Comparing total medical expenditure between patients receiving direct oral anticoagulants vs warfarin for the treatment of atrial fibrillation: evidence from VA-Medicare dual enrollees

Edwin S Wong, PhD; Nicolae Done, PhD; Molly Zhao, BA; Adam B Woolley, PharmD; Julia C Prentice, PhD; and Hillary J Mull, PhD

What is already known about this subject

- Newer direct oral anticoagulants (DOACs) are an alternative to warfarin for the treatment of atrial fibrillation.
- DOACs have been shown to be either noninferior or superior to warfarin on a variety of outcomes in clinical trials.

What this study adds

- Knowledge is incomplete about the generalizability of previous findings from trial settings to real-world patient populations that differ in factors such as socioeconomic status and comorbidity.
- This study presents new evidence comparing total medical expenditure among Veterans Affairs Health Care System patients receiving warfarin and DOACs.

Author affiliations

Edwin S Wong, PhD, VA Puget Sound Health Care System, Seattle, WA, and Department of Health Services, University of Washington, Seattle. Nicolae Done, PhD, and Molly Zhao, BA, Center for Healthcare Organization and Implementation Research (CHOIR), VA Boston Healthcare System, Boston, MA. Julia C Prentice, PhD, Center for Healthcare Organization and Implementation Research (CHOIR), VA Boston Healthcare System, Boston, MA, and Department of Psychiatry, Boston University, Boston, MA. Adam B Woolley, PharmD, Northeastern University, Boston, MA. Hillary J Mull, PhD, Center for Healthcare Organization and Implementation Research (CHOIR), VA Boston Healthcare System, Boston, MA, and Department of Surgery, Boston University, Boston, MA.

AUTHOR CORRESPONDENCE:

Edwin S Wong, 206.277.4703;
eswong@uw.edu

J Manag Care Spec Pharm.
2021;27(8):1056-66

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ABSTRACT

BACKGROUND: Direct oral anticoagulants (DOACs) are an alternative to warfarin for treatment of atrial fibrillation (AF). Evidence demonstrating the efficacy and safety of DOACs has primarily been from clinical trial settings. The real-world effectiveness of DOACs in specific nontrial populations that differ in age, comorbidity burden, and socioeconomic status is unclear.

OBJECTIVE: To compare total downstream medical expenditure between AF patients treated with warfarin and DOACs dually enrolled in the Veterans Affairs (VA) Healthcare System and fee-for-service Medicare.

METHODS: This was an exploratory treatment effectiveness study that analyzed VA administrative data and Medicare claims. We examined patients with an incident diagnosis for AF and initiated warfarin or DOAC treatment between 2012 and 2015. The primary outcome was total medical expenditure over 3 years following treatment initiation. To address potential informative censoring, we applied a multipart estimator that extends traditional 2-part models to separate differences between groups due to survival and cost accumulation effects. Inverse probability weighting was applied to address potential treatment selection bias.

RESULTS: We identified 31,276 and 17,021 patients receiving warfarin and DOACs, respectively. Mean unadjusted (SD) expenditure was higher for warfarin (\$56,265 [\$96,666]) compared with DOAC patients (\$32,736 [\$52,470]). Compared with patients receiving DOACs, adjusted 3-year expenditure was \$25,688 ($P < 0.001$) higher for patients receiving warfarin.

CONCLUSIONS: VA patients with AF initiating warfarin incurred markedly higher downstream expenditure compared with similar patients receiving DOACs. The benefits of DOACs found in previous clinical trials were present in this population, suggesting that these DOACs may be the preferred option for treatment of AF in older VA patients.

