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ORIGINAL RESEARCH

Direct Oral Anticoagulant Adherence of Patients With Atrial Fibrillation Transitioned from Warfarin

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BACKGROUND: Reduced time in international normalized ratio therapeutic range (TTR) limits warfarin safety and effectiveness. In patients switched from warfarin to direct oral anticoagulants (DOACs), patient factors associated with low TTR could also increase risk of DOAC nonadherence. We investigated the relationship between warfarin TTR and DOAC adherence in warfarin-treated patients with atrial fibrillation switched to DOAC.

METHODS AND RESULTS: Using data from the Veterans Health Administration, we identified patients with atrial fibrillation switched from warfarin to DOAC (switchers) or treated with warfarin alone (non-switchers). Logistic regression was used to evaluate association between warfarin TTR and DOAC adherence. We analyzed 128 605 patients (age, 71±9; 1.6% women; CHA_2DS_2-VASc 3.5±1.6); 32 377 switchers and 96 228 non-switchers. In 8016 switchers with international normalized ratio data to calculate 180-day TTR before switch, TTR was low (median 0.45; IQR, 0.26–0.64). Patients with TTR <0.5 were more likely to be switched to DOAC (odds ratio [OR],1.68 [95% CI,1.62–1.74], P<0.0001), as were those with TTR <0.6 or TTR <0.7. Proportion of days covered ≥0.8 was achieved by 76% of switchers at 365 days. In low-TTR individuals, proportion of days covered ≥0.8 was achieved by 70%, 72%, and 73% of switchers with TTR <0.5, 0.6, and 0.7, respectively. After multivariable adjustment, TTR <0.5 decreased odds of achieving 365-day proportion of days covered ≥0.8 (OR, 0.49; 0.43–0.57, P<0.0001), with similar relationships for TTR <0.6 and TTR <0.7. In non-switchers with TTR <0.5, long-term TTR remained low.

CONCLUSIONS: In patients with atrial fibrillation switched from warfarin to DOAC, most achieved adequate DOAC adherence despite low pre-switch TTRs. However, TTR trajectories remained low in non-switchers. Patients with low warfarin TTR more consistently achieved treatment targets after switching to DOACs, although adherence-oriented interventions may be beneficial.

Key Words: anticoagulation ■ atrial fibrillation heart ■ warfarin

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting up to 6 million Americans.[1] The associated loss of coordinated atrial activity leads to an increased risk of thromboembolic stroke,[2] and stroke prevention using anticoagulant therapy is a major focus of AF management.[3–5] Warfarin was first demonstrated to reduce stroke risk more effectively than aspirin in 1991,[6] and was the only available oral anticoagulant for AF until the approval of dabigatran, apixaban, rivaroxaban, and edoxaban between 2010 and 2015.[7–10] These direct oral anticoagulants (DOAC) provided comparable stroke reduction in AF with lower rates of major bleeding.

Warfarin time in international normalized ratio (INR) therapeutic range (TTR) is an established measure of the intensity of warfarin anticoagulation.[11] TTR can affect the effectiveness and safety of warfarin, and previous studies have suggested that a TTR greater than 0.58 is needed for patients with AF to benefit from warfarin therapy compared to aspirin alone.[12] In

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CLINICAL PERSPECTIVE

What Is New?

- Warfarin-treated patients with atrial fibrillation and low international normalized ratio time in therapeutic range (TTR) continue to have low TTRs over time.
- However, in warfarin users with low TTR switched to a direct oral anticoagulant, the majority achieved adequate direct oral anticoagulant adherence.

What Are the Clinical Implications?

- Warfarin-treated patients with low TTR may have more therapeutic coverage with direct oral anticoagulants.
- Low warfarin TTR should not be used as a direct surrogate for predicting drug adherence and should not be a barrier to switching from warfarin to direct oral anticoagulant therapy.

Nonstandard Abbreviations and Acronyms

DOAC	direct oral anticoagulant
PDC	proportion of days covered
TTR	time in therapeutic range

the United States and much of the world excluding integrated health care systems in Europe, system-wide TTRs are observed to be low,[13,14] including in clinical trial settings.[15,16] With DOACs demonstrated to be noninferior or superior to warfarin in preventing strokes with lower risk of major bleeding, the most recent combined American College of Cardiology/American Heart Association/Heart Rhythm Society and European Society of Cardiology guidelines recommend anticoagulating with a DOAC preferentially over warfarin in eligible patients, and use of a DOAC in patients who are unable to maintain a therapeutic INR level.[3,5]

Prior studies have shown that poor adherence to warfarin decreases TTR in AF.[17,18] Multiple patient-level factors, including sex, race, socioeconomic status, comorbidities, frailty, and medication burden also have been shown to affect TTR.[19–22] These factors may, in turn, affect adherence to other drugs. In patients with AF treated with warfarin, low TTR could then be a risk marker of subsequent reduced DOAC adherence. The projected DOAC adherence of patients with AF with low TTR switched from warfarin has not been evaluated. We therefore sought to characterize the relationship between TTR and clinical risk factors and post-switch DOAC adherence.

METHODS

We performed a retrospective cohort study using data from the US Veterans Health Administration between January 1, 2009 and September 30, 2018. Medical claims data and electronic health records were obtained from the Veterans Affairs (VA) National Patient Care Database,[23] the VA Decision Support System national pharmacy extract,[24] the VA Fee Basis Inpatient and Outpatient datasets, the VA Laboratory Decision Support System extract,[25] Medicare inpatient and outpatient institutional claims data (part A, part B, and carrier files),[26] and the VA Vital Status file, which provides validated mortality data by combining Medicare, VA, and Social Security Administration data.[27,28] The methods for data linkage have been previously described in detail.[29–31]

This study was approved by the local institutional review board (Stanford, CA) and the VA Research and Development Committee (Palo Alto, CA). These data were obtained with permission from the VA Corporate Data Warehouse and stored and analyzed on the VA Informatics and Computing Infrastructure. Data are not available to share because of data use agreements and restrictions on use of Veteran data, but access to the master files may be requested from VA Informatics and Computing Infrastructure by eligible investigators.

Cohorts

Figure 1 summarizes the analysis cohorts, study design, and timing of measurements. We identified a primary analysis cohort of patients with AF (*International Classification of Diseases, Ninth Revision [ICD-9*], 427.31 or 427.32; *International Classification of Diseases, Tenth Revision* [*ICD-10*], I48) switched from warfarin to DOAC (referred to throughout as switchers). We then excluded patients who (1) did not receive at least 30 days of DOAC prescription (ie, apixaban, dabigatran, edoxaban, or rivaroxaban); (2) filled a DOAC prescription outside the continental United States; (3) were prescribed ≥2 prescriptions from the DOAC class on the index prescription date; (4) did not have a primary or secondary AF diagnosis from 90 days before to 30 days after the index DOAC prescription; (5) had a history of a concomitant indication for anticoagulation (ie, *ICD-9/10* diagnosis of deep vein thrombosis, pulmonary embolism, or mechanical heart valve [Table S1] before index DOAC fill); and (6) did not have a warfarin prescription in the 120 days before the index DOAC prescription [Cohort selection diagram in Figure S1]. The date of index DOAC prescription was defined as the switch date.

We also created a parallel analysis cohort of patients who were not switched from warfarin to DOAC (referred to throughout as non-switchers), so that we could perform (1) a counterfactual analysis on

