

# Long-term effectiveness of catheter ablation in patients with atrial fibrillation and heart failure

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## Aims

Randomized trials suggest reductions in all-cause mortality and heart failure (HF) rehospitalizations with catheter ablation (CA) in patients with atrial fibrillation (AF) and HF. Whether these results can be replicated in a real-world population with long-term follow-up or varies over time is unknown. We sought to evaluate the long-term effectiveness of CA in reducing the incidence of all-cause mortality, HF hospitalizations, stroke, and major bleeding in AF–HF patients.

## Methods and results

In a cohort of patients newly diagnosed with AF–HF in Quebec, Canada (2000–2017), CA patients were matched 1:2 to controls on time and frequency of hospitalizations. Confounders were controlled for using inverse probability of treatment weighting. Multivariable Cox models adjusted for the presence of cardiac electronic implantable devices and medication use during follow-up, and the effect of time since CA was modelled with B-splines. For non-fatal outcomes, the Lunn–McNeil approach was used to account for the competing risk of death. Among 101 933 AF–HF patients, 451 underwent CA and were matched to 899 controls. Over a median follow-up of 3.8 years, CA was associated with a statistically significant reduction in all-cause mortality [hazard ratio 0.4 (95% confidence interval 0.2–0.7)], but no difference in stroke or major bleeding. The hazard of HF rehospitalization for CA patients, relative to non-CA patients, varied with time since CA ( $P=0.01$ ), with a reduction in HF rehospitalizations until approximately 3 years post-CA.

## Conclusion

Compared with matched non-CA patients, CA was associated with a long-term reduction in all-cause mortality and a reduction in HF rehospitalizations until 3 years post-CA.

## Keywords

Catheter ablation • Atrial fibrillation • Heart failure

## Introduction

Atrial fibrillation (AF) and heart failure (HF) frequently coexist<sup>1,2</sup> and are associated with an increased risk of all-cause mortality, HF hospitalizations, and stroke.<sup>1,3,4</sup> There is lack of consensus regarding optimal treatment for AF in patients with comorbid HF.<sup>1,3</sup> As pharmacological rhythm control therapies have not demonstrated long-term effectiveness in this population,<sup>5–8</sup> catheter ablation (CA) has been used to reduce AF burden and improve cardiac function.<sup>9–11</sup>

Current clinical guidelines recommend use of CA to treat AF in selected patients with HF, but specify that evidence supporting its use in this population is limited (Class IIb recommendation).<sup>12–14</sup>

Randomized trials, such as CASTLE-AF and AATAC, demonstrated that CA was associated with a reduction in HF rehospitalizations compared with medical therapy;<sup>9,10</sup> however, only CASTLE-AF showed a statistically significant decrease in all-cause mortality.<sup>9</sup> A recent sub-analysis from the CABANA trial suggested that among patients with HF, the risk of the combined endpoint of mortality, stroke, bleeding, and cardiac arrest may be reduced after CA compared with antiarrhythmic drugs (AADs).<sup>15</sup> On the other hand, CA did not appear to have an effect on stroke risk.<sup>9,10</sup> Furthermore, none of these trials assessed whether the benefit of CA may vary with time since CA.

While the results of randomized trials are encouraging, whether they are replicable in the real-world AF–HF population, persist in the

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### What's new?

- This real-world investigation of the effectiveness of catheter ablation (CA) in the atrial fibrillation (AF) population with comorbid heart failure (HF) included the largest cohort of AF-HF patients who underwent CA with the longest follow-up period.
- This study complements the results of randomized trials by accounting for the competing risk of death, medication use during follow-up (antiarrhythmic drugs and anticoagulation), repeat CA, and the time-varying effect of CA.
- Similar to the CASTLE-AF and AATAC trials, the present study demonstrated that CA is associated with a long-term reduction in all-cause mortality.
- The protective effect of CA against HF re-hospitalizations, however, was limited to 3 years post-CA.

long-term, or varies over time, remains to be determined. The objective of the present study was to evaluate the long-term effectiveness of CA in AF-HF patients in reducing the incidence of all-cause mortality, HF hospitalizations, and major morbidities [stroke/transient ischaemic attack (TIA) and major bleeding], in a real-life clinical context.

