ANMCO/SIC/SICI-GISE/SICCH Executive Summary of Consensus Document on Risk Stratification in elderly patients with aortic stenosis before surgery or transcatheter aortic valve replacement

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doi:10.1093/eurheartj/sux012
Aortic stenosis (AS) is one of the most common acquired valvular diseases in developed countries, and its impact on public health resources and assistance is increasing. A substantial proportion of elderly people with severe aortic stenosis is not eligible to surgery because of the advanced age, frailty, and multiple co-morbidities. Transcatheter aortic valve implantation (TAVI) enables the treatment of very elderly patients at high or prohibitive surgical risk considered ineligible for surgery and with an acceptable life expectancy. However, a significant percentage of patients die or show no improvement in quality of life (QOL) in the follow-up. In the decision-making process, it is important to determine: (i) whether and how much frailty of the patient influences the risk of procedures; (ii) how the QOL and the individual patient’s survival are influenced by aortic valve disease or from other associated conditions; and (iii) whether a geriatric specialist intervention to evaluate and correct frailty or other diseases with their potential or already manifest disabilities can improve the outcome of surgery or TAVI. Consequently, in addition to risk stratification with conventional tools, a number of factors including multi-morbidity, disability, frailty, and cognitive function should be considered, in order to assess the expected benefit of both surgery and TAVI. The pre-operative optimization through a multidisciplinary approach with a Heart Team can counteract the multiple damage (cardiac, neurological, muscular, respiratory, and kidney) that can potentially aggravate the reduced physiological reserves characteristic of frailty. The systematic application in clinical practice of multidimensional assessment instruments of frailty and cognitive function in the screening and the adoption of specific care pathways should facilitate this task.

Introduction

Aortic stenosis (AS) is one of the most common acquired valvular abnormalities in developed countries, with an increasing prevalence due to the ageing population.\(^1,3\) The prognosis of AS is relatively benign in the absence of symptoms; however, an incidence of sudden death between 1\(^\%\) and 3\(^\%\) must be taken into account. The onset of symptoms coincides with a dramatic reduction in life expectancy, with a median survival of 2-3 years in patients with angina or syncope and only 1-2 years in symptomatic patients with heart failure.\(^3,4\)

Surgical aortic valve replacement (SAVR) remains the gold standard of care;\(^5\) however, at least 40\(^\%\) of potential patients are not candidate because of the prohibitive nature of their co-morbidities and consequent perioperative risk.\(^6,7\) Consistent with the epidemiological changes, in clinical practice, about three-quarters of patients with isolated SAVR receive a bioprosthesis.\(^8\) Advanced age alone cannot be considered an obstacle to surgery, but medical options are limited. Elderly patients who do not receive a SAVR have a higher risk of mortality compared with those treated surgically.\(^9\) Isolated SAVR can be performed in octogenarians with low post-operative mortality\(^10\) and result in significant improvement in quality of life (QOL), symptoms, and functional capacity.\(^11\) In addition, cost-effectiveness analyses have shown that SAVR is convenient also for very elderly patients.\(^12\)

In the last years, transcatheter aortic valve implantation (TAVI) has emerged as a less invasive treatment strategy in high-risk patients, allowing the treatment of more complex, elderly patients, with severe symptomatic AS, previously considered ineligible for surgery.\(^13-15\) However, even today, a considerable percentage of these patients die or do not present a significant improvement in dyspnoea, fatigue, and functional impairment. This observation has raised a lively discussion on the need to identify and recognize the boundaries of indications for surgical and interventional procedures and, consequently, identify a possible futility in some patients.\(^16\) The decision-making process in this population is difficult because of co-morbidity, disability, frailty, and reduced life expectancy, and these factors, as well as traditional ones, should be considered in risk stratification. It is likely that TAVI will be used in an increasing number of AS patients, but its exact role alongside surgery will need to be defined in a judicious and evidence-based manner. The assessment by a multidisciplinary team is therefore essential to predict possible benefits and allow to make complex decisions with a clear communication to the patient. The decision that surgical treatment or with TAVI is useless/futile should include alternative routes to optimize the patient’s health state and to consider options for assistance to the terminal stages.\(^17\)

Heterogeneity and complexity

The peculiar feature of the elderly patient can be summarized in two words: phenotypic heterogeneity and complexity. In these two dimensions describe the effects of cardiovascular ageing, heart disease, lifestyle, and socio-environmental factors and three different entities: co-morbidity, disability, and frailty (Figure 1).\(^18\) Complexity considers not only the sum of all coexisting diseases and geriatric conditions but also their mutual interactions. From a conceptual point of view, therefore, the elderly person is in himself/herself a complex patient.
An accurate pre-operative/pre-procedural risk stratification in the elderly person should identify those who benefit from the intervention, exclude those who have a prohibitive risk, and identify those who need more intensive care in the post-operative period. In this sense, the ideal tool for risk stratification in the elderly person waiting for cardiac surgery should be reliable and targeted at easily obtainable variables. Any tool should be tested in a real-world ageing population with different degrees of frailty or disability, pointing out that the two concepts are interdependent but not synonymous. Pre-operative evaluation in the elderly patient should collect information on physical functional status, cognitive function, and non-cardiac co-morbidities of prognostic importance.19

