Population-level evaluation of ablation therapy in patients with atrial fibrillation and comorbid heart failure

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ABSTRACT

Atrial fibrillation (AF) and heart failure (HF) frequently coexist. The presence of both diseases further increases the risk of all-cause mortality, HF hospitalizations, and stroke compared to either disease individually. Pharmacologic therapy has limited effectiveness in this challenging subpopulation, therefore a minimally invasive rhythm control strategy, called catheter ablation (CA), has been used to treat AF in patients with HF. Randomized trials have shown CA is safe and reduces all-cause mortality and HF hospitalizations, however, current clinical guidelines recognize the evidence for CA use in the AF-HF population is limited. The aim of the present thesis is to evaluate treatment selection patterns, safety, and long-term effectiveness of CA in a real-world AF-HF population and address research and methodological gaps from randomized controlled trials.

Linked hospital discharge summary [Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (Med-Echo)] and claims [la Régie de l'assurance maladie du Québec (RAMQ)] administrative databases from Quebec, Canada were used to construct the AF-HF cohort (2000-2017). The final overall cohort consisted of 112,955 AF-HF patients, of which 700 patients underwent CA. Of patients with government prescription insurance coverage, 432 patients underwent CA of 101,931 AF-HF patients. Both the overall and medication cohorts included the largest number of CA patients with AF-HF studied till date.

Current clinical guidelines are nonspecific about the criteria for referral to CA in the AF-HF population. Thus, referral is dependent on the individual cardiologists' preference and the real-world treatment selection pattern is unknown. In the **first manuscript**, we characterize the real-world AF-HF population who underwent CA by identifying the clinical predictors for CA treatment. Overall, our study demonstrated that (1) CA was rarely used to treat AF in patients with

comorbid HF, (2) CA patients had a minimal number of comorbidities, and (3) women had a lower probability of treatment with CA.

Although a certain subset of the AF-HF population underwent CA, the structural differences in the heart of HF patients may make the procedure more technically challenging and potentially riskier to perform compared to patients without comorbid HF. Therefore, the **second manuscript** evaluates the safety of CA in the real-world AF-HF population by determining the incidence and potential risk factors for major adverse events (AEs) within 30 days of the procedure. Major periprocedural AEs included all-cause mortality, stroke (including transient ischemic attacks), pericardial effusion requiring drainage, vascular AEs, hemorrhage/hematomas, and pulmonary embolism. We found that in the largest cohort of AF-HF patients who underwent CA, the incidence of major AEs was low and comparable to rate of major AEs in randomized trials and real-world evaluations of procedural safety in the overall AF population, regardless of the presence of comorbid HF. Due to the limited number of AEs, identification of predictors was hypothesis generating and larger studies are warranted.

Randomized trial data suggests a reduction in all-cause mortality and HF hospitalizations with CA in selected patients, however, whether these results are replicable in a real-world population and persist in the long-term remains to be shown. The **third manuscript** investigated the long-term effectiveness of CA in AF-HF patients in reducing the incidence of: 1) all-cause mortality, 2) HF hospitalizations, and 3) major morbidities (stroke and major bleeding). Incidence density sampling (1 case: 2 controls) and inverse probability of treatment weighting were used to account for immortal time and confounding bias, respectively. Multivariable Cox models adjusted for the time-varying confounders of the presence of cardiac devices and medication use during the follow-up period. For non-fatal outcomes, the competing risk of death was accounted for using the

Lunn-McNeil approach. Further, the time-dependent effect of CA was modeled with a B-spline. After matching and weighting, CA was associated with a statistically significant reduction in all-cause mortality compared to non-CA patients. CA was also protective against HF hospitalizations for the first 3-years after the date of CA when modeled with a B-spline and adjusted for the competing risk of death. Although no difference in the risk of stroke and major bleeding was detected between CA and non-CA patients, larger studies are warranted.

Compared to previous prospective studies and randomized trials, the present thesis investigated treatment patterns, safety, and long-term effectiveness in the largest and longest cohort of AF-HF patients who underwent CA till date. In addition, the specific patient population investigated reflects those encountered real-world practice. Methodologically, the results from this thesis advance the knowledge gained from prior studies and randomized trials by illustrating the time-varying effects of CA over a long follow-up period for clinically relevant outcomes. Also, time-varying effects of medications and cardiac implantable electronic device use as well as the competing risk of mortality were included to better quantify the risk of a specific event, all of which fill methodological gaps present in current research on CA in AF-HF patients. Finally, results of the present thesis are important to better inform clinical practice guidelines for the treatment of this challenging subpopulation.

ABRÉGÉ

La fibrillation auriculaire (FA) et l'insuffisance cardiaque (IC) coexistent fréquemment et leur présence combinée confère un risque accru de décès, d'hospitalisations pour IC et d'accident vasculaire cérébral (AVC) par rapport à chaque maladie individuellement. Au sein de cette sous-population, le traitement pharmacologique a une efficacité réelle limitée et l'ablation par cathéter (AC), procédure non invasive de contrôle du rythme cardiaque, est utilisée pour soigner la FA chez les personnes souffrant d'IC. Des essais randomisés ont révélé que l'AC est sécuritaire et qu'elle diminue le taux de mortalité toutes causes confondues et d'hospitalisations pour IC. Toutefois, bien que les lignes directrices cliniques actuelles reconnaissent la pertinence de l'AC, son recours demeure modeste au sein de la population FA-IC. L'objectif de la présente thèse est d'évaluer les profils du choix de traitement, l'innocuité et l'efficacité à long terme de l'AC auprès d'une population FA-IC réelle, ainsi que de combler les lacunes en matière de recherche et de méthodologie des essais randomisés.

Le recoupement des bases de données administratives du Québec (Canada) sur les sorties d'hôpital [Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (Med-Echo)] et des réclamations [Régie de l'assurance maladie du Québec (RAMQ)] a permis de former une cohorte FA-IC (2000-2017). Au terme de l'exercice, la cohorte globale était composée de 112 955 patients FA-IC, dont 700 avaient subi une AC. Des 101 931 patients bénéficiant du régime d'assurance médicaments gouvernemental, 432 patients avaient subi une AC. Les deux cohortes (globale et sous le régime d'assurance médicaments) comportaient le plus grand nombre de patients FA-IC étudiés à ce jour.

Les lignes directrices cliniques actuelles ne décrivent pas avec précision les critères d'orientation vers une AC chez les patients FA-IC. Ainsi, la décision repose sur les préférences du

cardiologue et les profils de choix de traitement en pratique clinique sont encore inconnus. Le **premier manuscrit** dresse un portrait des caractéristiques de la population FA-IC ayant subi une AC, et ce, en identifiant les facteurs cliniques prédictifs du traitement par AC. Dans l'ensemble, notre étude a démontré que 1) le recours à l'AC pour soigner les patients aux prises avec de la FA et une IC est rare, 2) les patients ayant subi une AC présentent peu de comorbidités et 3) les femmes sont moins susceptibles de recevoir un traitement par AC.

Bien qu'un certain sous-groupe de la population FA-IC ait subi une AC, les différences structurelles du cœur chez les patients souffrant d'IC pourraient poser un plus grand défi technique et rendre la procédure plus risquée par rapport aux patients n'ayant pas d'IC. Par conséquent, le **deuxième manuscrit** porte sur l'évaluation de l'innocuité de l'AC au sein d'une population FA-IC réelle, et ce, en établissant l'incidence et les facteurs de risque possibles d'effets indésirables (EIs) graves au cours des 30 jours suivant l'intervention. Au nombre des EIs graves associés à la procédure, il y a la mortalité toutes causes confondues, l'AVC (y compris les accidents ischémiques transitoires), l'épanchement péricardique nécessitant un drainage, les EIs de nature vasculaire, les hémorragies et hématomes ainsi que l'embolie pulmonaire. Il s'est avéré qu'au sein de la plus importante cohorte de patients FA-IC qui avaient subi une AC, l'incidence d'EIs graves était faible et comparable à celle observée lors d'essais randomisés et d'évaluations d'innocuité des procédures dans l'ensemble de la population souffrant de FA, sans égard à la présence d'IC. En raison de la faible occurrence d'EIs, l'identification des facteurs prédictifs a servi à générer des hypothèses et justifie la tenue d'études de plus grande importance.

Les données issues d'essais randomisés suggèrent une diminution de la mortalité toutes causes confondues et des hospitalisations pour IC dans les cas d'AC chez certains patients. Toutefois, la reproductibilité et la constance à long terme de ces résultats au sein d'une population

réelle restent à démontrer. Le **troisième manuscrit** porte sur l'efficacité réelle à long terme de l'AC chez les patients FA-IC par le biais de la diminution de l'incidence : 1) de la mortalité toutes causes confondues, 2) des hospitalisations et 3) des comorbidités graves (AVC et hémorragies sévères). La méthode d'échantillonnage selon le taux d'incidence (1 cas : 2 témoins) et la pondération par l'inverse des probabilités de traitement ont permis de tenir compte du biais du temps immortel et du biais de confusion, respectivement. Des modèles multivariés de Cox furent ajustés pour des facteurs de confusion variant dans le temps lié à la présence de dispositifs cardiaques et à l'utilisation de médicaments pendant la période de suivi. Quant aux événements non mortels, le risque concurrent de décès a été pris en compte à l'aide de l'approche Lunn-McNeil. Enfin, l'effet variant dans le temps de l'AC a été modélisé à l'aide de B-splines et en tenant compte du risque concurrent de décès. Après le pairage et la pondération, l'AC était associée à une diminution statistiquement significative de la mortalité toutes causes confondues par rapport aux patients n'ayant pas subi d'AC. De plus, avec la modélisation à l'aide des B-splines et pondération pour le risque concurrent de décès, l'AC est apparue comme un facteur protecteur contre les hospitalisations pendant les trois années suivant la date de l'AC. Bien qu'aucune différence de risque d'AVC et d'hémorragies graves n'ait été décelée entre les patients ayant subi une AC et ceux n'en ayant pas subi, des études comportant plus de patients devront être menées.

Comparativement aux études prospectives et essais randomisés antérieurs, la thèse présentée ici porte sur les profils de traitement, l'innocuité et l'efficacité réelle à long terme dans la plus imposante cohorte, et avec le plus long suivi, de patients FA-IC ayant subi une AC à ce jour. De plus, la population étudiée est représentative de celles soignées en pratique clinique. Du point de vue de la méthode, les résultats de cette thèse contribuent à parfaire la connaissance issue des études et essais cliniques précédents par la démonstration de l'effet variant dans le temps de

l'AC sur une longue période de temps pour des événements cliniques d'intérêt. De plus, les effets variant dans le temps des médicaments et de l'utilisation de dispositifs cardiaques, ainsi que le risque concurrent de décès, furent inclus afin de mieux quantifier le risque d'événements spécifiques, ce qui comble les lacunes méthodologiques de la recherche actuelle traitant d'AC chez les patients FA-IC. Enfin, les résultats de la présente thèse sont importants pour mieux déterminer les lignes directrices en matière de pratique clinique pour le traitement de cette population complexe.

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CONTRIBUTIONS TO ORIGINAL KNOWLEDGE

I attest that the thesis work presented is my own original scholarship and represents an advancement in knowledge in the field of cardiovascular epidemiology. My co-supervisors and committee member were central throughout my research progress; however, the overarching design, statistical analysis, interpretations, and manuscript writing were my own. Our work was motivated by the emergence of a potential treatment option (CA) for a challenging population with both AF and HF, as well as important gaps in current research on this topic.

As the first and largest evaluation of CA in a real-world AF-HF population, the present thesis has the potential to influence clinical practice patterns and guidelines. From manuscript 1, we identified the specific clinical criteria used to select patients for CA. These results will provide clearer recommendations for referral in the clinical guidelines and will better inform clinicians considering CA as a treatment option for their AF-HF patients while highlighting lower rates for CA in women and patients with comorbidities. This is further supported by manuscript 2 which elucidates that CA is relatively safe to perform in AF-HF patients, despite the technical challenges. Finally, manuscript 3 validates the results of randomized trials in a real-world population and advances knowledge from the trials by more precisely determining the long-term effectiveness of CA with consideration for concurrent therapies, competing events, and potential variations in effectiveness over time. In addition, information on OAC and AAD prescription patterns in CA patients with AF and HF patients has not been previously evaluated, especially in the long-term. These results may strengthen clinical guideline recommendations and subsequent referrals for treatment with CA in select AF-HF patients and inform on medication practices after CA.

CONTRIBUTION OF AUTHORS

The research questions and study designs for the all manuscripts were developed by my co-supervisors (Drs. Louise Pilote and Vidal Essebag) and myself. In close partnership with my committee member (Dr. Michal Abrahamowicz) and my co-supervisors (Drs. Pilote and Essebag), I refined my research questions and developed my protocol with in-depth design and analysis plans. As we all had different proposals for design, the many discussions regarding the strengths and weaknesses of each approach further validated my final design and analysis choices. In addition, Dr Essebag's specific expertise in cardiac electrophysiology provided unique and necessary clinical insight.

The Quebec atrial fibrillation (AF) administrative database was created by my supervisor (Dr. Pilote) and my thesis was built on her teams' prior work. I helped acquire newer data and I was solely responsible for performing all statistical analyses, formulating overall messages, and drafting all manuscripts. My co-supervisors (Drs. Pilote and Essebag) and my committee member (Dr. Abrahamowicz) provided detailed and valuable comments and revisions on all manuscripts.

My co-author, Dr. Jacqueline Joza, provided additional substantive knowledge to my thesis proposal, results, and each manuscript. As a cardiac electrophysiologist, she has extensive experience performing AF ablations and was helpful to translate our results to clinical practice. Dr. Joza was involved in the original design, reviewed results, and revised all manuscripts.

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ABBREVIATIONS

AAD, antiarrhythmic drug

ACE, angiotensin converting enzyme

AE, adverse event

AF, atrial fibrillation

ARB, angiotensin II receptor blocker

CA, catheter ablation

CIED, cardiac implantable electronic device

CRT, cardiac resynchronization therapy

CVA, cerebrovascular accident

DOAC, direct-acting oral anticoagulation

EF, ejection fraction

HF, heart failure

HR, hazard ratio

ICD, implantable cardiac defibrillator

IPTW, inverse probability of treatment weighting

LV, left ventricle

LVEF, left ventricular ejection fraction

NYHA, New York Heart Association functional class

OAC, oral anticoagulation

PERD, pericardial effusion requiring drainage

PS, propensity score

TIA, transient ischemic attack

CHAPTER 1: INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) are two often co-existing conditions associated with considerable increases in morbidity and mortality.[1-3] The existence of one condition greatly increases the risk of developing the other.[4] It is estimated that 200,000 North Americans suffer from both diseases together.[5] HF promotes AF and AF aggravates HF, resulting in an increased risk of all-cause mortality, HF hospitalizations, and strokes compared to either disease alone.[6-8] Pharmacologic rhythm control therapies have shown reduced effectiveness in the AF-HF population,[1,9] therefore an alternative treatment option for this challenging subpopulation is necessary.

Catheter ablation (CA) with isolation of the pulmonary veins is a well-established treatment option for AF patients who are refractory to at least one class 1 or class 3 antiarrhythmic medication.[10] Although the procedure is increasingly used to treat patients with more comorbidities, a vast majority of CAs have been performed in patients with normal left ventricular systolic function.[11] However, the proportion of CAs performed in patients with reduced left ventricular ejection fraction (LVEF) or HF patients, has increased in the last decade.[11]

Although CA is more technically challenging due to the effects of HF on cardiac morphology, several studies showed that restoration of sinus rhythm by means of radiofrequency CA in patients with AF and HF is feasible and accompanied by clinical improvements, such as significant increases in left ventricular function.[11-13] Further, recent randomized controlled trials also indicated that CA reduced mortality and HF hospitalizations compared to pharmacologic rhythm and rate control therapy in a specified target AF-HF population.[12-14] Subsequently, clinical guidelines suggest the use of CA in AF patients with comorbid HF, however, recommendations are relatively non-specific.[15,16]

Although randomized trial results are promising, the present thesis addresses important gaps which are essential for CA to be considered a standard treatment option in AF-HF patients. First, the effectiveness and safety of AF-HF patients who underwent CA has not been evaluated in a real-world population, especially in long-term follow-up. Also, the clinical profile of AF-HF patients to be referred for CA has not been specifically described in the clinical guidelines, which may further limit potentially eligible patients from being referred to CA. In addition, randomized trials did not 1) account for the additional effects of medication use and cardiac devices on the incidence of outcomes, 2) accurately specify the association of CA with non-fatal outcomes, independent of the competing risk of all-cause mortality, 3) determine the time since CA that the procedure was protective against outcomes, and 4) describe OAC and AAD prescription patterns in the long-term. Filling these important gaps will better inform clinical practice and guidelines to improve treatment in the challenging AF-HF population.

Therefore, we conducted retrospective cohort study of AF patients with comorbid HF in Quebec who had CA, in order to determine the patient population treated with CA, safety, and long-term effectiveness.

1.1 Research objectives

Our specific objectives are to:

1. To identify clinical predictors and sex differences for treatment with CA in AF-HF patients.
2. To assess the safety of CA in AF-HF patients by determining frequency and potential risk factors for major AEs within 30-days post-CA.
3. To evaluate the long-term effectiveness of CA in AF-HF patients in reducing the incidence of a) all-cause mortality b) HF hospitalizations, and c) major morbidities (stroke/TIA and major bleeding).

CHAPTER 2: LITERATURE REVIEW

2.1 Atrial fibrillation, heart failure, and their coexistence

AF is the most common sustained cardiac rhythm disorder, affecting 1-2% of the population.[17] Strong associations exist between AF and increased risk of cerebral thromboembolism, development of HF, and increased mortality, notwithstanding the attributable burden on healthcare resources.[2,18-31]

HF is a common complication of many cardiovascular diseases[32] and is associated with substantial increases in morbidity and mortality.[33] It is estimated that >2.5 million North Americans are afflicted with HF and it develops in 700,000 patients each year.[34-36] Similar to AF, the burden and prevalence of HF is expected to rise due to the aging population and increased survival from cardiovascular disease.[2,19,33,37] Over the last 20 years, there has been significant progress in the management of HF patients.[38,39] However, despite recent advances, the mortality remains high with a 5-year survival rate of up to 50%, depending on the New York Heart Association (NYHA) functional class.[4,40,41]

AF and HF have similar risk factors and often coexist in the same population.[42] AF affects approximately 15-30% of patients with clinically overt HF.[43,44] Diagnosis of either AF or HF substantially increases the risk of diagnosis for the other.[45-48]

HF is one of the most powerful independent predictors of AF.[49] According to the Framingham Heart Study, there is a six-fold increased risk of developing AF in a HF patient.[2] HF enlarges the atrium through increasing filling pressure of the heart, augments sympathetic nerve activity, deregulates the intracellular calcium concentration, and leads to further degenerative fibrotic changes in the myocardium that markedly increase the risk of developing AF.[43,45] As

indicated in the SOLVD[50] and CHF-STAT[51] studies, prevalence of AF progresses with NYHA class, from 5% in NYHA class I patients to 50% in NYHA class IV patients.[43,44,50-55]

Likewise, adverse hemodynamic consequences of AF including chronically elevated heart rate, elevated cardiac filling pressures, irregular ventricular intervals, lack of effective atrial contraction, and AV dyssynchrony can impair ventricular function and lead to HF.[46,56,57] Approximately 25-50% of AF patients develop left ventricular dysfunction, a condition referred to as tachycardia-induced cardiomyopathy.[32,58-60]

2.2 Worsened outcomes with comorbid AF and HF

AF is an established independent risk factor for increased major morbidities and mortality in HF patients.[2,4,45] HF promotes AF and AF aggravates HF.[4] Previous studies have established that mortality risk substantially increases with the presence of both AF and HF, compared to either condition alone.[44,48,50,61] Macdonald et al showed that the 2-year risk of mortality was 39% higher in AF-HF patients compared to HF only patients.[62] Similarly, the Framingham Heart study showed incident AF with HF increased the risk of cardiovascular mortality (RR=1.5 to 1.9, adjusted).[49] SOLVD predicted a higher risk of all-cause mortality with AF and HF compared to only HF (RR=1.34, p=0.002).[50]

In addition, HF hospitalizations have been shown to increase with the addition of comorbid AF.[63] Aleong et al found a 2.2-fold increase in HF hospitalizations in AF-HF patients compared to HF only ($p<0.001$).[63] In HF patients who developed AF, HF hospitalizations increased by 2.9 times in the 1-year post AF diagnosis compared to the 1-year prior.[63]

Risk classification systems for stroke risk in AF populations, including $CHADS_2$ and CHA_2DS_2-Vasc scores, quantify comorbid HF as a 1-point increased risk, similar to diabetes and hypertension. However, several studies suggest these scores underestimate additional stroke risk

from HF.[6,23,48] The Framingham Heart Study found that AF-HF patients had a 4 times increased risk of thromboembolism compared to AF only patients.[23,48] In the PREFER registry, AF-HF patients had a statistically significant higher yearly stroke risk compared to AF only patients [1.3% vs 0.6% per year, respectively; p=0.007].[6]

Furthermore, anticoagulation (OAC) management may be tricky in this sub-population as a few studies have shown an increased major and clinically significant bleeding in patients with AF and HF.[6,64] The PREFER registry showed the incidence of major bleeding was higher in AF-HF compared to no HF (3.6% vs 2.5%, respectively; p=0.01).[6] The thromboEVAL study found a statistically significant interaction for major bleeding between AF subtypes with concomitant HF and OAC therapy [HR_{HF} 2.45 (1.51-3.98) vs $HR_{no\ HF}$ 0.85 (0.55-1.34), interaction 0.003].[64]

Other outcomes, including quality of life measures, exercise capacity, enlarged LV dimensions, lower left ventricular ejection fraction (LVEF), and increased BNP have also been shown to worsen.[65,66]

2.3 Rate versus rhythm control strategies

Management of AF-HF patients focuses on the restoration of sinus rhythm as well as the optimization of HF management.[52,53,55] CHF-STAT,[51] DIAMOND,[67] RACE,[68,69] AF-CHF,[1] and AFFIRM,[9] demonstrated that patients who converted to sinus rhythm had a better prognosis with 30% mortality compared to 60% mortality in patients who did not convert to sinus rhythm at 4 years (p=0.04).[51] The two therapeutic strategies aimed to treat AF-HF patients include rhythm control to restore or maintain sinus rhythm or rate control to optimize ventricular response rate.[52,53,55]

