Choice of Treatment for Aortic Valve Stenosis in the Era of Transcatheter Aortic Valve Replacement in Eastern Denmark (2005 to 2015)

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ABSTRACT

OBJECTIVES The aim of this study was to evaluate the choice of treatment for severe aortic valve stenosis in the era of transcatheter aortic valve replacement (TAVR) in Eastern Denmark.

BACKGROUND Until the early 21st century, the only therapeutic option for aortic valve stenosis was surgical aortic valve replacement (SAVR), but this has changed with the introduction of TAVR.

METHODS Using the East Denmark Heart Registry, the evolution of AVR over time was studied for the period 2005 to 2015.

RESULTS TAVR has since its introduction in 2007 seen steady growth, with currently more than 35% of AVR procedures—and 45% of isolated AVR procedures—being performed by transcatheter-based technology. The number of SAVR procedures remained rather stable over the study period and even saw a slight decline since 2012—there was a marked decrease in the age at which surgical bioprostheses are considered appropriate. The age profile of TAVR patients remained unchanged over the study period, with a recent trend toward more low- and intermediate-risk patients. Currently, patients age ≥80 years and/or with a Society of Thoracic Surgeons (STS) surgical risk score >6 are automatically referred for TAVR, and one-half of patients age 70 to 80 years with an STS risk score of 4 to 6 are treated with TAVR.

CONCLUSIONS The number of TAVR procedures has increased steadily in recent years, with a TAVR penetration rate of 35% in 2015 and close to 45% when considering isolated AVR. The number of SAVR procedures remained stable over the study period, and surgical bioprostheses are currently used at a much younger age than in 2005. (J Am Coll Cardiol Intv 2016;9:1152–8) © 2016 by the American College of Cardiology Foundation.

Patients with symptomatic, severe aortic valve stenosis (AS) are known to face a high mortality risk. With the onset of symptoms, 75% of patients succumb within 3 years if not treated (1). Until the early 21st century, the only therapeutic option for these patients was surgical aortic valve replacement (SAVR) (2), but this has changed with the introduction of transcatheter aortic valve replacement (TAVR) (3). TAVR has been shown to be a safe and effective alternative to surgical aortic valve replacement (SAVR) (4), particularly in patients who are at high surgical risk (5). The advantages of TAVR include minimized trauma, shorter hospital stay, and reduced risk of stroke (6). However, TAVR also has some disadvantages, such as higher procedural costs and the need for anticoagulation. Therefore, the decision to perform TAVR or SAVR should be individualized based on the patient’s characteristics and preferences (7).
replacement (TAVR). Since the first TAVR procedure performed by Cribier et al. (3) in 2002, the therapeutic management strategy for patients with severe AS has been revolutionized, especially for inoperable and high-risk patients (4–7). Recently, the number of TAVR procedures worldwide surpassed 200,000—the rate of TAVR is highest in Northwestern Europe with more than 50,000 TAVR procedures performed in Germany alone (8,9). In accordance, Scandinavian countries have been early adopters of this new technology and have played a pioneering role in introducing this technology to lower risk patients (10). In this update, we study the choice of treatment for patients with severe AS in the era of TAVR in Eastern Denmark (2005 to 2015), with additional focus on the potential impact of TAVR on SAVR.

METHODS

In Eastern Denmark, all SAVR and TAVR procedures are registered in the WebPATS East Denmark Heart Registry—registration is linked to reimbursement. All data are reported using standardized electronic data entry and are self-adjudicated by the sites. Mortality data were obtained from Landspatientregisteret and Danmarks Statistik (Copenhagen, Denmark). The indication for SAVR or TAVR is made at a daily heart team meeting. All referring hospitals in Eastern Denmark (population 2.6 million) participate in a daily video conference call centralized at Rigshospitalet and discuss potential cases for cardiac surgery, TAVR as well as complex percutaneous coronary intervention with a senior cardiac surgeon, interventional cardiologist, and noninvasive cardiologist. The aforementioned procedures are performed only at Rigshospitalet, Copenhagen University Hospital. Because rates of TAVR in Scandinavia are among the highest worldwide, we believe that these real-world data may provide useful information for physicians involved in aortic valve replacement (AVR) around the world. In this report, we give an overview of the evolution of SAVR and TAVR in the period 2005 to 2015, a period during which TAVR was introduced and saw fast growth.