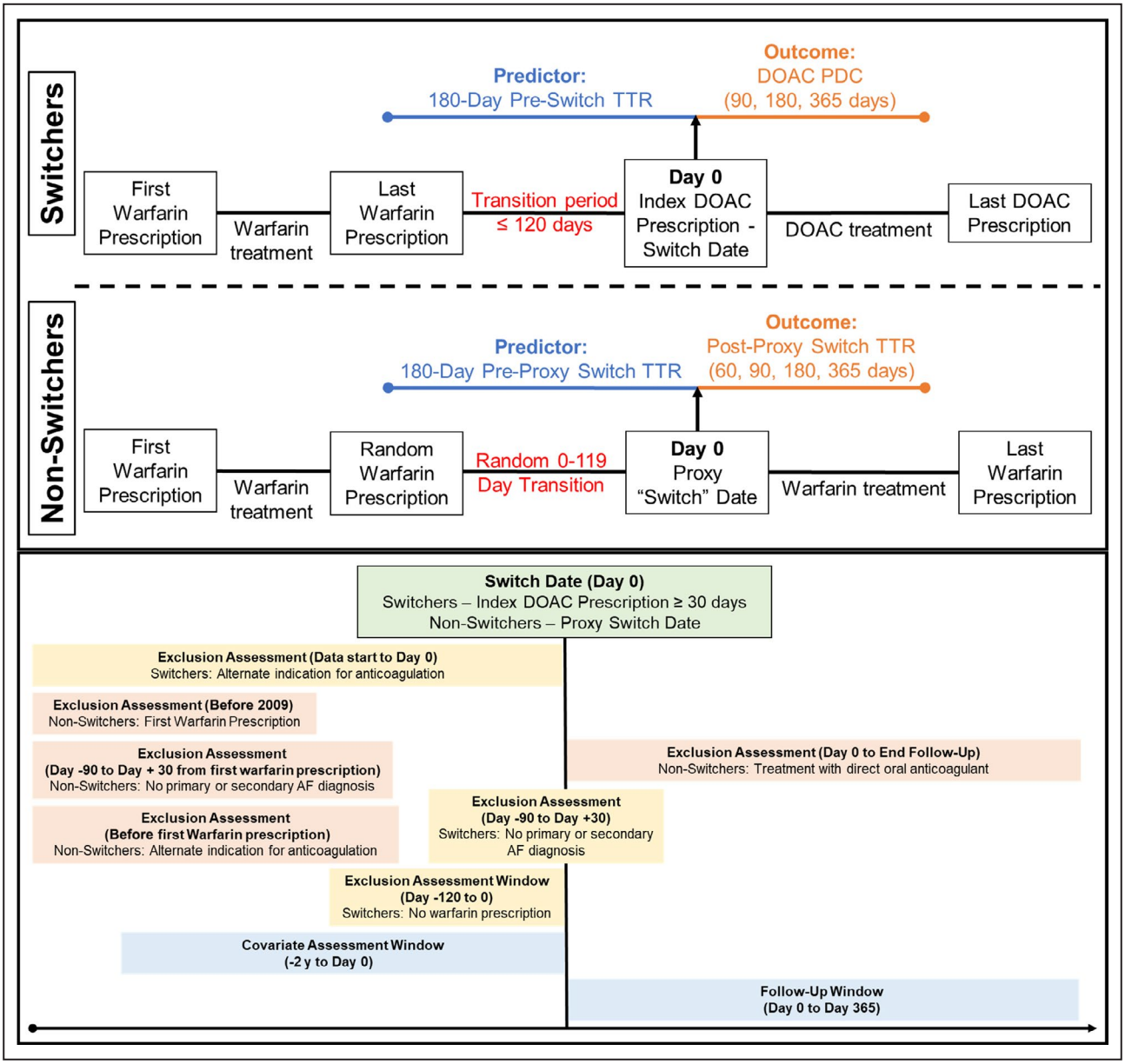

Figure. Study design

(**A**) The primary switcher analysis cohort consisted of patients on warfarin therapy who switched to a direct oral anticoagulant (DOAC) within 120 days of their last warfarin prescription. The warfarin time in therapeutic range (TTR) was calculated in the last 180 days with eligible international normalized ratio (INR) values leading up to the index DOAC prescription. The proportion of days covered by DOAC was calculated over the 90, 180, and 365 days after the initial DOAC prescription. The parallel non-switcher analysis cohort consisted of patients who never received a DOAC prescription. To perform parallel analyses, we assigned a semi-random proxy "switch" date by (1) randomly selecting one warfarin prescription over the course of treatment and (2) randomly choosing a date between 0 and 119 days after that prescription. Pre-switch time in therapeutic range was calculated in the last 180 INR-eligible days leading up to the proxy "switch" date, and post-switch time in therapeutic range was calculated over the 60, 90, 180, and 365 days after the proxy "switch" date. (**B**) Derivation of study population with timing of exclusion criteria, covariate assessment, and follow-up window. AF indicates atrial fibrillation; DOAC, direct oral anticoagulant; INR, international normalized ratio; and TTR, time in therapeutic range.

non-switchers and (2) pooled analyses on the switchers and non-switchers cohorts. For this cohort, we identified all patients with an AF diagnosis treated only with warfarin by excluding those who ever filled a DOAC prescription in the course of follow-up. We then excluded all patients who did not receive a warfarin prescription after 2009 (the commercial introduction of DOACs for AF) and matched the exclusion criteria from the switcher cohort as noted in Figure S2. We assigned a semi-random proxy switch date for non-switchers to mirror the DOAC switch date in the switcher cohort by (1) randomly selecting 1 warfarin prescription over the

course of treatment and (2) randomly choosing a date between 0 and 119 days after the prescription fill date. We additionally excluded patients who were not on warfarin therapy in the preceding 120 days using the previous warfarin prescription date and pill count.

Warfarin TTR

We ascertained TTR in the 180 days before index DOAC prescription or proxy switch date, which was measured as a continuous and dichotomous variable with a 0.5 cut point. We chose a primary threshold of TTR <0.5 to indicate poor INR control because TTRs in US health care systems tend to run lower than peer countries.[12–14] In non-VA US health care systems the mean TTR is 54%[14] while our prior work has shown that in the VA, mean TTR is higher at 59%, although still lower than many peer countries.[32] To perform secondary analyses, we also calculated TTR over the 90 and 365 days before switch. We additionally evaluated TTR cut points of 0.6 and 0.7 and their associated subsequent DOAC adherence. INR ineligible days included periods of inpatient hospitalization, excluding day of admission if the patient had been on warfarin within the previous 30 days. We calculated TTR using the Rosendaal method, which assigns an INR value to each day between successive measured INR values using linear interpolation.[11] The proportion of time in which the interpolated and measured INR values were between 2.0 and 3.0 equates to the TTR. TTR calculation began from the first measured INR after warfarin prescription. We interpolated INRs only if the duration between measured INR values was ≤56 days.

DOAC Adherence

DOAC adherence was ascertained by estimating the proportion of days covered (PDC) by DOAC. PDC over the 90, 180, and 365 days following index DOAC prescription were calculated and reported as a continuous and dichotomous variable with a 0.8 cut point, an established threshold for adherence.[33–35] PDC was defined as the total number of non-hospitalized days DOAC was supplied, based on prescription fill dates, pill counts, and prescribed administration frequency, divided by the observation period.[36,37] We stopped calculating PDC if after index DOAC prescription (1) a clinician cancelled the DOAC prescription without re-prescription in 14 days, (2) a different DOAC or warfarin was prescribed, or (3) the patient died.

We stratified post-switch PDC by pre-switch 180-day TTR < and ≥0.5, 0.6, or 0.7 and used multivariable logistic regression to determine the association between 180-day TTR <0.5, 0.6, or 0.7 and PDC ≥0.8 at 90, 180, and 365 days. To test whether health care system departure may have lowered PDC results, we also calculated PDCs only in patients who refilled their DOAC or filled an additional prescription after the index DOAC prescription during days unique to each PDC period (ie, days 1–90 for 90-day PDC, days 91–180 for 180-day PDC, and days 181–365 for 365-day PDC.)

Non-Switcher Analysis

To estimate TTR trajectory for switchers had they been maintained on warfarin (ie, the counterfactual) as opposed to transitioned to DOAC, we performed a counterfactual analysis in the non-switchers cohort. We chose to measure counterfactual TTR over warfarin PDC as the latter has not been established as a metric for warfarin treatment success. We stratified non-switchers by 180-day TTR before the proxy switch date (TTR < and ≥0.5, 0.6, or 0.7) and compared post-proxy switch TTR trajectories using TTR over the subsequent 60, 90, 180, and 365 days. To determine whether low TTR predicted switching to a DOAC, we pooled the non-switcher and switcher cohorts and determined the association between a TTR <0.5, 0.6, or 0.7 and switching to a DOAC.

Statistical Analysis

To determine associations between TTR <0.5, <0.6, or <0.7 and DOAC PDC ≥0.8 at 90-, 180-, and 365-days post-switch, we used a multivariable mixed-effects logistic regression model with a random intercept for the site of DOAC prescription. Covariates included patient demographics (age, race, sex), comorbidities (Charlson comorbidity index, diabetes, hypertension, prior stroke or transient ischemic attack, heart failure, prior myocardial infarction, coronary artery disease, peripheral vascular disease, and glomerular filtration rate), cardiovascular non-AF medications (antiplatelet, ACE inhibitor/angiotensin receptor blocker, diuretic, niacin/fibrates, statin), and cardiovascular AF medications (amiodarone, beta-blockers, calcium channel blockers, class I agents, class III agents, digoxin).

We also evaluated the association of TTR <0.5, 0.6, or 0.7 with switching to a DOAC using logistic regression with baseline covariates (as noted above) and propensity score adjustment using inverse probability of treatment weights.[38] Propensity scores were calculated using logistic regression to predict the probability of having TTR <0.5, <0.6, or <0.7 over the 60, 90, 180, and 365 days before the switch (or proxy switch) date based on baseline covariates. We assessed multiple TTR durations to additionally ensure model stability. Covariate weights were calculated as the inverse of the estimated propensity score for patients with TTR <0.5, <0.6, or <0.7, and the inverse of 1 minus the estimated propensity score for patients with TTR ≥0.5, ≥0.6, or ≥0.7. Balance diagnostics were assessed using standardized difference in baseline covariates before and after inverse probability of treatment weights (Table S2).

A standardized difference after inverse probability of treatment weights <0.1 is acceptable. Model fit was assessed by the Hosmer-Lemeshow goodness-of-fit and C statistic. The C-statistics ranged from 0.58 to 0.59 for 180-day TTR, and 0.59–0.61 for 365-day TTR.

Baseline characteristics were identified by previously described methods[31] and stratified by non-switchers and switchers. Differences in characteristics between non-switchers and switchers and TTR subgroups were assessed with the χ^2 test and 2-sample *t* test for categorical and continuous variables, respectively.