Co-morbidity is defined as the simultaneous presence of two or more diseases in the same patient, an event that increases with age.20 About 16% of patients >65 years have co-morbidity with two or more diseases, a percentage that increases to 35% in octogenarians.21 At this age, chronic co-morbidities are associated with a higher risk of death, rehospitalization, disability, and reduced QOL beyond those related to individual disorders. Co-morbidity plays a central role in the implementation of evidence-based medicine in clinical geriatrics, because trials have often excluded older subjects with co-morbidities, raising questions about the transferability of the results obtained in the geriatric populations.22 Co-morbidity also becomes crucial in influencing the diagnostic-therapeutic process, because the onset of symptoms can be different from the usual and makes the interpretation of symptoms and signs of the index disease more difficult.

The elderly candidate to heart surgery is, regardless of his death risk, susceptible to frequent serious complications. These often result in a cascade of negative events...
that converge to lose autonomy in carrying out the activities of daily living, leading to significant health-care costs and decreased QOL. This phenotype of reduced homeostatic physiological reserves and greater vulnerability to stressful events is described as frailty.\textsuperscript{23} The complex pathophysiological substrate of frailty is described in Figure 2.\textsuperscript{24} Frailty has been defined ‘a condition or syndrome that results from a multi-systemic reduction in homeostatic reserve, to the extent that the physiological systems are close to the threshold of symptomatic clinical failure. Consequently the frail person is at increased risk of disability and death for a minimum external stress’.\textsuperscript{25} The concept of frailty (although the two conditions are frequently overlapping) is not synonymous of disability nor is equivalent to the concept of co-morbidity (Figure 1).\textsuperscript{26}

Given this definition, there are basically two conceptual models of frailty: the ‘frailty phenotype’\textsuperscript{26} and the ‘clinical frailty phenotype’.\textsuperscript{27} The first substantially recognizes a set of five domains such as unintentional weight loss, muscle strength measured by handgrip, self-reported fatigue, gait speed, and self-reported physical activity.\textsuperscript{26} The second model is based on a ‘deficit accumulation model of frailty’ and has been built from a list multiple items, both functional and clinical, exploring the physical, cognitive, and independence in activities of daily living, with a final score ranging from 0 to 7 for increasing frailty.\textsuperscript{27} Both models have been tested in the stratification of the elderly patient’s surgical risk but also showing some of the limitations related to the complexity of their clinical routine implementation.

The negative impact of frailty on prognosis of cardiovascular diseases has been demonstrated in a wide range of conditions, including stable cardiovascular disease,\textsuperscript{28} heart failure,\textsuperscript{29} ischaemic heart disease and acute coronary syndromes,\textsuperscript{30} cardiac surgery,\textsuperscript{31,32} and TAVI.\textsuperscript{33,34}

\textit{Disability} is defined by the level of dependence in performing basic and instrumental activities of daily living, i.e. basic activities of daily living (BADL)\textsuperscript{35} and instrumental activities of daily living (IADL).\textsuperscript{36}

In the recent US TAVI guidelines,\textsuperscript{16} a specific section—\textit{Frailty and futility versus Utility}—was included, demonstrating that when deciding a therapeutic intervention in elderly subjects, the assessment of frailty and the risk of disability is a key variable for deciding the effectiveness and utility of the intervention itself.

Outcomes of surgical and interventional procedures in the elderly persons

\textbf{Results of surgical aortic valve replacement}

Overall, the outcomes of surgery for severe AS are excellent in patients with moderate-to-low surgical risk. A meta-analysis of 48 observational studies in 13 216 patients \(>80\) years, undergoing isolated aortic valve surgery\textsuperscript{36} showed an immediate post-operative mortality of 6.7% (5.8% for patients treated from 2000 to 2006 and 7.5% in patients treated from 1982 to 1999). The post-operative stroke rate was 2.4%, dialysis of 2.6%, and pacemaker implant 4.6%. The 1-, 3-, 5-, and 10-year mortality rates after isolated SAVR were approximately 12.4%, 21.3%, 34.7% and 70.3%, respectively. These data confirm that advanced age, as the only risk factor, cannot be considered a contraindication to conventional isolated SAVR. In the Society of Thoracic Surgeons (STS) database, mortality at 30 days after isolated SAVR over 80 years was 3.7% in low-risk patients but rose to 10% and 17%, respectively, in patients with STS score \(\geq 5\) and \(\geq 10\).\textsuperscript{37} Octogenarians also report improvements in symptoms and ventilricular function.\textsuperscript{38}