Categorical variables are reported as absolute values and percentages. Continuous variables are expressed as mean ± SD. Categorical variables were compared using chi-square or Fisher exact tests and continuous variables using Student t tests or Mann-Whitney U tests, as appropriate. All tests were 2-sided, and p values <0.05 were considered to indicate statistical significance. Kaplan-Meier survival curves were compared using the log-rank test. A multivariate Cox proportional hazards regression model was used to adjust for any confounding variables between the groups. The analyses were conducted using SPSS version 20.0 (IBM, Armonk, New York).

RESULTS

Between 2005 and 2015, a total of 5,149 SAVR procedures were performed in Eastern Denmark. Of these, 3,810 procedures were isolated SAVR (62.3%) or SAVR in combination with CABG. Trends in (A) overall aortic valve replacement (AVR), (B) isolated AVR, and (C) AVR plus revascularization in the period 2005 to 2015, as measured for the transcatheter AVR (TAVR) and surgical AVR (SAVR) groups.

Abbreviations and Acronyms

As = aortic valve stenosis
AVR = aortic valve replacement
SAVR = surgical aortic valve replacement
STS = Society of Thoracic Surgeons
TAVR = transcatheter aortic valve replacement

Trends in (A) overall aortic valve replacement (AVR), (B) isolated AVR, and (C) AVR plus revascularization in the period 2005 to 2015, as measured for the transcatheter AVR (TAVR) and surgical AVR (SAVR) groups. (A) Total number of procedures per year. (B,C) Percentage of annual procedures performed with the TAVR technology. *Combined TAVR and percutaneous coronary intervention (PCI) with no more than 3 months between the 2 procedures. CABG = coronary artery bypass graft surgery.
coronary artery bypass graft surgery (37.7%) for pure or mixed AS (Online Figure 1).

The number of SAVR procedures slightly increased (þ15%) from 2005 to 2012, but there is a downward trend since 2012. In 2007, TAVR was introduced in Eastern Denmark with the first 2 procedures. In 2012, the TAVR technology was used for 26.8% of all AVR procedures, and this percentage has increased to 36.4% by 2015 (Figure 1A). When considering isolated AVR, TAVR has been used in 44.4% of all cases in 2015, whereas 19.9% of all AVR procedures combined with coronary revascularization were performed by transcatheter-based technology (Figures 1B and 1C).

The populations treated with SAVR and TAVR are clearly different, with younger and lower risk patients treated mainly with SAVR. The median age of the SAVR group was 73 years, compared with 81 years for the TAVR group (Figure 2A)—the age distribution did not change substantially over time in the 2 groups (Figures 2B and 2C). The median Society of Thoracic Surgeons (STS) score of the SAVR group was 1.8, compared with 5.3 for the TAVR group (Figure 2D)—the distribution of this variable did change over time within the evaluated period. In 2005 and 2006, 4.6% of patients treated with SAVR were at high surgical risk (STS score >8) and 18.1% of patients had an STS score >4, whereas in the period 2013 to 2014, no single patient with an STS score >8 was treated with SAVR, and only 11.1% of all SAVR patients were at intermediate risk (STS score 4 to 8) (Figure 2E). Also for the TAVR group, there was an evolution from (very) high risk to lower risk patients over time, with 37.2% of TAVR patients having an STS score >8 in the period 2008 to 2009, compared with 14.9% of TAVR patients with an STS score >8 in the period 2013 to 2014 (Figure 2F; see also Online Figure 2 for logistic European System for Cardiac Operative Risk Evaluation score analysis).

When analyzing the SAVR population group, the patient age at which more biological than mechanical surgical prostheses were used markedly decreased, with the “cutoff” at an age of 68 years in 2005 to 2006 compared with an age of 61 years in 2013 to 2014. In total, 80.1% of all surgical aortic prostheses were bioprostheses in the period 2005 to 2006, compared with 85.5% in the period 2013 to 2014 (p < 0.01) (Figure 3).

