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Catheter Ablation for Atrial Fibrillation: Predicting Recurrence

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A thesis submitted in partial fulfillment of the requirements for the degree in Master of Science
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Abstract

Background

Catheter ablation has emerged as treatment for atrial fibrillation (AF). Health care-related variables have not been explored as predictors of first ablation outcome. Determining factors associated with arrhythmia recurrence may help select patients likely to benefit. The objective was to identify variables associated with recurrence following AF ablation.

Methods

Retrospective cohort design of 314 AF patients who had undergone first ablation. Follow-up visits occurred at 3, 6 and 12 months. Variables and the outcome of recurrence were modeled with Cox proportional hazards analysis.

Results/Conclusions

After mean follow-up of 239+/-125 days, 110/314 patients (35.0%) experienced recurrence. Adjusted Cox proportional hazards models demonstrated cardiomyopathy [HR (95% CI) = 1.97 (1.13-3.41)] was associated with arrhythmia recurrence. Conversely, height per cm increase [HR (95% CI) = 0.96 (0.94-0.99)], and targeted ablation outside the pulmonary veins [HR (95% CI) = 0.531 (0.29-0.98)] were associated with hazard reduction. Wait time was not associated with recurrence.

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Chapter 1

1   Introduction

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder. It is characterized by disorganized electrical impulses in the upper chamber of the heart, resulting in an irregular and rapid heartbeat that can occur in episodes or last continuously. An electrocardiogram (ECG) or rhythm recording demonstrating AF lasting at least 30 seconds is considered an episode.[1, 2, 3]

Overall, AF affects 1-2% of the population.[4] Among adults aged 55 years or younger the prevalence of AF is less than 1%, though it rises with age to nearly 10% in adults over 80. As the population ages, the absolute number of cases is expected to increase due to increased risk with age, combined with population aging. This presents a public health problem for planning future treatment capacity and resource utilization. AF increases the risk of stroke and is recognized as an independent predictor of morbidity and mortality in the setting of cardiovascular disease.[5, 6, 3]

Although the etiology of AF is incompletely understood, AF is primarily initiated by triggers within the pulmonary veins (PVs).[7, 8] Catheter ablation aims to electrically isolate the foci within the PV from the atria, thereby preventing the chaotic electrical signals from interrupting the normal conduction of the left atrium.[9] It has emerged as a treatment modality for symptomatic patients who have not responded to medication.[10, 11] Acute procedural success is indicated by the electrical isolation of the PVs. Long-term results are heterogeneous and demonstrate a high rate of recurrence of atrial arrhythmias following the procedure. Although there have been advances in the catheter ablation technique, recurrence rates remain as high as 50% post-ablation in more chronic forms of the condition.[12, 13]

PV reconnection, due to recovery of ablated areas or transient ablation related to poor catheter contact, has been postulated by several authors to be the cause of early recurrences.[14, 15, 16, 17] However, there is uncertainty of the cause of recurrence and the progressive attrition in success over time, even after acute success.[14, 15, 18] There has

been interest in identifying factors that contribute to arrhythmia recurrences after catheter ablation. Previous studies have assessed the impact of factors on the outcome of various catheter ablation techniques. However, contradictory results along with heterogeneous definitions of recurrence and blanking period lengths (i.e. the period of time between the procedure and when an arrhythmic episode is counted) across studies have not provided definitive conclusions. Variables that have been implicated as potential predictors of recurrence include: type of AF, increased left atrial diameter, decreased ejection fraction, hypertension, body size and left atrial fibrosis.[19, 20] Cardiac risk factors including hypertension, diabetes, obesity and obstructive sleep apnea have been shown to independently increase the incidence of AF. [21-24] These risk factors are also associated with structural and electrical remodeling of the atria that leads to AF development and progression. [25-27]

The purpose of this study was to examine the associations of pre-procedural clinical, procedural and post-procedural variables with recurrence after successful ablation for AF. Using broad inclusion criteria, including comorbid conditions, this study will be representative of patients encountered in clinical practice. Randomized trials provide data on efficacy of treatment, but are performed under tightly controlled conditions on a highly select subgroup of potential subjects. Catheter ablation is not effective for all patients and high recurrence rates following ablation is a major challenge. Pre-procedural screening of AF patients who are suitable for catheter ablation is critical for optimizing the success and safety of the procedure. Identifying factors that contribute to the recurrence of arrhythmia is of clinical importance to reduce healthcare costs and to avoid exposing patients to unnecessary procedures and related complications.

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Chapter 2

2 Literature Review

Cardiac arrhythmia refers to an irregular heartbeat. Of the several types, atrial fibrillation (AF) is the most common cardiac arrhythmia. In AF patients, disorganized electrical impulses in the atria cause an irregular and often rapid heartbeat. AF affects 1-2% of the population, though the prevalence rises with age.[1] The risk of stroke is increased in AF patients, and it is recognized as an independent predictor of morbidity and mortality in the setting of cardiovascular disease.[2] Patients are often highly symptomatic, though symptoms affect patients differently due to varying episode duration, disease processes, and comorbid conditions.[3] People with AF experience lower quality of life scores compared with the general population, healthy controls and other cardiovascular disease groups.[4]

2.1 Classification of atrial fibrillation

While there are several ways to categorize AF, there is agreement across several guidelines to classify AF as paroxysmal or persistent.[3] Paroxysmal AF is defined as recurrent AF that resolves within 7 days, while persistent AF describes AF that continues beyond 7 days. Persistent AF can be further defined as longstanding persistent if the AF has continued beyond one year, or permanent if treatment has failed or has been discontinued.

Although there is agreement in the categorization of AF, previous studies have employed various criteria to define type of AF. Furthermore, persistent and paroxysmal AF are not mutually exclusive. The transient and often variable nature of AF poses limits to categorization based on patterns. Patients can experience episodes consistent with both persistent and paroxysmal AF categories. It has been recommended to categorize the patient based on the dominant AF pattern.[3] However, there are not any investigations that specifically address the intra- or inter- observer reliability of the existing classifications. This is of interest because associations of type of AF and other

variables may be inconsistent in the current published literature due to variations in classification.

AF often occurs in patients with heart conditions, including heart disease, hypertension, lung disease, or those who have undergone cardiac surgery. However, 10% of patients with AF do not have an associated cardiac condition and were previously classified as "lone AF," while patients with concomitant heart conditions were distinguished as "secondary AF." The current recommendations advise against using this definition so treatment is not influenced.[3] Along with cardiac conditions, familial, genetic, behavioural factors and biochemical markers have been implicated as risk factors for AF.

2.2 Healthcare burden

Healthcare costs associated with AF have increased and are expected to continue rising as the population ages.[5] Although there is a paucity of Canadian AF cost and healthcare burden data, O'Reilly and colleagues published a national database study with data from fiscal year 2007/2008.[6] The authors estimated 22,823 (68 per 100,000 population) hospital admissions and 68,066 (174 per 100,000 population) emergency department visits nationally were directly attributable to AF. The average length of stay was 5.7 days, with an average admission cost of $6718. Nationally, the estimated total cost for the fiscal year was $223 million. Conditions related to previously diagnosed AF accounted for significantly higher costs and longer hospital admissions. The additional cost for AF as a comorbidity was $558 million. However, the province of Quebec (23% of the nation's population) does not contribute admissions data to the national database analyzed in this study, and Ontario is the only province to contribute complete emergency department and single day admissions data. The estimates are likely underestimated because the results were extrapolated to provinces with missing data solely on age and sex demographic data, without taking into account the varying risk profiles of Canadians across the country. In spite of problems with data quality, these estimates highlight the significant healthcare resource utilization and cost burden of AF.

2.3 Procedural and healthcare related factors

2.3.1 Medication

Management of AF has traditionally been medication-based, intended to either control heart rate or maintain sinus rhythm.[7] A rate control and anticoagulation strategy allows AF to recur or persist, but controls the ventricular rate during episodes to control symptoms and reduce the risk of stroke. Rhythm control attempts to restore and maintain sinus rhythm, though it can be very difficult to achieve in some patients using medications alone. There has been a lack of compelling evidence demonstrating rhythm control offers a survival advantage over rate-control strategies.[7]

2.3.2 Catheter ablation

Catheter ablation aims to electrically isolate the tissue where AF most frequently starts thereby preventing chaotic electrical signals from disturbing the normal conduction patterns.[10] Radiofrequency energy is delivered from the catheter, creating many small lesions to block the electrical conduction contributing to AF. Pulmonary vein isolation (PVI) is the most common ablation technique. The procedural end point is electrical isolation of the left and right pairs of pulmonary veins (PVs) from the left atrium.[11, 3]

Catheter ablation is a curative treatment for AF. Due to the infrequent but potentially serious risk involved, it is currently reserved for symptomatic paroxysmal AF patients who have not responded to at least one anti-arrhythmic medication.[3] Randomized, multicenter trials have demonstrated that while both medication and ablation therapies reduced AF burden, ablation results were markedly better.[8] Importantly, patients who underwent catheter ablation had higher quality of life scores and wellness scores and better exercise capacity than the patients on anti-arrhythmic drugs (AADs). Wazni and colleagues[9] trialled ablation as a first-line treatment approach instead of waiting for patients to become unresponsive to AADs and demonstrated comparable success rates, establishing that in some patients AADs are not required. These studies all demonstrated that adapting AF treatment strategies and considering ablation as a first or second line therapy is more effective than multiple AAD treatments. However, the

most recent guidelines for the management of AF continue to recommend ablation in paroxysmal AF patients only after they have failed at least one AAD, and recommend more limited use in persistent AF patients.[3]

There have been advances in the catheter ablation technique since its inception, but arrhythmia recurrence rates remain as high as 50% in persistent AF and post-ablation outcomes have not improved proportionately.[12, 13] Although the procedure has become more uniform across different health care centers, variations in end-points, definitions of recurrence and ultimately differences in procedural success persist as the search for improved outcomes continues. Direct comparisons across previous studies is difficult, and complicating matters, some studies include only off-AAD sinus rhythm as the definition of success, while others include patients maintaining sinus rhythm on AADs as successes. Clinical trials are often limited to a select group of patients and are not representative of patients seen in clinical practice.

