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Published in:
American Heart Journal

DOI (link to publication from Publisher):
10.1016/j.ahj.2021.09.010

Publication date:
2022

Document Version
Publisher's PDF, also known as Version of record

Temporal trends in utilization of transcatheter aortic valve replacement and patient characteristics: A nationwide study

Jarl E. Strange, MD[a], **Caroline Sindet-Pedersen, MSc, PhD**[a,b], **Gunnar H. Gislason, MD, PhD**[a,b,c], **Christian Torp-Pedersen, MD, DMSc**[d,e], **Kristian H. Kragholm, MD, PhD**[e], **Camilla Lundahl, MB**[e], **Emil L. Fosbøl, MD, PhD**[f], **Jawad H. Butt, MD**[f], **Lars Køber, MD, DMSc**[f], **Lars Søndergaard, MD, DMSc**[f], and **Jonas B. Olesen, MD, PhD**[a] *Hellerup, Denmark; Copenhagen, Denmark; Aalborg, Denmark*

Aim To investigate trends in the utilization of transcatheter aortic valve replacement (TAVR) and changes in the characteristics of patients undergoing first-time TAVR.

Methods Using Danish nationwide registers, we included all patients undergoing TAVR between 2008 and 2020. To compare patient characteristics, the study population was stratified according to calendar year of procedure: 2008-2010, 2011-2013, 2014-2016, and 2017-2020.

Results We identified 6,097 patients undergoing TAVR with year-by-year increases in TAVR penetration rate. Over time, the age of the patients remained stable (2008-2010: median age 82 year [interquartile range (IQR): 77-86] vs 2017-2020: median age 81 years [IQR: 77-85]). Moreover, there was an increase in male patients (2008-2010: 49.9% vs 2017-2020: 57.4%) and patients with diabetes (2008-2010: 14.2% vs 2017-2020: 19.2%). Conversely, a history of stroke (2008-2010: 15.8% vs 2017-2020: 13.1%), previous myocardial infarction (2008-2010: 22.4% vs 2017-2020: 10.0%), heart failure (2008-2010: 40.5% vs 2017-2020: 25.2%), and peripheral artery disease (2008-2010: 14.8% vs 2017-2020: 10.4) decreased among patients.

Conclusions TAVR utilization increased markedly in the years 2008-2020. Patients undergoing TAVR had less comorbidity over time while age remained stable. Thus, despite expanding to patients at lower surgical risk, TAVR is still offered mainly to older patients. (Am Heart J 2022;243:140–146.)

European guidelines list transcatheter aortic valve replacement (TAVR) as an option to treat symptomatic, severe aortic stenosis in elderly patients at increased surgical risk,[1] whereas in recent American guidelines, TAVR is an acceptable option across all surgical risk groups.[2] Randomized controlled trials (RCT) comparing TAVR to surgical aortic valve replacement (SAVR) in high-,[3,4] intermediate-,[5,6] and low-risk[7-9] patients have been conducted. As such, the expansion of TAVR into patients at lower surgical risk and younger age is an ongoing topic of interest.[10]

However, due to the strict inclusion and exclusion criteria of the RCT, these patients may not have been representative of actual practice patterns for patients ultimately undergoing TAVR and extrapolation of trial results to patients seen in everyday clinical practice becomes difficult. Importantly, a previous study highlighted the exclusion criteria for patients likely to have poor outcomes after TAVR in the low-risk RCT.[11] Further, transfemoral TAVR is now an acceptable treatment option for patients aged 65 to 80 considering the patient's life-expectancy and valve durability;[2] however, the mean age in the low-risk RCT were 79.2,[7] 74.1,[9] and 73.3 years,[8] respectively. If TAVR expands to not only patients at lower surgical risk, but also at younger age and longer life-expectancy, valve durability, future access to coronary arteries and complications such as conduction abnormalities become increasingly important.[10] This emphasises

