OPEN ACCESS

Original research

Association between catheter ablation of atrial fibrillation and mortality or stroke

Finn Akerström ,[1,2] Julie Hutter,[3] Emmanouil Charitakis ,[4] Fariborz Tabrizi,[5] Fahd Asaad,[1] Hamid Bastani,[1] Tara Bourke,[1,2] Frieder Braunschweig,[1,6] Nikola Drca,[1,2] Anders Englund,[5] Leif Friberg,[7] Per Insulander,[2] Anders Hassel Jönsson,[4] Göran Kennebäck,[1] Astrid Paul-Nordin,[1,2] Bita Sadigh,[1] Ott Saluveer,[1,2] Serkan Saygi,[1] Jonas Schwieler,[1,6] Emma Svennberg,[1,2] Jari Tapanainen,[8] Yusuf Türkmen,[1] Mats Jensen-Urstad[1,2]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2023-322883).

For numbered affiliations see end of article.

Correspondence to
Dr Finn Akerström, Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden;
finn.akerstrom@regionstockholm.se

This work was presented as an abstract at the EHRA 2023 Conference (Europace 2023;25:i167–i168).

Received 26 April 2023
Accepted 11 August 2023
Published Online First 1 September 2023

To cite: Akerström F, Hutter J, Charitakis E, *et al*. *Heart* 2024;**110**:163–169.

ABSTRACT

Objective Catheter ablation of atrial fibrillation effectively reduces symptomatic burden. However, its long-term effect on mortality and stroke is unclear. We investigated if patients with atrial fibrillation who undergo catheter ablation have lower risk for all-cause mortality or stroke than patients who are managed medically.

Methods We retrospectively included 5628 consecutive patients who underwent first-time catheter ablation for atrial fibrillation between 2008 and 2018 at three major Swedish electrophysiology units. Control individuals with an atrial fibrillation diagnosis but without previous stroke were selected from the Swedish National Patient Register, resulting in a control group of 48 676 patients. Propensity score matching was performed to produce two cohorts of equal size (n=3955) with similar baseline characteristics. The primary endpoint was a composite of all-cause mortality or stroke.

Results Patients who underwent catheter ablation were healthier (mean CHA_2DS_2-VASc score 1.4±1.4 vs 1.6±1.5, p<0.001), had a higher median income (288 vs 212 1000 Swedish krona [KSEK]/year, p<0.001) and had more frequently received university education (45.1% vs 28.9%, p<0.001). Mean follow-up was 4.5±2.8 years. After propensity score matching, catheter ablation was associated with lower risk for the combined primary endpoint (HR 0.58, 95% CI 0.48 to 0.69). The result was mainly driven by a decrease in all-cause mortality (HR 0.51, 95% CI 0.41 to 0.63), with stroke reduction showing a trend in favour of catheter ablation (HR 0.75, 95% CI 0.53 to 1.07).

Conclusions Catheter ablation of atrial fibrillation was associated with a reduction in the primary endpoint of all-cause mortality or stroke. This result was driven by a marked reduction in all-cause mortality.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Catheter ablation of atrial fibrillation is effective in reducing symptomatic burden; however, several studies on its long-term effect on mortality and stroke show conflicting results.

WHAT THIS STUDY ADDS

⇒ In this large real-world population study of consecutive patients who underwent catheter ablation at three major Swedish electrophysiology units between 2008 and 2018, we found a significant reduction in mortality or stroke in ablated patients and this was driven by a marked reduction in mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study results should encourage future randomised controlled trials to be conducted on the same topic, and if our findings are corroborated indication for catheter ablation will be strengthened for this patient group.

INTRODUCTION

Atrial fibrillation (AF) is the most frequent sustained arrhythmia with an estimated prevalence in adults of between 2% and 4%, which is expected to further increase due to extended longevity and improved screening.[1 2] AF is associated with an increased risk of mortality and morbidity related to stroke, heart failure and dementia. Moreover, AF is typically linked to impaired quality of life and has substantial socioeconomic implications.[3 4] Catheter ablation for AF is more effective than antiarrhythmic drug therapy in restoring sinus rhythm,[5 6] including in therapy-naïve patients, and has been associated with a significant improvement in quality of life.[7] Furthermore, in selected patients with heart failure, three randomised clinical trials (RCTs) found that AF ablation reduces mortality and hospital admissions.[8–10] However, whether ablation also improves clinical outcomes such as stroke and mortality in a general AF population has not been established. The CABANA (Catheter Ablation vs Antiarrhythmic Drug Therapy for Atrial Fibrillation) trial failed to show a reduction in the primary composite endpoint of death, stroke, serious bleeding or cardiac arrest when compared with medical therapy.[11] Several observational and registry studies have attempted to evaluate the effect of AF ablation on stroke and mortality risk with mixed results.[12–16] In addition, two meta-analyses of AF ablation RCTs showed contradictory results on clinical outcomes.[17 18]

Our aim was to evaluate the long-term effects of catheter ablation on the risk of all-cause mortality or stroke in patients with AF in a large real-world cohort followed up by national registries.

METHODS

Ablation patients

We included all consecutive patients who underwent first-time AF ablation between 1 January 2008 and 31 December 2018 at three high-volume electrophysiology centres (>300 AF ablations/year) in Sweden (Karolinska University Hospital, Stockholm; Arrhythmia Center, Stockholm; and Linköping University Hospital, Linköping). Patients were prospectively entered into local databases at the time of ablation, together with pertinent information and details about the procedure. Catheter ablation was indicated according to current national and international guidelines, and the electrophysiology procedures followed conventional and local standards as described previously.[19] All patients were on oral anticoagulants (OACs) (warfarin or novel OACs) for at least 3–4 weeks prior to the procedure and intraprocedural heparin was used to maintain activated clotting time (ACT) levels >300 s. Routine transoesophageal echocardiography was performed prior to the ablation to exclude intra-atrial thrombosis. In all cases, pulmonary vein isolation (PVI) was either performed with a radiofrequency (RF) catheter (point-by-point technique) or with a cryoballoon. Ablation in addition to PVI was carried out according to the operator's discretion and consisted of empirical lines, complex fractionated electrograms and substrate ablation. Major complications were defined as tamponade, vascular (requiring invasive treatment or blood transfusion), phrenic paralysis, stroke and death. Given the nature of the study (large sample registry study), we have limited detailed information on follow-up visits, arrhythmia monitoring and arrhythmia status. The patients were followed up according to standard of care, which in general consisted of regular cardiology clinics with 12-lead ECG and 24-hour Holter recordings 3, 6, 12 and 24 months following catheter ablation. For non-ablated patients, follow-up usually consisted of 6–12 months of follow-up with 12-lead ECG and 24-hour Holter recordings.