All analyses performed with SAS version 9.2 (Cary, NC) and STATA version 11.0 (College Station, TX). The senior author had full access to all study data and takes responsibility for its integrity and the data analysis.

RESULTS

The pooled analysis cohort included 128 605 patients (age, 71±9 years; 1.6% women; CHA_2DS_2-VASc 3.5±1.6), of whom 32 377 were switchers and 96 228 were non-switchers (Table 1). Switchers, compared with non-switchers, had a significantly higher proportion of patients with TTR <0.5 in the 90 days (61% versus 47%, *P*<0.0001), 180 days (57% versus 44%, *P*<0.0001), and 365 days (51% versus 40%, *P*<0.0001) preceding the switch date or proxy switch date. Low TTR was independently associated with switching to DOAC (Table 2); the magnitude of the association was similar using multivariable adjustment and inverse probability of treatment weights. Moreover, the association was similar across multiple cut points used to define TTR (<0.5, <0.6, <0.7; Table 2).

For the primary outcome analysis, there were 8016 switchers with necessary INR data to calculate TTR in the 180 days before switch date (mean age 71±9 years, 2% female, CHA_2DS_2-VASc 3.4±1.5). Of these, 92 patients (1%) were switched to edoxaban, 1924 (24%) to rivaroxaban, 2958 (37%) to apixaban, and 3042 to dabigatran (38%) (baseline characteristics are presented in Table S3). Median 180-day TTR prior to switch was 0.45 (interquartile range [IQR], 0.26–0.64), and 4532 switchers (57%) had a 180-day TTR <0.5 (TTR distribution is presented in Figure S3). Amongst these 8016 switchers, median 365-day PDC was 0.93 (IQR, 0.80–0.99), and 76% achieved PDC ≥0.8 after 365 days (PDC distributions are demonstrated in Figures S4–S6).

Switchers with a 180-day TTR <0.5 (n=4532, 57%), as compared to those with TTR ≥0.5 (n=3484, 43%), had lower PDC: 0.83±0.21 versus 0.89±0.16 at 365 days after switch (*P*<0.0001) (baseline characteristics by TTR category in Table S4). PDC ≥0.8 was achieved by 82%, 78%, and 70% of switchers with 180-day TTR <0.5 at 90, 180, and 365 days, respectively (Table 3). The PDC findings were similar when using TTR cut points of 0.6 and 0.7 (baseline characteristics and PDC reported in Tables S5 and S6).

After adjusting for covariates, 180-day TTR <0.5 was associated with lower odds of achieving 90-, 180-, and 365-day PDC ≥0.8 (odds ratio 0.65 [95% CI, 0.56–0.75], 0.53 [0.46–0.61], 0.49 [0.43–0.57], respectively, *P*<0.0001 for all). A similar relationship was observed with the TTR cut points of 0.6 and 0.7 (odds ratios are presented in Table 4).

In patients who refilled DOAC or filled an additional prescription after index DOAC prescription (ie, patients unlikely to have departed the health care system), PDCs were similar to the full switcher cohort (baseline characteristics and PDC values are presented in Table S7).

In the 44 697 non-switchers, the median 180-day TTR was 0.54 (IQR, 0.34–0.71) and 19 516 (44%) of these had TTR <0.5 (baseline characteristics in Table S8). In non-switchers with a pre-proxy switch date TTR <0.5, the post-proxy switch 180-day and 365-day TTR were significantly lower compared with non-switchers with pre-proxy TTR ≥0.5, (180-day TTR: 0.52±0.28 versus 0.66±0.25; 365-day TTR: 0.54±0.23 versus 0.67±0.20, *P*<0.0001 for all) (TTRs are presented in Table S9). The post-proxy switch date TTRs had similar relationships using TTR cut points of 0.6 and 0.7 (Table S9).

DISCUSSION

In patients with a history of AF in the Veterans Health Administration, those on warfarin therapy generally had low TTR. Of patients treated with warfarin, those who had a TTR <0.5 had higher odds of being switched to a DOAC compared with those who had TTR ≥0.5. In patients who had a TTR <0.5 before switching to a DOAC, 70% achieved adequate DOAC adherence at 1 year. These findings were similar in patients achieving higher TTR goals when using cutoffs of TTR <0.6 and <0.7. Low TTR was associated with lower likelihood of achieving DOAC adherence. In a counterfactual analysis, TTR in warfarin users was stable over time, and those with low TTR continued to have lower TTR over time.

Previous studies have demonstrated that low TTR limits the net therapeutic benefit of warfarin.[10–12] In patients treated with a DOAC, PDC ≥0.8 is associated with lower rates of stroke and mortality without increased bleeding.[33,35] Based on our findings of high post-switch DOAC adherence and minimal PDC increases with higher TTR cut-offs, low warfarin TTR should not be used as a direct surrogate for predicting drug adherence and should not be a barrier to switching from warfarin to DOAC therapy. The TTR trajectories findings in non-switchers suggests that clinicians should not expect patients with low TTR to have meaningful improvements if left on warfarin without other patient-oriented interventions.

Table 1. Baseline Characteristics Stratified by Switchers and Non-Switchers

Demographics	Full cohort (N=128 605)	Non-switchers (n=96 228)	Switchers (n=32 377)	*P* value
Age, y	72.9±9.8	73.1±10.0	72.1±9.1	<0.0001
Men	126 569 (98.4%)	94 752 (98.5%)	31 817 (98.3%)	0.01
Race				0.0003
White	112 870 (87.8%)	84 320 (87.6%)	28 550(88.2%)	
Black	12 027 (9.4%)	9172 (9.5%)	2855 (8.8%)	
Other/Unknown*	3708 (2.9%)	2736 (2.9%)	972 (3.0%)	
Hypertension	104 166 (81.0%)	77 435 (80.5%)	26 731 (82.6%)	<0.0001
Heart failure	44 834 (34.9%)	33 740 (35.1%)	11 094 (34.3%)	0.0092
Prior stroke/TIA	16 244 (12.6%)	12 120 (12.6%)	4124 (12.7%)	0.50
Prior MI	7145 (5.6%)	5859 (6.1%)	1286 (4.0%)	<0.0001
Diabetes	60 860 (47.3%)	45 015 (46.8%)	15 845 (48.9%)	<0.0001
Coronary artery disease	52 368 (40.7%)	39 748 (41.3%)	12 620 (39.0%)	<0.0001
Chronic kidney disease	44 729 (34.8%)	32 283 (33.6%)	12 446 (38.4%)	<0.0001
Peripheral vascular disease	11 946 (9.3%)	9168 (9.5%)	2778 (8.6%)	<0.0001
Charlson comorbidity index	2.6±1.9	2.6±1.9	2.56±1.8	<0.0001
$CHADS_2$ score	2.3±1.2	2.3±1.2	2.2±1.2	<0.0001
CHA_2DS_2-VASc score	3.5±1.6	3.6±1.6	3.5±1.5	<0.0001
0	2393 (1.7%)	1973 (2.1%)	420 (1.3%)	<0.0001
1	8702 (6.8%)	6655 (6.9%)	2047 (6.3%)	
2	21 757 (16.9%)	15 933 (16.6%)	5824 (18.0%)	
3	32 053 (24.9%)	23 457 (24.4%)	8596 (26.6%)	
4+	63 700 (49.5%)	48 210 (50.1%)	15 490 (47.8%)	
HAS-BLED score†	2.8±1.1	2.8±1.2	2.8±1.1	0.0002
Baseline medications				
Aspirin	26 039 (20.3%)	19 958 (20.7%)	6081 (18.8%)	<0.0001
$P2Y_{12}$ Inhibitor	31 966 (24.9%)	24 547 (25.5%)	7419 (22.9%)	<0.0001
ACE-I/ARB/ARNI	72 605 (56.5%)	52 858 (54.9%)	19 747 (61.0%)	<0.0001
Diuretic	68 818 (53.5%)	51 441 (53.5%)	17 377 (53.7%)	<0.0001
Niacin/fibrates	5999 (4.7%)	4723 (4.9%)	1276 (3.9%)	<0.0001
Statin	87 020 (67.7%)	63 374 (65.9%)	23 646 (73.0%)	<0.0001
Rhythm control agents				
Class 1	2559 (1.9%)	1653 (1.7%)	906 (2.8%)	<0.0001
Class 3	5729 (4.5%)	3546 (3.7%)	2183 (6.7%)	<0.0001
Amiodarone/dronedarone	37 263 (10.3%)	9700 (10.1%)	3563 (11.0%)	<0.0001
Rate control agents				
Digoxin	17 608 (13.7%)	12 864 (13.4%)	4744 (14.7%)	<0.0001
Beta blockers	89 225 (69.4%)	65 730 (68.3%)	23 495 (72.6%)	<0.0001
Calcium channel blockers‡	43 485 (33.8%)	32 166 (33.4%)	11 319 (35.0%)	<0.0001

Values are mean±SD or n (%). AAD indicates antiarrhythmic drug; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MI, myocardial infarction; and TIA, transient ischemic attack.

* Other indicates categorized as the above specified races or missing.

† Excludes labile international normalized ratio component.

‡ Non-dihydropyridine.

