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REVIEW

Clinical update

TAVI or No TAVI: identifying patients unlikely to benefit from transcatheter aortic valve implantation

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Transcatheter aortic valve implantation (TAVI) has spawned the evolution of novel catheter-based therapies for a variety of cardiovascular conditions. Newer device iterations are delivering lower peri- and early post-procedural complication rates in patients with aortic stenosis, who were otherwise deemed too high risk for conventional surgical valve replacement. Yet beyond the post-procedural period, a considerable portion of current TAVI recipients fail to derive a benefit from TAVI, either dying or displaying a lack of clinical and functional improvement. Considerable interest now lies in better identifying factors likely to predict futility post-TAVI. Implicit in this are the critical roles of frailty, disability, and a multimorbidity patient assessment. In this review, we outline the roles that a variety of medical comorbidities play in determining futile post-TAVI outcomes, including the critical role of frailty underlying the identification of patients unlikely to benefit from TAVI. We discuss various TAVI risk scores, and further propose that by combining such scores along with frailty parameters and the presence of specific organ failure, a more accurate and holistic assessment of potential TAVI-related futility could be achieved.

Keywords Aortic stenosis • Transcatheter aortic valve implantation • Futility • Risk scores

The advent of transcatheter aortic valve implantation (TAVI) signalled a paradigm shift for treating patients with severe aortic stenosis (AS). Not only has TAVI stimulated enormous development and innovation for a variety of transcatheter heart valve (THV) technologies, it has also resulted in a renewed interest in AS *per se*, with an intense focus on the comparative benefits of available therapeutic options. Current evidence points to the clinical superiority of TAVI vs. medical therapy in patients with critical AS deemed inoperable,[1] and TAVI is now deemed equivalent to conventional surgical aortic valve replacement (SAVR) in severe AS patients at high surgical risk.[2–4] Accordingly, there is now an ongoing quest to test the feasibility of TAVI in younger and lower surgical risk populations with AS.

Although research continues on the various technical aspects of TAVI (including device innovation, imaging-based procedural planning, procedural techniques and peri/post-procedural pharmacology), there is also an increasing recognition that some patients simply fail to derive a functional, morbidity, or mortality benefit post-TAVI. With ongoing scrutiny of the economic implications of TAVI, accurately identifying the subgroup of patients in whom TAVI is likely to be futile remains a priority. Given the known limitations of currently applied surgical risk algorithms for reliably predicting post-TAVI mortality,[5,6] there remains considerable interest in developing novel tools for predicting clinical futility post-TAVI. In parallel, there is an emerging consensus of the importance of a more holistic, multidisciplinary approach to pre-TAVI patient assessment, with careful attention to baseline frailty, mobility and cognition, in addition to a variety of comorbid medical conditions. Therapeutic futility is a generic term corresponding to a lack of medical efficacy. Although there is currently no uniform definition,[7] futility from a TAVI perspective is usually defined by the combination of death and/or absence of functional improvement during short-term follow-up post-procedure (6 months to 1 year).

This review aims to outline the patient factors and comorbidities currently known to be associated with a futile post-TAVI outcome,

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and thus help clarify which patients are unlikely to benefit from TAVI. The first part of the review focuses on specific non-cardiac and cardiac co-morbidities, whilst the second part discusses specific TAVI-related risk scores and global risk prediction.

Non-cardiac conditions and poor outcomes post-transcatheter aortic valve implantation

Severe chronic lung disease

The adverse prognostic effects that chronic lung disease (CLD) imparts upon post-TAVI clinical and functional outcomes have recently been described. Akin to the SAVR literature,[8] numerous national TAVI registries have confirmed that CLD patients undergoing TAVI (who account for about one-third of the TAVI population) are significantly more likely to demonstrate earlier mortality compared with those without CLD, irrespective of the type of valve inserted or procedural approach.[9–12] Although these data strongly suggest that pre-TAVI assessment should consider the presence of moderate–severe CLD as a marker of futility, the spectrum of CLD severity among potential TAVI recipients is broad, and these registry data do not necessarily outline which specific CLD patients are most likely to not benefit from TAVI. Therefore, analysing the relationship between CLD and a poor outcome post-TAVI requires a quantitative assessment of the severity of CLD.

Identifying futile outcomes among chronic lung disease-transcatheter aortic valve implantation candidates

Mok *et al.* evaluated the factors specifically associated with a poor outcome post-TAVI in patients with CLD (representing 30% of their study population).[13] Poor outcomes were defined as either mortality or lack of functional status improvement as evaluated by NYHA functional classification at 6-month follow-up. In over 40% of CLD patients, TAVI was judged to be futile, and close to one-third of CLD patients had died at 1-year follow-up (vs. $<$20% of non-CLD patients). A shorter distance walked during the 6-minute walking test (6MWT) was the main factor associated with poor outcomes. Approximately 75% of patients whose pre-TAVI 6MWT was $<$150 m died at follow-up compared with nearly 25% of patients whose baseline 6MWT yielded $\geq$150 m.

The outcomes of patients with CLD undergoing TAVI and SAVR were further examined in the PARTNER (Placement of Aortic Transcatheter Valve) trial.[14] This *post hoc* analysis confirmed the findings of Mok *et al.*, with CLD patients undergoing TAVI exhibiting greater mortality rates than those without CLD, although TAVI appeared to offer a better survival benefit than standard medical therapy alone in these patients. Poor mobility (defined as a distance $<$ 50 m during the 6MWT) and oxygen-dependency independently associated with greater mortality rates. Interestingly, other TAVI studies have also identified oxygen-dependency as an important marker of poorer outcomes (*Figure 1A*).

