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Policy Evaluation: Removal of Prior Authorization on Non-Vitamin K Oral Anticoagulants (NOACS)

Research Questions:

1) Did the utilization of oral anticoagulants change after removal of the prior authorization (PA) criteria?
2) Did the use of non-vitamin K antagonists oral anticoagulants (NOACS) for FDA approved indications increase after removal of the PA criteria? Did use of the NOACS in the presence of contraindications or precautions increase since removal of the PA policy?
3) What are the adherence rates of NOACS compared to warfarin?
4) Did the number of patients encountering a denied claim for a NOAC decrease after removal of the PA?

Conclusions:

- Utilization for the NOACs increased after removal of the PA criteria (from 37 unique members per member per month [PMPM] to 64 unique members PMPM). However, utilization remains low overall and this increase in use is consistent with clinical practice patterns. The use of NOACS for FDA approved indications was slightly lower after removal of the PA criteria compared to the control group (60% vs. 79%). However, there were more patients with an unknown indication in the study group as well, which is a limitation of the analysis. There were no significant concerns regarding use of a NOAC in patients with a contraindication or precaution after removal of the PA policy.
- Adherence to NOACS was not found to be higher compared to warfarin (> 80%).
- There were no denied claims for a NOAC after removal of the PA. Therefore, removal of the PA decreased a barrier to treatment with oral anticoagulants that was observed in the previous policy evaluation.

Recommendations:

- Evidence supports removal of clinical PA to improve access to NOACs.
- Continue to monitor appropriate use as utilization increases.

Previous recommendations:

1. Given the high risk to patients from anticoagulation disruption, the high incidence of disruption among patients encountering the prior authorization requirement and the apparent low use of the NOACS it is recommended the clinical PA for NOACS be discontinued.
2. It is recommended that a Retrospective DUR program be developed to monitor appropriate dosing and use in the presence of contraindications, as these remain a concern.
3. It is recommended the class utilization be reviewed again in one year given the evolving evidence and new drugs in the class.

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Background:

Warfarin has been the preferred and only oral anticoagulant for many decades. However, with the approval and increasing use of NOACS, warfarin may be less favorable in particular patients due to many drug-drug and drug-food interactions, required lab monitoring, and complicated dosing regimens. Currently, there are four NOACS available on the United States market including dabigatran (Pradaxa™), rivaroxaban (Xarelto™), apixaban (Eliquis™), and edoxaban (Savaysa™). The NOACS are indicated for prevention and treatment of venous thromboembolism (VTE), for prevention of stroke in non-valvular atrial fibrillation (NVAF), and for VTE prophylaxis in those patients undergoing orthopedic surgery**. Table 1** outlines the approved FDA indications for all oral anticoagulants.

Table 1. Oral anticoagulants and FDA approved indications [1-3, 8]

			Indications		
HSN code	**Brand**	**Generic**	**Orthopedic VTE prophylaxis**	**VTE treatment**	**Stroke prevention in NVAF***
Warfarin					
002812	Coumadin	Warfarin	Yes	Yes	Yes
NOACS					
035604	Pradaxa®	Dabigatran	Yes	Yes	Yes
035915	Xarelto®	Rivaroxaban	Yes	Yes	Yes
037792	Eliquis®	Apixaban	Yes	Yes	Yes
041672	Savaysa®	Edoxaban	No	Yes	Yes

HSN Code = hierarchical ingredient code list (HICL) sequence number as reported by First DataBank™
Abbreviations: AF: atrial fibrillation; NVAF: non-valvular atrial fibrillation; VTE: venous thromboembolism
**NVAF is defined as:* AF in the absence of prosthetic mechanical heart valves or hemodynamically significant valve disease, referring to a valve lesion severe enough to warrant surgical or percutaneous intervention or would have an impact on survival

