Quantifying the Shift Towards Transcatheter Aortic Valve Replacement in Low-Risk Patients: A Meta-Analysis

De Sciscio TAVR in Low-Risk Patients

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Abstract

Background – In recent years, use of transcatheter aortic valve replacement (TAVR) has expanded to include patients at intermediate- and low-risk cohorts. We sought to determine disease prevalence and treatment distribution including TAVR eligibility in low-risk patients across 37 advanced economies.

Methods and Results – Four systematic searches were conducted across MEDLINE, EMBASE, and the Cochrane database for studies evaluating disease prevalence, severity, decision-making and survival in patients with AS. Estimates of disease prevalence and treatment eligibility were calculated using stochastic simulation and population data for the 37 countries comprising the IMF 'advanced economies' index. Fifty-six studies comprising 42,965 patients were included across five domains: prevalence, severity, symptom status, treatment modality and outcome. The pooled prevalence in the general population aged 60-74 years and >75 years was 2.8% (95% CI: 1.4–4.1%) and 13.1% (95% CI: 8.2–17.9%), respectively – corresponding to an estimated 16.1 million (95% CI: 12.2–20.3) people in 37 advanced economies. Of these, an estimated 3.2 million (95% CI: 2.2–4.4) patients have severe AS with 1.9 million (95% CI: 1.3–2.6) eligible for surgical aortic valve replacement (SAVR). There are approximately 485,230 (95% CI: 284,547–667,353) high-risk/inoperable patients, 152,690 (95% CI: 73,410–263,000) intermediate-risk patients and 378,890 (95% CI: 205,130–610,210) low-risk patients eligible for TAVR.

Conclusions – With a prevalence of 4.5%, an estimated 16.1 million people aged ≥60 years across 37 advanced economies have AS. Of these, there are approximately 1.9 million patients eligible for SAVR and 1.0 million patients eligible for TAVR.

Introduction

Since the release of the first PARTNER trial, transcatheter aortic valve replacement (TAVR) has been widely accepted as the preferred approach for selected high-risk/inoperable patients with severe symptomatic aortic stenosis (AS).[1,2] In 2013, Osnabrugge and colleagues[3] modelled the number of high-risk patients eligible for TAVR in the general population aged ≥75 years. The authors identified approximately 290,000 candidates across 21 countries in Europe and North America. Since this report, the total number of TAVR procedures has grown to over 200,000 across more than 1,000 centers in 50 countries.[4] While surgical aortic valve replacement (SAVR) remains the primary modality for valve replacement in patients with severe AS,[5] the use of TAVR in lower-risk patients is increasing as clinical practice anticipates the results of ongoing trials. Most recently, Edwards Lifesciences received expanded indication approvals from the US Food and Drug Administration for the SAPIEN 3 and SAPIEN XT in intermediate-risk patients. Unfortunately, there is limited data detailing the distribution of lower-risk patients eligible for TAVR (or SAVR). Indeed, quantification of disease prevalence and treatment eligibility will facilitate data-driven decision-making with respect to resource allocation, operator training and financial reimbursement.

Accordingly, we sought to expand on previous modelling to determine disease prevalence, treatment distribution and survival outcomes for patients with severe AS aged ≥60 years. Using a mixed methodology of meta-analysis and stochastic simulation, our analysis estimates the number of patients with severe AS eligible for AVR across 37 countries comprising the International Monetary Fund's (IMFs) 2015 'advanced economies' index.

Methods

Four systematic searches were conducted across MEDLINE, EMBASE, and the Cochrane database for studies evaluating disease prevalence, severity, decision-making and outcomes in patients with AS. Search terms (and combinations thereof) included: 'aortic stenosis', 'valvular heart disease', 'prevalence', 'epidemiology', 'severe', 'symptomatic', 'surgical aortic valve' or 'SAVR', and 'transcatheter aortic valve' or 'TAVR'. Search results were limited to studies published in English during the 20-year period from January 1996 to December 2015. Citations were screened using the title and abstract, with the full article retrieved if it reported one or more of: disease prevalence in the general population, distribution of AS by severity with or without symptom status, SAVR and/or TAVR eligibility, risk profile in patients undergoing SAVR and postoperative mortality. Additional papers were identified from reference lists where appropriate. Studies were reviewed by two independent investigators at each

stage, with data extraction including study characteristics (i.e. author, year, journal, study design, enrollment period, inclusion criteria and AS definition), methodological quality and outcomes, as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Study quality was assessed using the Quality Index Assessment Criteria for Methodology of Studies, adopting a threshold of 12 for study inclusion.[6] Disagreements relating to study inclusion were solved by consultation with a third investigator. Only original peer-reviewed publications enrolling patients from advanced economies were included in the analysis.

