Diagnosis-to-ablation time predicts recurrent atrial fibrillation and rehospitalization following catheter ablation

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BACKGROUND Wait times for catheter ablation in patients with symptomatic atrial fibrillation (AF) may influence clinical outcomes.

OBJECTIVE This study examined the relationship between the duration from AF diagnosis to ablation, or diagnosis-to-ablation time (DAT), on the clinical response to catheter ablation in a large nationwide cohort of patients.

METHODS We identified patients with new AF who underwent catheter ablation between January 2014 and December 2017 using the IBM MarketScan databases. Cox proportional hazard models were used to estimate the strength of the association between DAT and the outcomes of AF recurrence and hospitalization at 1 year postablation.

RESULTS Among 11,143 AF patients who underwent ablation, the median age was 59 years, 31% were female, and the median CHA_2DS_2-VASc score was 2. Median DAT was 5.5 (2.6, 13.1) months. At 1 year postablation, 10.0% (n = 1116) developed recurrent AF. For each year increase in DAT, the risk of AF recurrence increased by 20% after adjustment for baseline comorbidities and medications (hazard ratio [HR] 1.20, 95% confidence interval [CI] 1.11–1.30). A longer DAT was associated with an increased risk of hospitalization (HR 1.08 per DAT year, 95% CI 1.02–1.15). DAT was a stronger predictor of AF recurrence postablation than traditional clinical risk factors, including age, prior heart failure, or renal failure.

CONCLUSION Increasing duration between AF diagnosis and catheter ablation is associated with higher AF recurrence rates and all-cause hospitalization. Our findings are consistent with a growing body of evidence supporting the benefits of prioritizing early restoration of sinus rhythm.

KEYWORDS Atrial fibrillation; Catheter ablation; Recurrence; Rehospitalization; Predictors

Introduction

Catheter ablation is an effective therapy for patients with symptomatic atrial fibrillation (AF) to improve quality of life and reduce morbidity.[1] However, the long-term success of AF catheter ablation remains suboptimal, with reported AF recurrence rates ranging from 20% to 50% at 1 year.[2] Given the natural history of AF and progressive remodeling of atrial substrate, timely catheter ablation may influence procedural success and rates of AF recurrence. The likelihood of restoring and maintaining sinus rhythm diminishes over time owing to the structural and electrical remodeling processes associated with long-standing AF.[3] Recent studies have given support to the hypothesis that timely AF ablation can slow the progression of AF from paroxysmal to persistent forms.[4] Furthermore, the recently published EAST-AFNET 4 (Early Treatment of Atrial Fibrillation for Stroke Prevention Trial) supports a strategy of rhythm control when applied earlier in the AF disease course to reduce the risk of adverse clinical outcomes.[5]

Diagnosis-to-ablation time (DAT), or the duration between AF clinical diagnosis and first catheter ablation, is an emerging clinical predictor of ablation success. Several observational studies have suggested that an inverse relationship exists between shorter DAT and AF recurrence following catheter ablation.[6] However, these studies were

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KEY FINDINGS

- This study sought to investigate an emerging predictor of clinical response to catheter ablation, diagnosis-to-ablation time (DAT), or the duration between atrial fibrillation (AF) diagnosis and ablation, in a large nationwide cohort of patients.
- Among 11,143 patients with newly diagnosed AF undergoing catheter ablation, the risk of AF recurrence at 1 year following catheter ablation increased by 20% and the risk of all-cause hospitalization increased by 8% for every year increase in DAT.
- The linear relationship between DAT and AF recurrence suggests that there is no threshold effect and that earlier ablation is more beneficial.

limited by either small sample size, single-center study design, or variable ability to adjust for important confounders such as antiarrhythmic medication use. Therefore, we examined the association between DAT and clinical outcomes in a large nationwide cohort of nonvalvular AF patients who underwent catheter ablation.

Methods

Study design and cohort

This study was a retrospective cohort analysis of patients aged 18 years and older with AF who underwent catheter ablation. Patients were identified in the Truven Health (IBM) MarketScan Commercial Claims and Encounters Database (2013–2017), which includes person-level information on healthcare utilization, diagnoses, and enrollment from multiple private-sector medical payers. Covered individuals include insured employees and their dependents, Consolidated Omnibus Budget Reconciliation Act (COBRA) individuals, and those with employer-provided Medicare Supplemental coverage.

Administrative codes from the International Classification of Diseases, Ninth Revision Clinical Modification (ICD-9-CM), Tenth Revision Clinical Modification (ICD-10-CM), and Tenth Revision Procedure Coding System (ICD-10-PCS) and Current Procedural Terminology (CPT) were used to construct the study cohort. Eligible patients were identified as those with incident nonvalvular AF, defined as the first inpatient or outpatient encounter with an AF diagnosis (ICD-9-CM 427.31; ICD-10-CM I48.0–I48.2, I48.91), who underwent catheter ablation (CPT 93656, 93657; ICD-9-CM 37.33, 37.34; ICD-10-PCS 02573ZZ, 02583ZZ, 025S3ZZ, 025T3ZZ) during the study period (January 1, 2014 to December 31, 2017). Patients were also required to have continuous healthcare coverage for at least 12 months pre–AF diagnosis and be at least 18 years of age.