Atrial fibrillation (AF) is the second most common cardiovascular condition that affects up to 6.1 million individuals in the United States.¹ One aspect of AF treatment focuses on preventing blood clots to reduce stroke risk. Traditionally, warfarin, a vitamin-K antagonist, has been used to reduce stroke risk. However, warfarin requires regular laboratory monitoring to ensure safety and efficacy, is associated with several adverse effects and drug/food interaction risks, and has low convenience ratings by patients.²

Newer direct oral anticoagulants (DOACs) are an alternative option that does not require laboratory monitoring because of their more predictable pharmacokinetics. DOACs

have been shown to be either noninferior or superior to warfarin on a variety of outcomes in clinical trials.^{3,4} In addition, DOACs may be cost-effective for certain patient populations.⁵ Much of the evidence demonstrating benefits of DOACs over warfarin has been in clinical trial settings, which may have limited generalizability in real-world practice. Studies comparing DOACs with warfarin in real-world settings have produced mixed results.⁶

The generalizability of findings from clinical trials to patients enrolled in the Veterans Affairs (VA) Healthcare System is unclear. VA patients have complex medication regimens and often obtain medications from VA and non-VA sources.⁷ Also, VA patients have greater socioeconomic challenges, a higher rate of substance abuse, and greater risk of cognitive impairment compared with the general population.⁷⁻⁹ These factors may reduce patients' ability to remain adherent to anticoagulation therapy. This is particularly important for DOACs, which have a shorter duration of blood thinning effect than warfarin, so missed doses leave a patient unprotected against stroke. Previous trials excluded individuals deemed unreliable or who had conditions compromising their ability to take DOACs safely, such as alcohol or drug abuse. Also, storage of DOACs such as dabigatran have stricter requirements, including the need for tight humidity control.

In addition, the VA population is older and has a high burden of illness, which may compromise the efficacy of DOACs compared with warfarin.¹⁰ A subanalysis of RE-LY, the pivotal dabigatran trial, found a trend toward more frequent major bleeding for patients aged 75 years and older on dabigatran compared with warfarin.¹¹ Although recent studies have demonstrated the safety of apixaban in AF patients with renal impairment,¹² a common condition in the VA population, warfarin has traditionally been the preferred anticoagulant for these patients.¹³ Unlike warfarin, there is no reliable approach to measuring blood levels of dabigatran; therefore, its impact on coagulation assays may not correlate to clinical outcomes.¹⁴

Previous studies have focused primarily on mortality and clinical outcomes such as stroke and bleeding events.¹⁵⁻²¹ Limited evidence on the downstream medical expenditure following initiation of pharmacotherapy for AF currently exists. Two studies compared total and stroke-/systemic embolism (SE)-related costs between AF patients treated with warfarin and those treated with apixaban, dabigatran, or rivoroxaban.^{22,23} Similar to existing research on clinical outcomes, these studies examined non-VA populations, so generalizability to VA enrollees with AF is unknown. Furthermore, a limitation of previous economic studies is differences in rates of death between patients receiving warfarin and DOACs was not accounted for.

All else being equal, if DOACs are at least comparable with warfarin in terms of reducing stroke and minimizing risk of adverse events such as bleeding, then downstream medical expenditure should be lower for patients prescribed DOACs who do not require regular laboratory monitoring. However, if the efficacy of DOACs compared with warfarin is different in the VA population compared with trial populations or adherence is suboptimal, then patients prescribed DOACs may instead incur higher downstream medical expenditure because of factors such as greater adverse events.

This study examined whether advantages of DOACs found in previous trials translated to the VA population by comparing total downstream medical expenditure over 3 years between AF patients treated with warfarin and DOACs. To address potential biases from differential attrition stemming from death, we applied a unique multi-part estimator that separated the expenditure differences between warfarin and DOAC patients due to respective survival and expenditure intensity effects. Our approach comprehensively captured patients' future expected medical resource use that is relevant for integrated health systems such as the VA, which is responsible for comprehensively managing care for its patient population.

