Journal of Thrombosis and Thrombolysis (2020) 50:739–745
https://doi.org/10.1007/s11239-020-02064-0

# The role of clinical pharmacy anticoagulation services in direct oral anticoagulant monitoring

**Aubrey E. Jones**[1,3] · **Jordan B. King**[2] · **Kibum Kim**[1] · **Daniel M. Witt**[1]

Published online: 21 February 2020


## Abstract

The role of dedicated anticoagulation management services (AMS) for patients receiving direct oral anticoagulant (DOAC) therapy is unclear. The objective of our study was to describe DOAC management in patients who were and were not managed by an AMS. We conducted a retrospective cohort study among patients with atrial fibrillation at the University of Utah Health (UUH) who received DOAC therapy between January 2013 and June 2016. Patients in the AMS group were managed by a pharmacist-led AMS whereas those in the non-AMS group were managed by other providers. The number and type of provider encounters and interventions related to DOAC therapy and a composite endpoint of thromboembolism, bleeding, and all-cause mortality were recorded. Overall, 90 and 370 patients were managed in the AMS and non-AMS groups, respectively. AMS group patients had greater chronic disease burden as measured by the Charlson comorbidity index. AMS group patients had more frequent DOAC-related encounters than non-AMS group patients but both groups had similar DOAC therapy intervention rates. Over half of patients in the AMS group received potentially duplicative interventions from their regular clinicians. The composite endpoint occurred in 18.9% and 13.5% of AMS and non-AMS group patients, respectively ($p=0.29$). Patients managed by AMS providers were more complex and had more frequent encounters regarding their DOAC therapy than those managed by non-AMS providers. However, there was evidence of duplicative DOAC therapy management efforts. No difference between AMS and non-AMS groups in the composite clinical endpoint was detected.

**Keywords** DOAC · Anticoagulation · Pharmacist management · Bleeding · NOAC

## Highlights

- Patients on direct oral anticoagulants (DOACs) referred to anticoagulation management services (AMS) tended to be more complicated.
- Duplicative efforts in DOAC management between AMS pharmacists and non-AMS providers are likely occurring.
- No difference in clinical endpoints between AMS and non-AMS groups were observed.
- Periprocedural planning interventions occurred commonly among patients on DOACs.
- Implications: More evidence is needed to fully determine the role of AMS services in DOAC monitoring and therapy.

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s11239-020-02064-0) contains supplementary material, which is available to authorized users.

✉ Aubrey E. Jones
Aubrey.e.jones@pharm.utah.edu

[1] Department of Pharmacotherapy, University of Utah, 30 South 2000 East, Salt Lake City, UT 84112, USA

[2] Population Health Sciences, University of Utah, Salt Lake City, UT, USA

[3] University of Utah College of Pharmacy, 30 South 2000 East, Salt Lake City, UT, USA

## Introduction

The use of direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban, edoxaban is increasing [1]. The primary advantages of DOACs over warfarin therapy are lower risk for intracranial hemorrhage, no requirement for routine laboratory monitoring, and fewer drug and dietary interactions [2, 3]. However, there are several factors that impact DOAC use: (1) need for dose adjustments or

switching to alternative anticoagulants in renal or hepatic impairment, (2) less certain drug-drug interaction management due to lack of standardized tests to monitor the anticoagulant effect, (3) differing dosing schedules and frequency based on therapeutic indication and specific DOAC used, (4) varied side effect profiles besides bleeding, (5) interruption of therapy for invasive procedures, and (6) significant costs compared to warfarin [4–7]. As a result, off-label DOAC prescribing is common [8–11] indicating a potential need for comprehensive patient and provider education and frequent patient follow up to mitigate the risk for harm during DOAC therapy.

