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Multimorbidity in Older Adults with Aortic Stenosis

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Synopsis

Aortic stenosis is a disease of older adults, many of whom have associated medical and aging-related comorbidities. With the aging of the population and the emergence of transcatheter aortic valve replacement as a treatment option, clinicians will increasingly be confronted with the intersection of aortic stenosis and multimorbidity. This convergence makes the evaluation, management, and treatment of aortic stenosis more complex in multiple ways. To optimize patient-centered clinical outcomes, new treatment paradigms are needed that recognize the import and influence of multimorbidity on patients with aortic stenosis. We review the prevalence of medical and aging-related comorbidities in patients with aortic stenosis, their impact on outcomes, and discuss how they influence management and treatment decisions.

Keywords

aortic stenosis; multimorbidity; comorbidity; geriatrics; frailty; cardiovascular disease; transcatheter aortic valve replacement; cardiac surgery

Introduction

Calcific aortic stenosis (AS) is generally a disease of older adults. A recent meta-analysis of seven population-based studies from Europe and North America found that the prevalence of AS in persons >75 years of age was 12.4% and the prevalence of severe AS was 3.4%.⁽¹⁾ As the population ages, the absolute number of patients with significant AS will rise substantially.

Within the aortic valve leaflets, an active biological process occurs to cause fibrosis and calcification, leading to restricted leaflet motion.⁽²⁾ As the aortic valve becomes

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progressively obstructed, maintenance of cardiac output imposes a chronic increase in left ventricular pressure that leads to hypertrophic ventricular remodeling and eventually diastolic and systolic dysfunction.(3,4) Symptoms such as shortness of breath and chest pain can be disabling, markedly reduce quality of life, and are associated with an average life expectancy of 2–3 years.(5–7) The only effective treatment for symptomatic severe AS is valve replacement.(3,8) However, surgery has significant risks, including stroke and death, and at least one-third of patients do not undergo surgery due largely to advanced age, left ventricular dysfunction, or associated comorbidities.(5,9,10)

Recently, a less invasive approach to valve replacement using balloons and catheters—transcatheter aortic valve replacement (TAVR)—has been introduced as a viable alternative for patients at high or prohibitive risk for surgery.(11–14) TAVR has been a transformative innovation, allowing for the treatment of many patients that previously did not have a therapeutic option. Based on current regulatory approval indications, recent estimates indicate that there are approximately 300,000 TAVR candidates in Europe and North America and almost 30,000 new TAVR candidates annually.(1) As indications for TAVR (based mostly on estimates of operative risk) are lowered, this number will substantially increase.

Primarily because of two forces—the aging of the population and the emergence of TAVR as a therapeutic option—clinicians increasingly face challenging scenarios that result from the intersection of AS and multiple comorbidities. These include multiple medical comorbidities as well as numerous aging-related, or geriatric, comorbidities. AS is often conceptualized as a mechanical problem (valve obstruction) requiring a mechanical solution (valve replacement). There can be a myopic focus on the valve as the singular cause of the patient's impairments (e.g. shortness of breath); accordingly, it is often assumed that once the valve is fixed the patient's symptoms will resolve and quality of life improve. The frequent occurrence of multiple, often severe, comorbidities influences—sometimes dramatically—this linear, simple diagnostic and treatment framework. Indeed, among patients with AS, medical and aging-related comorbidities influence health status, the determination of whether symptoms related to AS are present, estimates of procedural risk, and anticipated benefit from valve replacement. In short, these comorbidities are common and introduce a significant degree of complexity into the evaluation, management, and treatment of patients with AS.

Herein, we review aging-related and medical comorbidities commonly coexistent in patients with AS (Table 1). Their prevalence and impact on clinical outcomes depends on the population of patients with AS examined. Specifically, studies examining patients evaluated for and treated with TAVR include older patients with more numerous and more severe comorbidities. In that regard, where possible, we tried to include data from multiple different AS populations to provide perspective on the range of comorbidity prevalence and clinical effects.

Geriatric or Aging-Related Comorbidities

Frailty

Frailty is a geriatric syndrome characterized by an increased vulnerability to stressors due to impairments in multiple organ systems, particularly the cardiovascular and musculoskeletal systems.(15,16) Although frailty is a “system-wide” syndrome, there is mounting evidence for a bidirectional relationship between cardiovascular disease and frailty.(17) As such, frailty is not necessarily separate and distinct from AS. Rather, the heart failure that results from severe AS may impair functionality, mobility, eating habits, etc. in ways that contribute to the development or progression of frailty. Conversely, frailty may influence the timing of symptom onset, the severity of the clinical presentation, and the response to valve replacement in a patient with significant AS. These issues remain to be elucidated.

