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California Study of Ablation for Atrial Fibrillation : Re-Hospitalization for Cardiac Events (CAABL-CE)

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Abstract

Background: Catheter ablation (ABL) for non-valvular (NV) atrial fibrillation (AF) improves rhythm control. Our aim was to compare re-hospitalization for heart failure (HF), acute coronary syndrome (ACS), or recurrent AF among patients with NVAF who underwent ABL versus controls.

Methods: From the Office of Statewide Planning and Development (OSHPD) database, we identified all patients who had at least one hospitalization for AF between 2005-2013. Patients who subsequently underwent ABL were compared to controls (up to fivematched controls by age, sex and duration of AF between diagnosis and time of ABL). Cases with valve disease, open maze, other arrhythmias, or implanted cardiac devices were excluded. Pre-specified clinical outcomes including readmission for HF, ACS, severe or simple AF (severe = with HF or ACS; simple= without HF or ACS)were assessed using a weighted proportional hazard model adjusting for number of hospital admissions with AF before the ABL, calendar year of ABL, and presence of chronic comorbidities.

Results: The study population constituted 8338 cases and controls, with mean 3.5+ 1 patient-year follow up. In the ABL cohort, there was lower risk of re-hospitalizations for HF, HR=0.55(95%CI: 0.43-0.69,); ACS,HR=0.5(95%CI: 0.35-0.72,); severe AF [HR=0.86 (CI:0.74-0.99), and higher for simple AF, HR=1.25 (CI:1.18-1.33).

Conclusion: In patients with NVAF, although ABL is associated with increased risk of re-hospitalization for simple AF, ABL was associated with a significant reduction in the risk of re-hospitalization for HF, ACS and severe AF. These findingsrequireconfirmation in a prospective clinical trial.

Introduction

Atrial fibrillation (AF) is one of the most common causes of emergency department (ED) visits and hospitalizations and it is projected to affect more than 10 million Americans by 2050. The prevalence doubles with every decade of age, and morbidity is related to higher incidence of stroke, heart failure (HF) and re-hospitalization for recurrent AF episodes. HF develops in about a quarter of the patients diagnosed with AF, leading to higher mortality and there has been no decrease in this trend[1]. AF is also associated with higher risk of acute coronary syndrome (ACS), especially in women and those younger than 60 years of age. In patients presenting with ACS, associated AF increases long-term mortality compared to those without AF[2]. These findings translate to an increased health care economic burden, with an annual direct medical cost due to AF of about $3 billion more than those without AF[3].

Observational and registry data have demonstrated improved event free survival defined as non-recurrent AF > 30 seconds following ABL compared to medical management[4]. ABL is generally considered safe, but it does have certain peri-procedual complications;[5] here is an increase in HF hospitalization and recurrent arrhythmia early in the post-ABL course. However, due to advances in techniques and early recognition of these adverse effects, there has been a decreasing trend for all cause readmissions after ABL[6].

Ablation (ABL) as a first line therapy in the young is modestly cost effective with a gain of 0.06 quality-adjusted life years with an incremental cost of 3003 euros[7]. The cost effectiveness may be related to direct and indirect cost from improved quality of life and reduced hospitalizations.

Our aim was to assess the efficacy of ABL to reduce re-hospitalization for HF, ACS and recurrent AF compared to match controls in a large multi-ethnic patient population previously hospitalized for at least an episode of AF.

Methods

Data source:

California requires all non-federal hospitals in the state to report all hospitalizations and emergency department visits as well as ambulatory surgical encounters to the Office of Statewide Health Planning and Development (OSHPD). All clinical and demographic

Key Words

Atrial fibrillation Ablation, Heart Failure, Acute Coronary Syndrome

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characteristics of the individual are also recorded providing access to the co-morbidities. Since any hospitalization from any non-federal California hospital can be identified in a temporal relationship, the database is comprehensive for assessment of clinical outcomes of a procedure under investigation.