Anticoagulation management services (AMS) staffed by anticoagulation therapy experts have a well-recognized role in warfarin management [12–14]. However, the need for close monitoring during warfarin therapy stems from a narrow therapeutic index, the need for routine laboratory monitoring, and numerous dietary and drug interactions. Given the aforementioned advantages of DOAC therapy, the role of a dedicated AMS for DOAC management is unclear. One study in the Veterans Affairs (VA) health system showed that pharmacist interventions improved adherence to DOAC therapy but these interventions were not part of an AMS dedicated to managing DOAC patients and clinical endpoints of thromboembolism (TE) or bleeding were not examined [15]. Another study in a hospital setting evaluated the effect of a pharmacist led DOAC stewardship program and documented interventions in 36% of patients [16]. Interventions included discontinuing concurrent antiplatelet therapy, DOAC dose adjustments, and laboratory monitoring of DOAC anticoagulant response, but bleeding or TE endpoints were not evaluated [16].

Many health systems are trying to determine whether patients prescribed DOAC therapy need to be formally enrolled in existing AMS. The objective of our study was to describe the initial experience of managing DOAC therapy within an AMS and determine the effect, relative to non-AMS management (i.e., DOAC management provided by the prescriber), on health care utilization and anticoagulation-related endpoints.

## Methods

### Study setting and patients

This retrospective cohort study was conducted at University of Utah Health (UUH), a large academic healthcare system in the Western United States. Administrative data within the UUH Electronic Data Warehouse was used to identify a cohort of adult patients with a diagnosis of atrial fibrillation or atrial flutter who were prescribed DOAC therapy at UUH between January 2013 and June 2016. DOAC prescriptions were identified using the first outpatient order for any of the following, apixaban, dabigatran, edoxaban, or rivaroxaban; the cohort entry date was defined as the first DOAC prescription. Atrial fibrillation or flutter diagnosis of any type including paroxysmal, persistent, longstanding persistent, etc. was identified using ICD 9/10 codes (427.3x/I48.x) for any healthcare visit during the 365 days preceding the cohort entry date. After creating the cohort using administrative data, each patient record was manually reviewed to confirm DOAC status and collect study endpoints. We excluded patients with insufficient information to determine study endpoints, patients not receiving DOAC therapy, and cases where DOAC therapy was managed outside the UUH system as determined during manual chart reviews.

### Primary exposure

The primary exposure of interest was the intended DOAC management approach: pharmacist-led AMS versus non-AMS providers. We defined intended pharmacist-led AMS management as having two or more encounters with AMS providers documented in the electronic medical record between January 2013 and December 2017. The AMS approach included initial patient education followed by phone calls or chart reviews by a pharmacist at regular intervals. At the beginning of the observation period AMS guidelines suggested reviews every 3 months. During the study the suggested frequency of reviews was decreased to every 6 or 12 months for most patients. Phone encounters with AMS pharmacists entailed questions about adherence, bleeding or stroke concerns, and reminders about suggested labs such as serum creatinine and complete blood counts, when necessary. Patients with less than two encounters with AMS providers were categorized as being managed by non-AMS providers. Non-AMS providers included cardiologists, neurologists, or primary care providers, depending on who was primarily responsible for managing DOAC therapy, and could include multiple providers per patient. Patients were followed for two years, until DOAC therapy discontinuation, or death, whichever occurred first.

### Study endpoints

We assessed the number and type of encounters, interventions related to DOAC therapy, and clinical endpoints including thromboembolic events (ischemic stroke, transient ischemic attack, peripheral arterial embolism), any bleeding (major bleeding, clinically relevant non-major bleeding [CRNMB], or minor bleeding), and death from any cause during follow-up. First, we described the frequency and type of DOAC-related encounters that occurred within the AMS and non-AMS groups. Second, as some patients in the AMS group had potentially duplicative DOAC-related

encounters and interventions from their regular clinicians during routine care we described DOAC-related encounters provided by patients' regular clinicians within the AMS group. "Encounters" were defined as any visit or phone or electronic communication that directly addressed DOAC therapy issues. "Interventions" were defined as changes in DOAC therapy or management aimed at ensuring best quality care. We categorized DOAC therapy-related intervention types as one or more of the following: (1) addressing inappropriate DOAC dosing, (2) addressing changes in renal function, (3) addressing bleeding concerns, (4) evaluating potential DOAC treatment failures, (5) developing periprocedural plans, (6) managing drug interactions, (7) addressing insurance coverage or cost issues, (8) addressing adherence concerns, (9) discontinuing DOAC therapy, (10) managing side effects other than bleeding, and (11) "other" types of interventions.