2.3.3 Technique

Often the type of AF helps inform operators whether additional ablation lesions will likely be required and may help predict the response to the therapy. Isolation of the pulmonary veins alone is often sufficient to treat patients with paroxysmal AF, but suboptimal results are observed in patients with persistent AF.[14] Initial reports of persistent AF ablation demonstrated that PVI achieved arrhythmic resolution in 85% of paroxysmal AF patients compared to just 29% for persistent AF.[11]

Persistent AF requires elimination of initiating sites in the pulmonary veins, but also may entail ablation of sites in the left atrium that can cause AF to persist. In theory, AF is less likely to persist once modification to the atrial substrate, specifically 'rotor' sites, has occurred. Improvements in identifying these points with ablation techniques have resulted in enhanced success in persistent AF patients in some studies. In a small study of 74 patients with paroxysmal AF, Jais et al found that additional targeted ablation lines only in patients where AF or atrial flutter was inducible helped reach a success rate of 91%.[15] The endpoint was non-inducibility of AF and atrial flutter and additional lesions were performed until foci were uninducible. By tailoring the procedure to target foci in

each patient, unnecessary lesions were avoided. In contrast, a study of 144 paroxysmal and persistent patients by Leong-Sit and colleagues found that aggressive stimulation and subsequent ablation of induced arrhythmias was limited in predicting freedom from arrhythmia after ablation.[16] The authors found persistent AF was independently associated with recurrence (OR = 2.43) along with left atrial size (OR = 2.18).

Persistent AF episodes result in changes from electrical foci propagating AF to underlying electro-anatomical changes that further perpetuates AF. Willems et al[17] compared PVI alone to PVI and substrate modification of the left atrium in persistent AF patients. After a mean follow up time of 487 days, only 20% of persistent AF patients were free of recurrence, while 69% of patients who underwent the hybrid procedure remained in sinus rhythm. Gaita and colleagues[18] expanded these results to both paroxysmal and persistent patients and demonstrated the addition of linear lesions to PVI provides greater long-term success free from AF in both patient groups compared to PVI alone. In the paroxysmal AF group, there was not a significant difference in ablation strategy outcomes at 1 year follow-up, but the hybrid approach was significantly superior over long-term follow-up. This reinforces the notion that as AF duration increases so does substrate degradation and without intervention the arrhythmia progresses towards atrial changes that further perpetuates AF.[19] On-treatment analysis of the Conventional ablation for AF with or without focal impulse and rotor modulation (CONFIRM) trial suggested fewer AF ablation failures when all sources are eliminated, with a graded increase in recurrence of arrhythmia with more sources missed.[20]

In a sub-study of the CONFIRM trial, Baykaner and colleagues[21] identified stable AF sources in 97.1% of patients. Higher counts of concurrent stable sources per patient were associated with obstructive sleep apnea, enlarged left atrial (LA) diameter, obesity, and heart failure. Concurrent sources of AF observed in this study indicate a tailored approach is necessary. Indeed, single procedure freedom from recurrence was 90% in patients receiving targeted ablation compared to 44% for conventional ablation only.

Complex fractionated atrial electrograms (CFAEs) have been investigated as a target of ablation in persistent AF patients.[22] CFAEs are often slow "rotors" of continuous electrical conduction and representative of phenomena that facilitate AF. Andrade et al[23] found CFAE ablation alone resulted in high rates of early and late recurrence, with early recurrence also predicting late recurrence. However, a hybrid CFAE plus PVI procedure increased long term success without an increase in early recurrence. In contrast to the traditional approach of substrate modification, however, this international, randomized trial of ablation failed to detect any outcome advantage to substrate modification (roof line or mitral annulus line) over simple isolation of the pulmonary veins.[23] This has recently led to significant debate in the arrhythmia community regarding whether a simple pulmonary vein isolation is sufficient as initial approach to persistent AF, or whether some specific patient groups may be more amenable to some form of substrate modification.

Elayi et al[24] randomized longstanding persistent AF patients to 3 groups consisting of 2 different approaches to ablation and PV ablation plus targeting CFAEs. After one procedure, 61% of patients with the combination ablation approach of targeted CFAEs and ablation were in sinus rhythm without antiarrhythmic medications, while only 11% and 40% of those in the first two groups maintained sinus rhythm over a mean follow-up period of 16.4 months. However, the selective nature of patients enrolled in clinical trials may limit the generalizability of these studies.

While therapeutic strategies for targeting CFAEs remain to be exploited, new algorithms for mapping CFAEs are continually being developed but have not yet been used clinically.[25] Ablation procedures continue to advance, but the recurrence rate and predictors of recurrence remain inconsistent. Within randomized trials, one year recurrence rates following ablation for AF have ranged from 23-44%.[8,9,26] Evidence from clinical trials suggests that although persistent AF patients have higher rates of arrhythmia recurrence post-ablation, both paroxysmal and persistent AF patients may benefit from additional targeted ablation lesions.

2.3.4   Operator experience

Catheter ablation is a complex procedure and operator experience plays a key role in outcomes including complications. One study demonstrated a temporal trend in fewer complications with advanced operator experience, even in the absence of change to the ablation technique.[27] Fewer complications occurred over time, with a senior operators reporting fewer complications and shorter procedural durations than junior operators, although the difference was not statistically significant. Broader patient inclusion has been observed over time, along with advances in ablation technique, and improvements in operator skill with more ablations.[28]

2.3.5   Wait time

Catheter ablation requires specialized skill and is still performed in relatively few centers. Time waited for catheter ablation has not been explored, likely because wait times are not currently a widespread issue in the United States. However, long waiting lists for ablation, resulting in treatment delays, may be problematic in countries with a single payer healthcare system. In 2006, the Canadian Cardiovascular Society Access to Care Working Group and the Canadian Heart Rhythm Society published medically acceptable wait times for outpatient assessment and non-invasive investigations of a patient with AF of no longer than four to 12 weeks, depending on the urgency of the need for consultation, and no longer than 12 weeks for catheter ablation procedures in the absence of structural abnormalities.[29] Gillis and colleagues[30] examined wait times for AF patients to be assessed by a cardiologist or electrophysiologist in the Calgary Health Region (Alberta, Canada). The mean wait time was 80+/-55 days from referral date to an in-personal specialist visit. It is currently unknown how long Canadians wait for ablation procedures subsequent to the initial consultation or whether wait times impact procedural success.

2.4   Patient factors

Catheter ablation is constantly evolving, but no single approach to ablation has garnered full success, even in the short term. Most recurrences are presumed to result

from electrical reconnection at the pulmonary veins, though there is little evidence to suggest how or why it occurs.

2.4.1   Body size and left atrial size

Several factors interact to cause AF and there is evidence to suggest the same factors are implicated in the recurrence of AF. Incident AF is associated with advanced age, male sex, and conditions including hypertension.[31] More recently, additional conditions have been implicated in the initiation of incident AF, including obesity and sleep apnea.[32] Several large cohort studies have reported a positive linear association with BMI and risk of AF.[33-35] Furthermore, a meta-analysis of 5 population-based cohort studies including over 78,000 individuals observed a direct proportional increase in AF risk with increased BMI and found that obese individuals have a 49% higher risk of developing AF compared to their non-obese counterparts.[36] However, the authors failed to find an association between an increased AF risk in obese vs. non-obese individuals who had previously undergone cardiac surgery. Following catheter ablation, freedom from arrhythmia recurrence is not uniform and is reduced in patients with risk factors involved in AF initiation.[37, 38] However these results have not been consistent and it is unclear why some patients are more difficult to treat.

Obesity is a risk factor for many conditions linked to AF including hypertension, sleep apnea, and enlarged left atrium diameter.[36] It is unclear whether obesity itself is associated with AF because it is associated with many conditions implicated in the development of AF. Left atrial (LA) diameter is also strongly associated with height, and a larger left atrium has been linked to a higher risk of AF.[39] A larger LA diameter for height may be indicative of obesity-related processes.[40] LA diameter also tends to increase with age, though it may be more reflective of the pathophysiological changes that accompany advanced age, rather than chronologic age itself.[41] VASAN et al[39] found a graded increase in hazard of AF development from the 95th to 99th percentiles of LA diameter for height. There was a 4.4-fold hazard for subjects above the 99th percentile of LA diameter vs. those in the 95th percentile or less. Similarly, Wang et al[33] found that after risk adjustment, a 4% increase in risk of incident AF for each 1 unit BMI

increase observed in both sexes was eliminated after adjustment for LA size. Enlarged LA diameter is associated with many patient characteristics and disease processes.

Baykaner and colleagues[21] found remote sources of ectopic activity in the right atrium of obese patients, a location not typically targeted in ablation for AF. It is currently unknown if this area of activation is common in obese patients, but it may help explain the high rates of recurrence in this population.

2.4.2   Age

The prevalence of AF increases with age, and age-related changes in the heart are common.[41] Elderly patients are often excluded from clinical trials for AF ablation so it remains uncertain whether age is associated with the outcome of catheter ablation. An observational study found no difference in complication rates and AF control in patients grouped by age following catheter ablation (<65 years of age, age 65 to 74 years, age 75 year or older).[42] However, the outcome measure, AF control, included pharmacological measures, and reported lower recurrence rates. In this study, older patients were more likely to be female, and have structural heart disease or hypertension.

2.4.3   Cardiac-related conditions

Vaziri et al[40] found elevated blood pressure was significantly associated with increased left atrial size, even after adjusting for age and BMI. In this sample, BMI was the most powerful determinant of LA size. Hypertension creates an overload of volume and/or pressure, altering the atrial substrate and encouraging AF propagation.

Hypertrophy cardiomyopathy (HCM), a common heritable heart disease that can lead to heart failure, has presented a challenge for catheter ablation success for AF. Bassiouny et al[43] found a 39% success rate of single catheter ablation for cardiomyopathy patients. However, symptomatic improvements were observed. Persistent AF predicted higher recurrence rates. Di Donna and colleagues[9] found similar low success rates in cardiomyopathy patients undergoing initial catheter ablation for AF. After subsequent re-

ablation, the overall success was similar to that of patients without HCM after first ablation.