Warfarin TTRs have been observed to be poor in real world populations,[13,14,21] and even in the RE-LY and ARISTOTLE clinical trials, the mean TTR of the corresponding warfarin arms were only 0.64 and 0.62.[7,9] Despite being part of the largest integrated health care system in the United States with an extensive network of pharmacist-led specialized anticoagulant clinics, a large proportion of our cohort had TTR <0.5, well below the estimated threshold for net benefit from warfarin.[12] Combined with our findings that 70%

Table 2. Association of Low TTRs With Switching to a Direct Oral Anticoagulant

	Unadjusted*		Multivariable regression†		Propensity-adjusted with IPTW‡	
TTR	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
90-d TTR <0.5	1.75 (1.68–1.83)	<0.0001	1.80 (1.73–1.89)	<0.0001	1.75 (1.70–1.81)	<0.0001
180-d TTR <0.5	1.68 (1.60–1.76)	<0.0001	1.74 (1.66–1.83)	<0.0001	1.68 (1.62–1.74)	<0.0001
365-d TTR <0.5	1.56 (1.48–1.65)	<0.0001	1.62 (1.54–1.72)	<0.0001	1.61 (1.55–1.67)	<0.0001
90-d TTR <0.6	1.86 (1.78–1.95)	<0.0001	1.91 (1.82–2.00)	<0.0001	1.93 (1.78–1.89)	<0.0001
180-d TTR <0.6	1.77 (1.68–1.86)	<0.0001	1.82 (1.73–1.92)	<0.0001	1.73 (1.67–1.79)	<0.0001
365-d TTR <0.6	1.63 (1.54–1.73)	<0.0001	1.69 (1.59–1.79)	<0.0001	1.67 (1.60–1.74)	<0.0001
90-d TTR <0.7	1.84 (1.75–1.94)	<0.0001	1.87 (1.78–1.97)	<0.0001	1.75 (1.69–1.81)	<0.0001
180-d TTR <0.7	1.87 (1.76–1.98)	<0.0001	1.91 (1.80–2.03)	<0.0001	1.82 (1.75–1.88)	<0.0001
365-d TTR <0.7	1.83 (1.71–1.96)	<0.0001	1.89 (1.76–2.04)	<0.0001	1.78 (1.70–1.85)	<0.0001

IPTW, ind icates inverse probability of treatment weights; OR, odds ratio; and TTR, time in therapeutic range.
*Logistic regression model.
†Adjusted logistic regression model includes all baseline variables.
‡ Adjusted model includes all baseline variables with inverse probability of treatment weights. Propensity score model fit assessed by Hosmer-Lemeshow goodness-of-fit and C statistic:
TTR <0.5: P = 0.63, C-statistic=0.57 for 90-day TTR, P = 0.25, C-statistic=0.58 for 180-day TTR, P = 0.14, C-statistic=0.60 for 365-day TTR.
TTR <0.6: P = 0.61, C-statistic=0.57 for 90-day TTR, P = 0.18, C-statistic=0.58 for 180-day TTR, P = 0.16, C-statistic=0.59 for 365-day TTR.
TTR <0.7: P = 0.32, C-statistic=0.56 for 90-day TTR, P = 0.63, C-statistic=0.59 for 180-day TTR, P = 0.71, C-statistic=0.61 for 365-day TTR.

of patients with low TTR achieve DOAC adherence at 1 year, these data suggest that in real-world populations, patients could more frequently achieve their treatment targets on DOACs compared with warfarin. However, there is not available data to suggest that DOAC PDC fully stabilizes at 1 year and could continue to decrease over time.

While the 2019 Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation recommends switching patients from warfarin to a DOAC if they are unable to maintain a therapeutic INR,[5] they do not define TTR thresholds at which patients should be switched. The 2020 ESC Guidelines for the Diagnosis and Management of Atrial Fibrillation recommend considering switching to a DOAC or targeted TTR-based interventions for those with TTR <0.7.[3] In this study, we found that among switchers, 70% achieved DOAC adherence (PDC ≥0.8) at 1 year despite a pre-switch TTR <0.5. When including patients not achieving a TTR of 0.7, which is more common in high-performing peer countries, the proportion that had post-switch adherence was even slightly higher (73%). With wider availability of DOACs, a favorable safety profile, and availability of Factor Xa inhibitor reversal agents,[39] these findings provide support for proactive switching of patients with low TTR. However, in modern integrated health care systems with a high level of success with warfarin anticoagulation,[40] higher TTR thresholds for switching may be more reasonable.

Several factors can lead to low warfarin TTR, including medication adherence, dietary changes, interactions with other medications, variations in drug metabolism, or health care system support. However,

Table 3. DOAC Adherence of Switchers by TTR

Characteristics		TTR<0.5 (n=4532, 57%)	TTR≥0.5 (n=3484, 43%)	*P* value
Post-switch PDC				
90-d	(Mean±SD)	0.90±0.16	0.93±0.13	<0.0001
	(Median, IQR)	0.99, 0.12	0.99, 0.07	
180-d	(Mean±SD)	0.86±0.18	0.91±0.15	<0.0001
	(Median, IQR)	0.94, 0.19	0.97, 0.12	
365-d	(Mean±SD)	0.83±0.21	0.89±0.16	<0.0001
	(Median, IQR)	0.91, 0.23	0.95, 0.13	
Post-switch PDC≥0.8				
90-d		3331 (82%)	2676 (88%)	<0.0001
180-d		2910 (78%)	2420 (87%)	<0.0001
365-d		2250 (70%)	1967 (83%)	<0.0001

DOAC indicates direct oral anticoagulant; IQR, interquartile range; PDC, proportion of days covered; and TTR, time in therapeutic range.

Table 4. Association of Low Warfarin TTR With Direct Oral Anticoagulant Proportion of Days Covered ≥0.8

	TTR180<0.5			
	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
PDC 90≥0.8	0.63 (0.55–0.72)	<0.0001	0.66 (0.55–0.76)	<0.0001
PDC 180≥0.8	0.53 (0.47–0.61)	<0.0001	0.56 (0.49–0.64)	<0.0001
PDC 365≥0.8	0.56 (0.49–0.64)	<0.0001	0.51 (0.44–0.58)	<0.0001
	TTR180<0.6			
	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
PDC 90≥0.8	0.61 (0.53–0.72)	<0.0001	0.64 (0.55–0.76)	<0.0001
PDC 180≥0.8	0.49 (0.42–0.58)	<0.0001	0.52 (0.44–0.61)	<0.0001
PDC 365≥0.8	0.47 (0.40–0.55)	<0.0001	0.49 (0.42–0.57)	<0.0001
	TTR180<0.7			
	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
PDC 90≥0.8	0.66 (0.55–0.80)	<0.0001	0.71 (0.58–0.85)	0.0003
PDC 180≥0.8	0.51 (0.42–0.62)	<0.0001	0.54 (0.44–0.66)	<0.0001
PDC 365≥0.8	0.44 (0.36–0.53)	<0.0001	0.46 (0.37–0.56)	<0.0001

OR, indicates odds ratio; PDC, proportion of days covered; and TTR, time in therapeutic range.

Multivariable mixed-effects logistic regression model with random intercept for the site of DOAC prescription. Covariates included patient demographics (age, race, sex), baseline comorbidities (hypertension, diabetes, prior stroke or transient ischemic attack, heart failure, prior myocardial infarction, coronary artery disease, peripheral vascular disease, glomerular filtration rate, and Charlson comorbidity index), and medications (anti-platelet agents, anti-hypertensives, beta-blockers, calcium channel blockers, class I agents, class III agents, diuretics, statin, niacin/fibrates, and digoxin).

low TTR was associated with a lower likelihood of achieving PDC ≥0.8, which suggests a group of individuals with low TTR partially driven by challenges with medication adherence. The impact of poor DOAC adherence is not insignificant, and has been associated with higher mortality and stroke rates.[35] However, pharmacist-led DOAC education and monitoring has been shown to improve adherence,[33] and proactive enrollment of these high-risk patients could improve outcomes in this vulnerable population. For patients with low TTR continued on warfarin, targeted approaches including intensive calls and letters from anticoagulation centers and multi-dose drug dispensing have also been shown to help improve TTR over time.[41]

Limitations

These data have limitations owing to their observational nature. Patients who were selected to switch from warfarin to a DOAC were not random and may represent a group of patients who were less suited for warfarin therapy, which may underestimate TTR declines in the counterfactual group. While PDC is validated and frequently used for population-level DOAC adherence assessments, it may not capture true medication adherence. We could not directly ascertain warfarin dosing adherence outside of using TTR to estimate INR control, since PDC calculation relies on assumptions of fixed-dosed therapy, whereas warfarin dosing may be changed for a given day or week by an anticoagulation clinic pharmacist without a change reflected in the prescription or pill supply. We also do not assess DOAC non-persistence, which is another important measure of long-term anticoagulation success in AF. TTR measurement across the cohort is not uniform because of availability of INR values and variability in monitoring. SAMe-TT_2R_2 scores, used as a decision aid to identify warfarin treated patients who will have poor INR control,[19] were not calculated as we were unable to accurately ascertain tobacco use. Unidentified confounders may have informed the decision to switch from warfarin to DOAC. Variable baseline TTRs across health care systems may limit the generalizability of our findings. In addition, our cohort is predominantly male and is part of an integrated health care system.