The secondary endpoint was a composite of clinical events including thromboembolic events, any bleeding, and death from any cause as previously described. We also examined a composite of major endpoints (ischemic stroke, peripheral arterial embolism, major bleeding and death) and individual components of the composite endpoints. Each individual endpoint was identified by International Classification of Disease, 9th and 10th revision codes and/or death records from the State Population Database and verified during manual chart review.

Major and CRNMB were defined per International Society on Thrombosis and Haemostasis guidelines [17, 18]. All other bleeding was categorized as minor. Thromboembolic endpoints required objective confirmation via radiologic imaging (e.g., computed tomography scanning, magnetic resonance imaging, or ultrasound). Baseline characteristics were identified using the closest value proximal to the index DOAC prescription date, within one year.

### Statistical analysis

Baseline characteristics and endpoint measures were summarized using frequency and percentage for categorical variables, and mean and standard deviation (SD) for continuous variables. The chi-squared test of association and Student's *t* tests were used to compare differences in categorical and continuous variables between the AMS and non-AMS groups, respectively. Time to the composite clinical endpoint and composite of major endpoints were analyzed using a Kaplan–Meier product limit estimator from which patients were censored at the time of the first encounter with an individual endpoint or the end of the 2-year follow up period whichever came first. Hazard ratios of the endpoints comparing the AMS and non-AMS groups were estimated using Cox proportional hazard models. In order to control for the possible effects of more interventions occurring early following discharge for patients newly started on DOAC therapy, additional sensitivity analysis was performed using a follow-up start beginning 90 days after the initial discharge. Patients who had any endpoint during this initial 90-day period or whose follow-up was shorter than 90 days were excluded from this analysis. The regression model could not be adjusted for covariates because the number of endpoints was too small to include additional explanatory variables in the model. Instead the time-to primary composite endpoint regressed on the exposure to AMS was stratified by Charlson comorbidity index scores, 0 or 1 versus 2 or higher. Analyses were performed using Stata v. 15.0 (StataCorp LP, College Station, Tx) and SAS version 9.4 (SAS Institute, Cary, NC).

## Results

An initial cohort of 737 patients was identified from administrative queries. A total of 274 patients were excluded after manual chart review for the following reasons: lack of endpoint data in the chart (n = 42), not receiving DOAC therapy (n = 72), and managed outside of UUH system (n = 163) leaving a total of 90 and 370 patients in the AMS and non-AMS groups, respectively (Fig. 1).

Baseline characteristics were similar between groups (Table 1) except that patients in the AMS group had higher $CHA_2DS_2$-VASc scores, (p = 0.07), greater chronic disease burden per the CCI (p < 0.001), and were more likely to be prescribed apixaban (p = 0.002). AMS patients were also less likely to be prescribed rivaroxaban (p = 0.035) than those in the non-AMS group.

### DOAC-related encounters

Patients in the AMS group had more frequent DOAC-related encounters with AMS providers compared to non-AMS group providers (5.2 vs 3.7 per patient-year, p < 0.001) (Online resource, Table S1). Potentially duplicative DOAC-related encounters provided by regular clinicians in the AMS group occurred at a rate of 3.1 per patient-year.

