Characterization of Antithrombotic Regimens for Patients with Nonvalvular Atrial Fibrillation and Obesity Discharged from Cardiology Wards

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To cite: O'Byrne S, Tangedal K, Kennedy B, Semchuk W. Characterization of antithrombotic regimens for patients with nonvalvular atrial fibrillation and obesity discharged from cardiology wards. *Can J Hosp Pharm.* 2024;77(1):e3425. doi: 10.4212/cjhp.3425

ABSTRACT

Background: Despite data derived from observational studies, optimal anticoagulation strategies have yet to be established for patients with nonvalvular atrial fibrillation and obesity.

Objective: To describe direct oral anticoagulant (DOAC) regimens prescribed for adult patients with nonvalvular atrial fibrillation who weighed more than 120 kg.

Methods: This single-centre, retrospective cohort study, conducted in the Saskatchewan Health Authority – Regina Area, involved adult patients with body weight greater than 120 kg who had an indication for oral anticoagulation to treat nonvalvular atrial fibrillation and were discharged by a cardiologist between June 2019 and July 2021.

Results: A total of 62 patients were included (median weight 135 kg). At discharge, DOACs were prescribed for 57 (92%) of the patients and warfarin for 5 (8%). In numeric terms, patients receiving warfarin were at higher risk of thromboembolism or thrombosis; however, the small sample size limited the ability to draw conclusions.

Conclusions: Practice patterns in the Saskatchewan Health Authority – Regina Area indicated substantial use of DOACs for patients with body weight greater than 120 kg; however, for those with the highest weights, warfarin was still in use.

Keywords: atrial fibrillation, obesity, direct oral anticoagulants, anticoagulation, pharmacist interventions, pharmacist

RÉSUMÉ

Contexte : Malgré les données dérivées d'études observationnelles, les stratégies d'anticoagulation optimales n'ont pas été consolidées pour les patients atteints de fibrillation auriculaire non valvulaire et d'obésité.

Objectif : Décrire les schémas thérapeutiques d'anticoagulants oraux (ACO) prescrits aux patients adultes atteints de fibrillation auriculaire non valvulaire et qui pesaient plus de 120 kg.

Méthodes : Cette étude de cohorte rétrospective monocentrique menée dans l'office de la santé de la Saskatchewan à Regina a porté sur des patients adultes pesant plus de 120 kg qui avaient une indication de traitement anticoagulant oral pour traiter la fibrillation auriculaire non valvulaire et qui ont été renvoyés par un cardiologue entre juin 2019 et juillet 2021.

Résultats : Au total, 62 patients ont été inclus (poids médian, 135 kg). Au congé, des ACO ont été prescrits à 57 (92 %) des patients et de la warfarine à 5 (8 %) d'entre eux. En termes numériques, les patients traités par warfarine présentaient un risque plus élevé de thromboembolie ou de thrombose; cependant, la petite taille de l'échantillon a limité la capacité de tirer des conclusions.

Conclusions : Les modèles de pratique de l'office de la santé de la Saskatchewan à Regina indiquaient une utilisation importante des ACO pour les patients dont le poids corporel était supérieur à 120 kg; cependant, pour les personnes ayant le poids le plus élevé, la warfarine était toujours utilisée.

Mots-clés : fibrillation auriculaire, obésité, anticoagulants oraux, anticoagulation, interventions du pharmacien, pharmacien

INTRODUCTION

The direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban, and edoxaban are considered non-inferior or superior to warfarin in preventing stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF).[1] Compared with warfarin, DOACs have established advantages, including fewer drug or food interactions and fixed dosing, which entails only infrequent laboratory monitoring.[2] Obesity is a risk factor for NVAF and plays a causal role in other risk factors for this condition, including hypertension, diabetes mellitus, and heart failure, through cardiac remodelling and other physiological changes.[3,4] Although obesity increases the risk of NVAF by almost 50%, optimal oral anticoagulation for patients with NVAF and weight greater than 120 kg or body mass index (BMI) over 40 has not been established.[4-6] There is a concern that fixed doses may result in subtherapeutic DOAC concentration and suboptimal protection against preventable thromboembolic events for these patients.[7]

Recommendations from professional societies differ according to the patient population and may not align with real-world prescribing patterns.[8] Thrombosis Canada recommends that clinicians who are prescribing a DOAC for patients with weight over 120 kg or BMI over 40 inform them of the limitations of current data, although the organization also recognizes that observational studies have shown encouraging safety and efficacy results.[9] Landmark trials have shown that DOACs are as effective as warfarin for patients with obesity, but the trials cited by guidelines[1,9] included few patients with BMI greater than 30, and there was underrepresentation of those with BMI greater than 40. Recent systematic reviews have suggested no differences in rates of stroke or bleeding among patients with BMI up to 50.[10,11] Other meta-analyses and randomized controlled trials have had mixed results regarding reduction in stroke and mortality rates for patients with obesity, a phenomenon known as the "obesity paradox".[3]

