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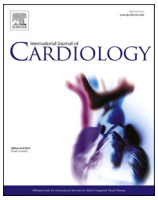

Patterns of aortic valve replacement in Europe and adoption by sex

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ABSTRACT

Objective: Management of patients with severe aortic stenosis (AS) may differ according to the patient sex. This study aimed to describe patterns of aortic valve replacement (AVR) for severe AS across Europe, including stratification by sex.

Methods: Procedure volume data for surgical aortic valve replacement (SAVR) and transcatheter aortic valve implantation (TAVI) for six years (2015–2020) were extracted from national databases for Austria, Czech Republic, Denmark, England, Finland, France, Germany, Norway, Poland, Spain, Sweden, and Switzerland and stratified by sex. Patients per million population (PPM) undergoing AVR per year were calculated using population estimates from Eurostat.

Results: Between 2015 and 2019, AVR procedures grew at an average annual rate of 3.9%. In 2020, the average total PPM undergoing AVR across all countries was 339, with 51% of procedures being TAVI and 49% SAVR. AVR PPM varied widely between countries, with the highest and lowest in Germany and Poland, respectively. The average total PPM was higher for men than women (423 vs. 258), but a higher proportion of women (62%) than men (44%) received TAVI. The proportion of TAVI among total AVR procedures increased with age, with an overall average of 96% of men and 98% of women aged ≥85 years receiving TAVI; however, adoption of TAVI varied by country.

Conclusions: The analysis of temporal trends in the adoption of TAVI vs. SAVR across Europe showed significant variations. Despite the higher use of TAVI vs. SAVR in women, overall rates of AV intervention in women were lower compared to men.

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List of abbreviations

AR	aortic regurgitation
AS	aortic stenosis
AVR	aortic valve replacement
CAD	coronary artery disease
DHT	dihydrotestosterone
EAPCI	European association of percutaneous cardiovascular intervention
LV	left ventricle
PPI	patients per million population
SAVR	surgical aortic valve replacement
TAVI	transcatheter aortic valve implantation

1. Introduction

Aortic stenosis (AS) is the most common valvular heart disease in developed countries, and its prevalence is expected to increase due to the aging of the population in industrialised countries [1]. There is some uncertainty about the relative frequency of AS in men versus women. Epidemiological studies have generally not found a difference in the incidence or prevalence of AS between the sexes [1]. However, AS tends to be underdiagnosed in women, and the prevalence may be higher in women than men in older age groups most likely reflecting the longer life expectancy of women [2].

There is also increasing evidence that there are differences between the sexes in terms of the pathophysiology, clinical presentation, and treatment of AS [3]. Studies have found differences in the management pattern for men and women with AS [4,5]. In particular, women are often diagnosed later than men and are less likely to undergo treatment [5]. With respect to aortic valve replacement (AVR) in patients with severe AS, [6] analysis of a European registry found that men are more likely to undergo surgical AVR (SAVR) and women are more likely to undergo transcatheter aortic valve implantation (TAVI) [4]. Separately, it is known that differences exist between European countries in the management of patients with severe AS, including the adoption rate of TAVI vs. SAVR [7].

Therefore, the aim of this database analysis was to describe the current patterns of AVR (SAVR and TAVI) use in different European countries, stratified by sex, and to evaluate changes over time.

2. Patients and methods

We extracted procedure volume data of SAVR and TAVI stratified by sex, from national statistical databases for 12 European countries: Austria, Czech Republic, Denmark, England, Finland, France, Germany, Norway, Poland, Spain, Sweden, and Switzerland (Suplementary Table 1). Where available, data acquired from six years between 2015 and 2020 were used to assess time trends in AVR. Data from 2020 were unavailable for England at the time of manuscript preparation.

The SAVR and TAVI codes used in the study are presented in Supplementary Table 2. In each case, the data sources provided information on volumes of procedures by patient sex and age group.

Table 1
Sources of data by country.

