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REVIEW

Treatment Decision in Aortic Stenosis—Look at the Valve but Do Not Forget the Ventricle

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Abstract

In patients with aortic stenosis, current guidelines recommend valve replacement therapy in case of severe valve narrowing in combination with symptoms and/or left ventricular dysfunction (ejection fraction < 50%). It is increasingly recognized that left ventricular ejection fraction offers a crude interpretation of a complex disease entity that is in need of refinement to optimize the timing of valve replacement therapy and patient outcome. In this state-of-the-art review article, we discuss the pathophysiological transition from left ventricular hypertrophy to other types of cardiac remodeling and myocardial fibrosis in response to progressive narrowing of the aortic valve, and how new imaging developments and biomarkers may help identify patients with a dismal outcome at earlier stages of disease. Also, the digital transformation of health care and novel analytical methods such as artificial intelligence that can help improve treatment decision is evaluated. This is in combination with the increased use of minimally invasive treatment modalities that may fulfill the goal of offering valve replacement in patients with aortic stenosis at earlier stages of disease and prior to the onset of symptoms but nevertheless at risk of left ventricular deterioration.

Keywords Aortic stenosis · Treatment decision · Treatment timing · Digital health

Introduction

Acquired aortic valve stenosis (AoS) is a degenerative valvular heart disease whose incidence increases with age [1, 2]. It exposes the left ventricle (LV) to a progressive increase in afterload, leading to changes in cardiac structure, function, and morphology (remodeling) [3–5]. Typically, the cardiomyocytes respond with an increase in cell size (myocyte hypertrophy) and consequently cardiac mass (left ventricular hypertrophy, LVH). LVH is considered an initially reversible and adaptive process to restore LV wall stress and maintain cardiac function, but may progress to irreversible changes with loss of function and, ultimately, death [6, 7]. This is explained by the fact that, in addition to an increase in myocyte cell size, LVH also entails deposition of collagen in the extracellular matrix, which is the hallmark of myocardial fibrosis [4, 5, 8, 9].

The genetic and molecular mechanisms governing cellular hypertrophy, collagen deposition, and the gross morphologic expression of cardiac remodeling remain poorly understood [10]. They have an insidious onset, which precede clinical manifestations and—when present—are associated with a dismal prognosis (heart failure, mortality) [6].

In general, the indication for aortic valve replacement (AVR) is primarily based upon the assessment of AoS severity in combination with global LV (dys)function and/or symptoms using binary cut-off criteria. Yet, the response of the heart to increased afterload occurs during the early phases of the disease (e.g., moderate AoS) when cardiac structure and function are normal and are presently not incorporated in treatment decision-making. It is conceivable that AVR in these intermediate phases safeguards the

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LV from future (irreversible) deterioration and may be beneficial from a patient and society perspective [11]. This premise has become particularly relevant with the advent and increased use of transcatheter aortic valve replacement (TAVR) that, at variance with surgical aortic valve replacement (SAVR), obviates the need of general anesthesia, large surgical access, cardiac arrest, and cardiopulmonary bypass although transcatheter valve durability is yet to be determined. In this article, we discuss the pathophysiological basis favoring early AVR in AoS and how the digital transformation of health care and novel analytical methods such as artificial intelligence (AI) may help improve treatment decision in a patient-centered approach.

Methods

In this state-of-the-art review, the authors used PubMed as the source of information to extract articles focusing on developments in detecting pathophysiological changes in cardiac function and morphology in response to AoS. Additionally, articles related to the digital transformation of health care and novel analytical methods to enhance treatment timing were analyzed. The abovementioned keywords and the following MeSH terms were used: left ventricular hypertrophy, remodeling, myocardial fibrosis, advanced imaging, echocardiography, cardiac ultrasound, cardiac magnetic resonance, computed tomography, biomarkers, left ventricular dysfunction, digital health, artificial intelligence, deep learning, transcatheter aortic valve replacement/implantation, and surgical aortic valve replacement. The quality and citations of individual manuscripts were reviewed and non-English papers were excluded. A total of 75 articles were published between 2010 and 2022; older articles ($n = 23$) were included because of their historical value related to the natural history and pathophysiological changes in AoS.

