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CARDIOVASCULAR DISEASE AND STROKE (S. PRABHAKARAN, SECTION EDITOR)

Anticoagulation Resumption After Stroke from Atrial Fibrillation

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Abstract
The goal of this paper is to review literature on the topic of anticoagulation resumption after stroke from atrial fibrillation. Following ischemic stroke, the average annual risk of recurrent stroke in a patient with a CHADS2 score of 9 is 12.2%%, translating to an average daily risk of 0.03%%. Oral anticoagulant therapy provides a 75% relative risk reduction. However, in the 2-week period immediately following an acute stroke, this daily risk appears to be elevated. The same period is associated with an increased risk of hemorrhagic transformation of ischemic stroke due to reperfusion, impaired autoregulation, and disruption of the blood-brain barrier. Use of thrombolytics and anticoagulants, baseline infarct size, presence of microhemorrhages, and evidence of hemorrhagic transformation further increases the risk of symptomatic hemorrhagic. The decision to resume anticoagulation early after ischemic stroke from atrial fibrillation must carefully balance the risks of hemorrhagic transformation with the risk of recurrent stroke. There are currently 4 trials in progress at present (OPTIMAS, ELAN, TIMING, and START) comparing different anticoagulant resumption protocols after stroke in patients on non–vitamin K oral anticoagulants. There are a number of major limitations of the studies to date on the timing of anticoagulation resumption on stroke in atrial fibrillation. For instance, they do not explicitly account for infarct size, presence/absence of hemorrhagic transformation, recanalization via mechanical thrombectomy, and bleeding diatheses such as liver synthetic dysfunction or thrombocytopenia. These factors are crucial in personalizing a treatment decision to an individual patient.

Keywords Atrial fibrillation · Hemorrhagic transformation · Cardioembolism · Non–vitamin K oral anticoagulants · Cerebral microhemorrhages

Introduction

Atrial fibrillation affects nearly 1% of the US population and is associated with an increased risk of stroke, systemic embolism, and death [1]. Stroke occurrence in atrial fibrillation carries an enormous economic burden and increases healthcare resource utilization [2]. Anticoagulation in the form of vitamin K or non–vitamin K antagonist oral anticoagulants reduces the risk of stroke by up to 75% [3, 4].

In the weeks following an acute ischemic stroke in patients with atrial fibrillation, the benefits of oral anticoagulant therapy on recurrent ischemic stroke prevention must be weighed against the increased risk of hemorrhagic transformation (HT) after ischemic stroke [5–7]. Thus, the decision represents a delicate balance between two competing possibilities—recurrent ischemic stroke and intracranial hemorrhage (ICH)—either of which could be devastating for the patient. Complicating this decision is that a recurrent stroke would ironically necessitate delaying anticoagulation yet further.

High-quality, randomized, controlled clinical trials have not yet conclusively addressed this issue, although a growing body of observational literature has provided some general principles and there are some recommendations in professional guidelines. The 2014 American Heart Association (AHA) "Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack" [8] recommend that

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for patients with stroke or transient ischemic attack (TIA) in the setting of AF, it is reasonable to start oral anticoagulation within 14 days of onset. In the presence of a high risk for hemorrhagic transformation, they state that it is reasonable to delay initiation of oral anticoagulation beyond 14 days. Each of these is a class IIa recommendation. The 2018 AHA Guidelines on the management of acute ischemic stroke [9] recommend against "urgent anticoagulation" while the European Heart Rhythm Society recommends resuming anticoagulation with a non–vitamin K antagonist oral anticoagulant (TSOAC) 1 day after TIA, 3 days after mild stroke, 6 days after a moderate stroke, and 12 days after a severe stroke [10].

In this review, we discuss the competing risks of recurrent stroke due to atrial fibrillation and risk of hemorrhagic transformation separately. Then, we attempt to assemble a set of recommendations to optimize secondary prevention based on the available evidence and informed by our own clinical experience. There have been a number of important additions to the literature during the past 3 years and we will particularly emphasize this recent literature in our review.