\textbf{Results of transcatheter aortic valve implantation in patients at high or prohibitive risk}

On the basis of two main randomized trials and various observational studies, recent guidelines\textsuperscript{1} indicate TAVI as an option of choice in patients deemed inoperable because a prohibitive risk (with results far superior to medical therapy alone) and a reasonable alternative to SAVR in those at high risk (Table 1).\textsuperscript{13-15,39-47}

In the PARTNER trial (Cohort A), which included patients with high operative risk,\textsuperscript{44} patients undergoing SAVR had a higher incidence of bleeding and a lower incidence of vascular complications, compared with those undergoing TAVI at 5 years. The percentage of residual aortic moderate and severe insufficiency was 14% in patients undergoing TAVI and 1% of patients undergoing SAVR (\(P < 0.0001\)) and, if moderate and severe, correlated with an increase in mortality.
The data of Registries confirm those of trials. In the GARY (Germany Aortic Valve Registry) hospital mortality was 5.2% and serious complications occurred in 5% in patients undergoing TAVI from 2011 to 2013. In the FRANCE TAVI Registry, enrolling 6827 patients undergoing TAVI in 2013 and 2014, the hospital mortality was 5.9%, the incidence of major bleeding was 9.3%, stroke 2.2%, need for pacemaker 15%, and severe aortic insufficiency 1.2%. The Italian OBSERVANT study analyzed propensity-matched patients undergoing TAVI or SAVR. The mean logistic EuroSCORE 1 was 10.2 in SAVR group and 9.5 in the TAVI group. No significant differences were recorded in mortality (13.6% and 13.8%), MACE rate (17.6% vs. 18.2%), and in hospitalizations for cardiac causes.

The recent STS-TVTR Registry confirms that typical TAVI patients are highly symptomatic, frail elderly with multiple co-morbidities, a high STS predicted risk of mortality (STS PROM) score, advanced functional class, and a poor health status. From 2012 to 2014, in-hospital mortality decreased from 5.3% to 4.4%, vascular complications from 5.6% to 4.2%, while stroke rates remained stable at 2.2%. In this Registry, ~16% of patients were aged >90 years. Although 30-day and 1-year mortality rates were statistically higher compared with younger patients, the absolute and relative differences were clinically modest. TAVI also improved QOL to the same degree in nonagenarians as in younger patients.

Results of transcatheter aortic valve implantation in low-intermediate risk patients

NOTION study randomized low-risk patients >70 years to SAVR or TAVI (STS score 2.9% vs. 3.1%). At 1 year, the primary endpoint (death, stroke, or myocardial infarction) showed no significant differences. Patients undergoing surgery had a better functional outcome and those who underwent TAVI had a significantly higher incidence of moderate or severe peri- or intraprosthesis regurgitation (15.7% vs. 0.9%, P < 0.001).

In PARTNER 2 study, patients at intermediate risk (mean STS score 5.8%, mean age 81.6 years) randomized to TAVI with self-expandable SAPIEN XT prosthesis and SAVR. There was no significant difference in the primary endpoint of death from any cause or disabling stroke at 2 years between the two groups. Another randomized trial, SURTAVI, designed to evaluate the safety and efficacy of TAVI in intermediate surgical risk patients, will evaluate 2500 patients with STS score between 4 and 10. The primary endpoint is composed of mortality and disabling stroke at 24 months. Patients will be followed for 5 years (www.clinicaltrials.gov).

Procedural complications of transcatheter aortic valve implantation

Mortality is strongly conditioned by periprocedural complications, represented by stroke (1-5%), pacemaker implantation (7-40%), and vascular complications (up to 20%). The improvement of the femoral approach techniques has resulted in a reduction in major bleeding. In a recent meta-analysis of randomized trials and observational studies, the incidence of stroke was 2.9%, regardless of the prosthesis used. That effect was not, however, different than in patients treated with SAVR.

The main Achilles heel of TAVI compared with SAVR is represented by periprosthetic leak, that, if moderate to severe, is one of the major predictors of mortality.

Numerous studies have shown that, for this complication,
results are in favour of surgery. In the recent PARTNER 2, the incidence and severity of paravalvular regurgitation after TAVI were more frequent compared with SAVR, and TAVI patients with moderate-to-severe paravalvular regurgitation at 30 days had a higher mortality at 2 years than those without or with mild regurgitation. Proper sizing of the annulus, a better understanding of the procedure and optimization of the immediate result, may lead to a gradual reduction in incidence of this complication.