Until the emergence of TAVR, frailty was largely incorporated into clinical decision making in the form of a subjective “eye-ball test.” Due to the general recognition that frailty is common and likely affects clinical outcomes, there is rapidly growing interest in how to incorporate the concept of frailty into risk assessment and treatment decisions for patients with AS.(8,18,19) Based on different definitions of frailty and the population examined, the prevalence of frailty in patients with severe AS ranges from approximately 20–84%.(13,20–23)

Some studies suggest that a single test, most commonly the 5 meter gait speed, provides the best prediction of clinical events post-valve replacement, whereas others suggest that an integrated frailty score has greater prognostic utility.(20,24) In patients >70 years of age referred for cardiac surgery, including valve surgery, a 5 meter gait time >6 seconds (46% of patients) was associated with a 3-fold increased hazard of in-hospital morbidity and mortality after adjustment for the STS-PROMM.(25) In a recent TAVR trial enrolling patients at prohibitive risk for surgery, 84% of patients had a 5 meter gait time >6 seconds. (13) A slower timed get up and go test and worse nutrition have also been associated with worse 30 day and 1 year mortality and cardiovascular event rates.(23) Among patients treated with TAVR, frailty as determined by an integrative score was associated with an 2.5-fold increased adjusted hazard of 1-year mortality and a higher 1-year rate of “poor outcome” (integrating mortality and quality of life).(26)

Beyond predicting increased mortality and cardiovascular event rates, frailty pre-TAVR predicts greater functional decline and loss of independence after TAVR.(22) Among patients >70 years of age undergoing TAVR, functional decline at 6 months post-TAVR (defined as dependence for 1 basic activities of daily living compared to pre-TAVR) occurred in 21% of patients. A multidimensional frailty score was able to predict this functional decline, whereas clinical risk scores such as the STS and EuroSCORE were not. This has important implications for predicting outcomes that matter to patients.

Across varying definitions of frailty, there is a consistent association between frailty and worse clinical outcomes after TAVR, including procedural morbidity and mortality, longer-term mortality, and progressive loss of independence. Frailty is generally not correlated with other clinical risk scores, so it adds new information to risk prediction.(23,25) Elucidating

how frailty should be incorporated into risk stratification and treatment decisions is an active area of ongoing research.(18,19)

Disability

The prevalence of disability in patients with AS also depends on the definition or instrument used and the population assessed. Among patients >70 years of age referred for cardiac surgery, the rate of having any disability was 5% using the basic activities of daily living scale, 32% using the instrumental activities of daily living scale, and 76% using the more sensitive Nagi scale.(20) Three or more disabilities (out of 7) on the Nagi scale was associated with a 3-fold higher unadjusted hazard of in-hospital morbidity or mortality. Among patients treated with TAVR, 23–29% were dependent for 1 basic activities of daily living.(22,24,26) In an inoperable TAVR trial cohort, 21% were dependent for 2 and 14% were dependent for 3 basic activities of daily living.(13) Among patients treated with TAVR, an increasing degree of dependence for basic activities of daily living is associated with increased 30-day and 1-year mortality.(23) Patients with AS undergoing TAVR also have a relatively high rate of mobility impairment. In one study, 25% of patients could not perform a 6 minute walk test.(26) In an inoperable cohort of patients, 18% had experienced a fall in the last 6 months.(13)

Cognitive Impairment

The prevalence of cognitive impairment in patients with AS undergoing TAVR has been reported to be 28–45%.(13,22,23,27) In a large cohort of 2137 patients from the PARTNER trial, each 1 point decrease in the Mini-Mental Status Examination score (MMSE) was associated with higher odds of poor 6-month and 1-year clinical outcome.(28) Other studies also show an association between cognitive impairment and increased mortality after TAVR and surgical AVR.(23,29) Schoenenberger et al. showed an association between pre-TAVR cognitive impairment and greater dependence in basic activities of daily living 6 months after TAVR.(22) Whether transcatheter versus surgical AVR has a differential impact on post-procedure cognitive function and whether embolic protection devices during TAVR can reduce post-procedure cognitive decline remain to be determined.

