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Impact of first-time detected atrial fibrillation after transcatheter aortic valve replacement: A nationwide study

Jeppe Kofoed Petersen [a,*,1], Emil Loldrup Fosbøl [a,1], Jarl Emanuel Strange [a,1], Morten Schou [b,1], Daniel Alexander Brems [a,1], Lars Køber [a,1], Lauge Østergaard [a,1]

[a] Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark
[b] Department of Cardiology, Herlev and Gentofte University Hospital, Copenhagen, Denmark

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ABSTRACT

Background: The prognostic implications of new-onset atrial fibrillation (AF) in conjunction with transcatheter aortic valve replacement (TAVR) is sparsely examined. Therefore, we aimed to examine the impact of first-time detected AF after TAVR on all-cause mortality and heart failure (HF).

Methods: With Danish nationwide data from 2008 to 2021, we identified all patients who underwent TAVR and were alive 30 days after discharge (index date). Patients were categorized into i) no AF; ii) history of AF; and iii) first-time detected AF within 30 days after discharge. From the index date, two-year rates of all-cause mortality and HF admissions were compared using multivariable adjusted Cox analysis.

Results: We identified 6,807 patients surviving 30 days beyond TAVR: 4,229 (62.1%) without AF (55% male, median age 81), 2,283 (33.6%) with history of AF (58% male, median age 82), and 291 (4.3%) with first-time detected AF (56% male, median age 81). Compared with patients without AF, adjusted analysis yielded increased associated hazard ratio (HR) of all-cause mortality in patients with history of AF (1.53 [95% confidence interval [CI], 1.32–1.77]) and in patients with first-time detected AF (2.06 (95%CI, 1.55–2.73]). Further, we observed increased associated HRs of HF admissions in patients with history of AF (1.70 [95%CI, 1.45–1.99]) and in patients with first-time detected AF (1.77 [95%CI, 1.25–2.50]).

Conclusion: In TAVR patients surviving 30 days beyond discharge, first-time detected AF appeared to be at least as strongly associated with two-year rates of all-cause mortality and HF admissions, as compared with patients with history of AF.

1. Introduction

Transcatheter aortic valve replacement (TAVR) is a well-established treatment intervention in patients with symptomatic, severe aortic stenosis,[1] and recent clinical trials have expanded the indication from elderly high-risk patients by showing benefit also in elderly patients with low surgical risk score.[2,3] As the number of TAVR procedures are increasing, [2,4–6] the risk of complications such as new-onset atrial fibrillation (AF) needs further investigation. Within 30 days of TAVR procedure, The Placement of Aortic Transcatheter Valves (PARTNER) trials have observed new-onset AF ranging from 0.6% to 9.1%.[2,7–9] These estimates have been extended in observational studies with new-onset AF rates of up to 50%.[10–14] While AF is a well-known risk factor for death and the development of heart failure (HF),[15,16] the impact of new-onset AF in conjunction with TAVR on the risk of mortality and HF is sparsely examined, and studies on the matter are mostly conducted on selected patient cohorts with highly heterogeneous estimates on both incidence and outcome measures.[10–13,17–21].

The present study examined the association between periprocedural AF in TAVR and the two-year risk of all-cause mortality and admission with HF.

2. Methods

2.1. Data sources

All Danish citizens are assigned a unique personal registration number, which enables linkage between administrative Danish

