SUPPLEMENT

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METHODS

Table S1. ICD-9/10 codes for effectiveness outcomes

Outcome	ICD-9 Codes	ICD-10 Codes
HF hospitalizations	428.0 (1, 2, 3, 9)	I50.1 (2, 3, 4, 9)
Cerebrovascular accident / transient ischemic attack and retinal infarct	433, 434, 435, 436, 362.3	I63, I64, G45, H34.1
Major Bleeding (intracranial bleeding, bleeding from the respiratory, gastrointestinal, or urinary tract)	362.8, 379.2, 430, 431, 432, 459, 530.7, 531.0 (2,4,6), 532.0 (2,4,6), 533.0 (2,4,6), 534.0 (2,4,6), 578	H35.6, H43.1, I61, K92.0 (1,2), K25.0 (2,4,6), K25.2 (4,6), K26.0 (2,4,6), K27.0 (2,4,6), K28.0 (2,4,6), K29.0

*No ICD-9/10 codes for mortality.

Table S2. RAMQ cardiac implantable electronic devices (CIEDS) codes

Device	Implant procedure codes	Follow-up
Pacemaker VVI	20577	0685
Pacemaker DDD	20579	0693
ICD (VVI or DDD)	0460	0313
CRT-D	20531	20517 and 0313
CRT-P	20531	20517 and 0685 or 0643

*Presence of CIEDs was be captured at implant or follow-up.

Inverse probability of treatment weighting (IPT-weighting)

Estimated PS score was calculated from a fitted multivariable logistic regression model that regresses the logit of probability of CA on predefined baseline characteristics [$e = P(Z = 1|X)$] (1). Variables identified to be clinically significant based on published research and are listed in figure 2.

Variables included in the PS model were: age, women, hypertension, diabetes mellitus, coronary artery disease, valve disease, renal disease, liver disease, vascular disease, prior stroke (including TIA), prior major bleeding, pacemaker, ICD, CRT, warfarin, DOACs, amiodarone, sotalol, class 1 AADs, beta blockers, digoxin, and diuretics. Age at baseline was modeled as a linear variable and was compared to age modeled flexibility using multiple knots (fractional polynomials). Age at baseline modeled as a linear variable had the lowest deviance (-2log likelihood) and was incorporated into the PS model (2, 3). Weights were stabilized and estimated the average treatment effect in the treated (ATT) (4-7).

To create the IPT-weights, subjects were weighted by the inverse of the probability of receiving the treatment that the subject received (1/PS for treated and 1/(1-PS) for untreated subjects)(8, 9), creating a pseudo-population in which measured baseline characteristics are independent of treatment status. Estimates were transformed to estimate the average treatment effect in the treated and stabilized ($W_{i,ATT,stabilized} = Z_i \Pr(Z=1) + \frac{(1-Z_i)e_i \Pr(Z=0)}{1-e_i}$). Stabilization was used as a mitigation strategy for having treated subjects with a low probability of treatment and untreated subjects with a high probability of treatment resulting in extremely large weights, increasing the variables of the effect estimates.

To assess the success of the PS model to remove systematic differences between treatment groups, standardized mean differences (SMD) were used to compare proportions and means between treatment groups conditional on the PS. Balance between treatment groups was achieved if the variables in the PS model had a SMD value of <0.1 when treatment groups were compared. For variables in the PS model in which the SMDs were >0.1, we also adjusted for these variables in the multivariable Cox model creating a doubly robust model. Balance and PS overlap was also assessed with a density plot (Figure S2).

CA patients also as controls

CA patients could also be controls if the time until CA was greater than the time at risk for the matched case. For CA patients who were also controls, a later CA was incorporated in the Cox model as a binary time-varying exposure.