Cardiac Performance and Hemodynamics

The function of the heart is to offer and maintain sufficient output of blood to meet the metabolic demands of the peripheral tissues (and itself) for which it needs large quantities of oxygen and adenosine 5-triphosphate (ATP). In normal conditions, ATP is mainly generated via fatty acid oxidation [4, 12]. In case of stress (e.g., increased afterload), the heart switches to other energy substrates via the upregulation of glucose uptake and glycolysis while reducing fatty acid oxidation, thereby mimicking fetal cardiac metabolism, to maintain function [13–15].

Cardiac output depends on the complex interplay between cardiac filling (preload), contractility and arterial resistance (afterload), and the autonomic nervous system [16, 17]. In healthy conditions, LV filling is associated with small changes in diastolic pressure reflecting preserved diastolic function (i.e., myocardial relaxation). In illness such as AoS, the LV is exposed to an increase in afterload and intracardiac pressures and, thus, myocardial wall tension (Fig. 1a, b). The general view is that—in accordance with the law of Laplace [cardiac wall tension (T) = intracardiac pressure (P) × cardiac radius (r)/2 × wall thickness (h)]—the LV myocardium responds with "compensatory" hypertrophy to maintain wall tension within a normal range [7]. However, the concept that LVH is needed to maintain cardiac output is subject of debate as clinical observations reveal that not all patients with AoS have LVH on echocardiography upon presentation [18]. Also, longstanding experimental findings indicate that hypertrophy may not be needed for normalization of wall tension [10, 19].

Myocardial Hypertrophy and Cardiac Remodeling

The heart responds to physiologic (e.g., exercise) and pathologic stress (e.g., AoS) by an increase in cardiomyocyte cell size (hypertrophy) and a change in cardiac morphology (remodeling). Interestingly, the heart has the ability to make the distinction between physiologic and pathologic stress as different molecular and cellular signaling pathways are activated [3, 10, 20]. In clinical practice, the increase in cardiomyocyte cell size cannot be measured. Yet, non-invasive imaging allows the measuring of myocardial thickness as a marker of mass as well as the global morphologic structure and changes (remodeling) of the heart [21].

The effects of myocardial hypertrophy on the ventricular cavity and hence global morphology vary. LVH may be associated with an increase, decrease, or no change in ventricular volume. To account for the proportionality between wall thickness and ventricular volume, distinction is made between three phenotypes of remodeling, namely concentric remodeling, concentric hypertrophy, and eccentric hypertrophy [3]. Concentric remodeling is defined by an increase in relative wall thickness (i.e., wall thickness relative to end-diastolic diameter) with normal cardiac mass (g/m^2). Concentric hypertrophy is defined by an increase in relative LV wall thickness and cardiac mass with little or no change in LV volume due to the addition of sarcomeres in parallel and lateral growth of cardiomyocytes. Eccentric hypertrophy is defined by an increase in cardiac mass with increased LV volume (with normal, decreased, or increased relative wall thickness) due to the addition of sarcomeres in series and longitudinal cell growth. In short, concentric hypertrophy is characterized