In respiratory medicine, studies involving COPD patients have developed a number of risk assessment tools for morbidity and mortality.[15,16] A distance of $<$150 m during the 6MWT remains a strong predictor of 3-year mortality in COPD patients. Poor exercise capacity and oxygen-dependency have been identified as the two most important factors determining a poor outcome post-TAVI among CLD patients. While some discrepancies exist regarding the specific 6MWT distance cut-off determining prohibitive risk, it seems that there is a very high likelihood of a poor post-TAVI outcome in those patients unable to walk at least 100 m during the 6MWT. Oxygen-dependent CLD patients are also at very high risk of poor outcomes, and a very thoughtful and extensive evaluation should be undertaken before accepting these patients for TAVI (*Table 1*). Baseline spirometric variables are associated with pulmonary complications post-TAVI;[13] however, no threshold has been shown yet to be predictive of futility.

Chronic kidney disease

Given the inevitable decline in renal function with increasing age, CKD is present in 30–50% of potential TAVI candidates, with a stepwise association demonstrated between the CKD severity and early and late mortality post-TAVI.[17] In fact, 1-year mortality rates in those with severe CKD exceed 30%,[18] and the presence of CKD has been consistently associated with poorer outcomes post-TAVI across several national registries,[9,10,12,19] and in a large-scale meta-analysis.[20] However, patients with advanced CKD were systematically excluded from randomized trials evaluating the feasibility of TAVI,[1–3] with the reliance on several large-scale multicentre analyses to identify CKD as likely marker of post-TAVI futility. Furthermore, given both the broad spectrum of CKD as well as its high prevalence in the TAVI population, isolating the subpopulation of CKD patients least likely to benefit from TAVI has been challenging.

Predicting poor outcomes among chronic lung disease-transcatheter aortic valve implantation candidates

Allende *et al.* pooled the clinical results of over 2000 patients who underwent TAVI, with the aim of evaluating factors predictive of poorer outcomes within the CKD population.[21] The presence of more advanced CKD, defined as an eGFR $<$ 30 mL/min was independently associated with 30-day post-TAVI mortality, as well as late cardiac and non-cardiac mortality. However, the presence of atrial fibrillation and dialysis-dependence were factors independently associated with mortality in advanced CKD patients (*Table 1*). Of note, the mortality rate among patients with advanced CKD and atrial fibrillation was $\sim$40% at 1 year, and increased to $>$70% when combined with dialysis-dependence (*Figure 1B*). Pre-existing atrial fibrillation has been recognized as an important prognostic factor in TAVI, related to an increase in decompensated heart failure, thrombo-embolic, and bleeding events.[22]

Frailty

The contribution of mobility, cognition, and nutrition is increasingly being evaluated as a means of identifying potential TAVI candidates unlikely to benefit from the procedure. By assessing the degree of physiological reserve in response to a specific stressor, one can evaluate the degree of frailty.[23]

Although the precise definition of frailty remains the subject of debate, a recent systematic review identified a consistent association between frailty and an increased risk of morbidity, mortality, and functional decline post-cardiac surgery.[24] The concept of prospectively applying an objective frailty assessment in potential

