Rapid Review

Title: Timing of anticoagulation after recent ischaemic stroke in patients with atrial fibrillation

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I Summary

Background: About 13-26% of all acute ischaemic strokes are related to non-valvular atrial fibrillation (AF), the commonest cardiac arrhythmia globally. Deciding when to initiate oral anticoagulation in these patients is a longstanding, common and unresolved clinical challenge. Although the risk of early recurrent ischemic stroke is high in this population, early oral anticoagulation is suspected to increase the risk of potentially harmful intracranial haemorrhage, including haemorrhagic transformation of the infarct. This assumption, and current guidelines, are based on historical (mostly observational) data of populations treated using heparins, heparinoids or Vitamin K antagonists (VKA) to prevent recurrent ischaemic stroke. Randomized controlled trials have shown that direct oral anticoagulants (DOAC: apixaban, dabigatran, edoxaban and rivaroxaban) are at least as effective as VKA in primary and secondary prevention of AF-related ischemic stroke, with around half the risk of intracranial haemorrhage, but none of the DOAC trials included patients with recent ischaemic stroke. Clinicians therefore remain uncertain regarding when to commence DOACs after acute ischaemic stroke in patients with AF.

Recent developments: Recent prospective observational data and two small randomised trials investigated the risks and benefits of early DOAC initiation (most with a median delay of 3-5 days) in mild to moderate AF-associated ischaemic stroke. These studies reported that early DOAC treatment was associated with low rates of clinically symptomatic intracranial haemorrhages or surrogate haemorrhagic lesions on MRI, but a higher rate of recurrent ischemic stroke with later DOAC initiation (i.e. >7 or >14 days after index stroke).

Where next? Adequately powered randomised clinical trials comparing early to later oral anticoagulation with DOACs in ischaemic stroke associated with AF are justified to confirm acceptable safety and efficacy of this strategy. Four such randomized controlled trials (collectively planned to include around 9000 participants) are underway, using either single time cut-off points for early vs. late DOAC initiation, or selecting DOAC timing according to the severity and imaging features of the ischemic stroke; they should help determine the optimal timing to start DOACs after recent ischemic stroke and whether this should differ according to stroke severity. Results of these trials are expected from 2021.

II. Introduction

Cerebral embolism attributable to non-valvular atrial fibrillation (AF) accounts for 13-26%[1-3] of ischaemic strokes; this proportion increases with age[4]. Historical observational data report that the risk of early recurrence after AF-related ischaemic stroke might be as high as 13% in the first 10 days without anticoagulation, while early anticoagulation with heparins or warfarin was associated with lower rates of recurrence[5]. A meta-analysis of subgroups of patients with AF from RCTs using heparins within 48 hours of recent ischaemic stroke found a non-significant reduction in the risk of recurrent ischaemic stroke but a significantly increased risk of intracranial haemorrhage[6]. Vitamin K antagonists (VKA) are still recommended as first line therapy in patients with AF in many countries, although there is only limited historical randomised evidence for VKA in acute ischaemic stroke. Since 2010, four direct oral anticoagulants (DOAC: apixaban[7], dabigatran[8], edoxaban[9] and rivaroxaban[10]) have been approved for use in patients with (non-valvular) AF. Systematic Cochrane reviews and meta-analyses found that these DOAC have similar efficacy to VKA in primary and secondary prevention of stroke but have about half the rate of intracranial haemorrhage[11,12]. However, none of the RCTs comparing DOACs and VKA included patients with recent ischaemic stroke associated with AF – presumably because of concerns about the risk of haemorrhagic transformation of the ischaemic brain tissue or other intracranial haemorrhage.