From the [a]Department of Cardiology, Copenhagen University Hospital Herlev and Gentofte, Hellerup, Denmark, [b]The Danish Heart Foundation, Copenhagen, Denmark, [c]Department of Clinical Medicine, Faculty of Health and Sciences, University of Copenhagen, Copenhagen, Denmark, [d]Department of Cardiology and Clinical Research, Nordsjaellands Hospital, Hillerød, Denmark, [e]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark, [f]Department of Cardiology, The Heart Center, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

Submitted February 16, 2021; accepted September 20, 2021

Reprint requests: *Jarl E. Strange, MD, Department of Cardiology, Copenhagen University Hospital Herlev and Gentofte Hospital, Post 635, Gentofte Hospitalsvej 8, Hellerup 2900, Denmark.*

E-mail address: *Jarl.emanuel.strange.02@regionh.dk.*

0002-8703

https://doi.org/10.1016/j.ahj.2021.09.010

the need to conduct observational studies to facilitate knowledge on how TAVR is implemented in clinical practice of unselected patients.

Results from registers have previously shown trends in patient characteristics.[12-17] However, only one of these studies provides data beyond year 2015. Since 2015, results from intermediate- and low-risk trials have been published. Therefore, it is largely unclear if clinical practice has changed.

The purpose of this study was to investigate temporal trends in the utilization of TAVR and to examine changes in patient characteristics of patients undergoing first-time TAVR.

Methods

Data collection

All permanent Danish residents are assigned a unique personal identification number allowing for crosslinking at an individual level of information between the following nationwide administrative registers: The Danish Civil Registration System,[18] The Danish National Patient Register,[19] The Danish National Prescription Registry.[20] These registers have been described and used previously.[21] Lastly, a collective database with results of blood samples from 4 out of the 5 regions in Denmark was used: Provides data on hemoglobin, creatinine, and albumin levels. All blood samples within 1 year prior of TAVR procedure date were identified, and the result from the closest sample was defined as baseline level.

Study design and population

In this observational study, all patients undergoing first-time TAVR in Denmark between January 1, 2008 and the December 31, 2020 were included. Patients were stratified according to calendar year of procedure resulting in the follow year groups: 2008-2010, 2011-2013, 2014-2016, and 2017-2020.

Characteristics, comorbidities, comedication, and mortality

Cohabitant status is evaluated quarterly and the latest status prior to TAVR date was defined as baseline status. Living alone was defined as the only inhabitant at the address above the age of 18. Comorbidities 10 years prior to date of TAVR were identified using International classification of Diseases - 10th edition (ICD-10) codes (see Supplementary Table I for full list of diagnoses codes). Cancer was defined as a hospital contact within 3 years. Diabetes was defined as use of anti-diabetic drugs. Hypertension was defined as a diagnosis of hypertension or use of two or more blood pressure lowering drugs. Comedication was defined as prescription drugs dispensed 180 days prior to date of TAVR. Ninety-day mortality was evaluated for each year group.

Statistical analyses

Baseline characteristics are presented with numbers and percentages for categorical values and median and interquartile range for numerical values. To compare the different groups, the chi-squared test was used for categorical variable and the Kruskal-Wallis rank test was used for continuous variables. To assess temporal trends in comorbidities of the patients, the Cochrane-Armitage trend test was used for categorical values with 2 levels. For continuous variables such as blood sample values, a simple linear regression model was used to assess the linear association between the dependent variable (blood sample value) and independent ordered categorical variable (calendar year). The *P*-values provided throughout the manuscript are to be considered a support in the interpretation of the test results. They reflect the degree of unexpectedness of the observed test results under the null hypothesis of no differences between groups compared.[22]

Data management, statistical analyses, and figures were managed, performed, and created in SAS version 9.4 and in R.[23]

Results

Utilization of TAVR

Figure 1A illustrates procedure volume by calendar year. In total, 6,097 patients underwent first-time TAVR between 2008 and 2020 in Denmark. In 2008, 10.3 per 1,000,000 capita underwent TAVR compared with 167.0 per 1,000,000 capita in 2020.

