

Formulary Restrictions and Stroke Risk in Patients With Atrial Fibrillation

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Historically, stroke risk in patients with atrial fibrillation (AF) has been lowered by treatment with warfarin sodium. First approved for use in humans in 1954, warfarin is both efficacious—it has been shown to reduce the risk of stroke by up to 70% in patients with AF—and inexpensive.^{1,2} However, its use can be burdensome to patients because of numerous food and drug interactions requiring dietary and treatment restrictions and the need for ongoing laboratory testing and dose adjustment to achieve anticoagulant control. Consequently, patients taking warfarin are in the target therapeutic international normalized ratio range only about half of the time.^{3,4}

Recently introduced non-vitamin K antagonist oral anticoagulants (NOACs)—including dabigatran, rivaroxaban, and apixaban—provide more convenient therapeutic options and have demonstrated equivalent or superior efficacy compared with warfarin.⁵⁻⁹ However, NOACs are considerably more expensive and, until recently, lacked a reversal agent to mitigate the risk of life-threatening bleeding. Some health plans initially excluded NOACs from coverage or chose to restrict access to them through the use of prior authorization (PA) and step therapy (ST) requirements. Under PA, the health plan or pharmacy benefit manager must authorize a particular prescription before it can be covered. Under ST, also called “fail first,” patients must try and fail to reach therapeutic target on a lower-cost alternative, in this case warfarin, before receiving authorization for the originally requested medication. Both PA and ST are designed to promote formulary compliance, reduce unnecessary prescription drug use, and lower costs, but if not used judiciously, they can induce patients to delay treatment, switch to less effective medications, or become nonadherent and, as a result, experience adverse health effects.¹⁰⁻²⁰

Herein we examine the effect of the use of PA and ST on the utilization of NOACs among patients with newly diagnosed AF enrolled in Medicare Part D. We linked detailed, plan-level information on the coverage of NOACs in Part D plans to beneficiaries' medical and prescription drug claims. We tested the association between coverage restrictions and NOAC use, including initiation and adherence, and whether coverage restrictions were associated with elevated risk of stroke and bleeding.

ABSTRACT

OBJECTIVES: To determine the use of formulary restrictions (prior authorization and step therapy) on the use of non-vitamin K antagonist oral anticoagulants (NOACs) and their effect on health outcomes.

STUDY DESIGN: Longitudinal cohort study. We identified a sample of Medicare beneficiaries with an incident diagnosis of atrial fibrillation (AF) in 2011 to 2015 and followed them until the end of 2016 or death. We compared anticoagulant use and health outcomes associated with Medicare Part D plan coverage of NOACs.

METHODS: The primary outcomes were composite rates of death, stroke, transient ischemic attack, and systemic embolism. We used Cox proportional hazards models to estimate the association between formulary restrictions and adverse health outcomes.

RESULTS: Beneficiaries enrolled in Part D plans that restricted access to NOACs had a lower probability of NOAC use [30.2% vs 32.2%], worse adherence conditional on NOAC use [32.1% vs 34.3% adherent], and longer delays in filling an initial prescription [46% vs 55% filled within 30 days of AF diagnosis]. Beneficiaries in restricted plans had higher aggregate risk of mortality/stroke/transient ischemic attack (adjusted HR, 1.098; 95% CI, 1.079-1.118).

CONCLUSIONS: Limiting access to NOACs may exacerbate current underuse of anticoagulants and increase the risk of stroke among patients with newly diagnosed AF. Pharmacy benefit managers and Part D plans need to continuously review the appropriateness of formulary policies to ensure patient access to effective medications.

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TAKEAWAY POINTS

Non-vitamin K antagonist oral anticoagulants (NOACs) were documented to be equivalent or superior to warfarin at reducing stroke risk in patients with atrial fibrillation. Mixed findings have been reported on the impact of step therapy and prior authorization on patients' medication use and health outcomes across various drug classes.

- ▶ Step therapy and prior authorization policies were associated with reduced NOAC use and higher stroke rates among patients with new atrial fibrillation in Medicare.
- ▶ Pharmacy benefit managers and Medicare Part D plans need to continuously review the appropriateness of formulary policies to ensure patients' access to effective medications.

METHODS

Data

Through a reuse agreement with the National Bureau of Economic Research, we used data for a 20% random sample of fee-for-service Medicare beneficiaries. We linked data on enrollment, demographics, and parts A (inpatient), B (outpatient), and D (pharmacy) claims for patients with newly diagnosed AF from 2010 to 2016. Inpatient and outpatient medical claims provided information on *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis codes (*International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]* codes were included beginning October 2015) and Current Procedural Terminology procedure codes, dates of service, and spending. Part D claims provided information related to prescription drug claims, including National Drug Code, fill dates, and days supplied. Enrollment and claims data were supplemented with claim histories from the Chronic Conditions Data Warehouse, which identifies incident dates of diagnosed chronic health conditions and cardiovascular risk factors.

We linked the Part D claims to the plan characteristics file, which provided detailed information on each plan's formulary, benefit design, and utilization management policies, including PA and ST. We used this information to identify the formulary restrictions and cost-sharing requirements for each NOAC in the plan-year. To adjust for other aspects of plan quality, we linked the plan characteristic file with the annual Part D star performance rating provided by CMS.²¹ Star ratings, which range from 1 to 5, were designed to provide summary measures of how well Part D plans perform in terms of customer service, member experience, drug pricing, and patient safety.

Study Sample

The study sample consisted of beneficiaries with an incident diagnosis of AF (*ICD-9-CM* diagnosis code 427.31 or *ICD-10-CM* codes I48.0-I48.2, I48.91) between 2010 and 2015, based on at least 1 inpatient or 2 outpatient or carrier claims (**eAppendix Table 1** [eAppendix available at ajmc.com]). We excluded patients who died or had a stroke within 30 days of the index AF diagnosis and defined the index date as the date of the first AF medical claim (inpatient or outpatient). We required at least 1 year of follow-up data unless

the patient died within 364 days of the index AF diagnosis. We also required enrollment in a fee-for-service Medicare plan for at least 1 year before the incidence date to capture the health history. We excluded beneficiaries enrolled in Medicare Advantage plans due to incomplete capture of medical claims and those enrolled in a Part D plan through an employer because CMS waives Part D formulary submission requirements for these plans. Finally, we excluded patients with valvular heart disease,

end-stage chronic kidney disease, kidney transplant, dialysis, or hip or knee replacement surgery with a diagnosis of deep vein thrombosis or pulmonary embolism at any point during the study sample (**eAppendix Table 2**).