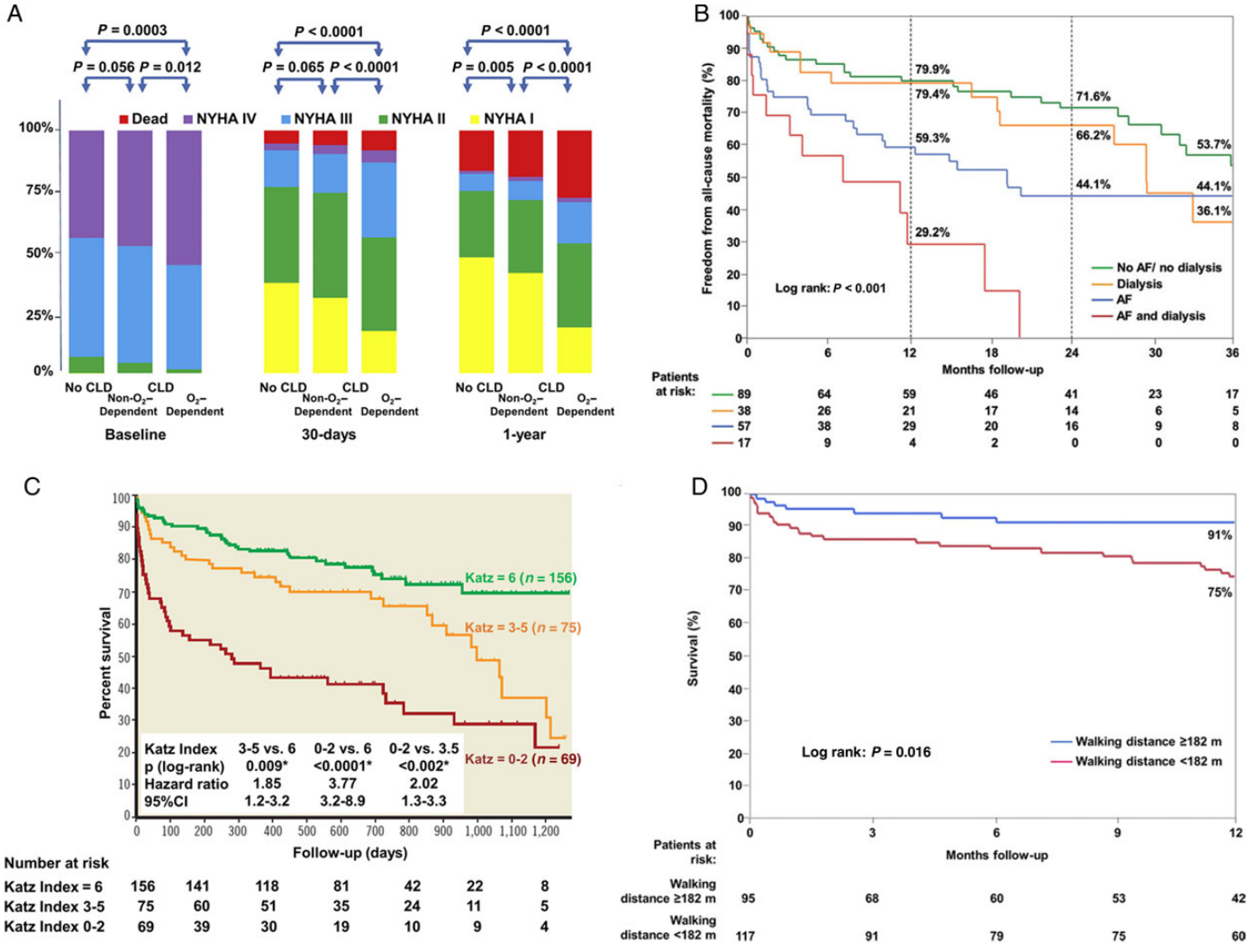

Figure 1 Non-cardiovascular factors linked with poorer outcomes following transcatheter aortic valve implantation. (*A*) Chronic and (oxygen-dependent) lung disease. Comparison at baseline, 30 days and 1-year post-transcatheter aortic valve implantation in those patients with no chronic lung disease, non-oxygen-dependent chronic lung disease and those with oxygen-dependent chronic lung disease (adapted from Dvir *et al.* with permission from the publisher).[14] (*B*) Chronic kidney disease. Kaplan–Meier survival curves at 3-year follow-up for all-cause mortality in patients with advanced chronic kidney disease, according to the presence of pre-existing atrial fibrillation and/or dialysis (adapted from Allende *et al.* with permission from the author).[21] (*C*) Survival depending on frailty status and its varying stages. Kaplan–Meier curves demonstrating the impact of the degree of frailty in the subgroups divided according to Katz index (0–2 severe disability, 3–5 moderate disability) on overall survival in transcatheter aortic valve implantation patients (adapted from Puls *et al.* with permission from the publisher).[30] Survival depending on functional status, assessed by the 6-min walking test. Kaplan–Meier survival curves at 1-year follow-up, according to mean distance walked during the 6-min walking test (< or ≥182 m) (adapted from Mok *et al.* with permission from the author).[13] CLD, chronic lung disease; AF, atrial fibrillation.

Table 1 Medical comorbidities and factors predicting poorer outcomes post-transcatheter aortic valve implantation

Medical comorbidity	Factors specifically associated with futility
CLD	6MWT < 150 m[13] Oxygen-dependency[14]
Advanced CKD	Atrial fibrillation[21] Dialysis dependence[21]
Frailty	>2 frailty indices (Katz activities of daily living + mobility status[a])[30]
Cardiovascular conditions	LVEF < 30% Pre-capillary or combined PH[b] (mean PAP > 25 mmHg)[44] Low trans-aortic gradient Impaired contractile reserve Low flow state (<35 mL/m^2)[40] Organic severe MR

6MWT, 6-min walk test; LVEF, left ventricular ejection fraction; PH, pulmonary hypertension; PAP, pulmonary artery pressures; MR, mitral regurgitation.
[a]Time taken to walk 5 m is >6 s.
Katz indices are: independence in feeding, bathing, dressing, transferring, toileting, urinary incontinence.
[b]Measured invasively. Combined PH defined as post-capillary PH (measured by LV end-diastolic pressure > 15 mmHg) with a diastolic pulmonary artery pressure ≥ 7 mmHg than LV end-diastolic pressure.

TAVI candidates, rather than an 'eyeball' test, was initially proposed in 2012,[25–27] and has been systematically assessed across several TAVI trials or registries. Although frailty assessed subjectively in a multicentre Canadian TAVI registry was independently associated with late mortality,[28] Stortecky *et al.* demonstrated that a multidimensional geriatric assessment (assessing cognition, nutrition, mobility, activities of daily living, and frailty) across 100 consecutive TAVI candidates significantly improved risk prediction compared with global risk scores.[27] Schoenenberger *et al.* prospectively demonstrated an index of frailty to strongly predict post-TAVI functional decline when adjusted for both the STS and EuroSCOREs.[29] The Katz index was evaluated in 300 consecutive TAVI patients within a single institution.[30] This frailty index was associated with early (30-day) and longer-term mortality (median observation period of 537 days), with a threshold Katz Index score of <6 predicting long-term mortality (*Figure 1C*). Green *et al.* recently reported on a PARTNER substudy evaluating the prognostic value of frailty (assessed using a composite of albumin levels, dominant handgrip strength, gait speed, and Katz index) in older TAVI recipients.[31] Poor outcome post-TAVI was defined as death, Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS) score <60 or a decrease of ≥10 points on the KCCQ-OS score from baseline to 1 year. Rates of all-cause mortality and poor post-TAVI outcome were significantly higher in the frail compared with non-frail TAVI recipients. A substudy from the US CoreValve trial characterized the health-related quality-of-outcomes status of over 400 patients who underwent trans-femoral TAVI with a self-expanding prosthesis.[32] A poor post-TAVI outcome was defined as death, a KCCQ-OS score of <45, or a decline in KCCQ-OS of ≥10 points at 6-month follow-up. Poor outcomes were reported in 39% of the population, with baseline wheelchair dependency, oxygen-dependency, low serum albumin (among several other factors) independently associating with a poor outcome. Also, a lower distance walked during the 6MWT has been associated with poorer outcomes (*Figure 1D*).[33] Although these data outline the importance of frailty as a risk factor determining poorer outcomes post-TAVI, there is currently little consensus on the optimal approach to assessing frailty in potential TAVI recipients. FRAILTY-AVR (Frailty Assessment Before Cardiac Surgery and Transcatheter Interventions; NCT 01845207) is an ongoing prospective cohort study ($n = 800$ patients recruited from 16 sites across Canada, USA, and France) designed to determine which frailty assessment tool is most predictive of mortality or major morbidity in elderly patients undergoing SAVR or TAVI.