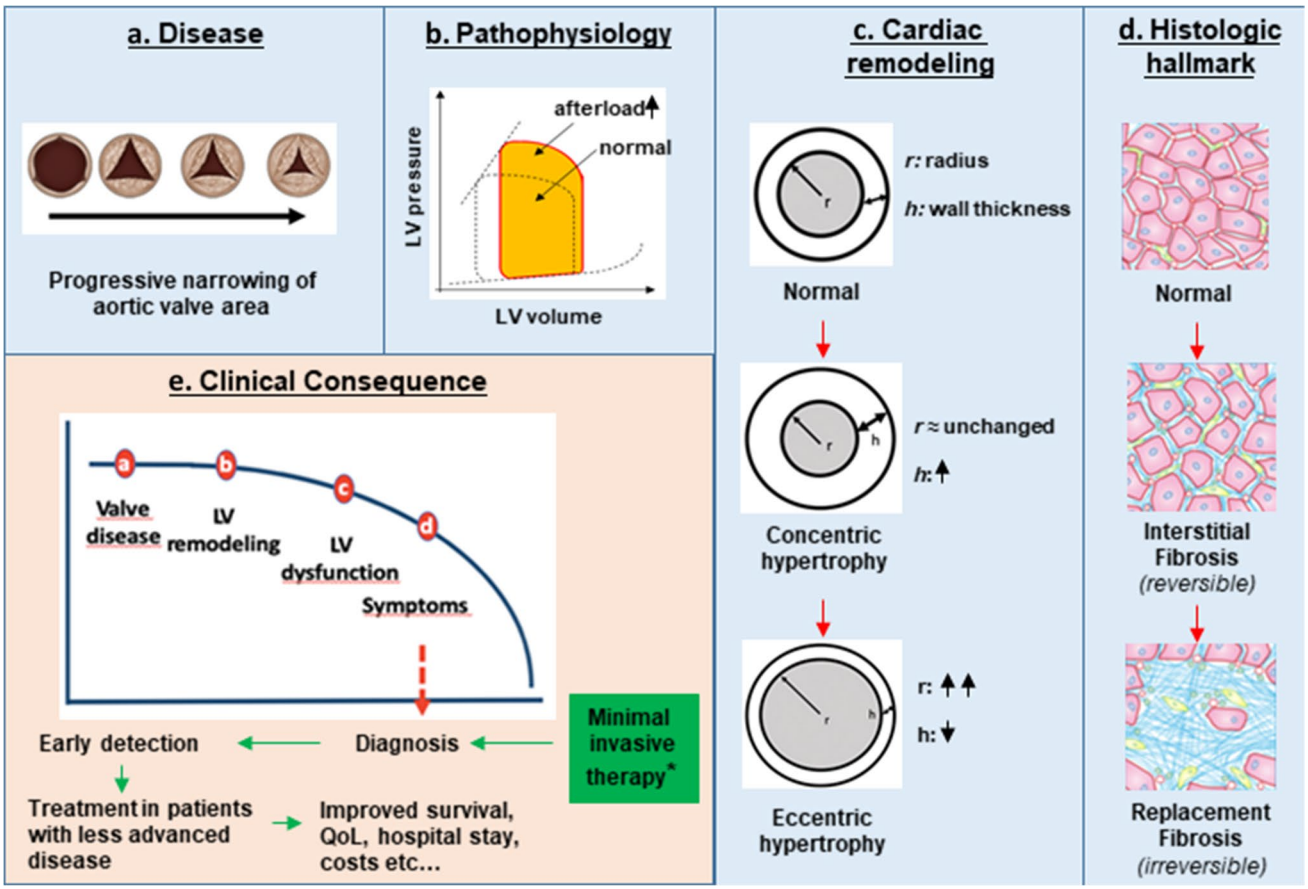

Fig. 1 Natural history of aortic valve stenosis. **a** Morphological features of progressive aortic valve stenosis. **b** Hemodynamic consequences for the left ventricle (increased left ventricular pressures). **c** Myocardial hypertrophy and cardiac remodeling. **d** Histologic hallmark of myocardial fibrosis. The drawing of the histologic hallmark, courtesy: de Boer et al., "Towards better definition, quantification and treatment of fibrosis in heart failure." *European Journal of Heart Failure* (2019) 21, 272–285. **e** Clinical consequences of aortic valve stenosis. Early identification of patients at risk of unfavorable outcome may improve clinical outcomes by the use of minimally invasive therapies at an earlier disease stage. *The concept of providing a minimal invasive therapy (i.e., transcatheter aortic valve implantation) at earlier stages of disease and prior to the onset of symptoms and/or development of (irreversible) myocardial damage cannot be recommended until sound longevity data of transcatheter valves are available (expected in the next 5–10 years)

by an increase in mass with no or little changes in volume while eccentric hypertrophy is characterized by an increase in both mass and volume (Fig. 1c).

The reason why one patient with AoS presents with one type of remodeling or the other and whether or not one precedes the other is unknown. Clinical observations indicate that in addition to the severity of valve stenosis, non-valve-related factors such as age [22], gender [23], and metabolic disorders (e.g., obesity [24], diabetes [25]) play a role in addition to ischemic heart disease [26] and arterial stiffening. For instance, it has been shown that the total amount of LV afterload in AoS (valvular plus arterial component or valvulo-arterial impedance) better correlates with LV wall thickness than AoS severity itself [27].