Country	Source
Austria	ÖGIS (Austrian Health Information System) [10–12]
Czech Republic	UZIS (Institute of Health Information and Statistics) [13,14]
Denmark	National Patient Register [15,16]
England	NHS Digital (National Health Service) [17–19]
Finland	THL (Institute of Health and Welfare) [20]
France	PMSI (Programme de Médicalisation des Systèmes d'Information) [21,22]
Germany	DESTATIS (German Federal Office of Statistics) [23,24]
Norway	National Patient Register [25–27]
Poland	NFZ (National Health Fund) [28,29]
Spain	RAE-CMBD (Registry of Specialized Health Activity) [30,31]
Sweden	National Board of Health and Welfare [32,33]
Switzerland	BFS (Federal Statistics Office) [34,35]

In Spain and Sweden, the data were available online. In Denmark, data were available online through 2018, and we directly requested the years 2019 and 2020 from the National Patient Register. In England and Norway, overall AVR data were available online, and codes distinguishing SAVR from TAVI were requested directly from NHS Digital in England and the Norwegian Directorate of Health. TAVI and SAVR data were available online in Switzerland, and specific data split by sex were sourced through a direct request to the Federal Statistics Office in Switzerland. In the other countries, data from the authorities responsible for providing data were requested.

Due to privacy protection, the number of patients in Denmark and Norway was not given for any combination of age and sex in cases where the combination comprises less than five patients. In contrast, for Spain, the number is not given if there are less than three patients. We imputed values where numbers were suppressed so that the sum of individual age and sex combinations added up to the total provided in the registry data. Procedure numbers are based on procedure type (SAVR or TAVI) and are not distinguished by disease aetiology; the data, therefore, contain both AS and aortic regurgitation (AR) procedures. Data sources for some countries report inpatient and outpatient activity, whereas others report only inpatient activity. We assumed that all valve procedures took place on inpatients. We also assumed that the database of each country provides a nearly complete picture of the SAVR and TAVI activity in each country.

We calculated patients per million population (PPM) undergoing AVR each year using estimates of population by sex and age group as published by Eurostat [8]. PPM is calculated by taking the number of patients treated in a country by procedure (SAVR or TAVI) in a year by gender and age combination (the patients) divided by the total number of people in the population for the same country in the year by gender and age combination (the population) [8]. Eurostat does not publish estimates from England's population, therefore data from the Office for National Statistics were used. In addition, Durko et al. [9] developed an incidence model to calculate the yearly number of AS patients per European country eligible for TAVI and, by inference, SAVR. We used this model to calculate the total incidence of AVR by country by assuming the same model applies to both sexes.

2.1. Data sources by country

Data sources for Austria [10–12], Czech Republic [13,14] Denmark [15,16], England [17–19], Finland [20], France [21,22], Germany [23,24], Norway [25–27], Poland [28,29], Spain [30,31], Sweden [32,33], and Switzerland [34,35] are summarised by country in Table 1. Additional details are provided in Supplementary Table 3.

2.2. Patient and public involvement statement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

3. Results

In 2020, across countries included in this study, the average PPM undergoing AVR was 339, with 51% of the procedures being TAVI and 49% SAVR. The AVR PPM varied widely across countries; in 2020, Germany was highest with 508 PPM (of which 60% were TAVI), and Poland was lowest with 174 PPM (of which 25% were TAVI). In 2020, for every country, PPM was higher for men than for women (Fig. 1), but a higher proportion of women received TAVI: on average, the PPM was 423 for men (of which 44% were TAVI), and the PPM for women was 258 (with 62% TAVI).

