Project Title:Management of Direct Anticoagulants to Lower Adverse Events in Atrial Fibrillation (AFLODL	
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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

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, Limitio ns)

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

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.

	DOAC		Warfarin		
Outcome and management model	**No. of patients with an event/ No. of patients (%)**	**% per year**	**No. of patients with an event/ No. of patients (%)**	**% per year**	**IP-weighted Hazard Ratio (95% CI)***
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)	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	1.- 0.85 (0.79,0.92)
Proa					

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Sex					
Male					
sual 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 = 823) Data-	94/327 (28.75)	16.80	174/496 (35.08)	16.60	1.08 (0.82,1.42)

Table 3. Hazard ratios for the primary outcomes, by covariate adjustment strategy.

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			

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) TE 842 532	**ID 350 BDC 1**	**842 532.5 16.64 0.5.959 re252.BT0.002 Tc -0.00**

	KP Northwest (Usual DOAC care)		KP Southern California (Data-driven DOAC care)		KP Colorado (Proactive DOAC care)	
	DOAC	Warfarin	DOAC	Warfarin	DOAC	Warfarin

7. List of