The anticoagulation prescribing patterns for patients with obesity and NVAF in the Saskatchewan Health Authority – Regina Area (SHA-Regina) are unknown. To provide insight into real-world data, the primary objective of this retrospective cohort study was to characterize oral anticoagulation regimens prescribed on discharge from cardiology wards for patients with NVAF (new onset or pre-existing) and body weight greater than 120 kg. The secondary objectives were to determine each patient's prevalence of risk factors for thromboembolism or bleeding using the CHADS2 and HASBLED scoring systems, to determine the proportion of patients with changes in anticoagulation regimen from admission to discharge, and to determine the proportion of patients with evidence in the medical chart of a pharmacist's involvement in the anticoagulation regimen.

METHODS

This study was conducted at Regina General Hospital, a 453-bed tertiary care hospital within SHA-Regina. Patients who had been discharged from the cardiology wards over a 2-year period (June 2019 to July 2021) with a prescription for an oral anticoagulant were identified using BDM Pharmacy software (BDM IT Solutions). Patients were screened against the following inclusion criteria using electronic and paper charts: age 18 years or older, diagnosis of NVAF and an indication for anticoagulation (based on the CHADS65 algorithm, as recommended by current Canadian guidelines[1]), body weight greater than 120 kg, and discharge by a cardiologist. Patients were excluded if they had indications other than NVAF for oral anticoagulation (e.g., left ventricular thrombus, mechanical valve, venous thromboembolism [VTE], cancer-associated thrombus), were transferred to another acute care facility, died during the index hospitalization, were receiving long-term hemodialysis, had creatinine clearance less than 15 mL/min on discharge, or were pregnant. Ethics approval was obtained through the SHA-Regina Research Ethics Board (REB-21-09) with a waiver of patient consent.

Descriptive statistics, calculated with Microsoft Excel 2016 software, were used to present the data. The data for categorical variables were presented as frequencies (numbers and percentages). Data for continuous variables were expressed as means with standard deviations or medians with interquartile ranges [IQRs]), depending on the data distribution.

RESULTS

Of the 1072 patients screened against inclusion and exclusion criteria, 62 (5.8%) were included in the analysis. The reasons for exclusion were as follows: 959 (89.5%) had body weight less than 120 kg, 29 (2.7%) had indications other than NVAF for oral anticoagulation, 10 (0.9%) were not discharged home, 9 (0.8%) were not discharged by a cardiologist, 1 (0.1%) had a mechanical valve, 1 (0.1%) had concomitant VTE, and 1 (0.1%) had creatinine clearance less than 15 mL/min.

Baseline characteristics of the study sample are presented in Table 1. The overall average CHADS2 score (as calculated by the researchers using patient data) was 2.2, and 22 patients had a CHADS2 score of 1. The average CHADS2 score was 3.2 for patients who received warfarin and 2.1 for those who received a DOAC. The average HASBLED score was 1.0 overall, 1.8 for patients who received warfarin, and 1.0 for patients who received a DOAC. Most patients (79%) weighed between 120 and 150 kg, and 68% had a diagnosis of atrial fibrillation before admission. Within this cohort, most anticoagulant regimens prescribed on discharge were DOACs (n = 57, 92%), with warfarin prescribed for a much smaller group (n = 5, 8%). The proportion of patients with body weight above 150 kg was higher in the warfarin group than the DOAC group (40% vs 19%). The highest individual weight was 243.2 kg, and this patient received warfarin. Most of the patients received apixaban (n = 30, 48%) or rivaroxaban (n = 20, 32%) (Figure 1).

Among the 62 patients, 29 had high risk of bleeding (previous stroke, age 75 or older, and concomitant antiplatelet therapy), and the majority of these (n = 27, 93%) received a DOAC, whereas the other 2 patients (7%) received warfarin. In patients with these risk factors, apixaban was the most common DOAC prescribed (n = 17, 59%).