Studies evaluating disease prevalence were included if they met the following criteria: (a) random sampling in a representative population, (b) diagnosis using objective echocardiographic assessment, and (c) outcomes reported by age category (or in a way that facilitates calculation of prevalence in the population aged ≥60 years). Studies directly or indirectly reporting disease severity were included if: (a) enrollment of patients was either random or consecutive and, (b) AS severity was determined by echocardiographic assessment. Studies directly or indirectly reporting AVR eligibility were included if: (a) enrolled patients had *a priori* defined severe AS, (b) symptom status was reported (with symptomatic AS defined by a clinical history of angina, syncope and/or congestive heart failure), and (c) intervention rate was reported for AVR as number of patients. Data pertaining to all-cause mortality were extracted from studies comparing outcomes in patients receiving SAVR or medical therapy. Studies reporting the risk profile of patients undergoing isolated SAVR were included if: (a) enrollment of patients was consecutive, (b) risk score was prospectively collected, and (c) patient risk was reported by category using a defined EuroSCORE threshold (or interval) or Society of Thoracic Surgery Predicted Risk Of Mortality (STS-PROM) score. Studies reporting TAVR eligibility were included if: (a) patients were referred for assessment of eligibility, (b) enrollment of patients was consecutive, and (c) enrollment was consistent with regional guidelines at the time of recruitment. The exclusion criteria reported in each individual study was not used to determine inclusion in the meta-analysis.

Studies were excluded if one or more of the following criteria applied: duplicate publication, subgroup analysis of a previously reported cohort, publication in the form of an abstract, case report, conference presentation or editorial, undefined recruitment protocol and/or unclear reporting of outcomes such that the relevant statistics could not be extracted or calculated. Where duplicated data was identified, the study with the largest sample was used. With respect to TAVR eligibility, studies performed in the United States prior to the release of PARTNER I (NCT00530894) findings were excluded due to stricter inclusion criteria which have since eased in line with earlier European trials.

Disease prevalence, represented as rate and 95% confidence interval (95% CI), was determined for each study population by extraction of sample size and patient number by age category. Thereafter, prevalence was evaluated as a pooled estimate using fixed and random-effects models, where appropriate. Patient progression to AVR was mapped using pooled estimates of: symptom status in patients with severe AS, risk score (EuroSCORE and/or STS-PROM) and as-treated intervention rates. Individual patient characteristics were not obtained. Estimates of disease prevalence and treatment eligibility were calculated using Monte Carlo methods (n=100,000) with probability distributions parametrized using the aforementioned pooled statistics. Population estimates for 2015, 2016 and 2020 were sourced for the 37 countries comprising the 2015 IMF 'advanced economies' index, namely: Australia, Austria, Belgium, Canada, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Iceland, Ireland, Israel, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, Netherlands, New Zealand, Norway, Portugal, San Marino, Singapore, Slovakia, Slovenia, South Korea, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States.[7-8] The number of patients eligible for TAVR was estimated for high-, intermediate- and low-risk using EuroSCORE and adopting the inclusion age of PARTNER II (NCT01314313) for high-to-intermediate risk and PARTNER III (NCT02675114) for low-risk patients. A separate analysis was performed using STS-PROM. The exclusion criteria for PARTNER was not modelled in the simulation.

Data analysis was conducted using R Studio (GNU General Public License). Weighted point estimate (PE) and risk ratio (RR) were calculated for the pooled study population, with results presented as weighted PE or RR and 95% CI. Fixed and random effects models utilized the inverse variance and DerSimonian-Laird methods, respectively. Statistical heterogeneity, a measure of variability across trials not due to chance, was assessed using the Cochran-Q and I^2 statistics. Moderate heterogeneity was considered to be present for an $I^2>50\%$ and $p<0.10$. Accordingly, conclusions were based on analysis using the random effects models. Sensitivity analysis was performed using the one-study exclusion method. A $\geq15\%$ modification of the pooled estimate was considered significant. Publication bias was assessed by inspection of funnel plots for asymmetry and Egger's regression test with $p<0.10$ considered significant.

Results

Of the 4,514 studies identified during the systematic search, with an additional 47 found through cross-referencing, 4,037 were excluded on initial review owing to inadequate diagnostic criteria, biased patient selection,

duplicate data, non-original publication and/or an unclear methodology (**Figure 1**). Following assessment of 524

full articles, 56 studies were included for analysis with 42,965 patients extracted (not including 141,905 patients

used for sensitivity analysis of preoperative risk score).

Characteristics of the studies used to estimate disease prevalence are presented in **Table 1** (*see supplementary*

material for prevalence studies that were excluded due to patient selection and/or disease classification). Disease

prevalence ranged from 1.3% to 7.8% for people aged 60-74 years and 2.6% to 22.8% for people aged ≥75 years.

The pooled prevalence was 2.8% (95% CI: 1.4–4.1%) and 13.1% (95% CI: 8.2–17.9%), respectively (**Figure 2a**).

The portion of AS classified as severe was reported in six of the nine populations ranging from 11.5% to 26.7%.

The pooled estimate was 19.9% (95% CI: 12.8–26.9%; **Figure 2b**).

