3-14-2023

Adverse Outcomes of Atrial Fibrillation Ablation in Heart Failure Patients With and Without Cardiac Amyloidosis: A Nationwide Readmissions Database Analysis (2015-2019)

Waqas Ullah
Thomas Jefferson University Hospitals

Max Ruge, MD
Thomas Jefferson University Hospitals

Alexander G. Hajduczok
Thomas Jefferson University Hospitals

Kirpal Kochar
Thomas Jefferson University Hospitals

Daniel R. Frisch
Thomas Jefferson University Hospitals

See next page for additional authors

Recommended Citation

Ullah, Waqas; Ruge, MD, Max; Hajduczok, Alexander G.; Kochar, Kirpal; Frisch, Daniel R.; Pavri, Behzad B.; Alvarez, René J; Rajapreyar, Indranee N.; and Brailovsky, Yevgeniy, "Adverse Outcomes of Atrial Fibrillation Ablation in Heart Failure Patients With and Without Cardiac Amyloidosis: A Nationwide Readmissions Database Analysis (2015-2019)" (2023). *Jefferson Hospital Staff Papers and Presentations.* Paper 26.
https://jdc.jefferson.edu/tjuhpapers/26

Authors

Waqas Ullah; Max Ruge, MD; Alexander G. Hajduczok; Kirpal Kochar; Daniel R. Frisch; Behzad B. Pavri; René J Alvarez; Indranee N. Rajapreyar; and Yevgeniy Brailovsky

European Heart Journal Open (2023) **3**, 1–10
https://doi.org/10.1093/ehjopen/oead026

ORIGINAL ARTICLE
Arrhythmia and electrophysiology

Adverse outcomes of atrial fibrillation ablation in heart failure patients with and without cardiac amyloidosis: a Nationwide Readmissions Database analysis (2015–2019)

Waqas Ullah *, Max Ruge, Alexander G. Hajduczok, Kirpal Kochar, Daniel R. Frisch, Behzad B. Pavri, Rene Alvarez, Indranee N. Rajapreyar, and Yevgeniy Brailovsky

Thomas Jefferson University Hospitals, 1100 11th Street, Philadelphia, PA 19107, USA

Received 23 November 2022; revised 22 January 2023; accepted 8 March 2023; online publish-ahead-of-print 14 March 2023

Handling Editor: Christian de Chillou

Editorial for this article: Eur Heart J Open 2023; https://doi.org/10.1093/ehjopen/oead027

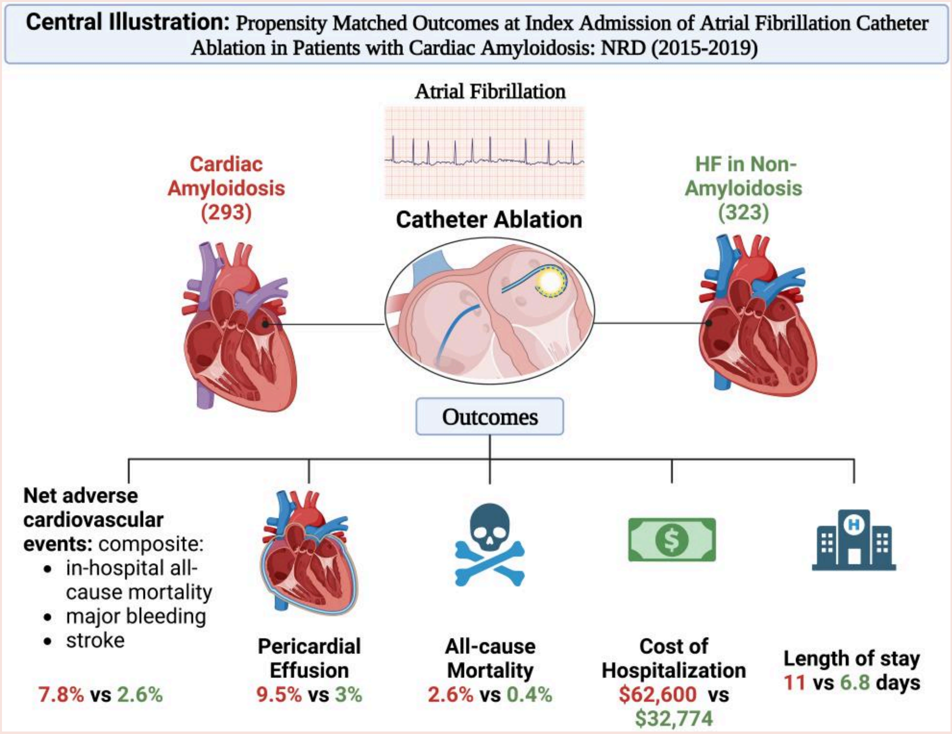
Aims Atrial fibrillation (AF) in patients with cardiac amyloidosis (CA) has been linked with a worse prognosis. The current study aimed to determine the outcomes of AF catheter ablation in patients with CA.

Methods and results The Nationwide Readmissions Database (2015–2019) was used to identify patients with AF and concomitant heart failure. Among these, patients who underwent catheter ablation were classified into two groups, patients with and without CA. The adjusted odds ratio (aOR) of index admission and 30-day readmission outcomes was calculated using a propensity score matching (PSM) analysis. A total of 148 134 patients with AF undergoing catheter ablation were identified on crude analysis. Using PSM analysis, 616 patients (293 CA-AF, 323 non-CA-AF) were selected based on a balanced distribution of baseline comorbidities. At index admission, AF ablation in patients with CA was associated with significantly higher adjusted odds of net adverse clinical events (NACE) [adjusted odds ratio (aOR) 4.21, 95% CI 1.7–5.20], in-hospital mortality (aOR 9.03, 95% CI 1.12–72.70), and pericardial effusion (aOR 3.30, 95% CI 1.57–6.93) compared with non-CA-AF. There was no significant difference in the odds of stroke, cardiac tamponade, and major bleeding between the two groups. At 30-day readmission, the incidence of NACE and mortality remained high in patients undergoing AF ablation in CA.

Conclusion Compared with non-CA, AF ablation in CA patients is associated with relatively higher in-hospital all-cause mortality and net adverse events both at index admission and up to 30-day follow-up.

