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CLINICAL OUTCOMES OF EARLY VERSUS DELAYED ANTICOAGULATION AFTER ISCHAEMIC STROKE WITH ATRIAL FIBRILLATION

TEREZA NOVOTNY[1]*, THIBAULT DELACROIX[2], AGNIESZKA ZIELINSKI[3]

Affiliation

[1]Department of Clinical Pharmacy, Vysocina Institute of Pharmaceutical Chemistry, Jihlava, Czech Republic
[2]Department of Internal Medicine, Loire Valley Institute of Pharmacy, Saumur, France
[3]Department of Clinical Pharmacy, Warmia Institute of Pharmaceutical Sciences, Olsztyn, Poland

*Corresponding author: Tereza Novotny, t.novotny@vipc.cz
ORCID iD: Tereza Novotny 0000-0001-2838-3291; Thibault Delacroix 0000-0001-4367-1187; Agnieszka Zielinski 0000-0001-0891-3283

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Abstract

Patients who have an ischaemic stroke caused by atrial fibrillation need long-term anticoagulation, but the best moment to start it in the first days after the event is uncertain. This narrative review examines what the published literature says about clinical outcomes of early versus delayed anticoagulation in this setting. It reports no new data and describes no patient series. The review covers the biological rationale, randomised trials of anticoagulants, observational cohorts on timing, and practical consensus rules. Observational evidence suggests that starting a direct oral anticoagulant within days is feasible in mild to moderate stroke, but confounding by indication and the lack of large randomised trials limit confidence.

1. INTRODUCTION

Atrial fibrillation (AF) is the commonest sustained cardiac arrhythmia and one of the best-established causes of ischaemic stroke. Population data from Framingham showed that it raised the risk of stroke roughly fivefold, independent of other vascular risk factors [1]. Strokes caused by AF tend to be larger and more disabling than those from other sources, and early death is more frequent [2, 3]. Once a patient has had such a stroke, the risk of another is substantial, and long-term oral anticoagulation is the intervention with the strongest evidence for lowering it [4, 5]. Guidelines from Europe and North America are clear on that point [6, 7, 8]. The difficulty lies elsewhere: exactly

when, in the days after the stroke, should treatment begin?

The question is a real dilemma and not a matter of preference. Anticoagulation started too late exposes the patient to early recurrence of embolism, which is highest in the first days and weeks after the index event [9, 10]. Started too soon, it risks turning a bland infarct into a haemorrhagic one or causing bleeding elsewhere in the brain, which can make a recovering patient much worse [11, 12]. For many years, clinical practice resolved this tension by waiting, often for two weeks or more, a habit based on experience and caution rather than controlled trials. As direct oral anticoagulants (DOACs) have become the standard of care, with lower intracranial bleeding than warfarin, the case for earlier starts has been debated again [13, 14].

This review examines what the published literature says about the clinical outcomes of early versus delayed anticoagulation after ischaemic stroke in patients with AF. It reports no new data, and no patient series is described. It covers the biological rationale for timing, the evidence from randomised trials and from observational cohorts, practical approaches to individual decisions, and the limitations of the existing evidence. Because the question was still being tested in randomised trials when this review was prepared, conclusions are necessarily provisional. Where evidence is observational, that is stated, since patients who were started early in cohorts were often those with smaller infarcts and a lower perceived bleeding risk [10, 14, 15].

2. BIOLOGICAL RATIONALE FOR TIMING

Cardioembolic stroke occurs when thrombus formed in the left atrial appendage travels to a cerebral artery. The source persists after the stroke, so the same mechanism can strike again, and the risk of recurrence in the first days is greater than the long-term yearly risk [3, 9, 16]. An early retrospective analysis of patients with non-valvular AF reported that recurrent embolism clustered in the first weeks after the first event [9]. Left alone, a patient with AF who has had an embolic stroke therefore remains exposed to a rapid early return of the problem. This is the main argument for starting anticoagulation without long delay, and it is supported by the observation that adequate anticoagulation is highly effective at preventing embolism once established [4, 5].

