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Transcatheter aortic valve implantation in the elderly: an umbrella review

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Abstract

Aim: The management of aortic stenosis has seen momentous changes thanks to the introduction of transcatheter aortic valve implantation (TAVI, i.e., transcatheter aortic valve replacement). Indications to TAVI have expanded progressively to intermediate- and low-risk patients, but trends in life expectancy have led to an increase of elderly but fit individuals with aortic stenosis eligible for TAVI.

Methods: We reviewed the current evidence base on TAVI in the elderly by conducting an umbrella review (i.e., overview of systematic reviews), based on a formal bibliographic search for systematic reviews on TAVI in elderly patients (≥ 65 years). Key, study, patient, procedural, and outcome data were extracted, and validity formally appraised with the Oxman-Guyatt index.

Results: From 71 citations, eight reviews were included (totaling 39 studies and 8579 patients): five systematic reviews, and three meta-analyses. Topics of interest were cognitive function before and after TAVI, predictive role of muscle mass and frailty on post-TAVI outcomes, comparative safety and effectiveness of TAVI, and role of rehabilitation to improve patient outlook after TAVI. Thirty-three additional studies were retrieved by means of snowballing, emphasizing the

role of multidimensional assessment of elderly patients scheduled for TAVI, in order to maximize its appropriateness, effectiveness, and safety.

Conclusion: It is crucial to consider frailty scores, as well as nutrition and functional status, in addition to established surgical risk scores, in elderly patients considered for TAVI to improve risk prediction, reinforcing the favorable impact of this therapy to improve cognitive function.

Keywords: Aortic stenosis, elderly, transcatheter aortic valve implantation, transcatheter aortic valve replacement

INTRODUCTION

Surgical aortic valve replacement (SAVR) has been for several decades the default management strategy for severe aortic stenosis in fit patients[1]. However, an ever increasing elderly population, often fraught with substantial comorbidities, has challenged in many cases the risk-benefit profile of surgery[2]. Accordingly, less invasive strategies were developed, including balloon aortic valvuloplasty[3].

Building upon developments in materials and procedures, and inspired by breakthrough results of stenting for coronary and endovascular procedures, transcatheter aortic valve implantation (TAVI), also called transcatheter aortic valve replacement (TAVR), was introduced by Alain Cribier almost two decades ago[4-6]. The successes of TAVI have been dramatic indeed, as poignantly summarized by the recent US Food and Drug Administration approval of new-generation devices for TAVI even in patients at low surgical risk[7]. However, TAVI continues to be considered and used mostly for elderly patients, given the uncertainty on long-term and very long-term device durability[8].

Despite the evidently favorable risk-benefit profile of TAVI in general, and in the elderly in particular, several areas of investigation and debate persist, typically focusing on indication, timing, procedural aspects, device choice, ancillary medical management, and post-procedural results[6]. We aimed at exploiting the synthesizing power of umbrella review studies to reconcile conflicting sources of evidence on TAVI in the elderly, in order to inform current practice and guide future research[9].

METHODS

This scoping umbrella review was conducted in keeping with best practice recommendations, and reported accordingly[9]. Specifically, we used a multifaceted approach for evidence accrual, avoiding a specific or restrictive definition of elderly. First, PubMed was searched using the following string: "{elderly OR octogenarian* OR octagenarian* OR nonagenarian* OR old OR aged OR [age AND (advanced OR old)]} AND transcatheter AND aortic AND valve AND (implantation OR replacement) AND systematic[sb]" up to 31 October 2019. Accordingly, any review detailing on, at least in part, nonagenarians, octogenarians, aged patients, or subjects with advanced or old age could be included, provided it also focused on TAVI. Thereafter, we used backward and forward snowballing to identify additional citations. Afterwards, potentially relevant citations were screened at the title/abstract level. Potentially relevant hits were then retrieved as full-texts.

We included systematic reviews (i.e., overviews of published clinical studies including two or more primary original reports) detailing TAVI in elderly patients (defined as people aged ≥ 65), irrespective of their focus on diagnosis, prognosis, device choice, procedural aspects, or outcomes, to avoid being overly restrictive. Several domains were abstracted, including review features, study aspects, and other details on included patients, procedures, and outcomes. Review validity was appraised with the Oxman and Guyatt Overview Quality Assessment Questionnaire[10]. All reviewing activities were performed by two independent reviewers, with divergences solved after consensus.

