Timing of anticoagulation therapy in patients with acute ischaemic stroke and atrial fibrillation

Maurizio Paciaroni1; Giancarlo Agnelli1; Walter Ageno2; Valeria Caso1
1Stroke Unit and Division of Cardiovascular Medicine, University of Perugia, Italy; 2Department of Internal Medicine, Insubria University, Varese, Italy

Summary
In patients with acute stroke and atrial fibrillation (AF), the risk of early recurrence has been reported to range between 0.1 % and 1.3 % per day. Anticoagulants are the most effective therapy for the prevention of recurrent ischaemic stroke in these patients, but randomised clinical trials have failed to produce any evidence supporting the administration of heparin within 48 hours from stroke onset as it has been associated with a non-significant reduction in the recurrence of ischaemic stroke, no substantial reduction in death and disability, and an increase in intracranial bleeding. As early haemorrhagic transformation is a major concern in the acute phase of stroke patients with AF, determining the optimal time to start anticoagulant therapy is essential. This review which focuses on the epidemiology of recurrent ischaemic stroke and haemorrhagic transformation in patients with acute ischaemic stroke and AF, proposes a model for decision making on optimal timing for initiating anticoagulation, based on currently available evidence.

Keywords
Atrial fibrillation, ischaemic stroke, secondary prevention, acute therapy

Introduction
Patients with acute ischaemic stroke and non valvular atrial fibrillation (NVAF) are at high risk of early recurrence. In these patients, anticoagulant therapy plays a major role in the prevention of recurrent ischaemic stroke. As early haemorrhagic transformation is a major concern in the acute phase of stroke associated to NVAF, the optimal time to start anticoagulant therapy is still a controversial issue. Actually, there are no comparative studies on the optimal timing of the start of anticoagulation in patients with acute ischaemic stroke and NVAF. Thus, such a decision hinges upon the assessment of the competing risks of early thromboembolic recurrences and haemorrhagic transformation.

Clinical guidelines do not have great levels of evidence but they make recommendations. The American Heart Association/ American Stroke Association guidelines recommend: 1) For most patients with a stroke or transient ischaemic attack (TIA) in the setting of AF, it is reasonable to initiate oral anticoagulation within 14 days after the onset of neurological symptoms (Class IIa; Level of Evidence B); 2) In the presence of high risk for haemorrhagic conversion (i.e. large infarct, haemorrhagic transformation on initial imaging, uncontrolled hypertension, or haemorrhage tendency), it is reasonable to delay initiation of oral anticoagulation beyond 14 days (Class IIa; Level of Evidence B) (1).

This opinion based review focuses on the epidemiology of recurrent ischaemic stroke and haemorrhagic transformation in patients with acute ischaemic stroke and NVAF and propose a model for decision making about the timing of start anticoagulation based on clinical epidemiology and clinical judgment.

Review methods
Data for this review were identified by searching PubMed or EM- BASE for single or combined terms including: non valvular atrial fibrillation, direct oral anticoagulants, acute stroke, secondary prevention, anticoagulation, heparin, heparinoid, low-molecular-weight heparin, warfarin, vitamin K antagonist, haemorrhagic transformation, intra-cerebral bleeding, symptomatic intra-cranial haemorrhage. Original research papers, clinical series, case reports and reviews were included. Our research covered all relevant data from January 1990 to March 2016. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this Review.

Risk of thromboembolic events in patients with acute stroke and AF
In the International Stroke Trial, the risk of recurrent stroke within 48 hours (h) from stroke onset in patients with AF was 4.8 % (2). Within 90 days, the risk of recurrent stroke, transient ischaemic attack (TIA) and systemic embolism was reported to be 7.6 % (3). Old age, large lesion size and atrial enlargement were reported to...
be predictive factors for ischaemic outcome events (4, 5). Small lesion size was inversely correlated with an ischaemic recurrence. Another risk factor for early recurrence could be the presence of an intracardiac thrombus. In patients with acute stroke, a presence of an atrial thrombus is evidenced in 17% of the patients using trans-esophageal echocardiography (TEE) compared to 1–2% using trans-thoracic echocardiography TTE (4, 6).

