Anticoagulation stewardship: Descriptive analysis of a novel approach to appropriate anticoagulant prescription

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Abstract

Background: Anticoagulants are a leading cause of morbidity among hospitalized patients, with prescription errors commonly reported. Literature surrounding anticoagulation stewardship is scarce despite its documented effectiveness in the antimicrobial realm.

Objective: To determine the proportion of accepted recommendations on inappropriate anticoagulant prescriptions suggested by a multidisciplinary anticoagulation stewardship program (ASP).

Methods: We conducted a descriptive cohort study of hospitalized patients using therapeutic anticoagulation at a large Canadian tertiary care center between September 1, 2019, and February 28, 2020. A multidisciplinary ASP, composed of physicians and pharmacists, was implemented on June 1, 2019. Patient-, anticoagulant-, and admission-related characteristics were collected. The primary outcome was the proportion of accepted ASP team recommendations by the prescribing team.

Results: A total of 381 patients were enrolled during the study period, resulting in 553 anticoagulant reviews (1.56 reviews/patient) by the ASP. The most common indications for anticoagulation were atrial fibrillation (n = 276, 72%) and venous thromboembolism (n = 84, 22%). Direct oral anticoagulants were most frequently prescribed (n = 253, 67%), followed by vitamin K antagonists (n = 88, 23%). Among the reviewed prescriptions, 355 of 553 (64%) generated a recommendation; 299 of 355 (84%) recommendations were accepted by the treating team. Dose adjustments were the leading category of recommendations (31%), followed by alerts regarding drug interactions (19%).

Conclusion: Inpatient anticoagulant prescriptions were optimized following recommendations by the ASP team. The most frequent types of prescription changes concerned dose adjustments and drug interactions. Further research is required to assess the effect of an ASP on clinical outcomes.
1 | BACKGROUND

Anticoagulants are among the most commonly prescribed medications in North America. They are primarily used for prevention of stroke in patients with atrial fibrillation and for prevention and treatment of venous thromboembolism (VTE). With an aging population, anticoagulant prescriptions are on the rise. National prescription trends in Canada from 2014 reached 7,000,000 oral anticoagulant prescriptions; a noteworthy increase from the 4,800,000 in 2008.

Anticoagulants are a leading cause of emergency department visits for adverse drug events, appearing in 14.9% of cases overall, and among patients aged >65 years, were the most frequent type of medications associated with such visits (4.5 [95% confidence interval, 2.3–6.7] per 1000 population). Appropriate dosing of anticoagulation is important to reduce events such as bleeding, cardiovascular hospitalizations, and all-cause mortality. One retrospective review assessing compliance with best-practice recommendations for all anticoagulant classes showed high rates of inappropriate prescribing, with 12% of “non-adherence” to indication and 36.5% of “nonadherence” to dose recommendations. Higher adverse drug events in the nonadherent group compared to the adherent group (34% vs 11%, respectively; odds ratio [OR], 3.9; 95% confidence interval [CI], 0.9–15.3; P = .05) were noted.

Over the past decade, there has been a shift toward favoring direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs). The introduction of several molecules, along with expanding indications and rapidly evolving literature, has contributed to the complexity of DOAC prescribing. Factors such as age, weight, kidney function, and medication interactions must be considered when prescribing DOACs. Furthermore, different indications can be associated with different dosing regimens. Consequently, inappropriate DOAC prescribing is reported: the Systematic Assessment of Geriatric Elements in Atrial Fibrillation cohort (which included 460 patients on a DOAC) demonstrated 23% and 13% inappropriate dosing, respectively. Another retrospective study of 770 patients on DOACs demonstrated 23% and 13% inappropriate dosing, respectively. Interestingly, underdosing of DOACs has been found to be the most common error.

Multidisciplinary stewardship programs have been effective in reducing inappropriate prescriptions in domains such as antimicrobials, another class of medications with previously elevated estimates of inappropriate use. The concept of stewardship originated from the discipline of infectious diseases in 1996, with the overarching aim to optimize antibiotic therapy. Within a few years, thousands of publications, including several guidelines, on antimicrobial stewardship became available, outlining various effects of stewardship programs such as reduced adverse events, decreased health care costs, and improved clinical outcomes.