Patients were excluded from the analysis if they had any of the following in the year prior to incident AF: valvular disease (ie, mitral or aortic disease [ICD-9-CM 394, 395, 396, 424.0, 424.1; ICD-10-CM I05, I06, I08.0, I08.1, I08.2, I08.3, I34, I35], tricuspid or pulmonary valvular disease [ICD-9-CM 397, 424.2, 424.3; ICD-10-CM I07, I08.1, I08.2, I08.8, I08.9, I36, I37] or valve surgery [ICD-9-CM 35.0, 35.1, 35.2, 35.96, 35.97, 35.99; 1.HS.80,1.HS.90, 1.HT.80, 1.HT.89, 1.HT.90, 1.HU.80, 1.HU.90, 1.HV.80, 1.HV.90]), previous history of AF (ICD-9-CM 427.31; ICD-10-CM I48.0-I48.2, I48.91), surgical maze procedure (CPT 33256, 32257, 33259, 33254, 33255, 33258, 33265, 33266; ICD-9-CM 37.33, 37.34; ICD-10-PCS 02560ZZ, 02570ZZ), or dialysis (CPT 90918-90999).

Variables

DAT was the primary predictor of interest, calculated as the number of days between the first AF diagnosis and the date of first catheter ablation. The primary analyses considered DAT as a continuous variable in years. Alternative cutoffs were also explored for descriptive purposes: $\leq$1 year vs $>$1 year, $\leq$2 years vs $>$2 years, and quartiles. The distribution of DAT is displayed in Supplemental Figure S1.

The primary outcome of interest was AF recurrence 1 year after index ablation. AF recurrence was defined as the first occurrence, following a 90-day blanking period, of a repeat ablation (CPT 93656, 93657; ICD-9-CM 37.33, 37.34; ICD-10-PCS 02573ZZ, 02583ZZ, 025S3ZZ, 025T3ZZ), or an emergency room visit, inpatient hospital visit, or electrical cardioversion (CPT 92960, 92961; ICD-9-CM 99.61, 99.62, 99.60; ICD-10-PCS 5A2204Z) with a primary diagnosis of AF. First all-cause hospitalization 1 year after index ablation was the secondary outcome, defined as the first inpatient hospital admission following the index ablation; transfers to other hospitals and admissions for rehabilitation were excluded. Patients without the event of interest were censored at the end of MarketScan enrollment coverage, or end of the study period (December 31, 2017).

Covariates included age at AF diagnosis, sex, comorbid conditions, and medication use. Comorbid conditions, assessed in the year prior to index AF diagnosis, were defined using validated algorithms (Supplemental Table S1). Medication use was extracted from the prescription drug claims filled by the patient during the 3 months prior to first catheter ablation; those without prescription drug coverage (6.8% of sample) were assigned to a missing category.

Statistical analysis

Characteristics were reported for the overall sample and DAT $\leq$1 year vs $>$1 year using proportions and frequencies for categorical variables and medians and interquartile ranges for continuous variables; differences were tested using χ^2 or Kruskal-Wallis tests, respectively. The AF recurrence and all-cause hospitalization 1-year event rates were calculated using Kaplan-Meier estimates, overall and by sex.

The relationship between DAT and outcomes was assessed using unadjusted and adjusted Cox regression models without competing risks to calculate hazard ratios (HR) and

95% confidence intervals (95% CI). Time 0 was set to the date of index AF catheter ablation. These models were repeated with the DAT predictor categorized as ≤1 year vs >1 year, ≤2 years vs >2 years, and quartiles. A sensitivity analysis was conducted using the more restrictive definition of the outcome AF recurrence, defined as a repeat ablation following a 90-day blanking period, using the same models.

This analysis was repeated within predefined subgroups, including preexisting heart failure (HF), presence of any comorbid renal disease, female sex, and AF subtype at diagnosis (ie, paroxysmal AF [ICD-10-CM I48.0] and persistent or chronic AF [ICD-10-CM I48.1, I48.2]) (Supplemental Table S2). We additionally tested for a difference in the associations with DAT by each of these subgroup indicators by including interactions between the subgroup variable and DAT variable for each outcome in separate outcome models. As a sensitivity analysis, we assessed the relationship between DAT and an alternate definition of AF recurrence, limited to electrical cardioversions for AF.

We tested the assumptions for the Cox proportional hazards model by examining the Schoenfeld residuals for rank and log time and the Kolmogorov-Type Supremum Tests (proportional hazards assumption) and graphing the Martingale residuals across continuous predictors (linearity assumption).[7] These criteria were met across models, including for all functional forms of DAT assessed. We calculated the effect of continuous DAT on estimated 1-year AF recurrence and plotted the estimated probability against the continuous DAT values, with a LOESS or locally weighted smoothing parameter = 0.8.[8,9]

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). The analysis was approved by the Duke University Institutional Review Board and conducted in accordance with the Declaration of Helsinki. Individual written informed consent was waived owing to the fully de-identified structure of the dataset.