In the subgroup of inoperable, symptomatic patients at excessive risk for TAVI, valvuloplasty balloon can be a procedure of choice or bridge for further treatment. In this context, valvuloplasty could also be used to verify whether the patient’s frailty is related to valvular disease or not.

Clinical risk assessment

Clinical and imaging parameters
Risk stratification has assumed a key role in patient selection and recent guidelines from the European Society of Cardiology have stressed the importance of a multidisciplinary ‘Heart Team’ approach to help determine this risk. Appropriate selection is critical for the success of aortic procedures and must take into consideration several clinical and anatomical factors, also in asymptomatic patients, in which treatment remains controversial.

Even patients with mild-to-moderate asymptomatic AS have an excess of mortality and cardiovascular events than the general population. Many parameters have been shown to have an important role in predicting adverse events and therefore considered useful for the prognostic stratification.

The echocardiographic parameters include speed of the transvalvular jet, average and maximum transvalvular gradients, changes of these parameters over time, degree of valve calcification, left ventricular hypertrophy, and excess mass compared with the predicted values (inappropriate mass) and increased left atrial systolic force. Main clinical parameters include coexistence of coronary artery disease, advanced age, diabetes mellitus, increased body mass index, worse functional capacity, cigarette smoking, and high arterial blood pressure.

Finally, biological parameters include increased serum levels of brain-type natriuretic peptide measured at baseline conditions and/or C-reactive protein.

A system to further improve the prognostic stratification of AS patients may also consist in the use of indexes alternative to the classical method of the equation of continuity, such as energy loss index, stroke work loss, and valvuloarterial impedance. A correct stratification must also include a quantification of aortic valve calcifications.

The assessment of systolic function and left ventricle (LV) geometry plays an important role in stratifying a patient’s prognosis. Ejection fraction remains normal for a long time even in the presence of a high chronic pressure overload, while myocardial contractility is reduced significantly. A reduced midwall shortening has been associated with the onset of symptoms and a worse prognosis. The use of recent technologies such as speckle tracking enables to analyse the reduced longitudinal myocardial deformation that identify the AS patients with the greatest risk to transit from the compensatory phase to the pathological remodelling and worst prognosis after valve replacement. In addition to subclinical deterioration of systolic function parameters, also the changes in LV geometry and hypertrophy are able prognosticators of poor outcome. The presence of an LV mass in excess with respect to the aforementioned theoretical values in the individual patient (inappropriate mass) identifies a subgroup of subjects at higher risk compared with subjects having the same degree of AS but appropriate LV mass. An intrinsic myocardial dysfunction in the presence of preserved ejection fraction and severe low flow/low gradient is of clinical and prognostic significance.

Clinical and echocardiographic prognostic scores
A useful method for more accurate risk stratification in patients with AS is based on multiparametric scores. Monin et al. first proposed a score based on three variables: female sex, the maximum speed of the transvalvular aortic jet, and baseline BNP. The SEAS score, validated in mild-to-moderate AS, is based on seven parameters: age, sex, smoking, heart rate, serum bilirubin, serum levels of C-reactive protein, and LV mass. The ‘CAIMAN–ECHO score’ validated in moderate-to-severe AS, is based on three echocardiographic parameters: aortic valve calcium score assessed with conventional transthoracic echocardiography (TTE), maximum speed of transvalvular aortic flow, and inappropriate mass, measured as the ratio of measured and predicted mass.

Role of imaging in patient selection before transcatheter aortic valve implantation or surgical aortic valve replacement

Multimodality imaging plays an essential role in patient selection and procedural planning, performance, and follow-up. In each of these steps, optimal imaging can help to enhance successful outcome. Non-invasive imaging methods used for the selection of patients for TAVI are echocardiography, computed tomography (CT), and, less frequently, nuclear magnetic resonance. There is variability in the preferred imaging protocols in individual institutions, as a result of institutional and individual experience and equipment, and patient characteristics. The aim of the imaging is to: (i) confirm the severity of aortic stenosis; (ii) evaluate the anatomical suitability of revalving procedure and vascular accesses; and (iii) evaluate associated cardiovascular diseases.

Baseline TTE is usually adequate to confirm severity based on ACC/AHA/ESC criteria. A rigorous methodology that takes into account the possible technical difficulties and sources of error is however necessary. In the elderly people, the frequent coexistence of LV dysfunction can cause a discrepancy between low gradients and reduced area (AS with low flow and low gradient). In doubtful cases, low-dose dobutamine stress and anatomical evaluation using planimetric transoesophageal echocardiography (TEE) (preferably with three-dimensional reconstruction) can help differentiate a true AS by a pseudo-stenosis and to assess contractile reserve.
The evaluation of the anatomic suitability for revalving procedure includes the study of the vascular iliofemoral axis accessibility and of the aortic valve. Multilayer CT is the method of choice for assessing the size of the vessel, inner diameter, tortuosity, degree and extent of calcification, presence of high risk of dissection of complex plaques. This information is required to express an opinion on the possibility of introducing and advancing the guides and catheters and to assess the risk of any vascular complications. In the case of apical access, TTE verify the absence of apical aneurysm with thrombosis that represents a contraindication to this approach.

