

# Precision Timing of Oral Anticoagulation After AF-Related Ischemic Stroke: Integrating Infarct Topography, Early Imaging Biomarkers, and Hemorrhagic Transformation Risk

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## ABSTRACT

**Background:** Atrial fibrillation (AF)-related ischemic stroke is one of the most preventable yet devastating cerebrovascular events, carrying a high risk of early recurrence if oral anticoagulation is delayed, but an equally concerning risk of hemorrhagic transformation (HT) if initiated too soon. The optimal timing for restarting anticoagulation remains one of the most clinically delicate decisions in acute stroke care. Traditional empirical rules, such as the 1–3–6–12-day framework, fail to integrate patient-level heterogeneity including infarct topography, reperfusion status, and advanced imaging markers that stratify bleeding versus recurrence risk. Recent randomized and observational data, along with precision neuroimaging, have reframed this timing dilemma into a precision-medicine challenge.

**Aim:** This review synthesizes the evolving evidence defining when to initiate oral anticoagulation after AF-related ischemic stroke through a precision lens—integrating infarct size, severity, vascular territory, and early imaging biomarkers such as diffusion-weighted lesion volume, microbleed burden, and the presence of parenchymal hematoma. It examines how hemorrhagic transformation subtypes, mechanical thrombectomy outcomes, and individualized imaging findings can refine timing beyond categorical heuristics. We also explore the interplay of pathophysiology, imaging-based risk assessment, and trial data (ELAN, TIMING, SoSTART, RAF) to propose a stratified, imaging-informed algorithm suitable for modern stroke units.

**Conclusion:** Evidence increasingly supports that early initiation of non-vitamin K oral anticoagulants (NOACs) may be safe in mild or moderate strokes with small infarcts and absent HT, while patients with large infarctions, significant mass effect, or parenchymal hematoma should undergo delayed initiation guided by serial imaging. Precision-based stratification—anchored in infarct topography, hemorrhagic risk biomarkers, and recanalization outcomes—represents the future of anticoagulation timing. By merging clinical severity, advanced imaging, and individualized risk profiling, neurologists can minimize both ischemic recurrence and hemorrhagic conversion, achieving a tailored, safe, and evidence-driven approach to secondary prevention.

**Keywords:** Oral Anticoagulation, AF-Related, Stroke

## INTRODUCTION

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia and contributes to approximately 15–20% of all ischemic strokes, conferring a fivefold increased stroke risk compared with individuals in sinus rhythm [1]. These cardioembolic strokes tend to be larger, more disabling, and carry a higher early recurrence rate if anticoagulation is not resumed promptly [2]. Conversely, premature initiation of anticoagulation in the setting of a fragile infarct bed and disrupted blood–brain barrier (BBB) can precipitate hemorrhagic transformation (HT), which significantly worsens morbidity and mortality [3]. Balancing these dual hazards—early recurrent ischemia versus secondary hemorrhage—represents one of the most challenging aspects of acute stroke management.

Historically, clinicians have relied on rule-of-thumb algorithms such as the “1-3-6-12 day rule,” recommending anticoagulation initiation 1 day after a transient ischemic attack (TIA), 3 days after a minor stroke, 6 days after a moderate stroke, and 12 days after a severe stroke [4]. While intuitive, this approach fails to consider key biological and radiological heterogeneity, including infarct volume, location, reperfusion status, and imaging evidence of microvascular injury. Advances in magnetic resonance imaging (MRI) and computed tomography (CT) now allow for more refined assessment of infarct topography, early blood–brain barrier integrity, and microbleed burden—factors that critically modify bleeding risk and should therefore influence timing decisions [5].

In recent years, randomized trials such as ELAN, TIMING, and SoSTART, along with prospective registries including RAF and CROMIS-2, have reshaped the evidence landscape. These studies suggest that early initiation of direct oral anticoagulants (DOACs) may be both safe and effective in selected patients, especially when guided by careful imaging and clinical stratification [6–8]. Yet, the optimal integration of these findings into daily clinical practice remains incomplete.

### **Aim:**

This review aims to synthesize the pathophysiological, imaging, and clinical determinants that influence the optimal timing of oral anticoagulation after AF-related ischemic stroke. By integrating data from contemporary trials, neuroimaging biomarkers, and stroke subtype analyses, we propose a precision-based framework that moves beyond arbitrary time thresholds toward individualized, evidence-informed decision-making in modern stroke care [9].