Results

Cohort characteristics

The study cohort included 11,143 patients with incident clinical AF who underwent catheter ablation. The median age was 59 (25th, 75th percentiles: 53, 64) years, 30.8% (n = 3431) were female, and the median CHA_2DS_2-VASc score was 2 (1, 3) (Table 1). The most prevalent comorbidities in the cohort were hypertension (60.2%, n = 6713), coronary artery disease (22.2%, n = 2474) and diabetes mellitus (19.2%, n = 2136).

The median DAT was 5.5 (2.6, 13.1) months. When stratified by DAT ≤1 and >1 year, the baseline medical comorbidities were similar between the 2 groups, with the exception of hypertension and cancer, which were more prevalent in the DAT >1 year group. Differences in baseline medications were not clinically significant between groups; however, longer DAT (>1 year) was associated with a higher frequency of class Ic and III antiarrhythmic medication use.

Clinical outcomes at 1 year

At 1-year postablation, 10.0% (n = 1116) developed recurrent AF. As DAT increased, there was a linear increase in the 1-year risk of AF recurrence postablation (adjusted HR 1.20 per DAT year, 95% CI 1.11–1.30; $P < .001$) (Figure 1). When DAT was assessed as a prespecified dichotomous variable (ie, 1- or 2-year cutoff values), the relationship with AF recurrence postablation remained consistent (Figure 2 and Table 2). As a sensitivity analysis, we assessed the relationship between DAT and an alternative definition of AF recurrence, limited to cardioversion for AF. At 1 year postablation, 3.0% (n = 331) had an electrical cardioversion for AF. When DAT was assessed as a continuous or categorical variable, the relationship between DAT and recurrent AF remained consistent in this analysis (Supplemental Table S3).

At 1 year after AF ablation, 16.5% (n = 1833), or approximately 1 out of 6 individuals, were admitted to the hospital. For every year increase in DAT, there was an 8% increased risk in all-cause hospitalization at 1 year (adjusted HR 1.08 per DAT year, 95% CI 1.02–1.15, $P = .007$) (Figure 1 and Table 2). Similar relationships were observed when DAT was stratified as a dichotomous variable.

Predictors of atrial fibrillation recurrence and hospitalization after ablation

Univariable and multivariable adjusted predictors of AF recurrence and all-cause hospitalization following catheter ablation are shown in Table 3. Independent predictors of AF recurrence postablation included DAT, peripheral vascular disease, and prior calcium channel blocker use. In the multivariable model, DAT remained a stronger predictor of AF recurrence when compared with traditional clinical risk factors, such as age, renal failure, or diabetes. With respect to all-cause hospitalization, both DAT and traditional risk factors (such as age, HF, chronic obstructive pulmonary disease, and diabetes) were independently associated with the outcome at 1 year.

Subgroup analysis

The association between DAT and outcomes was assessed in several prespecified subgroups. Interaction tests between DAT (continuous years and dichotomous <1 year) were not significant for any subgroup with either outcome (all $P > .10$). Although interaction terms between the DAT predictor and our subgroups of interest were not statistically significant, we report the several prespecified subgroups owing to their clinical relevance (Table 4).

DAT was significantly associated with AF recurrence postablation among patients with HF at baseline (n = 1232; adjusted HR 1.31 per DAT year, 95% CI 1.05–1.63, $P = .016$), among patients with renal disease (n = 494 excluding patients on dialysis; adjusted HR 1.48 per DAT year, 95% CI 1.08–2.01, $P = .013$) and among women (n = 3431; adjusted HR 1.21 per DAT year, 95% CI 1.05–1.38, $P = .008$).

Table 1 Baseline characteristics, stratified by diagnosis-to-ablation time at 1 year