Rate control medications, including beta-blockers, are central for the treatment of AF with reduced ejection fraction (Recommendation: class 1, evidence level A).[52,53,55] However, the

beneficial effects of these medications have been reduced with the coexistence of HF.[70-72] Studies found that increased survival with beta-blockers in the HF population is restricted to patients in sinus rhythm, even when the ventricular rate reduction was similar in AF and non-AF populations.[70-72]

The use of rhythm control medications is generally limited to amiodarone and dofetilide in the HF populations due to evidence of worse outcomes with other rhythm control agents in patients with reduced LVEF as described in the clinical guidelines.[52,53,55] Amiodarone is the most effective anti-arrhythmic drug (AAD) to maintain sinus rhythm, however it is associated with many side effects with long term use, including an increase likelihood of non-cardiac death.[73,74]

Large trials comparing pharmacological rhythm and rate control, including AFFIRM and AF-CHF, have demonstrated that rhythm control with AADs failed to show non-inferiority in cardiovascular and all-cause mortality and stroke risk (Table 1).[9,51] Further, these trials indicated that AADs may increase HF hospitalizations (Table 1).[1,9,51] It is hypothesized that the decreased effectiveness of AADs in the AF-HF population compared to AF alone may be due to decreased efficacy to convert and maintain patients in sinus rhythm as well as increased risk of adverse events (AEs).[1,9,51]

Table 1. Pharmacological Rhythm vs Rate Control Trials in AF-HF Patients

Author/ study title & year	Sample Size	Rhythm Control	Rate Control	Follow-up (months)	Outcomes (RR, 95% CI)		
					All-cause Mortality	HF Hospitalization	Stroke
AF-CHF[1] (2008)	1,376	Amiodarone ± DCCV	β-blockers + CCB	48	1.0 (0.8-1.2)	0.9 (0.7-1.0)	0.8 (0.4-1.4)
AFFIRM[9] Sub-study (2007)	788	AAD	β-blockers + CCB	42 (mean)	1.0 (0.8-1.2)	0.9 (0.8-1.0)	ND
CAFÉ-II[75] (2008)	61	Amiodarone ± DCCV	β-blockers + digoxin	12	1.0 (0.1-14.8)	ND	ND
RACE[68,76] Sub-study (2004)	261	DCCV ±Sotalol (± AADs)	CCB ±β-blockers	24	1.9 (0.8-4.3)	1.4 (0.5-4.3)	0.7 (0.6-2.0)

*Reference group- rate control; DCCV= direct current cardioversion (electrical); CCB= calcium channel blocker; ND= not done

2.4 Catheter ablation vs pharmacological therapy

CA, a minimally invasive intervention aimed to maintain sinus rhythm, offers a unique therapeutic strategy to decrease AF burden by modifying the arrhythmogenic substrate responsible for triggering and maintaining AF.[4,11] CA has been widely shown to reduce AF recurrence[1,77] and improve quality of life[11] when compared to AAD therapy in several randomized trials. In non-randomized studies, CA has also been associated with reductions in stroke risk, mortality, and major morbidities.[21,78-83]

CA in HF patients is more challenging due to: 1) enlarged left atria and larger pulmonary vein ostia resulting in the need for a larger area to be ablated and 2) many HF patients have persistent rather than paroxysmal AF, necessitating the targeting of extra non-pulmonary vein triggers.[84,85] Despite the technical challenges, CA has been successfully performed in patients with

HF with an improvement in surrogate outcome measures including: increased LVEF (weighted mean difference of 6.8%, p=0.0004), lower arrhythmia recurrence (29.6% vs 80,1%, p<0.001), better quality of life (weighted mean difference -9.1, p=0.007), and reduced NT-proBNP (mean difference -106.0, p<0.001).[11,68,86-92]

In addition, recently published randomized trials have investigated the efficacy of CA in AF-HF patients, including the outcomes of mortality, HF hospitalizations, and stroke.[10,12,13,62,89,93,94] Only CASTLE-AF showed a protective effect of CA for all-cause mortality compared to pharmacological rhythm and rate control therapy,[13] however the AATAC trial indicated a similar trend.[12] Similarly, a statistically significant reduction in HF hospitalizations was also observed in subjects who underwent CA.[12,13] Interestingly, the two studies that observed a protective effect from CA had pharmacological rhythm control as the control arm, instead of rate control only.[12,13] CA did not appear to have an effect on stroke risk.[10,12,13] (Table 2) Results were further supported by a sub-analysis of HF patients in the CABANA trial which also showed that CA reduced the incidence of a combined endpoint of all-cause mortality, stroke, and cardiac arrest [HR 0.6 (95% CI 0.4-1.1)].[14]

The majority of the AEs related to CA are acute or subacute procedure-related complications.[95] Reported complications include stroke or transient ischemic attacks (TIAs), pericardial effusion or cardiac tamponade, pulmonary vein stenosis, phrenic nerve injury with diaphragmatic paralysis, pneumothorax, heart valve damage, sepsis, atrio-esophageal fistula, vascular complications and death.[95] Results from a meta-analysis of 7 CA studies on HF patients show the overall procedural risk of complications is 4.8%, which is similar to the risk of CA without HF.[96]

Table 2. Randomized Controlled Trials on AF ablation in AF-HF patients

Author/ study title & year	N	Women	Medical Therapy	AF subtype	Follow-up (months)	Outcomes (RR, 95% CI)		
						All-cause Mortality	HF Hospitalization	Stroke
CASTLE[13] (2018)	363	14.3%	Pharmacological rhythm or rate control	Paroxysmal & persistent	Outcomes assessed at 37 months	0.5 (0.3-0.8)*	0.6 (0.4-0.8)*	0.5 (0.2-1.3)
PABA-CHF[10] (2008)	81	0.09%	AV node ablation with BiV pacing	Paroxysmal & persistent	6	ND	2.9 (0.1-69.8)	ND
AATAC[12] (2016)	203	25.6%	Pharmacological rhythm control (amiodarone)	Persistent with ICD/CRT-D implant	24	0.4 (0.2-1.0)	0.6 (0.4-0.8)*	ND
CAMTAF[93] (2014)	50	0.06%	Rate control (Beta blocker)	Persistent	6	0.3 (0.0-7.2)	ND	0.9 (0.1-14.0)
CAMERA-MRI[94] (2017)	66	0.09%	Optimal pharmacological therapy	Persistent	6	ND	0.2 (0.0-4.0)	ND
MacDonald et al[62] (2011)	41	22.0%	Optimal pharmacological therapy	Persistent	6	ND	1.7 (0.2-17.6)	2.6 (0.1-60.5)
ARC-HF[97] (2013)	52	19.2%	Rate control (beta blockers) ± Digoxin	Persistent	12	3.0 (0.1-70.4)	1.0 (0.2-4.5)	0.3 (0.0-7.8)

*Marks a statistically significant protective effect of CA; ND=not done; Studies assessing similar outcomes were included

2.5 Research gaps

European and American AF guidelines have no specific recommendations for CA utilization in AF-HF (compared to patients without HF) except for additional medical treatment for HF symptoms.[52,53,55] The results of randomized trials (Table 2)[10,12,13,62,93,94,97] are encouraging for treatment of AF-HF patients, however the translation of effect to the real-world population needs to be further elucidated.

Many of the patients with HF encountered in clinical practice do not meet the inclusion criteria of trials performed to date, as reflected by the high screening failures.[12,13,96] In the largest trial, CASTLE-AF, approximately 3000 patients were screened to yield a final study population of 363 patients.[13] With the trial criteria and the non-specificity of clinical guidelines, there needs to be a better description of patients eligible for the procedure. Also, the value and safety of CA in a broader range of AF patients with HF remains to be determined by further research studies.

The present thesis addressed analytical limitations of prior studies (randomized trials and observational). In time-to-event analyses, all studies assumed the effect of CA was constant over the entire follow-up period. However, the plausibility of the effect of CA remaining constant has not been investigated and may be false since AF recurrence is common in this population, necessitating repeat CA or medical therapy. This study modeled change in the adjusted hazard ratio (HR) for CA over follow-up to determine if and how the effectiveness of treatment may vary with time since CA. Also, covariates that prevent outcomes including implantable cardiac defibrillators (ICDs) (prevents mortality), cardiac resynchronization therapy devices (CRTs) (decreasing HF admissions), OAC (prevents strokes), and AAD medications (prevents AF recurrence) were not adjusted for in prior study models, especially as time-varying covariates. Randomized studies only reported use of devices or medications and did not account for its effect

on the outcomes.[10,13] Randomization only balances baseline measured and unmeasured confounding,[98-100] therefore the additional effects of medications or ICDs and CRTs during the follow-up period were not assessed. Similarly, the proportion of patients with repeat CA were reported, however the effect of repeat CA was not incorporated into the analysis. Most studies assessed a primary composite endpoint of mortality and a non-fatal outcome.[12,13] When outcomes were evaluated individually, the competing risk of mortality was not accounted for when assessing the risk of the non-fatal outcome. Without accounting for the competing risk of death, the effect of CA on the specific non-fatal outcome was not accurately assessed.

Lastly, follow-up time to capture the outcomes was relatively short from 6 months to 3 years with a maximum number of patients in the treatment group (CA) of 179 patients,[10,12,13,62,93,94,96,97] while the median follow-up post-CA in our AF-HF cohort is 5.5 years (IQR 2.7-9.5) for the 700 CA patients.

Therefore, this thesis used a real-world AF-HF population to address the methodological gaps present in the literature to assess the use, safety, and long-term effectiveness of CA. The outcome of the proposed thesis will build on the results of randomized trials and observational studies to better inform clinical guidelines for treatment of the AF-HF population with CA.

CHAPTER 3: DATABASE AND COHORT CREATION

3.1 Study design

We conducted a retrospective cohort study of the utilization, safety, and long-term effectiveness of CA therapy in AF-HF patients using Quebec administrative health care databases.

3.2 Study population and databases

The Quebec AF cohort consists of linked hospital discharge summary and claims databases, Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (Med-Echo) and la Régie de l'assurance maladie du Québec (RAMQ) respectively, and included patients discharged alive with a primary or secondary diagnosis of AF from April 1, 2000 to March 31, 2017. Patients' encrypted provincial health insurance numbers were used to link the Med-Echo and RAMQ data. Med-Echo is a hospital discharge summary database used to identify patients with AF, HF, related comorbidities, and non-fatal outcomes. Medical procedures, medication use, and mortality data are contained in the RAMQ claims database.

AF patients were defined as those admitted to hospital with a primary diagnosis or a major co-morbid (secondary) diagnosis of AF (International Classification of Diseases – 9th/10th (ICD-9/10) revision, code 427.3, 427.31, or 427.32 / I48). ICD-9/10 codes for AF have been previously validated to yield a positive predictive value of 89%.[101,102] To identify patients with AF not due to a reversible cause, we excluded patients with: 1) AF as a post-admission complication, 2) peri-operative AF (defined as having coronary artery bypass surgery, pericardial intervention, or structural cardiac repair within 30 days prior to their AF diagnosis); or 3) diagnosis of hyperthyroidism or thyrotoxicosis within the previous 12 months. Patients who are residents of chronic care facilities, and who do not have a valid health card number were excluded due to inconsistent medical information. The first date of AF admission was the date of entry into the AF

cohort.

To identify the subpopulation with co-existing HF, patients with a primary or secondary diagnosis of HF at hospitalization were included in the cohort. Validated ICD-9/10 codes have been used to capture this patient population (428.0, 428.1, 428.2, 428.3, 428.4, 428.9/ I50.1, I50.2, I50.3, I50.4, I50.8, I50.9).[103,104] Positive predictive values for HF diagnostic codes ranged from 84-100% for ICD-9 codes and 90-94% for ICD-10 codes.[104] Date of first HF admission is the date of HF diagnosis.

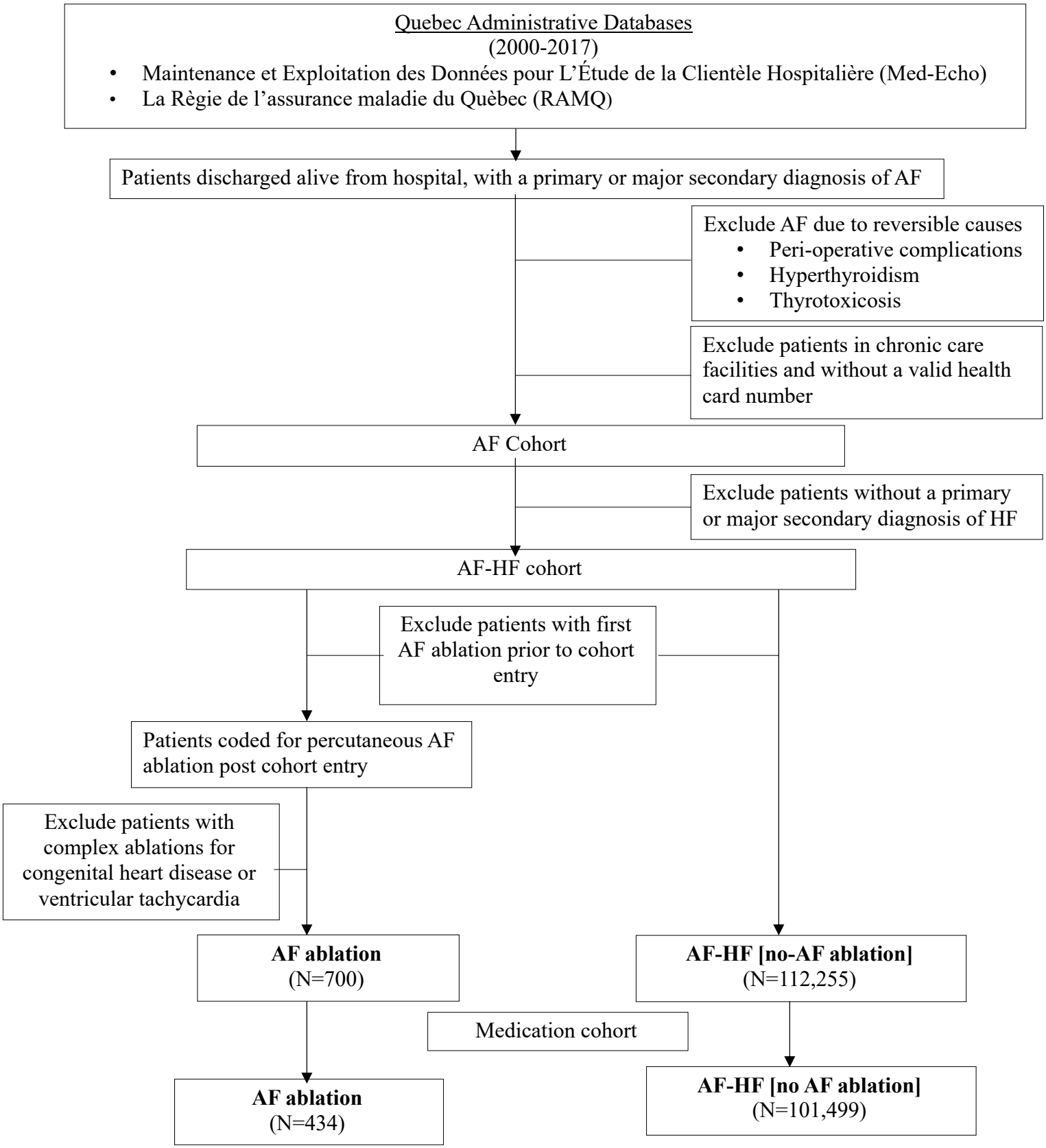
In addition, patients who underwent CA (section 3.4) prior to cohort entry (diagnosis of both AF and HF, section 3.3) were excluded from the cohort due to potential mixing of treatment effect. The duration of effectiveness of CA for the prevention of AF recurrences has not previously been quantified, however the present thesis specifically aims to evaluate CA *after* a patient also has HF.

An AF-HF cohort of 112,255 patients was created, of which 700 underwent CA (Figure 1).

3.2.1 Medication data

Medication prescriptions were captured from the medication claims data in RAMQ. The validity of prescription claims databases has been assessed and determined to be reliable for filling prescriptions.[105-107] In Quebec, all patients 65 years and older, and about half of patients 65 years and younger (without private coverage) are covered by the government drug insurance and have medication use captured in RAMQ.[107,108] Approximately 90% of patients in the AF-HF cohort had available medication information. The medication cohort consisted of 101,933 AF-HF patients, of which 434 underwent CA. The medication cohort was the primary cohort investigated for manuscripts 1 and 3 and the medication cohort was used as a sensitivity analysis for manuscript 2 (Figure 1).

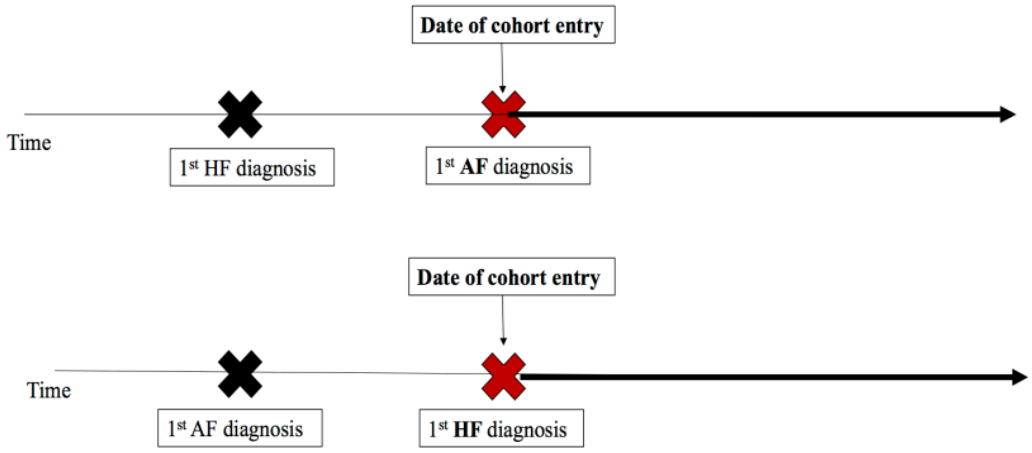
Figure 1. Cohort creation flow chart



3.3 Cohort Entry

To enter the AF-HF cohort, patients had both AF and HF. In order to capture patients only when they have both conditions, entry into the AF-HF sub-cohort was determined based on the date of first HF amongst patients in the AF cohort. As mentioned, patients enter the AF cohort on the date of first AF diagnosis. Patients with pre-existing HF (diagnosis of HF prior to first AF diagnosis) entered the AF-HF cohort on the date of first AF diagnosis. Patients who developed HF after pre-existing AF, entered the AF-HF cohort on the date of the first HF diagnosis. Patients diagnosed with first AF and first HF on the same date, entered the cohort on that date. (Figure 2)

Figure 2. Cohort entry



3.4 Identification of AF ablation

CA is a procedure performed by a trained electrophysiologist (cardiologist specializing in arrhythmias) and was identified by a provincial physician billing code for percutaneous AF ablation [CA] (RAMQ code 291). The date of CA was defined as the date of the procedure as billed in RAMQ. To exclude complex ablations for congenital heart disease or ventricular tachycardia (also billed under RAMQ code 291), date of CA was matched to date of AF admission (ICD-9/10 codes for AF). In addition, patients with any ICD-9/10 code for congenital heart disease

or a code for ventricular tachycardia at CA admission were excluded. Patients in Quebec undergoing CA are routinely admitted for at least 24 hours. By identifying date-matched admission for AF, all patients undergoing CA for AF will be captured.

Administrative coding validation for common cardiac procedures compared to a clinical registry (gold standard) demonstrated that procedure coded data elements are accurate, reflect interventions performed at the time of service, and therefore may be used for cardiovascular outcomes research.[109]

3.5 Measurement of covariates

Comorbidities was ascertained from hospital admissions documented in Med-Echo and captured using ICD-9/10 codes. Covariates chosen are clinically indicated from published literature[21,43,52,53,55,78,110] and reflect the severity of diseases and are associated with the outcomes. Clinical covariates investigated include CHA_2DS_2-Vasc variables (congestive heart failure, hypertension, diabetes, vascular disease, and prior stroke) and age as a continuous variable. When investigating the outcome of major bleeding, most HAS-Bled variables were also be incorporated into the models (hypertension, renal disease, liver disease, prior stroke, and prior major bleeding). Presence of a cardiac implantable electronic device (CIED) [pacemaker, implantable cardioverter defibrillator (ICD), and cardiac resynchronization therapy (CRT-D/P)] were recorded. Implantation of these devices occurs for HF patients and sometimes AF and will be markers for severity of disease.[52,53,55] ICDs and CRT-Ds are particularly important because they can prevent the primary outcome of mortality (manuscript 3). In the medication cohort, OACs, rate control, rhythm control, diuretics, ACEs, and ARBs were documented to complete the patient profile. Baseline covariates were captured within 1 year prior to cohort entry. Covariates were incorporated into the models as time-varying or time-fixed depending on the specific manuscript.

CHAPTER 4: MANUSCRIPT 1: SEX DIFFERENCES AND PREDICTORS FOR TREATMENT WITH CATHETER ABLATION IN PATIENTS WITH ATRIAL FIBRILLATION AND HEART FAILURE

4.1 Preface: Manuscript 1

Although there is a lack of consensus on the best management strategy for AF patients with comorbid HF, promising results from recent randomized trials indicate CA may be considered as a treatment option. Clinical guidelines recommending the use of CA in AF-HF patients are relatively non-specific, thus criteria for patient referral is based on individual cardiologists' preference. Therefore, in the first manuscript of the present thesis, entitled "Sex differences and predictors for treatment with catheter ablation in patients with atrial fibrillation and heart failure", we determined the incidences, sex differences, and time-updated predictors for CA treatment in the real-world AF-HF population.

Results of the present study demonstrated that CA is infrequently used to treat AF-HF patients, with a further reduced propensity for CA treatment amongst women. Although randomized trial results and clinical guidelines may increase the utilization of CA amongst AF-HF population, widespread use may be limited as a majority of the AF-HF population are older and have additional comorbidities (CHA_2DS_2-Vasc ≥ 2). Until future studies are conducted in patients whose clinical characteristics are more representative of the AF-HF population, utilization of CA is likely to remain low amongst AF-HF patients, however, the present study better describes the AF-HF patients undergoing CA.

An abstract of this work was accepted and presented as a poster at the Society for Epidemiologic Research (SER) Conference 2019 (June) in Minneapolis, Minnesota. The present manuscript has been submitted to the *Canadian Journal of Cardiology Open* (*CJC-O*).