## Methods

### Data sources and population selection

Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (Med-Echo) and la Régie de l'assurance maladie du Québec (RAMQ), hospitalization and physician claims databases from the province of Quebec, Canada, were used to create the AF-HF cohort. Methods for creation of a Quebec AF cohort (from 2000 to 2013) have been published.<sup>16–19</sup> For the current AF-HF cohort, we extended follow-up to include patients with a primary or major secondary diagnosis of AF between 1 April 2000 and 31 March 2017. The AF-HF cohort was limited to patients with a hospitalization recorded in Med-Echo with HF listed as either primary or major secondary diagnosis at admission [International Classification of Disease-9th and 10th Revisions (ICD-9/10) codes: 428.0-4, 428.9/150.1-4, 150.9]. Patients entered the AF-HF cohort at the date of their first HF admission. Patients with first CA prior to cohort entry were excluded. Only patients with available medication information were included (Quebec government prescription coverage includes all patients  $\geq 65$  years and all those without private prescription insurance). Cohort creation is described further in *Figure 1*. The study received institutional review board approval from the McGill University Faculty of Medicine (A05-M79-08B).

### Ascertainment of treatment with catheter ablation

Treatment and date of CA were identified by the billed procedure code for percutaneous AF ablation in RAMQ (code 291). To ensure the CA was for AF, the date of CA billed in RAMQ was matched to a hospital admission on the same date as CA (MED-Echo) (all patients undergoing CA in Quebec are admitted to a hospital). Only matched admissions with a primary or major secondary diagnosis of AF at hospital admission were included. To exclude complex ablations for congenital heart

disease and ventricular tachycardia (also billed under RAMQ code 291), patients with a primary or major secondary diagnosis of ventricular tachycardia or any diagnosis of congenital heart disease at CA admission were excluded.

### Incidence density sampling of matched non-catheter ablation controls

To avoid immortal time bias<sup>20,21</sup> and ensure the comparability of the follow-up between CA and non-CA groups, incidence density sampling was used to select matched non-CA controls. Specifically, each patient who underwent CA was matched to two randomly selected patients. Eligible potential controls were selected based on (i) time at risk (since being diagnosed with both AF and HF) before date of CA, (ii) frequency of previous all-cause hospitalizations, and (iii) presence of a recent hospitalization (within 6 months prior to match date). Number of hospitalizations is an indicator for severity of disease and thus, its inclusion as a criterion for matching further created comparability between cases and controls.

The index date (beginning of follow-up) was the date of CA for CA patients and the matched date for the control group.

### Inverse probability of treatment weighting

To control for measured confounders, inverse probability of treatment weightings (IPTWs) were calculated from the matched sample as the inverse propensity for receiving CA (logistic regression).<sup>22–24</sup> Baseline variables incorporated into the propensity score model were predefined and listed in *Figure 2*.<sup>22</sup>

