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A retrospective analysis of patients with AF and HF undergoing treatment with Drug Therapy vs Catheter ablation: *Which was better?*

THESIS

submitted in partial satisfaction of the requirements

for the degree of

MASTER OF SCIENCE

in Biomedical and Translational Science

by

Jennifer Maffre

Thesis Committee:

Professor Dr. Sheldon Greenfield, Chair

Professor Dr. Sherrie Kaplan

Associate Professor Dr. John Billimek

2018

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DEDICATION

To my kids, Mateo and Isa,

"*Nothing worth having comes easy*" -Theodore Roosevelt.

To my husband, parents, and my friends

humbled and grateful of their support in this endeavor

You make me possible.

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List of Abbreviations

Abbreviation	Definition
AF	Atrial Fibrillation
CCAE	Commercial Claims and Encounters
CCI	Deyo-Charlson Comorbidity Index
$CHADSVASC_2$ score	Score evaluated ischemic stroke risk in AF patients
CHF or HF	Congestive heart failure or HF
COPD	Chronic Obstructive Pulmonary Disease
CV	Cardiovascular
DRRA	Database Related Research Activity
GEE	Generalized estimating equation
HEMA	Health Economics and Market Access
HF	Heart Failure
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
IHD	Ischemic heart disease
IRB	Institutional Review Board
HFpEF	Preserved ejection fraction
HFrEF	Reduced ejection fraction
LVEF	Left ventricle ejection fraction
MI	Myocardial Infarction
OSA	Obstructive Sleep Apnea
PS	Propensity Score
PCD	Primary cillary dyskinesia
PVD	Peripheral vascular disease
TIA	Transient Ischemic Attack

LIST OF FIGURES AND TABLES

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ABSTRACT OF THE THESIS

A retrospective analysis of patients with AF and HF undergoing treatment with Drug Therapy vs Catheter ablation: Which was better?

By: Jennifer Maffre

Master of Science in Biomedical and Translational Science

University of California, Irvine, 2018

Professor Dr. Greenfield Irvine, Chair

Background: Atrial fibrillation (AF) and heart failure (HF) are common cardiac disorders associated with substantial morbidity, mortality, and economic cost. AF can lead to HF, and HF can lead to AF.

Hospital admissions for heart failure (HF) have been increasing over the past decade due to an aging population as well as longer survival of patients with chronic heart disease. Atrial fibrillation (AF) is present in up to 50% of patients with HF and both are associated with several common predisposing risk factors and a shared pathophysiology[1]

Patients with these two diseases may encounter conflicting opinions from physicians based on guidelines on what is the most effective disease management and treatment strategy. Treating AF to restore sinus rhythm has been shown to positively affect long and short-term outcomes in patients suffering from HF. Prospective studies have compared catheter ablation with rate or rhythm control drugs for AF treatment among patients with HF and between the studies had found the former approach to be superior

to the latter. One of the largest electrophysiology studies to date, is the Catheter Ablation versus Antiarrhythmic drug therapy for Atrial fibrillation (CABANA) trial. This study randomized more than 2,000 patients to either catheter ablation or drug therapy. It demonstrated catheter ablation as not having a clinical benefit in patients with heart failure. On the other hand, a second multicenter randomized controlled trial, showed that for patients suffering from heart failure, catheter ablation for treatment was associated with a significantly lower rate of death from any cause or hospitalization for worsening heart failure than drug therapy.[2] This proposed study aims to provide real-world evidence (RWE) on the treatment options and examine whether or not catheter ablation emerges as superior to drug therapy in a real-world setting.

Objectives: Compare the outcomes between two cohorts: ablation or drug therapy. Outcomes included inpatient admissions (all-cause, cardiovascular and AF), direct current cardioversions and treatment costs in the 12-month post-index period.

Methods/Study design: A retrospective analysis was performed on all adults with a primary or secondary diagnosis of HF and AF in an inpatient or outpatient setting between January 1, 2011 and September 30th, 2016. These patients were identified from the Truven Health MarketScan® Commercial Claims and Encounters (CCAE) (IBM Truven Health Analytics, Ann Arbor, MI). The index episode was defined as their first database recording with HF, defined as the patient's index date.

A search strategy, using hospital charge codes, allowed for creation of two separate treatment cohorts: catheter ablation cohort or drug cohort. The catheter ablation cohort consisted of a) patients who were >18 years of age, b) patients with a primary procedure of ablation in an inpatient setting with a primary diagnosis of AF and a secondary diagnosis of HF in an inpatient setting OR c) primary diagnosis of HF and a secondary diagnosis of AF in an inpatient setting. For the ablation arm, those who had a previous catheter ablation in the 12 month pre- index date or did not have continuous insurance coverage 12- month post index date were removed.

The drug therapy arm consisted of: a) patients >18 years of age, b) had a primary or secondary diagnosis of AF AND c) used a rhythm or rate control drug from 2011 to 2016 . Patients who had a catheter ablation procedure 12-month pre or post their index date were removed from the arm and considered for the ablation arm.

Statistical analysis was performed to assess outcomes. A propensity score matching was run comparing catheter ablation versus drug therapy on all study outcomes: inpatient admissions (all-cause, cardiovascular and AF) direct current cardioversions and financial costs. Separate Logistic regression models were estimated for all-cause, CV-related, and AF-related admissions) and a generalized linear model was estimated for the cost outcome.

Results

A total of 1,225,988 patients were assessed for eligibility, including HF as a primary or secondary diagnosis. Of those, 169, 846 also had a primary or secondary diagnosis of

AF. There were 9, 522 patients that qualified for the ablation cohort. Of this group 65% (6, 191) were retained after primary and secondary diagnosis exclusions were applied as well as all other exclusions regarding age, and previous surgeries. The drug cohort included 45, 748 patients. Following application of exclusion and inclusion criteria, there were 24, 265 remaining in this group.