* Corresponding author. Tel: +1215 955 6000, Fax: +215 503 4983, Email: waqasullah.dr@gmail.com

Graphical Abstract



Keywords Cardiac amyloidosis • Atrial fibrillation • Chronic heart failure

Introduction

The current prevalence of known atrial fibrillation (AF) in the USA is ∼5.2 million, estimated to rise to 12.1 million by 2030.[1] Atrial fibrillation is the most commonly encountered arrhythmia (in ∼70% of patients) with cardiac amyloidosis (CA).[2] This association has important clinical implications. Atrial fibrillation-related loss of atrial contribution to an already thickened and dysfunctional left ventricle is often poorly tolerated, which not only results in profound clinical deterioration but also leads to recurrent hospitalizations.[3] Atrial fibrillation in patients with CA is associated with a significant risk of intracardiac thrombi and stroke regardless of the CHA2DS2VASc score.[4] Moreover, CA patients with AF are often highly symptomatic and thus require individualized and expedited management.

However, given the complex interplay of AF and CA, the usual therapeutic options for AF management may not be as efficacious in these patients. Cardiac amyloidosis-associated atrial dilatation exponentially increases the risk of atrial thrombus, systemic embolism, and ischaemic strokes, which often interferes with the use of rhythm control strategies.[5] Similarly, the commonly used tachyarrhythmia medications such as digoxin, calcium channel blockers, and beta-blockers can lead to clinical and haemodynamic decompensation, adding further complexity to the management of AF. These considerations may make definitive management options (such as pulmonary vein isolation by radiofrequency or cryotherapy catheter ablation) more attractive. However, evidence on the safety and efficacy of catheter ablation in CA is also disputed and limited to small, underpowered single-centre studies.[6,7] To date, there has been no large-scale study to assess outcomes of AF catheter ablation in patients with HF with and without CA. Providers are often left to expert consensus and clinical experience to aid in decision-making.

Methods

Data source

Data were obtained from the Nationwide Readmissions Database (NRD), part of the Healthcare Cost and Utilization Project (HCUP). It was established by the federal–state–industry partnership and monitored by the Agency for Healthcare Research and Quality. The NRD is an all-payer database with more than 15 million discharge data points from 22 states of the USA. The unweighted data of NRD account for 49% and 51% of the total US hospitalizations and population, respectively. The NRD contains unique identification codes that can link patients across the same year, allowing us to capture readmission. Data are anonymized and hence exempted from the approval of the Institutional Review Board (IRB).

Study design and population

Using the International Classification of Diseases-10th Revision-Clinical Modification (ICD-10-CM) codes, all hospitalizations for catheter ablation for AF were identified between September 2015 and November 2019 (see Supplementary material online, *Table S1*). Of these, only patients with an admitting diagnosis of HF were isolated each year. Consistent with published literature, secondary diagnoses for CA were identified (CA-AF) and compared with patients with HF without associated amyloidosis (non-CA-AF). As data are annualized, hospitalizations in December from each year were excluded to enable 30-day outcomes for each index admission. The catheter ablation hospitalizations of patients with CA-AF

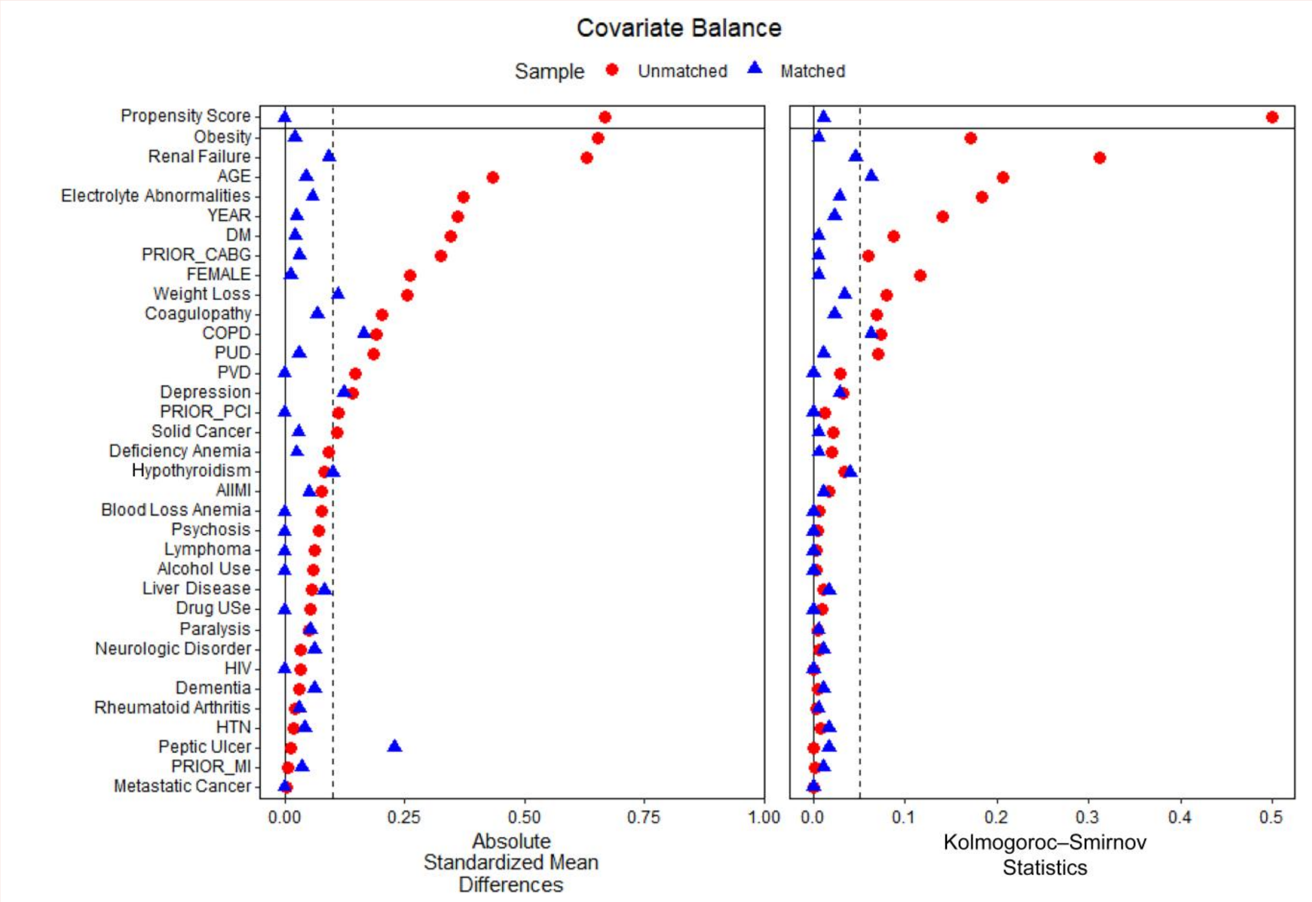


Figure 1 Propensity score matching analysis of 30-day readmission sample showing the standardized mean differences of major comorbidities showing no deviation beyond the allowable threshold (SMD 0.1 and KSS 0.05) (DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; RA, rheumatoid arthritis; HTN, hypertension; MI, myocardial infarction).

were compared with a matched sample of patients undergoing catheter ablation for non-CA-AF.