4.3 Manuscript

Population-level sex differences and predictors for treatment with catheter ablation in patients with atrial fibrillation and heart failure

Short title: Predictors of treatment with catheter ablation

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Word Count: 4,889/ 5,000 words

ABSTRACT

BACKGROUND: Current guidelines are relatively general regarding the type of heart failure (HF) patient who should be considered for catheter ablation (CA) of atrial fibrillation (AF).

OBJECTIVE: To identify clinical predictors and sex differences for treatment with CA in the AF-HF population.

METHODS: A population-based AF-HF cohort was created using Quebec administrative data (2000-2017). Patients were followed from the date of diagnosis of both diseases until date of CA or death. Predictors for CA, represented by time-varying covariates, were assessed in a multivariable Cox model, that accounted for the competing risk of death.

RESULTS: Among 101,931 AF-HF patients with available medication information [median age 80.7 years (IQR 73.9-86.3), 51.4% female, median CHA_2DS_2-Vasc 4 (IQR 3-4)]; only 432 (0.4%) underwent CA after a median of 0.8 years (IQR 0.1-2.7). Independent of multiple comorbidities and advanced age which were associated with a lower likelihood of CA, women were almost half as likely to have had a CA [26% women; aHR 0.6 (95% CI 0.4-0.7)]. Prior use of direct acting oral anticoagulants and antiarrhythmics, as well as the presence of an implantable cardioverter-defibrillator were also predictors for CA treatment ($p<0.05$ for all).

CONCLUSION: In a real-world population, CA was infrequently used to treat AF amongst patients with HF and the likelihood of CA was further reduced in women. As CA patients had few comorbidities, future studies need to be conducted to determine whether CA can be beneficial in subjects whose clinical characteristics are more representative of the AF-HF population.

Keywords: catheter ablation, atrial fibrillation, heart failure

BRIEF SUMMARY

The coexistence of atrial fibrillation (AF) and heart failure (HF) increase the risk of mortality and HF hospitalizations. Due to limited effectiveness of pharmacologic therapy and promising randomized trial results for catheter ablation (CA) of AF, our objective was to determine the population-based incidence, predictors, and sex differences for CA treatment amongst AF-HF patients. We found AF-HF patients infrequently underwent CA. Patients undergoing CA had few comorbidities and were half as likely to be women.

INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) frequently coexist with AF affecting approximately 15-30% of patients with clinically overt HF[1]. The presence of both diseases substantially increases the risk of all-cause mortality[2], HF hospitalization[1], and thromboembolism[3].

Treatment of this high-risk population is challenging with little consensus on an effective management strategy.[1,4] Pharmacological rhythm control strategies have failed to show a reduction in cardiovascular mortality, all-cause mortality, and stroke in large randomized trials, with an indication that antiarrhythmic medications (AADs) may increase HF hospitalizations.[5]

In the absence of effective pharmacological rhythm control options for AF patients with HF, catheter ablation (CA) for AF has emerged as a treatment option. Randomized trials, including CASTLE-AF and AATAC, have shown a reduction in HF hospitalizations in AF-HF patients with reduced ejection fraction (HFrEF) treated with CA compared to medical therapy.[6-8] CASTLE-AF also showed a statistically significant reduction in all-cause mortality,[7] where a mortality benefit was further supported in a subgroup analysis of the CABANA trial.[9] Although the results of randomized trials are encouraging, subjects who meet the strict inclusion and exclusion criteria may not reflect the AF-HF population encountered in clinical practice. Further, only 15-25% of study subjects included these trials were women and it is unclear if this CA treatment selection pattern persists in the real-world AF-HF population.[6,7]

Canadian clinical guidelines recommend CA as a second line treatment option for AF and do not have a specific recommendation for patients with comorbid HF (moderate quality of evidence).[10] American guidelines suggest referral may be reasonable in HFrEF patients with weak evidence of a benefit (level IIb).[11] In both sets of guidelines, however, no patient-specific

inclusions/exclusions are recommended for patients with HF.[10,11] Thus, criteria to select AF-HF patients for CA is based on the electrophysiologists' expert opinion and the real-world CA treatment pattern is unknown. The objective of the present study was to characterize the real-world patterns of CA use in HF patients by identifying clinical predictors and sex differences.

METHODS

Study design

A population-based cohort of patients with AF and HF was assembled using administrative databases to identify predictors for CA in Quebec, Canada between April 1, 2000 and March 31, 2017. The study received institutional review board approval from the McGill University Faculty of Medicine (A05-M79-08B).

Data sources and study population

First, the Quebec AF cohort was created from linked hospital discharge summary and physician claims databases, Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (Med-Echo) and la Régie de l'assurance maladie du Québec (RAMQ), respectively, as described previously.[12-14] Recent years of data, until 2017, were added.

To create the AF-HF cohort, only patients with a primary or secondary diagnosis of HF at hospitalization were included (International Classification of Disease-9th and 10th Revisions (ICD-9/10) codes:428.0-4, 428.9/ I50.1-4,8,9). Patients entered the cohort on the first date they had both diseases diagnosed. Patients with a CA prior to the cohort entry were excluded.

The main cohort was limited to a subset of AF-HF patients who had government prescription insurance coverage (medication cohort). In Quebec, all patients 65 years and older, and about half of patients 65 years and younger (without private coverage) are covered by the government prescription insurance and have medication prescriptions captured in RAMQ. In

sensitivity analysis, we included all patients with AF and HF, regardless of medication insurance coverage (overall cohort). Considering the first study on CA in AF-HF patients was published in 2008, an additional sensitivity analysis limiting the cohort duration from 2009 to 2017 was also conducted.

Outcome ascertainment

A provincial physician billing code for percutaneous AF ablation (RAMQ code 291) was used to identify CA. The date of CA was defined as the date of the procedure as billed in RAMQ. To exclude complex ablations for congenital heart disease or ventricular tachycardia (also billed under RAMQ code 291), date of CA was matched to date of AF admission (ICD-9/10 codes for AF) or a diagnosis code linked with CA in RAMQ. Further, patients with any diagnosis of congenital heart disease or a primary or major secondary diagnosis for ventricular tachycardia were also excluded.

Potential predictors

Potential predictors for CA therapy, considered in our analyses, include patient and procedure-specific factors of CA and variables that may act as markers of AF and HF disease severity (listed in table 1). The presence of potential predictors at cohort entry were identified from comorbidities listed at hospital admissions within the 1-year period prior to cohort entry. For patients who did not undergo CA on the date of cohort entry (date of diagnosis of AF and HF), comorbidities acquired during follow-up were represented in the prediction models as time-varying covariates. Since we investigated comorbidities corresponding to chronic diseases, a patient was considered exposed from the date of the first hospitalization that indicated the relevant diagnosis until the end of the follow-up period (comorbidities were listed as any diagnosis at admission). ICDs and CRTs acquired during follow-up were also incorporated as time-varying

covariates.

Any exposure to pertinent medications was also assessed using time-varying covariates described above. Although a patient may not have been on a medication throughout the follow-up, prior use of medications may predict CA: for example, patients who failed pharmacologic rhythm therapy may be referred for CA, as per clinical guidelines.[10,11]

In Quebec, the waiting period for CA (date CA was requested to date CA was performed) is approximately 3-6 months. Therefore, predictors first captured within less than 3 months prior to CA were excluded, based on the assumption that the decision to perform the CA for the patient had been already likely taken. A sensitivity analysis with a blanking period of 6 months prior to CA was also conducted.

Statistical analysis

In descriptive analyses, distributions of continuous variables were summarized with medians and interquartile ranges (IQR) and categorical variables were described by frequency and percentages. To assess sex differences in the AF-HF cohort amongst patients who underwent CA, differences in the distribution of continuous and categorical variables between men and women were compared by the Wilcoxon rank-sum test and Chi-squared test, respectively.

Predictors of CA were identified using multivariable Cox proportional hazards models, extended to account for the competing risk of all-cause mortality using the Lunn-McNeil approach.[15] In addition to age at cohort entry and sex, time-varying covariates were included in the multivariable model as potential predictors after potential collinearity between predictors was investigated. Selection criteria for prediction model was based on statistical significance ($p \leq 0.05$) and clinically significant predictors near statistical significance ($p \leq 0.1$). Backwards elimination was also performed to verify results from prediction model ($p \leq 0.05$). All analyses were first

conducted in the medication cohort (main analysis) and then, in sensitivity analysis, were replicated, for all study subjects including patients who had no data on medication use. An additional evaluation of predictors was conducted limiting the cohort to 2009-2017 and a comparison of baseline characteristics between patients who underwent CAs between 2000-2014 and 2015-2017 was also performed (supplement),

SAS software version 9.4 (SAS Institute, Cary, North Carolina) was employed for all analyses.

RESULTS

Among the 101,931 AF-HF patients with available medication information, 432 (0.4%) underwent CA within a median of 0.8 years (IQR 0.1-2.7) after cohort entry. The number of CAs performed per year increased, however, the low rate of CAs was relatively constant (Figure 1 and supplement).

Baseline characteristics

At cohort entry, patients with available medication information were a median of 80.7 years (73.9-82.3), 51.4% were women, and had a high median CHA_2DS_2-Vasc score of 4 (3-4). Only 2.5% of the population had an implantable cardioverter defibrillator (ICD) and 9.4% had a cardiac resynchronization therapy (CRT) device. Warfarin was the most frequently prescribed OAC (47.6%) and amiodarone the most frequent AAD (10.0%). Diuretics were prescribed in 69.5% of the population. (Table 1)

Sex differences

Although more than half (51.4%) of the AF-HF population were women, only 25.6% of CA patients were women. In the AF-HF cohort, the presence of most comorbidities, ICDs and CRTs, and the use of medications were less frequent in women than men, whereas men were

younger and had less hypertension, valve disease, and prior stroke (Table 2; p-values <0.05 for all comparisons). Despite the differences between men and women in the full cohort of patients with AF and HF, in the relatively small CA sub-population, there were no statistically significant differences in most patient characteristics except that women had less coronary artery disease, chronic renal failure, ICDs, and CRTs (Table 2). Overall, the shape of the distribution of CHA_2DS_2-vasc scores for CA and non-CA patients was similar between men and women, except the distribution was shifted to the right due to an extra point assignment for female sex (Figure 2a). The distribution of HAS-Bled scores was similar between the sexes for both CA and non-CA patients (Figure 2b). Independent of multiple comorbidities and advanced age, women were almost half as likely to undergo CA [adjusted Hazard Ratio (aHR) 0.6 (95% CI 0.4-0.7)].

Other predictors for CA

Presence of an ICD [aHR 3.3 (95% CI 2.2-5.0)], and a prior prescription for a DOAC [aHR 1.5 (95% CI 1.2-1.9)] and AADs [HR 1.9 (95% CI 1.5-2.4)] during follow-up were associated with higher likelihood of CA (Figure 3). On the other hand, advanced age, female sex, chronic obstructive pulmonary disorder, liver disease, renal disease, prior stroke (including transient ischemic attacks (TIA)), valve disease, coronary artery disease, prior bleeding, and diuretic use were associated with a lower probability of CA (Figure 3, p<0.05 for all). Predictors remained the same after comorbidities, medications, and devices first captured within 6-months prior to CA were excluded (not exposed) (Figure S1).

Sensitivity analyses

In the overall cohort of AF-HF patients, including those without medication information (N=112,955), 700 (0.6%) patients underwent CA (Figure S4). Comorbidities and procedures identified as predictors of CA were the same as in the medication cohort, except for the presence

of a CRT [aHR 0.72 (95% CI 0.53-0.97)], which was associated with non-use of CA only in the overall cohort (Figure S5).

Predictors for referral were the same in the cohort limited to 2009-2017 except for hypertension which was statistically significant predictor for non-referral to CA [aHR 0.73 (95% CI 0.54-0.98); Figure S2]. In addition, baseline characteristics between patients who underwent CA prior and post (including) 2015 demonstrated that there was only a statistically significant difference in the proportion of CA patients with renal disease, valvular disease, prior use of specific OAC therapy and angiotensin II receptor blockers (Table S3).

DISCUSSION

In this population-level assessment of CA in AF-HF patients, we demonstrated that: (1) CA is infrequently used to treat the AF-HF population (0.4%), (2) patients undergoing CA had few additional comorbidities, (3) were almost half as likely to be women, and, (4) were more likely to have had an ICD and been prescribed an AAD or DOAC.

Utilization of CA

Based on the promising results from recently published randomized trials, current clinical guidelines recommend the use of CA as second line therapy to treat symptomatic AF in patients with comorbid HF,[10,11] however, the present study demonstrated that <1% of the Quebec AF-HF population underwent CA in real-world practice. The utilization of CA in the AF-HF population is less than the rate of CA use in the general AF population (1.3-3.9%),[12,16,17] but similar to the present study, the frequency of the procedure increased over time.[13,18] The trend is expected to continue based on results of CASTLE-AF and CABANA trials with updates to the clinical guidelines.[6,7,10,11]

Although the use of CA in the AF-HF population may increase, the scope of its use may be limited due to the additional comorbidities that accompany HF. It is estimated that between 40% to 93% of patients with HF have 2 or more additional comorbidities.[4] In our study, more than 97% of patients had a CHA_2DS_2-VASC score ≥2, but decreased to 75% in patients who underwent CA. Previous evaluations characterizing the profile of patients undergoing CA have determined that patients were often younger and had fewer comorbidities, however, patients with higher risk scores (CHA_2DS_2-Vasc scores from <1 to ≤2) have increasingly been undergoing the procedure in recent years.[13,18] As a majority of AF-HF patients had a CHA_2DS_2-VASC score ≥2, few patients are likely to qualify for CA with current CA practices.

Sex differences

Large epidemiologic studies of the AF population found that women with AF are often older at disease onset,[19] have more hypertension,[20] previous stroke,[21] and valvular disease,[20] while men have more diabetes,[19,22] coronary artery disease,[20,22] and chronic obstructive pulmonary disorder,[20] all of which were mirrored in the present AF subpopulation with HF. Further, women with AF also have more adverse events from AADs,[23] higher stroke risk,[20,22] more disabling strokes,[22] and a higher cardiovascular mortality compared to men.[21] Despite the increased risk of events in women, which is further elevated with the addition of HF, only a quarter of CA patients were women. The disparity between sexes for treatment with CA, however, is not unique to the AF-HF population and several studies have shown that women are substantially less likely to have a CA in the general AF population.[13,21,24] Amongst AF patients treated with CA, it is estimated that <30% were women.[13,21,24] A similar trend of the unequal distribution of the sexes was demonstrated in randomized trials on CA in AF-HF patients, in which 14.3% and 25.6% of patients enrolled in CASTLE-AF[7] and AATAC,[6] respectively, were women.

It has been suggested that fewer women are treated with CA due to older age,[25] presence of comorbidities that reflect a more diseased substrate,[24,25] and 1.3 to 2.3-fold increased risk of procedural complications,[26] including tamponade[27] and vascular site complications.[27] There is also evidence that the CA procedure in women is more difficult to perform as they tend to have more non-pulmonary vein triggers and atrial fibrosis.[24.25] In addition, a study by Hoyt et al suggests that women may have a higher rate of prolonged hospitalization after CA than men.[26] Regardless, the women and men who underwent CA in the present study had similar patient characteristics, which may suggest that the strict criteria for CA may be based on the patient characteristics of men, who also comprise of the majority of subjects enrolled in randomized trials[6,7] which the clinical guidelines are based upon.[10,11]

Lower probability of CA with major comorbidities and advanced age

Elevated age, CHA_2DS_2-Vasc and HAS-Bled scores, and the presence of chronic obstructive pulmonary disorder have all been identified as predictors for an increased risk of complications post-CA, all-cause mortality in the AF population, and hospitalizations in patients with HF.[1,4] The high-susceptibility for adverse events and outcomes may explain the reluctance to proceed with CA in this high-risk population.

Presence of cardiac electronic implantable devices as predictors

The probability of CA was also reduced with the presence of a CRT device when patients <65 years were included in the cohort. It is possible that CRT was a marker for more advanced HF and more severe atrial disease which may have deterred from consideration of CA. Furthermore, CRT may have been associated with AV nodal ablation (rather than CA of AF) in some patients, to ensure biventricular capture in patients with AF.[28,29] In contrast, patients with an ICD (without

CRT) may be more likely to undergo CA for AF as it is common practice to consider device upgrade to CRT prior to AV node ablation.[28,29]

Medication use as predictors

Clinical guidelines recommend CA in symptomatic AF patients refractory to at least one AAD.[10,11] Although CA has increasingly been used as a first line therapy in patients with paroxysmal AF,[30] it remains likely that patients were prescribed an AAD prior to CA.[10,11] In addition, studies evaluating AAD prescription patterns demonstrated that patients treated by cardiac electrophysiologists were more likely to be prescribed an AAD, who in turn may be more likely to proceed with CA.[31,32]

DOACs were prescribed in <10% of the AF-HF population, however, 24% of patients who underwent CA had a prior prescription for DOACs. Given that DOACs are more likely to be prescribed by cardiologists,[33] DOAC use may be associated with management by a cardiologist who may be more likely to refer a patient for CA compared to a non-specialist. Patients on DOACs may be less likely to have comorbidities, such as renal disease, in which the efficacy and safety of DOACs has not been established.[10,11]

The use of diuretics has been shown to be a marker of advanced HF and worse prognosis in patients with HF.[34] Therefore, prior use of diuretics may be a surrogate marker for HF disease severity and results of the present study suggest that patients with more advanced HF (or diuretic use) were less likely to be treated with CA.

Limitations

Given the nature of the administrative databases used to characterize the type CA patients in the AF-HF population, potential clinical predictors for CA were missing such as: the type of AF (paroxysmal, persistent, and permanent), New York Heart Association (NYHA) class, and left

ventricular ejection fraction (LVEF). To account for severity of disease, we used proxy confounders such as the use of diuretics and presence of a CRT.

Medication information was only present for a subset of the population (patients >65 years or without alternate forms of drug insurance), therefore, the results may be less generalizable to the typically younger population treated with CA. In our study, we found that >90% of AF-HF patients had government prescription coverage, however only 65% of the patients treated with CA were covered. Although we could not investigate medications as predictors in the entire AF-HF population, the same patient characteristics were identified as predictors in the medication and overall cohorts.

The present study accounts for waiting time until CA (date of referral to date of CA) by blanking comorbidities first captured within 3 or 6 months prior to CA, however, waiting times may be longer than 6-months prior to date of CA.

CONCLUSION

In a real-world population, CA was infrequently used to treat AF amongst patients with comorbid HF and the likelihood of CA was further reduced in women. The frequency of CA, however, increased over time. Encouraging results from randomized trials and updates to clinical guidelines may increase the frequency of CA in the AF-HF population, however, the additional comorbidities that commonly coexist in the AF-HF population may prevent the widespread use of CA. Future studies need to be conducted in subjects whose clinical characteristics are more representative of the real-world AF-HF population to determine if CA should more frequently be considered as a treatment option for AF patients with comorbid HF.

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Table 1. Baseline characteristics

	All patients with available medication information (N=101,931) N (%)
Median age (IQR), years	80.7 (73.9-82.3)
< 65	6,801 (6.7)
65-75	22,133 (21.7)
≥75	73,057 (71.7)
Women	52,402 (51.4)
Hypertension	32,578 (32.0)
Diabetes mellitus	16,832 (16.5)
Coronary artery disease	27,323 (26.8)
Prior myocardial infarction	11,464 (11.2)
Valvular disease	27,831 (27.3)
Valve replacement	2,847 (2.8)
Chronic obstructive pulmonary disease	16,505 (16.2)
Chronic renal failure	14,456 (14.2)
Prior stroke (including transient ischemic attack)	2,095 (2.1)
Liver disease	2,241 (2.2)
Vascular disease	11,996 (11.8)
Prior major bleeding	4,155 (4.1)

Implantable cardioverter defibrillator	2,566 (2.5)
Cardiac resynchronization therapy	9,608 (9.4)
Median CHA_2DS_2-Vasc Score	4 (3-4)
Median HAS-BLED Score	1 (1-2)
Medications	
Oral anticoagulation	55,576 (54.5)
Warfarin	48,547 (47.6)
Direct oral anticoagulant	8,607 (8.4)
Dabigatran	2,999 (2.9)
Rivaroxaban	3,105 (3.0)
Apixaban	3,050 (3.0)
Antiarrhythmic medication	15,018 (14.8)
Amiodarone	10,152 (10.0)
Sotalol	3,333 (3.3)
Class 1 antiarrhythmic	2,443 (2.4)
Digoxin	25,140 (24.7)
Beta blocker	50,766 (49.8)
Angiotensin converting enzyme inhibitor	40,462 (39.7)
Angiotension II receptor blockers	18,324 (18.0)
Calcium channel blocker	17,646 (17.3)
Diuretic	70,839 (69.5)

*The table presents the distribution of patient characteristics at cohort entry and does not include the comorbidities, devices, and medications acquired during the follow-up period which is

included in the analysis. Prevalence of patient characteristics are lower since they are measured at time of initial AF-HF disease diagnosis and more patients develop the comorbidities over the time in the cohort.

Table 2. Sex differences in AF-HF patients with and without CA

	Non-CA patients (N=101,931) N (%)		**CA patients (N=432) N (%)**	
	Males 49,521 (48.6)	**Females 52,403 (51.4)**	**Males 322 (74.4)**	**Females 110 (25.6)***
Median age (IQR), years	78.5 (71.8-84.3)	82.6 (76.3-87.8)*	66.5 (58.4-71.6)	65.0 (60.6-73.0)
< 65	4,462 (9.0)	2,339 (4.5)*	140 (43.5)	54 (49.1)
65-75	13,357 (27.0)	8,776 (16.8)*	143 (44.4)	36 (32.7)*
≥75	31,769 (64.1)	41,288 (78.8)*	39 (12.1)	20 (18.2)
Hypertension	14,922 (30.1)	17,655 (33.7)*	83 (25.5)	27 (24.6)
Diabetes mellitus	8,820 (17.8)	8,012 (15.3)*	51 (15.8)	16 (14.5)
Coronary artery disease	14,905 (30.1)	12,418 (23.7)*	74 (22.7)	15 (13.6)*
Prior myocardial infarction	6,637 (13.4)	4,827 (9.2)*	42 (13.0)	7 (6.4)
Valvular disease	12,029 (24.3)	15,802 (30.2)*	98 (30.3)	40 (36.0)
Valve replacement	1,439 (2.9)	1,408 (2.7)*	5 (1.6)	2 (1.8)

Chronic obstructive pulmonary disease	9,071 (18.3)	7,434 (14.2)*	29 (9.0)	4 (3.6)
Chronic renal failure	7,679 (15.5)	6,777 (12.9)*	28 (8.7)	3 (2.7)*
Prior stroke (including TIA)	906 (1.8)	1,189 (2.3)*	1 (0.3)	0 (0.0)
Liver disease	1,258 (2.5)	983 (1.9)*	7 (2.2)	0 (0.0)
Vascular disease	6,662 (13.5)	5,334 (10.2)*	17 (5.3)	4 (3.6)
Prior major bleeding	2,514 (5.1)	1,641 (3.1)*	6 (1.9)	2 (1.8)
Implantable cardioverter defibrillator	2,091 (4.2)	475 (0.9)*	70 (21.7)	6 (5.5)*
Cardiac resynchronization therapy	5,447 (11.0)	4,161 (7.9)*	73 (22.7)	10 (9.1)*
Median CHA_2DS_2-Vasc Score	3 (3-4)	4 (4-5)*	2 (1-3)	3 (2-4)*
Median HAS-BLED Score	1 (1-2)	1 (1-2)*	1 (0-1)	1 (0-1)

*P-values of <0.05 are considered statistically significant. P-values compare males and females.