	Overall N = 11,143	DAT ≤1 year n = 8118	DAT >1 year n = 3025	*P* value
Age (years), median (IQR)	59.0 (53.0, 64.0)	59.0 (53.0, 64.0)	59.0 (53.0, 64.0)	.98
Female	3431 (30.8%)	2518 (31.0%)	913 (30.2%)	.40
Myocardial infarction	614 (5.5%)	442 (5.4%)	172 (5.7%)	.62
Congestive heart failure	1232 (11.1%)	906 (11.2%)	326 (10.8%)	.57
Coronary heart disease	2474 (22.2%)	1798 (22.1%)	676 (22.3%)	.82
Hypertension	6713 (60.2%)	4828 (59.5%)	1885 (62.3%)	.006
Peripheral vascular disease	719 (6.5%)	506 (6.2%)	213 (7.0%)	.12
Diabetes	2136 (19.2%)	1541 (19.0%)	595 (19.7%)	.41
Stroke or TIA	455 (4.1%)	319 (3.9%)	136 (4.5%)	.18
Dementia	24 (0.2%)	22 (0.3%)	2 (0.1%)	.04
Cerebrovascular disease	810 (7.3%)	575 (7.1%)	235 (7.8%)	.22
COPD	1967 (17.7%)	1453 (17.9%)	514 (17.0%)	.26
Renal disease	494 (4.4%)	358 (4.4%)	136 (4.5%)	.84
Cancer	787 (7.1%)	541 (6.7%)	246 (8.1%)	.007
$CHADS_2$-VASc, median (IQR)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.0, 3.0)	.04
$CHADS_2$-VASc score				.31
0	2185 (19.6%)	1619 (19.9%)	566 (18.7%)	
1	3174 (28.5%)	2312 (28.5%)	862 (28.5%)	
≥2	5784 (51.9%)	4187 (51.6%)	1597 (52.8%)	
Deyo-Charlson comorbidity index, median (Q1, Q3)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	1.0 (0.0, 2.0)	.67
Medications				
Beta blockers	6137 (55.1%)	4453 (54.9%)	1684 (55.7%)	<.001
Antiarrhythmic - class Ic	2330 (20.9%)	1689 (20.8%)	641 (21.2%)	<.001
Antiarrhythmic - class III	3323 (29.8%)	2358 (29.0%)	965 (31.9%)	<.001
Calcium channel blockers	2218 (19.9%)	1634 (20.1%)	584 (19.3%)	<.001
Digoxin	719 (6.5%)	533 (6.6%)	186 (6.1%)	<.001
ACEI/ARB	4057 (36.4%)	2899 (35.7%)	1158 (38.3%)	<.001
Antiplatelet	667 (6.0%)	494 (6.1%)	173 (5.7%)	<.001
Lipid-lowering medication	4133 (37.1%)	2893 (35.6%)	1240 (41.0%)	<.001
Diuretics	2093 (18.8%)	1443 (17.8%)	650 (21.5%)	<.001

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; DAT = diagnosis-to-ablation time; IQR = interquartile range; TIA = transient ischemic attack.

An exploratory analysis also assessed the relationship between DAT and AF recurrence by AF subtype at baseline. Data on AF subtype were available for only 23.6% (n = 2625) of the overall cohort, since ICD-10 diagnostic codes, which provide additional granularity on AF subtype, were only available after October 1, 2015. There was no statistically significant association between DAT and AF recurrence in persistent or chronic AF. However, among patients with paroxysmal AF, DAT was significantly associated with AF recurrence (adjusted HR 1.78 per DAT year, 95% CI 1.13–2.82, $P = .014$).

There were no differences in the 1-year risk of all-cause hospitalization by subgroup (Supplemental Table S4).

Discussion

In this analysis of 11,143 patients from a large nationwide United States cohort, a longer duration between incident AF diagnosis and catheter ablation was associated with an increased risk of AF recurrence postablation and all-cause hospitalization at 1 year. Specifically, for every year increase in DAT, the risk of AF recurrence at 1 year following catheter ablation increased by 20% and the risk of all-cause hospitalization increased by 8%. The linear relationship between DAT and AF recurrence suggests that there is no threshold effect and that earlier ablation is better. Furthermore, in the multivariable adjusted models, DAT was a stronger predictor of AF recurrence than traditional clinical risk factors, such as HF or diabetes. Finally, a longer DAT was associated with increased AF recurrence across important patient subgroups, including patients who were female or had HF or renal failure.

The results are consistent with prior studies that assessed the relationship between DAT and AF recurrence. A meta-analysis of 6 observational studies found that a DAT of 1 year or less was associated with a reduced relative risk of AF recurrence (RR 0.77; 95% CI 0.72–0.83, $P < .001$).[6] However, the individual studies of the meta-analysis were limited by relatively small cohort sizes, inconsistent adjustment for important covariates such as baseline medication use, and inclusion of patients that underwent ablation over a decade ago.[10,11] The current study complements the existing literature by assessing DAT in a more contemporary nationwide cohort that better reflects the current catheter ablation technology, such as use of next-generation electroanatomic mapping systems and contact force catheters, which are associated with increased likelihood of procedural success.[12]

Few studies have assessed the association between DAT and "hard" cardiovascular outcomes, and the results are