Risk of Ischemic Stroke in Atrial Fibrillation

Epidemiology

Atrial fibrillation is the most common arrhythmia in the USA [11]. It is a major cause of stroke with between 18 [12] and 33% [13] of all ischemic strokes attributable to it. The annual risk of stroke associated with atrial fibrillation can be estimated using the CHA_2DS_2-VASc Score [14]. This model uses demographic factors (age and sex), as well as aspects of a person's past medical history (congestive heart failure, hypertension, stroke/transient ischemic attack/thromboembolism, vascular disease, diabetes mellitus), to stratify a person's risk of stroke by assigning a score of between 0 and 9. A person with the highest score of 9 has a yearly risk of stroke of 12.2%. Assuming a linear risk, this equates to a daily risk of only 0.03% and a 14-day risk of 0.47%. However, this risk is likely to be non-linear after an ischemic stroke such that the risk may be as high as 8% in the 90 days following an acute event [15]. In a study of patients presenting with ischemic stroke, a 1-point increase in CHA_2DS_2-VASc Score conveyed an increased risk of recurrent event with an OR of 1.22 [16]. An additional consideration is that in addition to stroke, atrial fibrillation conveys a risk of visceral infarcts and limb ischemia when anticoagulation is held [17].

Pathophysiology

An important consideration when assessing the risk of ischemic stroke associated with cardioembolism is that it tends to be severe and lead to more disability than other subtypes [18, 19]. Although it can affect any artery in the brain, they tend to involve the large arteries [20] which, in turn, cause large areas of infarction. They have a particular predilection for the anterior and middle cerebral arteries [21]. Additionally, because the large arteries are involved, they tend to implicate the cortex meaning that the affected patient has deficits in higher brain functions leading to disabling outcomes such as aphasia, alexia, neglect, visuo-spatial impairment, and agraphesthesia in addition to motor impairments which are also common. Strokes associated with atrial fibrillation are twice as likely to be fatal as those not associated with atrial fibrillation [18] and when death does occur, it is more likely to be a result of neurological injury from the stroke itself [20].

Treatment

Vitamin K antagonist therapy (e.g., warfarin) reduces the risk of stroke in atrial fibrillation by approximately 60% when compared to antiplatelet therapy which reduces the risk by only 20% [4]. In the European Atrial Fibrillation Trial (EAFT) [22], 669 patients with non-valvular AF were randomized to warfarin (with a goal international normalized ratio [INR] of 3), aspirin, or placebo. Anticoagulation reduced the risk of the composite primary outcome (stroke, myocardial infarction, systemic embolism, or vascular death) with a hazard ratio (HR) of 0.53. The risk of stroke was reduced from 12 to 4%. Patients were enrolled within 3 months of the index stroke. In the patients who were eligible for anticoagulation, 46% were enrolled within 14 days of the index event. Oral anticoagulation was more effective than aspirin in reducing the risk of the primary outcome and this was largely attributed to a major reduction in the risk of recurrent strokes (HR 0.38).

In the International Stroke Trial of 3169 patients with atrial fibrillation [20], 784 were allocated to receive unfractionated heparin at a dose of 12,500 IU SC twice per day, 773 to receive 5000 IU SC twice per day, and 1612 were not administered heparin. Without anticoagulation, the risk of ischemic stroke in the ensuing 14 days was 4.9% and the risk of intracranial hemorrhage was 0.4%. In those administered the highest dose of heparin, the stroke risk was 2.3% while the risk of ICH rose to 2.8%. There was no statistically significant difference in the rates of any stroke (ischemic or hemorrhagic) or death between those treated with anticoagulation and those not treated with anticoagulation.

Non–vitamin K antagonist oral anticoagulants (NOACs) are reported to confer a lower risk of ICH than vitamin K antagonists particularly in people with history of prior stroke [23–25]. It is challenging to make assertions about this in the immediate post-stroke period as ARISTOTLE [26] (apixaban vs. warfarin in atrial fibrillation) excluded people with a stroke in the preceding 7 days, RE-LY [27] (dabigatran vs. warfarin in atrial fibrillation) and ROCKET-AF [28] (rivaroxaban vs.

warfarin in atrial fibrillation) excluded people with a stroke in the preceding 14 days or a severe stroke in the preceding 3–6 months, and ENGAGE AF-TIMI [29, 30] (edoxoban vs. warfarin in atrial fibrillation) excluded any patient with stroke within the preceding 30 days. All trials excluded patients with a history of ICH.

Predictors

In addition to the CHA_2DS_2-VASc Score, there are other factors that influence the risk of recurrent stroke [31••]. The risk of recurrent stroke may be increased in the presence of:

1) Non-paroxysmal atrial fibrillation [32];
2) Left atrial appendage thrombus [16];
3) Left atrial enlargement: A recent study showed that left atrial enlargement conveyed an increased risk of early recurrent events (odds ratio (OR) of 2.13) [16]. Additionally, left atrial enlargement has been shown as a predictor of stroke recurrence, independent of AF, in the Northern Manhattan Stroke Study [33].
4) High risk morphologies of the left atrial appendage;
5) Atrial dysfunction: Biomarkers of left atrial cardiopathy include left atrial size and amino-terminal pro-brain natriuretic peptide (NT-proBNP) [31••].
6) The presence of spontaneous echocontrast on transthoracic echocardiography (TTE); and
7) Severe mitral stenosis [34]