The counter-argument rests on the state of the infarcted brain. Within hours of an occlusion, the blood-brain barrier begins to break down and reperfusion, whether spontaneous or after thrombolysis, can allow blood to leak into the damaged tissue. A prospective multicentre study found that haemorrhagic transformation was common in the early days after ischaemic stroke, although most cases were asymptomatic and not associated with worse outcome [12]. Larger infarcts, higher stroke severity, high blood pressure and reperfusion therapy were among the predictors identified. Anticoagulation might convert a minor transformation into a symptomatic haematoma, and this concern is the basis for the traditional delay in treatment [11, 12].

Evidence from unselected stroke populations supports the view that early anticoagulation carries a bleeding price. The International Stroke Trial, which randomised nearly twenty thousand patients to aspirin, subcutaneous heparin, both or neither within 48 hours, found that heparin reduced recurrent ischaemic stroke but this was offset by an increase in haemorrhagic stroke [17]. A Cochrane review of anticoagulants against antiplatelet agents in acute ischaemic stroke likewise found no net benefit from early anticoagulation in general [18], and an individual patient data meta-analysis of heparins reached a similar conclusion [19]. These trials did not select patients with AF, the group in whom the embolic benefit is greatest, so they cannot settle the question for this population [17, 18, 19].

Two further considerations modify the balance. First, the benefit of anticoagulation may differ in AF because the embolic source is persistent and well defined. Second, the bleeding hazard depends heavily on the agent: warfarin carries a risk of intracranial bleeding that rises with intensity of anticoagulation [11], while DOACs roughly halve intracranial haemorrhage compared with warfarin in the

large trials [13]. The anticoagulant used in older timing studies, usually heparin followed by warfarin, was therefore less safe than the one given today. Because of this shift, data from the 1990s on heparin cannot be applied unchanged to current DOAC practice, and new evidence is needed [13, 17, 19].

3. ANTICOAGULANT EVIDENCE IN AF AND PRIOR STROKE

Warfarin was the first anticoagulant shown to prevent stroke in AF. A meta-analysis of randomised trials estimated that adjusted-dose warfarin reduced stroke by about two thirds compared with placebo, and was superior to antiplatelet therapy [4]. For patients who had already had a stroke or transient ischaemic attack (TIA), a Cochrane review concluded that anticoagulation was more effective than antiplatelet treatment for secondary prevention, at the cost of more major bleeding [5]. These findings settled the question of whether to anticoagulate, but they said nothing about when to begin after an acute stroke, since the patients in the trials were mostly enrolled months after the event [4, 5].

The four large randomised trials of DOACs against warfarin, RE-LY (dabigatran), ROCKET AF (rivaroxaban), ARISTOTLE (apixaban) and ENGAGE AF-TIMI 48 (edoxaban), established that these drugs were at least as effective as warfarin for stroke prevention with less intracranial bleeding [20, 21, 22, 23]. A meta-analysis of all four found that DOACs reduced stroke or systemic embolism by about a fifth and intracranial haemorrhage by about half compared with warfarin [13]. This difference in haemorrhage risk is precisely what makes earlier treatment more plausible. It does not, however, show that early treatment is safe, because the trials excluded patients with recent or severe stroke [20, 21, 22, 23].

Subgroup analyses focused on patients with a previous stroke or TIA. In each of the main trials, the relative benefit of the DOAC over warfarin in these patients was consistent with that in the overall population, and the absolute risk of recurrence was higher, so that the absolute benefit may have been greater [24, 25, 26]. These analyses are reassuring about long-term choice of agent in patients with prior stroke. They address patients who were generally stable and treated weeks to months after the event, and the key question of what happens in the first few days remains outside their scope [24, 25, 26]. They should not be used to support very early initiation.

One small randomised trial tackled the early period directly. It compared rivaroxaban with warfarin started within a few days of a mild AF-related stroke, and was designed to examine feasibility and safety, not to detect differences in clinical events [27]. The trial indicated that early treatment with a DOAC could be carried out within a randomised framework, and it provided pilot data for later work. Its size and the mild severity of the strokes enrolled mean that no conclusion about larger strokes can be drawn. The study is better viewed as a marker of direction than as a source of firm evidence on benefit or harm [15, 27].