In both men and women, AVR PPM increased with age to a peak in

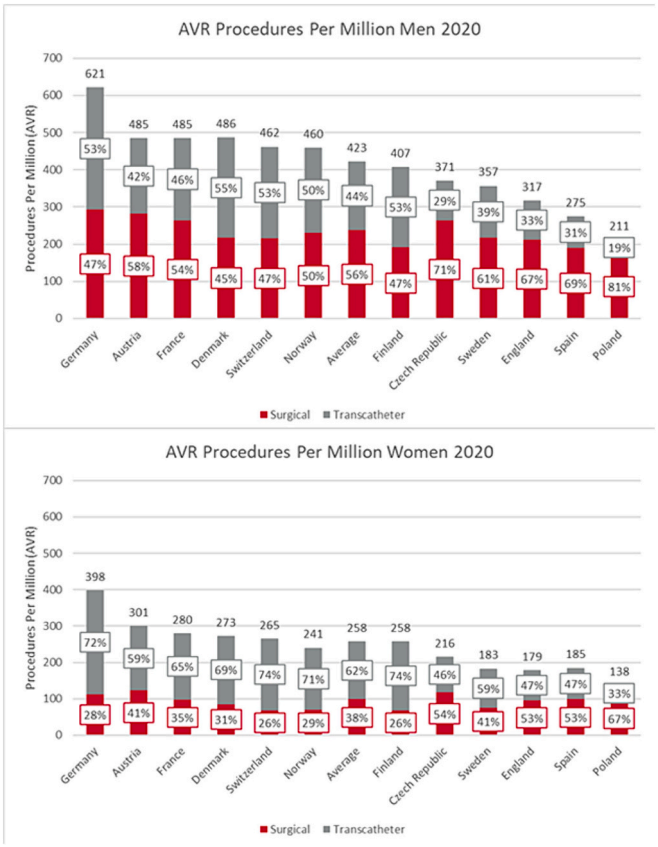

Fig. 1. Patients per million undergoing aortic valve replacement (AVR) procedures, and percentages undergoing each type of procedure (surgical AVR or transcatheter AV implantation), for each country.
Legend: AVR, aortic valve replacement.

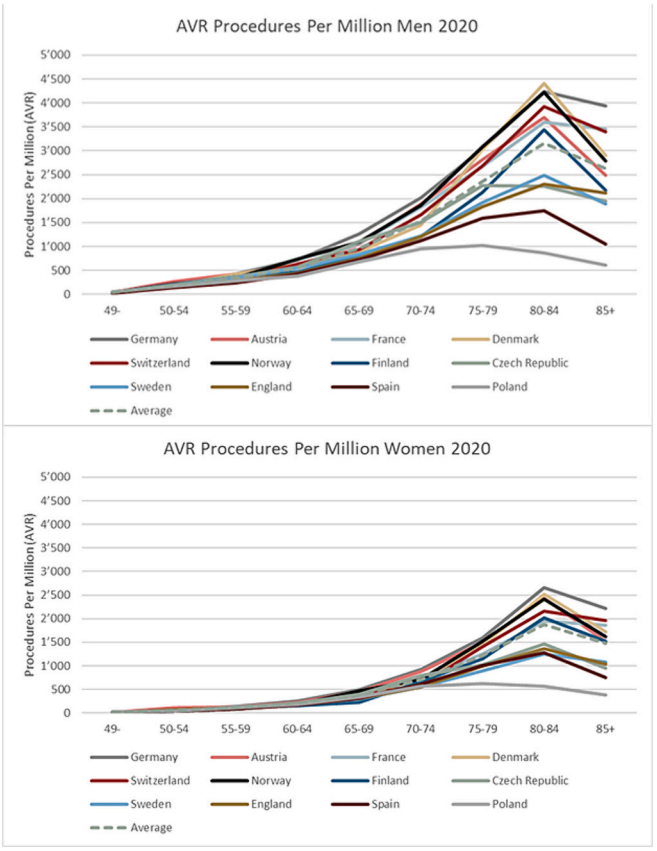

Fig. 2. Patients per million undergoing aortic valve replacement (AVR) procedures by patient age group, for men and women, for each country.
Legend: AVR, aortic valve replacement.

the age group 80–84 years (Fig. 2), after which treatment rates decreased, especially in Austria, Denmark, Finland, and Norway.