The propensity score matched (5,800 Ablation Group and 5,800 Drug Therapy) patients were included in the sub-analysis. The Ablation group had significantly lower odds of all-cause (odds ratio [OR] 0.393; 95% CI 0.206 - 0.747) and cardiovascular-related readmissions (OR 0.269; 95% CI 0.096- 0.754), and lower events of DCCV (OR 0.57; 95% CI 0.35–0.93) than those patients in the Drug therapy group.

Conclusion

In conclusion, comparing catheter ablation with drug therapy in HF patients treated for atrial fibrillation, catheter ablation was associated with lower odds of all-cause inpatient readmission. Patients treated with catheter ablation showed at 12-months to have a reduction in burden of atrial fibrillation in forms of lower re-admission rates (All causes, AF/CV-related) and reduced number of direct current cardioversions. There was no significant difference in costs for either group.

CHAPTER 1

Introduction

THE BACKGROUND AND FOUNDATION FOR THIS ANALYSIS

Hospital admissions for heart failure (HF) have been increasing over the past decade due to an aging population as well as longer survival of patients with chronic heart disease.[3] Atrial fibrillation (AF) is present in up to 50% of patients with HF and both are associated with several common predisposing risk factors and a shared pathophysiology [1] AF is the most common cardiac arrhythmia of clinical significance with an estimated prevalence of >33 million individuals globally.[4]

Treating AF, restoring sinus rhythm has shown to positively affect long and short-term outcomes in patients suffering from HF. Prospective studies have compared catheter ablation with rate or rhythm control drugs for AF treatment among patients with HF, and found the former approach to be superior to the latter. One of the largest studies to date, the CABANA trial (**C**atheter **Ab**lation versus **An**tiarrhythmic drug therapy for **A**trial fibrillation)[5] with over 2000 patients (n= 2204) randomized to either catheter ablation or drug therapy with a follow up of 5 years, showed that catheter ablation did not have a clinical benefit in patients with heart failure but catheter ablation participants showed a significant improvement in overall health defined as a positive change in self-assessment scores from MAFSI and AFEQT scores as compared to baseline.

Within the same timeframe, results from the CASTLE-AF trial, a different randomized control trial (n=397pts) with a follow up of 3 years, comparing ablation (n=200) to drug therapy (n=197) for AF treatment among patients with HF found the ablation group to have a significantly lower mortality rate, decreased incidence of hospitalization for worsening of heart failure, and decreased rate of death from cardiovascular causes in the catheter ablation group.[2] Therefore, it is possible that patients suffering from diseases may encounter conflicting guidelines on what is the most effective disease management and treatment strategy. Although several studies[1,2,6–8] ranging from a large observational study (n=100 pts) to a moderately sized prospective randomized trial (n=167) have found ablation treatment to be superior to drug therapy among patients with HF, real-world evidence comparing the two treatment modalities (ablation vs drug therapy) is limited and conflicting.

THE GAP

The proposed study aims to provide real-world evidence regarding the treatment options and examine if catheter ablation emerges superior to drug therapy in patients suffering from both AF and HF. The hypothesis is to understand from patients being treated with either therapy who will have the better outcome. In the following paper, I will explore the methods and results used to examine a medical claims database to segment into two groups treated with either drugs or catheter ablation and how that treatment affected a patients one year results. The current literature at the time of my analysis did not have an analysis of real world treatment results in this current patient

population nor interpret how this treatment affects patient's readmission rates or overall costs to the healthcare system.

CHAPTER 2 Background

Atrial fibrillation (AF) and congestive heart failure (HF) have been called the "two new epidemics of cardiovascular disease."[1] Atrial fibrillation and congestive heart failure are common cardiac disorders associated with substantial morbidity, mortality, and economic cost. AF can lead to HF, and HF can lead to AF. Patients with these two diseases may encounter conflicting guidelines on what is the most effective disease management and treatment.[2-5] Treating AF, restoring sinus rhythm has shown to positively affect long and short-term outcomes in patients suffering from HF.[6] Congestive heart failure was a powerful independent predictor of the occurrence of AF in the Framingham Study, in both symptomatic and asymptomatic LV dysfunction patients [9]

Prospective studies have compared catheter ablation with rate or rhythm control drugs for AF treatment among patients with HF and found the former approach to be superior to the latter, yet drugs are still the primary route for treatment in these patients. The largest study to date, the CABANA trial (Catheter Ablation versus Antiarrhythmic drug therapy for Atrial fibrillation) with n= 2204 patients randomized to either catheter ablation or drug therapy showed that catheter ablation did not have a benefit in patients with heart failure. Less than a year prior, results from a different multicenter randomized controlled trial CASTLE-AF, showed that specifically for

patients suffering from heart failure, catheter ablation (n=200) for treatment was associated with a significantly lower rate of death from any cause or hospitalization for worsening heart failure than drug therapy (n=197).[2]

Heart failure is straightforward in its mechanism. It is the hearts inability to pump blood outside of the heart. It is mainly caused by cardiovascular disease that inhibits the flow of blood to the heart. The heart muscle becomes stiff and therefore cannot contract enough to push blood out into circulation. Combine this with electrical abnormalities such as atrial fibrillation, the heart not only receives insufficient blood, its contractility is compromised due to the irregularity in electrical firing from the cardiac cells. This fibrillation and lack of enough blood to and from the heart lead to a list of clinical complications. Mortality and morbidity are higher among patients with atrial fibrillation and heart failure than among those with heart failure alone.[2] Drug therapy attempts to block certain ion channels at the cellular level to treat the irregular firing of the cells to therefore prevent the fibrillation. Catheter ablation treats the cluster of the cardiomyocyte cells within the tissue to decimate the irregular tissue and allow the normal heart to return to normal sinus rhythm.