Stroke and bleeding risk scores sit alongside the trials in guidelines. The CHA_2DS_2-VASc score, derived from a European survey, assigns points for heart failure, hypertension, age, diabetes, previous stroke, vascular disease and sex, and a patient who has already had an ischaemic stroke scores at least two, which in itself is enough to recommend anticoagulation [6, 28]. The HAS-BLED score estimates one-year bleeding risk from features such as uncontrolled hypertension, abnormal renal or liver function, bleeding history and age, and is intended to flag modifiable risk factors and not to deny treatment [29]. Both scores were developed in outpatient populations, so they say little about the first days after a stroke [6, 28, 29].

4. OBSERVATIONAL EVIDENCE ON TIMING

Observational studies provide most of the available data. The Early Recurrence and Cerebral Bleeding in Patients with Acute Ischemic Stroke and Atrial Fibrillation (RAF) study followed a large prospective cohort, and examined outcomes at 90 days in relation to the time of starting anticoagulation. The lowest rate of the composite of recurrence and major bleeding was seen in patients who started between four and fourteen days after onset, whereas starting very early or very late

was associated with worse results [10]. Many of the patients received heparins or vitamin K antagonists, so the findings reflect an earlier era of treatment. The pattern is consistent with the physiological argument for neither moving too fast nor waiting too long [10, 11].

A follow-up analysis from the same group concentrated on patients given non-vitamin K oral anticoagulants (NOACs, here DOACs), and found low rates of early recurrence and major bleeding when treatment was started in the first week or so after stroke [30]. A pooled analysis of several prospective cohorts in Europe and Asia, including more than five thousand patients, compared early with later initiation of DOACs in relation to stroke severity. It suggested that, in patients with mild to moderate stroke, starting a DOAC within about four days was not clearly linked to a higher rate of symptomatic intracranial haemorrhage [14]. The authors stressed that these were observational data and could not prove benefit [14, 30].

Registries from Japan add some further information. A multicentre study of patients with non-valvular AF analysed the three-month balance of benefit and risk of anticoagulation in relation to when it was begun and how severe the stroke was, and found that outcomes depended on both [31]. A later registry-based analysis of early DOAC initiation examined short-term outcomes according to the day on which the drug was started [32]. Taken as a group, these cohorts suggest that outcomes are not uniform across patients, and that stroke severity and infarct size matter more than a calendar day. They also show how difficult the data are to compare, as populations, drugs and definitions differ [10, 31, 32].

All of this evidence shares one fundamental weakness, confounding by indication. In real practice, clinicians start anticoagulants early in patients who look safe, with small infarcts, controlled blood pressure and no sign of haemorrhage, and delay in those who look fragile. Early starters therefore do better partly because they were healthier. Statistical adjustment cannot fully remove this bias, and a favourable result for early initiation may simply reflect careful selection by the treating team [10, 14, 30]. This is the central reason why the field has moved towards randomised comparisons, which were ongoing when this review was written, and why observational estimates must be treated cautiously [14, 15, 27].

The studies relevant to timing can be sorted into observational cohorts, randomised trials of anticoagulation in general or in the early period, large major trials of DOACs, and risk and guidance documents. They are summarised in table 1 and counted by type in fig. 1. What stands out is the preponderance of observational work on the specific question of timing, against a handful of randomised studies that either addressed a wider population or were too small to settle it [10, 14, 17, 27, 30]. Large trials of DOACs contribute the safety profile of the drug class, and guidance documents supply the practical rules. Each type of evidence answers a different part of the question, and none answers all of it [12, 13, 15].

