Evaluating the Effect of Carve-in or Carve-out Insurance Designs on Adherence to Oral Anticoagulation in Patients with Atrial Fibrillation: A Comparison of Medicare Advantage versus Medicare Fee-for-Service Insurance Plans

by

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Abstract

Atrial Fibrillation (AF) is a highly prevalent cardiac arrhythmia that affects nearly 6 million adults in the United States. AF quintuples the risk of stroke and this risk increases with age. Given the aging population in the US, AF-related stroke represents a significant public health burden. Treatment with oral anticoagulation (OAC) is the main intervention to prevent stroke in AF; however, nearly 50% of AF patients recommended to receive OAC, according to professional society guidelines, do not receive this therapy.

The literature shows that health insurance can affect initiation and adherence to OAC in AF patients, however there is limited information assessing to what extent different Medicare Part D insurance designs can affect adherence to OAC. Jung and colleagues suggest that insurance designs that carve-in pharmacy benefits with medical benefits such as Medicare Advantage Prescription Drug Plan (MA-PD) can improve medication adherence compared to plans that carve-out pharmacy benefits such as Stand-Alone Prescription Drug Plans (PDP). Insurers that provide carve-in benefits may be incentivized to improve adherence to OAC in order to offset medical costs that could be incurred through the development of a stroke.

In this study, we conducted multivariate logistic regression models among propensity-score matched samples to evaluate the effect of enrollment in PDP vs. MA-PD on OAC use and adherence.

We used 2014-2016 Medicare Claims Data from Centers of Medicare and Medicaid Services (PDP) and UPMC Health Plan data (MA-PD) for patients with AF. We found that enrollment in a PDP was associated with lower odds of OAC use (OR 0.59, 95% CI 0.50-0.69) and adherence (OR 0.68, 95% CI 0.60-0.76) compared to MA-PD. Our results suggest that insurance plans that carve-in pharmacy benefits can improve adherence to OAC and ultimately prevent downstream stroke events.

Public health significance: Determining the effect of Part D insurance design on OAC use and adherence is of major relevance because reducing OAC underuse in the US by half would avert 20,000 strokes annually and save Medicare $1 billion. Policymakers should consider the benefits of carve-in insurance designs in order to improve OAC use and adherence in the AF population.

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Preface

I would like to express my deepest gratitude for the support and guidance of my committee members Inmaculada Hernandez, Chester B. Good, Coleman Drake, and Samar R El Khoudary. Furthermore, I am incredibly grateful to Inmaculada Hernandez for the mentorship, instruction, and leadership throughout my academic journey. Additionally, I would like to thank Joseph Gabriel for providing assistance with the methods and statistical analysis, Alvaro San-Juan-Rodriguez for being a supportive colleague and friend throughout this master's program, Natasha Parekh for her support and encouragement in my professional development, and to Wendy He, Serena Guo, and many others—thank you for your advice and help along the way. Lastly, I would like to thank my family for their unwavering love and encouragement.

1.0 Introduction

1.1 Atrial Fibrillation

1.1.1 Epidemiology of Atrial Fibrillation

Atrial Fibrillation (AF) is a highly prevalent cardiac arrhythmia affecting nearly 33 million people globally, and between 3 to 6 million people in the United States (US).[1-4] The prevalence of AF is higher in older adults and increases with age.[2,5] For example, among those diagnosed with AF, an estimated 3 out of 4 individuals are between the ages of 65 to 85 years.[5] Furthermore, the prevalence of AF in persons younger than 55 years of age is 0.1%, whereas this prevalence increases to 3.8% and 10% in those 60 and 80 years of age, respectively.[2] Given the higher prevalence in older adults and the aging population in the US, the prevalence of AF is expected to triple by 2050.[6]

1.1.2 Stroke Risk in Atrial Fibrillation

AF is a cardiac arrhythmia characterized by an uncoordinated, rapid contraction of the atria, leading to ineffective atrial contraction.[7] In normal sinus rhythm, the heart beats in a coordinated manner where one electrical impulse, arising from the sinoatrial node (SA) in the right atrium, controls the contraction of the heart.[8] With AF, many different electrical impulses arise causing irregular atrial contraction and ventricular excitation.[7] In AF, a variety of manifestations such as an invariable ventricular rate, uncoordinated atrial contraction, sympathetic stimulation, and inconsistent ventricular filling can occur, leading to hemodynamic compromise.[7] Additionally, the presence of AF increases the risk of thrombogenesis—particularly in the form of an atrial thrombi in the left atrial appendage.[7,9]

As a result, the most common serious clinical consequence of atrial fibrillation is the development of an ischemic stroke or transient ischemic attack (TIA).[9-11]

AF is an independent and potent risk factor for stroke.[1,9-11] The presence of AF alone constitutes a 5-fold increase in the risk of stroke.[1,9-11] In the US, AF is responsible for the development of greater than 70,000 ischemic strokes annually,[12] and accounts for 15-20% of all ischemic strokes.[13] The risk of stroke due to AF increases with age,[1] and AF is the main cause of stroke in elderly patients.[14]

1.1.3 Clinical and Economic Burden of Stroke

In the US, there are nearly 800,000 stroke occurrences each year, and more than half of these events are new occurrences.[15] Stroke is a principal cause of death and disability in the US and may lead to dementia in up to 30% of stroke survivors.[16,17] The management of stroke is not limited to the acute setting and often requires long-term, post-stroke care, which represents a significant public health challenge.[18] In fact, nearly 50% of all patients who develop a stroke will experience moderate to severe impairment that requires special care and 10% will need supportive care from long-term care facilities.[18] Compared to non-AF related strokes, AF-related strokes are associated with poorer health outcomes.[9,19] Individuals with stroke due to AF experience longer hospital stays, higher 30-day mortality rates, lower 1-year survival rates, and experience a higher risk of stroke recurrence compared to individuals without AF.[9,19] Furthermore, even when constraining to a population with cardioembolic strokes, AF is still associated with the most severe outcomes.[19]

Stroke is associated with significant economic burden on the healthcare system. According to the American Heart Association, the annual direct cost of stroke is expected to reach $184 billion by 2030.[15,20] Additionally, the total annual cost, including direct and indirect costs, is expected to amount to $240 billion by 2030, corresponding to an 129% cost increase, compared to 2012 estimates.[20] The

presence of AF increases the costs of stroke hospitalizations thereby contributing to higher costs of care for AF patients.[14]

1.2 Oral Anticoagulation Treatment for Stroke Prevention

1.2.1 Treatment Options for Stroke Prevention in Atrial Fibrillation

In patients with AF, oral anticoagulation (OAC) is a mainstay treatment for stroke prevention. They work by inhibiting the biological pathways that promote clot formation.[21] OAC reduces the risk of stroke by 60%[22,23] and subsequently reduces the risk of death by 26%.[23] However, OAC is associated with an increased risk of bleeding. The use of OAC is recommended in individuals with AF who are determined to be at moderate to high risk of stroke as indicated by a CHA2DS2-VASc score of 2 or higher in men and a CHA2DS2-VASc score of 3 or higher in women.[24] CHA2DS2-VASc is a validated tool that predicts the risk of stroke in AF on the basis of eight components including congestive heart failure, hypertension, age, diabetes, previous history of stroke or TIA, vascular disease, and female sex[13].

There are two evidence-based, guideline recommended treatment options for OAC in AF patients: vitamin K antagonist therapy with warfarin and direct oral anticoagulants (DOACs). Previous literature has shown that the use of warfarin in the setting of AF reduces the annual stroke risk to less than 2%.[25] More recently, direct oral anticoagulants (DOAC) have been shown to be at least as efficacious or more efficacious than warfarin at preventing stroke occurrences.[26]

1.2.2 Trade-offs of Different Oral Anticoagulation Therapies

Warfarin is the oldest oral anticoagulation agent available and has been used for decades in the prevention of AF-related stroke and systemic embolism. It works by inhibiting the formation of a particular type of vitamin K, thereby reducing the synthesis of clotting factors that depend on vitamin K for generation.[27] Warfarin has a very narrow therapeutic index, requiring at least monthly monitoring of laboratory tests, and has major drug and food interactions that may present safety and efficacy issues.[27] On the other hand, DOACs are newer medications, approved since 2010.[27] There are four approved DOACs—dabigatran, rivaroxaban, apixaban, and edoxaban. They act on the coagulation cascade to prevent clot formation by directly inhibiting clotting factors Xa (rivaroxaban, apixaban, edoxaban) and thrombin (dabigatran).[27] The more stable pharmacokinetic profile of DOACs is an important advantage over warfarin, since they do not require routine monitoring nor dose adjustments and have fewer drug interactions.[27]

From an economic perspective, DOACs are more expensive than warfarin, because they are protected by patents.[7] In a study using data from a large, nationwide insurer, warfarin users spent $54 in out of pocket costs for 6 months of medication while DOAC users spent over $200 in the same period,[28] and insurer costs were over 10-times higher for DOACs.[28]

According to recent guidelines, DOACs are recommended over warfarin for the prevention of thromboembolism and stroke in patients with AF.[24] This recommendation was made based on evidence that DOACs are noninferior or superior to warfarin, with less severe bleeding risks.[24]

1.2.3 Real-World Initiation and Adherence to Oral Anticoagulation

Despite the benefit of stroke and systemic embolism prevention, OAC use in this population is still considered sub-optimal.[29,30] In the US, around 30-50% of high risk patients indicated to receive

OAC for stroke prevention do not receive this therapy.[30] And among OAC users, less than 50% adhere to therapy over time.[31] Lack of adherence is a major concern in stroke prevention because a single missed DOAC dose increases the risk of stroke.

