Project Title: Management of Direct Anticoagulants to Lower Adverse Events in Atrial Fibrillation (MODL-AF)	
Grant Number: 5R18HS026156-04	**Project/Grant Period:** 08-01/2018-05/31/2022
Principal Investigator: Jordan B King, PHMD, MS Phone number: 801-213-1331 Email: Jordan.King@hsc.utah.edu	**Business Officer:** Todd Bjorklund Phone number: 801-585-6946 Todd.bjorklund@osp.utah.edu
Organization: University of Utah 75 south 200 east Salt Lake City, UT 841128930 DUNS: 009095365 EIN: 1876000525A1	**Federal Project Officer:** Farzana Samad Phone number 301-427-1332 Farzana.samad@ahrq.hhs.gov
Acknowledgement of Agency Support	
This project was funded under grant number R18HS026156 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services (HHS). The authors are solely responsible for this document's contents, findings, and conclusions, which do not necessarily represent the views of AHRQ. Readers should not interpret any statement in this report as an official position of AHRQ or of HHS. None of the authors has any affiliation or financial involvement that conflicts with the material presented in this report.	

2.Structured Abstract (200 words maximum) Include five headings: purpose, scope, methods, results and key words

DOAC treatment practices can be broadly categorized as utilizing one of three delivery models: 1) usual care –prescriber provides care with no standardized system level service; 2) proactive care – anticoagulant specialists are proactively involved to comprehensively evaluate DOAC prescribing and adherence at the time of medication initiation and at pre-specified follow-up times; or 3) data-driven care–resources are focused and coordinated at the system level, relying on administrative reports to detect potential DOAC-related problems and, when detected, directing anticoagulant specialists to intervene. Recent publications indicate that proactive care improves DOAC care processes (e.g., appropriate prescribing and medication adherence) relative to usual care. However, whether either the data driven, or proactive DOAC care models contribute to reductions in observed rates of bleeding, stroke, and death relative to usual care is not known. Further, no study has compared outcomes between data-driven and proactive care models

3. Purpose (Objectives of the study)

The major goals of this project were:

1. Determine the comparative safety of DOAC care models.
2. Determine the comparative effectiveness of DOAC care models.
3. Assess the cost effectiveness of DOAC care models

4. Scope (Background, Context, Settings, Participants, Incidence, Prevalence)

Two in three patients with atrial fibrillation (AF) who receive oral anticoagulants to prevent stroke use a direct oral anticoagulant (DOAC). Between 2011 and 2019, the number of Medicare Part D members prescribed DOACs increased over 17-fold from 0.20 million to 3.5 million, compared to a decrease in warfarin users from 2.48 million to 1.74 million. The rapid increase in DOAC use relative to warfarin was driven in part by a perception that DOACs are simpler to use given their monitoring convenience (e.g., fewer laboratory measurements, lower drug/food interaction burden). Nonetheless, DOAC therapy is not immune to prescribing and behavior issues such as incorrect dosing or poor adherence. Some health care systems enrolled DOAC-treated patients in management services originally developed to manage patients taking warfarin. However, there are substantial differences between DOACs and warfarin, and there is little evidence to demonstrate that DOAC management services are effective to prevent clinical outcomes of stroke and bleeding.

Kaiser Permanente (KP) is an integrated healthcare delivery system and one of the nation's largest not for-profit health plans which provides care across eight distinct regions. Importantly, each KP region has its own local leadership, autonomy, and flexibility to establish health services. This autonomy, coupled with a paucity of evidence on how to best care for patients

using DOACs, resulted in substantially different approaches to DOAC management across the KP regions. Identifying the most effective DOAC management strategy is essential to guide allocation of healthcare resources. We sought to leverage the natural experiment that has arisen within KP to determine whether to determine whether different DOAC care models resulted in different anticoagulation-related outcomes of bleeding, stroke, and death.

5. Methods (Study Design, Data Sources/Collection, Interventions, Measures, Limitations)

This retrospective cohort study used clinical and administrative data from three KP regions: Northwest (KPNW), Southern California (KPSC), and Colorado (KPCO). Each region uses an electronic health record (EHR) to document and store health information which is then loaded into a Virtual Data Warehouse (VDW), a repository used for clinical research.

Within each region, we emulated a trial comparing the initiation of a DOAC (i.e., dabigatran, rivaroxaban, apixaban, or edoxaban) vs. warfarin among patients with AF. First, we used pharmacy dispensing records to identify patients initiating a medication of interest between August 1, 2016, and December 31, 2019, and created new-user cohorts, with the patient's first oral anticoagulant dispense defining the index date. We then excluded patients who: 1) were less than 18 years of age on the index date; 2) had less than 365 days of KP health plan membership prior to the index date (lapses of less than 45 days were allowed); 3) picked up two DOACs on the index date or picked up a DOAC and warfarin on the index date; or 4) who did not have a history of AF. Patients were censored at an outcome of interest, loss of KP membership, or December 31, 2020, whichever occurred first.

The primary outcome for this study was a composite of thromboembolic stroke, intracranial hemorrhage, gastrointestinal (GI) bleed, extracranial major bleed, or death. We defined each outcome according to validated claims-based algorithms from the Food and Drug Administration's Sentinel program.