Selection of patients:

After obtaining institutional approval, clinical characteristics, demographics, hospitalization, emergency department and ambulatory surgery encounters from non-federal hospitals listed in OSHPD database were utilized for this study. ICD 9 codes were used to identify encounter diagnoses of ABL (37.34), AF (427.31), atrial flutter (AFL) (427.32), supraventricular tachycardia (SVT) (427.0), ventricular tachycardia (VT) (427.1), open surgical ablation (SA) (37.33), and pacemaker/defibrillator implant (37.80-37.87). In addition, the Elixhauser comorbidity index (Healthcare Cost and Utilization Project V3.7) was applied for 29 major co-morbidities based on ICD-9-CM codes listed as present at the time of first admission with AF[8]. The ABL group was identified as those patients with ambulatory surgery encounters for ABL between Jan 1, 2005-Dec 31, 2013 associated with principal diagnosis of AF. We excluded those with AFL, SVT, VT, SA, valvular heart disease, dementia, human immunodeficiency disease, alcohol abuse, active cancer or psychosis. All cases that had pacemaker/defibrillator implant were also excluded. Patients who had no prior encounter diagnosis of AF before ABL were excluded because they represented healthier ambulatory patients whose symptom status was unknown. The date of ABL was the study date (SDT) for this case cohort [Figure 1].

Selection of matched controls:

The control group was selected by weighted matching based on age, sex, year of onset of AF, the pattern of health-facility encounters prior to ABL and number of AF hospitalizations before the SDT. For the control group, SDT was the corresponding interval after the first encounter diagnosis of AF to the date of ABL of the matched ABL case. We reviewed sample hospitalization records to verify the accuracy of the inclusions and exclusions.

End points:

The pre-specified clinical outcomes occurring after the date of ABL included re-hospitalization for HF (principal position), ACS (principal position), and AF (principal or secondary position). Re-hospitalization for AF included those who had the diagnosis in principal or secondary position. AF was considered as severe (principal position only to avoid double counting) or simple (any position) depending on presence or absence of ICD 9 codes for ACS (410.x, 411.1, 411.8x)[9] or HF respectively during the re-hospitalization. Since ablation can cause troponin elevation, ACS was considered an outcome, if occurred > 7 days and recurrence of AF or HF was an outcome if these occurred > 90 days after the SDT. Study design is shown in [Figure 1].

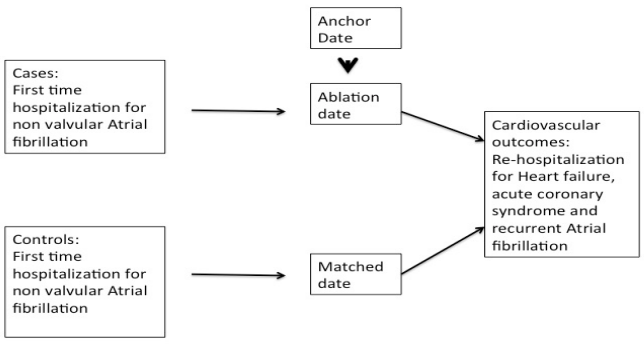

Figure 1: Study design

Statistics:

To reduce confounding effect of variables, various methods of matching have been used in observational studies. Propensity matching has been a surrogate for randomized clinical trials, however it reduces sample size of the cohorts (=power)[10]. Studies comparing the two methods (propensity score vs. simple multivariable regression) have shown no significant difference in the strength or statistical significance of associations between exposure and outcomes[11]. Since the majority of the patients with non-valvular AF (NVAF) have similar co-morbidities, regression model can be used to study the treatment effect in all patients undergoing ABL. We used weighted matching which averages multiple individuals in control group (5:1 in our study), providing 20% weight to each treated individual, providing equal number of patients in either group and reducing the variance of imbalance[10].

Outcomes in the ABL and No-ABL controls were analyzed using a weighted proportional hazard regression model with follow-up to Dec 31, 2013, adjusting for the number of prior admission with HF, and number of prior admissions with AF before ABL, calendar years, presence of specific chronic co-morbidities and demographics which were forced into the model. All co-morbidities were present at the SDT.

SAS version 9.3 was used for all statistical analyses. Continuous variables were expressed as mean + standard deviation. Categorical variables were presented as percentages. Uni-variate analysis was performed with a X^2 test for nominal variables; t test for continuous variables and Fisher's exact test was applied for outcomes fewer than 5 events per cell. A p-value < 0.05 was considered significant.

Results

The cohort comprised 8338 patients (4169 ABL and 4169 matched controls), median age 63 years, 72 % male, 79% Caucasian. Additional demographic features included 55% hypertension (HTN), 18% obesity, 17% diabetes mellitus (DM), 12% HF, 8% coronary artery disease (CAD), and 4% prior stroke. Patients were followed up for 3.5 + 1 patient-years. The control group had a significantly higher rate of co-morbidities [Table 1].