A variety of factors relating to patient demographics, medical history, and socioeconomic status influence adherence to OAC.[30,32-34] Factors associated with increased adherence to OAC include older age; presence of comorbidities related to an increased risk of stroke, such as hypertension, diabetes, and other cardiovascular diseases; and high health literacy.[30,31,35] Conversely, factors associated with low adherence to OAC include non-white race, alcohol use, dementia, and higher bleeding risk.[30,31,35]

1.3 Effect of Medicare Design on Medication Use and Adherence

Medicare is a federal health insurance program that provides coverage for the elderly and those with disabilities.[36] It currently covers 18% of the US population, and is the main source of insurance for individuals age 65 and older.[36] Medicare benefits are administered through 3 parts: Part A, which covers inpatient services and hospitalizations, Part B, which covers provider services, and Part D, which covers prescription drugs. Medicare beneficiaries can opt to enroll in traditional fee-for-service Medicare, in which the federal government provides coverage of parts A and B, or in Medicare Advantage (MA) plans. MA plans are administered by private insurance carriers and provide coverage of parts A, B, and usually D.[36] MA plans typically have lower cost-sharing for their beneficiaries compared to traditional Medicare and may offer coverage of services included under traditional Medicare, such as dental or vision services.[36] On the other hand, Medicare fee-for-service offers more access to a variety of providers and less administrative

burden for beneficiaries in terms of prior authorization requests and referrals. As of 2018, 34% of Medicare individuals were enrolled in a MA plan.[36] Younger and healthier beneficiaries are overrepresented in MA plans, while individuals with higher disease burden often opt for fee-for-service coverage.[37]

Medicare Part D is provided through private plans approved by the federal government. Medicare enrollees have two options for prescription coverage through Medicare Part D: 1) They can purchase a stand-alone prescription drug plan (PDP) to supplement coverage of hospitalizations and provider services through fee-for-service Parts A and B or 2) they can enroll in a Medicare Advantage plan that provides prescription drug coverage (MA-PD). For patients enrolled in Medicare fee-for-service Parts A and B and on a PDP plan, Medicare reimburses providers directly for services rendered, and the PDP plan covers outpatient prescription drugs. In other words, Medicare carries financial risk for medical services, while PDP sponsors bear risk for the provision of pharmaceutical services. Thus, there is no alignment of incentives (pharmacy benefits are carved out). In contrast, in an MA-PD benefit design, medical and pharmacy benefits are integrated; therefore, one insurer bears the risk of medical and pharmacy costs (pharmacy benefits are carved in). Since insurers within a MA-PD internalize medical and pharmacy costs, they may have an increased incentive to ensure proper utilization of evidence-based medications shown to improve health and economic outcomes.

Evidence from an economic model, created by Goldman and colleagues suggests that the type of Part D plan can have an effect on adherence due to the concept of substitutable services.[38] Based on this theory, if an integrated insurer (i.e. MA-PD) covers services that are substitutable, the integrated insurer will maximize use of one service in order to decrease the use of the other service. In the context of OAC use in AF population, proper use and optimal adherence to OAC

can prevent utilization of medical services for stroke treatment. In this case, OAC use and stroke care are substitutable services; therefore, MA-PD plans have a higher incentive to maximize the optimal use of OAC in order to decrease stroke events that result in costly hospitalizations. In other words, MA-PD plans are incentivized to improve OAC use and adherence because they benefit from cost-savings associated with averted stroke events. PDP plans, however, are not subject to these incentives because they do not provide medical services [38] To incentivize the use of medications that can prevent downstream events, such as OAC use in the prevention of stroke, MA-PD plans can use different strategies, including lowering copayments and initiating quality improvement measures across the continuum of care, to improve medication use.[38]

1.4 Objective

In this study, we sought to determine if OAC use and adherence differs between PDP beneficiaries and MA-PD beneficiaries. This is of capital relevance because decreasing OAC underuse by half would avert nearly 20,000 strokes annually.[39] In this retrospective cohort study, we matched AF patients enrolled in PDP to enrollees in MA-PD and compared OAC use and adherence between the two groups. We hypothesized that a higher proportion of MA-PD beneficiaries will use an OAC and have adherent OAC use compared to PDP beneficiaries because, unlike PDP plans, MA-PD plans benefit from cost-savings associated with averted stroke events.

2.0 Methods

2.1 Data Source and Study Population

To capture members enrolled in PDP, we obtained 2014-2016 claims data from a 5% random sample of Medicare beneficiaries provided by the Centers for Medicare and Medicaid Services (CMS). These data contained information on members enrolled in Medicare Parts A, B, and D. For members enrolled in MA-PD, we obtained 2014-2016 de-identified claims data from UPMC Health Plan. UPMC is an integrated delivery and financing system that provides insurance coverage to over 3 million members in Pennsylvania, Ohio, Maryland, and West Virginia. We selected our study population across both cohorts in the following steps: First, we selected patients with a diagnosis of AF in 2015 defined as one inpatient or two outpatient claims with an AF diagnosis in the first or second position (lists of International Classification of Diseases, Ninth Revision [ICD-9] and ICD, Tenth Revision [ICD-10] shown in supplementary appendix). The date of AF diagnosis was defined as our index date. Second, because DOACs are not recommended in valvular disease,[7] we excluded any patients with a diagnosis of valvular atrial fibrillation (ICD-9: 394.0, V43.3; ICD-10: I05.0, Z95.2)in 2015. Thirdly, we restricted the sample to those continuously enrolled for 12 months before index date, in order to have complete data to define covariates. We further limited the sample to beneficiaries who were continuously enrolled for 12 months after the index date to ensure we observed their prescription claims. Fourth, we excluded beneficiaries with a CHA2DS2-VASc score less than two because, in 2014-2016, professional society guidelines recommended OAC use in AF patients with a CHA2DS2-VASc score of 2 or greater. Finally, we limited our sample to beneficiaries located within Pennsylvania, where UPMC has the highest market share.