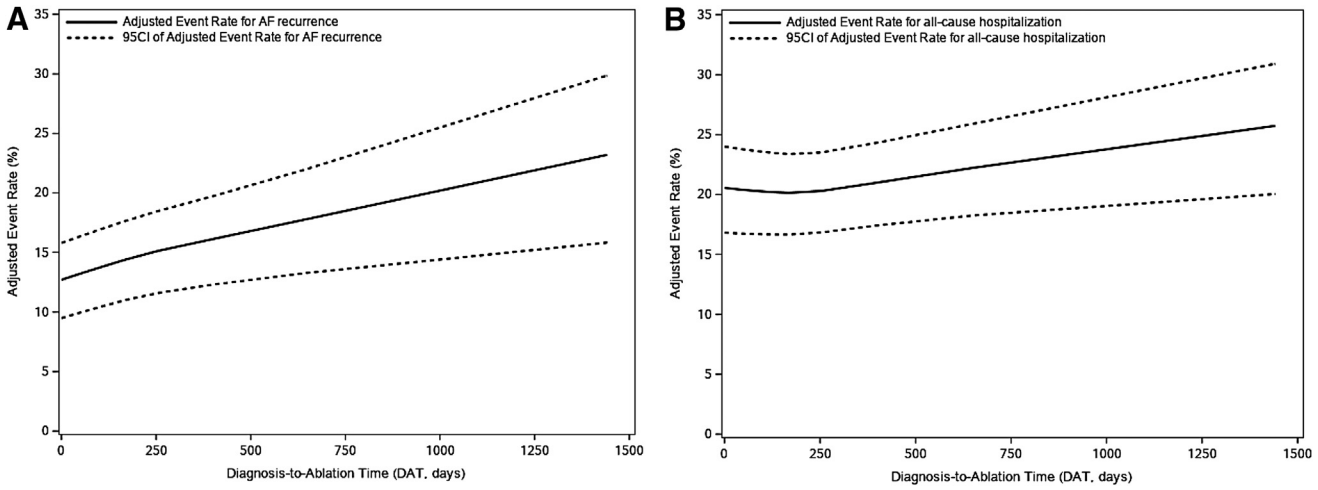

Figure 1 Adjusted event rates at 1 year for **A:** atrial fibrillation (AF) recurrence and **B:** first all-cause hospitalization. DAT = diagnosis-to-ablation time.

conflicting. For example, Bunch and colleagues[13] found that longer DAT was associated with an almost 3-fold increased risk of all-cause mortality and 2-fold increased risk of HF hospitalization at 1 year. In contrast, another study found no significant differences in all-cause mortality or HF hospitalization after adjustment for baseline covariates, except in the subgroup of patients with a history of HF.[14] While our study outcomes did not include the subset of hospitalizations related to HF, DAT was associated with all-cause hospitalization independently of traditional clinical predictors such as increasing age and increasing comorbidity burden.[15,16]

Interestingly, the current study cohort had a median DAT of 5.5 months, which is relatively short compared to prior studies. The shorter median DAT may be attributed to a more contemporary and younger study cohort, which may reflect improved access and availability of catheter ablation. Nevertheless, over 25% of the cohort had a DAT between 12 and 44 months. Our findings suggest that when DAT was assessed as a continuous variable, even monthly delays in ablation increased the risk of AF recurrence.

While DAT is conceptually an attractive candidate surrogate for atrial remodeling and progressive atrial myopathy that occurs during the natural history of AF,[17] the relatively short median DAT of the cohort suggests that some degree of maladaptive atrial remodeling may be present at the time of clinical AF diagnosis. That is, the precise date of AF genesis is undiscernible and AF may have already existed for variable periods of time prior to clinical diagnosis. Nevertheless, prior studies have investigated progressive atrial remodeling as the mechanistic link between DAT, greater resistance to successful AF ablation, and higher AF recurrence rates.[17–19]

Hussein and colleagues[17] found that a longer duration of AF preceding catheter ablation was associated with higher degrees of atrial remodeling suggested by atrial dilatation and increased serum biomarkers. Furthermore, the prospective multicenter DECAAF (Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation) study found a linear relationship between the degree of atrial fibrosis as identified by late gadolinium enhancement cardiac magnetic resonance imaging and AF

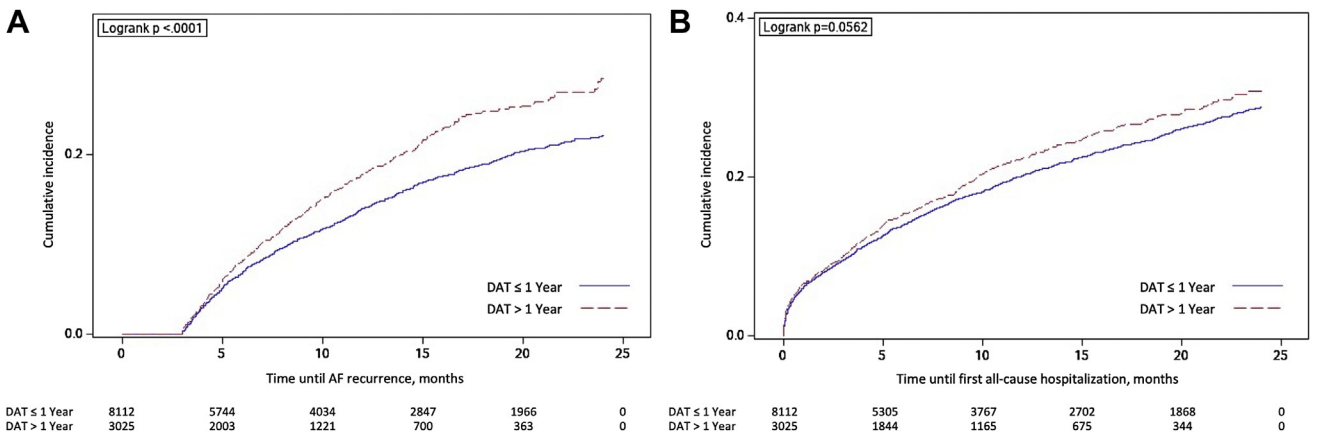

Figure 2 Product-limit failure curves for 1-year (**A**) atrial fibrillation (AF) recurrence and (**B**) first all-cause hospitalization, stratified by diagnosis-to-ablation time (DAT) ≤1 year and >1 year.

