Prescribing patterns of target-specific oral anticoagulants: an academic hospital perspective

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Target-specific oral anticoagulants have been rapidly adopted into clinical practice for stroke prophylaxis and venous thromboembolism treatment, raising concerns about off-label prescribing practices. We conducted a retrospective review of consecutive patients prescribed dabigatran, rivaroxaban or apixaban prior to inpatient hospitalization over an 18-month period to examine the off-label prescribing frequency, contraindications and related complications. Chart review included baseline demographics, hospital admitting service, outpatient prescribing service, renal function, therapeutic indication, echocardiographic findings, contraindications, major bleeding events and vital status. We identified 160 patients who received a target-specific oral anticoagulant prior to hospitalization. Over half (53.1%) of the patients received rivaroxaban, 43.7% received dabigatran and 3.1% received apixaban. Atrial fibrillation (68.1%) and venous thromboembolism treatment (25.6%) were the most common indications. Ninety percent of patients had a U.S. Foods and Drugs Administration (FDA)-approved indication for therapy. Major bleeding events occurred in 4.4% of patients. Cardiology was the most common prescribing and admitting service (43.8 and 31.3%), and more frequently adhered to FDA-approved indications (97 vs. 84%, $P = 0.01$). There were no significant differences between prescribing services regarding major contraindications ($P = 0.14$) and major bleeding events ($P = 0.77$). Off-label prescription rates for target-specific oral anticoagulants were infrequent and not associated with increased adverse events. *Blood Coagul Fibrinolysis* 26:767–771 **Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.**

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Introduction

Atrial fibrillation and venous thromboembolism (VTE) affect more than 3 million Americans annually, conveying significant morbidity and mortality [1,2]. Oral anticoagulants are the cornerstone of therapy for most patients. Warfarin, a vitamin K antagonist (VKA), had been the only oral anticoagulant available in the United States until 2010 when the U.S. Foods and Drug Administration (FDA) approved the target-specific oral anticoagulant (TSOAC) dabigatran for the prevention of stroke in nonvalvular atrial fibrillation [3]. Shortly thereafter, two additional TSOACs, rivaroxaban and apixaban, received regulatory approval for stroke prophylaxis in nonvalvular atrial fibrillation [4,5]. The use of rivaroxaban was further expanded to include VTE treatment and postoperative VTE prophylaxis in orthopaedic surgery, offering clinicians new treatment options [6,7].

Examination of trends in oral anticoagulant use between 2007 and 2011 shows rapid adoption of dabigatran into clinical practice with almost 17% of atrial fibrillation cases being treated with dabigatran by the end of 2011 [8]. Similarly, rivaroxaban has seen increases in its use [9,10]. Given the rapid rise in TSOAC prescriptions, there are concerns about off-label administration and potential complications arising from inappropriate prescribing [8]. Further complicating this is the relative inexperience of many providers with these new agents. Bleeding complications can be catastrophic given the lack of proven reversal agents [11].

On the basis of these concerns, we aimed to determine the characteristics of patients prescribed a TSOAC prior to inpatient admission to a university healthcare system and to assess conformation to FDA labelling for the TSOACs. We also attempted to determine any differences in prescription patterns between prescribing and admitting services.

Materials and methods

We conducted a retrospective study of consecutive patients admitted to the University of Utah Hospital, a 476-bed academic medical centre with more than 23 000 admissions annually, and its affiliated institution the Huntsman Cancer Hospital. Investigational review board approval was obtained prior to initiation of this study. All patients admitted for any reason from 1 March 2012 to 30 September 2013 were eligible for inclusion. A database

