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Review Article

Timing of Anticoagulation after Acute Ischemic Stroke in Patients with Atrial Fibrillation

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ABSTRACT: Patients with atrial fibrillation (AF) and ischemic stroke are at high risk for stroke recurrence. Early anticoagulation may reduce the risk of recurrent events but is usually avoided due to the risk of hemorrhagic transformation (HT). Current guidelines are based on empiric expert opinion. The assumed risk of HT is based on historical data from an older generation of anticoagulants. The direct oral anticoagulants (DOACs) have demonstrated lower risk of intracranial hemorrhage compared to older anticoagulants. However, the optimal timing of DOAC initiation after AF-related ischemic stroke has remained an area of clinical equipoise, as the pivotal phase III trials did not include patients in the early period after ischemic stroke. Multiple prospective studies and a few smaller randomized controlled trials evaluating the safety and efficacy of early versus delayed DOAC initiation have been completed. These studies have reported promising results of early DOAC initiation after acute ischemic stroke. However, a standardized documentation of HT rates on follow-up imaging with objective assessment criteria is missing from most of these studies. Larger randomized trials of early versus delayed DOAC are ongoing. A literature review was performed using keywords and Medical Subject Headings in MEDLINE/PubMed and Google Scholar databases. For each relevant paper, the bibliography was scrutinized for other relevant articles and journals. In this article, we review the risk of recurrent ischemic stroke and HT in patients with AF, pathophysiology, classification, predictors, natural history, and outcomes of HT and discuss the studies of early anticoagulation after AF-related ischemic stroke.

RÉSUMÉ : Moment propice de l'anticoagulation après la survenue d'un accident vasculaire cérébral ischémique chez les patients atteints de fibrillation auriculaire. Les patients atteints de fibrillation auriculaire (FA) qui ont subi un accident vasculaire cérébral (AVC) ischémique connaissent un risque élevé de récidive. Certes, l'anticoagulation précoce peut réduire le risque de nouvel AVC, mais elle est généralement évitée par crainte de transformation hémorragique (TH). Les lignes directrices actuelles reposent sur des opinions d'experts tirées d'inférences empiriques, et le risque estimé de TH repose sur des données historiques sur l'utilisation d'anticoagulants de première génération. Par contre, il a été démontré que les anticoagulants directs oraux (ADO) comportent un risque moins élevé d'hémorragie intracrânienne que les premiers anticoagulants. Toutefois, une incertitude absolue règne du point de vue clinique quant au moment propice de la mise en route du traitement par les ADO après la survenue d'un AVC ischémique lié à de la FA étant donné que les essais pivots de phase III ne comptaient pas de patients ayant subi un AVC ischémique récent. Bon nombre d'études prospectives et quelques essais comparatifs, à répartition aléatoire, de petite taille, portant sur l'évaluation de l'innocuité et de l'efficacité de l'emploi précoce des ADO comparativement à l'emploi tardif ont été menés à terme. D'après ces études, l'administration précoce d'ADO après un AVC ischémique aigu donne des résultats encourageants, mais la plupart d'entre elles n'ont pas de documentation uniforme à l'appui sur les taux de TH fondés sur des examens de suivi par imagerie et sur des critères objectifs d'évaluation. Par contre, des essais à répartition aléatoire, de plus grande taille, d'utilisation précoce d'ADO par opposition à utilisation tardive sont en cours. Par ailleurs, une recension de la documentation a été réalisée dans les bases de données MEDLINE-PubMed et Google Scholar, à l'aide de mots clés et de Medical Subject Headings; les chercheurs ont par la suite dépouillé minutieusement la bibliographie de chacun des articles jugés intéressants afin de trouver d'autres revues et articles pertinents. Seront donc examinés, dans l'article, le risque de nouvel AVC ischémique et de TH chez les patients atteints de FA; la physiopathologie, la classification, les facteurs prévisionnels, l'évolution naturelle et les résultats de la TH, ainsi que les études sur l'anticoagulation précoce après la survenue d'un AVC ischémique lié à de la FA.

Keywords: Atrial fibrillation; Ischemic stroke; Hemorrhagic transformation; Direct oral anticoagulant; Cardioembolic stroke; Intracerebral hemorrhage

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Atrial fibrillation and ischemic stroke

Atrial fibrillation (AF) is a major risk factor for ischemic stroke, associated with three to fivefold increased risk.[1] The rate of AF-associated ischemic stroke has tripled over the last few decades, and it is predicted to continue increasing in the future.[2] It is established that patients with AF who have suffered an ischemic stroke are at high risk for recurrence and require long-term anticoagulation. The risk of recurrent ischemic stroke ranges from 0.5% to 1.3% per day within the first 14 days after the index event based on retrospective observational studies.[3] AF-related ischemic stroke is disabling in 60% and fatal in 20% of cases.[4] A European epidemiological observational study demonstrated cardioembolic ischemic stroke is associated with the highest recurrence rate (22%; 95% CI 14–30) and lowest 2-year survival (55%; 95% CI 0.47–0.63) compared to other etiologies.[5] In patients with acute ischemic stroke and either known or newly diagnosed AF, the usual practice is to bridge with an antiplatelet agent until the patient is anticoagulated.[6,7] The timing of OAC initiation is often highly variable and opinion rather than evidence based. While earlier anticoagulation may reduce early recurrent ischemic stroke, it may also increase the risk of hemorrhagic transformation (HT), a serious early complication of ischemic stroke. Predictors of recurrent ischemic stroke in patients with AF include atrial thrombus, left atrial enlargement, left ventricular dysfunction, older age, larger infarct volume, and increasing CHA_2DS_2-VASc score, which is a clinical stroke risk score for patients with AF that includes heart failure, hypertension, age, diabetes mellitus, prior ischemic stroke, female sex, and other vascular diseases.[8–11] Most of these predictors are of limited use in informing the timing of anticoagulation, as they are also associated with an increased risk of HT. The competing rationales for early versus late anticoagulation make the optimal timing of anticoagulation after an ischemic stroke a persisting area of clinical equipoise.