Table 2 Association between diagnosis-to-ablation time with atrial fibrillation recurrence and first all-cause hospitalization at 1 year postablation

	AF recurrence						First all-cause hospitalization					
	Unadjusted model			Adjusted model[†]			Unadjusted model			Adjusted model[†]		
Predictor	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
DAT, per year	1.21	1.12–1.3	<.001	1.20	1.11–1.3	<.001	1.07	1.01–1.14	.020	1.08	1.02–1.15	.007
DAT >1 year	1.28	1.12–1.45	<.001	1.27	1.12–1.45	<.001	1.11	1–1.22	.05	1.10	1.00–1.22	.06
DAT >2 years	1.33	1.09–1.64	.006	1.33	1.08–1.63	.007	1.31	1.13–1.53	<.001	1.31	1.13–1.53	<.001
DAT quartiles[‡]												
Quartile 1	Ref.			Ref.			Ref.			Ref.		
Quartile 2	1.17	0.98–1.40	.08	1.18	0.99–1.41	.07	0.96	0.84–1.09	.51	1.01	0.89–1.15	.87
Quartile 3	1.36	1.15–1.61	<.001	1.37	1.15–1.62	<.001	0.91	0.80–1.03	.14	0.96	0.84–1.09	.53
Quartile 4	1.47	1.24–1.75	<.001	1.48	1.24–1.75	<.001	1.09	0.96–1.23	.20	1.13	1.00–1.29	.05

AF = atrial fibrillation; DAT = diagnosis-to-ablation time.

[†]Adjusted for age, sex, comorbidities, and baseline medications.

[‡]DAT quartiles. Q1: 0–2.57 months; Q2: 2.60–5.53 months; Q3: 5.56–13.1 months; Q4: 13.2–47.4 months.

recurrence rates postablation,[18] and Chelu and colleagues[19] correlated higher levels of atrial fibrosis with longer AF duration. More recently, AF arrhythmic burden quantified by continuous implantable loop recorder monitoring has been suggested as a marker of underlying atrial remodeling. In a prespecified subanalysis of the CIRCA-DOSE (Cryoballoon vs Irrigated Radiofrequency Catheter Ablation: Double Short vs Standard Exposure Duration) study, Andrade and colleagues[20] found that baseline AF episode durations of longer than 24 continuous hours were associated with a 3-fold increased odds of AF recurrence following cryoablation.

Importantly, unlike imaging and arrhythmic burden predictors of AF ablation outcome, DAT is a readily available and actionable risk marker. Thus, optimizing patient care processes that reduce the time to AF catheter ablation may improve rates of procedural success, patient quality of life, and clinical outcomes. For example, there is emerging evidence that catheter ablation earlier in the AF disease process may alter the natural history of AF, slow the progression from paroxysmal to persistent phenotypes, and decrease AF burden.[4,21] With regard to "hard" cardiovascular endpoints, the recently published EAST-AFNET 4 trial supports a rhythm control strategy when applied earlier in the AF treatment course.[5,22] Specifically, in a cohort of patients with recently diagnosed AF (<1 year since diagnosis), those randomized to an early rhythm control strategy had a lower composite risk of cardiovascular death, stroke, or hospitalization for worsening HF or acute coronary syndrome (HR 0.79, 95% CI 0.66–0.94; $P = .005$) compared to usual care, where over 80% of patients remained on a rate-control strategy.

Table 3 Univariate and multivariable predictors of catheter ablation outcomes at 1 year postablation

