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BRIEF COMMUNICATION

Trends in direct oral anticoagulant use in patients presenting with acute stroke

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Abstract

Acute ischaemic strokes occur despite the use of direct oral anticoagulants (DOACs). A retrospective review was conducted at a high-volume primary stroke centre over a 3-year period to assess the acute management of stroke presentations in patients prescribed DOACs. During the time period of the study, 103 of 195 anticoagulated stroke patients presented within the timeframe for thrombolysis and only 15 patients had DOAC plasma level assays performed. Of these 103, 5 received thrombolysis; however, DOAC level was not a factor in these cases.

Anticoagulation therapy reduces the risk of stroke for patients with non-valvular atrial fibrillation (NVAF) by approximately 60%.[1] Compared to traditional Vitamin K antagonists (VKA), direct oral anticoagulants (DOACs) offer benefits in terms of efficacy, safety and convenience and are being increasingly prescribed among the Australian population.[2] In 2018, 3.5 million Australians were prescribed a DOAC, with 15% year-on-year growth.[3]

Across recent pooled international data, 22.5% of patients who had an ischaemic stroke had been receiving anticoagulant therapy prior to stroke onset, with approximately 13% on DOACs and 72% on warfarin.[4] We previously showed that over a 5-year period from 2012 to 2017, one third of warfarinised patients with acute stroke were thrombolysed due to subtherapeutic international normalised ratio (INR) levels on presentation (INR ≤ 1.7) compared to only 1 out of the 19 patients taking DOACs who had received thrombolysis.[5] The lack of acute DOAC-level testing was identified as one of the potential barriers to providing intravenous thrombolysis to patients presenting with stroke while on DOACs. This may be further attributed to the lack of awareness of such assays by front-line clinicians, perceived delays to decision-making and the limited availability of appropriate training, staff or equipment in hospital pathology laboratories.

The anticoagulant effect of a DOAC is likely proportional to its plasma concentration, with consensus for safe thrombolysis based on specific plasma DOAC levels to determine 'on-therapy' status.[6] Although thrombin time (TT) and anti-Xa levels can exclude the presence of dabigatran and factor Xa inhibitors, respectively, they do not provide a reliable assessment of anticoagulant effect since results have insufficient correlation to specific drug levels.[7,8] Additionally, heparin-calibrated anti-Xa assays have limited sensitivity at lower drug concentrations and so cannot provide accurate levels to guide thrombolysis decision-making.[9]

At our centre, testing for plasma DOAC level was made available starting in early 2018. With the 2019 EXTEND trial expanding the thrombolysis window from 4.5 h up to 9 h, if accompanied by favourable perfusion imaging, this enabled a potentially greater proportion of patients access to thrombolysis therapy.[10] We aimed to examine the utility of acute DOAC-level testing in patients presenting with stroke while taking DOACs. We hypothesised an increased ordering of DOAC levels and increased intravenous thrombolysis in this cohort compared prior to 2018.

Consecutive patients presenting with a new diagnosis of ischaemic stroke, haemorrhagic stroke or transient

Conflict of interest: None.

Table 1 Demographics, clinical characteristics, comorbidities, stroke severity and treatment received in each direct oral anticoagulant (DOAC) group and warfarin

N (%) or median (IQR)	DOAC				Warfarin
	Combined (*n* = 195)	Apixaban (*n* = 120)	Rivaroxaban (*n* = 49)	Dabigatran (*n* = 26)	(*n* = 64)
Demographics					
Age, median (IQR) (years)	81 (75–88)	81 (75–88)	79.6 (74–84)	83.5 (78–87)	83 (76–87)
Female	83 (43)	55 (46)	22 (45)	6 (23)	23 (36)
Premorbid mRS > 3	41 (21)	37 (31)	4 (8)	0	2 (3)
Indication for DOAC					
Atrial fibrillation or flutter	170 (87)	106 (88)	38 (78)	26 (100)	50 (78)
Venous thromboembolism (VTE)	23 (12)	12 (10)	11 (22)	0	4 (6)
Mechanical valve replacement	0	–			10 (16)
Other (tachy-brady syndrome, not documented)	2 (1)	2 (2)	0	0	0
Clinical characteristics					
Haemorrhagic stroke	27 (14)	20 (17)	3 (6)	4 (15)	8 (13)
Ischaemic stroke	146 (75)	86 (72)	42 (86)	18 (69)	53 (83)
Transient ischaemic attack (TIA)	22 (11)	14 (12)	4 (8)	4 (15)	3 (4)
Presented within 4.5 h of stroke onset	72 (37)	45 (38)	16 (33)	11 (42)	29 (45)
Risk factors and comorbidities					
$CHAD_2DS_2$-VASc	5 (4–6)	5 (4–6)	6 (3–5)	5 (3.25–6)	4 (3–5)
Congestive heart failure	23 (12)				15 (23)
Hypertension	133 (68)				39 (61)
Diabetes mellitus	57 (29)				12 (19)
Past history of stroke/TIA/VTE	108 (55)				25 (39)
Vascular events	56 (29)				7 (11)
eGFR	67.5 (50–81.3)				54 (42.5–72.5)
Creatinine	82.5 (71–99)				103 (82.8–122)
Stroke severity					
Presentation NIHSS	3 (1–6)	3 (1–7)	3 (2–6.5)	3 (1–5.3)	8 (3–14)
Mild (NIHSS ≤ 4)	100 (51)	56 (47)	29 (59)	15 (58)	23 (36)
Moderate (NIHSS 5–15)	45 (23)	28 (23)	9 (18)	8 (31)	20 (31)
Severe (NIHSS ≥ 16)	14 (7)	9 (8)	4 (8)	1 (4)	13 (20)
Not documented	36 (18)	–			8 (13)
Reperfusion therapy received					
Thrombolysis only	4 (2)	1 (0.8)	0	3 (11.5)	3 (5)
Primary Endovascular Clot Retrieval (ECR)	5 (3)	3 (2.5)	1 (2)	1 (3.8)	2 (3)
ECR with thrombolysis	1 (0.5)	1 (0.8)	0	0	0