The American College of Chest Physicians (CHEST) guidelines for VTE issued an update in early 2016 recommending NOACS over warfarin for the initial and long-term treatment of VTE in patients without cancer. [4] Anticoagulation therapy in AF is supported by two American guidelines, the 2012 CHEST and the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) guidelines. Per the 2012 CHEST guidelines, chronic anticoagulation is recommended for those with a CHADS2 score of 1 or more. [5] The CHEST guideline recommends dabigatran 150 mg taken twice daily, the only FDA approved NOAC at the time, over a vitamin K antagonist (warfarin) for AF. The exception is for patients with valvular disease (mitral stenosis and prosthetic heart valves), in which warfarin is the only recommended oral anticoagulant. [5] According to the 2014 AHA/ACC/HRS guidelines for the management of patients with AF, warfarin is also the recommended oral anticoagulant for patients with valvular AF. [6] Generally, patients with mitral stenosis and prosthetic heart valves or valve repair were excluded from NOAC trials. The AHA/ACC/HRS guideline recommends either warfarin or a NOAC for those with NVAF and a CHA2DS2-VASc score of 2 or more. [6] In February 2017, AHA/ACC provided a focused update for managing patients with valvular heart disease. Warfarin is still indicated for patients with AF with rheumatic mitral stenosis and mechanical heart valves; these patients were excluded in studies with NOACS. [7] However, NOACS are reasonable alternatives for patients with AF and native aortic valve disease, tricuspid valve disease, or mitral regurgitation. [7]

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Other clinical scenarios in which warfarin may still be recommended over a NOAC include in those with end-stage chronic kidney disease (CKD) (CrCl <15 ml/min) or on hemodialysis. [6] NOACs excluding edoxaban and dabigatran may be considered in moderate to severe CKD, however, safety and efficacy have not been established. [6] Utilization of edoxaban, the newest NOAC on the market, has been low in part due its unique dosing parameters, which recommend avoiding therapy in patients with creatinine clearance greater than 95 mL/min. [8] Additionally, safety and efficacy have not been established in obese patients with a BMI ≥ 40 or weight ≥ 120 kg.

A reversal agent, idarucizumab (Praxbind™), was approved for bleeding associated with the direct thrombin inhibitor, dabigatran use in October 2015, which provided an additional safety net in the event of adverse bleeding effects associated with dabigatran therapy. There are other agents in clinical trials for reversal of Xa agents (apixaban, edoxaban, and rivaroxaban). [9]

Another theorized benefit of NOACs is easier administration and improved adherence over warfarin. A systematic review examined dosing frequency and medication adherence in chronic diseases showed that patients are more adherent with once-daily dosing compared to more frequently scheduled doses.[10] Although the difference in once versus twice daily was not as clear cut as once daily versus more complicated regimens requiring three to four times a day drug administration. [10] In a retrospective cohort analysis that included nearly 65,000 patients with AF initiated on warfarin or a NOAC (dabigatran, rivaroxaban, apixaban), the proportion of days covered (PDC) after 1 year of follow-up showed that 47.5% of patients prescribed a NOAC had a PDC of 80% or above compared to only 40.2% in the warfarin group ($p < 0.001$). [11]

The Oregon Health Plan (OHP) fee-for-service (FFS) removed the prior authorization (PA) criteria for the use of NOACs in May 2015 to enhance patient access to anticoagulant therapy. Initially, the OHP developed PA criteria for NOACS to limit use for FDA approved indications in people who were not a candidate for warfarin. The results of a PA policy evaluation in 2015 showed that a PA was requested for only 54 patients (56.3%) after a denied claim. In addition, only 57.3% of those patients received subsequent anticoagulation therapy within 14 days of the denied claim. This resulted in removal of the PA criteria for overall safety concerns. [12] Another recommendation was to complete retrospective DUR to assess the safe and appropriate use of NOACS.

The purpose of this evaluation is to examine change in utilization of oral anticoagulants and assess the impact of removing PA criteria on patient access to oral anticoagulants. This review will determine if patients are receiving appropriate therapy based on approval for FDA indications and as evaluate safety by screening for contraindications or precautions. Additionally, adherence will be assessed by calculating PDC.

Methods:

Patients were identified if they had a new paid FFS pharmacy claim for any NOAC in **Table 1** from July 1, 2014 through June 30, 2015 (control group) or from July 1, 2015 through June 30, 2016 (study group). Patients were excluded if they had Medicare Part D coverage as indicated by benefit packages BMM, BMD, MED or MND. Only new starts were included and were defined as the first FFS pharmacy claim for a NOAC or warfarin in the control or study period, without any prior FFS or CCO pharmacy claim for a NOAC or warfarin in the 90 days prior. The first claim was designated the index event. Patients were excluded if they were found to have less than 75% of combined FFS or CCO eligibility in the 12 months prior to the index event, in order to insure complete medical records for their prior diagnoses. The list of ICD9 & 10 codes for these diagnoses are referenced in **Tables 2** and **3**.