	AF recurrence						First all-cause hospitalization					
	Unadjusted			Adjusted			Unadjusted			Adjusted		
Predictor	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
DAT, years	1.21	1.12–1.3	<.001	1.20	1.11–1.3	<.001	1.07	1.01–1.14	.020	1.08	1.02–1.15	.007
Age, years	1.01	1–1.02	.001	1.01	1.00–1.01	.12	1.03	1.02–1.03	<.001	1.01	1.01–1.02	<.001
Female sex	1.06	0.94–1.21	.33	1.04	0.91–1.18	.55	1.11	1.01–1.23	.030	1.05	0.95–1.16	.31
Myocardial infarction	1.22	0.96–1.55	.10	1.07	0.82–1.40	.63	2.01	1.72–2.35	<.001	1.24	1.04–1.48	.019
Congestive heart failure	1.09	0.91–1.32	.35	0.99	0.82–1.21	.94	2.06	1.83–2.32	<.001	1.46	1.29–1.66	<.001
Coronary heart disease	1.20	1.05–1.37	.008	1.07	0.91–1.26	.39	1.79	1.63–1.98	<.001	1.22	1.08–1.38	.001
Hypertension	1.21	1.07–1.37	.002	1.09	0.96–1.25	.18	1.66	1.5–1.83	<.001	1.20	1.07–1.33	.001
Peripheral vascular disease	1.49	1.21–1.84	<.001	1.35	1.08–1.69	.007	1.70	1.46–1.99	<.001	1.14	0.97–1.35	.11
Diabetes	1.20	1.04–1.38	.013	1.08	0.93–1.26	.31	1.68	1.52–1.87	<.001	1.24	1.11–1.39	<.001
Stroke or TIA	1.22	0.92–1.61	.16	1.14	0.75–1.74	.53	1.85	1.54–2.22	<.001	1.36	1.03–1.81	.030
Dementia	1.40	0.45–4.35	.56	1.28	0.41–4.00	.67	2.86	1.54–5.33	.001	1.77	0.95–3.32	.07
Cerebrovascular disease	1.18	0.95–1.46	.13	0.91	0.65–1.27	.58	1.73	1.49–2	<.001	0.98	0.78–1.23	.86
COPD	1.13	0.97–1.31	.11	1.05	0.90–1.22	.56	1.73	1.56–1.92	<.001	1.39	1.25–1.55	<.001
Renal disease	1.13	0.86–1.49	.37	0.97	0.73–1.29	.83	2.08	1.76–2.46	<.001	1.30	1.09–1.55	.003
Cancer	1.24	1.01–1.54	.044	1.14	0.92–1.42	.23	1.45	1.25–1.7	<.001	1.17	1.00–1.37	.049
Beta blockers	1.28	1.12–1.46	<.001	0.98	0.86–1.11	.73	1.17	1.06–1.3	.003	1.22	1.10–1.35	<.001
Anti-arrhythmia drugs	1.15	1.01–1.3	.032	0.96	0.85–1.08	.49	1.03	0.94–1.14	.54	1.00	0.91–1.1	.95
Calcium channel blockers	1.23	1.08–1.4	.002	1.20	1.04–1.38	.014	1.19	1.07–1.32	.001	1.27	1.14–1.42	<.001
Digoxin	1.39	1.16–1.65	<.001	1.18	0.95–1.47	.13	1.43	1.25–1.64	<.001	1.27	1.09–1.49	.003

AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; DAT = diagnosis-to-ablation time; TIA = transient ischemic attack.

Table 4 Associations between diagnosis-to-ablation time and atrial fibrillation recurrence at 1 year postablation among subgroups

	AF recurrence					
	Unadjusted			Adjusted		
Predictor	HR	95% CI	*P* value	HR	95% CI	*P* value
Heart failure (n = 1232)						
DAT, years	1.30	1.04–1.61	.019	1.31	1.05–1.63	.016
DAT >1 year	1.50	1.02–2.19	.037	1.52	1.03–2.24	.034
DAT >2 years	1.40	0.75–2.60	.29	1.41	0.75–2.64	.29
DAT quartile						
Q1 (0–2.57 months)	Ref.			Ref.		
Q2 (2.60–5.53 months)	0.79	0.47–1.35	.40	0.83	0.48–1.45	.52
Q3 (5.56–13.1 months)	1.17	0.71–1.91	.55	1.19	0.72–1.98	.50
Q4 (13.2–47.4 months)	1.56	0.99–2.43	.05	1.61	1.02–2.54	.04
Renal disease (n = 494)						
DAT, years	1.52	1.13–2.04	.006	1.48	1.08–2.01	.013
DAT >1 year	1.70	0.97–2.97	.06	1.74	0.97–3.13	.06
DAT >2 years	1.96	0.96–4.02	.07	1.94	0.90–4.18	.09
DAT quartile						
Q1 (0–2.57 months)	Ref.			Ref.		
Q2 (2.60–5.53 months)	0.46	0.16–1.27	.13	0.48	0.17–1.37	.17
Q3 (5.56–13.1 months)	1.42	0.7–2.92	.33	1.32	0.62–2.83	.47
Q4 (13.2–47.4 months)	1.91	0.96–3.82	.07	1.93	0.93–4.01	.08
Female sex (n = 3431)						
DAT, years	1.21	1.06–1.38	.006	1.21	1.05–1.38	.008
DAT >1 year	1.20	0.95–1.52	.12	1.20	0.95–1.52	.13
DAT >2 years	1.40	0.99–2.00	.06	1.39	0.98–1.99	.07
DAT quartile						
Q1 (0–2.57 months)	Ref.			Ref.		
Q2 (2.60–5.53 months)	1.34	0.99–1.83	.06	1.28	0.93–1.75	.13
Q3 (5.56–13.1 months)	1.69	1.26–2.27	<.001	1.67	1.24–2.26	.001
Q4 (13.2–47.4 months)	1.46	1.07–2	.02	1.43	1.04–1.96	.03
Paroxysmal AF[†] (n = 2044)						
DAT, years	1.68	1.07-2.65	.03	1.78	1.13-2.82	.01
DAT >1 year	1.66	0.91–3.01	.10	1.72	0.94–3.14	.08
DAT quartile						
Q1 (0–2.57 months)	Ref.			Ref.		
Q2 (2.60–5.53 months)	0.91	0.59–1.4	.67	0.93	0.6–1.43	.73
Q3 (5.56–13.1 months)	1.57	1.04–2.36	.031	1.64	1.08–2.49	.02
Q4 (13.2–47.4 months)	1.12	0.48–2.62	.79	1.19	0.5–2.79	.70
Persistent or chronic AF[†] (n = 581)						
DAT, years	1.57	0.74–3.29	.24	1.57	0.71–3.48	.27
DAT >1 year	0.56	0.13–2.31	.42	0.55	0.13–2.34	.42
DAT quartile						
Q1 (0–2.57 months)	Ref.			Ref.		
Q2 (2.60–5.53 months)	2.11	1.03–4.35	.04	1.94	0.91–4.12	.09
Q3 (5.56–13.1 months)	1.90	0.89–4.04	.10	2.01	0.9–4.51	.09
Q4 (13.2–47.4 months)	1.22	0.27–5.46	.79	1.23	0.27–5.61	.79