AF and heart failure share many of the same risk factors. Bertgalia et al[45] found that structural heart disease was a predictor of early recurrence. Structural remodelling from heart failure results in atrial dilatation and widespread fibrosis, both of which perpetuate AF. The presence of structural heart disease precludes left atrial remodeling and enlargement, which are likely involved in the complex mechanisms resulting in early electrical reconnection of the PVs.

2.4.4   Obstructive sleep apnea

Obstructive sleep apnea (OSA) is associated with significant morbidity and mortality. It is associated with AF, obesity, older age and heart conditions. In multivariable analysis, Matiello and colleagues[46] found that severe obstructive sleep apnea (OSA) and enlarged LA diameter were independent risk factors for recurrence. However, significant differences were observed between OSA and non-OSA patients at baseline that suggests OSA patients have more advanced AF. The association between OSA and recurrence may be more complicated. Patients in the OSA group had high incidence of persistent AF, and higher BMI, along with higher rates of hypertension and structural heart disease. In this analysis, the treatment of OSA with continuous positive airway pressure (CPAP) did not affect the results. Conversely, Fein and colleagues[47] compared OSA CPAP-users to OSA non-users and non-OSA patients and found similar baseline characteristics. They found that OSA patients not treated with CPAP had more than a two-fold higher risk of recurrence after PVI. It is uncertain whether the acute effects of apnea events or the related structural changes predispose OSA patients to AF, and it may have important therapeutic implications.

2.5   Variations in existing literature

In a meta-analysis, the single factor that demonstrated a potential link to recurrence after ablation was type of AF.[48] This association was only observed in univariable analysis, and the disappeared when adjusted in multivariable analysis.

There is significant heterogeneity between studies investigating predictors of recurrence. Individual studies have found a variety of different associations between patient characteristics and recurrence, but the results are often not reproducible.

2.5.1   Type of atrial fibrillation

AF leads to both electrical and anatomical remodeling of the atrium which may facilitate the persistence of AF.[49] The degree and longevity of damage caused by atrial remodeling will consequently be reflective of the changes associated with more persistent AF. Wijffels and colleagues[50] demonstrated that induced AF will self-perpetuate over time – "AF begets AF". Over time, paroxysmal AF episodes can become longer-lasting and more difficult to treat, resulting in the progression from paroxysmal to persistent AF. Kerr et al[19] found that 25% of paroxysmal AF cases progressed to permanent AF within 5 years, accompanied by a significant increase in symptoms. This presents a challenge for the clinical categorization of AF. Paroxysmal AF describes short episodes less than one week in duration without the need for intervention. However, some longer lasting episodes may demonstrate the progression from paroxysmal to persistent AF, but complicate the clinical categorization. There is not consistent agreement with how paroxysmal and persistent AF should be defined, which limits the comparability between studies. Additionally, "permanent AF" patients have been included in studies even though they would actually be classified as persistent.[3] Permanent implies that treatment has ceased, but performing ablation on these patients calls into question the permanent AF category.

Indeed, some studies have found associations between AF type and recurrence of AF after catheter ablation, while others have not. Similarly, some studies have shown statistically significant differences in clinical and procedural variables in persistent and paroxysmal patient groups, while others have failed to find differences. This may be indicative of classification deviation.

2.5.2   Recurrence

Several studies have postulated that early recurrences are a result of incomplete ablation and residual PV conduction reinitiates AF.[51-53] A "blanking" period of 3 months following ablation is often used and has been recommended in international and national guidelines.[3] This constitutes a time where AF may recur but should not be considered a procedural failure unless it persists beyond this period, due to the assumption that post-ablation AF is more likely related to inflammation from the procedure itself as opposed to recurrent vein conduction. However, there is limited evidence for the blanking period and it may discount the importance of recurrences during this time.

The ablation procedure itself induces swelling that may cause transient conduction block during the procedure, only to resolve within days or weeks. Despite the 'acutely successful' procedure, lasting conduction block may not be achieved in some patients. Indeed, Bertaglia and colleagues[45] found a 46% relapse rate of atrial arrhythmias during the first three months of follow-up. Furthermore, the incidence of early recurrence is at a maximum shortly after the procedure which is perhaps indicative of acute thermal injury and subsequent recovery.[54] Joshi and colleagues[54] identified early recurrences in 65% of the patients with continuous monitoring. An earlier report of Oral et al[11] suggests only 31% of patients with early recurrence will have long-term freedom of AF.

Additionally, several studies have found associations between early recurrences within the blanking period and late recurrences.[23] Different blanking periods have been used which likely influence the reported recurrence rates in both clinical trials and observational studies. Moreover, some investigators prescribe patients AADs during the blanking period, while others do not, resulting in even greater variation.

In the CONFIRM sub-study of targeted ablation, Baykaner et al[21] calculated recurrence rates using two definitions of recurrence: AF only compared to AF and atrial tachycardias. Though not statistically significant, differences in proportions of

recurrence were observed, depending on which definition was employed. Higher recurrence rates were observed when the failure definition was widened. Predictors of recurrence may prove to be different even within the same study depending on the definition of recurrence.

Most studies have only examined outcomes within 1 year, though long-term data available suggest a continued risk of recurrence beyond one year. After acute procedural success, there is uncertainty of the "cause" of later recurrence and continued attrition observed with time.

2.6 Procedural risks

Although the risk of any complication has decreased as the procedure has advanced over time, no procedure is without risk. Currently, the risk of complication is 2-3%, with vascular access complications being the most common, while fatal complications are rare.[3,28] Prior to and following ablation, patients are prescribed blood thinners to reduce the risk of blot clots forming within the left atrium due to ablation, which can result in heart attack or stroke. Stroke is a risk of AF itself, but the procedural risks must be weighed against the potential benefits. Prevention of complications is based on antithrombotic therapy and adequate treatment of concomitant cardiac disease.

2.6.1 Stroke

The risk of stroke is not homogenous in AF patients. Well-established risk factors have been used to formulate scoring systems to evaluate the stratified risk of stroke.[55] The most widely used scoring system in AF research is the Cardiac Failure, Hypertension, Age >= 75, Diabetes, Stroke ($CHADS_2$) score.[56] Each of the risk factors is worth one point, except stroke or TIA which counts for two in a validating scoring system that correlates $CHADS_2$ score with stroke risk.

2.7 Conclusions

There has been interest in identifying factors that may contribute to AF recurrence after catheter ablation. Previous studies have assessed the impact of factors on the outcome

of various catheter ablation techniques. However, contradictory results along with heterogeneous definitions of recurrence and blanking periods across studies have prevented definitive conclusions. Variables that have been implicated as potential predictors of procedural failure include type of AF, increased left atrial diameter, hypertension, age, and obesity. These factors are also implicated in the development of AF.

Catheter ablation is not necessarily effective for all patients and high recurrence rates following ablation is a major challenge. Wait times for ablation have not been characterized and it is unknown whether time waited affects outcome. Pre-procedural screening of AF patients who are suitable for catheter ablation is critical for optimizing the success and safety of the procedure. Identifying factors that contribute to the recurrence of arrhythmia is of clinical importance to reduce healthcare costs and avoid exposing patients to unnecessary procedures and related complications.

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Chapter 3

3 Objectives

Recurrence of atrial arrhythmias following catheter ablation remains problematic. Understanding the relationship between the patient characteristics, procedural, health care factors and recurrence may facilitate the identification of patients most and least likely to benefit from the procedure.

The identification of key factors related to procedural failure may lower health care costs and avoid exposing patients to unnecessary procedures and related complications when minimal benefit is expected. The proposed study will provide insight into recurrence of arrhythmias following catheter ablation for atrial fibrillation in the Canadian context.

The literature reveals heterogeneity in both direction and strength of association of predictive factors. We aimed to contribute to the understanding of recurrence of arrhythmia following catheter ablation of AF, with the following specific objectives:

3.1 Research objective 1

- To determine the outcome of catheter ablation on AF recurrence after catheter ablation at University Hospital, London, Canada
- To assess the relationships between patient, procedural, and healthcare-related variables and the outcome of catheter ablation among AF patients undergoing initial catheter ablation

3.2 Research objective 2

- To compare the differences in baseline clinical and procedural characteristics and outcomes in paroxysmal vs. persistent AF patients undergoing initial catheter ablation

3.3 Other objectives

- To review the peer-reviewed literature on recurrence of atrial arrhythmias in AF patients who have undergone catheter ablation, and compare our findings to other published results

Chapter 4

4   Methods

The methods for the current study are detailed in Chapter 5 as a section of the integrated article. To avoid duplication, below is a summary of the methodology along with additional information beyond the scope of the article.

4.1   Research Design

Data from an atrial fibrillation clinical database started in 2009 at Arrhythmia Service at University Hospital (London Health Sciences Centre) was used for this retrospective cohort study. Data was recorded from AF patients enrolled prior to catheter ablation and include patient, treatment, and follow-up factors. Patients were routinely followed up at 3, 6 and 12 months post-ablation. All patients provided both informed consent for the procedure and permission for their data to be used in research studies. This study was approved by Western University Ethics Board for Health Sciences Research and LHSC Lawson approval (see Appendix 1). Prior REB approval 17108E (ROMEO #7075) was obtained for the creation of the database.

4.2   Study population

All patients from the database were included in the current study who had either symptomatic paroxysmal or persistent AF, had failed at least one anti-arrhythmic drug (AAD), and had not previously had a cardiac ablation procedure.[1] Patients were not excluded on the basis of comorbid conditions, including underlying cardiovascular disorders or structural abnormalities (hypertension, coronary artery disease and cardiomyopathies). Patients were enrolled with procedures and follow-up between 2009 and 2013 who had at least one follow-up visit.

4.3   Procedure

All patients underwent a standard pulmonary vein isolation ablation under either general anesthetic or deep sedation. Using an electroanatomic mapping system, a 3D anatomic map of the left atrium was created to guide the procedure. Circumferential ablation lesions were made to encircle both left and right pulmonary vein ostia. If the patient had persistent AF, was in AF during the procedure and it did not terminate during ablation, supplementary ablation lines were created as necessary by the operator to achieve electrical conduction block across the LA roof and/or in the mitral isthmus, at the discretion of the physician. Ablation effect was confirmed by reduction of local electrogram amplitude by at least 50% and at least 60 seconds of ablation at each ablation site.