Methods

STUDY DESIGN AND DATA SOURCES

This retrospective national cohort study used data from several sources. The primary source was administrative data from the VA's Corporate Data Warehouse, which contains extensive information tracking of all care delivered at VA facilities nationally. This includes data on patient demographics, diagnosis and procedure codes, health service utilization, and prescription drug fills. VA administrative data were linked to 2 sources of expenditure data. The first source was data from the VA Health Economics Resource Center, which contain medical encounter-level cost estimates constructed to be proportional to Medicare reimbursement rates for similar services.²⁴ The second source was the Managerial Cost Accounting System pharmacy extracts, which includes information on drug and dispensing costs.²⁵

VA data were linked to (1) Medicare claims, which include information on care received by patients through traditional fee-for-service Medicare and (2) the Medicare Part D Event File, which contains information on the cost of drugs reimbursed by Medicare. Medicare data were included to construct more complete measures of expenditure and to ensure completeness in the construction of baseline characteristics and acute events such as stroke

and acute myocardial infarction. Data from respective VA and Medicare sources were linked using unique patient identifiers.

Data from the VA External Peer Review Program were used to ascertain measures of primary care clinical quality.²⁶ These data were collected through chart abstraction of a random sample of patients at each VA facility. Quality data were aggregated to the facility level and linked to patient-level data through unique VA facility identifiers that capture where patients receive primary care.

STUDY SAMPLE

We identified 282,163 patients who received care from the VA and had at least 1 prescription fill for warfarin or a DOAC during the period between January 1, 2012, and December 31, 2015 (Figure 1). We defined the date of the first observed drug fill as the index date. We excluded 127,988 patients who did not have a diagnosis of nonvalvular AF (*International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification* [ICD-9-CM] codes 427.3, 427.31 and 427.32 before October 1, 2015, and ICD-10-CM code I48.x thereafter) in the 12 months before the index date.²⁷

Next, we excluded patients missing facility-level identifiers (n=604). To ensure that we had complete data on VA patients dually enrolled in fee-for-service Medicare, we excluded patients aged under 65 years on the index date or who were enrolled in a Medicare Advantage (MA) plan at any time between the index date and the end of the inclusion period (December 31, 2015; n=56,362), since individual claims are not available through MA. We then excluded patients with an index drug fill covered by Medicare (n=18,466) to ensure that the study sample consisted of patients that were more likely to have coagulation monitoring interactions through the VA.

Subsequently, we dropped 27,249 patients who switched or discontinued anticoagulants within 12 months after the index date. Patients who switched or discontinued anticoagulants before death and had less than a full year of expenditure did not contribute information to empirical models (see the Statistical Analysis subsection for more detail).

Finally, we excluded 3,197 patients with missing covariate data. The final study sample included 48,297 patients.

OUTCOMES

The primary outcome was total medical expenditure following initiation of anticoagulation treatment for AF over a period of up to 3 years. This included expenditures for utilization of inpatient services and outpatient services delivered within VA facilities. Inpatient care included acute and nonacute (eg, long-term care) services. VA expenditures

FIGURE 1 Sample Study Selection

AF=atrial fibrillation; DOAC=direct oral anticoagulant; VA=Veterans Affairs.

also included the costs of care contracted to non-VA providers. VA medical expenditures were summed with expenditures for medical services reimbursed by Medicare, which included inpatient, outpatient, and nursing home services. Patient-level medical expenditure was calculated from the date of initiation of anticoagulation until the earliest of the following: (1) date of death, (2) date of

the first anticoagulant switch, or (3) the end of available data (December 31, 2016).

In the secondary analysis, we examined expenditures on anticoagulants. Similar to medical expenditures, we summed the costs of all anticoagulants obtained by patients from the VA and through Medicare. Anticoagulant expenditure was calculated until the earliest of the 3 dates previously

described. All expenditures were calculated from the perspective of the public payer, reflecting the cost of medical services and paid for by the VA and Medicare. We adjusted expenditures for inflation using the Consumer Price Index (CPI), reflecting 2018 constant dollars.²⁸ Previous research has demonstrated that the general CPI exhibits better performance in adjusting for inflation compared with its medical component.²⁹

To facilitate analysis that accounts for mortality over the 3-year follow-up period, we partitioned total expenditure into 3 variables that captured expenditure in each of 3 follow-up years. These annual measures were accompanied by a count variable denoting years of survival. Data on survival were available for up to 5 years.