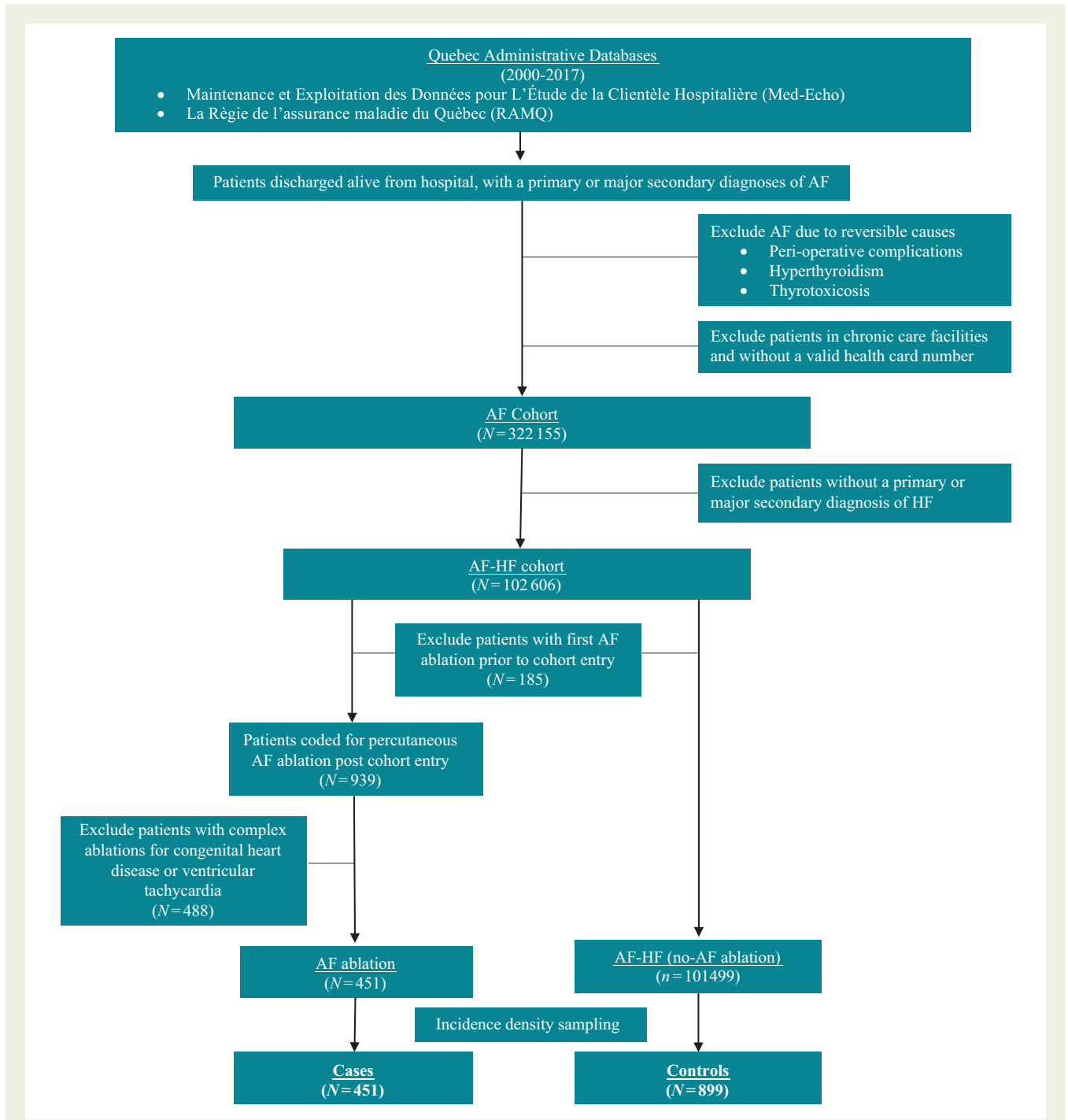
### Outcome ascertainment

Outcomes investigated were (i) all-cause mortality (primary endpoint), (ii) HF hospitalizations, (iii) stroke (including TIAs), and (iv) major bleeding (intracranial bleeding, or bleeding from the respiratory, gastrointestinal, or urinary tract) (ICD-9/10 codes listed in *Supplementary material online, Table S1*) and were analysed separately. Outcomes were identified from Med-Echo based on the primary diagnoses from hospitalizations and emergency department visits. Updated information on vital status until 31 March 2017 (end of cohort) and dates of death were obtained from both the Med-Echo and RAMQ databases.

### Statistical analyses

Standardized mean differences (SMDs) were calculated to compare the balance of covariates between cases and the matched controls in the IPTW sample.<sup>25</sup> For each covariate, an absolute SMD of  $<0.1$  was considered as evidence of a balanced distribution.<sup>25</sup> To ensure accurate adjustment for those variables that were *not* adequately balanced after IPTW, we included them as covariates in the final multivariable Cox model for the outcome.<sup>22,25</sup>

The associations of CA with the hazards of clinical endpoints were investigated using time-to-event analyses. In all analyses, Time 0 was defined as the index date, i.e. the date of the first CA for each CA case and his/her matched non-CA controls. Individual event time was defined as the time from the index date to the first event of interest and patients who had no event during the follow-up were right censored at the date of administrative end of the cohort (31 March 2017) or—for non-fatal outcomes—death of any cause, whichever came first. Crude cumulative incidence rates were calculated as the number of events per 100 person-years. In separate analyses, the associations of CA with each of the effectiveness outcomes was assessed with IPTW multivariable Cox models that additionally adjusted for the time-varying covariates, updated during the follow-up, indicating the current presence of implantable



**Figure 1** Cohort creation flow chart. AF, atrial fibrillation; HF, heart failure.

cardioverter-defibrillators (ICDs), cardiac resynchronization therapy (CRT), warfarin, direct-acting oral anticoagulants (DOACs), and AADs use during follow-up. As patients discontinued, restarted, and switched medications throughout the follow-up period, time-varying covariates accounted for current use of medications (separate time-varying covariates for warfarin, DOACs, and AADs). Current use was assumed from the time of the start of a prescription until 30 days after discontinuation. For the analyses of non-fatal outcomes, the Lunn–McNeil (cause-specific) approach was used to account for the competing risk of all-cause mortality.<sup>26</sup>

Results of the Cox and Lunn–McNeil analyses were presented in terms of adjusted hazard ratios (aHRs), with 95% confidence interval (CI).

