

Annual number of candidates for transcatheter aortic valve implantation per country: current estimates and future projections

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Aims

The number of transcatheter aortic valve implantation (TAVI) procedures is rapidly increasing. This has a major impact on health care resource planning. However, the annual numbers of TAVI candidates per country are unknown. The aim of this study was to estimate current and future number of annual TAVI candidates in 27 European countries, the USA and Canada.

Methods and results

Systematic literature searches and meta-analyses were performed on aortic stenosis (AS) epidemiology and decision-making in severe symptomatic AS. The incidence rate of severe AS was determined. Findings were combined with population statistics and integrated into a model employing Monte Carlo simulations to predict the annual number of TAVI candidates. Various future scenarios and sensitivity analyses were explored. Data from 37 studies ($n = 26\,402$) informed the model. The calculated incidence rate of severe AS was 4.4‰/year [95% confidence interval (95% CI) 3.0–6.1‰] in patients ≥ 65 years. AS-related symptoms were present in 68.3% (95% CI 60.8–75.9%) of patients with severe AS. Despite having severe symptomatic AS, 41.6% (95% CI 36.9–46.3%) did not undergo surgical aortic valve replacement. Of the non-operated patients, 61.7% (95% CI 42.0–81.7%) received TAVI. The model predicted 114 757 (95% CI 69 380–172 799) European and 58 556 (95% CI 35 631–87 738) Northern-American TAVI candidates annually.

Conclusion

Currently, approximately 180 000 patients can be considered potential TAVI candidates in the European Union and in Northern-America annually. This number might increase up to 270 000 if indications for TAVI expand to low-risk patients. These findings have major implications for health care resource planning in the 29 individual countries.

Keywords

Aortic valve stenosis • Epidemiology • Incidence • Transcatheter aortic valve implantation

Introduction

The growing elderly population and the concomitant age-related high prevalence of degenerative aortic stenosis (AS) have a major impact on society.^{1,2} Historically, a considerable proportion of patients with severe AS were denied surgical treatment due to advanced age and elevated operative risk. More recently, transcatheter aortic valve implantation (TAVI) has emerged as the preferred management

strategy for inoperable and high-risk patients, and consequently procedural volume has grown exponentially in recent years.³ This has important implications for health care resource planning. Our group previously estimated the number of potential high- and excessive-risk TAVI candidates based on practice patterns at that time.⁴ Since then, transfemoral TAVI has been shown to be non-inferior to surgical aortic valve replacement (SAVR) among intermediate-risk patients.^{5–12}

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Considering the results of the recent trials suggesting the extension of TAVI to patients at intermediate operative risk, our objectives were; (i) assess the prevalence of AS in patients above 65 years old; (ii) to systematically estimate the annual number of potential TAVI candidates under current practice, assuming unrestricted TAVI availability; and (iii) to predict the annual number of potential TAVI candidates if this technology further extends into low operative risk patients with severe AS.

Methods

Literature search

Separate systematic literature searches on the prevalence, symptom status, and clinical decision-making in severe AS were performed using Medline, Embase®, and Cochrane databases in January 2017. Pre-specified literature search strategies, without time restriction, were constructed using the following search terms: 'valvular heart disease', 'heart valve disease', 'aortic stenosis', 'aortic valve stenosis', 'prevalence', 'symptoms', 'symptomatic', 'asymptomatic', 'decision making', 'treatment decision' and 'heart team'. The literature search was carried out independently by two investigators (A.P.D. and M.M.) and targeted full-length articles published in peer-reviewed journals and congress abstracts. Relevant articles identified by cross-referencing were added manually. After duplicate removal in EndNote, all references were first screened for title and abstract, applying the following eligibility criteria: (i) prevalence: population above 65 years, AS severity assessed by echocardiography; (ii) symptoms: reporting of AS-related symptoms in those with severe AS; (iii) decision-making: studies reporting the current TAVI era decision-making process in severe AS. After screening, full-length manuscripts were carefully assessed for eligibility. The echocardiographic definition of AS was extracted from all studies, along with other essential information related to study design, including country, population characteristics, and risk categorization. The diagnosis of severe AS had to be aligned with contemporary guidelines: maximum jet velocity (V_{max}) ≥ 4.0 m/s; aortic valve area (AVA) ≤ 1.0 cm²; mean gradient ≥ 40 mmHg.^{12,13} The search on clinical decision-making in AS was directed to identify studies focusing on (i) the proportion of patients declined SAVR in the pre-TAVI era, and (ii) the proportion of patients treated with TAVI or medical therapy if declined SAVR. Data detailing the risk distribution among SAVR patients and contemporary TAVI utilization were also collected.

