PATTERNS OF ORAL ANTICOAGULANTS USE IN ATRIAL FIBRILLATION

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ABSTRACT

Background
Novel oral anticoagulants are available for the management of atrial fibrillation and are considered more convenient to use than warfarin.

Objective
The main objective of this study was to describe patterns of oral anticoagulant use in the 6 months period following the availability of dabigatran at our hospital.

Methods
A cross-sectional study was conducted in a single University hospital in the province of Québec, Canada. Medical records of subjects on oral anticoagulants for atrial fibrillation that were hospitalized between October 1st, 2011 and March 31th, 2012 were reviewed. Type of use (prevalent, incident and switch) and patient's characteristics of warfarin and dabigatran users were compared using Chi-squared and T-tests.

Results
In the 6-month period following dabigatran availability in the hospital, 59 patients (13%) were on dabigatran and 388 (87%) on warfarin. Mean $CHADS_2$ score, mean age and mean number of chronic medications were lower in the dabigatran group. The percentage of patients with coronary artery disease was lower and renal function was higher in the dabigatran group.

Conclusion
Dabigatran use remained low in the first 6 months period following the approval of dabigatran at our hospital, which could be explained by limited data on the efficacy and safety of this agent in subjects with multiple comorbidities.

Key Words: *Atrial fibrillation, anticoagulants, warfarin, novel anticoagulants, apixaban, dabigatran, rivaroxaban*

Non valvular atrial fibrillation (AF) is a common arrhythmia and is associated with significant risks of stroke and systemic thromboembolism.[1] Anticoagulation with vitamin K antagonists has been recommended over the past fifty years[2], and reduces the risk of stroke by about 60%.[3] Warfarin is effective, but has a narrow therapeutic index, is susceptible to many interactions, and requires monitoring of the international normalized ratio.[4] Novel oral anticoagulants (NOAC), such as dabigatran, rivaroxaban, apixaban and edoxaban, do not require frequent laboratory monitoring and are associated with fewer drug interactions than

warfarin.[5] The efficacy and safety of NOAC in AF has been investigated in four major trials.[6-9] Each NOAC was at least non-inferior to warfarin in terms of embolic events prevention and was associated with lower (dabigatran 110 mg twice daily, apixaban and edoxaban) or similar (dabigatran 150 mg twice daily and rivaroxaban) risks of major bleeding events.[6-9] However, patients at high-risk of bleeding were excluded from these studies. Recent Canadian guidelines favours NOAC over warfarin in AF.[10] Few studies have evaluated the effectiveness and safety of NOAC in "real clinical practice".[11,12] A publication by the *Institut national d'excellence en santé et en services sociaux* (INESSS) in the province of Quebec, Canada, describes the use of dabigatran and warfarin in subjects with non valvular AF, but the analysis was limited to outpatients.[13] The primary objective of this study was to describe patterns of oral anticoagulants use at the Centre Hospitalier Universitaire de Sherbrooke (CHUS) in the province of Québec, Canada.

METHODS

Study Design

This was a cross-sectional study. The medical archivist identified subjects who were hospitalized between October 1st, 2011 (i.e. when dabigatran became available on the hospital formulary) and March 31st, 2012; who had a documented diagnosis of AF (based on ICD-10 codes); and a prescription of warfarin, dabigatran or rivaroxaban (apixaban was not available during the study period). Only the first eligible hospitalization was selected.

To be included, subjects had to be at least 18 years old; with a diagnosis of non valvular atrial fibrillation or atrial flutter documented on the discharge summary; an oral anticoagulant prescribed during the hospitalisation and at discharge; and a complete discharge prescription documented in the electronic medical record (EMR). Subjects were excluded, based on information on the discharge summary, if they had a diagnosis of valvular heart disease (i.e. moderate to severe mitral stenosis), mechanical valve repair or replacement, congenital heart disease, uncontrolled hyperthyroidism, illicit drug use (amphetamines, cocaine or crack), drug intoxication (e.g. tricyclic antidepressant), orthopaedic surgery, another indication for anticoagulation (e.g. thromboembolic disease), atrial fibrillation following cardiac surgery or transient AF (i.e. lasting less than 48 hours, because we were interested in chronic treatment). The research ethics board of the institution approved this study, and the Director of Professional Services approved the retrospective review of medical charts without obtaining written informed consent from the subjects included.

Data Collection

EMRs were reviewed and data were obtained from the hospital discharge summary, laboratory reports, and discharge prescriptions.