Hemorrhagic Transformation

HT is a spectrum of ischemia-related brain hemorrhage, which varies from subtle heterogenous leakage of blood within the infarction to extensive hemorrhage within and beyond the infarction with and without mass effect.[12] HT can lead to clinical deterioration from increasing edema, mass effect, intraventricular extension, and hydrocephalus and ultimately can result in death.[13]

Pathophysiology

Understanding the mechanism of HT is a key element for predicting, preventing, treating, and prognosticating HT. The entire pathophysiology is still unclear. However, breakdown of the blood–brain barrier (BBB) is an essential component in the development of HT in ischemic stroke.[14,15] BBB disruption results from a series of cellular, metabolic, and inflammatory events led by reduction in energy and failure in the Na+-K+ ATPase activity, causing injuries to cerebral endothelial cells and impairment in autoregulation of the cerebral blood vessels.[16,17] It has also been suggested that the BBB disruption is time-dependent, and that the mechanism of early HT (≤24 hours) may be different than the late HT (>24 hours).[18] Reactive oxygen species, blood derived matrix metalloproteinases (MMP)-9, and the brain-derived MMP-2 may play critical roles in the mechanism of early HT. On the other hand, multiple factors could contribute to the late HT. This includes brain-derived MMP-9, MMP-3, inflammatory responses, vascular remodeling processes, and other proteases.[18]

Classification

Classification of HT is based on two components, the radiographic features of the hemorrhage and associated clinical changes. The term hemorrhagic infarction (HI) has emerged to describe subtle or confluent heterogenous blood within the infarcted tissue without mass effect. The term parenchymal hematoma (PH) describes the extensive homogamous hematoma within and beyond the infraction borders with mass effect.[19,20] In 1999, Fiorelli et al proposed the European Cooperative Acute Stroke Study (ECASS) classification system, which includes two subtypes of HI (HI-1: small petechiae along the margins of the infarct, and HI-2: confluent petechiae within the infarcted area but no space-occupying effect) and two subtypes of PH (PH-1: hematoma in 30% or less of the infarcted area with some slight space-occupying effect, and PH-2: hematoma in more than 30% of the infarcted area with substantial space-occupying effect).[21] The ECASS criteria do not clearly differentiate between PH within the area of infarction and PH remote from the infarction, nor do they include other types of hemorrhages such as intraventricular hemorrhage, subarachnoid hemorrhage, and subdural hemorrhage. The Heidelberg bleeding classification is a classification tool to grade HT that expands beyond the ECASS system by including and categorizing these previously non-classified hemorrhages.[22] The single standard definition of symptomatic HT in ischemic stroke has yet to emerge. As a result, variability in how HT is defined in stroke studies has impacted the reporting rate of symptomatic HT and makes comparing rates of HT between studies challenging.[22–27]

Risk of HT after Acute Ischemic Stroke

Most of the older studies on HT in patients with acute ischemic stroke were of limited sample size and/or study design, or derived from studies on thrombolysis. Additionally, the reported rates of HT after ischemic stroke are variable in different studies. This variability could be related to the differences in study design, the included populations, the definitions of HT, type and frequency of imaging, timing and sequence of scan used, and method of assessing and defining clinical worsening. The reported incidence of HT is up to 70% in autopsy studies.[28–31] On the other hand, the incidence of HT in computed tomography (CT) studies was variously reported over the last four decades, from few to 43% of consecutive patients.[12,30–35] A more recent large prospective study that examined the risk of early HT in patient with acute ischemic stroke by using systematic brain CT at baseline and 5 ± 2 days after stroke onset was conducted.[36] Early HT in patients with acute ischemic stroke, including both AF and non-AF-related infarcts, was observed to be about 9% within 5–7 days from the index event and, of these HT events, 3.2% were PH. The early Recurrence and cerebral bleeding in patients with Acute ischemic stroke and atrial Fibrillation (RAF) study was a prospective observational study which specifically examined the risk of HT in patients with AF-related ischemic stroke. The rate of HT was found to be higher, 13%: 8.8% HI and 4.2% PH.[8] A recent combined analysis from two large observational studies included 2183 patients and found that HT occurred in 11% on repeated imaging, with 3.1% of these being PH.[37] The reported incidence of HT varies based on type of study, type and frequency of imaging, and sequence of scan used.