The findings of the current study should be interpreted within the context of the following known limitations. The studied population was largely non-Hispanic White and of relatively high educational background, and it is possible that one of the care models described may have differential effects on outcomes in more diverse populations. If the diagnostic codes for the outcomes differ in sensitivity or specificity by DOAC vs. warfarin group or across regions, under- or overestimation of the true effect could be possible. We used outcome definitions validated by the Sentinel Program, and we have no reason to believe that coding of outcomes varied between DOAC and warfarin users, although inter-regional differences are possible. The findings may not be externally generalizable to health systems that have large out-of-system resource use, as most KP patients are incentivized to use in-network KP services. Because changes in warfarin therapy are not well-reflected in dispensing data, we could not reliably assess warfarin adherence. Low outcome rates in subgroups should be interpreted with caution.

6. Results (Principal Findings, Outcomes, Discussion, Conclusions, Significance, Implications)

During the no-cost extension year, overall, we finished the retrospective cohort analysis and wrote the manuscript, which is currently under review with co-authors (formatted for initial submission to *JAMA Internal Medicine*). We also finalized the cost-effectiveness model and worked towards completing the cost-effectiveness analysis. We met as a research team at least

monthly for planning calls, to review results of the retrospective analysis and discuss the assumptions for the cost-effectiveness model.

The manuscript flowing from Aim 1 compares the association of DOAC vs. warfarin initiation in on a composite outcome of thromboembolic stroke, intracranial hemorrhage, gastrointestinal bleed, extracranial major bleed, or death (see Table 1 below), stratified by DOAC management model. The primary inverse-probability of treatment weighted analysis indicates that DOAC initiators were significantly less likely than warfarin initiators to experience a composite of thromboembolic stroke, intracranial hemorrhage, gastrointestinal bleed, extracranial major bleed, or death in the two regions where system-level DOAC management services were available (KP Sourthern California and KP Colorado). In the region where a system-level DOAC management service was not available (KP Northwest), DOAC users still experienced fewer composite outcomes compared to warfarin users, but this association did not reach statistical significance. These results were robust in secondary analyses evaluating the components of the primary outcome (Table 1), subgroup analyses (Table 2), and sensitivity analyses (Table 3-4).

Table 1. Association of DOAC vs warfarin use and major clinical outcomes, by DOAC management model.

Outcome and management model	DOAC		Warfarin		IP-weighted Hazard Ratio (95% CI)*
	No. of patients with an event/ No. of patients (%)	% per year	No. of patients with an event/ No. of patients (%)	% per year	
Composite endpoint*					
Usual care	360/3297 (10.9)	5.38	637/2885 (22.1)	9.07	0.91 (0.79,1.05)
Data-driven model	2514/21891 (11.5)	6.10	2897/11734 (24.7)	10.54	0.85 (0.79,0.90)
Proactive care model	223/2089 (10.7)	5.08	534/2850 (18.7)	8.02	0.84 (0.72,0.99)
Thromboembolic stroke					
Usual care	34/3297 (1.0)	0.50	48/2885 (1.7)	0.67	0.97 (0.59,1.59)
Data-driven model	333/21891 (1.5)	0.80	194/11734 (1.7)	0.69	1.15 (0.92,1.43)
Proactive care model	32/2089 (1.5)	0.71	62/2850 (2.2)	0.91	0.84 (0.54,1.33)
Intracranial hemorrhage					
Usual care	6/3297 (0.2)	0.09	29/2885 (1.0)	0.40	0.22 (0.08,0.56)
Data-driven model	134/21891 (0.6)	0.32	185/11734 (1.6)	0.66	0.50 (0.38,0.65)
Proactive care model	5/2089 (0.2)	0.11	48/2850 (1.7)	0.70	0.19 (0.07,0.50)

Gastrointestinal bleed					
Usual care	45/3297 (1.4)	0.67	55/2885 (1.9)	0.77	1.21 (0.78,1.89)
Data-driven model	296/21891 (1.4)	0.71	277/11734 (2.4)	0.99	0.88 (0.72,1.08)
Proactive care model	47/2089 (2.2)	1.06	71/2850 (2.5)	1.04	1.19 (0.81,1.76)
Extracranial major bleed					
Usual care	45/3297 (1.4)	0.67	61/2885 (2.1)	0.85	1.09 (0.71,1.68)
Data-driven model	296/21891 (1.4)	0.71	296/11734 (2.5)	1.06	0.79 (0.65,0.97)
Proactive care model	48/2089 (2.3)	1.08	81/2850 (2.8)	1.19	1.03 (0.71,1.51)
Death					
Usual care	301/3297 (9.1)	4.42	549/2885 (19.0)	7.57	0.96 (0.82,1.11)
Data-driven model	2014/21891 (9.2)	4.79	2542/11734 (21.7)	8.95	0.85 (0.79,0.92)
Proactive care model	158/2089 (7.6)	3.49	414/2850 (14.5)	5.96	0.85 (0.70,1.03)

*Composite endpoint of thromboembolic stroke, intracranial hemorrhage, gastrointestinal bleed, extracranial major bleed, or death.
DOAC: direct oral anticoagulant; CI: confidence interval; IP: inverse propensity

Table 2. Association of incident DOAC vs warfarin use and the composite endpoint* in subgroups.