The AHA/ACC guidelines on managing patients with valvular heart disease advocate frailty assessment in addition to global risk scores when assessing procedural risk.[34] A simple questionnaire including six activities of daily life (independence in feeding, bathing, dressing, transferring, toileting, and urinary continence) in addition to the mobility/functional status (no walking aid or assistance required or 5-m walk in <6 s) are used for evaluating frailty. Those patients with at least two frailty indexes are considered to be at moderate-to-high risk for surgical valve intervention, and this could potentially apply to TAVI procedures (*Table 1*). Although frailty could sway potential SAVR candidates towards TAVI, predictive models combining clinical factors, and a frailty assessment will likely optimize the selection of TAVI candidates who are most likely to derive maximal benefit.

Cardiac conditions and poor outcomes post-transcatheter aortic valve implantation

Reduced left ventricular ejection fraction

The prevalence of left ventricular (LV) systolic dysfunction in TAVI candidates ranges between 6–11 and 27–46% when defined as LVEF ≤ 30% or LVEF between 30 and 50% respectively.[35]

The potential benefits vs. poor outcomes of TAVI in populations with depressed LVEF remain important and somewhat controversial. For example, in an Italian registry involving >660 patients who underwent TAVI with a self-expanding THV, a baseline LVEF < 40% was independently associated with early mortality.[36] A separate pooled analysis of over 3 700 patients who underwent TAVI with either a balloon- or self-expanding prosthesis identified a baseline LVEF of ≤40% was independently associated with death due to advanced heart failure or sudden cardiac death during a mean follow-up period of ~2 years.[37] Interestingly, a *post hoc* analysis from the PARTNER trial failed to identify a significant impact of a low baseline LVEF (defined as LVEF > 20% but <50%, mean LVEF of 36 ± 9%) on post-TAVI or post-SAVR outcomes.[38] However, it is likely that the systematic exclusion of patients with severely depressed LVEF of <20%, low trans-aortic gradients (mean trans-aortic gradients < 40 mmHg) and those with incomplete coronary revascularization may have diluted the adverse prognostic effect of low LVEF on post-procedural outcomes.

Low valve gradients, reduced stroke volume

Emerging evidence suggests that the LVEF itself may not accurately represent the true extent of myocardial dysfunction in the setting of severe AS. Rather, reduced trans-aortic flow may be a more important prognostic factor. Patients with severe AS without sufficient contractile reserve following stress echocardiography demonstrate operative mortality of the order of 22–36% with SAVR.[39] A separate *post hoc* analysis of the full PARTNER cohort demonstrated that a low-flow state (defined as stroke volume index $\leq$ 35 mL/m^2) independently associated with 2-year mortality, irrespective of LVEF.[40] Although the dynamic interaction between LVEF, trans-aortic flow and gradients is complex, TAVI in patients with reduced LVEF and low transvalvular gradients without contractile reserve is generally associated with a worse outcome than in patients with higher transvalvular gradients (*Table 1*, *Figure 2A* and *B*). The importance of assessing for the presence/absence of contractile reserve as a means of further risk-stratifying AS patients has been well described.[41] This usually requires dobutamine stress echocardiography (in those patients with an LVEF $\leq$ 40% and an aortic valve area $\leq$ 1.0 cm^2) to assess for an augmentation in stroke volume (of $\geq$20%), indicative of the presence of contractile reserve.[42] Further insights into these issues will come from the ongoing TOPAS registry (NCT01835028) evaluating clinical outcomes and prognostic markers in patients with low flow, low gradient AS.

Pulmonary hypertension

Pulmonary hypertension (PH) may or may not accompany heart failure or a low LVEF. Current conventional global risk-scoring algorithms however do not include the presence of PH or associated right ventricular (RV) dysfunction as adverse prognosticators. Therefore, our current knowledge of the impact of PH upon TAVI outcomes and possible procedural futility is based upon registry or single-centre reports.