Study outcomes

The primary outcome was net adverse clinical events (NACE), a composite of in-hospital all-cause mortality, major bleeding, and stroke. Secondary outcomes included components of NACE, pericardial effusion, cardiac tamponade, length of stay, and adjusted cost of hospitalization at both index admission and 30-day readmission (see Supplementary material online, *Table S2*).

Statistical methods

Demographics, hospital characteristics, comorbidities, and outcomes across the comparison cohorts (CA-AF and non-CA-AF) were displayed as proportions for categorical data and as mean with standard deviation (SD) and median with interquartile ranges (IQR) for scale variables. The variables used in matching included age, sex, major comorbidities, and all components of the Charlson comorbidity index (CCI) (except HF, which was the primary inclusion criteria for both comparison groups). The estimates of CCI were obtained using the proposed coding scheme by Deyo *et al.*[8] Two propensity score matching (PSM) analyses were obtained, one for the hospitalizations at the time of index catheter ablation procedure (index admission) and the other at 30-day follow-up of the same cohort (30-day readmission) (*Figure 1* and see Supplementary material online, *Figure S1*). A one/many near neighbour strategy with an allowable threshold of 0.1 absolute standardized mean difference (SMD) and 0.05 Kolmogorov–Smirnov Statistic (KSS) was adopted without replacement.

The unadjusted odds ratio (OR) with a 95% confidence interval (CI) for the overall sample was calculated using the Cochran–Mantel–Haenszel test. Adjusted association between the secondary diagnosis of CA among AF ablation groups and the clinical outcomes was assessed using multivariable logistic (categorical outcomes) and linear (continuous) regression models. The models were adjusted for varying hospital teaching status, the severity of illness, risk of mortality, and primary payer. Scale outcomes were compared using the independent *t*-test analysis of the mean and SD for normally distributed data and Wilcoxon–Mann–Whitney measures of the median and IQR for the non-normally distributed data. To estimate hospital cost (total expense for hospital services), the NRD-provided 'cost-to-charge ratio' variable was multiplied by the total inpatient charges (the total billed amount by the participating hospital) and was adjusted for inflation wages of January 2020 using the Bureau of Labor Statistics Consumer Price Index (adjusted cost).

The 30-day readmission was further classified as cardiovascular (CV) and non-CV readmissions for both comparison groups. Cardiovascular readmissions included acute HF exacerbation, ischaemic heart disease, and stroke. The non-CV readmission primarily focused on complications or systemic manifestations of amyloidosis, such as acute kidney injury (AKI), bleeding, hypertensive crises, sepsis, and other causes. Cumulative incidence function and log-rank test were used to compare the rate and timing of 30-day readmission between CA-AF and non-CA-AF groups. A *P*-value interaction analysis was performed to assess the impact of the teaching status of the hospital on index mortality across both groups. The alpha error threshold was set at a *P*-value <0.05. All analyses were performed using R 3.02 and SPSS 27.

Table 1 Unadjusted and propensity-matched demographic and baseline characteristics of study population undergoing ablation

	Crude analysis		Propensity score matching analysis	
	CA-AF (293)	Non-CA-AF (147 841)	CA-AF (293)	Non-CA-AF (323)
Sex				
Male	201 (68.5%)	90 304 (61.1%)	201 (68.5%)	237 (73.4%)
Female	92 (31.5%)	57 537 (38.9%)	92 (31.5%)	86 (26.6%)
Admission day				
Weekday	267 (91.3%)	127 593 (86.3%)	267 (91.3%)	261 (81.0%)
Weekend	25 (8.7%)	20 248 (13.7%)	25 (8.7%)	61 (19.0%)
Admission type				
Elective	224 (77.1%)	88 604 (60.1%)	224 (77.1%)	206 (64.1%)
Emergent	67 (22.9%)	58 818 (39.9%)	67 (22.9%)	115 (35.9%)
Teaching status				
Metropolitan non-teaching	24 (8.2%)	19 098 (12.9%)	24 (8.2%)	32 (10.0%)
Metropolitan teaching	265 (90.5%)	125 767 (85.1%)	265 (90.5%)	283 (87.5%)
Non-metropolitan hospital	<11	2976 (2.0%)	<11	<11
Area				
Large metropolitan area	225 (76.9%)	94 830 (64.1%)	225 (76.9%)	185 (57.2%)
Small metropolitan area	64 (21.9%)	50 035 (33.8%)	64 (21.9%)	130 (40.3%)
Micropolitan areas	<11	2934 (2.0%)	<11	<11
Payer				
Medicare	241 (82.5%)	97 989 (66.3%)	241 (82.5%)	266 (82.4%)
Medicaid	13 (4.5%)	8037 (5.4%)	13 (4.5%)	11 (3.3%)
Private insurance	31 (10.8%)	36 365 (24.6%)	31 (10.8%)	39 (12.2%)
Self-pay	<11	1656 (1.1%)	<11	<11
No charge	<11	339 (0.2%)	<11	<11
Other	<11	3356 (2.3%)	<11	<11
Location				
'Central' counties of metro areas of ≥ 1 million population	92 (31.3%)	36 057 (24.4%)	92 (31.3%)	69 (21.3%)
'Fringe' counties of metro areas of ≥ 1 million population	115 (39.4%)	44 920 (30.4%)	115 (39.4%)	93 (28.8%)
Counties in metro areas of 250 000–999 999 population	51 (17.3%)	32 734 (22.2%)	51 (17.3%)	68 (21.1%)
Counties in metro areas of 50 000–249 999 population	<11	13 181 (8.9%)	<11	51 (15.9%)
Micropolitan counties	<11	11 181 (7.6%)	<11	21 (6.7%)
Not metropolitan or micropolitan counties	15 (5.1%)	9504 (6.4%)	15 (5.1%)	20 (6.2%)
Risk of mortality				
Minor likelihood of dying	<11	44 455 (30.1%)	<11	49 (15.2%)
Moderate likelihood of dying	66 (22.5%)	44 185 (29.9%)	66 (22.5%)	90 (27.7%)
Major likelihood of dying	144 (49.2%)	42 752 (28.9%)	144 (49.2%)	136 (42.3%)
Extreme likelihood of dying	74 (25.2%)	16 449 (11.1%)	74 (25.2%)	48 (14.8%)
Severity class				
Minor LOF	<11	33 833 (22.9%)	<11	35 (10.8%)
Moderate LOF	61 (20.7%)	55 654 (37.6%)	61 (20.7%)	107 (33.1%)
Major LOF	161 (55.1%)	42 793 (28.9%)	161 (55.1%)	134 (41.4%)
Extreme LOF	66 (22.6%)	15 561 (10.5%)	66 (22.6%)	48 (14.8%)