	DOAC users		Warfarin users		IP-weighted Hazard ratio
Subgroup, region	**No. of patients with an event/ No. of patients (%)**	**% per year**	**No. of patients with an event/ No. of patients (%)**	**% per year**	**(95% CI)**
Age, years					
<65					
Usual care (n = 1,177)	35/727 (4.81)	2.35	41/450 (9.11)	3.68	1.16 (0.71,1.90)
Data-driven care (n = 6,764)	217/4,708 (4.61)	2.39	256/2,056 (12.45)	5.31	0.91 (0.72,1.16)
Proactive care (n = 825)	15/395 (3.80)	1.82	37/430 (8.60)	3.63	0.77 (0.41,1.46)
≥65 and <80					
Usual care (n = 3,425)	155/1,865 (8.31)	3.94	277/1,560 (17.76)	6.98	0.83 (0.67,1.03)
Data-driven care (n = 17,056)	1,048/11,378 (9.21)	4.70	1,168/5,678 (20.57)	8.36	0.83 (0.74,0.92)
Proactive care (n = 2,586)	87/1,144 (7.60)	3.37	214/1,442 (14.84)	5.91	0.67 (0.51,0.86)
≥80					
Usual care (n = 1,580)	170/705 (24.11)	13.48	319/875 (36.46)	16.45	0.95 (0.77,1.17)
Data-driven care (n = 9,805)	1,249/5,805 (21.52)	12.72	1,473/4,000 (36.83)	16.95	0.88 (0.80,0.96)
Proactive care (n = 1,528)	121/550 (22.00)	12.28	283/978 (28.94)	14.01	1.03 (0.82,1.29)

Sex					
Male					
Usual care (n = 3,399)	180/1,836 (9.80)	4.78	318/1,563 (20.35)	8.18	0.94 (0.77,1.15)
Data-driven care (n = 19,034)	1,347/12,432 (10.83)	5.74	1,537/6,602 (23.28)	9.97	0.87 (0.79,0.95)
Proactive care (n = 2,681)	107/1,172 (9.13)	4.29	273/1,509 (18.09)	7.73	0.75 (0.59,0.94)
Female					
Usual care (n = 2,783)	180/1,461 (12.32)	6.16	319/1,322 (24.13)	10.17	0.86 (0.71,1.06)
Data-driven care (n = 14,591)	1,167/9,459 (12.34)	6.57	1,360/5,132 (26.50)	11.27	0.82 (0.75,0.91)
Proactive care (n = 2,258)	116/917 (12.65)	6.12	261/1,341 (19.46)	8.34	0.95 (0.75,1.20)
Race-ethnicity					
Non-Hispanic White					
Usual care (n = 5,631)	325/3,027 (10.74)	5.27	580/2,604 (22.27)	9.13	0.87 (0.75,1.01)
Data-driven care (n = 20,280)	1,588/13,548 (11.72)	6.22	1,677/6,732 (24.91)	10.35	0.85 (0.78,0.93)
Proactive care (n = 4,142)	183/1,776 (10.30)	4.81	442/2,366 (18.68)	7.92	0.81 (0.68,0.97)
All other race-ethnicities					
Usual care (n = 515)	35/247 (14.17)	7.28	57/268 (21.27)	8.95	1.37 (0.86,2.18)
Data-driven care (n = 12,623)	871/7,817 (11.14)	5.90	1,187/4,806 (24.70)	10.93	0.83 (0.74,0.92)
Proactive care (n = 695)	32/259 (12.36)	6.74	87/436 (19.95)	8.97	0.90 (0.59,1.39)
Body weight, kg					
<60					
Usual care (n = 606)	58/327 (17.74)	9.82	99/279 (35.48)	16.35	0.87 (0.61,1.25)
Data-driven care (n = 4,050)	480/2,451 (19.58)	11.48	625/1,599 (39.09)	18.97	0.79 (0.68,0.92)
Proactive care (n = 663)	54/265 (20.38)	11.22	120/398 (30.15)	14.61	0.91 (0.65,1.28)
≥60					
Usual care (n = 5,576)	302/2,970 (10.17)	4.95	538/2,606 (20.64)	8.38	0.89 (0.76,1.04)
Data-driven care (n = 29,575)	2034/19,440 (10.46)	5.49	2,272/10,135 (22.42)	9.39	0.87 (0.81,0.94)
Proactive care (n = 4,276)	169/1,824 (9.27)	4.32	414/2,452 (16.88)	7.09	0.80 (0.66,0.97)
Creatinine clearance, mL/min					
<30					
Usual care (n = 240)	19/45 (42.22)	30.52	102/195 (52.31)	31.11	0.91 (0.48,1.75)
Data-driven care (n = 2,058)	211/549 (38.43)	29.78	716/1,509 (47.45)	29.70	0.84 (0.69,1.02)
Proactive care (n = 217)	15/37 (40.54)	26.23	75/180 (41.67)	28.83	0.65 (0.34,1.27)