Disease progression to SAVR and TAVR (for high-risk/inoperable patients) is reported in **Figure 3** (*see*

supplementary material for studies used to derive SAVR eligibility). Of those patients with severe AS, 71.2% (95%

CI: 63.3–79.2%) were symptomatic (**Figure 4**), with SAVR performed in 56.1% (95% CI: 48.4–63.9%) of

symptomatic patients and 28.8% (95% CI: 20.8– 46.7%) of asymptomatic patients (**Figure 5**). A further 39.9%

(95% CI: 32.4–47.4%) of non-operated asymptomatic patients progressed to SAVR within 2 years due to

development of symptoms necessitating surgical intervention. Of the patients who did not receive SAVR, 20.0%

(95% CI: 12.3–27.7%) were deemed eligible but refused. Irrespective of symptom status, SAVR was associated

with a significant reduction in mortality (up-to 2 years postoperatively) when compared to optimal medical therapy

(RR: 0.34 [95% CI: 0.24–0.48] and RR: 0.37 [95% CI: 0.18–0.78]; **Figure 6**). Of the patients who underwent

SAVR, 57.4% (95% CI: 41.3–73.6%) were classified as low-risk based on EuroSCORE assessment (**Figure 7**). The

characteristics of studies investigating TAVR eligibility are presented in **Table 2**. Of the high-risk/inoperable

patients referred for TAVR assessment, 56.0% (95% CI: 50.2–61.8%) were eligible (**Figure 8**), of which 84.6%

(95% CI: 79.0–90.2%) received TAVR with 15.4% (95% CI: 9.8–21.0%) refusing intervention.

The overall prevalence of AS in the study population was 4.5%, corresponding to an estimated 16.1 million

(95% CI: 12.2–20.3) people across the 37 advanced economies. Disease prevalence and AVR eligibility for 2015,

stratified by country and procedural type, are presented in **Tables 3 and 4**. By region, there is an estimated 7.5

million (95% CI: 5.7–9.5) people in Europe, 4.5 million (95% CI: 3.5–5.7) people in North America and 350,190

(95% CI: 266,950–440,760) people in Australasia with AS. Of these, an estimated 3.2 million (95% CI: 2.2–4.4)

people aged ≥60 years have severe AS. An estimated 1.9 million (95% CI: 1.3–2.6) patients with severe AS are

eligible to receive SAVR including 873,690 (95% CI: 596,290–1,208,500) in Europe, 515,690 (95% CI: 355,210–706,910) in North America and 40,950 (95% CI: 28,220–56,170) in Australasia. Applying age and risk profiles from the PARTNER trial series, 485,230 (95% CI: 284,547–667,353) patients at high-risk and aged ≥75 are eligible for TAVR including 231,490 (95% CI: 136,880–351,490) in Europe, 125,060 (95% CI: 73,710–190,060) in North America and 10,130 (95% CI: 6,010–15,420) in Australasia. An additional 152,690 (95% CI: 73,410–263,000) patients aged ≥75 years and at intermediate-risk are now eligible for TAVR with the recent shift in approved indications. Extending further to low-risk patients, adopting an inclusion age of ≥65 years as per PARTNER III, another 378,890 (95% CI: 205,130–610,210) patients would be candidates for TAVR. Analysis using population projections for the next 5 years[8] returns estimates of 331,359 (95% CI: 266,263–390,776) new cases of AS in 2016, with overall prevalence reaching 17.9 million patients (95% CI: 13.6–22.6) by 2020. Accordingly, there will be an estimated 2.1 million (95% CI: 1.4–2.9) patients eligible for SAVR and 1.1 million (95% CI: 0.6–1.7) patients eligible for TAVR by the end of this decade.

Pooled estimates remained stable on sensitivity analysis for all parameters except prevalence in the general population aged 60-74. On removal of the Taiwanese-based study by Lin and colleagues[11], adjusting prevalence to 1.4% (95% CI: 1.2–1.6%), 300,000 fewer patients with severe AS were eligible for SAVR. Despite this, the estimated number of TAVR candidates remained similar at 485,247 (95% CI: 286,170–740,191). In a second analysis, the proportion of SAVR patients classified as high-, intermediate- and low-risk was adjusted to 6.2%, 13.9% and 79.9%, respectively – based on a 2015 registry study that used STS-PROM score to classify 141,905 patients who underwent isolated primary SAVR in the US from 2002 to 2010.[51] Accordingly, the estimated number of patients eligible for TAVR in the high- and intermediate- risk groups was reduced by 39,185 (95% CI: 26,358–53,887) and 79,254 (95% CI: 40,043–132,524), respectively. The difference was shifted to the low-risk group, totaling 527,256 (95% CI: 304,308–814,868). No evidence of publication bias was identified on Egger's test for measures of prevalence, symptom status or AVR eligibility.

Discussion

This meta-analysis presents a quantitative analysis of the progression of severe AS, from diagnosis to intervention, extending the current understanding of patient distribution along the path to AVR. Moreover, this

study quantifies the breadth of disease burden in advanced economies highlighting the need for expansion in operational capacity and payer reimbursement.