Control patients

The control group was selected from the Swedish National Patient Register, which is based on civic registration numbers given to all residents in Sweden irrespective of citizenship, which are used by all authorities, hospitals, open care clinics and pharmacies. The present study used codes according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10 SE). A validation study found the positive predictive value for a diagnosis of stroke (I63) to be 98.6% and for AF (I48) 97%.[20] The civic registration numbers make it possible to follow every patient's medical history as well as purchases of prescribed drugs. The control group consisted of patients with a registered AF diagnosis (I48) at a hospital admission or outpatient clinic visit between 2008 and 2018. Patients with a previous diagnosis of catheter ablation (Nordic Medico-Statistical Committee (NOMESCO) code beginning with FPB or Swedish procedure code DF003) were excluded, as well as patients who had lived less than a year in Sweden prior to study inclusion.

Patient and public involvement

This research was conducted without patient involvement.

Matching

A total of 10 control patients per case were selected, matched by age and sex. For all patients in the ablation and control group, baseline characteristics including comorbidities, socioeconomic status and medications at baseline were collected from the Swedish National Patient Register, Statistics Sweden and Swedish Drug Register, respectively. Medication at baseline was defined as a filled prescription within 6 months before study inclusion. Information about medical events during follow-up was obtained from the Swedish National Patient Register and the Cause of Death Register. Baseline characteristics variables known to have a potential impact on the primary combined endpoint (all-cause mortality or stroke) and available from the registry databases were selected for propensity score matching. A total of 29 variables were included in the propensity score matching (online supplemental table 1).

The CHA_2DS_2-VASc (heart failure, hypertension, age, diabetes, stroke, vascular disease and gender) scores were calculated based on patient characteristics. The primary endpoint was a composite of all-cause mortality or stroke. Secondary endpoints were all-cause mortality, stroke, cardiovascular mortality and heart failure. The only variable with missing data was classification of level of education and those patients (n=410) were classified as having 'unknown' level of education.

Statistical analysis

Continuous variables are expressed as mean±SD or as median with IQR for skewed or non-normal data. Comparisons of means were made using Student's t-test for independent samples or Mann-Whitney U test for non-normal distributions. Categorical variables are expressed as absolute frequencies and percentages and compared with Pearson's X^2 test. Propensity scores were obtained for the likelihood of AF ablation through logistic regression. Matching of scores for cases and controls was made to the nearest neighbour in a 1:1 fashion with a calliper of 0.1. No replacements were used. Cox regression was used to evaluate the association between outcomes and AF ablation.

A falsification endpoint (the incidence of a new diagnosis of cancer) was used to detect the prognostically important differences in background risk factors between the cohorts that we were not able to detect from registry data and hence could not adjust for. A p value of <0.05 and a standardised difference of >0.1 were considered significant for all statistical tests. CIs are given as 95%. The statistical analyses were performed using Stata V.17.0.

RESULTS

Baseline characteristics

Over an 11-year study period, we included 5628 patients who underwent a first-time AF ablation at three EP sites. The ablation techniques were PVI only by RF point-by-point ablation (66.1%), cryoballoon PVI (23.8%) and PVI plus additional atrial ablation (10.1%). Major complications occurred in 1.9% of the patients. There were no deaths related to the procedures. One or more redo procedures were made among 30.9% of the patients during follow-up (table 1). Changes in ablation techniques over the study period included a larger proportion of cryoballoon being performed during the first half of the study period (32% in 2008–2013 vs 24% in 2014–2018) and the introduction of contact-force RF ablation catheters from 2014 and onwards. Throughout the whole study, ablation catheters and three-dimensional mapping system from Biosense Webster (Diamond Bar, California) were used in the vast majority (94%) of all RF

Table 1 Procedural characteristics (N=5628)

		n (%)
Hospital site	Karolinska University Hospital	2466 (43.8)
	Arrhythmia Center	1690 (30.0)
	Linköping University Hospital	1472 (26.2)
BMI	26.8 (24.5–29.9)	
Structural heart disease		627 (11.3)
AF type	Paroxysmal	3559 (66)
	Persistent	1282 (23.8)
	Long-standing persistent	547 (10.1)
Type of ablation	RF PVI only	2684 (64.7)
	Cryoballoon PVI only	1121 (27.0)
	RF PVI+additional ablation	345 (8.3)
Procedural duration (min)	171 (136–207)	
Major complications	Tamponade	34 (0.8)
	Vascular (requiring invasive treatment or blood transfusion)	9 (0.2)
	Phrenic paralysis	15 (0.4)
	Stroke	20 (0.5)

AF, atrial fibrillation; BMI, body mass index; PVI, pulmonary vein isolation; RF, radiofrequency.

ablation cases. The control group consisted of 48 676 patients with AF who had not undergone AF ablation, matched by age and sex to the study patients.

Compared with the control group, patients in the study group were healthier with less comorbidities, were more likely to be on an antiarrhythmic medication, had used healthcare resources to a greater extent and had a different socioeconomic status, characterised by a higher median disposable income and higher level of education. Propensity score matching resulted in two cohorts of equal size (n=3955) and similar characteristics (table 2 and online supplemental table 1). The proportion of patients on an OAC, as per pharmacy dispense records, throughout the study period showed a lower proportion of ablated patient on an OAC when compared with the control group (online supplemental table 2).

The falsification endpoint newly detected cancer disease occurred equally often among cases and controls (HR 1.06, 95% CI 0.92 to 1.23), indicating that any major residual confounding due to unaccounted comorbidity was unlikely. The mean follow-up was 4.5±2.8 years and there were no losses during follow-up due to the registry nature of the study. In the following, all comparisons refer to the propensity score-matched cohorts.