Figure 1B shows access point for TAVR procedures. Over time, there was a steady decrease in alternative access from 40% in the 2008-2010 group to 10% in the 2017-2020 group. This decrease was due to a steady increase in transfemoral approach from 60% in 2008-2010 to 90% in 2017-2020.

Overall, hospital length of stay of TAVR patients decreased. In 2008-2010 the median hospital length of stay was 9 days (interquartile range [IQR]: 6-14) compared with 3 days (IQR: 2-5) in 2017-2020.

Patient characteristics, comorbidity burden, and mortality

Table I shows the baseline characteristics of patients according to calendar year group. During the study period, there was no change in the patients' age at first-time TAVR. The patients in the 2008-2010 group had a median age of 82 years (IQR: 77-86) compared with patients in 2017-2020 with a median age of 81 years (IQR: 77-85). The proportion of patients younger than 70 years also remained stable with 26 (6.6%) patients in 2008-2010 and 232 (7.0%) patients in 2017-2020 (*P*-value for trend: .289). There was an increasing proportion of males receiving TAVR during the study period with 49.9% males

Table I. Baseline characteristics of TAVR patients by calendar year

	2008-2010	2011-2013	2014-2016	2017-2020	Total
No.	393	860	1,516	3,328	6,097
Male (%)	196 (49.9)	441 (51.3)	813 (53.6)	1,911 (57.4)	3,361 (55.1)
Age (y), median [IQR]	82 [77-86]	82 [77-85]	82 [77-85]	81 [77-85]	81 [77-85]
Aged below 70 y	26 (6.6)	55 (6.4)	103 (6.8)	232 (7.0)	416 (6.8)
Living alone (%)	208 (53.2)	446 (51.9)	758 (50.2)	1,539 (46.8)	2,951 (48.5)
Missing (%)	2 (0.5)	1 (0.1)	6 (0.4)	7 (0.5)	16 (0.3)
Hospital length of stay (median [IQR])	9 [6-14]	7 [5-10]	5 [3-7]	3 [2-5]	4 [2-7]
Comorbidities, No. (%)					
Bioprosthetic aortic valve	5 (1.3)	18 (2.1)	39 (2.6)	89 (2.7)	151 (2.5)
Stroke/systemic embolism	62 (15.8)	123 (14.3)	220 (14.5)	436 (13.1)	841 (13.8)
Myocardial infarction	88 (22.4)	134 (15.6)	192 (12.7)	334 (10.0)	748 (12.3)
Ischemic heart disease	267 (67.9)	491 (57.1)	794 (52.4)	1,322 (39.7)	2,874 (47.1)
Heart failure	160 (40.7)	308 (35.8)	481 (31.7)	839 (25.2)	1,788 (29.3)
Peripheral artery disease	58 (14.8)	130 (15.1)	186 (12.3)	345 (10.4)	719 (11.8)
Previous PCI	133 (33.8)	209 (24.3)	361 (23.8)	458 (13.8)	1,161 (19.0)
Previous CABG	44 (11.2)	81 (9.4)	63 (4.2)	97 (2.9)	287 (4.7)
Atrial fibrillation	134 (34.1)	336 (39.1)	560 (36.9)	1,105 (33.2)	2,135 (35.0)
Pacemaker	29 (7.4)	71 (8.3)	130 (8.6)	217 (6.5)	447 (7.3)
Diabetes	56 (14.2)	161 (18.7)	293 (19.3)	638 (19.2)	1,148 (18.8)
Chronic kidney disease	47 (12.0)	95 (11.0)	177 (11.7)	305 (9.2)	624 (10.2)
Previous bleeding	106 (27.0)	224 (26.0)	362 (23.9)	656 (19.7)	1,347 (22.1)
Chronic obstructive pulmonary disease	63 (16.0)	147 (17.1)	231 (15.2)	415 (12.5)	856 (14.0)
Cancer	29 (7.4)	73 (8.5)	137 (9.0)	361 (10.8)	600 (9.8)
Hemoglobin mmol/L (median [IQR])	7.4 [6.7-8.0]	7.5 [6.7-8.2]	7.1 [6.4-7.9]	7.3 [6.6-8.1]	7.3 [6.5-8.1]
Missing	260 (66.2)	491 (57.1)	581 (38.3)	803 (24.1)	2,135 (35.0)
Creatinine μmol/L (median [IQR])	91 [71-112]	84 [69-110]	91 [74-115]	88 [72-110]	88 [72-111]
Missing	258 (65.6)	486 (56.5)	579 (38.2)	801 (24.1)	2,124 (34.8)
Albumin g/L (median [IQR])	40 [35-42]	41 [36-43]	36 [31-40]	36 [32-40]	36 [32-40]
Missing	316 (80.4)	635 (73.8)	702 (46.3)	1,092 (32.8)	2,745 (45.0)
Comedication, No. (%)					
Oral anticoagulant	82 (20.9)	261 (30.3)	505 (33.3)	1,162 (34.9)	2,010 (33.0)
ADP receptor antagonist	104 (26.5)	177 (20.6)	379 (25.0)	837 (25.2)	1,497 (24.6)
Non-steroidal anti-inflammatory drug	46 (11.7)	92 (10.7)	135 (8.9)	234 (7.0)	507 (8.3)
Beta-blockers	209 (53.2)	488 (56.7)	806 (53.2)	1,536 (46.2)	3,039 (49.8)
Statin	260 (66.2)	535 (62.2)	924 (60.9)	2,083 (62.6)	3,802 (62.4)
Calcium channel blockers	129 (32.8)	292 (34.0)	488 (32.2)	1,084 (32.6)	1,993 (32.7)
Renin-angiotensin system inhibitors	184 (46.8)	439 (51.0)	809 (53.4)	1,798 (54.0)	3,230 (53.0)
Diuretics	184 (46.8)	336 (39.1)	577 (38.1)	1,113 (33.4)	2,210 (36.2)