Analysis

Meta-analyses were performed to create a pooled estimate for each specific question regarding AS epidemiology and clinical decision-making. Fixed- and random-effects models were used, applying the inverse variance method and the DerSimonian and Laird methods for the fixed- and random-effect analyses, respectively. Heterogeneity was tested by Cochran *Q* test and *I*² statistics. The exact method was used to calculate the 95% binomial confidence intervals for proportions derived from the included studies. Results were presented as Forest plots. All statistical analyses were performed using Stata software (version 12.0, StataCorp, College Station, TX, USA).

To estimate the number of annual TAVI candidates, first the annual number of newly diagnosed cases of severe symptomatic AS was determined. As prevalence is less useful in this regard, we determined the yearly incidence rate using the following equation: (Incidence rate) = (Prevalence)/(Average untreated disease duration). Prevalence was based on epidemiological reports on AS in

the general population.^{1,2,14–16} Average disease duration to death was determined using reports on the survival of untreated cases of severe symptomatic AS.¹⁷

A decision-making flowchart was built in TreeAge Pro (version 2016, TreeAge Software, Williamstown, MA, USA). Sequential steps of the flowchart were informed with distributions derived from the meta-analyses. Latest available census data on the population aged 65 years or older were collected for the USA, Canada, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the UK.^{18–20} Beta distributions were utilized at each step of the model and per-country estimates were determined using 10 000 Monte Carlo simulations. Results are presented as numbers of annual TAVI candidates per country along with their 95% confidence intervals (95% CI). When estimating the number of potential annual candidates in individual countries, local reimbursement policies were not considered, and unlimited TAVI availability was assumed.

Scenario and sensitivity analyses

To make future estimates, two scenario analyses were performed. Scenario 1: TAVI will be the treatment of choice in intermediate-risk patients, while SAVR–TAVI distribution in the low-risk group remains unchanged. Scenario 2: TAVI will become the treatment of choice in intermediate-risk patients and elderly (>75 years) low-risk SAVR candidates (representing approximately 50% of the low-risk population) will become TAVI candidates as well. The impact of prevalence and average disease duration on the annual numbers of the European and Northern-American candidates were assessed in separate sensitivity analyses.

Results

Epidemiology of symptomatic severe aortic stenosis

The search on AS prevalence generated 5355 articles (*Figure 1*). After duplicate removal, 4996 records were screened for title/abstract, and 145 were assessed for eligibility. Forty-one were included in the qualitative synthesis and finally five in the meta-analysis. The included studies reported on 16 514 patients from three continents. Studies were heterogeneous, especially with respect to age and echocardiographic definitions of AS. Study details are summarized in *Supplementary material online, Table S1*.

Heterogeneity was considerable after performing the meta-analysis [*I*² = 89.0%, *Q* = 36.3, *P* < 0.001 (*Supplementary material online, Figure S1*)]. The largest study specifically reporting AS prevalence in subjects ≥ 65 years was used in the decision-making model.² In a population of 13 349 patients, Nkomo reported a 0.8% (95% CI 0.7–1.0%) prevalence of severe AS (Nkomo, personal communication). This value was used for incidence rate calculations, and when divided by an average disease duration of 1.8 years,¹⁷ corresponded to an incidence rate of 4.4‰/year (95% CI 3.0–6.1‰).

Annual candidates for transcatheter aortic valve implantation

The number of potential annual TAVI candidates was estimated using the model presented in *Figure 2*. This model was informed by the results of separate meta-analyses (*Figures 3 and 4*).

Based on the analysis of 14 studies, we estimate that 68.3% (95% CI 60.8–75.9%) of patients with severe AS were symptomatic (Figure 3A, Supplementary material online, Table S2). Analysis of 20 studies (Supplementary material online, Table S3) revealed that in the pre-TAVI

era, 41.6% (95% CI 36.9–46.3%) of all severe symptomatic AS patients did not receive SAVR (Figure 3B). These patients were deemed to be possible TAVI candidates, though importantly an analysis of nine studies (Supplementary material online, Table S4) reporting on contemporary decision-making in this population demonstrated that 38.3% (95% CI 18.7–58.0%) of these patients were not offered TAVI and were assigned to medical therapy only. There was substantial variability among different countries in offering TAVI to inoperable patients (Figure 4).