Study endpoint comparison

The primary combined endpoint of stroke or all-cause mortality occurred in fewer patients in the ablation group than in the control group (174 vs 293 patients), with an HR of 0.58 (95% CI 0.48 to 0.69) (figure 1). This was driven by all-cause mortality (HR 0.51, 95% CI 0.41 to 0.64) (figure 2), whereas a statistically non-significant trend in favour of catheter ablation was observed for stroke, with 56 patients with stroke in the ablated vs 72 patients in the control group (HR 0.75, 95% CI 0.53 to 1.06) (figure 3). When excluding strokes <30 days postablation, the trend in favour of catheter ablation remained statistically non-significant (121 events; HR 0.83, 95% CI 0.51 to 1.04). Cardiovascular death was common, but in patients who underwent catheter ablation cardiovascular death was significantly reduced (55 patients in the ablated vs 122 patients in the control group), with an HR of 0.44 (95% CI 0.32 to 0.60). The primary combined endpoints for the first (2008–2013) and second (2014–2018) half of the study period had an HR of 0.62 (CI 0.50 to 0.77) and 0.51 (95% CI 0.37 to 0.72), respectively. A summary of the primary and secondary outcomes can be found in table 3. A separate outcome assessment considering significant covariates in the Cox regression analysis and using death as a confounding competing risk to stroke showed similar results (online supplemental table 3).

In a sensitivity analysis, only regarding patients with heart failure, the apparent benefit of catheter ablation was greater than in the overall cohort (HR 0.41, CI 0.28 to 0.61) for the primary combined endpoint of all-cause mortality or stroke. After exclusion of patients with a heart failure diagnosis prior to inclusion (full cohort n=45 402 and propensity score-matched cohort n=6544), there was a reduction in the incidence of de novo heart failure diagnoses among those who underwent catheter ablation than among those in the control group (HR 0.77, CI 0.61 to 0.98) (figure 4). During follow-up, almost twice as many ablated patients underwent direct-current cardioversions (DCCV) (following the 3-month blanking period) when compared with the control group (419 vs 269, p<0.001).

Of the 128 patients with stroke, 36 (28.1%) were not on an OAC at the time of stroke diagnosis (20 and 16 patients in the ablation and control group, respectively). However, some of these patients had no indication for OAC (CHA_2DS_2-VASc score=0), leaving a final of 24 (18.8%) patients with stroke (16 and 8 patients in the ablation and control group, respectively), not receiving an OAC despite treatment indication.

DISCUSSION

The main finding of this propensity matched case–control study was that AF ablation was associated with reduction in the primary endpoint of all-cause mortality or stroke. This result was driven by a marked decrease in all-cause mortality, in particular cardiovascular death, with stroke reduction showing a trend in favour of catheter ablation. The clinical benefit of ablation was greater in those with a previous diagnosis of heart failure, and the incidence of a de novo heart failure diagnosis was reduced in ablated patients.

During the last decade, several studies have evaluated whether catheter ablation can reduce mortality in patients with AF, both in RCTs and observational real-life cohorts, with conflicting

Table 2 Baseline characteristics before and after propensity score matching

		Full cohort (before PS score matching)				PS-matched cohorts			
		Controls (n=48 676)	Cases (N=5628)	P value	Std diff	Controls (n=3955)	Cases (n=3955)	P value	Std diff
Demographic characteristics on index date									
Age, years	Mean (SD)	61.1 (10.0)	59.9 (10.0)	<0.001	0.114	61.7 (9.5)	60.9 (9.7)	<0.001	0.077
	Median (IQR)	63 (56–68)	61 (54–67)			64 (57–68)	62 (55–68)		
Female	n (%)	14 902 (30.6)	1564 (27.8)	<0.001	0.062	1182 (29.9)	1168 (29.5)	0.731	0.008
Education	Elementary, n (%)	12 198 (25.1)	822 (14.6)	<0.001	0.374	652 (16.5)	657 (16.6)	0.952	0.013
	High school, n (%)	22 030 (45.3)	2243 (39.9)			1640 (41.5)	1617 (40.9)		
	University, n (%)	14 063 (28.9)	2538 (45.1)			1641 (41.5)	1661 (42.0)		
	Unknown, n (%)	385 (0.8)	25 (0.4)			22 (0.6)	20 (0.5)		
Income (KSEK/year)	Mean (SD)	273.2 (1418.6)	415.2 (934.1)	<0.001*	−0.118	469.3 (4842.9)	363.7 (649.8)	0.014*	0.031
	Median (IQR)	211.7 (143.9–305.8)	287.9 (192.8–419.7)			261.3 (178.2–362.8)	269 (179.3–394.5)		
Civil status	Alone, n (%)	21 863 (44.9)	2004 (35.6)	<0.001	0.191	1402 (35.4)	1435 (36.3)	0.439	−0.017
Born abroad	n (%)	6586 (13.5)	480 (8.5)	<0.001	0.160	352 (8.9)	367 (9.3)	0.557	−0.013
Healthcare utilisation during 10 years prior to index date									
Outpatient visits	Mean (SD)	8.1 (22.6)	12.1 (11.1)	<0.001*	−0.229	12.2 (43.2)	12.0 (10.2)	0.347*	0.001
	Median (IQR)	4 (1–10)	10 (6–15)			8 (4–14)	10 (5–15)		
Hospitalisation	Mean (SD)	2.9 (4.3)	4.4 (5.0)	<0.001*	−0.314	4.0 (5.2)	4.0 (4.5)	0.347	−0.001
Comorbidities prior to index date, n (%)									
Hypertension		21 002 (43.2)	2409 (42.8)	0.623	0.007	1927 (48.7)	1801 (45.5)	0.005	0.064
Heart failure		8166 (16.8)	738 (13.1)	<0.001	0.103	619 (15.7)	580 (14.7)	0.221	0.028
Ischaemic heart disease		6195 (12.7)	396 (7.0)	<0.001	0.192	322 (8.1)	316 (8.0)	0.804	0.006
Chronic kidney disease		1922 (4.0)	82 (1.5)	<0.001	0.154	75 (1.9)	67 (1.7)	0.498	0.015
Diabetes (type 1 and 2)		6804 (14.0)	396 (7.0)	<0.001	0.228	326 (8.2)	331 (8.4)	0.839	0.005
Drug prescriptions 6 months prior to index date, n (%)									
Amiodarone		721 (1.5)	887 (15.8)	<0.001	−0.526	432 (10.9)	423 (10.7)	0.744	0.007
Flecainide		1887 (3.9)	1220 (21.7)	<0.001	−0.553	678 (17.4)	653 (16.5)	0.452	0.017
Dronedarone		774 (1.6)	1104 (19.6)	<0.001	−0.612	500 (12.6)	540 (13.7)	0.183	−0.030
NOAC		4299 (8.8)	1982 (35.2)	<0.001	−0.671	1351 (34.2)	1269 (32.1)	0.050	0.044
Warfarin		14 486 (29.8)	3750 (66.6)	<0.001	−0.793	2562 (64.8)	2556 (64.6)	0.888	0.003
Digoxin		3965 (8.2)	328 (5.8)	<0.001	0.091	295 (7.5)	272 (6.9)	0.316	0.023