Abbreviations: ADP, adenosine diphosphate; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement.

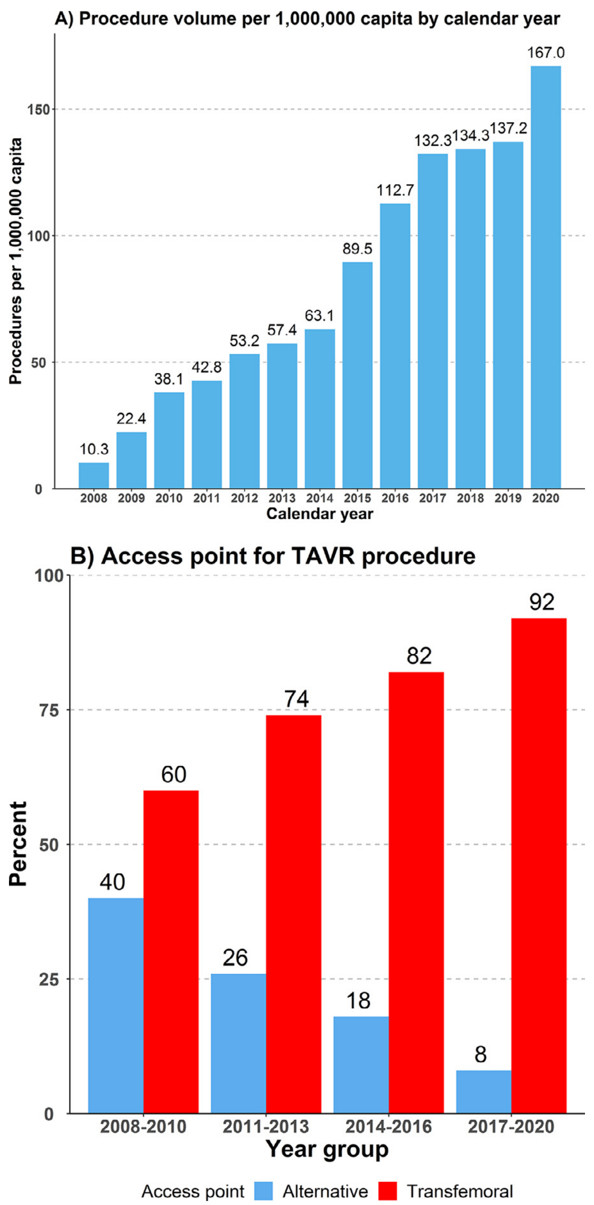
in 2008-2010 vs 57.4% in 2017-2020 (*P*-value for trend: <.001).