The daily risk of stroke is elevated after one ischemic event and is elevated for at least the 2 weeks after a first stroke [35]. Paciaroni et al. [36••] studied predictors of recurrent thrombotic events and major bleeding in patients with acute stroke and atrial fibrillation. The ALESSA score [37] assigns a score of 2 points for age > 80 and 1 point for each of age 70–79, ischemic lesions > 1.5 cm, and severe left atrial enlargement. A higher score predicts recurrent ischemic events at 90 days. Advanced imaging modalities, such as cardiac magnetic resonance imaging [38], may be used in select cases to highlight patients at particularly high risk of recurrent stroke owing to left atrial or left ventricular thrombi.

Risk of Symptomatic Hemorrhagic Transformation

Definition

In discussing hemorrhagic transformation after acute ischemic stroke, we use the European Cooperative Acute Stroke Study (ECASS) criteria which grade according to the appearance of an infarct on neuroimaging [39]. These criteria are summarized in Table 1.

Symptomatic hemorrhagic transformation has been defined different according to different studies. The SITS-MOST criteria [40] define symptomatic intracranial hemorrhage (sICH) as a local or remote type 2 parenchymal hemorrhage that occurs on the 22 to 36 h post-thrombolysis scan combined with an increase in NIHSS of 4 points or more from baseline or leading to death. The modified SITS-MOST criteria expand this definition to include hemorrhage in the intraventricular space or subarachnoid space in addition to intraparenchymal hemorrhage. These criteria are extrapolated beyond 36 h for the purposes of defining sICH in most studies.

Pathophysiology

Cardioembolic strokes confer a higher risk of hemorrhagic infarction (OR 2.36) and of parenchymal hematoma formation (OR 5.25) than non-cardioembolic strokes [5, 41, 42] even in the absence of anticoagulation. In a cardioembolic stroke, a large- or medium-sized artery is occluded by embolus which—with variability based on the degree of collateralization—leads to tissue death distal to the occlusion. After recanalization occurs, an area of infarcted tissue is then subject to reperfusion through an artery which may have regained its normal caliber though with a disrupted blood-brain barrier. Experimental models suggest that this reperfusion—particularly in the presence of anticoagulation—is one of the reasons for this hemorrhagic transformation [43] as is disruption of the blood-brain barrier as a result of ischemia [44]. Additionally, impaired cerebral autoregulation in the setting of acute ischemic stroke contributes to this risk [45]. By contrast, strokes of small vessel etiology involve arteries that have undergone lipohyalinosis or branch atheromatous disease and have reduced flow through them at baseline and smaller volumes of infarction than cardioembolic strokes. The risk of hemorrhagic transformation increases as infarct volume increases [46]. In patients with atrial fibrillation and a prior stroke, the risk of intracranial hemorrhage is higher than in those without prior stroke [47]. In general, early hemorrhagic transformation (within the first 48 h post-stroke) is likely related to early reperfusion, tissue plasminogen activator (tPA) use, or mechanical thrombectomy with recanalization of the affected vessel. Delayed hemorrhagic transformation is more likely to be related to the use of antithrombotic therapy (antiplatelet or anticoagulant therapy).

Epidemiology

When follow-up magnetic resonance imaging is performed, over two thirds of cardioembolic strokes have asymptomatic hemorrhagic transformation [48]. Within this group, 84% had petechial hemorrhage and 16% had parenchymal hematoma. When an ischemic infarct is larger than 10 cm^3, there is a

Table 1 European Cooperative Acute Stroke Study (ECASS) criteria for grading hemorrhagic transformation

Hemorrhagic infarction	
HI-1	Small petechiae without space-occupying effect
HI-2	More confluent petechiae without space-occupying effect
Parenchymal hematoma	
PH-1	Hemorrhage in < 30% of the infarcted area with mild space-occupying effect
PH-2	Hemorrhage in > 30% of the infarcted are with significant space-occupying effect

greater than 90% probability of some form of asymptomatic hemorrhagic transformation [48]. Another study [5] included 1125 patients with acute ischemic stroke (35% cardioembolic) via computed tomography of the brain performed 5 days post ischemic stroke. In this cohort, 8.7% had hemorrhagic transformation (5.5% hemorrhagic infarction and 3.2% parenchymal hematoma). Of the patients with parenchymal hematoma, 91.7% were dead or disabled at 3-month follow-up.

