial intelligence (AI) algorithms may support performance of auscultation by health practitioners and improve its accuracy.[71]

Nevertheless, several studies have shown the limits of auscultation both in terms of sensitivity and specificity, even when performed by experienced physicians.[72] This limited accuracy is a strong incentive to develop additional screening tools. Echocardiography is the main method to diagnose VHD. Due to logistical issues as well as cost concerns, it is not feasible to develop large population screening programmes using transthoracic echocardiography in accredited echocardiography laboratories. Point-of-care ultrasound (POCUS) or hand-held cardiac ultrasound devices are becoming widely available and offer the possibility of performing cardiac ultrasound at the point of care level.[73,74] Several studies have shown incremental benefits in identifying disease when these tests are added to the general physical examination, including among medical students.[75–78] However, the lack of trained personnel capable of acquiring adequate images and interpretating them accurately have hindered the adoption of POCUS in clinical practice. Point-of-care ultrasound should be a component of medical school curriculum, similar to the use of a stethoscope. Technology and AI may also overcome issues regarding both image acquisition and interpretation.[79]

It has been reported that AS can be detected with good accuracy based on the ECG recording and AI interpretation.[80] Biomarkers are attractive, but no specific biomarkers for the diagnosis of AS or MR are currently available.

Existing epidemiological data on VHD are scarce and out of date. Implementation of large-scale contemporary population-based studies in different geographical areas with systematic implementation of state-of-the-art diagnostic tools is of paramount importance to provide

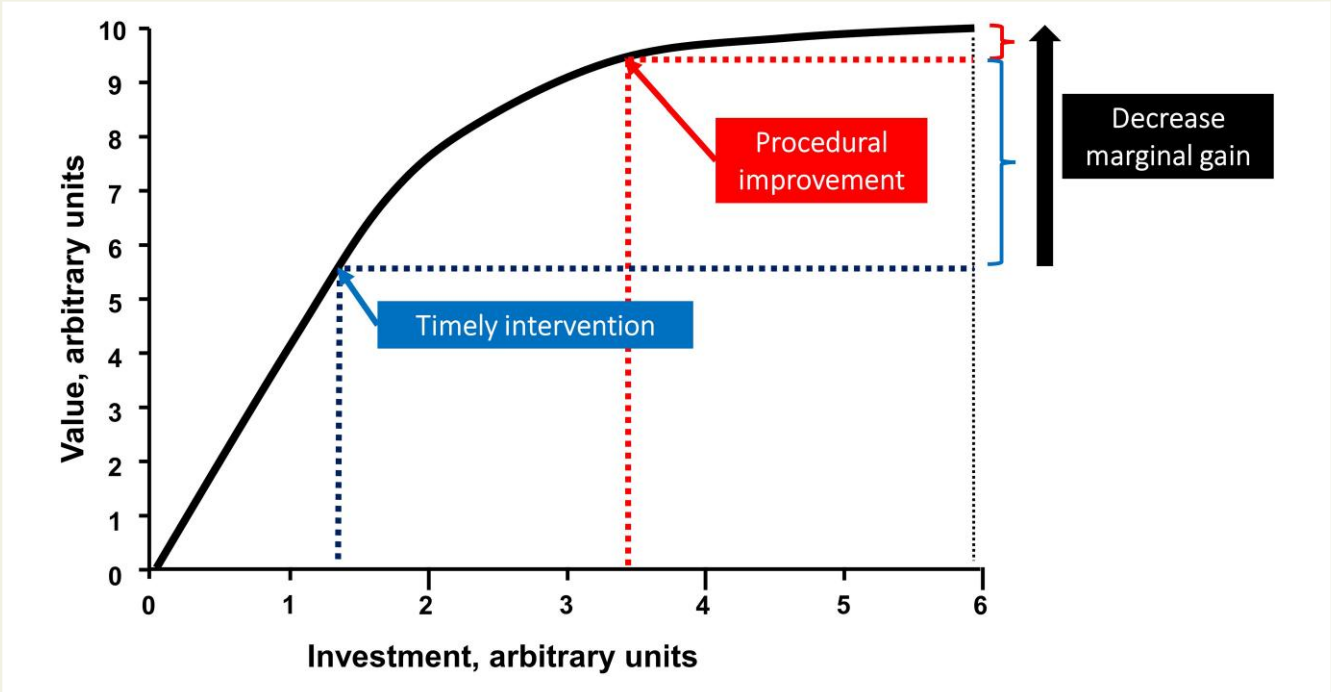

Figure 3 The importance of timely intervention. The marginal gain that can be obtained by improving timeliness of intervention markedly supersedes the marginal gain that can be expected by improving procedural results of surgical or transcatheter interventions and will have a much higher impact on public health.

accurate estimation and prediction of VHD burden in the years to come.