We categorized Part D plans into 2 groups based on their coverage of NOACs. Plans were defined as unrestricted if 1 or more NOACs were available without PA/ST and as restricted if all NOACs were subject to PA/ST or not covered by the plan (by 2013, all prescription drug plans covered at least 1 NOAC). We excluded a small number of beneficiaries who switched from an unrestricted to a restricted plan or vice versa after their AF diagnosis. The final study sample included 139,041 patients with incident AF, 36% of whom (n = 50,596) were enrolled in restricted plans.

Statistical Analyses

To estimate the direct impact of PA/ST on medication use, we counted the number of anticoagulant prescription fills (30-day equivalent) 1 year before the index date and after diagnosis for patients in restricted and nonrestricted plans. To control for differences in beneficiaries' cardiovascular risk and other characteristics that may influence anticoagulant use, we compared the medication adherence of patients in restricted plans vs those in unrestricted plans using multivariate logistic regression. The key independent variable was a binary indicator for a restricted plan as defined earlier. Other independent variables included beneficiary demographics (age, sex, race/ethnicity) and binary indicators for AF incidence year to control for time trends. Race/ethnicity was determined using the beneficiary race code in enrollment data from CMS and by applying an algorithm developed by the Research Triangle Institute that improves identification of Hispanic and Asian individuals based on name. To adjust for patients' socioeconomic status, we linked enrollment and claims data from their AF incidence year to zip code-level data on household income and education from the American Community Survey. We also controlled for 27 comorbid conditions identified in the Chronic Conditions Data Warehouse (**eAppendix Table 3**). These included binary indicators for previous diagnosis of stroke, acute myocardial infarction, congestive heart failure, hypertension, and diabetes (full model results are available from the corresponding author). To control for plan quality, we calculated the beneficiary-level mean star rating since incident diagnosis and created a binary variable indicating mean star rating above the median.

We also examined the association between formulary restrictions and clinical outcomes. The primary outcome was the composite risk of death or stroke, including ischemic stroke, hemorrhagic stroke, and transient ischemic attack (TIA). The secondary outcome was major bleeding, including gastrointestinal bleeding, intracranial bleeding, and bleeding from other sites. To focus on acute events, outcomes were identified using only inpatient or emergency department medical claims (see eAppendix Table 1 for associated ICD-9-CM and ICD-10-CM codes). We plotted unadjusted Kaplan-Meier curves of unadjusted rates of all-cause mortality, stroke, or TIA for patients in restricted vs unrestricted plans. We grouped patients into 3 subgroups based on their CHA₂DS₂-VASC (congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65-74 years, sex category) scores at AF incidence date (≤3, 4-5, or ≥6), and we used Cox proportional hazards models to test the association between PA/ST and all-cause mortality, stroke, and bleeding for each subgroup. Cox regressions included the same set of covariates as the logistic regression models for medication use.

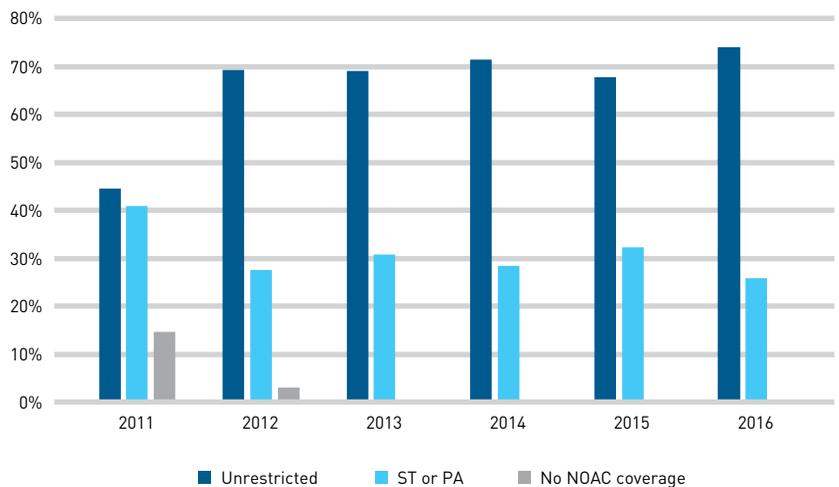
We ran several additional analyses to assess whether patients at higher cardiovascular risk differentially enrolled in less restrictive plans and whether the magnitude of effects we observed were consistent with clinical trial data. First, we predicted rates of NOAC use and stroke by plan type (eAppendix Table 4). Second, we estimated the association between anticoagulant use and adverse health outcomes for a subsample of patients without a history of anticoagulant use before their incident AF date (eAppendix Table 5). Finally, we compared predicted stroke rates using observed differences in NOAC use in the present sample with the effect sizes reported from clinical trial data (eAppendix Table 6).

RESULTS

Coverage of NOACs

Figure 1 reports the prevalence of formulary restrictions in our sample of Part D plans. Warfarin accounted for 94% of anticoagulant prescriptions for patients with AF in 2011 and remained the most frequently prescribed anticoagulant throughout the study period, although its share of use fell to 62% by 2016 (eAppendix Figure 1). The steady increase in NOAC prescriptions coincided with a decline in formulary restrictions. In 2011, 44% of plans covered NOACs without restrictions, 41% imposed PA or ST, and the remaining

FIGURE 1. Use of Formulary Restrictions on NOACs in Stand-alone Medicare Part D Plans, 2011-2016, Weighted by Enrollment



NOAC, non-vitamin K antagonist oral anticoagulant; PA, prior authorization; ST, step therapy.

TABLE 1. Summary Characteristics of Medicare Part D Plans With and Without Restrictions on NOACs*

Characteristic	Unrestricted plans (n = 5002)	Restricted plans (n = 1344)
Unique medications on plan formulary, n	1139	1234
Covered medications subject to ST or PA, %	21.1	21.2
Enhanced alternative plans, %	30.1	43.4
Mean star rating	3.34	3.26
Plans rated ≤ 2.5 stars, %	15.8	9.7
Plans rated 3-3.5 stars, %	62.7	77.1
Plans rated ≥ 4 stars, %	20.7	13.3

NOAC, non-vitamin K antagonist oral anticoagulant; PA, prior authorization; ST, step therapy.

*Stand-alone Part D plans, 2011-2016, weighted by enrollment.

15% excluded NOACs from the formulary altogether. However, by 2013 all the plans in the sample covered at least 1 NOAC, and the percentage of Part D plans imposing PA or ST decreased to 31% in 2013 and to 26% by 2016.

Importantly, unrestricted plans were similar to restricted plans in their coverage of all other medications (Table 1). The number of unique medications included in the formulary of restricted plans was similar to that in unrestricted plans (1234 and 1139, respectively), as was the fraction of formulary drugs subject to PA or ST (21% in both plan types). Unrestricted plans had slightly higher mean star ratings (3.34 vs 3.26, respectively) and were more likely to receive a star rating of 4 or higher (20.7% vs 13.3%, respectively) than restricted plans.