Predictors

Studies have shown that larger infarct, previous intracranial hemorrhage, and thrombocytopenia portend an increased likelihood of hemorrhagic transformation [6, 49]. The risk of hemorrhagic transformation increases after mechanical thrombectomy with longer times from symptom onset to thrombectomy [7]. One study suggested that the presence of hemorrhagic infarction 1 or 2 on imaging with no symptom correlate does not increase the risk of symptomatic hemorrhagic transformation after atrial fibrillation–related stroke [50].

In the International Stroke Trial, patients with atrial fibrillation who received therapeutic anticoagulation (un fractionated heparin at a dose of 12,500 IU BiD SQ) had a 2.8% risk of symptomatic intracranial hemorrhage in the 14 days after stroke [20]. A meta-analysis of IST, TOAST, FISS-tris, HAEST, and TAIST found that in all stroke subtypes, the risk of significant intracranial hemorrhage was 0.8% with the use of heparinoids and found no net benefit to treatment with anticoagulation in the acute phase after stroke [51]. This was supported by a subsequent meta-analysis of 24 trials using anticoagulation in the acute phase after ischemic stroke [52].

In the International Stroke Trial, patients with atrial fibrillation who received aspirin but no anticoagulation had a 0.4% risk of symptomatic intracranial hemorrhage in the 14 days after stroke [20]. Another meta-analysis of randomized trials of early anticoagulation (within 48 h) in patients presenting with acute cardioembolic stroke [53] found that early initiation of anticoagulation slightly reduced the risk of recurrent stroke within 14 days though the effect did not attain statistical significance (odds ratio [OR] 0.68; 95% CI 0.44–1.06, $P = 0.09$). However, there was an increased risk of symptomatic intracranial hemorrhage—2.5% in those treated with anticoagulation compared with 0.7% in those treated with antiplatelet therapy or placebo (OR 2.89; 95% CI 1.19–7.01, $P = 0.02$). There was no net difference in long-term disability or mortality.

Cerebral microhemorrhages (CMHs) are foci of hemosiderin deposition observed as focal hypointensities on iron-sensitive MRI sequences, including gradient echo T2* and susceptibility-weighted imaging which serve as a biomarker for small vessel angiopathies [54–56]. The pattern of CMH, coupled with other markers of small vessel disease including white matter hyperintensity and enlarged perivascular spaces, can be helpful to determine the specific underlying pathology. CMHs are present nearly exclusively in lobar regions in cerebral amyloid angiopathy (CAA) while in hypertensive angiopathy, there is a preference for the basal ganglia, pons, and cerebellum [54, 57]. In meta-analyses of patients with stroke and atrial fibrillation, the presence of CMHs correlated with increased ICH risk after stroke/TIA and the magnitude of risk increased as the number of CMHs increased; odds ratio of ICH was 2.68 (95% CI 1.19–6.01) when any CMH was present and 5.50 (95% CI 2.07–14.66) when greater than 5 CMHs were present [58•]. The number of CMBs correlated with both increased stroke risk and increased ICH risk after stroke/TIA in another study that did not consider atrial fibrillation status [59]. However, the effect size was greater for ICH than for ischemic stroke [59]. Risk of ICH was more closely associated with lobar than deep CMH in both of these studies, highlighting the importance of identifying the specific underlying microangiopathy (e.g., CAA vs. hypertensive) to correctly assess ICH risk.

Early Resumption of Anticoagulation After Stroke in a Patient with Atrial Fibrillation

The approach to early resumption of anticoagulation has been informed by a number of recent studies [15, 36••, 50, 60–62] examining the rates of recurrent stroke and symptomatic intracranial hemorrhage with early anticoagulation resumption for secondary prevention after atrial fibrillation–related stroke (Table 2).

A post hoc analysis of the Preventive Antibiotics in Stroke Study (PASS) reported on 192 patients taking anticoagulants at the time of enrollment (which was within 24 h of stroke onset). Of those patients, 157 had anticoagulation continued and 35 had anticoagulation discontinued (in 20, this was a temporary discontinuation for a median of 7 days). Their analysis suggested that there was a higher rate of thrombotic events by 90 days when anticoagulation is discontinued though this did not persist after adjustment for age and NIHSS score. Of particular note in this study, in the 27

Table 2 Recent studies of early anticoagulation after atrial fibrillation–related stroke. *NIHSS* National Institutes of Health Stroke Scale, *TIA* transient ischemic attack, *sHT* symptomatic hemorrhagic transformation, *TSOAC* XXXX, *NOAC* YYYY