≥30 and <50					
Usual care (n = 823)	94/327 (28.75)	16.80	174/496 (35.08)	16.60	1.08 (0.82,1.42)
Data-driven care (n = 5,394)	630/2,981 (21.13)	12.69	834/2,413 (34.56)	15.34	0.88 (0.78,1.00)
Proactive care (n = 809)	66/296 (22.30)	12.37	145/513 (28.27)	13.22	1.10 (0.81,1.49)
≥50					
Usual care (n = 4,804)	230/2,736 (8.41)	4.04	340/2,068 (16.44)	6.37	0.83 (0.70,1.00)
Data-driven care (n = 25,207)	1,625/17,653 (9.21)	4.76	1,305/7,554 (17.28)	6.88	0.85 (0.78,0.93)
Proactive care (n = 3,783)	138/1,698 (8.13)	3.75	305/2,085 (14.63)	5.95	0.77 (0.62,0.94)
CHADS2-Vasc score					
<2 (low stroke risk)					
KPNW (usual care; n = 655)	8/462 (1.73)	0.80	13/193 (6.74)	2.58	0.50 (0.20,1.24)
Data-driven care (n = 3,144)	59/2,406 (2.45)	1.22	25/738 (3.39)	1.29	0.70 (0.39,1.25)
Proactive care (n = 515)	3/294 (1.02)	0.45	8/221 (3.62)	1.45	0.36 (0.09,1.37)
≥2 (intermediate/high stroke risk)					
Usual care (n = 5,527)	352/2,835 (12.42)	6.19	624/2,692 (23.18)	9.57	0.91 (0.78,1.05)
Data-driven care (n = 30,481)	2,455/19,485 (12.60)	6.75	2,872/10,996 (26.12)	11.24	0.85 (0.79,0.91)
Proactive care (n = 4,424)	220/1,795 (12.26)	5.91	526/2,629 (20.01)	8.61	0.86 (0.73,1.01)
ATRIA bleed score					
<4 (low risk)					
Usual care (n = 3,504)	163/1,960 (8.32)	3.96	244/1,544 (15.80)	6.11	0.86 (0.69,1.06)
Data-driven care (n =20,173)	1,159/13,885 (8.35)	4.29	1,058/6,288 (16.83)	6.55	0.83 (0.75,0.92)
Proactive care (n = 3,077)	103/1,312 (7.85)	3.54	263/1,765 (14.90)	6.01	0.75 (0.59,0.95)
≥4 (intermediate/high risk)					
KPNW (usual care; n = 1,416)	149/569 (26.19)	15.07	321/847 (37.90)	18.54	0.95 (0.77,1.18)
Data-driven care (n = 8,206)	1,038/4,098 (25.33)	15.86	1,577/4,108 (38.39)	19.98	0.89 (0.81,0.97)
Proactive care (n = 1,027)	95/345 (27.54)	16.59	223/682 (32.70)	17.75	1.07 (0.83,1.39)

* Composite endpoint of thromboembolic stroke, intracranial hemorrhage, gastrointestinal bleed, extracranial major bleed, or death.
"Usual care" refers to KPNW, "Data-driven care" refers to KPSC, and "Proactive care" refers to KPCO.
DOAC: direct oral anticoagulant; CI: confidence interval; IP: inverse propensity; KPCO: Kaiser Permanente Colorado region; KPNW: Kaiser Permanente Northwest region; KPSC: Kaiser Permanente Southern California region

Table 3. Hazard ratios for the primary outcomes, by covariate adjustment strategy.			
	KP Northwest (Usual DOAC care)	**KP Southern California (Data-driven DOAC care)**	**KP Colorado (Proactive DOAC care)**
Outcome and adjustment strategy	**HR for DOAC vs. warfarin (95% CI)**	**HR for DOAC vs. warfarin (95% CI)**	**HR for DOAC vs. warfarin (95% CI)**
Composite endpoint*			
Crude	0.54 (0.47,0.61)	0.52 (0.49,0.54)	0.58 (0.50,0.68)
Minimally-adjusted**	0.62 (0.55,0.71)	0.57 (0.54,0.60)	0.66 (0.56,0.77)
Propensity score matching	0.85 (0.73,1.00)	0.85 (0.79.0.82)	0.83 (0.69,1.01)
Propensity score strata	0.87 (0.76,1.00)	0.83 (0.78,0.88)	0.84 (0.71,0.98)
Matching weight adjusted	0.90 (0.78, 1.04)	0.89 (0.83,0.94)	0.85 (0.72,1.00)
Primary analysis: IPTW (truncate to 99%ile)	0.91 (0.79,1.05)	0.85 (0.79,0.90)	0.84 (0.72,0.99)
Thromboembolic stroke			
Crude	0.61 (0.40,0.95)	0.92 (0.77,1.10)	0.69 (0.45,1.06)
Minimally-adjusted**	0.71 (0.46,1.11)	0.97 (0.81,1.16)	0.74 (0.48,1.14)
Propensity score matching	0.89 (0.50,1.56)	1.18 (0.91,1.52)	0.84 (0.51,1.39)
Propensity score strata	0.95 (0.58,1.54)	1.12 (0.81,1.37)	0.86 (0.55,1.35)
Matching weight adjusted	0.95 (0.58,1.55)	1.16 (0.94,1.43)	0.89 (0.56,1.40)
Primary analysis: IPTW (truncate to 99%ile)	0.97 (0.95,1.59)	1.15 (0.92,1.43)	0.84 (0.54,1.33)
Intracranial hemorrhage			
Crude	0.18 (0.07,0.43)	0.39 (0.31,0.48)	0.14 (0.06,0.35)
Minimally-adjusted**	0.20 (0.08,0.48)	0.41 (0.33,0.51)	0.16 (0.06,0.41)
Propensity score matching	0.23 (0.07,0.74)	0.53 (0.38,0.74)	0.15 (0.06,0.39)
Propensity score strata	0.22 (0.09,0.56)	0.50 (0.39, 0.65)	0.16 (0.06,0.40)
Matching weight adjusted	0.22 (0.08,0.61)	0.52 (0.40,0.68)	0.17 (0.07,0.43)
Primary analysis: IPTW (truncate to 99%ile)	0.22 (0.08, 0.56)	0.50 (0.38, 0.65)	0.19 (0.07,0.50)
Gastrointestinal bleed			
Crude	0.71 (0.48,1.05)	0.57 (0.49,0.67)	0.89 (0.62,1.29)
Minimally-adjusted**	0.79 (0.53,1.17)	0.60 (0.51,0.71)	0.99 (0.68,1.43)
Propensity score matching	0.96 (0.57,1.59)	0.96 (0.76,1.20)	1.16 (0.72,1.86)
Propensity score strata	1.06 (0.69,1.64)	0.94 (0.78,1.14)	1.20 (0.82,1.78)

