Systematic Review

Long term outcomes of transcatheter aortic valve implantation (TAVI): a systematic review of 5-year survival and beyond

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Background: Transcatheter aortic valve implantation/replacement (TAVI/TAVR) is becoming more frequently used to treat aortic stenosis (AS), with increasing push for the procedure in lower risk patients. Numerous randomized controlled trials have demonstrated that TAVI offers a suitable alternative to the current gold standard of surgical aortic valve replacement (SAVR) in terms of short-term outcomes. The present review evaluates long-term outcomes following TAVI procedures.

Methods: Literature search using three electronic databases was performed up to June 2017. Studies which included 20 or more patients undergoing TAVI procedures, either as a stand-alone or concomitant procedure and with a follow-up of at least 5 years, were included in the present review. Literature search and data extraction were performed by two independent researchers. Digitized survival data were extracted from Kaplan-Meier curves in order to re-create the original patient data using an iterative algorithm and subsequently aggregated for analysis.

Results: Thirty-one studies were included in the present analysis, with a total of 13,857 patients. Two studies were national registries, eight were multi-institutional collaborations and the remainder were institutional series. Overall, 45.7% of patients were male, with mean age of 81.5±7.0 years. Where reported, the mean Logistic EuroSCORE (LES) was 22.1±13.7 and the mean Society of Thoracic Surgeons (STS) score was 9.2±6.6. The pooled analysis found 30-day mortality, cerebrovascular accidents, acute kidney injury (AKI) and requirement for permanent pacemaker (PPM) implantation to be 8.4%, 2.8%, 14.4%, and 13.4%, respectively. Aggregated survival at 1-, 2-, 3-, 5- and 7-year were 83%, 75%, 65%, 48% and 28%, respectively.

Conclusions: The present systematic review identified acceptable long-term survival results for TAVI procedures in an elderly population. Extended follow-up is required to assess long-term outcomes following TAVI, particularly before its application is extended into wider population groups.

Keywords: Transcatheter aortic valve implantation; TAVI; survival; long-term; systematic review

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Introduction

As Western populations age, the prevalence of aortic stenosis (AS) is gradually increasing (1). In a select population, surgical aortic valve replacement (SAVR) is precluded by patient frailty and other comorbidities (2). The availability of transcatheter aortic valve implantation/replacement (TAVI/TAVR), pioneered in the early 2000s, has made a significant impact on survival for these patients (3-5). These early successes led to a number of trials, such as the PARTNER and US Pivotal trials, which compared TAVI, SAVR and standard treatment outcomes (*Figure 1*). As a result, TAVI is increasingly being considered as a less-invasive option for treatment of AS in younger and lower surgical risk patients, where SAVR is not necessarily contraindicated (6,7), although this is not without controversy (8).

While the short-term outcomes of TAVI have been well explored, limited studies have examined longer term results (9,10). Additionally, while much data has been published on SAVR survival beyond 5 years, there are relatively few studies (outside the Edwards and Medtronic trials) that present long-term, two-armed results with TAVI and SAVR. The present review aims to identify and analyze survival outcomes of studies which present 5-year of follow-up.

Methods

Literature search

Electronic searches were performed on Medline, Scopus and PubMed from dates of database inception to June 2017 using ("transcatheter aortic valve implantation" OR "transcatheter aortic valve replacement" OR "TAVI" OR "TAVR") AND ("survival" OR "long-term" OR "Kaplan-Meier"), either as keywords or MeSH headings. Records were systematically reviewed according to the inclusion and exclusion criteria by two independent authors (Adam Chakos, Ashley Wilson-Smith). A PRISMA diagram of the search process is presented in *Figure S1*.

Inclusion/exclusion criteria

Studies were included if 20 or more patients underwent TAVI (via any access approach and as a stand-alone or concomitant procedure), and where follow-up was for at least five years. Time-to-event data was required to be present in order to facilitate statistical analysis. Non-English studies, review articles, conference abstracts, editorials, letters, case reports and opinions were excluded. Only the most up-to-date study was included if duplicating studies were published for the same patient cohort.

Quality assessment of included studies

A modified quality appraisal schema, based on the Canadian National Institute of Health's Quality Assessment Tool for Case Series Studies, was used to evaluate all included studies (11). In short, studies were scored based on six main domains: clarity of objective, characteristics of the study population, description of the intervention, adequate outcome measures, suitable statistical analysis, and appropriate results/conclusions (quality is listed in *Table S1*). Studies were scored out of 16 points. Studies scoring 13–16 were categorized as high-quality, 10–12 medium-quality and below 10 were low-quality.

The primary outcome of interest is time-to-event survival data. Secondary outcomes of interest included short-term outcomes such 30-day mortality, 30-day stroke/CVA, permanent pacemaker (PPM) implantation and acute kidney injury (AKI). Definitions from the Valve Academic Research Consortium (VARC)-2 consensus were used where appropriate (12). Logistic EuroSCORE (LES) was recorded in preference to additive EuroSCORE and EuroSCORE II since the former was replaced by the logistic model and the latter was not widely reported as it has only been in use since 2012.

Statistical analysis

Baseline patient data, risk factors, operative details and operative outcomes were extracted by two independent researchers. Kaplan-Meier curves were digitized and iteratively computed to generate individual patient data, using the algorithm from Guyot and colleagues (13). Censoring was assumed to be constant unless the particular curve had a long follow-up of only minimal patients (in which case, censoring was manually entered). The death event and censoring data for the entire cohort was pooled and an overall survival curves calculated according to the Kaplan-Meier method using MATLAB R2016a [Natick, Massachusetts, US (14)]. Survival was also compared to the general population by utilizing life tables obtained from government sources specific to the majority of patients within the included studies (15-17). Specifically, weighted survival (according to patient numbers) for Italy, UK, Germany, Canada, US and Spain were used, accounting for