4.4   Follow up

Patients were followed on an ambulatory basis with clinical examinations at approximately 3, 6 and 12 months following the procedure. Clinic visits included ECG or 24-hour Holter monitor, symptom review and patient history updates. Additional clinical visits were scheduled if indicated by symptoms.

Arrhythmia-free survival was measured in days from the procedure until recurrence was documented or until censoring occurred. Data were censored at the last known follow-up visit in the outpatient clinic or at 400 days (one year with one month of run-out).

4.5   Variables investigated

Data was collected from patients at their first visit to the outpatient clinic prior to ablation and data was later verified by the research nurse against medical records.

4.5.1   Baseline sociodemographic and clinical data

Biological sex was recorded at the first arrhythmia clinic encounter prior to ablation. Patient age was derived as a whole number, in years, from the time between date of birth and procedure date. Type of AF was categorized as Paroxysmal AF (primarily

episodes that resolve within 7 days) and persistent AF (episodes continuing beyond 7 days).[1] Left atrial diameter (LAD) was measured (in mm) from echocardiography prior to ablation. Body mass index (BMI) was calculated as kg/m^2 from height (in cm) and weight (in kg) measurements at baseline. BMI was also analyzed as a categorical variable according to World Health Organization criteria: normal weight (BMI 18.5-25kg/m2), overweight (BMI 25-30 kg/m2) and obese (BMI greater than 30kg/m2).[3]

A measure of stroke risk, the $CHADS_2$ score, was calculated for each patient, with one point for each of: Cardiac Failure, Hypertension, Age >= 75, Diabetes, and two points for previous stroke or transient ischemic attack (TIA) for a theoretical range of 0 to 6. Because a small proportion of patients had higher scores, $CHADS_2$ scores were dichotomized as ≤ 1 (few risk factors; low risk of stroke) vs. ≥2 (more risk factors; higher risk of stroke).

Patients were asked about history of cormorbid conditions including hypertension, diabetes, prior stroke/TIA, coronary disease, cardiomyopathy, depression, alcohol use, sleep apnea and heart failure. Existing and previous health conditions were assigned as binary variables with yes or no responses.

4.5.2   Procedure-related variables

Procedure duration and fluoroscopy duration were each recorded during the procedure, in minutes. Additional areas for ablation were targeted if the patient was in AF during ablation and remained in AF after the initial pulmonary vein isolation, at the discretion of the treating physician. Specific targets include: LA roof line, CFAE, mitral isthmus line, tricuspid isthmus line. Cardioversion following the procedure was performed if patients remained in AF after substrate modification.

4.5.3   Healthcare-related

Wait time was calculated as months from the date the procedure was ordered to the scheduled procedure date, according the clinical records.

Anti-arrhythmia medications were discontinued prior to surgery. Because all patients had failed at least one medication, specific medications were not analyzed in this study.

4.6   Outcome

4.6.1   Recurrence

Recurrence was defined as at least one episode of documented atrial arrhythmia lasting more than 30 seconds at any time within the study period after one procedure. No blanking period was used in this study as there has been conflicting evidence of its validity. Therefore, arrhythmias were classified as recurrent even within the first few months of the procedure and patients who experienced recurrence were offered a second ablation.

4.6.2   Time to recurrence

Arrhythmia-free survival time was measured in days from procedure until recurrence was documented, or until censoring occurred. Patients were censored at their last visit to the outpatient clinic or at 400 days (one year with one month of run-out).

4.7   Statistical Analysis

All statistical analyses were performed in SAS v. 9.3.

Continuous variables were expressed as mean ± SD and categorical variables were expressed as counts and percentages. To compare paroxysmal and persistent AF patients at baseline, Student's *t*-test or the Wilcoxon rank-sum test were used to analyze continuous variables, as appropriate. Categorical variables were analyzed using the chi-squared test, or Fisher's exact test. Variables were tested for collinearity using Spearman correlations.

A Kaplan-Meier survival curve was created for the overall arrhythmia-free survival time. In univariable analyses, each clinical, procedural and healthcare-related variable was assessed for crude (unadjusted) association with recurrence. Continuous variables

were analyzed as both continuous and as categorical (dichotomized at the median). Cox proportional hazard regression models were then created to identify statistically independent predictors of procedural failure. Modelling was not 'data driven' (e.g. stepwise) but was guided by clinical knowledge. For example, likely confounders were identified and tested in models. These variables were determined from previous research, clinical experiences and face validity. All Cox proportional models tested were adjusted for age, sex, and type of AF regardless of significance level. Variables with $p \leq 0.2$ in univariable analyses were assessed in Cox proportional hazards models along with the identified confounders. The Cochran-Armitage trend test was used to test for an overall temporal trend with recurrence. Testing for temporal recurrence trends was a proxy to test the effect of operator experience. The level of statistical significance was set at 5 percent, two-tailed.

Linearity was tested by adding quadratic terms. To test the proportional hazards assumption, lambdas were inspected visually and tested with time-dependent covariates. In the results, the estimated effects of variables on AF recurrence are presented as hazard ratios (HR) and 95% confidence intervals (CI).

4.8   References

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Chapter 5

5 Integrated Article: Predictors of arrhythmia recurrence following catheter ablation for AF

Abstract

Background

Catheter ablation has emerged as more effective treatment for atrial fibrillation (AF) compared to anti-arrhythmic medications. Although the procedure continues to advance, recurrence of arrhythmias post-ablation remains high. Health care-related variables including wait time have not been explored as predictors of first ablation outcome. Wait times can be significant for non-urgent medical procedures in Canada.

Objectives

The primary objective was to identify patient, procedural, and health-care related factors associated with arrhythmia recurrences following catheter ablation for AF. The secondary objective was to compare baseline and procedural characteristics of patients with paroxysmal and persistent forms of AF.

Methods

314 consecutive patients with AF underwent first ablation for (83.4% paroxysmal AF, 16.6% persistent AF). Follow-up visits occurred at 3, 6 and 12 months. Variables and the outcome of recurrence were modeled with Cox proportional hazards analysis.

Results

After a mean follow-up of 239+/-125 days, 110 patients (35.0%) experienced arrhythmia recurrence after single ablation.

Adjusted Cox proportional hazards models demonstrated cardiomyopathy [HR (95% CI) = 1.97 (1.13-3.41)] was a predictor of arrhythmia recurrence. Conversely, height per cm

increase [HR (95% CI) = 0.96 (0.94-0.99)], and additional ablation targets [HR (95% CI) = 0.531 (0.29-0.98)] were associated with hazard reduction.

Conclusions

Clinical differences were observed in paroxysmal and persistent AF patients, though there was not a statistically significant difference in recurrence comparing these two groups. Cardiomyopathy and taller stature were predictive of recurrence. Targeted ablation outside the pulmonary veins when AF persisted beyond initial isolation was protective. Wait time for ablation was not associated with recurrence.

Predictors of arrhythmia recurrence after atrial fibrillation ablation

5.1 Background

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder. 1-2% of the population is affected by AF, and the prevalence increases with age.[1] In AF, chaotic electrical signals disrupt the normal conduction within the left atrium, resulting in irregular contractions of the cardiac chambers and potentially diminished cardiac output. AF increases the risk of stroke and is recognized as an independent predictor of morbidity and mortality in the setting of cardiovascular disease.[2]

AF can be classified as either paroxysmal or persistent. Paroxysmal AF is defined as recurrent episodes of AF resolving within 7 days.[3] Persistent AF is continuous AF lasting more than 7 days. However, the transient and often variable nature of AF poses limits to this categorization as patients can experience episodes of varying lengths. AF causes changes to the substrate of the atrium over time, creating an environment that favours AF.[4] Over time paroxysmal AF episodes can become longer-lasting and more difficult to treat, which indicates progression to persistent AF.[5]

The etiology of AF is incompletely understood. Triggers within the pulmonary veins have been implicated in the initiation and perpetuation of AF.[6] Catheter ablation has emerged as a treatment modality for symptomatic patients who have not responded to anti-arrhythmic medication.[7,8] AF ablation aims to electrically isolate the foci within the pulmonary veins from the left atrium. Electrical isolation of the PVs from the rest of the left atrium prevents the triggers from initiating AF.[9]

Catheter ablation aims to reduce the symptoms of AF by reducing or eliminating episodes and potentially changing sensory innervation which can reduce symptoms. Catheter ablation has not proven to reduce thromboembolic risk, whereas anticoagulation reduces the risk of stroke and is continued after ablation in patients who are at higher risk. Regardless of ambient risk, anticoagulation is prescribed for 1 month prior and 3 months after the ablation procedure to address the risk of clotting where ablation disrupts the integrity of the atrial surface. Though the procedure has been

refined over time, high recurrence rates following ablation remain a major challenge. Approximately 20-40% of patients experience arrhythmia recurrence after ablation.[10,11] PV reconnection, due to incomplete ablation, has been postulated by several studies to be the cause of early recurrences.[12,13] Many studies have justified the use of a "blanking period" of 1-3 months where recurrences may occur but are not counted as recurrences in the study until they occur beyond the blanking period. However, there is evidence to suggest early recurrence frequently results in later recurrence, questioning the use of such blanking periods.[14]

Identifying factors that contribute to the recurrence of arrhythmia is of clinical importance to reduce healthcare costs and avoid exposing patients to unnecessary procedures and related complications. Success rates have been lower in patients with persistent, compared to paroxysmal, AF even when a more aggressive ablation approach is used.[15] This is likely due to the electro-anatomical changes that result from long term and continuous AF.

Catheter ablation requires specialized skill and is performed in large health care centers.[16] The length of time waited for catheter ablation in has not been explored when determining predictors of recurrence. Lengthy wait lists result in treatment delays, which is often the case for non-urgent procedures in a single payer health care system. Paroxysmal AF can progress to persistent AF, which may then require extensive ablation to block conduction.[17]

Previous studies have identified many possible predictors of recurrence after ablation, though heterogeneous methodology and analyses have produced conflicting results. The primary objective of this study was to identify patient, procedural and health-care predictors of procedural failure following catheter ablation for AF. The secondary objective was to compare baseline and procedural characteristics of paroxysmal and persistent AF patients.

