



Valvular Heart Disease 2

The future of valvular heart disease assessment and therapy

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Valvular heart disease (VHD) is becoming more prevalent in an ageing population, leading to challenges in diagnosis and management. This two-part Series offers a comprehensive review of changing concepts in VHD, covering diagnosis, intervention timing, novel management strategies, and the current state of research. The first paper highlights the remarkable progress made in imaging and transcatheter techniques, effectively addressing the treatment paradox wherein populations at the highest risk of VHD often receive the least treatment. These advances have attracted the attention of clinicians, researchers, engineers, device manufacturers, and investors, leading to the exploration and proposal of treatment approaches grounded in pathophysiology and multidisciplinary strategies for VHD management. This Series paper focuses on innovations involving computational, pharmacological, and bioengineering approaches that are transforming the diagnosis and management of patients with VHD. Artificial intelligence and digital methods are enhancing screening, diagnosis, and planning procedures, and the integration of imaging and clinical data is improving the classification of VHD severity. The emergence of artificial intelligence techniques, including so-called digital twins—eg, computer-generated replicas of the heart—is aiding the development of new strategies for enhanced risk stratification, prognostication, and individualised therapeutic targeting. Various new molecular targets and novel pharmacological strategies are being developed, including multiomics—ie, analytical methods used to integrate complex biological big data to find novel pathways to halt the progression of VHD. In addition, efforts have been undertaken to engineer heart valve tissue and provide a living valve conduit capable of growth and biological integration. Overall, these advances emphasise the importance of early detection, personalised management, and cutting-edge interventions to optimise outcomes amid the evolving landscape of VHD. Although several challenges must be overcome, these breakthroughs represent opportunities to advance patient-centred investigations.

Introduction

Progress in the treatment of valvular heart diseases (VHDs) has been fostered by the development of invasive transcatheter approaches and supported by well designed randomised trials primarily focused on devices and procedures. The other paper in this Series reviews these recent advances.¹ However, a 2020 report from the National Heart, Lung, and Blood Institute highlighted substantial gaps in the delivery of and patient access to personalised care in VHD.² In this Series paper, therefore, we focus on priorities that will define the next decade of scientific research and clinical practice in VHD. These priorities include developing new avenues for screening and surveillance through digital health, artificial intelligence, and imaging; honing pre-procedure management via computational precision phenotyping and medical decision making; and probing innovative medical and bioengineering approaches for valve therapies.² Just as the COVID-19 pandemic revealed limitations in clinical care yet fostered innovation, we anticipate future advances stemming from technological and bioengineering breakthroughs will refine patient-centred care in VHD.

Digital medicine and artificial intelligence

The emergence of big data from computerised patient health records, mobile devices, sensors, wearable technologies, imaging techniques, and social networks is enabling the use of machine-learning algorithms that learn from such data and perform tasks autonomously.³

Specifically, convolutional neural network (CNN) models—a deep learning method for segmenting an image in a grid-based fashion to identify patterns for overall image comprehension—have enabled high algorithmic precision and accuracy.⁴

Artificial intelligence-powered digital tools for screening

Physical examination and cardiac auscultation are the cornerstones of clinical diagnosis and screening of VHD; however, compared with transthoracic echocardiography, cardiac auscultation alone achieves a sensitivity of only 40–70% for the detection of VHD.⁵ Machine learning can improve diagnostic yield by extracting features (eg, phonocardiography or electrocardiogram [ECG] signals from an electronic stethoscope) and learning to assign labels to clinical data. This learning process can be supervised or unsupervised. Briefly, supervised learning assigns given labels to data with information on the outcome or ground truth to develop a prediction model. By contrast, unsupervised learning seeks labels that could be assigned to data.

Artificial intelligence algorithms can extract acoustic features from audible heart sounds and murmurs or infrasound data (ie, sound waves with a frequency lower than the lower limit of human audibility—generally 20 Hz) using unfiltered phonocardiography data or digitally processed acoustic signals.^{6,7} The direct incorporation of these algorithms into electronic

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stethoscopes has shown promising results in prospective clinical studies⁸ (appendix p 1). Machine learning has also been applied to ECG for detecting VHD, specifically left-sided valvular lesions (aortic stenosis and mitral regurgitation), with acceptable accuracy^{9–11} (appendix p 1). Machine learning-augmented ECG has shown excellent discrimination for predicting moderate-to-severe or severe VHD, with the area under the receiver operating characteristic (AUROC) curve ranging from 0·80 to 0·91 (appendix p 1). Artificial intelligence has also been applied to assess cardiomechanical signals (ie, cardiac vibrations propagating to the chest wall) obtained using microelectromechanical system accelerometers and gyroscopes to classify VHDs.¹²

Artificial intelligence-augmented ECG monitors and other wearables appear promising as level 1 (community-based) screening tools for identifying patients with clinically significant VHD in the general population (unselected population; figure 1). However, with low overall prevalence of VHD, the positive predictive value of these models might be lower for individual target VHDs.¹⁰ The use of clinical features in addition to ECG data might overcome this limitation.¹¹ For example, the rECHOmmend study aimed to improve the accuracy of

CNN models by including patients with moderate-to-severe valvular diseases who also had structural changes, such as reduced ejection fraction (<50%) or ventricular septal thickness greater than 15 mm.¹¹ The CNN model was trained to identify the presence or absence of any valve lesion using ECG tracings and input data, including demographic and laboratory data. Although the model achieved the best performance when all inputs were considered, the AUROC remained high, at 0·91, when only age, sex, and ECG tracings were used. Similarly, in a multisite pooled analysis involving 77163 patients, a CNN model using ECG and demographic features identified moderate-to-severe VHD with receiver operating characteristic (ROC) curve values ranging from 0·77 to 0·88 for specific valve lesions and 0·84 for overall lesion detection.¹³ However, for most of these studies, training and validation have been restricted to retrospective datasets from hospital-based settings. Moreover, models have underperformed during external validation.¹³ Future studies must address the challenges associated with prospective implementation, use, generalisability, and overall impact on early detection, diagnostic throughput, and clinical outcomes in general population settings.

