Original Paper

Use of Synchronous, Interruptive Electronic Health Record–Embedded Medication Alerts to Improve Evidence-Based Medication Prescribing: Randomized Comparative Effectiveness Trial of Two Prescriber Alerts

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Abstract

Background: Antithrombotic stewardship is critical for reducing preventable harm from inappropriate anticoagulant prescribing. Electronic health record (EHR)–embedded clinical decision support (CDS) alerts can prevent prescribing errors at the point of care, but their real-world effectiveness is variable and often limited by alert fatigue and poor workflow integration. Whether augmenting interruptive medication alerts with just-in-time access to clinical pharmacists improves prescriber response remains unclear.

Objective: This study aimed to (1) compare the effectiveness of synchronous, interruptive direct oral anticoagulant (DOAC) prescribing alerts with and without an embedded clinical pharmacist referral option for correcting inappropriate new prescriptions within 7 days, and (2) evaluate the system-level impact of implementing synchronous DOAC alerts on inappropriate prescribing over time.

Methods: We conducted a prescriber-level randomized comparative effectiveness trial within a large US academic health system. Prescribers who placed an inappropriate ambulatory apixaban or rivaroxaban order were randomized to receive an interruptive EHR alert either with or without an embedded clinical pharmacist referral link. The primary outcome was any change to the prescription within 7 days. In parallel, a system-level interrupted time series analysis examined weekly proportions of inappropriate DOAC prescriptions (secondary outcomes) from 24 months before through 29 months after alert implementation. Exploratory outcomes included adverse events within 30 days and alert implementation metrics.

Results: Among 2082 prescribers writing DOAC prescriptions during the study period, 300 (14.4%) triggered at least one inappropriate prescription and were randomized; after prespecified exclusions, 758 alerts across 286 prescribers were analyzed. Overall, 28.9% (219/758) of alerts led to a prescription change within 7 days. The proportion of alerts leading to a prescription change did not differ between alerts with and without pharmacist referral (difference 1 percentage point [95% CI −7 to 9]). The system-wide proportion of inappropriate DOAC prescriptions exhibited a significant downward preimplementation trend (−0.04

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percentage points per week [95% CI −0.06 to −0.02]), followed by an immediate 3.5-percentage-point absolute reduction at alert launch (to 9.7%), with no subsequent slope change. Adverse events within 30 days were uncommon and similar across arms.

Conclusions: Adding an embedded pharmacist referral option to an interruptive DOAC prescribing alert did not increase short-term prescription changes. However, the implementation of synchronous, user-centered alerts was associated with a system-level reduction in inappropriate DOAC prescribing. These findings support a complementary digital stewardship model in which high-value, point-of-order alerts prevent routine prescribing errors, while clinical pharmacists focus on complex and longitudinal medication management.

Trial Registration: ClinicalTrials.gov NCT05351749; https://clinicaltrials.gov/study/NCT05351749

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KEYWORDS

clinical decision support systems; electronic health records; anticoagulants; medication errors/inappropriate prescribing; pharmacists; randomized controlled trial; antithrombotic stewardship

Introduction

Inappropriately prescribed anticoagulant medications are the leading cause of adverse drug events, with dosing errors and unrecognized drug-drug interactions contributing to preventable patient harm and health care resource use [1-3]. Health systems are increasingly investing in antithrombotic stewardship as a core patient-safety strategy to standardize prescribing, monitor therapy, and mitigate risk [4-6]. Population health approaches, including pharmacist-led dashboards, have reduced inappropriate direct oral anticoagulant (DOAC) medication prescriptions and even reduced adverse clinical event rates [7-10]. However, they are labor-intensive and typically only identify prescribing errors after an order has been placed.

Computerized clinical decision support (CDS) tools, including medication alerts, hold promise for preventing errors at the point of prescribing. However, the real-world impact of these interruptive alerts has been mixed, often limited by insufficient or inactionable information, workflow disruptions, and alert fatigue [11]. User-centered design, incorporating human-factors principles, has been proposed to improve alert acceptance and impact, yet prospective evaluations embedded in routine care remain scarce [12,13].

Because many prescribing-based CDS tools are ignored or overridden and contribute to alert fatigue, one component of antithrombotic stewardship that remains untested is the opportunity to connect prescribers with clinical pharmacists—either to collaborate on decision-making or to fully offload decision-making [14]. This collaboration, facilitated by CDS tools, could improve the utility of prescribing alerts while also better integrating pharmacists into just-in-time, point-of-care decision-making. However, no studies have yet examined the potential effectiveness of this type of CDS tool in antithrombotic prescribing, particularly when compared with more traditional best-practice alerts.

To better inform how health care systems might design prescribing CDS alerts to improve evidence-based prescribing, we developed and implemented a set of electronic health record (EHR)–embedded DOAC medication alerts, grounded in user-centered design principles. As part of this rollout, we aimed to evaluate 2 questions. First, using prescriber-level randomization, we compared whether adding a direct, in-line referral process for engaging clinical pharmacists in prescribing decisions increased the rate of prescribers changing inappropriate DOAC prescriptions beyond what alerts alone achieved. Second, in parallel, we used an interruptive time series analysis to prospectively evaluate the system-wide impact of implementing synchronous medication alerts on the system-level proportion of DOAC prescriptions that were inappropriate.

Methods

Study Overview and Setting

As part of a larger program testing several strategies to reduce inappropriate DOAC prescribing and improve evidence-based prescribing [15], we conducted a 2-arm randomized comparative-effectiveness trial of 2 DOAC medication alerts. Specifically, we randomized eligible prescribers to receive 1 of 2 types of CDS interruptive alerts whenever they ordered a DOAC prescription that did not follow the package label instructions. This study focused on inappropriate ambulatory DOAC prescriptions that occurred at the time of ordering within the EHR (ie, new DOAC prescriptions) rather than those that developed longitudinally for already existing prescriptions (eg, related to a change in renal function); the latter were addressed in a companion trial and the results of that study have been previously published [16].

Within a large, quaternary care health system in the midwestern United States, we initially implemented a series of medication alerts for patients with atrial fibrillation (AF) on August 1, 2022, and conducted a pilot study to examine the acceptability, accuracy, and feasibility of these alerts [13]. Subsequently, on April 12, 2023, we further implemented alerts for patients with venous thromboembolism (VTE). Prescribers were randomized (and thus entered the study) upon ordering their first inappropriate DOAC prescription for either AF or VTE after alerts were launched for patients managed in the ambulatory setting. This study includes both the pilot study and expanded trial periods, with continued clinician enrollment until December 15, 2024, the end of the trial. As is customary for most new EHR alerts within this health system, no specific communication or dissemination strategies were used, other than the single prestudy electronic message, described below.