This concept has started to emerge in the anticoagulation realm with hopes of achieving similar success, though there is still sparsity in the literature. In 2019, the Anticoagulation Forum published a guide on the core elements of anticoagulation stewardship programs emphasizing their necessity based on the complexity, variety, and dangers of the anticoagulant arsenal. Anticoagulation stewardship is defined as “coordinated, efficient, and sustainable system-level initiatives designed to achieve optimal anticoagulant-related health outcomes and minimize avoidable ADEs [adverse drug events] through: 1) the application of optimal evidence-based care, 2) the appropriate prescribing, dispensing, and administration of anticoagulants and related agents, and 3) the provision of appropriate patient monitoring and clinical responsiveness.”

We postulated that a multidisciplinary anticoagulation stewardship program (ASP), designed as per the principles set forth by the Anticoagulation Forum, would optimize anticoagulant prescriptions in the inpatient setting in a large 700-bed tertiary care center in Montreal, Canada.

2 | METHODS

We conducted a descriptive cohort study in adult patients receiving therapeutic doses of anticoagulants at our institution, the Jewish General Hospital, in Montreal, Canada, between September 1, 2019, and February 28, 2020. Anticoagulation status was determined via our hospital electronic prescription software. All patients prescribed therapeutic doses of any anticoagulant on units without dedicated clinical pharmacists, whether initiated before or during their admission, were included. Patients receiving prophylactic or intermediate-dose anticoagulation were excluded.

To optimize anticoagulation prescriptions, an ASP was implemented on June 1, 2019, at our institution. It consisted of three...
clinical pharmacists, one of whom had a background in internal medicine and antimicrobial stewardship, one in cardiology, and one in emergency medicine, sharing a full-time equivalent position, that is, one pharmacist per weekday, and a physician with expertise in thrombosis and anticoagulation and quality improvement. The Jewish General Hospital is composed of 20 units in total, 9 of which have a designated clinical pharmacist. All units receive initial prescription review of all medications, including anticoagulants, by the central pharmacy, and those with designated pharmacists receive additional ongoing clinical follow-up. The ASP pharmacists, in contrast to non-ASP clinical pharmacists, perform a more thorough and targeted assessment of prescriptions of therapeutic anticoagulants. The ASP reviewed prescriptions only on units without a designated pharmacist as a priority target while piloting the program. Appropriateness of prescriptions was judged on the basis of compliance with the most recent Canadian best-practice recommendations from Thrombosis Canada and the Canadian Cardiovascular Society. Criteria assessed for appropriateness were indication; dose; drug-drug interactions; monitoring; and patient characteristics including age, weight, creatinine clearance, and laboratory values. All prescriptions that included a therapeutic dose of any anticoagulant were reviewed, and any criterion for inappropriateness triggered a recommendation by the ASP team directed to the prescribing team. Recommendations were coded according to distinct categories.

The complete process of review is described in detail in Appendix S1.

Our primary outcome was the proportion of accepted ASP recommendations by the prescribing team leading to a prescription change. The proportion of prescriptions requiring a recommendation, proportions of recommendations and acceptance per category of recommendation, and proportions of recommendations and acceptance among different hospital units were also recorded. Clinical secondary outcomes were the occurrence of VTE, arterial thromboembolism (ATE), transfusion of >2 units of packed red blood cells (pRBCs), and/or death after an assessment by the ASP team during each patient’s first admission. VTE included objectively confirmed pulmonary embolism (PE) on computed tomographic pulmonary angiography and/or ventilation perfusion scan and deep vein thrombosis (DVT) on ultrasound Doppler study; ATE included radiologically proven cerebrovascular accident, acute mesenteric ischemia, and acute limb ischemia. All clinical outcomes were reviewed and adjudicated by two independent authors (DW, MK).

Patient-, anticoagulant- and admission-related characteristics were collected from electronic health records and included age; sex; medications; indication for anticoagulation; anticoagulant class, molecule, and dose; admission date; treating physician; hospital unit; and hospital length of stay. Laboratory data consisting of creatinine, hemoglobin, and platelet count at time of first admission along with the occurrence of transfusions, VTE, ATE, and/or death during the admission were also collected for each patient. Each patient was enrolled only once in the study, and data were collected until the occurrence of either (i) discharge from hospital or (ii) death. More than one review per patient was possible given that patients were actively followed throughout the course of their admission, and thus more than one prescription review and recommendation outcome could have been reported.

Descriptive statistics were used to describe patient and anticoagulant baseline characteristics as well as to measure primary and secondary outcomes. Approval for this study was obtained from our institution’s Department of Quality as requested by our Internal Ethics Committee.