Myocardial Fibrosis

Cardiomyocytes are embedded within the myocardial extracellular matrix (ECM), which constitutes approximately 25% of the total cardiac mass (Fig. 1d). It is a collagen network produced by fibroblasts with a honeycomb structure surrounding the individual cardiomyocytes and myocardial blood vessels [28, 29]. The ECM provides structural integrity and supports myocardial function via the handling and transmission of mechanical forces during the cardiac cycle.

Upon pathologic stress, fibroblasts [30] and collagen-secreting bone marrow–derived cells [31] differentiate into secreting myofibroblasts, leading to excess collagen

deposition within the ECM which is named myocardial interstitial fibrosis (MIF) [8, 32, 33]. In AoS, MIF is characterized by increased synthesis and deposition of collagen I more than III outweighing their degradation and removal [34]. MIF starts at the subendocardial layer and is initially diffuse and reversible [35]. The expansion of the ECM contributes to myocyte loss, stimulating replacement fibrosis (RF) that occurs at the site of eliminated myocytes and is focal and irreversible [4, 8, 32, 36] (Fig. 1d). According to cardiac magnetic resonance imaging studies in both symptomatic and asymptomatic AoS patients, RF may progress rapidly especially in association with advanced valve narrowing and established RF. Interestingly, upon the first sign of RF, further scarring accumulates as fast as 75% each year impairing myocardial performance and heralding a grim prognosis [9, 37–41]. Although RF seems equally prevalent in older (≥ 70 years) [18, 37, 40, 42, 43] and younger (< 70 years) [9, 38, 39] patients, age remains an important determinant of adverse outcome irrespective of RF [38, 44]. Presence or absence of bicuspid valve morphology seems unrelated to fibrosis development [38, 42].

An early functional or hemodynamic effect of myocardial fibrosis is stiffening of the left ventricle (LV) and, consequently, diastolic dysfunction [33]. The degree of stiffness depends on the amount of fibrosis and the mechanical properties of the collagen fibers. For instance, collagen type I that is more abundant in AoS exhibits greater stiffness due to altered cross-linking than collagen III [34, 45, 46]. In addition, realignment of collagen fibers affects the transmission of force generated by the cardiomyocytes and henceforth systolic function [47]. The varying degree of deposition and cross-linking offers the identification of MIF subphenotypes with different prognostic effects with patients exhibiting severe deposition and cross-linking faring the worst [33, 48]. In addition, myocardial stiffening is also explained by changes in the architecture of the cardiomyocyte cytoskeleton (protein isoforms), a response that varies from patient to patient [49, 50]. Regression of myocardial stiffening generally occurs after afterload correction but is indeterminate.

Myocardial Fibrosis Detection

The premise is that AVR may be beneficial in the early phase of disease to prevent myocardial deterioration, impairment of quality of life, heart failure, and death (Fig. 1e). It implies the tools to detect early (subclinical) changes of myocardial structure (fibrosis) and cardiac function and/or a more refined method of disease phenotyping elucidating which patients are at (increased) risk of LV deterioration or dismal prognosis [9, 42, 43].

Cardiovascular magnetic resonance (CMR) is currently the best tool for non-invasive detection of MIF and RF [51]. MIF can be detected by native (pre-contrast) T1 mapping as T1 times are prolonged in MIF due to the accumulation of water. Yet, clinical interpretation of T1 times is hindered by a significant overlap between diseased and healthy myocardium and dependence upon CMR settings such as field strength and sequence [52]. RF can be detected by the administration of gadolinium, an extracellular contrast agent that accumulates in areas affected by fibrosis reducing T1 times in comparison to regions of normal myocardium [51].