LOF, loss of function

Results

Selection of cases

A total of 19 218 224 AF hospitalizations between September 2015 and November 2019 were identified. Of these, 9 333 137 patients had a diagnosis of HF, and 42 150 patients had a secondary diagnosis of CA. A total of 148 134 patients of the initial AF group who underwent ablation were selected after excluding hospitalizations in December of each study year. Of these, 147 841 had HF without CA, and 293 patients had HF with CA. A PSM sample of 616

Table 2 Unadjusted and propensity-matched baseline comorbidities of study population undergoing ablation

	Crude analysis		Propensity score matching analysis	
	CA-AF (292)	Non-CA-AF (147 841)	CA-AF (292)	Non-CA-AF (323)
Coagulopathy	45 (15.3%)	9539 (6.5%)	45 (15.3%)	33 (10.1%)
COPD	52 (17.7%)	38 428 (26.0%)	52 (17.7%)	78 (24.2%)
Iron deficiency Anaemia	18 (6.1%)	4809 (3.3%)	18 (6.1%)	21 (6.7%)
Depression	19 (6.4%)	13 835 (9.4%)	19 (6.4%)	8 (2.4%)
Diabetes mellitus	24 (8.1%)	23 237 (15.7%)	24 (8.1%)	27 (8.4%)
Drug use	<11	2882 (1.9%)	<11	7 (2.2%)
Electrolyte abnormalities	122 (41.8%)	34 680 (23.5%)	122 (41.8%)	147 (45.5%)
Hypertension	233 (79.5%)	116 731 (79.0%)	233 (79.5%)	261 (80.8%)
Hypothyroidism	58 (19.8%)	25 127 (17.0%)	58 (19.8%)	59 (18.2%)
Liver disease	12 (3.9%)	5228 (3.5%)	12 (3.9%)	8 (2.4%)
Metastatic cancer	<11	912 (0.6%)	<11	2 (0.6%)
Neurologic disorder	<11	4249 (2.9%)	<11	7 (2.1%)
Obesity	21 (7.1%)	37 248 (25.2%)	21 (7.1%)	25 (7.7%)
Paralysis	<11	895 (0.6%)	<11	2 (0.6%)
Peripheral vascular disease	22 (7.4%)	10 333 (7.0%)	22 (7.4%)	13 (4.1%)
Peptic ulcer disease	62 (21.1%)	15 747 (10.7%)	62 (21.1%)	56 (17.4%)
Renal failure	169 (57.7%)	35 201 (23.8%)	169 (57.7%)	189 (58.6%)
Rheumatoid arthritis	21 (7.1%)	4614 (3.1%)	21 (7.1%)	13 (4.1%)
Solid cancer	18 (6.1%)	2835 (1.9%)	18 (6.1%)	10 (3.1%)
Weight loss	31 (10.6%)	4546 (3.1%)	31 (10.6%)	20 (6.2%)
Myocardial infarction	13 (4.6%)	5162 (3.5%)	13 (4.6%)	11 (3.4%)
Prior CABG	<11	14 199 (9.6%)	<11	12 (3.7%)
Prior MI	29 (10.1%)	16 208 (11.0%)	29 (10.1%)	40 (12.3%)
Dementia	<11	4471 (3.0%)	<11	<11

COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; MI, myocardial infarction.

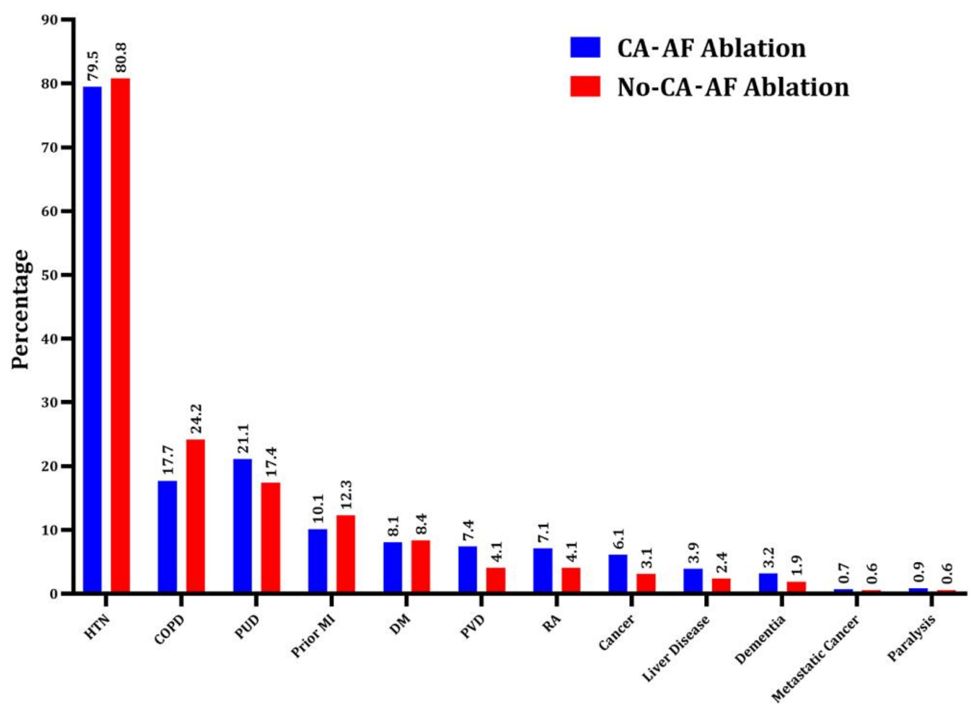


Figure 2 Baseline characteristics of propensity-matched sample at index admission CA-AF vs. non-CA-AF ablation groups (HTN, hypertension; COPD, chronic obstructive sleep apnea; PUD, peptic ulcer disease; MI, myocardial infarction; DM, diabetes mellitus; PVD, peripheral vascular disease; RA, rheumatoid arthritis).