### RESULTS

A total of 381 patients admitted to our hospital on therapeutic-dose anticoagulation were reviewed during the study period. More than one review was required in 74 of 381 (19%) patients, resulting in a total of 553 (1.56/patient) anticoagulant reviews performed by the ASP team. The median age of the population was 83 (range, 21-102) years, and 57% were women. The most common indications for anticoagulation were atrial fibrillation (n = 276, 72%), followed by VTE (n = 88, 23%) and prosthetic heart valves (n = 14, 4%). DOACs were the most frequently prescribed anticoagulants (n = 253, 67%), followed by VKAs (n = 88, 23%). All patient baseline characteristics are reported in Table 1.

In total, 355 of 553 (64%) reviews generated a recommendation during the study period, of which 141 of 355 (40%) occurred at the onset of the patient’s admission. A total of 299 of 355 (84%)

| Characteristic | Result (N = 381) |
|---------------|-----------------|
| Age, y. median (range) | 83 (21-102) |
| Female sex, n (%) | 216 (57) |
| Creatinine, µmol/L, mean ± SD | 100 ± 67 |
| Hemoglobin, g/L, mean ± SD | 112 ± 20 |
| Platelet count, ×10^9/µL, mean ± SD | 252 ± 115 |
| ASA use, n (%) | 77 (20) |
| NSAID use, n (%) | 12 (3) |
| Indications for anticoagulation, n (%) | |
| Atrial fibrillation | 276 (72) |
| Venous thromboembolism | 84 (22) |
| Prosthetic heart valve | 14 (4) |
| Acute coronary syndrome | 3 (1) |
| Cerebrovascular accident | 3 (1) |
| Arterial thromboembolism | 1 (0) |
| Type of anticoagulant, n (%) | |
| Direct oral anticoagulant | 253 (67) |
| Vitamin K antagonist | 88 (23) |
| Low-molecular-weight heparin | 35 (9) |
| Unfractionated heparin | 4 (1) |

Abbreviations: ASA, aspirin; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation.
recommendations were accepted by the treating team resulting in an intervention, the primary outcome of interest. Dose adjustments were the leading category of recommendations (112/355, 31%), drug interactions were the second most common (68/355, 19%), and third was ordering laboratory testing (46/355, 13%). The highest proportions of accepted recommendations were for initiation and interruption of anticoagulant (94%), including bridging recommendations and laboratory test (94%) categories; the lowest was for drug change (58%). The most common process of recommendation was a verbal discussion with the treating team, and the process of recommendation with the highest acceptance was verbal orders taken directly by the ASP pharmacist from the prescribing team (100%). Of 56 refused recommendations, nearly one-third (30%) concerned dose adjustments of DOACs and VKAs.

Figures 1 and 2 summarize the recommendations proposed by the ASP team.

Family medicine, geriatrics, and cardiology were the three admitting services that received the most recommendations, amounting to 24%, 19%, and 12%, respectively. Resultant changes, that is, recommendation acceptance, varied between these services and were 90% on the family medicine unit, 87% on the geriatrics unit, and 66% on the cardiology unit, the overall lowest acceptance. Units with the highest acceptance were general surgery (100%), cardiac surgery (93%), orthopedics (94%), and internal medicine (90%).

Secondary outcomes of VTE, ATE, transfusion, death following the initial review by the ASP team until patient discharge, and hospital length of stay (LOS) were as follows: 1 PE, no DVT, and no ATE; 11 of 381 (3%) transfusions of ≥2 units of pRBCs, 31 of 381 (8%) deaths, and mean hospital LOS of 24 days (SD ± 30 days).

4 | DISCUSSION

To our knowledge, our ASP is the first of its kind to be described in a large Canadian tertiary care center. While many other centers benefit from specialized anticoagulation pharmacists, none have published on the creation and implementation of an ASP. In pioneering such a program, we demonstrate optimization of anticoagulant prescriptions among hospitalized patients on therapeutic anticoagulation in our institution. Over a 6-month period, close to 300 prescriptions were improved to conform to Canadian best-practice recommendations. We noted both a high proportion (64%) of prescriptions requiring a recommendation, that is, meeting at least one inappropriate criterion, and a high proportion (84%) of acceptance of these recommendations, demonstrating an enthusiasm for anticoagulation stewardship from prescribers.