Author	Number	Days after stroke	Median NIHSS	Agent	Follow-up (days)	Warfarin		NOAC	
						Stroke/TIA	sHT	Stroke/TIA (%)	sHT (%)
Arihiro 2016 [60]	1137	< 7 (median 4)	8	Warfarin or NOAC	90	2.42%	91	2.74	0.21
Gioia 2016 [50]	60	< 14 (median 3)	2	Rivaroxaban	90	–	–	3.33	0
Seiffge 2016 [61]	204	Median 5 (TSOAC) and 4 (warfarin)	4	Warfarin or NOAC	90	4%	2%	2.60	0
Hong 2017 [63]	183	< 5	2	Warfarin or rivaroxaban	30	1.1%	0%	1.1	0
Paciaroni 2017 [36••]	1127	Median 7.66	7.7	NOAC (no edoxoban)	90	–	–	2.00	1.4
Wilson 2018 [62]	358	< 7 days	2	NOAC	90	–	–	1.40	0

patients with a severe stroke (NIHSS score > 15), anticoagulation was continued in 13 (48%) patients with no observed bleeding events [64]. Another study [65] retrospectively reviewed cases in which NOACs were administered to patients post-stroke via a structured protocol which was as follows: initiation of anticoagulation with a NOAC immediately in cases of TIA/minor stroke, in 3–5 days in cases of moderate strokes, and 1–2 weeks in patients with severe stroke. Only one case of symptomatic intracranial hemorrhage (0.4%) was detected during the variable follow-up period (duration of the hospitalization). Lack of post-hospital follow-up and lack of data on rates of recurrent stroke are major limitations of this study.

In a prospective observational study [36••] of 1127 patients of whom 33% were treated with each of dabigatran, rivaroxaban, or apixaban at a median of 8 days from stroke onset, 2.8% had recurrent stroke within the study period and 2.4% had bleeding events (1.4% attributable to symptomatic intracranial hemorrhage). This study found the lowest composite rate of recurrent stroke/major hemorrhage in those treated between 3 and 14 days after stroke (2.1%). The rate was 12.4% in those treated within 48 h and 9.1% in patients treated beyond 14 days after stroke onset. The study did not include patients presenting with transient ischemic attacks and exclusively analyzed patients treated with NOACs.

There are a number of major limitations of the studies to date on the optimal timing of anticoagulation resumption on stroke in atrial fibrillation. They do not explicitly account for stroke size, administration of thrombolysis, presence/absence of hemorrhagic transformation, recanalization via mechanical thrombectomy, and bleeding diatheses such as liver synthetic dysfunction or thrombocytopenia. These factors are crucial in personalizing a treatment decision to an individual patient.

Our Approach to Anticoagulation Resumption After Acute Ischemic Stroke in Patients with Atrial Fibrillation

- General principles:
  - Initiation or resumption of anticoagulation is favored after an ischemic stroke in a patient with atrial fibrillation for secondary stroke prevention (Fig. 1).
  - The decision about the timing of anticoagulation resumption/initiation complex should be tailored to an individual patient.
  - Recommendations to start anticoagulation at a time point after discharge are only observed by two thirds of patients [70] and the physician should bear this in mind when recommending extended time points for anticoagulation resumption.
- Management in the first 48 h post-stroke:

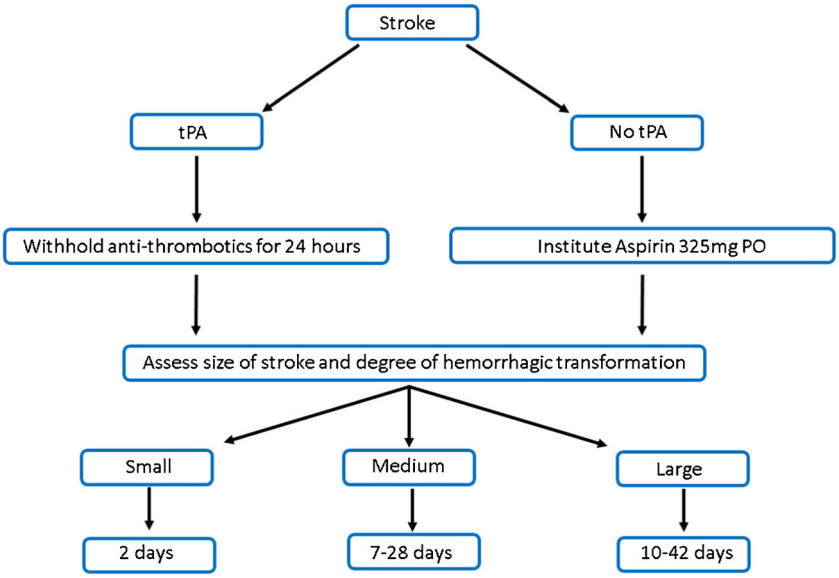

Fig. 1 Template for determining timing of anticoagulation post-acute ischemic stroke