According to the present guidelines for the management of AF, antiarrhythmic drugs (AADs) are the primary strategy for treating AF.[10] The American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS) guidelines on AF management recommends the use of catheter ablation for patients who are refractory or intolerant to at least 1 class I or III antiarrhythmic drug and have symptomatic paroxysmal AF (Class I, Level of Evidence A), symptomatic persistent

AF (Class IIa, Level of Evidence B-NR), or symptomatic long-standing (>12 months) persistent AF (Class IIb, Level of Evidence C-LD).[11] Since AF is a progressive disease that becomes more difficult to treat with increasing duration, during the time a patient has AF, their heart is modified either by electrical, contractile, and structural remodeling of the atria, which creates an environment for the propagation of the disease. All the while a patient is on drug therapy their atrial fibrillation and/or heart failure may progress making the drug therapy less effective and a candidate for ablation. Clinical trials and observational studies have demonstrated ablation to be more effective in supporting sinus rhythm and to be associated with better outcomes than antiarrhythmic medications in patients with symptomatic and paroxysmal AF.[6,7,12]

TREATMENT WITH DRUGS

According to AHA guidelines, for patients with HF appropriate treatment of their condition may need multiple medications, each treating a different symptom or contributing factor. These drugs may also have strict methods by which they need to be taken to be effective. A study comment on "*Medical doctors should not only focus on HF therapy, but comorbidities and polypharmacy should also influence therapeutic decision making*…" [13] This may lead to multiple prescriptions and the need to ensure the patient is taking the right prescription at the most effective time. Since AF is associated with an increased risk of stroke a blood thinner such as warfarin was the prescription of choice for cardiologists. As one writer describes it, "*Warfarin, one of*

the most inconvenient, dangerous and disliked drugs in the world, has remained vitally important for more than 50 years."[14]

Warfarin although effective has a track record of requiring constant monitoring and dosage adjustment with a long list of side effect and changes in quality of life. In 2010, other drugs like, rivaroxaban (Xarelto®), dabigatran etexilate (Pradaxa®) and apixaban (Eloquis®) were alternative blood thinners. These drugs are categorized as novel anticoagulants (NoACs) and although provide options to the current users of warfarin, have their own list of side effects and limitations in the treatment of AF and HF. For example, clinical trials have shown that rivaroxaban increased the patient's risk of experiencing a major bleeding event as compared to another oral coagulants. All drugs had increased risk of other bleeding complications and serious interactions with over the counter medication. These drugs have also shown an increased risk of gastrointestinal (GI) bleeding.[15]

In addition to the patients blood thinner prescription, a patient who is asymptomatic with heart failure needs to take an antiarrhythmic to manage AFib. To treat AFib, the drug therapy routine has multiple factors to consider that could affect a patient's daily routine.[16,17] The side effects include but are not limited to blurred vision, stomach pain, and other daily ailments that may impair a patient's day to day tasks (e.g. driving, exercise, leisure walking). These is only one class of drug that is recommended for the treatment of AF. Drugs like, flecainide acetate (Tambocor™), dofetilide, rythmol, and sotalol are all antiarrhythmics that could be given to a patient to try and suppress their arrhythmias. These drugs work at the cardiac cell level to

block certain sodium and calcium channels in order to control inappropriate cell conduction that cause the arrhythmia.

Due to side effects and changes in quality of life, patients prescribed medications may not take their medications allowing the AF to progress to a more severe state. Since AF or HF can affect a person at any age, the limitations of these drugs may cause a patient to look for alternative options.

TREATMENT WITH ABLATION

Catheter ablation is often recommended as an alternative to drugs for those patients who have failed drugs or cannot tolerate the side effects of their prescription.

Ablation of AF has two mechanistic goals: 1) to remove all potential triggers that may initiate or perpetuate AF; and 2) to alter the conduction properties of the atria (substrate modification) so that AF cannot be sustained even when triggered.[18] From the early 2000s, the mechanism of AF was not clearly understood. The predominant theory of the 20th century was that chaotic multiple re-entry circuits, following constantly varying lines of conduction block, perpetuate AF[18] After multiple debates and techniques to treat AF currently the belief is that the source of AF lies in the connection of the left atrium to the pulmonary veins and disconnecting that area electrically can result in the patient returning to sinus rhythm.

There are three types of ablation treatment for atrial fibrillation: surgical, radiofrequency and cryo. Surgical ablation via an open chest procedure known as the Maze procedure. Cardiac surgeons were the pioneers of surgical ablation of AF,

and in 1992 Cox's Maze-III procedure evolved from five years accumulated worldwide surgical experience and carefully conducted animal and human mapping studies. Initially the lesions were created by a “cut and sew” method through a median sternotomy. As a consequence this technique is extremely clinically effective, with maintenance of sinus rhythm reported by Cox at greater than 97%[19] and at 84.9% in a systematic review of 1553 patients in all published series up to 2004.[20] In addition both left atrial (LA) mechanical function and left ventricular function have been shown to improve this would be ideal for those also suffering from heart failure.

However, surgical ablation requires a high level of technical skill [19] and therefore as a result few centers in the world have been able to replicate the original Cox results. In addition, the mortality and morbidity associated with surgical ablation when compared to catheter ablation is comparable 7.2% vs 13.4%[2] but not without the need for additional training and procedure time. This type of procedure was not included in the analysis for this study and patients who received surgical treatment were excluded from the study.

Electrophysiology is the branch of physiology that deals with the electrical phenomena associated with nervous and other bodily activity, it involves measurement of voltage change or electric current from the single ion channel in cells to the entire heart. An electrophysiology study is a diagnostic procedure that looks at the electrical function of the heart to evaluate both the heart mechanical strength and rhythm. Catheter ablation is a comparatively new procedure for treating patients with AFib when compared to direct cardioversion treatment or surgical treatment. It began

to take shape after a publication in 1998 from a group of electrophysiologists in Bordeaux[21] calling out the pulmonary veins as sources for the arrhythmia.