The present study reports a disease prevalence of 2.8% and 13.1% in the general population aged 60-74 years and ≥75 years, respectively. Subsequent modelling estimates that 16.1 million people across 37 advanced economies have AS. Of these, 1.9 million patients are eligible for SAVR with 485,230 high-risk/inoperable patients eligible for TAVR. These figures underscore the growing disparity between the number of replacement procedures and clinical need for treatment. SAVR is projected to reach 500,000 cases per year by 2020.[52] Even if patient demand remained stable, this number is inadequate. Our analysis projects 17.9 million patients will have AS within 5 years, or approximately 331,300 new cases per year including 65,600 patients diagnosed with severe AS.

The data used to quantify each step of the analysis (from prevalence to TAVR eligibility) were extracted from studies performed in advanced economies. Accordingly, estimates of disease prevalence and patient eligibility were restricted to the 37 countries comprising the IMF advanced economies index. Inherent in the study design is the assumption that prevalence and intervention rates are generalizable across these countries. In reality, there are likely to be differences from one country to the next. Indeed, favorable reimbursement schemes and local decision-making may result in differing eligibility rates across countries. Moreover, the IMF advanced economies index represents less than 15% of the world's population.[8]

Distribution of patients along the AVR pathway raises a number of questions. The literature has consistently demonstrated mortality rates of up to 50% within 3-5 years from symptom onset in patients with severe AS.[53-55] Yet, this study reports that more than 40% of patients with severe symptomatic AS did not undergo SAVR. Equally surprising, less than 30% of patients with asymptomatic AS underwent SAVR despite at least a 25% reduction in mortality when compared to medical therapy. It should be noted that five of the six studies reporting outcomes for asymptomatic AS included patients with low LVEF. This cohort of asymptomatic patients is known to have poorer outcomes. Accordingly, their inclusion may have disproportionately influenced the observed mortality benefit with SAVR. Likewise, it may also have contributed to the finding that close to half of the asymptomatic patients treated with medical therapy progressed to SAVR within 2 years following symptom onset. Irrespective of symptom status, 20% of patients who received medical therapy did so because they refused surgical intervention. The reasons for treatment refusal were not explored in this study and may include reimbursement. Nevertheless, these data

underscore the disparity between the number of patients estimated as having AS and the number of patients undergoing SAVR over the past two decades.

With respect to TAVR, notwithstanding the rapid rise in adoption since the first procedure in 2002,[56] the present meta-analysis indicates that only 56% of high-risk/inoperable patients referred for TAVR were eligible. This is not entirely unexpected given that TAVR was initially reserved for contraindicated surgical patients. Using data from the German Aortic Valve Registry, Reinöhl and colleagues have shown an overall increase in the number of AVR procedures between 2007-2013 with TAVR increasing by 9,003 compared to a decrease in SAVR by 1,574.[57] The majority of this increase was seen in the cohort aged 80 years or more whereby a small reduction in SAVR was considerably outpaced by the increase in TAVR. This suggests that the two modalities are complementary with additional patients being treated beyond those who would have previously undergone SAVR. In contrast, TAVR in younger patients offset the reduction in SAVR suggesting that TAVR in the 'lower-risk' population will compete with SAVR. Of note, Germany has one of highest rates of TAVR adoption in Europe as a result of their TAVR-specific national diagnosis-related group reimbursement scheme. In 2013, Mylotte and colleagues[58] demonstrated a 3.3-fold increase in the number of TAVR procedures per million population in healthcare systems using TAVR-specific reimbursement schemes. In countries with lower rates of TAVR adoption, it is possible that TAVR has been limited to inoperable patients. Thus, a shift towards lower-risk patients will see TAVR compete directly with SAVR, with an estimated 530,000 patients being eligible for both TAVR and SAVR.

A significant barrier to TAVR adoption is the costs associated with device procurement and implantation. Moreover, the cost-effectiveness compared to SAVR is unclear. Analysis of the US CoreValve High-Risk Trial has demonstrated higher index admission and projected lifetime costs with TAVR when compared to SAVR ($11,260 and $17,849 increase per patient, respectively).[59] In contrast, transfemoral access was associated with lower costs and higher QALYs gained in PARTNER I – with TAVR being dominant over SAVR in 70.9% of bootstrap replicates (ICER<$50,000/QALY).[60]

Irrespective of treatment modality, the estimated number of patients in need of valve replacement presents a considerable challenge to policy makers. From a fiscal perspective, treating all patients eligible for valve replacement in this study would require a budget of at least $149.9 billion (95% CI lower bound) - calculated using mean 12-month cost from PARTNER I.[38] Aside from the direct financial costs of the procedure, additional treatment centers and operators would be required. Expansion of TAVR to low-risk patients may prompt a reduction

in device cost allowing for earlier intervention thus redirecting financial resources to training or infrastructure. Reductions in procedural time, hospital length of stay and rehabilitation days,[38] may allow for a higher throughput of patients – ultimately increasing the number of beds and staff available. However, it should be noted that the long-term durability of TAVR remains unknown following recent reports indicating deterioration within 10 years for the first generation of transcatheter valves.[61] Likewise, it remains unclear as to whether TAVR is, at the least, non-inferior to SAVR in the low-risk cohort. The purpose of the present study was to quantify current treatment patterns and estimate patient eligibility. Any decision to expand TAVR into younger, low-risk patients will require evidence of durability and outcomes comparable to SAVR. In the short-term, SAVR will likely remain the primary modality for valve replacement in this cohort – especially for younger patients and/or patients with asymptomatic disease.