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query was used to identify all patients with apixaban, rivaroxaban or dabigatran recorded on their admission medication reconciliation. For each inpatient admission, a clinical pharmacist or pharmacy resident is required to reconcile and document preadmission medications. We believe this to be a reliable method for identifying patients prescribed a TSOAC prior to admission. Two authors (S.A.J. and P.M.Y.) performed manual chart review and data extraction of all identified patients, using prespecified categories of age, weight, sex, hospital admitting service, outpatient prescribing service (if known), baseline creatinine and creatinine clearance (CrCl), admission creatinine and CrCl, indication for TSOAC therapy, echocardiography findings, major contraindications, vital status and major bleeding events. FDA-approved indications were determined by drug-specific package inserts. We classified major bleeding events according to the International Society on Thrombosis and Haemostasis definition [12]. We defined major contraindications as active bleeding; recent major bleeding; CrCl less than 30 ml/min; active liver disease (Child–Pugh Class B/C or hepatic transaminases more than three times the upper limit of normal range). We defined baseline creatinine as the lowest recorded creatinine within 6 months prior to admission, or if unavailable, the lowest recorded creatinine during admission. We calculated CrCl using the MDRD equation [13] followed by stratification into one of three ranges (<30, 30–50 or >50 ml/min). We also evaluated additional relative contraindications to TSOAC therapy: presence of a mechanical heart valve, haemodynamically significant valvular heart disease (moderate to severe mitral or aortic stenosis), medication interactions, thrombocytopenia (<90 000 platelets/μl), pregnancy, high bleeding risk and uncontrolled hypertension.

We used descriptive statistics to report rates of off-label use, indications for treatment, major and relative contraindications and major bleeding events. We also describe prescription patterns by prescribing service. We used Fisher's exact test or the Kruskal–Wallis test for comparisons of groups. All analyses were performed with Stata v12 (StataCorp, College Station, Texas, USA).

Results

We identified 160 patients who received dabigatran, rivaroxaban or apixaban prior to hospital admission. Median age was 65 years, median weight was 89 kg, median baseline creatinine was 0.88 mg/dl and median admission creatinine was 0.95 mg/dl (Table 1). Over half (53.1%) the patients received rivaroxaban, 43.7% received dabigatran and 3.1% received apixaban prior to admission. The indications for receiving a TSOAC were largely atrial fibrillation (68.1%) and VTE treatment (25.6%). Orthopaedic surgery related VTE prophylaxis was less common (0.6%). Other indications constituted the remaining 5.6%. Most (80.7%) patients treated for atrial fibrillation had an echocardiogram available to review. Haemodynamically significant valvular heart disease was rare (1.8%) in these patients. Ninety percent of

Table 1 Baseline characteristics of study population

Characteristic	Dabigatran $N=70$ (43.8%)	Rivaroxaban $N=85$ (53.1%)	Apixaban $N=5$ (3.1%)	Totals $N=160$
Age (years)				
Median	68	63	71	65
Interquartile range	58–74	52–73	61–75	55–74
Weight (kg)				
Median	91.3	86.7	75.5	88.9
Interquartile range	72.3–108.7	73.7–107	68.3–90.4	73–107
Male sex, no./total (%)	41 (58.6)	58 (68.2)	3 (60)	102 (63.8)
Baseline creatinine (mg/dl)				
Median	0.89	0.86	0.88	0.88
Interquartile range	0.76–1.05	0.7–1.1	0.68–1.57	0.72–1.08
Admission creatinine (mg/dl)				
Median	0.93	0.99	0.94	0.95
Interquartile range	0.77–1.06	0.75–1.28	0.7–1.67	0.76–1.19
Indication, no./total (%)				
Atrial fibrillation	65 (40.6)	41 (25.6)	3 (1.9)	109 (68.1)
VTE treatment	4 (2.5)	37 (23.1)	–	41 (25.6)
VTE prophylaxis	–	1 (0.6)	–	1 (0.6)
Other	1 (0.6)	6 (3.8)	2 (1.3)	9 (5.6)
Prescribing service, no./total (%)				
Cardiology	45 (28.1)	22 (13.8)	3 (1.9)	70 (43.8)
Family medicine	3 (1.9)	–	–	3 (1.9)
Haematology/Oncology	1 (0.6)	17 (10.6)	–	18 (11.3)
Infectious disease	1 (0.6)	–	–	1 (0.6)
Internal medicine	2 (1.3)	8 (5.0)	1 (0.6)	11 (6.9)
Neurology	1 (0.6)	–	–	1 (0.6)
Orthopaedic surgery	–	1 (0.6)	–	1 (0.6)
Plastic surgery	–	1 (0.6)	–	1 (0.6)
Pulmonary	1 (0.6)	3 (1.9)	–	4 (2.5)
Unknown	16 (10.0)	32 (20.0)	1 (0.6)	49 (30.6)
Vascular surgery	–	1 (0.6)	–	1 (0.6)