When the proportional hazards assumption was violated ( $P < 0.05$ )<sup>27</sup> for a given outcome we employed flexible B-spline modelling of the time-dependent effect to describe how the aHR for CA varied with increasing time since CA.<sup>28–30</sup> The pointwise 95% CIs were calculated with 500 bootstrap resampling.<sup>30–33</sup>

R version 3.6.0 (RStudio, Inc. Boston, MA, USA) was employed for all analyses.

### Sensitivity analyses

Sensitivity analyses were conducted to account for repeat CAs, shorter medication discontinuation periods, and confounding by indication.<sup>34–38</sup>

## Results

The presence of both AF and HF were identified in 101 933 medication insured patients, of whom 451 (0.4%) who underwent CA were matched to 899 matched controls. Overall, the CA patients were younger and had fewer comorbidities compared with patients who had no CA (Table 1). However, after IPTW, the distributions of all potential confounders included in the propensity score model were balanced between cases and controls (age 65.5 ± 11.0 vs. 61.6 ± 11.6 years; 24% vs. 20% women; CHA<sub>2</sub>DS<sub>2</sub>-Vasc score 3.2 ± 2.3 vs. 2.9 ± 2.1; SMD < 0.1 for all covariates shown in Figure 2).

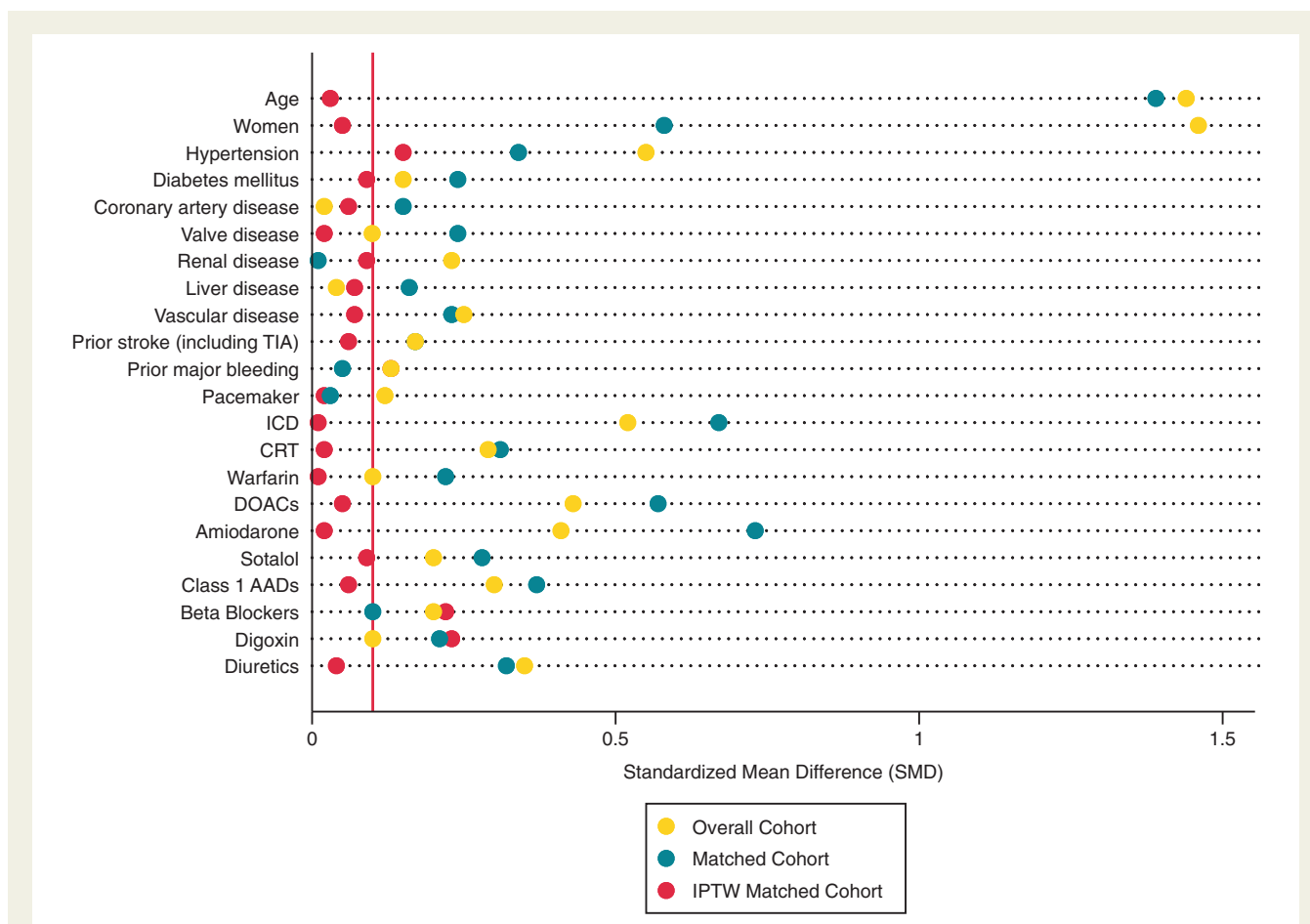
### All-cause mortality

Over a median follow-up time of 3.8 years [interquartile range (IQR) 1.7–7.7], 21 (4.7%) CA patients and 171 (19.0%) non-CA patients died (Table 2). In multivariable IPTW Cox model, with adjustment for additional time-varying covariates, CA was associated with a

statistically significant reduction in the hazard of all-cause mortality [aHR 0.4 (95% CI 0.2–0.7)] compared with non-CA patients (Table 2). Consistent with these results, comparison of the IPTW Kaplan–Meier curves showed the sustained reduction in mortality over the follow-up period (log-rank P-value = 0.004; Figure 3).

### Heart failure hospitalizations

A total of 70 (15.5%) CA patients had an HF hospitalization compared with 272 (30.3%) of non-CA patients, with an incidence of 4.6 and 6.8 HF hospitalizations per 100 person-years (P=0.002 for log-rank), respectively (Table 2). Within 30 days of CA, 3 (0.6%) of CA patients died (two patients died during CA hospitalization and one patient died post-discharge).<sup>39</sup> In multivariable analyses, with an additional adjustment for the competing risk of all-cause mortality, there was no statistically significant difference in HF hospitalizations between CA and non-CA patients across the follow-up period [aHR 1.2 (95% CI 0.8–1.6)]. However, Figure 4 shows how the aHR associated with CA (black curve) varies with time elapsed since the date of CA (horizontal axis) and indicates a statistically significant reduction in HF hospitalizations during the first 3 years after CA, when the 95% CI (dashed curves) remain below 1.0 (P=0.01; Figure 4). The time-