Therapy was changed before discharge for 11 patients (25% of those who had been receiving some form of anticoagulation at the time of admission). Therapy was changed from warfarin to a DOAC for 7 patients, DOAC dose was adjusted for 3 patients, and the initial DOAC was changed to another DOAC for 1 patient. The following reasons were documented for these changes: DOAC dose too low (n = 1), regimen optimization with combination antiplatelet usage

TABLE 1. Baseline Characteristics of the Study Population

Characteristic	Group; No. (%) of Patients[a]		
	Total (*n* = 62)	DOAC (*n* = 57)	Warfarin (*n* = 5)
Age (years) (mean ± SD)	62 ± 11	62 ± 11	66 ± 5
Sex, female	11 (18)	10 (18)	1 (20)
Weight (kg) (median and IQR)	135 (124.9–147.9)	134 (124.8–147)	137 (124–202)
120–150 kg	49 (79)	46 (81)	3 (60)
> 150 kg	13 (21)	11 (19)	2 (40)
Creatinine clearance[b] (mL/min) (mean ± SD)	142 ± 52	131 ± 46	100 ± 29
> 50 mL/min	61 (98)	56 (98)	5 (100)
30 to 50 mL/min	1 (2)	1 (2)	0 (0)
15 to < 30 mL/min	0 (0)	0 (0)	0 (0)
AF before admission	42 (68)	39 (68)	3 (60)
CHADS2 score[c] (mean ± SD)	2.2 ± 1.1	2.1 ± 1.1	3.2 ± 1.1
Heart failure	29 (47)	25 (44)	4 (80)
Hypertension	59 (95)	54 (95)	5 (100)
Prior stroke	6 (10)	5 (9)	1 (20)
Diabetes mellitus	31 (50)	26 (46)	5 (100)
Vascular disease	24 (39)	19 (33)	5 (100)
HASBLED score[d] (mean ± SD)	1.0 ± 1.0	1.0 ± 1.0	1.8 ± 1.1
Concomitant use of antiplatelet agents[e]	15 (24)	14 (25)	1 (20)
ASA	6 (10)	6 (11)	0 (0)
Clopidogrel	8 (13)	7 (12)	1 (20)
Ticagrelor	3 (5)	3 (5)	0 (0)
Concomitant NSAID	1 (2)	1 (2)	0 (0)
Documented antithrombotic allergy or intolerance	0 (0)	0 (0)	0 (0)

AF = atrial fibrillation, ASA = acetylsalicylic acid, DOAC = direct oral anticoagulant, IQR = interquartile range, NSAID = nonsteroidal anti-inflammatory drug, SD = standard deviation.

[a]Except where indicated otherwise.

[b]Calculated using weight-adjusted Cockcroft–Gault equation.

[c]CHADS2 score was calculated as the sum of the following risk factors: history of heart failure (1 point), hypertension (1 point), diabetes mellitus (1 point), age ≥ 75 years (1 point), prior stroke or transient ischemic attack (2 points).

[d]HASBLED score was based on the following risk factors: hypertension (systolic blood pressure > 160 mm Hg within 3 days before discharge), abnormal renal function (kidney transplant, serum creatinine > 200 µmol/L), abnormal liver function (aspartate aminotransferase or alanine aminotransferase > 3 times upper limit of normal, bilirubin > 2 times upper limit of normal), stroke (any stroke), bleeding (previous hospitalization for bleeding, history of a drop in hemoglobin greater than 20 g/L or requiring blood transfusion), labile international normalized ratio (time in therapeutic range < 60%), elderly (age > 65 years), drugs (concomitant NSAID or antiplatelet agent), and substance use (alcohol use > 8 drinks per week).

[e]The individual antiplatelet numbers sum to more than the total because 2 patients were receiving dual antiplatelet therapy (one with the combination of ASA and clopidogrel, the other with the combination of ASA and ticagrelor).

for acute coronary syndrome (*n* = 3), and labile international normalized ratio (*n* = 2). For 5 patients, no reason was stated.

For all of the included patients, only dosages approved by Health Canada were used; serum levels of anti-Xa or DOAC were not used to determine dosing. None of the patients received concomitant inhibitors of the cytochrome P450 3A4 isozyme or P-glycoprotein.

Pharmacist involvement was documented for 4 (80%) of the 5 patients who received warfarin and 18 (32%) of the 57 who received a DOAC. Pharmacists intervened a total of 10 times for patients with high risk of bleeding (previous stroke, age 75 or older, and concomitant antiplatelet therapy); this represented 34% of high-risk patients. Education was the most commonly documented intervention, and pharmacists were engaged in stopping, changing, and continuing anticoagulation. Pharmacists intervened by changing warfarin to a DOAC in 2 cases.