Prior to SDT, hospitalizations for AF with at least one episode of AF < 2 years were higher in ABL than control groups (81.1% vs. 77.4%, p<0.0001); the rates of hospitalization were not different (46.6% vs. 45.7%, p=ns) > 2 years prior to SDT. There was no difference between the mean number of any admission for AF before SDT between ABL and control groups (2.55 (CI 2.49-2.620 vs. 2.62 (CI 2.58-2.65), ns); however, the ABL group had more encounters

Table 1: Baseline characteristics

Characteristics		Cases (%)	Controls(%)	P value
Patient age at catheter ablation	18-34	1.9	1.8	0.4385
	35-49	13.4	12.4	
	50-64	46.2	46.4	
	65-79	35.6	36.0	
	80 or older	2.9	3.4	
Gender	Male	72.3	71.2	0.2717
Race/ethnicity	White	84.1	73.2	0.0000
Congestive heart failure		11.6	12.7	0.1502
Peripheral vascular disease		3.5	5.9	0.0000
Chronic pulmonary disease		12.9	15.9	0.0002
Diabetes		14.1	20.4	0.0000
Hypertension		58.1	51.1	0.0000
Renal failure		3.2	7.7	0.0000
Liver disease		1.2	2.4	0.0000
Coagulopathy		1.9	1.8	0.4385
Obesity		17.0	18.4	0.1178
Coronary artery disease		6.7	9.6	0.0000
Stroke/TIA		4.7	3.8	0.0528

TIA-Transient ischemic attack

for the principal diagnosis of AF < 2 years prior to the SDT (1.04 (CI: 1-1.08) vs. 0.84 (CI: 0.82-0.86), p< 0.0001)[12] [Table 2].

Regarding HF admissions before SDT, the proportion of patients in ABL and control groups, respectively, who were hospitalized for at least one episode of HF < 2 years prior to SDT was not different (9.2% vs. 10.3%, ns); there were more patients (5.6% vs. 6.8%, p=0.02) in the control group > 2 years prior to SDT, with fewer number of admissions in ABL vs. control groups within two years prior to SDT (0.23 (CI:0.2-0.25) vs. 0.33 (CI:0.31-0.35), p<0.0001). The ABL group had fewer encounters for the principal diagnosis of HF <2 years prior to SDT (0.03 (CI:0.03-0.04) vs. 0.04 (CI:0.04-0.05), p< 0.0001) [Table 2].

Clinical Outcomes:

In the ABL vs. control groups, HF hospitalization occurred in 162 vs. 309 patients within 5 years: 53 vs. 39 within 90 days and 117 vs. 287

Table 2: Episodes of Atrial fibrillation and Heart failure prior to date of ablation.

Number of episodes from index hospitalization to anchor date	Ablation (mean)	CI	Controls (mean)	CI	P value
All atrial fibrillation	2.55	(2.49,2.62)	2.62	(2.58,2.65)	0.0907
Number of encounters with Principal Diagnosis of AF within 2 years prior to ablation	1.04	(1,1.08)	0.84	(0.82,0.86)	0.0000
Number of admissions w/ CHF DX prior to ablation	0.23	(0.2,0.2)	0.33	(0.31,0.5)	0.0000

CHF- Congestive heart failure DX- Diagnosis

between 90 days – 5 years, respectively. After multivariate analysis, although there was an initial 31% increase of HF in ABL group within 90 days of SDT, (HR 1.69 (CI:1.02-2.62) p=0.02), there was a 30% reduction in ABL group within 5 years after SDT, (HR 0.7 (CI: 0.57-0.86), p=0.001). This outcome was mainly due to a 45% decrease of HF occurring 90 days after SDT in the ABL group, (HR 0.55(CI: 0.43-0.69), p<0.0001) [Table 3], [Figure 2A].

Table 3: Results comparing ablation vs. no ablation for non -valvular atrial fibrillation.