Large studies from both Europe and Northern-America confirmed that most patients undergoing SAVR are at low risk.^{21,22} In the Society of Thoracic Surgeons (STS) data set comprising 141 905 patients undergoing SAVR, 6.2% (95% CI 6.1–6.3%), 13.9% (95% CI 13.8–14.1%), and 79.9% (95% CI 79.7–80.1%) of all patients were at high (STS-PROM > 8%), intermediate (4–8%), and low (<4%) operative risk.

A recent study from Denmark reported that among the severe symptomatic AS population traditionally treated with SAVR, 100% of high-risk, 68.2% (95% CI 61.6–74.2%) of intermediate-risk, and 9.9% (95% CI 7.8–12.6%) of low-risk patients undergo TAVI.²³

Ultimately, our model estimated the number of potential TAVI candidates to be 114 757 (95% CI 69 380–172 799) in Europe and 58 556 (95% CI 35 631–87 738) in Northern-America per annum (Take home figure, A).

Scenario and sensitivity analyses

In Scenario 1, where all intermediate-risk patients receive TAVI while SAVR remains the preferred treatment for low-risk patients, the annual number of potential TAVI candidates would increase only by 7%, meaning 122 402 (95% CI 74 208–185 127) annual candidates in Europe and 62 467 (95% CI 38 170–93 322) in Northern-America (Supplementary material online, Figure S2). In Scenario 2, if TAVI becomes the choice of treatment for all intermediate-, and for elderly low-risk patients, the model predicted a 50% further increase in

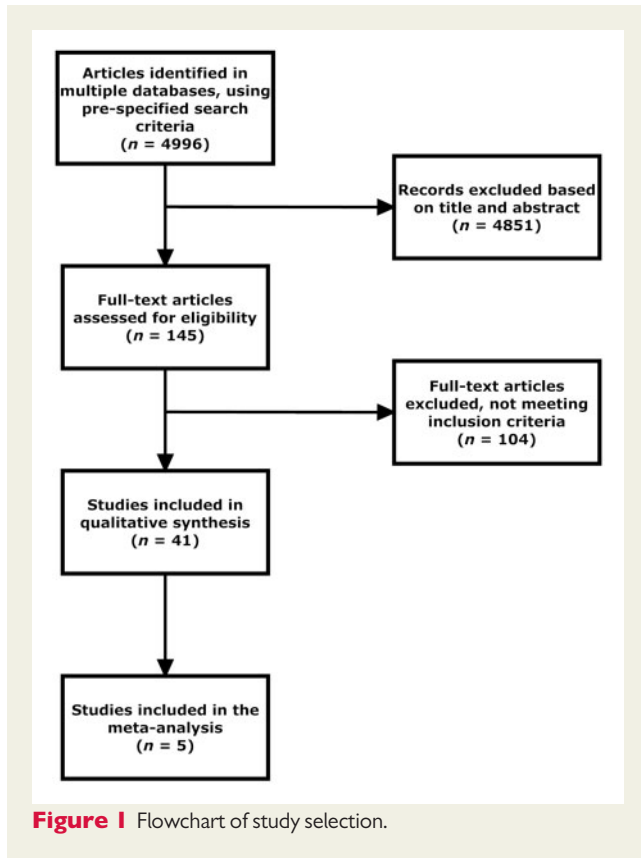


Figure 1 Flowchart of study selection.