Table 2. FDA labeled indications for NOACS

	ICD-9 Code	ICD-10 Code
Atrial Dysfunction		
Atrial fibrillation & atrial flutter, supraventricular premature beats	427.3x, 427.61	I4891, I4892, I491
Thromboembolic Events		
Phlebitis & thrombophlebitis	451.xx, 453.xx, V12.51, 415.1x, V12.55	I8000, Z86718, I2690, I2699, T800XXA, T81718A, T8172XA, T82817A, I2690, I2692, I2699, Z86711
Orthopedic Procedures		
Total knee arthroplasty, Total hip arthroplasty	81.54-81.55; V43.65, 81.51-81.53; V43.64, 820xx	Z96659, Z96649
Acute Coronary Syndrome		
Cardiac device in situ	V45.xx, V45.81, V45.82, 413.x, 410.xx	Z959, Z950, Z95810, Z95818, Z95.1, Z9861, I208, I201, I208, I209, I2109, I2119, I2111, I2129, I214, I213

Table 3. Contraindications or precautions for NOACS

	ICD-9 Code	ICD-10 Code
Valve Replacement		
Heart valve replaced by transplant , Heart valve replaced by other means	V42.2 , V43.3	Z953, Z952
Valvular Disease/Dysfunction		
Other congenital anomalies of heart	746.xx, 394.x, 397.x	Q2xx, I050, I051, I052, I058 , I060, I061, I062, I068, I069, I071, I072, I078, I080, I088, I089, I091, 10XXX, I0989
Cardiac		
Acute & subacute endocarditis, Aortic aneurysm & dissection	421.x, 441.xx	I330, I39, I339, I7100-17103, 1711-1719
Cranial Bleeding		
Subarachnoid hemorrhage, Intracerebral hemorrhage, Other & unspecified intracranial hemorrhage	430, 431, 432.x	I609, I619, I621, I6200, I629
Gastrointestinal		
Esophageal varices with bleeding, ulcers, hemorrhages	456.0, 456.20, 459.0, 530.21, 531.xx-535.xx, 578.x	I8501, I8511, R58, K2211, K25x-K29xx, K920-K922

Hematologic and Circulatory		
Hemorrhagic disorder due to intrinsic circulating anticoagulants, coagulation defects	286.5x, 790.0x, 790.92, 286.xx	D68311, D68312, D68318 , R710, R718, R791, D6x-D6xxx
Hepatic		
Chronic liver disease & cirrhosis	571.xx	K7XX-K7xxx
Kidney Disease		
Chronic kidney disease	585.x	N18x
Other		
Purpura & other hemorrhagic conditions	287.xx, 442.xx	D473, D69x-D69xx, I72x