During an electrophysiology study, several catheters are placed within the heart chambers by way of the groin introducer sheaths to observe the electrical function of the heart via diagnostic mapping and through pacing maneuvers. Since the first treatment cases of atrial fibrillation, patients who are non-responsive to drug therapy or have failed various classes of drugs have been referred to an electrophysiologist for further treatment. Ablation therapy is a treatment to treat arrhythmias like atrial fibrillation while at times eliminating the need medications.

Most ablation treatment or catheter ablation discussed in my paper, were radiofrequency ablations, where a physician using a catheter with a platinum tip electrode connected to an radiofrequency generator, sends radiofrequency energy to the heart in an attempt to destroy (ablate) the arrhythmic tissue.[22] Like most technologies' catheter ablation has evolved, current treatment options range from radiofrequency energy to cryoablation energy. Cryoablation therapy like radiofrequency ablates using extreme cold to destroy tissue, where a balloon is inserted via the groin, and expanded around the ostium of the pulmonary vein, a cryogenic freezing unit that is connected to the balloon catheter cools the balloon to form ice crystals within cells disrupting the membrane and causing cellular death. [23]

The current guidelines for physicians to use catheter ablation is as a secondary method of treatment for patients who have failed drug therapy or are unable to handle the medication due to another illness (i.e. renal deficiency or failure). For this analysis when discussing catheter ablation in the database used, the

ICD9/ICD10 codes do not distinguish between the cryoablation or radiofrequency (RF) ablation. Therefore, for the analysis performed in this study, catheter ablation encompasses both modalities. It is possible that most of the patients in this cohort have also failed a drug and is considered a limitation of the study design to be discussed in a later section.

STUDY OBJECTIVE

To compare the impact of AF treatments (ablation vs. drug therapy) on HF patients

PRIMARY OBJECTIVES:

These are important variables to understand the rate of re-admission rates between the two groups to see which treatment had the highest incidence of hospital admissions and the nature of the admission. Upon matching the by all covariates listed in Table 1 age, gender, insurance type and geographical region, the two matched groups were assessed for the following:

1. To assess and compare the 12-month post-index period all-cause inpatient readmission among patients with AF who underwent ablation vs. medication therapy.
2. To assess and compare the 12-month post-index period cardiovascular (CV)-related inpatient readmission among patients with AF who underwent ablation vs. medication therapy.
3. To assess and compare the 12-month post-index period AF-related inpatient readmission among patients with AF who underwent ablation vs. medication therapy.

4. To assess and compare the 12-month post-index period direct current cardioversion (DCCV) among patients with AF who underwent ablation vs. medication therapy.
5. To assess and compare the 12-month post-index period costs (all-cause inpatient, outpatient, emergency room, office visits, and prescription medication) among patients with AF who underwent ablation vs. medication therapy.

In summary, the current guidelines favor drug therapy but is this the best treatment for those patients suffering from HF and AF? Should the guidelines be revised to allow for patients suffering from this composite to be treated with catheter ablation to improve their health. In the following chapter, I will discuss how the groups were identified in the database and how variables for covariates were selected and why.

CHAPTER 3: RESEARCH METHODS

LITERATURE REVIEW

The literature review was performed using multiple strategies. The literature search was begun using keywords and MeSH terms originally provided in studies of interest (atrial fibrillation AND Heart failure) limiting to the last 10 years, in English and human trials resulted in 10 articles in PubMED. The limit of only the last 10 years was due to the fact catheter technology was still a novel treatment and the studies

only had a small number of patients. After this search, a sub search for studies aiming to answer the similar question of HF patients being treated for AF provided further information on statistics and treatment options resulted in an additional 5 studies. An independent search on PubMed, Scopus, Google Scholar were used to find other studies that were similar in the primary objective as well as the patient population. These studies were used to validate the list of comorbidities listed as well as to control the group for geographical location.[9] All studies were used within this body of text as references.

Data Sources

This study has used a commercial claims database from January 1, 2010 to December 31, 2016 contained in the IBM Truven Health MarketScan® Commercial Claims and Encounters (CCAE) database and Truven Medicare Supplemental database (IBM Truven Health Analytics, Ann Arbor, MI). The MarketScan® Commercial Claims and Encounter and Medicare Supplemental database is medical and prescription drug insurance claims database for more than 138 million individuals in the US enrolled in employer-sponsored health insurance plans. The database includes information on inpatient admissions, outpatient services, prescription drugs, enrollment, and costs associated with the provision of healthcare services. To protect patient-identity, all data was made available in a de-identified format. A unique encrypted recipient identification number was used to link data files.

The use of MarketScan database was reviewed by the New England Institutional Review Board (IRB) and was determined to be exempt from broad IRB approval, as this research project did not involve human subjects research.

A blanking period of 3-months was applied as the post-index treatment window as treatment stabilization period for primary objective assessment for ablation arm as at times patients may need to return due to relapse of arrhythmia.

Index event for ablation and drug therapy cohorts were restricted to January 1, 2011 to December 31, 2016, and the 12-month post-index criteria was relaxed. This allowed patients to be followed until they were lost to follow-up or occurrence of event.

Missing Data

Any patient file that was incomplete for any variable in the database was excluded, this resulted in a total loss of 5.2% of patients after the first assessment. Therefore, all patients after this filter was applied to the data had complete data files from January 1, 2011 to December 2016.

Study Population

There were two cohorts in this study: Ablation and Drug Therapy cohorts. Upon receiving approval of this study and the use of the Truven Database was granted, it was searched for patients that met either the ablation cohort or the drug cohort.

The first part of this study was to identify patients with primary or secondary diagnosis of HF in an inpatient or outpatient setting between January 1, 2009 and September 30, 2016, using ICD-9/ICD-10 procedure codes. Upon this identification, patients with primary (or secondary) diagnosis of AF in an inpatient or outpatient setting between January 1, 2011 and September 30, 2016 were sorted out. Any patients who had either primary or secondary diagnosis of AF in the prior 2-year period of index episode (inpatient or outpatient) were removed as it was considered out of scope for this study.