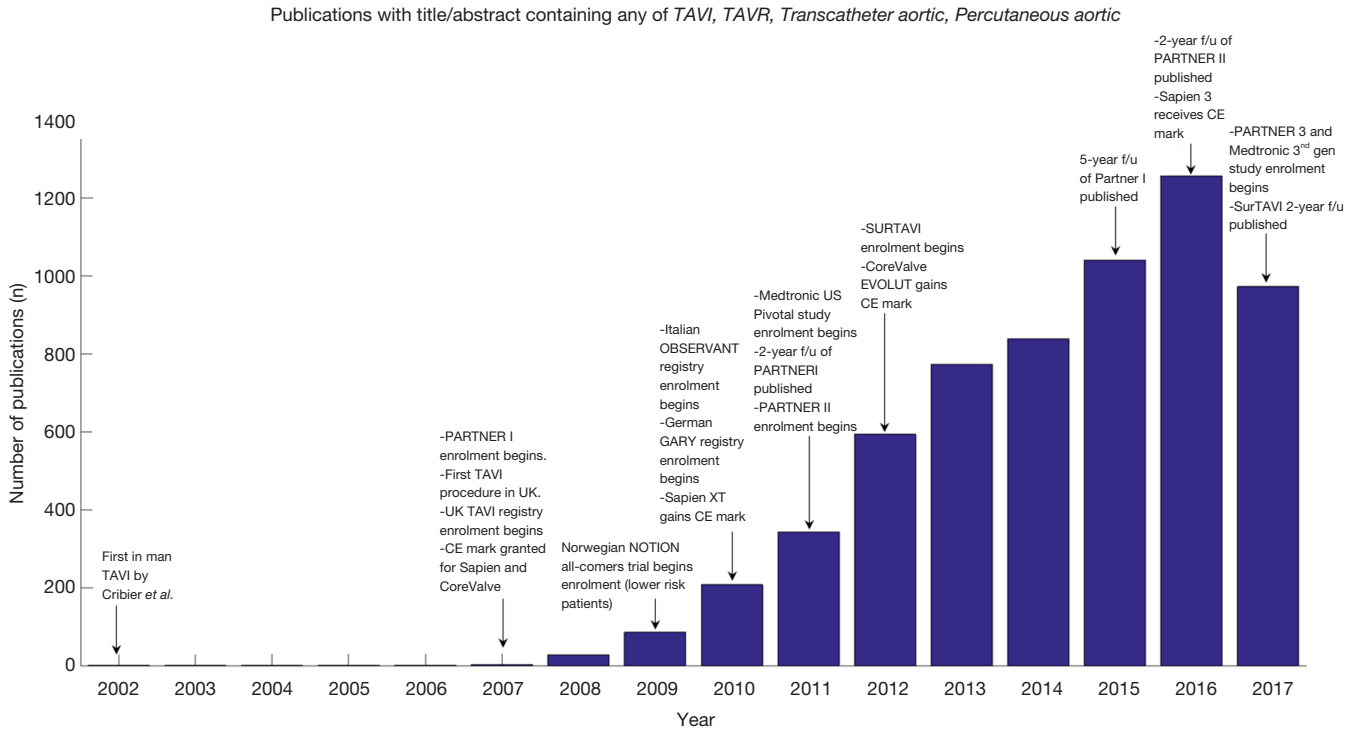

Figure 1 Timeline of publication rate annotated with significant events since the introduction of TAVI. Number of publications by year extracted from PubMed. TAVI, transcatheter aortic valve implantation; TAVR, transcatheter aortic valve replacement.

93% of all included patients.

Results

Overall 5,194 records were identified in the literature search. Following application of the inclusion and exclusion criteria, 31 studies were included for analysis, with a total of 13,857 patients. The median number of patients per study was 120 (interquartile range 60–292) with median follow-up of 5 years (interquartile range 5–6 years, mean follow-up 5.6 years). These studies included 23 single-center studies (6,10,18-38) and 8 multi-center studies (39-46), where 14 were retrospective and 15 had prospective enrolment. The studies were conducted in the UK, Italy, Germany, US, Canada, Spain, Israel, Denmark and Sweden. Seven studies were deemed high-quality studies, 19 as medium-quality and 5 as low-quality. Kaplan-Meier survival for patients in the three study groups was calculated and results are presented in *Figure S2*.

The mean age for the entire cohort was 81.5±7.0 years, with 45.7% males. Pre-operative LES was the most widely available risk statistic among included studies, reported for 91% of the total cohort, with a mean value of 22.1%±13.7%. Pre-operative Society of Thoracic Surgeons (STS) score was reported for 50% of the cohort at a mean risk value of 9.17%±6.61%. Baseline characteristics and comorbidities (such as hypertension, LVEF%, cardiac history and interventions) recorded across more than half of the included studies are summarized in *Table 1* and fully detailed in *Table S2*.

Multiple types of valves were used, which was reported by 84% of studies. For those studies which specified valve type, 64.7% of reported patients received an Edwards valve (Sapien, Sapien XT, Sapien 3), 33.5% received a Medtronic valve (CoreValve, Evolut R) and 1.7% of patients received a different type (Lotus or JenaValve). Valve delivery approach was specified for 92% of included patients. Where specified, 68.5% of approaches were transfemoral, 34.8% were transapical, 2.6% were trans-subclavian and 1.9% were trans-aortic (and other) approach type.

Aggregated survival rates at 1-, 2-, 3-, 5-, and 7-year were 83%, 75%, 65%, 48%, and 28%, respectively. The overall survival curve derived from reconstructed individual patient data is shown in *Figure 2*.

Table 1 Summary of patient baseline characteristics

Characteristics	Data
Total patients (n)	13,857
Males (%)	6,327 (45.7%)
Age (mean ± SD)	81.5±7.0
Logistic EuroSCORE (mean ± SD) %	22.1±13.7
STS score (mean ± SD) %	9.17±6.61
Hypertension	81.7% (5,447/6,667)
Diabetes mellitus	28.2% (3,414/12,104)
Dyslipidaemia	61.9% (2,318/3,743)
Peripheral vascular disease	28.7% (3,571/12,440)
Pre-operative LVEF (%)	53.5±15.1
Pulmonary disease	25.7% (3,243/12,605)
Previous cerebrovascular accidents	12.1% (1,539/12,704)
Previous CABG	22.0% (1,093/4,962)
Previous percutaneous intervention	22.2% (2,138/9,628)
Previous myocardial infarction	20.1% (2,253/11,184)
Renal disease	18.2% (2,191/12,019)
History of atrial fibrillation	26.0% (1,814/6,981)

Where applicable, data is reported as percentage and the fraction of the total surveyed for a particular comorbidity. SD, standard deviation; STS, Society of Thoracic Surgeons; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass graft.

Patients were further grouped according to their LES as either moderate (LES ≤20) or high-risk (LES >20) and the respective results are shown in *Figure 3*. Risk factors and outcomes reported in more than half of the included studies were included for analysis in this review - a summary is presented in *Table 1*. Kaplan-Meier curves generated for high-, medium-, and low-quality studies are presented in *Figure S2*.

Post-operative 30-day mortality was 8.4% (12,913 patients). Other widely reported post-operative outcomes included incidence of 30-day cerebrovascular accident (2.8% of 10,881 patients), AKI (14.4% of 7,963 patients) and requirement for PPM implantation (13.4% of 11,599 patients). Other operative and post-operative details were insufficiently presented to facilitate statistical analysis (*Table S3*).

Discussion

TAVI trials, expanding indications and criticisms

Since introduction in 2002, TAVI has been used at increasing rates, with over one-hundred thousand procedures performed worldwide (47). Much of the clinical outcomes have been captured in a range of trials and registries, including the Edwards-sponsored PARTNER trials, Medtronic-sponsored Pivotal and SURTAVI trials, UK TAVI registry (UK), GARY registry (Germany), OBSERVANT registry (Italy) and NOTION trial (Norway) (3,48-54).

In 2011, the seminal PARTNER IA and IB randomized controlled trials, using Edwards' balloon-expandable valve, established the non-inferiority of TAVI compared to SAVR and the superiority of TAVI compared to medical management (55). These favorable results energized TAVI advocates, with more studies subsequently commenced. The validation of the Edwards valve encouraged Medtronic to develop their model, with similarly favorable results from their Pivotal RCT subsequently published in 2014 (50). Both trials recruited high-risk patients (or non-surgical candidates in PARTNER IB), establishing the clinical legitimacy of utilizing TAVI in these patients (34,56). Despite early differences in TAVI and SAVR outcomes seen in the PARTNER IA trial, at five-years these differences have dissipated. However, TAVI's higher rate of vascular complications and paravalvular leak persisted at five years, raising concerns. SAVR patients in PARTNER I had higher rates of major bleeding post-operatively and in the long term (34,49,56,57).