All potential screening strategies need to be carefully designed and evaluated: methods used, setting and population targeted, cost, psychosocial impact, and even more critically impact on outcome.[81] The underpinning principle of a screening/early detection strategy is access to care, especially access to primary care providers. Such access is often deficient and heterogeneous, related to health care coverage, physicians' demography, and underserved rural or remote areas, among others. Access to primary care professionals needs to be improved in order for any screening strategy to be fully effective and efficient. Similarly, access to echocardiography when VHD is suspected needs to be optimized. Lack of access to echocardiography has been identified as one major barrier by GPs to diagnosing VHD.[82]

How to improve timely intervention and state-of-the-art management?

With improvements in surgical and post-operative care and the development and maturation of many transcatheter therapies, most valvular interventions can be performed at a relatively low risk. Notwithstanding the importance of continuing to improve interventional outcomes, marginal gains are expected to be relatively modest. In contrast, optimizing the timing of intervention and avoiding late presentation will have a major impact on outcomes at the population level (*Figure 3*). As highlighted in the prior section, late presentation and undertreatment are the main drivers of increased mortality and morbidity of patients with VHD and a major area for improvement.

Education of physicians

Among the potential reasons explaining the undertreatment of patients with VHD, insufficient physicians' knowledge regarding the management and timing of intervention has been highlighted in a survey of physicians.[31] This survey, using cased-based scenarios, showed a gap in knowledge and the critical need to develop continuous medical education programmes dedicated to VHD. These programmes should target not only cardiologists but also primary care providers as they are the initial contact, often the individual ordering an echocardiogram and making the diagnosis of VHD. National and international societies of cardiology should cooperate with primary care provider organizations to develop training programmes adapted to their needs and specific environment. Education of community cardiologists is also critical and should be performed in parallel. These programmes should focus on the importance of screening, assessment of VHD severity, the need for regular follow-up, the recognition of symptoms, the availability of transcatheter therapies, and a better understanding of the risk/benefit ratio of valvular interventions.

Valvular heart disease clinics and referral pathways

As the evaluation and management of patients with VHD becomes more complex, development of dedicated heart valve clinics and VHD teams should be promoted as highlighted both in the European and the North American guidelines on VHD.[83,84] Several publications have suggested a beneficial role of heart valve clinics.[85] Although the concept seems sound, the level of evidence remains low, and formal demonstration of the benefit of valve clinics on outcome is complex and unlikely to occur. Various definitions of heart valve clinics have been proposed as well as who should be part of the structure.[86] In our opinion, we should place emphasis on two major points: (i) access

to cardiologists with expertise in VHD and (ii) development of VHD referral pathways that are adapted to each specific environment. A cardiologist with expertise in VHD is the cornerstone of a VHD clinic, and access to these cardiologists should be promoted, especially in remote areas.[87,88] Requirement for a multidisciplinary expertise as the basis of every VHD clinic may lead to an excessive centralized system which may be potentially overwhelmed with limited added value for the majority of patients with VHD. The VHD expert cardiologist should have access to high-quality echocardiography to accurately assess the severity of the valve disease, its consequences, and to guide the timing of interventions. As part of the VHD pathways, the VHD expert cardiologist should have access to tertiary centres and more advanced multidisciplinary VHD clinics (composed of core members of surgeon, interventional cardiologist, advanced imaging specialists, heart failure specialists, intensivist, and valve nurse) and facilities performing transoesophageal echocardiography, computed tomography imaging, or magnetic resonance imaging for the evaluation of complex patients. Valvular heart disease pathways should be implemented according to local constraints, population density, and environment. Hub and spoke models or hub, spoke, and node models are equally valuable depending on the environment (*Figure 4*). Rural environments, small countries with concentrated populations in urban environment, or large countries with wide-spread populations require specific and different VHD pathways. Valvular heart disease referral pathways should be implemented based on local health care needs from bottom to top rather than pyramidally imposed in a systematic manner to all regions/areas from top to bottom.