A single-centre experience of over 400 TAVI patients identified a pulmonary artery systolic pressure of 50 mmHg (measured non-invasively) as an optimal cut-off to predict post-TAVI outcomes.[43] In a more detailed study, O'Sullivan *et al.* characterized the impact of PH on TAVI outcomes based on several invasive haemodynamic parameters.[44] Patients were dichotomized according to the presence of PH (mean pulmonary artery pressure [PAP] $\geq$ 25 mmHg) or not. Those with PH were further stratified according to post-capillary PH (LV end-diastolic pressure $>$ 15 mmHg) or pre-capillary PH (LV end-diastolic pressure $\leq$ 15 mmHg). In patients with post-capillary PH, if the diastolic pressure difference between the pulmonary artery and left ventricle was normal ($<$7 mmHg) or elevated ($\geq$7 mmHg), they were further classified as having isolated PH or combined PH, respectively. Compared with patients with no PH, higher 1-year post-TAVI mortality was present in those with both pre-capillary and combined PH but not in those with isolated PH. The presence of combined PH was a strong predictor of 1-year mortality in a multivariable analysis (*Figure 2C*). These data support the role of a comprehensive baseline evaluation of the mechanisms contributing to PH in patients considered for TAVI. This may help better identify which patients with heart failure and or PH are more likely to experience a satisfactory vs. poor outcome post-TAVI. Furthermore, evaluating RV function is also likely to yield important prognostic information. Whilst RV function may be affected differently according to pre- vs. post-capillary PH, ultimately it is RV function that likely dictates clinical outcomes in patients with PH.

Severe mitral regurgitation

Mitral regurgitation (MR) can be classified as organic (intrinsic valve-related pathology) or functional (MR secondary to adverse LV remodelling). Overall, the prevalence of moderate–severe MR in the TAVI population varies between 2 and 33%, with some degree of organic MR being present in close to 50% of TAVI recipients.[45] A major challenge in determining the prognostic importance of MR in patients undergoing TAVI is the high degree of variability in MR grading across sites. As such, the actual prognostic impact of significant MR upon TAVI outcomes remains controversial. For example, some studies demonstrated moderate–severe MR to adversely impact 30-day and long-term survival, despite the fact that nearly 50% of these moderate–severe MR patients experienced an improvement in MR severity post-TAVI.[46,47] On the contrary, a PARTNER *post hoc* analysis indicated that moderate–severe MR was adversely prognostic at 2 years post-SAVR but not post-TAVI.[48] Nombela-Franco *et al.* recently reported a meta-analysis comprising eight studies and over 8000 patients to assess the clinical impact and changes of moderate–severe MR in TAVI recipients.[49] Moderate–severe MR was associated with both higher 30-day and 1-year mortality post-TAVI, although the degree of MR improved in 50% of individuals (*Figure 2D*). However, significant heterogeneity was observed across studies, possibly related to variability in pre-procedural MR grading. It is important to note that the presence of organic MR is unlikely to diminish following TAVI.

In summary, identifying the non-cardiac and cardiovascular factors leading to poor outcomes post-TAVI remains a challenging and unresolved issue. With regards to non-cardiac conditions, a large body of evidence supports that CLD, CKD, and frailty predict futility post-TAVI. However, it remains difficult to deny TAVI on the basis of a single variable related to respiratory of renal function. In addition, assessing the large number of indices of frailty requires a comprehensive but time-consuming geriatric evaluation, thereby compromising its routine use in practice. A multi-disciplinary Heart Team is fundamental for a global, holistic patient assessment, especially for more specific frailty assessments. The implication of geriatricians is of particular importance in this setting. Furthermore, given the frequency of concomitant CLD in potential TAVI candidates, regular dialogue with a thoracic physician would also seem useful, and other disease specialists should be involved in accordance with the presence/absence of relevant comorbidities. Concerning cardiac conditions, available data suggest that low LVEF cannot be used as an isolated factor for determining futility post-TAVI. Rather, the presence of a low flow state, severe PH (especially pre-capillary or combined), and severe organic MR are cardiovascular factors that should be considered in the clinical decision-making process of potential TAVI candidates. Furthermore, studies have demonstrated the adverse impact of pre-existing or new-onset atrial fibrillation (AF) on post-TAVI morbidity and mortality.[28,50] Similar data have been demonstrated when examining the impact of AF post-SAVR.[51] However, AF *per se* more likely represents a marker of advanced underlying cardiac disease such as heart failure, multi-valvular