* Corresponding author at: Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 København Ø, Denmark.
E-mail address: jeppe.kofoed.petersen@regionh.dk (J.K. Petersen).
[1] This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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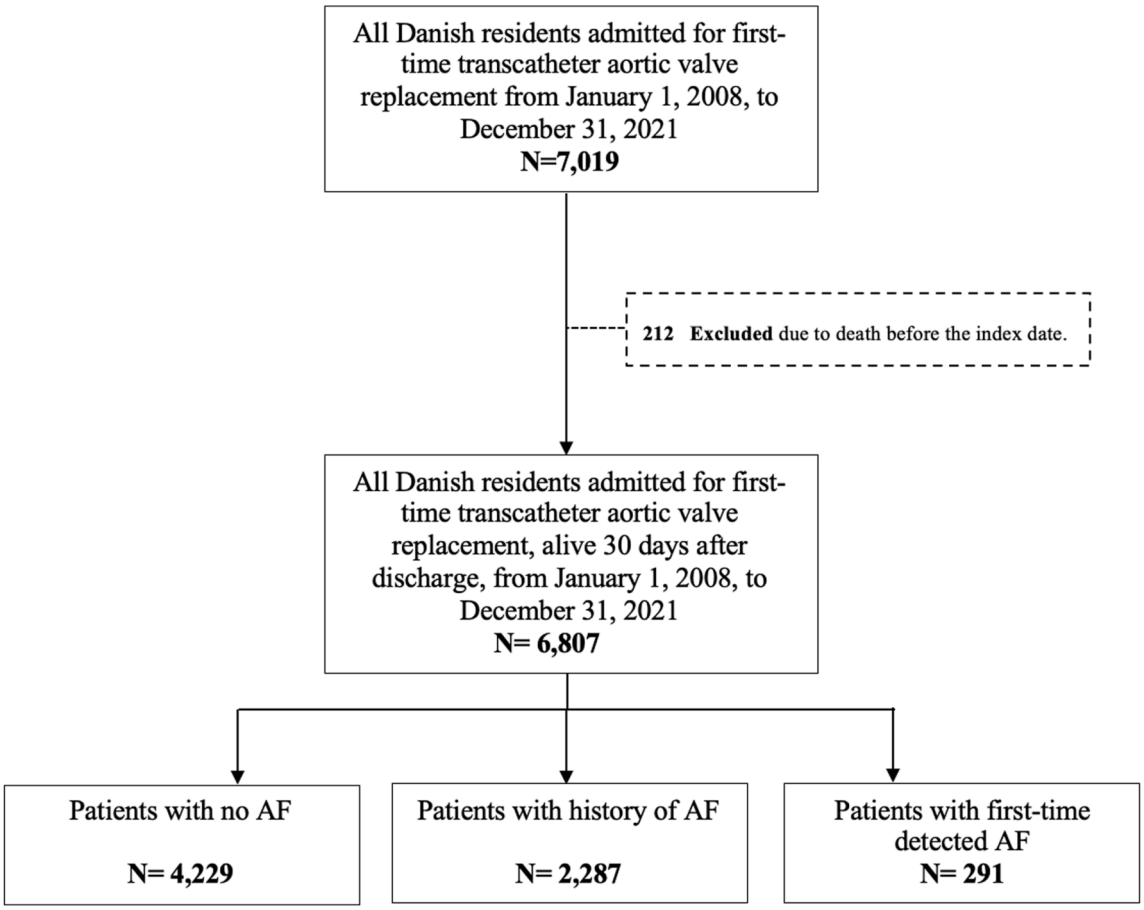

Fig. 1. Flow chart.

registries and clinical registries on a nationwide basis. Tax-financed healthcare is provided to all Danish citizens. This study used the following registries: 1) The Danish National Patient Registry (DNPR), which holds records on all hospital admissions since 1977 and outpatient visits since 1995, with discharge diagnoses based on the International Classification of Diseases (ICD) (ICD-8 and ICD-10 codes) and surgical procedures classified according to The Nordic Medico-Statistical Committee since 1996; [22] 2) The Civil Registration System, which holds information on sex, vital-status, migration, and birth date;[23] 3) The Danish National Prescription Registry, which keeps records on all claimed drug prescriptions since 1995;[24] 4) The Danish Registry of Causes of Death, which contains information about the date of death.[25].