Prior to the commencement of the randomized trial, all inappropriate DOAC prescriptions in the health system were

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captured on a population health DOAC Dashboard. Clinical pharmacists within the anticoagulation clinic regularly reviewed these inappropriate prescriptions and recommended prescription changes when clinically indicated (clinical pharmacists do not have independent prescribing authority in this health system). To ensure study fidelity, inappropriate DOAC prescriptions included in the study were suppressed on the DOAC Dashboard for at least 14 days while the study was being conducted. This allowed us to measure the impact of the medication alerts on changes to prescriptions flagged as inappropriate for up to 14 days without interference from the clinical pharmacists using the DOAC Dashboard.

Ethical Considerations

This study was reviewed by the University of Michigan Medical Institutional Review Board and approved with a waiver of documented informed consent for the prescriber and patient, given the study's focus on improving standards of care and minimal risk. Prior to the August 1, 2022, launch, all prescribers were informed about the trial through a system-wide electronic message and given the opportunity to opt out. Only one provider elected to opt out of the study. The trial is registered at ClinicalTrials.gov (NCT05351749), and details of the overarching study have been previously published [15].

Participant Eligibility and DOAC Prescription Assessment

All prescribers who ordered an eligible ambulatory DOAC prescription (ie, an inappropriate DOAC prescription) and did not opt out of study participation were included in the trial. Prescriptions written in the emergency department, inpatient setting, skilled nursing facility, or written by study team members were excluded. All eligible DOAC prescriptions written for adult patients (age 18 years or older) in the ambulatory setting by prescribing clinicians at Michigan Medicine were assessed for appropriateness immediately upon order.

At the time an apixaban or rivaroxaban prescription was written by a prescriber, the medical information for the patient being prescribed the DOAC medication was automatically checked through Our Practice Advisory framework in the Epic EHR to determine whether the DOAC prescription met the Food and Drug Administration (FDA) package label recommended criteria or whether there was a significant drug-drug interaction as defined by the Anticoagulation Forum (Multimedia Appendix 1). If the prescribed DOAC did not match the FDA recommendation or contained a significant drug-drug interaction, the prescriber received a medication alert before placing the prescription order. This alert informed the prescriber of the potential error and suggested ways to align the prescription with FDA dosing recommendations. Detailed information about the alert format and description of the alert logic/algorithm has been published elsewhere [13]. Briefly, we designed the alerts using a 3-phase, user-centered process with iterative feedback and design enhancements from end users.

After the trial was initiated, a protocol amendment was made to exclude patients receiving nirmatrelvir/ritonavir for COVID-19. This combination medication is known to interact with DOACs; however, a system-wide process, independent of our study, was implemented to instruct patients on adjusting their anticoagulant while taking nirmatrelvir/ritonavir. As such, these instances of inappropriate DOAC prescribing due to a drug-drug interaction were excluded from the study.

Randomization

Prescribers with eligible prescriptions were randomized once, at their first instance of an inappropriate apixaban or rivaroxaban prescription. Prescribers were randomized with equal probability to 1 of 2 medication alerts: (1) medication alert that included a direct link for clinical pharmacist review and support; or (2) medication alert without a direct link for clinical pharmacist review and support. Other than the link for pharmacist review, medication alerts were identical in the 2 arms (Multimedia Appendix 2). Permuted block randomization was implemented via computer scripts built into the EHR for prescriber-level randomization. Randomization was stratified by trainee versus primary care versus specialists. The trial was clustered at the prescriber level, as prescribers were each only randomized once (upon first eligible prescription order) but may have had multiple inappropriate DOAC prescriptions during the trial. Once randomized, prescribers remained consistently within their assigned arm (ie, receiving the same type of alert). Prescribers were aware of their assignment. However, the analytic team was blinded to randomization.

Data Sources and Collection

The EHR system provided all study data to be analyzed, including (1) prescription-level trial data (for each of the inappropriate DOAC prescriptions triggering alerts) during the trial and (2) system-level data (for all appropriate and inappropriate DOAC prescriptions) pre- and postimplementation of the medication alerts.

For the analysis of our primary research question of comparative effectiveness of the 2 medication alerts, we collected information at the prescription-level between August 1, 2022, and December 15, 2024 (29 months), including details of the DOAC prescription triggering an alert and the type of alert that was triggered. We also collected data on the patient's medication details on day 7 following the alert to determine whether any DOAC medication changes were made within the 7-day window. Patient characteristics at the time of the alert were also collected: gender, age, weight, presence of impaired renal function (based on creatinine clearance [CrCl] level as calculated by the Cockcroft-Gault equation [17] using actual body weight and actual serum creatinine values), and specific diagnosis (VTE vs AF). For prescriber characteristics, we collected prescriber role (trainee vs primary care vs specialist), provider type (physician, physician assistant, nurse practitioner, or resident), and frequency of DOAC prescriptions by the provider in the year prior to the trial initiation. All data were retrieved from the EHR through custom-built reports. One prescription usually corresponded to one alert, to which a prescriber responded by selecting options shown on the alert, dismissing the alert, or canceling the original order. Some prescriptions, however, triggered multiple medication alerts of the same type (eg, the identical alert reappeared if a prescriber dismissed the alert and

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then canceled and reentered the same medication); in such cases, only the final instance of the alert per prescription was analyzed.

For the second research question on the overall impact of the introduction of the medication alert system on inappropriate prescribing, we collected system-level data on all DOAC prescriptions (including appropriate and inappropriate) over time, starting 24 months before the trial began. For this analysis, we used a 14-day observation window, starting on the date of initial prescribing, to identify the total number of DOAC prescriptions and the number of inappropriate DOAC prescriptions. We used the same criteria for inappropriate DOAC prescriptions as were used in this study's first research question. These data were collected from the DOAC Dashboard reporting tool built into the EHR. Consistent with the first research question, this study population was also limited to ambulatory patients, excluding prescriptions written during inpatient hospital stays or emergency department visits. We analyzed weekly data between the week of August 2, 2020, and the week of December 15, 2024.

Hypotheses and Outcome Measures

Primary Research Question: Comparative Effectiveness of Alerts

Clinical pharmacists working in the anticoagulation clinic are experts in evidence-based DOAC prescribing and are highly regarded within our health system, as demonstrated by their prior work with the population health DOAC Dashboard [8]. As such, we hypothesized that prescribers randomized to receive DOAC medication alerts that included a referral option for clinical pharmacist review would remedy a higher proportion of inappropriate DOAC prescriptions than prescribers randomized to medication alerts without the clinical pharmacist referral option.