There have been other reports outside of North America showing benefits of ASPs, albeit limited in numbers. Perlman et al. reported on the impact of a pharmacist-led initiative to improve DOAC use in hospitalized patients. This clinical pharmacists’ team, in collaboration with coagulation specialists, did a retrospective evaluation of the appropriateness of DOAC prescriptions among 585 patients.

In their case, 36% of medication orders for DOACs required a recommendation by the clinical pharmacist, with 76% of these leading to a change by the physician. While our proportions of accepted recommendations were comparable, our recommendation proportions were higher, possibly explained by the fact that we reviewed all anticoagulants classes rather than restrict our program to DOACs only. Much of the literature on inappropriate anticoagulation prescriptions pertains to DOACs; however, other classes of anticoagulation are susceptible to errors and thus ASPs targeting all classes of anticoagulation will yield more significant results. Expanding ASPs to ambulatory populations could be of interest since a significant proportion of recommendations occurred at the time of admission, highlighting that inappropriate anticoagulant prescriptions are pervasive in the outpatient setting as previously reported. In fact, a prior study noted off-label dosing of DOACs in 9.4% of outpatients in a Michigan collaborative (Michigan Anticoagulation Improvement Initiative) and by means of a programmed alert prompting direct
contact with the prescribing physician, meaningful prescription changes were made in 63% of cases. There is also emergence of technologies to aid and support oversight of DOAC prescription and compliance with best practices.

Recent prospective studies have analyzed the impact of anticoagulation stewardship on adherence to guidelines and on clinical outcomes of safety and efficacy. Dreijer et al conducted two before-and-after interventional studies in which the intervention was the addition of an ASP team. The first study revealed significantly higher overall adherence during the intervention period (497/660, 75.3%) compared to the usual care period (395/623, 63.4%) (OR, 1.76; 95% CI, 1.38-2.24). The second noted a reduction, albeit nonsignificant, from 14.3% to 13.1% during the intervention period of the composite end point of one or more bleeding episodes or one or more more thrombotic events from hospitalization until 3 months after. Note that all-cause mortality in this latter study was significantly lower during the intervention period (81/945, 8.6% vs 108/941, 11.5%; OR, 0.72; 95% CI, 0.53-0.98). These results highlight that increasing appropriateness of anticoagulant prescriptions, as was done in our study, can lead to improved safety and efficacy outcomes, including all-cause mortality.

A limitation of our study is its retrospective, single-center design. Access to clinical pharmacists with interest in anticoagulation, along with certain prescribing privileges, is readily available at our institution, allowing for minimal implementation challenges for our ASP. This likely contributed to our impact, which may not be easily reproduced in other centers. Interinstitutional consultation, along with presentation of our model by means of conferences, workshops, and publication, are potential mitigation strategies to increase availability. Another limitation was that our study was not designed to detect clinical end points as a primary outcome, and thus conclusions regarding the impact of our ASP on safety and efficacy of anticoagulants cannot be inferred. Finally, in the absence of a control group, we cannot rule out the possibility that secular trends improving prescribers’ habits influenced our results; however, no consistent trend in prescription appropriateness over time was detected, and our study period was rather short for this to have occurred. We also cannot definitively state that all of the prescription changes, in particular within certain categories such as dose adjustment for VKAs, would not have occurred without the ASP, as prescribers may have taken similar actions in its absence. Future, larger prospective studies examining these issues are warranted. We plan a further study to determine clinical outcomes among patients with accepted stewardship recommendations compared to those with refused recommendations. Our program will be extended to our institution’s affiliated rehabilitation and long-term care centers to ascertain its impact among patients who are hospitalized beyond the acute care setting.

5 | CONCLUSION

We demonstrate that anticoagulation stewardship leads to optimization of anticoagulant prescriptions in hospitalized patients on therapeutic doses of anticoagulation. Dose adjustments and drug interactions comprised categories of recommendations with the highest acceptance, narrowing down areas for future more targeted studies. Larger, prospective studies measuring the impact of anticoagulation stewardship in expanded settings and on clinical outcomes are required.

AUTHOR CONTRIBUTIONS

MK and RK were primary contributors to manuscript redaction, followed by HM and DW. NK contributed to data collection. SK reviewed the manuscript and provided administrative support.

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RELATIONSHIP DISCLOSURE

The authors of this study do not have any conflicts of interest to declare related to this work.

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**SUPPORTING INFORMATION**

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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