**Figure 2** Standardized mean differences comparing CA and non-CA patients. All SMDs < 0.1 considered balanced. CA, catheter ablation; IPTW, inverse probability of treatment weighting; SMD, standardized mean difference.

**Table 1** Baseline characteristics

	Before matching and IPTW <sup>b</sup>	After matching and IPTW <sup>b</sup>		Standardized mean difference <sup>c</sup>
	All AF-HF patients (N = 101 933)	Cases (N = 451)	Controls (N = 899)	
Age (years), mean (SD) <sup>a</sup>	79.6 (9.4)	65.6 (11.0)	61.6 (11.6)	0.03
<65	6.7%	38%	55%	-0.52
65-75	21.7%	11%	12%	0.01
≥75	71.6%	44%	28%	0.35
Women <sup>a</sup>	51.4%	24%	22%	0.05
Hypertension <sup>a</sup>	31.9%	72%	65%	0.15
Diabetes mellitus <sup>a</sup>	16.5%	37%	33%	0.09
Coronary artery disease <sup>a</sup>	26.8%	55%	52%	0.06
Prior myocardial infarction	11.2%	33%	24%	0.20
Valvular disease <sup>a</sup>	27.3%	25%	26%	0.02
Valve replacement	2.8%	9%	12%	0.08
Chronic obstructive pulmonary disease	16.2%	27%	27%	0.02
Chronic renal failure <sup>a</sup>	14.2%	29%	25%	0.09
Prior stroke (including TIA) <sup>a</sup>	2.1%	2%	1%	0.06
Liver disease <sup>a</sup>	2.2%	9%	11%	0.07
Vascular disease <sup>a</sup>	11.8%	19%	17%	0.07
Prior major bleeding <sup>a</sup>	4.1%	11%	7%	0.13
Pacemaker	12.3%	20%	19%	0.02
Implantable cardioverter-defibrillator <sup>a</sup>	2.5%	29%	29%	0.01
Cardiac resynchronization therapy <sup>a</sup>	9.4%	34%	33%	0.02
CHA <sub>2</sub> DS <sub>2</sub> -Vasc score, mean (SD)	3.8 (1.3)	3.2 (2.3)	2.8 (2.0)	0.04
HAS-BLED score, mean (SD)	1.5 (0.9)	1.8 (1.4)	1.5 (1.6)	0.07
Medications				
Oral anticoagulation	54.5%	90%	93%	0.10
Warfarin <sup>a</sup>	47.6%	65%	66%	0.01
DOACs <sup>a</sup>	8.4%	38%	40%	0.05
Dabigatran	2.9%	15%	16%	0.03
Rivaroxaban	3.0%	18%	18%	0.01
Apixaban	3.0%	12%	8%	0.14
Amiodarone <sup>a</sup>	10.0%	58%	59%	0.02
Sotalol <sup>a</sup>	3.3%	16%	13%	0.09
Class 1 antiarrhythmics <sup>a</sup>	2.4%	19%	20%	0.06
Digoxin <sup>a</sup>	24.7%	28%	39%	0.23
Beta blockers <sup>a</sup>	49.8%	81%	72%	0.22
Angiotensin-converting enzyme inhibitors	39.7%	59%	63%	0.09
Angiotensin II receptor blockers	17.9%	20%	22%	0.05
Calcium channel blockers	17.3%	23%	19%	0.10
Diuretics <sup>a</sup>	69.5%	72%	70%	0.04

