Appropriateness of Direct Oral Anticoagulant dosing in relation to renal function at hospital discharge.

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Background

Atrial Fibrillation (AF) is a common type of cardiac arrhythmia mainly affecting the elderly.[1] In 2014–15, there were 58,608 hospitalisations for AF in Australia (430 hospitalisations per 100,000 people aged over 35 years).[2] The irregular heart rhythm in AF causes blood pooling in the atria and the formation of clots that can travel to the brain which can cause a stroke.[3] AF is associated with an increased risk of hospitalisations, morbidity and mortality.[1] For these reasons, anticoagulation is recommended.[4] The $CHA_2DS_2VAS_c$ score is a risk assessment tool to determine whether anticoagulation is required to prevent embolism[1].

Warfarin has historically been used for oral anticoagulation in this patient group, however it has several clinical limitations (dietary and drug interactions, consistent monitoring and narrow therapeutic index).[3] Warfarin's use has declined since the development of direct oral anticoagulants (DOACs). Dabigatran and Rivaroxaban are PBS approved for the prevention of thrombotic events in non-valvular AF.[5] DOACs have overcome some of the clinical limitations to prescribing Warfarin as they have more convenient dosing regimens, less drug interactions and do not require INR monitoring.[3] Anticoagulants are considered high-risk medications and are associated with adverse drug events such as haemorrhagic stroke and gastrointestinal haemorrhage.[6] DOACs require dose adjustment based on factors such as renal function and age.[3] Inappropriate DOAC dosing can lead to increased stroke or bleeding risk.[6]

Anticoagulant prescribing practises in Australia since the introduction of DOACs have not been extensively described.

Aim

To assess the appropriateness of DOAC dosing in relation to renal function for patients with AF discharged from a large metropolitan health network.

Methods

- This study was a retrospective cross sectional study.
- Patients admitted between June 2013 to June 2017 with a discharge diagnosis of AF (ICD-10-AM code I48) and prescribed Rivaroxaban or Dabigatran at discharge were included. Diagnosis data and validated prescription data from electronic medical records were linked using SAS v9.4.
- Dosing appropriateness was assessed by comparing the dose prescribed on discharge against the patient's last eGFR and age in accordance with the Therapeutic Guidelines.
- Standard dose Rivaroxaban (20mg/day) was considered appropriate if eGFR >50mL/min and reduced dose Rivaroxaban (15mg/day) was appropriate if eGFR was 30-49mL/min. Dabigatran 110mg twice daily was considered appropriate if age > 75years and eGFR 30-50mL/min or 150mg twice daily (age <75 years and eGFR >50mL/min).
- Discharge doses were then classified as either appropriate, inappropriate (subtherapeutic, supratherapeutic) or contraindicated (eGFR <30mL/min).

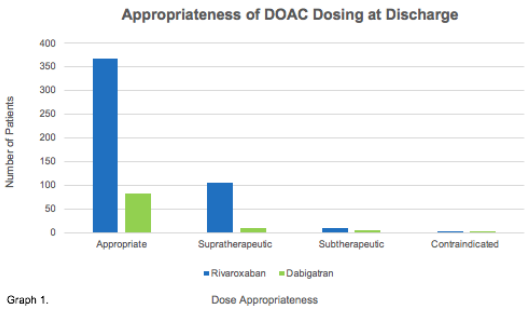
Results

609 patients were included in the study. Patient characteristics are presented in Table 1.