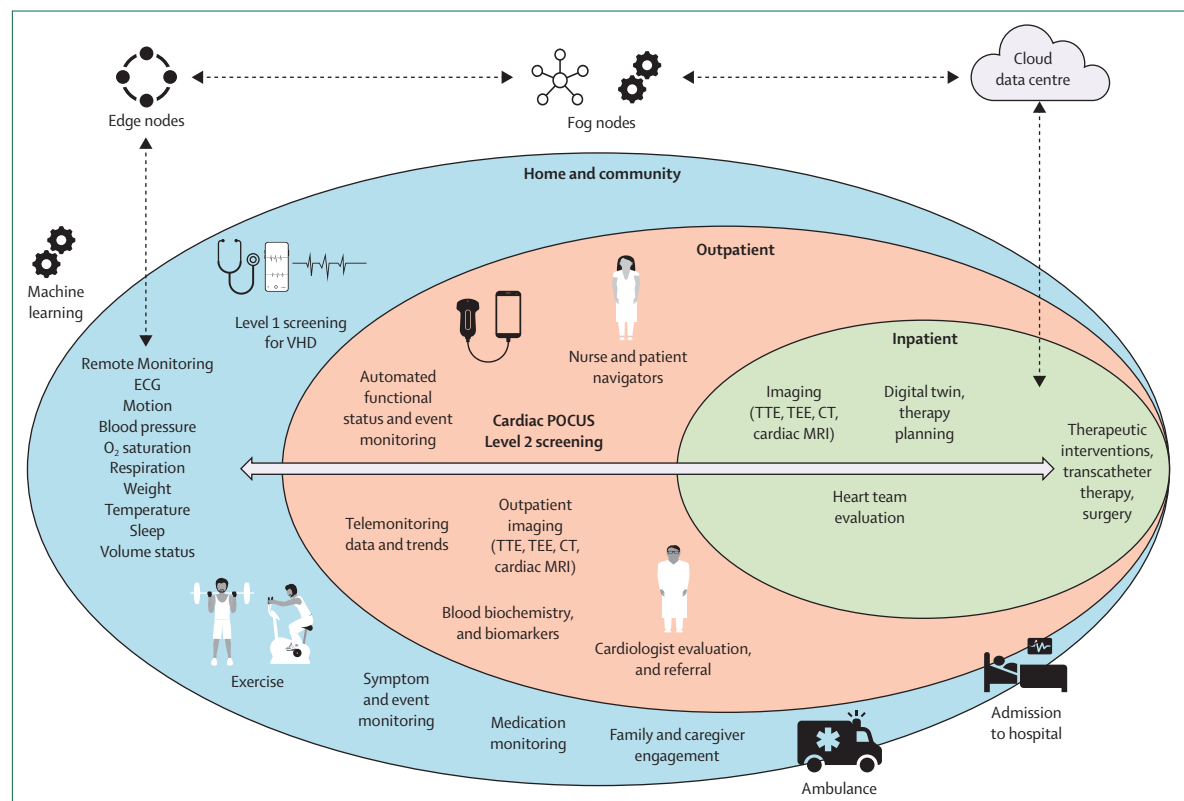


Figure 1: Digital innovations in care delivery for valvular heart disease

The schematic conceptualises machine learning techniques using ECG, wearable devices, and physiological sensor-based data for screening, individualised care coordination, and follow-up strategies. Screening in communities can be triggered with the use of wearables, devices, and remote patient monitoring systems. The appropriate triggers can lead to specialised consultations, with additional screening (using cardiac POCUS imaging techniques) and optimisation of downstream testing, evaluation, and timing of interventions. ECG=electrocardiogram. VHD=valvular heart disease. POCUS=point-of-care ultrasound. TTE=transthoracic echocardiogram. TEE=transesophageal echocardiogram.

Artificial intelligence-driven monitoring and access to care

Remote patient monitoring by use of wearable devices, such as smartwatches or smartphone-based mobile health apps and telehealth applications, is a rapidly growing field.¹⁴ Sensors can be deployed in garments or worn at the chest and wrist areas, and artificial intelligence techniques can be used to help monitor physical activity and related physiological parameters such as heart rate, respiration, oxygen saturation, blood pressure, and weight.¹⁵ Specifically, for patients with chronic VHD, such devices can provide efficient individual-level monitoring of physiological changes and symptoms over the disease course (figure 1).

Physiological parameters measured via wearable devices can provide a quantitative and objective assessment of functional capacity, potentially equivalent to the predictive value of 6-min walk tests and other frailty assessment methods.^{16,17} Several remote-monitoring devices have received regulatory approval for artificial intelligence-based algorithms that continuously monitor, for example, symptoms, physiological signals, and ECG.¹⁸ Longitudinal use of such remote patient monitoring in VHD could help ascertain clinical and haemodynamic stability or early deterioration when physical activity diminishes, specifically in patients with severe asymptomatic valve disease. Conversely, for patients already on waiting lists for surgical or transcatheter procedures, remote monitoring can identify subsets of patients at risk of rapidly worsening symptoms or outcomes so that therapies can be expedited.¹⁹ For example, the Royal Brompton and Harefield NHS Clinical Group implemented digital remote patient monitoring to identify and prioritise patients needing surgery for valvular disease or requiring coronary artery bypass graft, myectomy, or ascending aortic surgery. Of 525 patients who enrolled and were monitored through the app, 51 (9.71%) were flagged as being at risk and were escalated, resulting in surgery dates being brought forward for 45 (88.2%) patients.¹⁹ Wearable devices can also facilitate remote health care for patients discharged to home after undergoing transcatheter aortic valve replacement (TAVR) and can provide access to cardiac rehabilitation and monitor patient-reported outcomes.²⁰

Artificial intelligence-augmented cardiac imaging

Over the past few years, there have been three key advances in cardiac ultrasound, aided by the emergence of miniaturisation, three-dimensional (3D) and four-dimensional (4D) imaging, artificial intelligence use for image acquisition, automated quantification measurements, and decision support for automated interpretation. The first key advance is point-of-care ultrasound (POCUS), which has performed better than traditional auscultation methods of evaluating VHD, even when conducted by medical professionals who are not cardiologists (eg, nurses).²¹ For patients referred with suspected VHD,

cardiac POCUS is, thus, well suited as a level 2 (outpatient) screening tool for early detection (figure 1). In a randomised clinical trial that assessed patients with known structural heart disease, adding POCUS to the clinical evaluation resulted in earlier referral for valvular intervention and decreased the risk of admission to hospital and mortality.²² Recently developed artificial intelligence tools can guide novice users in the acquisition of high-quality images using POCUS and diagnose VHDs from limited echocardiography views.^{23,24} For example, using such tools to train non-expert health-care workers (eg, nurses, medical students, and clinical officers) in underserved areas might be helpful in ultrasound screening for rheumatic heart disease in endemic areas.²⁵

Another key advance in cardiac ultrasound is the application of artificial intelligence to cart-based equipment and picture archiving and communication systems. Deep learning techniques can automate the segmentation of cardiac chambers and leaflet segmentation in B-mode images, estimation of Doppler tracing, calculation of cardiac chamber volumes and function (ejection fraction and global longitudinal strain), and evaluation of valve morphology and motion in two-dimensional images.^{26,27} Besides improving accuracy in the assessment of valvular lesion severity, machine-learning models might help the development of personalised recommendations for subsequent echocardiographic examinations as part of follow-up screening, specifically for patients with non-severe lesions.²⁸ Regarding 3D and 4D imaging, several commercial software programmes have been developed for the automated quantitative analysis of aortic and mitral valve apparatus.²⁹ However, further software development is needed for more complex and comprehensive assessments—eg, to differentiate mechanisms of regurgitant lesions, such as leaflet prolapse, perforation, tethering, and chordal rupture.