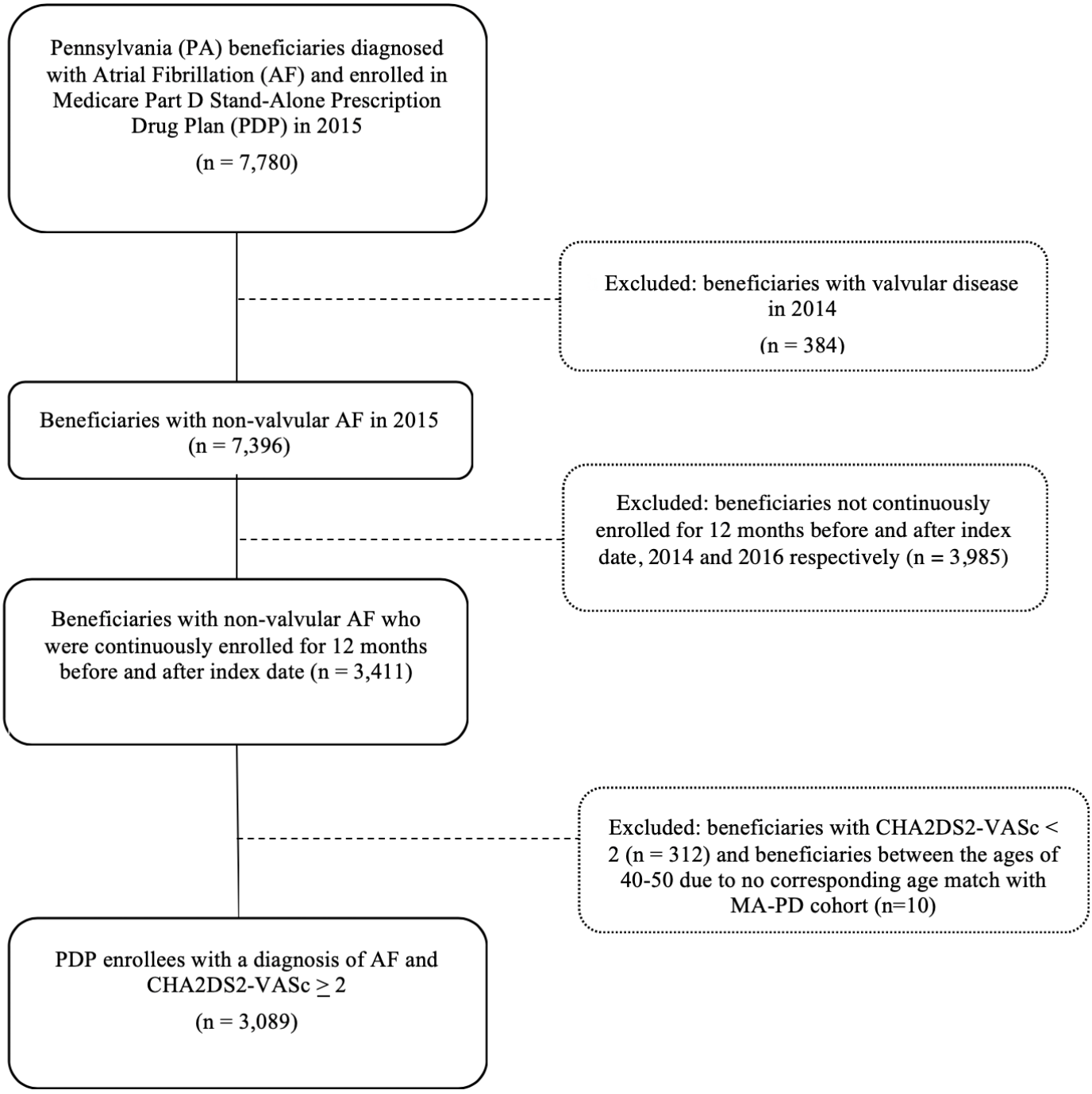

Figure 1 Sample Selection (PDP Cohort)

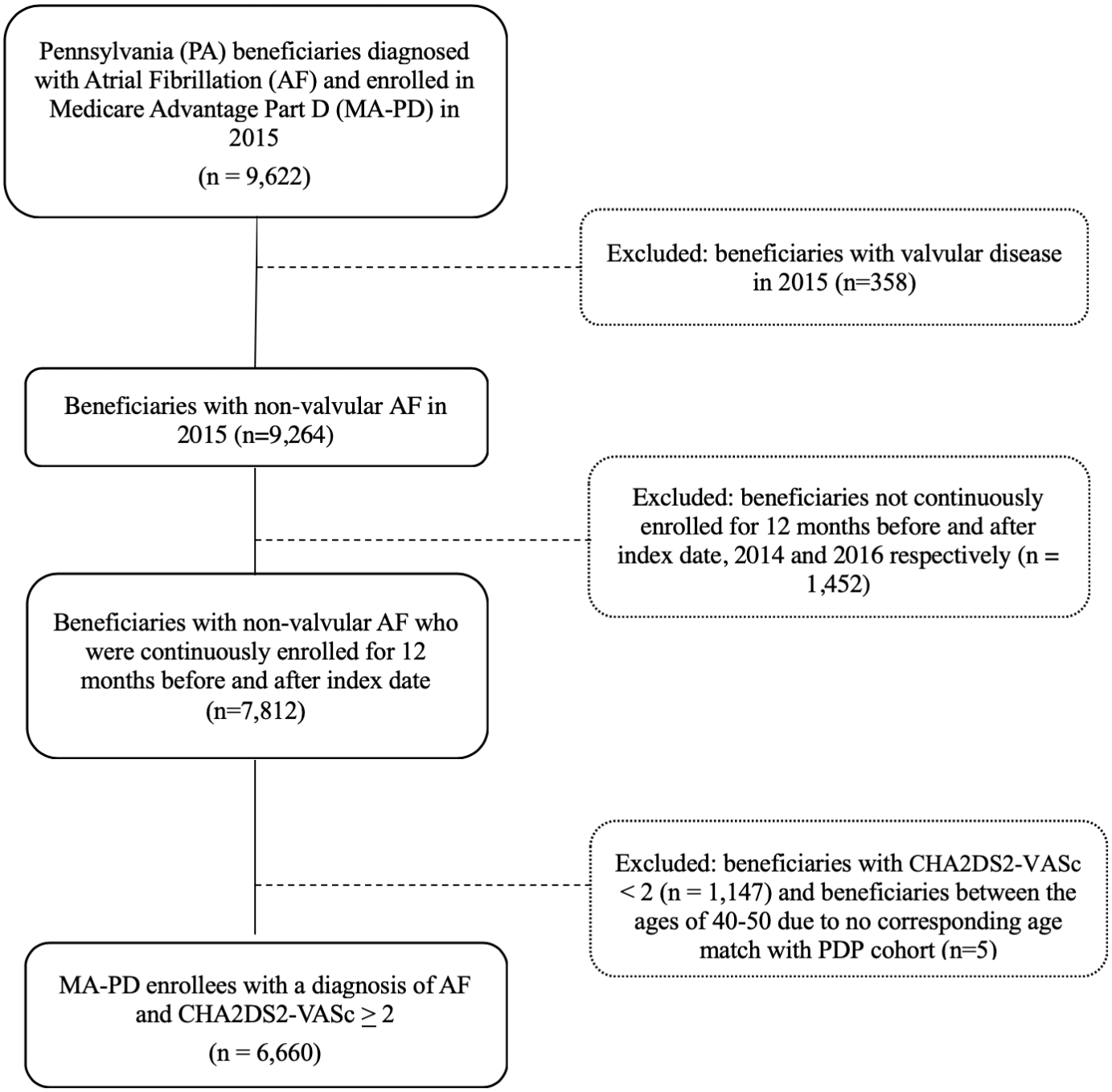

Figure 2. Sample Selection (MA-PD Cohort)

2.2 Outcomes

We evaluated two primary outcomes: OAC use and OAC adherence. OAC use was defined as having at least 1 fill of any OAC after index date. OAC adherence was defined as having greater than or equal to 80% days covered with OAC. To calculate the number of days covered with OAC, we extracted all prescriptions for warfarin, apixaban, edoxaban, dabigatran, and rivaroxaban filled after index date. Then, using dates of fill and days of supply for each prescription, we created a supply diary for 360 days (12 months) after the index date, and counted the number of days that each subject had possession of OAC in the 360 days after index date. We defined adherent individuals as those who had greater than or equal to 288 (80% of 360) days covered, since 80% is the most commonly used threshold in the literature to define medication adherence .[30,40,41]

In secondary analyses, we defined OAC use and adherence separately for warfarin and DOACs. We used the same definitions as in primary analyses but only used prescription claims for warfarin and DOACs, respectively.

2.3 Covariates

In order to minimize potential confounding effects, we controlled for a comprehensive set of demographic and clinical characteristics. Demographic characteristics included binary indicator for sex and discrete categories for age (>80 or $\leq$80). Binary clinical covariates included indicators for prior history of congestive heart failure (CHF), hypertension (HTN), acute myocardial infarction (AMI), renal disease, liver disease, diabetes, stroke or TIA, intracranial hemorrhage (ICH), major bleeding, prior use of nonsteroidal anti-inflammatory drugs, antiplatelet drugs, or anticoagulants, CHA2DS2-VASc score and HAS-BLED score. Chronic diseases and history of bleeding were measured in the

year before the index date using ICD-9 and ICD-10 codes (list of diagnosis codes included in Supplementary Appendix). CHA2DS2-VASc score is a risk stratification tool used to measure the risk of stroke in patients with AF.[7] To calculate CHA2DS2-VASc score, CHF, HTN, diabetes, vascular disease, ages 65-74, and female sex were all assigned one point. Age of 75 years or older and prior history of stroke/TIA or thromboembolism were all assigned two points. The CHA2DS2-VASc score was then derived as the sum of all points.[7] We also calculated a HAS-BLED score, which is a validated prediction tool used to measure the risk of bleeding.[42] The HAS-BLED score is calculated as the sum of 8 factors: HTN, abnormal renal or liver function, stroke, history of bleeding, international normalized ratio (INR), age 65 or older, concomitant use of antiplatelets or NSAIDS and excess alcohol use. The higher the score, the greater the risk of bleeding.[43] Since Medicare claims data do not contain information on INR levels, we calculated HAS-BLED scores as the sum of 8 factors, excluding labile INR. Prior medication use was measured in the six months before the index date. Non-steroidal anti-inflammatory drugs were defined as filling a prescription for diclofenac, ibuprofen, naproxen, ketoprofen, fenoprofen, flurbiprofen, piroxicam, meloxicam, mefenamic acid or indomethacin. Lastly, antiplatelets were defined as filling a prescription for aspirin, clopidogrel, prasugrel, dipyridamole, ticlopidine or ticagrelor. In addition to demographic and clinical characteristics, we also collected information regarding average copayment for OAC for beneficiaries who received a prescription for OAC prior to index date. We collected copayment information because copayment can serve as a mediator in these analyses.