Anticoagulant Use

A primary concern when using observational claims data to assess health outcomes is that plan choice may be correlated with

TABLE 2. Sample Characteristics of Medicare Beneficiaries Enrolled in Restricted and Unrestricted Plans, 2011-2015

Characteristic	Plan-year coverage of NOACs		
	Unrestricted (n = 88,445)	Restricted or off formulary (n = 50,596)	T test for equal means (P)
Demographics			
Mean age in years at incidence date	76.5	77.8	<.001
Male sex, %	43.0	42.0	<.001
Race/ethnicity, %			
White	85.8	89.1	<.001
Black	6.31	4.72	<.001
Asian	1.71	1.37	<.001
Hispanic	4.21	3.30	<.001
Other	1.96	1.56	<.001
Socioeconomic status (zip code–level mean)			
Household income, median, \$	54,598	58,359	<.001
High school graduate, %	78.5	79.8	<.001
Bachelor's degree, %	20.9	23.2	<.001
Mean star rating (1-5 stars)	3.44	3.30	<.001
Mean CHA ₂ DS ₂ -VAsc score	4.39	4.49	<.001
CCW history of cardiovascular risks, %			
Acute myocardial infarction	8.56	8.52	.796
Heart failure	46.5	46.1	.199
Ischemic heart disease	65.1	66.9	<.001
Stroke/transient ischemic attack	21.7	22.2	.029
Hypertension	90.9	91.9	<.001
CCW history of other comorbidities, %			
AD	8.51	8.42	.561
AD-related disorders, senile dementia	20.4	20.0	.027
Anemia	62.5	65.4	<.001
Asthma	18.1	18.2	.815
Benign prostate hyperplasia	19.6	21.3	<.001
Cancer, breast	5.95	7.09	<.001
Cancer, colorectal	3.88	4.18	.007
Cancer, endometrial	1.16	1.19	.723
Cancer, lung	2.70	3.13	<.001
Cancer, prostate	5.74	6.67	<.001
Cataract	70.5	73.7	<.001
Chronic kidney disease	34.2	33.9	.287
Chronic obstructive pulmonary disease	38.4	38.2	.352
Depression	37.8	35.6	<.001
Hip/pelvic fracture	5.29	5.65	.004
Hyperlipidemia	82.2	84.8	<.001
Hypothyroidism	27.6	29.4	<.001
Osteoporosis	25.1	27.6	<.001
Rheumatoid arthritis/osteoarthritis	62.5	64.2	<.001

(continued)

unobserved factors that affect medication use and outcomes, including health status. Given the similarities in restricted and unrestricted plans aside from their coverage of NOACs, it is not surprising that we found little evidence that beneficiaries differentially enrolled in the 2 plan types (Table 2). Beneficiaries in restricted plans were slightly older (1 year) at the time of their incident AF diagnosis and were less likely to be male and non-White, but they had similar rates of acute myocardial infarction, heart failure, heart disease, stroke, and TIA before their AF diagnosis.

Beneficiaries enrolled in unrestricted plans had modestly higher rates of NOAC use (32.2% vs 30.2% in restricted plans) and lower, but not statistically significantly different, use of warfarin (32.9% vs 33.3%, respectively). Conditional on NOAC use, beneficiaries in unrestricted plans had higher adherence rates (34.3% vs 32.1%) and shorter delays in filling an initial prescription. More than 55% of those in unrestricted plans filled their first NOAC within 30 days of AF diagnosis compared with 46% in restricted plans.

Regression results shown in Table 3 indicate that patients in restricted plans had lower use of NOACs. They had lower odds of receiving a NOAC (odds ratio [OR], 0.961; 95% CI, 0.937-0.986) after an initial AF diagnosis but no statistically significant difference in warfarin use. Plan-level differences in NOAC use varied markedly by race/ethnicity, with lower use among Black (OR, 0.786; 95% CI, 0.695-0.890), Hispanic (OR, 0.864; 95% CI, 0.753-0.993), and Asian (OR, 0.772; 95% CI, 0.625-0.955) individuals in restricted plans compared with White individuals. The association between formulary restrictions and NOAC use was more pronounced for those at higher risk of stroke, with lower use of NOACs among those at intermediate (CHA₂DS₂-VAsc score of 4 or 5: OR, 0.942; 95% CI, 0.907-0.978) and high (CHA₂DS₂-VAsc score ≥6: OR, 0.926; 95% CI, 0.879-0.977) stroke risk.

Health Outcomes

Figure 2 plots the cumulative incidence of mortality/stroke/TIA by plan type. Kaplan-Meier estimates of the composite risk of death, stroke, and TIA within 500, 1000, 1500, and 2000 days after the index date (defined as 30 days after the AF incidence date) were 21.9%, 37.7%, 51.0%,

and 62.4%, respectively, for beneficiaries in restricted plans compared with 20.2%, 34.9%, 46.4%, and 55.4%, respectively, for beneficiaries in unrestricted plans. In multivariate Cox regression analyses, patients in restricted plans also had higher risk of mortality/stroke/TIA (adjusted HR, 1.098; 95% CI, 1.079-1.118) (Table 3). Bleed rates were also higher, with an adjusted HR of 1.046 (95% CI, 1.014-1.079).

Table 3 reports adjusted HRs of adverse outcomes by sex, race, and CHA₂DS₂-VASc subgroups over a range of clinical end points (ischemic and hemorrhagic strokes, TIAs, and bleeding). The association between formulary restrictions and composite risk of death, stroke, and TIA was slightly stronger for women (OR, 1.102; 95% CI, 1.078-1.128) compared with men (OR, 1.091; 95% CI, 1.060-1.122) and for Black patients (OR, 1.139; 95% CI, 1.062-1.222) compared with White patients (OR, 1.091; 95% CI, 1.071-1.112). We also found that the impact of PA/ST was greater for hemorrhagic stroke (OR, 1.109; 95% CI, 1.020-1.206) relative to ischemic stroke (OR, 1.082; 95% CI, 1.026-1.142) and for intracranial bleeds (OR, 1.103; 95% CI, 1.011-1.203) relative to gastrointestinal bleeding (OR, 1.030; 95% CI, 0.994-1.068) in the full sample.

DISCUSSION

We studied the association between formulary restrictions on the use of NOACs and associated clinical outcomes among Medicare beneficiaries with an incident diagnosis of AF. Although formulary restrictions have been shown to reduce use of the targeted drug or medical service, there is some concern that substitution to an alternative therapy is often incomplete.¹¹⁻¹⁶ The present results seem to validate this concern in the case of AF, as we found that restricting access to NOACs by either requiring PA/ST or not covering them at all reduced the likelihood of using these medications by approximately 2 percentage points (PP) and lowered overall anticoagulant use by 1.3 PP among Medicare beneficiaries with incident AF. In addition, formulary restrictions reduced mean adherence rates by 2.2 PP among NOAC users and reduced the probability of filling a first prescription within 30 days of AF incidence by 9.1 PP among new NOAC users. Lower use and delayed initiation of NOACs were associated with elevated risks of stroke and bleeding, consistent with data from clinical trials and other observational studies.