Figure 2 illustrates changes in selected patient comorbidities over time. Overall, cardiovascular comorbidity burden decreased among patients. Notably, the proportion of patients with a history of myocardial infarction decreased significantly from 22.4% in 2008-2010 to 10.0% in 2017-2020 (*P*-value for trend: <.001). A decrease was observed in the proportion of patients with a history of peripheral artery disease from 14.8% in 2008-2010 to 10.4% in 2017-2020 (*P*-value for trend: <.001). Lastly, a history of heart failure also decreased from 40.7% in 2008-2010 to 25.2% in 2017-2020 (*P*-value for trend: <.001). Consequently, significant decreases in revascularization procedures were observed (Figure 2). No clinically significant changes were observed for history of atrial fibrillation or previous pacemaker implantation (Figure 2).

Regarding non-cardiovascular diseases, there was a significant increase in patients with diabetes (2008-2010: 14.2% vs 2017-2018: 19.4%, *P*-value for trend: .030). A decrease in the proportion of patients with chronic obstructive pulmonary disease (COPD) was observed from 16.0% in 2008-2010 to 13.2% in 2017-2020 (*P*-value for trend: .003). For baseline blood sample values, there were no significant changes in hemoglobin and creatinine levels across year groups (hemoglobin *P*-value: .588, creatinine *P*-value: .503). However, there was a decrease in albumin levels across year groups (albumin *P*-value: <.001).

Ninety-day mortality after TAVR decreased with 36/393 (9.2%), 64/860 (7.4%), 54/1,516 (3.6%), and 113/3,328

Figure 1A and B,



Procedure volume and access point. Utilization of transcatheter aortic valve replacement showing TAVR penetration rate by calendar year and access site by calendar year. *TAVR*, transcatheter aortic valve replacement.

(3.4%) deaths in year groups 2008-2010, 2011-2013, 2014-2016, and 2017-2020, respectively.

Discussion

In this nationwide cohort study of unselected, first-time TAVR patients, the main findings can be summarized as: During the study period (i) TAVR penetration rate increased (ii) The proportion of males undergoing TAVR increased, while the age of patients remained stable. (iii) The proportion of patients with cardiovascular comorbidities and previous revascularization procedures decreased except for atrial fibrillation which remained stable. (iv) Hospital length of stay decreased and the proportion of transfemoral access increased.