Primary Outcome: Prescriptions Changed

For our primary research question, the primary outcome was the proportion of medication alerts that resulted in any prescription change within 7 days of the alert. Medication alerts were considered to have resulted in a "change" if any change was made in terms of dosage, frequency, and/or medication being prescribed when compared to the initial order that triggered the alert. To assess this outcome, for each prescription, we compared the DOAC medication that triggered the alert with the medication details 7 days after the alert, and then coded the alert as resulting in a change or not. Cases in which the incorrectly dosed anticoagulant order was canceled, and no further anticoagulant order was placed over the subsequent 7 days were coded as changes. When the data retrieved from the EHR were unclear for determining the outcome, cases were reviewed manually by a study team member (MF), who was blinded to assignment and did not participate in further analysis. Prespecified potential moderators for the comparative effectiveness of the medication alerts were also explored.

Exploratory Outcomes

Per our study protocol, we also examined several exploratory outcomes based on the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) implementation evaluation framework [15,18] that were related to our primary research question. These included the proportion of DOAC-treated patients and DOAC-prescribing providers who triggered an alert ("Reach"); the proportion of prescribers that implemented at least one prescription change during the study period (a secondary measure of "Adoption"); the percentage of changes made as recommended in the alert and the percentage of alerts with a pharmacist referral option that resulted in a pharmacist referral ("Implementation Fidelity"); the number and proportion of a randomly selected sample of alerts that were deemed clinically inappropriate by 2 independent clinical pharmacist adjudicators ("Implementation Fidelity"); 30-day rates of clinical adverse events, including major and clinically-relevant nonmajor bleeding events ("Clinical Effectiveness"); and overtime changes in the proportion of prescriptions that triggered an alert that were changed during the study period ("Maintenance").

Beyond those implementation outcomes prespecified in our protocol paper, we also report several further outcomes, again all in line with the RE-AIM framework: the distribution of new versus existing prescriptions that triggered an alert ("Reach"); the number and percentage of clinical pharmacist referrals that resulted in medication prescription changes beyond the prespecified 7-day evaluation window ("Implementation Fidelity"); the number/percentage of times prescribers documented justification for not following an alert-recommended medication change ("Implementation Fidelity"); and integration of the alerts into posttrial routine clinical practice ("Maintenance").

Second Research Question: System-Level Change in Inappropriate DOAC Prescribing

Our second research question examined the system-level impact of implementing DOAC medication alerts (regardless of type) on the proportion of inappropriate DOAC prescriptions ordered over time. We hypothesized that implementing these alerts would reduce inappropriate prescribing across the system.

Secondary Outcome: The Proportion of Inappropriate Prescriptions

To evaluate our second research question, our secondary outcome was the proportion of system-wide DOAC prescriptions deemed inappropriate. This proportion was computed as the number of inappropriate DOAC prescriptions divided by the total number of DOAC prescriptions written by prescribers (regardless of whether they had been randomized in the trial). This outcome was calculated weekly starting 105 weeks (2 years) before initiation of the medication alerts and continuing through the end of the study period, or for 53 months (4 years and 5 months) in total.

Statistical Analysis

Analytic methods for our 2 research questions are described below. All analyses were conducted using Stata 19 (StataCorp LLC) and statistical significance was assessed as P value <.05 using 95% CIs, unless otherwise noted.

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Primary Research Question: Comparative Effectiveness of Alerts

Analyses for Primary Outcome

For the first research question, we compared the main effect of 2 medication alerts for inappropriate prescriptions (alerts that included a clinical pharmacist referral option vs similar alerts without the referral option) on our primary outcome, the proportion of alerts that resulted in a prescription change within 7 days. Mixed-effects logistic regression models were conducted with fixed effects for alert type (a treatment) and clinician role (a stratification variable; trainee vs primary care vs specialists), and an unstructured covariance matrix for residual errors. The unit of analysis was the prescription, and a prescriber-level random effect was included to account for clustering of prescriptions within prescribers. To account for patients with multiple prescriptions during the study period, sensitivity analyses including a patient-level random effect were also conducted.

Moderator Analyses for Comparison of Alerts

We also explored moderators of the comparative effectiveness of medication alerts (with and without pharmacist referral option) to evaluate whether certain types of prescribers, patients, and/or prescriptions might benefit most from certain alerts. These included 2 prescriber-level moderators (specialty vs primary care providers and number of DOAC prescriptions before the study divided into tertiles), 4 moderators of patient characteristics at the time of an alert (patient age, presence of impaired renal function, polypharmacy [5 or more prescribed medications], and specific diagnosis [VTE vs AF]), and 2 prescription-level moderators (apixaban vs rivaroxaban, dose too high vs too low). As part of our analyses for a companion trial [16], we added one further post hoc moderator (near vs farther from cutoff threshold values). Each moderator was assessed separately by including it in the primary analysis model as an interaction with a treatment. 90% CIs were used to assess significance.

Analyses for Exploratory Outcomes

Reach and secondary measures of adoption were assessed descriptively across study arms. Clinical effectiveness and implementation fidelity were also assessed descriptively, both across and between treatment arms. Maintenance was assessed by adding a fixed effect for time and a time-by-treatment interaction to the primary analysis model to evaluate whether the effect of alerts or the difference between arms on changes to inappropriate DOAC prescriptions changed over time.

Power and Sample Size

As described in the protocol paper [15], for our primary research question comparing the effectiveness of the 2 types of alerts, assuming 600 patients/alerts across 300 prescribers, prescriber-level intraclass correlation coefficient (ICC) of 0.1, and a type 1 error rate of 5%, we had 94% power to detect the difference in the proportion of prescription changes of 0.55 versus 0.40 (risk ratio of 1.45) for alerts with versus without a pharmacist referral options.

Second Research Question: System-Level Change in Inappropriate DOAC Prescribing

To evaluate the effectiveness of the overall alert system implemented in the trial on overall levels of inappropriate DOAC prescribing, we conducted an interrupted time-series analysis (ITSA) with a single intervention of the medication alert commencement. Trends in the proportions of DOAC prescriptions deemed inappropriate were analyzed using an ordinary least-squares time-series regression model with Newey-West SEs, with autocorrelation adjusted for using the Cumby-Huizinga test. We compared the proportion of inappropriate DOAC prescriptions, pre- and postimplementation of the alert system (weeks 1-105 vs weeks 106-229) by evaluating shifts in the level (intercept) immediately after the intervention and in the slope preintervention versus postintervention.