Risk of haemorrhagic transformation in patients with acute ischaemic stroke and AF

In patients with acute ischaemic stroke, the risk of early haemorrhagic transformation is about 9%. The cardioembolic nature of acute stroke is an independent risk factor for the occurrence of parenchymal haematoma (PH), the type of haemorrhagic transformation associated with increased mortality and disability (7). In a study including 300 patients with cardioembolic acute stroke, about 7% had a PH type haemorrhagic transformation within seven days. In the period between 48–72 h from stroke onset and 90 days, the risk of symptomatic haemorrhagic transformation was about 4%. Large lesion size was an independent risk factor for symptomatic intra-cerebral bleeding (3, 7). Age is associated with increased risks for both haemorrhagic transformation of acute ischaemic stroke (8) and recurrent stroke (9).

Early anticoagulation and the risk of thromboembolic events or intra-cerebral bleedings

Randomised clinical trials failed to produce any evidence supporting the administration of heparin within 48 h from stroke onset in patients with acute ischaemic stroke (10–13). A meta-analysis involving 4,624 patients with acute cardioembolic stroke, mainly with AF, showed that in these patients, early anticoagulation was associated with a non-significant reduction in recurrence of ischaemic stroke, no substantial reduction in death and disability, and an increase in intracranial bleeding (14, 15). Vitamin K antagonists (given 2–3 days post-stroke to achieve a therapeutic anticoagulation level by days 5–7) were shown to be associated with substantially fewer recurrent stroke events over the following weeks with no excess of risk of symptomatic intra-cerebral haemorrhages (16). Early treatment (during hospitalisation) with anticoagulants was found to reduce stroke recurrence, mortality and disability (17–19). The RAF study showed that in patients with acute stroke and AF, the best time for initiating anticoagulation treatment for secondary stroke prevention was 4 to 14 days from stroke onset (3).

Type of anticoagulant

In the RAF study, 14.7% of the patients received low-molecular-weight heparin (LMWH) alone at therapeutic dose, 37.8% vitamin K antagonists, 12.1% direct oral anticoagulants, and 36.0% LMWH followed by vitamin K antagonists. The type of anticoagulant used after the index stroke in patients with AF was associated with the composite of recurrent stroke, TIA, systemic embolism and symptomatic intracerebral bleeding (3). Patients treated with oral anticoagulants alone had a better outcome compared to those treated with LMWH followed by oral anticoagulants or with LMWH alone. This last treatment led to a significantly higher risk of outcome events compared with the other treatments. About 7% of the patients treated with oral anticoagulants alone had an outcome event compared to 16.8% and 12.3% of those treated with LMWHs alone or followed by oral anticoagulants, respectively (p=0.003). The unfavourable results with LMWH alone or before warfarin were accounted for by an increased risks of symptomatic intracranial bleeding when treatment was initiated in the first days from index event. However, it cannot be excluded that low-risk patients might have been selected for oral anticoagulant strategy. Other studies found that in patients with acute stroke and AF, heparin or enoxaparin bridging increased the risk for serious bleeding (20–22).