The anatomy of aortic cusps must have certain characteristics that make it suitable for the proper anchoring of the bioprosthesis. The bicuspid valve is a relative contraindication to TAVI. CT is the method of choice for the risk of spontaneous aortic dissection or of an incorrect opening of the bioprosthesis due to the elliptical orifice. A mildly calcified aortic valve is also a contraindication to TAVI for the risk of spontaneous aortic dissection or fibroelastica deficiency. The TTE/TEE are the methods of choice for the anatomical and functional assessment of mitral regurgitation. Severe pulmonary hypertension and right ventricular dysfunction represent a contraindication for TAVI. The TTE/TEE are the methods of choice for the study of this associated pathology.

Conventional and new pre-procedural risk scores
Surgical risk stratification requires objective and reliable methods. Of the many risk scores published over the years, those most frequently used for the estimation of short-term mortality risk in adult cardiac surgery are basically three: the EuroSCORE II (online calculator http://www.euroscore.org/calc.html), the STS score (online calculator http://riskcalc.sts.org/stswebriskcalc/#/calculate version 2.81), and the ACEF score. While the EuroSCORE II and ACEF are models applicable for the estimation of the risk of both coronary artery bypass surgery to valvular procedures or combined interventions, STS score offer separate models for isolated valve surgery or in combination with myocardial revascularization. The use of these risk scores is recommended by the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) and the American Heart Association/American College of Cardiology (AHA/ACC) guidelines.

The EuroSCORE was developed over 15 years ago, mainly in candidates for bypass coronary artery, while only one-third of patients were candidate for valve surgery. Considering the year of publication, the EuroSCORE I is defined ‘out of date’ by the authors and should not be used in favour of the updated version, the EuroSCORE II in which some new variables have been introduced while others have been modified. The STS risk score, unlike the EuroSCORE, was developed to identify the risk of death or perioperative complications, taking into consideration the specific type of intervention, coronary surgery, mitral, aortic, or combined.

The main features of a risk score are the power of discrimination—the ability to differentiate between low- and high-risk patients—and calibration—the ratio between observed and predicted mortality. Table 2 shows the characteristics of EuroSCORE, EuroSCORE II and STS score. A difference between these scores is that the calculation algorithms for EuroSCORE (I and II) and ACEF score are freely available but not periodically updated to the progressive change of patient’s clinical characteristics, while the algorithms of the STS risk scores are not freely available, but are regularly updated on the basis of the STS database. In SAVR, the performance of these algorithms is satisfactory for predicting the risk of category (high or low risk), with areas under the receiver-operating characteristics (ROC) curve ranging between 0.7 (fair discrimination) and 0.8 (good discrimination), even in octogenarians. These models tend to show more performance problems in
calibration, in particular in the assessment of patients usually defined as ‘high’ and ‘very high’ risk. In high-risk patients, EuroSCORE, EuroSCORE II, and ACEF overestimate mortality, while STS score tends to underestimate the risk. With regard to the medium- and long-term mortality, these scores show little satisfactory performances both in discrimination (AUC between 0.6 and 0.7) and in calibration.

Several studies have recently addressed the issue of the applicability of these risk scores to TAVI candidates. Overall, the acceptable discrimination allows to estimate with good approximation risk category, but poor calibration performance prevents from using these scores to estimate the individual operative mortality, especially in the high-risk category. In several studies, an average area under the curve around 0.6–0.7 was observed, a lower performance that could be obtained with surgery. EuroSCORE II and STS score performance was assessed in a meta-analysis of patients undergoing SAVR or TAVI. In the SAVR group, the difference between observed and expected mortality was not statistically significant with EuroSCORE II, while for the STS score the relationship was closer to 1. On the contrary, both the EuroSCORE II and the STS score have underestimated the risk of death in patients undergoing TAVI, confirming problems with calibration of these scores in this procedure.

The proportion of patients considered at high surgical risk on the basis of a single score (EuroSCORE II >7%, logistic EuroSCORE >20% and STS score >10%) and the correlation between scores were assessed in patients considered at high surgical risk based on a multiparameter stratification and candidates for TAVI. About half of the patients did not reach the value of high-risk threshold on the basis of the only score. The correlation between logistic EuroSCORE, EuroSCORE II, and STS was modest.

A recent analysis of the PARTNER trial suggests that performances for prediction of mortality with STS score and the logistic EuroSCORE are even less satisfactory (AUCs <0.6) for both SAVR and TAVI in very elderly patients. In summary, traditional risk scores seem to be inadequate as the only way to identify older patients with severe symptomatic AS at high risk and candidates for TAVI. There is a need to develop and validate specific score for this population.