Results

Results for Primary Research Question: Comparative Effectiveness of Alerts

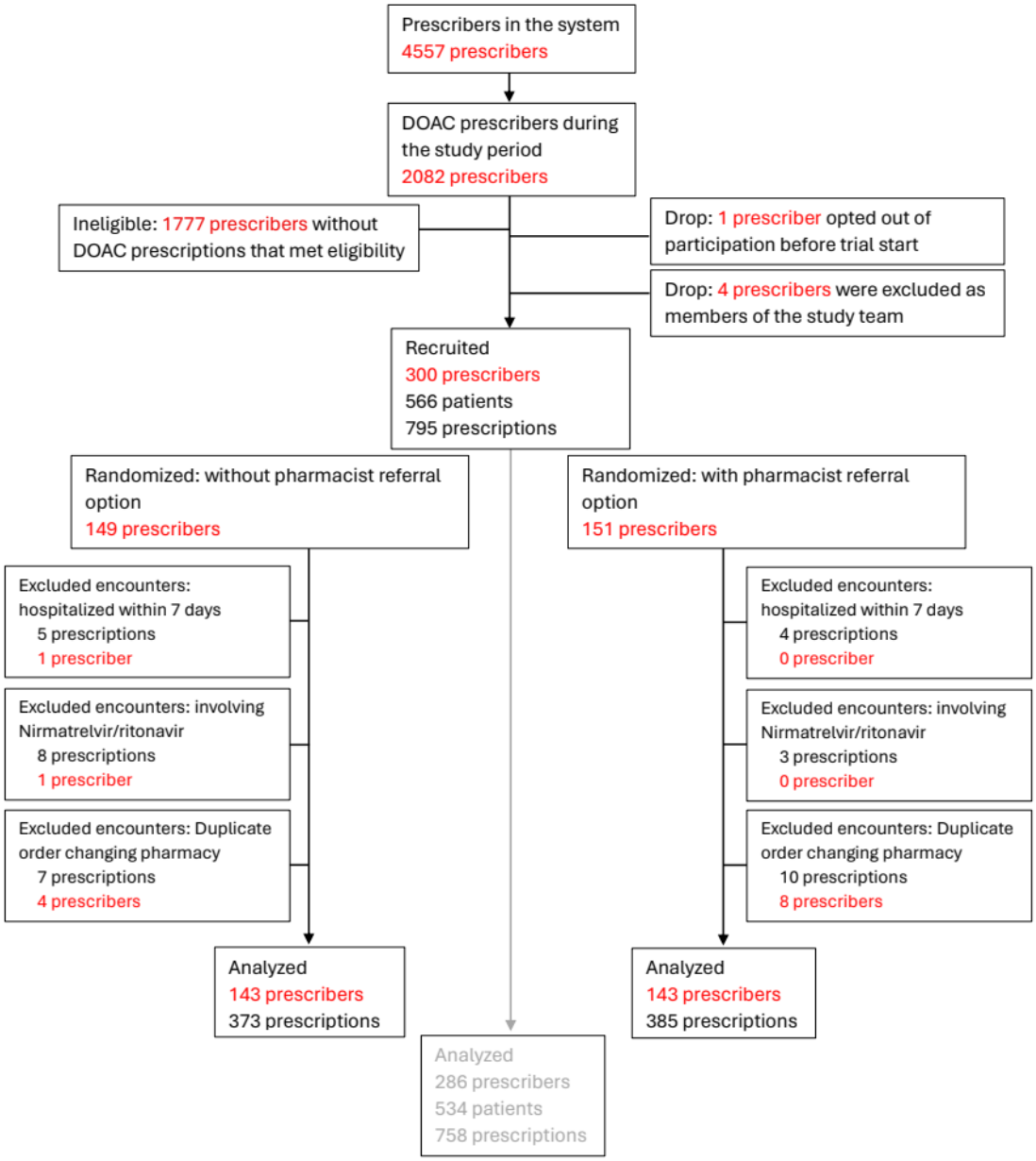
Alerts and Participants

During the trial, 2082 prescribers within the health system prescribed a DOAC medication. Prior to the start of the study, 1 (0.05%) prescriber opted out, and 4 (0.2%) were excluded due to study affiliation. During the study period, 300 (14.4%) prescribers had at least one inappropriate DOAC prescription that triggered an alert, resulting in their randomization to either of the 2 alert groups. Among all 20,470 patients with an active ambulatory DOAC prescription during the study period, 566 (2.8%) triggered at least one alert.

The 300 randomized prescribers triggered a total of 795 inappropriate prescription alerts; of these, 37 (4.7%) were excluded from analyses due to patient hospitalization within 7 days of the alert, concomitant use of nirmatrelvir/ritonavir, or a technical error (eg, an alert was triggered by a duplicate order of an existing appropriate prescription when the prescriber intended to change the designated pharmacy). After these exclusions, subsequent analyses included 758 prescriptions that triggered alerts for 286 prescribers (Figure 1; Multimedia Appendix 3) [19]. Most alerts occurred in patients with existing DOAC prescriptions (653/758, 86.1%), while a minority involved new DOAC prescriptions (105/758, 13.9%).

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram. Prescribers were excluded when all alerts associated with them were excluded for the specified reasons and an alert associated with a prescriber no longer existed. DOAC: direct oral anticoagulant.



Prescriber Characteristics

Of 286 randomized prescribers included in the analysis, 32 (11.2%) were trainees, 149 (52.1%) were primary care clinicians, and 105 (36.7%) were specialist clinicians. Most prescribers were attending physicians (68.9%), followed by nurse practitioners (15.7%), residents (11.2%), and physician assistants (4.2%; Table 1). Relative to the population of DOAC prescribers without an alert, these 286 prescribers who received alerts comprised more primary care clinicians (52% vs 16%) and fewer residents (11% vs 40%). Prescribers with one or more DOAC alerts had a higher median volume of pretrial DOAC prescriptions than prescribers without any DOAC alerts (median 48 vs 5; Table S1 in Multimedia Appendix 4).

The randomized prescribers had one or more alerts triggered by their prescriptions during the trial: 148 (51.8%) prescribers received a single alert, while 138 (48.2%) received multiple alerts (range 2-20; median 3, IQR 2-5). Of the 138 prescribers who had multiple alerts, 75 had a single alert triggered by multiple patients, 16 had multiple alerts for a single patient, and 47 had patients that triggered both single and multiple alerts.

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Table 1. Provider-level characteristics by alert randomization.