Clinical Predictors of HT

Several clinical factors have been described in association with development of HT. Recognizing these clinical variables might

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be helpful for clinicians to anticipate and stratify the risk of HT in individual patients. However, it is unknown if early anticoagulation in the presence of these clinical parameters further increases the risk of new and/or progressive HT. The size of infarction is independently associated with HT.[38] Larger ischemic infarct volume is associated with mass effect and vascular compression, both of which increase vascular permeability and therefore HT risk. Higher National Institutes of Health Stroke Scale (NIHSS) scores indicate severe stroke and larger infarct which increase the risk of HT.[39] Further, cardioembolic stroke and AF-related ischemic stroke tend to be severe and related to large vessel occlusion (LVO).[40] Compared to other subtypes, cardioembolic stroke associated with AF has been associated with the highest risk of HT.[41] Additionally, hyperglycemia may worsen the BBB disruption by inducing systemic stress and enhancing circulating factors that damage BBB which increases the risk of HT.[42–44] The effect of high blood pressure (BP) on the risk of HT has been documented, especially in patients with larger infarcts who received thrombolytic therapy.[45] High BP is considered an modifier of the risk of HT through its interaction with other predictors.[41] Another factor found to be associated with HT is high body temperature in the first 24 hours after stroke onset.[46,47] Moreover, low-density lipoprotein cholesterol level with and without statin has correlated with the risk of HT.[48,49] Finally, reperfusion therapies, including thrombolysis and endovascular therapy, are all associated with an increased rate of HT.[41,50–54] However, a recent prospective observational study has shown that acute reperfusion therapies using thrombolysis and/or EVT prior to initiating anticoagulation did not influence the risk of recurrent ischemic stroke(s) and HT.[55]

Radiographic Predictors of HT

Non-contrast CT/CT Angiography (CTA)/CT Perfusion (CTP)

Early ischemic changes, including loss of gray–white matter differentiation, hypodensity (hypoattenuation) of brain parenchyma, presence of edema or mass effect, and low Alberta Stroke Program Early CT Score (ASPECTS) of ≤7 on baseline CT scan, appear to increase the risk of HT.[56–59] Another CT marker associated with HT is the hyperdense middle cerebral artery sign.[60] Patients with hyperdense middle cerebral artery sign, LVO, poor collateral flow, lower clot burden scores, and severe hypoperfusion with large core in CTP tend to have severe stroke and early ischemic changes, and thus, higher risk of HT.[61–63]

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is more sensitive than CT for detection of HT after acute ischaemic stroke,[64,65] especially with adding the susceptibility weighted imaging, which is highly accurate in detecting blood products. A low volumetric apparent diffusion coefficient and large diffusion weight imaging on baseline MRI are associated with an increased risk of HT.[45,66–68] Additionally, multiple radiological markers in MRI have been associated with HT including poor fluid suppression on fluid-attenuated inversion recovery (FLAIR) from extravasation of contrast into CSF leading to hyperintensity of the CSF space, which has been labeled Hyperintense Acute Reperfusion Marker (HARM),[69] sulcal hyperintensity on FLAIR,[70] parenchymal enhancement on post-contrast T1,[71–73] signs of disrupted BBB,[74,75] and finally, cerebral microbleeds (CMBs). A recent meta-analysis has shown that patients with ≥5 CMBs are at higher risk of hemorrhage than those with fewer or no CMBs – patients with <5 CMBs (2.48%; 95% CI 1.2–6.2; $p = 0.001$).[76] At this point, however, MRI screening is not routinely performed prior to initiation of anticoagulation and this finding has not changed clinical practice.

Serological Biomarkers Predictive of HT

Matrix Metalloproteinases

Several studies have demonstrated that increased expression of MMP-9 is associated with an increased risk of HT after reperfusion.[77–79] Similar studies have shown that elevated MMPs correlate with disrupted BBB and HT in experimental stroke models regardless of whether or not thrombolysis is received. This observation is likely secondary to the fact that MMP has the potential to degrade the basal lamina of the vascular endothelium.[80] However, the role of MMPs in the setting of anticoagulant-associated bleeding is unknown.

Leukocyte RNA

Inflammation and immune response after ischemic stroke may also influence the risk of HT by promoting peripheral leukocytes activation, adhesion, migration, and potentially BBB disruption.[81,82] Preliminary data suggest the risk of HT in patients with stroke can be stratified by RNA expressed in circulating leukocytes within 3 hours of stroke onset. A panel of six genes associated with subsequent HT has been identified.[18,83] Of note, these data are driven from patient with early HT after thrombolysis, thus the role of leukocyte RNA in the setting of anticoagulation-related bleeding remains unclear.

Natural History and Outcomes of HT

HT is part of the spectrum of ischemia-related brain hemorrhage associated with a wide range of clinical significance. Most studies of the significance of HT come from thrombolysis trials. The relationship between PH-2 and clinical and functional outcomes has been established, but this is not the case for HI-1, HI-2, and PH-1.[84] A retrospective study indicated that any PH independently predicted mortality at day 30 and day 90.[13]. Conversely, a post hoc analysis of European Cooperative Acute Stroke Study I (ECASS I) indicated that only PH-2 was associated with an increased risk of neurological deterioration at 24 hours (OR 18.0; 95% CI 6.0–56.0) and 90 day mortality (OR 11.4; 95% CI 3.7–36.0).[21] Another post hoc analysis of the ECASS II study demonstrated that PH-2 was associated with approximately 50% mortality.[85] This analysis and others revealed that HI-1 and HI-2 were not associated with unfavourable outcomes.[21,85,86] Similarly, another prospective study assessed the outcomes of early HT after ischemic stroke and found that only PH was independently associated with a higher risk of mortality and functional disability.[36] Conversely, a more recent prospective study revealed that both PH (OR 1.79; 95% CI 1.00–3.27; $p = 0.05$) and HI (OR 1.75; 95% CI 1.21–2.53; $p = 0.003$) were associated with death and disability.[37] However, quantifying the impact of HT, especially HI, on functional outcome is challenging as the independent contribution of HT to clinical worsening remains uncertain,[87] and evidence from high quality studies is lacking.