Table 1. Included systematic reviews on TAVI in the elderly

Ref.	PubMed ID	Focus	Studies	Patients	Highlights
Anand *et al.*[11]	28927173	Frailty	10	4592	Frailty is a significant predictor of adverse events after TAVI
Fink *et al.*[12]	26192563	Cognitive function	1	64	Cognitive function may be impaired after TAVI
Furukawa *et al.*[13]	25916404	Frailty	6	1023	Frailty is a significant predictor of adverse events after TAVI
Lai *et al.*[14]	25785192	Cognitive function	6	349	Cognitive function remains stable or improves after TAVI
Mohammadi *et al.*[15]	26728319	Effectiveness of TAVI	NA	NA	TAVI impacts favorably on morbidity and mortality in elderly patients with AS
Ribeiro *et al.*[16]	28071146	Rehabilitation	5	292	Cardiac rehabilitation improves functional capacity and QoL after TAVI
Sepehri *et al*[17]	25199821	Frailty	3	378	Frailty is a significant predictor of adverse events after TAVI
Soud *et al.*[18]	30915667	Muscle mass	8	1881	Skeletal muscle area appraised with CT is a significant predictor of adverse events after TAVI

CT: computed tomography; NA: not applicable; QoL: quality of life; TAVI: transcatheter aortic valve implantation; AS: aortic stenosis

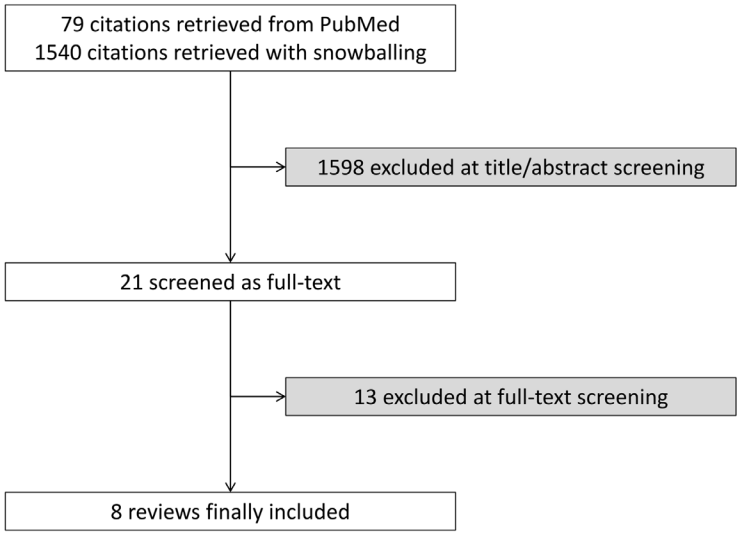

Figure 1. Review profile, detaling study search and selection

RESULTS

From an initial set of 1619 citations, a subset of 21 were retrieved as full-texts, finally yielding eight reviews, totaling 39 primary studies and 8579 patients [Table 1 and Figure 1][11-18]. Five were systematic reviews only, and the remaining three also provided meta-analysis results[11,16,18]. The topics of interest were cognitive function before and after TAVI[12,14], predictive role of muscle mass and frailty on post-TAVI outcomes[11,13,17,18], comparative safety and effectiveness of TAVI[15], and role of rehabilitation to improve patient outlook after TAVI[16]. Review quality ranged from high validity and low risk of bias for five reviews[11,12,16-18], to low validity and high risk of bias in three reviews[13-15] [Table 2], with lack of adequate reporting being the most common limitation.