[y] The baseline table presents the distribution of patient characteristics at cohort entry and does not include the comorbidities and devices acquired during the follow-up period which is included in the analysis.

FIGURE LEGENDS

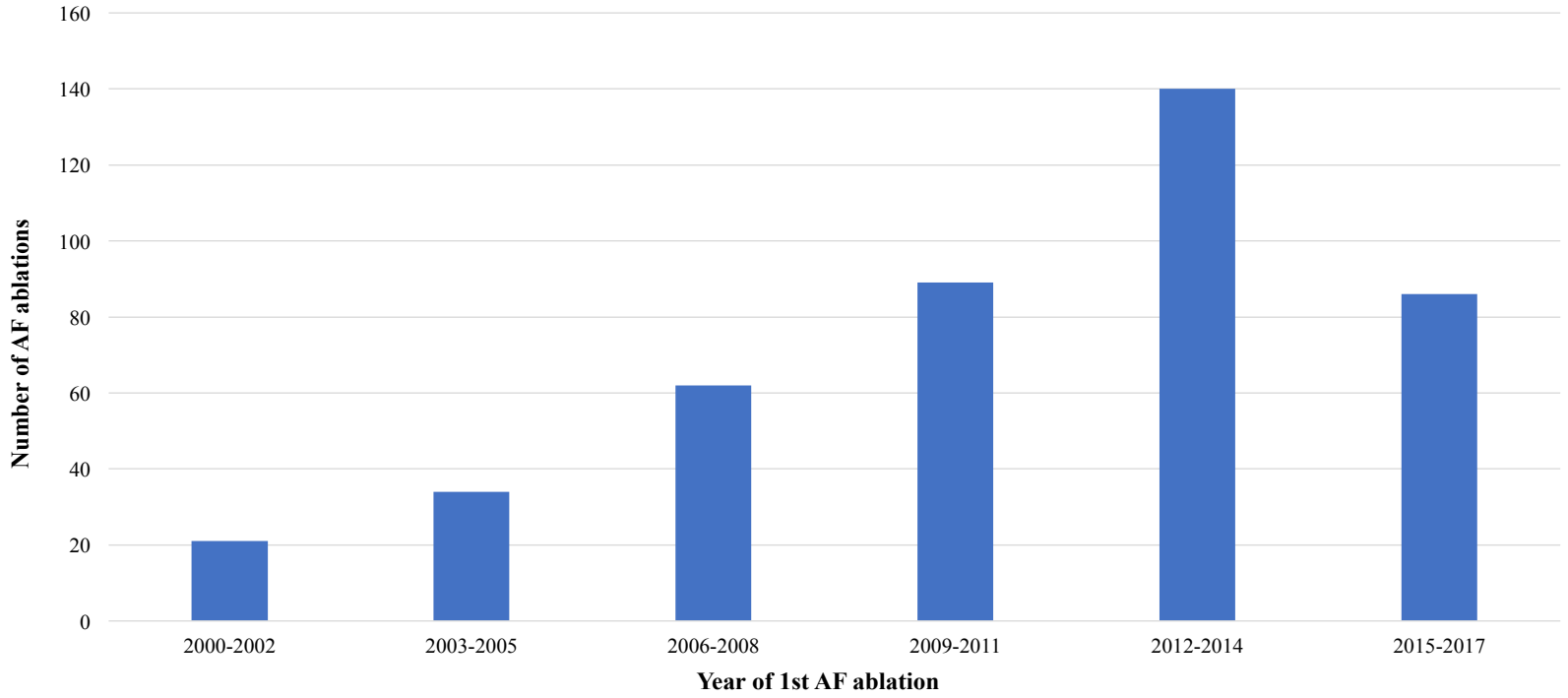
Figure 1. Number of AF ablations over time (N=432)

Figure 2a. Distribution of $CHADS_2$ scores by sex

Figure 2b. Distribution of HAS-Bled scores by sex

Figure 3. Predictors for referral to AF ablation

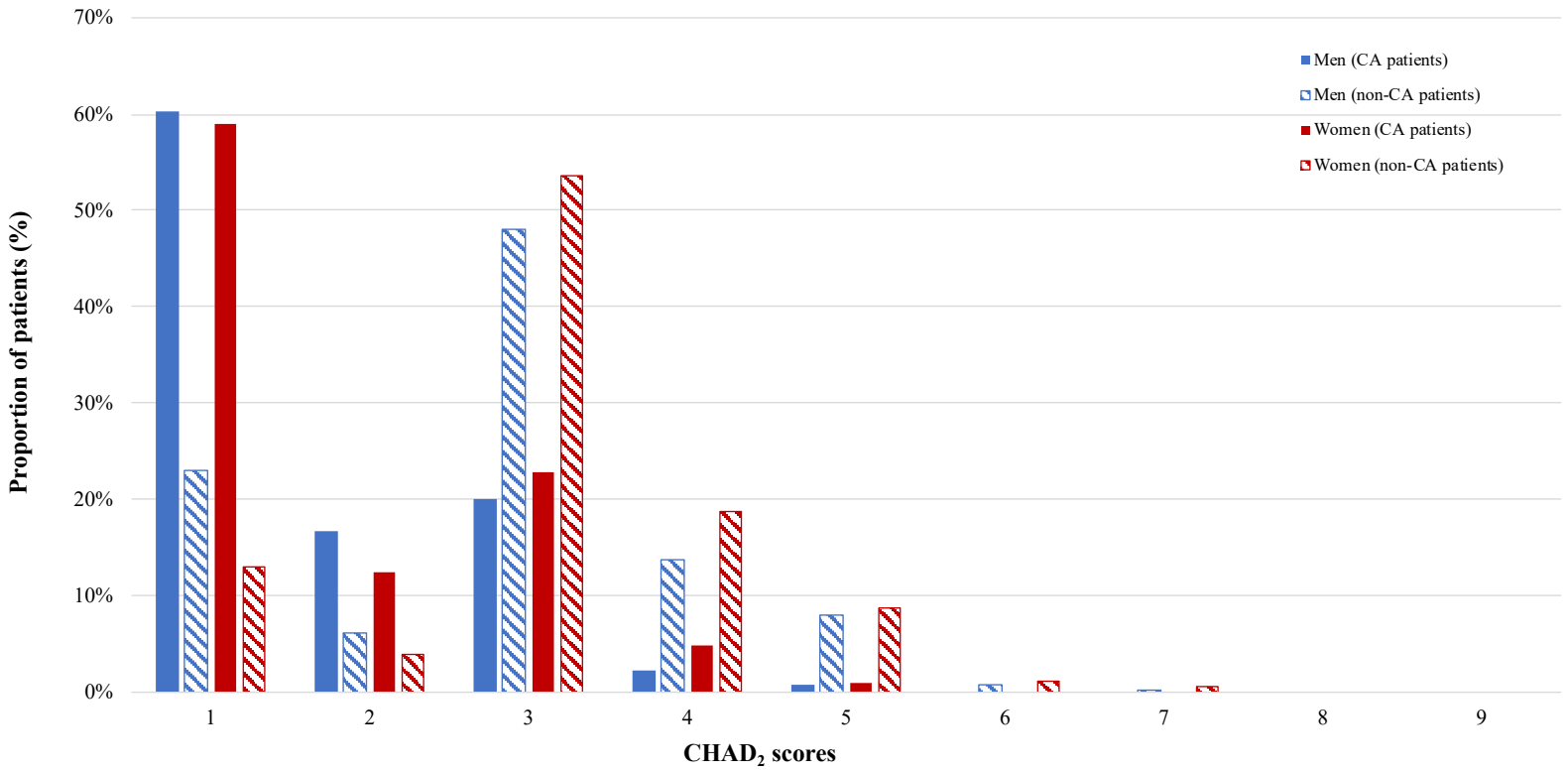
Figure 1. Number of AF ablations over time (N=432)



	2000-2002	2003-2005	2006-2008	2009-2011	2012-2014	2015-2017
Number of AF ablations (%)	21 (0.16)	34 (0.19)	62 (0.26)	89 (0.24)	140 (0.27)	86 (0.13)
Number of AF-HF patients	13,454	17,813	24,236	36,529	52,349	66,509

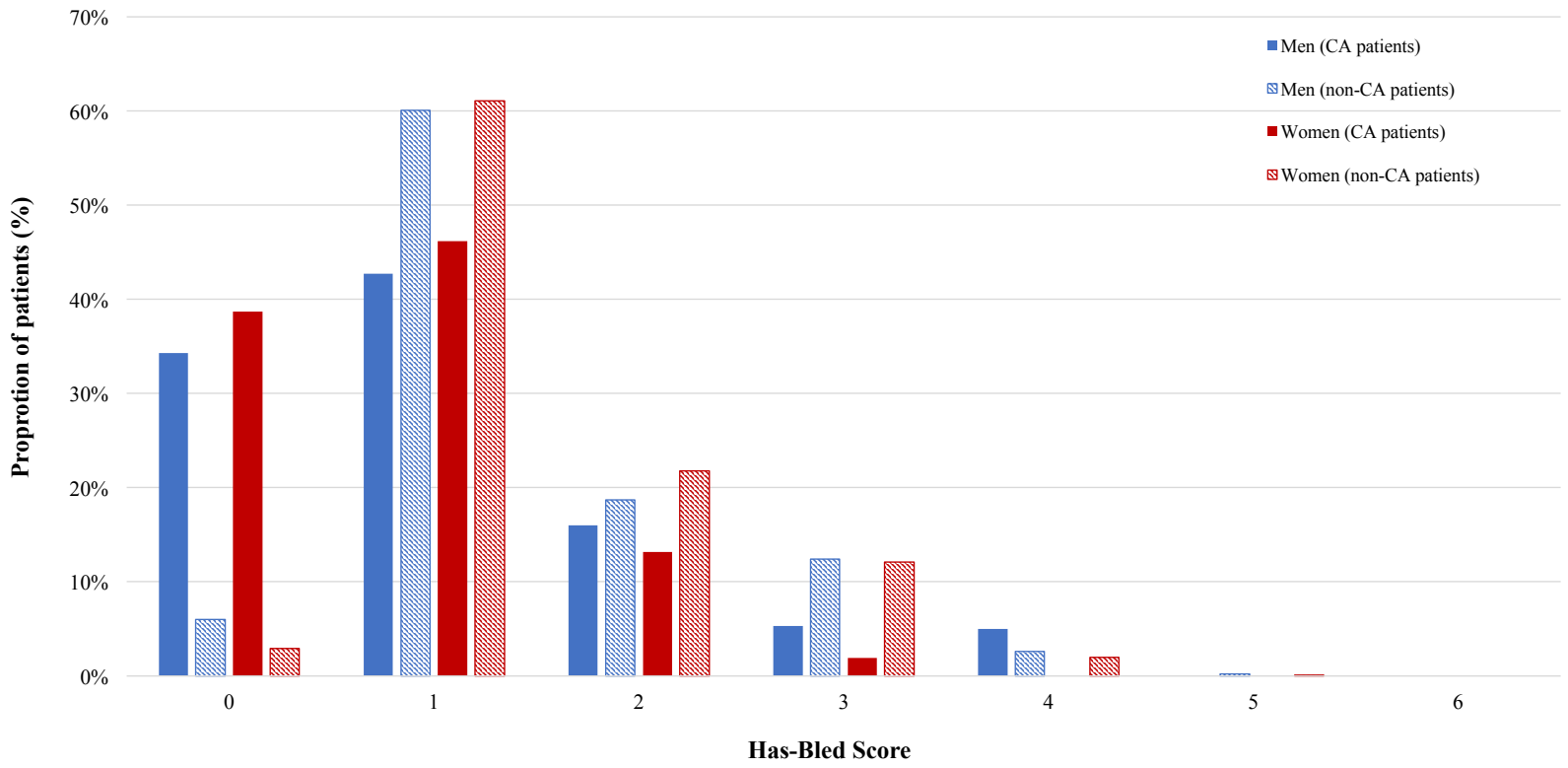
*The number of AF ablations for 2015-2017 is an underestimate because AF ablations after March 31, 2017 were not included in the cohort.

Figure 2a. Distribution of $CHADS_2$ scores by sex at baseline



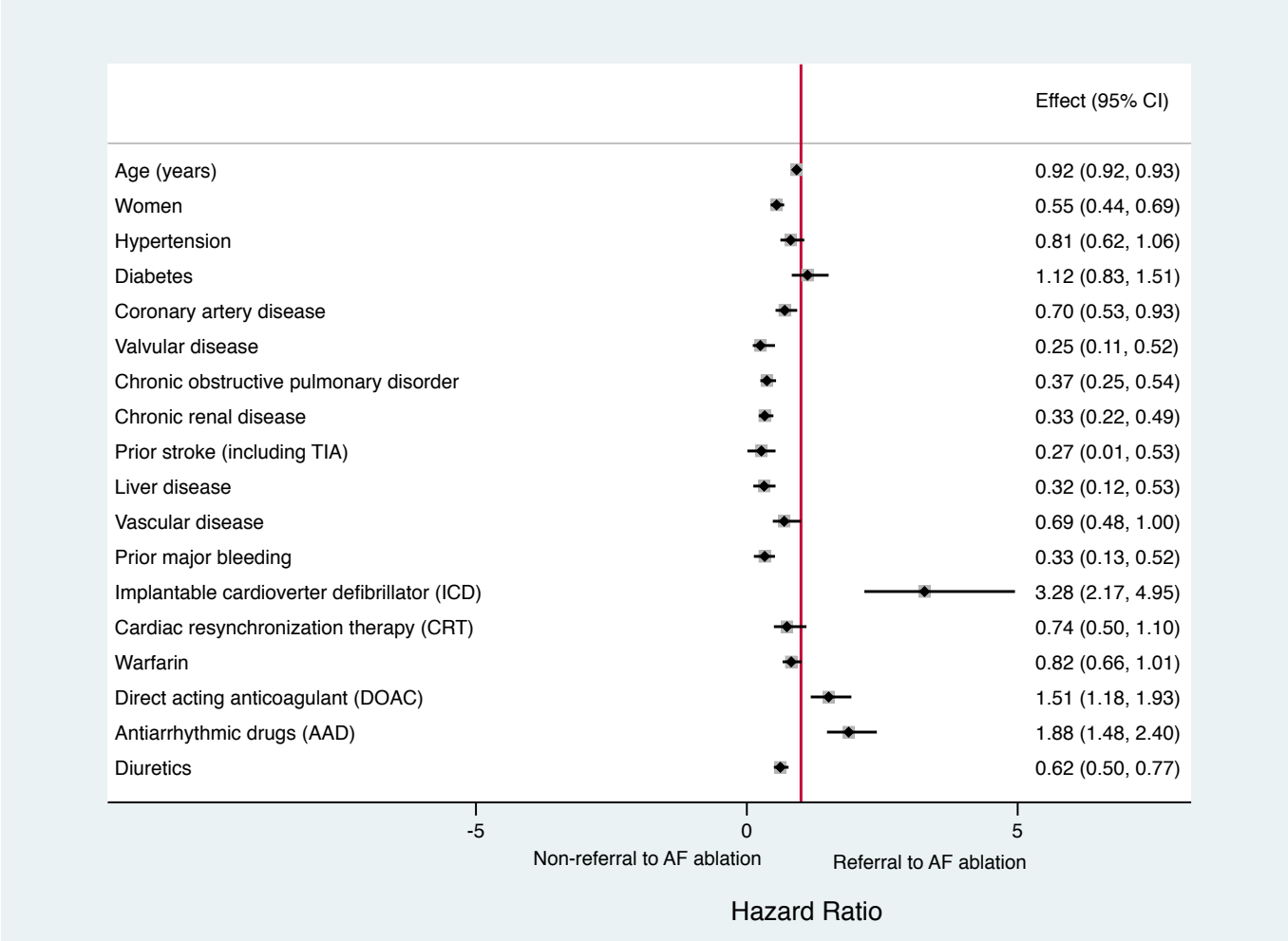
*Baseline was measured at cohort entry and does not account for the increase in $CHADS_2$ score during follow-up period as more comorbidities were acquired.

Figure 2b. Distribution of HAS-Bled scores by sex at baseline



*Baseline was measured at cohort entry and does not account for the increase in HAS-Bled score during the follow-up period as more comorbidities were acquired.

Figure 4. Predictors for AF referral



*Comorbidities first captured within 3-months prior to AF ablation or end of follow-up were excluded.

4.3 Supplementary appendix

SUPPLEMENT

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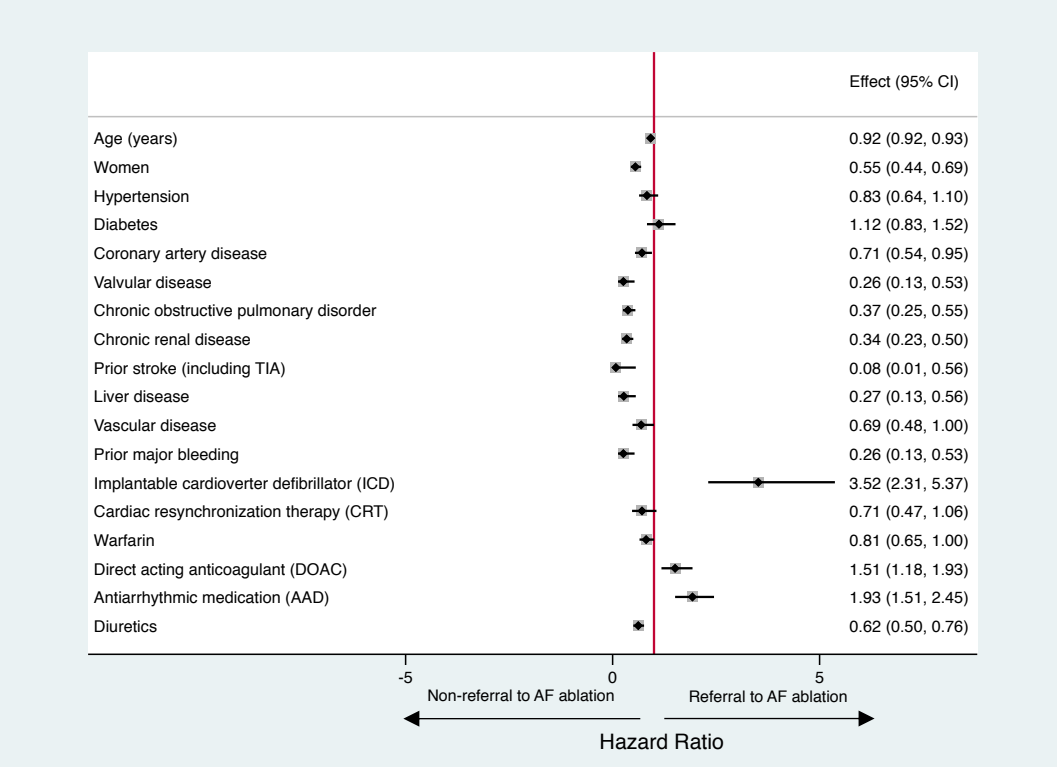
Sensitivity analysis #1: Backwards elimination

Backwards elimination was performed eliminating potential predictors p-values ≤0.05. Diabetes (p=0.54), hypertension (p=0.27) and presence of a CRT (p=0.10) were sequentially removed from the model. Due to the strength of the associations, predictors for treatment and non-treatment to CA were the same in both the overall Cox model and the model from backwards elimination (covariates of diabetes, hypertension, and presence of CRT not included).

Sensitivity analysis #2: Identification of predictors with a 6-month blanking period

Figure S1. Predictors for AF ablation with a 6-month blanking period (N=101,931)

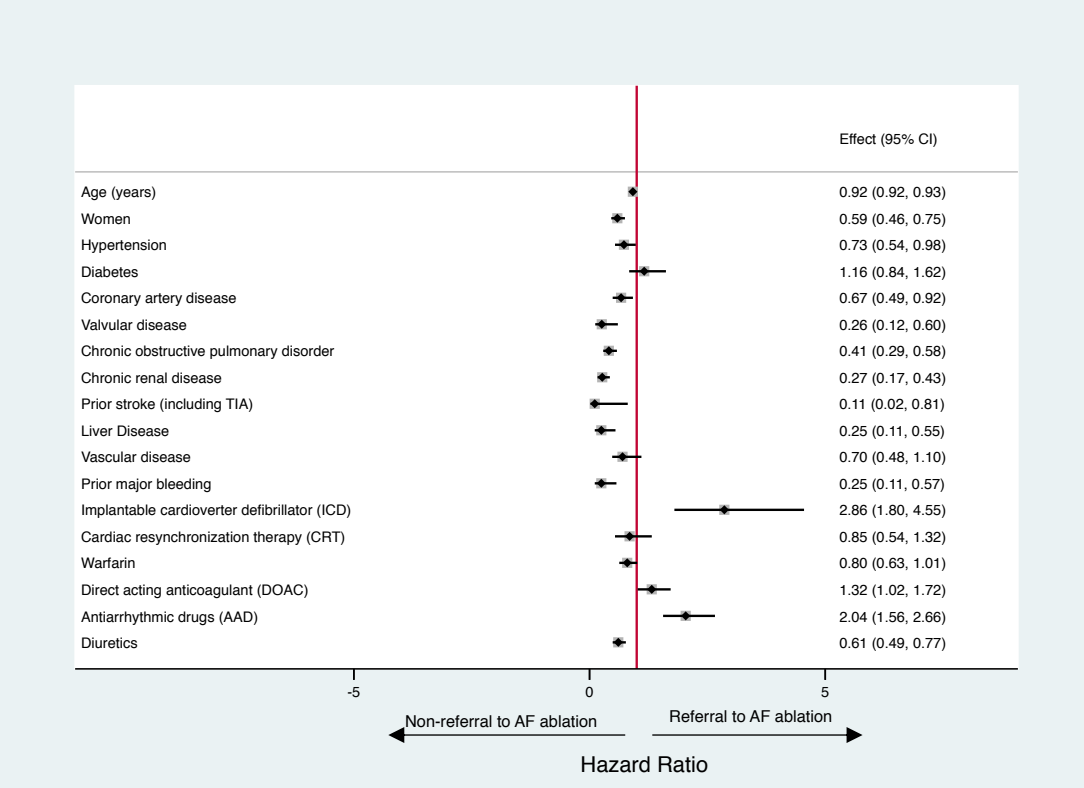


*Comorbidities first captured within 6-months prior to AF ablation or end of follow-up were excluded.