Adherence with direct oral anticoagulants compared to warfarin

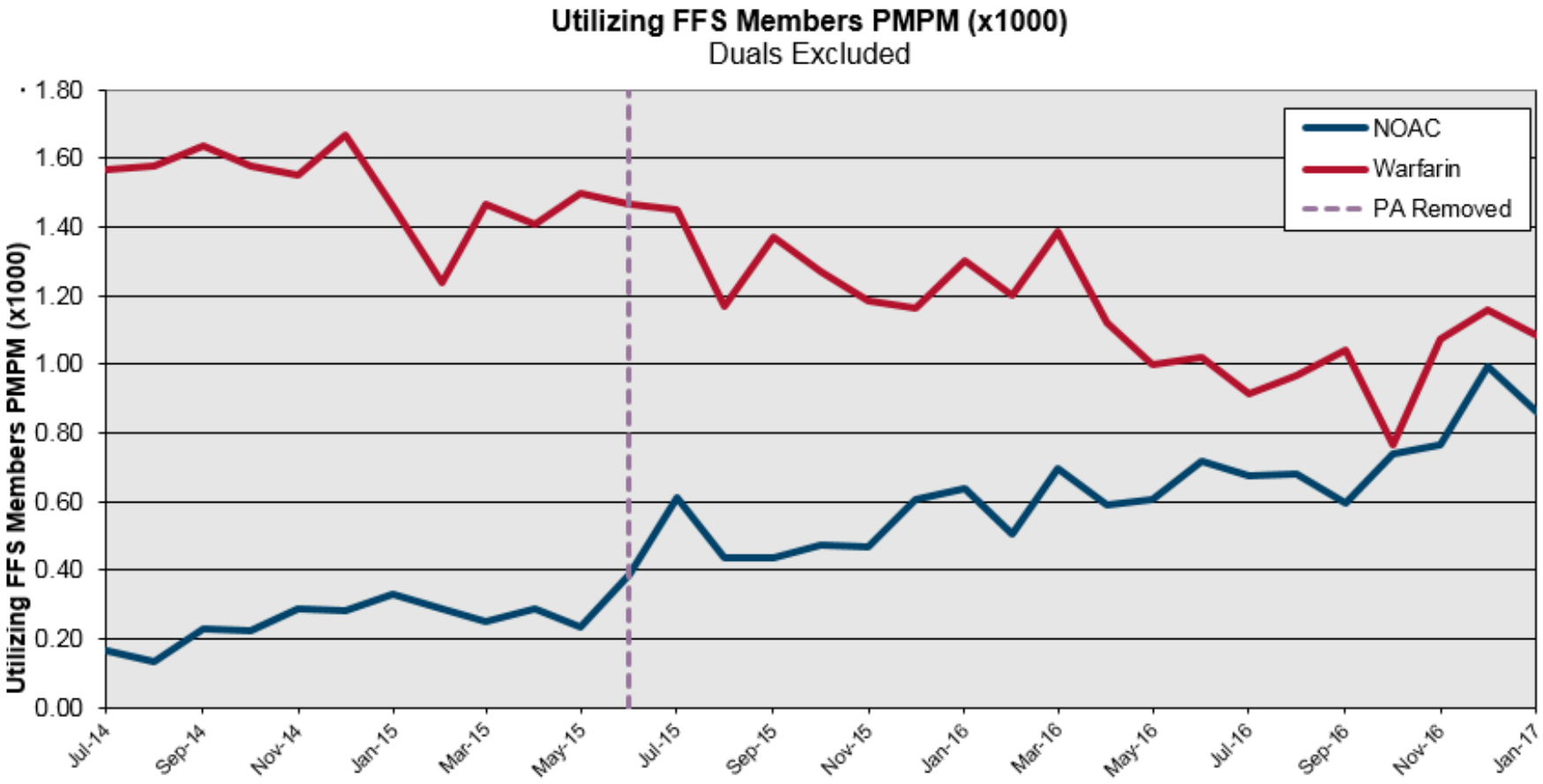
A different group of patients was selected using similar parameters to identify new therapy starts, but days' supply was an additional metric to assist with assessment of adherence. Patients were selected if they had a new start paid FFS pharmacy claim for any NOAC or warfarin listed in Table 1 from July 1, 2014 through June 30, 2015 (control group) or from July 1, 2015 through June 30, 2016 (study group). Patients were once again excluded if they had Medicare Part D coverage. New starts were defined as the first FFS pharmacy claim for a NOAC in the control or study period, without any prior FFS or CCO pharmacy claim for a NOAC in the 90 days prior. The first claim was designed the index event. Patients were then excluded if they were found to have less than 75% of combined FFS or CCO eligibility in the 3 months after the index event, in order to be sure of having complete records of their subsequent medications.

Finally, adherence in the form of PDC was calculated by adding the days' supply for all anticoagulant claims in the 90 days following the new start claim and dividing by 90. "All anticoagulants" means any anticoagulant from Table 1 and from any source, i.e. FFS or CCO.

Results:

Figure 1 depicts the trend of oral anticoagulant utilization per individual agent for the unique FFS patients with paid claims on a per-member-month (PMPM) basis. Each month the count of unique patients with a FFS claim for warfarin or NOAC was counted and divided by the number of total enrolled FFS patients in that month. Those with dual eligibility were excluded. Warfarin was the most utilized anticoagulant; ranging from 94 patients per 1000 FFS members to 187 patients per 1000 FFS members per month. Utilization of NOACS seemed to increase and warfarin decreased right around the time of removal of the PA criteria (June to July 2015). The difference in utilization between warfarin and the NOACS decreased substantially since 2014. The utilization for NOACS from June to July for the PMPM went from 37 to 64 patients. Note that the overall utilization remains low.

Figure 1. Utilization of oral anticoagulants



After excluding patients with <75% of days of combined FFS and coordinated care organization eligibility from 12 months prior to the index month to 3 months after the index month (for a total of 16 months), 155 patients with new-start FFS pharmacy claims for a NOAC were included in the study. Of these patients, there were no patients with a denied claim.

Table 4 displays the patient demographics. Patients (n = 44 in control and n = 111 in study groups) ranged in age from 19 to 64 years old. The mean age was 51.6 years old in the control group and 46.3 years old in the study group. There were more females (51.4%) in the study group compared to the control group (43.2%).