Like PARTNER IA, the three-year follow-up of the US Pivotal trial (again with a 7.5% difference required for inferiority) found similar mortality between SAVR and TAVI, the same issues of vascular complications and valvular regurgitation (including para-valvular leak) and reported higher incidence of re-intervention in TAVI. SAVR patients in the Pivotal trial also had higher rates of major bleeding and AKI compared to TAVI. Unlike the Edwards valve, significant need for PPM implantation compared to SAVR persisted at three years in the CoreValve trial (58). Neither product demonstrated valvular deterioration at late follow-up, allaying early concerns regarding the long-term durability of TAVI valves due to device crimping for implantation (59).

Given the success demonstrated by the PARTNER I and US Pivotal trials, TAVI procedure rates increased

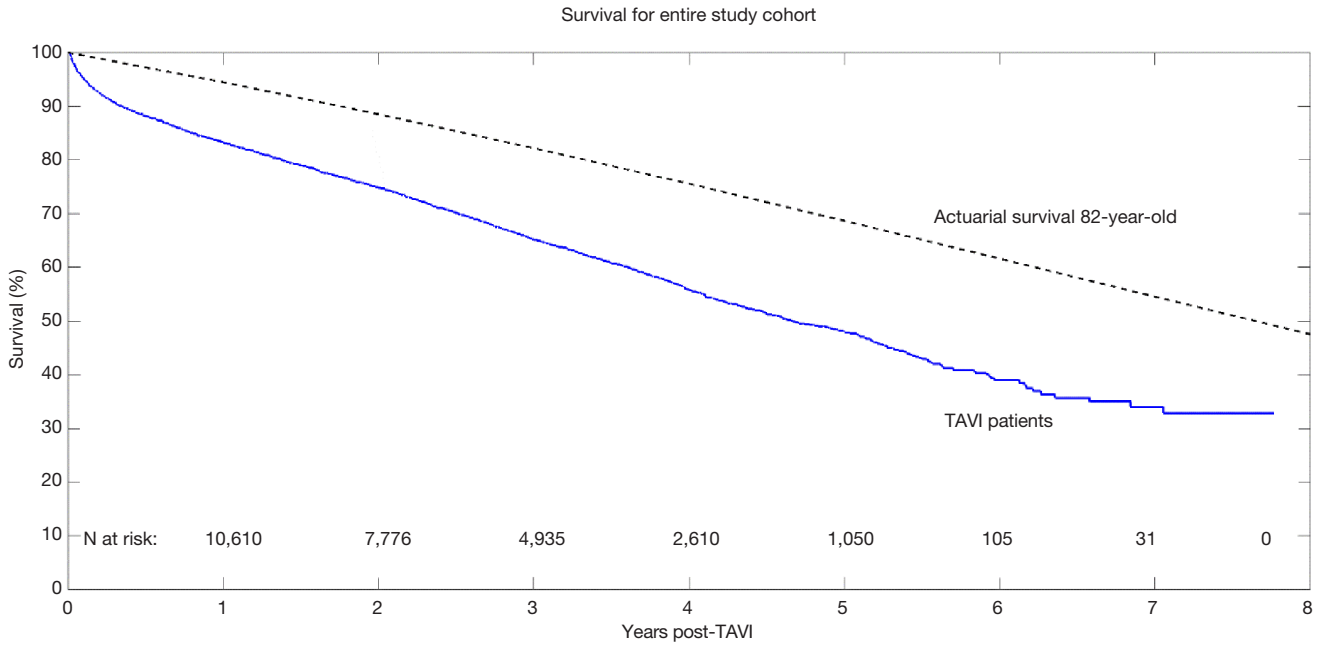

Figure 2 Aggregated long-term survival of patients receiving transcatheter aortic valve replacement. The expected survival curve for a general-population 82-year-old (calculated from the national life tables relevant to the included studies) is also plotted.

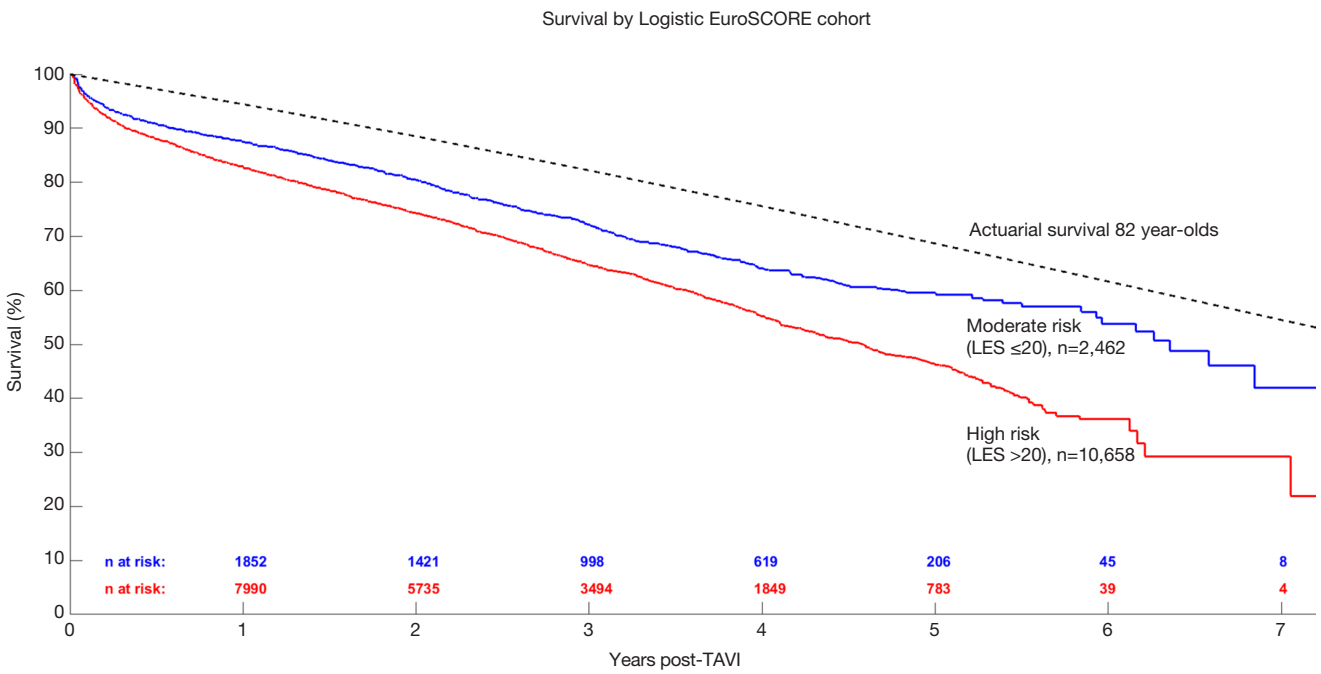

Figure 3 Long-term survival of patients receiving transcatheter aortic valve replacement, stratified according to high risk (logistic EuroSCORE >20, in red) or moderate risk (logistic EuroSCORE ≤20, in blue). LES, logistic EuroSCORE.

and began to be expanded to intermediate-risk cohorts by practitioners. The development of the newer generation Edwards (Sapien XT) and Medtronic (CoreValve Evolut R) devices, along with the need to validate results in lower-risk cohorts formed the basis for the PARTNER II and SURTAVI trials (Edwards and Medtronic, respectively), which examined patients with STS operative risk scores up to 8% (PARTNER II) and 15% (SURTAVI) and enrolled more than twice the number of patients as the original Edwards and Medtronic trials. The mean STS scores in PARTNER II and SURTAVI were approximately 5.8%±2.0% and 4.5%±1.6%, respectively (49,51). This new wave of RCTs (now in moderate-risk patients) again established the short-term non-inferiority of TAVI compared to SAVR. However, the same issues of vascular complications, paravalvular leak and requirement for re-intervention persisted in both Edwards and Medtronic trials (along with continued high rates of post-operative PPM in the CoreValve trial) (49,51).