Table 1. Clinical Characteristics of Patients Included

	Rivaroxaban N = 486	Dabigatran N = 123
Age		
Mean (SD)	73 (12)	76 (12)
Median (IQR)	74 (67 - 83)	78 (69 - 84)
> 75 years, % (n)	50 (250)	64 (79)
Gender, % (n)		
F	54 (233)	49 (61)
Co-morbidity, % (n)		
CCF	22 (111)	26 (32)
HT	38 (191)	38 (48)
Diabetes	15 (77)	25 (31)
Stroke, Systemic embolism, Venous thromboembolism	11 (53)	30 (37)
MI, IHD, Peripheral arterial disease, Atherosclerosis	17 (85)	18 (22)
Renal and Liver Disease	3 (17)	13(16)
Prior bleeding	4 (20)	10 (12)
Medications, % (n)		
Aspirin	17 (83)	12 (15)
Beta Blockers	65 (326)	66 (82)
ACEi/A2RB	48 (239)	58 (72)
CCB	17 (85)	23 (29)
Statin	41 (208)	63 (78)
Diuretics	33 (168)	36 (45)
Digoxin	19 (96)	22 (27)
Amiodarone	12 (61)	8 (10)
NSAIDs	3 (13)	3 (4)
CHA2DS2VASC score , % (n)		
Median (IQR)	3 (2-4)	3 (2.8- 4)
0 --- 1	18 (87)	9 (11)
2 -- 3	60 (293)	49 (61)
> 4	22 (106)	41 (51)
HASBLED score ,% (n)		
Median (IQR)	3 (1-2)	3 (1-3)
0 --- 1	21(169)	29 (36)
2 -- 3	58 (282)	62 (76)
> 4	7 (35)	9 (11)
LOS , % (n)		
Median (IQR)	4 (2-7)	4 (2-8)
0 --4	60 (289)	55 (68)
5--9	27 (135)	24 (30)
≥ 10	13 (62)	20 (25)

Dosing appropriateness is shown in Graph 1.



Graph 1.

Overall, prescribed dose on discharge were appropriate for 472 (78%) patients. For the 137 (22%) patients whose prescribed dose was inappropriate, 117 (85%) doses were supratherapeutic, 16 (12%) were subtherapeutic and 4 (3%) contraindicated.

Discussion

Supratherapeutic DOAC dosing is a concern because the risk of bleeding outcomes increases.[3] 19% of all patients received a supratherapeutic dose, with Rivaroxaban (22%) being the most common. Several case reports of bleeding complications with supratherapeutic dosing of Rivaroxaban and Dabigatran have been reported in the literature. [8] Patients with severe renal impairment are particularly vulnerable to these effects.[8]

Greater than 50% of patients were over 75 years of age and female. Patients discharged with Rivaroxaban had a median age of 74, consistent with median age of patients in the pivotal ROCKET-AF study. [6]

The recommendations for $CHA_2DS_2VAS_c$ score have changed overtime. The current therapeutic guidelines recommend, patients with a score of zero to one have a low stroke risk and therefore anticoagulation is of marginal benefit. [4] 16% of all patients with a CHA2DS2VASc score of zero to one in our study were anticoagulated.

Four patients received a DOAC on discharge despite its use being contraindicated based on renal function. Three of those four patients were prescribed Rivaroxaban. In the two landmark clinical trials for AF, those with several renal impairment were excluded as the risk of thromboembolic and bleeding complications were increased. [8]

Strengths

Data was collected from a large metropolitan hospital network which provided an adequate sample size and represented a diverse patient demographic.

DOAC prescribing was assessed against the therapeutic guidelines which contains nationally recognised practice guidelines for stroke prevention.

Limitations

Renal function was measured using eGFR rather than Cockcroft- Gault equation which the 2 landmark AF studies used.[6,7] In some cases, eGFR may overestimate renal function and overestimate appropriateness of DOAC dosing.[8]

Long-term follow-up data were not available therefore clinically important outcomes associated with the doses prescribed could not be monitored.

Apixaban was not included in the study as the complete appropriateness of dosing couldn't be assessed as there was no weight of patients.

Clinical pharmacist interventions weren't directly assessed which may impacted the results.

Conclusion

Study results showed that most patients received an appropriate dose of Rivaroxaban or Dabigatran at discharge. Inappropriate doses were mostly supratherapeutic, which may increase patient's bleeding risk.

Our study shows there is room for improvement in optimizing DOAC dosing for stroke prevention in the setting of AF.

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