In the large phase III clinical trials on the prevention of stroke in patients with NVAF, anticoagulant treatment was started only after seven days or more from the stroke onset (23–27). In RAF study, patients who received a direct oral anticoagulant were found to have low risk for both symptomatic intracranial bleeding (2.1%) and ischaemic event (4.3%) (3). Non vitamin K anticoagulants (NOACs) were specifically tested in the acute phase of stroke only in studies with reduced sample size (28–30). Nomura et al. (29), evaluating 50 patients with acute stroke and NVAF who where started on a NOAC at a median of two days after admission, did not find differences in new ischaemic lesions on MRI-DWIs (26% vs 28%) or haemorrhagic transformation (30% vs 39%) between patients treated with NOAC or warfarin. Shibazaki et al. (28) found that in 41 patients (25 males; mean age 76.2 years; 39 with stroke, and 2 with TIA) who started NOAC within a median of two days (Interquartile Range 1–6) from acute stroke, no symptomatic intra-cranial bleeding was observed. Arihiro et al., in 475 patients with AF who initiated NOACs within four days from stroke onset, reported a three-month cumulative rate of stroke/systemic embolism of 2.84% and a rate of major bleeding of 2.61% (31). It should be taken into account that patients with acute stroke were excluded from all randomised studies that evaluated NOACs in the prevention of stroke in patients with NVAF (32). Therefore, the decision to use NOACs in this phase should be carefully made. In 53 patients with minor stroke [National Institutes of Health Stroke Scale (NIHSS) score ≤3] without AF and evidence of acute infarction on magnetic resonance imaging treated with dabigatran within 24 h of onset, none experienced symptomatic haemorrhagic transformation (33).

Risk stratification for thromboembolic events or intra-cerebral bleedings in patients with acute stroke and AF

In patients with acute stroke and NVAF, most clinicians would like to be able to identify those patients at high risk for early recurrence, who may be potential candidates to prompt anticoagulation, to justify the risk of cerebral bleeding associated with early
anticoagulant treatment. Several risk factors could be used to estimate the risk of recurrence or cerebral bleeding.

**CHA₂DS₂-VASc score**

CHA₂DS₂-VASc score (2 points for a history of stroke or age ≥75 years and 1 point for age 65 to 74 years, history of hypertension, diabetes, cardiac failure, vascular disease and female sex) was developed to improve risk stratification for stroke in NVAF patients (9). In patients with acute stroke and AF, the RAF study found that CHA₂DS₂-VASc score was a predictive factor for the composite primary outcome event (ischaemic recurrence and symptomatic haemorrhagic transformation) within 90 days from stroke onset (3). However, CHA₂DS₂-VASc score was a predictive factor for both ischaemic recurrent event or symptomatic cerebral bleeding and therefore it cannot be considered alone for stratifying the risk for adverse outcome in patients with acute stroke and AF (▶Figure 1).

**Lesion size**

The size of the lesion is considered a main risk factor for haemorrhagic transformation (7). Large lesions were associated with high rates of symptomatic cerebral bleeding as well as of stroke recurrence (▶Figure 2). Conversely, small lesions were associated with low rates of symptomatic cerebral bleeding as well as of stroke recurrence (3). Indeed, small ischaemic lesions, especially subcortical, could be caused by other underlying aetiologies other than cardioembolism, including small vessel disease which is associated with a lower risk of recurrence. European Heart Rhythm Association (EHRA) guidelines suggest classifying the severity of stroke in accordance with the NIHSS: less than 8 = mild; between 8 and 16 = moderate; more than 16 = severe (34). We believe that lesion size on neuroimaging is more precise than NIHSS. For example, patients with a NIHSS of 10 to 12 could have a small lesion in the thalamo-capsular region.

**Left atrium size**

Several studies found that moderate to severe 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 (4, 35). Furthermore, atrial dilatation is correlated with the severity of stroke (36). In a large prospective study with a median follow-up of four years, 65 patients out of 529, had recurrent stroke (5). In multivariate models, moderate-severe left atrial enlargement was associated with greater risk of recurrent stroke compared with normal left atrial size (adjusted hazard ratio 2.83, 95% confidence interval 1.03–7.81). Furthermore, in patients with AF and acute stroke, severe atrial enlargement was associated with early stroke recurrence (4). Future studies are needed to evaluate whether left atrial enlargement could be used to drive prompt anticoagulant therapy in patients with acute stroke and AF to reduce the risk of recurrence.