Valvular heart disease centres of excellence

Once an intervention is considered, it should be performed in a centre with the potential to offer all treatment modalities with proof of excellent outcomes, which should be used to define a VHD centre of excellence. These two components are critical. Availability of all therapeutic options limit bias performance of 'what is available' vs. 'what is the best for a patient in accordance with patients' preference'. Achievement of excellent results requires the implementation of a multidisciplinary VHD team working closely together to best serve patients' interest. In these VHD centres of excellence, the multidisciplinary VHD clinics will evaluate the need, timing, and type of intervention. Specialized clinics as the TAVI/surgical aortic valve replacement (SAVR) clinic or mitral/tricuspid clinic should be embedded into these VHD structures (*Figure 4*). The patient should be at the centre of the decision-making process, and incorporating the patient's 'voice' should be a priority. Education is the cornerstone of patients making informed decisions and is a key component of this patient-centred approach. Goals and preferences of the patient should be carefully explored, therapeutic options and their respective risks and benefits clearly explained, and a shared decision-making process promoted.[89]

A record of VHD centres of excellence adjusted for case mix outcomes should be publicly available and benchmarked. It is critical to highlight that centre's volumes and centre's outcomes are not interchangeable, although a significant overlap exists. Many studies have shown that centre volume is usually associated with better outcome after surgery or transcatheter therapies.[55,90] In a recent US study,