The combination of T1 mapping and late gadolinium enhancement (LGE) allows the calculation of the extracellular volume (ECV) fraction, which is the space occupied by the ECV relative to the cardiomyocyte tissue and reflects the total interstitial space. The relation between ECV and MIF is, however, equivocal [53, 54]. Also, an increase in ECV fraction is a non-specific marker as it is seen not only in AoS but also in myocardial inflammatory and infiltrative disease and ischemia [55, 56]. Interpretation of CMR images, hence, demands the integration of patient demographics (age, gender) and clinical context [57]. LGE and ECV assessments do not provide qualitative information of collagen fibers [54]. This may be achieved with diffusion tensor CMR (DF-CMR) by assessing cardiac microstructure at a cellular level but is currently in an experimental phase [58]. In addition to the need of robust clinical expertise (settings, interpretation), CMR is cumbersome (e.g., patients with cardiac devices and/or claustrophobia), expensive, and not bedside available. Whether cardiac computed tomography (CCT) with iodine-based contrast administration will replace CMR for 3D ECV quantification remains to be seen [59].

Myocardial Dysfunction Detection

At variance with CMR, echocardiography is broadly available, simpler to perform, and—similar to CMR—extensively validated. Accordingly, it is the ideal clinical tool for the detection of disease, its effects on cardiac function and morphology plus evolution. With respect to the evaluation of cardiac function, several markers are available with those of diastolic dysfunction preceding those of systolic dysfunction. They are sensitive but non-specific, thereby requiring incorporation of the past medical history, comorbidities, age, and gender for the proper interpretation of their relationship with disease.

Currently, guidelines recommend LVEF < 50% as cut-point for AVR in some clinical scenarios (AoS with low

flow or asymptomatic AoS) [60]. LVEF is a measure of the volumetric changes during the cardiac cycle and is defined by the end-diastolic minus end-systolic volume (EDV-ESV) relative to the EDV (EDV-ESV/EDV). As such, it is a crude proxy of global cardiac function that, moreover, is affected by the loading conditions of the heart at the moment of assessment (e.g., volume status/preload, blood pressure/afterload), inotropy (e.g., B-blockers), and associated valvular disease (e.g., mitral or aortic regurgitation/LV pre- and afterload) in addition to eventual morphologic changes due to the disease for which the patient is referred for examination (e.g., small cavity size due to LVH in AoS). Also, LVEF does not provide information on regional myocardial function.

For that reason, myocardial strain analysis using speckle tracking echocardiography (STE) may be more helpful [61]. Strain analysis using speckle tracking is based upon the myocardium (speckle pattern) allowing the assessment of motion and deformation (i.e., strain) of different myocardial regions and, as such regional and global and myocardial (dys)function [62, 63]. Strain is the change in dimension of an object (e.g., tissue) from its reference or resting state when subjected to a load. STE offers a multidirectional evaluation of the myocardium in the radial, circumferential, and longitudinal axis obviating the need of beam alignment with the motion direction of the myocardium. Of all STE-derived measures, global longitudinal strain (GLS) is the most robust and reproducible parameter. It measures systolic shortening of the LV wall capable of unveiling functional changes when the LVEF is still normal [64–66]. Yet and similar to LVEF, GLS is a relative measure of global LV function that depends on the loading conditions of the heart (*preload*, *afterload*), contractility, heart rate, and morphologic changes (remodeling) of the heart. In addition, its value is automatically generated by vendor-specific software precluding comparison of values derived from different machines [67].

Instead of measuring deformation (strain), one can also assess the rate at which deformation occurs (strain rate). Strain rate is less dependent on loading conditions but is limited by insufficient reproducibility due to the need of correct alignment of the tissue Doppler signal with cardiac tissue (angle dependency) and spatial resolution[68]. Early findings indicate that the 3D ultrasound shear-wave elasticity imaging for the quantification of myocardial stiffness may help identify patients with AoS at different levels of risk [69, 70]. In the absence of a technique unmistakably elucidating the state and etiology of myocardial (dys)function, the integration of the information derived from various (and serial) imaging techniques (CMR, echocardiography) in combination with patient's history and laboratory findings (below) may at present be the best approach for more refined prediction of symptom onset and outcome and, thus, the timing of AVR.