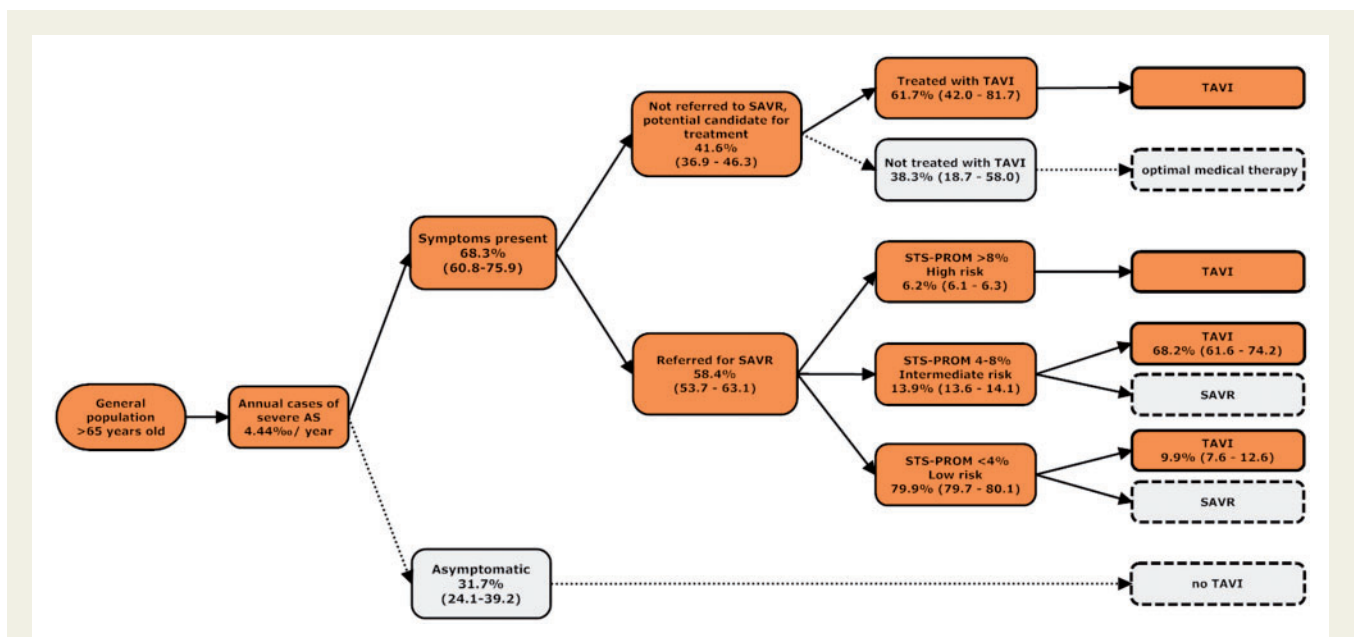


Figure 2 Model for the estimation of annual transcatheter aortic valve implantation candidates. AS, aortic stenosis; SAVR, surgical aortic valve replacement; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI, transcatheter aortic valve implantation.