- If a patient receives tissue plasminogen activator (tPA), antithrombotic therapy should be withheld for 24 h.
- If a patient does not receive thrombolytic therapy, they should receive aspirin at a dose of 325 mg.
- Reversal of thrombolysis should be undertaken if a patient develops intracranial hemorrhage within the first 36 h post-tPA.
- Anticoagulation reversal should be considered in patients with symptomatic hemorrhagic transformation who were on anticoagulation at the time of admission. The need for reversal should be determined on the basis of the prothrombin time (PT)/international normalized ratio (INR) for patients on warfarin, the activated partial thromboplastin time for patients on dabigatran and on the basis of an assay of antifactor Xa activity (for patients on rivaroxaban, edoxoban, or apixaban).
- Treating providers may consider holding off on anticoagulation treatment in the first 48 h from an ischemic stroke in the setting of atrial fibrillation unless there is another strong indication for early initiation (such as mechanical heart valve, left ventricular thrombus, or left ventricular assist device (LVAD) in-situ).

• Management after 48 h post-stroke:

- The goal of management is to resume anticoagulation as soon as the risk of symptomatic hemorrhagic transformation is low enough to no longer outweigh the risk of a potentially disabling recurrent ischemic event.
- Previous reports have suggested using infarct size as the primary determinant of the risk of hemorrhagic transformation [71], and therefore, they suggested delay to anticoagulation in patients with large strokes (defined as involving the complete territory of the MCA, ACA, or PCA, two cortical superficial branches or more than one arterial territory).
- As a general schema, it is reasonable to start anticoagulation after 2 days in patients with small strokes, 7–10 days in those with moderate-sized strokes, and 10–14 days in those with large strokes (Fig. 2). One reasonable schema [5] for defining stroke size is outlined in Table 4.
- Strokes associated with atrial fibrillation are often multifocal. In determining the risk of hemorrhage, it is our practice to use the size of the largest infarct to predict the risk of hemorrhage as opposed to the total infarct volume in the case of multifocal infarcts.
- In the presence of hemorrhagic transformation, it is reasonable to delay anticoagulation further. A delay in the setting of hemorrhagic transformation is reasonable since it was not associated with an increased risk of ischemic events (cerebral or systemic) in one study [72]. We have outlined a schema for this based on whether there is HI-1, HI-2. PH-1, or PH-2 in Fig. 2.
- If there is a recurrent stroke during the waiting period, it may be reasonable to delay anticoagulation resumption based on the size of the new stroke as well as the degree of hemorrhagic transformation.
- The CHA_2DS_2-VASc score has been used to estimate patients' daily risk of stroke but it also positively correlates with the risk of hemorrhage [73]. It also correlates with stroke risk in patients without atrial fibrillation [74]. Thus, we do not suggest using it to aid with decisions around the timing of anticoagulation.
- While waiting to resume anticoagulation, aspirin should be administered as a "bridge" since it has been shown to reduce early recurrent events in patients with atrial fibrillation [75, 76].

- There are several instances when it may be reasonable to start anticoagulation prior to the recommended time point due to an extremely high risk of ischemic stroke or systemic embolic off anticoagulation. These include:

  - Mechanical heart valve as these convey a particularly high risk of systemic embolism when off anticoagulation and even in the setting of spontaneous intracerebral hemorrhage; the optimal time to initiation of anticoagulation has been suggested to be within 4 to 7 days [77].
  - Hypercoagulability associated with malignancy. The OASIS-CANCER study [78] of 268 patients with cancer-associated stroke reported that serum markers of hypercoagulability correlated with mortality; patients with a d-dimer of > 9.06 μg/ml had a median survival of only 66 days post-stroke. Anticoagulation in these patients was independently associated with survival.
  - Left ventricular thrombus
  - Left ventricular assist device (LVAD)
  - Left atrial thrombus
  - Acute deep venous thromboembolism
  - The risk of ischemic stroke is higher after myocardial infarction (MI) [79, 80]. When an ischemic stroke occurs in the setting of atrial fibrillation and recent MI, it may be necessary to administer anticoagulation earlier if deemed necessary.

