Evaluation of bleeding rates for patients taking direct oral anticoagulants under a guided prescribing system

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Background

Direct Oral Anticoagulants (DOACs), including dabigatran, apixaban and rivaroxaban, have been in use in Australia for almost a decade. Their use has increased over the years, however there is limited local real-world usage data and many clinicians remain concerned about monitoring and availability of reversal agents, with idarucizumab for dabigatran being the only available agent.

At Northern Health, the prescription of DOACs for both inpatients and outpatients require approval by the Haematology Department. This involves the treating team creating a record in "Guidance®", a guided prescribing system, of treatment details and relevant patient characteristics. Applications are reviewed by the Haematology registrar, consultant or pharmacist. Retrospective review of approvals provides opportunity for evaluation of DOAC use in the local setting.

Aim

To evaluate DOAC usage in patients who were initiated treatment at least three months prior to the audit, following prescription via a guided prescribing system at Northern Health. Bleeding and thrombosis rates were assessed.

Methods

A retrospective cohort study was conducted of DOAC prescriptions entered into the Guidance® system from September 2013 to August 2016 at Northern Health. This preliminary analysis presents data from September 2013 to August 2014.

Patients were included if DOAC therapy was initiated at least three months prior to the audit. Duplicate records were removed. Patients were excluded if they lived outside the catchment area and had no follow-up (i.e. out-patient appointments) after DOAC approval.

Data extraction included patient characteristics: age, weight, renal function (eGFR), concurrent CYP3A4 or PGP inhibitor/inducers, concomitant antiplatelet therapy, previous venous thromboembolism (VTE), cerebrovascular accident (CVA), or ischemic heart disease (IHD). In patients with atrial fibrillation (AF), a CHADSVASC score for stroke risk was collected, if available. DOAC therapy details included indication, dose and therapy duration.

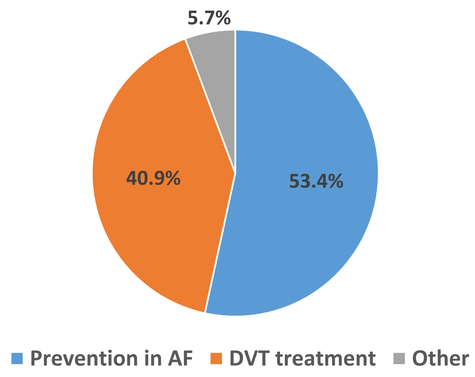
Medical records were reviewed to identify subsequent admissions or emergency presentations for DOAC-related adverse events (haemorrhage) and thrombosis.

Results

Between September 2013 to August 2014, 99 treatment episodes were recorded in Guidance®. Eleven patients met the exclusion criteria; 88 patients were included in the study (Table 1). Rivaroxaban was the most frequently prescribed DOAC. The most common indications for DOAC use were stroke or embolism prevention in the setting of AF (n=47) or VTE treatment (n=36) (Figure 1).

Table 1, Figure 1: Direct oral anticoagulant use: agents and indications

N=88	N (%)
DOAC agent	
Apixaban	11 (12.5)
Dabigatran	15 (17.0)
Rivaroxaban	62 (70.5)
Indication	
Stroke/embolism prevention in AF	47 (53.4)
DVT Treatment	36 (40.9)
Other	5 (5.7)



Patients prescribed rivaroxaban were younger and had a higher median eGFR than those prescribed apixaban or dabigatran, while patients on apixaban weighed less (Table 2). Median duration of therapy was similar across groups.

Table 2: Baseline patient demographics across the three DOAC agents

Median (IQR)	Total cohort (n=88)	Apixaban (n=11)	Dabigatran (n=15)	Rivaroxaban (n=62)	P value*
Age, years	65.5 (51-74)	83 (78.5-87)	83 (79-86.7)	59 (45-68.7)	**<0.001**
Weight, kg	78.8 (68-92)	62.3 (56-66)	86.6 (56-66)	83 (69-93)	**0.026**
eGFR, mL/min	86.5 (69-90)	61 (54-68)	61 (55-66)	90 (79-90)	**0.001**
Duration of therapy, months	12 (5-33)	12 (3-30)	12 (8-28)	12.5 (5-30)	0.654

*Calculated using Kruskal-Wallis independent samples test

There were seven adverse events identified: six bleeding events (total rate 6.8%) and one thrombosis event (total rate 1.6%) (Tables 3, 4).