5.2   Methods

This study was a retrospective cohort design using data from a prospectively collected atrial fibrillation clinical database by the Arrhythmia Service, London Health Sciences Centre. The database was initiated in 2009 and contains data on patient demographics, medical history, treatment, and follow up. Demographic and clinical data were collected at the time of first consult. Patients were routinely followed-up at approximately 3, 6 and 12 months post-ablation. Patients were referred by family physician, internist or cardiologist from across Southwestern and Northern Ontario to London Health Sciences Centre, a regional referral centre for AF ablation. All patients provided both informed consent for the procedure and permission for their data to be used in research studies. This study was approved by Western University Ethics Board for Health Sciences Research.

5.2.1   Study population

All patients were included this study from the database who had either symptomatic paroxysmal or persistent AF, had failed to maintain sinus rhythm on at least one anti-arrhythmic drug (AAD), and had not previously undergone an ablation for cardiac arrhythmia. Patients were not excluded on the basis of comorbid conditions, including those with underlying cardiovascular disorders or structural abnormalities (hypertension, coronary artery disease and cardiomyopathies).

5.2.2   Procedure

Prior to the procedure, all antiarrhythmic drugs were discontinued and patients received anticoagulation for 1 month prior and 3 months after ablation to reduce the risk of periprocedural thromboembolic events. Under general anesthetic or deep sedation, patients underwent standard pulmonary vein ablation. Catheters were introduced into the right atrium, right ventricle, and coronary sinus from the right femoral vein. Transseptal puncture was performed under fluoroscopy to obtain access to the left atrium. A circular mapping catheter and ablation catheter were then advanced to the left atrium. To reduce thermal risk to the adjacent esophagus, an esophageal temperature

probe was inserted. In most cases, a 3D anatomic map was created using an electroanatomical mapping system of the left atrium integrated with previously obtained CT images. Circumferential ablation lesions were made to encircle left and right pulmonary vein ostia in pairs. If AF did not terminate during pulmonary vein isolation, supplementary ablation lines were created as necessary. Specific additional ablation approaches included: mitral isthmus line (from the mitral annulus to the left inferior pulmonary vein), LA roof line (connecting the superior pulmonary veins across the superior posterior wall of the left atrium), and ablation of complex fractionated atrial electrograms (CFAEs), or a combination of these procedures. Electrical signals were observed during ablation for reduction in amplitude by at least 50% and lesions were at least 60 seconds in duration. All procedures took place between January 2009 and May 2013.

5.2.3   Follow up

Patients were followed on an ambulatory basis in the arrhythmia service outpatient clinic. Patients underwent clinical examination at approximately 3, 6 and 12 months after the ablation procedure. Clinic visits included ECG, or 24-hour Holter monitor, symptom review, patient history and medication updates. 24-hour Holter monitors were used prior to 3- and 12-month visits. Event recorders were used prior to the 6 month clinic visit. Additional clinical visits were scheduled if indicated by symptoms.

Arrhythmia-free survival time was measured in days from the procedure until recurrence was documented or until censoring occurred. Data were censored at the last known follow-up visit in the outpatient clinic or at 400 days (one year with one month of run-out).

5.2.4   Recurrence

Recurrence was defined as at least one episode of documented arrhythmia (AF or atypical flutter) lasting more than 30 seconds at any time during follow-up. Atypical left atrial flutter was included in the recurrence definition.

A blanking period was not used in this study as there has been conflicting evidence for its validity. AF or atypical flutter at any time during follow up was recorded as procedural failure.

5.2.5   Variables investigated

5.2.5.1   Baseline sociodemographic and clinical data

Sociodemographic and clinical variables investigated included: age (in years), sex, height (in cm) and weight (in kg). Body mass index (BMI) was calculated (in kg/m^2) from baseline height and weight measurements. BMI is also expressed as a categorical variable according to the World Health Organization's categorization (Normal: <25 kg/m2, Overweight: 25–29.99 kg/m2, Obese ≥30 kg/m2).[18]

Type of AF was categorized as paroxysmal (episodes resolved within 7 days) or persistent (episodes persisted beyond 7 days).[3] Left atrial diameter (LAD) was measured (in mm) from echocardiography prior to ablation. CHADS2 scores were calculated for each patient (1 point each for Cardiac Failure, Hypertension, Age >= 75, Diabetes, 2 points for Stroke).[19] Due to small numbers of patients with higher scores, this variable was dichotomized as ≤1 and ≥2.

Patients were asked about their history of comorbid conditions including: hypertension, diabetes, prior stroke/transient ischemic attack (TIA), coronary disease, cardiomyopathy, depression, history of alcohol abuse, sleep apnea, and heart failure. Cardiomyopathy was defined as deterioration in the ability of the heart to contract. Although there are variants of cardiomyopathy, there was no distinction in type of cardiomyopathy in this study. Existing and previous health conditions were assigned as binary variables with yes or no responses.

5.2.5.2   Procedure-related variables

Procedural variables included: procedure duration (in minutes) and fluoroscopy duration (in minutes). If sinus rhythm was not achieved after pulmonary vein isolation, non-

pulmonary vein triggers were identified and targeted for ablation. Specific targets include: LA roof line, CFAE, mitral isthmus line, tricuspid isthmus line. Cardioversion following the procedure was performed if patients remained in AF post-ablation.

5.2.5.3   Healthcare-related variables

Wait time (in months) was calculated as the number of months from the date the procedure was ordered to the scheduled procedure date.

5.2.6   Statistical analysis

All statistical analyses were performed in SAS v. 9.3.

Continuous variables were expressed as mean ± SD and categorical variables were expressed as counts and percentages. To compare paroxysmal and persistent AF patients at baseline, Student's *t*-test or Wilcoxon rank-sum test were used to analyze continuous variables, as appropriate. Categorical variables were analyzed using the chi-squared test, or Fisher's exact test. Variables were tested for collinearity using Spearman correlations.

A Kaplan-Meier survival curve was created for the overall arrhythmia-free survival time. In univariable analyses, each clinical, procedural and healthcare-related variable was assessed for crude (unadjusted) association with recurrence. Continuous variables were analyzed as both continuous and as categorical (dichotomized at the median) in form. Cox proportional hazard regression models were then created to identify statistically independent predictors of procedural failure. Modelling was guided by clinical knowledge. Likely confounders were identified and tested in models. These variables were determined from previous research, clinical experiences and face validity. All Cox proportional models tested were adjusted for age, sex, and type of AF regardless of significance level. Variables with $p \leq 0.2$ in univariable analyses were assessed in Cox proportional hazards models along with identified confounders. The Cochran-Armitage trend test was used to test for an overall trend over time with recurrence. Testing for temporal recurrence trends was a proxy to test the effect of operator experience. The level of statistical significance was set at 5 percent, two-tailed.

Linearity was tested by adding quadratic terms. To test the proportional hazards assumption, lambdas were inspected visually and tested with time-dependent covariates. In the results, the estimated effects of variables on AF recurrence are presented as hazard ratios (HR) and 95% confidence intervals (CI).

5.3   Results

5.3.1   Baseline clinical characteristics

314 patients with AAD-refractory, symptomatic AF were included in this study. The mean patient age was 57.7+/-10.1 years, 27.1% were female, mean BMI was 29.7+/-5.1. Hypertension was present in 149 patients (47.45%), 12.4% had heart failure, and 10.8% had cardiomyopathy. Paroxysmal and persistent AF patients had similar baseline clinical and echocardiographic characteristics (Table 1), though persistent AF patients had a higher BMI (32.7+/-5.5 vs. 29.1+/-4.8, p < 0.0001), a larger left atrial diameter (47.5+/-5.8 vs. 41.2+/-5.5 mm, p < 0.0001), and more often had heart failure (28.9% vs. 9.2%, p < 0.0001).

5.3.2   Procedural and healthcare characteristics

The mean duration of wait from time of booking to procedure date was 8.3+/-4.3 months. The mean procedure duration was 231.2+/-59.3 minutes. Mean fluoroscopy duration was 21.8+/-12.5 minutes. Additional foci and atrial substrate modification were targeted for ablation in 76 patients (24.2%). These included LA roof line (16.0%), complex fractionated atrial electrograms (CFAEs) (11.8%), mitral isthmus line (3.2%), and the tricuspid isthmus line (20.4%). Ablation targets outside the PVs occurred more frequently in persistent compared to paroxysmal AF patients (78.9% vs. 13.4%, p < 0.0001).

5.3.3   Univariable analysis

After a mean follow-up duration of 239.5 +/- 125.0 days, 110 patients (35.0%) experienced arrhythmia recurrence after single PVI (see Figure 1). On univariable

analysis, the hazard of recurrence was not statistically significant for persistent vs. paroxysmal AF patients [HR (95% CI) = 1.22 (0.76-1.97), p=0.03]. Mean time waited to procedure, in months, was not associated with recurrence [HR (95% CI) = 0.99 (0.95-1.01), p=0.62]. Cardiomyopathy was the only variable associated with increased hazard of recurrence [HR (95% CI) = 1.77 (1.07-2.94), p=0.03]. Tests for temporal trends of recurrence by procedure year were not significant.

5.3.4   Multivariable analysis

The final Cox proportional hazards model included age, sex, type of AF, LA diameter, height, weight, cardiomyopathy, fluoroscopy duration and additional ablation targets (see Table 4). The multivariable analysis identified three variables as independent predictors of arrhythmia recurrence: height [HR per cm (95% CI) = 0.96 (0.94-0.99), p = 0.01], presence of cardiomyopathy [HR (95% CI) = 1.97 (1.13-3.41), p = 0.02], and additional ablation targets [HR (95% CI) = 0.53 (0.29-0.98), p = 0.04].

5.4   Discussion

5.4.1   Principal study findings

In the present study of 314 persistent and paroxysmal AF patients, cardiomyopathy, shorter height, and not requiring additional ablation to achieve sinus rhythm during the procedure were statistically independent predictors of recurrence. In the healthcare context, procedure wait time was not predictive of recurrence. The recurrence rate of persistent AF patients compared to paroxysmal AF patients did not reach statistical significance, though there were statistically significant differences in patient and procedural characteristics of these two groups. Comparing patients at baseline, a higher proportion of persistent compared to paroxysmal AF patients had AF risk factors including obesity and comorbid conditions.