2.2. Study population

From January 1, 2008, to December 31, 2021 we identified all patients with first time admission for TAVR (Procedure code: KFMD11, KMFD12, and KMFD14). The population was grouped into: 1) Patients without AF (ICD-8 codes: 42,793 and 42794; ICD-10 code: I48) prior to or within 30 days after TAVR, 2) patients with history of AF, and 3) patients with first-time detected AF between TAVR admission date and 30 days after discharge. In line with the Valve Academic Research Consortium 3 (VARC-3) definition of periprocedural AF,[26] first-time detected AF was determined as a diagnosis code of AF within 30 days after the TAVR procedure with no prior history of AF. The diagnosis code of AF has previously been validated with a positive predictive value (PPV) of 95%.[27].

2.3. Covariates

Patients' medical history was defined as a primary or secondary inpatient or outpatient diagnosis code given any time prior to the admission date (Supplementary Table 1 for ICD diagnosis codes) with the exceptions of hypertension and diabetes, which were identified using claimed drug prescriptions as described previously.[28,29] Pharmacotherapy was defined by claimed prescriptions within six months prior to the admission date (Supplementary Table 2 for Anatomical Therapeutic Chemical Classification System codes).

2.4. Outcomes and follow-up

The primary outcome was all-cause mortality. The secondary outcome was hospital admissions with a diagnosis of heart failure (HF) (ICD-10 codes: I50, I110, I130, I132). The HF diagnosis code has previously been validated with a PPV of 76–81% for inpatients.[27 30] Patients were followed from the index date (index date being 30 days after the date of discharge) until the date of the respective outcomes, a maximum of two years of follow-up, or 31 December 2021, whichever came first.

2.5. Statistics

Patient characteristics were presented as counts and percentages for categorial variables and medians with interquartile ranges (IQRs) for continuous variables. Absolute risks of all-cause mortality were estimated using the Kaplan-Meier estimator, and crude differences between groups were assessed using the log-rank test. Absolute risks of HF admissions were estimated using the Aalen-Johansen estimator, taking the

Table 1
Baseline characteristics.

	No AF N = 4,229	History of AF N = 2,287	First-time detected AF N = 291
Demographics			
Male, N (%)	2303 (54.5)	1317 (57.6)	163 (56.0)
Age, median years [IQR]	81.1 [76.3–84.9]	81.9 [77.6–85.3]	81.3 [76.6–85.0]
Calendar period, N (%)			
2000–2005	507 (12.0)	287 (12.6)	69 (23.7)
2006–2011	1495 (35.4)	906 (39.6)	118 (40.6)
2012–2017	2227 (52.7)	1094 (47.8)	104 (35.7)
TAVR modality, N (%)			
Transapical	353 (8.4)	262 (11.5)	69 (23.7)
Ministernotomy	130 (3.0)	64 (2.7)	10 (3.4)
Transfemoral	3746 (88.6)	1961 (85.8)	212 (72.9)
During admission for TAVR			
Pacemaker implantation, N (%)	488 (11.5)	263 (11.5)	47 (16.2)
Admission time, median days [IQR]	5 [3–8]	6 [2–8]	11 [2,6–18]
Medical history prior to the index date*, N (%)			
HAS-BLED, Median [IQR]	3 [2,3]	3 [2,3]	3 [2,3]
CHA_2DS_2-VASc, Median [IQR]	4 [3–5]	5 [4–6]	4 [3–5]
Hypertension	2780 (65.7)	1877 (82.1)	214 (73.5)
Myocardial infarction	700 (16.6)	434 (19.0)	44 (15.1)
Chronic heart failure	927 (21.9)	900 (39.4)	72 (24.7)
Permanent pacemaker	254 (6.0)	339 (14.8)	17 (5.8)
CABG	393 (9.3)	230 (10.0)	28 (9.6)
PCI	977 (23.1)	546 (23.9)	55 (18.9)
Stroke (ischemic/ hemorrhagic)	508 (12.0)	367 (16.1)	35 (12.0)
Diabetes	765 (18.1)	494 (21.6)	47 (16.2)
Peripheral artery disease	299 (7.1)	193 (8.4)	20 (6.9)
Chronic kidney disease	372 (8.8)	287 (12.6)	23 (7.9)
Malignancy	942 (22.3)	485 (21.2)	48 (16.5)
Liver disease	130 (3.1)	69 (3.0)	6 (1.7)
COPD	593 (14.0)	388 (17.0)	36 (12.4)
Pharmacotherapy six months prior to the index date*, N (%)			
Statins	2760 (65.3)	1419 (62.1)	175 (60.1)
Beta blockers	1617 (38.2)	1561 (68.3)	147 (50.5)
Loop diuretics	1841 (43.5)	1500 (65.6)	146 (50.2)
Calcium channel blockers	1421 (33.6)	738 (32.3)	193 (33.7)
RAS inhibitors	2289 (54.1)	1261 (55.1)	152 (52.2)
Aspirin	2305 (54.5)	620 (27.1)	142 (48.8)
$P2Y_{12}$ inhibitors	1176 (27.8)	387 (16.9)	64 (22.0)
OAC	296 (7.0)	1868 (81.7)	77 (26.5)