Study Limitations

With respect to estimating patient numbers, measures of uncertainty were incorporated at each step to calculate intervals representing the likelihood of the final estimates. For TAVR eligibility, estimates may disproportionately represent European experience as risk profile was determined using EuroSCORE. The decision to use EuroSCORE for the primary analysis was based on the greater number of included studies reporting EuroSCORE relative to STS-PROM. The decision to include studies that used hospital-based eligibility criteria and not a specific trial standard (i.e. the PARTNER exclusion criteria) was based on the desire to provide findings that represent broader clinical practice.

For estimates of postoperative survival, the concomitant effect of coexisting disease could not be directly assessed. While risk profile measures like EuroSCORE or STS-PROM score may be used as a surrogate for AVR patients, these scores do not capture every characteristic that may affect outcomes. Unfortunately, individual patient data was not provided to enable matching or reporting of sex-based and racial/ethnic-based differences. Additionally, patients receiving medical therapy were not stratified by risk. Accordingly, patients who refused SAVR were included in estimates of SAVR eligibility but not TAVR eligibility.

Although studies in this analysis used echocardiography to identify AS classification criteria varied. The influence of differing methodologies on estimates of disease prevalence, severity and symptom status should be considered when interpreting the results of this study. Heterogeneity was explored by comparison of study characteristics, assessment of funnel plot asymmetry and Egger's linear regression method, where appropriate. The

repeatedly high I^2 statistic increases the uncertainty of the patient estimates with each successive step in the simulation. Sensitivity analysis was employed in the case of prevalence in the general population aged 60-74 years. Likewise, a separate analysis was performed substituting EuroSCORE for STS-PROM. The reduction in estimated SAVR candidates with a change in the initial prevalence parameter highlights the limitations of the modelling approach, specifically the dependence on the methodologies of the studies comprising the meta-analysis.

In conclusion, the present study adopted a mixed methodology of meta-analysis and stochastic simulation to quantify the growing burden of AS, specifically the progression of severe AS to AVR. Based on AHA/ACC guidelines, 4.5% of people aged ≥60 years have AS or 16.1 million people across 37 advanced economies. Of these, approximately 1.9 million patients with severe AS are candidates for SAVR. For high-to-intermediate risk patients aged ≥75 years, approximately 637,000 patients are eligible for TAVR. A further 379,000 patients would be eligible following expanded indication approval to include the low-risk cohort. Given the trend towards TAVR in lower-risk patients, together with an ageing population, healthcare systems must look at ways to accommodate the increase in patient numbers, operator shortage and hospitalization of untreated patients with severe AS.

Disclosures

No conflicts to report

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Table 1 Characteristics of studies included to determine prevalence of severe AS

Author., Year	[#]n	Study location	Inclusion period	Recruitment method	Recruitment population	Consecutive recruitment	Population characteristics	AS criteria (Doppler Echo)
[9]Iivanainen et al., 1996	501	Helsinki, Finland	1990-1991	Invitation	Helsinki Ageing Study (n=651) - 77% inclusion rate	Yes	Aged ≥75yrs Female: 73%	**Mild AS:** V_{ratio} ≤0.55, AVA: ≤1.5cm^2 **Moderate AS:** V_{ratio} ≤0.45, AVA: ≤1.2cm^2 **Severe AS:** V_{ratio} ≤0.35, AVA: ≤0.8cm^2
[10]Stewart et al., 1997	5,201	North Carolina, California, Maryland, Pennsylvania, USA	1989-1990	Random selection	Cardiovascular Health Study - 57% inclusion rate	n/a	Aged ≥65yrs Female: 57%	**AS:** Vmax >2.5m/s
[11]Lin et al., 2005*	2,850	Taipei, Taiwan	2004	Referral	Routine health review and/or non-cardiac surgery	Yes	Aged 20-97yrs Female: 41%	**Mild-moderate AS:** gradient >20mmHg **Severe AS:** gradient ≥50mmHg
[12]Nkomo et al., 2006*	13,349	Minnesota, USA	1990–2000	Prospectively recorded echo	Olmsted County Cohort (n=16,501) - 90% inclusion rate	Yes	Aged ≥18yrs Female: 51%	**Mild AS:** Vmax 2.5-3m/s, AVA: >1.5cm^2 **Moderate AS:** Vmax 3-4m/s, AVA: 1-1.5cm^2 **Severe AS:** Vmax ≥4m/s, AVA <1.0cm^2
[13]Van Bemmel et al., 2010	81	Leiden, Netherlands	1997-1999	Invitation (at 90yrs)	Leiden 85-plus Study (n=277)	Yes	Aged 90yrs Female: 67%	**Mild AS:** gradient <25mmHg **Moderate AS:** gradient 25-40mmHg **Severe AS:** gradient >40mmHg

