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CASE REPORT

# Early recurrence of ischaemic stroke of cardioembolic cause and delayed anticoagulation: a case report

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## Abstract

**Introduction:** Anticoagulation therapy is used for the management of atrial fibrillation to prevent new clots from developing. However, neurologists face the challenge of when to initiate/reintroduce treatment after a recent episode of stroke without increasing haemorrhagic risk, especially if the stroke is large and/or complicated with haemorrhagic transformation.

**Case presentation:** This report describes the case of a 72-year-old man who had an ischaemic stroke of the right posterior cerebral artery. The patient had permanent atrial fibrillation, discovered in hospital. He was not on chronic anticoagulation therapy before stroke. His anticoagulation therapy was postponed due to a haemorrhagic lesion, leading to new ischaemic stroke. The patient suddenly had right hemiplegia with aphasia for which a mechanical thrombectomy was performed but complicated by embolization into the left posterior cerebral artery with failure of thromboaspiration of this clot. Finally, the patient presented with intracranial hypertension due to ischaemic lesions and died 3 days after his readmission.

**Conclusion:** When to start anticoagulation therapy after ischaemic stroke is an unresolved question but should be discussed at least twice weekly in a stroke unit based on the clinical evolution of the patient.

**Keywords:** anticoagulation, atrial fibrillation, cardioembolic, haemorrhagic transformation, ischaemic stroke.

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## Introduction

Atrial fibrillation is a frequent and well-established aetiology of ischaemic stroke[1] with a high risk of recurrence.[2] Management of this pathology relies mainly on anticoagulation therapy to prevent new clots from developing. Neurologist dilemma is when to start or restart the treatment after a recent episode of stroke without increasing the haemorrhagic risk. The guidelines of the European Society of Cardiology (ESC) recommend commencement of treatment at baseline based on the National Institutes of Health Stroke Scale (NIHSS)[3]; this expert consensus recommendation may become evidence-based depending on the results of the ongoing studies, probably by 2023. This issue is even more problematic when the stroke is large and/or complicated with haemorrhagic transformation. In these cases, anticoagulation is more delayed despite the embolic risk. We report here a case where anticoagulation therapy was postponed due to a haemorrhagic lesion, leading to new ischaemic stroke.

## Case presentation

A 72-year-old male patient was first admitted to the acute stroke unit in Lariboisière Hospital, Paris, France, at the end of September 2019 for the management of ischaemic stroke of the right posterior cerebral artery. His medical history included arterial hypertension, type 2 diabetes mellitus and dyslipidaemia.

The patient had an unusual headache and psychomotor slowing 5 days before hospitalization. He also scratched a parked car in a non-traumatic accident 2 days before presenting at hospital. Because of persistent symptoms, he went to the emergency room, where left homonymous lateral hemianopsia and left hemineglect were noted. A CT scan confirmed a semi-recent ischaemic stroke in the right posterior cerebral artery with haemorrhagic transformation.

The patient had permanent atrial fibrillation, discovered in hospital. During hospitalization in our stroke unit, atrial

fibrillation was monitored. No intracardiac thrombus was noted in the transthoracic echocardiography, but a reduced left ventricular ejection fraction (LVEF, 45%) of probably ischaemic cause was detected. Cardiovascular risk factors were managed (LDL cholesterol at 0.7 g/L under pravastatin 20 mg and HbA1c at 6.6% under metformin 700 mg twice daily). After a complete work-up that ruled out other stroke causes, especially atheroma, a diagnosis of stroke of cardioembolic cause was made. Ten days after admission, a CT scan revealed a smaller but persistent haemorrhagic transformation. Given this complication, curative anticoagulation therapy was delayed and the patient was discharged and given antiplatelet therapy. The patient was not on chronic anticoagulation therapy before his stroke.

Two days after hospital discharge, the patient presented suddenly with a right hemiplegia with aphasia. A cerebral MRI showed a recent ischemic stroke of the left middle cerebral artery with thrombus in the proximal part of the artery (M1). No intravenous thrombolysis was conducted because of the recent stroke and the haemorrhagic transformation. A mechanical thrombectomy was performed and allowed a complete reperfusion of the left middle cerebral artery territory 4 hours after the beginning of symptoms. However, the procedure was complicated by embolization into the left posterior cerebral artery (fetal origins of both posterior cerebral artery) with failure of thromboaspiration of this clot.

Follow-up in the resuscitation department was marked by an unfavourable evolution as the patient presented with intracranial hypertension due to ischaemic lesions in the left, middle and posterior cerebral artery despite thrombectomy. The patient did not undergo any decompressive hemicraniectomy because of the major lesions and died 3 days after readmission.

## Statement of ethics

Written informed consent was obtained from the next-of-kin of the patient for publication of this case report. Authors have deidentified all data to ensure patient confidentiality.

# Discussion

The present case showed that a delay of anticoagulation therapy due to haemorrhagic transformation of a first ischaemic stroke finally led to an early recurrence in another vascular territory. Haemorrhagic risk was considered higher than embolic risk because of persistent bleeding into the ischaemic lesion on CT-scan, leading to postponing anticoagulation therapy.