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Table 4. Demographics of Study Population for NOACS

	Control Group		Study Group	
N=	44		111	
Mean age (range)	51.6	(25-64)	46.3	(21-64)
< 19		0.0%		0.0%
19-64	44	100.0%	111	100.0%
> 64		0.0%		0.0%
Female	19	43.2%	57	51.4%
White	25	56.8%	47	42.3%

Table 5 displays the diagnoses for the patients with paid NOAC index claims. The majority of patients in both the control and study groups had a FDA labeled indication. However, the overall percentage went down slightly after removal of the PA criteria (79.5% to 60.4%). There were also slightly fewer patients with a contraindication or precaution in the study group (36.9%) compared to the control group (43.2%). However, the percentage of patients who had valvular disease/dysfunction, cardiac, and gastrointestinal events were higher in the study group.

Table 5. Use of NOACS by Diagnosis in year prior and after index event

	Control Group		Study Group	
N=	44		111	
FDA Indications	**35**	**79.5%**	**67**	**60.4%**
Atrial Dysfunction (atrial fibrillation & flutter, etc)	20	45.5%	34	30.6%
Thromboembolic Events (phlebitis & thrombophlebitis)	12	27.3%	33	29.7%
Orthopedic Procedures (knee or total hip arthoplasty)	5	11.4%	4	3.6%
Acute Coronary Syndrome (cardiac device in situ)	9	20.5%	23	20.7%
Unknown indication	9	20.5%	44	39.6%
Contraindications and Precautions	**19**	**43.2%**	**41**	**36.9%**
Valve replacement	1	2.3%	1	0.9%
Valvular Disease/Dysfunction	2	4.5%	7	6.3%
Cardiac (eg acute & subacute endocarditis, aortic aneurysm, etc)		0.0%	1	0.9%
Cranial Bleeding (eg subarachnoid hemorrhage, intracerebral hemorrhage, etc)	2	4.5%	4	3.6%
Gastrointestinal (esophageal varices w/ bleeding, ulcers, hemorrhages)	3	6.8%	17	15.3%

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*FDA Indications and Contraindications are not mutually-exclusive

The proportion of days covered (PDC) was characterized by index drug for both the control and study groups in **Table 6.** Among the control group, apixaban, dabigatran, and warfarin had an average PDC of 80-86%. For apixaban and warfarin, the adherence average in the study group were almost unchanged. Dabigatran adherence in the study group, however, had a difference of 15.6% lower average PDC compared to the control group. Rivaroxaban adherence was similar to both the control and study groups, but had the lowest average PDC among the oral anticoagulants. There were no claims for edoxaban.

Table 6. Adherence to oral anticoagulants (measured by the PDC)

	Control Group		Study Group	
	Patient Count	Avg PDC	Patient Count	Avg PDC
Index Drug N=	428		459	
APIXABAN	14	84.0%	61	82.3%
DABIGATRAN ETEXILATE MESYLATE	6	80.6%	8	64.4%
RIVAROXABAN	43	64.1%	114	63.0%
WARFARIN SODIUM	365	86.2%	276	83.4%

Denied claims

There were no denied claims identified for a PA or PDL denial after removal of the PA policy. This was the desired effect of removing the PA criteria.

Discussion:

This evaluation demonstrated an increase in utilization of the NOACS since removal of the NOAC PA. The increase in utilization was observed around the time the PA criteria was removed. Meanwhile, warfarin utilization trended downwards. Several changes in practice during the time frame of the study group selection may have contributed to increased utilization of NOACS. A reversal agent for dabigatran (idarucizumab) was approved and CHEST guidelines for VTE recommended NOACS over warfarin in non-cancer patients.[4] Because NOACS require minimal clinical monitoring, this may be an appealing factor for both the provider and the patient. There is also more data that the NOACs are associated with less severe bleeding compared to warfarin. As providers are becoming more comfortable with using these agents in a variety of patient populations, we would expect an increase in utilization consistent with clinical practice.

The majority of patients using NOACs seem to have an appropriate diagnosis for use. While the PA ensured that these medications were used for FDA approved diagnoses only, this does not seem to be a concern since the PA was removed. The main contraindications or precautions identified were gastrointestinal related (ulcers, previous gastrointestinal bleed, varices, etc.). While these are risk factors for bleeding, they are also a concern with the use of warfarin and there is not enough information from the data to fully capture the risk versus benefit of anticoagulation in each patient. Lastly, there were 7 patients on a NOAC with valvular disease. While, these agents are not preferred in valvular disease, trials excluded patients with significant mitral stenosis and prosthetic heart valves, but not necessarily those with other types of valvular heart disease.