Table 3 Proportion of major outcomes on index admission and 30-day readmission in patients who underwent ablation in CA-AF vs. non-CA-AF

	Crude index admission		PSM index admission		PSM 30-day readmission	
	Odds ratio	*P*-value	Odds ratio	*P*-value	Odds ratio	*P*-value
NACE	2.28 (1.54–3.39)	<0.0001	4.21 (1.7–5.20)	<0.0001	2.38 (1.01–5.71)	0.02
Mortality	2.52 (1.24–5.10)	0.017	9.03 (1.12–72.70)	<0.0001	4.28 (1.15–15.9)	0.04
Major bleeding	2.39 (1.34–4.27)	0.005	2.71 (0.94–7.80)	0.09	0.89 (0.19–4.09)	0.81
Stroke	1.76 (0.56–5.52)	0.54	1.78 (0.52–6.02)	0.55	1.59 (0.48–6.52)	0.85
Pericardial effusion	1.93 (1.31–2.85)	0.001	3.30 (1.57–6.93)	0.002	1.72 (0.53–5.58)	0.53

NACE, net adverse clinical events (a composite of in-hospital all-cause mortality, major bleeding, and stroke)

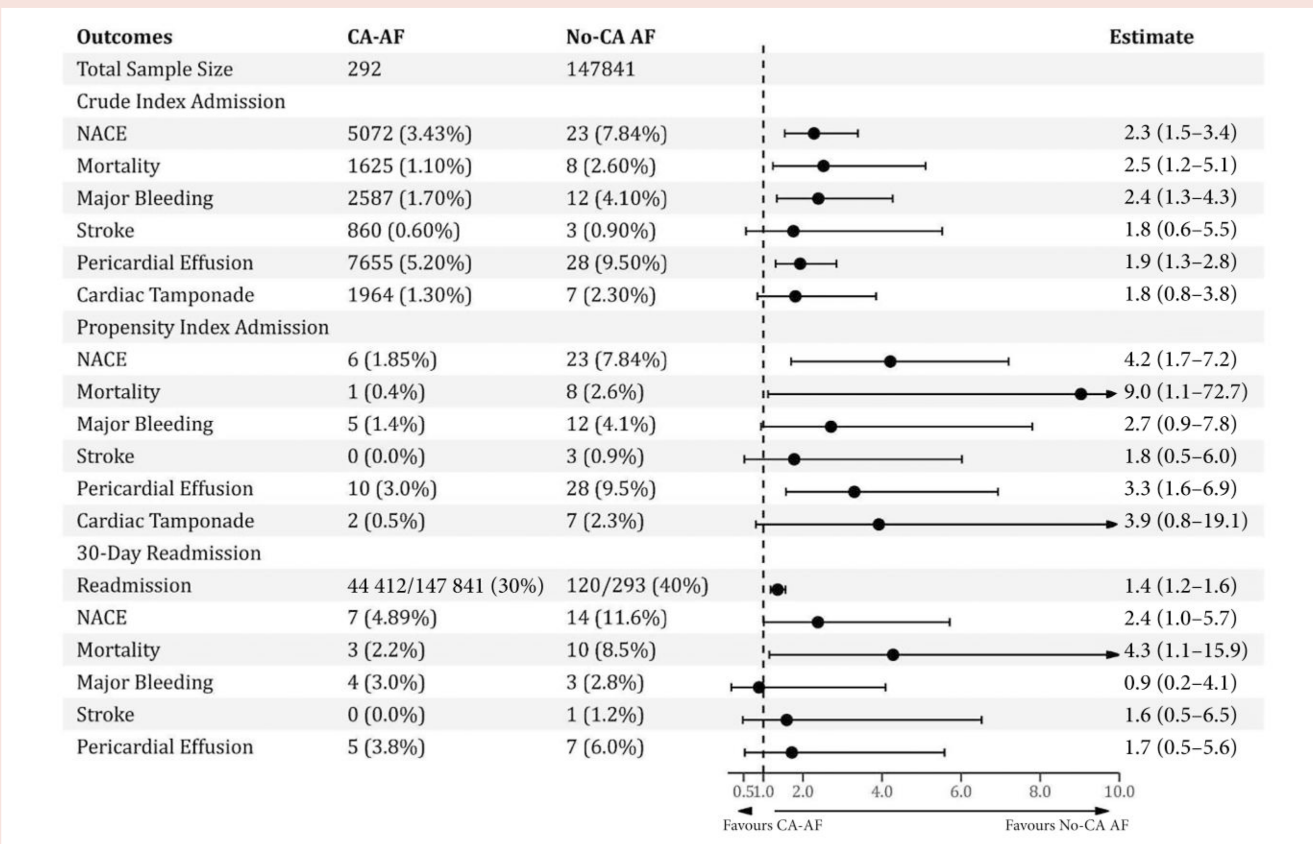


Figure 3 Forest plot showing the odds of index admission and 30-day readmission rate in CA-AF vs. non-CA-AF. The dotted line presents the null line (OR = 1), the horizontal line indicates the 95% confidence interval, and the solid circle indicates the point estimates.

patients (293 CA-AF and non-CA 323) was selected for adjusted analysis.

Baseline characteristics

Baseline demographics, hospital characteristics, and comorbidities of all AF ablation hospitalizations stratified by the secondary diagnosis of CA are described in *Tables 1* and *2*. On crude analysis, the CA-AF group had a lower percentage of emergent (22.9% vs. 39.9%) admissions compared with the non-CA-AF group. The non-CA-AF patients were less likely to be supported by Medicare (66.3% vs. 82.5%) and more likely to belong to micropolitan counties than their CA-AF counterparts. The proportion of major components of the CCI was significantly higher among the CA-AF vs. non-CA-AF group, including coagulopathy (15.3% vs. 6.5%), peptic ulcer disease (21.1% vs. 10.7%), renal failure (57.7% vs. 23.8%), rheumatoid arthritis (7.1% vs. 3.1%), and solid organ cancer (6.1% vs. 1.9%).