**Atrial thrombosis**

Despite the lack of a proven risk/benefit assessment in favour of early anticoagulation, several studies using either TTE or TEE recommend using anticoagulation for patients with an atrial
thrombus detected by echocardiography, in order to reduce the risk of stroke recurrence (37).

**Hints for decision making**

In clinical practice, patients with acute stroke and NVAF present with different possible scenarios that are detailed in ▶ Table 1 and ▶ Figures 3–6.

- Scenario A: lesion with low risk of recurrence and low risk of haemorrhagic transformation;
- Scenario B and C: lesions with high risk of recurrence and low risk of haemorrhagic transformation;
- Scenario D: lesion with low risk of recurrence and low risk of haemorrhagic transformation but a bleeding in posterior fossa could have poor prognosis; it should be noted that our suggestions related to this scenario are not supported by firm evidence and are essentially extrapolated from data in patients with spontaneous intracranial haemorrhage (38).
- Scenario E: lesion with high risk of recurrence and moderate risk of haemorrhagic transformation;
- Scenario F: lesion with high risk of recurrence and high risk of haemorrhagic transformation but this patient has a severe clinical picture.

We suggest the following key points:

1. Randomised clinical trials failed to produce any evidence supporting the administration of anticoagulants in patients with acute ischaemic stroke within 48 h from stroke onset. Thus, aspirin should be administered in this time frame to all patients.
2. After the exclusion of haemorrhagic transformation with CT or MRI performed at 48–72 h from stroke onset, the best timing for initiating anticoagulation treatment for secondary stroke prevention seems to be between 4 and 14 days from stroke onset.
Figure 3: Possible scenarios regarding lesion size performing CT scan or MRI in patients with acute ischaemic stroke and AF (small subcortical lesion, multiple small cortical-subcortical lesions).

Figure 4: Possible scenarios regarding lesion size performing CT scan or MRI in patients with acute ischaemic stroke and AF (small cortical lesion, small posterior lesion).

Figure 5: Possible scenarios regarding lesion size performing CT scan or MRI in patients with acute ischaemic stroke and AF (medium lesion, large lesion).
3. Starting with oral anticoagulants appears to be the best treatment option because patients treated with oral anticoagulants alone seem to have a better outcome compared to those treated with LMWH alone or LMWH followed by oral anticoagulants.

4. CHA2DS2-VASc score does not seem useful to stratify the risk of adverse outcome in patients with acute stroke and NVAF because it correlates with either ischaemic or haemorrhagic events.

5. Concerning lesion size, we consider reasonable to start anticoagulant therapy after 4 days in scenarios A, B and C; after 7 days in scenario E and after 14 days in patients with scenarios D and F.

6. It is reasonable to consider all the patients with stroke in posterior fossa as scenario D because even if the lesion is small, haemorrhagic transformation could determine a poor prognosis.

7. In the presence of high risk for haemorrhagic conversion (i.e. some cases with large infarct, haemorrhagic transformation on initial imaging or uncontrolled hypertension), delaying initiation of oral anticoagulation beyond 14 days could be considered.

8. In patients with acute stroke, left atrial enlargement is an independent marker of recurrent stroke. Future studies are needed to evaluate whether left atrial enlargement could be used to drive prompt anticoagulant therapy in patients with acute stroke and NVAF to reduce the risk of recurrence.

9. A future randomised study assessing for the efficacy of direct oral anticoagulants in the acute phase of stroke in patients with NVAF is warranted.

Conflicts of interest
M. Paciaroni received honoraria as a member of the speaker bureau of Sanofi-Aventis, Boehringer Ingelheim, Bayer and Pfizer.

G. Agnelli received honoraria as a member of the speaker bureau of Boehringer Ingelheim and Bayer. The other authors report no conflicts of interest.

References


Paciaroni et al. Timing of anticoagulation in acute stroke and AF