2.4 Statistical Analysis

We compared baseline covariates between PDP and MA-PD cohorts using chi-square tests and two-sample t-tests as appropriate. Categorical data were reported as frequencies and proportions and continuous variables were reported as means.

We used a propensity score matching approach in order to mitigate confounding. To calculate the propensity score, we conducted a logistic regression that regressed type of Part D plan (PDP vs MA-PD) against all covariates listed above except for HAS-BLED score, CHA2DS2-VASc score, and ICH. We did not include these variables because HAS-BLED and CHA2DS2-VASc scores are calculated using covariates already included and ICH is included in the prior bleeding covariate. After generating a propensity score, we used the nearest neighbor matching method, where we matched 1 member from PDP to 1 member from MA-PD with similar propensity scores. We calculated standardized differences in covariate means to ensure all covariates were balanced among matched groups. We defined good balance between groups as standardized differences with absolute values less than 10%.[44] Finally, we constructed conditional logistic regressions on the matched samples to assess the effect of insurance type on outcomes, while controlling for covariates specified earlier. All statistical analyses were performed using statistical software SAS 9.4 (SAS Institute, INC., Cary, NC, USA).

2.4.1 Subgroup Analyses

We conducted subgroup analyses for incident OAC users, defined as study participants who had no fills for any OAC in the six months before index date. Additionally, for the outcome of OAC adherence, we conducted three separate subgroup analyses restricting the sample to beneficiaries who

used any OAC, warfarin only, and DOAC only. OAC, warfarin, and DOAC users were defined as having at least one prescription claim for the respective medication after the index date.

2.4.2 Sensitivity Analyses

In sensitivity analysis, we controlled for average copayment paid for OAC. We did not include this variable in primary analyses because average copayment paid for OAC may serve as a mediator in the causal relationship between Medicare Part D plan and OAC use and adherence.

3.0 Results

3.1 Baseline Characteristics

Our final sample contained 3,089 PDP beneficiaries and 6,660 MA-PD beneficiaries who met all inclusion criteria. The propensity score matched samples included 3,089 beneficiaries in each treatment group.

Table 1 shows the comparison of baseline characteristics before and after propensity score matching across our study sample. Before propensity score matching, PDP beneficiaries were more likely to have prevalent chronic conditions such as CHF, HTN, renal disease, diabetes, prior history of stroke or TIA, previous ICH, and major bleeding compared to MA-PD beneficiaries. Additionally, compared to MA-PD beneficiaries, more PDP beneficiaries used NSAIDs concomitantly, and had higher average copayment for OAC. After propensity score matching, we achieved balance for all covariates (standardized difference <0.10).

Table 1. Baseline Characteristics of Study Cohorts Before and After Propensity Score Matching

	Before Propensity Score Matching			After Propensity Score Matching		
Variable—n (%)	PDP (n=3,089)	MA-PD (n=6,660)	P-value*	PDP (n=3089)	MA-PD (n=3089)	Standardized Difference in Covariate Means
Demographics						
Age group			0.73			-0.01
≤80	289 (9.32)	638 (9.57)		289 (9.36)	277 (8.96)	
> 80	2,800 (90.35)	6,022 (90.35)		2800 (90.64)	2812 (91.03)	
Female sex	1,896 (61.38)	3,142 (47.18)	<.0001	1896 (61.38)	1910 (61.83)	-0.01
Clinical Characteristics						
HAS-BLED score[a]			<.0001			n/a
0-1	1,686 (54.58)	4,547 (68.27)		1686 (54.58)	1712 (55.42)	
2-3	1,331 (43.09)	2,036 (30.57)		1331 (43.09)	1330 (43.06)	
≥4	72 (2.33)	77 (1.16)		47 (1.52)	47 (1.52)	
CHF[b]	973 (31.50)	1,453 (21.82)	<.0001	973 (31.50)	887 (28.71)	0.06
HTN[b]	2,684 (86.89)	4,328 (64.98)	<.0001	2684 (86.89)	2683 (86.86)	0
MI[b]	86 (2.78)	152 (2.28)	0.14	86 (2.78)	74 (2.40)	0.02
Renal disease[b]	779 (25.22)	1,227 (18.42)	<.0001	779 (25.22)	745 (24.12)	0.03
Liver disease[b]	61 (1.97)	110 (1.65)	0.26	61 (1.97)	57 (1.85)	0.01
Diabetes[b]	1,132 (36.65)	2,176 (32.67)	0.0001	1132 (36.65)	1124 (36.39)	0
Stroke or TIA[b]	630 (20.39)	1,030 (15.45)	<.0001	630 (20.39)	585 (18.94)	0.04
Intracranial Hemorrhage[b]	230 (7.45)	406 (6.10)	0.01	230 (7.45)	276 (8.93)	n/a
Prior bleeding[b]	792 (25.64)	1,293 (19.41)	<.0001	792 (25.64)	794 (25.70)	0
Concomitant medications						
NSAIDs[c]	216 (7.00)	336 (5.05)	0.0001	216 (6.99)	223 (7.22)	-0.01
Anticoagulants[c]	608 (19.68)	1350 (20.27)	0.4882	1815 (58.76)	1822 (58.98)	0
Antiplatelets[c]	271 (8.77)	554 (8.32)	0.4743	271 (8.77)	248 (8.03)	0.03
Average copayment for OAC in USD-n (SD)	94.27 (203.10)	33.98 (50.76)	<.0001	96.31 (205.3)	31.32 (48.44)	n/a

Notes:

Data are expressed as *n* (%) unless otherwise specified

**P* values were derived from Chi-squared and Student's *t* tests

CHF= congestive heart failure; HTN=hypertension; MI= myocardial infarction; TIA= transient ischemic attack, NSAIDs= non-steroidal anti-inflammatory drug

[a]Because Medicare claims data do not contain information on INR levels, we calculated a modified HAS-BLED score that did not include labile INR

[b]CHF, HTN, MI, renal disease, liver disease, diabetes, stroke or TIA, intracranial hemorrhage, and prior bleeding were defined using their respective ICD-9 and ICD-10 codes in the year prior to the index date

[c]Medication use was defined in the year prior to the index date

3.2 Unadjusted Results for the Overall Sample

Table 2 shows the proportion of patients across each cohort that had at least one fill of OAC, warfarin, and DOAC and were adherent to each medication before and after propensity score matching. A higher proportion of MA-PD beneficiaries (75%) had at least one fill of an OAC after an AF diagnosis compared to PDP beneficiaries (70%). Additionally, nearly 40% of MA-PD beneficiaries were adherent to OAC medications compared to 33% of PDP beneficiaries. Likewise, between 2-5% more MA-PD beneficiaries used warfarin and DOAC compared to PDP beneficiaries and roughly 2% more MA-PD beneficiaries were adherent to warfarin or DOACs.

Table 2. Proportion of Beneficiaries with OAC Use and Adherence in Overall Sample

	Overall Sample Before Matching		Overall Sample After Matching	
Variable – n(%)	**PDP (n=3089)**	**MA-PD (n=6660)**	**PDP (n=3089)**	**MA-PD (n=3089)**
OAC Use	2167 (70.15)	4965 (74.55)	2167 (70.15)	2348 (76.01)
Adherent OAC use	1028 (33.28)	2686 (40.33)	1028 (33.28)	1269 (41.08)
Warfarin Use	1334 (43.19)	3044 (45.71)	1334 (43.19)	1405 (45.48)
Adherent Warfarin Use	595 (19.26)	1573 (23.62)	595 (19.26)	723 (23.41)
DOAC Use	862 (27.91)	2184 (32.79)	862 (27.91)	1065 (34.48)
Adherent DOAC Use	431 (13.95)	1028 (15.43)	431 (13.95)	513 (16.61)

Notes: This table shows proportion of beneficiaries across each cohort that had at least one prescription claim for an OAC, warfarin, and DOAC in the post-index period and were adherent to each medication. Adherence was defined as greater than or equal to 80% of days covered with the respective drug in a 360-day period(PDC $\geq$0.8).

3.3 Adjusted Results for the Overall Sample

Table 3 shows the adjusted odds ratios for adherence to any OAC, warfarin, and DOAC as well as use of any OAC, warfarin and DOAC in the overall sample. Results showed that enrollment in PDP was associated with lower odds of having at least one fill for any OAC during the study period (OR 0.59, 95% CI 0.50-0.69) compared to MA-PD. Additionally, PDP enrollment was associated with lower odds of adherence to OAC (Odds ratio [OR] 0.68, 95% CI 0.60-0.76) compared to MA-PD. Enrollment in PDP was also associated with lower odds of having at least 1 fill for warfarin (OR 0.79, 95% CI 0.68-0.91) and adherence to warfarin (OR 0.79, 95% CI 0.69-0.91). Similar results were seen for DOAC.