Artificial intelligence can also assist in the interpretation of cardiac CT and MRI findings. For example, artificial intelligence techniques can aid image acquisition, reduce image reconstruction times, and facilitate automated slice positioning—improving the quality of images and accuracy of cardiac chamber segmentation—as well as enhance the automatic localisation of landmarks.²⁶ Artificial intelligence tools for CT are increasingly used in preoperative planning, with prospective studies showing the value of automated artificial intelligence tools in prosthesis sizing and procedural planning, specifically for TAVR.³⁰ For cardiac MRI, artificial intelligence techniques can potentially improve automated tissue characterisation for the quantification of myocardial replacement fibrosis (late gadolinium enhancement) and interstitial fibrosis (extracellular volume by T1 mapping), the key prognostic features in severe VHD.^{31,32} Moreover, combining methods for extracting pixel-level information that is not visible to the naked eye (radiomics) with artificial intelligence techniques might enable the detection of myocardial

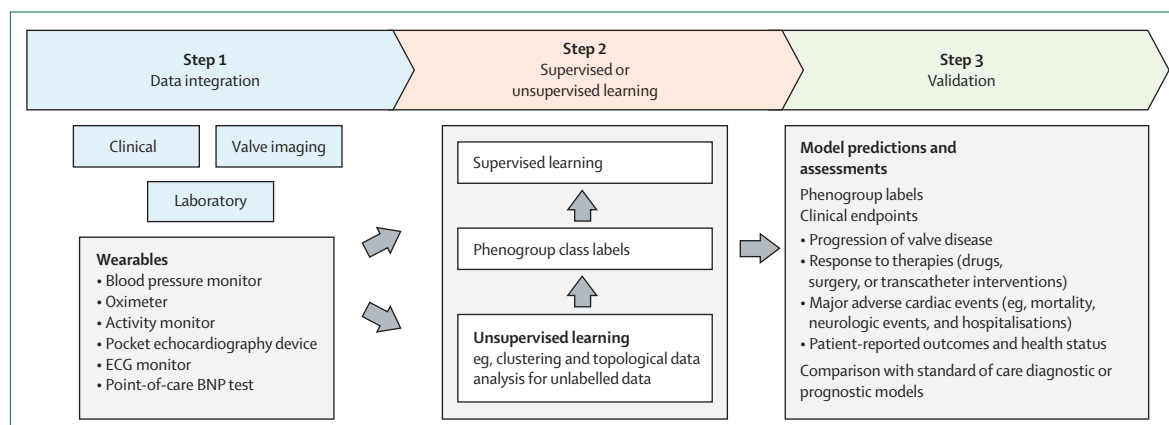


Figure 2: Use of machine-learning approaches to refine the taxonomy of valvular heart diseases

Unlike the conventional description of heart valve lesion severity (eg, mild, moderate, or severe), which uses a small number of imaging features, unsupervised machine-learning approaches integrate diverse data to develop meaningful subgroups (clusters) and biological networks (topological maps) associating disease severity with distinct outcomes. After the unsupervised learning is used to develop phenogroup labels, a supervised machine-learning classifier can assign a new patient to the phenogroup class label, which might be particularly useful when patients have conflicting clinical data or imaging measurements. ECG=electrocardiogram. CNN=convolutional neural network. AVR=aortic valve replacement.

changes without requiring contrast agents for image enhancement.³³

Machine learning for precision phenotyping of VHD

Unsupervised machine learning offers various methods for partitioning patients into comparable subgroups or phenotypic presentations. For instance, whereas aortic stenosis severity has previously been evaluated on the basis of valve-related factors, unsupervised machine learning enables the integration of structural, functional, and haemodynamic data to segregate patients into unique groups, also referred to as clusters, to highlight differences in cardiac remodelling patterns and prognoses (figure 2).³⁴ Another technique, network analysis, depicts patient groups as nodes, with connections between the nodes (appearing as lines) representing the strength of similarities between multiple clinical features. These networks can depict disease progression and severity patterns over time. For example, network analysis suggested that a distinct subgroup of patients with aortic stenosis might have had systolic dysfunction before developing severe aortic stenosis.³⁵ Although this finding is consistent with clinical observations,³⁶ such pathophysiological information is often overlooked in the traditional understanding of aortic stenosis, whereby left ventricular dysfunction is conventionally suggested to occur only after the development of severe aortic stenosis.

Unsupervised machine learning also provides a superior characterisation of the risk continuum across different aortic stenosis presentations.^{35,37,38} Such characterisation might aid in identifying patients with aortic stenosis who are at risk of developing clinical events despite non-severe or discordant echocardiographic findings and help reclassify patients more consistently

than the current guideline-recommended aortic stenosis severity groups.³⁷ Another advantage of unsupervised machine learning is that it facilitates the addition of clinical data to echocardiographic information, aiding in comprehensive patient comorbidity assessment—an element often missed when dealing with echocardiography data alone.³⁸ Beyond aortic stenosis, unsupervised machine learning has also been used to reclassify and identify distinct subgroups of patients with mitral and tricuspid regurgitation.^{39–42} Although these novel phenotyping strategies have not been extensively validated, such insights could lead to new grading systems for VHD severity and progression, to improve the timing of intervention.