Blood Biomarkers of LV Wall Stress and Fibrosis

The simplest technique—from a patient and hospital management perspective—for the detection of early myocardial dysfunction and/or fibrosis undoubtedly is the assessment of molecular markers by blood analysis. The most obvious ones are natriuretic peptides that are known to increase in response to pressure overload and cardiomyocyte stretch [71, 72]. This has been documented in patients with asymptomatic AoS and normal LVEF [73, 74]. Elevation of natriuretic peptides in such patients may, hence, reflect an already more advanced state of disease (myocardial dysfunction/fibrosis) suggesting the need of detecting disease at more earlier stages (e.g., aortic sclerosis detected via auscultation during routine GP examination or general health care control programs) and/or the need of markers unveiling cardiac dysfunction at such a stage. Since myocardial fibrosis precedes LV dysfunction, biomarkers of fibrosis may be helpful. High-sensitivity troponin-I (hsTnI) concerns a highly specific marker of myocardial injury that is associated with LGE and impaired outcome (i.e., AVR and death) [75]. As such, hsTnI is used to identify patients at risk for LGE and who might benefit from early AVR in the Early Valve Replacement Guided by Biomarkers of Left Ventricular Decompensation in Asymptomatic AoS (EVOLVED) trial [76]. Other candidate markers are galectin-3 (Gal-3) and collagen biomarkers (e.g., procollagen type III amino terminal peptides), which have been shown to be associated with heart failure and death [53, 77–79]. Their role in the management of patients with AoS remains elusive. Gal-3 did not outperform GLS and NT-proBNP in the prediction of prognosis in patients with AoS, and the correlation of the collagen biomarkers with myocardial fibrosis is subject of debate. This also holds for many other candidate markers including suppression of tumorigenicity 2 (ST2), C-reactive protein (CRP), and growth and differentiation factor-15 (GDF-15) [80]. Similar to other diagnostic challenges in medicine, the diagnostic value of blood biomarkers increments when interpreted in relation with other (clinical) factors. Chin et al. [44] recently demonstrated that hsTnI combined with other routine variables independently predicts presence of myocardial fibrosis and adverse outcome. Based on these variables, they developed the Aortic Stenosis Risk Score with high-risk patients carrying a tenfold higher risk of adverse outcome (death, heart failure, or new symptoms) as compared to low-risk patients, with a median time to event of 1.5 years.

The Role of Digital Health in the Early Detection of AOS

Acknowledging that the early detection of (*reversible*) myocardial fibrosis will remain questionable also when using CMR, one may consider shifting care to the early detection of AoS and its effects on LV performance and upstream cardiac remodeling. Digital health technology (DH) has the potential to revolutionize the early diagnosis of AoS by converging information and communication technologies in health care systems and society [81, 82]. This has become a credible possibility thanks to innovations in the domain of (1) sensors or detection tools of biomedical signals (*invasive*, *non-invasive*, *remote*), (2) transfer and storage of data, (3) analytical methods (*artificial intelligence* (*AI*) and *deep learning* (*DL*) in particular), and (4) computer power (e.g., quantum computing) [83–87].

AI-enabled analysis of the 12-lead ECG and heart sounds are exemplar of how DH can be helpful for the purpose defined above (Fig. 2). Digitization of biomedical signals has namely opened a vast array of novel data engineering (*feature extraction*, *input*) and analysis techniques (*relationship between input data*, *output*) unveiling "hidden" patterns that remain undetected by the human brain [84–86]. Human ECG analysis is based upon a visual semi-quantitative interpretation (*feature extraction plus relationship*) whose accuracy is dictated by experience and expertise. Computer or AI-enabled ECG analysis is based upon a set of predefined rules and, hence, a truncated pattern or feature recognition and assessment of those features with other patient-derived biomedical data (e.g., echocardiography), which is fully automated and unbiased (*no* a priori *hypothesis*). A number of observations have now shown that AI-enabled ECG analysis using DL and convolutional neural networks (CNN) is capable to detect AoS. Moreover, this does not only hold for the detection of AoS but also a host of other cardiac conditions of importance for the management of patients with AoS such as the detection of LVH, LV systolic and diastolic dysfunction, mitral regurgitation, silent atrial fibrillation, pulmonary capillary pressure, and pulmonary hypertension [85–91].