Based on aggregated data for all countries from 2015 to 2019, AVR procedures grew at an average annual rate of 3.9%. Looking at the type of procedure over the same time period, TAVI grew at an average annual rate of 16.0%, whereas SAVR declined by 3.0%.

Moreover, a general trend was noted for a higher treatment rate for men than women: the ratio of men to women of each country was more pronounced in younger age groups (2.2, 1.9, and 1.6 in the age groups 70–74, 75–79, and 80–84, respectively).

The proportion of TAVI among total AVR procedures increased with increasing age in both men and women (Fig. 3). We used Durko et al.'s model [9] model to calculate the total number of AVR procedures in patients aged ≥65 years, which was to be around 45,000 in Germany in 2019, compared to treatment of 37,439 patients, indicating that only 83% of all patients were treated. However, when this model was applied to sex-disaggregated data, 109% of men and only 63% of women were treated, indicating a large discrepancy.

4. Discussion

The dataset from our study shows clearly distinct patterns of treatment for AS between the sexes. Key findings were first, that across Europe, more men were treated per million population than women, and second, that a higher percentage of women than men received TAVI.

Assuming AV disease affects both sexes similarly [1], the observation that population-normalised procedure rates are higher in men would allow concluding that women are undertreated for AV disease.

There is evidence that AS may not affect men and women equally. Recently, Schafstedde et al. demonstrated that higher levels of the male sex hormone dihydrotestosterone (DHT) were associated with adverse myocardial remodelling in patients with severe AS [36]. Several studies have found that men may have an increased risk of calcific AS or aortic sclerosis [37,38]. The AGES-Reykjavik study found severe AS present in 8.5% of men and 4.0% of women aged ≥70 years using CT calcification as a marker [37]. In contrast, a few studies have suggested a higher rate among certain subgroups of women, [37,39] while others have found no difference between the sexes [1,40]. In the Tromsø study, 55% of 141 patients with mild, moderate, or severe AS were men, with no difference between the sexes [1]. A more recent study, in which the incidence of AS was analysed using multiple echocardiographic examinations over a median period of 2.8 years, found no difference between the sexes among patients who were initially free of AS and subsequently developed the disease [40].

The ambiguity as to whether men may have a higher risk of developing AS compared to women may be at least partially explained by differences in how the disease affects the sexes. A recent review indicated that AS is higher in calcium in men and they tend to exhibit more cardiac fibrosis, although the outcomes are worse in women when fibrosis is present [41]. Men exhibit higher valvular calcification than women for the same degree of AS; thus, solely using calcium load to assess AS severity may overlook the disease in women [41].

Furthermore, in response to AS, men developed dilated left ventricular (LV) remodelling and features related to heart failure with reduced ejection fraction. In contrast, women developed more hypertrophic LV remodelling with features associated with heart failure with preserved ejection fraction [42].

Differences in the degree of calcification and LV remodelling may cause differences in the frequency and timing of diagnosis of AS between sexes. Along these lines, a study reviewing the frequency of valvular