### DOAC-related interventions

The overall proportion of patients receiving DOAC therapy interventions was similar in the AMS and non-AMS groups (71.1% vs 74.9%, p = 0.30) (Online resource Table S1). The overall proportion of AMS group patients receiving potentially duplicative DOAC therapy interventions from their regular clinicians was 57.8%. The rate of DOAC therapy interventions per patient -year was 1.1 per patient-year in both the AMS and non-AMS groups (p = 0.69). Potentially duplicative DOAC-related interventions provided by regular

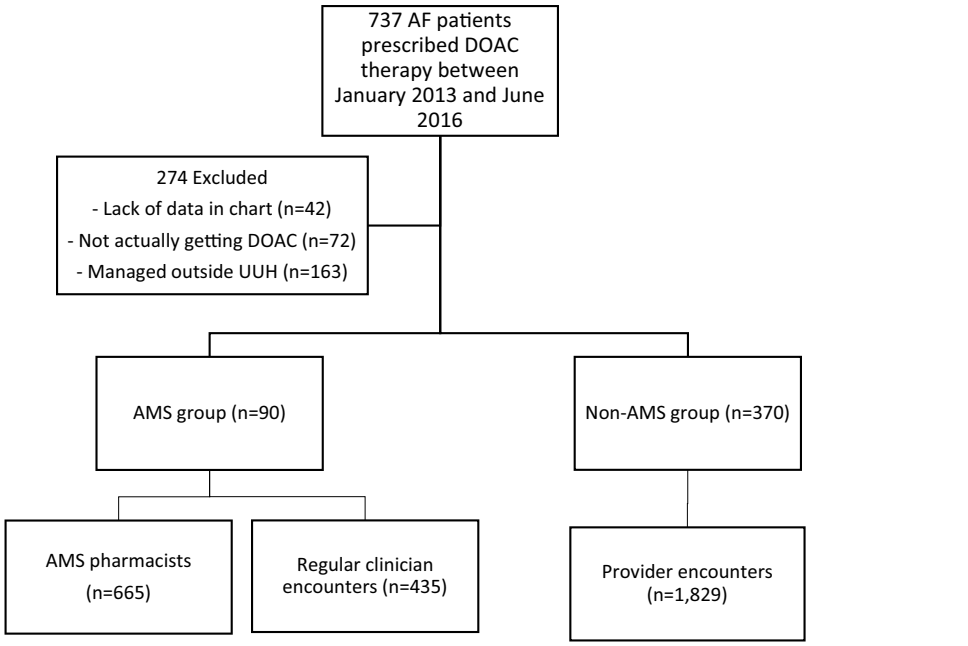


**Fig. 1** Flowchart of group allocation of atrial fibrillation patients prescribed DOAC therapy in the University of Utah Health System. *AMS* anticoagulation management service, *DOAC* direct oral anticoagulant, *UUH* University of Utah Health

**Table 1** Characteristics of atrial fibrillation patients prescribed DOAC therapy in the University of Utah Health System

| | AMS group n = 90 | Non-AMS group n = 370 | p-value |
|---|---|---|---|
| Age, mean (SD) | 68.9 (11.0) | 67.1 (12.0) | 0.19 |
| Gender—Male (%) | 285 (62.2) | 229 (61.9) | 0.88 |
| Race—Caucasian (%) | 83 (92.2) | 340 (91.9) | 0.92 |
| $CHA_2DS_2$-VASc, mean (SD) | 3.0 (1.5) | 2.7 (1.6) | 0.07 |
| Charlson Comorbidity Index, mean (SD) | 3.0 (3.1) | 1.7 (2.1) | < 0.001 |
| Creatinine clearance < 50 mL/min (%) | 8 (8.9) | 23 (9.4)[a] | 0.89 |
| DOAC Type (%) | | | |
| Apixaban | 49 (4.4) | 135 (36.5) | 0.002 |
| Rivaroxaban | 31 (34.4) | 172 (46.5) | 0.04 |
| Dabigatran | 15 (16.7) | 81 (21.9) | 0.27 |

[a]117 values were missing, creatinine clearance calculated using Cockcroft-Gault equation and actual body weight)

*DOAC* direct oral anticoagulant; *AMS* anticoagulation management service; *SD* standard deviation

clinicians in the AMS group occurred at a rate of 0.7 per patient-year.

