Patient screening for early detection of aortic stenosis (AS)—review of current practice and future perspectives

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Abstract: In Europe, approximately one million people over 75 years suffer from severe aortic stenosis (AS), one of the most serious and most common valve diseases, and this disease burden is increasing with the aging population. A diagnosis of severe symptomatic AS is associated with an average life expectancy of 2–3 years and necessitates a timely valve intervention. Guidelines for valve replacement therapy have been established but only a proportion of patients with symptomatic AS actually receive this life-saving treatment. The decision for valve intervention in asymptomatic patients with severe AS is often more challenging and likely results in fewer patients receiving treatment in comparison to their symptomatic counterparts. This article reviews the epidemiology and clinical manifestations of AS, the associated economic burden of AS to the healthcare system, the diagnosis of AS and the possible mechanisms for the introduction of routine screening in elderly patients. Elderly patients typically visit healthcare providers more frequently than younger patients, thereby providing increased opportunities for *ad hoc* AS screening and this, along with raising patient awareness of the symptoms of AS, has the potential to result in the earlier diagnosis and treatment of AS and increased patient survival.

Keywords: Aortic stenosis (AS); valvular heart disease; transthoracic echocardiography (TTE); auscultation, screening

Introduction

The burden of heart valve disease (VHD) is rising due to an increased life expectancy in the elderly population (1-4). Degenerative aortic stenosis (AS) is associated with a high mortality if diagnosed late and if no valve replacement therapy is performed (5). In patients with an established diagnosis of AS however, only two-thirds of those meeting guideline recommendations for valve replacement therapy actually receive treatment, with failure to intervene due mostly to an overestimation of the risks involved, underestimation of symptoms or misclassification of the severity of stenosis (6,7). Recent data shows that most patients are only diagnosed when they develop symptoms, as this precipitates referral of the patient for echocardiography (8). Valve replacement therapy may have
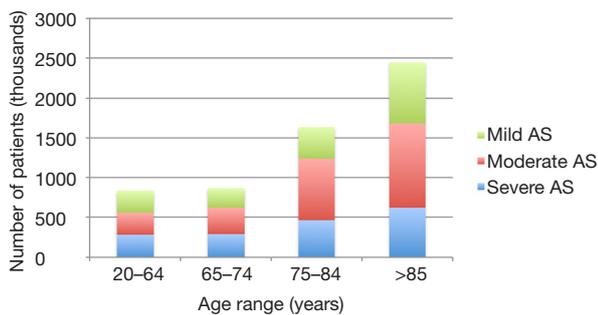
Figure 1 Estimated number of patients in Europe with severe, moderate and mild AS (Edwards Lifesciences, data/references on file). AS, aortic stenosis.

been indicated in a subset of these patients even before the onset of symptoms, not only in those with impaired left ventricular ejection fraction (LVEF <50%) or in those whom exercise testing unmasks symptoms but also in those with very severe AS (V_{max} >5.5 m/s), severe valve calcification and evidence of fast progression, pulmonary hypertension or markedly elevated brain natriuretic peptide (BNP) levels (9). Furthermore, there is accumulating evidence for the clinical benefit of early intervention in all patients with asymptomatic severe AS (10,11) as symptom-onset may well represent an arbitrary timepoint in the course of the disease (12). Certainly, outcomes deteriorate in proportion to myocardial response, particularly where there is replacement fibrosis, and recovery is sub-optimal in these patients (13). As AS follows a long indolent course over years during which patients are unaware of their condition and mortality rates increase dramatically soon after onset of symptoms, both patient and physician awareness need to be increased and methods of early diagnosis rates and referral need to be improved (14). The first presentation of AS is frequently in the primary care setting and, as a result, family physicians/general practitioners (GPs) play a key role in timely diagnosis and referral of patients with suspected VHD (15). The following article tries to evaluate the status and future perspectives of patient screening for AS.