An Italian multicentre study enrolling patients undergoing TAVI identified a previous stroke, creatinine clearance, and pulmonary hypertension as independent predictors of death at 1 year and calculated a score that showed a better performance than the STS score.

The TAVI2 score has been developed in a study of patients thought to be at high or prohibitive surgical risk. Variables independently associated with mortality at 1 year include: porcelain aorta, anaemia, low ejection fraction, recent myocardial infarction, male gender, mean aortic gradient >70 mmHg, age >85 years, creatinine clearance <30 mL/min. For each variable, a score was assigned and the sum identified the predicted risk of death at 1 year. The TAVI2 score showed improved power of discrimination and calibration compared with logistic EuroSCORE, EuroSCORE II, and the STS score.

The OBSERVANT study (Efficacy And Effectiveness of AVR-TAVI Procedures For the Treatment Of Symptomatic Severe Aortic Stenosis) has proposed another 30 days death risk score in patients undergoing TAVI. Seven independent variables related to the risk of death at 30 days were identified and integrated into a risk score.

**Multidimensional assessment**

In recent years, the availability of new techniques has extended to an older and frail population effective AS
treatments, however, currently used risk scores do not seem to be adequate in these patients. Therefore, it seems necessary to include other variables—i.e. co-morbidities and geriatric conditions—to improve risk stratification and compare the results of the procedures. Functional status is a multidimensional variable and also includes the ability of an individual to carry out daily activities within all functional domains. An overall assessment of functional status often requires multiple validated instruments, but on the other hand, a too complex battery may be little applicable and useful in clinical settings. The major open issues are the uncertainty of an operational definition of ‘frailty’ and what measurement tools to validate and use. However, there is no doubt that cardiac risk assessment of elderly people with heart disease should be performed, taking into account two fundamental points: (i) the instrument is valid, reproducible, and easy to use and (ii) is able to further stratify perioperative risk.

The European Valve Academic Research Consortium (VARC) described the importance of measuring clinical benefits such as functional status, but acknowledged the uncertainty that accompanied the choice of various measuring instruments and the overall lack of standardization. The Canadian Cardiovascular Society has also encouraged the use of an ‘objective assessment of function and neuro-cognitive Frailty’ to evaluate candidates for TAVI. Without providing an operational definition, the American Heart Association (AHA) recommended to include a functional assessment in the selection of elderly TAVI candidates.

Different tools have been proposed to identify frailty. The frailty index includes five easily detectable characteristics: muscle strength (handgrip), gait speed, weight loss, exhaustion, and level of activity. The subject that has no deficiency in any item is considered ‘robust’, ‘pre-frail’ if it has a deficit in one or two, ‘frail’ if it is positive in three or more of the items. The predictive value of frailty is independent of co-morbidities and clinical disability. The identification of frailty in the elderly people should not be made only for prognosis but should lead to ‘pre-rehabilitation’ interventions that have proven effective in the prevention of functional decline and mortality.

It is still debated whether disability and cognitive impairment should be considered frailty domains or just modulating factors that catalyse the transition from frailty to manifest disability.

The clinical evaluation of frailty as accumulation of deficits requires the evaluation of up to 70 symptoms, signs, morbidities, disability, and frailty, and for this reason, a simplified version was developed. However, disability, generally defined as difficulty or dependency in ADL or IADL, should be distinguished from frailty. Disability is more accurately conceptualized as a negative outcome associated with frailty or as an entirely separate entity. The International Academy Nutrition and Aging Frailty Task Force prefers the functional approach, stating that co-morbidity and disability must be separated from frailty.

A simple means for identification of frailty is the Short Physical Performance Battery (SPPB), which consists of three items: reduced gait speed, weakness in standing up from a chair, and reduced balance in three positions. A score from 0 to 4 is assigned to each item, where a total score >5 of 12 indicates the presence of frailty. The SPPB predicts the risk of disability and death in the elderly general population and with heart failure. As an alternative to these composite scores, individual variables such as gait speed on 4-5 m distance and handgrip force have been proposed as a single valid, simple, and reliable marker of frailty.

Several instruments and measures to assess the various components of functional status, QOL, disability, cognitive impairment, and various measures of frailty have been considered in pre-operative evaluation before TAVI.

In PARTNER study, TAVI resulted in significant improvement in NYHA Class and QOL, without reporting results on disability.

Another study reported that elderly patients undergoing TAVI were significantly more likely to develop clinically significant cognitive decline than those who underwent SAVR, but it is difficult to determine whether the results can be attributed to old age, reduced level of education, co-morbidity, or to the different treatment.