### **Pathophysiological Overview**

The decision to initiate oral anticoagulation after an acute ischemic stroke hinges on an intricate interplay between two opposing biological processes—thrombogenesis and hemorrhagic vulnerability. In atrial fibrillation, embolic material forms due to atrial stasis, leading to large-vessel occlusion and cerebral ischemia. Within hours of vessel occlusion, a cascade of ischemic injury unfolds: cytotoxic

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edema, excitotoxicity, and inflammatory activation result in endothelial dysfunction and compromise of the blood–brain barrier (BBB) [10]. The BBB disruption evolves dynamically over the first days, reaching its peak between days 2–5, which coincides with the highest risk period for hemorrhagic transformation if anticoagulation is introduced too early [11].

On the other hand, delaying anticoagulation increases the risk of recurrent embolic stroke—estimated at 0.5–1.3% per day during the first two weeks post-event in untreated AF patients [12]. The timing dilemma thus represents a balance between recurrent ischemia from persistent cardioembolic risk and hemorrhagic complications due to evolving tissue frailty. Pathophysiological insights suggest that infarct size, cortical involvement, and reperfusion dynamics are the dominant biological modifiers of this trade-off [13]. Small, deep (lacunar) infarcts with preserved vascular autoregulation have a lower risk of hemorrhagic conversion compared to large cortical infarcts, which exhibit more profound BBB damage and inflammatory response [14].

Moreover, reperfusion therapies—thrombolysis or mechanical thrombectomy—modulate this relationship. Successful recanalization restores perfusion but can exacerbate oxidative stress and microvascular leakage, predisposing to parenchymal hematoma in fragile tissue beds [15]. Conversely, failure of reperfusion maintains ischemic penumbra vulnerability, promoting recurrent embolization risk. Therefore, any timing recommendation must account for the evolving neurovascular unit—a dynamic entity influenced by stroke size, reperfusion status, systemic inflammation, and hemodynamic stability [16].

Understanding these biological trade-offs underscores why uniform time-based rules are suboptimal. Instead, anticoagulation initiation should be synchronized with biological readiness, evidenced by stabilized BBB integrity, absence of hemorrhagic transformation, and resolution of edema on follow-up imaging [17]. This physiologic framework forms the rationale for integrating neuroimaging biomarkers and individualized risk assessment into modern timing algorithms for anticoagulation initiation.

### **Stroke Phenotyping That Alters Timing**

Stroke severity and anatomical phenotype exert a critical influence on the optimal timing of oral anticoagulation after atrial fibrillation–related ischemic stroke. The degree of neurological impairment, the volume and location of infarction, and the presence of secondary complications directly modulate both recurrent embolic and hemorrhagic transformation (HT) risks [18]. The National Institutes of Health Stroke Scale (NIHSS) remains the most widely applied clinical index to approximate infarct burden. Patients with minor strokes (NIHSS  $\leq 5$ ) generally harbor smaller infarcts and limited BBB disruption, supporting safe early anticoagulation within the first 3–4 days. In contrast, those with moderate (NIHSS 6–15) or severe strokes (NIHSS  $> 15$ ) often demonstrate large territorial infarctions and unstable hemodynamics, necessitating delayed initiation—typically beyond 7–14 days [19].

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Infarct volume is another crucial determinant. Advanced imaging allows quantification of ischemic core using diffusion-weighted MRI (DWI) or CT perfusion maps. Studies such as RAF-NOAC and ELAN have demonstrated that patients with infarct volumes <25 mL tolerated early initiation of DOACs with minimal hemorrhagic risk, whereas large infarcts (>60 mL) were associated with higher rates of parenchymal hematoma and symptomatic ICH when anticoagulated within the first week [20,21].

Topographical distribution further refines this risk stratification. Cortical infarcts, particularly in the middle cerebral artery (MCA) territory, are more prone to hemorrhagic transformation than lacunar or deep subcortical lesions, where microvascular integrity is relatively preserved [22]. Posterior circulation strokes (brainstem or cerebellar) often demonstrate less severe BBB disruption, although mass effect and hydrocephalus can delay safe anticoagulation in large cerebellar infarcts [23].

Finally, concomitant pathologies—such as leukoaraiosis, cerebral amyloid angiopathy (CAA), or extensive white matter disease—further modify bleeding risk profiles. Patients with these substrates exhibit impaired microvascular resilience and higher microbleed burdens, which should inform more cautious, imaging-guided initiation strategies [24].

Thus, precise phenotyping based on clinical severity, infarct volume, and vascular territory allows neurologists to transition from rigid chronological timing toward pathophysiologically tailored anticoagulation, aligning therapy with each brain's biological recovery trajectory [25].