Clinical aspects and burden of AS

Clinical presentation and epidemiology

Moderate or severe VHD is present in approximately 13% of patients aged ≥75 years, with the most common conditions being AS and mitral regurgitation (1). According to a recently published meta-analysis, 12.4% of subjects aged >75 years suffer from AS and 3.4% from severe AS (4). AS develops over years and shares commonalities with the pathophysiology of atherosclerosis, where an inflammatory process leads to progressive leaflet-thickening and calcification (sclerosis) with an associated narrowing of the aortic valve orifice and increase in afterload (16). Patients with bicuspid aortic valves, the most common congenital cardiac anatomy (with a prevalence of approximately 1%), are prone to accelerated valve calcification and make up the majority of the population undergoing valve replacement therapy below the age of 60 years (17). Based on echocardiographic findings (transvalvular gradient, flow velocity and effective orifice area), the degree of AS usually progresses as an asymptomatic condition from mild or moderate to severe. The occurrence of typical symptoms in patients with severe AS (shortness of breath, angina and dizziness/syncope) is usually considered the appropriate timepoint for intervention as the maximum life expectancy in these patients is about 5 years and disease mortality exceeds the peri-operative risk of valve replacement intervention (5,9). Although most patients are symptomatic by the time of diagnosis, a major problem is that the symptoms patients' typically exhibit are not specific for AS, and are frequently attributed to other common conditions of the elderly, especially chronic obstructive pulmonary disease (COPD), ischaemic heart disease or neurocardiogenic syncope (4,18). The threshold for screening and referral, therefore, must be low.

Burden of AS to the healthcare system

AS is associated with a significant financial burden to healthcare systems. Published evidence on AS diagnosis rates are sparse, but assumptions can be made based on AS prevalence data from population-based studies. The estimated number of cases of severe, moderate and mild AS in Europe is shown in *Figure 1*. In the US, AS accounts for an estimated 1.5 million patients—about 500,000 patients with severe stage disease and 250,000 patients with symptomatic disease (19). This burden of disease will increase further with ageing of the population. According to a recent analysis by Moore *et al.*, aortic valve disease is associated with an estimated 10.2 billion USD incremental annual healthcare spending, including 10,816 USD/year per asymptomatic patient and 12,789 USD/year per symptomatic patient in the US (20). A

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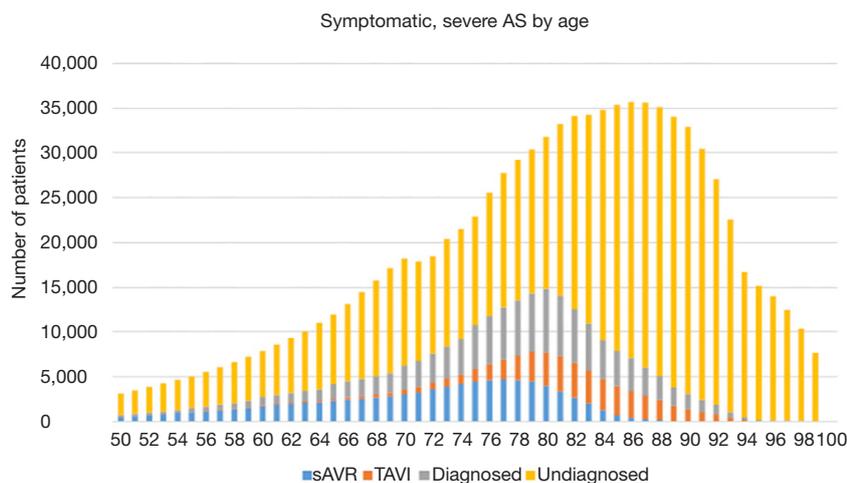
Figure 2 Estimated number of patients being diagnosed with severe symptomatic aortic stenosis in the European Union by age and the proportion of patients remaining undiagnosed or undergoing SAVR or TAVI (Edwards Lifesciences, data/references on file). SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; AS, aortic stenosis.

European perspective on direct costs of AS is provided by Veronesi *et al.*, who compared the cost of illness for a period of 2 years before an index hospitalisation for AS with costs of the two subsequent years in a cohort of 919 patients hospitalised between 2007–2011 in Italy. In patients who received surgical valve replacement, direct costs decreased from 28,365 EUR to 8,002 EUR after the intervention, indicating a significant cost burden of untreated severe AS patients (21). Patients with severe AS are costly to care for due to repeated hospitalisation and the need for heart failure therapies (cheap generics*)* (22).