Characteristic	All (N=286), n (%)	No pharmacist referral option (N=143), n (%)	Pharmacist referral option (N=143), n (%)
Provider role			
Resident	32 (11.2)	16 (11.2)	16 (11.2)
Primary care	149 (52.1)	73 (51.1)	76 (53.2)
Specialty	105 (36.7)	54 (37.8)	51 (35.7)
Provider type			
Nurse practitioner	45 (15.7)	23 (16.1)	22 (15.4)
Physician	197 (68.9)	99 (69.2)	98 (68.5)
Physician assistant	12 (4.2)	5 (3.5)	7 (4.9)
Resident	32 (11.2)	16 (11.2)	16 (11.2)
DOAC[a] prescriptions pretrial			
Fewer (0-5; 1st tertile)	98 (34.3)	48 (33.6)	50 (35.0)
Medium (6-20; 2nd tertile)	94 (32.9)	50 (35.0)	44 (30.8)
More (21-86; 3rd tertile)	94 (32.9)	45 (31.5)	49 (34.3)

[a]DOAC: direct oral anticoagulant.

Patient Characteristics

Patient characteristics at the time of alerts, including age, weight, gender, presence of impaired renal function, and polypharmacy (ie, 5 or more prescribed medications), were balanced between study arms (Table 2). During the trial, 758 prescriptions were included across 534 unique patients. Among the 534 patients, 460 (86.1%) patients were managed by a single provider, 35 (6.6%) patients were managed by multiple providers who were randomized to the same study arm, and 39 (7.3%) patients were managed by at least one provider randomized to each study arm. These 39 patients were counted in both arms for comparing patient characteristics.

Table 2. Patient characteristics by alert randomization[a].

Characteristic	All (N=758)	No pharmacist referral option (N=373)	Pharmacist referral option (N=385)
Age, mean (SD)	81.2 (10.2)	81.0 (10.8)	81.4 (9.6)
Age (years), n (%)			
>70	672 (88.7)	327 (87.7)	345 (89.6)
Weight (kg), mean (SD)	77.7 (19.6)	77.0 (20.7)	78.3 (22.1)
Sex, n (%)			
Female	393 (51.9)	201 (53.9)	192 (49.9)
Polypharmacy, n (%)	657 (86.7)	309 (82.8)	348 (90.4)
Impaired renal function (CrCl[b] ≤ 60), n (%)	582 (76.8)	276 (74)	306 (79.5)
VTE[c] (vs AF[d]), n (%)	22 (2.9)	15 (4)	7 (1.8)
Apixaban (vs rivaroxaban), n (%)	549 (72.4)	255 (68.4)	294 (76.4)

[a]All values are n (%) unless otherwise specified.

[b]CrCl: creatinine clearance.

[c]VTE: venous thromboembolism.

[d]AF: atrial fibrillation.

Reasons for Alerts and Alert Fidelity

The majority of alerts were triggered by an inappropriate prescription for apixaban (528/758, 69.7%), followed by a prescription for rivaroxaban (194/758, 25.6%), drug-drug interaction contraindications (26/758, 3.4%), and inappropriate use of a starter pack (10/758, 1.3%; Table 3).

Of 758 alerts included in analyses, 47 (6.2%; 28 without a referral option and 19 with a referral option) alerts were found to have been sent in error. In all cases, these alerts were triggered when prescriptions used free-text instructions and when dosing and frequency were not captured in structured data elements, resulting in erroneous alerts. We excluded these cases in a sensitivity analysis to ensure robustness of the main study

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findings. After excluding these 47 alerts, independent clinical pharmacists' adjudication found no additional alerts were sent in error.

With respect to pharmacists' engagement among prescribers, of 385 alerts that included a link to the pharmacist referral option, the pharmacy referral was requested directly through the alert in 14 (3.6%) alerts.

Table 3. Reasons for alerts by alert randomization.

Reasons for alerts and prescribed DOAC[a]	All (N=758), n (%)	No pharmacist referral option (N=373), n (%)	Pharmacist referral option (N=385), n (%)
Dose too low			
Apixaban	425 (56.1)	194 (52.0)	231 (60.0)
Rivaroxaban	85 (11.2)	45 (12.1)	40 (10.4)
Dose too high			
Apixaban	103 (13.6)	49 (13.1)	54 (14.0)
Rivaroxaban	109 (14.4)	62 (16.6)	47 (12.2)
Contraindication: AF[b]			
Apixaban	4 (0.5)	2 (0.5)	2 (0.5)
Rivaroxaban	10 (1.3)	6 (1.6)	4 (1.0)
Contraindication: VTE[c]			
Apixaban	11 (1.5)	7 (1.9)	4 (1.0)
Rivaroxaban	1 (0.1)	1 (0.3)	0 (0.0)
Starter pack refill			
Apixaban	6 (0.8)	3 (0.8)	3 (0.8)
Rivaroxaban	4 (0.5)	4 (1.1)	0 (0.0)

[a]DOAC: direct oral anticoagulant.

[b]AF: atrial fibrillation.

[c]VTE: venous thromboembolism.

Prescription Changes (Overall and by Study Arm)

Overall, 219/758 (28.9%) medication alerts for inappropriate initial DOAC prescriptions resulted in any prescription change within 7 days from the alert being sent. Importantly, 13 patients switched from one anticoagulant to another in response to medication alerts: 7 from a DOAC to another DOAC, 1 from a DOAC to warfarin, and 5 from a DOAC to another non-DOAC (Table S2 in Multimedia Appendix 4). Of 286 prescribers, 47.9% (n=137) made a change in response to at least one of their alerts. In the 14 patients for whom a clinical pharmacist referral was placed from the medication alert, no prescription changes occurred beyond 7 days that directly related to the referral.