In particular, Anand *et al.*[11] performed a systematic review and meta-analysis appraising the prognostic impact of frailty in patients undergoing TAVI, including a total of 10 studies and 4592 patients. They concluded that frailty proved to be a significant predictor of adverse events after TAVI. Similar findings were reported by prior reviews such as the systematic review conducted by Furukawa *et al.*[13], encompassing six primary studies and 1023 patients, and the one authored by Sepehri and colleagues, totaling three studies and 378 subjects[17]. A relatively similar focus was chosen by Soud *et al.*[18], who pooled eight studies including 1881 to appraise the predictive usefulness of appraising skeletal muscle mass by means of computed tomography (CT). CT-derived muscle area showed a significant prognostic

Table 2. Validity appraisal of included systematic reviews on TAVI in the elderly

Ref.	Search methods stated	Search for evidence comprehensive	Inclusion criteria reported	Selection bias avoided	Validity criteria reported	Validity criteria appropriate	Combination methods appropriate	Combination methods coherent	Conclusions supported by results	Overall rating
Anand *et al.*[11]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High validity
Fink *et al.*[12]	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	High validity
Furukawa *et al.*[13]	No	NA	No	NA	No	NA	NA	NA	NA	Low validity
Lai *et al.*[14]	Yes	Yes	No	NA	No	NA	NA	NA	NA	Low validity
Mohammadi *et al.*[15]	No	Yes	No	Unclear	No	NA	NA	NA	NA	Low validity
Ribeiro *et al.*[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High validity
Sepehri *et al.*[17]	Yes	Yes	Yes	Yes	Yes	Yes	NA	NA	NA	High validity
Soud *et al.*[18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High validity

NA: not applicable; TAVI: transcatheter aortic valve implantation

role in patients undergoing TAVI. Cognitive function before and after TAVI was the topic of interest of Fink *et al.*[12] (who included only one study and 64 patients undergoing TAVI) and Lai *et al.*[14] (who overviewed six studies and 349 subjects). Notably, they found that cognitive decline is common among elderly patients with severe aortic stenosis awaiting TAVI, whereas this procedure is not associated with significant worsening in cognitive function (which can actually improve after TAVI). Finally, Mohammadi *et al.*[15] reviewed several studies on TAVI in elderly patients to gauge the effectiveness and safety of this procedure, whereas Ribeiro *et al.*[16] reported the results of a meta-analysis spanning five studies and 292 patients on the use of cardiac rehabilitation following TAVI, concluding that this protected discharge approach may improve functional capacity and quality of life.

Given the limited scope of the systematic reviews retrieved with a focused umbrella review approach, we also explored by means of snowballing other bibliographic sources, highlighting several important primary studies on the indications, subtleties, and outlook of TAVI in elderly patients [Table 3]. In total, 33 reports were shortlisted, including as many as 30,657 subjects. Specifically, three were reviews, one was a qualitative study, 26 were observational studies, and three were diagnostic studies. The focus of reports varied, ranging from frailty appraisal tools to the electrical risk score, N-terminal pro-brain natriuretic peptide levels, oxygen consumption formulas, diagnosis of bicuspidy, nutritional status, grip strength, cognitive function, balloon aortic valvuloplasty, postoperative delirium, and prehabilitation/rehabilitation. Overall, these reports highlight the importance of multidimensionally considering every elderly patient with aortic stenosis considered for TAVI, in order to maximize appropriateness, maximize effectiveness, and minimize risk.

DISCUSSION

The present umbrella review, aiming at summarizing the evidence base for TAVI in elderly patients, has the following implications: (1) While TAVI has been offered mostly to patients at high surgical risk with advanced age, the evidence thus far accrued on TAVI in elderly subjects is relatively limited; (2) Frailty and cognitive function were the most commonly covered topics, with reports highlighting the importance of considering frailty scores on top of standard surgical risk scores to improve the accuracy of risk prediction and ensuing decision-making, and promising data in favor of TAVI as a means to improve cognitive function; and (3) Other studies, elicited from a scoping appraisal of the scholarly literature on TAVI in elderly patients, highlighted the importance

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Table 3. Selected studies on TAVI in the elderly