CONCLUSIONS

In patients with AF treated with warfarin, most had low TTRs. Of those who switched to a DOAC, most low and high TTR patients achieved the desired DOAC

adherence threshold. However, TTR trajectories remained low in patients with low TTR who stayed on warfarin. Patients with low TTR may have more therapeutic coverage with DOACs, although adherence-oriented interventions may still be beneficial.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S9
Figures S1–S6

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Supplemental Material

Table S1. ICD codes for cohort exclusion.

	ICD-9 Codes	ICD-10 Codes
Mechanical Heart Valve	35.20, 35.22, 35.24, 35.26, 35.28, V43.3	CM: Z95.2, Z95.4, T82.0X PCS: 02RF0JZ, 02RF4JZ, 02RG0JZ, 02RG4JZ, 02RH0JZ, 02RH4JZ, 02RJ0JZ, 02RJ4JZ
Deep Vein Thrombosis	451.1, 451.11, 451.19, 451.81, 451.83, 451.89, 451.9, 453.2, 453.4, 453.40, 453.41, 453.42, 453.5, 453.50, 453.51, 453.52, 453.7, 453.72, 453.8, 453.82, 453.83, 453.84, 453.85, 453.86, 453.87, 453.89, 453.9	I80.10-13, I80.X, I82.2X, I82.4X, I82.5X, I82.62X, I82.72X, I82.A1-2, I82.B1-2, I82.C1-2, I82.89, I82.9
Pulmonary Embolism	415.0, 415.11, 415.13, 415.19, 416.2	I26.0, I26.02, I26.09, I26.9, I26.92, I26.99

ICD-9,10 = International Classification of Diseases, 9th edition and 10th edition; CM: Clinical Modification; PCS: Procedure Coding System

Table S2. Covariate standardized mean differences before and after IPTW for TTR < 0.5 in warfarin treated patients.

Covariates	TTR 60		TTR 90		TTR 180		TTR 365	
	Before IPTW	After IPTW	Before IPTW	After IPTW	Before IPTW	After IPTW	Before IPTW	After IPTW
Age	-0.211	-0.143	-0.227	-0.150	-0.239	-0.157	-0.242	-0.159
Male	0.020	0.020	0.022	0.020	0.032	0.035	0.030	0.029
Race								
White	-0.020	-0.008	-0.018	-0.002	-0.013	0.003	-0.018	-0.0002
Black	0.006	-0.008	0.001	-0.016	-0.008	-0.026	-0.007	-0.025
Hypertension	0.120	0.110	0.122	0.110	0.101	0.090	0.087	0.074
Heart Failure	0.037	0.029	0.026	0.015	-0.013	-0.035	-0.013	-0.040
Prior Stroke/TIA	0.035	0.033	0.030	0.028	0.016	0.011	0.011	0.012
Prior MI	-0.055	-0.057	-0.054	-0.060	-0.059	-0.058	-0.047	-0.056
Diabetes	0.066	0.063	0.066	0.058	0.032	0.021	0.032	0.017
Coronary Artery Disease	-0.004	-0.008	-0.012	-0.016	-0.032	-0.046	-0.020	-0.037
Chronic Kidney Disease	0.111	0.102	0.105	0.101	0.066	0.051	0.053	0.035
Peripheral Vascular Disease	-0.018	-0.021	-0.020	-0.024	-0.031	-0.046	-0.027	-0.043
Charlson Comorbidity Index	0.028	0.011	0.017	0.011	-0.038	0.011	-0.037	-0.056
$CHADS_2$ Score	-0.005	-0.006	-0.018	-0.006	-0.062	-0.006	-0.066	-0.056
CHA_2DS_2-VASc Score	-0.008	-0.007	-0.023	-0.018	-0.068	-0.057	-0.070	-0.060

Covariate standardized mean difference determined between patients with TTR < 0.5 or TTR ≥ 0.5, before and after inverse probability of treatment weighting. Guidelines suggest 0.1 as acceptable cutoff for standardized mean difference.

Table S3. Baseline characteristics of switchers with 180-day warfarin time in INR therapeutic range.

Demographics	Total (N = 8,016)
Direct Oral Anticoagulant	
Edoxaban	92 (1%)
Rivaroxaban	1,924 (24%)
Apixaban	2,958 (37%)
Dabigatran	3,042 (38%)
Age	70.3 ± 8.9
Male	7,857 (98.0%)
Race	
White	6,981 (87.1%)
Black	750 (9.4%)
Other/Unknown	285 (3.6%)
Hypertension	6,793 (84.7%)
Heart Failure	2,713 (33.8%)
Prior Stroke/TIA	1,089 (13.6%)
Prior MI	442 (5.5%)
Diabetes	3,817 (47.6%)
Coronary Artery Disease	3,247 (40.5%)
Chronic Kidney Disease	2,753 (34.3%)
Peripheral Vascular Disease	689 (8.6%)
Anemia	1,036 (12.9%)
Obstructive Sleep Apnea	
Charlson Comorbidity Index	
$CHADS_2$ Score	2.2 ± 1.2
CHA_2DS_2-VASc Score	3.4 ± 1.5
HAS-BLED Score*	
Aspirin	1,663 (20.8%)
$P2Y_{12}$ Inhibitor	2,062 (25.7%)
ACE-I/ARB/ARNI	4,898 (61.1%)
Diuretic	4,275 (53.3%)
Niacin/Fibrates	316 (3.9%)
Statin	5,625 (70.2%)
Rhythm Control Agents	
Class 1 AAD	274 (3.4%)
Class 3 AAD	505 (6.3%)
Amiodarone/Dronedarone	1,082 (13.5%)
Rate Control Agents	
Digoxin	906 (11.3%)
Beta Blockers	5,923 (73.9%)
Calcium Channel Blockers‡	2,864 (35.7%)

Values are mean ± SD or n (%). AAD indicates antiarrhythmic drug; ACE, Angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; MI, Myocardial infarction; TIA: Transient ischemic attack

***Excludes labile international normalized ratio component.**

‡Non-dihydropyridine

Table S4. Baseline characteristics of switchers with low and high warfarin time in INR therapeutic range (TTR).

Characteristics	TTR < 0.5 (N = 4,532, 57%)	TTR ≥ 0.5 (N = 3,484, 43%)	P-value
Age, years (mean ± SD)	69.9 ± 9.0	70.8 ± 8.8	<0.0001
Male	4,437 (97.9%)	3,420 (98.2%)	0.41
Race			<0.0001
White	3,866 (85.3%)	3,115 (89.4%)	
Black	504 (11.1%)	246 (7.1%)	
Other/Unknown	162 (3.6%)	123 (3.5%)	
CHA_2DS_2-VASc Score (mean ± SD)	3.5 ± 1.5	3.4 ± 1.5	0.0072
Cardiovascular Medication Burden* (mean ± SD)	6.4 ± 1.8	6.3 ± 1.8	0.0007

TTR: Warfarin Time in INR Therapeutic Range
***Numeric sum of cardiac prescriptions at time of DOAC initiation (DOAC, warfarin, aspirin, P2Y12 inhibitor, ACE-I/ARB/ARNI, diuretic, statin, ezetimibe, niacin/fibrates, rhythm control agents, rate control agents)**

Table S5. Baseline characteristics and subsequent direct oral anticoagulant proportion of days covered of switchers for warfarin time in INR therapeutic range (TTR) below or above 0.6.

Characteristics		TTR < 0.6 (N = 5,620, 70%)	TTR ≥ 0.6 (N = 2,396, 30%)	p-value
Age, years (mean ± SD)		70.1 ± 9.0	70.8 ± 8.6	0.0006
Male		5,501 (97.9%)	2,356 (98.3%)	0.18
Race				<0.0001
White		4,808 (85.6%)	2,173 (90.7%)	
Black		605 (10.8%)	145 (6.1%)	
Other/Unknown		207 (3.7%)	78 (3.3%)	
CHA_2DS_2-VASc Score (mean ± SD)		3.4 ± 1.5	3.4 ± 1.5	0.06
Cardiovascular Medication Burden* (mean ± SD)		6.4 ± 1.8	6.3 ± 1.8	0.01
Post-Switch PDC				
90-Day	(mean ± SD)	0.91 ± 0.16	0.93 ± 0.13	<0.0001
	(median, IQR)	0.99, 0.12	0.99, 0.07	
180-Day	(mean ± SD)	0.87 ± 0.18	0.91 ± 0.14	<0.0001
	(median, IQR)	0.94, 0.18	0.97, 0.12	
365-Day	(mean ± SD)	0.83 ± 0.21	0.89 ± 0.16	<0.0001
	(median, IQR)	0.91, 0.22	0.95, 0.13	
Post-Switch PDC ≥ 0.8				
90-Day		4,188 (83%)	1,863 (88%)	<0.0001
180-Day		3,680 (79%)	1,701 (88%)	<0.0001
365-Day		2,868 (72%)	1,398 (84%)	<0.0001

DOAC: Direct Oral Anticoagulant, PDC: Proportion of Days Covered, SD: Standard Deviation, IQR: Interquartile Range
***Numeric sum of cardiac prescriptions at time of DOAC initiation (DOAC, warfarin, aspirin, P2Y12 inhibitor, ACE-I/ARB/ARNI, diuretic, statin, ezetimibe, niacin/fibrates, rhythm control agents, rate control agents)**

Table S6. Baseline characteristics and subsequent direct oral anticoagulant proportion of days covered of switchers for warfarin time in INR therapeutic range (TTR) below or above 0.7.