Artificial intelligence for risk stratification and therapy planning

Machine learning has recently been shown to complement or outperform existing risk models (eg, EuroSCORE II, Society of Thoracic Surgery models, and the National Inpatient Sample TAVR score model) in predicting mortality, prolonged ventilation, and renal failure following valve surgery or interventions.^{43–45} Improved risk stratification will allow health-care providers to more accurately assess a patient's risk of morbidity and mortality when undergoing valve replacement.^{44,45}

Surgical strategy (repair or replacement) mainly depends on the cardiac surgeon's expert assessment. Machine learning can combine the valve characteristics (assessed during preoperative valve analysis and obtained from preoperative and perioperative echocardiographic data) of large numbers of patients and correlate these characteristics with outcomes.⁴⁶ Artificial intelligence can also guide the surgeon or cardiologist in selecting optimal procedural scenarios. For example, automated measurement of the aortic and mitral annulus perimeters, allowing

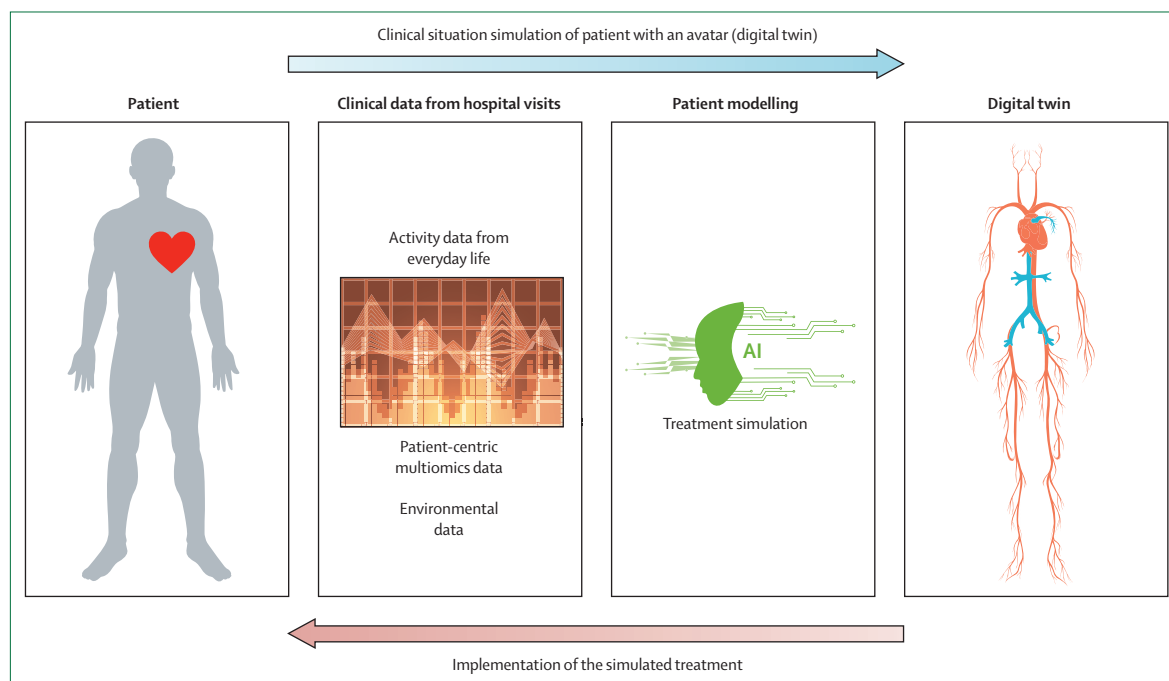


Figure 3: Suggested pipeline for developing, planning, and predicting the efficacy of therapy for valvular heart disease before real-world implementation
 A digital twin of an individual can be constructed using patient-centred multimodal data and used to simulate treatment outcomes, making it possible to predict the efficacy of therapy (blue arrow). Simulation results from the digital twin make it possible to implement the most effective treatment (red arrow), thereby maximising cost-effectiveness and efficacy. AI=artificial intelligence.

the selection of transcatheter aortic or mitral valve implantation, is feasible within seconds and with error similar to or smaller than that arising from interoperator variability.⁴⁷ Similarly, artificial intelligence can rapidly simulate the outcomes of MitraClip (Abbott, Abbott Park, IL, USA) interventions for different scenarios (eg, differing locations and numbers of MitraClips).⁴⁸ Using advanced imaging techniques (eg, real-time intraoperative video kinematic evaluation of the right ventricle), artificial intelligence can also predict right ventricle function following chest closure after pulmonary valve replacement in patients with tetralogy of Fallot, thus providing a decision-making tool to support the medical team during open-chest surgery.⁴⁹

In health care, a digital twin is a virtual representation of an individual generated using comprehensive datasets relating to that individual. The digital twin has become a powerful concept since the emergence of technology to collect patient data (eg, vital signs from smartwatches) during hospital visits and everyday life. Appropriate statistical models are applied to plan treatment and follow disease progression in an individualised manner.⁵⁰ Computational planning using digital twins is a step towards individualising decisions regarding when to offer surgery or intervention, as treatments are often costly or invasive (figure 3; panel 1).

Digital therapeutics provide information and communications for technology-based interventions to manage disease. An example is the application of digital

therapeutics to improve patient adherence to hypertension control.⁵³ In VHD, digital therapeutics-based exercise intervention has shown the potential to optimise outcomes.⁵⁴ Using digital therapeutics and digital twins could reduce the unnecessary expenditure of health resources, facilitate the monitoring of patients with limited health-care access, and maximise the outcomes of costly or invasive procedures.

Limitations and barriers to the adoption of artificial intelligence techniques

Inherent limitations and barriers to implementing digital and artificial intelligence techniques are presented in panel 2.^{56–58} The advent of large language models such as generative pre-trained transformer presents a new opportunity for a democratised artificial intelligence landscape. With billions of parameters, these models enable the handling of complex tasks and excel at transfer learning by fine-tuning their abilities through exposure to diverse data sources such as images and videos. The algorithmic fidelity, ethical implications, and privacy concerns surrounding these architectures have been topics of debate.⁵⁹ Nevertheless, the judicious integration of image-based models with the electronic medical records and outcomes of existing patients could enhance procedure planning and interventional strategy selection by improving creative discussion in heart team meetings and facilitating clear communication with patients.

Panel 1: Digital twins in valvular heart disease: opportunities and challenges

Digital twins offer a promising solution for clinicians and patients in precision cardiovascular medicine, especially when dealing with complex valvular conditions and individual treatment strategies. Digital twins are computational models that serve as avatars of patients and can aid clinicians in optimising treatment options. Digital twins can be constructed by leveraging various imaging technologies, providing insights into valve structure, haemodynamics, and the systemic milieu. Digital twins can facilitate virtual procedures, such as transcatheter aortic valve replacement in severe aortic stenosis, enabling clinicians to establish the optimal placement and sizing of valves and identify potential post-procedure complications, including paravalvular regurgitation.⁵¹ Cloud-based simulation software creates digital copies of the heart and its valves to optimise procedural outcomes.

