

Aortic Stenosis in the Elderly

Disease Prevalence and Number of Candidates for Transcatheter Aortic Valve Replacement: A Meta-Analysis and Modeling Study

Ruben L. J. Osnabrugge, MS,* Darren Mylotte, MD,†‡ Stuart J. Head, MS,*
Nicolas M. Van Mieghem, MD,§ Vuyisile T. Nkomo, MD, MPH,|| Corinne M. LeReun, MS,¶
Ad J. J. C. Bogers, MD, PhD,* Nicolo Piazza, MD, PhD,†# A. Pieter Kappetein, MD, PhD*

Rotterdam, the Netherlands; Montreal, Quebec, Canada; Galway and Cork, Ireland; Rochester, Minnesota; and Munich, Germany

- Objectives** The purpose of this study was to evaluate the prevalence of aortic stenosis (AS) in the elderly and to estimate the current and future number of candidates for transcatheter aortic valve replacement (TAVR).
- Background** Severe AS is a major cause of morbidity and mortality in the elderly. A proportion of these patients is at high or prohibitive risk for surgical aortic valve replacement, and is now considered for TAVR.
- Methods** A systematic search was conducted in multiple databases, and prevalence rates of patients (>75 years) were pooled. A model was based on a second systematic literature search of studies on decision making in AS. Monte Carlo simulations were performed to estimate the number of TAVR candidates in 19 European countries and North America.
- Results** Data from 7 studies (n = 9,723 subjects) were used. The pooled prevalence of all AS in the elderly was 12.4% (95% confidence interval [CI]: 6.6% to 18.2%), and the prevalence of severe AS was 3.4% (95% CI: 1.1% to 5.7%). Among elderly patients with severe AS, 75.6% (95% CI: 65.8% to 85.4%) were symptomatic, and 40.5% (95% CI: 35.8% to 45.1%) of these patients were not treated surgically. Of those, 40.3% (95% CI: 33.8% to 46.7%) received TAVR. Of the high-risk patients, 5.2% were TAVR candidates. Projections showed that there are approximately 189,836 (95% CI: 80,281 to 347,372) TAVR candidates in the European countries and 102,558 (95% CI: 43,612 to 187,002) in North America. Annually, there are 17,712 (95% CI: 7,590 to 32,691) new TAVR candidates in the European countries and 9,189 (95% CI: 3,898 to 16,682) in North America.
- Conclusions** With a pooled prevalence of 3.4%, the burden of disease among the elderly due to severe AS is substantial. Under the current indications, approximately 290,000 elderly patients with severe AS are TAVR candidates. Nearly 27,000 patients become eligible for TAVR annually. (J Am Coll Cardiol 2013;62:1002-12) © 2013 by the American College of Cardiology Foundation

Aortic stenosis (AS) is the most common valvular heart disease in developed countries, and its impact on public health and health care resources is expected to increase due to aging Western populations (1,2). Each year, approximately 67,500 surgical aortic valve replacements (SAVR) are performed in the United States (3). Studies describing the prevalence of AS are scarce and report disparate results (3% to 23%) (4,5), and currently there is no systematic overview

of population-based studies that have assessed the prevalence of AS.

See page 1013

The emergence of transcatheter aortic valve replacement (TAVR) has renewed interest in the epidemiology of AS.

From the *Department of Cardiothoracic Surgery, Erasmus University Medical Center, Rotterdam, the Netherlands; †Department of Interventional Cardiology at McGill University Health Center, Montreal, Quebec, Canada; ‡Galway University Hospital, Galway, Ireland; §Department of Interventional Cardiology, Erasmus University Medical Center, Rotterdam, the Netherlands; ||Division of Cardiovascular Diseases, Department of Internal Medicine, Mayo Clinic, Rochester, Minnesota; ¶Self-employed biostatistician, Carrigaline, County Cork, Ireland; and the #Department of Cardiovascular Surgery, German Heart Center, Munich, Germany. Dr. van Mieghem is

a member of the steering committee of the SURTAVI trial sponsored by Medtronic. Dr. Nkomo is co-investigator of the PARTNER II trial, sponsored by Edwards Lifesciences. Ms. LeReun received fees from Medtronic. Dr. Piazza is a proctor and consultant for Medtronic; and a member of the steering committee of the SURTAVI trial. Dr. Kappetein is a member of the steering committee of the SURTAVI trial. All other authors have reported they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 21, 2013; revised manuscript received April 8, 2013, accepted May 8, 2013.

In particular, these data may be important to predict the number of TAVR candidates, service development, financial planning, and physician training. In addition, estimates of potential TAVR candidates at intermediate and low surgical risk are not available. Several factors must be considered when estimating the number of TAVR candidates: the percentage of patients with severe AS who are symptomatic; the proportion of patients with symptomatic severe AS who do not undergo SAVR and could thus be considered TAVR candidates; and the percentage of those patients referred for TAVR who actually receive a transcatheter valve.

Therefore, we sought to assess the prevalence of AS in the general elderly population (age ≥ 75 years) through a systematic review and meta-analysis of population-based studies. The second objective was to systematically estimate the number of elderly patients who are TAVR candidates in both the European countries and North America.

Methods

Studies were identified through a systematic search of MEDLINE and EMBASE in February 2012. Keywords included “valvular heart disease,” “heart valve disease,” “aortic stenosis,” “aortic valve stenosis,” “epidemiology,” “incidence,” “prevalence,” and “survey.” No time restrictions were applied. Reference lists of selected studies and (systematic) reviews were examined, and the related article feature in PubMed was used to maximize relevant study identification.

All titles and abstracts were screened independently by 2 investigators using the following criteria: 1) the publication was an original full-length manuscript in a peer-reviewed journal; 2) the publication reported numbers of AS cases and sample size or the prevalence of AS in the general elderly population (≥ 75 years of age); and 3) AS and AS severity was diagnosed with echocardiography (6,7). The definition of AS used in each study was extracted, as was other relevant information including study location, inclusion period, and patient characteristics. After excluding manuscripts on the basis of title and abstract, the remaining full-text manuscripts were carefully assessed and were evaluated according to the criteria. If overlap between studies existed, only the publication with the largest population was included. Disagreement on study inclusion was solved by consensus.

For each included study, the prevalence rate of AS and its 95% binomial confidence interval (CI) was calculated based on the numbers of subjects in the sample and the number of patients with AS. These rates were subsequently combined to produce a pooled prevalence rate of both AS and severe AS. Both fixed- and random-effects models were used, and results of the appropriate model are presented as Forest plots. The fixed-effects model was performed using the inverse variance method and the random-effects model with the DerSimonian and Laird method. Heterogeneity was assessed by the Cochran Q test and I^2 statistics, derived from the inverse

variance fixed-effects model (8). All analyses were performed with Stata SE version 12.0 (StataCorp, College Station, Texas).

Estimation of TAVR candidates.

To estimate the number of elderly patients who could potentially be treated with TAVR under current indications, we performed a second literature search on clinical decision making in patients with severe AS.