Abbreviations: AF: Atrial fibrillation; IQR: Interquartile range; TAVR: Transcatheter aortic valve replacement; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention; COPD: Chronic obstructive pulmonary disease; RAS: Renin angiotensin system; MRA: Mineralocorticoid receptor antagonists, OAC: Oral anticoagulants.
***Index date:** 30 days after TAVR discharge.

competing risk of death into account, and crude differences between groups were assessed using Gray's test. Cause-specific Cox regression models were used to compare the rates of outcomes between groups, and results were reported with hazard ratios (HRs) and 95% confidence intervals (CI). The models were adjusted for comorbidities assessed relevant for the respective outcomes. The model examining mortality included the following covariates: age, sex, calendar year, diabetes, hypertension, chronic HF, myocardial infarction, chronic kidney disease, malignancy, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, and prior stroke. The model examining HF admissions included the same covariates as the aforementioned with the exception of COPD and stroke. The group without AF served as reference in all models. The assumption of proportional hazards were investigated using Martingale's residuals and reported if violated. Age and calendar year were included as continuous variables in the regression analysis as they fulfilled the criteria of linearity. Sex and age were tested as effect modifiers of AF on the main outcome, showing no interaction ($p > 0.05$). All statistical analyses were performed using the SAS statistical software (version 9.4,Cary, NC, USA) and R (version 3.6.1 The R Foundation, Vienna,Austria). Level of statistical significance were recognized by a P-value < 0.05.

2.5.1. Sensitivity and subgroup analyses

To test the robustness of our findings, three supplementary analyses were conducted. First, to test the difference between AF groups, history of AF was considered the reference group in adjusted models when examining the two-year rates of outcomes. Second, we examined a cohort only including patients with transfemoral TAVR (procedure code: KFMD14). Third, we examined the associated two-year rate of HF hospitalizations after excluding all patients with known chronic HF.

2.6. Ethics

In Denmark registry-based studies that are conducted for the sole purpose of statistics and scientific research do not require ethical approval or informed consent by law. However, the study is approved by the data responsible institute (Capital Region of Denmark – Approval number: P-2019–191) in accordance with the General Data Protection Regulation (GDPR).

3. Results

3.1. Study population and baseline characteristics

Between January 1, 2008, and December 31, 2021, we identified 6,807 patients who survived 30 days beyond their first-time TAVR admission (Fig. 1 illustrates the study population selection). Of these patients, 4,229 (62.1%) had no AF (54.5% male, median age 81, IQR 76–85), 2,287 (33.6%) had a history of AF (57.6% male, median age 82, IQR 78–85), and 291 (4.3%) presented with first-time detected AF within 30 days after TAVR (56.0% male, median age 80, IQR 74–85) (Table 1). In patients with a history of AF, the median time from their first AF diagnosis to TAVR admission was 4.46 years (IQR 0.96 – 10.22). Overall, patients with history of AF presented with the highest proportions of comorbidities (Table 1). Patients with first-time detected AF more commonly received TAVR by transapical access and generally had longer admission times (median days 11, IQR 6–19) compared with patients without AF (median days 5, IQR 3–8) and history of AF (median days 6, IQR 3–9).