A comparison of DOAC therapy interventions categorized by provider type is shown in Fig. 2. In total 325 patients received 795 interventions. Periprocedural planning interventions were commonly provided by AMS pharmacists, regular clinicians caring for AMS group patients, and non-AMS providers. Compared to AMS-group pharmacists, non-AMS providers were more likely to provide interventions relating to bleeding risk (2.7% vs. 8.0%, p = 0.018) and discontinuation of DOAC therapy (0.6% vs. 14.0%, p < 0.01). Regular clinicians caring for AMS group patients frequently provided interventions that were also being provided by AMS pharmacists.

The difference between the AMS and non-AMS group patients' primary composite endpoint was not statistically significant (18.9% vs. 13.5%, p = 0.29) (Table 2). Bleeding of any severity occurred more frequently in the AMS group (18.9% vs 10.5%, p = 0.03) as did gastrointestinal (GI) tract bleeding (7.8% vs 1.6%, p = 0.005). All other differences in clinical endpoints between groups were not statistically significant.

The 2-year cumulative incidence of the primary composite endpoint from the Kaplan–Meier estimator was higher in

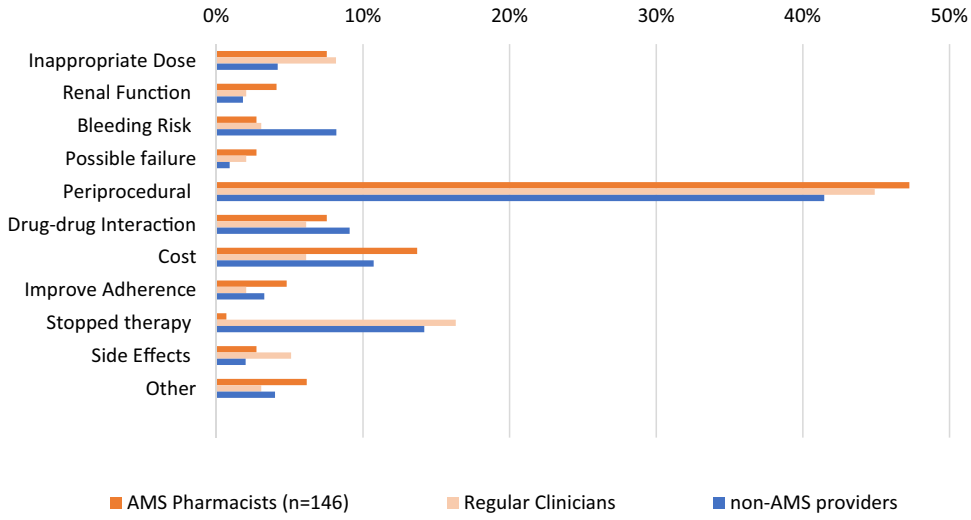


**Fig. 2** Direct oral anticoagulant therapy interventions categorized by provider type

**Table 2** Outcomes of direct oral anticoagulant therapy among patients with atrial fibrillation managed in the University of Utah Health System categorized by anticoagulation management service status

| | AMS group n = 90 | Non-AMS group n = 370 | p-value |
|---|---|---|---|
| Composite endpoint (%) | 17 (18.9) | 50 (13.5) | 0.29 |
| Bleeding | | | |
| Any severity (%) | 17 (18.9) | 39 (10.5) | 0.03 |
| Major bleeding (%) | 1 (1.1) | 2 (0.5) | 0.48 |
| CRNMB (%) | 10 (11.1) | 22 (6.0) | 0.08 |
| Minor bleed (%) | 6 (6.7) | 15 (4.1) | 0.29 |
| Bleeding type | | | |
| Gastrointestinal tract bleeding (%) | 7 (7.8) | 6 (1.6) | 0.005 |
| Hematuria (%) | 0 | 8 (2.2) | 0.17 |
| Hematoma (%) | 1 (1.1) | 2 (0.5) | 0.48 |
| Epistaxis (%) | 6 (6.7) | 13 (3.5) | 0.18 |
| Other bleeding types (%) | 3 (3.3) | 10 (2.7) | 0.73 |
| Stroke (%) | 0 | 4 (1.1) | 0.59 |
| Death (%) | 0 | 7 (1.9) | 0.35 |