Medical Comorbidities

Chronic Obstructive Pulmonary Disease

The presence and severity of associated lung disease influences the management, treatment, and outcomes of patients with AS.(3) In patients with significant lung disease, it can be difficult to discern whether symptoms of shortness of breath are due to the AS, lung disease, or a combination of both. The prevalence of lung disease ranges from less than 10% in those undergoing surgical AVR to almost 60% in inoperable patients undergoing TAVR.(11,13,30,31) Among patients treated with TAVR, up to 30% have oxygen-dependent lung disease.(13)

In a study of 2,553 patients included in the PARTNER trial, COPD was present in 43% and was associated with increased 1-year mortality (23.4% vs. 19.6%, $p=0.02$).(31) Among those with COPD, oxygen dependence and poor mobility were each independently

associated with increased mortality. These findings are supported by large TAVR registry studies from the United States, United Kingdom, and France.(32–34) COPD has also been shown to be an independent risk factor for mortality among patients treated with surgical AVR.(35)

Pulmonary hypertension

Pulmonary hypertension (PH) is present in 50–65% of patients with severe AS and is classified as severe in up to 15–25%.(30,36–38) In patients treated with surgical AVR or TAVR, PH has been associated with increased mortality, morbidity, and resource utilization after valve replacement.(30,37–40) Among patients with moderate or severe PH treated with TAVR, oxygen dependent lung disease, inability to perform a 6 minute walk, impaired renal function, and lower aortic valve mean gradient were independently associated with increased 1-year mortality.(38) A risk score including these factors was able to identify patients with a 15% versus 59% 1-year mortality. There are somewhat conflicting data as to whether an increased pulmonary vascular resistance exacerbates the risk associated with an elevated pulmonary artery systolic pressure.(38,41) In asymptomatic patients with severe AS, exercise induced PH is associated with increased cardiac event rates during follow-up.(42)

Chronic Kidney Disease

The prevalence of chronic kidney disease depends on the definition used and specific AS population studied, but ranges from less than 10% to >50%.(12,34,43,44) Chronic kidney disease is associated with increased mortality after TAVR and surgical AVR.(33,45,46) End-stage renal disease is less common but occurs in 2% of surgical AVRs and up to 4% of patients in the U.S. TAVR registry, where it is associated with a 66% increase in the hazard of 1-year mortality.(34,46) Acute kidney injury after valve replacement is also associated with increased mortality and may occur less commonly after TAVR compared to surgical AVR.(14,47)

Chronic Liver Disease

Chronic liver disease is relatively uncommon in patients treated for AS; in the recent PARTNER and CoreValve trials, it was 2–3%.(12,13) Nevertheless, it was associated with a 2-fold higher adjusted hazard of mortality in the overall study cohort treated with surgical AVR or TAVR.(45) Other studies have demonstrated that liver disease is associated with increased risk of early mortality after TAVR.(48) Larger studies are needed to elucidate how the severity of liver disease affects peri-procedural morbidity and early and late mortality.

Anemia

The prevalence of anemia in many TAVR treated populations is greater than 50%.(49–51) In a multicenter study of 1,696 TAVR patients, preoperative anemia was independently associated with increased 1-year mortality, particularly in those with pre-operative hemoglobin <10 g/dL (HR 2.78, 95% CI 1.60–4.82).(50) Anemia is also associated with worse functional status and quality of life before and after TAVR.(51)

Diabetes Mellitus

The prevalence of diabetes mellitus in patients with AS has increased over time and is as high as 42% in recent, older, higher risk cohorts.(13,14,46,52) Many studies have demonstrated that diabetes is associated with increased mortality after surgical AVR or TAVR.(33,53,54) According to a post-hoc analysis of PARTNER trial patients, there was a survival benefit, no increase in stroke, and less renal failure in diabetic patients treated with TAVR compared to surgical AVR.(52) However, this survival benefit with TAVR among diabetic patients was not observed in the CoreValve sub-group analysis.(14)

Cardiac and vascular comorbidities

There is a very high prevalence of associated cardiac and vascular comorbidities in patients with AS, including heart failure, atrial arrhythmias, hypertension, coronary artery disease, cerebrovascular disease, and peripheral vascular disease. A detailed treatment of these comorbidities is beyond the scope of this article. The presence and severity of each of them contributes to the procedural and long-term risk of patients treated with surgical or transcatheter valve replacement. Coronary disease, in particular, adds complexity to management decisions regarding whether, when, and how to revascularize a patient with severe AS.(55)