Specifically, we searched for studies that reported: 1) the percentage of patients with severe AS who experienced symptoms; 2) the percentage of patients with symptomatic severe AS who did not undergo SAVR and could thus be considered potential TAVR candidates; and/or 3) the percentage of those patients referred for TAVR who actually received a transcatheter valve. As TAVR is an approved therapy for patients at high operative risk, we also determined the proportion of elderly high-risk patients (The Society of Thoracic Surgery–Predicted Risk Of Mortality [STS-PROM] score $\geq 10\%$) undergoing SAVR (9), and the percentage of patients who would be considered TAVR-eligible. In anticipation of current and potential future trials in lower risk groups, estimates of the proportion of intermediate- and low-risk patients were also derived. For all studies, the point estimate and 95% binomial CI were calculated.

These data were combined to produce a pooled percentage estimate for each individual search. In each case, a fixed- or random-effects model was used and heterogeneity was assessed. To calculate national estimates of the number of patients with AS and TAVR candidates, we obtained population demographic data focusing on the elderly (≥ 75 years of age) for the following nations: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, the Republic of Ireland, Luxembourg, Norway, Poland, Portugal, Spain, Sweden, Switzerland, the Netherlands, the United Kingdom, Canada, and the United States (10–12). The annual number of new TAVR candidates was calculated using the number of people ages 75 years old in 2011 in the individual countries.

A flowchart was built in TreeAge Pro 2011 (TreeAge Software, Williamstown, MA). The probabilities in the flowchart were based on the pooled estimates from the systematic literature searches. Beta distributions were used and 10,000 Monte Carlo simulations were performed to estimate the number of elderly patients who are eligible to undergo TAVR, along with its 95% percentile CI.

To account for the heterogeneous nature of the studies, sensitivity analyses were performed. In particular, the proportion of patients receiving TAVR after referral for TAVR assessment was determined using European studies alone and then by combining European and U.S. studies. This analysis was performed to account for the different adoption of TAVR in the United States, where until

Abbreviations and Acronyms

AS	= aortic stenosis
CI	= confidence interval
SAVR	= surgical aortic valve replacement
STS-PROM	= The Society of Thoracic Surgery Predicted Risk Of Mortality
TAVR	= transcatheter aortic valve replacement

recently TAVR was only used in the context of clinical trials. In a second sensitivity analysis, we varied the percentage of high-risk SAVR-eligible patients who undergo TAVR.

Results

The systematic literature search yielded 1,523 studies. After the title and abstract were screened, 1,408 studies were excluded because they did not focus on the epidemiology of disease. After assessing full-text articles, another 109 studies were excluded because they were not performed in the general elderly population, AS was not assessed, or because it was not an original publication. After the inclusion of an additional study through cross-referencing, our final analysis consisted of 7 studies, with a total of 9,723 elderly patients (Fig. 1) (1,4,5,13-16). The characteristics of these studies are outlined in Table 1. The 7 studies reported the prevalence of AS in 9 study populations on 3 continents. The study periods ranged from 1989 to 2009. All studies had a cross-sectional character, and most were part of larger population-based cohort studies. In all 7 studies, echocardiography was used to diagnose AS, although definitions of AS and its severity were variable (Table 1).

The combined prevalence of AS in the elderly was reported in 6 studies and ranged from 2.6% to 22.8%

(Fig. 2A) (4,5,13,15,16). The pooled prevalence was 12.4% (95% CI: 6.6% to 18.2%) using a random-effects model ($I^2 = 98.5\%$; $Q = 337.70$, $p < 0.001$). The prevalence of severe AS in the elderly was reported separately in 5 studies and ranged from 1.2% to 6.1% (Fig. 2B) (1,4,13,14,16). The pooled prevalence of severe AS was 3.4% (95% CI: 1.1% to 5.7%) using a random-effects model ($I^2 = 85.7\%$; $Q = 27.99$, $p < 0.001$).

These estimates of the prevalence of AS in patients ≥ 75 years old correspond to approximately 4.9 million elderly patients with AS in the European countries and 2.7 million in North America. If only symptomatic severe AS is considered, this translates to 1.0 million elderly patients in the European countries and 540,000 in North America. In 2011, 8.5% of the population in the 19 European countries was ≥ 75 years of age, and this number is expected to increase to 10.7% in 2025 and 16.6% in 2050 (11). In North America, similar increases in the population demographics of the elderly are expected (2025, 8.3%, and 2050, 11.8%) (10,12). These numbers correspond to approximately 1.3 million and 2.1 million patients with symptomatic severe AS in the 19 European countries in 2025 and 2050, respectively. In North America, there will be an estimated 0.8 million and 1.4 million patients with symptomatic severe AS in 2025 and 2050, respectively.