Therefore, recent studies have focused their interest on the concept of frailty and its importance in risk stratification before SAVR or TAVI. Afifalo et al. have shown in elderly patients undergoing coronary and valvular surgery that a low gait speed on 5 m identified a subpopulation at high-risk mortality and morbidity. The speed of <0.83 m/s was chosen as the optimal threshold based on ROC curves. Importantly, gait speed had an incremental value when combined with the STS score in predicting incidence of mortality/morbidity. There was tendency towards interaction for female patients and those undergoing SAVR, both of which had a much higher relative risk in the presence of frailty.

Lee et al. and Südermann et al. defined frailty as a dependency in walking, disability in ADLs, or dementia, a definition that includes more a concept of disability than frailty. Südermann et al. defined frailty as an aggregate of 35 criteria reporting a prevalence of 50%.

In another study, Afifalo et al. observed a prevalence of 46% and 20% of frailty, using respectively, gait speed and Fried index, and a 5% prevalence of ADL disability; the measurement of gait speed alone was superior to the other scales in predicting outcomes.

Some studies have been conducted specifically on patients undergoing TAVI. Ewe et al. found that one-third of patients undergoing TAVI were frail according to Fried index and that frailty was among the most powerful predictors of death, myocardial infarction, stroke, or heart failure at 9 months. Frailty was not a significant predictor of outcome if defined only according to subjective judgement of the physician in the study by Rodes-Cabau et al. Green et al. observed that frailty was predictive of 1-year mortality, but not at 30 days. There was a trend towards increased risk for major bleeding, vascular complications, and length of stay in frail patients. A gait speed of 0.50 m/s was selected as the optimal threshold, slower than the 0.65-0.85 m/s reported in other settings. The
authors observed that >80% of their patients would be considered frail if they had used the traditional cut-off values. Only 19%–35% of patients were able to complete the gait speed test. This significant percentage of non-walkers, larger than usually reported for other cohorts, may reflect the heavy burden of morbidity and disability in patients undergoing TAVI. The impossibility to complete gait speed test was an indicator of advanced frailty or ADL disability.

In another study, where the vast majority of patients were able to complete the timed-up-and-go (TUG) test (which requires getting up from a chair and walk 3 m), 61% were able to do it in faster than 20s. The frailty composite index used included TUG test, limitation of mobility, BADL and IADL disability, cognitive impairment, and nutritional assessment. Frailty was predictive of a three- to four-fold increase of functional decline in BADL at 6 months and higher incidence of cardiac and cerebral adverse events at 1 year. A trend for frailty and mortality was observed, which was stronger at 30 days compared with 1 year, although the number of events was small.

In all these studies, the overall approach to the evaluation of frailty aimed at predicting morbidity and mortality following TAVI involved the use of multidimensional assessment tools, including cognitive function, gait, nutritional status, and activities of daily living.34,139

The presence of disability is uncommon in the cardiac surgery population, partly because disabled patients are less likely to be considered for surgery. Therefore, the scales of disability for basic ADL are relatively insensitive to screen elderly patients in this context. Higher level disability scales such as the Nagi Scale are more sensitive and better predict outcomes. An interaction between frailty and disability was still observed, with the prognostic weight of frailty which decreases progressively in patients with more advanced stages of disability.32

An attempt to combine clinical risk scores and geriatric evaluation is reported in recent guidelines, where frailty indices proposed include gait speed and disability indicators such as those that contribute to the ADL score (Table 1). Frailty is summarily stratified as follows: not frail (able to carry out all ADL and to walk 5 m in <6 s), pre-frail (unable to perform one ADL or to walk 5 m >6 s), and moderately-severely frail (unable to perform >2 ADL). In addition to this risk classification, it would be appropriate to defer any kind of intervention in patients with reduced life expectancy.

In summary, it is not yet clear whether the standard of frailty assessment tools (frailty index) or surrogate measures, such as single physical performance test (gait speed, SPPB, and handgrip) are sufficiently valid if used alone, or if these measures should be combined with disability (inability to walk, low albumin, and ADL disability), a cognitive and nutritional screening or psychoemotional state to better discriminate the risk.126

In clinical practice, the feasibility of variables and speed of execution are fundamental as much as the reliability of the instruments themselves. Future studies should aim to develop more reliable and reproducible ways to identify frailty and validate its use to estimate risk and expected benefits.

Recent studies incorporate measures of frailty such as CoreValve, and Partner II. FRAILTY-AVR (NCT01845207) compared different frailty instruments to determine which is more predictive in high-risk patients with AS undergoing TAVI and SAVR. A European register (European CGA-TAVI registry) has been scheduled for the same purpose.