Patient Characteristics

Patient characteristics were described according to demographic data (i.e. gender, age, body mass index) and medical history (i.e. hypertension, diabetes, heart failure, stroke or transient ischemic attack [TIA], coronary artery disease [CAD], peripheral artery disease [PAD], dementia, history of fall, cardioversion, cirrhosis, history of major bleeding [as described by the SPORTIF III criteria for major bleeding][14], peptic ulcers, renal insufficiency [based on the estimated glomerular filtration rate (eGFR) evaluated by the Cockcroft-Gault [CG] formula], and $CHADS_2$ score). Liver enzymes (aspartate transaminase [AST] and alanine transaminase [ALT]) were categorized as either normal, or elevated when higher than twice the upper limit of normal. Concomitant use of antiplatelets, antifungal azoles (excluding fluconazole), NSAIDs, amiodarone/dronedarone, carbamazepine, diltiazem, phenythoin, proton pump inhibitor (PPI), rifampin, ritonavir, selective serotonin reuptake inhibitors (SSRI), serotonin/norepinephrine reuptake inhibitors (SNRI), statins, verapamil was assessed. We also described the healthcare unit of admission and length of hospital stay.

Patterns of use were described among all users of any oral anticoagulant in the 6-month period following dabigatran approval at our hospital. Type of use was categorized in three

types: prevalent use (i.e. patient already on oral anticoagulant before hospitalization), incident use (i.e. new prescription of oral anticoagulant during hospitalization), or a switch (i.e. patient switched from one oral anticoagulant to another during hospitalization).

Statistical Analysis

Patterns of use were described using proportions with 95% confidence intervals (CI) for categorical variables and means with standard deviations for continuous variables. Baseline characteristics of warfarin users were compared to those of dabigatran users with Chi-squared tests for categorical variables or T-tests for continuous variables. Fisher's exact tests were used when the number of subjects was too low.

RESULTS

In the study period, 808 inpatients had a diagnosis of AF and were prescribed an oral anticoagulant. Three hundred sixty-one subjects were excluded (45.0%): 223 patients because of unavailability of complete discharge prescriptions, and 140 because of valvular heart disease (*see Figure 1*). Four hundred forty-seven patients met our eligibility criteria: 59 (13%) were on dabigatran, and 388 on warfarin. About 71%, 25% and 3% of patients on dabigatran were prevalent users, incident users, and switchers, respectively. Similar proportions were found in the warfarin group (*see Table 1*).

FIG. 1 Study Flow Diagram

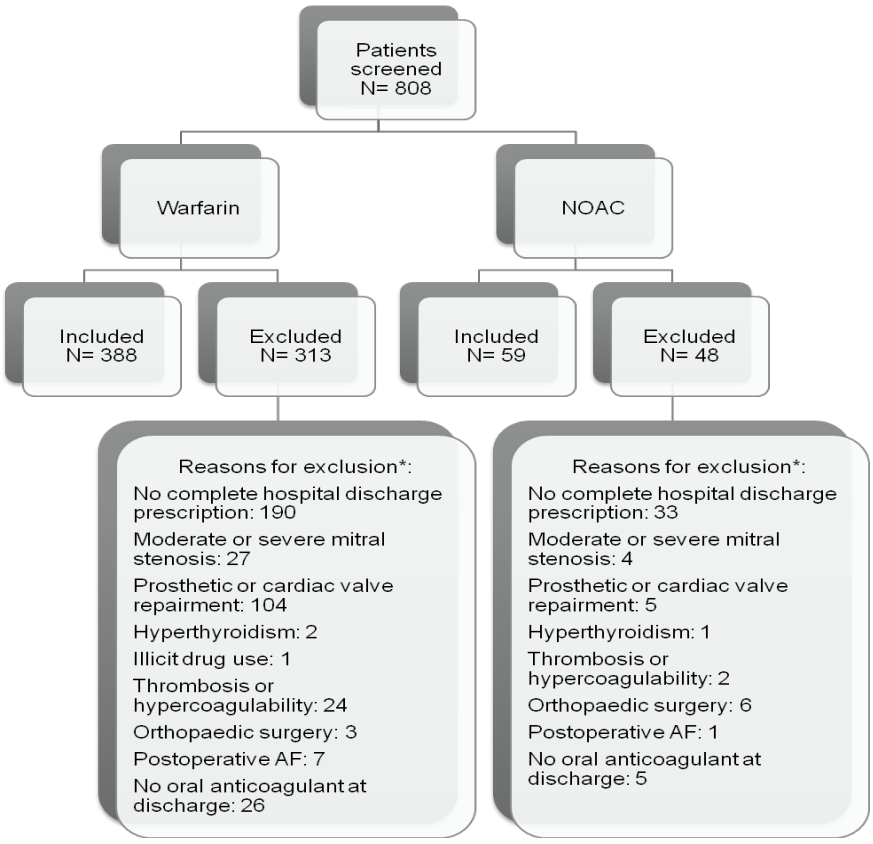

Figure 1 Legend:
*A patient may have more than one reason for exclusion
AF: atrial fibrillation; NOAC: novel oral anticoagulants.