Ref.	PubMed ID	Design	Patients	Highlights
Amofah (2016)	26635329	Observational study	143	Sleep is disturbed in patients with AS, and may improve after SAVR and TAVI, albeit less with the latter
Bogdan (2016)	27159658	Observational study	150	Albumin predicts long-term outcomes after TAVI
Bordoni (2015)	26378413	Observational study	224	Repeat BAV is a reasonable management strategy in elderly patients who are not candidate for TAVI
Boreskie (2019)	31543187	Review	NA	Prehabilitation may be beneficial in patients with AS awaiting TAVI
Cavalcante (2017)	29212513	Observational study	113	Cardiac amyloidosis is common in elderly patients with AS and predicts adverse outcomes after TAVI
Ciuca (2017)	28585899	Observational study	62	Cognitive impairment is common in elderly patients with AS but is not significantly impacted by TAVI
de Thézy (2017)	29187325	Diagnostic study	49	The G8 tool is a useful screening scale for frailty in elderly patients with AS
Drudi (2018)	29344620	Observational study	1035	Depression is common in patients awaiting TAVI, and it predicts adverse outcomes, especially if persisting after the procedure
Eide (2015)	25644851	Observational study	143	Postoperative delirium is less common with TAVI than with SAVR in octogenarians
Elgendy (2019)	30569661	Observational study	6680	TAVI is associated with similar mortality but less morbidity than SAVR in nonagenarians with AS
Gertz (2014)	23704061	Diagnostic study	51	Oxygen consumption is best estimated with a modified mathematical formula
Goldfarb (2018)	29976568	Observational study	1158	Preprocedural nutritional status is associated with mortality in older adults undergoing TAVI or SAVR
Green (2012)	22331630	Observational study	102	Gait speed is associated with ADL in elderly patients with AS
Instenes (2018)	28396186	Qualitative study	10	Postoperative delirium is common after TAVI and SAVR, and its memories persist long-term
Kagase (2018)	29301641	Observational study	927	Grip strength predicts long-term outcomes after TAVI
Kamga (2013)	24579438	Observational study	30	The SHERPA frailty score in an independent predictor of post-TAVI outcome
Kim (2019)	31587128	Diagnostic study	2583	CT can reliably recognize bicuspid AS in the elderly
Lindman (2016)	27113148	Review	NA	Multimorbidity is common in elderly patients with AS
Mentias (2019)	31668118	Observational study	13,544	Outcomes of TAVI in nonagenarians have improved by considering the impact of early complications on long-term events
Murata (2019)	31462606	Observational study	58	Ventilatory efficacy predicts long-term outcomes after TAVI
Nagura (2019)	30599060	Observational study	1004	Post-procedural valvuloarterial impedance is not associated with increased mortality after TAVI
Oh (2019)	31514956	Observational study	261	Long-term outcomes are similar with TAVI and SAVR in low-risk elderly patients
Okoh (2019)	30618060	Observational study	1160	Discharge disposition impacts on post-TAVI outcomes
Olsen (2017)	27036955	Observational study	65	TAVI improves self-reported global health and generic physical health and quality of life
Orvin (2014)	24481462	Observational study	36	TAVI impacts favorably on functional performance and cognitive function
Piccirillo (2018)	30237702	Observational study	40	The 12-lead-ECG-derived electrical risk score predicts long-term outcomes after TAVI
Rabinovitz (2016)	26936468	Observational study	302	Admission Norton scale score independently predicts post-TAVI mortality
Raposeiras-Roubín (2016)	27573609	Observational study	54	NT-proBNP predicts long-term outcomes after TAVI
Russo (2014)	23757283	Observational study	78	Early cardiac rehabilitation enhances independence, mobility, and functional capacity after TAVI
Schoenenberger (2013)	23008508	Observational study	106	Post-TAVI functional decline is predicted by frailty scores
Urena (2015)	25466975	Observational study	435	Arrhythmias are common in elderly patients with AS and predict post-TAVI adverse events
Zalenska-Kociecka (2019)	30718946	Review	NA	AKI is common in patients undergoing TAVI and can be predicted by means of multidimensional risk appraisal
Zemedkun (2015)	25982494	Observational study	54	A low-dose contrast protocol for CT is associated with reduced contrast volume in patients with AS

ADL: activities of daily living; AKI: acute kidney injury; AS: aortic stenosis; BAV: balloon aortic valvuloplasty; CT: computed tomography; NT-proBNP: N-terminal pro-brain natriuretic peptide; SAVR: surgical aortic valve replacement; SHERPA: Score Hospitalier d'Evaluation du Risque de Perte d'Autonomie; TAVI: transcatheter aortic valve implantation; NA: not applicable

of multidimensional appraisal and management of these subjects, while confirming the promising role of TAVI in comparison to medical therapy, balloon aortic valvuloplasty, and SAVR in elderly patients.