Gastrointestinal bleed			
Matching weight adjusted	1.00 (0.65,1.54)	1.02 (0.85,1.24)	1.18 (0.79,1.75)
Primary analysis: IPTW (truncate to 99%ile)	1.21 (0.78,1.89)	0.88 (0.72,1.08)	1.19 (0.81,1.76)
Extracranial major bleed			
Crude	0.64 (0.44,0.94)	0.54 (0.46,0.63)	0.80 (0.56,1.14)
Minimally-adjusted**	0.71 (0.48,1.04)	0.56 (0.48,0.66)	0.89 (0.62,1.27)
Propensity score matching	0.85 (0.52,1.40)	0.88 (0.70,1.10)	1.02 (0.65,1.60)
Propensity score strata	0.93 (0.61,1.42)	0.85 (1.70,1.02)	1.04 (0.72,1.52)
Matching weight adjusted	0.89 (0.59,1.36)	0.92 (0.76,1.12)	1.04 (0.71,1.53)
Primary analysis: IPTW (truncate to 99%ile)	1.09 (0.71,1.68)	0.79 (0.65,0.97)	1.03 (0.71,1.51)
Death			
Crude	0.54 (0.47,0.62)	0.49 (0.46,0.52)	0.55 (0.46,0.66)
Minimally-adjusted**	0.63 (0.55,0.73)	0.54 (0.51,0.58)	0.63 (0.52,0.76)
Propensity score matching	0.92 (0.78,1.10)	0.85 (0.78,0.92)	0.85 (0.67,1.07)
Propensity score strata	0.93 (0.80,1.08)	0.82 (0.77,0.88)	0.84 (0.69,1.02)
Matching weight adjusted	0.98 (0.84,1.14)	0.89 (0.83,0.95)	0.85 (0.70,1.04)
Primary analysis: IPTW (truncate to 99%ile)	0.96 (0.82,1.11)	0.85 (0.79,0.92)	0.85 (0.70,1.03)

* Composite endpoint of thromboembolic stroke, intracranial hemorrhage, gastrointestinal bleed, extracranial major bleed, or death.
** Age and sex only.
CI: confidence interval; DOAC: direct oral anticoagulant; HR: hazard ratio; IPTW: inverse propensity treatment weighting; KP: Kaiser Permanente

Table 4. Association of incident DOAC vs warfarin use and the composite endpoint* by sensitivity analysis.

	DOAC users		Warfarin users		Hazard ratio
Analysis, DOAC care model	**No. of patients with an event/ No. of patients (%)**	**% per year**	**No. of patients with an event/ No. of patients (%)**	**% per year**	**(95% CI)**
Primary analysis					
Usual care (N=6,182)	360/3297 (10.9)	5.38	637/2885 (22.1)	9.07	0.91 (0.79,1.05)
Data-driven program (N=33,625)	2514/21891 (11.5)	6.10	2897/11734 (24.7)	10.54	0.85 (0.79,0.90)
Proactive care program (N=4,939)	223/2089 (10.7)	5.08	534/2850 (18.7)	8.02	0.84 (0.72,0.99)

