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# Importance of frailty and comorbidity in elderly patients with severe aortic stenosis

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The progressive aging of the population has risen awareness and concern about the impact of geriatric syndromes on both clinical outcomes and health-related quality of life in elderly patients, as well as issues regarding the rising economic burden associated with healthcare.[1,2] Recent studies have demonstrated frailty and other geriatric syndromes such as functionality, dependency and comorbidity can identify the most vulnerable patients, thus allowing to better estimate the individual prognosis in terms of disability, readmission and mortality.[3,4] Such information should also be considered in the decision making process, ensuring the benefit derived from each treatment in each patient, optimizing the resources and avoiding futility.

Frailty is the aggregation of subclinical physiological conditions leading to heightened vulnerability in case of stressing situations. It is defined as impairment in multiple, interrelated organ systems causing decreased homeostatic reserve and increased vulnerability to stress.[5] Measures of frailty, even after adjustment for age and comorbidity, are highly predictive of worse outcomes, including death, incident disability, and hospitalization in patients with heart disease.[6] The concept of frailty lacks a widely accepted definition despite being a well-recognized entity among clinicians.[7] Although frailty is associated with advanced age, it is not confined to older populations nor does advanced age equate to frailty. Measures of frailty inherently work to distinguish highly vulnerable patients from those who are not, even among older adults.[8] The so-called "eyeball test," an overall assessment of the patient from the doorway, is often used by clinicians to intuitively qualify this vulnerability. Frailty may have multiple manifestations and may be difficult to identify and manage.[9] Weakness, decreased mobility, and limitation to perform routine physical activities are common in frailty patients. Performance measures represent aspects of physical function that are associated with routine daily activities that are important for maintaining independence in older adults.[10] Early detection of frailty may be a window of opportunity for intervention and a key factor for improving clinical outcomes in elderly patients with cardiovascular disease. These measures include multiple dimensions of health and aging, such as disease processes, nutritional status, cardiorespiratory fitness, and psychological state, and provide a global assessment of physical function.

Frailty and comorbidity are clinical manifestations of two distinct aging-related processes, involving diminished functional reserve and accumulation of pathological processes. Moreover, frailty and comorbidity often overlap in the elderly and lead to impairment in quality of life and functional status, also entailing worse prognosis. Wong et al reported that among community dwelling seniors who are frail 82% have comorbidities, 29% have disability in at least one activity of daily living, and 93% have disability in at least one instrumental activity of daily living.[11]

There are many scenarios in day-to-day clinical practice in which frailty assessment can provide valuable prognostic information, allowing clinicians to define optimal care pathways for their patients. Ideally, frailty is not a reason to withhold care but rather a means to structure care in a more patient-centered fashion. A guiding principle is that frailty, disability, and comorbidity are inter-related but distinct entities.[5] A second principle is that there is no definitive gold standard test for frailty, but rather an assortment of tools that reflect one or more domains of frailty.[9,12,13] Multi-domain tools do not necessarily provide incremental value above single-domain tools, and ease of implementation may be an important factor for adoption. A third principle is that frailty is a continuous spectrum, and specific cutoffs used to dichotomize frailty status in a group of patients may not be applicable in another group. Defining the optimal tool set to

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measure frailty is a high priority.

Aortic Stenosis (AS) has become the most frequent type of valvular heart disease in developed countries.[14] Its impact on health care resources and prevalence is expected to increase due to aging population. Although studies describing AS prevalence may report diverse results it seems that in elderly population severe AS may affect up to 4,6% and 8,1% in patients older than 75 and 85 years respectively.[15,16] Patients usually remain asymptomatic for a long time. However, once they develop symptoms, disease progression accelerates and prognosis is substantially worse.[17]

Regarding the treatment and management options for severe symptomatic AS there are no proven medical treatments to prevent or delay disease progression. Aortic valve replacement (AVR) or Transcatheter aortic-valve implantation (TAVI) are the only effective treatments recommended by ESC and ACC/AHA guidelines, offering not only symptomatic relief, but also improving long-term survival. Ballon aortic valvuloplasty should not be used as a substitute for AVR or TAVI due to high recurrence rates of AS; however, it may still be considered as a bridge to subsequent AVR or TAVI.[14] Currently, TAVI is indicated in patients with severe symptomatic AS prohibitive surgical risk who are not deemed suitable for AVR as assessed by a 'heart team' and who are likely to improve their quality of life with a life expectancy greater than one year after consideration of all their comorbidities (Class I Recommendation) and appears to be a reasonable alternative to surgical AVR in high surgical risk patients with indication for AVR (Class IIa Recommendation).[14] Some studies have demonstrated TAVI to be superior to medical therapy in patients with severe AS deemed inoperable,[18] and comparable to surgery in recent studies including patients of high[19] and intermediate risk.[20–22]