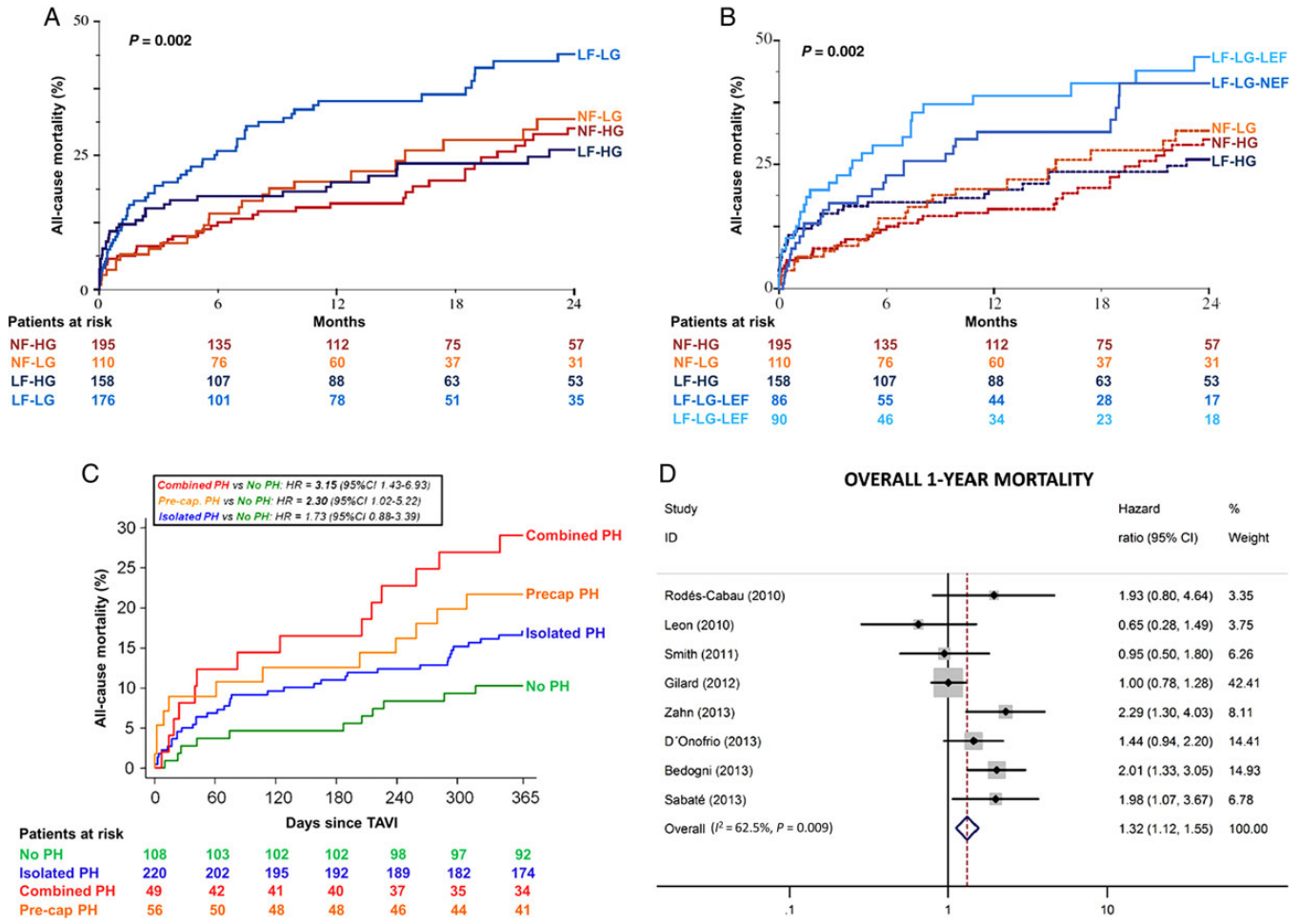

Figure 2 Cardiovascular factors linked with poorer outcomes following transcatheter aortic valve implantation. (*A*) The influence of trans-aortic flow and gradients on 1-year mortality post-transcatheter aortic valve implantation. Normal flow was defined as stroke volume indexed for body surface area $>$ 35 mL/m^2, and a high gradient was defined as mean transaortic gradient $\geq$ 40 mmHg, low gradient $<$ 40 mmHg. (*B*) The added influence of left ventricular ejection fraction upon 1-year mortality post-transcatheter aortic valve implantation. Low ejection fraction defined as left ventricular ejection fraction $<$50%, normal ejection fraction defined as left ventricular ejection fraction $\geq$50% (*A* and *B* adapted from Le Ven *et al.* with permission from the author).[64] (*C*) The influence of pulmonary hypertension on 1-year post-transcatheter aortic valve implantation mortality. Kaplan–Meier analysis of death at 1-year comparing transcatheter aortic valve implantation patients with isolated post-capillary pulmonary hypertension, combined post- and pre-capillary pulmonary hypertension, pre-capillary pulmonary hypertension, and patients without pulmonary hypertension (adapted from O'Sullivan *et al.* with permission from the publisher).[44] (*D*) The influence of mitral regurgitation on 30-day post-transcatheter aortic valve implantation mortality. Forest plot showing individual adjusted and pooled analysis for both balloon- and self-expandable valves. The size of the squares represents the percentage of the contribution of each study in the final result and is equivalent to the % weight of each study included in the meta-analysis. The lines represent the confidence interval of the odds ratio or hazard ratio (95%). The rhombus represents the final effect of the studied factor (significant mitral regurgitation) on mortality (adapted from Nombela-Franco *et al.* with permission from the author).[49] LF, low flow; LG, low gradient; HG, high gradient; NF, normal flow; PH, pulmonary hypertension; LEF, low ejection fraction.

Table 2 Transcatheter aortic valve implantation-specific risk scores and their specific features

Risk score	Number of patients	End point	Predictive factors[a]	c-statistics
PARTNER[58]	2137	6-month death or poor outcome[b]	*Positive predictors*: history of major arrhythmia, serum creatinine, and oxygen-dependent lung disease *Inverse predictors*: diabetes mellitus, mean aortic valve gradient, mini-mental status exam, and KCCQ Overall Summary Score	Derivation: 0.66 Validation: 0.64
FRANCE 2[59]	3833	30-day or in-hospital mortality	Age $\geq$ 90 years, BMI $<$ 30 kg/m^2, NYHA class IV, PH, critical haemodynamic state, $\geq$2 pulmonary oedema presentations/year, respiratory insufficiency, dialysis, and non-transfemoral access	Derivation: 0.67 Validation: 0.59
TARIS[61]	845	1-year mortality	BMI, low eGFR (per mL/min/1.73 m^2), low Hb (per g/dL), PH, low mean baseline trans-aortic gradient, LVEF $<$ 45%	Derivation: 0.66 Validation: 0.60 Sensitivity analysis: 0.71[c]