Table 3. Adjusted Odds Ratios for OAC Use and Adherence, Overall and by OAC Type

	Adjusted Odds Ratio for PDP vs. MA-PD (n=3089)
Use of OAC	0.59 (0.50-0.69)
Adherent OAC use	0.68 (0.60-0.76)
Use of Warfarin	0.79 (0.68-0.91)
Adherent Warfarin use	0.79 (0.69-0.91)
Use of DOACs	0.67 (0.58-0.77)
Adherent DOACs use	0.82 (0.71-0.95)

Notes: This table shows the adjusted odds ratios for use and adherence to any OAC, warfarin, and DOAC, respectively. Use of any OAC, warfarin, and DOAC was defined as having at least 1 fill of the respective drug in the post-index period (after AF diagnosis). Adherent use of OAC, warfarin, and DOACs was defined as greater than or equal to 80% of days covered with the respective drug in a 360-day period. All analyses were adjusted for covariates specified within the manuscript and compared use and adherence outcomes among PDP beneficiaries and MA-PD beneficiaries with MA-PD as the reference group.

3.4 Subgroup Analyses for Incident OAC Users

3.4.1 Proportion of Beneficiaries with OAC Use and Adherence

Table 4 shows the proportion of beneficiaries who used an OAC and were adherent to OAC among incident OAC users (no fill for any OAC 6 months prior to index date), before and after propensity score matching. After propensity score matching there were 1,272 beneficiaries in both cohorts and 44% of MA-PD beneficiaries had at least 1 fill for an OAC compared to 34% of PDP beneficiaries. Likewise, 17% of MA-PD beneficiaries had adherent OAC use compared to 13% of PDP beneficiaries.

Table 4. Proportion of Beneficiaries with OAC Use and Adherence

	Incident OAC users Subset Before Matching		Incident OAC users Subset After Matching	
Variable – n(%)	**PDP (n=1274)**	**MA-PD (n=3039)**	**PDP (n=1272)**	**MA-PD (n=1272)**
Use of OAC	429 (33.67)	1404 (46.20)	428 (33.65)	559 (43.95)
Adherent OAC use	162 (12.72)	539 (17.74)	162 (12.74)	215 (16.90)

Notes: This table shows the proportion of beneficiaries with OAC use and adherence in incident OAC users across PDP and MA-PD cohorts, before and after propensity score matching. OAC use was defined as at least 1 prescription claim for an OAC in the post-index period. Adherent OAC use was defined as greater than or equal to 80% of days covered with an OAC in a 360-day period.

3.4.2 Adjusted Results for OAC Use and Adherence among Incident Users

Table 5 shows results of OAC use and adherence among incident OAC users. Results showed that among incident OAC users, PDP enrollment was associated with lower odds of having at least one fill for an OAC during the study period (OR 0.66, 95% CI 0.56-0.77) compared to MA-PD. With regards to adherence, PDP enrollment was associated with lower odds of adherence to OAC (OR 0.70, 95% CI 0.55-0.88) compared to MA-PD.

Table 5. Adjusted Odds Ratios for OAC Use and Adherence in Incident OAC Users

Variable – n(%)	**Odds ratio (95%CI) for MAPD vs PDP (n=1272)**
Use of OAC	0.66 (0.56-0.77)
Adherent OAC use	0.70 (0.55-0.88)

Notes: This table shows the adjusted odds ratios for use and adherence to any OAC among incident OAC users. Incident OAC use was defined as no OAC use in the 6 months prior to AF diagnosis. All analyses were adjusted for covariates specified within the manuscript and compared adherence among PDP beneficiaries and MA-PD beneficiaries with MA-PD enrollment as the reference group.

3.5 Subgroup Analyses for Adherence among OAC Users, Warfarin Users, and DOAC Users

We conducted three, additional subgroup analyses to evaluate adherence outcomes among OAC users, warfarin users, and DOAC users. We evaluated OAC adherence for patients who filled at least one prescription for an OAC in the post-index period (OAC users); warfarin adherence in those who filled at least one prescription for warfarin in the post-index period (warfarin users) and DOAC adherence in those who filled at least one prescription for DOAC in

the post-index period (DOAC users). Among each group of users, we evaluated adherence to each respective medication using the same methodology in the main analyses.

3.5.1 Subgroup Analyses in OAC Users

3.5.1.1 Proportion of beneficiaries with Adherent OAC Use

Table 6 shows the proportion of patients who were adherent to OAC among those who had at least one fill for any OAC in the post-index period. Before propensity score matching there were a total of 4,965 MA-PD beneficiaries and 2,167 PDP beneficiaries who filled at least 1 prescription for an OAC in the post-index period. After propensity score matching there were 2,166 beneficiaries across both cohorts and more MA-PD beneficiaries were adherent to OAC (56%) compared to PDP beneficiaries (47%).

Table 6. Proportion of Beneficiaries with Adherent OAC Use among OAC Users

	OAC users Subset Before Matching		OAC users Subset After Matching	
	PDP	**MA-PD**	**PDP**	**MA-PD**
Variable – n(%)	**(n=2167)**	**(n=4965)**	**(n=2166)**	**(n=2166)**
Adherent OAC use	1028 (47.44)	2686 (54.10)	1027 (47.41)	1211 (55.91)

Notes: This table shows the proportion of beneficiaries with adherent OAC use among OAC users before and after propensity score matching. Adherent OAC use was defined as greater than or equal to 80% of days covered with an OAC in a 360-day period.

3.5.1.2 Adjusted Odds Ratios for Adherent OAC use Among OAC Users

Table 7 shows the adjusted odds ratio for adherent OAC use among OAC users. Compared to MA-PD beneficiaries, enrollment in PDP was associated with lower odds of adherent OAC use

(OR 0.71, 95% CI 0.63-0.80) among those who filled at least one prescription for an OAC in the post-index period.

Table 7. Adjusted Odds Ratios for Adherent OAC Use Among OAC Users

Variable – n(%)	Odds ratio (95%CI) for PDP vs MA-PD (n=1272)
Adherent OAC use	0.71 (0.63-0.80)

Notes: This table shows the adjusted odds ratios for adherent OAC use (greater than or equal to 80% of days covered with an OAC in 360-day period) among OAC users, defined as at least 1 fill for an OAC in the post-index period. All analyses were adjusted for covariates specified within the manuscript and compared adherence among PDP beneficiaries and MA-PD beneficiaries with MA-PD enrollment as the reference group.

3.5.2 Subgroup Analyses in Warfarin Users

3.5.2.1 Proportion of Beneficiaries with Adherent Warfarin Use

Table 8 shows the proportion of beneficiaries who were adherent to warfarin among those who had at least one fill for warfarin in the post-index period. Before propensity score matching there were a total of 2,781 MA-PD beneficiaries and 1,305 PDP beneficiaries who filled at least 1 prescription for warfarin in the post-index period. After propensity score matching, there were 1,304 beneficiaries across both cohorts and more MA-PD beneficiaries were adherent to warfarin (58%) compared to PDP beneficiaries (46%).

Table 8. Proportion of Beneficiaries with Adherent Warfarin Use among Warfarin Users

	Warfarin Users Subset Before Matching		Warfarin Users Subset After Matching	
Variable – n(%)	**PDP (n=1305)**	**MA-PD (n=2781)**	**PDP (n=1304)**	**MA-PD (n=1304)**
Adherent Warfarin use	595 (45.59)	1536 (55.23)	594 (45.55)	757 (58.05)

Notes: This table shows the proportion of beneficiaries with adherent warfarin use among warfarin users before and after propensity score matching. Warfarin users were defined as beneficiaries with at least 1 fill for warfarin in the post-index period. Adherent warfarin use was defined as greater than or equal to 80% of days covered with warfarin in a 360-day period.

3.5.2.2 Adjusted Odds Ratios for Adherent Warfarin Use Among Warfarin Users

Table 9 shows the adjusted odds ratios for adherent warfarin use among warfarin users. Compared to MA-PD beneficiaries, enrollment in PDP was associated with lower odds of adherent warfarin use (OR 0.59, 95% CI 0.51-0.68) among those who filled at least one prescription for warfarin in the post-index period.