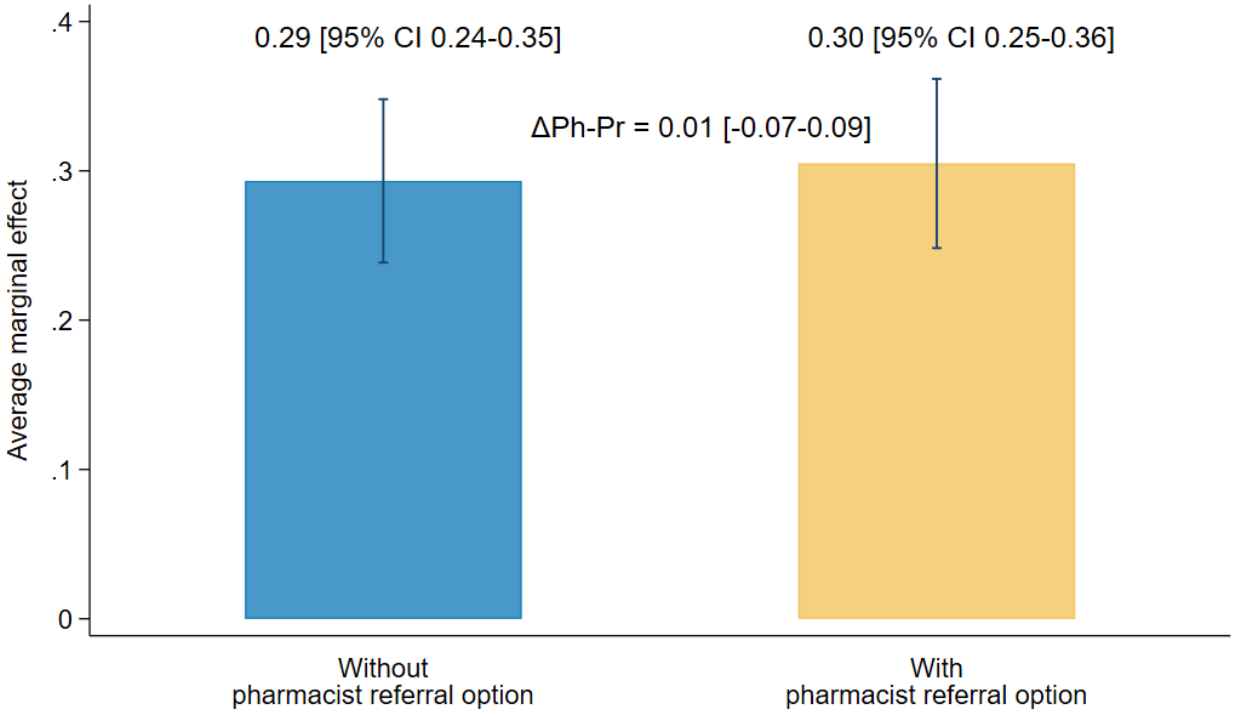
Over the 29-month study, the percentage of alerts resulting in a prescription change stayed largely level, from 29% in month 1 to 31% in month 29 (estimated linear marginal effect of time = 0.1 percentage points per month, 95% CI –0.3 to 0.5 percentage points per month).

The percentage of medication alerts that resulted in a prescription change did not differ across the 2 study arms (difference=1 percentage point higher for alerts with a pharmacist referral option, 95% CI 7 percentage points lower to 9 percentage points higher, *P*=.77; Figure 2). Sensitivity analyses, including analyses that dropped erroneous alerts and that included a patient-level random effect to account for multiple alerts per patient, found similar, nonstatistically significant differences between the 2 arms (Tables S3-S5 in Multimedia Appendix 4). The comparative effectiveness of the 2 medication alerts did not differ by prespecified moderators, except for the reasons for alerts (Table S6 in Multimedia Appendix 4). The alerts with a pharmacist referral option were more effective for dose-too-high alerts (13 percentage points higher for alerts with a pharmacist referral option), compared to dose-too-low alerts (2 percentage points lower); the difference in differences was 15 percentage points (90% CI 2 to 28 percentage points higher).

Medication alerts continued to be used throughout the 29-month study period. After operational review, the decision was made to continue use of the EHR alert that included the clinical pharmacist referral option after completion of the study.

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Figure 2. Change to direct oral anticoagulant prescription by medication alerts: average marginal effect by study arm.



Appropriateness of Prescription Changes (Overall and by Study Arm)

Of the 219 alerts that resulted in a prescription change, 213 (97.3%) led to a recommended medication change, while 6 (2.7%) alerts led to a change not recommended by the alert. Prescribers in all 6 (100%) cases provided a justification for not making the recommended change. When reviewed by the research team, 3 of the 6 (50%) changes were deemed clinically appropriate medication changes and 3 (50%) were clinically inappropriate. One inappropriate change occurred in the arm with a pharmacist referral option (0.3%) and 2 in the arm without (0.5%).

Adverse Events (Overall and by Study Arm)

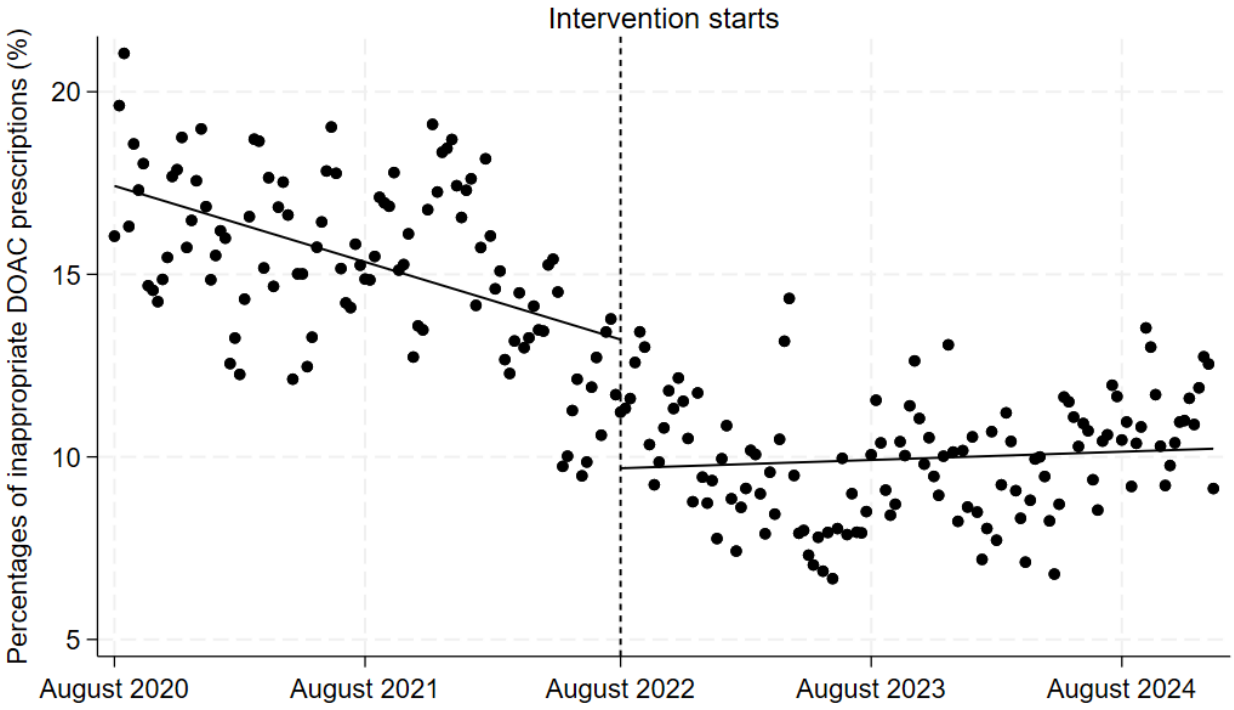
Within 30 days of an alert being sent, we identified 42 adverse events (related to 39 [5.1%] alerts). Of the 39 alerts that led to one or more adverse events, 16 (41%) involved bleeding or clotting events, and the remaining 23 (59%) did not involve bleeding or thrombotic events. The 16 adverse events involving bleeding or clotting were evenly split across study arms (9 events in alerts with a pharmacy referral option and 7 events in alerts without a pharmacy referral option). After the study, 2 clinical experts reviewed these 16 adverse events to evaluate whether they were (1) related to medication mismanagement, and/or (2) had any potential relationship to alert recommendation or study arm. In total, 2 bleeding events were adjudicated as being related to inappropriate medication management (one event in each study arm [0.3%]). In both cases, the alert recommended that the prescriber reduce the rivaroxaban dose, but the medication was not changed within 7 days.