- There are left atrial and left atrial appendage (LAA) markers associated with increased risk of stroke associated with atrial fibrillation. We do not suggest using these to inform timing of anticoagulation in clinical practice. These factors include:

  - Elevated amino-terminal pro-brain natriuretic peptide (NT-proBNP)
  - Increased left atrial size
  - Reduced LAA flow velocity
  - Spontaneous echocardiographic contrast
  - "Non-chicken wing" morphology of the left atrial appendage
  - Atrial fibrosis
  - Elevated P wave terminal force in lead V1 (on electrocardiography)

- There may be instances wherein starting anticoagulation later than the recommended time point is prudent such as:

  - In patients who have other risk factors for intracranial hemorrhage (e.g., poorly-controlled hypertension or CAA), we recommend that the underlying risk factor be addressed or anticoagulation delayed further. While the presence of deep CMH may increase the long-term risk of intracerebral hemorrhage, it may be reasonable to initiate anticoagulation after cardioembolic stroke in the presence of deep CMHs, particularly if the blood pressure is controlled. Patients with probable CAA and/or a prior lobar intraparenchymal hemorrhage should probably not be placed on long-term anticoagulation; alternative approaches like left atrial appendage closure in the early period after ischemic stroke require further study.
  - In patients who are felt to be at particularly high risk for hemorrhagic transformation (e.g., moderate to large infarct, CMBs, or petechial hemorrhage present), we suggest repeating brain imaging 48–72 h after resuming anticoagulation to exclude clinically silent hemorrhage.
  - In patients who are at high risk for both recurrent ischemic stroke and intracranial hemorrhage, percutaneous occlusion of the left atrial appendage has not been adequately investigated [81] and should be further studied since the safety of combined short-term systemic anticoagulation and dual antiplatelet therapy after left atrial appendage closure procedures has not been established.

- Other considerations:

  - When a patient with atrial fibrillation has an ischemic stroke while on anticoagulation, one important question

Table 3 Ongoing clinical trials comparing early versus late initiation of anticoagulant therapy in acute ischemic stroke in patients with atrial fibrillation. *OPTIMAS* Optimal TIMing of Anticoagulation After Acute Ischaemic Stroke, *ELAN* Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial Fibrillation, *TIMING* TIMING or Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation, *START* Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation

Trial	NCT	Intervention	Early	Late
OPTIMAS [66]	03759938	Any NOAC	< 4 days	7–14 days
ELAN [67]	03148457	Any NOAC	Mild: < 48 h Moderate: < 48 h Severe: 7 days	Mild: 3 days Moderate: 6 days Severe: 12 days
TIMING [68]	02961348	Any NOAC	< 4 days	5–10 days
START [69]	03021928	Any NOAC	4 arms: days 3, 6, 10, and 14 post-stroke	