Cr, creatinine; CLD, chronic lung disease; BMI, body-mass index; NYHA, New York Heart Association; PH, pulmonary hypertension; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; LVEF, left ventricular ejection fraction.
[a]Those with associations of $P < 0.05$.
[b]Defined as Kansas City Cardiomyopathy Questionnaire Overall Summary Scale score $\leq$ 45 or $\geq$10-point decrease compared with baseline.
[c]Following the addition of frailty.

disease, and more extensive vascular disease. Moreover the interaction between AF, anti-thrombotic therapies, bleeding, and ischaemic events is complex and difficult to reconcile solely on the presence or absence of AF. Furthermore, it is unlikely that any single cardiovascular factor is sufficient to identify a group of patients for whom TAVI is likely to be truly futile. Rather, the combination of several factors will likely determine a prohibitive risk post-TAVI (*Table 1*), and it is therefore attractive to combine these in multivariate risk scores. In situations whereby the role of TAVI is not clear, or due to persisting signs of clinical decompensation possibly attributable or enhanced by underlying severe AS, balloon aortic valvuloplasty as a 'bridging strategy' has been shown to be effective in selected patients.[52,53]

Transcatheter aortic valve implantation-risk scores predicting poor outcomes post-transcatheter aortic valve implantation

Clinical risk assessment in potential TAVI candidates has been based largely on the STS and EuroSCORE (including EuroSCORE 2) which were actually developed to predict short-term risk following cardiac surgery, based largely on the extent of baseline medical comorbidities.[54,55] Although these risk scores have been applied in TAVI population, their utility for this purpose is limited given their frequent discordance and modest correlations with 30-day and mid-term post-TAVI outcomes.[5,6,56] Furthermore, it is now well accepted that in current TAVI populations, accurately measuring procedural outcomes should not only include procedure-related clinical events but also account for quality of life and levels of functionality. As such, defining a poor post-TAVI outcome has been recently proposed to combine both mortality and quality-of-life measures within a single composite endpoint.[57]

This endpoint definition was applied to the PARTNER trial as a means of identifying patients at high risk for a poor outcome post-TAVI.[58] Quality of life was assessed using the Kansas City Cardiomyopathy Questionaire Overall Summary (KCCQ-OS) scale (range 0–100), and a poor 6-month post-TAVI outcome was subsequently defined as death, KCCQ-OS score $<$45, or $\geq$10-point decrease in KCCQ-OS score compared with baseline), and identified in 33% of patients. The most important baseline predictors of poor outcomes included reduced exercise capacity (measured using 6MWT), lower baseline mean aortic valve gradients, oxygen-dependent CLD, CKD, and poor baseline cognition, whereas the STS score was not a significant predictive factor. Despite the inclusion of two indices of functional and cognitive capacity, this model demonstrated moderate discrimination (*c*-indices of 0.66 and 0.64 in derivation and validation cohorts respectively), and was able to identify 10% of patients with a $\geq$50% likelihood of a poor post-TAVI outcome. These findings suggest that the assessment of frailty according to a limited number of is not sufficient to achieve a reliable prediction of futility post-TAVI. At the time of data collection for PARTNER, additional factors important in the multi-geriatric assessment of patients were not collected, which might have negatively biased the predictive model. A risk calculator from PARTNER has recently been developed, providing online assistance to clinicians for objective risk estimations for potential TAVI recipients (*Table 3*).

Another risk score was developed by Iung *et al.* using the FRANCE 2 cohort ($n = 3833$ consecutive patients), to predict 30-day post-TAVI mortality.[59] Up to nine pre-procedural factors associated with 30-day mortality were identified: age $\geq$ 90 years, body mass index $\leq$ 30 kg/m^2, NYHA functional class IV, PH, a critical hemodynamic state, $\geq$2 admissions for pulmonary oedema within the prior year, dialysis-dependence, respiratory insufficiency, and a non-trans-femoral approach. Each factor was weighted and a

Table 3 Integrated approach for estimating transcatheter aortic valve implantation-specific risk and futility

Criteria	Low risk	Intermediate risk	High risk	Prohibitive risk
PARTNER TAVI score[a], OR FRANCE 2 TAVI score	<25% risk of mortality or lack of QOL improvement at 6 months Risk score: 0 (30-day mortality risk < 5%)	25–50% risk of mortality or lack of QOL improvement at 6 months Risk score: 1–5 (30-day mortality risk 5–15%)	>50% risk of mortality or lack of QOL improvement at 6 months Risk score: 6–7 (30-day mortality risk 15–25%)	Risk score ≥ 8 (30-day mortality risk > 25%)
Frailty[b]	None	1 index	≥2 indices	≥4 indices
Specific major organ system compromise not to be improved post-TAVI[c]	None	1 organ system	2 organ systems	≥3 organ systems

[a]http://h-outcomes.com/tavi-risk-calculator/.
[b]Frailty based on Katz Index (independence in feeding, bathing, dressing, transferring, toileting, and urinary incontinence)[30] and independence in ambulation (walk 5 m in <6 s).
[c]Examples of major organ system compromise:[34] Cardiac—severe LV systolic or diastolic dysfunction or RV dysfunction, and fixed pulmonary hypertension; CKD stage 3 or worse; pulmonary dysfunction with FEV1 < 50% or DLCO < 50% of predicted; CNS dysfunction (dementia, Alzheimer's disease, Parkinson's disease, and CVA with persistent physical limitation); GI dysfunction—Crohn's disease, ulcerative colitis, nutritional impairment, or serum albumin < 3.0; cancer—active malignancy; and liver—any history of cirrhosis, variceal bleeding, or elevated INR in the absence of VKA therapy.