AF, atrial fibrillation; DOACs, direct oral anticoagulants; HF, heart failure; IPTW, inverse probability of treatment weighting; SD, standard deviation; TIA, transient ischaemic attack.

<sup>a</sup>Predefined variables included in the propensity score model.

<sup>b</sup>The prevalence of covariates for the overall cohort at measured at cohort entry and the prevalence of covariates in the matched and IPTW cohorts are measured on the date of AF ablation (cases) or matched date (controls).

<sup>c</sup>Standardized mean difference <0.10 denotes balance for baseline characteristics between AF ablation and no AF ablation patients.

dependent HR estimate (black curve in *Figure 4*) suggests reduced hazard of HF hospitalization starts shortly after CA, reaches about 50% risk reduction in 1-2 years after CA, but then becomes gradually weaker and disappears after approximately 5 years (*Figure 4*).

## Stroke and major bleeding

Nine (2.0%) CA patients had a stroke (including TIA) compared with 41 (4.6%) of non-CA patients. Major bleeding events occurred in 10 (2.2%) of CA patients and 46 (5.1%) of non-CA patients. Over the follow-up period, no statistically significant difference was detected

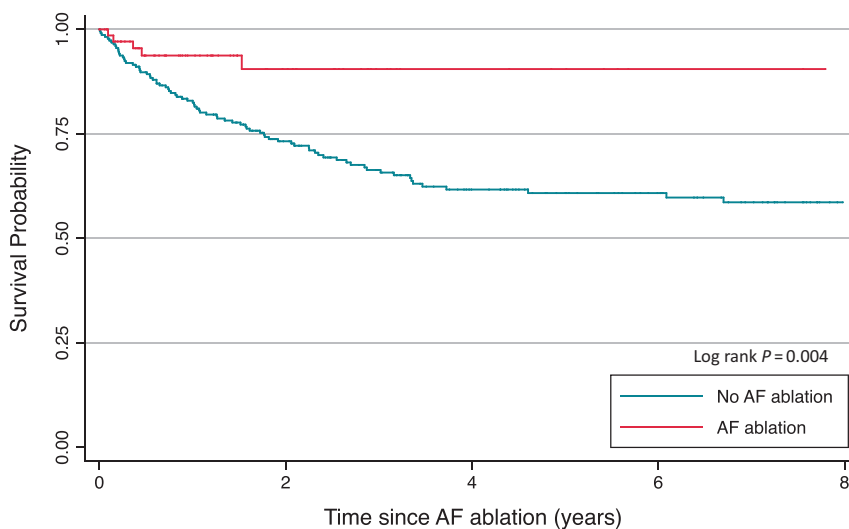
**Table 2** Incidence of outcomes

	N	Event rate, N (%)	Incidence rate per 100 person-years	Adjusted hazard ratio	95% confidence interval
All-cause mortality					
Cases	431	21 (4.6)	1.2	0.4 <sup>a</sup>	0.2–0.7
Controls	899	171 (19.0)	3.5		
Heart failure hospitalizations					
Cases	431	70 (15.5)	4.6	1.2 <sup>a,b</sup>	0.8–1.6
Controls	899	272 (30.3)	6.8		
Stroke (including TIA)					
Cases	431	9 (2.0)	0.5	1.4 <sup>a,b</sup>	0.56–3.7
Controls	899	41 (4.6)	0.9		
Major bleeding					
Cases	431	10 (2.2)	0.6	1.8 <sup>a,b</sup>	0.7–4.7
Controls	899	46 (5.1)	1.0		

ATT, average treatment effect in the treated; CRT, Cardiac resynchronization therapy; DOACs, direct oral anticoagulants; ICD, implantable cardioverter-defibrillator; IPTW, inverse probability of treatment weighting; TIA, transient ischaemic attack.