*CRNMB* clinically relevant non-major bleeding

the AMS group compared to the non-AMS group (18.0% vs. 14.1%), but the difference was not statistically significant (log-rank test, p-value = 0.45). The hazard ratio for AMS vs. non-AMS groups for the primary composite endpoint was 1.25 (95% confidence interval [CI] 0.70–2.24) (Fig. 3a). When analysis was limited to the composite of major endpoints, the log-rank test result remained statistically insignificant (p = 0.22), but the cumulative incidence was lower in the AMS group than the non-AMS group (1.3% vs. 3.6%) with a hazard ratio of 0.33 [95% CI 0.04–2.59] (Fig. 2a). Sensitivity analysis starting patient follow-up from 90 days after the index DOAC prescription date had a nominal influence on the cumulative incidences and hazard ratios (Fig. 2b).

The primary composite endpoint hazard ratio estimate for AMS vs. non-AMS groups stratified by CCI score 0 or 1 was 2.34 (95% CI 1.08–5.09], whereas the hazard ratio estimate in patients with CCI scores 2 or more was 0.66 (95% CI 0.27–1.62) (Online resource Figure S1). The direction of association in endpoint hazard ratios associated with baseline CCI scores were consistent when the patient follow-up started 90 days following the index DOAC prescription (data not shown).

## Discussion

This is among the first studies to measure endpoints of patients prescribed DOACs who were and were not managed by an AMS. Our results demonstrate that patients prescribed DOAC therapy received frequent contacts related to their anticoagulation therapy from healthcare providers regardless

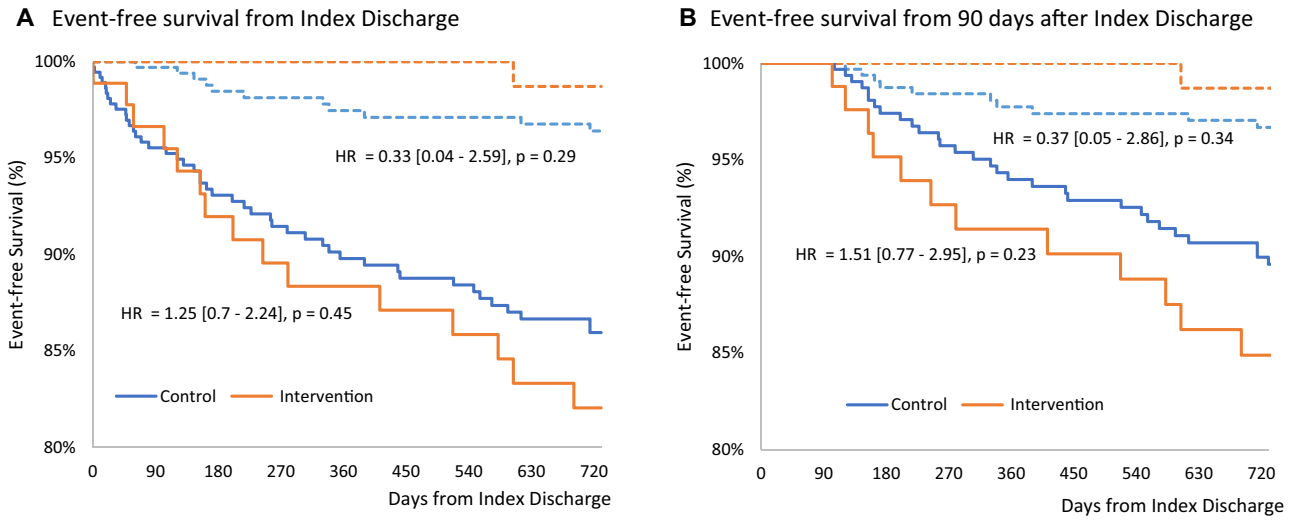


**Fig. 3** Kaplan–Meier estimates of event-free survival and hazard ratio [95% confidence interval] from Cox-proportional hazard regression models. *Orange lines* estimates for anticoagulation management service group; *Blue lines* estimates for non-anticoagulation management service group; *Solid lines* primary composite endpoint including ischemic stroke, transient ischemic attack, peripheral arterial embolism, major bleeding: clinically relevant non-major bleeding, minor bleeding and death; *Dotted lines* composite of major endpoints including ischemic stroke, peripheral arterial embolism, major bleeding and death; *HR* hazard ratio