5.4.2   Cardiomyopathy

Evidence regarding the efficacy of ablation for AF in cardiomyopathy patients is limited, and often it is an exclusion criterion in clinical trials. In a small study of 61 patients with

hypertrophic cardiomyopathy and AF, Di Donna and colleagues[20] found that 72% of patients who underwent catheter ablation experienced recurrence after a single procedure. High rates of recurrence were also observed by Santangeli et al[21] in a study of 43 AF patients with hypertrophic cardiomyopathy. After one procedure, 47% of patients had arrhythmia recurrence within one year. After long term follow-up of a median of 42 months, 51% of patients remained in AF, even after repeat procedures.

In the current study, 34 (10.8%) AF patients had cardiomyopathy, with a higher proportion observed among persistent compared to paroxysmal AF patients (17.3% vs. 9.5%), though statistical significance was not reached. Cardiomyopathy increased the hazard of recurrence and remained a statistically significant predictor of recurrence after adjustment in the multivariable model. The definition of cardiomyopathy in this study was broad and included different types. Although severity of disease may be different across patients due to the inclusive definition, the increased hazard of recurrence aligns with previous studies.

5.4.3   Height

Height has been implicated in incident AF. In a large cohort study of older US adults, Rosenberg and colleagues[22] found that independent of sex, increased height was significantly associated with the risk of incident AF. There is evidence to suggest tall stature may be associated with the initial development of AF, though the results from the current study suggest that recurrent AF is associated with shorter height. Increased height (per centimeter) was associated with a small reduction in hazard of arrhythmia recurrence after catheter ablation for AF.

5.4.4   Non-pulmonary vein ablation targets

Isolation of the pulmonary veins is the cornerstone of treatment in both paroxysmal and persistent patients. However, targeting additional ablation foci has not been consistently associated with reduced recurrence.[15,23] In the STAR AF II trial[23], persistent AF patients were assigned to one of three procedure variants: pulmonary vein isolation alone, or pulmonary vein isolation with the addition of either isolation of complex fractionated atrial electrograms or linear ablation across the left atrial roof and mitral valve isthmus.

No reduction in the rate of recurrent AF was detected when additional ablation areas were created in conjunction with pulmonary vein isolation.

In the current study, additional targets for ablation were guided by the persistence of AF after pulmonary vein isolation and not limited to a specific subset of patients. 24.2% of patients required additional targeted ablation to achieve sinus rhythm. Among these patients, 35/76 had paroxysmal AF (13.4% of paroxysmal patients) and 41/76 were persistent AF (78.9% of all patients with persistent AF) patients (p<0.0001). However, the addition of targeted ablation lesions was associated with nearly a 50% decrease in the hazard of recurrence [HR (95% CI) = 0.53 (0.29-0.98)]. Recurrence rates in paroxysmal patients compared to persistent patients did not reach statistical significance.

5.4.5   Procedure wait time

In the Canadian context, the absence of association with procedure wait time and recurrence of arrhythmia after catheter ablation suggests that even though patients waited a mean of 8.3 months, there was not enough evidence to suggest they are at increased risk of recurrence. As the population ages and more Canadians are affected by AF, wait times are likely to increase. It is relevant to understand this relationship to plan healthcare resources appropriately.

5.4.6   Limitations

Arrhythmia recurrence may have been underestimated in this study. Patients were not monitored continuously and therefore asymptomatic or nocturnal episodes may have been undetected. It is unlikely that short, asymptomatic episodes would be recorded at the regularly scheduled clinic visits. Event recorders were used prior to scheduled visits for each patient to collect more comprehensive data and minimize ascertainment bias. It is possible that events requiring patients to seek emergency medical attention were not captured, as data were not collected from outside departments or facilities. Therefore, the actual recurrence rate including minor episodes is almost certainly higher than

reported. However, the clinical significance of minor or asymptomatic episodes, and the bias posed by their omission, is unclear.

The technique for ablation was not uniform across all patients in the study population. All patients underwent PV isolation, though additional ablation areas were targeted at the discretion of the treating physician if sinus rhythm was not achieved through PV isolation alone.

This study is also limited by its observational nature. It was non-randomized and from a single center with a group of expert operators. Patients who were ultimately ablated and included in this study were chosen for the procedure by a physician. The number of patients excluded prior to ablation is uncertain.

Additional outcome measures, such as quality of life and AF-specific symptom assessment, would have provided more information about relevant outcomes after ablation. Ablation aims to reduce symptoms by eliminating AF altogether, though documented arrhythmia recurrences do not provide information on symptoms. Patients with documented arrhythmia post-ablation may still have an improved quality of life from a reduction of symptoms. Time to recurrence is just one method for evaluating procedural failure. Arrhythmia burden, or the frequency and severity of symptoms, may be an important factor to patients, though more difficult to assess clinically.

It is important to note that this study did not use a blanking period as some studies have previously. Several studies have found associations between early recurrences and later recurrences[24] and it is hypothesized that early recurrences are a result of incomplete ablation and thus should be counted as such.[25,26]

5.5   References

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Table 1: Baseline clinical characteristics of AF patients presenting for initial ablation

	All	Paroxysmal AF	Persistent AF	P value*
	(*n*=314)	(n=262)	(n=52)	
Age, years	57.7 (10.1)	57.9 (10.3)	57.0 (8.7)	0.57
Sex, female	85 (27.1%)	75 (28.6%)	10 (19.2%)	0.16
Weight, kg	92.0 (17.9)	89.7 (16.6)	103.8 (19.7)	<0.0001
Height, cm	176.0 (10.0)	175.6 (10.1)	178.0 (9.2)	0.11
BMI, kg/m^2	29.7 (5.1)	29.1+/-4.8	32.7 (5.5)	<0.0001
BMI category				<0.0001
Normal weight	54 (17.2%)	49 (18.7%)	5 (9.62%)	
Overweight	129 (41.1%)	118 (45.0%)	11 (21.2%)	
Obese	131 (41.7%)	95 (36.3%)	36 (69.2%)	
LA diameter, mm	42.3 (6.0)	41.2 (5.5)	47.5 (5.8)	<0.0001
CHADS2 score, dichotomized				0.52
0 or 1	246 (78.3%)	207 (79.0%)	39 (75.0%)	
More than 1	68 (21.7%)	55 (21.0%)	13 (25.0%)	
Comorbid conditions				
Hypertension	149 (47.45%)	121 (46.2%)	28 (53.85%)	0.31
Diabetes	31 (9.9%)	23 (8.8%)	8 (15.4%)	0.14
Prior stroke/TIA	32 (10.2%)	29 (11.1%)	3 (5.8%)	0.25
Coronary disease	17 (5.4%)	12 (4.6%)	5 (9.6%)	0.14
Cardiomyopathy	34 (10.8%)	25 (9.5%)	9 (17.3%)	0.10

Depression	10 (3.2%)	8 (3.1%)	2 (3.9%)	0.77
History of alcohol use	17 (5.4%)	13 (5.0%)	4 (7.7%)	0.43
Sleep apnea	39 (12.4%)	29 (11.1%)	10 (19.2%)	0.10
Heart failure	39 (12.4%)	24 (9.2%)	15 (28.9%)	<0.0001

Data expressed as mean (SD) or count (%) of patients

*P≤0.05 considered statistically significant

Table 2 - Procedural characteristics of initial ablation procedure in paroxysmal and persistent AF patients

	All	Paroxysmal AF	Persistent AF	P value*
	(*n*=314)	(n=262)	(n=52)	
Procedure duration, min	231.2 (59.3)	224.5 (55.5)	264.6 (66.8)	<0.0001
Fluoroscopy duration, min	21.8 (12.5)	21.2 (12.7)	24.5 (11.4)	0.09
Additional targets ablated	76 (24.2%)	35 (13.4%)	41 (78.9%)	<0.0001
LA roof line	50 (16.0%)	25 (9.5%)	25 (48.1%)	<0.0001
CFAE	37 (11.8%)	14 (5.3%)	23 (44.2%)	<0.0001
Mitral isthmus line	10 (3.2%)	4 (1.5%)	6 (11.4%)	0.002
Tricuspid isthmus line	64 (20.4%)	53 (20.2%)	11 (21.2%)	0.88
Cardioversion required post-ablation	18 (5.7%)	8 (3.1%)	10 (19.2%)	<0.0001
Wait time, months	8.3 (4.3)	8.4 (4.4)	7.7 (3.6)	0.28