Early Anticoagulation after AF-related Ischemic Stroke

Older studies focused on heparins for early anticoagulation, perhaps due to its rapid onset of action compared with vitamin K antagonists (VKA) which can take several days to reach to therapeutic level. However, in the last decade, four direct oral anticoagulants (DOACs) have been demonstrated to have a lower long-term risk of intracranial hemorrhagic complications compared

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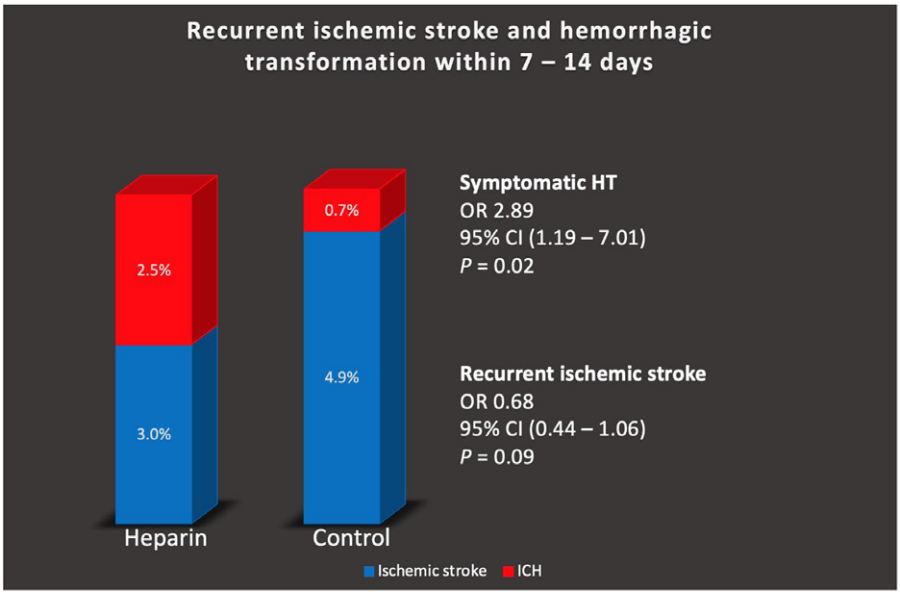

Figure 1: Absolute event rates of recurrent ischemic stroke and symptomatic HT associated with early LMWH after acute ischemic stroke. HT=hemorrhagic transformation; ICH=intracerebral hemorrhage; LMWH=low molecular weight heparin.

to older anticoagulants, and these are now the standard of care for stroke prevention in non-valvular AF.[88–91] In a meta-analysis, DOACs were associated with a 52% significant reduction of intracranial hemorrhage compared to warfarin.[92] In the following sections, we discuss studies of anticoagulation initiation within 14 days of an ischemic stroke or transient ischemic attack.

Early Heparin Initiation after Acute Ischemic Stroke

Among patients who were not on any antithrombotic therapy in the International Stroke Trial, 4.9% developed recurrent ischemic events within 2 weeks of the index stroke onset.[93] A dose-dependent reduction in the recurrent ischemic strokes was noted in the unfractionated heparin (UFH) groups, but that benefit was offset by an increase in HT. A meta-analysis indicated that initiating low molecular weight heparin (LMWH) within 24–72 hours after ischemic stroke (regardless of the mechanism) for 7–30 days was associated with no reduction in recurrent ischemic stroke rates, but a trend to more symptomatic HT, and a significant increase in major extracranial bleeding.[94] The Heparin in Acute Embolic Stroke Trial (HAEST) compared LMWH and aspirin initiation within 30 hours of stroke onset. Recurrent ischemic events within 14 days of the index stroke occurred 7.5% and 8.5% in patients that received LMWH and aspirin, respectively.[95] Starting LMWH within 30 hours of AF-related ischemic stroke was associated with an increased rate of symptomatic HT and extracranial hemorrhage.[95] A meta-analysis of seven trials of parenteral anticoagulants (UFH, LMWH, heparinoids) started within 48 hours of acute cardioembolic stroke indicated recurrent ischemic events within 7–14 days were similar to those in patients treated with aspirin or placebo (3.0% vs. 4.9%; OR 0.68; 95% CI 0.44–1.06; $p = 0.09$), but symptomatic HT was more frequent (2.5% vs 0.7%; OR 2.89; 95% CI 1.19–7.01; $p = 0.02$), (Figure 1).[96]