AS: awareness and diagnosis rates

The biggest catalyst for the implementation of successful disease screening measures is to increase public, patient and physician awareness of AS. According to a recently published survey in almost 9,000 subjects aged ≥60 years across nine European countries, only 2% of the respondents expressed concerns about VHD. In contrast, 28% of study patients were concerned about cancer and 25% about Alzheimer's disease. When patients were asked about their knowledge of AS, 92% of respondents had no knowledge of the condition or provided an incorrect definition. Interestingly, when provided with information about AS, about 5% of patients reported greater level of concern and had recognised symptoms in themselves (23).

The low awareness of AS symptoms and their importance was confirmed in another study of patients after diagnosis with severe AS, in which only 27–56% reported awareness of 1 of 3 main AS symptoms (shortness of breath, angina and dizziness/syncope), 69% reported awareness of two symptoms and only 16% reported awareness of all three symptoms (24). As the occurrence of symptoms usually defines the timing of valve replacement therapy in patients with severe AS, a low level of symptom awareness in previously diagnosed and undiagnosed patients could contribute to undertreatment or a significant delay in treatment and premature death (*Figure 2*). With this in mind, a variety of patient awareness campaigns are underway to help patients with the early identification of typical AS symptoms (25).

Diagnostic evaluation

Patients presenting with symptoms of advanced AS, including angina, dyspnoea and syncope, have a much higher mortality rate than asymptomatic patients. When patients present as a medical emergency, an initial diagnostic work-up should include an electrocardiogram, complete blood count, basic metabolic profile, coagulation studies, troponin, BNP and a chest radiograph (26). Essential diagnostic tests for AS, which can be performed in any medical environment, are auscultation and transthoracic echocardiography (TTE),
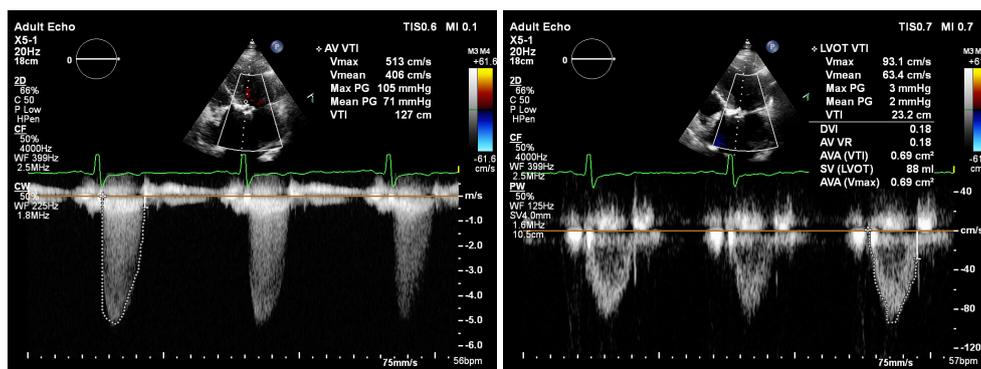
Figure 3 Echocardiology images for aortic valve sclerosis (left panel) and severe aortic stenosis (right panel).

which are discussed in detail below.