Data expressed as mean (SD) or count (%) of patients

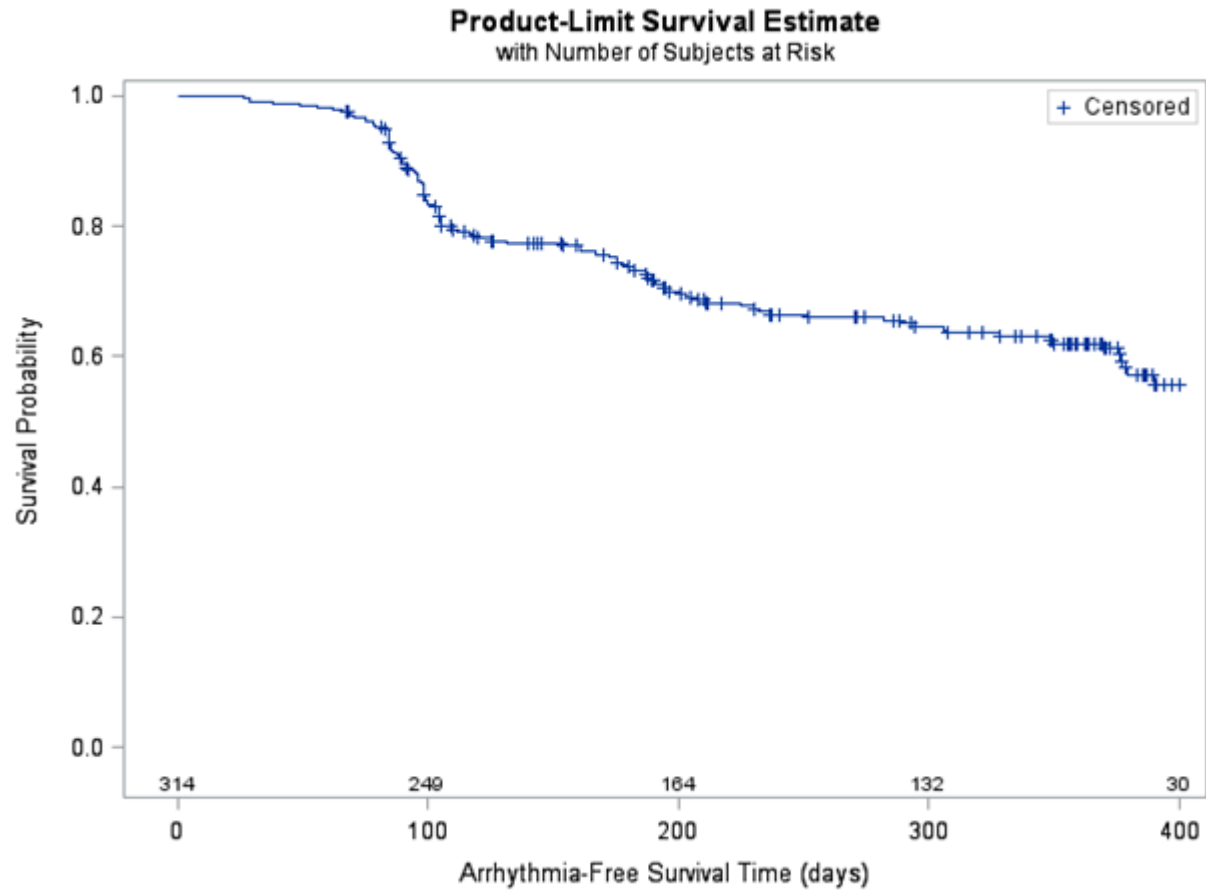*P≤0.05 considered statistically significant

Figure 1 Kaplan-Meier survival curve: Freedom from recurrence after initial AF catheter ablation

Table 3. Univariable analysis of clinical, procedural and healthcare-related variables and their association with recurrence

	HR (95% CI)	*P* value
Age, years	1.00 (0.98-1.01)	0.65
age > median	0.92 (0.63-1.34)	0.67
Sex, female	1.12 (0.73-1.70)	0.61
Persistent AF	1.22 (0.76-1.97)	0.41
Weight, kg	1.00 (0.99-1.01)	0.59
weight > median	1.05 (0.72-1.53)	0.80
Height, cm	0.99 (0.97-1.00)	0.11
height > median	0.69 (0.46-1.02)	0.06
BMI, kg/m^2	1.03 (0.99-1.07)	0.11
BMI>median	1.15 (0.79-1.68)	0.46
BMI category		
Normal weight	1.0 (reference)	--
Overweight	1.35 (0.75-2.42)	0.31
Obese	1.63 (0.91-2.90)	0.10
LA diameter, mm	1.02 (0.98-1.05)	0.33
LA diameter>median	1.00 (0.69-1.45)	1.00
CHADS2 score	1.26 (0.82-1.95)	0.29
Comorbid conditions		
Hypertension	1.03 (0.71-1.50)	0.88
Diabetes	1.26 (0.69-2.30)	0.45
Prior stroke/TIA	0.97 (0.52-1.81)	0.92

Coronary disease	1.10 (0.48-2.50)	0.83
Cardiomyopathy	1.77 (1.07-2.94)	0.03
Depression	1.24 (0.46-3.38)	0.67
History of alcohol abuse	1.66 (0.84-3.28)	0.15
History of smoking	1.28 (0.84-1.94)	0.26
Sleep apnea	1.28 (0.74-2.21)	0.38
Heart failure	0.99 (0.56-1.77)	0.98
Procedure duration, min	1.00 (1.00-1.00)	0.51
Duration>median	1.23 (0.85-1.80)	0.27
Fluoroscopy duration, min	1.02 (1.00-1.03)	0.02
Fluoroscopy time>median	1.27 (0.87-1.86)	0.21
Additional targets ablated	0.89 (0.56-1.40)	0.60
LA roof line	0.82 (0.47-1.43)	0.47
CFAE	0.82 (0.44-1.54)	0.54
Mitral isthmus line	0.97 (0.36-2.63)	0.95
Tricuspid isthmus line	1.37 (0.90-2.10)	0.14
Cardioversion required post-ablation	1.51 (0.70-3.25)	0.29
Wait time, months	0.99 (0.95-1.03)	0.62
months waiting > median	0.86 (0.59-1.25)	0.43

HR= Hazard ratio

Table 4. Adjusted Hazard Ratios (HR) from multivariable Cox proportional hazards model

	HR (95% CI)	*P* value
Age, years	0.99 (0.97-1.01)	0.49
Sex, female	0.76 (0.41-1.42)	0.39
Persistent AF, present	1.44 (0.76-2.70)	0.26
LA diameter, mm	1.02 (0.98-1.05)	0.43
Height, cm	0.96 (0.94-0.99)	0.01
Weight, kg	1.00 (0.99-1.02)	0.55
Cardiomyopathy, present	1.97 (1.13-3.41)	0.02
Fluoroscopy duration, min	1.02 (1.00-1.03)	0.01
Additional ablation areas targeted to achieve sinus rhythm, yes	0.53 (0.29-0.98)	0.04

HR= Hazard ratio

Chapter 6

6 Discussion

The current study included 314 patients with drug-refractory paroxysmal or persistent AF who underwent first catheter ablation. Clinical, procedural, and health care –related factors were evaluated to assess their association with arrhythmia recurrences following ablation. Cardiomyopathy and shorter stature were predictive of recurrence. Targeted ablation of areas outside the pulmonary veins when AF persisted beyond the isolation of the pulmonary veins was a protective factor. There was not enough evidence to suggest a difference in the recurrence rate of paroxysmal compared to persistent AF patients. Wait time for the procedure was not associated with recurrence.

6.1 Cardiomyopathy

Cardiomyopathy presents a challenge for the long term success of catheter ablation for AF, as observed in this study. Cardiomyopathy was an independent predictor of recurrence. This is complicated by the fact that AF is much more common in patients with hypertrophic cardiomyopathy compared to the general population (25% vs. 1-2%).[1] In the current study, 34/314 (10.8%) patients had cardiomyopathy. A higher proportion of persistent patients had concurrent cardiomyopathy (17.3%) in comparison with paroxysmal AF (9.5%), though it did not reach statistical significance. The definition of cardiomyopathy in the current study was inclusive to different types of cardiomyopathies, though variations have similar symptoms and all affect the ability of the heart muscle to contract. However, variation in disease severity may exist.

Evidence regarding the efficacy of ablation for AF in cardiomyopathy patients is limited, as comorbid conditions are often excluded from clinical trials. In this study, AF patients with cardiomyopathy had increased hazard of recurrence and remained a statistically significant predictor of recurrence after adjustment in the multivariable model. A multicenter study consisting solely of cardiomyopathy patients with AF, Di Donna and colleagues found that 44 of 61 patients (72%) experienced recurrence after the first procedure.[2] After a subsequent ablation in 32 patients, the overall recurrence rate was

33%. In that study, multivariable Cox regression models indicated the independent predictors of AF recurrence were increased left atrial volume and New York Heart Association (NYHA) functional class, which classifies heart failure according to symptom severity. The current study did not include NYHA functional class, though it may have provided additional information about the severity of cardiomyopathies among AF patients.

Santangeli et al[3] also observed high rates of recurrence among patients with cardiomyopathies. In a small study of 43 AF patients with hypertrophic cardiomyopathy, 47% of patients had arrhythmia recurrence within one year after a single procedure. AF triggers outside the pulmonary veins were identified in all patients and were responsible for late recurrences during subsequent re-ablation. In the present study, AF triggers outside the pulmonary veins were identified and ablated when AF continued after the initial isolation of the pulmonary veins. Though after adjusting for cardiomyopathies, additional ablation reduced the hazard of recurrence in the current study.

6.2   Body size

The results of this study suggest increased height (per centimeter) was associated with reduced hazard of recurrence after catheter ablation. Height was consistently associated with recurrence, even after adjustment.

Height has been implicated in the development of AF, though taller stature has been associated with the initial development of AF. Rosenberg and colleagues[4] found that after adjustment for sex, increased height was significantly associated with the risk of incident AF. In modeling the risk of AF development, they found that the higher risk among males was completely attenuated for by the inclusion of height. However, no such relationship has been observed between height and recurrence of AF in patients who have undergone catheter ablation.

A significant proportion of patients in this study were overweight and obese. Indeed, 82.8% of the patients in this study were overweight or obese, according to the WHO defined body mass index categories.[5] The mean BMI of patients in this study was 29.7

kg/m^2, which is nearly obese. Overweight and obese categories of BMI each had an increase in hazard of recurrence compared to the normal BMI category, though statistical significance was not reached. Therefore, there was not enough evidence to suggest BMI was associated with arrhythmia recurrences following catheter ablation in the current study. A larger sample size may have yielded significant results. The elevated BMIs found in AF patients in this study are similar to those observed in population-based studies of incident AF.[6]

Tedrow and colleagues[7] observed a large cohort of women and found that the risk of incident AF was linearly associated with increasing BMI. Among women who became obese during the study period, there was a 41% increase in AF development, compared to non-obese women. The risk of AF among those who became obese exceeded that of the women who were obese at baseline and remained obese. Importantly, those who were obese and decreased their BMI below 30 did not differ from the risk of non-obese women at baseline who remained non-obese. This study suggests a reversibility of obesity-associated AF risk increase. Rosengren et al[8] came to the same conclusion in a cohort of males. Risk factor reduction plays an important role in mitigating the development of AF, though little is known about whether it plays a role in reducing AF recurrence.