Table 9. Adjusted Odds Ratios for Adherent Warfarin Use Among Warfarin Users

Variable – n(%)	**Odds ratio (95%CI) for PDP vs. MA-PD (n=1304)**
Adherent Warfarin use	0.59 (0.51-0.68)

Notes: This table shows the adjusted odds ratios for adherent warfarin use among warfarin users. Warfarin users were defined as beneficiaries with at least 1 fill for warfarin in the post-index period. Adherent warfarin use was defined as greater than or equal to 80% of days covered with warfarin in a 360-day period. All analyses were adjusted for covariates specified within the manuscript and compared adherence among PDP beneficiaries to MA-PD beneficiaries with MA-PD enrollment as the reference group.

3.5.3 Subgroup Analyses in DOAC Users

3.5.3.1 Proportion of Beneficiaries with Adherent DOAC Use

Table 10 shows the proportion of patients who were adherent to DOACs among those who had at least one fill for any DOAC in the post-index period. Before propensity score matching there were a total of 2,184 MA-PD beneficiaries and 862 PDP beneficiaries who filled at least 1 prescription for DOACs in the post-index period. After propensity score matching there were 862 beneficiaries across both cohorts and fewer MA-PD beneficiaries were adherent to a DOAC (46%) compared to PDP beneficiaries (50%).

Table 10. Proportion of Beneficiaries with Adherent DOAC Use among DOAC Users

	DOAC Users Subset Before Matching		DOAC Users Subset After Matching	
Variable – n(%)	**PDP (n=862)**	**MA-PD (n=2184)**	**PDP (n=862)**	**MA-PD (n=862)**
Adherent DOAC use	431 (50.00)	1028 (47.07)	431 (50.00)	393 (45.59)

Notes: This table shows the proportion of beneficiaries with adherent DOAC use among DOAC users before and after propensity score matching. DOAC users were defined as beneficiaries with at least 1 fill for a DOAC in the post-index period. Adherent DOAC use was defined as greater than or equal to 80% of days covered with a DOAC in a 360-day period.

3.5.3.2 Adjusted Odds Ratios for Adherent DOAC Use Among DOAC Users

Table 11 shows the adjusted odds ratios for adherent DOAC use among DOAC users. Compared to MA-PD enrollment, enrollment in PDP was associated with no difference in the odds of adherent DOAC use (1.18, 0.97-1.45).

Table 11. Adjusted Odds Ratios for Adherent DOAC Use Among DOAC Users

Variable – n(%)	Odds ratio (95%CI) for PDP vs MA-PD (n=1304)
Adherent DOAC use	1.18 (0.97-1.45)

Notes: This table shows the adjusted odds ratios for adherence to DOACs among DOAC users. DOAC users were defined as beneficiaries with at least 1 fill for a DOAC in the post-index period. Adherent DOAC use was defined as greater than or equal to 80% of days covered with a DOAC in a 360-day period. All analyses were adjusted for covariates specified within the manuscript and compared adherence among PDP beneficiaries to MA-PD beneficiaries with MA-PD enrollment as the reference group.

3.6 Sensitivity Analyses

In sensitivity analyses we adjusted for the average copayment of OACs in the overall sample. When adjusting for average copayment, the point estimates for all use and adherence outcomes were smaller compared to the main analysis. Enrollment in a PDP was associated with lower odds of OAC use (OR 0.76, 95%CI 0.64-0.92), and no difference in use of warfarin (OR 0.90, 95%CI 0.77-1.05) or DOAC (OR 0.85, 95%CI 0.72-1.00). For adherence outcomes, enrollment in PDP was associated with lower odds of adherence to any OAC (OR 0.69, 95%CI 0.62-0.78) and no difference in adherence to warfarin (OR 0.90, 95%CI 0.77-1.06) or DOACs (OR 0.93, 95%CI 0.77-1.13).

Table 12. Adjusted Odds Ratio for Use and Adherence Outcomes After Adjusting for Copayment

	Adjusted Odds Ratio for PDP vs. MA-PD (n=3089)
Use of OAC	0.76 (0.64-0.92)
Adherent OAC use	0.69 (0.62-0.78)
Use of Warfarin	0.90 (0.77-1.05)

Table 12 Continued

Adherent Warfarin Use	0.90 (0.77-1.06)
Use of DOACs	0.85 (0.72-1.00)
Adherent DOAC use	0.93 (0.77-1.13)

Notes: This table shows the adjusted odds ratios for use and adherence to any OAC, warfarin, and DOAC in the overall sample, after controlling for the average copayment of OAC. Use of OAC, warfarin, and DOACs was defined as having at least 1 fill of the respective drug in the post-index period (after AF diagnosis). Adherent use of OAC, warfarin, and DOACs was defined as greater than or equal to 80% of days covered with the respective drug in a 360-day period. All analyses were adjusted for average copayment and covariates specified within the manuscript and compared use and adherence among PDP beneficiaries and MA-PD beneficiaries with MA-PD enrollment as the reference group.

4.0 Discussion

In this retrospective cohort study, we examined how OAC use and adherence differed between Medicare beneficiaries enrolled in PDP and MA-PD plans. We found that, compared to MA-PD, enrollment in PDP was associated with 40% lower odds of OAC use and 32% lower odds of OAC adherence. We observed similar associations between insurance type and adherence to warfarin; however, the association between type of plan and DOAC adherence was not significant. In sensitivity analyses, we found that adjusting for copayment of an OAC led to smaller effect sizes of the outcomes which supports the mediator role of copayment in the relationship between insurance type and OAC use and adherence.

Our study is consistent with the extensive body of literature showing that, across data sets and regions, only half of AF patients who are recommended for OAC according to guidelines, actually receive it. Prior research has evaluated how type of Part D coverage affects use and adherence to medications other than OACs. A study by Jung and colleagues evaluated how enrollment in MA-PD or PDP affects adherence to statin medications. They found that enrollment in MA-PD was associated with 2% higher adherence to statins compared to PDP enrollees, but this difference was determined to be clinically negligible.[38] This study evaluated data from 2007, and reflected the early phase of Medicare Part D which was implemented in 2006. Since implementation, Medicare Part D has grown to adopt strategies and infrastructure to enhance medication adherence and other outcomes-focused metrics. Our data contain more recent years and may reflect these changes over the years. Using CMS claims data from 2007, Erten and colleagues compared use and adherence of guideline-recommended prescription medications in diabetes patients enrolled in PDP versus MA-PD.[45] They found enrollment in MA-PD was associated with increased use of guideline-recommended therapy in diabetes patients but lower adherence compared to PDP. Our study aligns with the finding that MA-PD enrollment is

associated with higher use of guideline recommended therapy; however, we observed higher adherence in MA-PD beneficiaries. Erten and colleagues only included patients who were enrolled in Medicare fee-for-service in 2005 and either maintained coverage or switched to an MA-PD plan. This presents a selection bias, since some beneficiaries who would be newly eligible were not included. Our study is an important contribution to this existing literature because it uses more recent data and focuses on a therapeutic class where continued adherence is crucial for success of therapy.

Our findings support our hypothesis that beneficiaries enrolled in MA-PD would have higher use of and adherence to OAC compared to PDP beneficiaries. The higher OAC use and adherence observed among MA-PD beneficiaries may reflect the financial incentives of MA-PD plans to improve guideline-recommended OAC use because they benefit from cost-savings associated with costly stroke events. This finding supports the economic model proposed by Goldman and colleagues which suggests that an integrated insurer, who provides substitutable services, can maximize use of one service in order to decrease the use of the other substitutable service.[38] In the context of OAC use for stroke prevention, MA-PD as an integrated insurer can achieve optimal use of OAC in order to offset the use of services and resources associated with stroke care.

The results of our study carry important implications for policy, payer, and patient-stakeholders to consider how insurance designs can affect adherence and health outcomes. Due to the financial alignment of MA-PD plans, there may be better infrastructure and systems in place to improve OAC use and adherence because of the benefit of averted stroke events and costs. To further evaluate this mechanism, future research needs to evaluate the specific features of benefit design or care-coordination within these plans that may lead to improved adherence outcomes. Additionally, future research should evaluate how clinical outcomes, such as stroke events or hospitalizations related to AF, differ among MA-PD and PDP beneficiaries.

This paper is subject to some limitations. First, claims data can only provide us with the filling history of a patient but cannot provide us with information regarding if the medication was taken or

taken as prescribed. In the same vein, if a patient were to receive OAC via cash or free samples we would not have access to that information which could lead to an underestimation of adherence in our study. Secondly, this study included data from 2014-2016. Over the years, uptake to DOAC agents has increased due to development of reversal agents, increased clinician comfortability, better safety profile, and guideline changes that recommend DOACs over warfarin for stroke prevention.[24,38] As a result, a continuation of this study with more recent years of data could provide updated information. Thirdly, although we attempted to control for bias through propensity score matching and adjusted analyses there may be residual confounding since PDP patients generally represent a sicker and older population.[46] Fourth, we only observed beneficiaries within Pennsylvania which limits our generalizability to other geographic locations. Lastly, we observed characteristics of beneficiaries excluded from our study and noticed they differed from included beneficiaries. Tables 7 and 8 show characteristics for included beneficiaries compared to excluded beneficiaries across MA-PD and PDP cohorts. Compared to included beneficiaries, excluded beneficiaries in both MA-PD and PDP cohorts were sicker, with a higher bleeding risk and a greater prevalence of comorbidities. As such, our results may not serve as a wholly representative depiction of PDP and MA-PD enrollees.