In acute AF-related ischaemic stroke, the risk of both early recurrent ischaemic stroke[5] and haemorrhagic transformation[13] are highest in the days immediately after the index stroke; integrity of the microvasculature is lost, in part caused by degradation of the basal lamina and extracellular matrix,[14,15] leading to disruption of the blood-brain-barrier[16] and haemorrhagic transformation of ischemic brain tissue, ranging from petechial haemorrhage (HI) to more severe parenchymal haematoma (PH)[17]. Haemorrhagic transformation (HI or PH) is reported in about 9% of patients with acute ischaemic stroke and, like ischaemic stroke recurrence, is associated with large ischemic lesions; PH is associated with large cardioembolic lesions and acute recanalization therapies[18]. It is suspected (though not proven) that early initiation of anticoagulation might exacerbate or cause parenchymal haemorrhage, with potentially serious clinical consequences[18], through these mechanisms. This concern has led clinicians to delay anticoagulation, though the independent contribution of haemorrhagic transformation of the infarct to clinical worsening remains uncertain[19] and randomised clinical trial evidence is not

available. A lack of consensus for when to start oral anticoagulation (particularly with DOACs, the current usual standard of care) is shown by a recent online survey among UK stroke physicians, in which 95% were uncertain about the optimal timing[22]. In this Rapid Review, we summarize and critically review current guidelines, recently published new data from observational and small randomised studies, and give an overview of ongoing investigator-initiated randomized controlled trials of oral anticoagulation timing after AF-related ischaemic stroke.

III Guidelines

Current guidelines are imprecise and inconsistent regarding when and how to start oral anticoagulation after AF-related ischaemic stroke (see Panel). The "1-3-6-12 days rule" was introduced in 2013 by the European Heart Rhythm Association/European Society of Cardiology (EHRA/ESC)[28] because of evidence that larger infarcts (causing more severe stroke syndromes) are more likely to undergo haemorrhagic transformation.[18] Although the time points and definitions of stroke severity are based only on expert consensus, this guideline has been adopted, with some variations, by various countries and societies (including ESC/EHRA, ESO, Canada, Australia, Middle East and North Africa; see panel). The 2018 guidelines of the American Heart Association/American Stroke Association (AHA/ASA) on early management of patients with ischaemic stroke recommend starting oral anticoagulation between 4-14 days after onset of neurological symptoms[27] based on findings from the prospective observational Early Recurrence and Cerebral Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation (RAF) study of 1029 consecutive patients with acute ischemic stroke and known or newly diagnosed AF, in which only 12% of the patients were treated with DOAC [29]; they also recognise the need for trials of early DOACs. UK guidelines recommend that for people with "disabling" ischaemic stroke that OAC should be deferred until at least 14 days from onset but earlier for non-disabling strokes at the discretion of the clinician (United Kingdom, NICE-endorsed National clinical guideline for stroke[30]). A German guideline states that the efficacy of DOAC has not been proven within <14 days after a recent stroke (S3 guidelines 2015[31]). We found only guidelines from the pre-DOAC area for Japan (published as a supplement of the Journal of stroke and cerebrovascular disease: Shinohara et al 2011) while in India (published as a supplement of the Annals of Indian Academy of Neurology: Prasad et al 2011) and Latin America, EHRA/ESC and AHA/ASA

guidelines are widely used[34]. Repeated brain imaging prior to starting anticoagulation in patients with moderate and severe strokes to evaluate haemorrhagic transformation is recommended only by the ESC/EHRA guidelines[26], without supporting evidence. Bridging (i.e. treatment after stroke onset until start of oral anticoagulation) with low-molecular weight heparins is not recommended by the majority of guidelines, while the UK guidelines recommend using aspirin 300mg/day prior to starting oral anticoagulants. All guidelines state that the level of evidence is low (mainly Grade C – expert opinion) and that future studies are needed. Only the European Stroke Organisation-Karolinski Stroke Update (ESO-KSU)[35] and the ASA/AHA[27] guidelines cited observational data (from the RAF study) to inform their recommendations. Importantly, none of the guidelines distinguish between use of VKA and DOAC despite important differences in pharmacodynamics: for example, while, it may take 2-4 days after first intake of a VKA to achieve a therapeutic international normalised ratio of >2.0, therapeutic anticoagulation is achieved on the first day after initiating a DOAC.