**Arrows mark the magnitude and direction for predictors.

Sensitivity analysis #3: Identification of predictors: Sub-cohort (2009-2017)

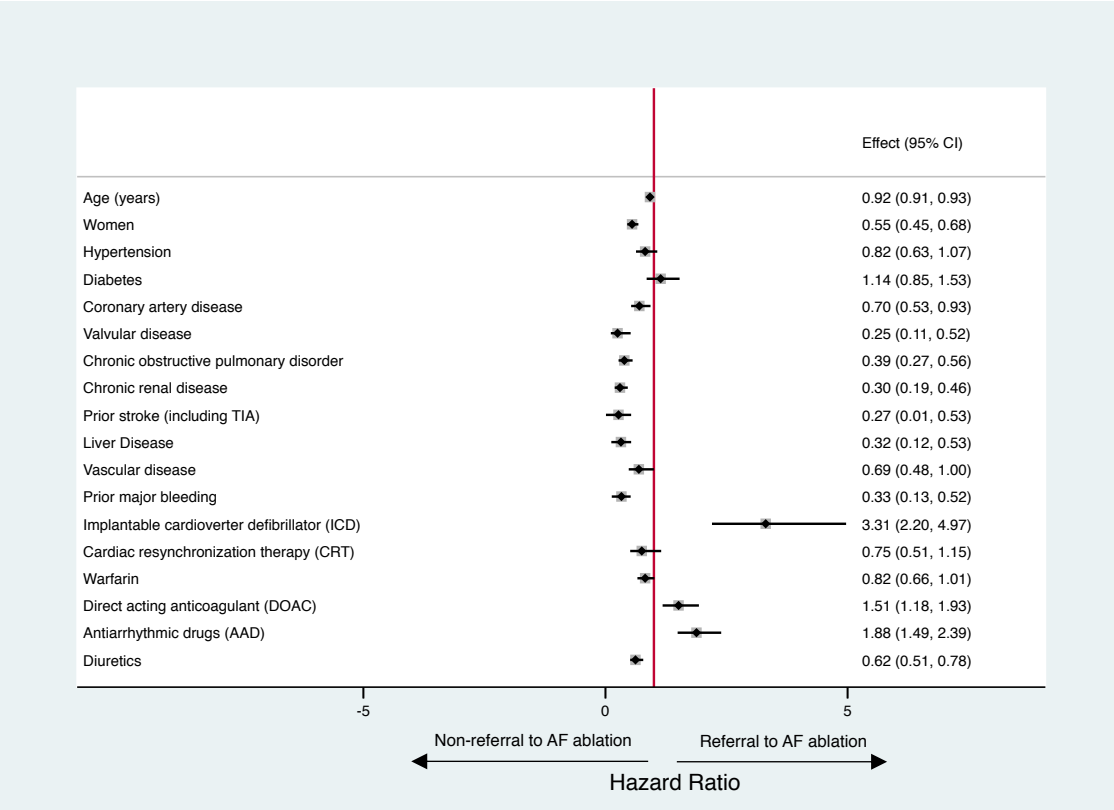
Figure S2. Predictors for AF ablation post 2009 (N=75,531)



*Comorbidities first captured within 6-months prior to AF ablation or end of follow-up were excluded.
**Arrows mark the magnitude and direction for predictors.

Sensitivity analysis #4: Identification of predictors without heart transplant and LVAD patients

Figure S3. Predictors for AF ablation excluding patients with a heart transplant or left ventricular assist device (LVAD) (N=101,906)



*Comorbidities first captured within 6-months prior to AF ablation or end of follow-up were excluded.
**Arrows mark the magnitude and direction for predictors.

Sensitivity analysis #5: Replication of analyses in overall cohort (N=112,955)

Table 1. Baseline characteristics for overall cohort

	All patients (N=112,955)
Median age (IQR), years	80.2 (72.7-86.1)
< 65	11,502 (10.2%)
65-75	23,939 (21.2%)
≥75	77,514 (68.6%)
Women	56,595 (50.1%)
Hypertension	35,830 (31.7%)
Diabetes mellitus	18,716 (16.6%)
Coronary artery disease	30,185 (26.7%)
Prior myocardial infarction	12,707 (11.2%)
Valvular disease	30,269 (26.8%)
Valve replacement	3,222 (2.9%)
Chronic obstructive pulmonary disease	17,985 (15.9%)
Chronic renal failure	15,781 (14.0%)
Prior stroke (including TIA)	2,289 (2.0%)
Liver disease	2,538 (2.2%)
Vascular disease	13,174 (11.7%)
Prior major bleeding	4,632 (4.1%)
Pacemaker	13,685 (12.1%)

Implantable cardioverter defibrillator (ICD)	3,167 (2.8%)
Cardiac resynchronization therapy (CRT)	10,795 (9.6%)
Median CHA_2DS_2-Vasc Score	4 (3-4)
Median HAS-BLED Score	1 (1-2)

*P-values of <0.05 are considered statistically significant. P-values compare patients underwent CA to patients who did not.

[y] The baseline table presents the distribution of comorbidities at cohort entry and does not include the covariates acquired during the follow-up period which is included in the analysis.

Figure S4. Number of AF ablations in the overall cohort over time (N=700)

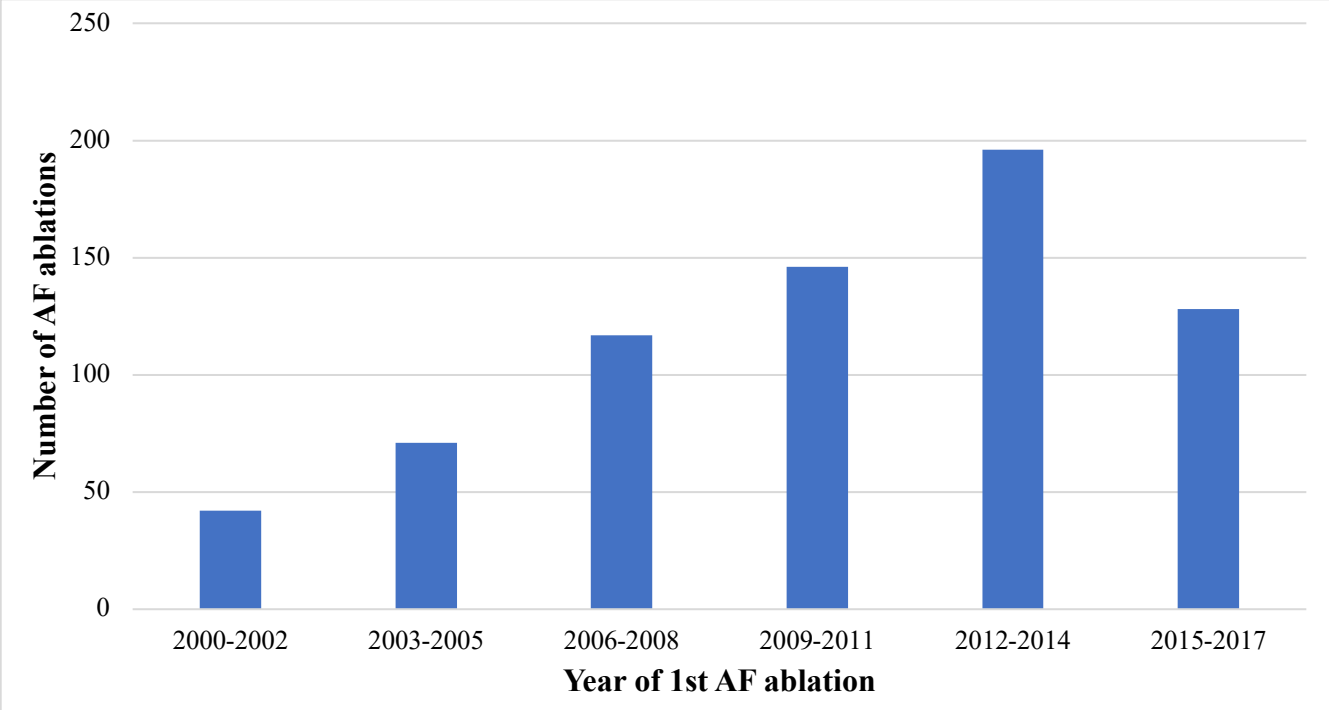
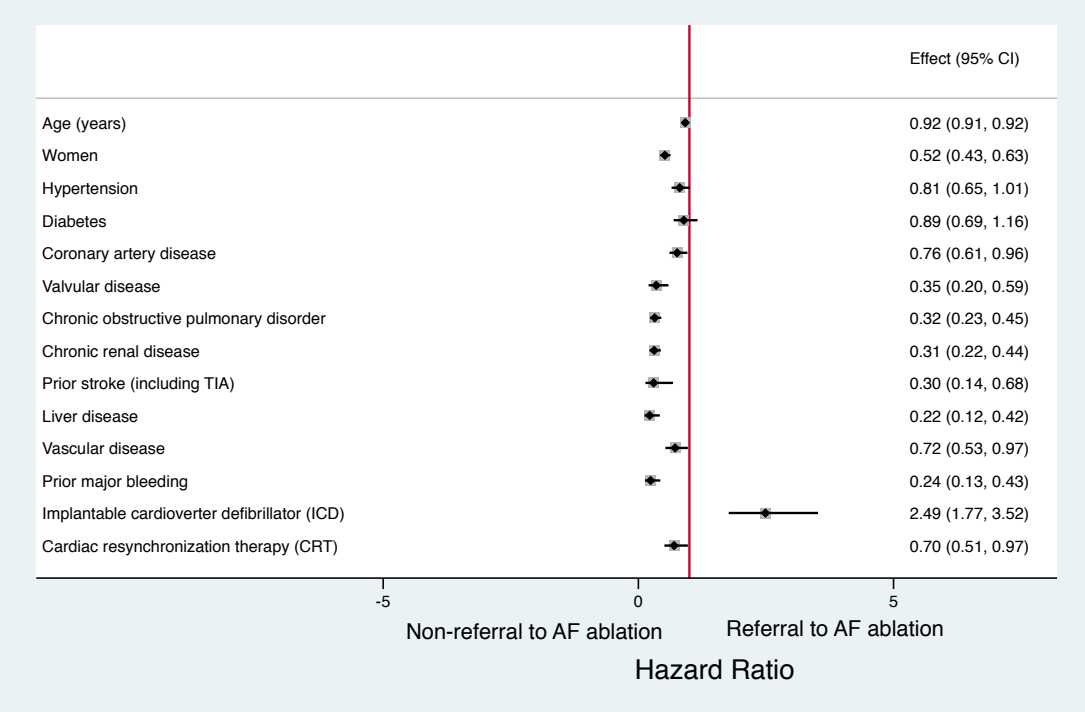


Figure S5. Predictors for AF ablation in the overall cohort (N=112,955)



*Comorbidities first captured within 6-months prior to AF ablation or end of follow-up were excluded.
**Arrows mark the magnitude and direction for predictors.

Table S2. Model Diagnostics: Alkaine's Information Criterion (AIC)

Figure Number	Cohort / sub-cohort	AIC (No Covariates)	AIC (Covariates)	Difference in AICs (No Covariates-Covariates)
3	Main (Medications with a 3-month blanking period)	9034.279	7863.221	1171.058
S1	Medications with a 6-month blanking period	9034.279	7881.215	1153.064
S2	Post 2009	8750.271	7554.032	1196.239
S3	Exclusion of patients with a heart transplant and LVAD	8962.588	7799.748	1162.840
S5	Overall Cohort	14728.925	12854.527	1871.398

*A difference of ≥4 AIC points is considered relevant.

Table S3. Comparison of baseline characteristics between CA patients (2000-2014 vs 2015-2017)

	Patients with CA performed between 2000-2014 (N= 383)	**Patients with CA performed between 2015-2017 (N=86)**
Median age (IQR), years	67.2 (61.4-73.0)	67.6 (59.4-73-6)
< 65	144 (37.6)	34 (39.5)
65-75	169 (44.1)	34 (39.5)
≥75	70 (18.3)	18 (20.9)
Women	91 (23.8)	22 (25.6)
Hypertension	238 (62.1)	48 (55.8)
Diabetes mellitus	128 (33.4)	25 (29.1)
Coronary artery disease	185 (48.3)	36 (41.9)
Prior myocardial infarction	103 (26.9)	20 (23.3)
Valvular disease	136 (87.7)	19 (12.3)*
Valve replacement	36 (9.4)	1 (1.2)*
Chronic obstructive pulmonary disease	85 (22.2)	18 (20.9)
Chronic renal failure	103 (26.9)	13 (15.1)*
Prior stroke (including transient ischemic attack)	7 (1.8)	2 (2.3)
Liver disease	24 (6.3)	5 (5.8)
Vascular disease	72 (18.8)	9 (10.5)
Prior major bleeding	20 (5.2)	4 (4.7)

Implantable cardioverter defibrillator	205 (27.4)	18 (20.9)
Cardiac resynchronization therapy	117 (30.6)	22 (25.6)
Median CHA_2DS_2-Vasc Score	3 (2-4)	4 (3-4)
Median HAS-BLED Score	2 (1-2)	1 (1-2)
Medications		
Oral anticoagulation	328 (85.6)	79 (91.9)
Warfarin	235 (61.4)	23 (26.7)*
Direct oral anticoagulant	123 (32.1)	61 (70.9)*
Dabigatran	48 (12.5)	8 (9.3)
Rivaroxaban	50 (13.1)	33 (38.4)*
Apixaban	34 (8.9)	24 (37.9)*
Antiarrhythmic medication	235 (61.4)	43 (50.0)
Amiodarone	178 (46.5)	30 (34.9)
Sotalol	41 (10.7)	11 (12.8)
Class 1 antiarrhythmic	54 (17.4)	15 (17.4)
Digoxin	74 (19.3)	13 (15.1)
Beta blocker	268 (70.0)	56 (65.1)
Angiotensin converting enzyme inhibitor	179 (46.7)	40 (46.5)
Angiotension II receptor blockers	58 (15.1)	0 (0.0)*
Calcium channel blocker	63 (16.5)	14 (16.3)
Diuretic	253 (66.1)	52 (60.5)

P-values compare the distribution of characteristics in CA performed between 2000-2014 and 2015-2017. P-values <0.05 are marked with an asterisk (*) to denote statistical significance.
‡Results are presented as N(%).
†The comparison used the medication cohort.

CHAPTER 5: MANUSCRIPT 2: POPULATION-LEVEL EVALUATION OF MAJOR ADVERSE EVENTS AFTER CATHETER ABLATION IN PATIENTS WITH ATRIAL FIBRILLATION AND COMOBID HEART FAILURE

5.1 Preface: Manuscript 2

The following manuscript entitled "Population-level evaluation of major adverse events after catheter ablation in patients with atrial fibrillation and comorbid heart failure" presents the incidence and potential risk factors associated with periprocedural complications within 30 days of CA for patients with AF and comorbid HF in Quebec, Canada between 2000 and 2017. As CA is increasingly used to treat AF in patients with HF, an assessment of periprocedural AEs in the real-world population is essential.

The present study is the largest assessment of safety among AF-HF patients who underwent CA (N=700). Our results support the increasing frequency and widening indication for the procedure in AF-HF patients as the rate of major AEs is relatively low and comparable to the AE rate in the general AF population. In addition, the present study identifies risk factors for major AEs following CA in patients with AF and HF, which is of vital importance when referring patients for the procedure. Readers, however, should remain cautious as univariate logistic regressions were used to identify predictors due to the low event rate, therefore the results are hypothesis generating.

The abstract was submitted to the Latin American Heart Rhythm Society (LAHRS) for a poster presentation in September 2019 (Guadalajara, Mexico). The manuscript is press in the *Journal of Cardiovascular Electrophysiology* (2 October 2019).

5.2 Manuscript

Population-level evaluation of complications after catheter ablation in patients with atrial fibrillation and heart failure

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ABSTRACT

OBJECTIVE: To assess the safety of CA in AF-HF patients by determining frequency and potential risk factors for adverse events (AEs) within 30-days post-CA.

BACKGROUND: Catheter ablation (CA) has been increasingly used to treat atrial fibrillation (AF) in patients with heart failure (HF), however, its safety at the population-level has yet to be evaluated.

METHODS: A population-based cohort of AF-HF patients who underwent CA in Quebec, Canada (2000-2017) was constructed using administrative databases. Major AEs included all-cause mortality, cerebrovascular accident (CVA), pericardial effusion requiring drainage (PERD), vascular AEs, hemorrhage/hematoma, and pulmonary embolism. Univariate logistic regression models were employed to assess potential risk factors for major AEs.

RESULTS: Of 700 AF-HF patients who underwent CA [median age 64.5 years (IQR 56.2-71.0), 22.0% female, and median CHA_2DS_2-Vasc 3 (IQR 2-4)], 14 (2.0%) patients developed 16 major AEs within 30-days of CA. Hemorrhage/hematoma was the most frequent major AE (4 patients; 0.6%) followed by all-cause mortality, CVA/TIA, PERD, and vascular AEs (3 patients each; 0.4%). Coronary artery disease [OR 3.9 (95% CI 1.2-12.3)] and age ≥65 years [OR 3.1 (95% CI 1.1-9.8)] were identified predictors for the composite outcome of major AEs. More than half of patients (57.2%) underwent a second CA within a median of 0.8 (IQR 0.2-2.2) years from date of first CA.

CONCLUSION: CA performed in the AF-HF population portends a relatively low incidence of major AEs. A larger study is required to determine whether certain patient factors are independently associated a higher risk of post-CA AEs.

KEYWORDS: catheter ablation, atrial fibrillation, heart failure, adverse events

CONDENSED ABSTRACT

In recent years, the use of catheter ablation (CA) has expanded to the treatment of atrial fibrillation (AF) in challenging subpopulations, including patients with comorbid heart failure (HF), however, CA may be more technically challenging to perform in HF patients, further increasing the risk of periprocedural adverse events (AE). The present study determines the population level frequency and risk factors for adverse events in patients with heart failure undergoing catheter ablation for atrial fibrillation. The incidence of major adverse events was relatively low (2.0%). Older age and coronary artery disease were identified as predictors for major AEs.

ABBREVIATIONS

AE, Adverse events

AF, Atrial fibrillation

CA, Catheter ablation

CRT, Cardiac resynchronization therapy

CVA, Cerebrovascular accident

DOAC, Direct acting oral anticoagulant

HF, Heart failure

ICD, Implantable cardioverter defibrillator

PERD, Pericardial effusion requiring drainage

INTRODUCTION

Catheter ablation (CA) of atrial fibrillation (AF) can be associated with significant periprocedural adverse events (AEs) such as cerebrovascular accidents (CVA), cardiac tamponade or pericardial effusion requiring drainage (PERD), vascular AEs, pulmonary embolism, hemorrhage/hematoma, and all-cause mortality (1-5). The reported incidence of major AEs is low in this patient population, ranging from 1% to 6% (1, 6-19).

In recent years, the use of CA has expanded to the treatment of AF in challenging subpopulations, including patients with comorbid heart failure (HF). Randomized trials have shown that treatment with CA is associated with reduced all-cause mortality and HF hospitalizations in patients with AF and HF (20-22). Nevertheless, CA in HF patients may be technically more challenging due to 1) left atrial enlargement resulting in the need for a larger area to be ablated, 2) hypertrophy of atrial myocytes and atrial fibrosis, and 3) a higher prevalence of persistent rather than paroxysmal AF (23). These structural differences may require longer dwell time in the left atrium for delivery of sufficient ablation to obtain pulmonary vein isolation, which may result in an increased risk of major AEs. In addition, two studies indicated that HF may increase the risk of periprocedural major AEs after CA for AF (7, 10).

Results from a meta-analysis of 8 randomized trials evaluating CA in patients with AF and HF show the overall procedural risk of complications to be 4.8%, which is similar to the risk in AF patients who underwent CA, regardless of HF presence (22, 24, 25). Although the results of randomized trials suggest CA is safe in patients with comorbid HF (8, 20), a real-world population-level assessment of periprocedural AE incidence is warranted. The objective of the present study is to assess the safety of CA in AF-HF patients by determining the incidence and potential risk factors for major AEs within 30 days of the CA procedure.

METHODS

Study Design

A population-based cohort using administrative databases was constructed to evaluate the safety of CA among patients with AF and comorbid HF who underwent CA in one of 6 ablation centres in the province of Quebec, Canada between April 1, 2000 and March 31, 2017. In Quebec, all CA procedures occur in dedicated academic electrophysiology laboratories located at 6 university-affiliated tertiary/quaternary care institutions each performing a broad range of complex ablation and device procedures. The study received institutional review board approval from the McGill University Faculty of Medicine (A05-M79-08B).

Data Sources and Population Selection

Linked hospital discharge and summary databases, Maintenance et Exploitation des Donnees pour l'Etude de la Clientele Hospitaliere (Med-Echo) and la Regie de l'assurance maladie du Quebec (RAMQ) respectively, were used to create the AF cohort. The description of the Quebec administrative AF cohort and its creation has been previously published (1, 26, 27) and the database has been updated with additional years of data through to 2017.

To identify the subpopulation with co-existing HF, patients with a primary or secondary diagnosis of HF at hospitalization were included in the cohort (International Classification of Disease-9th and 10th Revisions (ICD-9/10) codes: 428.0, 428.1, 428.2, 428.3, 428.4, 428.9/ I50.1, I50.2, I50.3, I50.4, I50.9) (28, 29). A patient was considered diagnosed with HF on the date of first hospital admission with a primary diagnosis for HF.

AF-HF patients who underwent CA were identified from billed procedure codes for CA of AF during a hospitalization with a primary admission diagnosis for AF (identified in Med-Echo). Patients who underwent complex ablations for congenital heart disease or ventricular tachycardia,

or who underwent first CA prior to HF diagnosis, were excluded. The final study population included only AF-HF patients who underwent first CA post-diagnosis of both diseases.