Ablation Cohort

To identify patients going into the ablation cohort, patients needed a primary procedure of ablation in an inpatient setting with primary diagnosis of AF with a secondary diagnosis of HF in an inpatient setting or primary diagnosis of HF with a secondary diagnosis of AF in an inpatient setting to be considered. For the ablation arm, the patients also needed to be at >18 years of age, if they have had a previous catheter ablation or did not have continuous insurance coverage they were removed.

Drug Therapy Cohort

For the drug therapy arm, those patients >18 years of age in age, who had a primary or secondary diagnosis of AF and had the usage of a rhythm or rate control drug from 2011 to 2016 were identified. If the patient had a catheter ablation procedure 12-month pre or post their index date they were removed from the arm and considered for the catheter ablation arm. The index episode was defined as their first database

recording with AF, while their index date was the date of their first prescription filled for an antiarrhythmic drug or heart failure drug whichever came first.

For prescriptions, medications considered in the database were:

- Heart Failure medication (measurement period: 365 days pre-index): Measured as number of distinct classes of HF medications filled in the 365 days pre-index period. HF medication classes include: angiotensin converting enzyme (ACE) inhibitors, beta blockers, digoxin, diuretics, Angiotension II receptor blockers, aldosterone antagonists.

- Anticoagulant medication (measurement period: 365 days pre-index): Measured as a "0/1 indicator" variable indicating whether a patient had used an anticoagulant in the pre-index period (=1) or not (=0). Anticoagulant medications include: warfarin, dabigatran, rivaroxaban, apixaban and edoxaban.

PATIENT CLINICAL CHARACTERISTICS/COVARIATES CONSIDERED

Patient clinical characteristic variables were measured using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9/10-CM) in the 12-month pre-index period. For the two comorbidity indices listed below, the individual comorbid conditions that the indices comprise were used as predictor variables within the statistical models. Individual comorbidities as listed under *Specific Clinical Characteristics* below were adjusted for in study analysis.[24–26] New York Heart Association (NYHA) class II, III, or IV heart failure is used to classify a patient with HF[27]

Study Measures

The primary independent variable was treatment status: catheter ablation or drug therapy. Main outcome measures of interest included readmission (all-cause, CV-related, AF-related), electrical cardioversion, and total healthcare cost. Implantation of a pacemaker or defibrillator and patients with cardiomyopathy were covariates of interest. In addition, total healthcare costs were assessed for both cohorts.

Statistical methods

Bivariate analyses were conducted with the Student's t-test and chi-squared test to examine any differences in the list of covariate characteristics between the ablation and drug therapy groups of patients. Categorical outcomes are presented as percentages. Multivariable adjusted analyses were conducted to examine study outcomes, where the variables adjusted for were age, sex, race, insurance type and geographical location. GEE with log link and gamma distribution was used for cost comparison. Separate logistic regression models were used to compare the 12-month incidence of readmission, and direct cardioversion rates after propensity matching. Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Data Analysis

Descriptive statistics were reported for all study variables. Means and standard deviations were reported for continuous variables and frequencies and percentages were reported for categorical variables. Bivariate statistical tests were conducted to examine and describe the differences between the two groups of patients in potential confounding factors such as patient demographics, clinical characteristics, and procedural characteristics.

Patients were matched to one another using the nearest neighbor technique, without replacement, enforcing a caliper of 0.10, with all study covariates included in the logistic propensity model. The standardized difference was used to assess the post-match balance of the variables which were included in the propensity score model. The propensity score was generated from a multivariable logistic regression and was equal to the predicted probability of undergoing catheter ablation or receiving drug therapy during the index hospital admission (date of admission). Variation in inclusion/exclusion criteria for primary objectives (12-month follow-up) were also considered. The PS model was made to fit through multivariable logistic regression in which the outcome was a binary indicator for the comparator (e.g., variable = 1 if patient is Ablation group, = 0 if patient is in medication group) and the study covariates served as predictors.

After matching, bivariate statistical analysis techniques were used to test for statistically significant differences in the outcomes between the comparators. The balance of covariate was assessed using standardized differences, with any

difference more than 25% considered to be significant. For primary objectives 1-4, logistic regression was used with the main independent variable of interest being treatment status (ablation or medication). For primary objective 5 (cost differences), generalized linear model (GLM) model was used to compare total cost among the two matched groups. In all analyses, a two-sided $P < 0.05$ was the threshold by which differences were statistically significant. All analyses were conducted using SAS for Windows, Version 9.4 (SAS Institute Inc., Cary, NC).

Considering that the issue of selection bias is probable in observational research, propensity score matching was conducted to better control for any bias, where patients were matched for all covariates to ensure the treatment being analyzed was the only difference between cohorts. First, propensity matching was conducted on the sample of patients that constituted the final sample (post-inclusion/exclusion) to examine costs. Costs considered were (all-cause inpatient/outpatient LOS, emergency room, office visits, and prescription medications) associated with index admission date. Second, inpatient readmission outcome (all-cause, CV-related, AF-related) between the two groups was examined. Finally, for DCCV occurrence in the subsequent 12-month follow-up period was analyzed to observe which group had the higher number of cardioversions after a patient's index date.

As mentioned previously any patient file that was found to have a missing data field was excluded in the analysis, therefore all patients that were retained in the bivariate analysis and the propensity matched group had complete data files in the study timeframe. The covariates used in the adjustment matched those used in

adjustment to the larger randomized controlled trials to mimic the analysis used in the two studies both pre and post matching. In the next section, I will discuss the results of the study and the interpretation of those results.