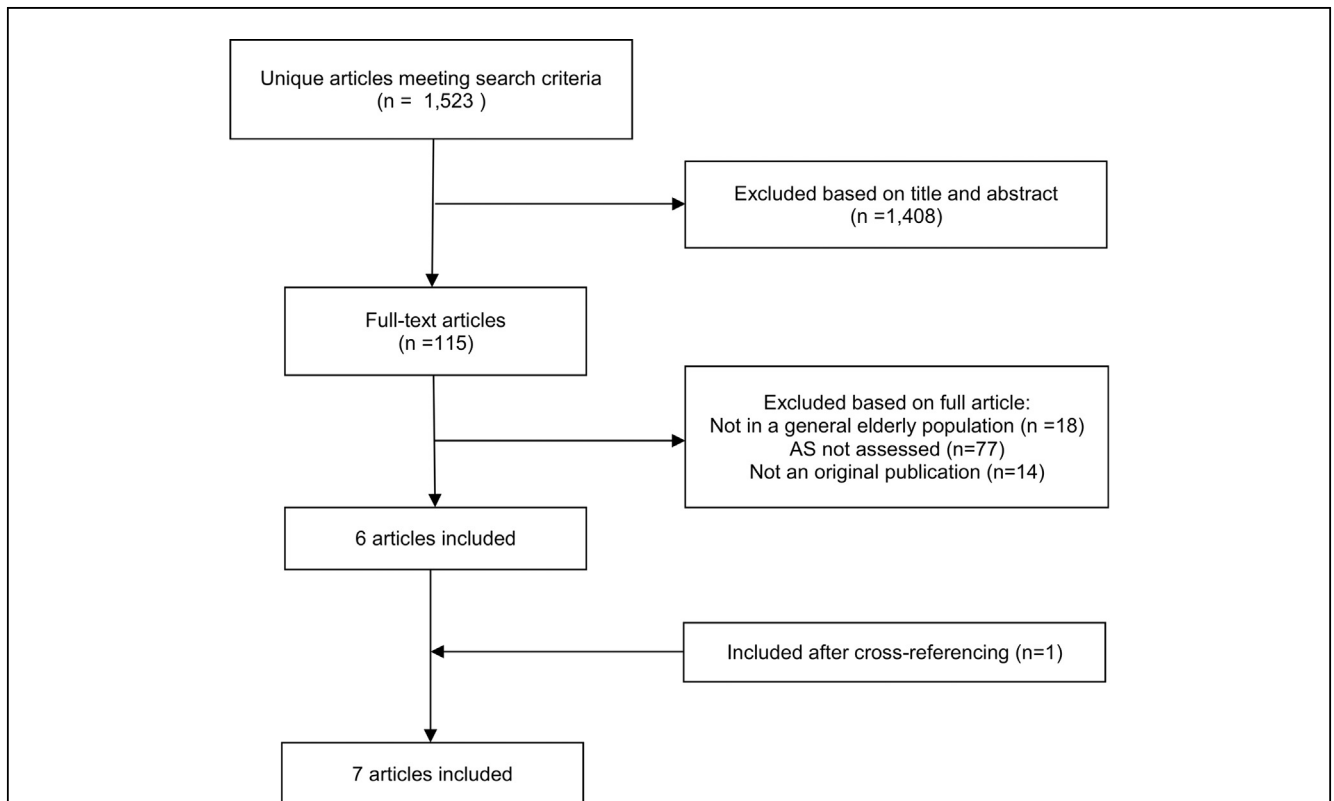


Figure 1 Flowchart of Study Selection

AS = aortic stenosis.

Table 1 Main Study Characteristics of the Included Studies

First Author (Year), Study, Country	Study Design, Study Period, Population, % Men	Age (yrs) Category in meta-Analysis	Recruitment Method, Examination Period	Response Rate (%), Reasons for Exclusion	Diagnostic Method, AS Definition
Lorz (1993), Switzerland	Cross-sectional study, 70–96 yrs (n = 129), 43% men	70–96, mean 80 ± 6.6 (n = 129)	Random selection within community and nursing homes. 1990	51%; death, unable to contact, and “other reasons”	Doppler echo; all AS: thickening of cusps, V _{max} >1.7 m/s level, or systolic separation of cusps <15 mm
Lindroos (1993), Helsinki Ageing Study, Finland	Cross-sectional substudy of larger population-based study, >55 yrs (n = 552), 28% men	75–86 (n = 476)	Random selection in population register. 1990–1991	From complete cohort 84 (9.3%) persons had died, 21 (2.3%) could not be contacted, and 144 (16%) refused; 77% agreed with substudy.	Doppler echo; moderate AS: VR ≤0.35 and AVA 1.0–1.2 cm ² ; severe AS: VR ≤0.35 and AVA ≤1.0 cm ² ; critical AS: VR ≤0.35 and AVA ≤0.8 cm ²
Stewart (1997), Cardiovascular Health Study, USA	Cross-sectional substudy of larger population-based study, >65 yrs (n = 5,201), 43% men	>75 (n = 1,736)	Random selection from 4 communities of Medicare-eligible patients. 1989–1990	57%; reasons not stated. Also, subjects with AVR (n = 23), MVS/MVR/both (n = 37), BAV (n = 4), AVE (n = 2), or inadequate echo data (n = 25) were excluded.	Doppler echo; all AS: thickened leaflets with reduced systolic opening and V _{max} >2.5 m/s
Lin (2005), Taiwan	Cross-sectional analysis, 20–97 yrs (n = 3,030), 59% of 2,850 group were men	>80 (n = 82)	Persons undergoing routine physical checkups; those with severe health conditions were excluded. Examination period NR.	NR	Doppler echo; all AS: leaflet thickening with reduced systolic opening, gradient ≥20 mm Hg; severe AS: gradient >50 mm Hg
Nkomo (2006),* Olmsted County Cohort, USA	Cross-sectional substudy of larger community study, >18 yrs (n = 16,501), 49% men	>75 (n = 6,663)	Patients who underwent echocardiography in affiliated hospital. 1990–2000	90% of population received care at affiliated hospital.	Doppler echo; Mild AS: V _{max} 2.5–3 m/s and AVA 1.5–2 cm ² ; Moderate AS: V _{max} 3–4 m/s and AVA 1–1.5 cm ² ; Severe AS: V _{max} >4 m/s and AVA <1.0 cm ²
Van Bommel (2010), Leiden 85-Plus Study, the Netherlands	Cross-sectional substudy of larger population-based study, >90 yrs (n = 18), 33% men	>90 (n = 81)	All inhabitants of Leiden >85 yrs were invited. At 90 yrs participants were invited for echo examination. 1997–1999	13% of total participants (n = 705) refused to participate; 71% of 277 participants eligible for echo were not able to visit study center.	Doppler echo; mild AS: gradient <25 mm Hg; moderate AS: gradient 25–40 mm Hg; Severe AS: Gradient >40 mm Hg
Vaes (2012), BELFRAIL (BF _{C80+}), Belgium	Cross-sectional analysis of population-based study, >80 yrs (n = 556) 37% men	>80 (n = 556)	29 general practitioners in 3 regions included >80 yr olds. 2008–2009	Severe dementia and medical emergency patients were excluded.	Doppler echo; mild AS: AVA >1.5 cm ² ; moderate AS: AVA 1.0 cm ² –1.5 cm ² ; severe AS: AVA <1 cm ²

*Only the Olmsted County community study was included in this analysis. Of the 3 pooled population-based studies in this publication, only the Cardiovascular Health Study was eligible and is included in this systematic review (Stewart et al. 1997). The other 2 studies did not meet the selection criteria because the population studied was too young.

AS = aortic stenosis; AVA = aortic valve area; AVE = aortic valve endocarditis; AVR = aortic valve replacement; echo = echocardiography; MVS = mitral valve stenosis; MVR = mitral valve replacement; NR = not reported; VR = velocity ratio; V_{max} = peak velocity.