Haemorrhagic transformation occurs spontaneously in about 7–10% of ischaemic stroke cases[4] and is even more frequent after thrombolytic treatment,[5] which was not the case of our patient. This complication has been described to be associated with a poorer functional outcome at 90 days (death or disabling) and not necessarily due to the early embolic recurrence.[6] Physiopathology is not clear but a haemorrhagic transformation seems to occur more often in the presence of a large ischaemic lesion[4,6] and to be associated with atrial fibrillation. In this context, appropriate management of patients is needed, as was provided to our patient.

It is clearly established that anticoagulation therapy prevents ischaemic stroke recurrence and allows improvement of survival.[7] Some scores have been developed in order to stratify patient risk[8,9] but can be difficult to rely on. In our case, the patient had a CHAD2S2-VASc score of 5, indicative of an embolic risk of 6.7% by year, whereas the HAS-BLED score was 3 with the haemorrhagic risk being at 5.8% by year. Nonetheless, the risk rate measured per year is not useful in assessing risk during the first few weeks. Accordingly, anticoagulation was planned but postponed to 3 or 4 weeks because of the stroke size and haemorrhagic transformation.

The decision of when to start anticoagulation therapy after ischaemic stroke of cardioembolic cause is challenging. The guidelines of the Heart Association/American Stroke Association suggest that anticoagulation treatment for secondary stroke prevention is better initiated 4–14 days from stroke onset.[10] Additionally, patients treated with oral anticoagulants alone, particularly a direct oral anticoagulant, have better outcomes compared with patients treated with low molecular weight heparins alone or before oral anticoagulants.[11,12] Some studies have shown that anticoagulants were probably safe to start at an early stage of the stroke as no recurrence of ischaemic or haemorrhagic stroke was noted when the treatment was started between 7 and 14 days.[9,13,14] The ESC/European Stroke Organization (ESO) guidelines recommend initiation of anticoagulation therapy based on the severity of stroke determined using the NIHSS score.[3] For mild stroke, anticoagulants can be started 3 days after the event. Treatment should be initiated 6 days after moderate stroke, whilst it can be delayed for 12 days in case of severe stroke. Although it is recommended to start after 12 days, the ESC/ESO guidelines suggest, in severe stroke, to repeat brain imaging to determine optimal initiation,[3] as we did. Data from a multicentre real-world cohort study conducted in the United States amongst 1289 patients suggest that the risk of ischaemic or haemorrhagic complication does not differ whenever anticoagulation is started. They found no significant difference in the rate of combined outcome (10%) when anticoagulation was started at less than 4 days, between 4 and 14 days, and more than 14 days after stroke.[15]

Anticoagulation therapy could have been started earlier in our case, but the patient had factors favouring delayed anticoagulation, especially a haemorrhagic transformation. Additionally, brain imaging was repeated as suggested by the ESC/ESO guidelines. These recommendations on brain imaging are based on expert consensus as most patients included in studies have a low haemorrhagic risk and, to our knowledge, no evidence-based medicine can help to answer the question of when it is safe to start anticoagulation after haemorrhagic

transformation. Embolic and haemorrhagic risks can sometimes be balanced. In those cases, the therapeutic choice and delay to start anticoagulant therapy rely mostly on the practitioner's judgment.

Another challenge was to know whether the embolic risk of this patient was underestimated. A reduced LVEF is associated with a higher embolic risk with a cut-off value usually below 40% *versus* 45% in our patient. Whilst transoesophageal echocardiography is not part of the routine exploration, it might have changed our decision if a thrombus was observed. Furthermore, the initial NIHSS was low (at 4), with this clinical score being more reliable than morphological results such as ischaemic lesion size seen on CT-scan. Haemorrhagic transformation influenced our decision, leading to postponement of treatment. Getting as much information as possible on both ischaemic and haemorrhagic risks is crucial to decide whether to initiate treatment or not.

## Conclusion

When to start anticoagulation therapy after ischaemic stroke is a question that must be discussed at least twice a week in a stroke unit. Fortunately, the majority of patients do not experience any ischaemic recurrence or haemorrhagic transformation. The negative survival outcome of this case might change our future approach in the management of other similar cases. In parallel, this case should not change our practice in terms of systematically introducing anticoagulation therapy earlier in a similar situation. Indeed, it is highly improbable that the same exact case will be encountered and anticoagulation treatment remains with a high risk of complications. Importantly, when to start anticoagulation therapy is an unresolved question that needs discussion and very careful evaluation of both embolic and haemorrhagic risks.

Finally, the results of six ongoing clinical trials comparing early *versus* late initiation of anticoagulation therapy (ELAN, NCT03148457; START, NCT03021928; OPTIMAS, NCT03759938; TIMING, NCT02961348; ERSAF, NCT03749057; PILOT, NCT03433235) will help improve decision-making. However, relying on the physician's own medical judgment is important as patients with a haemorrhagic transformation and/or a large infarct size are often excluded from such studies.

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