The NOTION trial in Norway also examined TAVI mortality in lower risk groups by virtue of its "all comers" nature. That RCT used the same 1:1 randomization for 280 patients receiving TAVI and SAVR and patients had a mean STS score of 3.0%±1.7%. The CoreValve was used and like the US Pivotal and SURTAVI trials, no statistically significant difference in mortality, stroke, or MI at 2 years between methods was found. Complications with respect to TAVI and SAVR were the same as the Pivotal and SURTAVI trials (52,60,61).

Results of the PARTNER II trial raised concern over whether the findings of these RCTs reflect real-world outcomes, and whether it can potentially introduce bias in favor of TAVI. Some criticism of the PARTNER II trial raised concerns that treatment in the SAVR arm was not representative of current surgical practices and included undetailed concomitant interventions, although 15% of the SAVR cohort did undergo contemporary SAVR with a minimally invasive approach. However, it should be noted that the SAVR cohort also included patients that underwent concomitant mitral or tricuspid repair or coronary grafting (62).

A new generation of Edwards and Medtronic valves have now been launched (Sapien 3 and EVOLUT R, respectively) and the PARTNER 3 and US clinical trial NCT02701283 RCTs are presently recruiting to investigate their use in low operative mortality risk patients (STS <4% for PARTNER 3, risk of mortality <3% at 30 days for Medtronic RCT) (63,64). Earlier studies also studied TAVI beyond the context of calcific AS, in pure aortic regurgitation patients (65,66), bicuspid aortic valve and (as in a number of our included studies) valve-in-valve for both redo-TAVI or SAVR (6,25,32,67,68).

TAVI is undoubtedly growing in usage across the world and as the results of these newer generation trials become available and potentially address earlier concerns, TAVI will inevitably be applied in a broader context to lower risk patients. Although national registries such as the UK TAVI trial report minimal "EuroSCORE creep" with time, later follow up from the recent Edwards and Medtronic trials showing durability and sustained favorable outcomes (as the earlier trials demonstrated) will likely lead to wider adoption in lower-risk cohorts and a noticeable risk score creep (69).

Cost effectiveness of TAVI

In addition to demonstrating the clinical effectiveness of TAVI, much has been published on its cost-effectiveness and financial sustainability for widespread adoption. These studies have used methods such as incremental cost effectiveness ratio (ICER), decision-analytic and Markov models to compare TAVI to SAVR and standard treatment. Analysis in the context of a government health system (the UK NHS) using data from the PARTNER I trials and extrapolated into the future calculated TAVI to cost anywhere from 2–5 times that of medical management (70,71) but highlighted that TAVI achieves markedly better survival outcomes. Quality-adjusted life-years (QALY) analysis of PARTNER I and other national registries demonstrated that TAVI still fell within the cost limits set by the NICE guidelines used under the NHS and thus, is a suitable (and superior) treatment to medical management in the case of inoperable AS (70-73).

While TAVI has been evaluated as cost-effective in patients who are not candidates for surgery, it has yet to be shown to be financially sustainable in high-risk patients who can undergo a much more economical surgical AVR procedure. A significant driver of the cost-difference between SAVR and TAVI is the high device cost compared to surgical valves (74). When the cost of the device is discounted from the analysis, TAVI becomes comparable to SAVR, owing particularly to the reduced intensive care unit and hospital stay required for TAVI (42). It has also been noted that TAVI requires more extensive diagnostic work-up (2), which may further offset the benefit of reduced hospital stay. Additionally, it is not clear whether all cost analyses accounted for costs associated with the higher re-intervention and re-admission rates of TAVI compared to

SAVR. However, Freeman and colleagues found in their analysis that when re-intervention and re-admission rates were considered, the cost per QALY for TAVI remained below the NICE threshold for coverage under the NHS, highlighting the potential long-term economic benefit of TAVI (73).

Long-term outcomes

A key factor in adoption of any new surgical procedure or device is its long-term efficacy. While the short-term results have been well studied, limited data exists regarding long-term outcomes following TAVI. The present review of nearly 14,000 cases found survival at 5 years to be 48%. When compared against the actuarial survival of 82-year-old, the aggregated results demonstrate poorer survival outcomes and a marginally worse Kaplan-Meier rate (after the initial attrition in the first year post-operatively). Mack and colleagues followed a small cohort of nonagenarians receiving TAVI in the US and found that their survival at 5 years to be approximately 30%, which was consistent with the expected age- and sex-matched actuarial survival in this elderly cohort (33).

Limitations

Firstly, a wide range of TAVI models and generations were included in the present analysis, which could not be accounted for. Secondly, the data presented in this review included series from the early TAVI era, where the learning curve associated with the uptake of this technology could have influenced these results. The likely evolution of patient selection, the procedure itself, and post-operative management is likely to have had an effect on survival outcomes in contemporary TAVI applications. It is also acknowledged that the heterogeneity in patient selection and procedural variations may have also affected outcomes. Finally, the method used to re-construct patient data from Kaplan-Meier survival curves assumed constant censoring and this may have impacted on the computed patient data.

Conclusions

It is widely anticipated that as results of newer generation device trials become available, TAVI will be applied in a broader context to lower risk patients. As TAVI registries continue to mature and grow, particularly all-comers registries like the UK TAVI registry, a clear case profile for TAVI may be brought in to focus. Additionally, as newer valve designs and device manufacturers enter the market, the economic case for TAVI will undoubtedly improve. However, future cost analyses must be included the procedural workup and long-term follow-up treatments. Despite the aggregated results identified in the present analysis, it is abundantly clear that extended data is required to clarify the long-term outcomes of TAVI.

Expert opinion 1 (Sameer Arora, John P. Vavalle)

In this study, Chakos and colleagues report an exhaustive aggregation of studies with reported follow-up of 5 years or more after TAVR. The aggregated survival at 5- and 7-year follow-up after TAVR was 48% and 28%, respectively. The study population largely represents a high-surgical risk category with more than 80% of the patients at high-surgical-risk with the mean STS >9. Additionally, most of the included studies were of initial experiences of TAVR, and therefore, do not take into consideration the improvements in prostheses and operator experiences in recent years. However, this study provides a benchmark for the more recent TAVR experiences and will help us to evaluate if improvements in prostheses performance and operator experiences has led to improvement in overall outcomes, which we expect it has.

In the US, TAVR is now recommended for patients with severe AS and high or inoperable-surgical risk, and is an alternative to surgery for intermediate-risk patients. Although the authors found a reduced survival for post-TAVR patients when compared to a general population of similar mean age, this does not take into account the co-morbidities that made the patient high or extreme risk for surgery. This highlights the overall morbidity of many of these patients undergoing TAVR, and supports the notion that a less invasive approach is favored for this group.

This study now helps set the stage for the next frontier of TAVR—low surgical risk patients. As we move towards an “all-comers” treatment paradigm for TAVR, there are several important unanswered questions. These include durability of the valve, higher rates of PPM, paravalvular leak, and long-term survival. As we await the results of the randomized trials of low risk patients, this study provides further support to pushing the envelope towards low risk. One thing is certain, TAVR is here to stay, and its rapid growth will only accelerate; however, we must use caution to not expand its use to low risk patients until we are certain of the long-term outcomes.