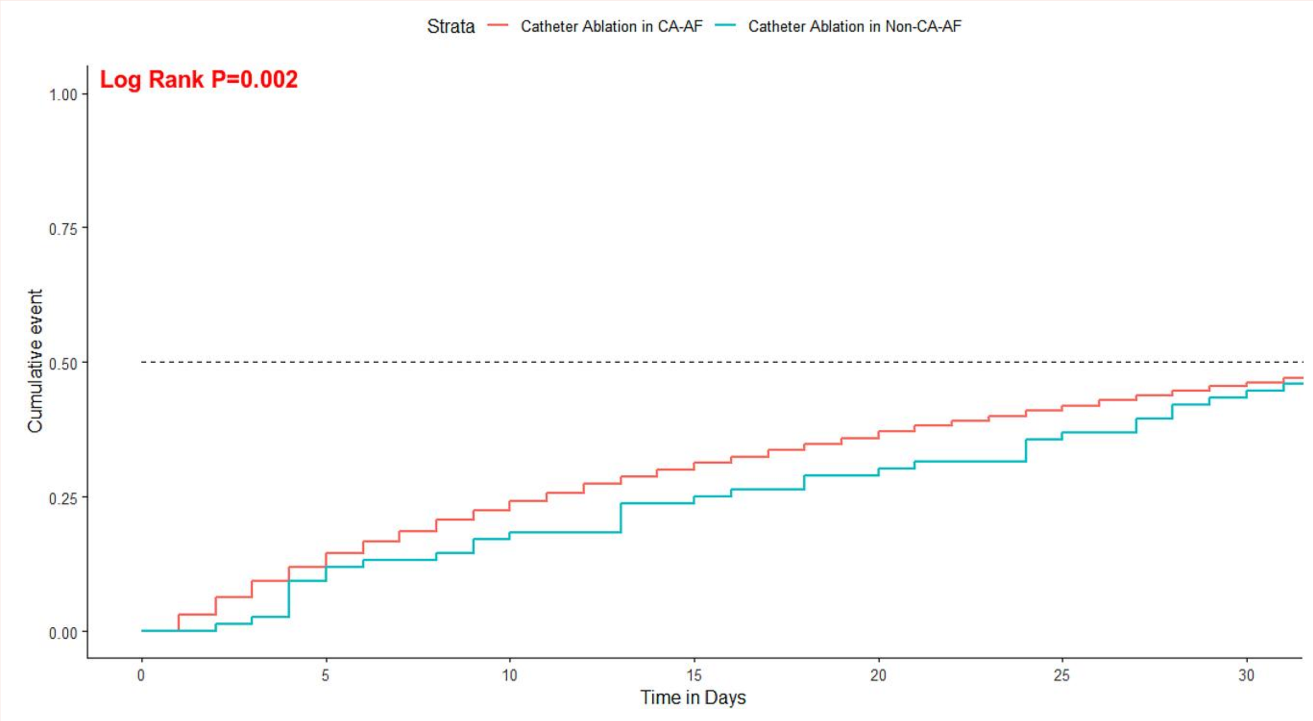


Figure 4 Kaplan–Meier estimates of cumulative 30-day readmission rate for the overall cohort (without PSM) shows a significantly lower readmission rate in patients undergoing ablation in the non-CA-AF group compared with the CA-AF group.

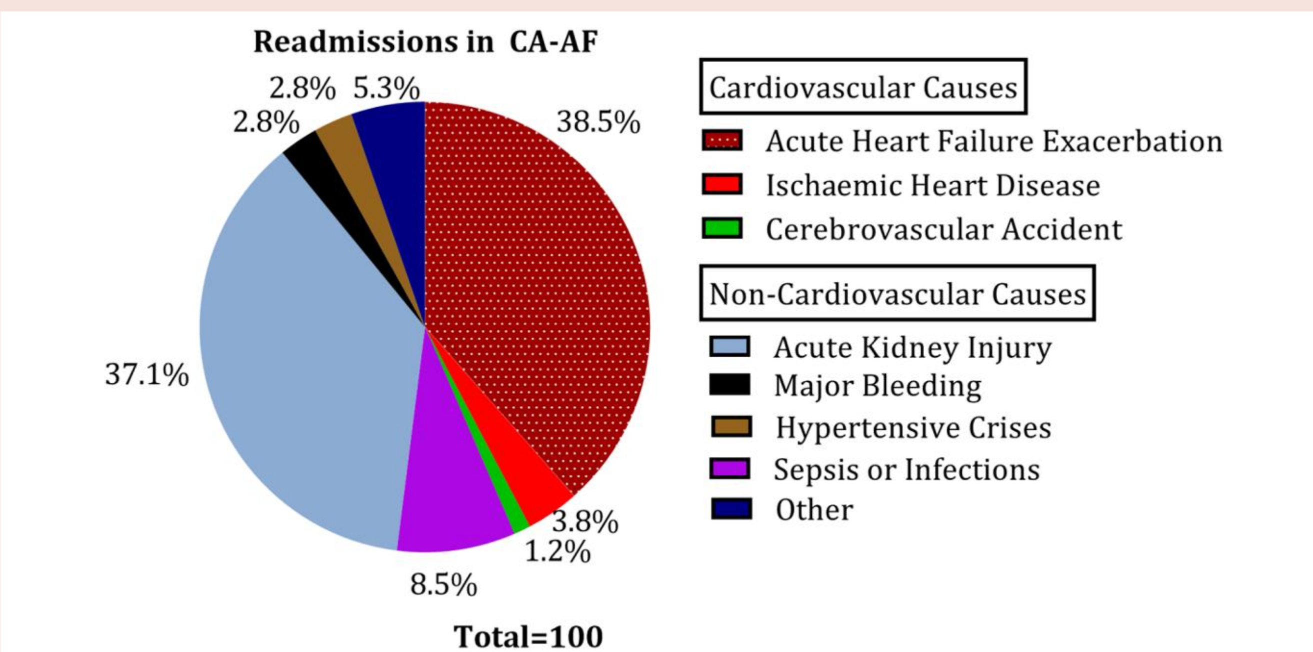


Figure 5 Causes of 30-day readmission in patients who underwent ablation for CA-AF.

After matching, a balanced group of non-CA-AF populations was selected for adjusted analysis. Among CA-AF vs. non-CA-AF, baseline characteristics were comparable, including the proportion of female patients (31.5% vs. 26.6%), Medicare payer (82.5% vs. 82.4%), and metropolitan teaching hospital admissions (90.5% vs. 87.5%). CA-AF patients more commonly had 'extreme likelihood of mortality' (25.2% vs.

14.8%) and 'severe loss of function' (22.6% vs. 14.8%). The components of CCI and other major baseline comorbidities were not significantly different between the two matched groups (*Figure 2*).

Crude analysis of the overall population

In the entire unmatched cohort, the odds of NACE, mortality, pericardial effusion, and major bleeding were significantly higher in patients with (vs. without) CA-AF undergoing ablation. The odds of ischaemic stroke and cardiac tamponade were not significantly different between the two groups (*Table 3*). CA-AF ablation group had a higher mean length of stay and greater adjusted cost of hospitalization (see Supplementary material online, *Table S3*).