Complete case analysis.					
Usual care (n = 4,735)	298/2420 (12.3)	6.09	551/2315 (23.8)	9.94	0.91 (0.78,1.06)
Data-driven care (n = 27,219)	2114/17139 (12.3)	6.60	2572/10080 (25.5)	11.02	0.85 (0.80,0.92)
Proactive care (n = 3,943)	195/1587 (12.3)	5.85	473/2356 (20.1)	8.74	0.88 (0.74,1.05)
Exclude patients with prior event.					
Usual care (n = 5,806)	312/3,102 (10.06)	4.92	570/2,704 (21.08)	8.60	0.89 (0.76,1.03)
Data-driven care (n = 31,865)	2,249/20,706 (10.86)	5.73	2,692/11,159 (24.12)	10.20	0.84 (0.78,0.90)
Proactive care (n = 4,530)	184/1,909 (9.64)	4.54	468/2,621 (17.86)	7.53	0.82 (0.68,0.98)
Early outcome events only.					
Usual care (n = 6,182)	104/3,297 (3.15)	12.95	140/2,885 (4.85)	20.08	0.97 (0.73,1.28)
Data-driven care (n = 33,625)	838/21,891 (3.83)	15.79	678/11,734 (5.78)	24.06	0.94 (0.83,1.07)
Proactive care (n = 4,939)	79/2,089 (3.78)	15.62	146/2,850 (5.12)	21.32	0.94 (0.70,1.25)
Late outcome events only.					
Usual care (n = 5,877)	256/3,147 (8.13)	3.84	497/2,730 (18.21)	7.09	0.88 (0.75,1.04)
Data-driven care (n = 31,633)	1,676/20,702 (8.10)	4.08	2,219/10,931 (20.30)	8.10	0.82 (0.76,0.89)
Proactive care (n = 4,650)	144/1,982 (7.27)	3.29	388/2,668 (14.54)	5.84	0.81 (0.67,0.99)

* Composite endpoint of thromboembolic stroke, intracranial hemorrhage, gastrointestinal bleed, extracranial major bleed, or death.
See eMethods for more detailed descriptions of each sensitivity analysis.
“Usual care” refers to KPNW, “Data-driven care” refers to KPSC, and “Proactive care” refers to KPCO.
DOAC: direct oral anticoagulant; CI: confidence interval; IP: inverse propensity; KPCO: Kaiser Permanente Colorado region; KPNW: Kaiser Permanente Northwest region; KPSC: Kaiser Permanente Southern California region

1. **Key Outcomes or Other Achievements**

Our analysis included a robust comparison of baseline patient characteristics between DOAC and warfarin initiators in each KP region. Overall, 44 746 patients met our

eligibility criteria and were included (6,182 patients at KPNW [n=3,297 DOAC and n=2,885 warfarin], 33 625 patients at KPSC [n=21 891 DOAC and n=11 734 warfarin], and 4,939 at KPCO [n=2,089 DOAC and n=2,850 warfarin]). DOAC-treated patients were modestly more likely to be younger, male, Non-Hispanic White, former or never smokers, >60 kg in weight, and have hypertension – these patterns were observed in all regions (Table 5). The most common DOAC used in all regions was dabigatran (84%-93%).

Table 5. Selected characteristics of DOAC and warfarin users across three DOAC management models, before weighting and multiple imputation.

	KP Northwest (Usual DOAC care)		KP Southern California (Data-driven DOAC care)		KP Colorado (Proactive DOAC care)	
	DOAC	**Warfarin**	**DOAC**	**Warfarin**	**DOAC**	**Warfarin**
No. of patients*	N=3297	N=2885	N=21891	N=11734	N=2089	N=2850
Dabigatran	3061 (93.0)	-	20044 (91.6)	-	1749 (83.8)	-
Apixaban	149 (4.5)	-	1379 (6.3)	-	251 (12.0)	-
Rivaroxaban	83 (2.5)	-	457 (2.1)	-	86 (4.1)	-
Year of index date						
2016	225 (6.8)	567 (19.7)	1728 (7.9)	3883 (33.1)	190 (9.1)	543 (19.1)
2017	720 (21.8)	1074 (37.2)	5474 (25.0)	4441 (37.9)	524 (25.1)	998 (35.0)
2018	1004 (30.5)	776 (26.9)	6933 (31.7)	2062 (17.6)	606 (29.0)	748 (26.3)
2019	1348 (40.9)	468 (16.2)	7756 (35.4)	1348 (11.5)	769 (36.8)	561 (19.7)
Demographics						
Age, years	71.3 (10.6)	73.9 (10.1)	72.2 (11.1)	74.2 (10.9)	72.5 (10.5)	74.6 (10.3)
Female Sex	1461 (44.3)	1322 (45.8)	9459 (43.2)	5132 (43.7)	917 (43.9)	1341 (47.1)
Non-Hispanic White	3027 (91.8)	2604 (90.3)	13548 (61.9)	6732 (57.4)	1776 (85.0)	2366 (83.0)
Lives in a census tract where:						
>20% of residents have less than a high school degree	386 (11.7)	330 (11.4)	6002 (27.4)	3659 (31.2)	206 (9.9)	367 (12.9)
Annual household income <$50,000 USD	1097 (33.3)	968 (33.6)	3448 (15.8)	2110 (18.0)	416 (19.9)	679 (23.8)
Health Behaviors						
Current tobacco use	131 (4.0)	132 (4.6)	722 (3.3)	339 (2.9)	92 (4.4)	136 (4.8)
Alcohol abuse	136 (4.1)	97 (3.4)	976 (4.5)	486 (4.1)	81 (3.9)	83 (2.9)
Physiologic Variables						
Weight, kg	201.9 ± 53.1	203.5 ± 58.3	191.9 ± 52.8	187.1 ± 53.4	188.3 ± 49	188.7 ± 51.9
BMI, kg/m^2	31.1 ± 7.3	31.7 ± 8.4	29.8 ± 7	29.5 ± 7.2	28.9 ± 6.5	29.6 ± 7.1
Systolic BP, mm Hg	127.1 ± 17.5	126.7 ± 18.1	127.8 ± 16.3	126.9 ± 16.6	123.2 ± 16.8	124.4 ± 17