Expert opinion 2: a step back to reexamine the evidence? (Tom C. Nguyen, Abhijeet Dhoble)

In the study, Chakos and colleagues present data on TAVI survival from 31 studies involving 13,857 patients. The authors found that the aggregated survival rates at 1-, 2-, 3-, 5-, and 7-year were 83%, 75%, 65%, 48%, and 28%, respectively. The mean age of the study population was 82 years. When compared to the actuarial survival of an 82-year-old healthy person, survival post-TAVI was poorer. This study represents the first systematic review of TAVI investigating long-term actuarial survival. The authors should be congratulated for their novel approach in exploring TAVI durability compared against an actuarial cohort. The authors further stratified patients into intermediate and high-risk categories. Expectedly, high risk patients experienced worse survival. These findings raise a question on widespread global acceptance of TAVI. It is to be noted that the present study included only registries and studies with longer term follow up, which included mostly high-risk patients with mean STS score of 9.17%±6.61%. Some of the patients included were treated as early as 2005, likely with the 1st generation TAVI devices.

The PARTNER 1B (inoperable) study that included patients with mean age of 83 years and mean STS of 11.7% showed 5-year mortality of 93.6% in medically managed patients, and 71.8% in TAVI group (56). The risk of death at 5 years was 67.8% in the TAVI group compared with 62.4% in the SAVR group (hazard ratio 1.04, P=0.76) in the PARTNER 1A (high risk) cohort (34). Additionally, a Mayo Clinic study showed that the asymptomatic patients with severe AS has 5-year mortality of 43% irrespective to whether they undergo SAVR. The same study also found that the 1-, 2-, and 5-year probabilities of remaining free of surgery or cardiac death were 80%, 63% and 25%, respectively (75). These high-quality data suggest that AS is a potentially fatal disease if left untreated, and mortality remains high even if the patient is treated.

The findings of this study should raise the question of global TAVI acceptance without better quality data supporting durability. This is particularly true as TAVI evolves into intermediate and lower risk cohorts where durability data is scant. Longer term follow-up data from randomized intermediate and low risk PARTNER and CoreValve trials will potentially shed light on the durability of this technology. Until then, it is prudent to step back and continue to actively reexamine the evidence for TAVI.

Expert opinion 3: taking two birds (durability and lower risk) with one stone (younger patients): next TAVI challenge (Giuseppe Tarantini)

TAVR has rapidly become the treatment of choice for AS patients at extreme or high surgical risk, and the results of recent randomized trials have now broadened TAVR indications to lower risk subjects. Nevertheless, the common risk scores used in clinical practice are accurate to predict the outcome of patients treated surgically but not by TAVI (1). The point is why? Unlike surgical series (76), in TAVI series, the progressive decrease in mean risk score value across studies is not paralleled by a significant change in TAVR patients mean age, which steadily remained above 80 years. Data on younger patients are lacking and is difficult to find. In ongoing trials, the entry criteria remain with the heart team. Considering the previously reported disconnection between risk and age—I would expect to see data still related on patients older than 80 years.

Granted that, in our opinion, future TAVR research should concentrate on outcomes of younger patients. Performing TAVR in <75-year-old subjects will allow us to get the eagerly awaited data on prostheses durability, which remains the last strong argument against transcatheter therapy. This, of course, has to be done by means of randomized controlled trials against SAVR. However, in order to compete with the excellent results of SAVR in younger patients, TAVR has to guarantee a 30-day mortality and stroke-rate around 1%, major vascular complications rate <3%, and new PM implantation rate <10%. Furthermore, the hemodynamic performance of transcatheter devices in the setting of bicuspid AS has to improve (especially in terms of paravalvular leakage), since this anatomical finding will dramatically increase in frequency as we move to younger subjects.

TAVR has walked a long and exciting road since the first patient was treated in 2002, but there is still much to walk before we can safely and effectively offer transcatheter therapy to every AS patient.

Expert opinion 4: 'times they are a-changin' (Matthias Thielmann, Daniel Wendt)

Since TAVI has been introduced in 2002 into clinical practice, it has successfully evolved (with more than 100,000 procedures worldwide) to become a main-stream

therapeutic option for symptomatic patients with severe AS. Initial evidence for TAVI came from first industry-sponsored clinical trials but also from several national registries considering patients who were deemed to be inoperable or non-surgical candidates as well as patients presenting with a high surgical risk. With growing experience, further developed TAVI devices and further evidence from more recent trials (although most of them still industry-initiated, -sponsored, and -controlled), the indication has and is going to shift to lower risk patients.

Aside from the euphoria around TAVI regarding its application and criticisms, the question of TAVI long-term performance and outcomes is as yet uncertain. First insights from initial randomized trials and registries were quite limited in the face of patient's age and comorbidities and present long-term data are still rare and limited in their validity and interpretation. Nevertheless, there is certainly no doubt that long-term performance and outcomes are and will become the major determinant for TAVI treatment—particularly in the lower risk, younger patients.

The present systematic review by Chakos and colleges of long-term outcomes of TAVI encompassing nearly 14,000 TAVI patients derived from 31 worldwide studies and national registries showed an aggregated 5-year survival of 48% and a 7-year survival of 28%. This is the first systematic review of TAVI that has been investigated on long-term survival in this fashion. By comparing the actuarial survival against an age-matched population, survival post-TAVI was significantly inferior, particularly in the high-risk group. This is at first not unexpected given the patient population and comorbidities. Nevertheless, when comparing the long-term survival of SAVR with a similar age- and gender-matched population, Wendt and colleges (77) could clearly demonstrate a non-inferiority of SAVR over a similar long-term period.

Of important note, not only long-term survival, but also quality of life, incidence of repeat intervention rate, transvalvular gradients, prosthesis valve areas, and structural valve deterioration over a long-term follow-up are major important determinants which will play a key role when younger and lower risk patients are going to be considered for a TAVI treatment instead of SAVR. Therefore, much longer and lager follow-up studies are needed to objectively judge whether TAVI is superior to SAVR and should therefore be offered and recommended to a younger and lower risk patient clientele.

'*And the first one now will later be last—for the times they are a-changin*'—freely adapted from Bob Dylan.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