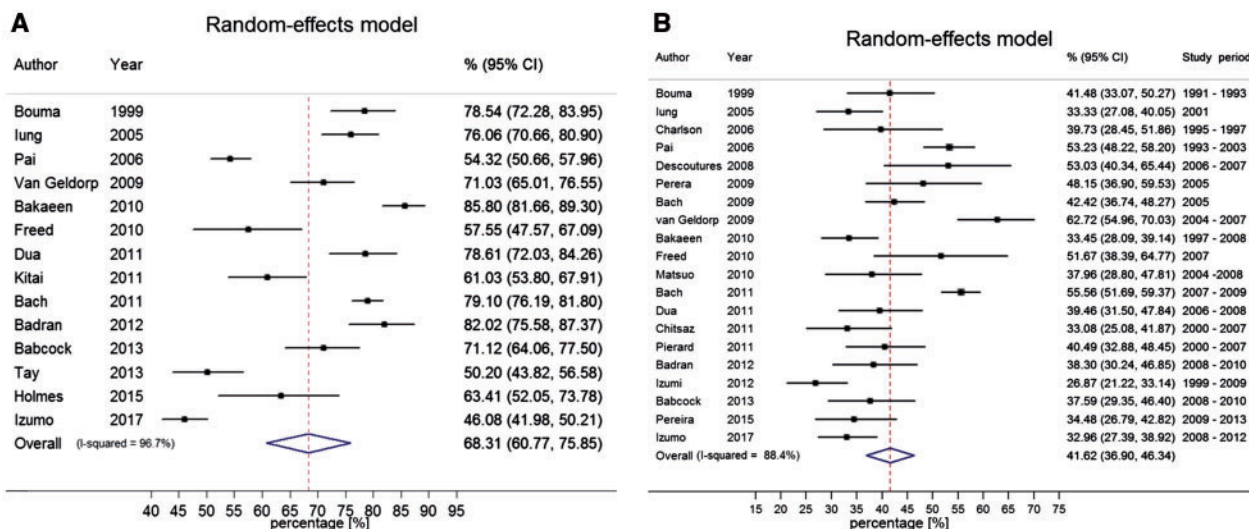


Figure 3 Forest plots of the different steps in the model. (A) Prevalence of symptoms in patients with severe aortic stenosis. (B) Percentage of patients not receiving surgical aortic valve replacement despite having severe symptomatic aortic stenosis. AS, aortic stenosis; CI, confidence interval; SAVR, surgical aortic valve replacement.

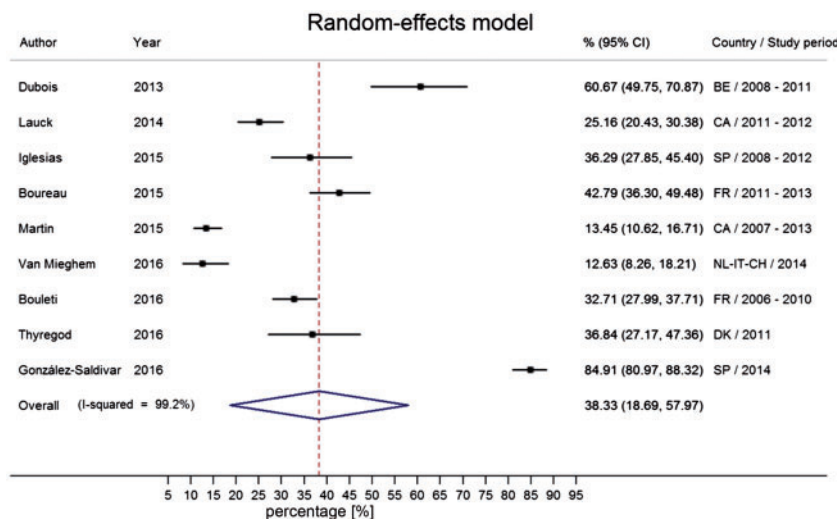


Figure 4 Percentage of patients not considered for surgical aortic valve replacement, who are also not treated with transcatheter aortic valve implantation. BE, Belgium; CA, Canada; CH, Switzerland; CI, confidence interval; DK, Denmark; FR, France; IT, Italy; NL, Netherlands; SAVR, surgical aortic valve replacement; SP, Spain; TAVI, transcatheter aortic valve implantation.

annual candidates compared to the base case analysis [177 462 (95% CI 110 059–260 576) and 90 135 (95% CI 56 740–131 605) for Europe and Northern-America, respectively]. The per-country estimates for Scenario 2 are demonstrated in *Take home figure, B*. Sensitivity analyses on the impact of average disease duration and prevalence are displayed in *Supplementary material online, Figure S3*.

Discussion

In this meta-analysis and modelling study, we estimate a yearly incidence rate of severe AS of 4.4%₀₀/year in the general population ≥ 65 years of age. Approximately 40% of symptomatic severe AS patients do not undergo SAVR. Although the policy of offering TAVI

A

COUNTRY	ANNUAL CANDIDATES (95% CI)
USA	51998 (31357-78241)
Canada	6826 (4118-10312)
Austria	1892 (1137-2871)
Belgium	2431 (1470-3652)
Bulgaria	1726 (1046-2604)
Croatia	956 (573-1434)
Czech Republic	2259 (1367-3393)
Denmark	1261 (764-1910)
Estonia	293 (179-441)
Finland	1314 (792-1983)
France	14632 (8886-22012)
Germany	20466 (12237-31180)
Greece	2718 (1656-4089)
Hungary	2108 (1276-3179)
Ireland	717 (435-1073)
Italy	15784 (9538-23700)
Latvia	460 (279-693)
Lithuania	655 (393-992)
Netherlands	3614 (2185-5481)
Norway	998 (597-1503)

COUNTRY	ANNUAL CANDIDATES (95% CI)
Poland	7008 (4195-10581)
Portugal	2516 (1535-3776)
Romania	4035 (2451-6065)
Slovakia	906 (549-1372)
Slovenia	444 (267-664)
Spain	10274 (6153-15470)
Sweden	2279 (1377-3448)
Switzerland	1756 (1059-2650)
United Kingdom	13787 (8293-20807)
European Union	114757 (69380-172799)
Northern America	58556 (35631-87738)