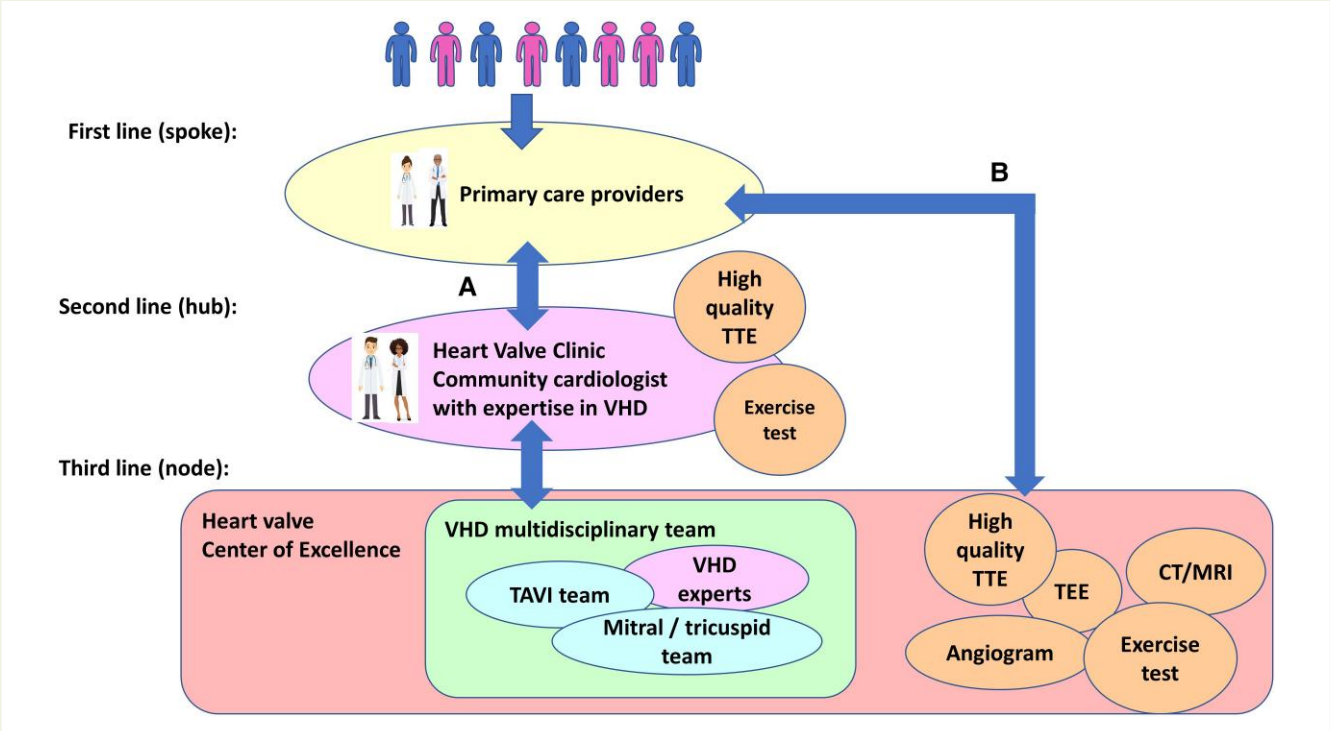

Figure 4 Proposed referral pathways based on local needs and environment. In pathway *A*, the patient is referred by the primary care provider to a local cardiologist with expertise in valvular heart disease and access to high-quality transthoracic echocardiography. Based on his assessment, he will continue the care and management of the patient or if needed will refer him to the tertiary centre/ valvular heart disease centre of excellence he is affiliated to. In pathway *B*, the patient is directly referred by the primary care to a tertiary centre he is affiliated with which will perform the evaluation and management. Valvular heart disease centre of excellence is composed of valvular heart disease experts both cardiologists and surgeon with access to all imaging modalities and surgical and transcatheter therapies. VHD, valvular heart disease; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; CT, computed tomography; MRI, magnetic resonance imaging.

the increase in the number of centres performing TAVI has resulted in a dilution of the number of cases per centre and was associated with unintended consequences on procedural quality and increased hazard of mortality, clearly demonstrating that centres' volumes are a marker of experience, expertise, and consequently outcomes.[91] However, the relationship between outcome and volume is more complex, and several studies have reported excellent case-mix adjusted outcomes in medium-sized centres and mis-classification of hospitals' performances when only volumes are taken into consideration.[92,93] Operator volumes are also important to consider. Importantly, so-called high-volume centres in one country may be considered as low-volume in a different country (and vice versa).[94] Thus, the definition of a VHD centre of excellence should be based more on adjusted outcomes than case volumes. It is nevertheless critical that international and national scientific societies establish minimal thresholds per centre and per operator adapted to national specificities to avoid deleterious and uncontrolled dissemination of centres and to guarantee experience and expertise of the centres. In parallel, national agencies should establish centre requirements regarding infrastructure and environment including on-site cardiac, vascular surgery, interventional neurology, and heart team, and monitor quality based on case-mix adjusted outcome and not only on volume. Ability for centres to treat patients with complex anatomy, to offer multiple approaches, and to master multiple devices should also be considered as quality indicators. Finally, accounting for the marked decline in post-procedural mortality especially for TAVI due to patients' selection, treatment of low-risk individuals, improvement in technology, simplification of the procedures, and standardization of post-procedural management, there is a need to develop more sophisticated quality indicators as the number of days spent alive at home outside of a hospital or a skilled nursing facility for both transcatheter and surgical interventions.[92,95] The development of other patient-centred quality indicators should be encouraged.

The AATS/ACC/ASE/SCAI/STS (American Association for Thoracic Surgery, American College of Cardiology, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons) have proposed and organized the system of care for patients with VHD by dividing centres into two tiers: Level I (comprehensive centres performing all commercially approved interventions and surgical procedures) and Level II (primary performing at least transfemoral TAVI and surgical procedures as SAVR).[96] Despite the distinction, an emphasis is placed on the need for both tiers to provide excellent adjusted outcomes. The US health care system is unique with a significant proportion of centres performing a low number of interventions. Such two-tier system might facilitate access to care and avoid elderly and frail patients needing to travel far from their home but exposes patients to low-volume centres and potentially worse outcomes as observed with TAVI dispersion. A health care system organization centring around VHD centres of excellence is likely preferable as long as the number of centres and their capacities are appropriately calibrated avoiding deadly waiting times.