Yet, the performance of those models and, hence, clinical utility depend not only on the AI model and architecture but also on the quality and completeness of the input data as well as the specificities of the population from which the data stem from (*age*, *gender*, *ethnicity*, *baseline demographics*, *antecedents* and *comorbidity*, etc.). These models may in theory detect the measures of interest such as LV hypertrophy and function and markers of upstream remodeling such as atrial fibrillation and pulmonary hypertension in populations these models have been developed. It remains to be seen whether they perform similarly in patients who were

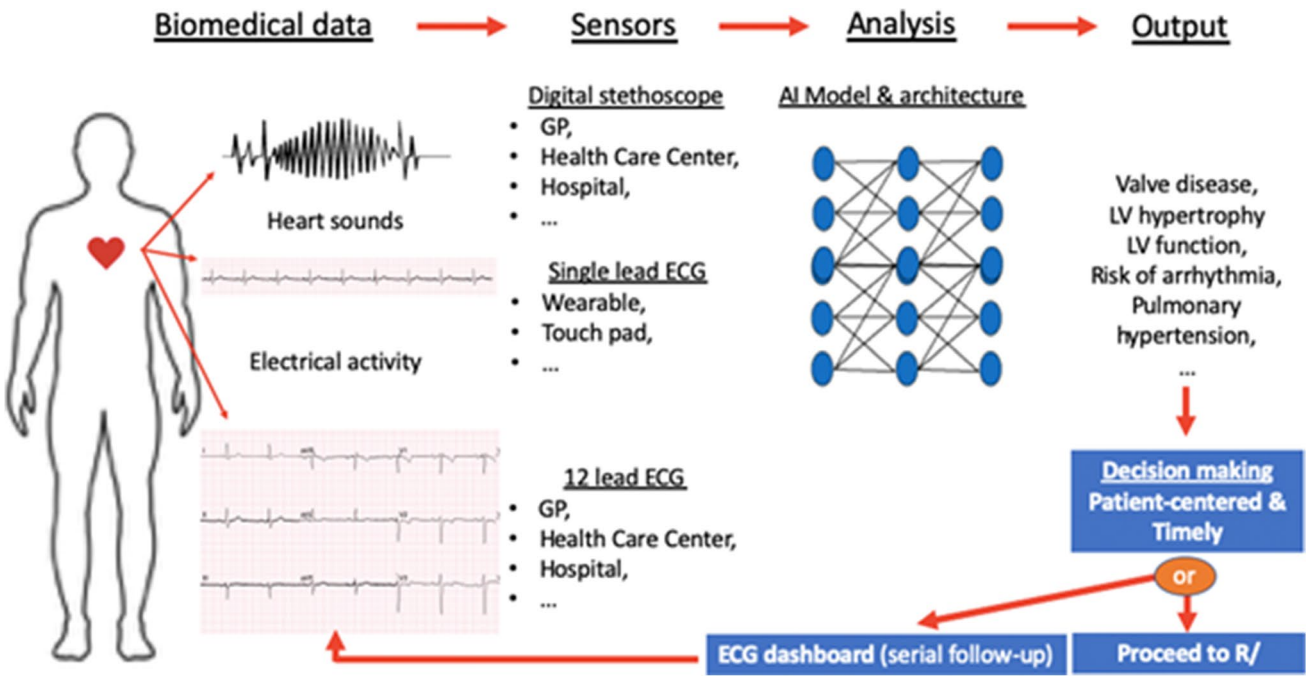

Fig. 2 Role of digital health in the early detection of aortic stenosis. Biomedical data are collected at different locations (at home, GP practice, hospital, etc.) using different tools or sensors. Subsequently, the data are transferred and analyzed to exploit the capacity of artificial intelligence to identify features within these data and their relation with structural heart changes which would normally remain unrecognized by clinical interpretation and/or regular statistical analysis

not used for model development (e.g., seen for a different reason at a different time and region).

Also, AoS is a disease with a relatively low prevalence. Consequently, when applied as an ambulatory screening tool in the general population (i.e., performed by general practitioners), the likelihood of a positive test will be low, of which a substantial number will be false positive. As such, the positive predictive value (PPV) will be low, and the negative predictive value (NPV) high. In other words, these models will serve well to exclude but not to confirm AoS. Unawareness of a high false-positive test rate may overwhelm the health care system by an inappropriate referral for echocardiography. This may be circumvented by the ambulatory AI-enabled heart sound analysis using the digital stethoscope (comparable to the expert cardiology heart sound analysis (Chorba et al., deep learning) to stratify patients for echocardiography and cardiology consultation in case a murmur is classified as AoS) (Fig. 2, [90, 92–94]). In the absence of such a murmur, patients with a false-positive test result might be followed more carefully since they are at a greater risk of developing AoS than those with true-negative test result [90].