Regarding clinical practice in Eastern Denmark in the period 2013 to 2014, we report an overall TAVR penetration rate of 26.0%, meaning that about 1 in 4 AVR procedures were performed by TAVR technology. A more in-depth analysis revealed that the majority of AS patients age $\geq$80 years and/or with an STS surgical risk score >6 were treated with TAVR, and about one-half of AS patients age 70 to 80 years and an STS risk score of 4 to 6 were treated with TAVR in the period 2013 to 2014 (Figure 4).

When comparing mortality for the TAVR and SAVR populations age 70 to 85 years with an STS risk score <6 in the period 2010 to 2014, the Kaplan-Meier survival curves in Figure 5 demonstrate that mortality rates were similar for both treatment groups (hazard ratio: 1.01; 95% confidence interval: 0.71 to 1.41; p = 0.977). Because both groups were significantly different on some variables, a multivariate Cox proportional-hazards regression model was used to adjust for these confounding variables. The hazard ratio adjusted for the covariates age, previous coronary artery bypass graft surgery, chronic kidney
disease, and STS score was 0.76 (95% confidence interval: 0.54 to 1.13; \(p = 0.189\)).

From 2007 to 2015, a total of 821 patients were treated with TAVR. The majority of patients (93%) were treated using the transfemoral approach. In 761 patients, self-expandable TAVR technology was used (Figure 6). As indicated in Figure 6, there is a clear downward trend in length of hospital stay, major vascular complications, and 30-day and 1-year mortality, with a mean length of stay of 4.7 days, a major vascular complication rate of 4.1%, and a 30-day mortality rate of 2.0% for the entire TAVR population (n = 196) treated in 2015.

**DISCUSSION**

The number of TAVR procedures in Denmark and around the world has increased steadily in recent years, and it is now routine practice at many centers, particularly in Northwestern Europe and North America. As reported earlier by Mylotte et al. (8), the number of TAVR procedures more than doubled in most European countries from 2009 to 2011. And both our data as well as the German AQUA (Institut für Angewandte Qualitätsförderung und Forschung im Gesundheitswesen) registry (9) show that the number of TAVR procedures has once more doubled since 2011. However, the adoption of TAVR across the different nations varies widely, mainly because of differences in reimbursement policies (8). As reported by Eggebrecht et al. (9), TAVR penetration in Germany evolved from 29.4% in 2011 to 44.5% in 2014. In accordance, we report in this study that TAVR penetration in Eastern Denmark increased from 20.1% in 2011 to 36.4% in 2015. In comparison, the annual volume of SAVR remained rather stable over the study period (2005 to 2015) and even slightly declines since 2012. Overall, the total number of AVR procedures increased, with more than 50% over the study period, which can be ascribed to aging of the population as well as increased awareness of the new transcatheter treatment option for severe AS in older patients and, as a result, an increased number of referrals of this specific patient population.

Remarkably, the age profile of TAVR patients treated in Eastern Denmark has remained unchanged over time (Figure 2)—a similar pattern has been reported in Germany with >95% of all TAVR patients being 70 years of age or older (9). In contrast, we report a clear trend toward treatment of intermediate- (and low-) risk patients, in line with current practice in most countries as well as with the trend seen in large randomized controlled trials (PARTNER I [Placement of AoRtic TraNscathetER valves] : STS score 11.8 vs. PARTNER II intermediate risk [S3i] STS score 5.3%) (5,11). Clearly, in the future, there will be a need for randomized controlled trials including not only low-risk patients but also younger patients (<75 years of age).

In Eastern Denmark, AS patients age ≥80 years and/or with an STS surgical risk score >6 are currently automatically referred for TAVR, and about one-half of patients age 70 to 80 years with an STS risk score of 4 to 6 are currently treated with TAVR. The expectation is that TAVR will further expand its indication to
younger and lower risk patients. The recent randomized controlled NOTION (Nordic Aortic Valve Intervention) trial reported that TAVR is as safe and effective as SAVR at 2 years for lower risk patients (10), but larger randomized trials with newer generation TAVR devices and longer term follow-up are needed before TAVR can be adopted as the first-choice treatment for an all-comers AS population.