These findings are particularly concerning given that anticoagulants are substantially underused in community practice.²² A recent initiative to improve outpatient cardiac care in the United

TABLE 2. (Continued) Sample Characteristics of Medicare Beneficiaries Enrolled in Restricted and Unrestricted Plans, 2011-2015

Characteristic	Plan-year coverage of NOACs		
	Unrestricted (n = 88,445)	Restricted or off formulary (n = 50,596)	T test for equal means (P)
Use of anticoagulants: since AF incidence date, %			
NOACs	32.2	30.2	<.001
Proportion of days covered	57.2	56.9	.278
Proportion of adherent anticoagulant use	34.3	32.1	<.001
Filled first NOAC claim in ≤30 days ^a	55.5	46.1	<.001
Warfarin only	25.3	26.0	.004
Proportion of days covered	59.6	57.4	<.001
Proportion of adherent users	33.7	30.3	<.001
Filled first claim in ≤30 days ^b	60.2	58.9	.105
Use of anticoagulants: 1 year before AF incidence date, %			
NOACs	8.05	6.09	<.001
Proportion of days covered	19.2	21.7	<.001
Warfarin only	0.17	0.16	.062
Proportion of days covered	34.7	32.4	<.001
All-cause mortality rate, %	34.4	39.9	<.001
Stroke and bleeding, %			
Stroke	5.17	5.88	<.001
Ischemic	3.99	4.54	<.001
Hemorrhagic	1.61	1.88	<.001
Transient ischemic attack	4.59	5.23	<.001
Major bleeding	15.2	16.2	<.001
Intracranial	1.70	1.93	.003
Gastrointestinal	11.8	12.4	.001
Other	2.73	2.97	.011

AD, Alzheimer disease; AF, atrial fibrillation; CCW, Chronic Conditions Data Warehouse; CHA₂DS₂-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65-74 years, sex category; NOAC, non-vitamin K antagonist oral anticoagulant.

^aNew NOAC users only (n = 18,332).

^bNew warfarin users only (n = 15,865).

States found that only 60% of patients at high thromboembolic risk (CHADS₂ [congestive heart failure, hypertension, age ≥75 years, diabetes, stroke] score ≥2) were treated with warfarin or NOACs.²³ A retrospective analysis of more than 94,000 patients with an acute ischemic stroke who had a known history of AF found that 84% did not receive guideline-recommended therapeutic anticoagulation preceding the stroke or had anticoagulation levels that were not in the therapeutic range.⁴ Our results suggest that limiting access to NOACs may exacerbate the underuse of anticoagulants and increase the risk of stroke and bleeding for those at high thromboembolic risk. These findings are particularly germane to women with AF, who are at greater risk when taking warfarin, and minority groups, for whom NOACs are relatively underprescribed.²⁴⁻²⁶

Although common, the use of PA, ST, and other utilization management strategies is controversial. Health plans and pharmacy

TABLE 3. Associations Between Restricted Access to NOACs and Anticoagulant Use and Clinical Outcomes, Overall and by Patient Subgroup*

Access to NOACs: ST/PA vs unrestricted	Medication use				Clinical outcomes					
	Any NOAC use	Any warfarin use	Any of: died, stroke, or TIA	All-cause mortality	Ischemic stroke	Hemorrhagic stroke	TIA	Major bleeding	Intracranial	Gastrointestinal
All patients										
	0.961*** (0.937-1.086)	0.988 (0.963-1.013)	1.098*** (1.079-1.118)	1.115*** (1.095-1.137)	1.082*** (1.026-1.142)	1.109** (1.020-1.206)	1.081*** (1.028-1.136)	1.046*** (1.014-1.079)	1.103** (1.011-1.203)	1.030 (0.994-1.068)
Patient subgroups										
Male sex (n=59,273)	0.983 (0.946-1.022)	1.002 (0.963-1.042)	1.091*** (1.060-1.122)	1.110*** (1.078-1.144)	1.087* (0.994-1.190)	1.125* (0.987-1.282)	1.094** (1.007-1.188)	1.037 (0.989-1.087)	1.157** (1.016-1.316)	1.003 (0.948-1.062)
Female sex (n=79,769)	0.943*** (0.912-0.975)	0.977 (0.944-1.010)	1.102*** (1.078-1.128)	1.119*** (1.092-1.146)	1.080** (1.011-1.155)	1.097* (0.983-1.224)	1.073** (1.008-1.142)	1.051** (1.008-1.095)	1.055 (0.938-1.187)	1.048** (1.001-1.097)
White (n=120,958)	0.983 (0.957-1.009)	0.977* (0.950-1.004)	1.091*** (1.071-1.112)	1.106*** (1.084-1.128)	1.077** (1.016-1.142)	1.116** (1.019-1.222)	1.088*** (1.031-1.147)	1.040** (1.006-1.076)	1.118** (1.017-1.229)	1.022 (0.983-1.062)
Black (n=7970)	0.786*** (0.695-0.890)	1.139** (1.021-1.271)	1.139*** (1.062-1.222)	1.170*** (1.087-1.260)	0.999 (0.827-1.207)	0.988 (0.701-1.394)	1.113 (0.910-1.363)	1.067 (0.948-1.202)	0.988 (0.689-1.418)	1.067 (0.935-1.218)
Hispanic (n=2202)	0.864** (0.753-0.993)	1.093 (0.949-1.258)	1.084* (0.987-1.191)	1.124** (1.017-1.242)	1.101 (0.854-1.418)	1.019 (0.675-1.539)	1.022 (0.789-1.322)	1.150* (0.984-1.345)	1.196 (0.808-1.771)	1.159 (0.968-1.388)
Asian (n=2520)	0.772** (0.625-0.955)	1.003 (0.785-1.281)	1.265*** (1.088-1.470)	1.351*** (1.150-1.588)	1.17 (0.801-1.708)	1.171 (0.649-2.115)	0.829 (0.512-1.340)	1.101 (0.853-1.421)	0.892 (0.483-1.647)	1.047 (0.782-1.401)
CHA ₂ DS ₂ -VASC score ≤3 (n=42,154)	0.998 (0.954-1.044)	0.986 (0.938-1.036)	1.146*** (1.098-1.195)	1.169*** (1.118-1.224)	1.125* (0.984-1.285)	1.104 (0.917-1.330)	1.094 (0.969-1.234)	1.037 (0.971-1.108)	1.149 (0.950-1.390)	1.021 (0.945-1.103)
CHA ₂ DS ₂ -VASC score of 4 or 5 (n=60,960)	0.942*** (0.907-0.978)	0.976 (0.940-1.014)	1.083*** (1.055-1.112)	1.110*** (1.079-1.141)	1.04 (0.959-1.128)	1.092 (0.965-1.235)	1.022 (0.946-1.103)	1.044* (0.997-1.093)	1.064 (0.936-1.209)	1.033 (0.979-1.089)
CHA ₂ DS ₂ -VASC score ≥6 (n=35,927)	0.926*** (0.879-0.977)	0.992 (0.944-1.043)	1.090*** (1.059-1.123)	1.094*** (1.061-1.129)	1.100** (1.011-1.197)	1.128 (0.976-1.304)	1.130*** (1.045-1.223)	1.052* (0.995-1.112)	1.122 (0.964-1.306)	1.032 (0.970-1.099)