[14]Eveborn et al., 2012*	3,273	Tromsø, Norway	1994	Random selection (aged 55-74yrs) Invitation (5-8% aged 25-84yrs)	Tromsø Study (n=10,542)	n/a	Aged 25-84yrs Female: 49%	**Mild AS:** gradient 15–29mmHg **Moderate AS:** gradient 30–49mmHg **Severe AS:** gradient ≥50mmHg
[15]Malouf et al., 2012≠	360	Minnesota, USA	1988–1997	Prospectively recorded echo	Olmsted County Cohort	Yes	Age: 74 ± 14yrs Female: 56%	**Mild AS:** AVA: >1.5cm^2 **Moderate AS:** AVA: 1.0-1.5cm^2 **Severe AS:** AVA: <1.0cm^2
[16]Leibowitz et al., 2013	498	Jerusalem, Israel	2005-2006	Random selection	Jerusalem Longitudinal Cohort Study (n=1,222)	n/a	Aged ≥85yrs Female: 53%	**AS:** Vmax >2.5m/s
[17]Rezzoug et al., 2015	567	Wallony, Brussels, Flanders, Belgium	2008-2009	Referral	Routine health review (29 GP clinics)	Yes	Aged ≥80yrs Female: 63%	**Mild AS:** AVA: >1.5cm^2 **Moderate AS:** AVA: 1.0-1.5cm^2 **Severe AS:** AVA: <1.0cm^2

AS = Aortic Stenosis, AVA = aortic valve area, Vmax = peak velocity, V$_{ratio}$ = velocity ratio;

*portion of the study population extracted (patients aged ≥60 yrs); #number of patients included in meta-analysis (not total study sample); ≠included for severity classification

Table 2 Characteristics of studies included to determine TAVR eligibility

Author Year	n	Study location	Inclusion period	Referral criteria	Consecutive enrollment	Patient characteristics	Valve system
[40]Otten et al., 2008	100	Rotterdam, Netherlands	2005-2007	Severe symptomatic AS Aged ≥75yrs or EuroSCORE >20	Yes	Age: 82 ± 8yrs Female: 57% EuroSCORE: 17 ± 11	CoreValve
[41]Himbert et al., 2009	160	Paris, France	2006-2008	Severe symptomatic AS High-risk/inoperable EuroSCORE >20 (STS-PROM ≥10) Life expectancy >1yr	Yes	Not-reported	SAPIEN
[42]De Carlo et al., 2010	166	Pisa, Italy	2007-2009	Severe symptomatic AS High-risk/inoperable	Yes	Age: 83 (7)yrs Female: 53% EuroSCORE: 21.1	CoreValve
[43]Ragani et al., 2010	85	Brighton, UK	2007-2009	Severe AS Inoperable	Yes	Age: 81 ± 7yrs Female: 45% EuroSCORE: 21±17	CoreValve
[44]Saia et al., 2010	98	Bologna, Italy	2007-2008	Severe symptomatic AS Inoperable	Yes	Age: 82 ± 7yrs Female: 60% EuroSCORE: 25.3 ± 14.5	SAPIEN and CoreValve
[45]Bainey et al., 2013	170	Ontario, Canada	2008-2011	Severe symptomatic AS High-risk/inoperable	Yes	Age: 82.1 ± 6.5yrs Female: 53% STS-PROM: 10.5 ± 7.6	SAPIEN
[46]Dubois et al., 2013	163	Leuven, Belgium	2008-2011	Severe symptomatic AS High-risk/inoperable Advanced age + one coexisting illness	Yes	Age: 83 ± 5yrs Female: 56%	SAPIEN

[47]Hong et al., 2014	60	Seoul, Korea	2011-2012	Severe symptomatic AS High-risk/inoperable EuroSCORE >20 (STS-PROM ≥10)	Yes	Age: 80 ± 5yrs Female: 58% EuroSCORE: 18.4 ± 14.3	CoreValve
[48]O'Sullivan et al., 2014	105	Dublin, Ireland	2009-2012	Severe AS High-risk/inoperable	Yes	Age: 83.2 ± 20.8yrs Female: 38%	Not-specified
[49]Iglesias et al., 2015	149	Madrid, Spain	2008-2012	Severe symptomatic AS Indication for AVR	Yes	Age: 83.7 ± 5.9yrs Female: 57% EuroSCORE: 19.8 ± 12.3	SAPIEN
[50]Pilgrim et al., 2015	442	Bern, Switzerland	2007-2010	Severe symptomatic AS High-risk/inoperable	Yes	Age: 83 (8)yrs Female: 52% EuroSCORE: 19.1	SAPIEN and CoreValve

AS = Aortic Stenosis, AVR = Aortic Valve Replacement, STS-PROM = Society of Thoracic Surgery Predicted Risk Of Mortality; *Continuous variables expressed as mean ± SD or median; categorical variables expressed as percentage*