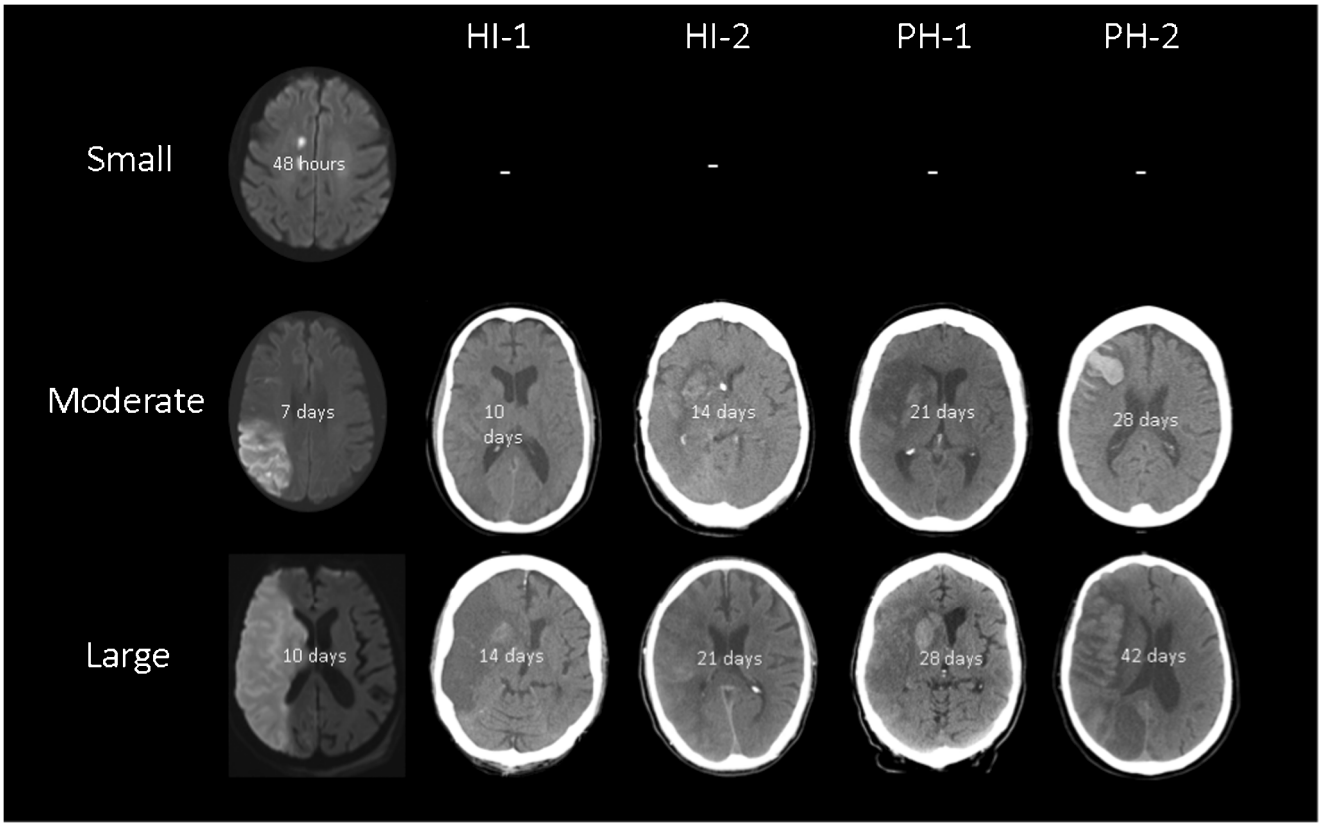

Fig. 2 Suggest times from stroke onset to consider anticoagulation resumption based on size of stroke bed and degree of hemorrhagic transformation

that can impact the timing of anticoagulation resumption is the causation etiology of the index ischemic stroke including:

Non-adherence to anticoagulation
Subtherapeutic anticoagulation despite full adherence
International normalized ratio < 2 on warfarin due to medication interaction or vitamin K ingestion
Under-dosing of non–vitamin K antagonist oral anticoagulant

Table 4 Definitions for small, medium, and large strokes according to the schema of Paciaroni et al. [5]. *MCA* middle cerebral artery, *PCA* posterior cerebral artery, *ACA* anterior cerebral artery

Size	Definition
Small	< 1.5 cm in the anterior or posterior circulation
Medium	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 (PCA), in a cortical superficial branch of the anterior cerebral artery (ACA)
Large	Involving the complete territory of MCA, PCA, or ACA, in two cortical superficial branches of MCA, in a cortical superficial branch of MCA associated to the MCA deep branch, or in more than 1 artery territory

Other mechanisms such as infectious endocarditis, atherosclerosis, small vessel disease, and hypercoagulability (e.g., malignancy and hyeprcoagulable state).

– Susceptibility-weighted imaging on MRI is exquisitely sensitive for blood products in the infarcted tissue bed. A CT without contrast is adequate to make the determination of what degree of hemorrhagic transformation has taken place. If susceptibility-weighted imaging is used to this purpose, it should be interpreted cautiously since it may over-estimate the burden of clinically relevant hemorrhagic transformation.
– When initiating warfarin therapy, bridging with heparin infusion or low molecular-weight heparin injections until the INR is therapeutic is often performed; however, in the setting of an acute stroke, bridging may be associated with more hemorrhagic complications [82] and is not currently recommended.

Conclusion

Future studies of anticoagulation resumption after stroke from atrial fibrillation will provide information on this subject in the

era of widespread tPA use, mechanical thrombectomy, and non–vitamin K antagonist oral anticoagulants. There are currently 4 clinical trials in progress comparing early versus late anticoagulation in patients with acute cardioembolic ischemic stroke: OPTIMAS (OPtimal TIMing of Anticoagulation After Acute Ischemic Stroke) [66], ELAN (Early Versus late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillatioN) [67], TIMING (TIMING of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation) [68], and START (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation) [69]. The enrollment criteria for these trials are summarized in Table 3.

While additional study is needed to precisely refine our understanding of the optimal timing of resumption of anticoagulation after atrial fibrillation-associated stroke, the general principles which should guide this decision are now reasonably clear. The use of good judgment to balance the risks on an individual basis is essential. Additionally, it is particularly important when approaching this question in clinical practice to involve the patient and their family in the decision-making process. The discussion should recognize that there are risks to resuming anticoagulation even at delayed time points and even the resumption of anticoagulation does not confer full protection against the threat of recurrent stroke.

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Compliance with Ethical Standards

Conflict of Interest Brian Mac Grory, Shane Flood, Matthew Schrag, Maurizio Paciaroni, and Shadi Yaghi declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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