of whether they were being managed by an AMS. Common DOAC therapy interventions included periprocedural planning, drug interaction management, insurance coverage or cost issues, and dose adjustments. The number and types of interventions made by the different provider types indicated that duplication of effort in DOAC management may be occurring between AMS pharmacists and regular clinicians. These results could indicate that lack of clear role delineation regarding DOAC therapy may result in suboptimal communication between AMS pharmacists and regular clinicians. With regard to periprocedural anticoagulation planning this could result in patients receiving the same instructions multiple times which could be reassuring, or conflicting instructions which could cause confusion. AMS pharmacists were more likely to address insurance coverage and medication cost issues than either non-AMS group or regular clinicians. Interventions for inappropriate DOAC doses constituted only a small fraction of total interventions.

We were not able to detect a discernable benefit of AMS care over non-AMS care regarding clinical endpoints in patients receiving DOAC therapy. In fact, there were slightly more bleeding episodes in the AMS cohort compared to the non-AMS cohort, particularly GI bleeding events. Patients in the AMS group tended to have higher CCI scores and worse renal function than those in the non-AMS group and, therefore, may have been at higher bleeding risk. When endpoint results were stratified by CCI score, patients with low chronic disease burden managed by AMS pharmacists were twice as likely to experience adverse endpoints than those in the non-AMS group. A possible explanation for this observation is that AMS pharmacists were more likely to ask patients about and document episodes of bleeding than providers in the non-AMS group. Conversely, there was evidence that patients with higher chronic disease burden managed by AMS pharmacists had lower risk of experiencing adverse endpoints but the confidence interval associated with this estimate was wide and included evidence of both benefit and harm. Additional studies with larger samples sizes are needed to confirm this observation.

Limitations of this study included the small sample size, especially in the AMS group, and thus the small number of endpoints limiting statistical power and ability to perform adjusted analyses. Additionally, this was a retrospective study and information pertaining to DOAC therapy was often not well documented and it was unclear in some instances whether DOAC therapy was actually discussed. Changes in treatment practices over the study period, particularly with regard to DOAC management during left atrial ablation procedures and the recommended frequency of encounters in the AMS group may also have influenced our results. In addition, DOACs were analyzed as a class and we acknowledge that there are differences between individual DOACs that could have influenced the results.

## Conclusion

Patients receiving DOAC therapy managed by AMS pharmacists tended to be higher risk and received more frequent interventions regarding their DOAC therapy than those

managed by non-AMS providers. However, some of this may represent duplicative efforts. Due to the small sample size, and low rate of endpoints, no differences were detected between AMS and non-AMS groups in clinical endpoints. Additional studies with larger samples sizes and more clearly defined AMS services for patients on DOACs are required to definitely demonstrate the benefit or cost of a dedicated AMS. Additionally, the most effective mix of AMS interventions for patients on DOAC therapy has yet to be determined, and it is possible that periodic bioinformatic-driven interventions such as drug interaction management, adherence monitoring, and periprocedural planning may lend themselves well to DOAC therapy management compared to the close monitoring AMS provide for patients receiving warfarin.

**Funding** This study was funded by a grant provided by the American Society for Health-System Pharmacists Foundation (ASHP) and by grant number R18HS026156 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

## Compliance with ethical standards

**Conflict of interest** Dr. Witt reports grant funding from Roche Diagnostics. The rest of the authors declare they have no conflict of interest.

