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
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 CHAD2DS2-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 pre-
scribed DOAC increased by 21% over the study period. Indications for DOAC use were primarily AF (88%) and
venous thromboembolism (VTE) (12%). The CHA\textsubscript{D}2\textsubscript{DS\textsubscript{2}}-VASc score was generally comparable across
DOAC and warfarin groups (5 vs 4), with patients pre-
scribed 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 warfar-
in 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 test-
ing performed in eight patients (8/17, 47%) to assess
suitability for safe thrombolysis as per Australian Stroke Guidelines.\textsuperscript{11} Two patients had plasma DOAC levels
below the expected ‘on-therapy’ range; however, nei-
ther received thrombolysis after consideration of symp-
tom 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 elec-
tive procedure. This patient presented with a stroke
1 week later and was ultimately not deemed an appropri-
ate 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 deter-
mined 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 pro-
cedure (Table S4).

### Discussion

Our results suggest that patients taking oral anticoagu-
lants 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 com-
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.\textsuperscript{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.\textsuperscript{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 throm-
bolysis due to ‘mild or resolving symptoms’. Import-
antly, 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 ongo-
ing trials exploring the benefit of thrombolysis in mild
strokes.\textsuperscript{14,15} Second, there is increasing evidence to suggest an
association between low DOAC levels and increased stroke
incidence and severity.\textsuperscript{16,17} Third, a DOAC level outside of
the expected ‘on-therapy’ range should prompt the clini-
cian to search for an explanation, most commonly medica-
tion non-adherence (30% in our cohort).

The inappropriate dosing of DOAC continues to be a
problem, with our rate of inappropriate dosing in keep-
with findings in the literature.\textsuperscript{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 guide-
lines 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. Further dissemi-
nation 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, war-
ranting 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 proto-
col 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 sam-
ple 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 inap-
propriate 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 adher-
ence 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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References

1 van Walraven C, Hart R, Singer D, Laupacis A, Connolly S, Petersen P et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation. JAMA 2002; 288: 2441.
2 Ntaios G, Papavasileiou V, Diener HC, Makaritsis K, Michel P. Nonvitamin-K-antagonist oral anticoagulants in patients with atrial fibrillation and previous stroke or transient ischemic attack: a systematic review and meta-analysis of randomized controlled trials. Stroke 2012; 43: 3298–304.
3 Australian Commission on Safety and Quality in Health Care. Medication Without Harm – WHO Global Patient Safety Challenge. Australia’s Response. Sydney: ACSQHC; 2020.
4 Seiffge D, De Marchis G, Koga M, Paciarotti M, Wilson D, Cappellari M et al. Ischemic stroke despite oral anticoagulant therapy in patients with atrial fibrillation. Ann Neurol 2020; 87: 677–87.
5 Valente M, Leung S, Wu P, Oh D, Tran H, Choi P. Ischaemic stroke and transient ischaemic attack on anticoagulants: outcomes in the era of direct oral anticoagulants. Intern Med J 2020; 50: 110–13.
6 Moll S. Do plasma levels of direct oral anticoagulants correlate with hemorrhagic and thrombotic complications? Hematologist 2018; 15.
7 Cuker A, Siegal D, Crowther M, Garcia D. Laboratory measurement of the anticoagulant activity of the non–vitamin K oral anticoagulants. J Am Coll Cardiol 2014; 64: 1128–39.
8 Sarode R. Direct oral anticoagulant monitoring: what laboratory tests are available to guide us? Hematology 2019; 2019: 194–7.
9 Shin H, Cho M, Kim R, Kim C, Choi N, Kim S et al. Laboratory measurement of apixaban using anti-factor Xa assays in acute ischemic stroke patients with non-valvular atrial fibrillation. J Thromb Thrombolysis 2017; 45: 250–6.
10 Ma H, Campbell B, Parsons M, Churilov L, Levi C, Hsu C et al. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. N Engl J Med 2019; 380: 1795–803.
11 Stroke Foundation. Clinical Guidelines for Stroke Management. Melbourne, Australia: 2021 [cited 2021 Nov 11]. Available from URL: https://informme.org.au/guidelines/clinical-guidelines-for-stroke-management
12 Dwyer M, Francis K, Peterson G, Ford K, Gall S, Phan H et al. Regional differences in the care and outcomes of acute stroke patients in Australia: an observational study using evidence from the Australian Stroke Clinical Registry (AuSCR). BMJ Open 2021; 11: e040418.
13 Connolly S, Milling T, Eikelboom J, Gibson C, Curnutte J, Gold A et al. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. N Engl J Med 2016; 375: 1131–41.
14 Tan S, Choi P. Mild in name but not in nature. Stroke 2021; 52: 2005–6.
15 ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 Feb 29 – Identifier NCT02398656. A Randomized Controlled Trial of TNK-TPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion (TEMPO-2): 2015 Mar 20 [cited 2022 Mar 6]; [about 5 screens]. Available from URL: https://clinicaltrials.gov/ct2/show/record/NCT02398656
16 Nosíl V, Petrovičová A, Skorňová I, Bolek T, Dlhá J, Stančiaková L et al. Plasma levels of direct oral anticoagulants in atrial fibrillation patients at the time of embolic stroke: a pilot prospective multicenter study. Eur J Clin Pharmacol 2022; 78: 557–64.
17 Rizos T, Meid A, Huperez A, Dumschat C, Purrucker J, Foerster K et al. Low exposure to direct oral anticoagulants is associated with
ischemic stroke and its severity. *J Stroke* 2022; **24**:88–97.
18 Sanghali S, Wong C, Wang Z, Clive P, Tran W, Waring M et al. Rates of potentially inappropriate dosing of direct-acting oral anticoagulants and associations with geriatric conditions among older patients with atrial fibrillation: the SAGE-AF study. *J Am Heart Assoc* 2020; **9**: e014108.
19 Ruiz Ortiz M, Muñiz J, Raña Míguez P, Roldán I, Marín F, Asunción Esteve-Pastor M et al. Inappropriate doses of direct oral anticoagulants in real-world clinical practice: prevalence and associated factors. A subanalysis of the FANTASIIA registry. *EP Europace* 2017; **20**: 1577–83.
20 Tran H, Joseph J, Young L, McRae S, Curnow J, Nandurkar H et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. *Intern Med J* 2014; **44**: 525–36.

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