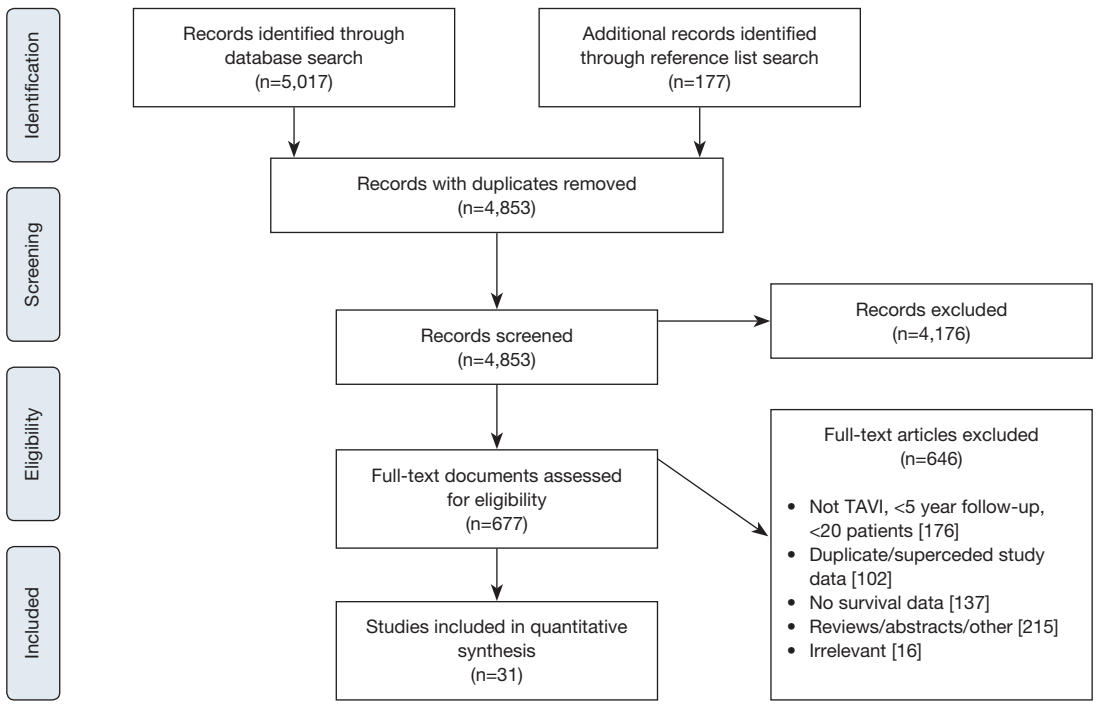

Figure S1 PRIMSA flow chart detailing the literature search process for TAVI outcomes at 5 years and beyond.

Table S1 Study detail

Author	Year of publication	Country	Recruitment years	Patients (n)	Follow up (year)	Study design	IHE quality
Barbanti	2015	Italy	2007–2009	353	5	MC, P	M
Barone-Rochette	2014	Belgium	2005–2012	40	5	SC, P, C	M
Bouleti	2017	France	2006–2010	253	6	SC, P, C	H
Brunner	2017	Canada	2005–2014	133	6.5	MC, R	L
Buzzatti	2017	Italy	2007–2015	558	7	SC, R	M
Chen	2016	US	2009–2013	60	6	SC, R	L
Codner	2015	Israel	2008–2015	360	5	SC, P	M
D'Onofrio [1]	2016	Italy	2007–2013	338	6	SC, R, C	M
D'Onofrio [2]	2016	Italy	2008–2015	44	5	MC, P	M
Engborg	2017	Denmark	2008–2012	128	6	SC, R, C	M
Escarcega	2015	US	2007–2014	511	5	SC, P, C	M
Gotzmann	2015	Germany	2008–2012	212	5	SC, P	M
Huded	2016	US	2008–2015	263	5	SC, R, C	M
Johansson	2016	Sweden	2008–2014	166	6	SC, R, C	H
Logstrup	2013	Denmark	2006–2010	81	5	SC, R	L
Lopez-Aguilera	2017	Spain	2008–2015	217	8	SC, P	M
Ludman	2015	UK	2007–2012	3,974	6	MC, R	H
Mack [1]	2015	US	2007–2013	90	5	MC, R, C	M
Mack [2]	2015	Canada, Germany, US	2007–2009	348	5	RCT, MC, P	H
Munoz-Garcia	2015	Spain	2008–2013	364	6	SC	M
Penkalla	2015	Germany	2008–2013	593	5	SC, P, C	M
Pilgrim	2015	Switzerland	2007–2010	257	5	SC, P, C	M
Poulin	2016	Canada, US	2007–2013	102	5	MC, R	L
Ruparelia	2016	Italy	2007–2015	829	5	SC, R, C	M
Salinas	2016	Spain	2008–2012	79	5.5	SC, P, C	H
Salizzoni	2016	Italy	2007–2012	1,904	5	MC	M
Santarpino	2015	Germany	2009–2013	364	5	SC, R	L
Schymik	2015	Germany	2008–2012	1,000	6	SC, P, C	H
Toggweiler	2013	Canada	2005–2007	88	5.5	SC, P	H
Unbehaun	2014	Germany	2008–2013	104	5	SC, R, C	M
Ye	2015	Canada	2007–2013	42	7	SC, P, C	M

IHE, Institute for Health Economics, Canada; SC, single-centre study; MC, multi-centre study; R, retrospective study; P, prospective study; C, consecutive patient recruitment.

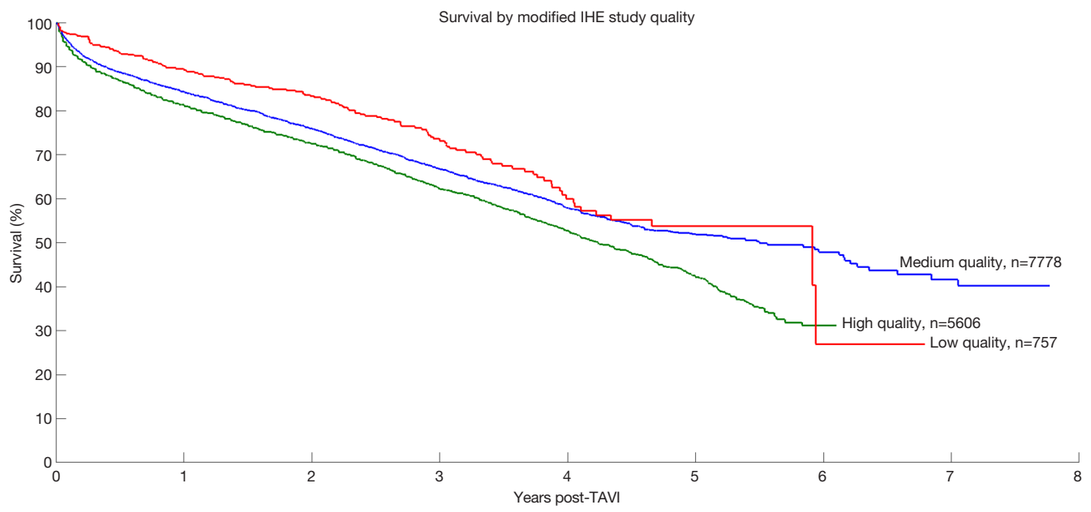

Figure S2 Survival of TAVI patients stratified by study quality according to our modified Canadian IHE guideline. IHE, Institute for Health Economics, Canada.