DISCUSSION

In SHA-Regina, most patients with NVAF and body weight over 120 kg were receiving a DOAC at the time of discharge, including some who had been receiving warfarin before admission. The Subcommittee on Control of

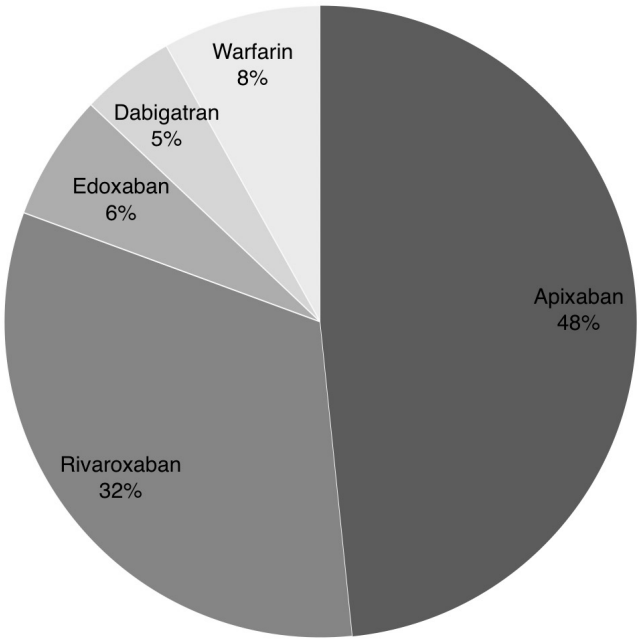

FIGURE 1. Anticoagulation regimens prescribed at discharge ($n = 62$).

Anticoagulation of the International Society on Thrombosis and Haemostasis (ISTH) released a guidance document for DOACs in patients with obesity and NVAF, which suggested that DOACs should not be used for patients with body weight greater than 120 kg because clinical data from this patient population are limited.[8] For the treatment of VTE, the ISTH Subcommittee on Control of Anticoagulation released a communication in 2021 recommending rivaroxaban or apixaban, regardless of weight.[6] Although the patients in our study did not have VTE, apixaban and rivaroxaban were used for many of them. Data from meta-analyses and phase 3 clinical trials support the use of primarily apixaban and rivaroxaban in patients with BMI up to 50, because these drugs had greater efficacy than warfarin in stroke prevention, with fewer incidents of major bleeding.[2,11-13] Numerically, body weights were higher for patients who received warfarin, the highest being 243 kg. This observation may suggest that practitioners are more comfortable prescribing a drug with a surrogate measure for efficacy in patients with extremely high weight.

There is evidence of lower rates of stroke and death in patients with obesity and NVAF, a phenomenon known as the obesity paradox. Small retrospective studies have shown similar, worse, and even better outcomes in these patients.[3,14-16] One proposed explanation for better outcomes is that patients may be younger and healthier when obesity is the primary cause for NVAF relative to patients with causes of NVAF such as age or alcohol consumption, which typically worsen outcomes.[3] This population (patients with obesity and NVAF) is also hypothesized to have cardiovascular comorbidities at a younger age and may receive cardioprotective treatment or follow-up earlier.[3] Further research may clarify how the obesity paradox affects outcomes in this population.

In our study, pharmacists were commonly involved in patient education, which highlights the role of these professionals in shared decision-making regarding choice of anticoagulant, which is crucial for understudied populations. High-risk patients and those receiving warfarin at the time of discharge had higher rates of pharmacist intervention, which suggests that pharmacists prioritized these patients. Pharmacist involvement may have been underestimated, given that documentation may fail to capture verbal conversations or discussions during interdisciplinary rounds. Further research is needed to determine the extent to which pharmacists support evidence-based anticoagulation regimens and improved patient-centred care.

The small sample size limited our ability to compare medication regimens. No outcome data were gathered, which prevented conclusions regarding regimen safety and efficacy. The study design relied on the accuracy of chart-based documentation, which prevented us from understanding the reasoning behind medication choices. We could not calculate BMI because patient heights were unavailable, and high body weight alone does not necessarily indicate obesity; as such, our interpretation of the data was based solely on reported body weight.[9] However, the study population was unique, given that the majority of patients weighed between 120 and 150 kg (median 135 kg). These results will help to resolve the paucity of data regarding prescribing of anticoagulation at these weights.

CONCLUSION

Despite unclear guidance for the use of DOACs for NVAF in patients with obesity, practice patterns in SHA-Regina indicate substantial use of DOACs in patients with body weight greater than 120 kg, as well as consideration of warfarin for patients with higher weights. Our study provides real-world insight into anticoagulation prescribing patterns in patients with NVAF and body weight greater than 120 kg, but large-scale randomized clinical trials are needed to further evaluate the efficacy and safety of DOACs in these patients.

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Competing interests: For activities unrelated to the study reported here, Kirsten Tangedal has received speaker's honoraria from the Canadian Cardiovascular Pharmacists Network and support for meeting attendance from the Canadian Society of Hospital Pharmacists (CSHP); at the time of manuscript submission, she was president of the Saskatchewan Branch of CSHP. No other competing interests were declared.

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Funding: None received.

Submitted: November 23, 2022
Accepted: November 11, 2023
Published: March 13, 2024