Comorbidities and the Evaluation and Treatment of Aortic Stenosis

The number, type, and severity of comorbidities substantially influence the evaluation, management, and treatment of patients with AS. As documented above, comorbidities—and often many of them together—are common in patients with AS. They can make it difficult to distinguish the “asymptomatic” from the “symptomatic” patient. An older adult may curtail certain activities and attribute developing limitations to “normal aging” when in fact they are signs of new onset heart failure. In contrast, a patient with limited mobility, deconditioning, and oxygen-dependent lung disease may be short of breath for several reasons making it difficult to ascribe symptoms to the AS. Moreover, the relative contribution of AS versus associated comorbidities to a patient’s health status can be difficult to discern. This is important and relevant as it likely has implications for the anticipated benefit that will accrue from valve replacement. Thus, patients whose symptoms are largely unrelated to AS are unlikely to derive significant benefit from valve replacement. Finally, the number and severity of associated comorbidities has implications for procedural risk from valve replacement and for whether a transcatheter or surgical approach is most appropriate.

The emergence of TAVR as a treatment option for patients with AS at increased surgical risk has coincided with the emergence of multidisciplinary heart valve teams as the centerpiece for making these complex and challenging management and treatment decisions.(8,56,57) Relevant to our focus here, it is clear that the number and severity of medical and geriatric comorbidities must be incorporated into the decision making process about whether and how the valve should be replaced.(8,56,58) We have moved beyond the “eye-ball test” to incorporate aging-related comorbidities into our decision making process; multiple objective tests of frailty and disability have been shown to improve risk prediction estimates beyond

clinical factors alone.(19,23,25) Nonetheless, further studies are needed to elucidate how these factors should be considered in our treatment decisions.

TAVR has been a life-saving therapy for many who were previously not treated for their AS. However, even after TAVR, up to 30% of these patients are dead by 1 year and 20% survive but have no significant improvement in their quality of life.(11,18,59) Further, it is clear that medical and aging-related comorbidities substantially influence these outcomes. Moving forward, we need to develop new and better ways to incorporate comorbidities not only into our procedural risk estimates, but into our assessment of the likelihood for longer-term benefit (defined holistically) from valve replacement.(58) How and to what extent various comorbidities influence post-valve replacement survival, quality of life, repeat hospitalizations, and functionality requires further study. Ultimately, we need to consider how to treat the whole patient, not just a mechanical problem with a mechanical solution.

Conclusion

AS is a disease of older adults, most of whom have associated medical and aging-related comorbidities. With the aging of the population and the emergence of TAVR as a treatment option, clinicians will increasingly be confronted with the intersection of AS and multimorbidity. This convergence makes the evaluation, management, and treatment of AS more complex in multiple ways. To optimize patient-centered clinical outcomes, new treatment paradigms are needed that recognize the import and influence of multimorbidity on patients with AS. The simplistic framework of a mechanical solution for a mechanical problem must be replaced by a more refined, nuanced, and holistic treatment paradigm.

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Key points

1. Medical and aging-related comorbidities are very common in older patients with calcific aortic stenosis.
2. Due to the aging of the population and the emergence of transcatheter aortic valve replacement as a therapeutic option, clinicians increasingly face challenging scenarios that result from the intersection of aortic stenosis and multiple comorbidities.
3. Among patients with aortic stenosis, medical and aging-related comorbidities influence health status, interpretation of the presence and etiology of symptoms, estimates of procedural risk, and anticipated benefit from valve replacement.
4. The number, type, and severity of comorbidities substantially influence the evaluation, management, and treatment of patients with aortic stenosis.
5. Awareness and incorporation of the influence of comorbidities on outcomes after valve replacement is critical to treating the patient and not just fixing the valve.

Table 1

Prevalence of Geriatric and Medical Comorbidities in Aortic Stenosis

Condition	Prevalence [*]
Disability	5–76%
Frailty	20–84%
Cognitive Impairment	28–45%
Chronic Obstructive Pulmonary Disease	8–59%
Pulmonary Hypertension	47–65%
Chronic Kidney Disease	3–57%
End Stage Renal Disease	2–4%
Chronic Liver Disease	2–3%
Anemia	49–64%
Diabetes	20–42%

* Prevalence is highly dependent on the population examined and the definition used for the condition, particularly for disability and frailty.