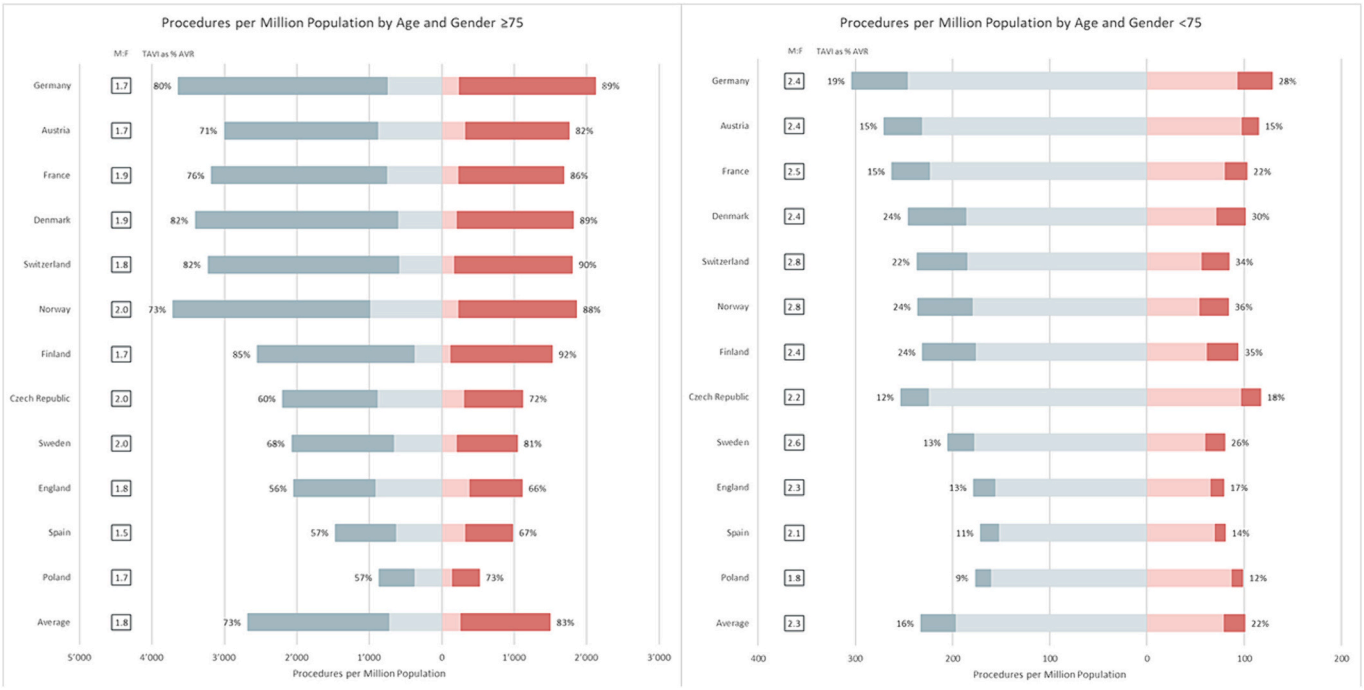

Fig. 3. Average patients per million by sex, age category and therapy in 2020 (except England 2019) for all countries combined.
Legend: Data for men are displayed to the left, data for women are displayed to the right; solid colours represent transcatheter aortic valve implantation (TAVI), semi-transparent colours surgical aortic valve replacement (SAVR).

heart disease diagnosis in a community found that men were more frequently diagnosed than women. Similarly, a study using national data from Sweden found that for each 5-year age group, more men than women were diagnosed with AS [43]. This would be in accordance with a study from Denmark. Analysing the timing of diagnosis of all diseases in Denmark, found that the age of first hospital diagnosis was, on average, higher in women [44]. These observations are mirrored in the present study, which shows that women in each age group are treated less with AVR than men. It may be speculated that a later manifestation or disease diagnosis can explain these findings. In addition, women tend to perceive their disease as less severe and undergo fewer diagnostic tests as they are more hesitant and are less frequently referred to a specialist [45].

Our study did not capture the reasons for the choice of procedure (TAVI versus SAVR), so it is unclear why proportionally more women underwent TAVI. This finding was seen across all age groups and all countries. The same finding was made in another study [4]. Several possible reasons could help explain this difference. It has been shown previously that women with severe AS tend to be diagnosed at an older age than men, have more symptoms, and are often at higher surgical risk [4,5]. In addition, women tend to have a smaller aortic annulus, with a greater risk of patient-prosthesis mismatch (PPM) during SAVR [46]. Although PPM can be significantly reduced by aortic root enlargement during SAVR, this approach is more suitable for young patients at low-risk profiles [47] and it does not necessarily improve long-term clinical outcomes, as per Kulik A et al. study [48]. Therefore, TAVI may be considered a more suitable intervention for women.