In Quebec, medication information is available for patients with government prescription insurance coverage, which includes all patients ≥65 years and patients <65 years without private coverage. To assess the potential association between medication use and major AEs, a sub-analysis was completed for patients with government prescription coverage.

Potential Predictors

Potential predictors of AEs included age, female sex, hypertension, diabetes mellitus, vascular disease, abnormal renal and/liver function, cerebrovascular accidents including transient ischemic attacks (CVA/TIA), prior major bleeding event, and the presence of a cardiac electronic implantable device (implantable cardioverter defibrillator (ICD) and cardiac resynchronization therapy (CRT)). In patients with government prescription insurance, medications including oral anticoagulation (warfarin and direct acting oral anticoagulation (DOACs)), antiarrhythmics, diuretics, and other cardiac medications, were investigated for a potential association with major AEs. All potential predictors were time-fixed and measured within 12 months prior to date of index (first) CA. To account for temporal trends in treatment, including improvements to technology and techniques, year of CA (categorized into 3, 6, and 9-year periods) and a comparison of prior and post 2014 (introduction of contact force and uninterrupted OAC use in Quebec, Canada) was also investigated.[30]

Adverse Events

A composite outcome of any major AE within 30 days after the CA was investigated, as well as, in separate analyses, the incidence of each specific outcome. Major AEs included all-cause mortality, CVA/TIA, pericardial effusion requiring drainage (PERD), vascular adverse events,

hemorrhage/hematomas, and pulmonary embolism (AE codes listed in Supplementary Table S1). PERD (including cardiac tamponade) is defined via physician billing for pericardial drainage (RAMQ procedure billing codes 0597 and 9334). Vascular AEs are defined as any injury to blood vessels, accidental punctures, AV fistula, injury to the retro-peritoneum, vascular complications requiring surgery, and vascular complications following a procedure. Cause of in-hospital death was determined in RAMQ from diagnostic codes linked to the code for death declaration (RAMQ 9200). Non-major AEs include any diagnosis that was not considered a major AE. AEs were captured from ICD-9/10 diagnoses recorded in Med-ECHO as a discharge complication from CA hospitalization and from subsequent hospitalizations or emergency department visits within 30-days of CA procedure. AF and HF listed at discharge were not included as post-procedural complications.

Statistical Analysis

Continuous variables were reported as a median and interquartile range (IQR), with differences between patients who had a major AE and those who had a non-major or no AE compared by the non-parametric Wilcoxon rank-sum test. For categorical variables, frequency distributions were reported, with differences assessed by the Chi-squared test. Incidence of each major and non-major AEs were documented as composite outcomes and individually. In addition, the incidences of specific major AEs during hospitalization were compared at discharge and from discharge to 30-days post-date of CA using the log-rank test. For patients with multiple CAs, the McNemar's test was used to compare the frequency of major AEs between the first and second CA. A two-tailed p-value of <0.05 determined a statistically significant difference.

Due to the low incidence of major AEs, multivariable analyses were not possible. Therefore, a series of univariate logistic regression models, each investigating the association of a

specific comorbidity or patient characteristic with the binary composite outcome of any major AE within 30 days post-CA were conducted. The results were summarized by un-adjusted Odds Ratios with 95% confidence intervals. A p-value <0.05 for a two-tailed Wald chi-square test marked a statistically significant predictor and a $0.05<p<0.1$ was interpreted as a trend towards an association.

Stata statistical software (StataCorp LLC, College Station, TX; 2017, release 15) was employed for all analyses.

RESULTS

Patient characteristics

Among the 112,955 patients in the AF-HF cohort, 700 (0.6%) patients underwent CA and were included in the study. Patients who underwent CA had a median age of 64.5 (IQR 56.2-71.0) years and 22.0% were female. The median CHA_2DS_2-Vasc score was 3 (IQR 2-4) and the median modified HAS-Bled score was 1 (IQR 0-2) (Table 1). Among 469 patients with medication coverage, during the 12-month period prior to index CA, 55.0% of patients received at least one prescription for warfarin, 39.2% were prescribed DOACs, and 44.4% were prescribed amiodarone.

Incidence of Adverse Events after the procedure

A total of 16 major AEs developed in 14 (2.0%) patients during 30 days after the CA. Hemorrhage and hematoma was the most frequent major AE, followed all-cause mortality, CVA/TIA, vascular AEs, and PERD (Table 2). No patient had a pulmonary embolism (Table 2). Vascular AEs were more likely to occur during CA hospitalization and post-procedural hemorrhages were more likely to occur post-discharge from CA than during CA hospitalization (Figure 1).

The incidence of non-major AEs is listed in Table 2. Forty-six (6.6%) patients had a non-major AE (56 AEs), with readmission for HF (10 patients, 1.4%) and arrhythmias (6 patients, 0.9%) being the most common.

Predictors of major post-procedural AEs

In the overall cohort, in separate univariate models, the presence of coronary artery disease [OR 3.9 (95% CI 1.2-12.3)] and age ≥65 years [OR 3.1 (95% CI 1.1-9.8)] were statistically significant predictors for the composite outcome of any major AE within 30-days post-CA. There was no statistically significant association between year of CA (2/210 vs. 12/490 patients had an AE post vs. pre-2014; OR 0.4, 95% CI 0.1-1.7, p=0.2) and other potential predictors with the outcome of major AEs (p>0.05 for all). Age ≥75 years [OR 12.7 (95% CI 1.1-53.6)] and chronic obstructive pulmonary disease [OR 8.0 (95% CI 1.7-35.5)], as well as increased value of the modified HAS-BLED score [OR 2.6 (95% CI 1.2-5.9)] were predictors for post-procedural all-cause mortality. The estimated median time to death was 4 days (IQR 3-12) from date of CA. Of the 2 in-hospital deaths, the reported causes of death were acute respiratory failure and nodular lymphoma. The cause of death for the one patient who died out-of-hospital could not be captured in the database. We did not identify any statistically significant predictors for the other individual major AE.

Among the 462 medication-insured patients, none of the medications investigated were associated with an increased incidence of major AEs, that occurred in only 7 patients (1.5%) of those patients.

Repeat CAs and AEs

More than half (57.2%; 401 patients) of the AF-HF patients with the first CA, had a repeat CA within a median of 295 (IQR 83-795) days from the index CA. Only 1 (0.2%) patient had a

major AE of CVA/TIA and PERD within 30-days after the repeat CA. PERD occurred during the hospitalization for the second CA and CVA/TIA was the primary diagnosis at readmission. Five patients had a non-major AE post repeat CA.

DISCUSSION

In the largest cohort of AF-HF patients who underwent CA, the incidence of periprocedural major AEs was low (2.0%), and age ≥65 years and presence coronary artery disease were associated with a higher risk of AEs. Overall, our results are consistent with AE incidence in randomized trials on CA in AF patients with comorbid HF, as well as prior population-level assessments of CA safety in patients who underwent the procedure, regardless of the presence of HF.

Consistency with randomized trials of CA in patients with AF and HF

Randomized trials on CA in AF-HF patients found overall complication rates between 3% to 15% (Table 3), of which our study was at the lower end (5, 20, 21, 31-35). Most trials with a higher rate of major AEs had less than 50 CA patients and were older studies (Table 3) (31-33). Similarly, our study found a trend towards a reduction in the proportion of patients with major AEs in more recent procedures (2009-2017) compared to remote procedures (2000-2008). Although AE incidence was higher (7.8%) in the largest and most recent trial, CASTLE-AF (N=179), it is likely attributable to complications being collected throughout the follow-up period (37 months), instead of the 30-day assessment period in our study (20).

The incidence of individual major AEs in randomized trials varied from 0% to 7%, which corresponds to the individual AE results in the present study (Table 3). Unlike our study, none of the trials reported post-procedure deaths, however, CASTLE-AF and AATAC included all-cause mortality as a primary outcome and therefore 30-day mortality was not reported (20, 21).

In addition to the incidence rates, the patient population enrolled in randomized trials was different to the real-world population investigated in the present study. A greater proportion of patients had hypertension and a prior stroke in CASTLE-AF compared to the present study (hypertension: 72% vs. 55.0%; prior stroke: 12% vs. 2.0%; CASTLE-AF vs. present study), however a larger proportion of patients were on diuretics in the present study (65.0%) compared to both the CASTLE-AF (55%) and AATAC (45%) trials (20, 21). The distribution of other baseline characteristics was similar across randomized trials and the real-world population investigated in the present study.

Major AEs in AF patients undergoing CA with or without comorbid HF

Although prior evaluations of the incidence of major AEs in AF patients who underwent CA included a low proportion of patients with comorbid HF (0.4% to 18%), the incidence of major AEs between 1% to 6% did not differ from the present study which only included patients with comorbid HF (1, 6, 7, 10-19, 36). Only 2 studies indicated that HF was a predictor for major AEs [univariate HR 5.2 (95% CI 2.0-13.4)] (7-10), however the comparable incidence between the present study and safety evaluations of all AF patients undergoing CA seems to indicate no increase in AE risk with the addition of HF. In addition to the presence of HF, the HF population who underwent CA was older and had a higher prevalence of all comorbidities compared to a prior study using the Quebec and Ontario AF cohorts which assessed the incidence major AEs in all AF patients who underwent CA (1). Despite more comorbidities in AF-HF patients undergoing CA and additional technical challenges of CA due to morphology changes in HF patients, the comparable rates of major AEs suggest that CA is safe to perform in AF patients with comorbid HF.

Predictors of major AEs

Advanced age has consistently been identified as a predictor of major AEs amongst patients undergoing CA, regardless of the presence of HF (1, 10, 15). Coronary artery disease, however, was only identified as predictive of hemorrhage complications in Bertaglia et al [OR 5.6, 95% CI 1.6-20.1)] (6). Although the present study found that coronary artery disease was predictive of the composite outcome of major AEs, it was not a statistically significant predictor for postprocedural hemorrhage and hematoma or any other individual AE.

The ROCKET-AF (37) and ARISTOTLE (38) trials have identified chronic obstructive pulmonary disorder as a predictor of all-cause mortality in the AF population. In addition, HAS-BLED risk score has been identified as a predictor of long-term adverse outcomes, including mortality, in the AF population as well as other cardiovascular diseases and post-cardiac procedures (39). Although the present study could not capture the precise cause of death, it is possible that post-CA deaths in the high-risk AF-HF population are attributable to the increased risk of death due to comorbid disease, rather than the CA procedure itself.

Limitations

Whereas the advantage of this population-based study is that it assesses the real-world safety of CA in the entire AF-HF population in Quebec, the use of administrative databases has limitations. Important immeasurable clinical factors for severity of HF, including New York Heart Association (NYHA) class, and procedural variables, including radiofrequency time and energy could not be investigated. AEs may be also underreported in administrative databases; however, the major AEs have a higher likelihood of being captured due to the need for additional treatments or interventions that are easily identified by physician procedure billings (in a single payer public provincial healthcare system). In addition, while death is reliably captured in our administrative

cohort, the date of out-of-hospital death and cause of death could not be precisely determined from the data.

Although this is the largest study of AF-HF patients undergoing CA, a multivariable regression to identify predictors of major AEs was not conducted due to the low incidence of major AEs. Therefore, the identification of major AE predictors had to be limited to univariate analyses, implying our study should be considered as mostly hypothesis generating. Future studies should perform multivariable analyses to identify *independent* predictors of post-CA AE's.

CONCLUSION

In this population-level evaluation of CA safety in patients with AF and HF, CA was associated with a relatively low incidence of major AEs. Repeat CA was common in patients with HF; however repeat procedures were performed without increased risk of AEs. A larger study is required to determine whether certain patient factors are associated with a higher risk of post-CA AEs in patients with AF and HF.

PERSPECTIVES

Clinical Competencies

In the largest study of CA patients with both AF and HF, the incidence periprocedural major AE was relatively low and comparable to the AE incidence in all CA patients, regardless of the presence of comorbid HF. Further, clinicians may consider CA relatively safe to perform in the select AF-HF patients referred for CA.

Translational outlook

Future studies with a larger sample size are warranted to identify predictors of major AEs among AF-HF patients who underwent CA.

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FIGURE LEGENDS

Figure 1. Major adverse events at index catheter ablation

Table 1. Baseline characteristics

	All patients (N=700)	**Patients with a major adverse event (N=14)**	**Patients with other or no adverse events (N=686)**
Median age (IQR), years	64.5 (56.2-71.0)	68.0 (59.2-74.1)	64.3 (56.2-71.0)
< 65	366 (52.3)	4 (28.6)	362 (52.8)
65-75	237 (33.9)	7 (50.0)	230 (33.5)
≥75	97 (13.9)	3 (21.4)	94 (13.7)
Women	154 (22.0)	5 (35.7)	149 (21.7)
Hypertension	385 (55.0)	9 (64.3)	376 (54.8)
Diabetes mellitus	189 (27.0%	2 (14.3)	187 (27.3)
Coronary artery disease	295 (42.1)	10 (71.4)	285 (41.6)*
Prior myocardial infarction	167 (23.9)	6 (42.9)	161 (23.5)
Valvular disease	209 (29.9)	3 (21.4)	206 (30.0)
Valve replacement	50 (7.1)	1 (7.11)	49 (7.1)
Chronic obstructive pulmonary disease	126 (18.0)	3 (21.4)	123 (17.9)
Chronic renal failure	141 (20.1)	3 (21.4)	138 (20.1)
Prior stroke (including TIA)	14 (2.0)	0 (0.0)	14 (2.0)
Liver disease	42 (6.0)	1 (7.1)	41 (6.0)
Vascular disease	101 (14.4)	2 (14.3)	99 (14.4)
Prior major bleeding	37 (5.3)	1 (7.1)	36 (5.3)

Pacemaker	91 (13.0)	1 (7.1)	90 (13.1)
Implantable cardioverter defibrillator (ICD)	171 (24.4)	6 (42.9)	165 (24.1)
Cardiac resynchronization therapy (CRT)	198 (28.3)	6 (42.9)	192 (28.0)
Median CHA_2DS_2-Vasc Score	3 (2-4)	3 (2-4)	3(2-4)
Median HAS-BLED Score	1 (0-2)	2 (1-3)	1 (0-2)
Year of procedure	2011 (2007-2014)	2008 (2007-2013)	2011 (2007-2014)*
2000-2008	230 (32.9)	8 (53.3)	222 (32.4)
2009-2017	470 (67.1)	7 (46.7)	463 (67.6)
Median length of ablation hospitalization	1 (1-2)	3 (1-4)	1 (1-2)
Medications	N=469	N=7	N=462
Oral anticoagulation	407 (86.8)	5 (71.4)	402 (87.0)
Warfarin	258 (55.0)	4 (57.1)	254 (55.0)
DOACs	184 (39.2)	1 (14.3)	183 (39.6)
Dabigatran	56 (11.9)	0 (0.0)	56 (12.1)
Rivaroxaban	83 (17.7)	0 (0.0)	83 (18.0)
Apixaban	58 (12.4)	1 (14.3)	57 (12.3)
Amiodarone	208 (44.4)	3 (42.9)	205 (44.4)
Sotalol	52 (11.1)	0 (0.0)	52 (11.3)
Class 1 antiarrhythmics	69 (14.7)	1 (14.3)	68 (14.7)

Digoxin	87 (18.6)	1 (14.3)	86 (18.6)
Beta blockers	324 (69.1)	6 (85.7)	318 (68.8)
Angiotensin converting enzyme (ACE) inhibitors	219 (46.7)	4 (57.1)	215 (46.5)
Angiotension II receptor blockers (ARB)	58 (12.4)	1 (14.3)	57 (12.3)
Calcium channel blockers	77 (16.4)	0 (0.0)	77 (16.7)
Diuretics	305 (65.0)	5 (71.4)	300 (64.9)

*P-values of <0.05 are considered statistically significant. P-values compare patients who had a major AE to patients with other or no AEs.

†Values in the table are presented as N (%).

Table 2. Adverse Events within 30 days of index AF ablation

Adverse Events	**Number of patients with an Adverse Event**
Major Adverse Events	**14 (2.0)**
Hemorrhage/Hematoma	4 (0.6)
Vascular AEs	3 (0.4)
PERD	3 (0.4)
CVA (including TIA)	3 (0.4)
All-cause mortality	3 (0.4)
Pulmonary Embolism	0 (0.0)
Other Adverse Events	**46 (6.6)**
Cardiac	26 (3.7)
Myocardial infarction	3 (0.4)
Acute and subacute infective endocarditis	0 (0.0)
AEs of cardiac and vascular prosthetic devices, implants and grafts	3 (0.4)
AF (post-discharge)	4 (0.6)
HF (post-discharge)	10 (1.4)
Heart Block	2 (0.3)
Arrhythmias	6 (0.9)
Other cardiac AEs	3 (0.4)
Non-cardiac adverse events	21 (3.0)
Respiratory AEs	3 (0.4)

Gastrointestinal hemorrhage	3 (0.4)
Renal AEs	3 (0.4)
Infection	4 (0.6)
Other non-cardiac AEs	12 (1.7)
Other admissions that are not related to the ablation procedure	**2 (0.3)**

*A patient may have multiple AEs.

†Values in the table are presented as N (%).

Table 3. Incidence of major adverse events in randomized trials

Study, Year	**CA patients (N)**	**All major AEs [N(%)]**	**All-cause mortality [N(%)]**	**CVA/TIA [N(%)]**	**Effusion / Tamponade [N(%)]**	**Hemorrhage / Hematoma [N(%)]**	**Vascular AEs [N(%)]**	**Pulmonary embolism [N(%)]**
Samuel et al. (2019)	700	14 (2.0)	3 (0.4)	3 (0.4)	3 (0.4)	4 (0.6)	3 (0.4)	0 (0.0)
CASTLE* (2018)	179	14 (7.8)	Primary outcome- not included as an complication	7 (3.9)	3 (1.7)	3 (1.7)	1 (0.6)	0 (0.0)
CAMERA-MRI (2017)	33	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	0 (0.0)	(0.0)
AATAC (2016)	102	3 (3.0)	Primary outcome- not included as a complication	0 (0.0)	1 (1.0)	2 (2.0)	0 (0.0)	0 (0.0)

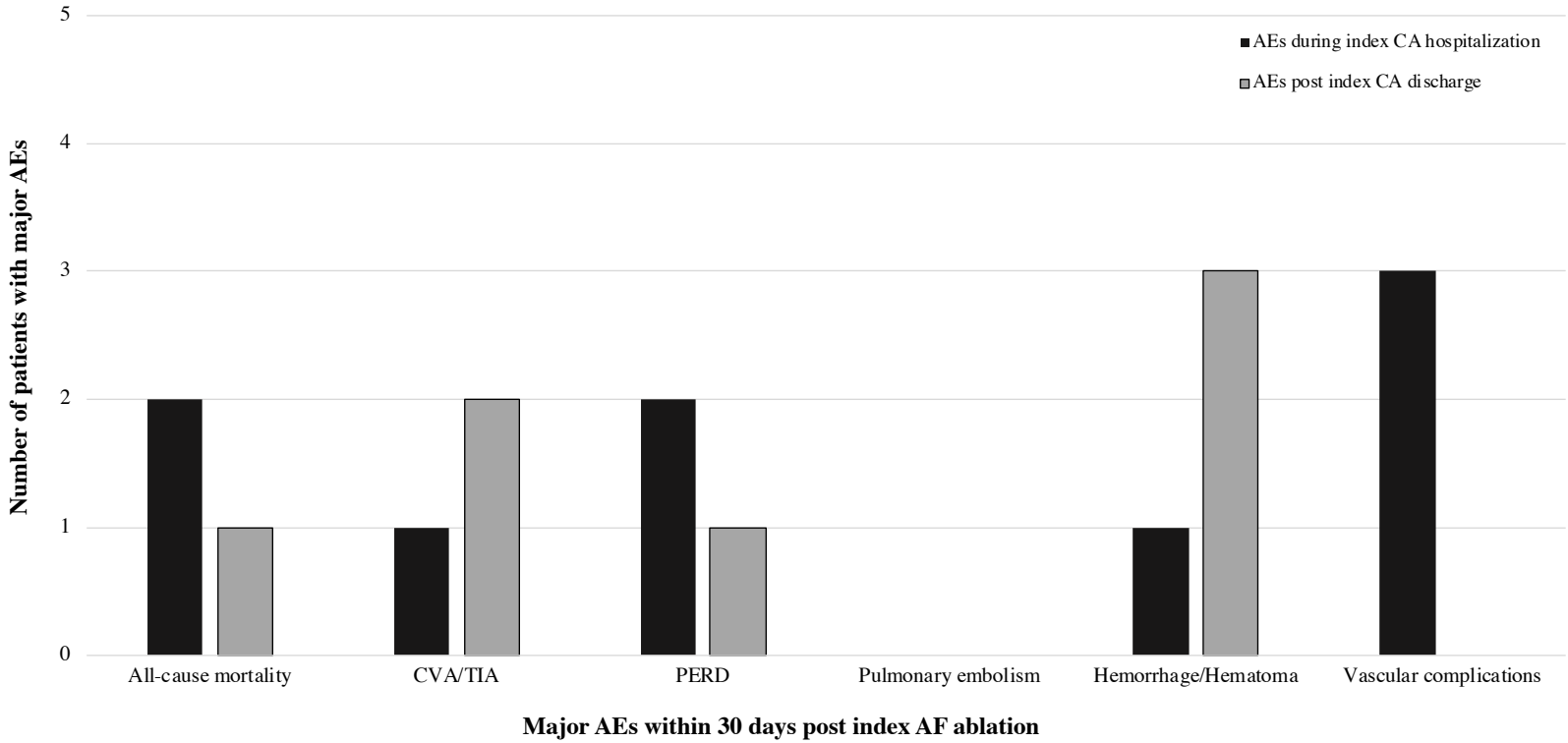
CAMTAF (2014)	26	2 (7.7)	0 (0.0)	1 (3.8)	1 (3.8)	0 (0.0)	0 (0.0)	(0.0)
MacDonald et al (2011)	27	3 (11.1)	0 (0.0)	1 (3.7)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)
PABA-CHF (2008)	41	6 (14.6)	0 (0.0)	0 (0.0)	1 (2.4)	3 (7.3)	2 (4.9)	0 (0.0)

*AEs measured throughout follow-up period of study.

†ARC-HF did not present complication results in publication.

‡Values in the table are presented as N (%).

