Direct Oral Anticoagulants in the Real World: Insights into Canadian Health Care Providers' Understanding of Medication Dosing and Use

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Abstract

Background: Direct-acting oral anticoagulant (DOAC) use is increasing in Canada. This study evaluated nurse, staff physician, and resident physician understanding of DOAC dosing and administration.

Methods: An electronic survey was distributed to health care providers (HCPs) at a hospital in Ontario, Canada. The questions discussed oral anticoagulant indications, dose adjustments, storage and administration, and counselling.

Results: A total of 52 responses were received: 3 from nurses, 1 from a nurse practitioner, 21 from staff physicians (Hematology, Thrombosis Medicine, General Internal Medicine, Neurology), 25 from resident physicians, and 2 unspecified respondents. Twenty-four respondents (46%) felt comfortable or very comfortable prescribing DOACs. Only 15 (29%) knew that dabigatran should not be exposed to moisture and 13 (25%) knew that higher doses of rivaroxaban should be taken with food.

Conclusion: HCP understanding of DOACs is variable. Though they express comfort with DOACs, their self-reported knowledge of dosing, administration, and patient counselling is incomplete.

Résumé

Contexte: L'utilisation d'anticoagulants oraux directs (AOD) est en hausse au Canada. La présente étude évalue la connaissance qu'ont les infirmières et les médecins (membres du personnel et résidents) de l'administration et du dosage des AOD.

Méthodologie: Un sondage en ligne a été effectué auprès des fournisseurs de soins de santé (FSS) d'un hôpital en Ontario, Canada. Les questions portaient sur les indications, l'adaptation posologique, l'entreposage et l'administration des anticoagulants oraux, ainsi que la démarche de conseil au patient.

Résultats: Les 52 répondants se répartissent ainsi : 3 infirmières; 1 infirmière praticienne; 25 médecins membres du personnel (hématologie, thrombose, médecine interne générale et neurologie); 25 médecins résidents. Deux répondants n'ont pas précisé leur statut. Vingt-quatre répondants (46 %) se sentent à l'aise ou très à l'aise de prescrire des AOD. Seulement 15 répondants

(29 %) savaient que le dabigatran ne doit pas être exposé à l'humidité et 13 (25 %) savaient que les doses plus élevées de rivaroxaban devaient être prises avec de la nourriture.
Conclusions: La connaissance qu'ont les FSS des AOD est variable. Les FSS se disent à l'aise de travailler avec les AOD, mais, d'après ce qu'ils rapportent, leur savoir en matière de dosage, d'administration et de conseil au patient comporte des lacunes.

In recent years, an increasing number of direct oral anticoagulants (DOACs) have become available. DOACs appear to be effective, safe, and convenient alternatives to warfarin.[1–8] The 4 available DOACs in Canada are dabigatran, apixaban, rivaroxaban, and edoxaban and are approved by Health Canada for the prevention of stroke and systemic embolism in patients with atrial fibrillation and for treatment and secondary prevention of venous thromboembolism (VTE).

DOACs come with specific recommendations for storage and administration. Dabigatran should not be exposed to moisture as this results in its breakdown and loss of potency.[9,10] Moreover, dabigatran should be taken as a whole capsule, and not crushed or chewed. Modifying the capsule can lead to increased absorption and potentially increased risk of bleeding.[9] Rivaroxaban at higher doses should be administered with food.[10] If it is taken when fasting, its bioavailability is reduced by one third, thereby resulting in potentially increased risk of thrombosis.[11]

Given that laboratory monitoring of DOACs is not routinely performed, it is crucial to ensure that these medications are administrated according to manufacturer's recommendations. It is unclear whether DOACs are appropriately prescribed for indications currently approved by Health Canada, and whether patients are advised on optimal administration. Ideally, HCPs should counsel patients about appropriate DOAC use, however their understanding of this issue is unknown. To determine the level of understanding of administration and indications for DOACs, we conducted a cross-sectional study of HCPs at a Canadian hospital using a survey questionnaire.