#### Hemorrhagic Transformation (HT) Risk

Hemorrhagic transformation (HT) represents the most feared complication following ischemic stroke and remains the principal limiting factor for early initiation of anticoagulation. HT occurs in approximately 15–40% of ischemic strokes, but only a subset—classified as parenchymal hematoma (PH)—carries significant clinical deterioration and mortality risk [26]. The Heidelberg Bleeding Classification provides a structured framework to distinguish radiological subtypes: hemorrhagic infarction (HI1/HI2) reflects petechial bleeding without space-occupying effect, while parenchymal hematoma (PH1/PH2) denotes confluent hematoma with or without mass effect [27]. This categorization is essential because therapeutic implications differ substantially: anticoagulation may be cautiously resumed in HI lesions but should be deferred in PH forms until hematoma stabilization is confirmed on serial imaging [28].

The timing and likelihood of HT are influenced by multiple synergistic factors. Infarct size and cortical involvement are the strongest predictors—larger infarcts create wider zones of microvascular rupture and reperfusion injury [29]. Additional risk enhancers include advanced age, uncontrolled hypertension, hyperglycemia, prior anticoagulant exposure, and successful reperfusion therapy (IVT or mechanical thrombectomy), each of which augments BBB permeability and promotes extravasation of blood products [30]. Furthermore, delayed recanalization or fluctuating cerebral perfusion pressures

can trigger reperfusion injury and secondary hemorrhagic conversion even several days after stroke onset [31].

Neuroimaging markers have become indispensable in refining hemorrhagic risk estimation. MRI susceptibility-weighted imaging (SWI) and gradient-echo sequences detect microbleeds and superficial siderosis—hallmarks of microangiopathic fragility—while perfusion CT and MRI perfusion maps assess capillary leakage and delayed transit time [32]. A high burden of cerebral microbleeds (>5 lesions), particularly in lobar regions, is associated with increased intracerebral hemorrhage risk after anticoagulation, especially in patients with probable cerebral amyloid angiopathy [33].

In summary, individualized HT risk profiling should precede anticoagulation initiation. Integrating lesion subtype (HI vs PH), infarct topography, and microbleed burden enables clinicians to define a “safe window” for therapy resumption. Precision in timing stems not merely from the number of days post-stroke but from objective evidence of vascular stabilization and imaging-based hemorrhagic quiescence [34].

### **Imaging Biomarkers to Guide Start**

Neuroimaging has revolutionized the precision of anticoagulation timing after atrial fibrillation-related ischemic stroke by providing direct visualization of infarct characteristics, tissue viability, and hemorrhagic risk. Advanced imaging biomarkers—derived from magnetic resonance imaging (MRI) and computed tomography (CT)—are now central to tailoring therapy, as they quantify the extent of ischemic injury and vascular integrity far more accurately than clinical scales alone [35].

Diffusion-weighted imaging (DWI) remains the gold standard for defining the ischemic core. Quantitative DWI lesion volume correlates strongly with hemorrhagic transformation risk; infarcts <25 mL typically exhibit safe profiles for early anticoagulation, while those >60 mL show significantly higher rates of parenchymal hematoma when treated within 7 days [36]. Apparent diffusion coefficient (ADC) thresholds and ASPECTS (Alberta Stroke Program Early CT Score) on non-contrast CT similarly stratify infarct burden, helping to individualize initiation windows in settings without MRI access [37].

**Perfusion imaging** adds another dimension by differentiating between the irreversibly infarcted core and salvageable penumbra. A large mismatch ratio (e.g., >1.8) with low hypoperfusion intensity (<0.5) suggests viable tissue and lower hemorrhagic conversion probability, permitting earlier anticoagulation [38]. Conversely, high hypoperfusion intensity ratios and extensive delayed time-to-maximum (Tmax) prolongations signal endothelial stress and greater bleeding potential [39].

Beyond ischemic core and perfusion metrics, microbleed assessment using susceptibility-weighted or gradient-echo MRI sequences refines hemorrhagic risk evaluation. Patients with >5 microbleeds—particularly lobar—show higher intracranial bleeding rates under oral anticoagulation, necessitating

either delayed initiation or preference for NOACs over warfarin to minimize ICH risk [40]. Moreover, superficial siderosis, a marker of cortical microangiopathy or probable cerebral amyloid angiopathy, flags those at exceptional risk for hemorrhagic complications [41].

Recent studies also highlight blood–brain barrier permeability imaging using dynamic contrast-enhanced MRI or CT perfusion leak metrics as predictive of HT evolution. High permeability indices in peri-infarct regions correlate with subsequent hemorrhagic transformation, suggesting that this emerging biomarker could become pivotal in guiding safe anticoagulation timing [42].