patients had an FDA-approved indication for TSOAC therapy. Twelve patients (7.5%) received a TSOAC for an off-label indication: nonorthopaedic surgery related VTE prophylaxis, valvular atrial fibrillation, portal vein thrombosis, cerebral vein thrombosis, left ventricle thrombus, antiphospholipid antibody associated skin ulcer, atrial tachycardia, and orthopaedic ankle surgery related VTE prophylaxis. An additional four patients (2.5%) received VTE treatment with dabigatran, which was an off-label indication at the time of our analysis [14].

None of the patients had a baseline CrCl less than 30 ml/min. Five patients had a CrCl less than 30 ml/min at the time of admission; of these, two were continued on dose-reduced dabigatran. The calculated CrCl for these two patients was 23 and 25 ml/min, respectively. Active liver disease was present in five (3.1%) patients at the time of admission; one patient received rivaroxaban and one patient received dabigatran while hospitalized. Major bleeding events were identified in 4.4% of patients upon admission, including gastrointestinal bleeding (1.9%); subdural haematoma (1.3%); haemorrhagic stroke (0.6%); and leg ulcer haemorrhage (0.6%). At the time of our review, 11.9% of patients had died since their index admission.

Relative contraindications were identified in 32.5% of patients (Table 2). Medication interactions accounted for the largest proportion of relative contraindications, with 24.4% of patients receiving one or more interacting medications during their hospitalization. Thrombocytopenia was noted in 2.5% of patients. Review of echocardiograms identified 4.3% of patients to have haemodynamically significant valvular heart disease, and mechanical heart valves in 2.2% of patients. Of these patients, 4.3% were receiving TSOAC therapy for atrial fibrillation and 2.2% for other indications. Uncontrolled hypertension was present in 0.6% of patients.

Cardiology was the most common prescribing service accounting for 43.8% of patients, followed by haematology/oncology (11.3%), internal medicine (6.9%) and other specialty services (7.5%). Identification of the prescribing service could not be determined during chart review for 30.6% of patients. The hospital admitting services were similarly distributed with the cardiology, haematology/oncology and internal medicine services responsible for 31.3, 15 and 15%, respectively. We found no significant differences between prescribing services in regard to major contraindications ($P = 0.14$) and major bleeding events ($P = 0.77$). Significant differences between prescribing services with respect to FDA-approved indications ($P < 0.001$) were identified. Cardiology was more likely than other services to adhere to FDA-approved indications (97 vs. 84%, $P = 0.01$), and family medicine less likely (33 vs. 91%, $P = 0.03$).

Table 2 Relative and major contraindications present on admission

	Number of patients (%)
Relative contraindications	
Medication interaction	45 (28.1)
Antiarrhythmic agent	3 (1.9)
Antiepileptic drug	2 (1.3)
Antimicrobial agent	6 (3.8)
Antiplatelet agent	8 (5.0)
Nondihydropyridine calcium channel blocker	17 (10.6)
NSAID	16 (10.0)
Thrombocytopenia <90 k	4 (2.5)
Valvular heart disease	4 (2.5)
Mechanical heart valve	2 (1.3)
Uncontrolled hypertension	1 (0.6)
Other	2 (1.3)
Major contraindications	
Major bleeding event	7 (4.4)
CrCl <30 ml/min	5 (3.1)
Active liver disease	5 (3.1)