Propensity score matching analysis at index admission

The PSM cohort mirrored the findings of the unadjusted analysis (*Figure 3*, Central Illustration). At index admission of ablation, there were 7.8% inpatient NACE and 2.6% in-hospital deaths in the CA-AF group compared with 1.85% NACE and 0.4% deaths in patients with no CA. In adjusted analysis, CA-AF (vs. without CA-AF) was significantly associated with a higher likelihood of NACE (aOR 4.21, 95% CI 1.7–5.20) and all-cause inpatient mortality (aOR 9.03, 95% CI 1.12–72.7). Similarly, the adjusted odds of pericardial effusion in CA-AF (9.5%) were significantly higher than in non-CA-AF (3.0%) patients (aOR 3.30, 95% CI 1.57–6.93). There was no significant difference in the risk of stroke (aOR 1.78, 95% CI 0.52–6.02) and cardiac tamponade (aOR 3.92, 95% CI 0.810–19.06) between the two groups (*Table 3*). The post-ablation mean length of hospital stay in days (11.5 ± 17 vs. 6.8 ± 6.3, $P < 0.0001$) and adjusted cost of hospitalization ($62 600 ± 53 006 vs. $32 774 ± 17199, $P < 0.0001$) were also significantly higher among the CA-AF patients compared with non-CA-AF (see Supplementary material online, *Table S4*).

Propensity score matching analysis at 30-day readmission

Thirty-day readmission was also higher following AF ablation hospitalization with (vs. without) secondary diagnosis of CA (40% vs. 30%; OR 1.36, 95% CI 1.18–1.56, $P = 0.02$) using the PSM analysis. Contrary to the index admission, there was no difference in the risk of pericardial effusion (aOR 1.72, 95% CI 0.53–5.58) between the CA-AF and non-CA-AF patients. The incidence of 30-day NACE (aOR 2.38, 95% CI 1.01–5.71) and mortality (aOR 4.28, 95% CI 1.15–15.9) remained higher among patients with CA-AF ablation group compared with non-CA-AF. The risk of stroke remained similar irrespective of follow-up (*Figure 3*).

Causes of readmission

The higher overall readmission rate in the CA-AF group was largely driven by differences in readmissions after 7 days of discharge from index ablation (log-rank test, $P = 0.002$) (*Figure 4*). The overall readmission events related to CV vs. non-CV-related causes in the CA-AF were (43% and 57%, respectively). Among the non-CA-AF group, the rates of CV-related (30.9%) readmissions were significantly lower than the non-CV causes (69.1%, $P < 0.0001$). The largest contributor to CV-related re-hospitalization was acute HF exacerbation (38.5% in CA-AF vs. 30.0% in non-CA-AF, $P = 0.02$), followed by acute kidney injury (37% in both groups, $P = 0.98$) (*Figures 5* and see Supplementary material online, *Figure S2*).

Interaction analysis based on the teaching status of hospital

The association between in-hospital mortality at index admission in patients with CA (vs. without CA) was not modified by the hospital's teaching status (P-interaction = 0.723) (see Supplementary material online, *Figure S3* and *Table S5*).

Discussion

In the current study, we report the largest evidence on the estimated prevalence of CA, CA-related AF, and outcomes of catheter ablation in CA-AF. Overall, our findings suggest that after matching for components of a well-validated comorbidity index (CCI), CA-AF patients undergoing ablation were associated with a higher risk of net adverse clinical events and all-cause mortality at index admission and 30-day readmission. CA-AF patients were also associated with a higher rate of healthcare resource utilization, as indicated by increased inflation-adjusted mean hospitalization cost and mean length of hospital stay. The 30-day readmission rate in the CA-AF group was also higher by 1.36 times compared with the non-CA-AF ablation group, primarily driven by cardiovascular causes, most notably acute HF exacerbations. The greatest risk of readmission was after the first week of discharge from the index ablation admission. The risk of stroke was similar in both groups.

Prior literature on catheter ablation in patients with AF and CA has discrepant results, primarily because of their small sample size and reporting of heterogeneous unadjusted outcomes from single-centre studies.[6–9] Barbhaiya et al. were the first to write their experience of 18 CA patients, among which seven patients with atrial tachycardia (AT) or AF who underwent left atrial (LA) ablation. The CA-AF cohort had a larger low-voltage left atrial area, a higher number of inducible atrial tachyarrhythmia, and a greater 1-year recurrence rate of AT/AF (83%) compared with an age- and sex-matched control of the non-CA-AF group (14%).[5] By contrast, Black-Maier and Tan et al. (13 patients each) reported 40% and 75% recurrence-free survival in the CA-AT/AF cohort at 1 year, respectively.[6,9] Taken together, these studies were underpowered and non-specific due to their small sample sizes and inclusion of patients with all types of atrial arrhythmias rather than CA-AF only. Recently, the study by Donnellan et al. was the largest and most comprehensive analysis of patients with CA-AF. A total of 72 patients with CA-AF were included, of whom 24 had catheter ablation compared with 48 medically treated patients.[10] On a 2:1 matched analysis, the ablation group (vs. medical group) had a significantly lower incidence of mortality (29% vs. 75%) and re-hospitalization, while both groups had an equal stroke rate. The overall 3-year AF recurrence rate was found to be 58%.[9] However, the generalization of these findings was also limited, as only patients with transthyretin cardiac amyloidosis (ATTR-CA) were included, and the greatest benefits were obtained in patients with stages I and II ATTR-CA. Moreover, the comparison group was a medically treated cohort rather than a matched cohort of non-CA patients. By contrast, we are reporting a wide range of adjusted outcomes in the largest available population of all types of CA-associated HF.

Mechanistically, the higher incidence of AF in CA could be explained by the disruption of the typical interatrial conduction system either through direct infiltration of insoluble amyloid fibrils within the atrial tissue or indirectly through the promotion of atrial fibrosis.[11] Moreover, CA-associated left ventricular (LV) diastolic dysfunction and higher LV filling pressures increase the risk of LA dilatation, which can serve as a substrate for AF. Prolonged atrioventricular conduction times from involvement of the conduction system can result in diastolic regurgitation across the atrioventricular valves and adversely affect atrial filling pressure, further contributing to AF. The impaired LV relaxation, coupled with the loss of the late diastolic atrial component of the LV filling (due to AF), makes these patients exquisitely prone to haemodynamic deterioration and HF exacerbations. Whether AF ablation can ameliorate the need for recurrent hospitalizations for acute decompensated HF in CA patients and reduce healthcare costs remains unknown thus far. Our study is the first to demonstrate that a higher percentage of CA patients after AF ablation was readmitted with acute HF exacerbations and was associated with higher adjusted costs and length of stay than HF patients with no CA.