## References

1. Barnes GD, Lucas E, Alexander GC, Goldberger ZD (2015) National trends in ambulatory oral anticoagulant use. Am J Med 128(12):1300-1305 e1302. https://doi.org/10.1016/j.amjmed.2015.05.044
2. Mohammad I, Korkis B, Garwood CL (2017) Incorporating comprehensive management of direct oral anticoagulants into anticoagulation clinics. Pharmacotherapy 37(10):1284–1297. https://doi.org/10.1002/phar.1991
3. Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J (2016) Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. J Thromb Thrombolysis 41(1):206–232. https://doi.org/10.1007/s11239-015-1310-7
4. Pradaxa® [Package Insert]. Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT (2015)
5. Xarelto® [Package Insert]. Janssen Pharmaceuticals, Inc, Titusville, NJ (2011)
6. Eliquis® [Package Insert]. Bristol-Myers Squibb Company, Princeton, NJ (2012)
7. Savaysa® [Package Insert]. Daiichi Sankyo Co, Tokyo (2015)
8. Barra ME, Fanikos J, Connors JM, Sylvester KW, Piazza G, Goldhaber SZ (2016) Evaluation of dose-reduced direct oral anticoagulant therapy. Am J Med 129(11):1198–1204. https://doi.org/10.1016/j.amjmed.2016.05.041
9. Gibson CM, Smith CB, Davis S, Scalese MJ (2018) Assessment of apixaban prescribing patterns for nonvalvular atrial fibrillation in hospitalized patients. Ann Pharmacother 52(1):54–59. https://doi.org/10.1177/1060028017726795
10. Howard M, Lipshutz A, Roess B, Hawes E, Deyo Z, Burkhart JI, Moll S, Shilliday BB (2017) Identification of risk factors for inappropriate and suboptimal initiation of direct oral anticoagulants. J Thromb Thrombolysis 43(2):149–156. doi:https://doi.org/10.1007/s11239-016-1435-3
11. Whitworth MM, Haase KK, Fike DS, Bharadwaj RM, Young RB, MacLaughlin EJ (2017) Utilization and prescribing patterns of direct oral anticoagulants. Int J Gen Med 10:87–94. doi:https://doi.org/10.2147/IJGM.S129235
12. Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, Song F (2007) Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anticoagulation therapy: a systematic review and economic modelling. Health Technol Assess 11(38):iii-iv, ix-66
13. Witt DM, Sadler MA, Shanahan RL, Mazzoli G, Tillman DJ (2005) Effect of a centralized clinical pharmacy anticoagulation service on the outcomes of anticoagulation therapy. Chest 127(5):1515–1522. doi:https://doi.org/10.1378/chest.127.5.1515
14. Chiquette E, Amato MG, Bussey HI (1998) Comparison of an anticoagulation clinic with usual medical care: anticoagulation control, patient outcomes, and health care costs. Arch Intern Med 158(15):1641–1647
15. Shore S, Ho PM, Lambert-Kerzner A, Glorioso TJ, Carey EP, Cunningham F, Longo L, Jackevicius C, Rose A, Turakhia MP (2015) Site-level variation in and practices associated with dabigatran adherence. JAMA 313(14):1443–1450. https://doi.org/10.1001/jama.2015.2761
16. Perlman A, Horwitz E, Hirsh-Raccah B, Aldouby-Bier G, Fisher Negev T, Hochberg-Klein S, Kalish Y, Muszkat M (2019) Clinical pharmacist led hospital-wide direct oral anticoagulant stewardship program. Isr J Health Policy Res 8(1):19. https://doi.org/10.1186/s13584-019-0285-9
17. Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the S, Standardization Committee of the International Society on T, Haemostasis (2005) Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 3(4):692–694. https://doi.org/10.1111/j.1538-7836.2005.01204.x
18. Kaatz S, Ahmad D, Spyropoulos AC, Schulman S, Anticoagulation SC (2015) Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. J Thromb Haemost 13(11):2119–2126. https://doi.org/10.1111/jth.13140