Outcomes	Cases (% person yrs.)	Controls (% person yrs.)	Hazard Ratio (CI)	P value
Heart failure (<5 years)	1.1	2.1	0.7 (0.57-0.86)	0.001
<90 days	5.3	3.8	1.69(1.02-2.62)	0.02
90 days-5 years	0.8	2.1	0.55(0.43-0.69)	<0.0001
Acute coronary syndrome (7 days- 5 years)	0.4	0.9	0.59(0.43-0.82)	0.002
7-90 days	1.3	1.5	1.26(0.56-2.84)	ns
90 days-5 years	0.3	0.8	0.5 (0.35-0.72)	<0.0001
Atrial fibrillation 90 days-5 years	17	8.6	1.77(1.63-1.93)	<0.0001
Simple AF	15.3	7	1.88(1.72-2.06)	<0.0001
Severe AF	2.8	4.1	0.86(0.74-0.99)	0.03

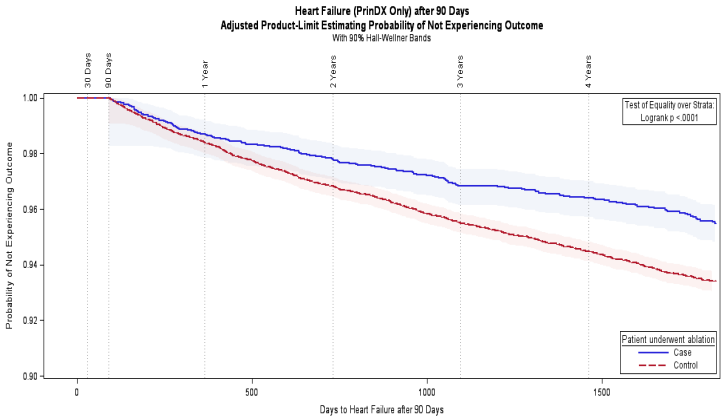

Figure 2A: Probability of not experiencing outcomes (Y axis), Days of follow up (X axis) A- Congestive heart failure

Hospitalization for ACS in ABL vs. control groups occurred in 61 vs. 131 patients, within five years: 13 vs. 15 patients < 90 days and 48 vs. 117 between 90 days – five years, respectively. After multivariate analysis, there was a 41% reduction in ABL group within 5 years after SDT (HR 0.59 (CI: 0.43-0.82), p=0.002), mainly due to a 50% decrease occurring >90 days after SDT in ABL group, (HR 0.5(CI: 0.35-0.72), p<0.0001), without a difference in ACS at <90 days ([Table 3] and [Figure 2B].

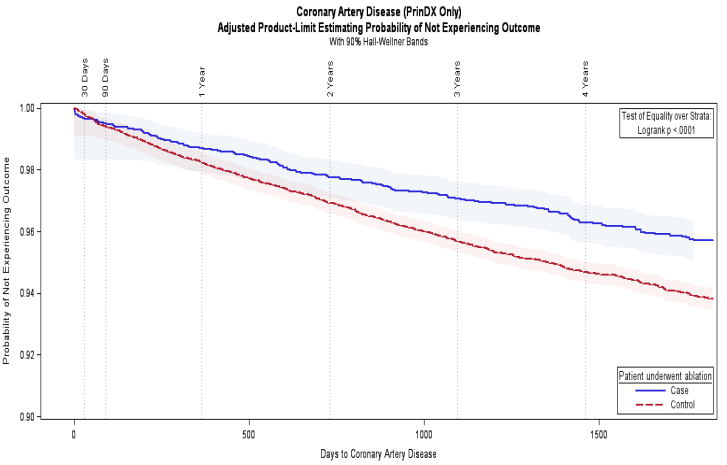

Figure 2B: Probability of not experiencing outcomes (Y axis), Days of follow up (X axis); B-Acute coronary syndrome

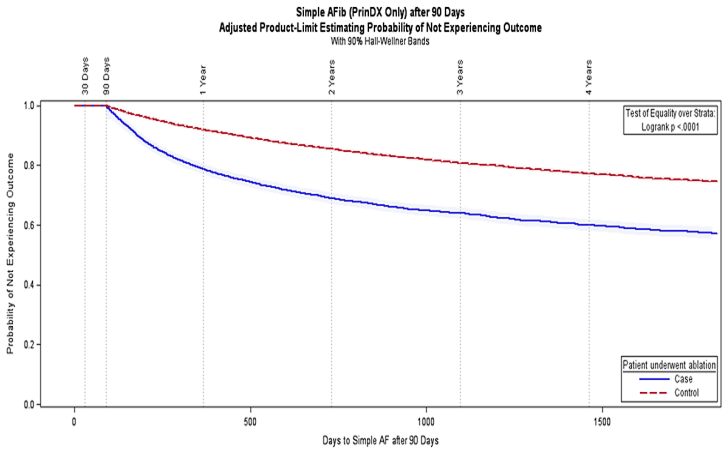

Figure 2C: Probability of not experiencing outcomes (Y axis), Days of follow up (X axis)C- Simple Atrial fibrillation