B

COUNTRY	ANNUAL CANDIDATES (95% CI)
USA	80076 (50754 - 117242)
Canada	10516 (6597 - 15332)
Austria	2919 (1834 - 4266)
Belgium	3740 (2332 - 5533)
Bulgaria	2642 (1660 - 3903)
Croatia	1468 (926 - 2165)
Czech Republic	3465 (2174 - 5078)
Denmark	1938 (1215 - 2850)
Estonia	456 (286 - 673)
Finland	2006 (1253 - 2953)
France	22607 (14305 - 33372)
Germany	31596 (19915 - 46723)
Greece	4190 (2649 - 6144)
Hungary	3262 (2038 - 4807)
Ireland	1106 (701 - 1610)
Italy	24368 (15255 - 35894)
Latvia	709 (442 - 1040)
Lithuania	1009 (639 - 1494)
Netherlands	5524 (3467 - 8126)
Norway	1537 (957 - 2236)

COUNTRY	ANNUAL CANDIDATES (95% CI)
Poland	10797 (6732 - 15971)
Portugal	3892 (2423 - 5802)
Romania	6224 (3872 - 9189)
Slovakia	1391 (879 - 2050)
Slovenia	681 (428 - 1004)
Spain	15783 (9919 - 23317)
Sweden	3526 (2230 - 5166)
Switzerland	2696 (1715 - 3949)
United Kingdom	21133 (13305 - 30852)
European Union	177462 (110059 - 260576)
Northern America	90135 (56740 - 131605)



Take home figure Estimated annual numbers of transcatheter aortic valve implantation candidates in different countries. (A) Under current indications; (B) if transcatheter aortic valve implantation indications expand into the low-risk category.

is highly variable among different countries, approximately 60% of these inoperable patients can be considered potential TAVI candidates. Among patients traditionally treated with SAVR, a substantial number are now considered potential TAVI candidates, predominantly in the high- and intermediate-risk category. Based on epidemiological data and decision-making studies, there are approximately 115 000 and 58 000 annual candidates for TAVI in the EU and in Northern-America, respectively.

These findings have a major impact on health care resource planning. Knowing the number of potential candidates aid health care systems preparing for the future needs. Human resource and hospital volume requirements can be forecasted, along with the expected budgetary requirements.²⁴ Moreover, these numbers help the industry tailor their production capacity to the future demands.

Epidemiology of severe symptomatic aortic stenosis

The prevalence of severe AS is largely age-dependent, with a marked increase ≥ 75 years of age.^{1,2} Logically, the same correlation is true for incidence rate. The 0.8% prevalence of severe AS might seem relatively low compared to other reports.^{14–16} This reflects the fact that prevalence was determined in a larger population (≥ 65 years) containing fewer elderly (≥ 75 years) subjects. Additionally, epidemiological studies often only report the combined prevalence of moderate-severe AS, while we used a more strict AS definition.² To eliminate the effect of heterogeneity observed in the studies reporting AS prevalence (Supplementary material online, Figure S1), we decided to use only the largest and most reliable study for the model. This decision conferred the further advantage of determining the prevalence and average disease duration of AS in the same, US population. In addition, it is reassuring that the calculated incidence rate of 4.4%/year used in this study is in harmony with the only previous report on severe AS incidence from the Tromsø study ($4.9 \pm 0.81\%$ /year).¹

Under-treatment and under-diagnosis of aortic stenosis

A sizeable number of patients with the diagnosis of severe symptomatic AS are not treated invasively. Recent data from the OxVALVE Population Cohort Study (Oxfordshire, UK) suggest that AS is underdiagnosed in some cases.²⁵ In this population-based study, involving 2500 individuals aged ≥ 65 years, participants were screened for undiagnosed valvular heart disease with transthoracic echocardiography. Although subjects with pre-existing valvular heart disease were excluded, a considerable number of AS patients were identified, predominantly in the lower socioeconomic classes. Based on these findings, the 'therapeutic gap' in AS might be even larger than previously anticipated.