Table 3 Prevalence of AS in the general population aged ≥60yrs

Country	Aortic Stenosis	Severe AS	Eligible for SAVR
Australia	**295,712 (226,107-372,421)**	**58,849 (40,826- 80,437)**	**34,578 (23,799-47,538)**
Austria	134,901 (102,575-170,563)	26,846 (18,459-36,857)	15,775 (10,766-21,805)
Belgium	**180,667 (137,212-228,532)**	**35,955 (24,656-49,446)**	**21,126 (14,409-29,251)**
Canada	480,853 (367,347-604,926)	95,691 (66,265-130,373)	56,225 (38,684-77,093)
Cyprus	**12,163 (9,307-15,298)**	**2,420 (1,690-3,292)**	**1,422 (985-1,943)**
Czech Republic	149,495 (114,316-187,965)	29,747 (20,719-40,370)	17,480 (12,076-23,915)
Denmark	**82,816 (63,254-104,197)**	**16,479 (11,450-22,438)**	**9,683 (6,673-13,247)**
Estonia	21,862 (16,602-27,651)	4,350 (2,992-5,971)	2,556 (1,744-3,533)
Finland	**90,954 (69,370-114,679)**	**18,100 (12,523-24,720)**	**10,635 (7,312-14,623)**
France	1,117,420 (848,647-1,414,286)	222,413 (152,287-306,733)	130,686 (88,684-181,424)
Germany	**1,529,513 (1,157,064-1,939,629)**	**304,438 (208,059-420,453)**	**178,877 (121,139-249,001)**
Greece	205,612 (155,563-261,091)	40,917 (27,905-56,548)	24,041 (16,256-33,441)
Hong Kong	**97,987 (74,708-123,670)**	**19,501 (13,506-26,685)**	**11,459 (7,863-15,777)**
Iceland	3,824 (2,922-4,822)	761 (527-1,039)	447 (307-615)
Ireland	**49,222 (37,671-61,922)**	**9,795 (6,830-13,289)**	**5,756 (3,982-7,859)**
Israel	79,789 (60,862-100,522)	15,877 (10,989-21,667)	9,330 (6,419-12,832)
Italy	**1,202,143 (910,283-1,523,895)**	**239,248 (163,346-330,570)**	**140,579 (95,229-195,484)**
Japan	2,838,264 (2,152,427-3,594,256)	564,840 (386,311-778,508)	331,893 (225,343-460,078)
Latvia	**33,382 (25,343-42,210)**	**6,642 (4,569-9,118)**	**3,903 (2,662-5,389)**
Lithuania	49,018 (37,163-62,070)	9,754 (6,679-13,418)	5,731 (3,896-7,940)
Luxembourg	**6,835 (5,206-8,631)**	**1,360 (941-1,861)**	**799 (548-1,100)**
Malta	6,376 (4,874-8,023)	1,269 (882-1,725)	745 (514-1,019)
Netherlands	**249,164 (190,297-313,669)**	**49,577 (34,401-67,501)**	**29,130 (20,070-39,905)**

New Zealand	54,478 (41,630-68,556)	10,841 (7,525-14,757)	6,370 (4,396-8,733)
Norway	**68,233 (52,101-85,951)**	**13,578 (9,419-18,529)**	**7,978 (5,492-10,951)**
Portugal	186,634 (141,740-236,160)	37,139 (25,420-51,025)	21,824 (14,838-30,191)
San Marino	**529 (401-670)**	**105 (72-145)**	**62 (42-86)**
Singapore	53,114 (40,675-66,774)	10,569 (7,395-14,307)	6,210 (4,315-8,457)
Slovakia	**61,858 (47,332-77,757)**	**12,309 (8,592-16,690)**	**7,233 (5,011-9,864)**
Slovenia	32,688 (24,941-41,241)	6,505 (4,488-8,892)	3,822 (2,620-5,263)
South Korea	**551,545 (421,061-694,339)**	**109,768 (76,096-149,490)**	**64,498 (44,369-88,319)**
Spain	766,704 (580,322-972,528)	152,576 (104,508-210,222)	89,648 (60,924-124,428)
Sweden	**155,088 (118,237-195,792)**	**30,862 (21,359-42,155)**	**18,135 (12,446-24,948)**
Switzerland	125,436 (95,435-158,507)	24,969 (17,172-34,227)	14,671 (10,009-20,244)
Taiwan	**248,178 (189,762-312,434)**	**49,387 (34,299-67,160)**	**29,022 (19,958-39,766)**
United Kingdom	949,884 (723,886-1,197,791)	189,044 (130,372-258,725)	111,085 (75,996-153,019)
United States	**3,928,656 (3,001,571-4,942,710)**	**781,773 (542,923-1063,142)**	**459,344 (316,429-628,430)**