Methods

Study Population

An electronic questionnaire examining HCP understanding of oral anticoagulant indications, dosing, administration, storage was distributed to physicians in different specialties, nurses, and nurse practitioners. The physician groups included: hematologists, thrombosis specialists, neurologists, internists, and resident physicians.

Data Collection

The electronic questionnaire was sent via email. Data collected included demographics, understanding of oral anticoagulant: (1) indications; (2) dosing and dose-adjustment based on renal function and age; (3) storage; and (4) administration. Additional data was collected about how HCPs counsel patients and how often they prescribe oral anticoagulants. Questionnaires were completed anonymously and no identifying data was collected outside of the participant's occupation. Participation in this survey was voluntary. This study was approved by the Hamilton Integrated Research Ethics Board.

Statistical Analysis

Descriptive statistics was used to identify the proportion of HCPs with understanding of appropriate oral anticoagulant indication, dosing, and dose-adjustment based on age and renal function. HCPs' comfort level with prescribing oral anticoagulants, and the frequency with which they prescribe oral anticoagulants, was also assessed using descriptive statistics.

Results

Participant Characteristics

The survey was sent to 300 potential respondents and 52 responses were received: 3 from nurses, 1 from a nurse practitioner, 21 from staff physicians, 25 from resident physicians, and 2 did not specify their profession. The speciality of the staff physicians included: 10 General Internal Medicine; 5 Neurology; 5 Thrombosis; and 1 Hematology. Twenty-two of the 25 residents were from Internal Medicine and 3 were from Neurology. Respondents had a mean of 11.8 years of experience and median of 5.5 years of experience in their field, respectively.

HCPs' Knowledge Base about Oral Anticoagulants

Only 10% of the respondents correctly identified the approved indications for all 3 DOACs available in Canada. Only 15 (29%) knew that dabigatran should not be exposed to moisture and 27 (52%) knew that it should not be crushed. Thirteen participants (25%) knew that higher doses of rivaroxaban should be taken with food. Forty-three of the participants (83%), 38 (73%), and 42 (81%) adjusted the dose of dabigatran, rivaroxaban, and apixaban, respectively, for renal function. However, only 38 (73%) calculated renal function using the widely accepted Cockcroft-Gault formula. The rest used a laboratory reported e-glomerular filtration rate or creatinine alone. Thirty-one of the

respondents (60%) and 29 (56%) adjusted the dose of dabigatran and apixaban, respectively, for age. Additional questions and respondents' answers regarding dose adjustments are listed in Table 1.

Table 1. Questions and Respondent's Answers Regarding Which Drug(s) Can Be Safety Administered Based on the Renal Function and Age

Oral Anticoagulant	Number	%
Renal Function: CrCl 30–50 mL/min		
Warfarin	48	92
Dabigatran 150 mg BID	11	21
Dabigatran 110 mg BID	29	56
Rivaroxaban 20 mg OD	8	15
Rivaroxaban 15 mg OD	36	69
Apixaban 5 mg BID	18	35
Apixaban 2.5 mg BID	37	71
Correct answers: all except rivaroxaban 20 mg OD		
Renal Function: CrCl 15-30 mL/min		
Warfarin	49	94
Dabigatran 150 mg BID	0	0
Dabigatran 110 mg BID	1	2
Rivaroxaban 20 mg OD	0	0
Rivaroxaban 15 mg OD	13	25
Apixaban 5 mg BID	2	4
Apixaban 2.5 mg BID	28	54
Correct answers: warfarin and apixaban 2.5 mg BID up to creatinine clearance 25 ml/min		
Renal Function: CrCl <15 mL/min		
Warfarin	46	88.5
Dabigatran 150 mg BID	0	0
Dabigatran 110 mg BID	0	0
Rivaroxaban 20 mg OD	0	0
Rivaroxaban 15 mg OD	2	4
Apixaban 5 mg BID	1	2
Apixaban 2.5 mg BID	7	13.5
Correct answer: only warfarin		
Age > 80 years old		
Warfarin	46	88.5
Dabigatran 150 mg BID	5	10
Dabigatran 110 mg BID	32	31.5
Rivaroxaban 20 mg OD	19	36.5
Rivaroxaban 15 mg OD	29	56
Apixaban 5 mg BID	12	23
Apixaban 2.5 mg BID	41	79
Correct answers: all except dabigatran 150 mg BID		