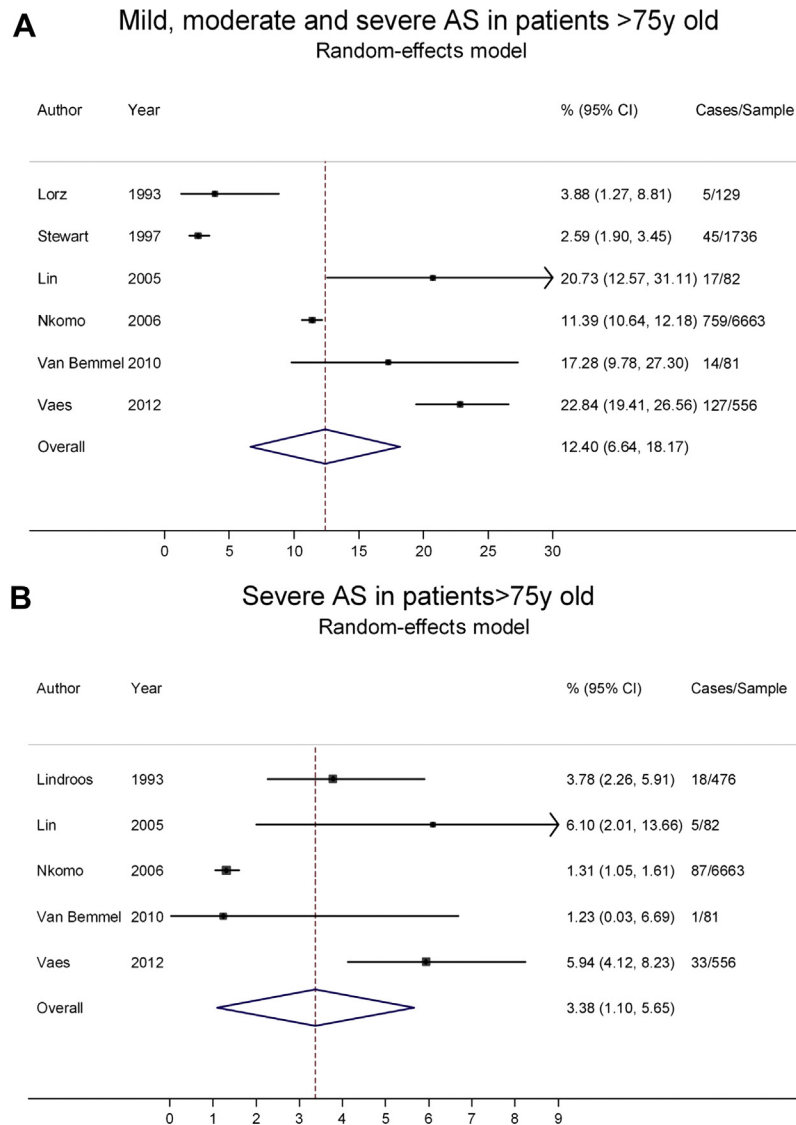


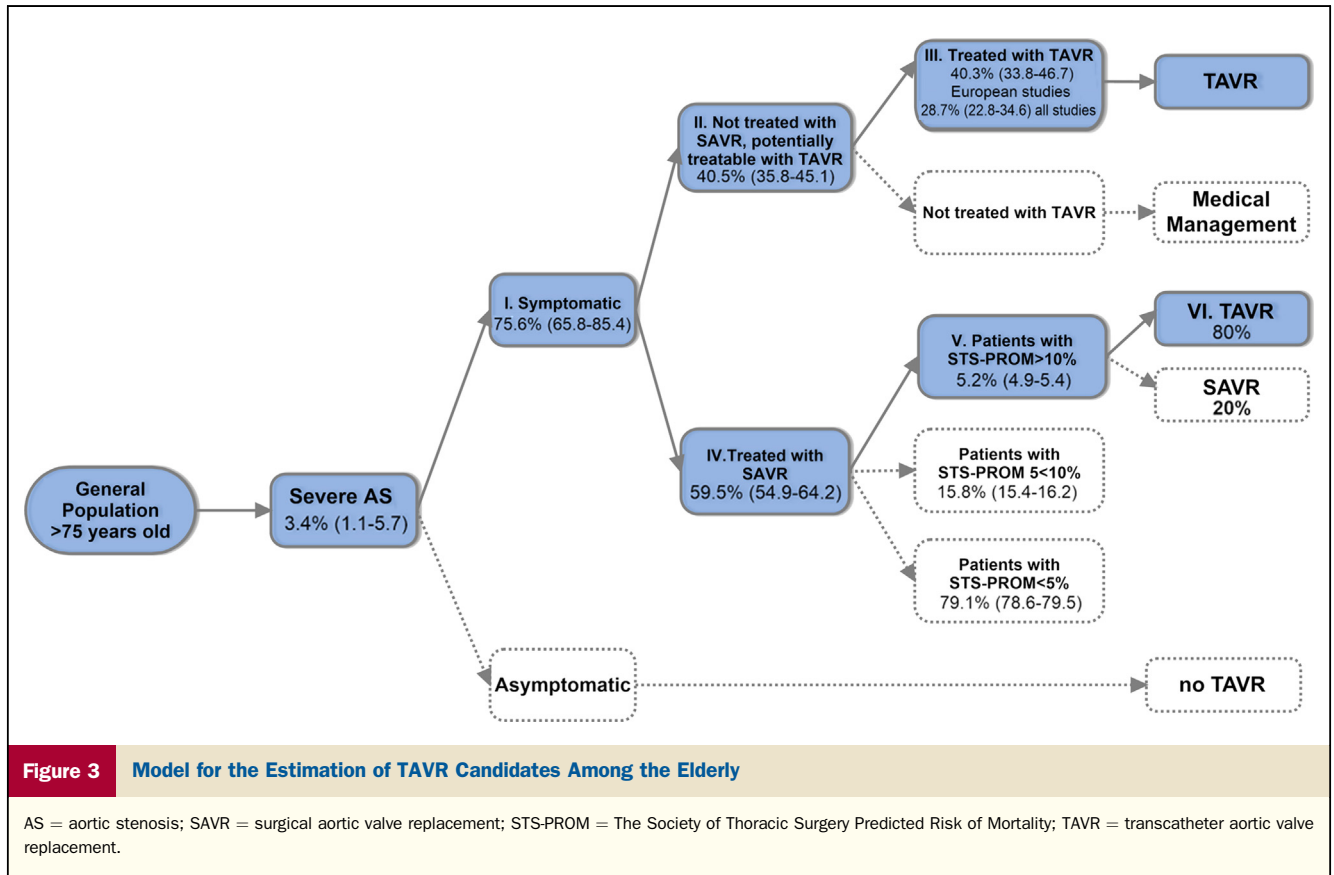
Figure 2 Forest Plots on the Prevalence of AS

(A) Mild, moderate, and severe aortic stenosis (AS) in the elderly, using a random-effects model. $I^2 = 97.1\%$, $Q = 140.25$, $p < 0.001$. (B) Severe AS in the elderly, using a random-effects model. $I^2 = 85.7\%$, $Q = 27.99$, $p < 0.001$. CI = confidence interval.

Estimates of TAVR candidates. The number of elderly patients who could potentially benefit from TAVR was estimated using the model outlined in Figure 3, with inputs from the systematic search and meta-analyses (Fig. 4). Seven studies reported the percentage of patients with severe AS who were symptomatic, resulting in a pooled estimate of severe symptomatic AS of 75.6% (95% CI: 65.8% to 85.4%) (Fig. 4A, Online Table 1). Of these patients with symptomatic severe AS, 40.5% (95% CI: 35.8% to 45.1%) did not undergo SAVR and thus could be considered candidates for TAVR (Fig. 4B, Online Table 2). Nine studies reported the percentage of patients referred for TAVR who actually received a transcatheter valve (Online Table 3). Three of these studies were performed in Europe, and 6 in the United States. The pooled

percentage including both European and U.S. studies was 28.7% (95% CI: 22.8% to 34.6%) (Figs. 4C and 4D, respectively). The European pooled percentage was 40.3% (95% CI: 33.8% to 46.7%), whereas the U.S. pooled percentage was 24.4% (95% CI: 18.9% to 29.8%). In total, 12.3% of patients with symptomatic severe AS at prohibitive surgical risk are TAVR candidates.