Figure 1. Major adverse events at index CA



AE= adverse event, AF= atrial fibrillation, CA= catheter ablation, CVA/TIA= cerebrovascular accident/transient ischemic attack, PERD= pericardial effusion requiring drainage

Section 5.3 Supplementary appendix

SUPPLEMENT

Table S1. Objective 2: ICD-9/10 codes for major adverse events

Adverse Event	ICD-9 Codes	ICD-10 Codes
Cerebrovascular accident / transient ischemic attack	433, 434, 435, 436, 362.3	I63, I64, G45, H34.1
Pericardial effusion requiring drainage (RAMQ code 291 and ICD-9/10 codes)	423.0 423.3	I31.0 (1, 2, 4, 8, 9)
Pulmonary embolism	415.1, 415.0	I269, I260
Post procedural hemorrhage / hematoma	998.11 (2), 459.0	R58, T810
Vascular comorbidities	997.7, 442.3, 998.6, 447.9, 444.2	I724, I728, I770, I743, T817

*No ICD-9/10 codes for mortality.

CHAPTER 6: MANUSCRIPT 3: LONG-TERM EFFECTIVENESS OF CATHETER ABLATION IN PATIENTS WITH ATRIAL FIBRILLATION AND HEART FAILURE

6.1 Preface: Manuscript 3

In the final manuscript entitled "Long-term effectiveness of catheter ablation in patients with atrial fibrillation and heart failure" we evaluated 1) the long-term effectiveness of CA in AF-HF patients reducing the incidence of all-cause mortality, HF hospitalizations, and major morbidities and 2) assessed the long-term use of OACs in AF-HF population with and without CA.

This manuscript is the first real-world study investigating the effectiveness of CA in the AF-HF population, and it includes the largest cohort of AF-HF patients who underwent CA with the longest follow-up period. Also, descriptive information on long-term prescription patterns for OACs use in AF-HF patients who underwent CA has not previously been investigated. To closely model a randomized trial by eliminating immortal time bias and reducing baseline confounding, incidence density sampling and IPT-weighting were used, respectively. Compared to the randomized trials, the present manuscript also more accurately captured the effectiveness of CA on individual non-fatal outcomes by accounting for the competing risk of death and adjusted by time-varying medication, ICD, and CRT use throughout follow-up which may influence the incidence and timing of outcomes. In addition, splines modeling the variations in hazards over time since CA determined that CA was protective for a limited time-period after the procedure and captured the approximate protective duration. Only AF-HF patients with available medication information at time of CA or match date (non-CA patients) were included in manuscript 3 to minimize residual confounding from the missing medication information in the overall cohort.

In addition to randomized trials, our study results suggest that CA should be considered as a treatment option in select patients with AF and HF due to long-term reductions in all-cause mortality and HF hospitalizations post-CA. The results of this study are of vital importance and have the potential to influence clinical guidelines and change clinical practice for treatment of this challenging AF subpopulation. Future studies are warranted to determine if the effectiveness of CA persists in patients with more advanced HF.

Abstracts for this work was presented as a poster at the European Society of Cardiology (ESC) Congress 2019 (August) in Paris, France and the Canadian Heart Rhythm Society (CHRS) Conference 2019 (September) in Montreal, Quebec and as a moderated poster at the Canadian Cardiovascular Society Congress (CCC) 2019 (October) in Montreal, Quebec. This manuscript was re-submitted to the *European Heart Journal* (*EHJ*).

6.2 Manuscript

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

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ABSTRACT

AIMS: Randomized trials suggest reductions in all-cause mortality and heart failure (HF) re-hospitalizations with catheter ablation (CA) in patients with atrial fibrillation (AF) and HF. Whether these results are replicable in a real-world population during 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 modeled 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 [HR 0.4 (95% CI 0.2-0.7)], but no difference in stroke or major bleeding. The hazard of HF re-hospitalization for CA patients, relative to non-CA patients, varied with time since CA (p=0.01), with a reduction in HF re-hospitalizations until approximately 3 years post-CA.

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

KEYWORDS: catheter ablation, atrial fibrillation, heart failure, adverse events

INTRODUCTION

Atrial fibrillation (AF) and heart failure (HF) frequently coexist (1, 2) and are associated with an increased risk of all-cause mortality, HF hospitalizations, and stroke (1, 3, 4). There is lack of consensus regarding optimal treatment for AF in patients with comorbid HF (1,3). As pharmacologic rhythm control therapies have failed to demonstrate effectiveness in this population (5-8), the use of catheter ablation (CA) as an option has increased in prominence (9-11).

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) (12-14). Randomized trials, such as CASTLE-AF and AATAC, demonstrated that CA was associated with a reduction in HF re-hospitalizations compared to medical therapy (9, 10), however, only CASTLE-AF showed a statistically significant decrease in all-cause mortality (9). In addition, 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 with CA compared to antiarrhythmic drugs (AADs) (15). On the other hand, CA did not appear to have an effect on stroke risk (9, 10). 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 long-term, or vary over time, remains to be assessed. 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 ischemic attack (TIA) and major bleeding), in a real-life clinical context. A secondary objective was to describe long-term OAC use after CA.

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 (16-19). For the current AF-HF cohort, we extended follow-up to include patients with a primary or major secondary diagnosis of AF between April 1, 2000 to March 31, 2017. The AF-HF cohort was limited to patients with a hospitalization recorded in Med-Echo with HF listed as the 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/ I50.1-4, I50.9). 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 ≥ 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 CA

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). 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 tachycardias (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-CA controls

To avoid immortal time bias (20, 21) and ensure the comparability of the of 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 2 randomly selected patients. Eligible potential controls were selected based on 1) time at risk (since being diagnosed with both AF and HF) before date of CA, 2) frequency of previous all-cause hospitalizations, 3) 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 (IPTW)

To control for measured confounders, inverse probability of treatment weights (IPTW) were calculated from the matched sample as the inverse propensity for receiving CA (logistic regression) (20-24). Baseline variables incorporated into the propensity score (PS) model were predefined and listed in Figure 2 (22).

Outcome ascertainment

Outcomes investigated were 1) all-cause mortality (primary endpoint), 2) HF hospitalizations, 3) stroke (including TIAs), and 4) major bleeding (intracranial bleeding, or bleeding from the respiratory, gastrointestinal, or urinary tract) [ICD-9/10 codes listed in Table S1] and were analyzed separately. Outcomes were identified from Med-Echo based on the primary

diagnoses from hospitalizations and emergency department visits. Updated information on vital status until March 31, 2017 (end of cohort) and dates of death were obtained from both the Med-Echo and RAMQ databases.

Statistical analyses

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

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 (March 31, 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 IPT-weighted multivariable Cox models that additionally adjusted for the time varying covariates, updated during the follow-up, indicating the current presence of implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy (CRT), warfarin, direct acting anticoagulants (DOACs), and antiarrhythmic drugs (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 for non-fatal outcomes, the Lunn-McNeil (cause-specific) approach was used to account for the competing risk of all-cause mortality (26). Results of the Cox and Lunn-McNeil analyses were presented in terms of adjusted hazard ratios, with 95% CI.

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

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

Sensitivity analyses

Sensitivity analyses were conducted to account for repeat CAs, shorter medication discontinuation periods, and confounding by indication (34-38).

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 substantially fewer comorbidities compared to patients who had no CA (Table 1). However, after IPT-weighting, 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_2DS_2-Vasc score 3.22.3 vs 2.92.1; SMD<0.1 for all covariates shown in Figure 2.

All-cause mortality

Over a median follow-up time of 3.8 years (IQR 1.7-7.7), 21 (4.7%) of CA patients and 171 (19.0%) of non-CA patients died (Table 2). Within 30 days of CA, 3 (0.6%) of CA patients died (2 patients died during CA hospitalization and 1 patient died post-discharge) (39). In multivariable IPT-weighted Cox model, with adjustment for additional time-varying covariates, CA was associated with a statistically significant reduction in hazard of all-cause mortality [aHR 0.4 (95% CI 0.2-0.7)] compared to non-CA patients (Table 2). Consistent with these results, comparison of the IPT-weighted Kaplan-Meier curves showed the sustained reduction in mortality over the follow-up period (log-rank p-value=0.004; Figure 3). Indeed, the time-dependent test indicated no violation of the PH assumption for the association of CA with all-cause mortality (p=0.48; Figure S2), confirming the mortality reduction among the CA patients did not vary systematically with increasing time since CA.

HF hospitalizations

A total of 70 (15.5%) CA patients had a HF hospitalization compared to 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). 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, there was a statistically significant deviation from the proportional hazards assumption for the association between CA and HF hospitalization (p-value=0.009; Figure S3), indicating that the strength of this association varies with time since CA. Figure 4 shows how the adjusted HR 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 5). The time-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 to 2 years after CA, but then becomes gradually weaker and disappears after approximately 5 years (Figure 4).

Stroke (including TIA) and major bleeding events

Nine (2.0%) CA patients had a stroke/TIA compared to 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 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 modeled [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 for medications [all sensitivity analyses are presented in the supplement].

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: (1) CA was associated with a long-term reduction in all-cause mortality, (2) CA was protective against HF hospitalizations for only 3-years post-procedure, (3) approximately 60% of CA patients were anticoagulated within 1 year post-CA, which reduced to 40% at 5 years, and these rates were similar for non-CA patients.

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 (9). Further, 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] (9). 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)] (10). Additional studies have shown CA is associated with reduced AF burden (restoration and maintenance of sinus rhythm) and NT-proBNP, and increased left ventricular ejection fraction (LVEF), 6-minute walk distance and quality of life measures (9, 10, 40-43), which may indicate improvements in AF and HF disease and subsequently a mortality reduction with CA. As described in subgroup analyses of the AFFIRM and AF-CHF trials, maintenance of sinus rhythm is associated with a lower risk of mortality (5, 6, 44) and specifically for CA, Ullah et al found that recurrent AF after CA strongly predicted mortality in AF-HF patients (45).

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 (9). In addition, randomization only balances baseline confounding, however, the present study also accounted for time-varying confounders during follow-up, including ICD, CRT, OAC, and AAD therapies, all of which could affect the association between CA and all-cause mortality.

HF hospitalizations

Both the CASTLE-AF and AATAC trials showed that HF hospitalizations reduced in CA patients compared to those on medical therapy (9, 10), 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 (9, 10), 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)] (9). 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 (46).

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 96% relative reduction in AF/atrial tachycardia recurrence (44). 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/TIA 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] (45) and no statistically significant difference for stroke risk between treatment groups (9, 40, 43, 47). 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 (15, 16).

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 (15, 16). 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 (NYHA) 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 database and could not be adjusted for in the 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 confidence intervals, due to low number of events, make the comparisons less conclusive, and the time-dependent effect of CA could not be accurately tested and modeled.

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.

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FIGURE LEGEND

Figure 1. Cohort creation flow chart

Figure 2. Standardized mean differences comparing CA and non-CA patients

Figure 3. Kaplan-Meier curve for all-cause mortality

Figure 4. Time-dependent effect of CA for HF hospitalizations

Table 1. Baseline characteristics

	Before matching and IPTW§	**After matching and IPTW§**		
	All AF-HF patients (N=101,933)	**Cases (N=451)**	**Controls (N=899)**	**Standardized Mean Difference****
Mean age (SD), years*	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*	51.4%	24%	22%	0.05
Hypertension*	31.9%	72%	65%	0.15
Diabetes mellitus*	16.5%	37%	33%	0.09
Coronary artery disease*	26.8%	55%	52%	0.06
Prior myocardial infarction	11.2%	33%	24%	0.20
Valvular disease*	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*	14.2%	29%	25%	0.09
Prior stroke (including TIA)*	2.1%	2%	1%	0.06
Liver disease*	2.2%	9%	11%	0.07

Vascular disease*	11.8%	19%	17%	0.07
Prior major bleeding*	4.1%	11%	7%	0.13
Pacemaker	12.3%	20%	19%	0.02
Implantable cardioverter defibrillator (ICD)*	2.5%	29%	29%	0.01
Cardiac resynchronization therapy (CRT)*	9.4%	34%	33%	0.02
Mean CHA_2DS_2-Vasc Score (SD)	3.8 (1.3)	3.2 (2.3)	2.8 (2.0)	0.04
Mean HAS-BLED Score (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*	47.6%	65%	66%	0.01
DOACs*	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*	10.0%	58%	59%	0.02
Sotalol*	3.3%	16%	13%	0.09
Class 1 antiarrhythmics*	2.4%	19%	20%	0.06
Digoxin*	24.7%	28%	39%	0.23
Beta blockers*	49.8%	81%	72%	0.22

Angiotensin converting enzyme (ACE) inhibitors	39.7%	59%	63%	0.09
Angiotension II receptor blockers (ARB)	17.9%	20%	22%	0.05
Calcium channel blockers	17.3%	23%	19%	0.10
Diuretics*	69.5%	72%	70%	0.04

*Predefined variables included in the propensity score model.

[§]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).

** Standardized mean difference (SMD) <0.10 denotes balance for baseline characteristics between AF ablation and no AF ablation patients.

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	0.2-0.7
Controls	899	171 (19.0)	3.5		
Heart failure hospitalizations					
Cases	431	70 (15.5)	4.6	1.2**	0.8-1.7
Controls	899	272 (30.3)	6.8		
Stroke (including TIA)					
Cases	431	9 (2.0)	0.5	1.4**	0.56-3.7
Controls	899	41 (4.6)	0.9		
Major bleeding					
Cases	431	10 (2.2)	0.6	1.9**	0.8-4.7
Controls	899	46 (5.1)	1.0		

*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 weighted with stabilized ATT weights.

**Hazard ratios were also adjusted for the competing risk of all-cause mortality.

Figure 1. Cohort creation flow chart

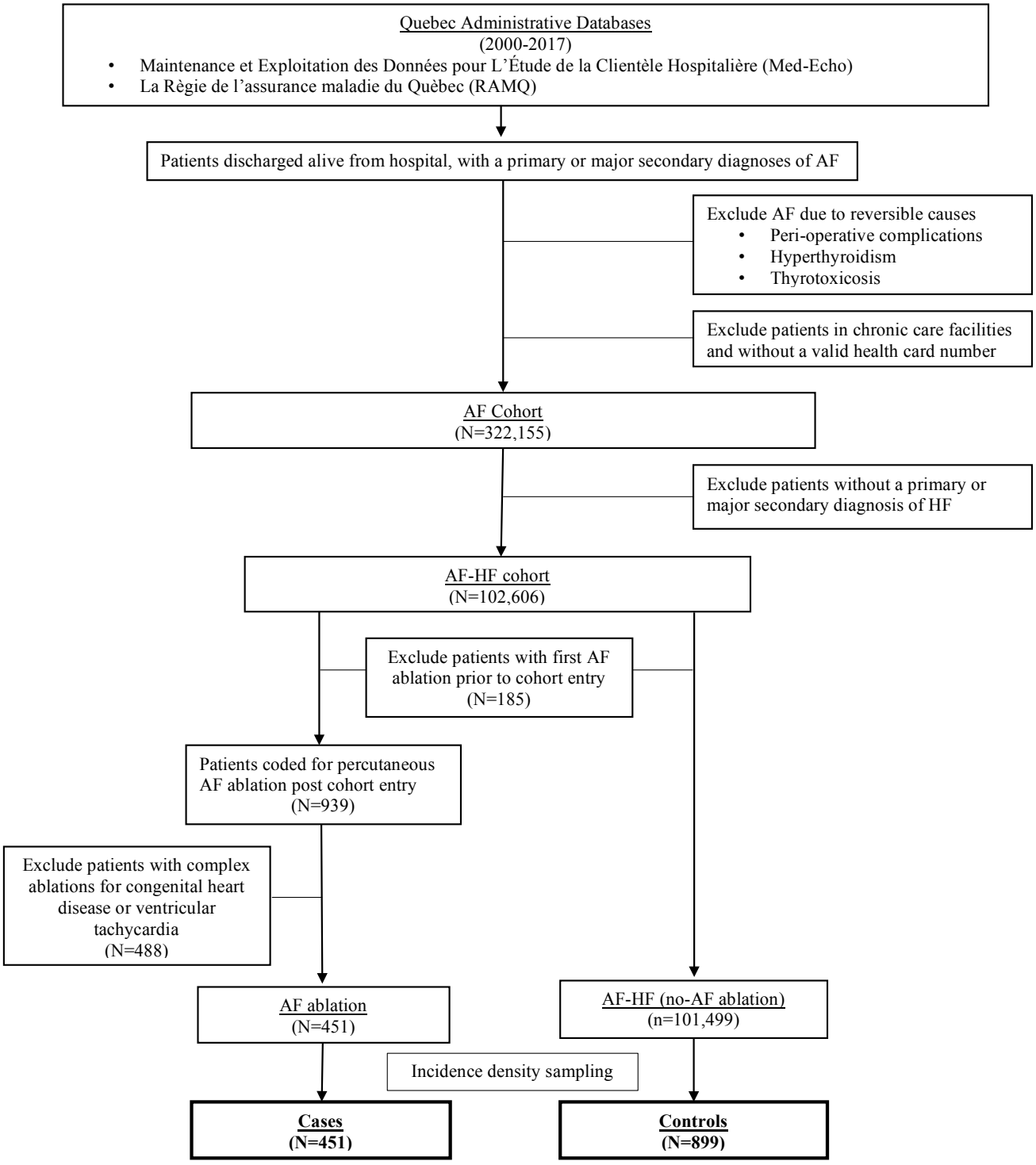
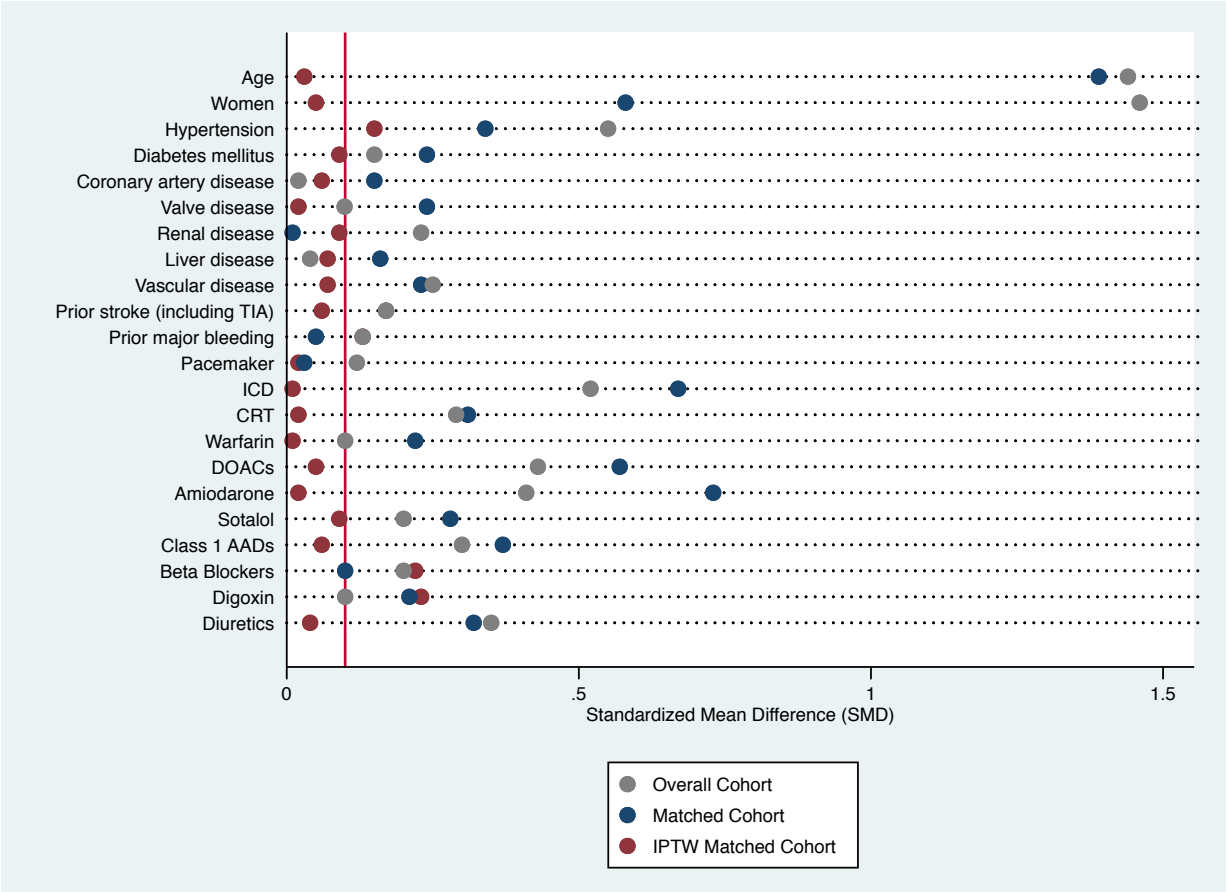
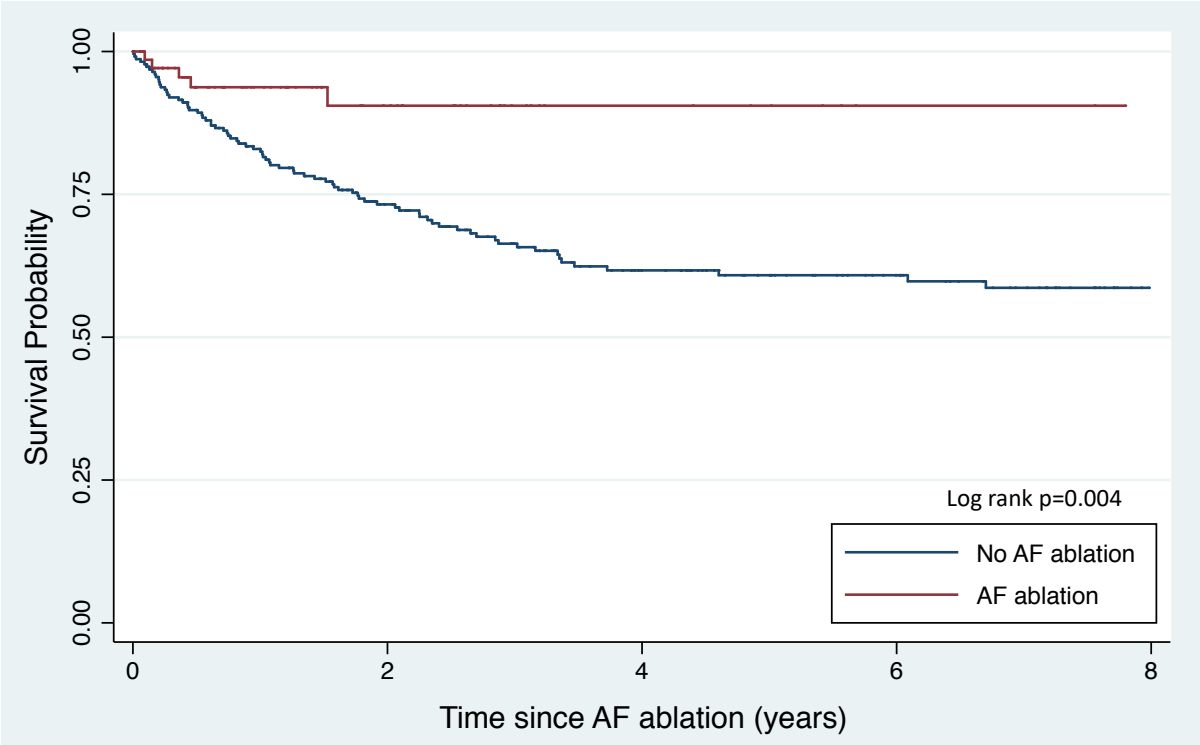