Table 4 Number of patients with severe symptomatic AS eligible for TAVR

Country	High-risk/inoperable (≥75yrs)	Intermediate-risk (≥75yrs)	Low-risk (≥65yrs)
Australia	**8,595 (5,087-13,081)**	**2,705 (1,299-4,659)**	**6,870 (3,732-11,040)**
Austria	4,137 (2,443-6,295)	1,302 (627-2,244)	3,222 (1,748-5,193)
Belgium	**5,610 (3,320-8,526)**	**1,765 (850-3,028)**	**4,280 (2,328-6,870)**
Canada	13,795 (8,164-20,947)	4,340 (2,082-7,458)	11,063 (5,999-17,804)
Cyprus	**338 (200-513)**	**106 (51-182)**	**277 (150-446)**
Czech Republic	4,080 (2,416-6,195)	1,284 (617-2,206)	3,414 (1,845-5,486)
Denmark	**2,348 (1,389-3,570)**	**738 (355-1,267)**	**1,947 (1,055-3,135)**
Estonia	676 (401-1,027)	213 (102-366)	515 (280-826)
Finland	**2,646 (1,566-4,009)**	**833 (401-1,432)**	**2,131 (1,156-3,430)**
France	34,837 (20,494-53,058)	10,959 (5,251-18,842)	26,521 (14,385-42,635)
Germany	**48,621 (28,745-73,889)**	**15,298 (7,336-26,307)**	**36,606 (19,867-58,771)**
Greece	6,646 (3,929-10,114)	2,090 (1,009-3,585)	4,979 (2,717-7,999)
Hong Kong	**2,885 (1,704-4,389)**	**908 (436-1,556)**	**2,231 (1,207-3,586)**
Iceland	111 (65-168)	35 (17-60)	88 (48-141)
Ireland	**1,362 (803-2,068)**	**429 (206-738)**	**1,120 (606-1,801)**
Israel	2,298 (1,360-3,498)	723 (348-1,246)	1,823 (989-2,932)
Italy	**38,459 (22,697-58,469)**	**12,105 (5,809-20,841)**	**28,975 (15,723-46,582)**
Japan	89,452 (52,843-135,992)	28,142 (13,539-48,333)	68,655 (37,183-110,057)
Latvia	**1,030 (609-1,567)**	**324 (155-555)**	**790 (429-1,266)**
Lithuania	1,539 (912-2,338)	484 (234-827)	1,163 (632-1,865)
Luxembourg	**205 (121-312)**	**64 (31-111)**	**159 (87-256)**
Malta	177 (105-269)	56 (27-96)	148 (80-239)
Netherlands	**7,154 (4,232-10,887)**	**2,252 (1,082-3,868)**	**5,798 (3,139-9,338)**

New Zealand	1,539 (910-2,335)	484 (233-833)	1,255 (680-2,021)
Norway	**1,966 (1,167-2,997)**	**619 (297-1,064)**	**1,594 (863-2,566)**
Portugal	5,815 (3,437-8,826)	1,829 (884-3,142)	4,449 (2,425-7,118)
San Marino	**17 (10-25)**	**5 (3-9)**	**13 (7-20)**
Singapore	1,362 (804-2,071)	428 (207-736)	1,149 (623-1,851)
Slovakia	**1,650 (976-2,505)**	**519 (250-892)**	**1,366 (739-2,200)**
Slovenia	975 (576-1,480)	307 (147-527)	753 (408-1,210)
South Korea	**15,522 (9,164-23,590)**	**4,884 (2,352-8,420)**	**12,545 (6,768-20,205)**
Spain	24,165 (14,319-36,701)	7,603 (3,655-13,076)	18,334 (9,972-29,419)
Sweden	**4,586 (2,706-6,983)**	**1,443 (693-2,475)**	**3,694 (1,995-5,935)**
Switzerland	3,812 (2,245-5,811)	1,199 (576-2,065)	2,977 (1,614-4,791)
Taiwan	**7,023 (4,159-10,670)**	**2,209 (1,059-3,791)**	**5,524 (2,999-8,898)**
United Kingdom	28,577 (16,905-43,477)	8,993 (4,317-15,475)	22,576 (12,227-36,245)
United States	**111,205 (65,763-168,903)**	**34,991 (16,813-60,098)**	**89,736 (48,766-143,992)**

Figure 1 Search methodology

Figure 2 Forest plots showing prevalence of severe AS; (upper) AS in general population aged ≥60 years; random effects models (n=26,320); (lower) proportion of AS classified as severe; random effects models (n=1,484)

Figure 3 Map of disease progression to SAVR (includes TAVR pathway for high-risk/inoperable patients); as-treated analysis (n=42,965)

Figure 4 Forest plot showing the proportion of severe AS patients reported as symptomatic; random effects models (n=9,658)

Figure 5 Forest plot showing the proportion of patients with severe AS who underwent SAVR; random effects models (n=8,034)

Figure 6 Forest plot showing all-cause mortality in patients treated for severe AS (AVR vs. medical therapy); random effects models (n=3,061)

Figure 7 Forest plot showing the risk profile (EuroSCORE) of patients treated with SAVR; random effects models (n=2,770)

Figure 8 Forest plot showing the eligibility of high-risk/inoperable patients referred for TAVR; random effects models (n=1,698)