Auscultation

Chest auscultation represents an important tool to support the diagnosis of suspected heart valve disease. However, the widespread use of echocardiography over the past decades has led to a decline of the utility of auscultation in primary care institutions. AS characteristics, as detected by auscultation, are mid-systolic, diamond-shaped murmur, which radiates along the aortic outflow tract (right-sided subclavian region) with a maximum intensity in the area of the right upper sternal border. In some patients, a characteristic systolic murmur can also be detected at the level of the apex (Gallavardin phenomenon), which could erroneously raise suspicion of mitral valve disease. Progressive AS is associated with changes in the characteristics of the S2 (paradoxical split or softening of murmur). There appears to be a suboptimal correlation between the intensity of the systolic murmur and the severity of AS, as systolic or diastolic function might deteriorate over time, resulting in a decrease of the ejection fraction (27). A high-pitched systolic ejection click can be detected in some patients with bicuspid aortic valves. Unfortunately, there are very few published data on the relationship between findings on heart murmurs and their echocardiographic correlation with AS. In a subcohort of the OxValve population cohort study, 251 patients without previous diagnosis of VHD underwent cardiac auscultation by two GPs and findings were compared to TTE in an investigator-blinded evaluation. Auscultation was shown to have a sensitivity of only 32% and specificity of 67% for diagnosing mild VHD, which increased to 43% and 69% for significant VHD, respectively (28). Interestingly, clinical examination—despite its limitations—may have a predictive value in terms of outcome in AS. Bodegard *et al.* studied a cohort of apparently healthy middle-aged men (aged 40–59 years), including 23.4% subjects with systolic murmurs, followed for up to 35 years. In those subjects with a low-grade murmur, there was a 4.7-fold, age-adjusted increase in risk of aortic valve replacement and an 89.3-fold increase in risk for those with moderate-grade murmur (29). When asked about cardiac auscultation performed by their GP, approximately half of the male patients and one-third of the female patients (<60 years of age) reported auscultation at every, every second or every third visit (23). These data were confirmed by data from a recent survey in 153 GPs from France, Germany and the UK, where only 62% performed auscultation routinely in elderly patients. In the UK and Germany, cardiac auscultation in symptomatic patients was only performed in 38% and 40% of elderly patients, respectively (30). These findings suggest that there may be a significant proportion of patients in any practice who have valve disease that is undetected and they are not, therefore, referred for echocardiography (31).

Echocardiography

Echocardiography is the primary tool for diagnosis, evaluation and risk stratification of valve disease. As most valve pathology develops gradually over time, echocardiographic screening can deliver accurate detection and risk stratification of patients at all stages of disease. Even when aortic sclerosis rather than stenosis is found (see *Figure 3*), which is present in one out of four persons

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aged ≥65 years and nearly half of patients aged >80 years (32,33), this may lead to improved patient care. Although previously thought to be benign, the degree of calcification in aortic sclerosis both predicts risk of progression to AS and also reflects increased cardiovascular risk due to atherosclerosis (34-37). Furthermore, systematic screening with echocardiography in the community not only identifies valve disease but also cardiomyopathy and heart failure. Based on echocardiography performed in >6,000 randomly selected patients aged >45 years from 16 GP-practices in the UK, 26% of patients were diagnosed with VHD and ~3% of patients with unheralded heart failure (38).

Patient referral

Once a patient has been diagnosed with severe AS, the treating clinician should adhere to treatment guidelines and refer the patient for intervention. However, several studies have reported non-adherence to clinical guidelines and have cited discrepancies between the decision to treat patients and current scientific recommendations occurring in up to 42% of patient cases (7,39-42). Reasons cited for non-adherence for to treatment guidelines included over and under use of AS interventions and lack of diagnostic data to make an informed treatment decision (40). Results of the IMPULSE Study, which is gathering data over a 12-month period on physician decisions to treat patients with newly diagnosed severe AS, is eagerly awaited and could help to serve the creation of a clinical care pathway to improve the timely management of these patients (8).

Feasibility and effectiveness of as screening in general practice

General considerations

Systematic disease screening in the primary care setting appears to be a valuable opportunity to identify patients with VHD and, in particular, AS (31). In Germany, 43% of 420,000 practicing physicians work in ambulatory care and each of the about 60,000 GPs is visited by an average of 243 patients/week (43). In the US, 52% of all patient visits are recorded in the primary care setting. In the age-group of patients aged ≥75, 89% of patients had visited their physician at least once within the previous 6 months (86% of patients in the age group of 65–74 years) (44). These numbers indicate a high intensity of patient-GP