The treating physicians may also have considered data from studies suggesting that women have better outcomes after TAVI than after SAVR [49]. In addition, patient preference could also influence the choice of procedure. In particular, the Valve-for-Life initiative of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) focuses on reducing inequities of access to the treatment of valvular heart diseases, and more initiatives should highlight the need for more focus on undertreatment in women.

4.1. Future research direction

Our analysis revealed that sex-related disparity exists in the treatment of AS across European countries, where men undergo AVR more frequently than women, while TAVI is more preferred in women, especially in older ones. However, the specific reasons for these disparities couldn't be captured. Further research is necessary to uncover the sex-related differences in AS considering valvular characteristics, clinical presentation, diagnosis, and treatment (SAVR vs. TAVI). This exploration is crucial to ensure optimal patient safety and outcomes, guiding the development of personalized medical approaches in AS management.

4.2. Limitations

This study relied on publicly available information about procedure types and volumes across European countries. Although efforts were made to identify data sources from all European countries, in some countries, including Belgium, Ireland, Italy, Netherlands, and Portugal, these efforts were not successful. Furthermore, clinical outcomes were not obtained or reported in this study.

Another limitation is that we requested data from the statistical agencies for the procedures performed, but not for the treatment of AS. Therefore, the procedure numbers will also include AVR to treat AR. A comparison of data for France (PMSI) including only cases of AS [50] versus our dataset from the same source but including all aetiologies suggests that in 2019, AR comprised 29% of SAVR cases (growing from 24% in 2011) and 4% of TAVI cases (a reduction from 5% in 2011). Those AR cases are included in this paper and may affect the strength of the observations specifically related to sex differences in treatment. Finally, the study does not account for comorbidities, such as coronary artery disease (CAD), influencing the treatment choice between SAVR and TAVI.

5. Conclusions

Our study described the total number of AVR procedures (SAVR and

TAVI) between 2015 and 2020 in 12 European countries, including stratification by sex. The results revealed a considerable variation in the utilization of AVR procedures between countries, with a lower rate of AVR in women than in men with severe AS. However, the use of TAVI has increased in recent years, and women are treated with TAVI more often than men.

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Statement of ethics

No ethical approval was required for the anonymised data analysis.

CRediT authorship contribution statement

Sabine Bleiziffer: Supervision, Conceptualization. **Clare Appleby:** Validation, Supervision, Investigation. **Victoria Delgado:** Visualization, Supervision, Resources, Data curation. **Helene Eltchaninoff:** Supervision, Resources, Formal analysis, Data curation, Conceptualization. **Catherine Gebhard:** Visualization, Resources, Investigation, Data curation. **Christian Hengstenberg:** Visualization, Validation, Methodology, Data curation, Conceptualization. **Wojtek Wojakowski:** Validation, Supervision, Resources, Investigation, Data curation, Conceptualization. **Nathan Petersen:** Resources, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Jana Kurucova:** Supervision, Resources, Funding acquisition, Conceptualization. **Peter Bramlage:** Writing – review & editing, Writing – original draft, Supervision, Resources, Conceptualization. **Tanja K. Rudolph:** Visualization, Validation, Supervision, Investigation, Conceptualization.

Declaration of competing interest

Nathan Petersen and Jana Kurucova are employees of Edwards Lifesciences, a manufacturer of TAVI and SAVR valves. Peter Bramlage is a research consultant and received funding for performing clinical research into the safe use of aortic valves by Edwards Lifesciences. Sabine Bleiziffer and Tanja Rudolph have held lecture and were part of advisory boards which were held and compensated by Edwards Lifesciences. No specific payment was associated with the development of this manuscript.

All authors read and approved the final version of manuscript for publication in international journal of cardiology.

Data availability statement

The data underlying this article will be shared upon reasonable request to the corresponding author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.131996.

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