As mentioned above, the current practice of the management of patients with AoS is guideline-based using cut-off values for treatment decision that in turn stem from survival data from populations in which all patients are considered similar based upon the presence of AoS. This is known to be a simplification of a complex reality. AI has been used to differentiate various subgroups of patients with a similar degree of AoS but with different prognoses or disease progressions. With respect to prognosis, three subgroups of patients with AoS were identified by cluster analysis: one with predominant cardiac dysfunction and high cardiovascular mortality, one comprising mostly elderly patients with prevalent comorbidities and increased cardiac and non-cardiac mortality, and a third subgroup of mainly "healthy" AoS patients with the best prognosis [95]. In high-risk patients with AoS such as those with concomitant pulmonary hypertension, cluster analyses identified subgroups with different prognoses based on alterations in left and right heart morphology [96]. With respect to disease progression, two pathways from mild-to-severe AoS have been uncovered by topological data analysis using cross-sectional echocardiographic data: one associated with preserved LV function and little LVH and the other with depressed LV function and increased LV mass [97]. Upstream adverse cardiac remodeling beyond the left ventricle (mitral valve apparatus, pulmonary circulation, tricuspid valve and right ventricle) is associated with impaired clinical outcomes [98]. These findings suggest that different molecular adaptive mechanisms may be involved in AoS progression and that different phenotypes are associated with different degrees of myocardial disease across the spectrum of AoS severity. AI may, thus, help refine treatment decision by offering AVR to those at risk of adverse events. In those with a benign prognosis, serial ECG assessment allows the creation of a patient-specific dashboard that helps expose a change in risk and, hence, timely treatment decision-making (Fig. 2). Whether an AI-enabled approach with its intrinsic limitations mentioned above and its complexity to execute will outperform regular echocardiographic follow-up remains to be determined.

In summary, we propose that adequateness of AoS treatment is based on specific individual characteristics and disease/patient interaction, thereby relying on the identification of those patients who will benefit the most from invasive treatment (utility vs. futility) as well as the appropriate time of intervention (early invasive vs. watchful waiting) in order to improve prognosis. In the foreseeable future, TAVR (relative to SAVR) may become the preferred therapy for AoS in lower risk patients at earlier stages of disease to prevent irreversible cardiac damage. In the absence of sound data on transcatheter valve durability, however, this cannot be recommended in contemporary practice yet. Identification and characterization of fibrosis in AoS patients may provide important prognostic clues, but adequate tools for this assessment are currently neither adequately validated nor ready for widespread use (availability, cost). Furthermore, although this information may shed some light in disease pathophysiology and progression, their implications in treatment (i.e., treatment/disease/patient interaction) are not clear and therefore, at the present time, treatment decisions should rely on the early detection of the disease through refined diagnostic tools such as the automatic ECG analysis together with automatic auscultation and accurate disease characterization and phenotyping. This, however, would implicate strict protocols that address appropriate referral for echocardiography to avoid overloading of the available resources. Given the likelihood of high sensitivity but low specificity of these diagnostic tools, it may be reasonable to combine both the automated ECG analysis and the smart stethoscope and refer for further testing only those with both tools pointing towards a high probability of severe AoS. Regardless, clinical expertise should always be above any AI tool and physicians should be aware that patients' symptoms and clinical evaluation may warrant further investigation irrespective of screening results. Finally, the success of envisioned DH programs including the AI-enabled analysis of data collected by simple diagnostic tools to detect AoS at earlier stages will depend on the quality and robustness of such DH programs that will still need to demonstrate clinical benefit and cost-effectiveness and promote equity. In addition, the creation of awareness of VHD in the community and among physicians remains pivotal in the proper management of this health care problem in addition to research on pharmacological approaches to temper disease progression [99].

Author Contribution All authors met the following three criteria: (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; and (3) final approval of the version to be published.

Data Availability Not applicable.

Code Availability Not applicable.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication All authors consented for publication of the manuscript.

Conflict of Interest The authors declare no competing interests.

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