The evolution of TAVI has been momentous, and, since the first pioneering cases, TAVI is challenging the role of SAVR even in low-risk patients[6]. These successes depend on major refinements in diagnostic tools (e.g., CT angiography for precise sizing), patient preparation, device improvements, ancillary management approaches, and post-procedural management[19-26]. These refinements and the fact that TAVI was initially validated in trials enrolling mostly high-risk patients with advanced age would suggest that all major issues concerning TAVI in the elderly have been solved[6]. This is of course false, and substantial research is still ongoing on several related topics. For instance, the aspects of cost utility and futility remain actively debated, as well as all issues pertinent to patient preparation, device selection, predilation vs. postdilation, embolic protection, and post-procedural antithrombotic therapy[6,11-15,27-30].

The present umbrella review, albeit limited in comparison to other umbrella reviews authored by our research group given the limited scope of the available evidence base, highlights the importance of frailty assessment to predict short-term complications and long-term results of TAVI in the elderly, the emerging role of cognitive assessment before TAVI and prevention of cognitive decline due to TAVI complications, and the usefulness of cardiac rehabilitation in all old patients with severe aortic stenosis undergoing TAVI. Further evidence highlights the importance of assessing in a multidimensional fashion the presence of comorbidities, nutritional status, grip strength, gait speed, and overall functional status, while confirming the favorable clinical performance at short- and mid-term follow-up of TAVI, without discounting the niche role of balloon aortic valvuloplasty in patients at prohibitive risk, and the pivotal function of SAVR in fit patients.

Limitations of this umbrella review are of course those typical of overviews of reviews, including the risk of ecological fallacy[9]. In addition, while studies on TAVI usually enroll mostly patients with advanced age, only a limited set of systematic reviews explicitly aimed at the topic of TAVI in the elderly. Accordingly, further reviews are eagerly awaited to more poignantly summarize the evidence base for this important topic in structural heart disease. Focusing on the definition of elderly, our definition of elderly as aged ≥ 65 years is quite arbitrary, especially in the context of TAVI, which is often performed in much older subjects[31,32]. However, this remains a common pragmatic definition for many patients, non-specialists, and decision-makers[32]. In addition, by default, umbrella reviews have limited room to select primary studies from included reviews. Similarly, having an unrestrictive approach at TAVI indication (e.g., stenosis, regurgitation, and valve-in-valve) risks mixing "apples with oranges" and providing overly heterogenous results. Most importantly, the TAVI landscape continues to change, shifting from prohibitive and high-risk patients, to subjects at intermediate or low risk. Another crucial evolution has centered on devices, which evolved from the crude Cribier-Edwards device to current-generation, low-profile and fully repositionable/retrievable ones[21]. However, as stated above, by definition, umbrella reviews cannot limit inclusion to a given group of primary studies. Accordingly, we can only let readers subset the included systematic reviews/studies according to the specific features they are most interested in, when wishing to apply to specific patient subgroups the findings of our umbrella review.

In conclusion, the scholarly literature on TAVI continues to accrue, reaffirming the favorable risk-benefit balance of this breakthrough technology in patients with severe aortic stenosis, including selected low-risk subjects. Our umbrella review, including eight systematic reviews, 39 primary studies, and 8579 patients, highlights the importance of considering frailty scores, as well as nutrition and functional status, in addition to established surgical risk scores in elderly patients considered for TAVI to improve risk prediction, reinforcing the favorable impact of this therapy to improve cognitive function.

DECLARATIONS

Authors' contributions

Designed the review, performed all reviewing activities and drafted the manuscript: Antonazzo B, Biondi-Zoccai G

Participated in review design, supervised all reviewing activities, and provided critical contributions to the manuscript: Marullo AGM, Frati G, Ronzoni S, Chiariello GA, Versaci F, Giordano A

All authors eventually approved it in its final version.

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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