CHAPTER 4 RESULTS

STUDY COHORT

A total of 1, 225, 988 patients who had a primary, secondary, or admitting diagnosis of AF for index ablation performed between January 1, 2011, and December 31, 2016, were identified in the Truven database. After screening for eligibility, the catheter ablation cohort included 6, 191 patients while the drug therapy group had 24,265 patients. Before matching the two groups, there were significant differences in study characteristics observed between the two treatment groups (Table 1). The catheter ablation group had significantly more patients with a CHA2DS2-VASc score of 2 or higher than that of the drug therapy group (CA Group 59% vs DT Group 56%; $P<0.05$). The catheter ablation group had significantly more patients with diabetes (CA Group 17.36% vs DT 12.96%; $P<0.05$) and hypertension (CA Group 63.91% vs 20% in the drug therapy group). Please refer to Table 1 for patient characteristics for each group.

PRIMARY OBJECTIVE ANALYSES

In the unadjusted analysis, all-cause, CV-related, and AF-related hospital readmissions were significantly different between the catheter ablation and drug

therapy groups (Table 2). After multivariable adjustment using survey logistic regression, the catheter ablation group was associated with 61% lower odds of all-cause inpatient readmission (OR 0.39 [95% CI 0.27–0.76]) and 73% lower odds of CV-related readmission (OR 0.27 [95% CI 0.21–0.96]) than the drug therapy group in the 12-month period after the index date (Table 2). When comparing outcomes during the blanking period (0–3 months), the catheter ablation group had 58% lower odds of all-cause readmission (OR 0.21 [95% CI 0.22–0.79]) and 62% lower odds of CV-related readmission (OR 0.38 [95% CI 0.15–0.95]) than the drug therapy group (Table 2). Before adjusting for covariates, the catheter ablation group had a significantly lower occurrence of DCCV than the drug therapy group at all time points (Table 2). After multivariable adjustment, results for DCCV significantly favored the catheter ablation group over the drug therapy group, with 44% lower odds at 0–12 months (OR 0.565 [95%CI 0.42–0.88]),

Results from Student's t-test indicated unadjusted mean total costs to be significantly lower in the Catheter ablation group than the Drug therapy group (CA: $19,729 vs DT: $22, 038; P<0.0022) (Table 2). After multivariable adjustment using GEE, the mean total costs were similar between the Catheter ablation and drug therapy groups (CA: $21,287 vs DT: $23,330) (Table 2). Unadjusted mean supply costs were significantly lower in the Catheter ablation group than the Drug therapy group (Catheter Ablation: $11, 523 vs Drug Therapy $11, 481; P<0.0001) (Table 2). After GEE adjustment, mean supply costs were similar between the treatment groups (Catheter Ablation: $9,832 vs Drug Therapy: $9,787) (Table 2).

Comparing catheter ablation with drug therapy in patients with heart failure and atrial fibrillation, catheter ablation was shown to be associated with lower rates of all-cause inpatient readmission and shorter length of stay. A reduction in burden of atrial fibrillation in forms of lower re-admission rates (AF/CV-related), direct current cardioversions, and visits to the emergency room were also higher in the drug treatment cohort. In comparison to the large randomized controlled studies mentioned in the background section, CASTLE-AF and CABANA, this study had a comparable mix of patients in age and risk of stroke. This cohort of patients were also similar in that patients who were treated by drugs had a higher rate of cardiovascular related and all cause re-admissions than those treated by catheter ablation. In the Truven database, overall patient QoL surveys are conducted, like the CABANA trial had this been performed at baseline and then later in the patients treatment plan, it would have been interesting to observe any differences.

However, from the clinical results, this study shows that patients who suffer from HF and are being treated for their AF symptoms should consider catheter ablation as a primary treatment. In the following section I plan on discussing the gaps in these analysis, key learnings of the analysis, and other suggestions on results.

CHAPTER 5 Discussion

This is the first study to demonstrate, from a real-world perspective, the clinical advantage of catheter ablation when compared to traditional drug therapy. This study used both multivariable regression analysis as part of primary outcome analysis where propensity matching was used to alleviate selection bias that may have affected primary analysis study results. Unlike clinical trials wherein randomization controls for selection bias, observation data is susceptible to such bias due to lack of randomization. Though it is difficult to fully control for selection bias without randomization, a common method to alleviate its effect in observational research is through propensity matching.[30] When comparing the real world database results to those of the clinical trials mentioned in the background section the patient characteristics of all studies were comparable.[5,7]

STUDY LIMITATIONS

Limitations of the current study include those that are inherent with a retrospective observational study design. This includes the possibility of inadvertent patient selection bias and unidentified confounding variables. Though multivariable analyses were used to adjust for measured confounders, there could be other factors influencing outcomes that could not be adjusted for. Patients who may have had a readmission at a different hospital would not have been captured in the Truven database. The operator's level of experience was not considered in the regression analyses as it is unavailable in the database. This represents a possible unidentified covariate. Variation in adoption and experience in catheter ablation could influence procedures and therefore study results. Study results could have

been affected by billing and coding errors in the database records. As the data period includes data from ICD-9 era (wherein ICD-9-CM diagnosis code of 427.31 refers to AF), information on AF type (paroxysmal, persistent, etc.) was also not available and not sure how severity of the arrhythmia might have also influenced study results.

As this was a study sponsored by my company, the types of questions I was able to analyze was limited. With open access to the data, I would have expanded the primary endpoint to be a composite of death, worsening of heart failure and readmission rates. This was not performed due the limitation in access to the data as well as guidance from my sponsor Johnson and Johnson to limit to a short-term measure such as readmission rates. Additionally, like the referenced larger randomized controlled trial I would have wanted to follow up these patients until lost to follow up. This I believe would have given me at least 3 years if not 5 year follow up data for all patients in the study. As this study is planned to be formatted for a formal publication it may be an option.

Lastly all data analysis required the use of SAS and a server-based analysis file, this was limiting as learning the SAS code and structure took time away from the data analysis and therefore required my limiting the amount of analysis performed in order to meet the primary objective within the time frame of this semester. Another limitation of SAS was its inability of my inability to generate comparison graphs of the propensity match samples that I felt would have been beneficial for illustrating the groups matched samples and the types of patients that

ended up without a match. For example, since the catheter ablation group had patients who failed drugs or were unwilling to take drugs, the timing of that patient's catheter treatment would have been much sooner than those who followed the recommended guidelines of drug treatment failure than catheter ablation.