interaction in the elderly population and these interactions are, therefore, a significant opportunity for the detection of undiagnosed VHD. However, there appears to be an impact of patient age on the patient-physician interaction in primary care, as older patients receive less counselling, are asked fewer questions, are less often provided with health education and are more often monitored for treatment compliance only (45). Furthermore, data from the US National Ambulatory Care Survey (1997–2010) reveals, that medical specialist primary care physicians take care of older patients (mean age 61 years), managing mostly chronic disease (51%), whereas generalist primary care physicians treat younger patients (mean age 55.4 years) dedicating their time to the care of new health problems (40.5%). Generalist primary physicians might not, therefore, encounter in daily practice a high number of patients where VHD is likely to be present (46). Still, disease screening measures for cardiovascular and non-cardiovascular conditions, such as arterial hypertension, diabetes or prostate- and colorectal cancer are well-established in the primary care setting as non-invasive diagnostic tools are readily available and screening measures are not considered as time-consuming or costly (47-50). However, the usefulness of any disease screening measure in an elderly population needs to be thoroughly assessed based on the expected disease prevalence in a particular age group, costs and feasibility of screening (for example, level of invasiveness and time-consumption) as well as an evaluation of potential patient benefits from existing treatment options for a particular condition, but also in light of patient comorbidities, expected effects of treatment on life-expectancy and quality of life. Generally, a high level of sensitivity and specificity is required to ensure that a condition is not missed or erroneously suspected in a considerable number of patients—with an associated impact on patient health and costs (51). Data from Germany suggests, that patients aged ≥65 years of age make up 32% of all visits to primary care physicians (19% for patients aged 65–74 years and 13% for patients aged ≥75 years), indicating that a GP in Germany has about 320 patient encounters per month with a patient aged >65 years and about 120 encounters with a patient aged ≥75 years of age (43,52). Based on an AS-prevalence rate of 12.4% in subjects >75 years of age, an estimated 15 patients with any grade of AS and four patients with severe AS could be potentially identified with dedicated measures on a monthly basis in general practice (4).

Screening for AS symptoms and cardiac auscultation

Systematic screening for symptoms in elderly patients represents the most simplistic approach to the diagnosis of advanced stages of AS. Even though, typical AS symptoms can be of multiple origin, it has been shown, that dizziness/pre-syncope results in the majority of cases from cardiovascular conditions (57%) and less frequently from other reasons, such as adverse drug effects (23%), peripheral vestibular disease (14%) and psychiatric illness (14%) (53). Dyspnoea represents the reason for ~1% of all non-procedure-related visits of patients >65 years of age to GPs in Germany (52). Dyspnoea in general practice can be attributed in about 50% of cases to acute respiratory infections, bronchial asthma or COPD, but only in about 4–6% of cases to heart failure and up to 2% of cases to cardiac arrhythmias, conditions which do potentially coincide with AS (54). Patient visits in general practice are due to chest pain/angina in up to 3% of cases, the majority of which occur in the patient group of 45–64 years of age (39.3%), followed by patients aged 65–74 years (18.5%) and patients aged >75 years (12.2%). With up to almost half of all visits caused by musculoskeletal problems, cardiovascular conditions represent the second most frequent reason for chest pain/angina (55). As chest pain in patients with AS is usually the result of reversible myocardial ischemia due to macro-/microvascular disease, the diagnostic pathway needs to rule out other pathological conditions first, in order to establish the diagnosis of AS as the underlying cause (56).

For decades, stethoscopes have been essential tools in clinical patient evaluation. However, data from the US, Canada and UK indicate, that a correct assessment of a heart murmurs was only made in about 25% of patients by internal medicine residents, indicating a lack of emphasis for auscultation in teaching and practice (57,58). On the other hand, accurately diagnosed abnormal auscultatory findings are not necessarily confirmed by echocardiography as shown by McBrien *et al.* In almost 4,000 patients undergoing hip surgery, a systolic murmur was detected in 22.7% of cases, but a diagnosis of AS could be only confirmed in 30% of patients by echocardiography (65.4% mild, 23.5% moderate and 11% severe) (28,59). Even though the overall sensitivity of cardiac auscultation appears low for diastolic murmurs (0.21–1.00), sensitivity for systolic murmurs is higher (0.67–1.00), supporting the usefulness of auscultation as a relevant diagnostic tool particularly for the detection of patients with AS (58). Another relevant limitation of the utility of cardiac auscultation in general practice is the timing of a patient-physician interaction in daily clinical routine, which appears to be in the range of 10–20 minutes in 75% of visits (60). As auscultation mandates an appropriate preparation—such as a warm/quiet room, an examination table/bed and a sufficiently exposed patient chest—and the short patient-physician interaction does not necessarily support a skillful auscultation with the objective to identify VHD (61).