Table S2 Patient characteristics (including patient sub-groups where the study divided up the cohort)

Study (first author)	Patient grouping (where applicable)	Patients (n)	Males	Age, mean ± SD, years	Patient risk scoring				Risk factors										
					STS	Logistic EuroSCORE	NYHA III, IV	Risk group[1]	HTN	DM[2]	DL	PVD	Pre-op LVEF (%)	Pulmonary disease[3]	Hx CVA[4]	Hx CABG	Hx PCI[5]	Hx MI	Renal[6]	Hx AF
Barbanti	N/A	353	157	81.5±6.3	9.5±10	19.5±11.9*	70	M^	267	107	–	96	50.6±12.3	91	18	54	106	77	37	5
Barone-Rochette	N/A	40	23	83±5	9.1±5.6	26±17	23	H	28	10	22	20	50±17	1	10	17	10	10	–	12
Bouleti	N/A	253	136	81±8	8±5.9	23.3±14	216	H	185	80	131	43	49.6±13.6	90	20	–	–	–	8	102
Brunner	Low PVR	61	38	80.4±8.5	–	–	–	–	–	–	–	–	–	24	–	–	–	–	–	–
	High PVR	72	33	80.3±8.3	–	–	–	–	–	–	–	–	–	25	–	–	–	–	–	–
Buzzatti	No post-TAVI AR	294	134	80.6±7.6	6.4±4.7*	17.5±12.4*	18	M	–	95	–	–	53±13	75	36	–	–	–	200	–
	Mild AR post-TAVI	264	117	80.6±6.9	6.1±3.7*	17.5±11.9*	18	M	–	77	–	–	54±14	65	38	–	–	–	197	–
Chen	Improved LVEF	30	18	81.5±8	11.6±5.6	–	30	H	–	–	–	11	35.2±6.5	16	4	11	7	11	–	9
	Persistent poor LVEF	30	21	81.5±6	11.8±4.3	–	30	H	–	–	–	11	39.2±5.9	18	6	17	13	13	–	12
Codner	N/A	360	157	82.1±6.9	7.5±4.7	19.5±11.2	343	M	332	122	312	59	–	76	66	71	140	30	–	113
D'Onofrio [1]	TF TAVI	233	126	80.5±7	–	12.5±1.7	166	M	209	62	139	13	54.9±12.9	71	28	–	72	45	116	80
	TA TAVI	105	55	80.2±6.1	–	19.2±5.5	72	M	97	29	71	20	55±10.9	27	15	–	37	21	59	36
D'Onofrio [2]	Aortic valve	44	25	77±10	12.3±8	28±16.6	44	H	37	9	–	12	52±12.6	11	–	–	–	–	4	8
Engborg	No PPM	87	34	79.9±6	–	17.9±12.5	73	M	60	16	40	–	48.9±14	21	8	13	18	16	11	19
	Post TAVI PPM	41	24	82.1±4.2	–	15.5±10.8	35	M	27	7	20	–	53.4±11.5	8	3	9	7	9	7	13
Escarcega	TA TAVI	115	54	84±6	10.9±4.5	–	–	H	106	32	86	62	51±13	39	27	41	–	19	57	46
	TF TAVI	396	202	82±8	9.2±4.4	–	–	H	351	131	299	106	52±13	115	53	123	–	74	195	159
Gotzmann	N/A	212	101	80±6	–	22±16	194	H	–	–	–	–	55±12	212	–	32	–	46	–	73
Huded	CVD	51	30	82.3±6.6	8.7±3.7	–	–	H	42	25	37	20	55±11	15	9	30	7	–	16	25
	No CVD	212	105	83.2±8.2	8.7±4.5	–	–	H	177	82	132	34	52±15	62	21	67	25	–	63	83
Johansson	N/A	166	85	80±9	–	23±15	35	H	–	40	–	86	–	29	13	81	52	17	11	–
Logstrup	TA TAVI	59	26	80.1±6.83	–	9.98±2.64[a]	42	–	35	7	–	–	–	–	–	6	21	15	–	–
	TF TAVI	22	11	82.2±7.29	–	8.62±3.4[a]		–	8	2	–	–	–	–	–			6	–	–
Lopez-Aguilera	PPM post-TAVI	39	23	78±4	10.7±8.4	14.5±8.7	–	M^	24	13	15	–	62±12.5	–	–	–	–	–	5	9
	No PPM post-TAVI	178	79	78±7	11.6±10.5	16±10	–	M^	120	51	87	–	58±132	–	–	–	–	–	20	45
Ludman	N/A	3974	1883	81.3±7.6	–	21.9±13.7	–	H	–	866	–	1,025	–	892	325	–	851	892	268	–
Mack [1]	N/A	90	46	91.81±1.79	11.63±6.05	–	80	H	80	18	–	31	53.1±11.7	20	35	27	–	16	7	–
Mack [2]	N/A	348	201	83.6±6.8	11.8±3.3	29.3±16.5	328	H	–	–	–	148	52.5±13.5	151	95	147	116	92	38	80
Munoz-Garcia	No AKI	308	122	79.2±6.4	–	18±11	270	M	254	133	160	49	60.2±15	109	36	25	87	52	68	–
	AKI	58	28	79.9±4.5	–	18.3±14	49	M	47	17	29	12	61.7±13.4	20	16	7	16	7	14	–
Penkalla	No CAD, no PCI	285	83	79.6±6.67*	9.6±7.04*	26.3±17.3*	3.3±0.5	H	–	61	–	161	55.4±10.1*	–	56	0	–	–	–	91
	Non-significant CAD, no PCI	232	88	81±7.4*	11.6±9.3*	30.6±19.7*	3.3±0.5	H	–	83	–	160	50.4±13.9*	–	59	0	–	–	–	70
	Significant CAD, PCI	76	21	82.3±5.9*	12.6±8.4*	34.2±24.8*	3.4±0.5	H	–	16	–	50	51.7±15.2*	–	15	0	–	–	–	13
Pilgrim	N/A	257	113	83±7	5.1	22.4	155	H^	201	62	155	64	51±14	–	23	54	58	47	–	66
Poulin	No PPM	61	36	83.3±7.6*	–	18.9±12.5	55	M	52	17	48	7	54±11.7	9	–	27	–	–	–	–
	PPM post-TAVI	41	23	82.7±8.5*	–	20±15.2	35	H	32	13	31	8	54.3±12.1	4	–	17	–	–	–	–
Ruparelia	TF TAVI	703	281	83.3±7.5	8.4±8.7	21.6±16.2	–	H	562	207	387	162	–	162	98	134	141	129	267	96
	Other access (OAS)	126	64	78.7±24.2	11.8±11.9	28.5±19.5	–	H	98	45	79	79	–	43	21	32	35	31	49	21
Salinas	N/A	79	36	82.3±6.1	5.9±2.9	16.9±9.1	–	M	63	33	38	10	55.4±11.8	19	13	5	27	9	16	31
Salizzoni	N/A	1904	757	81.7±6.2	9.2±7.6	21.1±13.7	1,536	H	1,553	573	–	674	53.5±12.4	468	171	–	267	371	152	414
Santarpino	N/A	364	158	82±6	–	26±17	3.1±0.4	H	339	207	–	98	54±14	105	–	–	–	–	171	–
Schymik	TA TAVI	413	202	81.5±5.8	–	24.3±16.2	–	H	–	–	–	91	55.8±5.8	60	61	–	–	63	35	–
	TF TAVI	587	233	82.1±5.1	–	22.6±16.2	–	H	–	–	–	64	57.5±14.1	63	90	–	–	66	38	–
Toggweiler	N/A	88	47	83±7	9.3±5.0*	–	–	H	61	22	–	–	58.3±11.1*	23	14	–	–	69	47	45
Unbehaun	N/A	104	63	78.7±8.3*	17.7±12.0*	59.7±31.1*	68	H	–	34	–	72	25.0±7.5*	–	29	27	25	–	6	38
Ye	N/A	42	28	80.5±9.8	9.1±4.0*	–	39	H	–	10	–	13	56.5±13.8*	4	7	19	–	–	9	–