3.2. All-cause mortality

The cumulative two-year incidence of all-cause mortality was 8.8%, 19.0%, and 20.6% for patients without AF, patients with history of AF, and patients with first-time detected AF, respectively (crude $p < 0.001$ for difference) (Fig. 2). Compared with patients without AF, adjusted analysis yielded an increased associated rate of all-cause mortality in patients with history of AF (HR 1.53 [95% CI, 1.32–1.77]) and in patients with first-time detected AF (HR 2.06 [95% CI, 1.55–2.73]) (Fig. 3).

3.3. Heart failure admission

The cumulative two-year incidence of hospital admission with HF was 5.7%, 18.6%, and 13.7% for patients without AF, patients with history of AF, and patients with first-time detected AF, respectively (crude $p < 0.001$ for difference) (Fig. 4). Compared with patients without AF, adjusted analysis yielded an increased associated rate of HF admissions in patients with history of AF (HR 1.70 [95% CI, 1.45–1.99]) and in patients with first-time detected AF (HR 1.77 [95% CI, 1.25–2.50]) (Fig. 3).

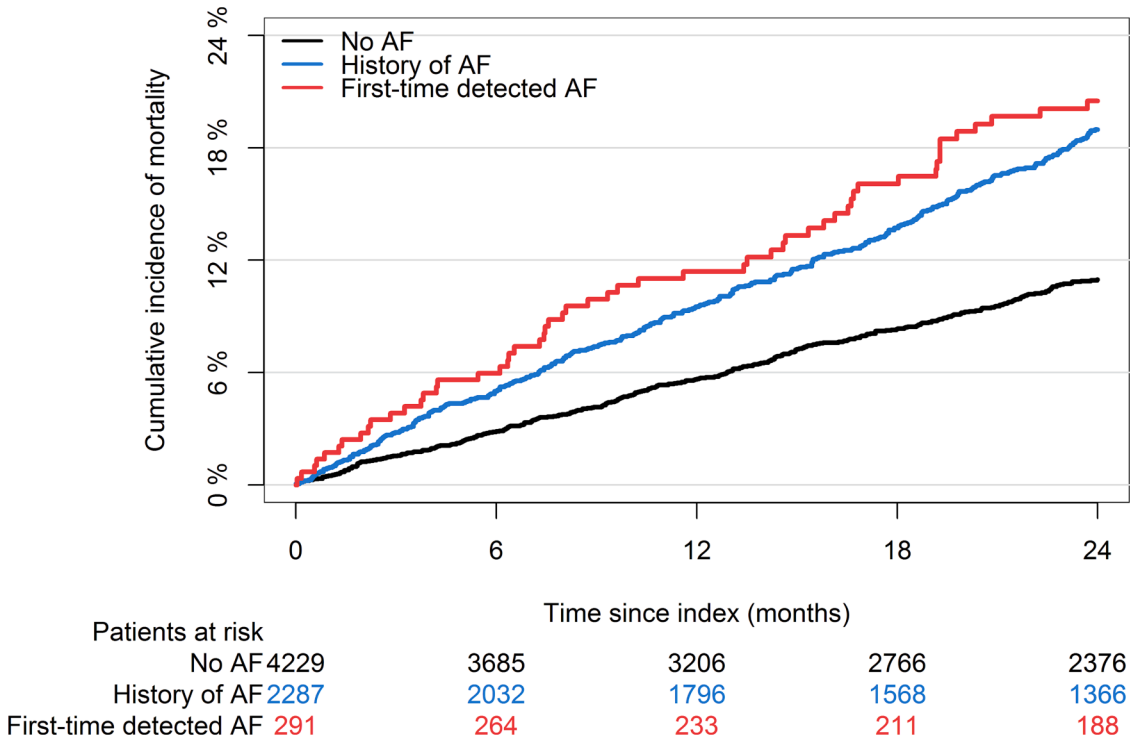

Fig. 2. Two-year cumulative incidence of all-cause mortality This figure shows the two-year cumulative incidence of all-cause mortality in patients undergoing transcatheter aortic valve replacement (TAVR) and no atrial fibrillation (AF), history of AF, and first-time detected AF, with follow-up starting 30 days after TAVR discharge.

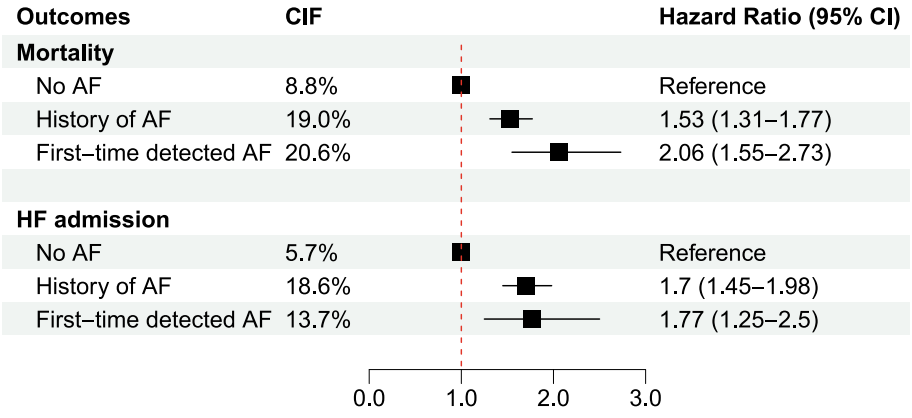

Fig. 3. Forest plot of two-year outcome rates This figure shows the two-year cumulative incidence frequencies (CIF) and adjusted hazard ratios of all-cause mortality and heart failure (HF) admission according to study groups. The model examining mortality included the following covariates: age, sex, calendar year, diabetes, hypertension, chronic HF, myocardial infarction, chronic kidney disease, malignancy, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, and prior stroke. The model examining HF admissions included the same covariates as the aforementioned except for COPD and stroke.