Figure 2. Standardized mean differences comparing CA and non-CA patients



*AF ablation vs no AF ablation. All SMDs <0.1

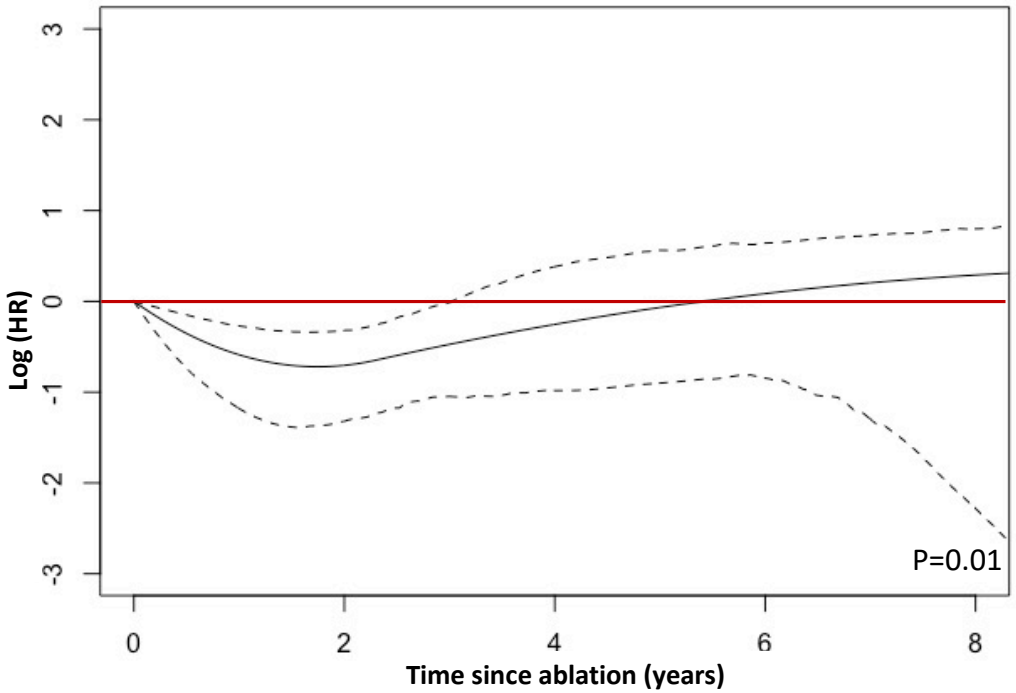
Figure 3. Kaplan-Meier curve for all-cause mortality



	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

*Kaplan meier curve was IPTW weighted and adjusted for hypertension, prior bleeding, beta blockers, and digoxin at baseline.

Figure 4. Time dependent effect of CA for HF hospitalizations



	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

*Adjusted for time-varying covariates and the competing risk of all-cause mortality, as well as IPTW weighting.
⊤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.

6.3 Supplementary appendix

SUPPLEMENT

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References

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 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. Age at baseline was included as a linear variable in the PS model [lowest deviance (-2log likelihood)] (2, 3) compared age modeled flexibility using multiple knots (fractional polynomials). Weights were stabilized and estimated the average treatment effect in the treated (4-7).

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

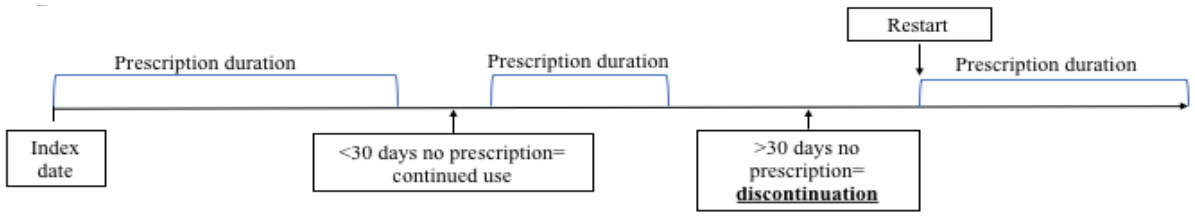
The primary objective of the present study was to assess single procedure effectiveness; however, patients may have undergone additional CAs during the follow-up period. To account for additional procedures, two separate sensitivity analyses were performed. The first approach censored a patient on date 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 (8-10). 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 (10, 11). 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 (12). 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) (12, 13). 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 (12, 13).

RESULTS

Testing the proportional hazards assumption

Figure S2. All-cause mortality

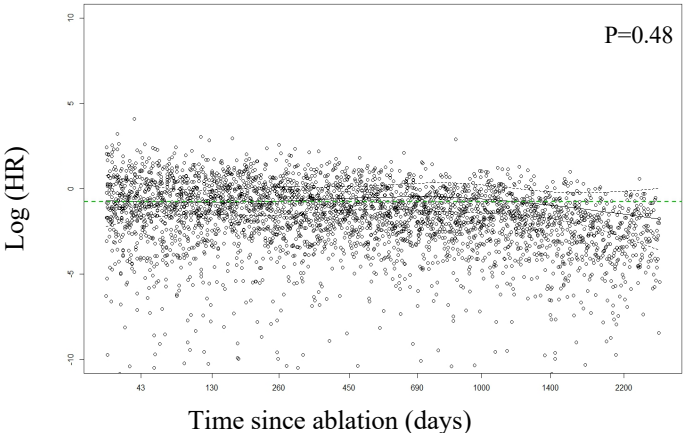


Figure S3. HF hospitalizations

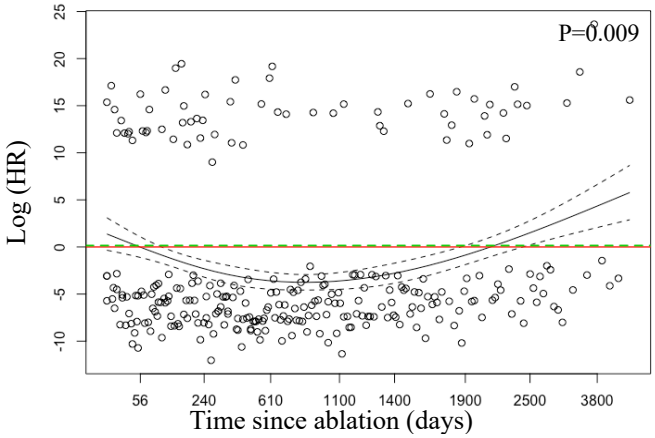


Figure S4. Stroke/TIA

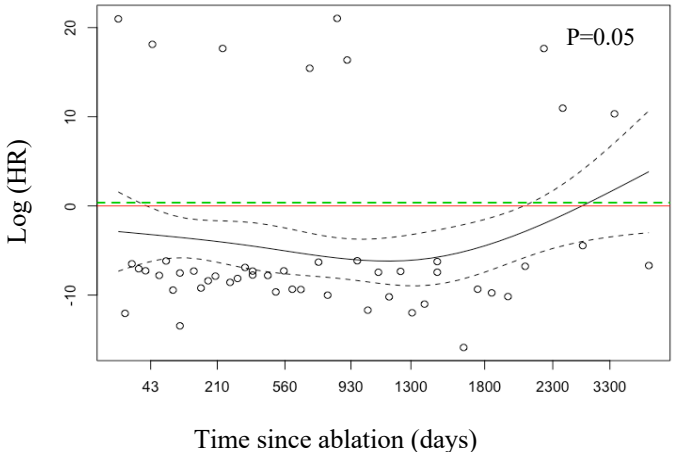
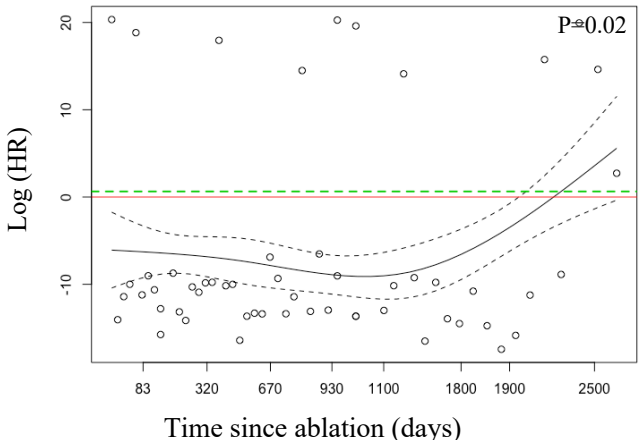


Figure S5. Major bleeding



*Figures S2 to S5 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 (14). 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) (14). 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 (0.85-1.70)	1.19 (0.85-1.68)
Stroke/TIA	1.44 (0.56-3.72)	1.48 (0.56-4.78)	1.47 (0.56-4.76)
Major bleeding	1.89 (0.75-4.74)	1.92 (0.76-4.79)	1.91 (0.76-4.77)

*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 (0.84-1.68)
Stroke/TIA	1.44 (0.56-3.72)	1.43 (0.55-3.71)
Major bleeding	1.89 (0.75-4.74)	1.88 (0.74-4.73)

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 (12, 13). 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 (15), 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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CHAPTER 7: DISCUSSION

7.1 Summary of findings

A retrospective population-level cohort was created using administrative data to investigate the utilization, safety, and long-term effectiveness of CA in AF-HF patients in Quebec, Canada between April 2000 to March 2017. Among 112,255 AF-HF patients, 700 (0.6%) underwent CA and among those with medication coverage (N=101,499), 434 (0.4%) had a CA. The set of studies presented in this thesis are the first real-world evaluation of CA in AF-HF patients and it contains the largest number of CA patients with the longest follow-up post-CA.

In manuscript 1, patients were followed from AF-HF disease onset (cohort entry, section 3.3) to date of CA to determine the incidence of CA, sex differences, and criteria for treatment with CA. Of 101,499 patients, very few (434 patients; 0.4%) underwent CA and the median time from cohort entry to CA was 0.8 years (IQR 0.1-2.7). Patients who underwent CA were younger, had few additional comorbidities, and were half as likely to be women [26% women; aHR 0.6 (95% CI 0.4-0.7)]. Presence of an ICD and any prior prescription for a DOAC or AAD were identified as predictors for CA treatment ($p<0.05$ for all). Results were similar when replicated in the overall cohort of 112,255 patients. Thus, there exists a knowledge gap for the use of CA in this population since CA patients are younger, have fewer comorbidities, and unlikely to be women which does not represent most the AF-HF population

Amongst the select population characterized in the first manuscript, the second manuscript determined that 3.0% of AF-HF patients who underwent CA had a major AE within 30-days post CA. Hemorrhage/hematoma was the most frequent major AE (4 patients; 0.6%) followed by all-cause mortality, CVA/TIA, PERD, and vascular AEs (3 patients each; 0.4%). No patient had a pulmonary embolism. Univariate logistic regressions identified age≥ 65 years and the presence of

coronary artery disease as predictors for the combined endpoint of a major AE, however, these results were hypothesis generating. Approximately 60% of CA patients had a repeat CA over the follow-up period, but only 1 patient had a major AE at repeat procedure. Overall, the incidence of major AEs in the AF-HF population is relatively low and is similar to the general AF population, with and without HF. This suggests that CA is relatively safety to perform in AF patients with comorbid HF.

After establishing the type of patient treated with CA in real-life population and that it is safe to perform in these select patients, the final manuscript investigated the long-term effectiveness of CA to reduce all-cause mortality, HF hospitalizations, and major morbidities (stroke/TIA and major bleeding). Incidence density sampling was used to match each CA patient to 2 controls based on time till CA and number of hospitalizations (451 CA and 899 non-CA patients). Over a median follow-up of 3.8 years, CA was associated with a statistically significant reduction in all-cause mortality [aHR 0.4 (95% CI 0.2-0.7)], but not for stroke and major bleeding. The hazard of HF re-hospitalization for CA patients, relative to matched controls, varied with time since CA (p=0.01), with a reduction in HF re-hospitalizations until approximately 3 years post-CA. Repeat CAs occurred in 58% of CA patients, but did not alter conclusions about the effectiveness of CA. Also, a similar proportion of CA and non-CA patients were anticoagulated during a 5-year follow-up period (approximately 60%), however, the OAC use is lower than general AF population, particularly among CA patients. Our findings confirmed the results from randomized trials which showed the CA reduced all-cause mortality and HF hospitalization in AF-HF patients, but, our longer-term results enhance these findings to suggest the protective effect for HF hospitalizations is temporary and lasts at least 3 years after the procedure.

7.2 Methodological strengths

Several methodological techniques were employed to more accurately capture the true effectiveness of CA in a real-world population and improve upon the results of randomized trials. To prevent immortal time bias and balance baseline confounding, incidence density sampling and IPT-weighing, respectively, were used. Incidence density sampling matched CA patients to non-CA patient on time from cohort entry (disease onset) to CA which was a surrogate for disease progression. Additional matching on number of hospitalizations before CA further ensured CA and non-CA patients had a similar disease severity. After IPT-weighting, most measured confounders were balanced between CA and non-CA patients. The few unbalanced comorbidities were further adjusted for in the Cox regressions.

Randomization, however, only balances measured and unmeasured baseline confounding.[98-100] Therapeutic management for AF and HF are complex and necessitate a management strategy which uses a combination of therapies. In addition to the effects of CA on all-cause mortality, HF hospitalizations, and strokes, concurrent therapies during follow-up can also potentially prevent these outcomes. ICDs prevent mortality, CRTs can improve HF symptoms, OAC therapy prevents strokes, and AADs have been shown to convert patients to sinus rhythm which has been indicated a reduction in mortality and improve HF.[9,15,55,111,112] The present study accounted for the association of these covariates with the outcomes during follow-up, which isolated the individual effectiveness of CA.

Many studies and randomized trials investigate non-fatal outcomes as a composite outcome with mortality or do not account for the competing risk of death. Neither approach accurately determines the association of CA on the individual outcome. Effectiveness of the procedure may be different for the outcomes of all-cause mortality and HF hospitalization; therefore, a combined

outcome prevents the detection of these differing associations. Similarly, investigation of a single non-fatal outcome without accounting for competing risks, also does not differentiate the individual association of the procedure with the outcome and death, since patients may die before they have an opportunity to get the procedure and are censored at death, further reducing the number of patients at risk for the outcome.[113-115] The present study uses the Lunn-McNeil (cause-specific) approach to account for the competing risk of death for non-fatal outcomes to isolate the association of CA on the individual non-fatal outcome, instead of mixing effects with a combined outcome or a single outcome without adjustment for competing risks.

Finally, all prior studies assumed the effectiveness of CA was constant over time with the use of Cox proportional hazards. Intrinsically, this has been shown to be untrue since more than half of the population had repeat CA. Although a repeat CA is likely due to AF recurrence, which could not be measured in the present study, recurrence may lead to more symptomatic HF. Therefore, the plausibility of constant effectiveness of CA over time is questionable. The present study investigated the variation in hazards over time since the procedure with a B-spline and 95% confidence intervals were calculated from 500 bootstrap resampling. Due to the large sample size and long follow-up, our study determined that the protective effect of CA was constant for all-cause mortality, however, HF hospitalizations were reduced for a minimum of 3 years post-CA. The duration of effectiveness of CA has not been previously quantified in the AF-HF population or the general AF population from trials or observational studies. This methodological strength directly advances knowledge about the use of CA in the long-term.

7.3 Limitations

Whereas the advantage of this population-based study assesses the real-world use, safety and effectiveness of CA in the entire AF-HF population, the use of administrative databases has

limitations. First, important immeasurable factors including type of AF (paroxysmal, persistent, or permanent), NYHA class, and LVEF are not contained in the database. These factors mark the severity of disease and have been shown to affect prognosis. To account for severity of disease, we used proxy confounders including diuretic, ICD, and CRT use, which are treatments for patients with advanced HF. In addition, we conducted a confounding by indication sensitivity analysis.

Despite the large sample size of CA patients compared to prior studies, the number of major AEs, strokes/TIA, and major bleeding events were limited. Subsequently, there was not enough power to identify predictors for major AEs (manuscript 2) and to detect associations for CA with the hazard of strokes/TIA and major bleeding events (manuscript 3). In addition, the limited number of events prevented the potential time-dependent effect of CA from being investigated for stroke/TIA and major bleeding (manuscript 3). Therefore, the results for these analyses were hypothesis generating and should be interpreted with caution.

Medications including OACs, AADs, and rate control drugs have important effects on the outcome, however, medication information is only present for a subset of the population (patients >65 years or without alternate forms of drug insurance). Although approximately 90% of the AF-HF population were included in the medication cohort, only 75% of patients who underwent CA had medication insurance at baseline (cohort entry). Consequently, the results from medication cohort may be less generalizable to the typical CA population as they are older and may have differing effects from treatments and medications than the overall CA population. In turn, results from the overall cohort without the inclusion of medication information had additional residual confounding from a lack of adjustment for medication use. The unmeasured confounding from missing medication information prevented the overall cohort from being used in manuscript 3 due

to high confounding bias.

It should also be noted, that medication use is based on prescriptions dispensed rather than prescriptions consumed. Although a patient may stop their medication soon after its dispensation, in Quebec, each prescription period is 30 days, which limits the extent of residual confounding from medication use.

AF and HF diagnoses at hospitalizations determine inclusion into the cohort. It has been shown that up to one-third of AF patients are not captured in administrative databases using this approach,[101] however due to frequent hospitalizations for HF,[104] patients with co-morbid AF are more likely to be captured within our database. Lastly, disease onset for both AF and HF likely occurred before hospitalization, but patients were only included when the diseases were severe enough to require hospitalization.

7.4 Clinical implications

In contrast to the reduced effectiveness of pharmacologic therapy, the promising results of randomized trials on CA have made the procedure a potentially viable therapeutic option for the challenging AF-HF population. The series of studies presented in this thesis further enhance the results from trials and establish that the safety and effectiveness of CA translates to the real-world AF-HF population.

Current Canadian Cardiovascular Society (CCS) AF guidelines do not have a specific recommendation for CA with AF-HF patients and state “we believe that the existing recommendation to pursue catheter ablation as a second-line treatment for symptomatic patients applies to this group”.[15] The focused update to the American guidelines in 2019 only states “AF catheter ablation may be reasonable in selected patients with AF and HF”.[16] Neither set of guidelines advises on the clinical profile of “selected” patients. Manuscript 1 helps to define a

"selected" patient and informs physicians about the clinical characteristics have been considered when referring patients to CA. Physicians can also be more comfortable to refer selected patients because the incidence of periprocedural AEs was low and comparable to the CA in the general AF population (manuscript 2).

Both guidelines assert the level of evidence towards the effectiveness of CA in AF-HF patients is limited and suggest that CA may "potentially lower mortality rate and reduce hospitalization from HF".[15,16] As the largest cohort with the longest post-CA follow-up period, our results demonstrate that CA reduces the incidence of the individual outcomes of all-cause mortality and HF hospitalizations, independent of concurrent cardiac device (ICD and CRT) and pharmacologic therapies (OAC and AAD). This strengthens the evidence of the effectiveness of CA with a more precise evaluation of protection from the procedure alone over the long-term.

Beyond the trials and guidelines, our study suggests that the alleviation of severe HF symptoms necessitating hospitalization post-CA is present for a minimum of 3 years, after which time a patient may need to seek additional therapy. Further, clinicians should be aware that more than half (approximately 60%) of AF-HF patients may have a repeat CA. In addition, although manuscript 3 did not assess the effectiveness of OAC use post-CA, it provides valuable insight to clinicians that management with an OAC was not different between CA and non-CA patients. Randomized trials including OCEAN (NCT02168829) and ODIn-AF (NCT02067182) will further elucidate the need for OACs use post-CA in high stroke risk patients.

Overall, our studies support the use of CA in AF-HF patients, however, clinicians should acknowledge that evidence for the use of the CA is limited. As in the present study, more than 90% of AF-HF patients are either elderly, female, or have many additional comorbidities, and such

patients are less well represented in current studies. Confirmation of whether CA is equally safe and effective in sicker patient populations will require further research.

7.5 Opportunities for future research

Although our study significantly advances knowledge about CA to treat AF-HF patients, it also indicates there is much more research to be done. First, replication of our studies with information on LVEF and NYHA class would 1) further classify patients eligible for the procedure, 2) determine if HF severity is a predictor for periprocedural AEs, and 3) evaluate the differences in effectiveness of CA by HF severity. In addition, information on AF recurrences and changes LVEF can be used to determine if the reduction in in these outcomes varies over time since CA. This could help inform about the reasons for the decrease in mortality or the temporary reduction in HF hospitalizations. Also, larger studies are necessary to be able to evaluate the association between CA and stroke and bleeding events and identify predictors for periprocedural AEs. In addition, future studies could also investigate the number of recurrent HF hospitalizations.

The results of the trials and the present set of studies are encouraging, however, all the AF-HF patients investigated were heathier than the majority of the AF-HF population. For CA to be considered as a standard and widespread treatment option for AF patients with comorbid HF, studies of patients with more comorbidities, advanced age, and more severe HF are warranted.

7.6 Conclusions

In the largest cohort of CA patients with AF and HF, CA was relatively safe to perform and was associated with a reduction in all-cause mortality in the long-term. CA also reduced HF hospitalizations, however, the protective effect of the procedure only persisted for a minimum of 3 years post-CA. These results suggest the CA may be considered as an appropriate treatment option for AF-HF patients, however, patients selected for the procedure are younger, mostly male,

and have minimal additional comorbidities which is not generalizable to most AF-HF patients. Therefore, future studies investigating whether the safety and effectiveness persists among patients who are more representative of the majority of the AF-HF population are warranted.

CHAPTER 8: REFERENCES

References were listed at the end of each individual manuscript (chapters 4-6) and were formatted in accordance to the guidelines of the specific scientific journal it was submitted to. References for the remainder of the thesis (chapters 1-3 and 7) are listed below:

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