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Non-adherence is one factor that may impact overall utilization of oral anticoagulants. This study showed similar adherence rates between the control group and the study group for most of the oral anticoagulants, except for dabigatran. Compared to warfarin, apixaban had a similar adherence rate. One limitation with comparing NOACS to warfarin is that warfarin dosing is variable among individuals, which may skew the PDC in comparison to NOACS. The PDC of rivaroxaban remained low at about 64% despite removal of the PA policy, which was interesting since maintenance dosing of rivaroxaban is only once daily. The safety and bleeding data for apixaban may be a consideration when weighing the benefits of using a once or twice daily dosing NOAC such as rivaroxaban. Rivaroxaban has been noted in a previous study for use in patients with a history of medication non-adherence. [15] Perhaps the patients in this study continued to be non-adherent regardless if the medication was only once daily dosing, which accounted for the low adherence rate in **Table 6**.

Study Limitations:

Since this study was a retrospective analysis using claims data, there may be some inconsistencies in use of the coding system for indications. Also patients may have multiple indications identified within the timeframe of the study and there is no way to associate the use of anticoagulation for a particular indication. It is unclear what valvular disease a patient may have since mitral stenosis and mechanical heart valves were contraindicated, but other valvular diseases were acceptable for NOAC use. . The validation of the measures using claims data such as demographics are considered reliable. The validation for PDC for adherence rates have some limitations; it was difficult to determine the exact reasons for each individual person without delving further into medical charts. The limitation of using PDC is that adherence data may be compromised if days supplied is incorrectly added or if other human errors were introduced. Also the PDC does not show if the patients actually consumed the medication. In terms of eligibility churn, by indicating inclusion with at least 75% coverage under an FFS or CCO, the data captured an appropriate sample for this study.

References:

1. DailyMed - PRADAXA- dabigatran etexilate mesylate capsule. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ba74e3cd-b06f-4145-b284-5fd6b84ff3c9. Accessed October 29, 2016.

2. DailyMed - ELIQUIS- apixaban tablet, film coated. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e9481622-7cc6-418a-acb6-c5450daae9b0. Accessed October 29, 2016.

3. DailyMed - XARELTO- rivaroxaban tablet, film coated XARELTO- rivaroxaban. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=10db92f9-2300-4a80-836b-673e1ae91610. Accessed October 29, 2016.

4. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for vte disease: Chest guideline and expert panel report. *Chest*. 2016;149(2):315-352. doi:10.1016/j.chest.2015.11.026.

5. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic therapy and prevention of thrombosis, 9th ed: american college of chest physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2_suppl):e531S-e575S. doi:10.1378/chest.11-2304.

6. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary. *J Am Coll Cardiol*. 2014;64(21):2246-2280. doi:10.1016/j.jacc.2014.03.021.

7. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients with Valvular Heart Disease. 2017;1-59. DOI:10.1161/CIR.0000000000000503.

8. DailyMed - SAVAYSA- edoxaban tosylate tablet, film coated. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e77d3400-56ad-11e3-949a-0800200c9a66. Accessed October 29, 2016.

9. Connolly SJ, Milling TJ, Eikelboom JW, et al. Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors. *N Engl J Med*. 2016;375(12):1131-1141. doi:10.1056/NEJMoa1607887.

10. Dosing Frequency and Medication Adherence in Chronic Disease - jmcp.2012.18.7.527. http://www.jmcp.org/doi/pdf/10.18553/jmcp.2012.18.7.527. Accessed March 30, 2017.

11. Brown JD, Shewale AR, Talbert JC. Adherence to Rivaroxaban, Dabigatran, and Apixaban for Stroke Prevention in Incident, Treatment-Naïve Nonvalvular Atrial Fibrillation. *J Manag Care Spec Pharm*. 2016;22(11):1319-1329. doi:10.18553/jmcp.2016.22.11.1319.

12. Anticoagulant DERP Summary Report_archive - 2016_07_28_AnticoagulantDERPSummaryReport.pdf. http://www.orpdl.org/durm/meetings/meetingdocs/2016_07_28/archives/2016_07_28_AnticoagulantDERPSummaryReport.pdf. Accessed February 5, 2017.

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