3.4. Sensitivity and subgroup analyses

Three supplementary analyses were performed. First, when patients with history of AF were considered the reference group in adjusted models, first-time detected AF showed an increased associated hazard of mortality [1.35 (95% CI 1.01–1.80)] and a statistically insignificant difference for HF admission [1.04 (95% CI 0.74–1.47)] (Supplementary Fig. 1). Second, when examining patients undergoing transfemoral TAVR only, we included 5,919 subjects: 3,746 (63.3%) without AF, 1,961 (33.1%) with history of AF, and 212 (3.6%) with first-time detected AF. In this subgroup, the outcomes rates were similar as compared with the results of the main analyses (Supplementary Fig. 2). Third, after excluding those with a previous diagnosis of chronic HF we identified 4,908 patients: 3,302 (67.3%) without AF, 1,387 (28.3%) with history of AF, and 219 (4.5%) with first-time detected AF. In this subgroup, we observed an increased associated rate of incident HF-admission in patients with history of AF (HR 2.09 [95% CI, 1.64–2.66]) and in patients with first-time detected AF (2.08 [95% CI, 1.29–3.35]) compared with patients without AF.

4. Discussion

In this nationwide cohort study, we examined the impact of first-time detected AF after TAVR on the two-year rate of all-cause mortality and HF admission. The study had two main findings: First, around 4% of patients undergoing TAVR were diagnosed with first-time detected AF within 30 days, which appeared to be at least as strongly, or even higher, associated with all-cause mortality compared with a history of previous AF. Second, first-time detected AF carried an increased associated rate of HF that appeared similar as of that in patients with history of AF. This analysis remained robust for incident HF as well.