*Mann-Whitney U test.
KSEK, 1000 Swedish krona; NOAC, non-vitamin K antagonist oral anticoagulants; PS, propensity score; Std diff, standardised differences.

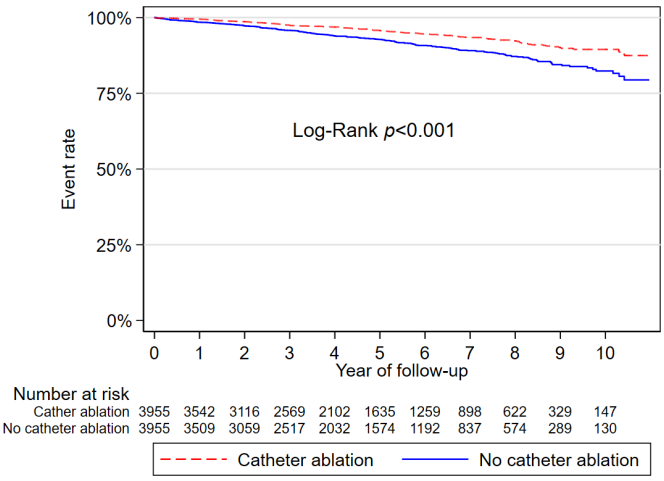

Figure 1 Combined primary endpoint of all-cause mortality or stroke after propensity score matching in patients with atrial fibrillation treated medically or with catheter ablation.

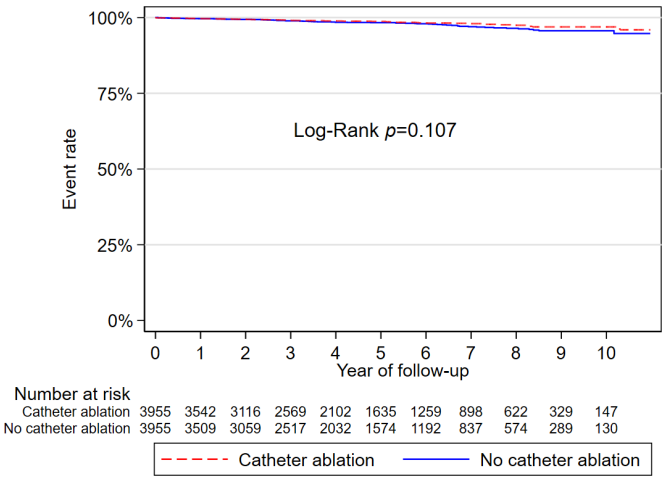

Figure 3 Stroke in the propensity score-matched cohorts in patients with atrial fibrillation treated medically or with catheter ablation.

results.[11–16] To date, the CABANA trial is the only large RCT to include a general AF population randomised to catheter ablation or medical therapy.[11] The trial failed to show a significant benefit of catheter ablation (HR 0.86, CI 0.65 to 1.15) for the composite primary endpoint of death, disabling stroke, serious bleeding or cardiac arrest. However, in the on-treatment analysis, there was a clear benefit for catheter ablation on all-cause mortality (HR 0.67, CI 0.50 to 0.89) and stroke (HR 0.60, CI 0.42 to 0.86).

In published observational case–control studies, majority have found that catheter ablation is associated with a reduction in mortality and stroke. For instance, Noseworthy *et al*[21] used a large administrative database to identify 183 760 patients who would fit the CABANA enrolment period and estimated that, for the 73.8% who were potentially trial-eligible, there was a significant reduction in the CABANA composite endpoint (HR 0.70, CI 0.63 to 0.77). Another study using discharge and surgical records from California non-federal hospitals reported a significantly lower mortality (HR 0.59, CI 0.45 to 0.77) and ischaemic stroke (HR 0.68, CI 0.47 to 0.95). On the contrary, a propensity score-matched cohort study based on the outcome registry

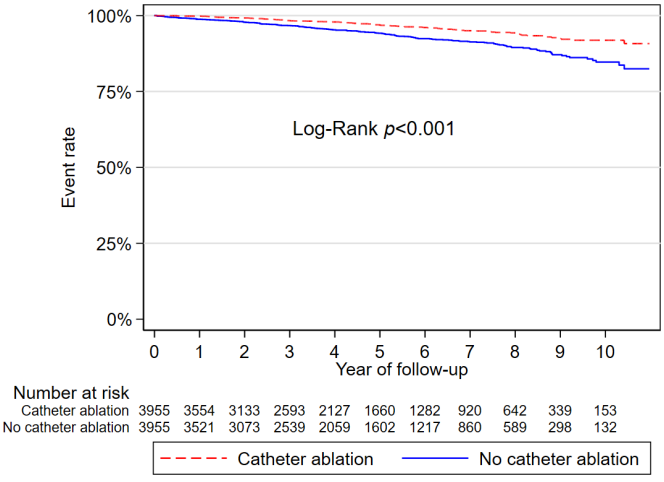

Figure 2 All-cause mortality in the propensity score-matched cohorts in patients with atrial fibrillation treated medically or with catheter ablation.

for better informed treatment of atrial fibrillation (ORBIT-AF) found no difference in all-cause and cardiovascular deaths nor neurological events during 1 year of follow-up.[13] Similarly, a Taiwanese cohort study of 846 patients who underwent AF ablation between 2003 and 2009 matched with 11 324 AF controls found no difference in mortality, hospitalisation for heart failure or stroke during a 3.5-year follow-up.[12]