Digital twins can be used to evaluate borderline cases, such as asymptomatic older patients with severe mitral regurgitation who might or might not benefit from the MitraClip procedure. Using more expansive models of the heart, such as those developed by The Living Heart Project, digital twins can simulate and forecast potential cardiac failure, enabling early valve repair and personalised treatment strategies.⁵² This approach ensures that only patients who require intervention undergo procedures, avoiding unnecessary risks for those who tolerate their condition well.

Although digital twins show great potential, the current models have limitations. These models primarily focus on the structural aspects of the heart and some haemodynamic factors while neglecting the systemic milieu, which can substantially influence valve function. Additionally, the slow evolution of most valvular heart diseases (VHDs) requires serial follow-ups for accurate twin creation, which might not be feasible in the near future. The reliability of digital twins heavily depends on the data used to create them, making them potentially biased, particularly in under-represented populations.

Despite these challenges, digital twins offer considerable room for improvement and development. Digital twins can be valuable tools in clinical practice, especially as technology advances, allowing for more comprehensive and accurate models of VHD. The complexity of cardiovascular structures and patients' unique characteristics highlight the need for personalised treatment strategies, with digital twins potentially playing a vital role in guiding clinicians' decisions.

Although it remains uncertain whether digital twins provide a clear advantage over conventional models in predicting outcomes for diverse populations, ongoing developments and research in this area are promising. As technology evolves and more data become available, digital twins could revolutionise precision medicine and improve individualised cardiovascular care for patients in the coming years.

Therapeutic innovations for VHD

To date, no medical treatment has been shown to prevent or reverse VHD. Furthermore, as VHD is a multifactorial disease involving genetic factors, molecular immune pathways, haemodynamic factors, and shear stress, its pathophysiology is complex. Therefore, the continued search for pathways to prevent VHD progression remains a hot topic due to the important clinical implications of this condition. The accelerating blending of artificial intelligence, digital health, and imaging could aid early VHD detection and timely therapeutic intervention.

Therapeutic pathways for mitral valve disease

Primary mitral regurgitation due to myxomatous degeneration results from the recruitment of monocyte-derived macrophages, which induce extracellular matrix remodelling, causing valve thickening and prolapse.⁶⁰ Various molecular pathways are implicated at a cellular level, but further investigation is needed to identify potential pharmacological targets.⁶¹ Understanding the distinction between syndromic factors (eg, resulting from genetic syndromes) and non-syndromic factors contributing to mitral valve prolapse is essential. For instance, in conditions such as Marfan syndrome, TGF- β signaling could be key, and blocking

angiotensin 2 receptors might limit aortic dilation and the associated progression of mitral valve prolapse.⁶¹

For secondary mitral regurgitation, targets within the extracellular matrix include SERT activity in interstitial cells and serotonin receptor signalling, which accelerate mitral valve remodelling.⁶² Serotonin has been implicated in the development of secondary mitral regurgitation in patients with myocardial infarction.⁶³ Application of cyproheptadine, a serotonin antagonist, in a sheep model of inferior myocardial infarction reduced maladaptive remodelling of the mitral valve, with lower severity of mitral regurgitation in treated animals than in controls.⁶⁴ Although this observation has not been fully validated in clinical studies, elevated concentrations of circulating serotonin have been reported in patients following myocardial infarction,⁶⁵ suggesting a target for future research.

Therapeutic pathways for calcific aortic valve

Calcific aortic stenosis is an active process initiated by inflammatory damage to valvular endothelial cells (VECs), leading to fibrosis and calcification. Aortic valve leaflets comprise three layers: the fibrosa, which is arranged towards the aortic wall; the elastin-rich ventricularis, which is oriented towards the left ventricle; and the spongiosa, the middle layer of the leaflet. Valvular

Panel 2: Barriers to digital and artificial intelligence techniques in valvular heart disease care

Wearable tools and digital health

Wearable technology studies have shown promising results in valvular heart disease (VHD) care but have limitations due to the under-representation of particular populations, study design heterogeneity, and the need for long-term, meaningful clinical results. The COVID-19 pandemic highlighted disparities in telemedicine access, particularly for older individuals, Asian people, Black people, Latinx individuals, non-English speakers, women, and individuals on low incomes. Reproducibility is hindered by varied interventions, differing devices, and evolving technology. Additionally, data quality from wearables faces challenges from technical issues, user-related factors, and the absence of standardisation. Moreover, the digital divide—the growing gap between groups due to unequal access to digital technologies—disproportionately affects older people, disabled people, people with low socioeconomic status, and people living in rural communities. To address these disparities, efforts are needed to improve broadband internet access, the affordability of digital tools, language accessibility, and form accessibility. Tailoring digital health solutions to patient context and communication preferences, promoting digital literacy, and recognising the digital divide as a social determinant of health are essential steps toward achieving health equity. Future clinical studies should focus on under-represented populations and assess the accuracy and validity of wearable devices through structured frameworks to enhance the equitability of digital health.

Artificial intelligence techniques

Machine learning algorithms are inherently susceptible to biases, and the scarcity of high-quality data that include specific patient groups, such as women and people from minoritised ethnic groups, presents a considerable obstacle to patient-centred machine learning research and decision making. Additionally, the black box nature of artificial intelligence algorithms raises concerns about transparency in the decision-making process. Although explainable artificial intelligence methods can provide reasoning for artificial intelligence predictions, these explanations might only focus on specific aspects of the model's decision. In complex cases, the explanations might not be comprehensive enough to fully

capture the reasoning behind a diagnosis or classification. For example, imagers might need to rely on their own expertise to validate or interpret artificial intelligence-generated explanations, adding an additional layer of complexity. Moreover, the successful implementation of artificial intelligence requires skilled professionals who can develop, implement, and maintain artificial intelligence solutions, but health-care organisations might face challenges in recruiting and training staff with the necessary expertise. Finally, the integration of artificial intelligence raises ethical considerations about the potential impact of this technology on patient autonomy and the question of who takes responsibility for artificial intelligence-driven decisions. Ensuring that artificial intelligence adheres to ethical guidelines and regulatory requirements is crucial for building trust in artificial intelligence-driven solutions.

Specific strategies for VHD

The development of robust artificial intelligence tools will require the prospective collection of high-quality data for various heart valve patient groups, including detailed valve-specific data (eg, valve characteristics during surgical valve analysis and imaging data) and complete follow-up. Validations need to be performed in diverse settings, with the inclusion of mortality, morbidity, and valve-specific outcomes (eg, reoperation, recurrent regurgitation, and structural valve deterioration). Furthermore, methods for ethical data collection, data governance, patient permission, and data sharing between institutions with additional privacy and data safety issues are important considerations.⁵⁵ Currently, the EU medical device regulation mandates medical device companies to assess the clinical outcomes of their devices. For example, the Heart Valve Society AVIATOR registry, a network that includes patients with regurgitant aortic valves or root aneurysms, allows clinicians to collaborate with medical device companies to collect high-quality data. If data inclusion in large prospective registries (that include patient-reported outcome measures) becomes a prerequisite for reimbursement, there could be meaningful opportunities to improve real-time clinical decision making for patients with VHD.