Comparison with other registries

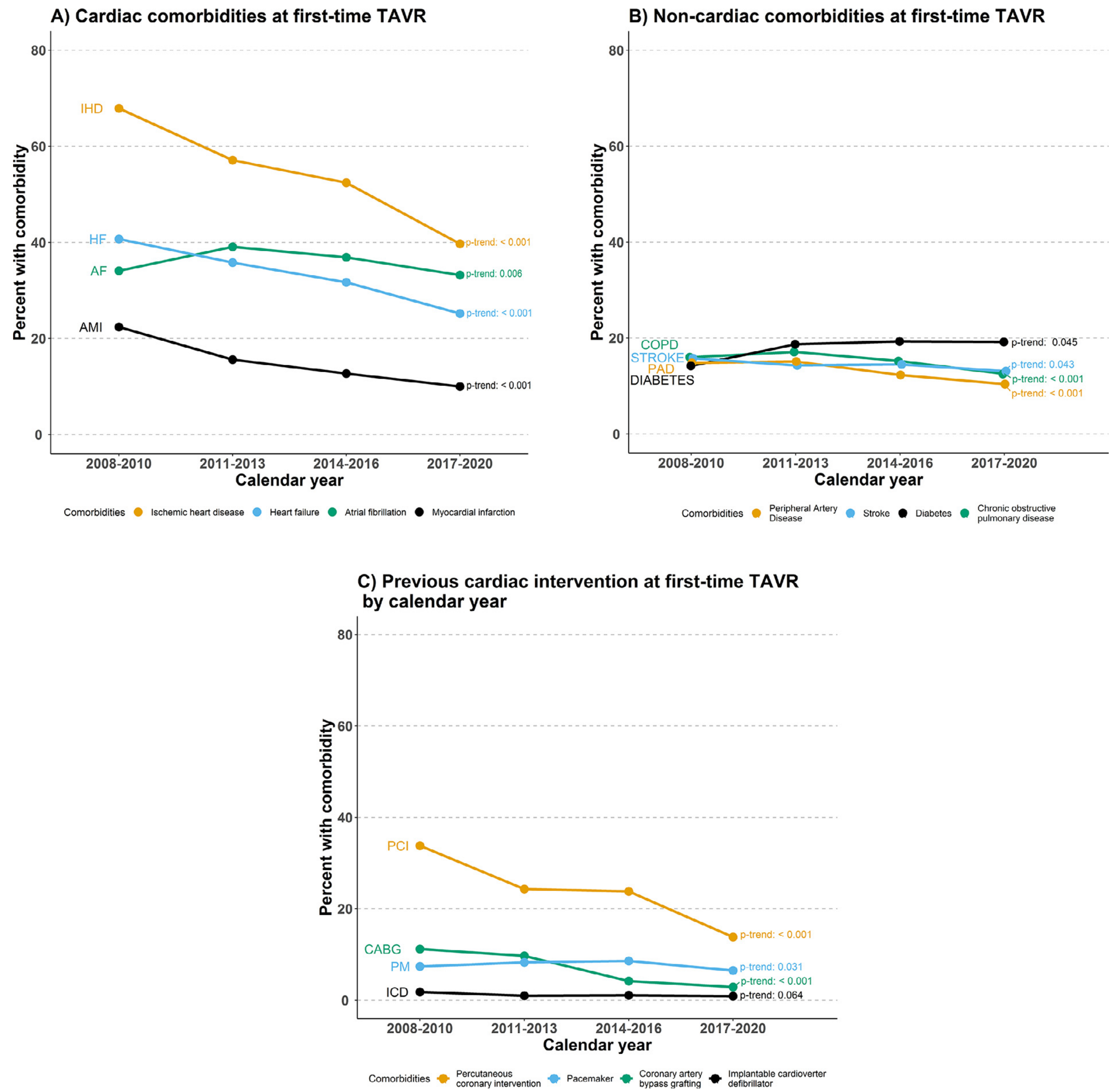
Other registers[12-17] have assessed trends in patient characteristics of TAVR patients, however, trends beyond year 2015 have only been sparsely investigated despite the publication of pivotal RCT studies evaluating TAVR vs SAVR in intermediate- and low-risk patients from 2015 to 2019.[5,6,8,9]

The marked increase in TAVR procedure volume is consistent with all other registries.[12-17] The UK TAVI registry recorded 3,980 total TAVR procedures with 2,9 procedures per 1,000,000 capita performed in 2007-2008 and 20.0 procedures per 1,000,000 capita in 2012.[15] Utilization in France also markedly increased with 21.3 procedures per 1,000,000 capita in 2010 (FRANCE 2) vs 64.6 procedures per 1,000,000 capita in 2015 (FRANCE TAVI).[12] The Swiss-TAVI registry recorded 26.2 procedures per 1,000,000 capita in 2011 vs 150.6 per 1,000,000 capita in 2015.[13] In Germany, there was a 20-fold increase between 2008 and 2014.[16] Lastly, although the STS/ACC TVT could not report exact numbers of TAVR procedures citing regulatory concerns of TAVR procedures performed as part of investigational trials, 14.6 procedures per 1,000,000 capita were recorded in 2012 compared to 222.4 per 1,000,000 capita in 2019.[17] We only included first-time TAVR procedures and the total number of TAVR procedures in Denmark is therefore slightly higher than what we report. Further increases in utilization is likely even for areas with a current high utilization rate as TAVR is now an acceptable option across all surgical risk groups and new indications may be on the horizon.[24,25]