To assess the proportion of elderly SAVR patients who was deemed to be at high surgical risk, we used a study that reported on all elderly SAVR patients in the United States between 1999 and 2007 (17). Among elderly patients undergoing isolated SAVR, 5.2% (95% CI: 4.9% to 5.4%) were at high risk (STS-PROM $\geq 10\%$), 15.8% (95% CI: 15.4% to 16.2%) at intermediate risk (STS-PROM 5% to



10%), and 79.1% (95% CI: 78.6% to 79.5%) at low risk (STS-PROM <5%). A recent study showed that in a group of operable patients with a EuroSCORE (European System for Cardiac Operative Risk Evaluation) ≥ 15 , approximately 80% were treated with TAVR (18).

In 2011, there were 39,316,978 people ≥ 75 years of age in the European countries and 21,182,683 in North America (10-12). Combining these figures with the Monte Carlo simulations in the model (Fig. 3), we estimated that a total of 292,000 high- or prohibitive-risk elderly patients with symptomatic severe AS are candidates for TAVR. Specifically, there are 189,836 (95% CI: 80,281 to 347,372) TAVR candidates in the European countries and 102,558 (95% CI: 43,612 to 187,002) in North America. Annually there are 17,712 (95% CI: 7,590 to 32,691) new TAVR candidates in the European countries and 9,189 (95% CI: 3,898 to 16,682) in North America. The total and annual number of TAVR candidates in the individual countries is presented in Figures 5 and 6, respectively.

The intermediate surgical risk group comprises approximately 145,000 elderly patients with symptomatic severe AS. Specifically, there are 94,730 (95% CI: 40,574 to 171,896) patients at intermediate risk in the European countries and 50,733 (95% CI: 22,148 to 90,451) in North America. The low surgical risk group includes approximately 730,000 patients with symptomatic severe AS. Specifically, there are

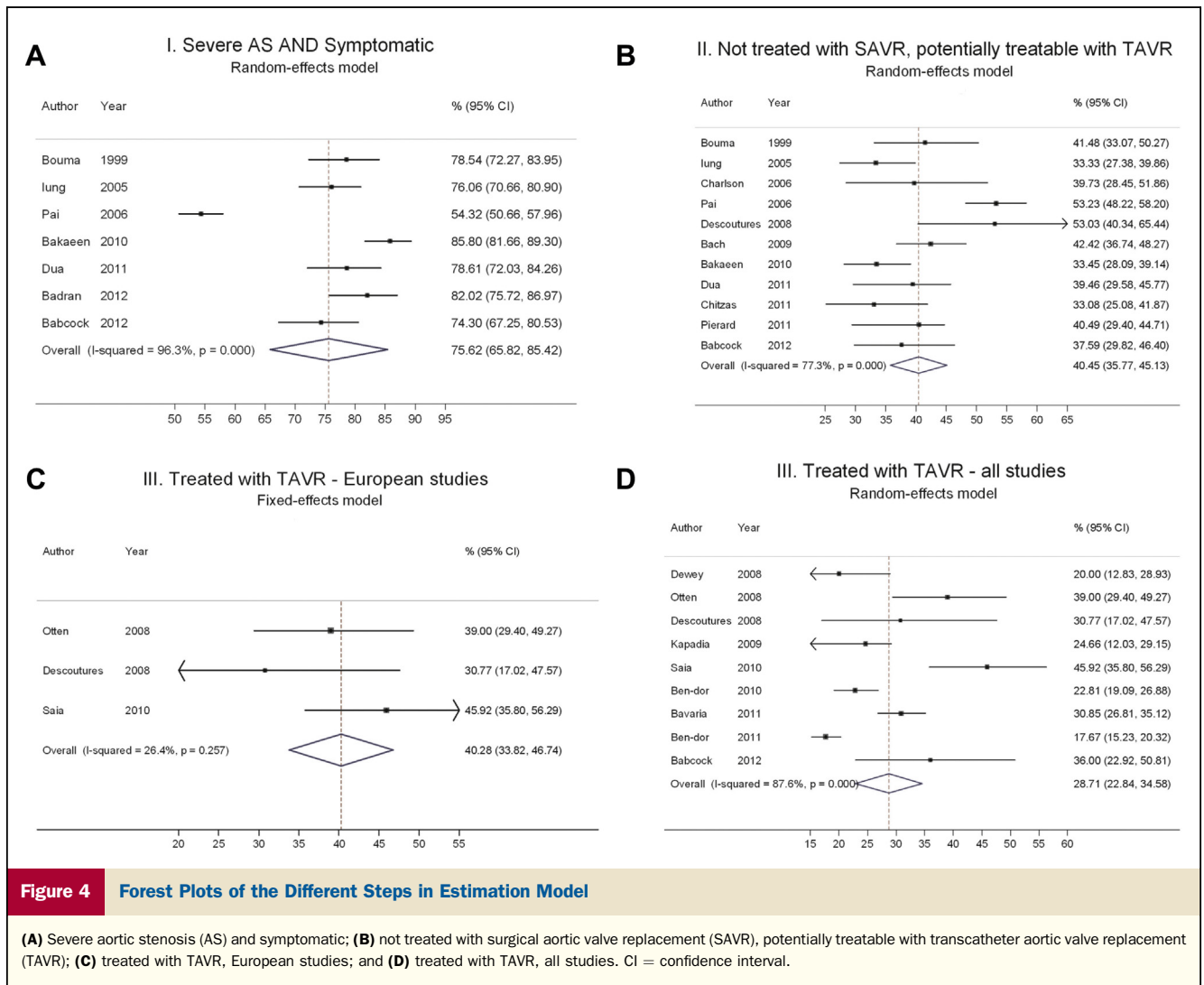
477,314 (95% CI: 206,798 to 862,958) patients at low-risk in the European countries and 255,272 (95% CI: 108,549 to 460,026) in North America.

Sensitivity analyses. In the pre-specified sensitivity analysis that varied the proportion of patients receiving TAVR after referral for TAVR assessment according to study location (28.7%, 95% CI: 22.8% to 34.6% in Europe and the United States combined), we estimated that approximately 220,000 patients are TAVR candidates. Of these, 142,658 (95% CI: 61,065 to 263,795) candidates lived in the European countries and 76,962 (95% CI: 32,805 to 140,673) in North America.

In the sensitivity analysis varying the percentage of high-risk operable patients who would undergo TAVR, the total number of TAVR candidates was 277,570 (95% CI: 119,406 to 512,707) assuming that 50% would undergo TAVR whereas there were 302,865 (95% CI: 129,433 to 550,562) candidates if all the high-risk patients would undergo TAVR. Finally, we estimated that the total number of patients with symptomatic severe AS in the intermediate-risk category was 145,936 (95% CI: 62,802 to 263,340), and 733,861 (95% CI: 310,623 to 1,302,586) in the low-risk category.

Discussion

The current study found that the prevalence of AS in the elderly (≥ 75 years of age) is 12.4%, and severe AS is present



in 3.4%. Among elderly patients with severe AS, 75.6% are symptomatic, and 40.5% of these patients are not treated surgically. From those, 40.3% are potentially treated with TAVR. In total, 12.3% of the prohibitive risk group are TAVR candidates. Among patients undergoing SAVR for severe symptomatic AS, 5.2% are high risk and 80% of those are potential TAVR candidates. Based on these data, we estimated that there are currently approximately 190,000 and 100,000 TAVR candidates in the European countries and North America, respectively. Each year, approximately 18,000 new TAVR candidates emerge in the European countries and 9,000 in North America.