IV Early anticoagulation in AF-related ischemic stroke

Historical observational data suggest that the early recurrence risk was 1.3% per day after recent AF-related ischaemic stroke[5]. Observational studies have identified age, large ischemic lesion size and atrial enlargement as risk factors for recurrent AF-related ischaemic stroke [29,36,37]. The presence of an atrial thrombus is rare [36,38], but, if detected, is associated with a high recurrence rate[36]. Large infarction is also a risk factor for haemorrhagic transformation.[18] Clinical scores including CHA_2DS_2-Vasc[39] (predicting the risk of ischaemic events) and the HAS-BLED[40] (predicting the risk of haemorrhagic events) are commonly used to determine the risk of ischaemic or haemorrhagic events in patients with AF receiving oral anticoagulants, but these scores are not designed for use in the acute stroke setting, have modest predictive value, and share many components (e.g. hypertension, age, previous ischaemic stroke) that are highly prevalent in ischaemic stroke populations. Indeed, a central clinical dilemma in stroke medicine is in assessing, differentiating and balancing the risks of ischaemic and haemorrhagic brain injury.

In patients with AF and a recent ischaemic stroke (who are at high risk for both recurrent ischaemia and haemorrhagic transformation), DOAC treatment (which should reduce ischaemia with a lower bleeding risk than VKA) is a promising strategy. However, individual

net clinical benefit will vary according to patients' absolute risk of these events, which might differ according to the timing of treatment (with early treatment likely to reduce the risk if ischaemic stroke but potentially increasing that of intracranial haemorrhage). The generally higher mortality and morbidity of intracranial haemorrhage compared to recurrent ischaemic stroke is also an important consideration.

Prior studies focused on heparins for early anticoagulation due to rapid onset of anticoagulant activity compared to VKA (which take several days to achieve full therapeutic anticoagulation), but found a non-significant reduction in early recurrence but a significant increase in haemorrhagic transformation[6]. Based on data from older studies from the early DOAC (RAF[29], 12% patients on DOACs) or pre-DOAC (VISTA collaboration[41], none taking treated with a DOAC) eras, the optimal time point to start anticoagulants might be between 4-14 days after stroke onset,[29] though the RAF study included mixed treatment protocols with low molecular weight heparin (LMWH) and warfarin as well as NOACs, and had insufficient statistical power to determine benefit of earlier anticoagulation with NOACs. Moreover, earlier (2-3 days post stroke) initiation (of VKA) was associated with fewer recurrent ischemic strokes in the VISTA prospective cohort study of 1644 ischaemic stroke patients with AF[41]. Recently, two small RCTs and several prospective observational studies focused on the early use of DOACs.

Randomized controlled trials of early DOACs in ischaemic stroke or TIA

In a randomized trial of 195 patients[42] with mild stroke (median National Institutes of Health Stroke Score 2 (IQR 0-4)) rivaroxaban was not superior to warfarin started within 5 days after a recent mild AF-related ischaemic stroke (defined as infarct size on DWI of less than 1/3 of MCA territory, 1/2 of ACA territory, 1/2 of PCA territory or 1/2 of one cerebellar hemisphere). The primary outcome of new ischaemic or haemorrhagic lesions on follow-up MRI did not differ between groups (rivaroxaban: 49.5% vs. warfarin: 54.5%: p=0.49). There was no difference in clinical outcomes (each group had one clinical ischaemic stroke while there were no symptomatic haemorrhages) but given the small sample size this study lacked statistical power so the results should be considered hypothesis-generating. The Dabigatran following acute transient ischemic attack and minor stroke II (DATAS-2, NCT02295826) trial[43] randomised 301 patients with transient ischaemic attack or minor stroke (NIHSS<9 points, DWI lesions <25ml) but without diagnosed AF to receive either aspirin or dabigatran within 72 hours of stroke onset for 30 days. The primary outcome was symptomatic parenchymal haemorrhage at 5 weeks on follow-up MRI. There were no primary outcome

events in either group (asymptomatic haemorrhage occurred in 7.8% of the dabigatran group vs 3.5% of the aspirin group, not significant). However, these data provide only indirect evidence as patients did not have diagnosed AF so might have a different risk of recurrent ischaemic stroke and haemorrhagic transformation. Nevertheless, these small trials provide some reassurance of safety for rivaroxaban or dabigatran started early in patients with mild to moderate ischaemic stroke (NIHSS <9 points).