Results for Second Research Question: System-Level Change in Inappropriate DOAC Prescribing

We conducted a secondary analysis of both alerts in aggregate to determine how they impacted the proportion of inappropriate DOAC prescriptions over time across the full health system (Figure 3; Table S7 in Multimedia Appendix 4). Two years prior to initiating the DOAC medication alerts, the baseline proportion of inappropriate DOAC prescribing was estimated at 17.4%. Prior to the implementation of the medication alerts, this proportion decreased by an average of 0.04 percentage points per week (95% CI –0.06 to –0.02 percentage points). Immediately after starting the medication alerts, inappropriate prescriptions decreased by 3.5 percentage points (95% CI –5.2 to –1.8 percentage points), to 9.7%. Since the alert implementation, the proportion of inappropriate prescribing has remained largely static (postintervention slope of 0.004 percentage points per week, 95% CI –0.01 to 0.02 percentage points).

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Figure 3. Time series plot of the proportion of inappropriate direct oral anticoagulant (DOAC) prescriptions with an intervention of the medication alert commencement.



Discussion

Principal Findings

This paper reported on 2 linked evaluations designed to inform health system use of interruptive alerts to improve evidence-based medication prescribing. First, within one large health system, we randomized prescribers who wrote at least one inappropriate DOAC prescription to receive 1 of 2 real-time interruptive EHR alerts, with and without an embedded referral option for clinical pharmacist assistance. The goal was to determine whether the referral option improved the effectiveness of alerts. While we were pleased to see that nearly 30% of alerts resulted in an inappropriate prescription being modified within 7 days, including the clinical pharmacist referral option did not increase the number of inappropriate prescriptions modified. However, our second evaluation showed that implementing this alert system was likely effective at improving the overall rate of appropriate DOAC prescribing. Specifically, the medication alerts were associated with a 3.5-percentage-point reduction in the absolute rate of inappropriate DOAC prescribing, an effect that was largely sustained over the following 2 years. Given a 20%-30% increased risk of bleeding and thromboembolic complications with inappropriate DOAC dosing [20], this could be associated with a substantial reduction in patient harm.

Implications for Designing Antithrombotic Stewardship Systems

The neutral finding from our comparison of 2 types of interruptive medication alerts, including one that attempted to more efficiently integrate clinical pharmacists into clinical decision-making, provides important insight into how medication safety interventions should be designed and deployed. Most notably, although a clinical pharmacist referral pathway was well aligned with existing antithrombotic stewardship models in this health system, prescribers infrequently used it. Specifically, fewer than 1 in 20 alerts with an option for clinical pharmacist review used this option. Given the low use rate, it is not surprising that clinicians presented with the alert including a referral option responded at a similar rate to clinicians presented with an alert that did not include the referral option. Rather, the design of alerts themselves, which included a clear explanation of the specific dosing error, the consequence of that error, and specific information on how to change the prescription, was most likely the primary driver of the changes that were made to inappropriate DOAC prescriptions. Importantly, the low use of the clinical pharmacist referral option could also be influenced by the location and relative lack of visual prominence in the alert design and choice architecture. This underpins the need to engage in a user-centered design process to maximize impact and minimize fatigue related to interruptive CDS alerts [12].

Our results complement—and extend—the antithrombotic stewardship literature, specifically demonstrating the value of pharmacist-enabled population management tools. Prior multicenter evaluations of DOAC dashboards (asynchronous, noninterruptive alerts) in the Veterans Health Administration and in our academic center found that clinical pharmacist review of dashboard-identified cases reduced off-label dosing and, in some settings, was associated with fewer thromboembolic events [8,9]. In those programs, clinical pharmacists primarily worked after the order was placed, contacting prescribers to correct therapy. By contrast, this trial moved the stewardship intervention “upstream” to the moment of prescriber ordering. And the overwhelming majority of inappropriate DOAC

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prescriptions that changed did not require clinical pharmacist involvement. Simultaneously with the implementation of these upstream alerts, we saw a sharp drop in unsafe prescribing, with less downstream labor required for clinical pharmacists to review dashboard-identified off-label prescribing. However, fewer than 1 in 3 inappropriate DOAC prescripts were changed after the interruptive medication alert. This suggests a potentially complementary model: synchronous point-of-order alerts prevent errors before a patient ever picks up an inappropriate prescription, while clinical pharmacist-staffed population dashboards remain valuable for longitudinal surveillance and complex follow-up. This is notable given our recently completed trial of asynchronous EHR messaging, which targeted either prescribers or clinical pharmacists. While there was no statistical difference in the overall rate of DOAC prescribing change between the 2 arms, the clinical pharmacists appear to apply more nuanced decision-making when identifying which patients should have their DOAC prescription changed. As such, continued involvement of clinical pharmacists in ambulatory antithrombotic stewardship efforts remains well justified.

Importantly, although this study was not designed to evaluate population management DOAC dashboards, our results provide observational evidence of the combined effect of dashboards and interruptive medication alerts. Specifically, the health system where this study took place adopted a clinical pharmacist-run DOAC dashboard in 2020. As such, the preimplementation downward slope in inappropriate prescribing we observed is likely due to the effects of this dashboard. Furthermore, the slow but steady reduction in inappropriate DOAC prescribing is also consistent with previous reports in which clinical pharmacists use dashboards to curate caseloads and close care gaps over time. In the Veterans Health Administration experience, earlier and more intensive adoption of the dashboard correlated with larger declines in off-label dosing [9]; our own prealert trend likely reflects similar pharmacist-driven gains. The step change we detected at the onset of synchronous alerts suggests that changing where and when the signal is delivered—at order entry rather than via retrospective review—can further improve the efficient prescribing of appropriate medications. In practical terms, this means fewer wasted dispensations and faster remediation for patients, benefits echoed in evaluations of role-tailored CDS and human factors–informed alert design.