To understand the impact of risk factor reduction on AF patients who had undergone catheter ablation, Pathak and colleagues[9] compared AF patients enrolled in a clinical risk factor management therapy program and those who were given information on risk factor management. Management was aimed at aggressively treating and managing blood pressure, weight, cholesterol, blood sugar for diabetics, sleep apnea, smoking, and excessive alcohol use. Patients enrolled in risk factor management therapy experienced better long term outcomes after catheter ablation on both first procedure and last procedure they underwent for catheter ablation. Reductions in left atrial volumes were observed in both groups. They concluded that the modification of risk factors that promote atrial substrate changes associated with AF can help maintain sinus rhythm post-ablation. However, the study aggressively aimed to reduce all risk factors at once, so it does not provide insight to the relative contribution of each

individually. It does provide evidence to suggest AF patients may achieve better outcomes through positive lifestyle changes. Similarly, a recent study observed that weight reduction and risk factor management in overweight individuals with AF resulted in a reduction of the AF symptom burden.[10] Body mass was not measured over time in this study and it is not known whether changes in body mass may have an effect on recurrence after cathether ablation for AF.

6.3 Non-pulmonary vein ablation targets

While pulmonary vein isolation is the cornerstone of treatment in both paroxysmal and persistent patients, targeting additional foci outside the pulmonary veins has not been consistently associated with reduced recurrence.[11, 12] Verma et al did not find a benefit associated with performing additional ablation lesions in persistent AF patients.[13] In that study, patients were randomly assigned to receive either pulmonary vein isolation alone or combined with ablation of CFAEs or linear ablation of the left atrial roof and mitral valve isthmus.

The present study targeted the same areas for ablation as the study by Verma et al[13] though only when arrhythmia persisted after standard pulmonary vein isolation. The addition of targeted ablation lesions to select patients was associated with nearly a 50% decrease in hazard of recurrence [HR (95% CI) = 0.53 (0.29-0.98)]. This finding is similar to that of on-treatment analysis of the CONFIRM trial, which suggested fewer AF recurrences when all ectopic sources are eliminated, with a graded increase in recurrence of arrhythmia with more sources missed.[14] Likewise, Gaita and colleagues, found that the addition of linear ablation lesions resulted in a lower recurrence rate in both paroxysmal and persistent AF patients compared to pulmonary vein isolation alone.[15]

Clinically relevant conclusions may be drawn about the optimal ablation strategy in these patients. Ablation in addition to the pulmonary veins was associated with a statistically significant arrhythmia-free survival benefit in the current study. However, assigning patients to receive additional ablation without evidence to suggest conduction

outside the pulmonary veins may not be an ideal ablation strategy. More extensive ablation can cause scarring and may be pro-arrhythmic. Indeed, areas of incomplete ablation or where conduction block has not been achieved may promote arrhythmia recurrence.[16]

6.4　　Type of atrial fibrillation

Most published studies of catheter ablation have involved patients with paroxysmal AF. Small studies of persistent AF have reported higher recurrence rates than those in studies of paroxysmal AF.[17, 18] Catheter ablation in patients with persistent AF remains controversial. Although there were differences in paroxysmal and persistent AF patients at baseline, there was no evidence of a statistically significant difference in hazard of recurrence in persistent compared to paroxysmal AF in crude or adjusted models examined. While a large variety of approaches to PVI exist for persistent AF patients, recurrence rates have varied drastically from as low as 9% to 92%.[19, 20]

6.5　　Wait time

To the best of our knowledge, this is the first study we are aware of that examined waiting time as a predictor of recurrence in catheter ablation for AF. In the Canadian context, the absence of association with procedural wait time and recurrence of arrhythmia after catheter ablation suggests that even though patients are waiting a mean duration of 8.3 months, 5 months longer than the recommended Canadian target for ablation procedures, they are not at increased risk of recurrence. As the population ages and more Canadians are affected by AF, wait times are likely to increase. It is relevant to gain insight on this relationship to plan healthcare resources appropriately.

The measure included in this study only included the duration of time from the scheduling date to the ablation date. It does not account for the duration of time waited prior to the decision to ablate, which may be highly variable.[21] Knudtson et al[22] have proposed that it is likely that patients face the greatest wait-related risk in the earlier phases of care, before the disease is adequately characterized. The complex pathway to ablation includes several individual time intervals, including access to primary care,

access to specialist consultation, the decision to treat (including wait time for diagnostic tests and subsequent consultations), and finally, the wait time to ablation. I this study, only the final interval was included for analysis. By measuring different wait times, it may be possible to examine where in the healthcare pathway the wait times are unacceptable or may be contributing to inferior patient outcomes.

6.6   Impact of definitions

6.6.1   Recurrence

The definition of recurrence is heterogeneous in the existing literature. It is possible that the definition of outcome impacted the results of the study. A "blanking" period of 1-3 months following ablation is sometimes used in studies, which allows patients to experience recurrence without identifying them as procedural failures. However several studies have found associations between early recurrences and later recurrences.[23] It is hypothesized that early recurrences are a result of incomplete ablation and subsequent re-conduction.[24, 25] Therefore, allowing blanking periods may underestimate the true recurrence rate. Documented AF or atypical flutter any time post-ablation was considered recurrence of arrhythmia in this study. A blanking period was not used.

Including only AF recurrence, instead of atypical flutter and AF, a lower overall recurrence rate would have been reported. Different results in the literature may be partially attributable to the definitions used in each particular study. Definitions may be further complicated by not counting recurrences if sinus rhythm could be maintained on anti-arrythmia medications following ablation.

6.6.2   Type of atrial fibrillation

Although there is agreement in the general definitions of paroxysmal and persistent AF, there are variations in how it can be clinically defined. Paroxysmal AF consists of recurrent episodes of AF resolving within 7 days, while persistent AF is continuous beyond 7 days.[26] However, the transient and often variable nature of AF poses limits to this categorization as patients can experience episodes of varying lengths. Additionally,

AF causes changes to the substrate of the atrium over time, creating an environment that favours AF.[27, 28] Paroxysmal AF can progress to persistent AF and may not be captured in observational or retrospective studies of clinical records. Differences in studies may be partly due to the somewhat subjective categorization of AF type. Without continuous monitoring, AF classification is based on clinical evaluations, patients' symptoms and short-term monitoring.

6.7   Limitations

This study included a relatively large number of patients, though some baseline characteristics had small counts. Ablation is constantly evolving, and although this center experienced no major changes in ablation equipment, the procedure itself is constantly being refined.

Arrhythmia recurrence may have been underestimated in this study. Patients were not continually monitored and asymptomatic recurrences may not be recorded at regularly scheduled clinic visits. Therefore, the actual recurrence rate may be higher than reported due to imperfect monitoring. 24-hour Holter, or loop event recorders were used to assess the rhythm status of patients at each follow-up visit. Events that occurred outside monitoring in a different facility or in an emergency room setting would not be captured. Data was not collected outside the department. Only documented arrhythmia events were included as failures. More aggressive monitoring may have captured more recurrences, but in the absence of symptoms, there is little evidence that these events are clinically significant.

This study is also limited by its observational nature. It was non-randomized and from a single center with a group of expert operators. Patients who were ultimately ablated and included in this study were chosen for the procedure by a physician. The number of patients excluded prior to ablation is uncertain, as is the reason.

Additional measures of outcomes, such as quality of life, arrhythmia burden, and AF-specific symptom assessment, would have provided more information about relevant outcomes after ablation. Documented arrhythmia recurrences do not provide

information on symptoms. Even patients with documented arrhythmia post-ablation may have an improved quality of life from a reduction of symptoms.

6.8   Clinical Implications

An optimal strategy for the ablation of AF has yet to be established. This study provides additional evidence in support of a tailored approach for catheter ablation. All patients underwent PVI, though additional triggers were identified and ablated if sinus rhythm was not achieved after PVI alone. However, because not every patient underwent the same procedure, the individualized nature of the procedure itself may have affected the results of this study, though the results are comparable to previous studies.

Bottoni and colleagues[29] recently published the results from a multicenter study of 218 patients who had failed one or more attempts at catheter ablation for either paroxysmal or persistent AF over a ten year period. Although the ablation strategy changed over the study period, the results suggest that after failed catheter ablation and the subsequent initiation of other antiarrhythmic therapies, only 15% of patients reported worse outcomes compared to their pre-ablation period. A drawback to this study is that pre-ablation status was self-reported and subject to recall bias as the mean time since ablation was 5 years. However, it is still indicative that patients had a positive outlook after ablation for AF. Similarly, Wokhlu et al[30] found quality of life improvements at 2 years post-ablation in patients with and without recurrence.

Because of the high recurrence rates still observed in AF patients following ablation, it is important to balance patient characteristics, symptoms and risks of ablation. Stratification by factors may help with patient selection for the procedure and to inform the risk-benefit ratio.

6.9   References

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Appendices

1. Ethics Approval

LAWSON HEALTH RESEARCH INSTITUTE

FINAL APPROVAL NOTICE

RESEARCH OFFICE REVIEW NO.: R-12-336

PROJECT TITLE: Development of a clinical predictive model for arrhythmia recurrence following pulmonary vein isolation for atrial fibrillation

PRINCIPAL INVESTIGATOR: Dr. Lorne Gula

DATE OF REVIEW BY CRIC: August 22, 2012

Health Sciences REB#:   102765

Please be advised that the above project was reviewed by the Clinical Research Impact Committee and the project:

Was Approved

PLEASE INFORM THE APPROPRIATE NURSING UNITS, LABORATORIES, ETC. BEFORE STARTING THIS PROTOCOL. THE RESEARCH OFFICE NUMBER MUST BE USED WHEN COMMUNICATING WITH THESE AREAS.

Dr. David Hill
V.P. Research
Lawson Health Research Institute

All future correspondence concerning this study should include the Research Office Review Number and should be directed to Sherry Paiva, CRIC Liaison, Lawson Health Research Institute, 750 Baseline Road, East, Suite 300.

cc: Administration

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Poster Presentations:

Thomas K, Wright GA, Skanes AC, Klein GJ, Gula LJ. The use of Ibutelide to Improve Atrial Fibrillation Ablation Outcomes. Poster presentation. Vascular (Canadian Cardiovascular Conference), Montreal, Canada. October 18, 2013.

Wright GA, Thomas K, Skanes AC, Klein GJ, Gula LJ. Is body habitus a risk factor for atrial fibrillation and does it affect outcome of AF ablation? Poster presentation. Vascular (Canadian Cardiovascular Conference), Montreal, Canada. October 18, 2013.