Discussion

When new medications enter the market, it is common for physicians to prescribe them for off-label indications [15]. TSOACs are not an exception and convey significant risk if not prescribed or monitored appropriately. In a large database review, Kirley *et al.* [8] reported substantial off-label use of dabigatran. To our knowledge, we present the first consecutive case series from an academic medical centre to assess TSOAC prescription patterns. Observed rates of off-label TSOAC use in our study (10.6%) were lower than previously reported (37%); none would have been considered off-label if treated with warfarin [8,16]. Major contraindications to TSOAC therapy (significant renal insufficiency, active liver disease and active or recent bleeding) were present in 10.6% of patients upon admission, although in our series, only one patient was inappropriately continued on TSOAC therapy. Dose-reduced dabigatran (75 mg twice daily) was continued briefly in one patient with active hepatitis and in two patients with CrCl between 15 and 30 ml/min after inpatient admission. Notably, dabigatran dose-reduction has not been evaluated in clinical trials; instead, it is based upon small pharmacological studies [17]. Despite relative contraindications being frequently observed (32.5%), no direct adverse outcomes were identified in these patients. Major bleeding events were uncommon (4.4% of patients) and similar to the major bleeding event rates observed in TSOAC clinical trials [18–20]. Mortality was high (47.4%) in patients admitted to the haematology/oncology service, but no deaths were directly attributable to TSOAC therapy. Further evaluation of prescription patterns demonstrated significant differences between prescribing services. Cardiology was significantly more likely to adhere to FDA-approved indications than other services (97 vs. 84%, $P = 0.01$). Family medicine adhered to FDA-approved indication less often (33 vs. 91%, $P = 0.03$), although this difference was statistically significant, the total number of prescriptions was low ($n = 3$).

There are several possibilities that may explain our findings. First, prior to the FDA approval of dabigatran, there was an institution-wide educational initiative led by

the University of Utah Healthcare Thrombosis Service to educate healthcare providers on the appropriate use of these medications [21]. It is possible that this initiative decreased the rates of off-label usage of these medications, although it is foreseeable in a large medical centre that such an initiative may not reach all providers. Second, the University of Utah Medical Center has a large cardiac electrophysiology division that aggressively manages atrial fibrillation. In our study, atrial fibrillation was the most common indication for TSOAC therapy and nearly half (47.5%) of the patients were either admitted to the inpatient cardiology service or prescribed a TSOAC by an outpatient cardiologist for atrial fibrillation. This may have introduced selection bias into the study design. Alternatively, the initial FDA-approved indication for all of the TSOACs was stroke and systemic embolization prophylaxis in nonvalvular atrial fibrillation; our results may reflect thoughtful and appropriate prescribing patterns within our institution rather than selection bias. Third, oral anticoagulants are recognized as high-risk medications [22]. This fact may have deterred the early adoption of TSOACs by prescribers who do not routinely order oral anticoagulant therapy. Last, even with clear FDA-approved indications (prophylaxis/treatment of thromboembolism associated with atrial fibrillation, cardiac valve replacement, myocardial infarction, pulmonary embolism and venous thrombosis), less common clinical scenarios necessitating oral anticoagulation have historically been treated with warfarin (Coumadin) [16,23]. The paucity of evidence for TSOAC use in these conditions may also have deterred their early adoption.

The strengths of our study include a consecutive series of patients with manual chart review to determine the specific indication(s) and contraindication(s), and serious adverse events related to TSOAC use. The manual chart review may offer more insight than prior database analysis of self-reported prescribing information that may not accurately capture or report these data [8]. Weaknesses of our study include single-centre design, small sample size and retrospective design, and included individuals were limited to inpatient admission status. The sample size may be underpowered to detect significant differences in prescribing patterns or complications attributable to TSOACs. The aforementioned unique features of the University of Utah hospitals may limit this study's generalizability to other practice settings.