IQR, interquartile range; mRS, modified Rankin Score; NIHSS, National Institutes of Health Stroke Scale.

ischaemic attack (TIA) to Box Hill Hospital, while prescribed anticoagulation, between January 2018 and December 2020 were included for analysis. Patient demographics and clinical parameters were extracted from hospital electronic medical records and departmental databases. These variables included age, sex, premorbid modified Rankin score (mRS), type of event and subjective reporting of adherence to DOAC. Risk factors and comorbidities were collected based on the components of the $CHAD_2DS_2$-VASc score (including congestive heart failure, hypertension, diabetes mellitus, history of stroke or TIA and vascular disease) and renal function.

Severity of stroke symptoms was classified according to the National Institutes of Health Stroke Scale (NIHSS) as follows: mild (NIHSS ≤ 4), moderate (NIHSS 5–15) and severe (NIHSS ≥ 16). For patients who presented within the window for thrombolysis, timing of the last DOAC dose and plasma DOAC level were extracted, where available. All analyses were performed using Microsoft Excel and SPSS statistics.

Over the 3-year period, 276 patients were included, with 17 patients excluded due to incorrect categorisation (anticoagulant naïve prior to index event) or having incomplete medical records. Of the remaining 259 patients, 25% (64/259) were taking warfarin, whereas 75% (195/259) were taking a DOAC – apixaban (62%), rivaroxaban (25%) and dabigatran (13%).

Eighty-six per cent (168/195) of patients presented with ischaemic stroke or TIA, and 14% (27/195)

presented with haemorrhagic stroke. The number of patients presenting *per annum* with stroke while prescribed DOAC increased by 21% over the study period. Indications for DOAC use were primarily AF (88%) and venous thromboembolism (VTE) (12%). The $CHAD_2DS_2$-VASc score was generally comparable across DOAC and warfarin groups (5 vs 4), with patients prescribed DOAC having better median renal function (eGFR) than the warfarin group (67.5 vs 54) (Table 1).

Overall, 53% (103/195) of patients with ischaemic stroke symptoms presented within 9 h from the time they were last known to be well or normal. Five (5/103, 4.9%) of these patients received thrombolysis compared to three (3/64, 5%) in the warfarin cohort, with the same percentages (3%) from both the DOAC and warfarin cohorts transferred for primary endovascular clot retrieval (ECR). Among the five DOAC patients who were thrombolysed, two patients received idarucizumab for dabigatran reversal, whereas the other three had presented with DOAC suspension for more than 48 h (while in the peri-procedural period or due to bleeding risk). Primary exclusion reasons for the 98/103 patients who did not receive thrombolysis were mild or rapidly resolving symptoms (45%), premorbid mRS > 3 (22%), established computed tomography changes (8%) and perceived increased bleeding risk (due to recent procedure, stroke or bleeding event) (7%) (Table S1).

The remaining 17 patients had reported their last DOAC intake within 48 h, with plasma DOAC-level testing performed in eight patients (8/17, 47%) to assess suitability for safe thrombolysis as per Australian Stroke Guidelines.[11] Two patients had plasma DOAC levels below the expected 'on-therapy' range; however, neither received thrombolysis after consideration of symptom severity (mild with NIHSS 1) and the potential for other differential diagnoses, such as a seizure. There were no clear reasons identified to account for their low DOAC levels.