![FIGURE 4 TAVR Penetration Rate in Eastern Denmark for the Period 2013 to 2014](image)

The absolute values are the numbers of patients per age and surgical risk category; the numbers in parentheses indicate the percentage of this specific patient category treated by transcatheter aortic valve replacement (TAVR) technology. STS = Society of Thoracic Surgeons.

![FIGURE 5 Baseline Characteristics and Kaplan-Meier Survival Analysis for All Patients 70 to 85 Years of Age With Low- or Intermediate-Risk Profile (Society of Thoracic Surgeons Risk Score < 6) Treated With Transcatheter or Surgical Aortic Valve Replacement in the Period 2010 to 2014](image)

Hazard ratio (HR) with 95% confidence interval. CABG = coronary artery bypass graft surgery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack.
The Kaplan-Meier survival analysis in Figure 5 indicates that TAVR is at least as safe as SAVR when used in the low- to intermediate-risk group, and both the adjusted hazard ratio calculated in this study of 0.76 as well as the lower 1-year mortality rate in the TAVR (4.9%) versus SAVR (7.5%) group in the NOTION trial (10) indicate that TAVR might even have better mortality outcomes than SAVR. However, this needs to be confirmed in larger randomized controlled trials.

Concerning the choice of a mechanical or biological prosthesis for patients treated with SAVR, we noted a marked decrease in the age at which aortic bioprostheses were considered appropriate. A possible explanation for this observation could be that surgeons, as well as patients, are increasingly considering the option of transcatheter valve-in-valve intervention in case of a degenerated surgical bioprosthesis (12). Moreover, this is in line with the current guidelines for the management of patients with valvular heart disease (13).

When analyzing the approach and outcomes of our TAVR program in Eastern Denmark, we observe that the vast majority of patients were treated using the transfemoral approach, even in the early period of TAVR. In contrast, the rate of nontransfemoral TAVR has been typically much higher (20% to 40%) in other national registries such as AQUA, FRANCE-2 (French Aortic National CoreValve and Edwards 2), UK-TAVI (United Kingdom Transcatheter Aortic Valve Implantation), and STS/American College of Cardiology TTV (Transcatheter Valve Therapy) Registry for the period 2007 to 2012 (9,14–16). In parallel with the treatment of more intermediate-risk patients with fewer comorbidities and less peripheral vascular disease, we also see now worldwide that transfemoral TAVR accounts for the vast majority of TAVR procedures (12). As shown in Figure 6, we also report continuously improving outcomes with regard to hospitalization length, major vascular complication, and mortality rates. This can partially be ascribed to a less complex patient population undergoing treatment but also to increased operator experience as well as the use of lower profile, next-generation TAVR devices. In addition, our team switched from general to local anesthesia in June 2015, resulting in a marked shortening of length of stay (mean 4.1 days after the switch to local anesthesia). Finally, we report a 30-day mortality rate of 2.0% for the entire TAVR population (n = 196) treated in 2015 and a 30-day mortality rate of only 1.2% for the low- and intermediate-risk group (n = 164)—these numbers are in line with the 30-day outcomes reported for the PARTNER II trial (11).

**STUDY LIMITATIONS.** This study reports data for Eastern Denmark, describing the therapeutic evolution for severe AS for a total population of 2.6 million people. The centralized organization in this part of the European Union is in one sense an advantage, as the overall patient evaluation and data handling and reporting are very stable for the studied period. However, this also implies that the data reported in this study are single-center data. Another potential limitation of this study is that the overall majority of patients were treated using self-expandable TAVR technology, with 75% of patients being treated with CoreValve (Medtronic, Minneapolis, Minnesota).

**CONCLUSIONS**

In Eastern Denmark, AS patients age ≥80 years and/or with an STS surgical risk score >6 are automatically referred for TAVR, and about one-half of patients age 70 to 80 years with an STS score of 4 to 6 are currently treated with TAVR. In general, almost one-half of isolated AVR procedures are currently performed using transcatheter-based technology. The number of SAVR procedures has slightly decreased since 2012, and surgical aortic bioprostheses are currently used at a much younger age (cutoff 60 years) than in 2005.

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KEY WORDS aortic valve replacement, aortic valve stenosis, surgery, transcatheter

APPENDIX For supplemental figures, please see the online version of this article.