COVARIATES

We ascertained an extensive set of variables related to outcomes among patients treated with oral anticoagulants, measured using VA administrative data linked with VA facility-level survey data and Medicare claims. These data included variables measured at baseline capturing patient demographics, stroke risk, fall risk, bleeding risk, history of hemorrhage, comorbidity, use of prescription medications, and clinical quality of patients' usual care facilities.

Stroke risk measures included the CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior transient ischemic attack or stroke, vascular disease, age 65-74, sex category) score, which is used by the American College of Cardiology and the American Heart Association to determine anticoagulation therapy recommendations. The CHA₂DS₂-VASc is considered a gold standard for estimating stroke risk.³⁰

Measures of bleeding risk included the validated ATRIA, HAS-BLED,

TABLE 1 Frequency of Patients by Prescribed Anticoagulant

Index drug	n	%
Apixaban	7,579	15.69
Dabigatran	4,985	10.32
Edoxaban	12	0.02
Rivaroxaban	4,445	9.20
Warfarin	31,276	64.76
Total	48,297	100.00

and HEMORR₂HAGES measures.³¹⁻³³ Construction of HAS-BLED omitted labile international normalized ratio (INR) values due to the lack of available data for newly diagnosed AF patients. This modified HAS-BLED score has been shown to identify patients at high bleeding risk despite lacking INR values.³⁴ As in previous research, construction of HEMORR₂HAGES excluded genetic factors, which were unavailable in administrative data.³⁵

Demographics included age, sex, and race/ethnicity. Comorbidities included 30 indicator variables denoting the presences of conditions within the validated Agency for Healthcare Research and Quality Comorbidity Software. Prescription medications included 20 indicator variables denoting whether patients were prescribed cardiac-related and other medications at baseline.

Clinical quality included variables denoting the percentage of a facility's eligible patients meeting clinical practice guidelines (eg, percentage of patients with blood pressure <140/90 mm Hg). We added quality indicators to proxy for facility-level prescribing practices that potentially influenced whether patients were prescribed warfarin or DOACs.

PROPENSITY SCORE WEIGHTS

We applied inverse probability of treatment weighting (IPTW) to address potential nonrandom assignment of anticoagulation therapy. Weights were constructed as the inverse of propensity scores estimated using generalized boosted machine (GBM), a machine learning approach that models the probability of initiating treatment with warfarin (compared with DOACs) using an ensemble of regression trees. The key advantage of GBM is facilitation of the inclusion of nonlinear transitions and interactions of covariates into the propensity score model to achieve greater covariate balance.³⁶ Predictors in the propensity score model included patient characteristics and facility-level measures of quality presented in the previous subsection.

STATISTICAL ANALYSIS

For statistical analysis, we first described the proportion of patients surviving to each year using the Kaplan-Meier estimator. Next, we presented univariate statistics of expenditure in each year and in total across the 3 years. The primary analysis separately examined medical and anticoagulant expenditure using a multipart estimator developed by Basu and Manning (2010). This approach estimates differences in total 3-year medical or anticoagulant expenditure between AF patients prescribed warfarin and DOACs.³⁷ This estimator accounts for differences in expenditures that arise from censoring due to death or end of study follow-up. In the first part, we used a parametric survival model to estimate the survival and hazard functions denoted $S_j(X)$ and $h_j(X)$. The second part modeled expected expenditures in a given year among patient-year observations where death was observed, denoted $\mu_{2j}(X)$, using a generalized linear model (GLM). Finally, the third part required

modeling expected expenditures in a given year among patient-year observations where a full year of expenditure was observed, denoted $\mu_{2j}(X)$, also using a GLM.