The prevalence of AS. Our estimates of the prevalence demonstrate that the overall burden of disease due to AS in the general elderly population is substantial. Population demographics clearly show that Western populations are aging, thereby further increasing the impact of AS. No effective medical therapy is available for patients with AS, and if not treated by intervention, the estimated 5-year survival of severe AS is only 15% to 50% (7). These data

suggest that the treatment of AS in the elderly will have an increasing impact on public health and health care resource consumption in the future.

Based on echocardiographic diagnosis, we found that severe AS occurs in 12.4% of the general elderly (≥ 75 years of age) population. Previous autopsy series and a study based on aortic valve diagnoses in Medicare claims have reported AS prevalence estimates of 9.2% and 16%, respectively (19,20). Our pooled prevalence of AS (12.4%) is lower than the estimates from Medicare claims, but covered a lower age group and did not include diagnoses of aortic regurgitation. The methodological differences between studies are likely to account for the variability in AS estimates.

We explored heterogeneity by assessing the individual study characteristics, but the limited number of studies prevented separate analyses. The heterogeneity is reflective of different diagnostic definitions for AS, dissimilar recruitment methods, and varying study periods (Table 1). Study participation was only 50% to 60% in 2 studies, making their results vulnerable for selection bias (5,15). In

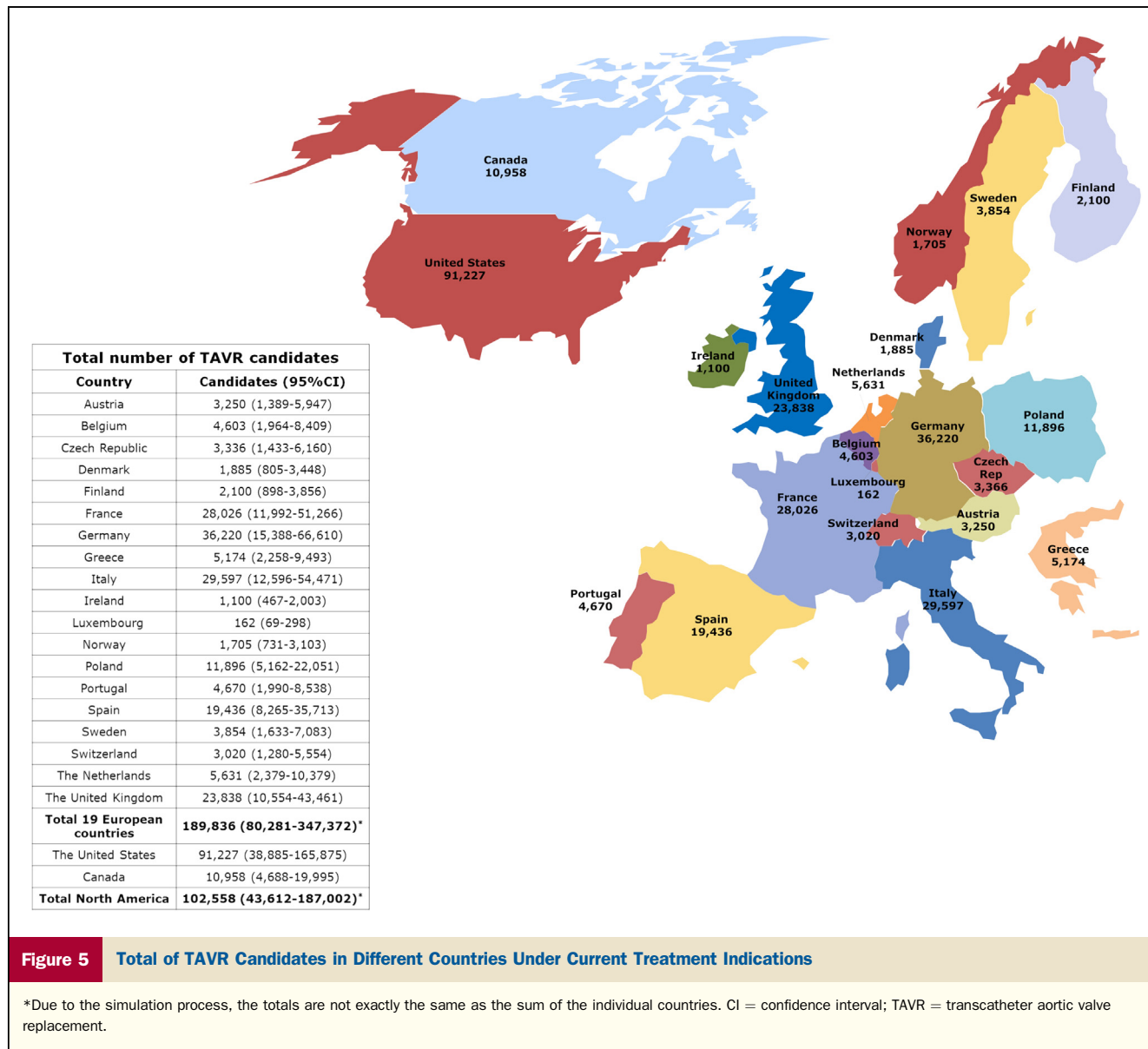


Figure 5 Total of TAVR Candidates in Different Countries Under Current Treatment Indications

*Due to the simulation process, the totals are not exactly the same as the sum of the individual countries. CI = confidence interval; TAVR = transcatheter aortic valve replacement.

1 study, AS was diagnosed using clinically indicated echocardiography (1). That might have caused a lower prevalence rate of AS. Moreover, improvements of echocardiographic techniques and interobserver variability might have had an influence on the prevalence rates and heterogeneity.

The number TAVR candidates. Nearly 40.5% of all patients with symptomatic severe AS did not undergo SAVR (Fig. 4B). Possible explanations for the lower than expected rates of SAVR include excessive operative risk, advanced age, comorbidities, and patient preference (21,22). TAVR is a safe, effective, and less invasive treatment strategy for a highly selected proportion of the patients who do not undergo SAVR (23), represented by the 40.3% of patients who underwent TAVR (Fig. 4C). The treatment decisions reflect heart team discussions, in which (interventional) cardiologists and cardiac surgeons combine

risk models with additional factors such as frailty, porcelain aorta, and vessel tortuosity (24).