Hence those patients who were unmatched, I believe, are those patients who failed a drug previously and were still symptomatic requiring further treatment. If that is the case, these patients are similar to those patients in the drug therapy group and the grouping should be changed to be three treatment groups: catheter ablation only, drug therapy, and drug therapy failure plus catheter ablation. However I suspect considering the importance of these diseases in the general population and the number of patients who are affected by it, that a study like this will probably be published soon.

APPENDIX A: BIBLIOGRAHPY

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Figure 1. PATIENT SELECTION DIAGRAM

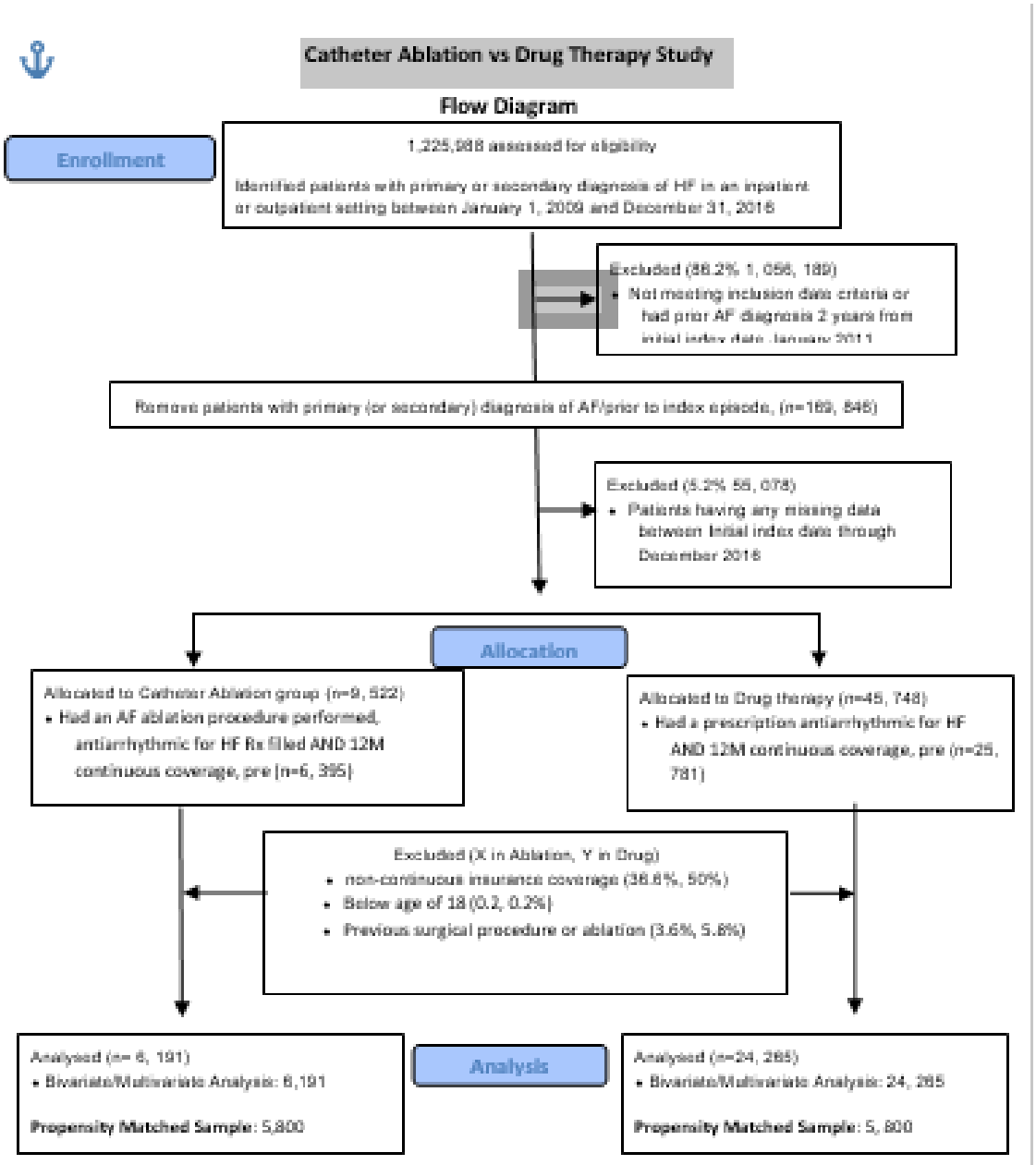

Table 1 PRE-AND POST-MATCH SAMPLE CHARACTERISTICS AND STANDARDIZED DIFFERENCES

Variable		Before Propensity Score Matching [A,B]			After Propensity Score Matching [A,B]		
	CA (n=6191)	DT (n=24,265)	P-value[+]	Standardized Difference**	CA (n=5800)	DT (n=580	Sta nd ard
Age, y							
18-49	10.50	10.23	0.9143	0.0087	7.35	8.09	-0.0276
50-59	23.44	17.84	0.1821	0.1389	19.12	22.79	-0.0904
60-69	37.61	39.77	0.5642	-0.0443	38.24	41.18	-0.0601
70+	28.45	32.16	0.5125	-0.0809	35.29	27.94	0.1586
Sex							
Female	35.90	32.75	0.2192	0.0664	38.24	33.09	0.1076
Race							
Non-White	8.30	12.57	0.0623	-0.14	12.5	11.76	0.0225
Other	1.95	6.14	0.0192	-0.2137	7.35	5.88	0.0592
Marital status							
Married	76.19	67.54	0.0623	0.1932	68.38	69.12	-0.0159
Single	21.86	26.32	0.4325	-0.1044	24.26	25.00	-0.0171
CCI score							
0	58.85	63.16	0.1433	-0.0884	59.56	61.03	-0.0301
1	26.13	23.68	0.2915	0.0566	21.21	22.06	0.1197
≥2	15.02	13.16	0.4629	0.0535	16.94	13.21	0.1029
CHA_2DS_2-VASc score							
0	13.92	18.42	**0.0355**	-0.1225	13.97	56.62	-0.1938
1	27.59	25.15	0.3711	0.0556	31.62	29.21	0.0479
≥2	58.49	56.43	0.4743	0.0415	56.66	47.06	0.1922
Other Comorbidities							
OSA	21.00	16.96	0.4410	0.1032	19.12	16.18	0.0772
Obesity	12.94	8.77	0.0923	0.1344	7.35	11.03	-0.1275
Diabetes	18.56	14.04	**0.0324**	0.1227	18.38	16.91	0.0386
Hypertension	63.74	56.43	**0.0270**	0.1496	59.56	56.62	0.0596
COPD	12.21	9.65	0.4735	0.0821	10.29	11.76	-0.047
Renal disease	4.27	2.05	0.1409	0.1275	2.21	5.15	-0.1568