AF, atrial fibrillation; CHA₂DS₂-VASC, congestive heart failure, hypertension, age ≥75 years, diabetes, stroke, vascular disease, age 65-74 years, sex category; NOAC, non-vitamin K antagonist oral anticoagulant; PA, prior authorization; ST, step therapy; TIA, transient ischemic attack.

*P < .10; **P < .05; ***P < .01.

*Models adjust for patient demographics, comorbidities, zip code-level income and education, mean plan star rating, and year of AF diagnosis. The key independent variable is a binary indicator for continuous enrollment in a restricted plan since incident AF diagnosis. Table displays odds ratios of anticoagulant use and HRs of clinical outcomes, with 95% CIs in parentheses.

benefit managers contend that the PA process reduces waste and unnecessary use. However, physicians often object that these policies are overused, impose administrative burden, and undermine their clinical decision-making.²⁷ In addition, physicians, pharmaceutical manufacturers, and patient advocates argue that these policies can induce patients to delay treatment, switch to less effective medications, or become nonadherent in some cases and, as a result, experience adverse health effects. The evidence on this is mixed; some studies find that PA, ST, and other restrictions lead to nonadherence and worse health outcomes,⁹⁻¹⁴ whereas others find no effects.¹⁵⁻¹⁷ Although encouraging the use of less expensive alternatives in a therapeutic class may be warranted in many contexts, our study highlights a particular class in which PA/ST may be harmful to patients.

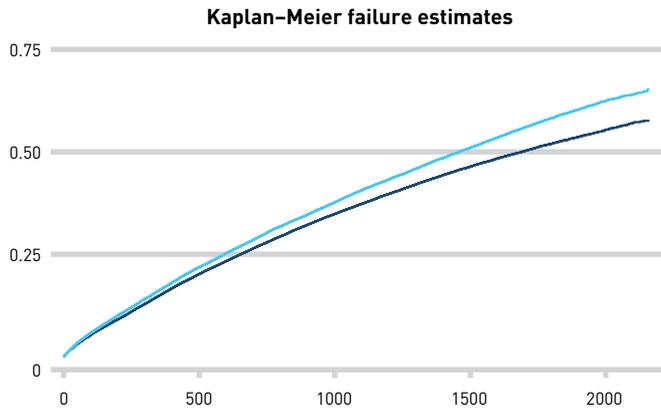
A recent economic analysis comparing apixaban with warfarin found that apixaban was clinically superior for patients with AF and

was cost-effective by current US norms but not cost-saving.²⁸ This exemplifies the near-universal trade-off between cost and quality resulting from medical innovation. Medicare and most commercial health insurance plans typically base coverage decisions of new medical technologies on evidence of effectiveness rather than on cost-effectiveness or any other direct measure of value.²⁹ Yet the continued growth in health care spending heightens pressure on manufacturers to demonstrate the clinical and economic value of their products. Broad and increasing use of formulary restrictions raises concern that there are other therapies besides NOACs for which restricting access may be clinically and/or economically counterproductive.

Limitations

This study has several limitations. Because Part D is a voluntary program, these results may be biased if beneficiaries at higher

FIGURE 2. Cumulative Failure Rate of the Composite Outcome of Death, Stroke, and Transient Ischemic Attack by Formulary Restriction on NOACs^a



Number at risk					
■ Unrestricted	88,445	62,624	31,389	12,455	2151
■ Restricted	50,596	35,359	18,447	7966	1635

NOAC, non-vitamin K antagonist oral anticoagulant; PA, prior authorization; ST, step therapy.

^aThe index date is 30 days after incident diagnosis of atrial fibrillation.

cardiovascular risk are more likely to enroll in plans that restrict access to potentially more effective, higher-cost therapies. We found no evidence that Medicare beneficiaries differentially enrolled in Part D plans based on the coverage of NOACs. Furthermore, the goal of this study was not to evaluate the efficacy of the medications, which has been well established in clinical trials, but rather to assess how plan-level policies designed to restrict access to these drugs affected medication use and clinical outcomes in real-world populations. These questions can be answered only by observational studies.

Because we relied on medical claims, we lacked clinical detail such as the type of AF, ejection fraction, and smoking histories. Observational studies using registries and single-center electronic medical records typically provide more clinical detail than those relying on administrative data. In addition, we restricted the analyses to stand-alone Part D prescription drug plans due to the lack of medical claims for Medicare Advantage and Part D plans. The latter may have stronger financial incentives to provide generous drug coverage if keeping enrollees healthy leads to savings in medical costs.

CONCLUSIONS

PA and ST policies are most effective when there is clear evidence that a service is being overused or misused and when patient safety and cost implications indicate that it is helpful or appropriate. Nonetheless, their use can be costly for payers, manufacturers, physicians, and patients. A recent study estimated that drug utilization

management costs \$93.3 billion annually in the United States.³⁰ Given the administrative and economic burden on providers and the risk to patients, it may be more effective to identify and educate outlier physicians rather than impose these policies on all providers and their patients. All payers, not just Part D sponsors, need to continuously review the use and appropriateness of formulary policies to ensure that beneficiaries have access to clinically beneficial medications. ■

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Technical Appendix

Supplemental Methods

eAppendix Table 1. ICD9 and ICD10-CM Codes Used in Defining Stroke and Bleeding

eAppendix Table 2. ICD9 and ICD10-CM Codes Used in Defining Conditions for Sample Exclusion

eAppendix Table 3. Conditions Defined by the Chronic Conditions Warehouse (CCW)

eAppendix Table 4. Predicted NOAC Use and Stroke Risk by Formulary Restrictions

eAppendix Table 5. Adjusted Hazard Ratio by Anticoagulant Use and Formulary Restrictions

eAppendix Table 6. Observed Stroke Rates versus Predictions from RCT Data

eAppendix Figure 1. Selection of Study Sample

eAppendix Figure 2. Utilization of anticoagulants among atrial fibrillation patients in Medicare PDP plans

Supplemental Methods

Definition of drug adherence measures

We calculated the proportion of days covered (PDC) by creating an array of days covered based on the fill dates and days supplied for each fill since the first prescription date. The numerator of the PDC was defined as the total days covered since the first fill after incident diagnosis until the end of the measurement period, defined as the earlier of date of death or December 31st, 2016. The denominator was defined as total number of days between incident diagnosis and the end of the measurement period. The PDC was truncated at 1.00 and overlapping days of prescription fills in the array were not duplicated when calculating total days covered.