Prospective observational studies

Several non-randomized, prospective observational studies have explored potential risks and benefits of early anticoagulation in AF-related ischemic stroke. Three studies included patients with a recent ischaemic stroke and AF that were followed-up for at least 3 months for clinical outcome events (recurrent ischaemic stroke and intracranial bleeding): a Swiss study (NOACISP) [44] included 204 participants; the Japanese SAMRUAI-NVAF study[45] included 1192 Japanese patients; and the international (Europe and Asia) RAF-NOAC study[46] included 1127 patients. All of these studies enrolled a considerable proportion (75%, 41% and 100%, respectively) of patients receiving DOACs. Key study characteristics are summarized in table 1. All studies included older patients (median age 76-79 years) with mainly minor to medium severity strokes (median NIHSS 3-8 points) and a median delay between ischaemic stroke and start of DOAC of 5 days. The annualized risk of recurrent ischaemic stroke was consistently between 7.7%/year to 8.5%/year (figure 1). While NOACISP and SAMRUAI-NVAF found low rates of symptomatic intracranial haemorrhage (1.3%/year and 0.9%/year respectively; figure 1), the annualized rate was considerably higher in RAF-NOAC (6.4%/year). However, although the majority of intracranial haemorrhages in this study occurred in patients started <3days after ischemic stroke, the relationship of these haemorrhages to early treatment is uncertain because they occurred after 30 days. Two of the studies reported increased rates of recurrent ischaemic strokes when DOACs were started late (NOACISP: 5.1%/year if started ≤day 7 vs. 9.3%/year if started >7 days, (not significant); and 2.1% vs 9.1% within the first 3 months if started between 3-14 days compared to >14 days in RAF-DOAC, p<0.001).

Four single-centre observational studies[47-50] reported on the timing of starting DOACs and short term clinical and radiological outcomes (i.e. prior to discharge from the acute care hospital) : all studies reported early initiation of DOAC (1-3 days) in patients with minor to medium stroke (NIHSS of <9 points Ref 42 or <8 points Ref 40 and 41) or small-to-medium sized infarcts (<1/3 of the affected arterial territory Ref 43) with low rates of symptomatic

and asymptomatic intracranial haemorrhages or recurrent ischaemic strokes (table 1). Two additional studies including 147[47] and 60 [49] patients, respectively, found that, despite early initiation, haemorrhagic transformation of the infarct (present prior to the start of DOAC) worsened in only a few patients (1/15[45] vs 5/25[47]).

All of these observational studies have limitations: they are prone to selection bias (ie, patients judged at low-risk of haemorrhage more likely to be started early, and higher risk patients started late); initiation of DOACs was not standardized (although timing in most studies was guided by infarct size and stroke severity); and they were biased towards milder strokes (median NIHSS scores mainly 3-8) and smaller infarcts (generally <1/3 of the affected arterial territory). Nevertheless, these studies all show that DOACs are started early in routine clinical practice across different countries and ethnicities, with low rates of intracranial haemorrhage (including haemorrhagic transformation).

V Future directions

Randomised controlled trials of early DOAC treatment

The ongoing clinical uncertainty and promising early DOAC observational studies have prompted several randomized, controlled clinical trials investigating early vs. late initiation of DOACs in patients with AF-related ischaemic stroke: ELAN (NCT03148457, Switzerland); OPTIMAS (UK), TIMING (NCT02961348, Sweden) and START (NCT03021928, USA) (see table 2). A key challenge for such trials is to include a sufficient sample size to assess differences in the risk of adverse outcome events related to the timing of oral anticoagulation. All four trials include composite primary outcomes including combinations of cerebral ischaemic and/or haemorrhagic events, three of which include either vascular or all-cause mortality. While using a composite endpoint including ischaemic stroke and intracranial haemorrhage as an outcome should increase the number of outcome events (thereby potentially increasing statistical power), early DOAC might have opposite effects on these components (i.e. reducing recurrent ischaemia, but possibly increasing intracranial haemorrhage), which could reduce any net treatment effect, potentially increasing the probability of a neutral result. Nevertheless, showing equivalent safety and efficacy for early DOAC treatment compared with late treatment would also be likely to change clinical practice in favour of early treatment given the likely convenience for patients (i.e. earlier hospital discharge), physicians (i.e. improved compliance and continuation of anticoagulant medication started in the acute hospital) and the health economic advantage for healthcare systems.