A decreased hospital length of stay was observed during our study period. Similar results have been reported from Germany.[16] However, as stated in a previous reply, only data from 1 hospital stay was reported in Germany and transfers to another hospital due to complications is not reflected in the total hospital length of stay.[26] Compared to the respective time periods evaluated in the UK TAVI registry, FRANCE 2 and FRACE TAVI registry and STS/ACC TVT registry, the hospital length of stay was either similar or slightly shorter in our study population.

We found a year-by-year increase in transfemoral approach and decrease in alternative accesses. While the offset percentage of 60% being performed with a transfemoral access in 2008-2010 in our study was lower compared to other studies, a trend toward increased use of transfemoral sheath access was reported in Germany (transfemoral in 2011: 63.3% vs 2014: 77.7%) and

Figure 2A-C



Comorbidity burden at first time TAVR. Percentage of patients with a medical history of comorbidities and previous cardiac intervention by calendar year. *P*-values are provided from the Cochrane-Armitage trend test. *TAVR*, transcatheter aortic valve replacement.

France (transfemoral in 2010: 75.2% vs 2015: 83.0%).[12,16] Other registries report minor year-by-year increases and decreases in the percentage of transfemoral TAVR procedures, however, in all studies the transfemoral access strategy was the most common (UK TAVI, 76.1% in 2012; STS/ACC TVT registry, 95.3% in 2019; Swiss-TAVI, 92.1% in 2015).[13,15,17]

In our study, the proportion of patients with ischemic heart disease, prior myocardial infarction, heart failure, and peripheral artery disease decreased reflecting the transition toward treating lower risk patients. Interestingly, only the UK TAVI registry did not report changes in these comorbidities nor overall Logistic EuroSCORE.[15] In the Swiss-TAVI registry, only the proportion of patients with COPD decreased, but patients trended toward lower STS-PROM scores.[13]

The importance of study periods becomes apparent when considering comorbidity burdens; In the evaluated time periods of the respective registries, only results from the high-risk RCT trials were available except for the STS/ACC TVT registry. Interestingly, overall median age decreased from 84 years from ≤2013 to 80 years in 2019, while median STS-score decreased from 6.91 to 4.38 in the same period.[17] It is also reported that the proportion of males undergoing TAVR increased from 48.9% from ≤2013 to 55.8% in 2019 which is consistent with findings from our study. The study reported different comorbidities compared to our study making further comparisons of patient characteristics difficult.

Over time, 90-day survival increased among patients. Although survival/mortality was evaluated at different timepoints for the registers making direct comparisons difficult, all studies reported increased survival throughout the respective study periods. The lesser comorbidity burden of patients, improvements to procedural devices, and increased operator experience over time may all influence the results.