BID = twice daily; CrCl = creatinine clearance; OD = once daily

Forty-nine of the respondents (94%) and 27 (52%) correctly responded that the International Normalized Ratio (INR) was elevated in patients on warfarin and rivaroxaban, respectively. However, 22 (42%) and 20 (38%) incorrectly stated that INR was elevated in patients taking dabigatran and apixaban, respectively. Questions and respondents' answers regarding anticoagulant reversal strategies are listed in Table 2.

Table 2. Questions and Respondent's Answers Regarding which Oral Anticoagulant's Effect Can Be Reversed Using Each Reversal Agent

Oral Anticoagulant	Number	%
Vitamin K		
Warfarin	51	98
Dabigatran	0	0
Rivaroxaban	0	0
Apixaban	0	0
Correct answer: only warfarin		
FFP		
Warfarin	41	79
Dabigatran	7	13.5
Rivaroxaban	7	13.5
Apixaban	6	11.5
Correct answer: only warfarin		
PCC		
Warfarin	45	86.5
Dabigatran	18	35
Rivaroxaban	20	38
Apixaban	20	38
Correct answers: all except dabigatran (activated PCC more effective)		

FFP = fresh frozen plasma; PCC = prothrombin complex concentrate.

HCPs' Comfort Level, Counselling, and Prescription Patterns

Twenty-four of the respondents (46%) felt comfortable or very comfortable prescribing DOACs. Twenty of the participants (38%) felt somewhat comfortable, while 5 (10%) felt very uncomfortable, and 3 (6%) did not specify their comfort level. Discomfort with prescribing DOACs was attributed to challenges with reversal of bleeding (31%), lack of knowledge about food or drug interactions (25%), lack of knowledge about appropriate dosing and administration (25%), lack of knowledge about appropriate indications (17%), challenges with dosing in the setting of renal impairment (21%), and bleeding risk (19%).

When counselling patients around DOACs: 51 (98%) discussed the indication; 51 (98%) discussed bleeding; 33 (64%) discussed medication administration (e.g., frequency, with or without meals); 36 (69%) discussed drug interactions; 33 (64%) discussed food interactions; and only discussed ways to improve

adherence (e.g., use of alarms or calendars). The prescribing pattern of HCPs per month is listed in Table 3.

Table 3. How Often Do HCPs Prescribe Each Oral Anticoagulant Each Month

Frequency Per Month	Never	< 5	5–10	10–20	>20	Blank
Warfarin	7	13	12	10	5	5
Dabigatran	11	27	8	1	0	5
Rivaroxaban	8	26	7	2	4	5
Apixaban	9	25	9	3	1	5

Discussion

Our study demonstrates that despite HCPs' self-expressed comfort with use of DOACs, their knowledge of oral anticoagulant indications, dosing, administration, and storage is suboptimal. HCPs have a unique opportunity to improve patients' understanding and comfort with medication; it is therefore vital that they have accurate information about oral anticoagulants, and can convey this information effectively to their patients.