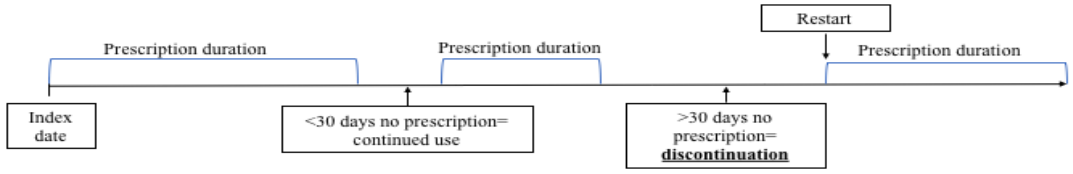
Sensitivity analysis #1: Repeat ablations

The primary objective of the present study was to assess single procedure effectiveness; however, patients may have undergone additional CAs during the follow-up period. To account for additional procedures, two separate sensitivity analyses were performed. The first approach censored a patient on date of repeat CA. As an alternative to censoring, an additional binary time-varying dummy variable for repeat CA was created to indicate a patient was exposed to repeat procedure from the date of repeat CA till the end of follow-up.

Sensitivity analysis #2: Shorten time to discontinuation

Current medication-use for warfarin, DOACs, and AADs was incorporated as a binary time-varying variable in the Cox regression analysis, assigned value of 1 from the start date of the first prescription until discontinuation. Discontinuation was determined as a period of >30 days after the end of a prescription (Figure S1). A 30-day window has previously been used in similar medication studies performed with RAMQ data (10-12). The length of a prescription in Quebec is 30 days, therefore if a patient has not filled a prescription within the 30-day window post the end of the prior prescription, the medication has most likely been discontinued. In addition, the 30-day window also accounts for the residual effects of amiodarone and OACs on the outcomes (12, 13). After discontinuation, a patient may be exposed to the medication again with additional prescriptions. As a sensitivity analysis, the discontinuation window was decreased from 30 days to 14 days after the end of the prior prescription.

Figure S1. Discontinuation



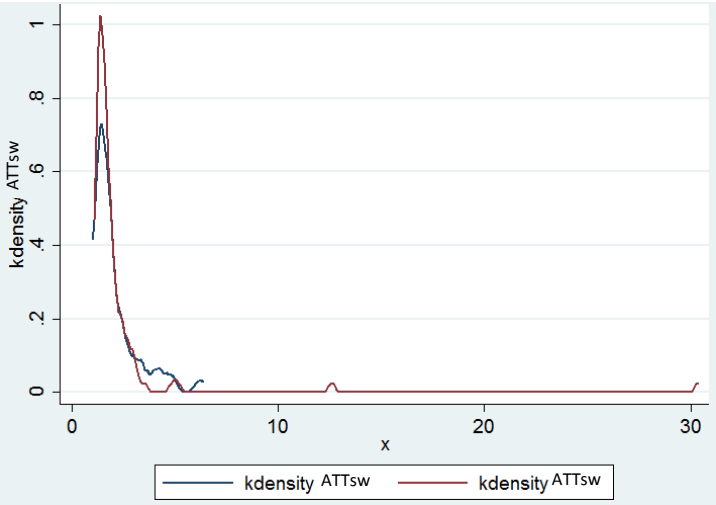
Sensitivity analysis #3: Confounding by indication

To evaluate the robustness of our findings as a result of a hypothetical unobserved confounder (confounding by indication), a simulation-based sensitivity analyses proposed by Greenland adapted for cohort studies was performed (14). A proposed hypothetical risk factor (ie. NYHA class IV) was chosen that is less frequent in CA patients compared to non-CA patients. We varied the assumptions about 1) the effect of the confounder on the outcomes (HR) and 2) the strength of the confounder association with CA (difference in the prevalence of the confounder between CA and non-CA patients) (14, 15). HRs were calculated for each combination of assumptions after adjustment for the (simulated) unobserved confounder to determine the prevalence of unobserved confounder necessary to meaningfully change the resulting HR for CA, and thus substantially affect the final conclusion (14, 15).

RESULTS

Kernal density plot for IPT-Weighting

Figure S2



The kernel density plot of the average treatment effect in the treated stabilized weights (ATTsw) demonstrates a large region of overlap between AF ablation (red line) and no-AF ablation (blue line) patients. The difference between the few observations in the AF ablation group that did not overlap were a result of the AF ablation patients being younger.