Characteristics		TTR < 0.7 (N = 6,524, 81%)	TTR ≥ 0.7 (N = 1,492, 19%)	P-value
Age, years (mean ± SD)		71.1 ± 8.6	70.1 ± 9.0	<0.0001
Male		6,393 (98.0%)	1,464 (98.1%)	0.74
Race				<0.0001
White		5,622 (86.2%)	1,359 (91.1%)	
Black		668 (10.2%)	82 (5.5%)	
Other/Unknown		234 (3.6%)	51 (3.4%)	
CHA_2DS_2-VASc Score (mean ± SD)		3.4 ± 1.5	3.4 ± 1.5	0.20
Cardiovascular Medication Burden* (mean ± SD)		6.4 ± 1.8	6.3 ± 1.8	0.06
Post-Switch PDC				
90-Day	(mean ± SD)	0.91 ± 0.15	0.93 ± 0.13	<0.0001
	(median, IQR)	0.99, 0.11	1.00, 0.07	
180-Day	(mean ± SD)	0.87 ± 0.18	0.91 ± 0.15	<0.0001
	(median, IQR)	0.95, 0.18	0.97, 0.11	
365-Day	(mean ± SD)	0.84 ± 0.20	0.90 ± 0.17	<0.0001
	(median, IQR)	0.92, 0.21	0.96, 0.12	
Post-Switch PDC ≥ 0.8				
90-Day		4,885 (83%)	1,166 (88%)	<0.0001
180-Day		4,319 (80%)	1,062 (88%)	<0.0001
365-Day		3,377 (73%)	889 (85%)	<0.0001

DOAC: Direct Oral Anticoagulant, PDC: Proportion of Days Covered, SD: Standard Deviation, IQR: Interquartile Range
***Numeric sum of cardiac prescriptions at time of DOAC initiation (DOAC, warfarin, aspirin, P2Y12 inhibitor, ACE-I/ARB/ARNI, diuretic, statin, ezetimibe, niacin/fibrates, rhythm control agents, rate control agents)**

Table S7. Baseline characteristics and subsequent direct oral anticoagulant proportion of days covered (PDC) of switchers with additional prescription fill by warfarin time in INR therapeutic range (TTR).

Characteristics		TTR < 0.5 (N = 4,433, 56%)	TTR ≥ 0.5 (N = 3,419, 44%)	p-value
Age, years (mean ± SD)		69.8 ± 9.0	70.6 ± 8.7	<0.0001
Male		4,338 (98.0%)	3,355 (98.1%)	0.40
Race				<0.0001
White		3,777 (85.2 %)	3,052 (89.3 %)	
Black		496 (11.2 %)	245 (7.2 %)	
Other/Unknown		160 (3.6 %)	122 (3.6 %)	
CHA_2DS_2-VASc Score (mean ± SD)		3.5 ± 1.5	3.4± 1.5	0.0097
Cardiovascular Medication Burden* (mean ± SD)		6.5 ± 1.7	6.4 ± 1.7	0.0010
Post-Switch PDC				
90-Day	(mean ± SD)	0.91 ± 0.16	0.93 ± 0.13	<0.0001
	(median, IQR)	0.99, 0.12	0.99, 0.07	
180-Day	(mean ± SD)	0.87 ± 0.18	0.91 ± 0.14	<0.0001
	(median, IQR)	0.94, 0.18	0.97, 0.12	
365-Day	(mean ± SD)	0.83 ± 0.20	0.89 ± 0.16	<0.0001
	(median, IQR)	0.91, 0.22	0.95, 0.13	
Post-Switch PDC ≥ 0.8				
90-Day		3,290 (82%)	2,640 (88%)	<0.0001
180-Day		2,884 (78%)	2,397 (87%)	<0.0001
365-Day		2,230 (70%)	1,947 (83%)	<0.0001

DOAC: Direct Oral Anticoagulant, PDC: Proportion of Days Covered, SD: Standard Deviation, IQR: Interquartile Range
***Numeric sum of cardiac prescriptions at time of DOAC initiation (DOAC, warfarin, aspirin, P2Y12 inhibitor, ACE-I/ARB/ARNI, diuretic, statin, ezetimibe, niacin/fibrates, rhythm control agents, rate control agents)**

Table S8. Baseline characteristics of non-switchers with low and high time in INR therapeutic range (TTR).

Characteristics	TTR < 0.5 (N = 19,516, 44%)	TTR ≥ 0.5 (N = 25,181, 56%)	P-value
Age, years (mean ± SD)	71.9 ± 10.4	73.2 ± 10.0	<0.0001
Male	19,196 (98.5%)	24,802 (98.4%)	0.26
Race			<0.0001
White	16612 (85.1%)	22511 (89.4%)	
Black	2343 (12.0%)	1937 (7.7%)	
Other/Unknown	561 (2.9%)	733 (2.9%)	
CHA_2DS_2-VASc Score (mean ± SD)	3.6 ± 1.6	3.5 ± 1.6	<0.0001
Cardiovascular Medication Burden (mean ± SD)*	5.2 ± 2.0	5.0 ± 1.9	<0.0001

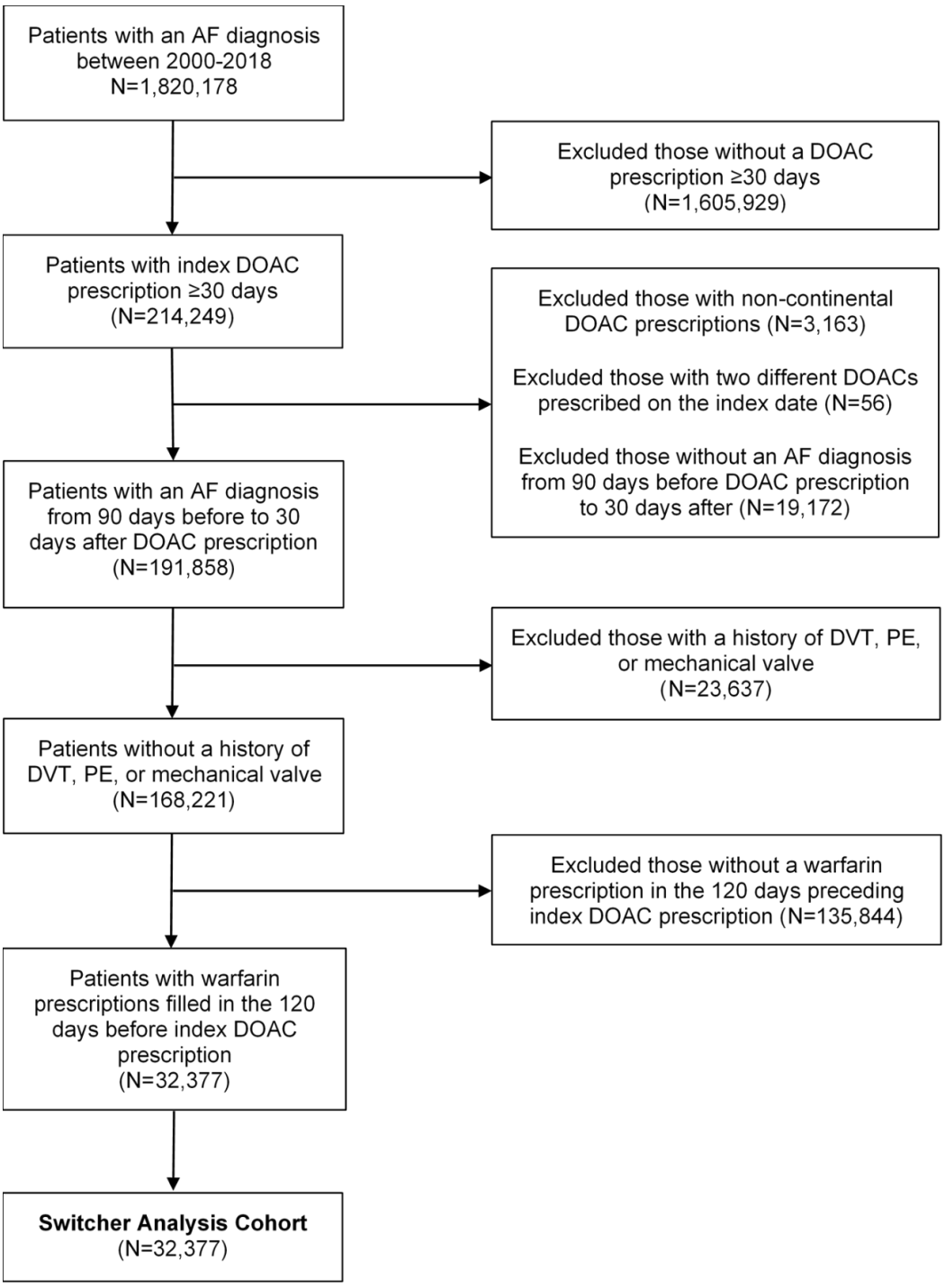
TTR: Warfarin Time in INR Therapeutic Range
***Numeric sum of cardiac prescriptions at time of DOAC initiation (DOAC, warfarin, aspirin, P2Y12 inhibitor, ACE-I/ARB/ARNI, diuretic, statin, ezetimibe, niacin/fibrates, rhythm control agents, rate control agents)**

Table S9. Warfarin time in INR therapeutic range (TTR) trends of non-switchers by 180-day pre-proxy switch TTR cut-points.