Our results in consecutive real-world patients are in line with the on-treatment CABANA results and are strengthened by the large number of patients, the long duration and completeness of follow-up, and the lack of endpoint adjudication bias due to the use of data from national registries. In our study, ablated patients with heart failure obtained a particularly large reduction in the primary endpoint and the development of de novo heart failure was significantly reduced in the catheter ablation group. This AF–heart failure interaction is a possible explanation for the observed reduction in all-cause mortality and is in line with previous findings from three RCTs.[8–10] While a decreased stroke risk may offer another possible explanation for better survival, we did not find a significant difference in stroke between the study groups. However, for reasons not known, there was a significant proportion of patients (18.8%) who were not on an OAC at the time of stroke diagnosis despite a CHA_2DS_2-VASc score ≥1, the majority being ablated patients. Furthermore, the proportion of patients on an OAC was lower in the ablated patients compared with the control group (67.2% vs 82.6% at the end of follow-up) (online supplemental table 2). One may speculate that the physician and/or patient misbelief that OAC is no longer needed after AF ablation led to drug discontinuation in some of these cases and may explain why there was no significant stroke reduction in the ablation group.

In our study, the ablation group represents consecutive first-time AF ablations from three major EP centres in Sweden and not from a national health registry, which makes this study different from the other previously published case–control registry studies. The positive results may therefore have been influenced by the inclusion of only high-volume centres. Studies have shown that high-volume centres have a lower complication rate and recent clinical trials have largely involved high-volume academic centres.[22] Our study period (2008–2018) covers a period of several technological advances in AF catheter ablation, such as contact-force sensing catheters (used in approximately half of the ablation group) and one-shot devices

Table 3 Primary and secondary clinical outcomes in patients with atrial fibrillation receiving catheter ablation versus controls

	Full cohort before propensity score matching (n=54 311)			Propensity score-matched cohorts (n=7910)		
	Events (n)	HR* (95% CI)	P value	Events (n)	HR* (95% CI)	P value
Primary outcome						
Combined all cause-mortality or stroke	6728	0.30 (0.26 to 0.34)	<0.001	466	0.58 (0.48 to 0.69)	<0.001
Secondary outcomes						
All-cause mortality	5503	0.27 (0.23 to 0.31)	<0.001	363	0.51 (0.41 to 0.64)	<0.001
CV mortality	2583	0.25 (0.20 to 0.32)	<0.001	177	0.44 (0.32 to 0.60)	<0.001
Stroke	1670	0.38 (0.30 to 0.48)	<0.001	128	0.75 (0.53 to 1.07)	0.107
Heart failure†	3456	0.47 (0.41 to 0.55)	<0.001	280	0.77 (0.61 to 0.98)	0.032

*HR using non-catheter ablation as the reference.
†Excludes patients with a heart failure diagnosis prior to inclusion (full cohort n=45 402 and propensity score-matched cohort n=6544).
CV, cardiovascular.

such as cryoballoon. This may also explain our positive results in comparison with some older case–control studies[12 13] as well as the CABANA study with an earlier inclusion period.[11]

An interesting finding was that almost twice as many patients in the catheter ablation group underwent DCCV. Most likely this reflects a dedication to sinus rhythm maintenance in this patient group, although we do not have data on rhythm status during follow-up. Therefore, our results may be interpreted as a rhythm versus rate strategy comparison, showing a clear benefit for rhythm control. This is in line with the recent EAST-AFNET 4 (Early Rhythm-Control Therapy in Patients with Atrial Fibrillation) trial which demonstrated that early rhythm control therapy was associated with reduction in the composite endpoint of death from cardiovascular causes, stroke or hospitalisation with worsening heart failure or acute coronary syndrome.[23] Nevertheless, our study aimed to compare therapeutic strategies, that is, ablation or no ablation, which is a more relevant clinical question than the effectiveness in sinus rhythm restoration by catheter ablation per se.

Limitations

This is a retrospective registry-based study which shows associations but cannot establish causal relationships. Moreover, given the study design, it cannot eliminate all potential differences between the treatment groups. Before propensity score matching, the two study groups differed in almost all baseline characteristics analysed, and despite adjustments possible unknown confounders may exist which may boost the effect of catheter ablation. Nonetheless, using cancer diagnosis as a falsification endpoint, without any clear relationship to the type of treatment studied, we could not show a significant difference between the groups. Another limitation is the incompleteness of medical records, which commonly leads to underestimation of comorbidities, although in theory balanced across both treatment groups. Also, one may speculate that more specialised and continuous medical attention was given to ablated patients, which in turn may lead to both an overall improved healthcare but also higher registration of medical events, which may have affected the observed ablation benefit in both directions. Furthermore, AF subtype is not commonly coded in the medical records and could not be included in the study subanalysis and we can therefore not make any conclusions on the benefits of catheter ablation on specific AF subtypes.

Finally, there have arguably been significant advancements in catheter ablation during the study period which may have affected the outcomes. However, when we analysed the first and second half of the study period, the primary combined endpoint showed similar positive results for catheter ablation.

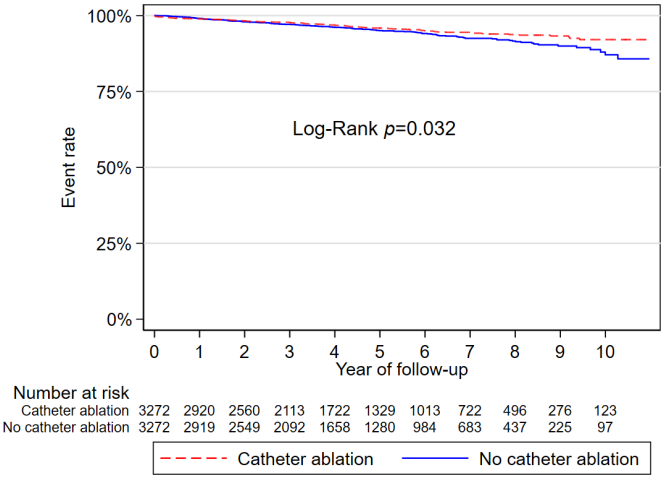

Figure 4 Heart failure in the propensity score-matched cohorts in patients with atrial fibrillation treated medically or with catheter ablation.