TABLE 1 Patient characteristics in Group 1

Characteristics	Warfarin (n=388)	Dabigatran (n=59)	P value
Type of use, n(%)			
Prevalent	306 (78.9)	42 (71.2)	
Incident	79 (20.4)	15 (25.0)	
Switch	3 (0.8)	2 (3.3)	
Mean age (years), ±sd	80.03 ± 9.37	72.51 ± 14.84	<0.001
Age ≥75 years, n(%)	296 (76.5)	29 (48.3)	<0.001
Male Gender, n(%)	178 (45.9)	27 (45.8)	0.987
Body mass index[1]	28.1 ± 6.5	29.3 ± 7.9	0.189
$CHADS_2$ score, mean ±sd	2.76 ± 1.25	2.34 ± 1.39	0.018
$CHADS_2$ score ≥2, n(%)	343 (88.4)	40 (67.8)	<0.001
eGFR[1,2], mean ±sd	53.04 ± 26.46	72.07 ± 33.21	<0.001
eGFR[2] <30 mL/min, n(%)	61 (16.0)	2 (3.4)	<0.001
Elevated liver enzymes	11 (3.4)	0 (0.0)	0.214
Hypertension	317 (81.7)	48 (81.4)	0.949
Diabetes	151 (38.9)	21 (35.6)	0.625
Heart Failure	140 (36.2)	16 (27.1)	0.150
Coronary artery disease	214 (55.0)	20 (34.0)	0.002
Peripheral artery disease	174 (45.0)	25 (41.7)	0.633
Stroke/transient ischemic attack	106 (27.3)	16 (27.1)	0.974
Dementia	76 (19.6)	5 (9.0)	0.039
Cirrhosis	6 (1.5)	2 (3.4)	0.285
Fall	39 (10.1)	0 (0.0)	0.011
Cardioversion	16 (4.1)	5 (8.5)	0.141
Peptic ulcers	16 (4.1)	1 (1.7)	0.364
Major bleeding	22 (5.7)	3 (5.1)	1.000
Healthcare unit, n(%)			0.104
Cardiology	117 (30.2)	19 (32.2)	
Internal medicine	107 (27.6)	17 (28.8)	
Family medicine	85 (21.9)	11 (19.0)	
Neurology	9 (2.3)	5 (8.5)	
Length of stay, mean days ±sd	13.52 ± 14.48	9.71 ± 9.41	0.051
Acetylsalicylic Acid	85 (21.9)	11 (18.6)	0.570
Antiplatelet therapy[3]	20 (5.2)	1 (1.7)	0.336
Amiodarone or dronedarone	43 (11.1)	4 (6.8)	0.492
Carbamazepine	1 (0.3)	0	-
Diltiazem	66 (17.0)	20 (33.9)	0.002
Itraconazole or posaconazole or voriconazole	2 (0.5)	0	-
NSAIDs	6 (1.5)	2 (3.4)	0.285
Phenytoin	3 (0.8)	1 (1.7)	-
Proton pump inhibitor	233 (60.1)	32 (54.2)	0.397
Rifampin	0	0	-
Ritonavir	0	0	-
SSRIs or SNRIs	61 (15.1)	6 (10.2)	0.266
Statins	262 (67.5)	33 (55.9)	0.08
Verapamil	6 (1.5)	0	-
Mean number of drugs at discharge ±sd	12.54 ± 4.48	10.92 ± 4.97	0.011

1. Because of missing data, means were calculated for 382 patients on warfarin and 58 patients on NOAC.
2. Estimated glomerular filtration rate calculated with Cockcroft-Gault formula.
3. Clopidogrel, prasugrel, ticagrelor or ticlopidine.