In total, 15 patients underwent plasma DOAC-level testing, with a median turn-around time from drawing blood samples to results of 71 min (interquartile range 46.5–143) (Table S2). Within this group, 12 patients were rejected for thrombolysis based on having DOAC levels within the 'on-therapy' range. Three patients had low DOAC levels – two for no clear reason as described earlier and one with low apixaban levels who had forgotten to recommence the DOAC after stopping it prior to an elective procedure. This patient presented with a stroke 1 week later and was ultimately not deemed an appropriate thrombolysis candidate due to a premorbid mRS of 4.

Of the 195 patients prescribed a DOAC, 30% (59/195) were non-adherent to guideline-based DOAC prescribing. Of these, incorrect dosing (42%), medication suspension due to adverse bleeding or peri-procedural management (36%) and patient non-compliance (22%) were given as reasons for non-adherence to DOAC (Table S3). Suspension of DOAC occurred when determined by clinicians to have adverse effects of bleeding, including gastrointestinal bleeding (12%) and epistaxis (7%). DOACs were also withheld peri-procedurally for a median period of 5 days, depending on the type of procedure (Table S4).

Discussion

Our results suggest that patients taking oral anticoagulants who present to hospital with an acute stroke are much more likely to have been prescribed a DOAC than warfarin. This is consistent with the increasing trend of DOAC use over warfarin in the general community. Until recently, plasma DOAC level has not been an assay commonly available in stroke centres, and this remains the case in most, if not all, regional hospitals receiving acute stroke patients.[12] While empiric reversal of dabigatran with idarucizumab is an established strategy prior to thrombolysis, the reversal agent for apixaban and rivaroxaban is comparatively much more complicated to administer and not available in Australia.[13]

There are three considerations for DOAC-level testing in acute stroke patients. First, although no patients were thrombolysed based on a DOAC level below the 'on-therapy' range during the study period, 45% of DOAC patients with stroke had not been considered for thrombolysis due to 'mild or resolving symptoms'. Importantly, two patients who presented within the given time frame and had sufficiently low plasma DOAC levels despite recent DOAC ingestion were not considered for thrombolysis due to their mild stroke symptoms. Acute stroke decision-making requires careful consideration of risks and benefits, yet we must remain cognisant that mild strokes can result in significant disability, with ongoing trials exploring the benefit of thrombolysis in mild strokes.[14,15] Second, there is increasing evidence to suggest an association between low DOAC levels and increased stroke incidence and severity.[16,17] Third, a DOAC level outside of the expected 'on-therapy' range should prompt the clinician to search for an explanation, most commonly medication non-adherence (30% in our cohort).

The inappropriate dosing of DOAC continues to be a problem, with our rate of inappropriate dosing in keeping with findings in the literature.[18,19] A median of 5 days of DOAC being withheld prior to procedures in our cohort of stroke patients is concerning – while this is unlikely to be a situation specific to our centre, further

data from other Australian centres would be helpful to gauge the extent of this problem. Clear Australian guidelines have existed in relation to DOAC peri-procedural and bleeding management since 2014, with stopping DOAC 3 days prior to a major surgery recommended in patients with normal renal function.[20] Further dissemination of this information beyond physicians to include surgeons and proceduralists may be required, as some of these peri-operative strokes are potentially preventable.

In our cohort, urgent plasma DOAC-level tests were conducted in 15 patients, with a median turn-around time to results of 71 min. Of the patients who reported prior DOAC ingestion in the last 48 h, just under half (47%) had plasma DOAC-level tests performed, warranting an increase in testing frequency among this cohort. Despite having a turn-around time in the lower range of what we previously found among metropolitan hospitals, for the levels to be practically useful and to maximise the effectiveness of thrombolytic therapy, a faster turn-around time is required. To this end, a protocol with the pathology laboratory was established in early 2021 to expedite urgent DOAC level analysis in acute stroke patients, reducing the median plasma DOAC-level turn-around time to 52 min for urgent samples on a recent audit following the protocol implementation.

In conclusion, we found the utilisation of DOAC plasma-level assays to be low in relation to the number of patients presenting with acute stroke while taking DOAC. There remain considerable challenges with inappropriate DOAC dosing and evidence of unnecessarily prolonged periods of DOACs being withheld prior to elective procedures, which may have contributed to patients' ischaemic stroke. Apart from boosting adherence to guideline-based prescribing and improving peri-procedural communication to patients, increasing DOAC-level testing in this cohort of patients may allow more eligible patients to receive thrombolytic therapy for stroke.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site:

Table S1 Exclusion reasons for potential candidates for thrombolysis (eligible based on timeframe)
Table S2. Plasma DOAC levels and eligibility for thrombolysis as per Australian Stroke Guidelines
Table S3. Reasons for non-adherence to DOAC
Table S4. Peri-procedural suspension of DOAC