Conclusion

TSOACs offer several potential advantages over the narrow therapeutic window encountered with warfarin, specifically the avoidance of frequent laboratory monitoring and dose adjustments, fewer interactions with food and other medications and more predictable pharmacology. Despite these advantages, the TSOACs require judicious prescribing to avoid unnecessary risks of anticoagulant therapy. Contrary to our initial impressions, anecdotal experience and published reports, our findings suggest that off-label prescribing generally occurred at low rates. Continued administration in the presence of major contraindications was rare in the inpatient setting. No serious adverse events other than major bleeding were directly attributable to TSOAC therapy in our study. Widespread adoption of these agents should be expected, as additional therapies are developed and evidence on their safety and efficacy accumulates. Prescribers need to remain aware of major contraindications and therapeutic limitations.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 US Department of Health and Human Services. Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism 2008. Available at: http://www.ncbi.nlm.nih.gov/books/NBK44178. Accessed 21 May 2014.
2 Naccarelli GV, Varker H, Lin J, Schulman KL. Increasing prevalence of atrial fibrillation and flutter in the United States. *Am J Cardiol* 2009; **104**:1534–1539.
3 Walsh S. FDA approves Pradaxa to prevent stroke in people with atrial fibrillation. 19 October 2010. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm230241.htm. Accessed 23 June 2014.
4 Walsh, S. FDA approves Xarelto to prevent strokes in people with common type of abnormal heart rhythm. 4 November 2011. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm278646.htm. Accessed on 21 May 2014.
5 Walsh, S. FDA approves Eliquis to reduce the risk of stroke, blood clots in patients with nonvalvular atrial fibrillation. 28 December 2012. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333634.htm. Accessed 21 May 2014.
6 Yao S. FDA expands use of Xarelto to treat, reduce recurrence of blood clots. 2 November 2012. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm326654.htm. Accessed on 21 May 2014.
7 Jefferson E. FDA approves Xarelto to reduce risk of blood clots after hip, knee replacements. 5 July 2011. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm261839.htm. Accessed on 21 May 2014.
8 Kirley K, Qato DM, Kornfield R, Stafford RS, Alexander GC. National trends in oral anticoagulant use in the United States, 2007 to 2011. *Circ Cardiovasc Qual Outcomes* 2012; **5**:615–621.
9 Luger S, Hohmann C, Kraft P, Halmer R, Gunreben I, Neumann-Haefelin T, *et al.* Prescription frequency and predictors for the use of novel direct oral anticoagulants for secondary stroke prevention in the first year after their marketing in Europe: a multicentric evaluation. *Int J Stroke* 2014; **9**:569–575.
10 Yan X. Prescribing patterns of novel oral anticoagulants following regulatory approval for atrial fibrillation in Ontario, Canada: a population-based descriptive analysis. *Canad Med Assoc J* 2013; **185**:1479–1480.
11 Siegal DM, Garcia DA, Crowther MA. How I treat target-specific oral anticoagulant-associated bleeding. *Blood* 2014; **123**:1152–1158.
12 Schulman S, Kearon C, and the Subcommittee on Control of Anticoagulation of the Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in nonsurgical patients. *J Thromb Haemost* 2005; **3**:692–694.
13 Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, *et al.* Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem* 2007; **53**:766–772.

14 Lewis M. FDA approves Pradaxa (dabigatran etexilate mesylate) for treatment and reduction in the risk of recurrence of deep venous thrombosis and pulmonary embolism. 2 April 2014. Available at: http://us.boehringer-ingelheim.com/news_events/press_releases/press_release_archive/2014/04-07-14-fda-approves-pradaxa-dabigatran-etexilate-mesylate-treatment-reduction-risk-of-recurrence-deep-venous-thrombosis-pulmonary-embolism.html. Accessed on 17 June 2014.
15 Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med* 2006; **166**:1021–1026.
16 Bristol-Myers Squibb. Coumadin (warfarin) U.S. Full Prescribing Information. October 2011. Available at: http://packageinserts.bms.com/pi/pi_coumadin.pdf. Accessed on 6 April 2015.
17 Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 2010; **49**:259–268.
18 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, *et al.* Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009; **361**:1139–1151.
19 Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, *et al.* Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011; **365**:981–992.
20 Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, *et al.* Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011; **365**:883–891.
21 Schulman S, Crowther MA. How I treat with anticoagulants in 2012: new and old anticoagulants, and when and how to switch. *Blood* 2012; **119**:3016–3023.
22 Wysowski DK, Nourjah P, Swartz L. Bleeding complications with warfarin use: a prevalent adverse effect resulting in regulatory action. *Arch Intern Med* 2007; **167**:1414–1419.
23 Martinelli I, De Stefano V. Extra-abdominal venous thromboses at unusual sites. *Best Pract Res Clin Haematol* 2012; **25**:265–274.