Regarding re-hospitalization for AF >90 days up to 5 years after SDT, there was a marginal increase in recurrence of all AF (simple and severe) in ABL vs. controls (HR 1.12 (CI: 1.05-1.19), p<0.0001), mainly attributable to simple AF (HR 1.25 (CI:1.18-1.33), p<0.0001)[Table 3], [Figure 2C]. There was a 14% reduction in severe AF (HR 0.86 (CI: 0.74-0.99), p=0.03) [Table 3], [Figure 2D] in the ABL group compared to controls.

Discussion

The major findings of this study are that re-hospitalization for HF, ACS and severe AF was reduced in patients undergoing ABL compared to the control group. However re-hospitalization for simple AF was increased in patients who had ABL. Our study group is diverse, reflecting the multi-ethnic population of California and comprised a wide age range. The majority of patients were between 50-79 years old and Caucasian males. Although California population is multi ethnic (Caucasians 44%; Hispanics 33%, Blacks 0.06%; Asians 15% and miscellaneous 7.9%), our findings are consistent with our prior report that hospitalization for AF has been higher for Caucasians, and they also have higher ABL rate[5]. As previously described, HTN was highly prevalent, with a proportion of other risk factors such as DM, CAD, HF comparable to prior investigations[13]. More

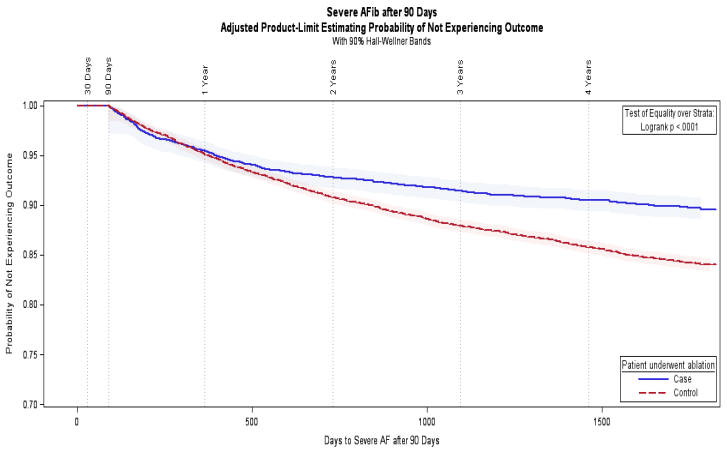

Figure 2D: Probability of not experiencing outcomes (Y axis), Days of follow up (X axis)D-Severe Atrial fibrillation.

patients had recent hospitalization for episodes of AF in ABL group, even though there was no difference in the number of admissions per patient. Patients had at least 2.5 hospitalizations, especially for principal diagnosis of AF before they underwent ABL; those with recent HF episodes were less likely to receive ABL, especially if HF was the principal diagnosis for that hospitalization.

A reduction in long-term HF readmissions in ABL group:

HF and AF often co-exist due to similar risk factors and co-morbidities[14]. In patients with HF, AF worsens pump function and augments mortality[15]. Additionally, HF is a cause for frequent hospitalizations in those with AF and is also associated with increased mortality[1]. Impaired atrial function in AF contributes to reduced peak oxygen consumption and cardiac output, in particular if heart rate is high;[16] Peak oxygen consumption and cardiac output are restored with return of sinus rhythm[17]. However, medical management for rhythm control has been ineffective in improving survival or reducing HF[18]. In contrast, restoration of sinus rhythm by ABL has shown improved survival and reduced HF episodes compared to non-ablated patients, in studies of AF patients with HF and reduced ejection fraction[19-21]. Preliminary results of CABANA trial indicate reduced cardiovascular hospitalization, though details of these results are not yet available. Our large study supports this finding as reflected by fewer HF hospitalizations in the ABL group. After ABL, AF episodes are known to recur at < 90 days; therefore, by convention episodes occurring after this blanking period are considered irrelevant for therapeutic failures[22]. We anticipated a higher rate of HF hospitalization at < 90 days as previously reported, possibly from peri-procedural fluid administration, inflammation and recurrent AF episodes. Our study revealed a higher rate of HF hospitalization at < 90 days; but despite this result, long term HF readmissions were 30% lower, mainly due a 45% reduction of these episodes after 90 days and through our five year follow up.