Early VKA Initiation after Acute Ischemic Stroke

Randomized controlled trials (RCTs) and observational studies of early anticoagulation after stroke, including patients initiated on VKA and DOACs, are summarized in Table 1. Data from RCTs evaluating the timing of VKA initiation after ischemic stroke in patients with AF are limited. The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) study was a prospective observational study of initiating anticoagulant after stroke/TIA in patients with AF.[97] A total of 650 patients were started on warfarin at a median of 3 days after stroke/TIA onset. There was no reported ICH prior to hospital discharge; however, systematic neuroimaging was not performed. The early Recurrence and cerebral bleeding in patients with Acute ischemic stroke and atrial Fibrillation (RAF) study was a prospective observational study.[8] VKA alone was initiated in 37% of patients, with another 36% started on LMWH therapy before receiving VKA. Timing of anticoagulation was at the discretion of the treating physician, varying from 1 to 90 days after stroke. The optimal net clinical benefit of composite outcomes for anticoagulation initiation was 4–14 days after stroke onset. Conversely, data from 1644 patients in the Virtual International Stroke Trials Archive (VISTA) indicated that early VKA initiation, within 2–3 days after stroke onset, was associated with lower recurrent ischemic events without an increase in symptomatic ICH.[98] Finally, the Clinical Relevance Of Microbleeds In Stroke-2 (CROMIS-2) study assessed the effect of oral anticoagulant timing in patients with AF and stroke.[99] Timing of anticoagulation was determined by the treating physicians and then retrospectively dichotomized into early (0–4 days) and late (≥5 days or never started) groups. Of 1355 patients prescribed an oral anticoagulant, 26% started early and 74% started late. Both groups had similar rates of recurrent ischemic events and ICH. Most patients (65%) were treated with warfarin, and 24% received bridging heparin therapy.

Early DOACs Initiation after Acute Ischemic Stroke

RCTs and observational studies of early anticoagulation after stroke, including patients initiated on VKA and DOACs, are summarized in Table 1. In the pivotal phase III DOAC trials, more than 70,000 patients were randomized; however, patients were not eligible immediately after ischemic stroke (exclusion ranged from 7 to 30 days after onset).[88–91] Moreover, among all the randomized patients, only 30% had previous stroke or TIA and the number of patients randomized early after stroke has never been published but is likely to be small.[92] DOACs are now the standard of care for stroke prevention in AF patients.[6,7] The optimal timing after ischemic stroke is a highly

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Table 1: Studies of early initiation of oral anticoagulants after atrial fibrillation-related ischemic stroke

Study	N	NIHSS and infarct size	Median time from onset to anticoagulation initiation	Follow-up period	HT	Recurrent ischemic events
Randomized controlled trials of early DOAC initiation post-stroke						
AREST trial[103]	88 (41 received apixaban)	Mean NIHSS 6.5; (29.3% TIA, 29.3% small, 41.5% medium)	Stratified based on infarct size and agent (apixaban vs. warfarin)	CT/MRI at day 14 and day 180	**Symptomatic:** 2.1% (warfarin) and 0% (apixaban) **Asymptomatic:** 10.6% (warfarin) and 12 · 2% (apixaban, p = 0.82)	19.2% (warfarin) and 14 · 6% (apixaban, p = 0.58)
The Triple AXEL trial[101]	195 (95 received rivaroxaban)	Median NIHSS 2; Median infarct volume 2.6 ml	2 days	MRI at week 4	**Symptomatic:** None (both groups) **Asymptomatic:** 28.7% (warfarin) and 31 · 6% (rivaroxaban, p = 0.50)	1.1% (warfarin) and 1 · 1% (rivaroxaban, p > 0.99)
DATAS II*[102]	305 (153 received dabigatran)	Median NIHSS 1; Median infarct volume 1.0 ml	1 day	MRI at day 30	**Symptomatic:** None (both groups) **Asymptomatic:** 3.5% (ASA) and 7 · 8% (dabigatran) (RR, 2.3; 95% CI 0.78–6.9)	2.7% (ASA) and 3.9% (dabigatran) (RR, 1.49; 95% CI 0.41–5.39)
Observational studies including systematic brain imaging following early DOAC initiation post-stroke						
Alrohimi et al[109]	101 (all received dabigatran)	Median NIHSS 1; Median infarct volume 0 ml	2 days	CT at day 7	**Symptomatic:** None **Asymptomatic:** 6 (6%)	4 (4%)
Alrohimi et al[110]	100 (all received apixaban)	Median NIHSS 4; Median infarct volume 4.0 ml	2 days	CT at day 7	**Symptomatic:** None **Asymptomatic:** 3 (3%)	13 (13%)
A.I. Al Bakr et al[111]	120 (37 received DOAC)	Median NIHSS 7; (46% small, 54% large)	No overall median reported. 80% within 14 days of stroke onset	CT scan at 3 – 6 months	32 (27%), including 8 (7%) who developed a parenchymal hematoma, but the majority of these were related to warfarin with/without heparin	5 (4.2%): all were not on DOAC
Gioia et al[108]	60 (all received rivaroxaban)	Median NIHSS 2; Median infarct volume 7.9 ml	3 days	MRI at day 7	**Symptomatic:** None **Asymptomatic:** 8 (13.3%)	2 (3.3%)
M. Cappellari et al[112]	147 (all received DOAC)	Mean NIHSS 8.2; (54% small, 22% medium, 24% large, 15% posterior circulation)	3 · 3 days (≤3 days for 97 patients; ≤7 days for all patients)	CT scan at day 7	**Symptomatic:** 1 patient (0.7%) **Asymptomatic:** 7 patients (4.7%)	None
K. Shibazaki et al[113]	41 (all received DOAC)	Median NIHSS 3	2 days	MRI at week 2	**Symptomatic:** None **Asymptomatic:** 31%	None
Observational studies without systematic brain imaging following early DOAC initiation post-stroke						
SAMURAI-NVAF study[104]	1137 (475 received DOAC)	Median NIHSS 4; (29.9% small, 56.3% medium, 13.8% large)	4 days	3 months	0.32% (warfarin) and 0.22% (DOAC)	2.58% (warfarin) and 2.82% (DOAC) (aHR, 1.12; 95% CI 0.50–2.47)
RAF-NOACs study[105]	1127 (all received DOAC)	Mean NIHSS 8; (41% small, 33% medium, 22% large)	No overall median reported 80% within 15 days of stroke onset	3 months	1.6%	2.8%
NOACISP registry[106]	204 (155 received DOAC)	Median NIHSS 4; no information on infarct size	5 days (≤7 days for 100 of DOAC-treated patients)	3–6 months	1 patient (1.3%/y), who was in the warfarin group	6 patients (7.7%/y), 2 received DOAC ≤ 7 days (5.1%/y) vs 2 received DOAC > 7 days (9.3%/y) (p = 0.53) and 2 in the warfarin group (11.3%/y)
CROMIS-2 study[99]	1355 (475 received DOAC)	Median NIHSS 4; (8% small, 18% large)	11 days (≤4 days for 358 of patients)	3 months	0.6%/y (combined DOAC and warfarin)	5.7%/y (combined DOAC and warfarin)