There is a lack of consensus and a paucity of data around the effect of patient education around oral anticoagulants. A 2013 systematic review evaluating the impact of supplemental patient education on outcomes did not support patient education as a mechanism to improve outcomes. The systematic review's conclusions were limited by poor quality evidence, and did not include patients on DOACs.[12] Subsequent studies have shown that greater patient education about warfarin therapy was associated with better overall anticoagulant control, which might be predictive of better outcomes.[13–15] The TREAT randomized trial compared a theory driven intervention using patient interviews, focus groups, educational booklet, self-monitoring diary, and worksheet with usual care.[14] It found that the educational intervention significantly improved anticoagulation control in patients taking warfarin, and concluded that improving patient education is essential to improve the efficacy and safety of anticoagulation.[14] A cluster-randomized trial assessed the impact of patient education on knowledge about treatment; it compared patients who received education consisting of a video, a brochure, and a questionnaire with a control group who only received the brochure.[15] It found that patient education resulted in markedly improved safety-related patient knowledge.[15]

Previous studies have shown similar findings of knowledge gap about oral anticoagulants among HCPs.[16,17] In a study by Couris et al., HCPs including physicians, pharmacists, and dieticians were surveyed using questions about drug and dietary interactions with warfarin.[16] The authors concluded that additional training and improved knowledge base about drug-dietary interactions among HCPs are crucial to provide adequate patient counselling and possibly optimized clinical outcomes.[16] Ferguson et al. utilized a paper-based survey distributed during a cardiovascular meeting to assess nurses' knowledge about warfarin-drug interactions and advise on warfarin dietary interactions, administration, monitoring, and duration of anticoagulation.[17] They found that there was very poor knowledge about warfarin anticoagulation among nurses.[17]

Several "real-world" studies have examined the safety and efficacy of DOACs in patients with atrial fibrillation.[18–22] Single-arm observational studies examining the real-world use of rivaroxaban in patients with atrial fibrillation[20,21,24,25] and a 2017 systematic review[26] confirmed the safety and efficacy outcomes observed in the ROCKET AF.[7] However dabigatran appears to perform differently outside of the randomized controlled trial setting. A 2016 systematic review of 7 post-marketing observational studies, which included 34,8750 patients with atrial fibrillation taking dabigatran, found that dabigatran at either dose showed no benefit over warfarin in prevention of stroke.23 This finding differs from data reported by the RELY trial, which demonstrated that compared with warfarin, higher dose dabigatran significantly reduced the risk of stroke and systemic embolism.[6] This raises the possibility that inappropriate use of dabigatran in clinical practice is contributing to its loss of clinical efficacy. Observational studies[22,27] and a 2017 systematic review[28] examining the real-world use of apixaban in patients with atrial fibrillation confirmed the safety and efficacy outcomes observed in the ARISTOTLE.[8]

Our study has some limitations. First, there is a potential for selection bias as we surveyed HCPs at one hospital on a volunteer basis and had a low response rate. The knowledge base of responders may have been different from that of non-responders. Five of the respondents were experts in thrombosis; HCPs' knowledge might be more subpar if sampling is performed at a centre with no thrombosis expertise. A national study is needed to get a more accurate picture of Canadian practitioners' understanding of DOACs. However, our study provides an initial look into an area where quality improvement appears to be badly needed. Second, due to its small sample size, our study could not compare the groups demonstrating appropriate understanding relative to those that did not. A larger study may yield information on the impact of specialty and years in practice. Third, as with any cross-sectional study, our study only offers a snapshot of the current practice. Nonetheless, our study is the first of its kind to describe HCPs' knowledge of DOAC indications and administration, and paves the way for future studies examining the impact of educational programs on medication literacy.

Conclusions

Though HCPs express comfort with prescribing DOACs, our study raises concerns around their self-reported knowledge of DOACs use. DOACs are a widely prescribed class of drugs, which can cause serious side effects if not prescribed and

taken correctly. It is essential that HCPs provide patients with accurate information and counselling around DOACs, in order to optimize safe and efficacious use. Future studies should focus on educational strategies to improve HCPs' knowledge base in this area, and associations between medication literacy and the safety and efficacy of DOACs.

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