Findings from this trial also align with prior work in human factors and user-centered design research, demonstrating that CDS interventions are most effective when they are timely, informative, actionable, and embedded directly within clinical workflows [12,21,22]. In this context, dashboard-based review and point-of-order alerts should be viewed as complementary rather than competing strategies within a comprehensive antithrombotic stewardship program. This aligns with prior studies highlighting the importance of tailoring CDS to individual clinician roles (eg, prescribers and clinical pharmacists), which can mitigate alert fatigue and improve evidence-based medication prescribing [14].

It is important to consider the resources used and the costs of developing, implementing, and sustaining CDS interventions. For this study, we made a significant resource investment to design the medication alerts using a 3-stage, user-centered design process [23]. We partnered with an external software development company to elicit end user feedback on iterative medication alert designs. In the future, this could be accomplished internally, but ideally would still use multiple rounds of end user feedback and iterative design modifications. We programmed and implemented the medication alert through our normal EHR enhancement processes, avoiding excess cost or resource use. Although rarely used during this trial, engaging clinical pharmacists in our anticoagulation clinic typically requires about 1 hour to review a case and make a medication recommendation. This aligns with ongoing work by this existing team of 4 clinical pharmacists within the ambulatory anticoagulation management service. As such, a health system with an existing EHR and clinical pharmacists actively engaged in antithrombotic stewardship can implement and sustain a CDS stewardship intervention similar to the one in this trial with a one-time, modest investment of resources.

This study also contributes to the broader literature on alert fatigue and CDS stewardship. Numerous studies have shown that excessive interruptive alerts lead to overrides and diminished effectiveness, even when alerts target clinically important safety issues [14]. Our findings reinforce recommendations that prioritize high-value alerts, suppress duplicative or low-yield notifications, and tailor interventions by clinical role. The relatively high acceptance rate of the medication alert in this study likely reflects prior investment in user-centered design, clear presentation of rationale, and concrete prescribing recommendations [23]—features that have been shown to increase clinician trust and adherence to CDS guidance [12]. Future analyses will examine whether there are further ways to tailor when and which medication alerts are delivered.

Limitations

Several limitations should be considered when interpreting this study's findings. First, this randomized trial was conducted within a single academic health system with an established antithrombotic stewardship program. While this system was suppressed to enable robust evaluation of the primary outcome in our provider-level randomized trial, the intervention effects still reflect this broader context. Thus, the findings may not be generalizable to other systems without preexisting antithrombotic stewardship. Second, the primary outcome for our comparative effectiveness study focused on prescription changes within 7 days and may not capture delayed but appropriate modifications, such as changes in patient clinical status (eg, fluctuations in renal function and new comorbidities).

Third, for our system-level evaluation, other quality improvement efforts adjacent to anticoagulant prescribing may have influenced prescriber behavior. While we intentionally suppressed DOAC medication alerts on the DOAC Dashboard during this study period to isolate the effect of synchronous, interruptive medication alerts, the spillover effect from other quality improvement efforts cannot be completely excluded. Specifically, these other causes may be responsible for some of the reduction in inappropriate prescribing around the time of alert system implementation or may have improved the overall

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rate of prescription change following alerts. However, the short timeframe during which the drop in inappropriate prescribing occurred (captured by the intercept shift) and its alignment with the alerts being activated strongly suggest that this specific action was likely responsible for much of the change. Further, while other efforts may have improved prescriber behavior change following an alert, we do not believe these other efforts are likely to have had any effect on our comparative effectiveness evaluation, as exposure to these other efforts was likely evenly distributed across treatment arms. Additionally, we were unable to capture the total time spent by clinical pharmacists reviewing cases that were referred through the medication alert. Finally, the secondary research question of a system-level change in response to the medication alert relied on an ISTA rather than patient- or clinician-level randomization. As such, we can only comment on associations between the introduction of the medication alerts and change in inappropriate DOAC prescribing.

Conclusion

In summary, this randomized trial demonstrates that while adding a clinical pharmacist referral pathway to interruptive alerts did not lead to high levels of clinical pharmacist engagement or improve short-term prescription change rates, implementing well-designed, synchronous prescriber alerts was associated with substantially reduced inappropriate DOAC prescribing. Furthermore, these alerts reduced reliance on labor-intensive clinical pharmacist medication review. In total, these findings support an antithrombotic stewardship care delivery model that emphasizes both preventing prescribing errors and strategically deploying pharmacist expertise to maximize patient safety and efficiency. By shifting the inappropriate medication prescription intervention from a retrospective dashboard review to the moment of ordering—and by formally testing alert variants prior to broad deployment—this study addresses key knowledge gaps about how to deliver high-value anticoagulant stewardship while reducing unnecessary alert burden and focusing clinical pharmacist expertise where it is most needed.

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Data Availability

Datasets generated and analyzed in this study are available from the corresponding author upon reasonable request (deidentified).

Generative AI Use

The authors declare that no generative AI tools were used in the preparation of this manuscript.

Authors' Contributions

Conceptualization: GB, SNS, MPD, MSML
Data curation: SNS, SYC, GB, MSML, FJS, JE, MF
Formal analysis: SNS, GB, MSML, SYC, JE
Software: MSML
Writing – original draft: GB, SNS, FJS, SYC, MF, MPD, MSML
Writing – review & editing: GB, SNS, FJS, SYC, MF, MPD, MSML, JE, AS

Conflicts of Interest

SNS provided consulting to Pfizer. MSML is a consultant for the Anticoagulation Forum. GB received grant funding from Boston Scientific; provided consulting to Pfizer, Bristol-Myers Squibb, Janssen, Bayer, AstraZeneca, Sanofi, Anthos, Abbott Vascular, and Boston Scientific; and is on the board of directors of the Anticoagulation Forum. All other authors have no conflicts of interest to disclose.

Multimedia Appendix 1

Food and Drug Administration guidelines and drug-drug interaction chart.
[DOCX File , 14 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Sample alert message.
[DOCX File , 1084 KB-Multimedia Appendix 2]

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Multimedia Appendix 3

CONSORT-EHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1105 KB-Multimedia Appendix 3]

Multimedia Appendix 4

Supplementary results regarding provider-level characteristics, specific instances of anticoagulant switches by randomization arm, and changes to prescription by medication alert.
[DOCX File , 26 KB-Multimedia Appendix 4]

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Abbreviations

AF: atrial fibrillation
CDS: clinical decision support
CrCl: creatinine clearance
DOAC: direct oral anticoagulant
EHR: electronic health record
FDA: Food and Drug Administration
ICC: intraclass correlation coefficient
ITSA: interrupted time series analysis
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
VTE: venous thromboembolism

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