Using the method of recycled predictions, we calculated expected expenditure over the 3-year period as the sum of expenditure in each of 3 individual years, weighted by the probability of survival in each year. In each year, expected expenditure was calculated as the weighted average of adjusted expenditure conditional on (1) surviving the full year ($\mu_{2j}[X]$), and (2) dying within the year ($\mu_{1j}[X]$), with adjusted hazard rates serving as weights. Death dates are stochastic over the course of the year, so adjusted expenditure $\mu_{ij}(X)$ was calculated as the weighted sum of recycled predictions conditional on the proportion of the year survived, with empirical distribution of death times within the year serving as weights. Note that expected expenditure was calculated for all patient-year observations. For patients not alive for a given patient-year observation, expected expenditure was calculated out-of-sample.

We defined the treatment effect as the difference in expected 3-year expenditure attributable to treatment with warfarin relative to DOACs. We calculated this difference for each patient, which is a function of $\hat{\mu}_{1j}(X)$, $\hat{\mu}_{2j}(X)$, $\hat{S}_j(X)$, $H_j(X)$ and the difference in each of these quantities conditional on receiving warfarin and DOACs, respectively. Each of these quantities was calculated using the method of recycled predictions. Patient-level differences were then averaged to generate an average treatment effect ([Supplementary File 1](#), available in online article).

TABLE 2 Descriptive Statistics Between Patients Prescribed Warfarin and DOACs

	Warfarin n = 31,276	DOAC n = 17,021	SMD ^a
Demographics			
Age, mean (SD)	74.7 (7.8)	74.8 (7.8)	−0.008
Female, %	1.3	1.4	−0.006
Race: Black, %	7.4	6.5	0.036
Race: Other, %	2.9	2.7	0.012
Stroke risk, mean (SD)			
CHA ₂ DS ₂ -VASC score	3.9 (1.5)	3.8 (1.5)	0.016
Bleeding risk, mean (SD)			
ATRIA	3.4 (2.4)	3.3 (2.5)	0.037
HAS-BLED	2.4 (0.9)	2.4 (0.9)	0.011
HEMORR ₂ HAGES	2.7 (1.7)	2.8 (1.7)	0.028
Cardiovascular comorbidities, %			
Acute myocardial infarction	18.5	17.5	0.024
Congestive heart failure	40.0	39.5	0.010
Hypertension	90.7	90.7	0.000
Peripheral artery disease	24.4	24.2	0.005
Stroke or TIA	13.4	13.4	−0.001
Valvular heart disease	26.7	26.6	0.001
Venous thromboembolism	8.0	7.4	0.024
Hemorrhage, %			
Any hemorrhage	13.3	12.9	0.011
Markers of fall risk, %			
Excessive fall risk	21.4	21.2	0.005
Neurological disorders	10.0	10.2	−0.005
Mental health comorbidities, %			
Dementia	7.2	7.7	−0.017
Depression	18.5	18.2	0.009
Mental health comorbidities, %			
PTSD	10.8	10.9	−0.004
Substance abuse	2.4	2.3	0.010
Physical comorbidities, %			
Chronic pulmonary disease	41.0	39.9	0.021
Diabetes	46.8	45.0	0.036
Fluid/electrolyte disorders	28.6	27.3	0.029
Pulmonary circulatory disorders	11.6	11.0	0.021
Renal disease	21.8	20.2	0.039
Antihypertensives, %			
ACEI	45.1	43.7	0.028
Beta blockers	72.7	70.8	0.043
Calcium channel blockers	41.2	40.0	0.024
Diuretics	48.1	45.6	0.050
Other antihypertensive	12.7	11.7	0.031
Other cardiovascular medications, %			
Antiarrhythmics	11.6	12.0	−0.010
Angiotensin receptor inhibitors	14.9	14.8	0.001
Antilipemics	71.6	71.4	0.004
Antiplatelets	14.9	14.8	0.003
Other prescription medications, %			
Antianginals	19.3	17.9	0.036
Hypoglycemics	27.7	26.4	0.029
Insulins	16.6	15.2	0.039
Nonopioid analgesics	36.2	33.9	0.049
Opioid analgesics	35.2	33.2	0.043

^aEstimates reflect differences before rounding.