Table 1: Published evidence on the timing of anticoagulation after AF-related stroke

Study or source	Principal finding reported	Ref.
RAF cohort prospective, ninety-day outcomes	Fewest recurrences and bleeds when treatment started four to fourteen days after onset	[10]
Pooled DOAC cohorts mild to moderate stroke	Early DOAC start within about four days not clearly linked to more symptomatic haemorrhage	[14]
RAF-NOACs analysis	Low rates of early recurrence and major bleeding with DOAC started within a week	[30]
Japanese registries	Benefit and risk varied with timing and stroke severity	[31, 32]
Rivaroxaban versus warfarin ultra-early randomised trial	Small pilot trial showing early treatment feasible in mild stroke	[27]
International Stroke Trial and Cochrane review	Early heparin cut recurrence but extra haemorrhage offset the gain	[17, 18]
DOACs versus warfarin meta-analysis of four trials	Fewer strokes and about half the intracranial haemorrhage	[13]
Subgroups with previous stroke or TIA	Relative benefit of DOACs consistent with overall trials	[24, 25, 26]

Study or source	Principal finding reported	Ref.
Haemorrhagic transformation prospective multicentre study	Common early on, mostly asymptomatic	[12]
EHRA 1-3-6-12 rule	Start after one, three, six or twelve days by severity (consensus)	[15]

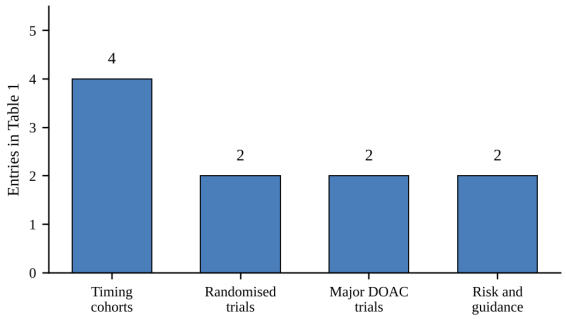


Fig. 1: Number of entries in table 1 by type of evidence

5. PRACTICAL DECISION-MAKING

In the absence of definitive trials, guidance rests on expert consensus. The European Heart Rhythm Association practical guide proposed a graded approach, often called the 1-3-6-12 rule, in which anticoagulation is begun after one day for TIA, three days for a mild stroke, six days for a moderate stroke and twelve days for a severe stroke, with imaging used to exclude haemorrhage before starting [15]. The 2020 European Society of Cardiology guideline accepts that timing should be individualised, and the American stroke guideline states that the optimal time is uncertain [6, 8]. Pharmacists and clinicians should understand that these timings are consensus-based, not trial-derived, and that they rest on the observational data above [6, 8, 15].

Several patient-level factors should shape each decision. Infarct size on computed tomography (CT) or magnetic resonance imaging is the most useful single indicator, and a repeat scan before starting treatment in moderate or severe strokes is common practice. Blood pressure should be controlled, since uncontrolled hypertension raises the risk of haemorrhage. Use of thrombolysis or thrombectomy, signs of haemorrhagic transformation, and the presence of a large or fluctuating deficit all favour waiting [8, 12, 15]. Risk scores give an overall picture: the CHA_2DS_2-VASc score estimates the stroke risk and the HAS-BLED score the bleeding risk, though neither was developed to time treatment after acute stroke [28, 29].

Choice of agent is a related decision. Guidelines now prefer a DOAC over warfarin in eligible patients with non-valvular AF, because of the lower intracranial bleeding rate [6, 7, 13]. DOACs reach full anticoagulant effect within a few hours, unlike warfarin, which needs days and overlap with heparin. Bridging with heparin is generally avoided in the acute period because it increases bleeding without clear benefit, and this was the lesson from the earlier heparin trials [17, 19]. Dose should follow the label criteria for age, weight and renal function, and interacting drugs should be checked. Adherence also needs attention, since DOACs have short half-lives and missed doses leave patients unprotected within a day [6, 15].

Pharmacists can add value at this stage. They can check dose criteria and interactions, confirm that renal function has been assessed, counsel patients and carers about bleeding signs and missed doses, and flag the need for review if the clinical picture changes. When AF is only found after the stroke, for example through prolonged cardiac monitoring, the same timing considerations apply, though identification of such patients depends on how hard one looks, with detection rates rising with the duration of monitoring [33]. A clear plan in the discharge summary, stating the date and criteria for starting anticoagulation if it has been deferred, helps avoid the opposite error of indefinite delay [15, 33].