Gait speed over 5 m has been added to the STS database. In this database, patients undergoing TAVI were classified in very slow walkers (<0.5 m/s), slow walkers (0.5–0.83 m/s), and normal walkers (>0.83 m/s), and 30-day all-cause mortality rates were 8.4%, 6.6%, and 5.4%, respectively (P <0.001). Each decrease of 0.2 m/s speed corresponded to an increase of 11% in 30-day mortality. Very slow walkers had 35% higher 30-day mortality compared with normal, longer hospital admissions and were less likely to be discharged home.144 Pending further results, it is reasonable to apply a decision algorithm based on an initial screening carried out with a gait speed test, followed by a more thorough multidimensional assessment in patients with indicative results of Frailty (Figure 3).147

**Conclusions**

TAVI enables the treatment of very elderly patients with severe AS considered ineligible for surgery and with an acceptable life expectancy, with good results in terms of survival and symptoms. However, many patients still develop complications and die or show no improvement in QOL at follow-up. These issues raise important questions on the need to identify and recognize the possible futility of treatments in some patients approaching the final stages of life, where the clinical condition is too advanced and in which even a technologically successful procedure is useless and does not improve health outcomes. Thus, in the decision-making process, it is important to determine: (i) whether and how much frailty affects the risk of the procedures; (ii) whether the QOL and the individual survival are influenced by aortic valve disease alone or from other factors; (iii) whether a geriatric specialist intervention to evaluate and correct co-morbid diseases, frailty, and disabilities can further improve outcomes.
Although *futility* may be invoked to justify the refusal to treat an individual patient, the threshold for the definition of futility itself is still not clear. In *inoperable* patients, therefore, a clear definition of the conditions that may adversely affect survival and QOL, despite the procedural success is essential to ensure that this therapy is properly used in patients who can benefit or not. These patients should receive targeted medical and palliative care.\(^{148}\)

As TAVI patients are usually very elderly, with high risk score, advanced functional class, and frailty,\(^{144,51}\) to assess the expected benefit of TAVI, a number of variables should be considered in addition to the traditional risk scores. The evaluation of patient’s complexity can provide a valuable prognostic contribution and assist cardiologists and cardiac surgeons in the definition of the optimal treatment in the individual patient.\(^{17}\) Moreover, complexity therefore is not a sufficient reason to refuse a certain treatment but rather a means to choose a personalized and more patient-centred care.

At present time, the evaluation of the operative risk is carried out using standard indices that have not been

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**Table 3** Pre-procedure screening recommendations. Modified from ref.\(^{150}\)

| Laboratory indices | Full blood count, serum urea, creatinine and electrolytes, C-reactive protein, serum transaminases, serum albumin, coagulation profile, blood culture, sputum culture, mid-stream urine, glycylated haemoglobin, human immunodeficiency virus, and hepatitis serology |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Physical indices   | Height, weight, and body mass index                                                                                                         |
| Clinical data to calculate logistic EuroSCORE or STS score | Detailed clinical history, examination and current medication list, 12-lead electrocardiography, echocardiography (transthoracic/transoesophageal), coronary angiography, peripheral vascular screening (contrast angiography/multidetector computed tomography), pulmonary function testing, and right heart catheterization |
| Clinical parameters of co-morbid conditions | Pulmonary function tests, carotid, and vertebral and abdominal ultrasonography |
| Frailty and cognitive function\(^a\) | Grip strength, graded exercise testing, walk test, physical activity level, and mini-mental score |
| Confirmation of aortic stenosis severity and assessment of associated pathology | Echocardiography (transthoracic/transesophageal), exercise stress testing, and stress echocardiography |
| Procedural planning | Multidetector computed tomography/transoesophageal echocardiography Aortic annulus: dimensions (minimal, maximal, and mean diameter; area; perimeter) and severity/distribution of calcification Other: Height of coronary arteries, sinus of valsalva dimensions, ascending aorta dimensions Iliofemoral vessels: minimal luminal diameter, tortuosity, calcium distribution Aorta: aortic plaque distribution, descending aortic tortuosity, proximal ascending aortic diameter |

STS, Society of Thoracic Surgeons. 
\(^a\)Fried frailty index.
calibrated to intercept all the risk factors of very elderly pa-
tients and do not estimate frailty with specific parameters.
An attempt is reported in the recent guidelines,2 where a combi-
nation of frailty (reduced gait speed), disability indic-
ators, and cognitive deficit are proposed. Probably the combi-
nation of traditional risk scores such as EuroSCORE II
and STS score with indices of frailty and co-morbidity could
better refine the assessment of the operative risk in SAVR,
and STS score with indices of frailty and co-morbidity could
combination of traditional risk scores such as EuroSCORE II
and STS score with indices of frailty and co-morbidity could
combination of frailty (reduced gait speed), disability indi-
ators, and cognitive deficit are proposed. Probably the
combination of traditional risk scores such as EuroSCORE II

Conflict of interest: none declared.

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