ACEI=angiotensin-converting enzyme inhibitor; CHA₂DS₂-VASC=congestive heart failure, hypertension, age ≥75, diabetes mellitus, prior transient ischemic attack or stroke, vascular disease, age 65-74, sex category; PTSD=posttraumatic stress disorder; SMD=standardized mean difference; TIA=transient ischemic attack.

Standard errors for treatment effect estimates were calculated using the Krinsky and Robb procedure. All statistical analyses were performed using Stata version 15.0 (StataCorp) and RStudio version 0.99.891 (RStudio Inc.). A nominal P value of 0.05 was used to assess all statistical hypotheses. This study was approved by the institutional review boards at the VA Boston Healthcare System and the VA Puget Sound Healthcare System.

Results

DESCRIPTIVE STATISTICS

Table 1 presents a tabulation of patients by DOAC. A total of 31,276 and 17,021 patients received warfarin and DOACs, respectively. Table 2 compares selected characteristics of patients receiving warfarin and DOACs. Standardized mean differences (SMDs) between groups were less than 0.1 for all variables after applying IPTW, a common threshold for

TABLE 3 Unadjusted Medical Expenditures by Follow-Up Year

	Mean	SD	25th percentile	Median	75th percentile	N
All						
Total 3 years	45,218	79,922	6,805	21,739	57,340	48,297
Year 1	32,423	65,582	4,532	13,830	38,925	48,297
Year 2	26,216	47,126	4,164	10,055	27,773	15,047
Year 3	27,149	55,042	4,073	9,947	27,991	6,803
Warfarin						
Total 3 years	56,265	96,666	10,864	30,361	72,052	31,276
Year 1	39,951	80,606	6,848	18,819	50,500	31,276
Year 2	28,568	50,412	4,484	11,095	30,507	12,686
Year 3	28,196	58,372	4,166	10,751	30,085	6,174
DOACs						
Total 3 years	32,736	52,470	4,034	14,558	40,504	17,021
Year 1	23,916	41,026	2,975	9,289	27,726	17,021
Year 2	22,060	40,352	3,587	8,154	23,102	2,361
Year 3	24,601	45,863	3,845	8,411	22,745	629

*All estimates are inflation adjusted to represent 2018 constant dollars.

DOAC = direct oral anticoagulant.

determining covariate balance.³⁸ [Supplementary Figure 1](#) (available in online article) presents SMDs for all covariates before and after IPTW.

On average, patients in both groups were aged nearly 75 years and predominately male. Patients had an average CHA₂DS₂-VASc of nearly 4, indicating high stroke risk. Cardiovascular comorbidities were common in both groups, including over 40% with congestive heart failure and 24% with peripheral artery disease. Nearly 11% of patients had a diagnosis of post-traumatic stress disorder, which is more common in a VA population. Before IPTW, the most substantial difference between groups was diagnosis of renal disease (warfarin = 25.3% vs DOAC = 14.0%). Other patient characteristics where meaningful differences between groups existed before IPTW included receipt of opioid (warfarin = 39.0% vs DOAC = 26.5%) and nonopioid (warfarin = 49.0% vs

DOAC = 27.7%) analgesics, diuretics (51.6% vs 39.1%), and ATRIA score (3.52 vs 3.06).