Results (Continued)

Table 3: Rates of adverse events between DOAC agents

Event, n (%)	Apixaban	Dabigatran	Rivaroxaban	P value*
Bleed	2 (18)	0 (0)	4 (6.5)	0.15
Thrombosis	0 (0)	0 (0)	1 (1.6)	0.99

*Calculated using Fishers' exact test

Table 4: Individual bleeding events

Bleeding Event	DOAC details	Time to event (days)
Vaginal bleeding	Rivaroxaban 20mg daily	87
Vaginal bleeding	Rivaroxaban 20mg daily	92
Nasal bleed	Rivaroxaban 20mg daily	87
Upper GI bleed	Rivaroxaban 20mg daily	153
Upper GI bleed	Apixaban 2.5mg bd	5
Haemorrhagic stroke	Apixaban 2.5mg bd	240
	Median (IQR)	**89.5 (87-138)**

One bleeding event was classified as major (ISTH 4)[1]: a fatal intracranial haemorrhage in an 89 year old female weighing <50kg, with a baseline eGFR of 45, and no history of CVA or VTE, who was on apixaban 2.5mg twice daily for AF.

The thrombosis event, a deep vein thrombosis (DVT), occurred in a patient on rivaroxaban 20mg daily for prevention of VTE, with a history of VTE, two years after DOAC initiation.

Three patients were receiving concurrent CYP3A4 inhibitors: one taking verapamil (also a PGP inhibitor), one taking diltiazem, and one taking long-term erythromycin. There were twelve patients receiving aspirin, including two patients taking dual antiplatelet therapy and one patient on aspirin/dipyradimole. None of the bleeding events occurred in patients taking concomitant CYP3A4/PGP inhibitors or antiplatelet medications.

Eighteen patients had a history of VTE, and 23 had a history of CVA or IHD. Despite 47 patients receiving DOACs for AF, a CHADSVASC score was only available for seven patients (median CHADSVASC 4.5, moderate-high risk).

Discussion

In this cohort of patients treated with DOACs during 2013 and 2014, rivaroxaban was the most frequently prescribed agent. Haemorrhagic adverse events were identified in 6.8% of patients, with a median onset of approximately 3-months following commencement of therapy. The bleeding rates for rivaroxaban are comparable to EINSTEIN-EXT (6%)[2] and lower than ROCKET AF (14.9%).[3] Few adverse events were associated with apixaban or dabigatran, likely due to the small sample size. As this study progresses, we expect to obtain a more accurate reflection of events associated with long term DOAC therapy.

Study inclusion criteria required that DOAC therapy was initiated a minimum of three months prior to data extraction. This enabled the identification of most expected adverse outcomes, as a large proportion of adverse effects to DOACs (e.g. bleeding) occur within the first month of treatment;[4] in addition, most recurrent VTEs occur within three months of the first event.

The use of a guided prescribing tool, Guidance®, allowed for easy identification of patients prescribed a DOAC during the study period. Due to the requirement for Haematology Department approval for all DOAC prescribing, both inpatient and outpatient, we may be confident no patients were missed during the time period.

A limitation of this study is the retrospective design, relying on accurate and complete medical records. Collecting data from patients' electronic records may have led to missed events in patients who presented to another health service. We attempted to minimise this by excluding patients outside our catchment area who were not followed-up in clinic.

Conclusion

Rivaroxaban was the most frequently prescribed DOAC in the 88 patients analysed. The overall incidence of bleeding presentations was 6.8%; with one fatal bleed identified. Bleeding rates for rivaroxaban were similar to that of the published literature, likely due to patient selection via the guided prescribing system. Electronic decision support tools such as Guidance® may assist with evaluation of local prescribing data for medications such as direct oral anticoagulants.

References

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