Overall, our study utilized data from nationally representative Medicare populations and provided new evidence regarding the association of Medicare Part D coverage with adherence to OAC in AF patients. Given the significant public health burden of AF, stroke prevention with OAC is an important measure to improve management of AF patients and reduce the total clinical and economic burden. Our results suggest that insurance plans that carve-in pharmacy benefits can improve adherence to OAC and ultimately prevent downstream stroke events.

Appendix A : Diagnosis Codes for Covariates

Table 13. Diagnosis Codes for Covariates

Covariate	ICD-9 Codes	ICD-10 Codes
Congestive Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9	I09.81, I11.0, I13.0, I13.2, I50.1, I50.20, I50.21, I50.22, I50.23, I50.30, I50.31, I50.32, I50.33, I50.40, I50.41, I50.42, I50.43, I50.810, I50.811, I50.812, I50.813, I50.814, I50.82, I50.83, I50.84, I50.89, I50.9
Hypertension	362.11, 401.0, 401.1, 401.9, 402.00, 402.01, 402.10, 402.11, 402.90, 402.91, 403.00, 403.01, 403.10, 403.11, 403.90, 403.91, 404.00, 404.01, 404.02, 404.03, 404.10, 404.11, 404.12, 404.13, 404.90, 404.91, 404.92, 404.93, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 437.2	H35.031, H35.032, H35.033, H35.039, I10, I11.0, I11.9, I12.0, I12.9, I13.0, I13.10, I13.11, I13.2, I15.0, I15.1, I15.2, I15.8, I15.9, I67.4, N26.2
Diabetes	249.00, 249.01, 249.10, 249.11, 249.20, 249.21, 249.30, 249.31, 249.40, 249.41, 249.50, 249.51, 249.60, 249.61, 249.70, 249.71, 249.80, 249.81, 249.90, 249.91, 250.00, 250.01, 250.02, 250.03, 250.10, 250.11, 250.12, 250.13, 250.20, 250.21, 250.22, 250.23, 250.30, 250.31, 250.32, 250.33, 250.40, 250.41, 250.42, 250.43, 250.50, 250.51, 250.52, 250.53, 250.60, 250.61, 250.62, 250.63, 250.70, 250.71, 250.72, 250.73, 250.80, 250.81, 250.82, 250.83, 250.90, 250.91, 250.92, 250.93, 357.2, 362.01, 362.02, 362.03, 362.04, 362.05, 362.06, 366.41	E08.00, E08.01, E08.10, E08.11, E08.21, E08.22, E08.29, E08.311, E08.319, E08.321, E08.3211, E08.3212, E08.3213, E08.3219, E08.329, E08.3291, E08.3292, E08.3293, E08.3299, E08.331, E08.3311, E08.3312, E08.3313, E08.3319, E08.339, E08.3391, E08.3392, E08.3393, E08.3399, E08.341, E08.3411, E08.3412, E08.3413, E08.3419, E08.349, E08.3491, E08.3492, E08.3493, E08.3499, E08.351, E08.3511, E08.3512, E08.3513, E08.3519, E08.3521, E08.3522, E08.3523, E08.3529, E08.3531, E08.3532, E08.3533, E08.3539, E08.3541, E08.3542, E08.3543, E08.3549, E08.3551, E08.3552, E08.3553, E08.3559, E08.359, E08.3591, E08.3592, E08.3593, E08.3599, E08.36, E08.37X1, E08.37X2, E08.37X3, E08.37X9, E08.39, E08.40, E08.41, E08.42, E08.43, E08.44, E08.49, E08.51, E08.52, E08.59, E08.610, E08.618, E08.620, E08.621, E08.622, E08.628, E08.630, E08.638, E08.641, E08.649, E08.65, E08.69, E08.8, E08.9, E09.00, E09.01, E09.10, E09.11, E09.21, E09.22, E09.29, E09.311, E09.319, E09.321, E09.3211, E09.3212, E09.3213, E09.3219, E09.329, E09.3291, E09.3292, E09.3293, E09.3299, E09.331, E09.3311, E09.3312, E09.3313, E09.3319, E09.339, E09.3391, E09.3392, E09.3393, E09.3399, E09.341, E09.3411, E09.3412, E09.3413, E09.3419, E09.349, E09.3491, E09.3492, E09.3493, E09.3499, E09.351, E09.3511, E09.3512, E09.3513, E09.3519, E09.3521, E09.3522, E09.3523, E09.3529, E09.3531, E09.3532, E09.3533, E09.3539, E09.3541, E09.3542, E09.3543, E09.3549, E09.3551, E09.3552, E09.3553, E09.3559, E09.359, E09.3591, E09.3592, E09.3593, E09.3599, E09.36, E09.37X1, E09.37X2, E09.37X3,

Table 13 Continued

		E09.37X9, E09.39, E09.40, E09.41, E09.42, E09.43, E09.44, E09.49, E09.51, E09.52, E09.59, E09.610, E09.618, E09.620, E09.621, E09.622, E09.628, E09.630, E09.638, E09.641, E09.649, E09.65, E09.69, E09.8, E09.9, E10.10, E10.11, E10.21, E10.22, E10.29, E10.311, E10.319, E10.321, E10.3211, E10.3212, E10.3213, E10.3219, E10.329, E10.3291, E10.3292, E10.3293, E10.3299, E10.331, E10.3311, E10.3312, E10.3313, E10.3319, E10.339, E10.3391, E10.3392, E10.3393, E10.3399, E10.341, E10.3411, E10.3412, E10.3413, E10.3419, E10.349, E10.3491, E10.3492, E10.3493, E10.3499, E10.351, E10.3511, E10.3512, E10.3513, E10.3519, E10.359, E10.36, E10.37X1, E10.37X2, E10.37X3, E10.37X9, E10.39, E10.40, E10.41, E10.42, E10.43, E10.44, E10.49, E10.51, E10.52, E10.59, E10.610, E10.618, E10.620, E10.621, E10.622, E10.628, E10.630, E10.638, E10.641, E10.649, E10.65, E10.69, E10.8, E10.9, E11.00, E11.01, E11.10, E11.11, E11.21, E11.22, E11.29, E11.311, E11.319, E11.321, E11.3211, E11.3212, E11.3213, E11.3219, E11.329, E11.3291, E11.3292, E11.3293, E11.3299, E11.331, E11.3311, E11.3312, E11.3313, E11.3319, E11.339, E11.3391, E11.3392, E11.3393, E11.3399, E11.341, E11.3411, E11.3412, E11.3413, E11.3419, E11.349, E11.3491, E11.3492, E11.3493, E11.3499, E11.351, E11.3511, E11.3512, E11.3513, E11.3519, E11.3521, E11.3522, E11.3523, E11.3529, E11.3531, E11.3532, E11.3533, E11.3539, E11.3541, E11.3542, E11.3543, E11.3549, E11.3551, E11.3552, E11.3553, E11.3559, E11.359, E11.3591, E11.3592, E11.3593, E11.3599, E11.36, E11.37X1, E11.37X2, E11.37X3, E11.37X9, E11.39, E11.40, E11.41, E11.42, E11.43, E11.44, E11.49, E11.51, E11.52, E11.59, E11.610, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9, E13.00, E13.01, E13.10, E13.11, E13.21, E13.22, E13.29, E13.311, E13.319, E13.321, E13.3211, E13.3212, E13.3213, E13.3219, E13.329, E13.3291, E13.3292, E13.3293, E13.3299, E13.331, E13.3311, E13.3312, E13.3313, E13.3319, E13.339, E13.3391, E13.3392, E13.3393, E13.3399, E13.341, E13.3411, E13.3412, E13.3413, E13.3419, E13.349, E13.3491, E13.3492, E13.3493, E13.3499, E13.351, E13.3511, E13.3512, E13.3513, E13.3519, E13.3521, E13.3522, E13.3523, E13.3529, E13.3531, E13.3532, E13.3533, E13.3539, E13.3541, E13.3542, E13.3543, E13.3549, E13.3551, E13.3552, E13.3553, E13.3559, E13.359, E13.36, E13.39, E13.40, E13.41, E13.42, E13.43, E13.44, E13.49, E13.51, E13.52, E13.59, E13.610, E13.618, E13.620, E13.621, E13.622, E13.628, E13.630, E13.638, E13.641, E13.649, E13.65, E13.69, E13.8, E13.9
Ischemic Stroke	433, 434, 436	I63, I64.9
Transient Ischemic Atack	435	G45