Trial patients vs patients in everyday clinical practice

The PARTNER 1A study was published in June 2011.[3] In the TAVR arm, the median age was 84 years compared to 82 years in the 2011-2013 group in our study. The proportion of male sex was 57.8% in PARTNER 1A and 51.3% in our study. Overall, patients had a higher comorbidity burden in the PARTNER 1A with a higher proportion of patients with a history of coronary artery disease (PARTNER 1A: 74.9% vs our study: 57.1%), previous myocardial infarction (PARTNER 1A: 26.8% vs our study: 15.6%), peripheral artery disease (PARTNER 1A: 43.0% vs our study: 15.1%), and COPD (PARTNER 1A: 43.4% vs our study: 17.1%), while atrial fibrillation was similar (PARTNER 1A: 40.8% vs our study: 39.1%). The US CoreValve High Risk trial was published in 2014.[4] When comparing patients in the TAVR arm to patients in this study in the 2014-2016 group, the mean age of patients in the trial was 83 years compared to a median age of 82 years in our study. The proportion of male sex was 53.6% in the trial and 53.6% in our study. Again, trial patients had a higher comorbidity burden when compared to patients in our study (coronary artery disease, trial 75.4% vs our study 52.4%; previous myocardial infarction, trial 25.6% vs our study 12.7%; peripheral artery disease, trial 41.7% vs our study 12.3%; diabetes, trial 34.5% vs our study 19.3%). Some of these differences might be explained by underreporting in the registers used in our study.

The NOTION trial published in 2015 was the first trial enrolling patients at lower operative risk.[7] When comparing patients in the TAVR arm to patients in this study in the 2017-2020 group, NOTION patients were younger (NOTION mean age 79 years vs our study median age 81 years) while sex composition were clinically similar (NOTION 54% males vs our study 57.4%). NOTION patients had a lower comorbidity burden when compared to patients in our study with a lower proportion of patients with a history of myocardial infarction (NOTION: 5.5% vs our study 10.0%), peripheral artery disease (NOTION 4.1% vs our study 10.4%), and atrial fibrillation/flutter (NOTION 27.8% vs our study 33.2%). Patients were clinically similar regarding history of COPD (NOTION 11.7% vs our study 12.5%). However, the similarities of patients in the NOTION trial and patients in our study can be partially explained by the inclusion of patients represented in both the NOTION trial and our study as the NOTION trial included patients from Denmark and Sweden. The impact of the findings from the NOTION trial on clinical practice patterns in Denmark might explain, why patients in the intermediate risk trials (PARTNER 2A published 2016[5] and SURTAVI published 2017[6]) had a higher comorbidity burden than patients in our study in the 2017-2020 group.

More data are required to evaluate the impact of the PARTNER 3A trial and the Evolut Low Risk trial both published in May 2019.[8,9] As such, the transition to treat unselected low-risk patients with longer life-expectancy remains to be implemented in clinical practice. This highlights the need to monitor trends in patient characteristics and outcomes of unselected TAVR patients.

Limitations

Data on New York Heart Association and Canadian Cardiovascular Society scores were not available which could have provided insights in symptomatic trends of patients. Smoking habits, body mass index, and clinical measures of frailty were not available. Further, preprocedural echocardiography results were not available and trends in valve type could not be assessed. Information on surgical risk scores were unavailable in the registers used. Not all patients had an available sample for hemoglobin, creatinine, and albumin values with high proportions of missing data in early calendar years and the values in these groups may not be representative of all patients.

Conclusion

In this nationwide study, there was a significant year-by-year increase in the utilization of TAVR. Patients had a decreasing comorbidity burden most noticeable for cardiovascular comorbidities, while the age of patients at TAVR remained stable. Thus, despite expanding to patients at lower surgical risk, TAVR is still mainly offered to elderly patients with limited life-expectancy. Future studies should continue to evaluate when younger, low-risk patients are treated in everyday clinical practice and examine their characteristics.

Ethics

The present study was approved by the data responsible institution, Capital Region. We refer to approval number P-2019-191. In Denmark, retrospective registry-based cohort studies do not require further approval from the Research Ethics Committee System.

Funding

No extramural funding was used to support this work.

Disclosures

CTP: Grants from Bayer and Novo Nordisk not related to current study. ELF: Independent research grant from Novo Nordisk Foundation. LK: Speakers honorarium from Novartis, Novo, Boehringer and AstraZeneca. LS: Consultant fees and/or institutional research grants from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, SMT and Symetis. JBO: Speaker honoraria or consultancy fees from Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Novartis Healthcare, and Novo Nordisk. The other authors declare that they have no conflicts of interest relevant to the content of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2021.09.010.

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