Echocardiographic AS-screening—innovative concepts

As growth of healthcare expenditure is on the agenda of healthcare providers and payors, the overuse of costly diagnostic measures represents one of the areas of concern. On the other hand, the routine use of handy echo devices like the VScan should be on the agenda of medical education early on just like using the stethoscope. But, in most countries, performance of imaging is increasing at a rate of >10%/year (62) and cost of a TTE varies significantly between £66–425 in the UK and >2,000 USD in the US (63,64). Furthermore, there is often limited capacity for performing an echocardiogram in a timely manner. Even though the majority of echocardiographic studies ordered in the primary care setting appear to be appropriate, only about 20% of patient abnormalities are detected and only 2.5% findings were consistent with the suspected diagnosis and led to a change in patient management (65). Generally, echocardiographic screening should be restricted to symptomatic patients in order to increase the likelihood of detecting relevant cardiac pathologies (66). As degenerative AS is a disease of the elderly, systematic echocardiographic evaluations should mainly focus on subjects aged 65 or older, when the prevalence of AS starts to rise significantly (1). Routine-screening, therefore, could be targeting facilities such as nursery homes or institutions of assisted living, where mobile heart scanning clinics could be run by certified nurse practitioners or non-medical health professionals who are educated in echocardiography (67-69). Another promising approach represents patient screening during dedicated flu vaccinations in primary care, where the value of echocardiography screening is being tested in ongoing studies. For these settings, various mobile (miniaturised) echocardiogram devices are commercially available, allowing for earlier disease detection, triage improvement and facilitation of patient referral (*Figure 4*). However, even though these devices allow for a limited, but quite reliable echocardiography assessment of some conditions,

Figure 4 All-in-one handheld echocardiogram devices with electronic transducers [Chamsi-Pasha *et al.* (70). (A,B) Vscan with dual probe (A) and Vscan Extend (B) (image courtesy of GE Healthcare, Wauwatosa, WI); (C) Acuson P10, © Siemens Healthineers 2017 (used with permission), Siemens Medical Solutions Inc., Malvern, PA; (D) Iviz; (E) 180 Plus; (F) iLook; (G) Nano-Maxx (D,E,F,G images courtesy of FUJIFILM SonoSite Inc., Bothell, WA); (H) uSmart 3200T (image courtesy of Terason Division, Teratech Corporation, Burlington, MA); (I) Sonimage P3 (used with permission), Konica Minolta Healthcare Americas, Inc., Wayne, NJ.

the evaluation of VHD still represents one of the most limited functions in terms of correlation with TTE, mainly due to a lack of spectral Doppler and a lower image resolution (71). On the other hand, studies suggest the highest level of sensitivity for the detection of valvular stenosis with these hand-held devices (72).

As limitations in the accessibility to an echocardiogram performed by an experienced echocardiographer do exist, novel concepts of machine learning have shown promising results. Learning algorithms introduced into medical image analysis software could help not only to locate standard heart views but discriminate physiological from pathological conditions, thereby facilitating accurate image acquisition and interpretation in examinations performed by less-experienced personnel (73). While currently existing applications mainly enable an assessment of ejection fraction, myocardial wall motion and myocardial strain, their usefulness in the assessment of VHD has been only

described for mitral valve disease so far (74,75).

Conclusions

Severe AS is a common, but serious, complication that affects more than one million people aged ≥75 years in Europe and with an aging population the number of cases of severe AS will keep increasing (4). Without valve replacement therapy, patients with severe, symptomatic AS face an average life expectancy of 2–3 years and an increased risk of sudden death (76-78). More can, and needs, to be done to mitigate the impact of AS on society and the associated financial burden on healthcare resources. The first challenge is to increase the timely diagnoses of AS. Possible avenues to achieve this include the implementation of a screening programme in the elderly during visits to GPs or in residential care and/or raising awareness of disease symptoms in the patients themselves to open dialogues with their GPs/clinicians. Once diagnosed, physicians should follow treatment guidelines to ensure approach patient management, although currently only a proportion of patients are managed in this manner (40,79), but the creation of clear care pathways might improve adherence to treatment regimens.

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Footnote

Conflicts of Interest: M Thoenes and J Kurucova are employees of Edwards Lifesciences. The other authors have no conflicts of interest to declare.

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