Definition of clinical outcomes

Stroke, TIA, systemic embolism or bleeding events were determined based on an inpatient, outpatient or carrier claim for the condition, where the place of service was “inpatient” or “emergency room”, and with a primary or secondary diagnosis code as defined in eAppendix Table 1. We excluded claims with a primary discharge diagnosis of rehabilitation (*ICD-9* code V57 and *ICD-10* code Z51.89), or any additional diagnoses of trauma (*ICD-9* codes 800–804, 850–854 and *ICD-10* code S02).

Predicting NOAC use and stroke risk by formulary restrictions

To demonstrate that patient characteristics were balanced across plan types (restricted vs unrestricted), we predicted two key outcomes under the assumption that: 1) all beneficiaries were enrolled in unrestricted plans; or 2) all were enrolled in restricted (ST/PA) plans, assuming other covariates remained at their observed values. We predicted NOAC use and stroke rates using estimated parameters from logistic and Cox proportional hazard regressions.

The results, presented in eAppendix Table 4, compare observed versus predicted values for beneficiaries enrolled in unrestricted vs restricted plans. Under the assumption that “NOAC restricted” beneficiaries were enrolled in unrestricted plans, we predicted a 1.1 percentage point difference in NOAC use and -0.2 percentage point difference in stroke rates. The predicted differences in NOAC use and stroke were reduced by 40% and 66%, respectively compared to observed differences. Similarly, under the assumption that all beneficiaries were in restricted

plans, predicted NOAC use and stroke rates were reduced by 41% and 63%. Overall, the results suggested that formulary restrictions accounted for the majority of the differences in the key outcome variables conditional on observed patient characteristics.

Supplemental analyses on association between clinical outcomes and anticoagulant use in restricted vs unrestricted plans

To address the concern that Medicare beneficiaries at higher (unobserved) cardiovascular risk differentially enrolled in plans with more generous coverage of NOACs, we analyzed the association between health outcomes and anticoagulant use among new AF patients. We restricted the analysis to a subsample of 95,830 new anticoagulant users or non-users. The sample excluded patients with a history of anticoagulant use prior to their incident AF diagnosis or those who switched between warfarin and a NOAC. We categorized beneficiaries into 6 subgroups by anticoagulant use and plan coverage: non-adherent anticoagulant users (including non-users); adherent NOAC users; and adherent warfarin users. The three groups were further split into those enrolled in restricted and unrestricted plans. We used Cox proportional hazard models to estimate the risk of an adverse health outcome for each of the six subgroups.

eAppendix Table 5 shows the relative risk ratios by anticoagulant use and plan type, with non-adherent users in unrestricted plans as the reference group. Compared with the reference group, both NOAC and warfarin users had lower risk of mortality, stroke and bleeding, while NOAC users had superior outcomes to warfarin users in both restricted and unrestricted plans. These results provide no evidence of unmeasured confounding due to plan choice based on unobserved cardiovascular risk factors.

Predicting stroke rate differences across formulary restrictions using randomized clinical trial results

Using relative risk ratios of NOAC versus warfarin users^{5,6,7} and as well as warfarin users versus placebo from clinical trial data,¹ we computed “back-of-the-envelope” predictions of differences in stroke risk based on observed differences in NOAC use.

eAppendix Table 6 reports the difference in anticoagulant use across plan types and the predicted difference in stroke rates. NOAC use was 2.0 percentage points higher in unrestricted plans, while anticoagulant use was 0.7 percentage points higher. We used estimates from RCTs

to estimate the increase in stroke rates across plan types, assuming that among the 2.0% difference in NOAC use across plan types, 1.3% would not take an anticoagulant and 0.7% would use warfarin instead. We found the predicted difference in stroke rates between unrestricted and restricted plans is -0.40 percentage points, which was similar to the *observed* difference of -0.45 percentage points.

eAppendix Table 1. ICD9 and ICD10-CM Codes Used in Defining Stroke and Bleeding

Stroke or Systemic Embolism	ICD9-CM	ICD10-CM
Ischemic Stroke	433.x1, 434.x1, 436	I63.3, I63.4, I63.6, I66.0, I66.1, I66.2, I66.3, I66.9, I67.89
Hemorrhagic Stroke	430, 431	I60, I61
Systemic Embolism	444.x	I74
TIA	435.x	I67.84, G45.0, G45.1, G45.8, G45.9
Major Bleeding		
Intracranial Bleeding	432.x, 852.x, 853.x	I62
Gastrointestinal Bleeding	456.0, 456.20, 530.21, 530.7, 530.82, 531.0x, 531.2x, 531.4x, 531.6x, 532.0x, 532.2x, 532.4x, 532.6x, 533.0x, 533.2x, 533.4x, 533.6x, 534.0x, 534.2x, 534.4x, 534.6x, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.x	I85.01, I85.11, K22.11, K22.6, K22.8, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.x1, K31.811, K31.82, K52.81, K55.21, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.83, K57.93, K62.5, K66.1, K92.0, K92.1, K92.2
Bleeding from Other Sites	423.0, 459.0, 596.7, 599.71, 719.1x, 784.8, 786.3	I31.2, M25.00, M25.01, M25.02, M25.03, M25.04, N32.89, R31.0, R58

eAppendix Table 2. ICD-9, ICD-10-CM, and CPT Procedure Codes Used in Defining Conditions for Sample Exclusion