		TTR < 0.5 (N = 19,516, 44%)	TTR ≥ 0.5 (N = 25,181, 56%)	P-value
Pre-Proxy Switch 180-Day TTR				<0.0001
	(mean ± SD)	0.34 ± 0.18	0.79 ± 0.12	
	(median, IQR))	0.37, 0.29	0.77, 0.20	
Post-Proxy Switch TTR				
60-Day	(mean ± SD)	0.49 ± 0.36	0.66 ± 0.33	<0.0001
	(median, IQR)	0.48, 0.66	0.73, 0.58	
90-Day	(mean ± SD)	0.49 ± 0.33	0.66 ± 0.31	<0.0001
	(median, IQR)	0.50, 0.57	0.70, 0.53	
180-Day	(mean ± SD)	0.52 ± 0.28	0.66 ± 0.25	<0.0001
	(median, IQR)	0.53, 0.42	0.69, 0.36	
365-Day	(mean ± SD)	0.54 ± 0.23	0.67 ± 0.20	<0.0001
	(median, IQR)	0.56, 0.33	0.68, 0.27	
		TTR < 0.6 (N = 25,495, 57%)	**TTR ≥ 0.6 (N = 19,202, 43%)**	**P-value**
Pre-Proxy Switch 180-Day TTR				
	(mean ± SD)	0.34 ± 0.18	0.79 ± 0.12	
	(median, IQR))	0.37, 0.29	0.77, 0.20	
Post-Proxy Switch TTR				
60-Day	(mean ± SD)	0.52 ± 0.36	0.68 ± 0.33	<0.0001
	(median, IQR)	0.52, 0.66	0.77, 0.55	
90-Day	(mean ± SD)	0.52 ± 0.33	0.68 ± 0.30	<0.0001
	(median, IQR)	0.53, 0.54	0.72, 0.53	
180-Day	(mean ± SD)	0.54 ± 0.28	0.67 ± 0.25	<0.0001
	(median, IQR)	0.56, 0.41	0.70, 0.41	
		TTR < 0.7 (N = 31,332, 70%)	**TTR ≥ 0.7 (N = 13,365, 30%)**	**P-value**
Pre-Proxy Switch 180-Day TTR				<0.0001
	(mean ± SD)	0.39 ± 0.20	0.85 ± 0.10	
	(median, IQR))	0.43, 0.32	0.83, 0.17	
Post-Proxy Switch TTR				
60-Day	(mean ± SD)	0.54± 0.36	0.70 ± 0.32	<0.0001
	(median, IQR)	0.55, 0.66	0.80, 0.53	
90-Day	(mean ± SD)	0.54 ± 0.33	0.69 ± 0.30	<0.0001
	(median, IQR)	0.57, 0.54	0.75, 0.54	
180-Day	(mean ± SD)	0.56 ± 0.27	0.69 ± 0.24	<0.0001
	(median, IQR)	0.58, 0.40	0.72, 0.34	
365-Day	(mean ± SD)	0.58 ± 0.23	0.69 ± 0.19	<0.0001
	(median, IQR)	0.60, 0.31	0.71, 0.26	
	(median, IQR)	0.60, 0.31	0.71, 0.26	

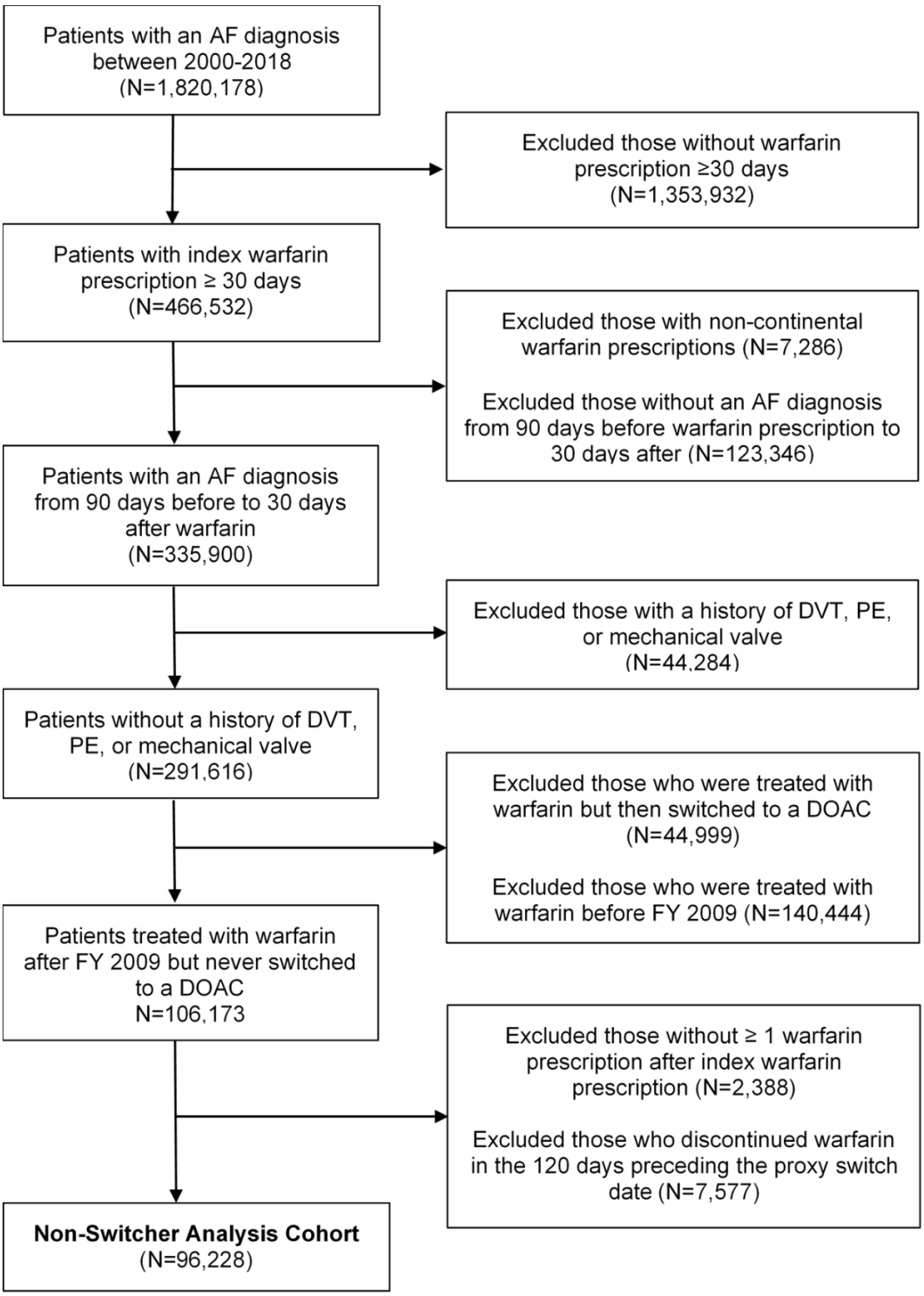
TTR: Warfarin Time in INR Therapeutic Range, SD: Standard Deviation, IQR: Interquartile Range
***Numeric sum of cardiac prescriptions at time of DOAC initiation (DOAC, warfarin, aspirin, P2Y12 inhibitor, ACE-I/ARB/ARNI, diuretic, statin, ezetimibe, niacin/fibrates, rhythm control agents, rate control agents)**

Figure S1. Switcher cohort selection diagram.



Inclusion and exclusion criteria used to select analysis cohort. AF indicates atrial fibrillation; DOAC: Direct Oral Anticoagulant; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolus.

Figure S2. Non-switcher cohort selection diagram.



Inclusion and exclusion criteria used to select analysis cohort. AF indicates atrial fibrillation; DOAC: Direct Oral Anticoagulant; DVT: Deep Vein Thrombosis; PE: Pulmonary Embolus.

Figure S3. Distribution of 180-day warfarin INR time in therapeutic range in switchers.