There are some important differences between trials: while OPTIMAS and TIMING use a binary definition of early treatment (≤4days) in all participants across the range of stroke severity, DOAC timing in the ELAN trial differs depending on the severity of the index stroke, based on the ESC, EHRA and ESO guidelines (Panel), which inform practice in Switzerland and other participating countries. START applies an adaptive design with 4 pre-defined time-to-treatment intervals from 2 to 14 days; response adaptive randomization will be used, modelling for ischaemic and haemorrhagic outcome events with an interim analysis after 100 subjects where new randomization probabilities will be calculated to favour the arms with the best risk profiles. Together, these trials aim to recruit up to 9000 patient; all trials are ongoing and results are expected from 2021. Differences in the trial designs will need to be considered when it comes to the interpretation of the results in a few years (e.g.

variation in how "early" DOAC initiation is defined). A pooled individual patient data analysis including data from all of these RCTs is planned, which should provide the best opportunity to determine the safety and efficacy of early DOAC treatment.

Other outstanding questions

Important yet unresolved questions concern starting anticoagulation in patients for whom DOACs are considered unsuitable (e.g. those with severely impaired renal function, contraindications to oral anticoagulants, or with severe, symptomatic haemorrhagic transformation (e.g. PH Type 2 (Figure 1). As DOACs are eliminated by the kidneys (ranging from 80% renal excretion for dabigatran to 27% for apixaban), caution is warranted in patients with renal impairment. The lower bleeding risk of DOAC as compared to warfarin was maintained with mild to moderate renal impairment (with appropriate dose reduction). However, patients with creatinine clearance <30 mL/ min were excluded from the RE-LY trial (dabigatran), the ROCKET AF/J-ROCKET AF trials (rivaroxaban), and from the ENGAGE-AF trial (edoxaban) trials; those with creatinine clearance <25 mL/min were excluded from the ARISTOTLE trial (apixaban). Thus, without adequate understanding of the risks of DOACs in patients with severe renal impairment or undergoing dialysis, DOACs should be avoided and VKAs used instead unless currently ongoing trials (i.e. NCT02942407) provide further insights. However, in patients with end-stage renal disease or undergoing dialysis, the indication and the benefit risk ratio of therapy with warfarin is also unclear, as randomized controlled trials excluded such patients

The potential roles of low dose DOAC, VKA, combined antiplatelet therapy or other antithrombotic strategies in patients with larger infarcts also remains uncertain. Left atrial appendage occlusion seems a promising option for patients with ischaemic stroke considered to have a contraindication to any form of OAC.[51] It is unlikely that currently planned RCTs will answer these questions in the very near future, and there is currently no expert consensus on how these patients should be managed. Further evidence might emerge from observational studies, but in the meantime decisions must be individualised based on careful consideration of the risks of ischaemic stroke and intracranial haemorrhage.

Another topic for investigation is the use of neuroimaging biomarkers to stratify and differentiate the risks of future ischaemia and haemorrhage. In 1490 patients anticoagulated after recent ischaemic stroke or TIA associated with AF, the baseline presence of cerebral

microbleeds (CMB, seen on GRE, T2* or SWI sequences) – found in 311 (21%) of participants - was independently associated with an increased risk of symptomatic intracranial haemorrhage (Adjusted HR 3.67, 95% CI 1.27-10.60, p 0.016)[52]. These findings support the hypothesis that CMB are a neuroimaging biomarker of a bleeding-prone arteriopathy specifically relevant for intracranial haemorrhage associated with anticoagulation. CMBs might also have relevance for haemorrhagic transformation risk, and for the optimal timing of OAC soon after ischaemic stroke, but there are no studies investigating this hypothesis. The relevance of cortical superficial siderosis, a much less common putative marker of cerebral amyloid angiopathy and associated ICH risk,[52] has not yet been investigated. Markers of cardiac anatomy and function might have relevance for the risk of recurrent cerebral embolism (e.g. transthoracic/transoesopagheal echocardiography) and merit investigation to help select patients for early DOAC treatment. For example, left atrial enlargement is an independent predictor of recurrent stroke of embolic subtype in patients with ischaemic stroke (even in patients without evidence of AF).[53,54] Subgroup analysis of completed RCTs may help further determine the role of brain and cardiac biomarkers to guide OAC.