Precision and personalized medicine

More options come at the expense of more complexity. If TAVI is the first-line treatment option in the elderly and SAVR the first-line option in younger patients, a large number of patients sit in a grey zone, and decisions need to be individualized based on the patient's comorbidities, anatomic and procedural/technical considerations, and personal preference.[97] The availability of valve-in-valve procedures has expanded and complexified the decision tree with multiple different possible permutations and sequences of aortic valve interventions, especially as TAVI is expending to low-risk and younger populations.[98] Better prediction of prosthesis durability at the individual level will be critical. One should keep in mind that long-term durability data of TAVI prostheses although promising are still scarce.[99–101]

For MR and to a lesser extent TR, choices are even more challenging due to disease heterogeneity and the more complex anatomy of the atrio-ventricular valves compared with the aortic valve. Multiple transcatheter devices with different designs and anatomical constraints are available. One size does not fit all, and there is critical need to develop tools to support the decision-making process and to select the best intervention for a given patient. Development of simulation models predicting the results of surgical and/or transcatheter interventions for a given patient is currently under development.[102]

Prediction should not be restricted to the results of interventions, and there is a critical need to predict disease progression, risk of occurrence of symptoms, and risk of occurrence of complications under medical management as well as after an intervention. Large prospective cohorts with associated biobank and long-term follow-up to better define the natural history of VHD disease combined with AI algorithms may provide new insights regarding individualized risk prediction. The multiple available 'omics' technologies may further refine the risk of disease progression and should be integrated into risk prediction models.[103]

Diffusion and access to technology

Diffusion of the technology across countries but also at a more regional level remains heterogeneous. Even a mature technology as TAVI still suffers from significant variability in access and waiting times.[34,36,53] Access should be improved, but it should not occur at the expenses of patients' outcomes as suggested with the broad diffusion of TAVI in the USA.[91] The referral and intervention pathways should be streamlined, but a centralized system in high-volume centres is likely the more effective way to guarantee the best patients' outcomes. This process should apply to surgical and transcatheter interventions.

Diffusion of less mature technologies should also be promoted but with safeguards. Promoting early access to innovative technology should be encouraged with careful monitoring and evaluation processes. It is interesting to note that despite the discordant results of the COAPT and MITRA-FR trials in patients with SMR,[69,70] real-life data regarding the profile of patients implanted, the processes to guarantee that patients are on optimal medical therapy, and the immediate and mid-term outcomes at the nationwide level are often lacking. It is expected that health care authorities should facilitate access to innovative technology while at the same time ensuring careful monitoring and evaluation of its implementation in real life. The main limitation of randomized controlled trials is generalizability, emphasizing the importance of real-life monitoring through large, dedicated registries. Indications and performance of interventions should rely on robust scientific evidence, and lack of real-life monitoring can lead to a major drift in clinical practice. These drifts have the potential to impact patient outcomes, the efficacy and cost-effectiveness of the procedure, and health care expenses. With constrained health care budgets, the medical community should be accountable of the use of expensive and scarce resources.

The missing piece—medical therapy

Compared with the significant advances in medical therapy in the treatment of atherosclerosis/coronary artery disease and heart failure,

medical therapies in VHD have been disappointing, and there is currently no medical therapy that can prevent or slow disease progression (*Figure 5*). The only recommended medical therapy in VHD is symptomatic treatment of heart failure and left ventricular dysfunction, especially in SMR and functional TR.[104] In other settings, medical therapy is only palliative, and symptoms or left ventricular dysfunction are Class I recommendations for intervention.[83,84]

Despite strong epidemiological links between AS and cardiovascular risk factors, especially elevated cholesterol, statins had no effect on AS progression.[105–107] There is a causal relationship between the presence/prevalence of AS and lipoprotein(a) [Lp(a)].[108] Trials are about to start using drugs specifically targeting Lp(a) reduction. Observational data have suggested a link between bone remodelling, osteoporosis, and AS progression. Unfortunately, two anti-osteoporotic drugs interfering in different bone turnover pathways (denosumab and alendronic acid) had no effect on AS progression.[109] There is a critical need to explore alternative pathways and mechanisms involved in AS progression to develop medical therapies. Aortic stenosis pathophysiology is likely different between men and women, the latter displaying less leaflet calcifications and more fibrosis for the same haemodynamic impairment and a different left ventricular response to the increased afterload.[65,110,111] It is possible that one drug may not be able to interfere with disease progression in all AS patients, or at all stages, and individualized medical therapy may be required. With the rapid expansion of TAVI and the marked decrease in the use of mechanical valves, bioprosthesis degeneration will become a major issue, and understanding the underlying mechanisms to develop dedicated therapies aiming at increasing bioprosthetic valve durability is of utmost importance.