Current and future trends in the numbers of candidates for invasive treatment

The annual number of TAVI procedures has been growing since its introduction, while at the same time the number of annual SAVR procedures remained more or less unchanged, or even increased.^{26–28} However, now TAVI has been demonstrated to be non-inferior to

SAVR in intermediate-risk patients this trend is changing and in some countries, annual TAVI numbers are exceeding the number of isolated SAVRs.^{8–12,29,30} Ongoing randomized-controlled trials are investigating TAVI in the low-risk group (PARTNER 3, NOTION-2, Medtronic Transcatheter Aortic Valve Replacement in Low Risk Patients; clinicaltrials.gov identifiers: NCT02675114, NCT02825134, and NCT02701283, respectively). The vast majority (80%) of AS patients currently treated with SAVR belong to this low-risk category.²² If results of these trials favour TAVI over SAVR, this will fundamentally change the number of annual TAVI candidates, as represented in our scenario analyses. Currently, aortic valve replacement is only indicated in asymptomatic AS if strict criteria are met.^{11–13} Recently, a multi-centre, randomized-controlled trial (EARLY TAVR, clinicaltrials.gov identifier: NCT03042104) was launched to compare TAVI and watchful waiting in patients with asymptomatic severe AS. Evidence favouring early TAVI in this group would result in a substantial increase in annual TAVI numbers. Beside this, current trends of increased bioprosthetic surgical heart valve utilization in younger patients will likely lead to growing numbers of valve-in-valve procedures in the future.

Factors limiting the expansion of transcatheter aortic valve implantation

There are several factors that might constrain expansion of TAVI. First of all, data on the long-term durability of transcatheter prostheses are still in accumulation.^{31–36} Unfavourable long-term results may prevent the expansion of TAVI indications towards the younger or lower-risk groups of patients. Additionally, in certain patient groups, mechanical prosthesis will remain the preferred option for aortic valve replacement.³⁷

Secondly, TAVI may be futile in some patients because of severe comorbidities precluding quality-of-life improvement or survival benefits.³⁸ It is important to assess the expected benefit for the individual patient in the Heart Team.³⁹

Moreover, health economic considerations and reimbursement decisions play a role in TAVI expansion.^{40–43} The cost-effectiveness profile of TAVI vs. SAVR in low-risk patients is unknown. The added benefits of TAVI in terms of quality-of-life and survival need to justify the higher costs. Both the effectiveness and costs in low-risk patients need to be studied carefully. Importantly, the large number of current and potential TAVI candidates presented in this study has a large budget impact on health care systems. Both cost-effectiveness and health care budget impact studies at national levels need to be considered in reimbursement policy decisions.

Study limitations

The use of a model based on currently available literature, containing multiple steps to estimate numbers has its inherent limitations. The determination of AS-related symptoms and SAVR- or TAVI-eligibility were based on the decision of individual physicians in each included study. The assessment of heterogeneity in the meta-analyses, and the confidence intervals—determined at each step in the model and presented along the final estimations—are aimed to represent this uncertainty.

According to the 2017 European Society of Cardiology: Cardiovascular Disease Statistics report, substantial differences exist

in health care systems among individual countries in Europe.⁴⁴ While predicting the number of potential TAVI candidates, this study did not consider the effect of local reimbursement or health insurance policies, regional differences in social background or life expectancy. It provides an insight into how many patients can potentially be candidates, combining all latest available epidemiological and clinical data, assuming unlimited TAVI availability.

As the yearly incidence rate of severe AS was calculated, both prevalence and average disease duration used for the calculation influence our estimations. The impact of these uncertainties was explored in sensitivity analyses.

Additionally, our estimations have a certain timeframe of validity. However, we are confident that our current and future predictions are valid unless robust data would show limited long-term TAVI durability in the future.

Conclusions

This study estimates the current and future potential number of TAVI candidates. An estimated 115 000 and 58 000 potential annual candidates are eligible for TAVI in Europe and Northern-America, respectively. These numbers will increase dramatically, up to 177 000 and 90 000 if ongoing clinical trials establish the evidence for TAVI in low-risk patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Conflict of interest: A.P.K.: principal investigator of the SURTAVI trial and also employee of Medtronic Inc.; N.V.M.: study chair of the SURTAVI trial sponsored by Medtronic Inc., and reports grants from Medtronic, Abbott, Boston Scientific and Claret Medical, outside the submitted work. All other authors declare that they have no conflicts of interest.

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