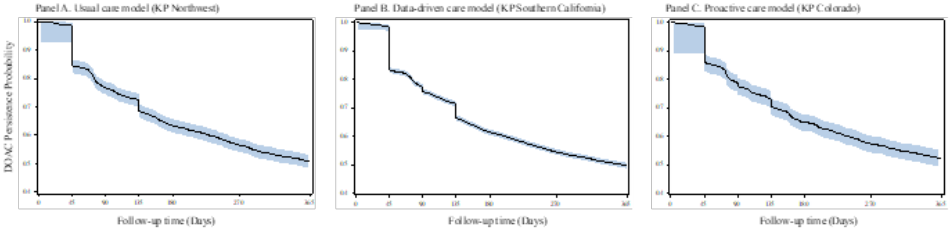
	KP Northwest (Usual DOAC care)		KP Southern California (Data-driven DOAC care)		KP Colorado (Proactive DOAC care)	
	DOAC	**Warfarin**	**DOAC**	**Warfarin**	**DOAC**	**Warfarin**
Diastolic BP, mm Hg	71.9 ± 12	70.4 ± 12	71.6 ± 11.9	68.8 ± 11.6	71.9 ± 10.7	71.5 ± 11.1
Serum glucose, mg/dL	118.3 ± 45.3	121.5 ± 46.7	131.2 ± 56	134.7 ± 59.2	109.8 ± 37.2	113.8 ± 43.1
Hemoglobin A1c, %	6.3 ± 1.2	6.5 ± 1.2	6.3 ± 1.2	6.5 ± 1.2	6.2 ± 1.1	6.4 ± 1.3
HDL cholesterol, mg/dL	50.4 ± 16.5	48.5 ± 15.8	49.8 ± 15.2	47.6 ± 14.6	51.2 ± 16.3	49.7 ± 16.2
LDL cholesterol, mg/dL	91.2 ± 37.5	87.9 ± 37.3	88.1 ± 33.6	82.5 ± 32.5	85.5 ± 33.3	80.8 ± 33
Total cholesterol, mg/dL	166.1 ± 43.1	159.7 ± 43.5	160 ± 41.5	153 ± 40.8	163.6 ± 40.9	157.9 ± 41.9
Creatinine Clearance, mL/min	91.7 ± 42.1	81.4 ± 43.7	84.4 ± 39.4	70.1 ± 41.2	80.5 ± 33.3	75.7 ± 37.4
AST, mg/dL	33.7 ± 23.8	36.2 ± 95.5	30.6 ± 40.5	32.3 ± 51.3	34.3 ± 76.3	38.4 ± 180.5
ALT, mg/dL	33.1 ± 30	35.7 ± 102.3	26.4 ± 30.6	26.7 ± 45.6	33.4 ± 60.9	36.2 ± 114.5
Stroke and Bleed Risk Scores						
CHA_2DS_2-VASc	3 [2-5]	4 [3-5]	4[2-5]	4 [3-5]	3 [2-5]	4 [3-5]
ATRIA stroke risk	6 [5-8]	7 [5-9]	7 [5-8]	8 [6-9]	7 [5-8]	7 [5-8]
ATRIA bleed risk	2 [1-3]	3 [1-5]	2 [1-3]	3 [1-6]	2 [1-3]	3 [1-4]
Medical Conditions						
Type of AF/Flutter						
Atrial flutter	30 (0.9)	8 (0.3)	107 (0.5)	28 (0.2)	47 (2.3)	30 (1.1)
Paroxysmal	1377 (41.8)	1066 (37.0)	9843 (45.0)	4605 (39.2)	1025 (49.1)	1178 (41.3)
Persistent	115 (3.5)	107 (3.7)	673 (3.1)	341 (2.9)	120 (5.7)	103 (3.6)
Chronic	286 (8.7)	256 (8.9)	944 (4.3)	914 (7.8)	119 (5.7)	177 (6.2)
Unspecified or unknown	1489 (45.2)	1448 (50.2)	10324 (47.16)	5846 (49.8)	778 (37.2)	1362 (47.8)
History of thromboembolic stroke	179 (5.4)	155 (5.4)	1055 (4.8)	442 (3.8)	153 (7.3)	173 (6.1)
History of GI bleed	6 (0.2)	16 (0.6)	87 (0.4)	91 (0.8)	19 (0.9)	42 (1.5)
History of Traumatic Intracranial Bleed	8 (0.2)	7 (0.2)	98 (0.5)	61 (0.5)	16 (0.8)	27 (1.0)
History of Extracranial Major Bleed	8 (0.2)	19 (0.7)	97 (0.4)	101 (0.9)	19 (0.9)	44 (1.5)
Diabetes mellitus	872 (26.5)	1053 (36.5)	7354 (33.6)	5113 (43.6)	506 (24.2)	844 (29.6)
Heart failure	845 (25.6)	977 (33.9)	5559 (25.4)	4900 (41.8)	568 (27.2)	997 (35.0)
Hypertension	2279 (69.1)	2113 (73.2)	17040 (77.8)	10011 (85.3)	1393 (66.7)	2114 (74.2)
History of myocardial infarction	258 (7.8)	245 (8.5)	1140 (5.2)	901 (7.7)	134 (6.4)	151 (5.3)
Peripheral artery disease	322 (9.8)	368 (12.8)	1637 (7.5)	1395 (11.9)	199 (9.5)	310 (10.9)
Moderate-severe liver disease	29 (0.9)	44 (1.5)	126 (0.6)	142 (1.2)	14 (0.7)	32 (1.1)
Moderate-severe renal disease	838 (25.4)	1086 (37.6)	6305 (28.8)	5746 (49.0)	656 (31.4)	1272 (44.6)