Myxomatous mitral valve disease is the most common aetiology of primary MR in western countries. Several genes have been identified.[112] Definitively more work needs to be done to understand the pathophysiology of this tissue disorder and possibly interfere with the underlying pathways to prevent progression of myxomatous MR.

Finally, the myocardial response to volume/pressure overload is highly variable with some individuals demonstrating a deleterious maladaptive response.[113] The mechanisms responsible for the myocardial response need to be better understood to potentially elucidate new therapeutic targets to delay disease progression.

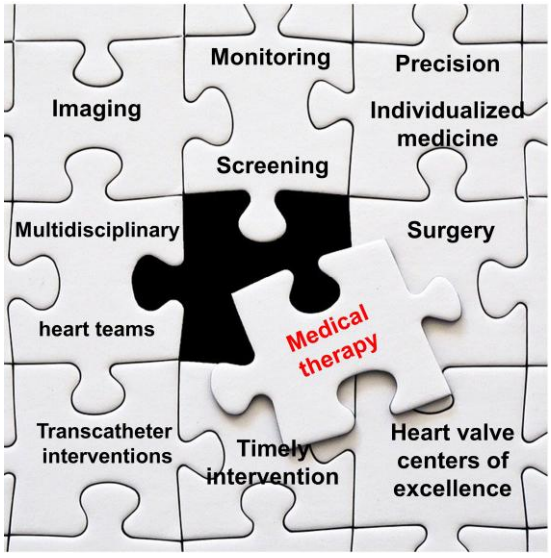

Figure 5 Need for medical therapies for valvular heart disease. There is an urgent need to develop medical therapies to stop or prevent the progression of heart diseases as well as the maladaptive myocardial response.

Conclusions

The field of VHD is rapidly evolving with major changes in the evaluation and management of patients with VHD and major advancements in treatment options with the availability of less invasive non-surgical interventions. With aging of the population, the incidence of VHD will continue to increase and VHD should be considered as the next epidemic in the cardiovascular field, affecting millions of people worldwide and having a major impact on health care systems. VHD has not received the attention it deserves from both the public and policymakers. VHD remains underdiagnosed, identified late, and often undertreated with inequality in access to care and treatment options. There is no medication that can prevent disease progression, and intervention is currently the only curative therapeutic option. But it does not have to be that way and solutions are at our doorstep (*Graphical Abstract*). Addressing the unmet needs of the VHD patient requires a multipronged approach directed at improving the detection of VHD earlier in the disease course, educating clinicians on the appropriate management and timing of intervention, developing VHD referral pathways that are adapted to each specific environment, and creating VHD centres of excellence with multidisciplinary teams with access to both surgical and transcatheter technologies, working closely together to best serve the patient's interest. Importantly, initiatives directed at the public and policymakers are needed to promote VHD awareness. Funding agencies should support VHD research to better understand the pathophysiology and natural history of VHD and the development of medical therapies aiming at preventing disease progression. A call for action as the one recently released by the Institute of Health Economics (https://www.ihe.ca/publications/heart-valve-disease-in-canada-recommended-components-for-a-national-strategy) or the ones published by the Global Heart Hub, Heart Valve Voice or the Valve for Life initiative should be encouraged. Addressing these gaps should be a public heath priority. The time to act is now.

Author contributions

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Data availability

No new data were generated or analysed in support of this research.

Conflict of interest

D.M.-Z. has received research grant from Edwards Lifesciences. H.B. received honoraria and travel support from Edwards Lifesciences and Actelion. M.E.-S. received consulting fees from Edwards LLC, Highlife, Artivon, and ChemImage. I.G.B. declares that there is no conflict of interest. A.V. declares that there is no conflict of interest. J.B. has received speaker fees from Edwards Lifesciences and Abbott. P.P. has received funding

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