The estimated large number of TAVR candidates has clinical, economic, and social implications. If the index admission costs (US \$72,000) of the PARTNER (Placement of Aortic Transcatheter Valves) trial are applied (25), treating all TAVR candidates would represent a budget impact of \$13.7 billion in the European countries and \$7.2 billion in North America. At a price of \$30,000, the total device turnover would be approximately \$8.7 billion. Although TAVR is cost effective in the United States for patients at high and prohibitive risk (25,26), data from other countries show that, for intermediate-risk patients, the costs of TAVR at 1 year are considerably higher than the costs of SAVR (27). Importantly, cost is not the only factor that determines the adoption of novel technologies such as TAVR (28). Reimbursement strategies, physician training,

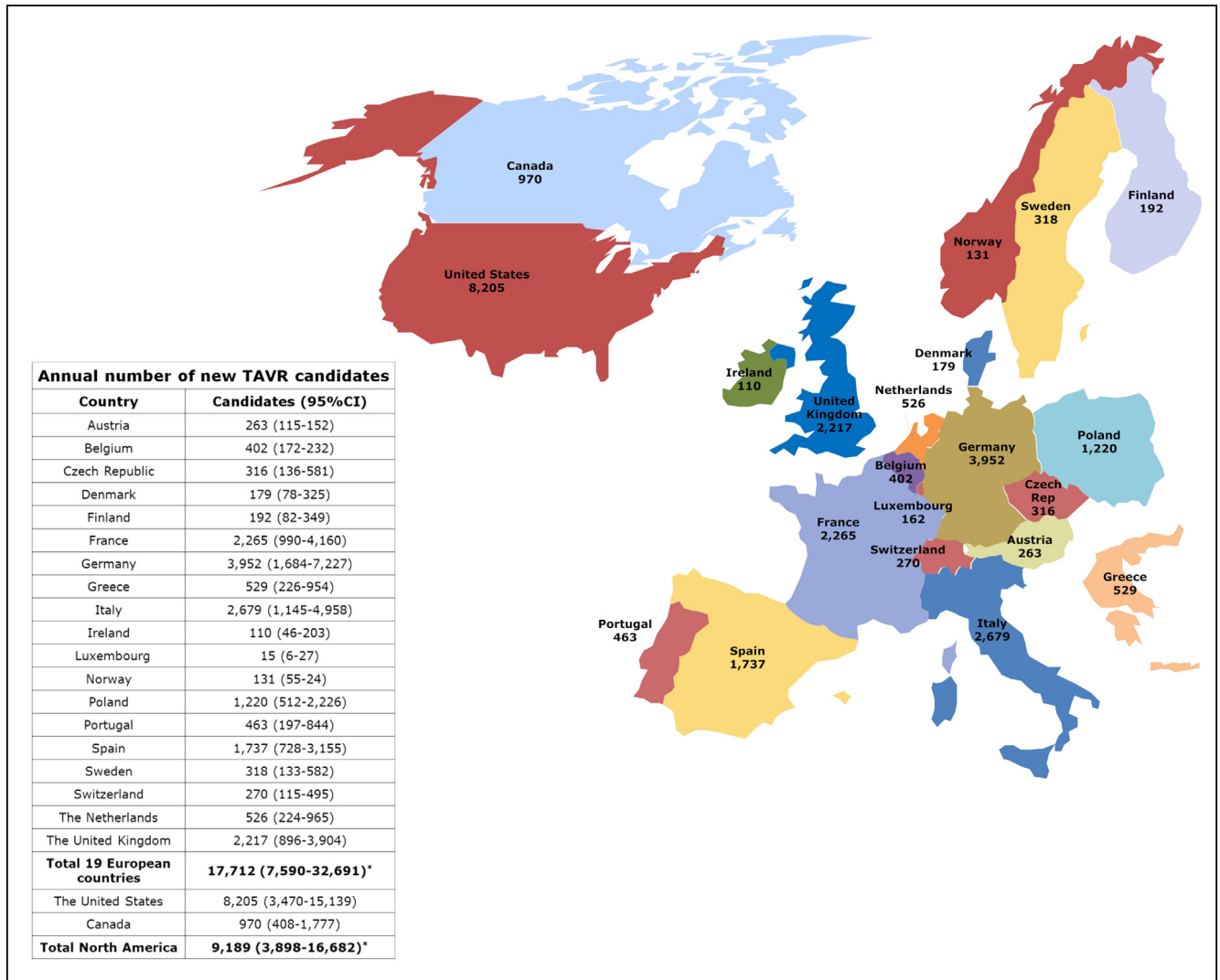


Figure 6 Annual Number of TAVR Candidates in Different Countries Under Current Treatment Indications

*Due to the simulation process, the totals are not exactly the same as the sum of the individual countries. CI = confidence interval; TAVR = transcatheter aortic valve replacement.

and health care culture may be related to the dissemination of this costly technology.

Despite budgetary concerns, current clinical trials are evaluating TAVR for patients at intermediate surgical risk (NCT01314313 and NCT01586910) (9,29). If TAVR proves to be noninferior to SAVR in this population, we estimate that a further 145,000 patients would become TAVR eligible. Indeed, there is some evidence that suggests that TAVR is already being performed in these intermediate-risk patients (18,30). Thus, our estimates of the impact of positive outcomes in the ongoing trials are likely to be conservative. In the future, TAVR may even compete with SAVR in patients at low surgical risk (30,31), a group that comprises 730,000 severe AS patients in the European countries and North America combined.

TAVR learning curve analyses show increasing proficiency with evidence of plateau after the first 30 cases (32).

In addition, governmental bodies mandate that each TAVR center performs at least 20 to 50 TAVR procedures per year (33–35). These requirements, combined with the figures from this study, are useful to estimate the number of TAVR centers and physicians who need to be trained in TAVR in the individual countries. For example, the 526 (95% CI: 224 to 965) new TAVR candidates per year in the Netherlands justify approximately 10 certified centers, assuming that each center performs 50 cases annually. Similarly, the 8,205 (95% CI: 3,470 to 15,139) new TAVR candidates per year in the United States suggest a requirement of approximately 165 certified TAVR centers.

The divergent standards of medical evidence required to introduce new therapies in Europe and the United States are likely to account for the difference in TAVR dissemination between the continents (36). Although the Edwards Sapien valve (Edwards Lifesciences, Inc., Irvine,

California) and Medtronic CoreValve (Medtronic, Inc., Minneapolis, Minnesota) both received the Conformité Européenne (CE) mark in 2007, the U.S. Food and Drug Administration used trial data to approve the Edwards Sapien valve for patients at prohibitive and high surgical risk only in November 2011 and October 2012, respectively. Consequently, TAVR has been performed with greater frequency and for a wider range of indications in Europe than in the United States. The studies on decision making in patients with AS reflect the commercial use of TAVR in Europe, whereas the U.S. studies display decision making in a time when TAVR use was restricted to clinical trials. These differences in practice are likely to disappear after the commercialization of TAVR in the United States and were taken into account in our sensitivity analyses.

Study limitations. Although we systematically searched the literature, relatively few reports on the prevalence of AS in the general population were identified. Additional population-based studies that use a unified echocardiographic definition of AS are warranted. The current study, however, reflects all of the currently available evidence on the prevalence of AS.

The estimation of TAVR candidates is as accurate as the currently available inputs and assumptions from the literature. However, we used sensitivity analyses to assess the influence of uncertain parameters. In addition, we included measures of uncertainty in each step of the model to calculate confidence intervals, representing the likelihood of the final estimates.