(*Continued*)

Table 1: (*Continued*)

Study	N	NIHSS and infarct size	Median time from onset to anticoagulation initiation	Follow-up period	HT	Recurrent ischemic events
RAF study[8]	1029 (93 received DOAC)	Mean NIHSS 9.2; (37% small, 36% medium, 27% large)	8 · 5 days for DOAC, 12 · 1 days for warfarin	3 months	77 events (7.6%)	37 (3.6%) symptomatic HT
Abdul-Rahim et al[98]	1300 (none received DOAC)	Median NIHSS 14; no information on infarct size	2 days	3 months	30 events (2.3%)	107 events (8.2%)
Paciaroni et al[107]	473 (314 received DOAC)	Mean NIHSS 6.8; (75.5% has lesion size > 1.5 cm)	12.3 days	3 months	20 events (4.2%)	18 events (3.8%)
Macha et al[126]	243 (all received DOAC)	Median NIHSS 5; (17% small or TIA, 70% medium, and 13% large)	From 1 · 7 days for small infarct or TIA to 6 · 7 days for large infarcts (≤7 days for of DOAC-treated patients)	In hospital	**Symptomatic:** 1 (0.4%) **Asymptomatic:** 2 (0.8%)	No information on recurrent ischemic events
Deguchi et al[127]	300 (186 received DOAC)	Median NIHSS 7; no information on infarct size	3 days for DOAC and 7 days for warfarin	In hospital	**Symptomatic:** None **Asymptomatic:** 2 warfarin treated patients (1.4%)	None

N=number; NIHSS=National Institutes of Health Stroke Scale; HT=hemorrhagic transformation; DOAC=direct oral anticoagulant; TIA=transient ischemic attack; CT=computed tomography; MRI=magnetic resonance imaging; ASA=aspirin; RR=relative risk; aHR=adjusted hazard ratio; cm=centimeter.
* Patients without atrial fibrillation.

relevant clinical question, given the anticoagulant effect of these drugs begins within hours of administration.[100]

Randomized studies of early DOAC use post-stroke: There are only three published randomized trials assessing the safety of early DOAC administration after ischemic stroke. The Triple AXEL (Acute Stroke With Xarelto to Reduce Intracranial Hemorrhage, recurrent Embolic Stroke, and hospitaL stay) compared rivaroxaban ($n = 101$) to warfarin ($n = 94$) initiation within 5 days of cardioembolic stroke (median NIHSS score of 2 in both arms).[101] This study revealed similar recurrent ischemic stroke and HT rates in both groups. Incident radiographic HT detected on follow-up MRI was seen in 49.5% and 54.5% of patients receiving rivaroxaban and warfarin, respectively. The higher frequency of HT compared to previous studies is likely related to the higher sensitivity of MRI for petechial bleeding. The DATAS II trial (Dabigatran in Acute Transient Ischemic Attack and minor Stroke) randomized 305 patients *without AF* to dabigatran or aspirin within 72 hours of mild ischemic symptom onset.[102] There were no symptomatic HT events in either group, but asymptomatic HT detected with MRI was reported in 7.8% of the dabigatran group and 3.5% of the aspirin group (relative risk 2.22, [0.79, 6.21]). More recently, the Apixaban for Early Prevention of Recurrent Embolic Stroke and Hemorrhagic Transformation (AREST) trial randomized patients to apixaban or warfarin, but the timing of initiation was according to the infarct size.[103] The study was stopped early in 2019, after 91 patients had been randomized as DOACs have become the standard of care for most patients with AF-related stroke. One case of symptomatic HT occurred in the warfarin group. Incident radiographic HT was detected in 12.2% and 10.6 % of the apixaban and warfarin groups, respectively. Recurrent ischemic events were more common in both the apixaban (14.6%) and warfarin (19.2%) groups.