CONCLUSIONS

Catheter ablation of AF was associated with reduced all-cause mortality or stroke when compared with medical therapy in real-world Swedish patients. This result was driven by a marked decrease in all-cause mortality, with stroke reduction showing a trend in favour of catheter ablation.

Author affiliations
[1]Department of Cardiology, Karolinska University Hospital, Stockholm, Sweden
[2]Department of Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden
[3]Kerckhoff Heart and Thorax Center, Bad Nauheim, Germany
[4]Department of Cardiology and Department of Health, Medicine and Caring Sciences, Linköping University, Linkoping, Sweden
[5]Arrhythmia Center, Stockholm, Sweden
[6]Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden
[7]Department of Clinical Sciences, Karolinska Institutet, Stockholm, Sweden
[8]Department of Cardiology, Danderyd University Hospital, Stockholm, Sweden

Twitter Finn Akerström @finnakerstrom and Emmanouil Charitakis @mcharitakis

Contributors FAk, JH, MJ-U, PI, FB and ND designed the study. FAk, JH, EC and FT acquired the data. FAk, LF and EC performed the statistical analysis. FAk, MJ-U, ND, LF, JS, ES and FB were involved in the data interpretation. FAk drafted the manuscript, approved its final version and is guarantor for the content of the manuscript. JH, EC, FT, FAs, HB, TB, FB, ND, AE, LF, PI, AHJ, GK, AP-N, BS, OS, SS, JS, ES, JT, YT and MJ-U provided critical revision, editing and approval of the final manuscript.

Funding This study was supported by research grants from the Swedish Research Council (Vetenskapsrådet, 2019-06102 and 2021-00202), Swedish Heart-Lung Foundation (Hjärt-Lungfonden, 20190301, 20200537 and 202110302), Center for Innovative Medicine (FoUI-954510) and ALF (FoUI-954075) Region Stockholm.

Competing interests ND and AP-N have received speaker fees from Johnson & Johnson. FAk is a consultant for Johnson & Johnson and Abbott. MJ-U is a consultant for Johnson & Johnson and Medtronic and has received research grants from Medtronic. FB is a consultant for Medtronic and Biotronik and has received speaker fees from Biosense Webster, Biotronik, Boston Scientific, Abbott, Pfizer, Novartis, Amgen and Orion. ES has received institutional consulting fees from lecture fees from Bayer, Bristol-Myers Squibb-Pfizer, Boehringer Ingelheim, Johnson & Johnson and Merck Sharp & Dohme.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study involves human participants and was approved by Stockholm (Sweden) regional ethical review board (ID: 2016/147-31). This was a retrospective study where informed consent was not mandatory.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Requests should be made to FAk.

ORCID iDs
Finn Akerström http://orcid.org/0000-0003-0611-8416
Emmanouil Charitakis http://orcid.org/0000-0002-2514-5324

REFERENCES

1 Hindricks G, Portpara T, Dagres N, *et al*. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association of Cardio-Thoracic surgery (EACTS). *Eur Heart J* 2020;00:1–126.
2 Krijthe BP, Kunst A, Benjamin EJ, *et al*. Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. *Eur Heart J* 2013;34:2746–51.
3 Virani SS, Alonso A, Aparicio HJ, *et al*. Heart disease and stroke Statistics-2021 update: a report from the American heart association. *Circulation* 2021;143:e254–743.
4 Chugh SS, Havmoeller R, Narayanan K, *et al*. Worldwide epidemiology of atrial fibrillation: a global burden of disease 2010 study. *Circulation* 2014;129:837–47.
5 Wilber DJ, Pappone C, Neuzil P, *et al*. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA* 2010;303:333–40.
6 Morillo CA, Verma A, Connolly SJ, *et al*. Radiofrequency ablation vs Antiarrhythgmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA* 2014;311:692–700.
7 Andrade JG, Wells GA, Deyell MW, *et al*. Cryoablation or drug therapy for initial treatment of atrial fibrillation. *N Engl J Med* 2021;384:305–15.
8 Marrouche NF, Kheirkhahan M, Brachmann J. Catheter ablation for atrial fibrillation with heart failure. *N Engl J Med* 2018;379:492:417–27.:.
9 Di Biase L, Mohanty P, Mohanty S, *et al*. Ablation versus amiodarone for treatment of persistent atrial fibrillation in patients with congestive heart failure and an implanted device: results from the AATAC multicenter randomized trial. *Circulation* 2016;133:1637–44.
10 Parkash R, Wells GA, Rouleau J, *et al*. Skanes A et al.randomized ablation-based rhythm-control versus rate-control trial in patients with heart failure and atrial fibrillation: results from the RAFT-AF trial. *Circulation* 2022;145:1693–704.
11 Packer DL, Mark DB, Robb RA, *et al*. Effect of catheter ablation vs antiarrhythmic drug therapy on mortality, stroke, bleeding, and cardiac arrest among patients with atrial fibrillation: the CABANA randomized clinical trial. *JAMA* 2019;321:1261–74.
12 Chang C-H, Lin J-W, Chiu F-C, *et al*. Effect of radiofrequency catheter ablation for atrial fibrillation on morbidity and mortality: A nationwide cohort study and propensity score analysis. *Circ Arrhythm Electrophysiol* 2014;7:76–82.
13 Freeman JV, Shrader P, Pieper KS, *et al*. Outcomes and anticoagulation use after catheter ablation for atrial fibrillation. *Circ Arrhythm Electrophysiol* 2019;12:e007612.
14 Srivatsa UN, Danielsen B, Amsterdam EA, *et al*. CAABL-AF (California study of ablation for atrial fibrillation): mortality and stroke. *Circ: Arrhythmia and Electrophysiology* 2018;11.
15 Friberg L, Tabrizi F, Englund A. Catheter ablation for atrial fibrillation is associated with lower incidence of stroke and death: data from Swedish health registries. *Eur Heart J* 2016;37:2478–87.
16 Yang P-S, Sung J-H, Jang E, *et al*. Catheter ablation improves mortality and other outcomes in real-world patients with atrial fibrillation. *J Am Heart Assoc* 2020;9:e015740.
17 Zheng YR, Chen ZY, Ye LF, *et al*. Long-term stroke rates after catheter ablation or antiarrhythmic drug therapy for atrial fibrillation: a meta-analysis of randomized trials. *J Geriatr Cardiol* 2015;12:507–14.
18 Ravi V, Poudyal A, Lin L, *et al*. Mortality benefit of catheter ablation versus medical therapy in atrial fibrillation: an RCT only meta-analysis. *J Cardiovasc Electrophysiol* 2022;33:178–93.
19 Akerström F, Bastani H, Insulander P, *et al*. Comparison of regular atrial tachycardia incidence after circumferential radiofrequency versus cryoballoon pulmonary vein isolation in real-life practice. *J Cardiovasc Electrophysiol* 2014;25:948–52.
20 Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish nation inpatient register. *BMC Public Health* 2011;11:450.
21 Noseworthy PA, Gersh BJ, Kent DM, *et al*. Atrial fibrillation ablation in practice: assessing CABANA generalizability. *Eur Heart J* 2019;40:1257–64.
22 Cheng EP, Liu CF, Yeo I, *et al*. Risk of mortality following catheter ablation of atrial fibrillation. *J Am Coll Cardiol* 2019;74:2254–64.
23 Kirchhof P, Camm AJ, Goette A, *et al*. Early rhythm-control therapy in patients with atrial fibrillation. *N Engl J Med* 2020;383:1305–16.