A reduction in re-hospitalization for ACS in ABL group:

CAD is a risk factor for development of AF, possibly related to atrial ischemia or the impact of left ventricular dysfunction on left atrial pressure and size[13,23]. In addition, as shown in the meta-analysis by Guo et al, patients with AF are at higher risk of MI[24]; a similar increase was noted in the atherosclerosis in the communities study (ARIC)[25]. The mechanisms for the increased risk are multifactorial, including a higher prevalence of risk factors, coronary embolism, inflammation and coronary endothelial dysfunction[26-28]. Computerized tomography has shown a higher prevalence of subclinical CAD and coronary calcification in patients with AF than in controls with sinus rhythm[29]. While there is a small risk of MI following cardioversion, the long-term decrease in hazard of ACS by maintenance of sinus rhythm is unknown. Anticoagulation reduces risk of thromboembolism, however it has not been shown to decrease ACS events[30-32]. We defined ACS based on ICD 9 codes for ST elevation MI (STEMI), non-STEMI or unstable angina. Since the objective of ABL is to create therapeutic myocardial injury, elevated myocardial markers is expected in the peri-procedural phase[33]. Therefore, in accounting for clinical outcomes, we considered only the readmissions for ACS occurring > 7 days after ABL. Our study reveals a reduction in re-hospitalization for ACS, especially >90 days after procedure during long term follow up. This could

be due to improved rhythm control or improved management of CAD. Consistent with our study, in a group of patients with AF and CAD who underwent percutaneous intervention, ABL reduced ACS compared to controls[34]. To our knowledge, ours is the first and largest study to show a reduced risk for ACS for all AF patients undergoing ABL regardless of pre-existing CAD.

An overall increase in re-hospitalization for simple AF episodes but a reduction in re-hospitalization for severe AF in the ABL group:

Regarding recurrence of AF after ABL, the majority of studies define success as non-relapse of AF > 30 seconds in duration on a monitor[22]. However despite reduced AF burden, asymptomatic episodes have been reported to be more frequent following ABL. Hospitalization for AF is a significant burden for these patients and reduction would be a beneficial clinical outcome. In a study of Medicare beneficiaries, the increased utilization of ABL has been associated with decreased 30-day re-hospitalization[35]. Our study shows an overall increase in re-hospitalization for simple AF episodes, although severe AF defined as that associated with ACS or HF was reduced in the ABL group. Simple AF recurrence could represent a low risk patient group who are very sensitive to their symptoms with a low threshold to seek medical care including ABL. Our group also represents those who underwent ablation after at least one hospitalization for AF; these patients could represent a high risk patient population. The benefits for reduced re-hospitalization in the ambulatory patients undergoing ABL without any prior hospitalization for AF cannot be assessed from our study. An increased awareness of this finding could enhance ambulatory care management of this subset of patients.

There are several important strengths within our study. The current study represents the inclusion of a multi-ethnic population, as well as the calendar period when utilization of ABL advanced most rapidly. Though we did not have access to rhythm control or anticoagulation, our results of reduction in HF and ACS provide another possible benefit from ABL for AF.

Limitations

This study is a retrospective investigation with inherent limitations of that method. However, to our knowledge this is the first and largest matched case control study of a multi-ethnic population of ABL for AF for cardiac outcomes. It depends on the accuracy of ICD 9 codes, but the validity of the data is supported by periodic audits performed for billing. We have also reviewed sample charts to ensure accuracy of exclusion and inclusion criteria. We do not have access to the actual rhythm and drugs used for treatment of the patients before and after ABL or the details of ABL strategy.

Conclusion

In this large population-based matched multivariate analysis of hospitalized patients with a diagnosis of NVAF undergoing ABL, the procedure was associated with reduced re-hospitalization for HF, ACS, and severe AF but increased readmissions for simple AF.

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