CHF	14.53	13.45	0.6757	0.0311	16.18	13.97	0.0617
Other Arrhythmia[1]							
	32.53	21.10	0.0001	0.2604	16.67	23.61	-
Valvular disease	20.41	12.10	0.4702	0.2269	10.12	8.33	0 .
Cardiomyopathy	7.99	6.91	0.4730	0.0410	8.33	7.74	0 .
IHD	7.55	15.12	0.2454	0.0659	15.48	16.07	- 0
PVD	.94	3.89	0.9582	0.0029	4.76	3.57	0
PCD	.25	2.59	0.4918	0.0393	2.98	3.57	-
GEOGRAHPICAL							
South	8.52	36.99	<0.0001	-0.7218	44.44	40.97	0
North	11.04	6.58	0.3064	0.1582	5.56	8.33	-
East	61.05	20.09	<0.0001	0.9178	17.86	12.50	0
West	14.04	37.43	<0.0001	-0.5552	31.62	32.35	-

[A, B]Analysis performed using Student's t-test and the chi-squared test; Other arrhythmia[1] includes atrial flutter, paroxysmal supraventricular tachycardia, and atrioventricular nodal reentry tachycardia. [+]P-value less than 0.05 were considered significant. AF = atrial fibrillation; CI = confidence interval; CV = cardiovascular; DCCV = direct-current cardioversion; OR = odds ratio; CA = Catheter Ablation; DT = Drug Therapy. **The balance of covariate was assessed using standardized differences, with any difference more than 25% considered to be significant.

TABLE 2. TOTAL AND SUPPLY COSTS AFTER PROPENSITY MATCHING

	Bivariate Unadjusted Analysis			**Regression Analysis[B]**		
	CA (USD$)	DT(USD$)	P-value	CA (USD$)	DT(USD$)	95% CI
Analysis Cohort*	(n=6191)	(n=24,265)		5800	5800	
Total Cost	$19,729	$22,038	0.0022	$21,287	$23,330	0.9124
Supply Cost	$11,523	$11,481	<0.0001	$9,832	$9,787	1.0046

[A]Analysis performed using Student's t-test [* B] a generalized linear model used for analysis
*Cost (total and supply) includes only those costs associated with the index ablation procedure and/or admissions.

TABLE 3. HOSPITAL READMISSIONS (ALL CAUSE, CV RELATED, AF RELATED) IN THE PATIENT COHORT AFTER PROPENSITY MATCHING

Readmissions*[A]	CA (%)	DT (%)	P Value	OR	95% CI
Analysis Cohort	5, 800	5, 800			
All- Cause					
0-12 months	9.72	21.53	0.0089	0.393	0.206 - 0.747
0-3 months	4.17	15.28	0.0023	0.241	0.133 – 0.437
4-12 months	6.94	7.64	1	0.902	0.286 – 2.845
CV-related					
0-12 months	3.47	11.81	0.013	0.269	0.096 – 0.754
0-3 months	1.39	7.64	0.0196	0.170	0.046 – 0.636
4-12 months	2.78	4.17	0.7495	0.657	0.147 – 2.947
AF-related					
0-12 months	2.08	9.03	0.0179	0.214	0.059 – 0.784
0-3 months	1.39	6.94	0.0347	0.189	0.054 – 0.659
4-12 months	1.39	2.08	1	0.662	0.047 – 9.309

*Analysis performed using Logistic regression, for all-cause, CV-related, AF-related admissions; AF = atrial fibrillation; CI = confidence interval; CV = cardiovascular; OR = odds ratio; CA = Catheter Ablation; DT = Drug Therapy.

TABLE 4. DIRECT CARDIOVERSION IN THE PATIENT COHORT AFTER PROPENSITY MATCHING

Direct Cardioversion (DCCV)[A]	CA (%)	DT (%)	P Value	OR	95% CI
Analysis cohort (n)	5800	5800			
DCCV					
0-12 months	10.91	36.47	0.0769	0.56	0.345 – 0.927

DCCV = direct-current cardioversion; OR = odds ratio; CA = Catheter Ablation; DT = Drug Therapy. [A] Analysis done using Logistic regression

TABLE 5. ANTI-ARRHYTHMIC DRUGS (AADS) RHYTHM CONTROL AND RATE CONTROL DRUGS CONSIDERED FOR DRUG THERAPY COHORT

AAD Drugs	Rate-control drugs
1. Vaughan Williams class IA: a. Disopyramide b. Quinidine c. Procainamide 2. Vaughan Williams class IC a. Flecainide b. Propafenone 3. Vaughan Williams class III a. Amiodarone b. Bretylium c. Dofetilide d. Dronedarone e. Sotalol f. Ibutilide	1. Atenolol 2. Carvedilol 3. Digoxin 4. Diltiazem 5. Esmolol 6. Metoprolol 7. Verapamil 8. Propranolol 9. Acebutolol