Supplementary table 1: Full baseline characteristics of all variables used for propensity-score matching

		Full cohort (before propensity score matching)				Propensity score matched cohorts			
		Controls (n=48,676)	**Cases (n=5,628)**	***P***	**std-diff**	**Controls (n=3,955)**	**Cases (n=3,955)**	***P***	**std-diff**
Demographic characteristics on index date									
Age, years	mean (s.d.)	61.1 (10.0)	59.9 (10.0)	<0.001	0.114	61.7 (9.5)	60.9 (9.7)	<0.001	0.077
	median (IQR)	63 (56-68)	61 (54-67)			64 (57-68)	62 (55-68)		
Females		14902 (30.6%)	1564 (27.8%%)	<0.001	0.062	1,182 (29.9%)	1168 (29.5%)	0.731	0.008
Year of index date	2008	2,662 (5.5%)	263 (4.7%)	<0.001	0.200	155 (3.9%)	166 (4.2%)	1.0	0.021
	2009	2,814 (5.8%)	284 (5.0%)			194 (4.9%)	198 (5.0%)		
	2010	4,804 (9.9%)	475 (8.4%)			312 (7.9%)	316 (8.0%)		
	2011	4,587 (9.4%)	462 (8.2%)			287 (7.3%)	292 (7.4%)		
	2012	5,093 (10.5%)	524 (9.3%)			376 (9.5%)	369 (9.3%)		
	2013	4,974 (10.2%)	517 (9.2%)			374 (9.5%)	376 (9.5%)		
	2014	5,920 (12.2%)	610 (10.8%)			456 (11.5%)	458 (11.6%)		
	2015	5,751 (11.8%)	634 (11.3%)			468 (11.8%)	464 (11.7%)		
	2016	5,553 (11.4%)	739 (13.1%)			522 (13.2%)	517 (13.1%)		
	2017	3,635 (7.5%)	570 (10.1%)			40 (10.6%)	406 (10.3%)		

	2018	2,884 (5.9%)	550 (9.8%)			392 (9.9%)	393 (9.9%)		
Education	Elementary	12,198 (25.1%)	822 (14.6%)	<0.001	0.374	652 (16.5%)	657 (16.6%)	0.952	0.013
	High school	22,030 (45.3%)	2243 (39.9%)			1,640 (41.5%)	1,617 (40.9%)		
	University	14,063 (28.9%)	2538 (45.1%)			1,641 (41.5%)	1,661 (42.0%)		
	Unknown	385 (0.8%)	25 (0.4%)			22 (0.6%)	20 (0.5%)		
Income (KSEK/year)	mean (s.d.)	273.2 (1,418.6)	415.2 (934.1)	<0.001*	-0.118	469.3 (4,842.9)	363.7 (649.8)	0.014*	0.031
	median (IQR)	211.7 (143.9-305.8)	287.9 (192.8-419.7)			261.3 (178.2-362.8)	269 (179.3-394.5)		
Civil status	Alone	21,863 (44.9%)	2,004 (35.6%)	<0.001	0.191	1,402 (35.4%)	1435 (36.3%)	0.439	-0.017
Born abroad		6,586 (13.5%)	480 (8.5%)	<0.001	0.160	352 (8.9%)	367 (9.3%)	0.557	-0.013
Health care utilization during 10 years prior to index date									
No. of outpatients visits	mean (s.d.)	8.1 (22.6)	12.1 (11.1)	<0.001*	-0.229	12.2 (43.2)	12.0 (10.2)	0.347*	0.001
	median (IQR)	4 (1-10)	10 (6-15)			8 (4-14)	10 (5-15)		
No. of hospitlizations	mean (s.d.)	2.9 (4.3)	4.4 (5.0)	<0.001*	-0.314	4.0 (5.2)	4.0 (4.5)	0.347	-0.001
	median (IQR)	2 (0-4)	3 (5)			3 (1-5)	3 (1-5)		
No. of hospital days	mean (s.d.)	10.8 (25.9)	7.1 (11.0)	<0.001*	0.186	8.0 (12.9)	7.6 (12.0)	0.032	0.038
	median (IQR)	3 (0-13)	4 (1-9)			4 (1-10)	4 (1-9)		
Comorbidities prior to index date									
Hypertension		21,002 (43.2%)	2409 (42.8%)	0.623	0.007	1,927 (48.7%)	1801 (45.5%)	0.005	0.064