Prospective, non-randomized studies of early DOAC use post-stroke: The SAMURAI study included a total of 466 patients who were started on DOAC at a median of 4 days after stroke/TIA onset.[97] In those patients, the recurrent stroke/systemic embolism rate was 2.84% and the rate of major bleeding was 1.1% at day 90.[104] The Early Recurrence and Major Bleeding in Patients With Acute Ischemic Stroke and Atrial Fibrillation Treated With Non-Vitamin-K Oral Anticoagulants (RAF-NOACs) study examined 1127 patients, 80% of whom received DOAC within 15 days of stroke.[105] Recurrent ischemic events within 90 days occurred in 2.8% of patients, which was more common than the symptomatic cerebral bleeding rate of 1.6%. However, the lack of serial imaging may have led to an under-estimation of the rate of asymptomatic HT. The 'Novel Oral Anticoagulants in Ischemic Stroke Patients' (NOACISP) registry did not report an increased risk of symptomatic HT or recurrent stroke in 100 patients initiated on DOAC within 7 days of stroke onset.[106] In another study, the risk of recurrent stroke and hemorrhagic complication was found to be similar in patients with anterior and posterior circulation infarcts.[107] Symptomatic HT rate was higher in this cohort (4.2% and 3.7% in the anterior and posterior circulation, respectively), and potentially explained by the fact that warfarin and/or bridging heparin prior to DOAC administration was used.

Prospective studies including systematic brain imaging following OAC initiation post-stroke have generally been smaller. By using serial MRI pre- and post-treatment, a prospective assessment of the safety of rivaroxaban initiation at a median of 3 days after AF-related ischemic stroke demonstrated that asymptomatic petechial HT was common at baseline (25/60) and remained clinically silent despite immediate treatment with rivaroxaban.[108] A recent

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prospective, multicenter registry of dabigatran initiation within 14 days of acute minor ischemic stroke/TIA (NIHSS ≤ 3) onset in patients with AF has also been published.[109] A total of 101 patients (median NIHSS score was 1) were enrolled. The median time from ischemic symptom onset to dabigatran initiation was 2 days and this was not associated with any symptomatic HT, but asymptomatic HT evident on systematically acquired follow-up CT was seen in 6% of patients. Another recent prospective study of apixaban initiation within 14 days of TIA/acute ischemic stroke regardless the size and severity has been completed.[110] A total of 100 patients (median NIHSS score was 4) were included. The median time from ischemic symptom onset to apixaban initiation 2 two days and this was not associated with any symptomatic HT, but incident radiographic HT evident on systematically acquired follow-up CT was seen in 3% of patients. Recurrent ischemic events occurred in 13 patients, 4 of which were associated with severe disability and 4 with mortality. One prospective study included 120 patients with AF-related stroke who received either DOAC or heparin/warfarin, 80% of which treated within 14 days.[111] HT occurred in 27%, including 7% whom developed a PH, but the majority of these were related to warfarin with/without heparin. A more recent study of 147 patients treated with DOAC within 7 days, HT was seen in 8 patients (asymptomatic in 7, and symptomatic in 1).[112] Another small MRI-based prospective study of 41 patients was completed.[113] Median NIHSS and time from onset to DOAC initiation were 3 and 2 days, respectively. Incident asymptomatic HT was observed in 11 patients, all of which were asymptomatic.

Guideline Statements and Current Practice

Current guidelines are inconsistent and provide limited advice with respect to the timing of DOAC initiation after AF-related ischemic stroke.[6,7,114–118] The European Heart Rhythm Association of the European Society of Cardiology (EHRA-ESC) endorsed the "1–3–6–12 days rule," which recommends timing of anticoagulation based on clinical severity and infarct size, but neither are well defined.[114] The 2021 guidelines of the American Heart Association/American Stroke Association (AHA/ASA) recommend starting oral anticoagulation immediately after TIA and 2–14 days after the index event for ischemic stroke.[7] In the same guideline statement, a delay in initiation beyond 14 days is recommended for patients considered to be at high risk of HT. Bridging therapy with heparins is considered a class III recommendation against (HARM) in the ESC guidelines.[115] An online survey indicated that 95% of physicians in the UK were uncertain when to start oral anticoagulation after cardioembolic stroke.[119]

Discussion

Standardized documentation of HT rates on follow-up imaging is missing from most studies of early anticoagulation. Studies including serial imaging data at baseline and following DOAC initiation have demonstrated the rate of incident asymptomatic HT to be as low as 3–6% in CT-based studies and up to 13% in MRI-based studies.[102,108–110,120] Even in cases with baseline HT prior to anticoagulation, DOAC initiation did not precipitate symptomatic HT. Conversely, early recurrent ischemic events were more common, all of which were symptomatic. Most of the recurrent ischemic events occurred within the first 14 days, suggesting the risk of ischemic events is highest early after the index event. In contrast to HT, which was detected incidentally on follow-up imaging and was not observed to independently influence the functional outcomes, recurrent ischemic events were always clinically evident and associated with poor functional outcomes.

The results from most observational studies suggest that symptomatic HT rates will likely be low in randomized trials of DOAC initiation post AF-related stroke. The low baseline event rate makes it difficult to predict the effect of DOAC initiation and also complicates studies aimed at risk stratification of patients with AF-related stroke. Conversely, recurrent ischemic stroke will potentially be the clinical outcome of interest in these RCTs. However, HT remains a critical complication to consider, as even a slight increase in frequency may outweigh any benefits of early anticoagulation. Although incident radiographic HT is asymptomatic and only detected incidentally on follow-up imaging, it likely shares a common mechanism and pathophysiological pathway with more severe symptomatic HT.[14,15] Clinicians tend to delay DOAC initiation in patients with larger infarcts, irrespective of the presence or absence of HT,[8,109-111] consistent with expert recommendations.[121] This practice of delaying DOAC administration due to concerns that patients with large infarcts are more prone to symptomatic HT appears reasonable at present. The absolute risk of HT, however, and the optimal timing in individual patients remains unknown. A follow-up neuroimaging scan before initiating DOAC is often used in clinical practice to assess infarct progression or hematoma expansion but whether these factors should guide decision, and how, remains unknown. Serial and systematic collection of HT rates constitute objective criteria which may be important surrogate markers even in larger trials, where the expected absolute number of symptomatic HT cases is likely to remain low.