*, these studies did not report mean ± SD, so the value reported here was calculated by the authors according to the method outlined by Wan *et al.* [2014] (78). ^, conflict exists between mean STS grouping (as per [1] below) and Logistic EuroSCORE grouping. EuroSCORE grouping takes precedence. [1], risk group defined primarily by mean Logistic EuroSCORE <20 (low to moderate risk: M) or ≥20 (high risk: H). Where Logistic EuroSCORE isn't given, STS>8 defined as high risk group. [2], where diabetes mellitus and insulin-dependent diabetes mellitus were reported separately, they were added together for the purposes of this review. [3], pulmonary disease includes reporting of COPD and pulmonary disease in general. Pulmonary hypertension was not recorded as pulmonary disease. [4], Hx CVA was recorded where studies indicated prior CVA specifically, as well as where "neurological dysfunction", "CVD (cerebrovascular dysfunction)" was reported. [5], PCI includes studies reporting PCI specifically and those reporting it under other names such as coronary angioplasty. [6], renal disease includes studies that reported renal disease specifically as well as those that reported disease by RIFLE criteria, creatinine>2 mg/dl, eGFR<60 ml/min or dialysis/renal replacement. Where multiple categories given (e.g., eGFR<60 mL/min and dialysis reported separately), the sum of these is reported. [a], Logstrup *et al.* (record 15) report EuroSCORE but do not specify whether it is according to the additive, logistic or EuroSCORE II classification. This result was not included in the overall EuroSCORE calculation for the whole cohort. STS, Society of Thoracic Surgeons risk score; NYHA, New York Heart Association functional group; HTN, hypertension; DM, diabetes mellitus; DL, dyslipidaemia; PVD, peripheral vascular disease; Hx CVA, history of cerebrovascular accident; Hx CABG, history of coronary artery bypass graft surgery; Hx PCI, history of percutaneous intervention; Hx MI, history of myocardial infarction; Hx AF, history of atrial fibrillation; M, low to moderate operative risk group; H, high operative risk group; TAVI, transcatheter aortic valve implantation.

Table S3 Patient operative details and outcomes

Study (first author)	Patient grouping (where applicable)	Patients (n)	Valve type[1]			TAVI approach					Procedural outcomes			
			Edwards	Medtronic	Other	TF	TA	TSub	TAortic	Other	PPM implant	AKI[2]	30-day stroke/CVA[3]	30-day mortality[4]
Barbanti	n/a	353	0	353	0	317	–	36	–	–	75	89	8	23
Barone-Rochette	n/a	40	40	0	0	25	15	–	–	–	–	–	–	10
Bouleti	n/a	253	186	67	0	171	82	–	–	–	36	1	10	27
Brunner	Low PVR	61	–	–	–	–	–	–	–	–	–	–	–	–
	High PVR	72	–	–	–	–	–	–	–	–	–	–	–	–
Buzzatti	No post-TAVI AR	294	137	76	81	251	25	14	4	–	–	–	–	21
	Mild AR post-TAVI	264	128	90	46	236	12	14	2	–	–	–	–	
Chen	Improved LVEF	30	30	0	0	M	M	0	0	0	–	–	–	–
	Persistent poor LVEF	30	30	0	0	M	M	0	0	0	–	–	–	–
Codner	n/a	360	97	258	5	308	31	19	1	1	58	59	–	14
D'Onofrio [1]	TF TAVI	233	255	83	–	233	–	–	–	–	66	35	7	11
	TA TAVI	105			–	–	105	–	–	–	11	39	3	4
D'Onofrio [2]	Aortic valve	44	32	12	0	28	16	0	0	0	0	1	0	2
Engborg	No PPM	87	25	62	–	–	–	4	–	–	0	–	–	3
	Post TAVI PPM	41	3	38	–	–	–	2	–	–	41	–	–	1
Escarcega	TA TAVI	115	–	–	–	–	115		–	–	4	36	5	22
	TF TAVI	396	–	–	–	396	–		–	–	34	52	21	17
Gotzmann	n/a	212	43	169	–	164	–	5	–	–	–	–	–	11
Huded	CVD	51	–	–	–	28	18		5	–	–	–	0	2
	No CVD	212	–	–	–	163	37	–	11	–	–	–	18	441
Johansson	n/a	166	168	0	19	76	92	–	–	–	15	7	5	7
Logstrup	TA TAVI	59	59	–	–	–	59	–	–	–	–	–	–	–
	TF TAVI	22	22	–	–	22	–	–	–	–	–	–	–	
Lopez-Aguilera	PPM post-TAVI	39	–	39	–	–	–	–	–	–	39	–	–	14
	No PPM post-TAVI	178	–	178	–	–	–	–	–	–	0	–	–	
Ludman	n/a	3974	2036	1897	41	2828	761	190	196	–	672	–	99	231
Mack [1]	n/a	90	86	4	–	–	–	–	–	–	–	7	2	10
Mack [2]	n/a	348	348	–	–	244	104	–	–	–	13	4	19	12
Munoz-Garcia	No AKI	308	–	308	–	277	–	30	1	–	71	0	–	4
	AKI	58	–	58	–	49	–	8	1	–	20	58	–	8
Penkalla	No CAD, no PCI	285	285	–	–	–	285	–	–	–	–	42	–	15
	Non-significant CAD, no PCI	232	232	–	–	–	232	–	–	–	–	34	–	9
	Significant CAD, PCI	76	76	–	–	–	76	–	–	–	–	11	–	2
Pilgrim	n/a	257	Mixed	Mixed	–	M	M	M	–	–	60	43	10	17
Poulin	No PPM	61	52	9	–	27	34	–	–	–	–	–	–	–
	PPM post-TAVI	41	38	3	–	23	18	–	–	–	–	–	–	–
Ruparelia	TF TAVI	703	–	–	–	703	–	–	–	–	68	166	12	29
	Other access (OAS)	126	–	–	–	–	–	–	–	–				
Salinas	n/a	79	79	–	–	64	15	–	–	–	3	14	2	10
Salizzoni	n/a	1,904	1,904	–	–	1,252	630	4	18	–	116	155	54	37
Santarpino	n/a	364	94	Mixed	Mixed	205	158	–	1	–	9	1	5	3
Schymik	TA TAVI	413	402	–	11	–	413	–	–	–	44	145	7	25
	TF TAVI	587	399	188	–	587	–	–	–	–	92	117	14	38
Toggweiler	n/a	88	88	–	–	64	24	–	–	–	6	1	1	0
Unbehaun	n/a	104	104	–	–	–	104	–	–	–	6	26	2	6
Ye	n/a	42	42	–	–	M	M	–	–	–	0	1	0	1

[1], various studies used different generations of the Edwards valve (e.g., Sapien, Sapien XT, Sapien 3) and Medtronic valve (e.g., CoreValve, Evolut R). These are not sub-divided here. [2], AKI includes studies which recorded AKI specifically according to VARC criteria as well as those that recorded other indicators/definitions of post-operative kidney injury, such as need for renal replacement therapy. Where AKI and renal replacement therapy were recorded separately, the combined number of patients is included here. [3], 30-day stroke/CVA includes those studies which recorded TIA, "neurological dysfunction", "stroke". Where only in-hospital outcomes were reported, these are recorded here. [4], 30-day mortality includes both in-hospital and post-discharge (but <30 day) mortality. Where only in-hospital outcomes were reported, these are recorded here. TF, trans-femoral; TA, trans-apical; Tsub, trans-subclavian; TAortic, trans-aortic; PPM, permanent pacemaker implant; AKI, acute kidney injury; CVA, cerebrovascular accident. M; mixed valve types, operative approaches used between those categories marked with "M".

References

78. Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol 2014;14:135.