	KP Northwest (Usual DOAC care)		KP Southern California (Data-driven DOAC care)		KP Colorado (Proactive DOAC care)	
	DOAC	**Warfarin**	**DOAC**	**Warfarin**	**DOAC**	**Warfarin**
Healthcare encounters during pre-index period						
Anticoagulant-related ambulatory visits	9 [5-15]	10 [5-18]	10 [5-17]	13 [7-21]	7 [4-11]	7 [4-11]
Emergency department visits	1 [0-2]	1 [0-2]	1 [0-2]	1 [0-2]	0 [0-1]	0 [0-1]
Hospitalizations	0 [0-1]	1 [0-1]	0 [0-1]	1 [0-1]	0 [0-1]	1 [0-1]

Numbers represent n (%), mean ± SD, or median [IQR] unless otherwise specified.
Complete set of characteristics available in eTable 4.
The index date was the date of first direct oral anticoagulant pharmacy fill; all values were collected in the one year prior to the index date.
*Does not add up to 100% in each region because some patients were on multiple DOACs (KPNW n=4; KPSC n=9; KPCO n=3).
AF: atrial fibrillation; ALT: alanine transaminase; AST: aspartate aminotransferase; BMI: body mass index; BP: blood pressure; DOAC: direct oral anticoagulant; GI: gastrointestinal; HDL: high-density lipoprotein cholesterol; KP: Kaiser Permanente; LDL: low-density lipoprotein cholesterol; USD: United States Dollars

The primary analysis results are as reported in section 3 above. For secondary outcomes, among DOAC initiators, we evaluated one-year medication adherence (using the proportion of days covered (PDC; i.e., how many pills "covered" the observed follow-up period) and medication persistence (i.e., how long a patient took their initiated treatment). There was no significant difference in the average PDC between the three DOAC care models; 65.5-72.4% of patients had a one-year PDC ≥80% depending on the underlying assumptions and DOAC care model. We found no significant difference in medication persistence across the three DOAC care models (Figure 1).

Figure 1. Medication persistence among DOAC users.



2. **How have the results been disseminated to communities of interest?**

The final results have been disseminated to co-authors, who are currently reviewing the manuscript prior to submission to *JAMA Internal Medicine.* We plan to disseminate our results internally to several stakeholder groups at Kaiser Permanente, including a scheduled presentation to the program-wide anticoagulation group in September, and to the lay public via press and social media outlets.

3. **What do you plan to do during the next reporting period to accomplish the goals?**

We are at the end of our no cost extension period. In the next 6 months, we will complete and publish results related to the Aim 1 and 2 cohort study of the safety and effectiveness of the different DOAC care models.

7. List of Publications and Products (Bibliography of Outputs) from the study. Follow the AHRQ Citation Style Format at https://www.ahrq.gov/funding/grant-mgmt/refstyle.html.

Jones AE, King JB, Kim K, Witt DM. The role of clinical pharmacy anticoagulation services in direct oral anticoagulant monitoring. J Thromb Thrombolysis. 2020 Feb 21. doi: 10.1007/s11239-020-02064-0. [Epub ahead of print] PMID: 32086703

T Delate, M Charlu, S Zhu, A Pai, NP Clark, DM Witt, JM King, JB King. Temporal trends in first-line anticoagulation therapy for cancer-associated venous thromboembolism. Thromb Res. 2020 Dec;196:367-370. doi: 10.1016/j.thromres.2020.09.008. Epub 2020 Sep 10.

JM King, T Delate, M Charlu, S Zhu, A Pai, NP Clark, DM Witt, JB King. P5590 Temporal trends in first line anticoagulation therapy for cancer-associated venous thromboembolism. European Heart Journal, Volume 40, Issue Supplement_1, October 2019, ehz746.0534, https://doi.org/10.1093/eurheartj/ehz746.0534

JB King, S Bhat, LJ Heath, CG Derington, Z Yu, NP Clark, DM Witt, K Reynolds, DT Lang, S Xu, BK Bellows. P5239 Cost-effectiveness of direct oral anticoagulants for cancer-associated venous thromboembolism. European Heart Journal, Volume 40, Issue Supplement_1, October 2019, ehz746.0212, https://doi.org/10.1093/eurheartj/ehz746.0212