For more on the Heart Valve Society AVIATOR registry <https://heartvalvesociety.org/AVIATOR/>

interstitial cells, components of all three layers, undergo fibrogenic and osteogenic transformation after initial inflammatory damage to VECs. In addition, injury promotes the accumulation of lipids, red blood cells, and immune cells, leading to further fibrosis and calcification of the valve leaflets. Hyperlipidaemia and other traditional risk factors for coronary artery disease and atherosclerosis are also associated with calcific aortic stenosis. For example, lipoprotein(a) has been associated with aortic valve calcification,⁶⁶ and a 2020 analysis of the FOURIER trial showed that treatment with a PCSK9 inhibitor, evolocumab, slowed the progression of aortic

stenosis.⁶⁷ To elucidate the role of lipid lowering in reducing the severity of aortic stenosis, studies are investigating the ability of statins (specifically, atorvastatin; NCT02679261), niacin (NCT02109614), pelacarsen (NCT05646381),⁶⁸ and PCSK9 inhibitor (NCT03051360) to reduce lipoprotein(a).

Nitric oxide in VECs plays an important role in maintaining the homeostasis of the valve leaflets. Valve injury depletes nitric oxide, inducing valve fibrosis and calcification by affecting NOTCH1 signalling, which is essential for proper aortic valve development.⁶⁹ In addition, nitric oxide inhibits RUNX2-dependent

calcification,⁷⁰ partly due to NOTCH1 activation. The effect of modifying nitric oxide-dependent pathways in aortic stenosis is being investigated in two clinical trials (appendix p 2; NCT02049203 and NCT02481258). Nitric oxide depletion activates DPP-4, which induces the osteogenic transformation of the aortic valve by limiting autocrine IGF-1 signalling.⁷¹ In addition, there is a sex-related difference in the degree of fibrosis versus calcification of the aortic valve; specifically, in women, there is upregulation of an inhibitor of calcification, which favours fibrosis rather than calcification during the development of aortic stenosis.⁷² In animal and retrospective human studies, inhibition of DPP-4 reduced the progression of valve calcification and fibrosis, and suppressed haemodynamic progression in aortic stenosis.^{73,74} Some DPP-4 inhibitors were found to be associated with slower progression of aortic stenosis in patients with diabetes.⁷⁴ Of these inhibitors, evogliptin penetrated the valve tissues most effectively. Therefore, a phase 2/3 multicentre double-randomised clinical trial (NCT0513177; appendix p 2) is testing whether evogliptin can reduce calcification of the aortic valves and the haemodynamic progression of aortic stenosis.

Another possible mechanism of calcific aortic stenosis is related to bone metabolism. RANKL is involved in the osteogenic transformation of valvular interstitial cells to osteoblasts and reduced secretion of proinflammatory cytokines.⁷⁵ In addition, altered calcium–phosphate metabolism seen in patients with chronic kidney disease has been associated with the development of calcific aortic stenosis. Some observational studies have suggested the role of bisphosphonates in decreasing osteoclastic activity and delaying calcific aortic stenosis.^{76,77} Similarly, warfarin has been shown to promote vascular and valvular calcification by inactivating vitamin K-dependent proteins.⁷⁸ One such vitamin K-dependent protein is matrix Gla, which inhibits the production of hydroxyapatite crystals and suppresses the expression of other osteogenesis-promoting proteins, such as TGF- β and BMP-2. However, despite promising observational data, prospective randomised studies addressing bone metabolism and matrix modulation have yielded disappointing results^{79,80} (appendix p 2), suggesting the need to look beyond these pathways.

Application of multiomics to find new molecular targets in VHD

Notwithstanding guidelines stressing the importance of disease progression in guiding treatment,⁸¹ echocardiography, the pillar of diagnosis for VHD, does not provide insights into whether or how the disease might evolve or suggest new therapeutic targets. The expansion of other domains of multiomics provides insights into the pathogenesis and progression of VHD, suggesting a possible precision approach (panel 3). For example, integrated spatiotemporal transcriptomic and proteomics analysis showed layer-specific pro-calcific,

pro-inflammatory pathways governing valve degeneration in aortic stenosis.⁸⁴

Several molecular targets, some of which are based on multiomics research, are under consideration as targets for novel pharmacological therapies for calcific aortic stenosis; such targets include NOX2, E-NPP 1, P2Y2, CDH11, PPAR γ , IL-6, and FABP4. Insights into therapeutic targets for VHD might come from precision phenotyping and the investigation of newer biological pathways via genomics, the typical starting point of multiomic approaches.⁸⁹ For example, a genome-wide association study identified sortilin—a type 1 membrane glycoprotein encoded by the *SORT1* locus—as a crucial mediator of aortic stenosis.⁹⁰ Similarly, a multiethnic genome-wide association study identified six novel genomic regions from the genetic profiles of individuals with atherosclerosis.⁹¹ With the genotyping of thousands or millions of individuals, the results of clinical trials might be predictable using genotypes as proxies for independent variables in randomised clinical trials (Mendelian randomisation). One example of this approach is the potential utility of lipoprotein(a) as a therapeutic target in aortic stenosis.⁹² Increasing our understanding of (personalised) VHD progression using multiomics approaches might be instrumental in the development of new pharmacotherapeutic targets (panel 3).

Surgical and interventional innovations

Heart valve replacement

Currently used heart valve replacements are either mechanical or biological prostheses. With the rise in TAVR, valve replacement in young and middle-aged patients comes with substantial risks of valve degeneration, reoperation, and mortality.⁹³ Over the past few years, decellularisation methods and anti-calcification treatments have changed, but they have not led to real improvement in outcomes. Both types of prostheses are non-viable substitutes that inherently lack the natural capacity of native heart valves to grow and adapt to changes in the haemodynamic environment throughout life.⁹⁴ New, more flexible, mechanical valves are in various stages of preclinical and clinical testing.⁹⁵ These flexible polymeric heart valves have two essential features. First, they are less thrombogenic and could function without (or with less) anticoagulation. Second, these valves can be used for transcatheter applications because of their flexibility. However, results from clinical trials are still awaited regarding their applicability in routine clinical practice.