Nevertheless, treatment decision in elderly patients with symptomatic AS remains a great challenge, mainly because of increased operative morbidity and mortality. It is well known that most octogenarian patients with severe AS refuse or are not proposed for neither TAVI nor AVR, despite a significant proportion could benefit from these interventional therapies.[23,24] In fact, both techniques may be performed in selected very elderly patients with relatively low mortality.[24,25] High surgical risk, however, is the most important factor associated with choice of conservative therapy in patients ≥ 80 years with severe AS,[24] which has been shown to entail worse prognosis. On the other hand, it is well known that interventional treatment does not improve the disease prognosis in all patients with symptomatic severe AS.[26] This, together with the current evaluation of the economic implications of TAVI, make a major issue identifying those patients in whom TAVI is likely to be futile.[27]

In elderly patients with AS a detailed case history is of crucial importance to assess symptoms and to evaluate for associated comorbidities. Traditional risk scores, including The Society for Thoracic Surgeon Predictive Risk of Mortality (STS PROM) and logistic European System for Cardiac Operative Risk Evaluation (logistic EuroSCORE) have proven insufficient to predict events in elderly patients with severe AS. Advanced age has important implications, as typically these patients have several comorbid conditions that increase, in addition to advanced age, the risk of interventional treatments. Therefore, functional status and a comprehensive assessment of non-cardiac conditions or comorbidities are of crucial importance. Moreover, interventional treatment does not always improve nor even change the prognosis of all patients. Therefore, some factors other than those inherent to the surgical risk have shown to have prognostic significance.[28] Concerning cardiac conditions, it is necessary to evaluate cardiac function and coronary anatomy. Available data suggest that low left ventricular ejection fraction (LVEF) may predict a higher risk and poor prognosis but cannot be used as an isolated factor for determining prognosis after intervention. The presence of a low flow state, severe pulmonary hypertension (especially pre-capillary or combined), and severe organic mitral regurgitation are cardiovascular factors that should be carefully considered in the decision-making process. Furthermore, pre-existing atrial fibrillation may have an adverse impact on post-TAVI morbidity and mortality.

On the other hand, in patients with AS there is an increasing perception that frail patients and those with more comorbidities do not benefit from interventional treatment in terms of morbidity and mortality, but also from a functional point of view.[27] Green, *et al*.[29] designed a score to evaluate frailty in older patients with symptomatic AS undergoing TAVI. Serum albumin, gait speed, grip strength and dependency for daily life activities were included. Patients with worse scores had worse prognosis. Impaired gait speed showed to be associated with dependence, also entailing higher 30-day mortality after TAVR.[30]

Regarding comorbidities, some non-cardiac conditions impact prognosis in the short and in the long term irrespective of the treatment.[31] Most important refer to chronic lung disease, present in one third of patients, entailing higher mortality specially in case of oxygen-dependency and poor mobility, and chronic kidney disease, also present in up to one half of patients. Some other specific predictive factors have been identified, such as pulmonary hypertension, anaemia and body mass index. Martinez-Sellés, *et al*.[26]

demonstrated that patients with high comorbidity (Charlson comorbidity index ≥ 5) which is present in 15% of octogenarian patients with severe AS, have a poor prognosis in the short term, mainly related to non-cardiac death. In such patients, interventional therapy was not associated with better prognosis. Also, some scoring systems based on variables with prognostic impact in the short and long term have been recently developed,[32] allowing patients to be accordingly classified in different risk levels, entailing important differences in mortality during follow up.

In conclusion, there is substantial evidence to support the utility of frailty assessment in patients with diverse forms of cardiovascular disease. The value of frailty as a prognostic marker is well demonstrated and can guide cardiovascular care as well as decision making process. Considering the above, there is an emerging consensus of the importance of a more holistic and multidisciplinary approach and assessment. Evaluation of elderly patients with symptomatic severe AS is challenging and continuously evolving. Traditional risk assessment has proven to be insufficient, thus considerations regarding frailty, comorbidities and disability, with prognostic impact and often not included in commonly used risk scores, are of great importance as they can improve decision-making. Such conditions, when present, entail worse prognosis, irrespective of AS per se, and should be considered in order to avoid futility. In short, these patients may benefit from a comprehensive assessment performed by a multidisciplinary team focused on the patient, and not only on AS, which may be only one of the many problems/diseases of the patient.

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