UNADJUSTED RESULTS

Survival was lower among warfarin patients, with 73.5% of patients alive at the end of year 3 compared with 80.8% of DOAC patients. Mean years of follow-up were 1.48 years (interquartile range [IQR] = 0.70–2.24 years) and 1.24 years (IQR = 0.56–1.74 years) for patients receiving warfarin and DOACs, respectively. Across all patients, mean (SD) unadjusted total 3-year medical expenditure was \$56,265 (\$96,666) for the warfarin group compared with \$32,736 (\$52,470) for the DOAC group (Table 3). Mean medical expenditures were higher in the warfarin group compared with the DOAC group among patients who were alive at the start of each year of follow-up. For warfarin patients, medical (SD) expenditures declined from \$39,951

(\$80,606) in year 1 to \$28,196 (\$58,372) in year 3. For DOAC patients, medical (SD) expenditures were similar across years, ranging from \$23,916 (\$41,026) in year 1 to \$24,601 (\$45,863) in year 3. Similar to mean medical expenditure, median estimates were higher for warfarin patients compared with DOAC patients.

Across all patients, mean (SD) unadjusted 3-year anticoagulant expenditure was \$220 (\$537) for the warfarin group compared with \$1,445 (\$1,270) for the DOAC group ([Supplementary Table 1](#), available in online article). Among patients who were alive at the start of each year of follow-up, mean and median anticoagulant expenditures declined in each year but were lower in the warfarin group in all 3 years.

ADJUSTED RESULTS

AF patients treated with warfarin had 0.52 fewer expected years of survival (95% CI = −0.695 to −0.349; [Supplementary Table 2](#), available in online article). Warfarin patients also had higher expected annual medical expenditure in years of death (\$9,461, 95% CI = \$5,207 to \$13,716) and survival over the full year (\$10,588, 95% CI = \$9,392 to \$11,784). Combining estimates for each of these model parts yielded average expected 3-year medical expenditure of \$72,026 (95% CI = \$70,131 to \$73,921; Table 4). Three-year medical expenditure was estimated to be \$25,688 (95% CI = \$23,122 to \$28,254) greater for warfarin, compared with DOAC patients.

In the secondary analysis, warfarin patients had lower expected anticoagulant expenditure during years of death (−\$346, 95% CI = −\$393 to −\$300) and survival over the full year (−\$900, 95% CI = −\$922 to −\$878). Combining estimates from the multipart model yielded an average expected 3-year

TABLE 4 Estimated Total Expenditure and Between Group Differences in Expenditure Over 3 Years

Quantity	Mean	SE	Lower 95% CI	Upper 95% CI
Medical expenditure				
Expenditure difference ^a	25,688	1,309	23,122	28,254
Total expenditure ^b	72,026	967	70,131	73,921
Anticoagulant expenditure				
Expenditure difference ^a	-1,849	31	-1,910	-1,788
Total expenditure ^b	1,162	16	1,131	1,193

^aExpenditure difference represents difference in expected total 3-year expenditure for warfarin vs DOAC patients.
^bTotal expenditure represents average expected expenditure across all patients.
^cAll estimates are inflation adjusted to represent 2018 constant dollars.
DOAC = direct oral anticoagulant; SE = standard error.

expenditure of \$1,162 (95% CI=\$1,131 to \$1,193; Table 4). Three-year anticoagulant drug expenditure was \$1,849 (95% CI=-\$1,910 to -\$1,788) lower for warfarin, compared with DOAC patients.

Discussion

This study compared downstream expenditures among VA-Medicare dual enrollees who were newly diagnosed with AF and initiated warfarin or DOAC therapy. Limited evidence exists that examines the downstream economic implications of drug therapies for treatment of AF. Previous research demonstrating the efficacy of DOACs compared with warfarin with respect to clinical outcomes suggests lower downstream costs associated with DOAC treatment.³⁹ However, this evidence is primarily from trial settings where the characteristics of patients differ from those in real-world settings.

Findings indicate warfarin patients have statistically significant and substantially greater expected medical expenditure over the 3-year period following treatment initiation, representing approximately 36% of the mean total expenditure. This difference

stemmed from warfarin patients (1) incurring greater expenditure during years when patients survive the full year and (2) incurring greater expenditure during years when death occurs. Greater expenditure in both of these cases is potentially due to health service utilization related to greater rate of stroke and bleeding events among warfarin compared with DOAC patients, as shown in previous research.^{6,18,21,22} Higher medical expenditure among warfarin patients was accompanied by lower anticoagulant drug expenditure. However, the magnitude of this difference was substantially smaller than differences in medical expenditure.