VI Conclusion

Oral anticoagulation using DOAC effectively prevents recurrent ischaemic stroke in patients with AF. However, how soon DOACs should be recommended after ischaemic stroke is unclear; current guidelines vary between different organisations and countries and have been created on the basis of expert consensus rather than on strong evidence. Observational data show that many stroke physicians start DOACs earlier than the timeframe tested in the large randomized controlled trials and that this may be effective and acceptably safe, although needs to be confirmed in future randomised trials. Where possible, people with very recent AF-related ischaemic stroke (i.e. within the first 2-4 days) - without contraindications to anticoagulation - should be randomised to a suitable clinical trial. Where this is not possible, clinicians will need to weigh up potential risks and benefits and work within the imprecise and inconsistent advice offered by guidelines (figure 2 – grade of recommendation B, level of evidence 2a). Current accepted practice, based on consensus rather than empirical evidence, suggests a delay in people with more severe stroke and larger areas of infarction. A CT brain scan prior to commencing OAC can also clarify the severity and pattern of haemorrhagic

transformation, so is often performed in clinical practice, but whether and how haemorrhagic transformation should guide OAC remains unknown.

The ongoing clinical trials should help establish whether early initiation of DOACs is safe, prevents recurrent ischaemic stroke, shortens hospital stay or improves the continuity of anticoagulant treatment. These trials will also highlight whether adjusting the timing of anticoagulation according to infarct size or clinical severity of the index stroke is necessary to reduce the risk of clinically harmful haemorrhagic transformation (which might be overestimated in the DOAC era). We suggest that every effort should be undertaken to include patients into these trials in order to answer the important open clinical questions.

VII Search strategy and selection criteria

We searched PubMed from Jan 1, 2016 to July 20, 2018 using the following search terms: "ischaemic stroke OR ischemic stroke AND atrial fibrillation OR non-valvular atrial fibrillation OR AF AND oral anticoagulation OR direct oral anticoagulants OR new oral anticoagulants OR novel oral anticoagulants OR DOAC OR NOAC OR dabigatran OR rivaroxaban OR apixaban OR edoxaban". In addition, we searched our personal records and abstracts from recent international conferences (i.e. European Stroke Organisation Conference 2018 and others) for relevant publications or data. For the section on early anticoagulation, we selected publications presenting original data and published in English. In addition, we searched in Pubmed, personal records and internet search engines (google) using the terms "guidelines", "secondary prevention", "stroke", "atrial fibrillation" and "oral anticoagulation or DOAC or direct oral anticoagulants" to identify guidelines from relevant organisations (national or international expert committees).

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DJW: speaking honoraria: Bayer AG

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Figures, panels and tables:

<u>Panel:</u> National and international guideline recommendations on timing of anticoagulation after ischaemic stroke associated with AF.

AHA/ASA

The AHA/ASA guidelines recommend that starting OAC within 4-14 days after ischemic stroke is reasonable for most patients. However, patients with haemorrhagic transformation may be considered for a later start.

European Society of Cardiology (ESC) and European Heart Rhythm Association (EHRA) Endorsed by the European Stroke Organisation (ESO) 2016[26] and 2018.[55]Recommends giving anticoagulants 1 day after onset of transient ischaemic attack, after 3 days in patients with minor stroke (NIHSS<8), after 6 days in those with mild stroke (NIHSS 8-15), and after 12 days in those with severe stroke (NIHSS >15).

Canadian Stroke best practice recommendations 2017[56]

Follows ESC/EHRA recommendations

Australian Guidelines for stroke management 2017 (accessed online: www. strokefoundation.org.au)

Recommends giving anticoagulants 1 day after onset of transient ischaemic attack, after 5-7 days in patients with moderate stroke (not defined), and after 10-14 days in those with severe stroke (not defined).