Future Directions

The question of optimal timing to start DOAC will remain unanswered until randomized trials of early versus delayed DOAC are completed (Table 2).[122–125] Ongoing trials include LASER (Lixiana Acute Stroke Evaluation Registry, NCT03494530), TIMING (Timing of Oral Anticoagulant Therapy in Acute Ischemic Stroke With Atrial Fibrillation: a Prospective Multicenter Registry-based Non-inferiority Randomized Controlled Clinical Trial, NCT02961348), ELAN (Early Versus Late Initiation of Direct Oral Anticoagulants in Post-ischaemic Stroke Patients With Atrial fibrillation, NCT03148457), START (Optimal Delay Time to Initiate Anticoagulation After Ischemic Stroke in Atrial Fibrillation, NCT03021928) trials, and OPTIMAS (OPtimal TIming of Anticoagulation After Acute Ischemic Stroke, NCT03759938).

Patients in the above-named trials are randomized to a DOAC, initiated as early as 48 hours and up to 5 days after onset, or delayed to 6–14 days. The primary endpoint in these trials is the composite of recurrent ischemic stroke and symptomatic HT. While using a composite endpoint will increase the number of events and statistical power, the contrasting outcomes could potentially dilute the net treatment effect (i.e., early initiation might potentially reduce recurrent stroke but increase symptomatic HT, and vice versa) and lead to a neutral primary outcome result.

The observed current practice of delaying DOAC initiation in patients with larger infarcts is relevant to the ongoing RCTs, where randomization is either stratified by infarct volume/size[123] ELAN, NCT03148457 and/or includes arms with relatively broad initiation time windows of several days, extending up to 14 days after symptom onset.[122,124] OPTIMAS, NCT03759938 This form of stratification by

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Table 2: Ongoing randomized trials assessing the safety and efficacy of early versus delayed oral anticoagulant initiation after AF-related ischemic stroke

	LASER[122]	ELAN	OPTIMAS	TIMING[124]	START[123]
NCT number	NCT03494530	NCT03148457	NCT03759938	NCT02961348	NCT03021928
Intervention arm (early)	≤5 days after ischemic stroke	≤48 h after minor and moderate stroke or at day 6 + 1 day after major stroke	≤4 days after ischemic stroke	≤4 days after ischemic stroke	**Adaptive trial design:** Time to treatment delay of 3, 6, 10, or 14 days after mild/moderate ischemic stroke. 6, 10, 14, or 21 days after severe ischemic stroke
Control arm (delayed)	Between day 6 and 14 after ischemic stroke	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 14 after ischemic stroke	Between day 5 and 10 after ischemic stroke	
Follow-up period	90 days	30 days (secondary outcomes at 90 days)	90 days	90 days	30 days (secondary outcomes at 30 and 90 days)
Including patients with HT	Yes	Yes	Yes	Yes	Yes
Using systematic imaging	Yes	No	No	No	No
Primary outcome	Incident radiographic HT	Composite of major bleeding, recurrent ischemic stroke, systemic embolism and/or vascular death	Composite of recurrent symptomatic ischaemic stroke, symptomatic intracranial haemorrhage, and systemic embolism	Composite of recurrent ischemic stroke, symptomatic intracerebral hemorrhage, or all-cause mortality	Composite of recurrent ischemic stroke, systemic embolism, and major bleeding
Included biomarkers	Ability of leukocyte RNA to predict HT is included as a secondary outcome	————————————	————————————	Cardiovascular biomarkers (Troponin, NT-proBNP, and GDF-15)	————————————
Sample size	150	2000	3478	3000	1500
Estimated end of study	December 2022	October 2021	September 2022	Not updated	August 2021
Treatment	Edoxaban	Any of the DOACs	Any of the DOACs	Any of the DOACs	Any of the DOACs

NCT=The National Clinical Trial number; h=hours; HT=hemorrhagic transformation; DOAC=direct oral anticoagulant; NT-proBNP=N-terminal pro b-type natriuretic peptide; GDF-15=growth/differentiation factor-15.

infarct volume or by having broad initiation time windows where the decision to time the treatment at the treating physician's discretion, even in the context of randomization, may play a role in introducing a bias. It may also limit the understanding of whether the timing of DOAC initiation should be adjusted based on infarct size and/or clinical severity of the index event to reduce the risk of HT. While these trials are expected to advance the field, the broad randomization windows, the contrast effect of used composite outcomes, and lack of systematic imaging post-treatment in most of the trials may leave some clinical equipoise and also facilitate continuation of current practice patterns based on expert opinion.

Conclusions

Currently available data suggest that early DOAC initiation after AF-related stroke is safe and perhaps even efficacious. However, this needs to be confirmed by ongoing randomized trials of early versus delayed DOAC initiation.

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