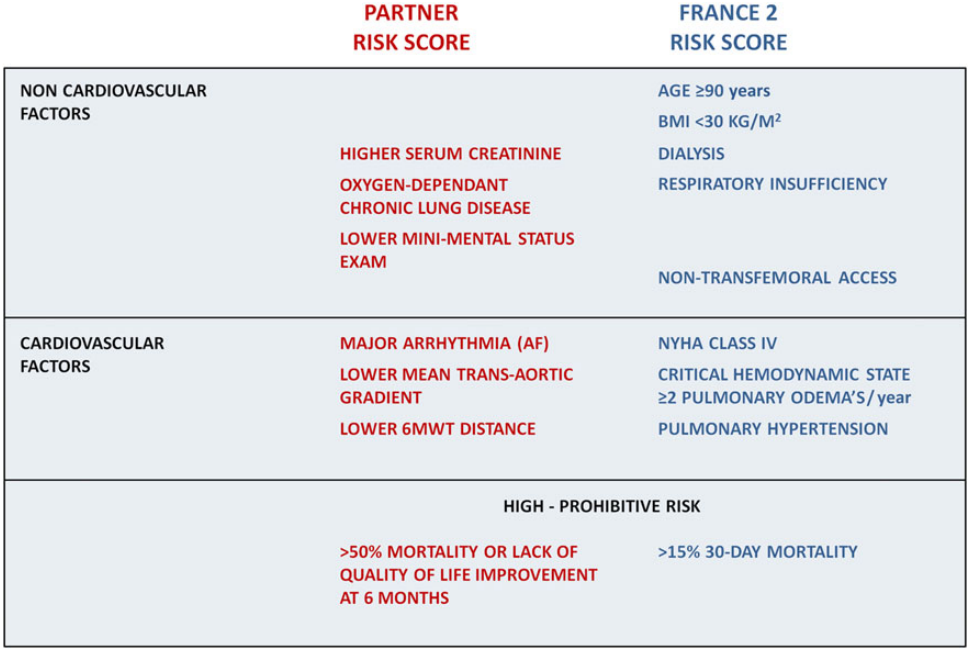

Figure 3 Cardiovascular and non-cardiovascular factors linked with transcatheter aortic valve implantation-related futility featured within the PARTNER and FRANCE 2 transcatheter aortic valve implantation-risk score models. 6MWT, 6-min walk test; BMI, body-mass index; Cr, creatinine; CLD, chronic lung disease; AF, atrial fibrillation.

21-point scale was constructed. Mortality rates < 5% or >40% were observed among patients with the lowest and highest risk scores, respectively. *c*-indices of 0.67 and 0.59 were observed in the derivation and validation models, respectively, suggesting modest predictive capacity. A limitation of this model was the lack of inclusion of frailty and functional assessment. Other models developed to predict risk post-TAVI have also been reported,[60–62] with variable limitations and prognostic capacity (summarized in *Table 2*).

A common theme emerging from these models, however, are their superiority to the STS and EuroSCORE, and the importance of integrating a comprehensive assessment of frailty and function as a means of improving both the relevance and accuracy of predicting TAVI-associated outcomes in a high-risk population.

These current limitations outline the potential interest of new TAVI-specific risk scores including a quantitative rather than binary coding of comorbities and indices of frailty. A number of

indices of frailty are associated with outcome. However, the addition of a limited number of them leads only to a moderate improvement in the predictive value of multivariate models. Therefore routinely assessing frailty in clinical practice would likely be a compromise between a multidimensional approach versus more isolated and simplistic tests. Even with such refinements of risk scores, concerns remain regarding the possibility to accurately assess the contribution of each patient characteristic to outcome in the heterogeneous high-risk population.[63]

In the absence of an ideal TAVI risk score, we propose in *Table 3* and *Figure 3* an integrated approach for risk evaluation of a futile outcome in TAVI candidates. This proposal uses a similar structure as the current AHA/ACC guidelines on the management of patients with valvular heart disease,[34] but introduces the use of risk scores specifically developed for TAVI candidates.

Conclusions

Advancements in innovation and technology have equipped us with the ability to successfully treat patients suffering the most advanced stages of AS who have traditionally been deemed inoperable or too high-risk for conventional SAVR. Despite enthusiasm for high rates of device-related procedural success, the success of monitored anesthesia care without the need for endotracheal intubation, and relatively low rates of procedural mortality, the sobering reality is that a substantial portion of these individuals fail to derive long-term functional improvement post-TAVI. Accordingly, considerable interest lies in the ability to better identify those individuals least likely to derive benefit from TAVI. An emerging consensus on the importance of frailty as a predictor of procedural success following a range of cardiovascular procedures, and incorporating a more holistic approach to baseline assessment is likely to better identify those patients in whom TAVI is likely to be futile. The development of multivariate risk scores combining variables reflecting cardiac and non-cardiac conditions and frailty appears attractive in this setting. However, substantial work remains to be done to achieve standardized definitions of a limited number of variables which can be easily collected during routine practice and to test the incremental predictive value of such models. Our fascination with technological refinements will continue to push the boundaries for treating the once untreatable chronic cardiovascular diseases. However as physicians, we must remember to resist the temptation of blindly offering novel therapies to all patients, and to honour the principle of first 'doing no harm.'

Authors' contributions

R.P., J.R.-C. acquired the data, conceived and designed the research, and drafted the manuscript. B.I., D.C. Made critical revision of the manuscript for key intellectual content.

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