	ICD-9-CM	ICD-10-CM
Valvular Heart Disease	394.0, 394.2, 396.0, 396.1, 396.8, V42.2, V43.3	I05.0, I05.2, I08.0, I08.8, Z95.2, Z95.3, Z95.4
End-Stage Chronic Kidney Disease	585.5, 585.6, 404.x2, 404.x3	I13.11, I13.2, N18.5, N18.6
Kidney Transplant	V42.0	Z48.22, Z94.0
Dialysis	V45.11, V56.x	Z49.x, Z99.2
Deep Vein Thrombosis	451.1x, 451.2, 451.81, 451.83, 451.84, 451.89, 451.9, 452, 453.4x, 453.5x, 453.9	I80.1x, I80.20x, I80.21x, I80.22x, I80.23x, I80.29x, I80.3, I80.8, I80.9, I81, I82.40x, I82.41x, I82.42x, I82.43x, I82.44x, I82.49x, I82.4Yx, I82.4Zx, I82.50x, I82.51x, I82.52x, I82.53x, I82.54x, I82.59x, I82.5Yx, I82.5Zx, I82.91
Pulmonary Embolism	415.x	I26.0x, I26.90, I26.92, I26.99, T80.0XXA
	ICD9 Procedure	ICD-10 Procedure
Valvular Heart Disease	3510, 3511, 3512, 3513, 3514, 3510, 3520, 3521, 3522, 3523, 3524, 3525, 3526, 3527, 3528	02QF0ZZ, 02QG0ZZ, 02QH0ZZ, 02QJ0ZZ, 027F04Z, 027F0DZ, 027F0ZZ, 02NF0ZZ, 027G04Z, 027G0DZ, 027G0ZZ, 02NG0ZZ, 027H04Z, 027H0DZ, 027H0ZZ, 02NH0ZZ, 027J04Z, 027J0DZ, 027J0ZZ, 02NJ0ZZ, 02RF07Z, 02RF08Z, 02RF0JZ, 02RF0KZ, 02RF47Z, 02RF48Z, 02RF4JZ, 02RF4KZ, 02RG07Z, 02RG08Z, 02RG0JZ, 02RG0KZ, 02RG47Z, 02RG48Z, 02RG4JZ, 02RG4KZ, 02RH07Z, 02RH08Z, 02RH0JZ, 02RH0KZ, 02RH47Z, 02RH48Z, 02RH4JZ, 02RH4KZ, 02RJ07Z, 02RJ08Z, 02RJ0JZ, 02RJ0KZ, 02RJ47Z, 02RJ48Z, 02RJ4JZ, 02RJ4KZ, 02RG37Z, 02RG38Z, 02RG3KZ, 02RG3JZ
Hip Replacement	8151	0SR9019, 0SR901A, 0SR901Z, 0SR9029, 0SR902A, 0SR902Z, 0SR9039, 0SR903A, 0SR903Z, 0SR9049, 0SR904A, 0SR904Z, 0SR907Z, 0SR90J9, 0SR90JA,

		0SR90JZ, 0SRB0J9, 0SRB0JA, 0SRB0JZ, 0SRB0KZ
Knee Replacement	8154	0SRC07Z, 0SRC0J9, 0SRC0JA, 0SRC0JZ, 0SRC0KZ, 0SRD07Z, 0SRD0J9, 0SRD0JA, 0SRD0JZ, 0SRD0KZ, 0SRT07Z, 0SRT0J9, 0SRT0JA, 0SRT0JZ, 0SRT0KZ, 0SRU07Z, 0SRU0J9, 0SRU0JA, 0SRU0JZ, 0SRU0KZ, 0SRV07Z, 0SRV0J9, 0SRV0JA, 0SRV0JZ, 0SRV0KZ, 0SRW07Z, 0SRW0J9, 0SRW0JA, 0SRW0JZ, 0SRW0KZ
	CPT	
Valvular Heart Disease		33999, 0257T, 0258T, 0259T, 33405, 33425, 33426, 33427, 33430, 0262T, 33475, 33460, 33463, 33464, ,33465, A4680, A4690, A4706, A4707, A4708, A4709, A4730, A4740, A4750, A4755, A4802, A4870, A4890, A4918, E1520, E1530, E1540, E1550, E1560, E1575, E1580, E1590, E1600, E1610, E1615, E1620, E1625, E1636, G0365, G0392, G0393, G8081, G8082, G8085, S9335, 90935, 90937, 90940, 93990, 36800, 36810,36815
Hip Replacement		27090, 27091, 27125, 27130, 27132, 27134, 27236, 27137, 27138
Knee Replacement		27438, 27446, 27447, 27486, 27487, 27488

eAppendix Table 3. Conditions Defined by the Chronic Conditions Warehouse (CCW)

Acquired Hypothyroidism	Cancer, Colorectal	Diabetes
Acute Myocardial Infarction	Cancer, Endometrial	Glaucoma
Alzheimer's Disease	Cancer, Lung	Hip / Pelvic Fracture
Alzheimer's Disease, Related Disorders, or Senile Dementia	Cancer, Prostate	Hyperlipidemia
Anemia	Cataract	Hypertension
Asthma	Chronic Kidney Disease	Ischemic Heart Disease
Atrial Fibrillation	Chronic Obstructive Pulmonary Disease	Osteoporosis
Benign Prostatic Hyperplasia	Heart Failure	Rheumatoid Arthritis / Osteoarthritis
Cancer, Breast	Depression	Stroke / Transient Ischemic Attack

eAppendix Table 4. Observed vs Predicted NOAC Use and Stroke Rate

	NOAC Use			Stroke Rate		
	Unrestricted (N=88,445)	ST/PA (N=50,596)	Difference	Unrestricted (N=88,445)	ST/PA (N=50,596)	Difference
Observed	32.2%	30.2%	2.0%	5.2%	5.9%	-0.7%
Predicted, Unrestricted	32.2%	31.0%	1.1%	4.9%	5.2%	-0.2%
Predicted, Restricted	31.4%	30.2%	1.2%	5.3%	5.6%	-0.3%

eAppendix Table 5. Adjusted Hazard Ratio of Adverse Health Outcomes by Anticoagulant Use and Formulary Restrictions

	Non-Adherent	NOAC Adherent		Warfarin Adherent	
	Restricted (N=31,996)	Unrestricted (N=3,791)	Restricted (N=1,815)	Unrestricted (N=2,638)	Restricted (N=1,488)
Died, Stroke, TIA	1.093*** (1.070 - 1.117)	0.610*** (0.562 - 0.662)	0.554*** (0.492 - 0.624)	0.770*** (0.716 - 0.829)	0.874*** (0.802 - 0.954)
All-Cause Mortality	1.110*** (1.085 - 1.136)	0.595*** (0.544 - 0.652)	0.503*** (0.438 - 0.577)	0.791*** (0.732 - 0.855)	0.880*** (0.802 - 0.966)
Ischemic Stroke	1.088** (1.018 - 1.163)	0.599*** (0.474 - 0.758)	0.614*** (0.445 - 0.847)	0.535*** (0.414 - 0.690)	0.764* (0.580 - 1.006)
Hemorrhagic Stroke	1.145** (1.031 - 1.273)	0.564*** (0.387 - 0.824)	0.661* (0.408 - 1.070)	0.683** (0.474 - 0.983)	0.906 (0.603 - 1.360)
TIA	1.088*** (1.021 - 1.158)	0.730*** (0.600 - 0.889)	0.847 (0.657 - 1.091)	0.863 (0.712 - 1.045)	1.007 (0.802 - 1.264)
Major Bleeding	1.052** (1.011 - 1.095)	0.663*** (0.584 - 0.753)	0.818** (0.695 - 0.962)	0.801*** (0.708 - 0.907)	1.002 (0.867 - 1.157)
Intracranial	1.190*** (1.066 - 1.327)	0.602*** (0.412 - 0.879)	0.757 (0.473 - 1.210)	0.691* (0.470 - 1.014)	0.937 (0.613 - 1.433)
Gastrointestinal	1.027 (0.981 - 1.074)	0.665*** (0.575 - 0.769)	0.818** (0.678 - 0.986)	0.755*** (0.653 - 0.873)	0.946 (0.800 - 1.120)
Other	1.064 (0.966 - 1.171)	0.728** (0.542 - 0.976)	0.852 (0.584 - 1.242)	1.071 (0.820 - 1.400)	1.192 (0.862 - 1.649)