Abbreviations: AST: aspartate aminotransferase; ALT: alanine aminotransferase; NOAC: novel oral anticoagulants; NSAIDs: Nonsteroidal Anti-inflammatory Drugs; SSRIs: Selective serotonin reuptake inhibitors; SNRIs: Serotonin/Norepinephrine reuptake inhibitors

Patient characteristics of subjects are shown in Table 1. About half of the subjects were females. The mean $CHADS_2$ score, age and the number of drugs at discharge were lower in patients receiving dabigatran, while the mean eGFR was lower in patients receiving warfarin. Patients on dabigatran less frequently had CAD, dementia, a history of falls and more frequently had a prescription of diltiazem. Other characteristics were similar between the two groups.

DISCUSSION

This study describes inpatient use of oral anticoagulants in patients with non valvular AF in the 6 months period following the availability of dabigatran on our hospital formulary. Prescriptions of dabigatran were infrequent, possibly because clinicians are hesitant to prescribe dabigatran in hospitalized patients who have multiple comorbidities. In fact, dabigatran has not been studied extensively in this population. Patients on dabigatran were younger, possibly because they have less co-morbidity and because the drug was mainly reimbursed by private insurances during the study period.

The percentage of subjects on diltiazem was higher in the NOAC group, but we found that it was more frequently prescribed in the absence of CAD. In fact, the percentage of subjects with CAD was lower in dabigatran users. The association between dabigatran and an increased risk of myocardial infarction[6] might have led prescribers to prefer warfarin for CAD patients. It is reassuring to observe that estimated renal function was higher in subjects who were prescribed dabigatran, but two subjects were prescribed this drug in the presence of a creatinine clearance lower than 30mL/min, which is a contraindication for this drug.

Few studies have described "real-world" dabigatran use in AF. A publication from l'INESSS in Quebec, Canada, describes new users of dabigatran or warfarin in patients with non valvular AF, using administrative databases. Their study period was between April 2011 and April 2012, included more subjects (7680 on dabigatran and 5160 on warfarin), and concerned outpatients.[13] Our patients on warfarin were older, while our patients on dabigatran were younger than the ones described in the INESSS report. Dabigatran was more frequently prescribed by cardiologists, a finding that we did not observe, but that could be explained by the fact that we only included hospitalized patients.

Our study has a number of limitations. First, data were collected retrospectively and a high number of patients were excluded because of incomplete discharge prescriptions. Secondly, apixaban, edoxaban and rivaroxaban were not available during the study period, and dabigatran was reimbursed under certain restrictions by public insurances, which limits external validity of our results.

In conclusion, dabigatran use was low in hospitalized patients with AF. Limited data on the efficacy and safety of NOAC in patients with several comorbidities might explain this and should be investigated. Our study is ongoing to assess predictors of NOAC prescriptions in new users of oral anticoagulants over a 3 years period.

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REFERENCES

1. Agence canadienne des médicaments et des technologies de la santé. Safety, Effectiveness, and Cost-Effectiveness of New Oral Anticoagulants Compared with Warfarin in

Preventing Stroke and Other Cardiovascular Events in Patients with Atrial Fibrillation [En ligne]. Ottawa: L'Agence; 2012 [December 5, 2012]. Available: http://www.cadth.ca/media/pdf/NOAC_Therapeutic_Review_final_report.pdf

2. Cairns JA, Connolly S, McMurtry S, Stephenson M, Talajic M. Canadian Cardiovascular Society Atrial Fibrillation Guidelines 2010: Prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. Can J Cardiol 2011;27:74-90.
3. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857-67.
4. Wisler JW, Becker RC. A guidance pathway for the selection of novel anticoagulants in the treatment of atrial fibrillation. Crit Pathw Cardiol 2012;11:55-61.
5. Hickey K. Anticoagulation management in clinical practice: preventing stroke in patients with atrial fibrillation. Heart Lung 2012;41:146-56.
6. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
7. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91.
8. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365:981-92.
9. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369:2093-104.
10. Skanes AC, Healey JS, Cairns JA, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. Can J of Cardiol 2012;28:125-36.
11. Sørensen R, Gislason G, Torp-Pedersen C, et al. Dabigatran use in Danish atrial fibrillation patients in 2011: a nationwide study. BMJ open 2013;3:e002758.
12. Larsen TB, Rasmussen LH, Skjoth F, et al. Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol 2013;61:2264-73.
13. Institut national d'excellence en santé et en services sociaux (INESSS). Portrait de l'usage du dabigatran chez les personnes assurées par le régime public d'assurance médicaments. Available at : http://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Medicaments/INESSS_Portraitdusage_Dabigatran.pdf Accessed December 30, 2013.
14. Olsson SB. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): randomised controlled trial. Lancet 2003;362:1691-8.