Follow-up matters after anticoagulation begins. Patients should be told to report new headache, worsening weakness, drowsiness or visible bleeding promptly, since these may signal haemorrhage and need urgent imaging. Blood pressure targets should be maintained, and review at one to three months allows reassessment of dose, adherence, renal function and tolerability. Where treatment has been withheld for a brief period because of a large infarct, a scheduled repeat scan can help decide when it is safe to begin [8, 15]. These steps are simple, but they are the part of care that determines whether the benefit seen in

trials reaches the patient who is actually at home [6, 8, 15].

Antiplatelet therapy is sometimes used as a stopgap while anticoagulation is deferred. The evidence for this is weak, since aspirin is much less effective than anticoagulation for preventing cardioembolic stroke in AF, and combined treatment increases bleeding risk [4, 5]. Many guidelines therefore discourage routine use of aspirin as a substitute and suggest it be considered only for patients in whom anticoagulation is contraindicated, though practice varies between centres and between countries. Where aspirin is given, it is normally stopped when anticoagulation starts, to avoid unnecessary additive bleeding risk [4, 6, 7].

6. LIMITATIONS AND FUTURE DIRECTIONS

The principal limitation is that the key question was still unresolved by randomised evidence at the time of writing. Observational cohorts are exposed to confounding by indication and to differences in definitions, drugs and imaging, and the pooled analyses do not remove these problems [10, 14, 30]. Patients with the largest infarcts, the ones who most need guidance, are underrepresented in the cohorts, because they are rarely started on treatment early. The older trials of heparin used drugs that are no longer standard, and the major DOAC trials excluded the patients of greatest interest [17, 20, 21]. Finally, this review is narrative and did not follow a formal systematic protocol.

Generalisability is a further problem. The cohorts reviewed here come mainly from Europe, Japan and North America, in centres with stroke units, rapid imaging and access to DOACs. In settings where anticoagulation is monitored poorly, where DOACs are unaffordable, or where scanning is limited, the balance of risks may differ, and consensus rules built on high-resource practice may not apply. Patients with prosthetic valves or significant mitral stenosis were excluded from the DOAC trials and need warfarin, so the timing evidence for DOACs does not cover them [6, 7, 20]. Older and frailer patients, the typical people with AF-related stroke, are less well represented than younger participants [2, 3, 13].

Several developments would improve the situation. Randomised trials comparing early with later DOAC initiation, stratified by infarct size, are the obvious priority, and should report both ischaemic and haemorrhagic outcomes over at least ninety days [14, 27]. Imaging-based decision tools could replace the day-count rules with criteria tied to infarct volume and haemorrhage risk [12, 34]. Studies of patients treated by thrombolysis or thrombectomy are needed, as are data from lower-income settings where DOACs are costly and warfarin monitoring is hard [6, 35]. Until the trials report, consensus timing rules and individual judgement remain the best available approach [15, 31].

7. CONCLUSION

The timing of anticoagulation after AF-related ischaemic stroke balances two real dangers: early recurrent embolism and haemorrhagic transformation of the infarct [9, 12]. Evidence from large trials proves that anticoagulation prevents stroke in AF and that DOACs cause less intracranial bleeding than warfarin [13, 20, 21, 22, 23]. Observational cohorts suggest that starting treatment within a few days is acceptable in mild to moderate stroke, and that very early or very late starts may do worse [10, 14, 30].

Even so, these data are open to confounding, and consensus timing rules based on stroke severity are the main guide in practice [15, 31, 32]. Pharmacists can support safe use by checking dose, interactions and adherence, and by making sure the plan for starting treatment is documented [6, 33]. Randomised trials of early against later DOAC initiation, with outcomes stratified by infarct size, are needed before the question can be considered settled [14, 27].

8. ABBREVIATIONS

AF-Atrial fibrillation, DOAC-Direct oral anticoagulant, NOAC-Non-vitamin K oral anticoagulant, ICH-Intracranial haemorrhage, TIA-Transient ischaemic attack, NIHSS-National Institutes of Health Stroke Scale, CT-Computed tomography, EHRA-European Heart Rhythm Association, ESO-European Stroke Organisation, RAF-Early Recurrence and Cerebral Bleeding in Patients with Acute Ischemic Stroke and Atrial

Fibrillation

9. FUNDING

Nil

10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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