<sup>a</sup>Hazard ratio adjusted baseline covariates of hypertension, prior major bleeding, and antiarrhythmic medications (amiodarone, sotalol, and Class I antiarrhythmic medications) and time-varying covariates of warfarin, DOACs, and antiarrhythmic medications as well as the presence of an ICD or CRT. Hazard ratios were IPTW with stabilized ATT weights.

<sup>b</sup>Hazard ratios were also adjusted for the competing risk of all-cause mortality.



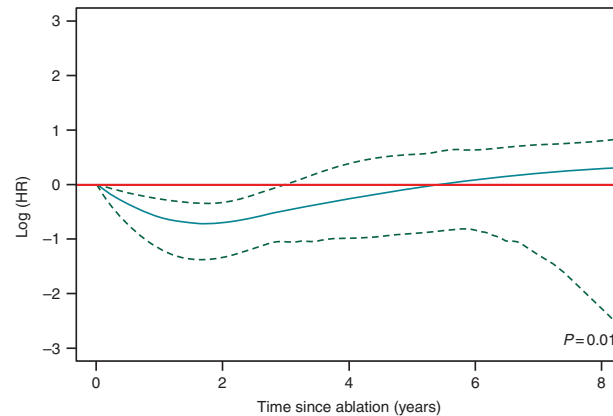
	0 Years	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years	7 Years	8 Years
AF ablation	451	437	368	294	263	226	194	168	138
No AF ablation	899	876	712	615	534	464	436	381	327

**Figure 3** Kaplan–Meier curve for all-cause mortality. Kaplan–Meier curve was IPTW and adjusted for hypertension, prior bleeding, beta blockers, and digoxin at baseline. AF, atrial fibrillation; IPTW, inverse probability of treatment weighting.

for the hazards of either stroke/TIA or major bleeding in CA and non-CA patients (Table 2). The hazards of both outcomes appeared to vary over time since CA ( $P < 0.05$ ), however, due to the low event rate, the time-dependent effect could not be modelled (Supplementary material online, Figures S4 and S5).

### Sensitivity analyses

More than half (58.9%) of CA patients had a repeat CA within a median of 0.8 years (IQR 0.3–2.02). Results and conclusions were consistent with the main results presented above, after (i) accounting for repeat CAs and (ii) adjustment for a 14-day discontinuation period



	0 Years	1 Year	2 Years	3 Years	4 Years	5 Years	6 Years	7 Years	8 Years
AF ablation	451	357	291	231	201	175	152	127	106
No AF ablation	899	739	623	524	438	375	332	300	262

**Figure 4** Time-dependent effect of CA for HF hospitalizations. Adjusted for time-varying covariates and the competing risk of all-cause mortality, as well as IPTW. Time at which the upper boundary of the 95% CI (dotted line) crossed 1.0 (red line; corresponding to no effect) was used to approximate the duration of the statistically significant protective effect of CA for HF hospitalizations. CA, catheter ablation; CI, confidence interval; HF, heart failure; IPTW, inverse probability of treatment weighting.

for medications (all sensitivity analyses are presented in the [Supplementary material online](#)).

## Discussion

The present study provides very long-term follow-up to evaluate the effectiveness of CA to reduce all-cause mortality, HF hospitalizations, stroke/TIA, and major bleeding among patients with both AF and HF. The main findings were that (i) CA was associated with a long-term reduction in all-cause mortality and (ii) CA was protective against HF hospitalizations for only 3-year post-procedure.

### All-cause mortality

The present study extends the findings of CASTLE-AF by demonstrating a statistically significant decrease in all-cause mortality with CA over the long-term.<sup>9</sup> Furthermore, estimates and precision for the mortality reduction were also very similar between studies [HR 0.5 (95% CI 0.3–0.8) for CASTLE-AF vs. aHR 0.4 (95% CI 0.2–0.7) for the present study].<sup>9</sup> The AATAC trial also trended towards a protective effect of CA for all-cause mortality with a comparable effect estimate [HR 0.4 (95% CI 0.2–1.0)].<sup>10</sup> The mortality reduction may be as a result of an improvement in the complex interplay between AF and HF, measured indirectly via a reduction in AF burden, N-terminal pro-b-type natriuretic peptide, and improvements in left ventricular ejection fraction (LVEF), 6-min walk distance, and quality of life measures.<sup>9,10,40–43</sup> As described in subgroup analyses of the AFFIRM and AF-CHF trials, maintenance of sinus rhythm is associated with a lower risk of mortality<sup>5,6,44</sup> and specifically for CA, Ullah et al.<sup>45</sup> found that recurrent AF after CA strongly predicted mortality in AF–HF patients.