AF = atrial fibrillation; COPD = chronic obstructive pulmonary disease; DAT = diagnosis-to-ablation time.

[†]Effects for models with DAT >2 years as the predictor could not be estimated. Only those with ICD-10 diagnosis coding (service dates October 1, 2015 – present) could be categorized as persistent, chronic, or paroxysmal AF.

Limitations

Limitations of the study include the retrospective nature of the study and the inability to exclude the possible unmeasured factors that may influence timing between AF diagnosis and ablation (such as regional access to ablation facilities, or socioeconomic factors). Factors influencing delays to AF diagnosis may attenuate the usefulness of DAT as a clinical marker of AF remodeling. Despite this, our study suggests that DAT is a reliable predictive marker of postablation outcomes. Second, since DAT was defined as time from first documented AF to the date of catheter ablation, AF may have already existed for variable periods of time before diagnosis. That is, it is possible that we may have underestimated DAT in some patients that were diagnosed with AF prior to enrolling in an insurance plan participating in the MarketScan database. To mitigate this possibility, we limited the cohort

inclusion criteria to patients with a minimum of 12 months of continuous insurance coverage prior to AF diagnosis.

Third, as this study used data from administrative claims, we were unable to adjust for known clinical and imaging predictors of ablation success, such as left atrial size, left atrial fibrosis, and body mass index, or AF treatment characteristics, including risk factor modification and extra lesion sets performed during the catheter ablation procedure. As AF subtype (ie, paroxysmal, persistent) was only available for a subset of the claims data with ICD-10 codes, our subgroup analysis may be underpowered. While Hussein and colleagues previously found an association between DAT and AF recurrence when assessed by electrocardiographic monitoring (including routine 12-lead electrocardiograms at scheduled clinic visits, Holter monitoring and continuous electrocardiogram monitoring when available through cardiac electronic implanted devices), our study did not find a similar association. This may be owing to the administrative definition of AF recurrence, which does not capture asymptomatic AF identified by electrocardiographic monitoring. That is, the study outcome of AF recurrence relied on administrative claims, rather than the traditional definition of >30 seconds of atrial tachyarrhythmia or AF recurrence. While the current study outcome may not be as sensitive as the >30-second definition of AF recurrence, AF recurrences defined through healthcare encounters are clinically meaningful and a relevant endpoint consistent with prior studies.[2,15] Furthermore, we would not expect differential detection or diagnostic bias in those with short or long DAT. Andrade and colleagues[23] have previously shown that the rate of AF recurrence at 1 year depends on the definition of the recurrence endpoint. For example, when employing a traditional AF recurrence definition of any atrial tachyarrhythmia >30 seconds, 43% of patients randomized to ablation in the EARLY AF (Early Aggressive Invasive Intervention for Atrial Fibrillation) trial experienced the endpoint at 1 year. However, when limited to *symptomatic* episodes, only 11% of postablation patients experienced AF recurrence, which is similar to our study (ie, 10% AF recurrence at 1 year).[23]

Fourth, our study cohort was derived from the MarketScan database, which primarily includes younger patients (age <65 years) with employer-provided health insurance. Thus, our results may not be necessarily generalizable to the older patients with AF, such as those enrolled in Medicare. Additionally, we were unable to obtain mortality data for the study cohort from the MarketScan database, and our estimates of AF recurrence may be overestimated in the presence of competing risk.

Conclusion

Shorter duration between AF diagnosis and catheter ablation is associated with lower AF recurrence rates and all-cause hospitalization. These results are consistent with a growing body of evidence supporting emphasis on early restoration of sinus rhythm in AF as an important determinant of both prognosis and quality of life.

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Ethics Statement: The analysis was approved by the Duke University Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

Data Availability: The data that support the findings of this study are available from the IBM MarketScan Research Databases under license. Data will be shared upon reasonable request with permission of IBM MarketScan.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2021.11.012.

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