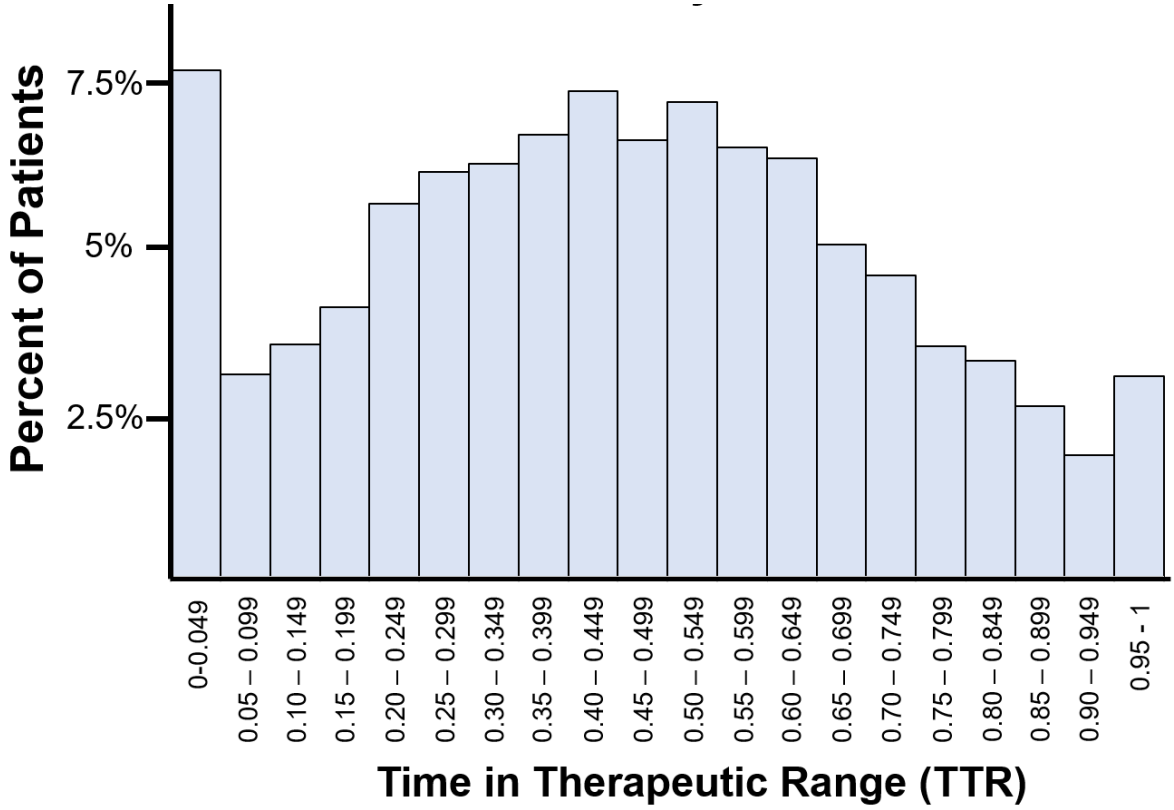


Figure S4. Distribution of 90-Day proportion of days covered in switchers.

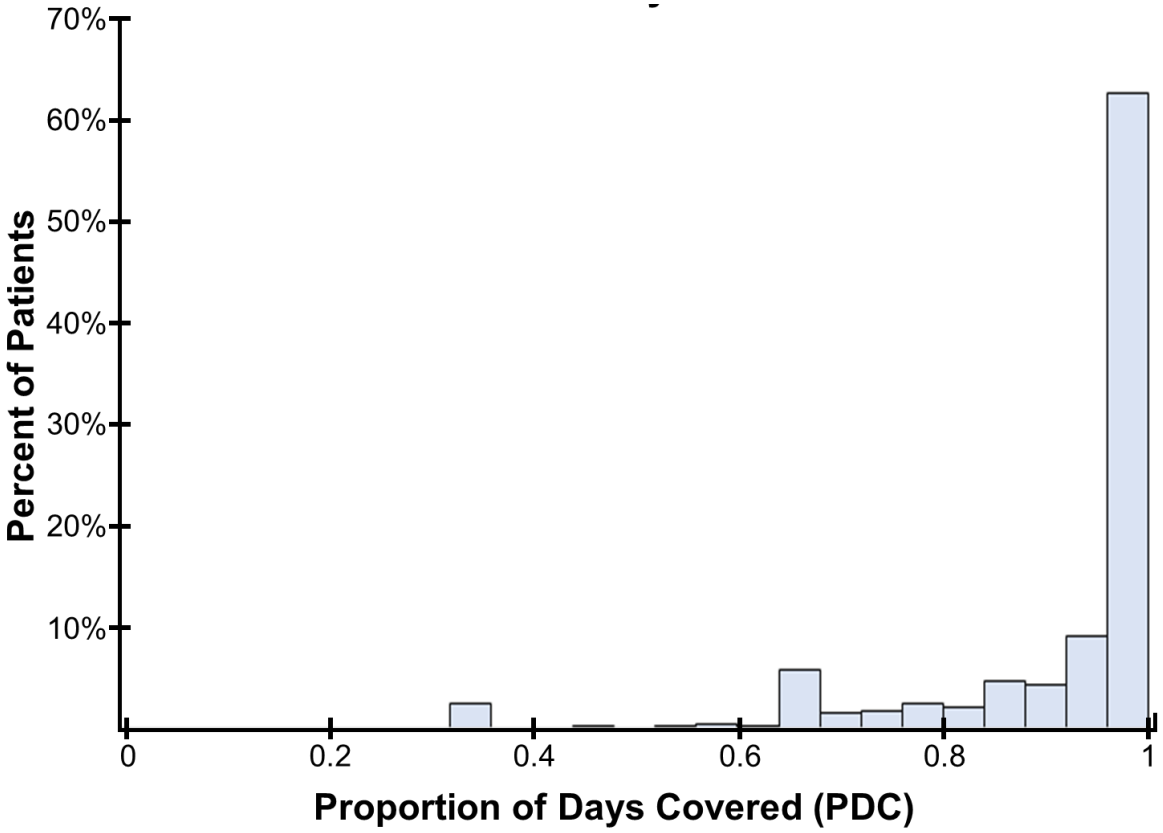


Figure S5. Distribution of 180-Day proportion of days covered in switchers.

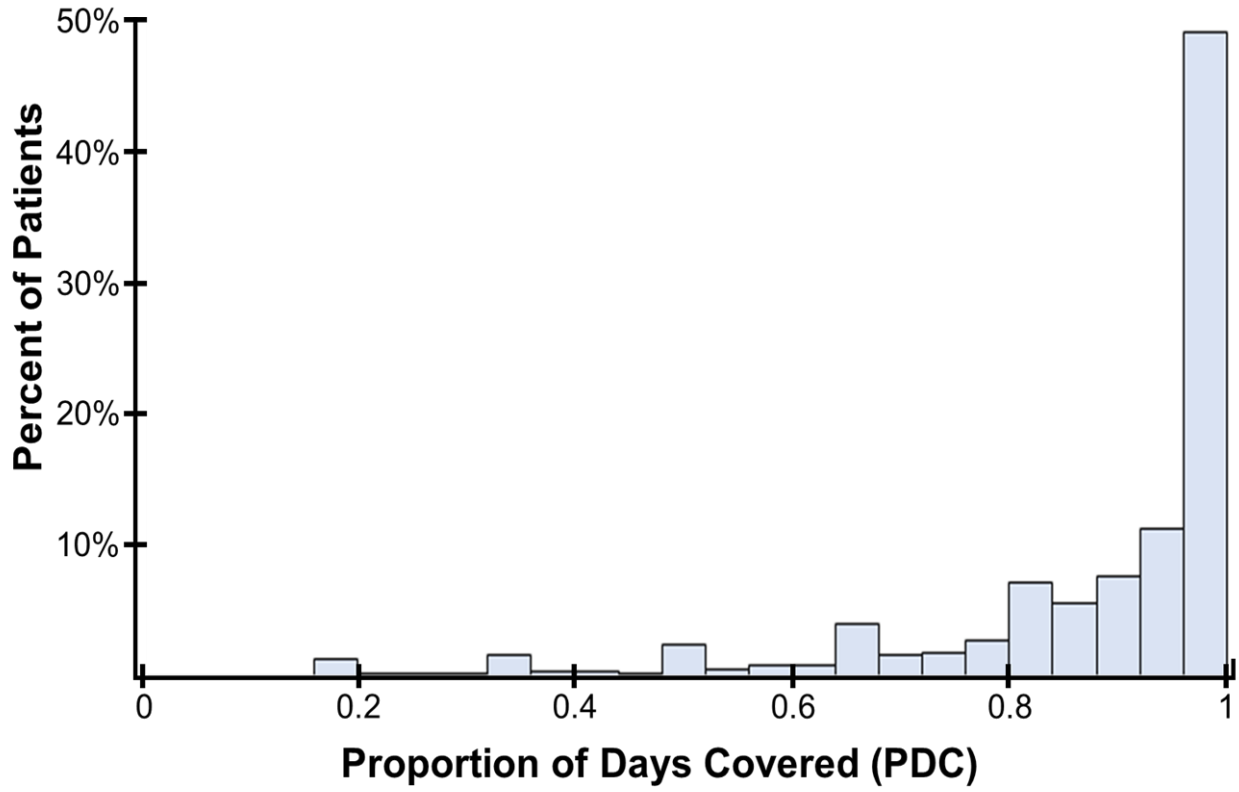


Figure S6. Distribution of 365-Day proportion of days covered in switchers.