For valvular prostheses, the absence of growth and remodelling potential is even more problematic when replacing valves in paediatric patients with congenital cardiac defects (eg, tetralogy of Fallot), who inevitably need reoperations due to somatic growth. In young adults, the benefit of having a viable replacement valve is evident from the improved long-term outcomes reported

Panel 3: Multiomics in valvular heart disease: projections and pitfalls

To date, haemodynamic and structural research have been the main ways of understanding valvular heart disease (VHD). Recent large-scale omics research has provided biochemical and molecular insights into VHD, mainly focusing on aortic stenosis. Proteomics and metabolomics have shown promising potential for stratifying risk and identifying therapeutic targets for VHD. For example, in patients with aortic stenosis who have diabetes, plasma proteomics revealed a pro-inflammatory and pro-fibrotic milieu that might worsen their condition.⁸² Metabolomics showed that higher lysophosphatidic acid concentrations in stenotic valves correlated with faster haemodynamic progression.⁸³ Such findings can help predict which individuals are at higher risk of future adverse events. Moreover, omics studies have identified novel molecular targets for aortic stenosis. Transcriptomics revealed increased *DPP4* transcription in stenotic aortic valves, suggesting the potential of this molecule as a therapeutic target.⁷¹ Inhibition of *DPP4* has shown promise in treating aortic stenosis.⁷⁴

The use of multiple omics domains, known as multiomics, enables a comprehensive understanding of valvular disease, revealing the distinct pathways driving aortic stenosis and carotid atherosclerosis. Recent research using proteomics and vesiculomics (extracellular vesicle proteomics) to analyse biospecimens of human carotid arteries and stenotic aortic valves showed that although atherosclerosis and aortic stenosis share common pathophysiology, distinct pathways drive each condition (eg, Notch signalling in carotid atherosclerosis and Wnt signalling in aortic stenosis).⁸⁴ These findings suggest that although some drugs might work on both atherosclerosis and aortic stenosis, others might only be effective in one of these disease processes. Vesiculomics also provides a basis for developing novel diagnostic strategies, as extracellular vesicles are now the focus of disease monitoring and therapeutic material delivery.

Genomics, the typical starting point of multiomics studies, has also provided new tools for the development of therapeutic targets of VHD, such as the use of genome-wide association studies to predict the results of randomised clinical trials. Human genotypes are inherently randomised as individuals can receive one of two alleles for each gene from their parents. These genotypes can be used as proxies for independent variables in randomised clinical trials, a process named Mendelian randomisation, which can then be used to assess causality. For example, if the effect of statins on aortic stenosis is in question, we could take advantage of genotypes associated with LDL cholesterol, such as *LDLR* or *PCSK9* variants. In addition, although targeting LDL was not proven to be effective in randomised trials,⁸⁵ Mendelian randomisation showed that LDL remained an adequate therapeutic target,⁸⁶ raising questions about the design of former trials to investigate the effects of LDL lowering and suggesting that the use of drugs such as *PCSK9* inhibitors might remain a viable therapeutic strategy.

Despite the novel insights from omics studies, the mechanisms of VHD remain complex. In vitro, computer-based, and animal experimental studies might not accurately reflect human physiology. For example, although lipoprotein(a) has been shown to have a causal effect on Mendelian randomisation,⁸⁷ deeper investigation of an observational cohort showed that lipoprotein(a) was only associated with the initiation of aortic valve calcification, not with its progression.⁸⁸ In addition, although mouse models of aortic stenosis are used to mimic VHD, there are specific differences between mice and humans. For example, aortic stenosis rarely occurs in normocholesterolemic mice and only under conditions of very high hyperlipidaemia, a finding that is substantially different to the scenario in humans. Considering the complex mechanisms of VHD, the results of in vitro, ex vivo, or animal studies should ultimately be complemented with human studies.

when using a pulmonary autograft to replace a diseased aortic valve (Ross procedure), rather than a biological or mechanical prosthesis.⁹⁶ Furthermore, new surgical techniques to wrap or reinforce the autograft might circumvent autograft dilatation. The Ross procedure—the only therapy for patients with aortic stenosis that results in a life expectancy comparable to that of the normal population—might be incorporated in future guidelines as an option for aortic valve replacement in adults younger than 60 years.⁹⁷

In situ heart valve tissue engineering

Inspired by the natural capacity of human heart valves to grow and remodel, heart valve tissue engineering (HVTE) has been pursued to obtain viable valve prostheses without the need for donor tissue. Although technically feasible, engineering an autologous valve in vitro has proven complex. This process is subject to several translational challenges, including the long culture periods required for

cell expansion and tissue formation and the associated logistical and financial costs. Nevertheless, considering the large patient population needing heart valve replacements because of rheumatic heart disease in developing countries, a consensus document was published stating that any new technology should be affordable and broadly applicable.⁹⁸ Therefore, attention has shifted to the more direct in situ HVTE approach (figure 4), rather than implantation of autologous cellularised valves. The in situ approach uses resorbable valvular prostheses that temporarily restore valve function while gradually becoming cellularised and replaced by endogenous new valve tissue directly in the valve's functional site.¹⁰⁵ Such prostheses are available off the shelf and are projected to be cost-effective for paediatric and adult patients, as predicted using early health technology assessment.^{106,107}

One strategy to obtain viable valve prostheses is to use decellularised tissue valves, which can be stored until needed. Upon implantation, the tissue becomes