Middle East and North Africa consensus statement 2017[57]

Recommends giving anticoagulants 12 days after onset in patients with moderate-to-severe ischemic stroke (not defined), and after 2-3 weeks in patients with a large infarct (not defined)

European Stroke Organisation (ESO) and Karolinksa Stroke Update (KSU) 2016[35]

Recommends giving anticoagulants 4 days after onset in patients with mild stroke and small infarct size (lesion of ≤1.5 cm in the anterior or posterior circulation)), after 7 days in those

with moderate stroke and medium infarct size (lesion in a cortical superficial branch of middle cerebral artery (MCA), in the MCA deep branch, in the internal border zone territories, in a cortical superficial branch of posterior cerebral artery, in a cortical superficial branch of the anterior cerebral artery), and after 14 days in those with severe stroke and large infarct size (lesion involved the complete territory of MCA, posterior cerebral artery, or anterior cerebral artery, in 2 cortical superficial branches of MCA, in a cortical superficial branch of MCA associated to the MCA deep branch or in >1 artery territory)).

United Kingdom Royal College of Physician: National clinical guidelines for stroke, Fifth Edition 2016 (https://www.rcplondon.ac.uk/guidelines-policy/stroke-guidelines)

Recommends giving anticoagulants 2 weeks after onset of disabling stroke (not defined). Earlier treatment can be considered in patients with minor, non-disabling stroke, and a lower risk of haemorrhagic transformation (not defined).

Table 1: Summary of studies on early initiation of anticoagulants after ischemic stroke (annualized event rates [%/year] were calculated whenever possible using published data [number of observed events/follow-up period])

Study	***Study population***	***Age, stroke severity (both median) and infarct size***	***Timing of anticoagulation***	***Follow-up period***	***recurrent ischemic stroke***	***intracranial haemorrhage***
Observational studies with clinical follow-up of ≥3 month						
Seiffge et al 2016 (NOACISP, Reference 37)	204 patients (155 DOAC)	79 years NIHSS 4 points No information on infarct size	Median 5 days (65% of DOAC ≤7 days)	At least 3 month	7.7%/year (5.1%/year in DOAC ≤7 days vs. 9.3%/year in DOAC>7 days, ns)	1.3%/year
Arihiro et al 2016 (SAMURAI-NVAF, Reference 38)	1192 patients (466 DOAC)	78 years NIHSS 3 points 24% small infarcts, 48% medium infarcts, 28% large infarcts	Median 5 days for DOAC	3 month	8.5%/year (VKA) and 10.1%/year (DOAC, ns)	1.2%/year (VKA) vs. 0.8% /year (DOAC)
Paciaroni et al 2017 (RAF-NOAC, Reference 39))	1127 patients (all DOAC)	76 years NIHSS 8 points 41% small infarcts, 33% medium infarcts, 22% large infarcts	No overall median reported (8 days for dabigatran and rivaroxaban, 7 days for apixaban)	3 month	7.8%/year	6.4%/year
Observational studies with clinical follow-up < 3 month or imaging surrogate outcome markers						
Macha et 2016 (reference 43)	243 patients (all DOAC)	78 years, NIHSS 5 points 17% small infarct/TIA 70% medium infarcts 13% large infarcts	Median ranging from 1.7 days for small infarct/TIA up to 6.7 days large infarcts (89.7% of DOAC ≤7 days)	Not reported	Not reported	1 case of symptomatic and 2 cases of asymptomatic ICH
Cappellari et al 2016	147 patients (all DOAC)	79 years NIHSS 8 points	Median 3.3 days, all ≤7 days, 66% ≤3 days	7 days (CT scan)	No case observed	8 cases of asymptomatic ICH (7 new, 1 pre-DOAC)