Note: Excludes patients with no anticoagulant use history prior to AF incidence date or patients who had first claim 30 days after AF incidence date, and who had both NOAC and warfarin claims. Adherent anticoagulant use is defined as PDC at or above 80%. The reference group are the non-users or non-adherent users in unrestricted plans (N=54,102).

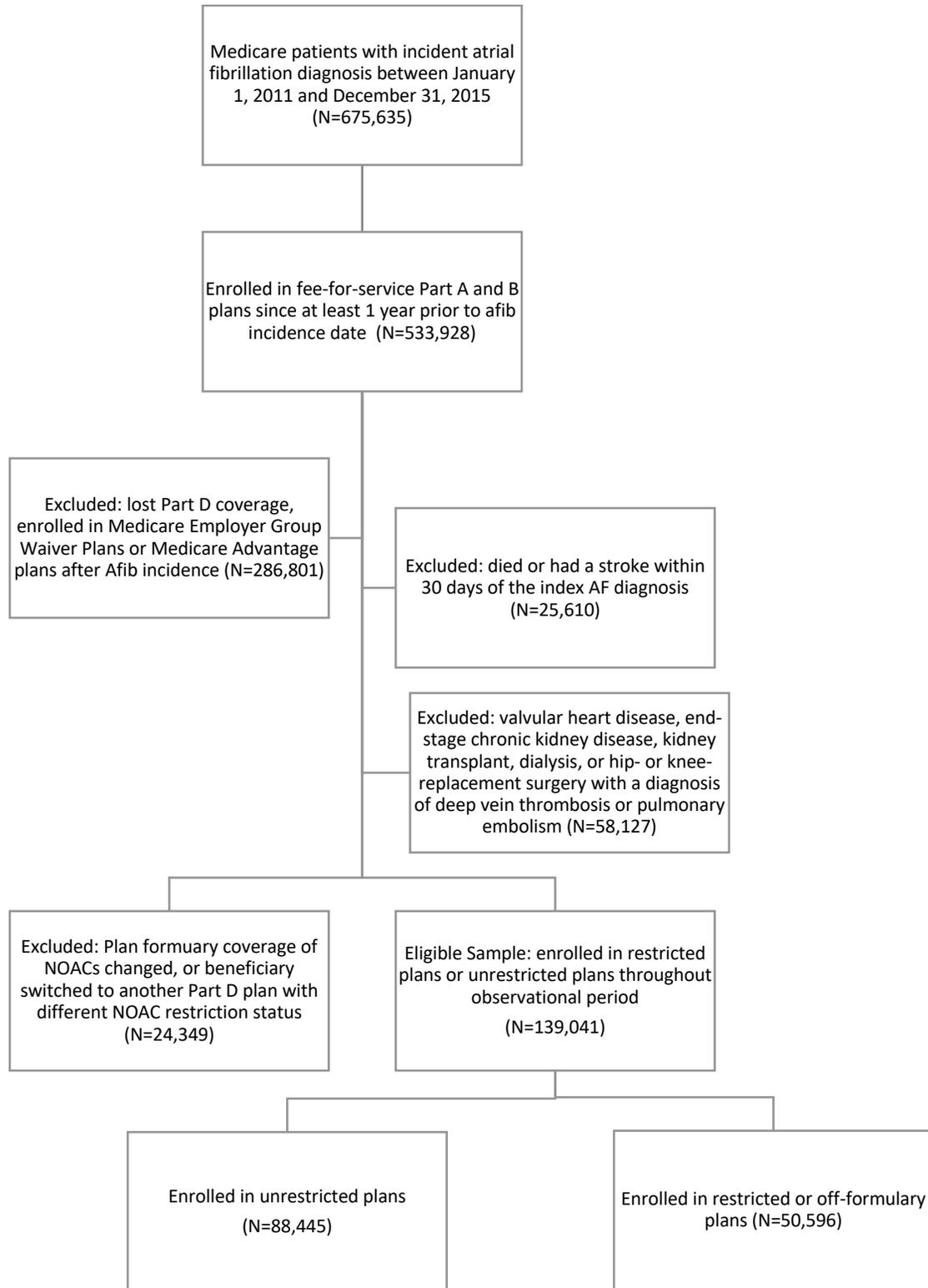
eAppendix Table 6. Predicting Differences in Stroke Rates Using RCT Data

Observed NOAC Use and Stroke Rate				
	NOAC	Warfarin Only	No Anticoagulant	All
Beneficiaries in Unrestricted Plans				
N. Obs.	28469	22338	37638	88,445
Anticoagulant use (%)	32.2	25.3	42.6	100
Beneficiaries in ST/PA Plans				
Restricted Subgroups (N)	15296	13132	22168	50,596
Restricted Subgroups (%)	30.2	26.0	43.8	100
Difference (Unrestricted – Restricted)				
Difference in Anticoagulant Use (%)	2.0	-0.70	-1.3	-
Prediction from RCT Data				
	NOAC	NOAC vs Warfarin	NOAC vs No Anticoagulant	All
Relative Risk from RCT	-	0.85*	0.18**	-
Predicted Difference in Stroke Rate (Percentage Points)	-	-0.006	-0.40	-0.40

Note: *Reported relative risk of stroke for NOACs versus warfarin are 0.79 (Apixaban), 0.79 (Rivaroxaban), 0.91 (Dabigatran), 0.79 (Edoxaban) from RCTs. We use 0.85 (the average of 0.79 and 0.91) in prediction.

** Since no RCT results for NOAC versus placebo are available, we use the multiplication of relative risks of NOAC vs warfarin and warfarin vs placebo to estimate the relative risk of stroke between NOAC versus no anticoagulant.

eAppendix Figure 1. Selection of Study Sample



eAppendix Figure 2. Utilization of anticoagulants among atrial fibrillation patients in Medicare PDP plans