Table 13 Continued

Thromboembolism	444, 444.9, 444.1, 415.1	I74, I26
Valvular Disease	394.0, V43.3	I05.0, Z95.2
Acute Myocardial Infarction	410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91	I21.01, I21.02, I21.09, I21.11, I21.19, I21.21, I21.29, I21.3, I21.4, I21.9, I21.A1, I21.A9, I22.0, I22.1, I22.2, I22.8, I22.9
Peripheral Vascular Disease	440.0, 440.2, 440.9, 441.3, 441.4, 441.5, 441.9, 443.9, 444.22, 444.81, 447.1, 443.81, 250.70, 433.10, 433.11, 433.30	I70.0, I70.2, I70.9, I71.3, I71.4, I71.8, I71.9, I73.9, I74.3, I74.5, I77.1, I79.8, E11.51, I65.2, I63.03, I63.13, I63.23, I65.8
Chronic Kidney Disease	016.00, 016.01, 016.02, 016.03, 016.04, 016.05, 016.06, 095.4, 189.0, 189.9, 223.0, 236.91, 249.40, 249.41, 250.40, 250.41, 250.42, 250.43, 271.4, 274.10, 283.11, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 440.1, 442.1, 572.4, 580.0, 580.4, 580.81, 580.89, 580.9, 581.0, 581.1, 581.2, 581.3, 581.81, 581.89, 581.9, 582.0, 582.1, 582.2, 582.4, 582.81, 582.89, 582.9, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.81, 583.89, 583.9, 584.5, 584.6, 584.7, 584.8, 584.9, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9, 586, 587, 588.0, 588.1, 588.81, 588.89, 588.9, 591, 753.12, 753.13, 753.14, 753.15, 753.16, 753.17, 753.19, 753.20, 753.21, 753.22, 753.23, 753.29, 794.4	A18.11, A52.75, B52.0, C64.1, C64.2, C64.9, C68.9, D30.00, D30.01, D30.02, D41.00, D41.01, D41.02, D41.10, D41.11, D41.12, D41.20, D41.21, D41.22, D59.3, E08.21, E08.22, E08.29, E08.65, E09.21, E09.22, E09.29, E10.21, E10.22, E10.29, E10.65, E11.21, E11.22, E11.29, E11.65, E13.21, E13.22, E13.29, E74.8, I12.0, I12.9, I13.0, I13.10, I13.11, I13.2, I70.1, I72.2, K76.7, M10.30, M10.311, M10.312, M10.319, M10.321, M10.322, M10.329, M10.331, M10.332, M10.339, M10.341, M10.342, M10.349, M10.351, M10.352, M10.359, M10.361, M10.362, M10.369, M10.371, M10.372, M10.379, M10.38, M10.39, M32.14, M32.15, M35.04, N00.0, N00.1, N00.2, N00.3, N00.4, N00.5, N00.6, N00.7, N00.8, N00.9, N01.0, N01.1, N01.2, N01.3, N01.4, N01.5, N01.6, N01.7, N01.8, N01.9, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N06.0, N06.1, N06.2, N06.3, N06.4, N06.5, N06.6, N06.7, N06.8, N06.9, N07.0, N07.1, N07.2, N07.3, N07.4, N07.5, N07.6, N07.7, N07.8, N07.9, N08, N13.1, N13.2, N13.30, N13.39, N14.0, N14.1, N14.2, N14.3, N14.4, N15.0, N15.8, N15.9, N16, N17.0, N17.1, N17.2, N17.8, N17.9, N18.1, N18.2, N18.3, N18.4, N18.5, N18.6, N18.9, N19, N25.0, N25.1, N25.81, N25.89, N25.9, N26.1, N26.9, Q61.02, Q61.11, Q61.19, Q61.2, Q61.3, Q61.4, Q61.5, Q61.8, Q62.0, Q62.2, Q62.10, Q62.11, Q62.12, Q62.31, Q62.32, Q62.39, R94.4
Liver Disease	571	K70, K71, K72, K73, K74, K75, K76
Alcohol or Drug Use Disorder	303, 304, 305	F10, F11, F12, F13, F14, F15, F16, F17, F18, F19
Intracranial Bleeding	430, 431, 432	I60, I61, I62

Table 13 Continued

Gastrointestinal Hemorrhage	530.7, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6,569.3, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84 , 562.02 ,562.03, 562.12, 562.13, 569.85, 578	K22.6, 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, K62.5, K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, K31.82, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.91, K57.93, K55.21, K92.0, K92.1, K92.2
Any bleeding event	430, 431, 432, 568.81, 599.7, 530.7, 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6,569.3, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84 , 562.02 ,562.03, 562.12, 562.13, 569.85, 578, 786.3, 626.2, 719.1, 372.72, 459, 784.7	I60, I61, I62, K66.1, R31, K22.6, 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, K62.5, K29.01, K29.21, K29.31, K29.41, K29.51, K29.61, K29.71, K29.81, K29.91, K31.811, K31.82, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.91, K57.93, K55.21, K92.0, K92.1, K92.2, R04.0, R04.2, N92.0, M25.0, M12.2, H11.33, R58

A.1 Other Covariate Definitions

Table 14. Other Covariate Definitions

Covariate measure	Definition
Use of antiplatelets	Filling a prescription for aspirin, clopidogrel, prasugrel, dipyridamol, ticlopidine or ticagrelor in the **six months before index date**
Use of NSAIDs	Filling a prescription for diclofenac, ibuprofen, naproxen, ketoprofen, fenoprofen, flurbiprofen, piroxicam, meloxicam, mefenamic acid or indomethacin in the **six months before index date**
Use of warfarin	Filling a prescription for warfarin in the **six months before index date**
Use of direct oral anticoagulants	Filling a prescription for dabigatran, rivaroxaban, apixaban or edoxaban in the **six months before index date**

Appendix B Information on Excluded Patients from Final Study Sample

Table 15. Comparision of Included vs. Excluded PDP Beneficiaries

Variable—n (%)	Included Beneficiaries (n=3,089)	Excluded Beneficiaries (n=803)
Demographics		
Age group		
≤ 80	289 (9.32)	60 (7.47)
> 80	2,800 (90.35)	743 (92.53)
Female sex	1,896 (61.38)	499 (62.14)
Clinical Characteristics		
HAS-BLED score		
0-1	1,686 (54.58)	383 (47.70)
2-3	1,331 (43.09)	383 (47.70)
≥4	72 (2.33)	37 (4.61)
CHF	973 (31.50)	375 (46.70)
HTN	2,684 (86.89)	685 (85.31)
MI	86 (2.78)	40 (4.98)
Renal disease	779 (25.22)	311 (38.73)
Liver disease	61 (1.97)	27 (3.36)
Diabetes	1,132 (36.65)	334 (41.59)
Stroke or TIA	630 (20.39)	183 (22.79)
Intracranial Hemorrhage	230 (7.45)	85 (10.59)
Prior bleeding	792 (25.64)	253 (31.51)
Concomitant medications		
NSAIDs	216 (7.00)	57 (7.10)
Anticoagulants	608 (19.68)	89 (11.08)
Antiplatelets	271 (8.77)	92 (11.46)
Average copayment for OAC in USD-n (SD)	94.27 (203.10)	54.71 (163.60)

Table 16. Comparision of Included vs. Excluded MA-PD Beneficiaries

Variable—n (%)	**Included Beneficiaries (n=6,660)**	**Excluded beneficiaries (n=1,338)**
Demographics		
Age group		
≤80	638 (9.57)	119 (8.88)
> 80	6,022 (90.35)	743 (91.12)
Female sex	3,142 (47.18)	640 (47.76)
Clinical Characteristics		
HAS-BLED score*		
0-1	4,547 (68.27)	836 (62.39)
2-3	2,036 (30.57)	471 (35.15)
≥4	77 (1.16)	33 (2.46)
CHF	1,453 (21.82)	490 (36.57)
HTN	4,328 (64.98)	919 (68.58)
MI	152 (2.28)	73 (5.45)
Renal disease	1,227 (18.42)	396 (29.55)
Liver disease	110 (1.65)	40 (2.99)
Diabetes	2,176 (32.67)	524 (39.10)
Stroke or TIA	1,030 (15.45)	234 (17.46)
Intracranial Hemorrhage	406 (6.10)	126 (9.40)
Prior bleeding	1,293 (19.41)	353 (26.34)
Concomitant medications		
NSAIDs	336 (5.05)	69 (5.15)
Anticoagulants	1350 (20.27)	224 (16.72)
Antiplatelets	554 (8.32)	142 (10.60)
Average copayment for OAC in USD-n (SD)	33.98 (50.76)	21.80 (41.68)

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