(reference 40)		54% small infarcts 22% medium infarcts 24% large infarcts				
Gioia et al 2016 (reference 42)	60 (all rivaroxaban)	74 years NIHSS 2 points Median DWI-lesion volume: 7.9ml	Median 3 days	MRI at 7 days	1 case	No symptomatic ICH, 8 asymptomatic HI
Deguchi et al 2017 (reference 41)	300 (186 DOAC)	77 years NIHSS 7 points No information on infarct size	DOAC: 3 days VKA: 7 days	Not reported	No case observed	2 intracranial ICH, 1 extracranial haemorrhage
Observational studies with a majority of patients receiving VKA or heparins						
Abdul Rahim et al 2014 (reference 34)	1,300 (pre-DOAC period)	73 years NIHSS 14 points No information on infarct size	Median 2 days	90 days	8.2% (107 events)	2.3% SICH (30 events)
Paciaroni et al 2015 (reference 23)	1029 patients (93 DOAC)	77 years NIHSS 9 points 37% small infarct 36% medium infarct 27% large infarct	Median 8.5 days (DOAC) vs. 12.1 days (VKA)	3 month	77 events (including TIA and systemic embolism)	37 events (including major extracranial haemorrhages)
Randomized controlled trials using DOAC						
Hong et al 2017 (Ref 42)	195 patients (95 rivaroxaban)	70 years NIHSS 2 Median DWI-lesion: 2.6ml	Median 2 days	4 weeks (MRI)	1 ischemic stroke	30 new haemorrhagic lesions (all asymptomatic)
Butcher et al (DATAS-2, results presented at ESOC 2018,	301 patients (151) dabigatran)	NIHSS 0-9. NB no patients had a diagnosis of AF	Within 3 days (72h)	5 weeks MRI	Ischaemic MRI lesions n=9 (6.3%)	New haemorrhagic lesions n=11 (7.8%; all asymptomatic)

not yet published)						

Table 2: Summary of key characteristics of ongoing randomized clinical trials investigating the early start of DOACs in patients with AF and a recent ischemic stroke.

	ELAN *"Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients with Atrial fibrillation"*	***OPTIMAS*** *"OPtimal TIMing of Anticoagulation after AF-associated acute cardioembolic ischaemic Stroke"*	***TIMING*** *"Timing of oral anticoagulant therapy in acute ischemic stroke with atrial fibrillation"*	***START*** *"Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation"*
Planned sample size	2000 NCT03148457	3474	3000 NCT02961348	1500 (1,000 mild/moderate 500 severe) NCT03021928
Intervention: early start	<48 hours after symptom onset (minor and moderate stroke) or at day 6 + 1 day after symptom onset (major stroke)	≤ day 4 after ischemic stroke	≤ day 4 after ischemic stroke	Adaptive trial design: time-to-treatment delay of 3, 6, 10 or 14 days in mild/moderate. 6,10,14 or 21 days in severe
Control: late start	Current recommendations (i.e. minor stroke after day 3 + 1 day, moderate stroke after day 6 + 1 day and major stroke after day 12 + 2 day).	between day 7 and day 14 after acute stroke	between day 5 and day 10 after acute stroke	
Follow-up period	30 days (secondary outcomes after 90 days)	90 days	90 days	30 days (secondary outcomes after 90 days)
Primary outcome	Composite outcome (major bleeding, recurrent ischaemic stroke, systemic embolism and/or vascular death)	Composite outcome (efficacy): recurrent ischaemic stroke, systemic embolism and/or vascular death. Principle safety outcome: major bleeding.	Composite outcome (recurrent ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality)	Composite of any CNS hemorrhagic or other major hemorrhagic events and the ischemic events of stroke or systemic embolism within 30 days of the index

				stroke
Patients with haemorrhagic transformation included	yes	yes	yes	yes
NIHSS exclusion criteria	No exclusion criteria	No exclusion criteria	No exclusion criteria	>3 and <23
Estimated end of study	10/2021	2021/22	12/2020	08/2021

Figure 1: Risk of recurrent ischemic stroke and intracranial haemorrhage in patients with atrial fibrillation and a recent ischemic stroke

Annualized rates (with 95% confidence intervals) of recurrent ischemic stroke (blue) and intracranial haemorrhage (orange) in prospective observational studies of patients receiving DOACs with at least 3 month of clinical follow-up (table 1). Data from Seiffge et al, 2016 (reference 42; Arihiro et al, 2016, reference 43; and Paciaroni et al, 2017, reference 44.

Figure 2 Timing of DOAC start – recommendations and RCTs

XX We recommend enrolment of eligible patients with ischaemic stroke and AF in one of the randomized controlled trials is emphasized. If this is not possible, data from recent prospective observational studies and small randomized controlled trials provide some guidance with limited evidence.

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