In the present study, the large sample size and the length of follow-up increased power to detect a significant difference. In CASTLE-AF,

the mortality benefit of CA only emerged at 3 years of follow-up.<sup>9</sup> In addition, randomization only balances baseline confounding, however, the present study also accounted for time-varying confounders during follow-up, including ICD, CRT, oral anticoagulant, and AAD therapies, all of which could affect the association between CA and all-cause mortality.

### Heart failure hospitalizations

Both the CASTLE-AF and AATAC trials showed that HF hospitalizations reduced in CA patients compared with those on medical therapy<sup>9,10</sup>; however, the results of the present study suggest that this protective effect of CA does not persist in the long-term. The end of follow-up was 2 years for AATAC and 3 years for CASTLE,<sup>9,10</sup> which is within the protective period of at least 3 years as identified in the present study [3.8 years (IQR 1.7–7.7)]. Perhaps with a longer follow-up, the trials would have also detected an increasing number of HF hospitalizations among CA patients. Regardless, the hazards for HF hospitalizations was similar during the protective period for the present study (lowest point, HR ~0.5) and CASTLE-AF [HR 0.6 (95% CI 0.4–0.8)]. In addition to the time-dependent effect, our results further enhance those of randomized trials by accounting for the competing risk of death and medication, ICD, and CRT use over the follow-up which may have prevented the outcome.<sup>46</sup>

The reduction in HF hospitalizations has been attributed to decreased AF recurrence after CA in AF–HF patients. A stratified pooled analysis of randomized trial results showed that CA led to a mean relative reduction of 96% in AF/atrial tachycardia recurrence.<sup>44</sup> Although the present study was not able to investigate AF recurrences, almost 60% of patients underwent a repeat CA which may indicate AF recurrence necessitating a repeat procedure.

## Stroke/transient ischaemic attack and major bleeding

Similar to the present study, there was also a low incidence stroke/TIA in randomized trials [stratified pooled analysis of randomized trials: 2.8% vs. 4.7%; our study: 2.0% vs. 4.6%; CA vs. non-CA, respectively]<sup>45</sup> and no statistically significant difference for stroke risk between treatment groups.<sup>9,40,43,47</sup> This is similar to results in AF patients with and without HF, in which the reduction in stroke risk after CA was not statistically significant.<sup>15,16</sup>

The present study is the first to investigate association between CA and major bleeding in AF–HF patients and found no statistically significant difference. This is also similar to the results of studies of AF patients who underwent CA, regardless of comorbid HF.<sup>15,16</sup> Although no statistical difference was detected between CA and non-CA patients in all studies, the estimates for both stroke and bleeding trended in opposite direction from randomized trials. Analogous to HF hospitalizations, the difference in effect may be due to randomized trials having shorter follow-up, not accounting for the competing risk of mortality, and a potential time-dependent effect.

## Limitations

Important immeasurable factors that mark severity of disease including type of AF (paroxysmal, persistent, or permanent), AF burden, New York Heart Association class, and LVEF were not contained in the database. To account for severity, we adjusted for diuretic use and presence of cardiac implantable electronic devices. In addition, we conducted a confounding by indication sensitivity analysis. Also, procedural information such as technologies and ablation strategies used were not contained in Quebec administrative databases and could not be adjusted for in analyses.

Medication information is only present for a subset of the population (90% of AF–HF population and 75% of CA patients). Therefore, the results for the medication cohort may be less generalizable to the typical population referred to for the CA procedure as they are older and may have differing effects from treatments and medications.

For both stroke and bleeding events, wide CIs, due to low number of events, make the comparisons less conclusive, and the time-dependent effect of CA could not be accurately tested and modelled.

## Conclusion

In a large cohort of patients with AF and HF, treatment with CA was associated with a long-term reduction in all-cause mortality. Although CA was also associated with a reduction in HF hospitalizations, the protective effect lasted for approximately 3 years after the procedure. The results of the present study suggest that CA may be particularly beneficial in the select AF–HF patients referred for CA; however, it remains to be investigated if the protective effect persists among patients with more advanced HF.

## Supplementary material

Supplementary material is available at *Europace* online.

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**Conflict of interest:** V.E. has received honoraria from Biosense Webster Inc., St. Jude Medical, Medtronic Inc., Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, and Servier. All other authors have nothing to disclose.

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