The difference in total 3-year medical expenditure between groups translated to \$714 per patient per month (PPPM). In comparison, Amin et al found that patients treated with warfarin incurred \$68 greater in costs related to stroke/SE and \$239 greater in major bleeding-related costs compared with patients treated with apixaban.²² Gupta et al examined total health care cost differences between warfarin and 3 DOACs, only finding statistically significant differences between warfarin compared with

rivaroxaban (warfarin lower by \$346 PPPM).²³

Taken together, our findings demonstrate the downstream economic benefit of DOACs compared with warfarin for incident cases of AF in VA patients aged 65 years and over. These findings coincide with results of previous studies demonstrating the clinical efficacy of DOACs. The approximately \$8,563 lower expected per year medical expenditure among DOAC compared with warfarin patients exceeds the higher annual costs of anticoagulant prescriptions estimated in this study (\$616). Lower annual medical expenditure estimated in this study also more than offsets higher annual prescription costs between the DOAC dabigatran and generic warfarin (\$1,354 vs \$113) found outside of the VA.^{40,41}

Study findings present differences on average across the VA population; however, the economic benefit of DOACs may differ within subgroups such as patients with kidney disease where the clinical efficacy is less clear.

Findings from this study also address concerns that the results from trial settings may not translate to real-world settings such as the VA. The economic benefit of DOACs materialized even in a population with known challenges to medication adherence and greater prevalence of comorbid conditions. Our results are one component that stakeholders such as pharmacy benefits management services should consider when maintaining prescription formularies and determining prescription prices. The results are also of relevance for administrators responsible for projecting expected costs of care for a given patient population.

LIMITATIONS

This study has several limitations. First, by design, our study focused on the population of VA patients, in part

to determine whether previous findings of DOAC efficacy translate to this population. Findings from this study should be generalized accordingly.

Second, we classified patients initiating 1 of 5 DOACs into a single category due to power considerations. It is possible that the economic benefits of DOACs compared with warfarin in this study may differ across DOAC classes.

Third, we applied machine learning tools to develop a propensity score model using an extensive set of patient covariates to address potential selection bias in treatment choice. Other omitted variables influencing choice of pharmacotherapy may confound study results.

Fourth, nursing home expenditures in the VA capture postacute care and long-term care but only include the former in Medicare due to reimbursement policies.⁴²

Finally, we examined dual VA-FFS Medicare enrollees to increase completeness in data capturing medical expenditure. It is possible differences in the costs of care received outside of the VA and Medicare between groups may influence estimates in this study and may include long-term care services paid for by Medicaid.

Conclusions

Among VA patients over age 65 years with incident AF, total medical expenditure in the 3 years following initial diagnosis was markedly greater for patients treated with warfarin compared with DOACs. This aligns with previous evidence that demonstrates the clinical benefits of DOACs in randomized trials and other non-VA populations. Study findings are of relevance to stakeholders charged with administering pharmacy benefits and measuring the expected costs of care for patients with this increasingly common condition.

DISCLOSURES

This study was funded by a VA Health Services Research and Development Investigator Initiated Research Award (IIR 15-139). Support for VA/CMS data was provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, VA Information Resource Center (Project Numbers SDR 02-237 and 98-004). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs, the University of Washington, Northeastern University, and Boston University. The authors declare no conflicts of interest.

This research includes data obtained from the VHA Office of Performance Measurement (17API2), which resides within the Office of Analytics and Performance Integration (API), under the Office of Quality and Patient Safety (QPS; formerly known as RAPID).

An oral presentation documenting a subset of the findings from this study was presented at the 2020 AcademyHealth Annual Research Meeting, delivered virtually on July 29, 2020.

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