Testing the proportional hazards assumption

Figure S3. All-cause mortality

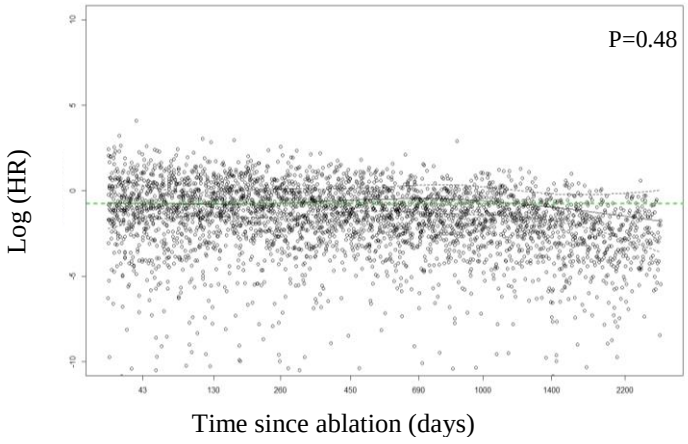


Figure S4. HF hospitalizations

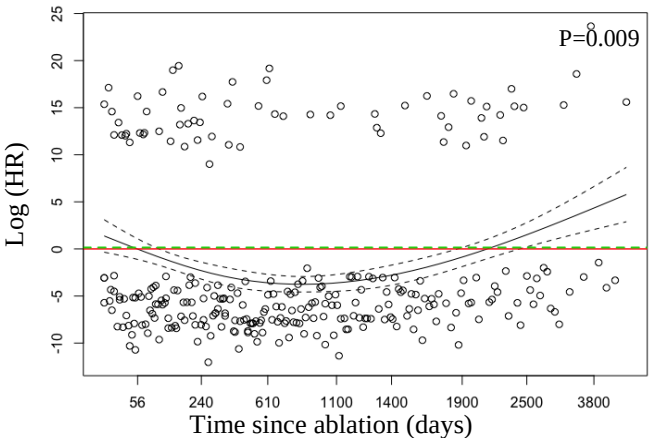


Figure S5. Stroke/TIA

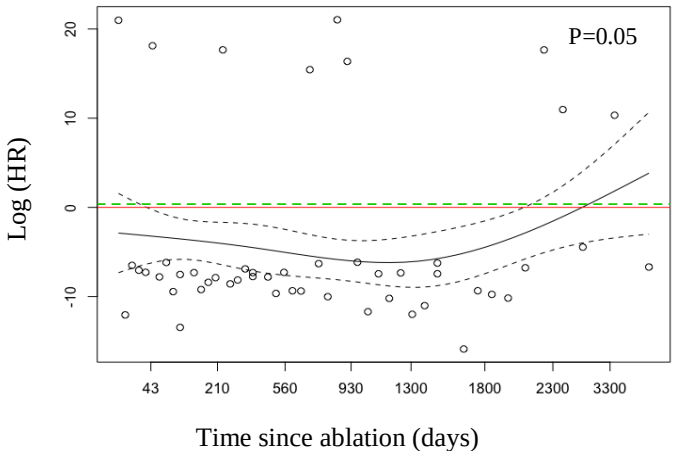
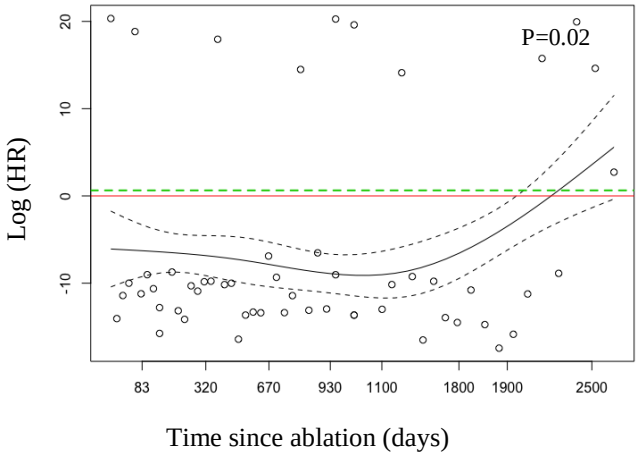