Previous studies on the impact of new-onset AF after TAVR on the risk of mortality has presented conflicting results. In a post-hoc analysis on the PARTNER 3 trial, including patients at low surgical risk, early-

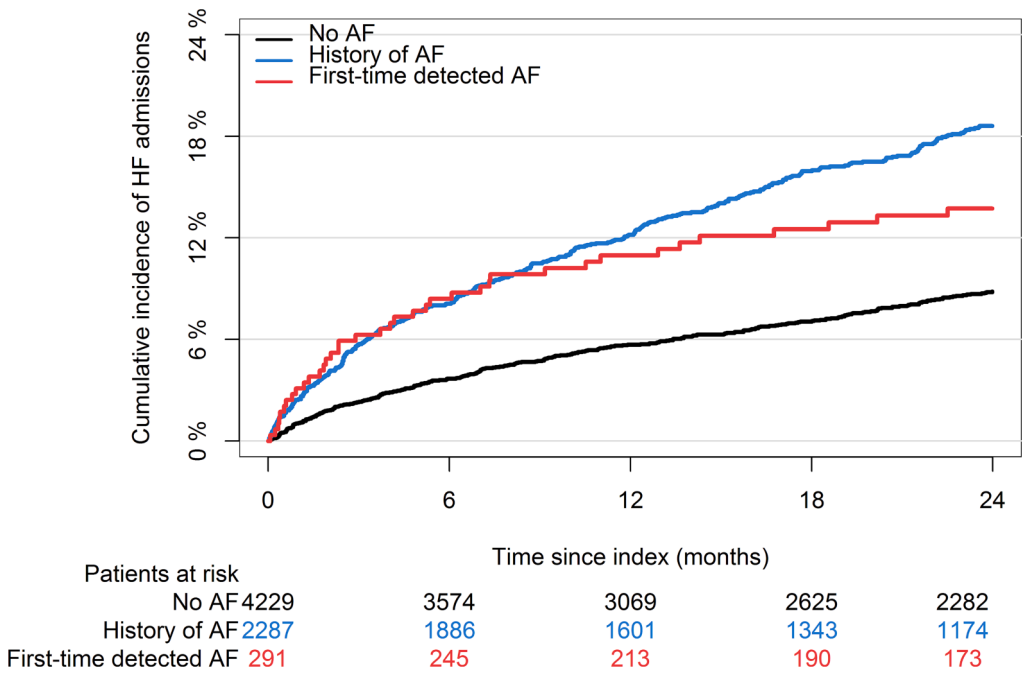

Fig. 4. Two-year cumulative incidence of admissions with heart failure This figure shows the two-year cumulative incidence of admissions for heart failure in patients undergoing transcatheter aortic valve replacement (TAVR) and no atrial fibrillation (AF), history of AF, and first-time detected AF, with follow-up starting 30 days after TAVR discharge.