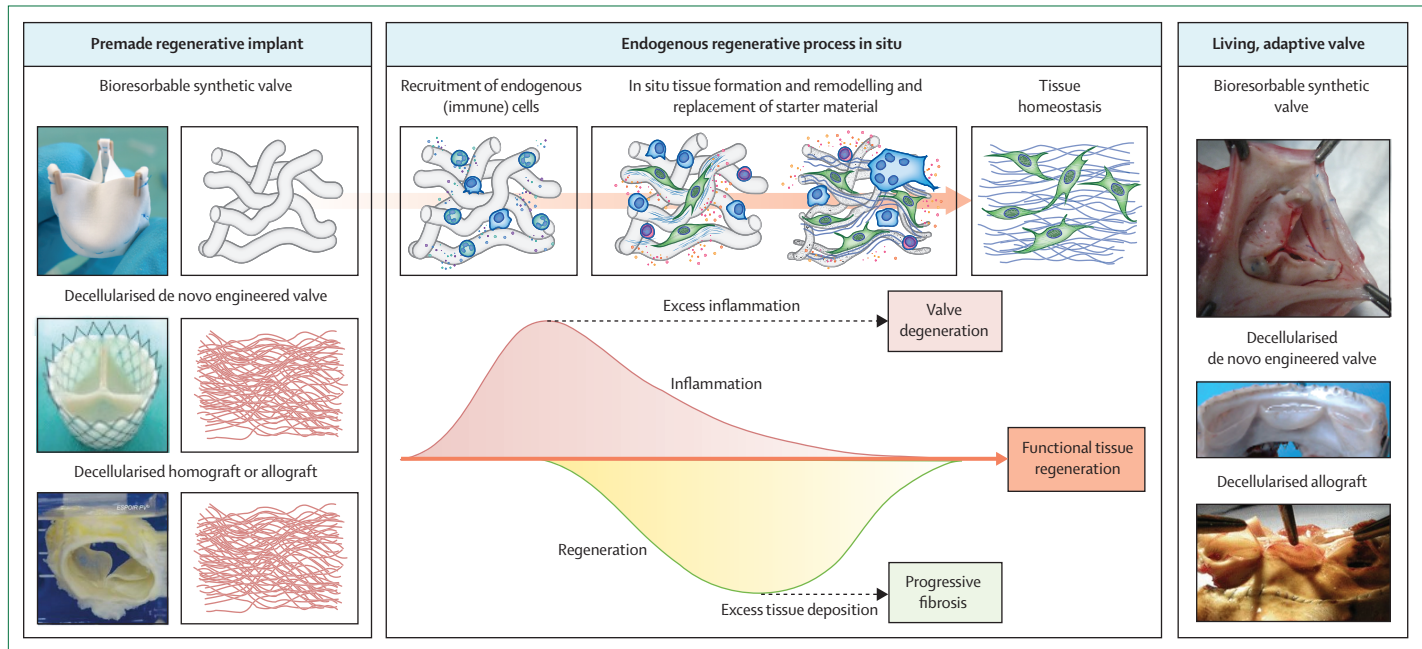


Figure 4: In situ heart valve tissue engineering

Upon implantation, an acellular valvular implant induces an inflammatory response. When harnessed correctly, this inflammatory response triggers a phased tissue regenerative response initiated by the recruitment of endogenous cells, which colonise the porous valvular microstructure. In situ, the cells resorb or remodel the implanted graft material and lay down new endogenous tissue, generating an autologous living valve with the potential to grow and remodel. Schematic adapted from de Kort and colleagues⁹⁹ by permission of the authors. Valve photographs reproduced from Uiterwijk and colleagues¹⁰⁰ by permission of the authors; Kluin and colleagues,¹⁰¹ by permission of the authors; Emmert and colleagues,¹⁰² by permission of the American Association for the Advancement of Science; Boethig and colleagues¹⁰³ by permission of the authors, and Goecke and colleagues,¹⁰⁴ by permission of Elsevier.

recellularised by the patient's cells, enabling growth and remodelling according to the body's needs. For example, decellularised homografts are being evaluated in prospective clinical trials for use as aortic and pulmonary valve replacements in young adults, showing excellent results at 5 years and 2.5 years follow-up, respectively.^{108,109} Thus far, this strategy has only been used for homograft tissue because using decellularised and untreated xenograft valves led to early graft failure and high mortality.¹¹⁰

To avoid the need for donor valves, an alternative approach is to use decellularised de novo engineered tissue valves. These cell-grown valves produced in vitro are decellularised for storage and rapid availability. Such decellularised tissue-engineered valves show rapid repopulation with host cells when implanted in the pulmonary valve position in preclinical studies.¹¹¹ Computational modelling has been used to optimise the design of such valves, showing the remarkable predictability of long-term valve remodelling in vivo.¹⁰² In addition, these valves are compatible with transcatheter delivery.¹¹² The somatic growth of decellularised tissue-engineered valves has been shown in a recent preclinical study using lambs, thereby confirming one of the main goals of tissue-engineered heart valves.¹¹³

Another strategy to obtain a living valve replacement is to use resorbable synthetic valves. These valves comprise a resorbable synthetic valvular mesh that temporarily takes

over valve function. In situ, the synthetic mesh is infiltrated by host immune and tissue cells, leading to the gradual immunological erosion and replacement of the mesh by endogenous new tissue. Preclinical proof-of-concept studies have shown the feasibility of these techniques when using supramolecular elastomeric meshes for pulmonary valve replacement by either surgical or transcatheter implantation.¹⁰¹ These synthetic valves are in clinical trials for right ventricular outflow tract reconstruction in paediatric patients with congenital malformations. Early outcomes from these trials showed that 17 of 18 patients (median age 5 years [range 2–12]) were free of reintervention at 1 year of implantation, with one patient requiring valve replacement due to the development of progressive stenosis of the proximal conduit anastomosis.¹¹⁴

Although preclinical results are encouraging, there are few studies that present long-term remodelling data, and variability in preclinical outcomes has been reported.¹⁰⁰ Given that the outcome of HVTE is heavily dependent on a patient's regenerative capacity and immunological state, a personalised approach might be expected to be required for broad clinical applicability.⁹⁹ To date, tissue-engineered valves have only been tested in situ in small patient cohorts, and the influence of patient characteristics (eg, sex and age) remains to be elucidated. The use of predictive computational modelling, integrated with experimental models and incorporating patient-specific features (ie, digital twins) at both the tissue level (eg, anatomy and

local haemodynamics) and cellular level (eg, immunological and metabolic states), might aid patient-specific in situ HVTE. Effective collaboration between clinicians and engineers is indispensable to ensure that emerging technologies remain centred closely around patient needs and are broadly applicable and affordable.

Conclusions

In the future, the focus of VHD management will be likely to shift towards early detection and monitoring of disease progression through screening techniques. Digital medicine and artificial intelligence techniques applied to wearables, ECG, and miniaturised POCUS could enhance access to care and establish population-wide screening strategies. Artificial intelligence techniques and multiomic approaches could also help identify distinct patient phenotypes with varying severity, pathophysiological mechanisms, and therapeutic targets, thereby overcoming the challenges posed by the underlying biological heterogeneity of VHD progression. Ongoing pharmacotherapy clinical trials might lead to a new era in preventing VHD. The use of large databases and digital twin strategies for patients with established diseases could enable pre-emptive therapy planning. Furthermore, developing next-generation heart valves with repair, remodelling, and regenerative capabilities could revolutionise transcatheter and surgical strategies. Despite the barriers and challenges, these multidisciplinary approaches have the potential to substantially improve the morbidity and wellbeing of many patients worldwide and mitigate the growing burden of VHD.

Contributors

PPS conceived and designed the manuscript. All authors contributed equally to the literature search, manuscript development, writing, and final editing of the content.

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