Hyperlipidemia		357 (0.7%)	29 (0.5%)	0.065	0.028	23 (0.6%)	23 (0.6%)	1.000	0.000
COPD		2,356 (4.8%)	116 (2.1%)	<0.001	0.152	102 (2.6%)	91 (2.3%)	0.423	0.018
Heart failure		8,166 (16.8%)	738 (13.1%)	<0.001	0.103	619 (15.7%)	580 (14.7%)	0.221	0.028
Ischemic heart disease		6,195 (12.7%)	396 (7.0%)	<0.001	0.192	322 (8.1%)	316 (8.0%)	0.804	0.006
Chronic kidney disease		1,922 (4.0%)	82 (1.5%)	<0.001	0.154	75 (1.9%)	67 (1.7%)	0.498	0.015
Diabetes (type 1 and 2)		6804 (14.0%)	396 (7.0%)	<0.001	0.228	326 (8.2%)	331 (8.4%)	0.839	0.005
CHA_2DS_2-VASc		1.6±1.5	1.4±1.4	<0.001	0.162	1.6±1.3	1.5±1.4	<0.001	0.083
Drug prescriptions 6 months prior to index date									
Amiodarone		721 (1.5%)	887 (15.8%)	<0.001	-0.526	432 (10.9%)	423 (10.7%)	0.744	0.007
Flecainide		1,887 (3.9%)	1,220 (21.7%)	<0.001	-0.553	678 (17.4%)	653 (16.5%)	0.452	0.017
Sotalol		1,424 (2.9%)	389 (6.9%)	<0.001	-0.185	274 (6.9%)	265 (6.7%)	0.688	0.009
Dronedarone		774 (1.6%)	1,104 (19.6%)	<0.001	-0.612	500 (12.6%)	540 (13.7%)	0.183	-0.030
Betablocker		27,119 (55.9%)	4,051 (72.0%)	<0.001	-0.340	2,887 (73.0%)	2,801 (70.8%)	0.031	0.048
Calcium antagonist		1,179 (2.4%)	230 (4.1%)	<0.001	-0.094	157 (4.0%)	152 (3.8%)	0.772	0.007
Loop diuretic		6,741 (13.9%)	477 (8.5%)	<0.001	0.171	413 (10.4%)	389 (9.8%)	0.371	0.020
ACEI /ARB		20,871 (42.9%)	2,244 (39.9%)	<0.001	0.061	1,796 (45.4%)	1,681 (42.5%)	0.009	0.059
Antiplatelet		9,824 (20.2%)	554 (9.8%)	<0.001	0.293	335 (8.5%)	360 (9.1%)	0.321	-0.022

NOAC		4,299 (8.8%)	1982 (35.2%)	<0.001	-0.671	1,351 (34.2%)	1,269 (32.1%)	0.050	0.044
Warfarin		14,486 (29.8%)	3,750 (66.6%)	<0.001	-0.793	2562 (64.8%)	2,556 (64.6%)	0.888	0.003
Digoxin		3,965 (8.2%)	328 (5.8%)	<0.001	0.091	295 (7.5%)	272 (6.9%)	0.316	0.023
*Man-Whitney U test. ACE = angiotensin receptor enzyme inhibitor; ARB = angiotensin receptor blockers; COPD = chronic obstructive pulmonary disease; NOAC = non-vitamin K antagonist oral anticoagulants; std-diff = standardised differences.									

Supplementary table 2: Oral anticoagulation during the study period

Year	Full cohort (before propensity score matching)				Propensity score matched cohorts					
	Controls		Cases		Controls		Cases		Warfarin/NOAC	
	Warfarin	NOAC	Warfarin	NOAC	Warfarin	NOAC	Warfarin	NOAC	*P*	std-diff
2008	16.9%	0%	88.2%	0%	71.6%	0%	86.1%	0%	0.001	-0.361
2009	20.9%	0%	68.8%	0%	71.7%	0.3%	69.4%	0%	0.457	0.056
2010	23.9%	0.1%	65.8%	0%	70.4%	0%	65.8%	0%	0.072	0.099
2011	28.8%	0.2%	61.2%	0.2%	71.1%	0.3%	62.2%	0.2%	<0.001	0.191
2012	34.4%	1.5%	57.7%	3.1%	70.6%	3.1%	59.2%	3.2%	<0.001	0.246
2013	39.6%	5.2%	53.3%	6.3%	67.7%	7.9%	56.7%	5.8%	<0.001	0.288
2014	38.0%	9.1%	48.5%	13.0%	62.7%	15.5%	52.2%	12.2%	<0.001	0.309
2015	35.0%	14.4%	41.0%	21.7%	53.2%	25.2%	44.2%	20.9%	<0.001	0.296
2016	31.9%	20.2%	30.7%	32.0%	45.3%	34.6%	33.4%	31.0%	<0.001	0.352
2017	29.1%	25.9%	23.3%	40.0%	38.7%	43.1%	25.8%	39.4%	<0.001	0.382
2018	25.9%	31.7%	19.3%	45.8%	32.0%	51.3%	21.6%	45.8%	<0.001	0.375
F/U end	26.2%	29.3%	20.0%	45.0%	33.1%	49.5%	22.4%	44.8%	<0.001	0.360

Proportion of patients on oral anticoagulation as per pharmacy dispense records. Data is shown for the enrolled patients per year of the study period and at the end of follow-up (F/U) for all patients. NOAC = non-vitamin K antagonist oral anticoagulants; std-diff = standardised differences.

Supplementary table 3: Primary and secondary clinical outcomes in patients with atrial fibrillation receiving catheter ablation versus controls

	Full cohort before propensity score matching (n=54,311)			Propensity score matched cohorts (n=7,910)		
	No. events	**Hazard ratio* (95% CI)**	***P***	**No. events**	**Hazard ratio* (95% CI)**	***P***
Primary outcome						
Combined all cause-mortality or stroke	6,728	0.30 (0.26 – 0.34)	<0.001	466	0.55*** (0.46 – 0.67)	<0.001
Secondary outcomes						
All-cause mortality	5,503	0.27 (0.23 – 0.31)	<0.001	363	0.47*** (0.39 – 0.60)	<0.001
CV-mortality	2,583	0.25 (0.20 – 0.32)	<0.001	177	0.41*** (0.29 – 0.57)	<0.001
Stroke	1,670	0.38 (0.30 – 0.48)	<0.001	128	0.74**** (0.52 – 1.05)	0.095
Heart Failure**	3,456	0.47 (0.41 - 0.55)	<0.001	280	0.73 (0.57 – 0.92)***	0.009

*Hazard ratio using non-catheter ablation as the reference. **Excludes patients with a heart failure diagnosis prior to inclusion (full cohort n=45,402 and propensity score matched cohort n=6,544). ***Cox regression of propensity score matched cohort with covariates ****Using death as a confounding competing risk to stroke. CI = confidence interval; CV = cardiovascular.