onset postoperative AF (i.e., new-onset AF within 30 days of TAVR) yielded no significantly increased associated two-year risk of mortality (HR 1.03).[31] These findings, however, should be interpreted in light of the low surgical risk profile of the PARTNER 3 study cohort, which is hardly comparable to a nationwide cohort of TAVR patients enrolled during a>10 year time span. In contrast, cohort studies have identified increased risk of mortality in patients with new-onset AF after TAVR compared with patients without AF: one showed significantly increased risk of in-hospital mortality [odds ratio 1.57],[10] two studies found significantly increased one-year risk of mortality [HR 1.37–1.96],[12,13] and one yielded increased risk of two-year mortality [HR 2.06].[11] Only two of the aforementioned studies, however, included history of AF, and when comparing these with patients with first-time detected AF, one study identified no difference between groups [p = 0.22],[12] while the other observed a significantly increased hazard in patients with first-time detected AF [HR 1.35].[11] In accordance with previous findings, our data yielded an increased associated rate of mortality with a maximum of two years of follow-up in patients with first-time detected AF [HR 2.06]. Furthermore, compared with patients with a history of AF, our results demonstrate a higher associated rate of mortality in patient with first-time detected AF [HR 1.35]. These associations were substantial, even after adjustments for factors known to be associated with adverse outcomes, and the findings were consistent, irrespective of sex and calendar year ($p > 0.05$ for interaction). Notably, new AF in relation to a TAVR procedure may have occurred second to an unregistered precipitant (e.g., acute kidney injury, infection, etc.), that may have shifted the results towards an increased risk of mortality in this patient subgroup, causing a potential unregistered confounder. Overall, these results add to the sparse evidence on this matter and demonstrate the severity of first-time detected AF in patients with TAVR which should be taken into consideration in the clinical assessment of this patient subgroup.

Only one prior study has examined the risk of HF admissions in patients with first-time detected AF after TAVR.[11] This study reported increased adjusted risk of HF in patients with first-time detected AF compared with patients with history of AF and patients without AF. Our data identified that patients with first-time detected AF carry a higher associated rate of HF admissions relative to no AF [HR 1.77] but similar rate relative to history of AF [HR 1.04]. While causality between the risk of HF admissions and type of AF (i.e., history of AF and first-time detected AF) cannot be established in the context of the study design, our results contribute to the sparse knowledge on this matter and further emphasize the need for increased awareness in this high-risk group of patients. Further, there is merit in developing clinical risk prediction models for outcomes such as congestive HF; particularly given our relative and absolute risk estimates.

5. Strengths and limitations

The main strength of this study is the completeness of data, extracted from a nationwide Danish cohort with no loss to follow-up. The Danish registries have been extensively validated, providing a valid source of data, and both exposure and outcome variables hold high PPVs.[27,30,32].

Our study has some limitations. First, this is an observational study and therefore precludes that any causal inference can be made; thus, only associative conclusions can be drawn. Second, new-onset AF has been reported with highly variable estimates after TAVR, ranging from 0.6 to 50% following a TAVR procedure.[2,7–13] In the present study, estimates of first-time detected AF was infrequent (2.5%), however still within the ranges of previous findings. Speculations on these variations include the clinical significance and symptom burden of AF, which may influence hospital coding, rhythm-monitoring techniques, and criteria of diagnosis changing over the course of time. Further, our data cannot distinguish new-onset AF (i.e., AF developed secondary to TAVR) from first-time detected AF (i.e., patients with AF prior to TAVR admission but with first-time diagnosis). However, patients undergoing TAVR usually undergo extensive diagnostic work-up prior to TAVR and it is therefore unlikely that patients with first-time detected AF would have had an extensive burden of AF prior to TAVR admission. Third, data on critical clinical variables such as electrocardiogram, echocardiography, data on atrial size (to help distinguish timing of AF onset), smoking, and body mass index were not available. Likewise, data on type and duration of AF (paroxysmal or chronic AF), the accurate timing of AF onset (i.e.,

AF secondary to TAVR or existing, undiagnosed AF), and the burden of AF could not be determined.

6. Conclusions

In patients undergoing TAVR surviving 30 days beyond discharge, first-time detected AF was identified in about 3% of patients and appeared to be at least as strongly, or even more strongly, associated with two-year rates of all-cause mortality, as compared with patients with history of AF. Both history of AF and first-time detected AF carried an increased associated rate of HF admission compared with patients without AF. These findings illuminate a high-risk group of patients and emphasize the need for increased awareness and further research.

Conflicts of interest

Emil Loldrup Fosbøl: Independent research grant from Novo Nordisk Foundation.

Lars Køber: Speaker's honorarium from Bayer, Novatis, AstraZeneca, and Boehringer.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2023.101239.

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