Overall, there is a general reluctance to do ablation in these patients, mainly stemming from concerns around the greater risk of procedural complications, the shortened life expectancy of CA patients, and the unknown efficacy of ablation due to the scarcity of large-scale data and clinical experience. From the operator's standpoint, potential intolerance of high volumes of fluids during the radiofrequency catheter ablation and an expectation that the ablation will be more extensive than simply pulmonary vein isolation makes the procedure challenging. This could potentially explain the higher incidence of pericardial effusion, HF-related readmissions, and mortality seen in our study.

Patients with CA-AF have a higher risk of left atrial thrombus, which represents a significant roadblock to adopting rhythm control strategies in these patients. Some studies have shown that one-third of the patients with CA-AF have left atrial thrombus, which invariantly increases the risk of stroke.[3,4] However, in concordance with the recent reports, our study showed that CA-AF patients undergoing ablation were not associated with an increased risk of stroke compared to non-CA-AF patients.[10] This could plausibly be explained by the careful selection of ablation candidates and ruling out the presence of atrial thrombus before the procedure.

We also observed that AF ablation in CA (vs. without CA) was more prevalent at large metropolitan teaching hospitals (∼90% of cases) and was largely supported by Medicare. This could potentially reflect referral bias, where patients with a rare diagnosis are more likely to receive care at teaching hospitals, or these observations might indicate the disparities in healthcare resource availability. Patients hospitalized at large teaching centres are more likely to receive specialized care and a diagnostic workup for CA, leading to a high disease prevalence. Nonetheless, our sensitivity analysis demonstrated no impact of the teaching status of the institution on CA-AF-related mortality, indicating that the care quality might not differ significantly between different hospitals. Overall, our study demonstrated relatively worse outcomes in patients with (vs. without) CA-AF after ablation. However, further studies are needed to demonstrate the safety and efficacy of ablation vs. conservative therapy in patients with CA.

Limitations

Our findings should be interpreted with acknowledgment of certain limitations. Given the retrospective observational study design, selection bias and residual confounding are possible. For the same reason, we could not establish a causal relationship but could only report temporal associations between intervention and outcomes. Despite propensity matching on a wide range of demographics and comorbidities, CA carried an inherently higher risk of mortality outside the risk of procedure-related factors, and the impact of unmeasured covariates could not be determined. Given that only patients with HF were included, our findings cannot be extrapolated to patients with CA but no heart failure. The NRD is a readmission database linked to inpatient discharge records, so we could not capture events occurring outside the hospital and could not account for the competing risk of mortality arising in the community or ambulatory settings. Furthermore, the lack of data on disease severity, type of amyloidosis, type of catheter ablation, anatomical substrate identification, echocardiographic parameters, functional status, and medications used precluded our ability to perform a more robust adjusted and stratified analysis on these critical factors. Although all codes were verified using the standard recommended sources, and with reported prior literature, the possibility of inadvertent coding error due to the lack of coding precision for AF could not be entirely excluded. Furthermore, CA is under-recognized, so it is plausible that the perceived low incidence of AF ablation in CA patients may be due to under-diagnosis or under-coding.

Conclusions

Compared with HF patients without CA undergoing AF ablation, CA-AF was associated with worse outcomes: higher NACE and higher mortality at index admission and at 30 days from the index procedure. The risk of stroke remained similar between the two groups.

Lead author biography

Waqas Ulah, MD is currently working as a cardiovascular disease fellow at Thomas Jefferson University Hospitals, Philadelphia, USA. After graduating from Khyber Medical College, Peshawar, Pakistan in 2013, he served as a research associate at the University of Arizona, Tucson, AZ and Yale-Griffin Research Center, CT, USA. Waqas completed his internal medicine residency from Abington Jefferson Health in 2021. His interests are in coronary interventions and structural heart diseases.

Data availability

Data was taken from NRD that is publically available.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Funding

None declared.

Conflict of interest: None declared.

References

1. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the US adult population. *Am J Cardiol* 2013;**4**:e003839.
2. Mints YY, Doros G, Berk JL, Connors LH, Ruberg FL. Features of atrial fibrillation in wild-type transthyretin cardiac amyloidosis: a systematic review and clinical experience. *ESC Hear Fail* 2018;**5**:772–779.
3. El-Am EA, Dispenzieri A, Melduni RM, Ammash NM, White RD, Hodge DO, Noseworthy PA, Lin G, Pislaru SV, Egbe AC, Grogan M, Nkomo VT. Direct current cardioversion of atrial arrhythmias in adults with cardiac amyloidosis. *J Am Coll Cardiol* 2019; **73**:589–597.
4. Donnellan E, Elshazly MB, Vakamudi S, Wazni OM, Cohen JA, Kanj M, Hanna M, Baranowski B, Saliba W, Jaber W. No association between CHADS-VASc score and left atrial appendage thrombus in patients with transthyretin amyloidosis. *J Am Coll Cardiol EP* 2019;**5**:1473–1474.
5. Feng DL, Syed IS, Martinez M, Oh JK, Jaffe AS, Grogan M, Martinez MW, Syed IS, Hughes DA, Lust JA, Jaffe AS, Gertz MA, Klarich KW. Intracardiac thrombosis and embolism in patients with cardiac amyloidosis. *Circulation* 2009;**119**:2490–2497.

6. Barbhaiya CR, Kumar S, Baldinger SH, Michaud GF, Stevenson WG, Falk R, John RM. Electrophysiologic assessment of conduction abnormalities and atrial arrhythmias associated with amyloid cardiomyopathy. *Hear Rhythm* 2016;**13**:383–390.
7. Tan NY, Mohsin Y, Hodge DO, Lacy MQ, Packer DL, Dispenzieri A, Grogan M, Asirvatham SJ, Madhavan M, Mcleod CJ. Catheter ablation for atrial arrhythmias in patients with cardiac amyloidosis. *J Cardiovasc Electrophysiol* 2016;**27**:1167–1173.
8. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992;**45**:613–619.
9. Black-Maier E, Rehorn M, Loungani R, Friedman DJ, Alenezi F, Geurink K, Pokorney SD, Daubert JP, Sun AY, Atwater BD, Jackson KP. Catheter ablation of atrial fibrillation in cardiac amyloidosis. *Pacing Clin Electrophysiol* 2020;**43**:913–921.
10. Donnellan E, Wazni O, Kanj M, Elshazly MB, Hussein A, Baranowski B, Hanna M, Patel D, Trulock K, Martyn M, Menon V. Atrial fibrillation ablation in patients with transthyretin cardiac amyloidosis. *EP Europace* 2020;**22**:259–264.
11. Ridolfi RL, Bulkley BH. Hutchins GM: the conduction system in cardiac amyloidosis. Clinical and pathologic features of 23 patients. *Am J Med* 1977;**62**:677–686.