Figure S6. Major bleeding



*Figures S3 to S6 above use the cox.zph function in the survival package in R to test the proportional hazards (PH) assumption of Cox models for CA using schoenfeld residuals (16). Rejection of the PH assumption indicates a time-dependent effect for the corresponding variable. The red horizontal line placed at log(HR) of 0 marks a constant HR of 1 and the dashed green horizontal line denotes the Cox estimate assuming proportional hazards. A p-value of <0.05 denotes a statistically significant deviation from the proportional hazards estimate.

Using the PH diagnostic test, a time-dependent effect between exposure to CA and effectiveness outcomes was detected for HF hospitalizations (p=0.009) (16). For all-cause mortality, the distribution of residuals was relatively horizontal and clustered around the proportional hazards estimate. Results from the PH test informed the need for modeling the time-dependent effect of CA on HF hospitalizations. A B-spline was used to model this effect (main manuscript). Although the PH assumption was violated for stroke/TIA and major bleeding (p<0.05), the time dependent effect of CA could not be modeled for these outcomes due to the low event rate.

Sensitivity analysis #1: Repeat ablations

Table S3. Comparison of effect estimates for repeat CA

Outcome	aHR without repeat CA (95% CI)	aHR censored at time of repeat CA (94% CI)	aHR with repeat CA as a time-varying covariate (95% CI)
All-cause mortality	0.39 (0.23-0.66)	0.40 (0.24-0.69)	0.40 (0.24-0.69)
HF hospitalizations	1.18 (0.84-1.67)	1.20 (0.85-1.71)	1.19 (0.86-1.68)
Stroke/TIA	1.44 (0.56-3.72)	1.48 (0.56-4.78)	1.47 (0.56-4.76)
Major bleeding	1.89 (0.75-4.75)	1.92 (0.77-4.80)	1.91 (0.76-4.78)

*For each outcome, aHRs and 95% CIs for main analysis, repeat procedures censored, and repeat procedures incorporated as time-varying covariates are presented.

Compared to the HR estimate which does not account for repeat CA (main analysis), all-cause mortality HRs from censoring and time-varying covariate variables produced higher HR point estimates, however, the confidence intervals remained significant. Accounting for repeat ablations also did not change the conclusions for HF hospitalizations, stroke/TIA, and major bleeding.

Sensitivity analysis #2: Shortened discontinuation window

After shortening of discontinuation window to 14-days, the association between CA and the effectiveness outcomes were the similar to the main analysis with the 30-day discontinuation window. **Table S4.** presents the aHR with the 30-day and 14-day discontinuation windows.

	aHR 30-day window (95% CI)	aHR 14-day window (95% CI)
All-cause mortality	0.39 (0.23-0.66)	0.40 (0.24-0.66)
HF hospitalizations	1.18 (0.84-1.67)	1.18 (0.83-1.68)
Stroke/TIA	1.44 (0.56-3.72)	1.43 (0.55-3.71)
Major bleeding	1.83 (0.74-4.74)	1.84 (0.75-4.75)

Sensitivity analysis #3: Confounding by indication

To estimate the potential impact of an unmeasured confounder, such as the presence of NYHA class, on the main outcome of all-cause mortality, we used our simulation-based bias sensitivity analyses (14, 15). Simulation results indicated that, assuming – based on literature – HR of 1.68 (95% CI 1.33-2.11) for the association of NYHA with the mortality hazard (17), indicated that over 60% of CA patients, compared to 30% of non-CA controls, would need to have NYHA IV to alter the conclusion of a statistically significant reduction of all-cause mortality in CA patients compared to non-CA patients.

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