Conclusions

This systematic review and meta-analysis of population-based studies found that the prevalence of AS and severe AS among the elderly is 12.4%, and 3.4%, respectively. The overall burden of disease due to severe AS in the general elderly population is substantial. Our model showed that under the current indications approximately 290,000 elderly patients at high or prohibitive surgical risk could potentially be treated with TAVR in Europe and North America, and that each year there are approximately 27,000 new TAVR candidates. These estimates have considerable clinical, economic, and social implications.

Acknowledgments

The authors would like to acknowledge the suggestions by Rachele Busca, MS, PharmD, and Liesl C. Birinyi-Strachan, BS, PhD, from Medtronic.

Reprint requests and correspondence: Dr. A. Pieter Kappetein, Department of Cardiothoracic Surgery, Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands. E-mail: a.kappetein@erasmusmc.nl.

REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet* 2006;368:1005–11.
2. Jung B, Vahanian A. Epidemiology of valvular heart disease in the adult. *Nat Rev Cardiol* 2011;8:162–72.
3. Clark MA, Duhay FG, Thompson AK, et al. Clinical and economic outcomes after surgical aortic valve replacement in Medicare patients. *Risk Manag Healthc Policy* 2012;5:117–26.
4. Vaes B, Rezzoug N, Pasquet A, et al. The prevalence of cardiac dysfunction and the correlation with poor functioning among the very elderly. *Int J Cardiol* 2012;155:134–43.
5. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. *J Am Coll Cardiol* 1997;29:630–4.
6. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). *J Am Coll Cardiol* 2008;52:e1–142.
7. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2012;42:S1–44.
8. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
9. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol* 2012;60:1438–54.
10. Statistics Canada. 2012. Available at: <http://www.statcan.gc.ca/start-debut-eng.html>. Accessed November 16, 2012.
11. EUROSTAT. 2012. Available at: <http://epp.eurostat.ec.europa.eu/portal/page/portal/population/data/database>. Accessed November 16, 2012.
12. United States Census Bureau. 2011. Available at: <http://www.census.gov/popest/data/national/asrh/2011/index.html>. Accessed November 16, 2012.
13. Lin SL, Liu CP, Young ST, Lin M, Chiou CW. Age-related changes in aortic valve with emphasis on the relation between pressure loading and thickened leaflets of the aortic valves. *Int J Cardiol* 2005;103:272–9.
14. Lindroos M, Kupari M, Valvanne J, Strandberg T, Heikkilä J, Tilvis R. Factors associated with calcific aortic valve degeneration in the elderly. *Eur Heart J* 1994;15:865–70.
15. Lorz W, Cottier C, Gyr N. The prevalence of aortic stenosis in an elderly population: an echocardiographic study in a small Swiss community. *Cardiol Elderly* 1993;1:511–5.
16. van Bommel T, Delgado V, Bax JJ, et al. Impact of valvular heart disease on activities of daily living of nonagenarians: the Leiden 85-Plus Study, a population based study. *BMC Geriatr* 2010;10:17.
17. Brennan JM, Edwards FH, Zhao Y, et al. Long-term survival after aortic valve replacement among high-risk elderly patients in the United States: insights from The Society of Thoracic Surgeons Adult Cardiac Surgery Database, 1991 to 2007. *Circulation* 2012;126:1621–9.
18. Wenaweser P, Pilgrim T, Kadner A, et al. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. *J Am Coll Cardiol* 2011;58:2151–62.
19. Bach DS, Radeva JI, Birnbaum HG, Fournier AA, Tuttle EG. Prevalence, referral patterns, testing, and surgery in aortic valve disease: leaving women and elderly patients behind? *J Heart Valve Dis* 2007;16:362–9.
20. Sugiura M, Matsushita S, Ueda K. A clinicopathological study on valvular diseases in 3,000 consecutive autopsies of the aged. *Jpn Circ J* 1982;46:337–45.
21. Freed BH, Sugeng L, Furlong K, et al. Reasons for nonadherence to guidelines for aortic valve replacement in patients with severe aortic stenosis and potential solutions. *Am J Cardiol* 2010;105:1339–42.
22. Jung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? *Eur Heart J* 2005;26:2714–20.

23. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–607.
24. Osnabrugge RL, Head SJ, Bogers AJ, Kappetein AP. Towards excellence in revascularization for left main coronary artery disease. *Curr Opin Cardiol* 2012;27:604–10.
25. Reynolds MR, Magnuson EA, Lei Y, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results of the PARTNER (Placement of Aortic Transcatheter Valves) trial (cohort A). *J Am Coll Cardiol* 2012;60:2683–92.
26. Reynolds MR, Magnuson EA, Wang K, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the Placement of Aortic Transcatheter Valves (PARTNER) trial (cohort B). *Circulation* 2012;125:1102–9.
27. Osnabrugge RL, Head SJ, Genders TS, et al. Costs of transcatheter versus surgical aortic valve replacement in intermediate-risk patients. *Ann Thorac Surg* 2012;94:1954–60.
28. Mylotte D, Osnabrugge RL, Windecker S, et al. Transcatheter aortic valve replacement in Europe: adoption trends and factors influencing device utilization. *J Am Coll Cardiol* 2013;62:210–9.
29. Osnabrugge RL, Head SJ, Bogers AJ, Kappetein P. Patient selection for transcatheter aortic valve replacement: what does the future hold? *Expert Rev Cardiovasc Ther* 2012;10:679–81.
30. Lange R, Bleiziffer S, Mazzitelli D, et al. Improvements in transcatheter aortic valve implantation outcomes in lower surgical risk patients: a glimpse into the future. *J Am Coll Cardiol* 2012;59:280–7.
31. Webb JG. Mid-term follow-up after transcatheter aortic valve implantation. *Eur Heart J* 2012;33:947–8.
32. Alli OO, Booker JD, Lennon RJ, Greason KL, Rihal CS, Holmes DR Jr. Transcatheter aortic valve implantation: assessing the learning curve. *J Am Coll Cardiol Interv* 2012;5:72–9.
33. Centers for Medicare and Medicaid Services. 2012. Decision memo for transcatheter aortic valve replacement. Available at: [http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?ncid=257&ver=5&ncaname=transcatheter+aortic+valve+replacement+\(tavr\)&bc=aaaaaaaaaaaa&c](http://www.cms.gov/medicare-coverage-database/details/nca-proposed-decision-memo.aspx?ncid=257&ver=5&ncaname=transcatheter+aortic+valve+replacement+(tavr)&bc=aaaaaaaaaaaa&c). Accessed November 30, 2012.
34. Haute Autorité de Santé. 2011. Transcutaneous aortic valve implantation by the transfemoral or transapical route. Available at: <http://www.has-sante.fr>. Accessed November 30, 2012.
35. College voor zorgverzekeringen. 2011. Transcatheter aortaklepverving. Available at: <http://www.cvz.nl/hetcvz/zoeken?query=transcatheter+aortaklepverving>. Accessed November 30, 2012.
36. Kramer DB, Xu S, Kesselheim AS. Regulation of medical devices in the United States and European Union. *N Engl J Med* 2012;366:848–55.

Key Words: aortic stenosis ■ prevalence ■ transcatheter aortic valve replacement.

 **APPENDIX**

For supplementary tables and references, please see the online version of this article.