Collectively, these imaging parameters—lesion volume, perfusion mismatch, microbleeds, and BBB permeability—enable neurologists to evolve from empirical timing to imaging-driven anticoagulation decisions, ensuring that therapy is initiated at the moment of biological readiness rather than arbitrary chronology [43].

### **Reperfusion Era Nuances**

The widespread adoption of reperfusion therapies—intravenous thrombolysis (IVT) and mechanical thrombectomy (MT)—has profoundly altered the landscape of anticoagulation timing after atrial fibrillation–related ischemic stroke. While these interventions restore perfusion and salvage penumbral tissue, they also introduce new variables affecting the safety and timing of subsequent anticoagulation [44]. The interplay between reperfusion-related vascular fragility, contrast extravasation, and residual BBB dysfunction demands a more individualized strategy than traditional timing rules allow.

Following intravenous thrombolysis, the endothelium remains highly susceptible to leakage for 24–48 hours due to fibrinolytic disruption of the vascular basement membrane and degradation of tight junction proteins [45]. Therefore, immediate anticoagulation is contraindicated, and repeat imaging—typically at 24 hours—is mandated to rule out hemorrhagic transformation before reconsidering therapy. For minor strokes without HT, initiation at day 3–4 may be considered safe with NOACs, while moderate-to-severe infarcts usually necessitate a 7–14 day delay [46].

In the mechanical thrombectomy era, timing is further complicated by procedural factors such as the number of device passes, reperfusion success (TICI score), and periprocedural hemorrhage. Successful recanalization (TICI 2b–3) often correlates with smaller final infarct volumes, supporting earlier anticoagulation if post-procedural imaging shows no parenchymal hematoma [47]. However, contrast staining seen on immediate post-thrombectomy CT must be distinguished from true subarachnoid or parenchymal bleeding, as the former represents transient extravasation and usually resolves within 24–48 hours [48].

Patients undergoing combined IVT and MT carry an additive risk of HT, particularly when infarct volumes exceed 70 mL or when reperfusion occurs after prolonged ischemia. In such scenarios, clinicians should defer anticoagulation until a follow-up MRI or CT (at 3–5 days) confirms stability and absence of progressive edema or hemorrhage [49].

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Emerging data from post-reperfusion registries suggest that, in selected patients with small core infarcts and complete recanalization, initiating NOACs as early as 48–72 hours post-thrombectomy can reduce recurrent embolic events without increasing symptomatic ICH rates [50]. Nonetheless, these decisions must be anchored in imaging confirmation of tissue stability, not procedural success alone.

Ultimately, the reperfusion era necessitates a biologically adaptive framework, integrating both procedural and imaging data to identify the optimal anticoagulation window—balancing recanalization benefits against vascular vulnerability [51].

#### Evidence Synthesis: Early vs Later Start

The debate surrounding early versus delayed initiation of oral anticoagulation after AF-related ischemic stroke has been shaped by a blend of randomized controlled trials (RCTs) and large-scale observational registries. Historically, clinicians favored a conservative approach, postponing anticoagulation to mitigate hemorrhagic risk; however, recent data increasingly challenge this paradigm by demonstrating that earlier initiation of DOACs may be both safe and efficacious in appropriately selected patients [52].

The Early versus Late Initiation of Direct Oral Anticoagulants in Post-Ischemic Stroke Patients with Atrial Fibrillation (ELAN) trial, published in 2023, provided pivotal evidence. ELAN randomized over 2,000 patients to early ( $\leq 48$  hours for minor/moderate stroke; day 6–7 for major) versus late (day 3–4 or day 12–14) DOAC initiation. The composite outcome of recurrent ischemic stroke, systemic embolism, major bleeding, or vascular death was similar between groups, but the early-start cohort experienced a numerically lower recurrent stroke rate without increased symptomatic intracranial hemorrhage [53].

Similarly, the TIMING trial found that DOAC initiation within 4 days post-stroke was non-inferior to delayed initiation (5–10 days) for a composite of stroke, ICH, or all-cause mortality, supporting the safety of earlier therapy in mild-to-moderate infarcts [54]. The SoSTART trial, though smaller, reported comparable findings—early DOAC start (median 5 days) did not significantly increase symptomatic ICH risk, while trends favored reduced recurrent ischemia [55].

Observational data corroborate these findings. The RAF and RAF-NOAC studies demonstrated that anticoagulation initiated within 4–7 days reduced recurrent ischemic events without elevating bleeding rates, particularly when infarct volume was modest and no parenchymal hematoma was evident on imaging [56,57]. Importantly, CROMIS-2 highlighted that cerebral microbleed burden modifies risk—patients with  $>5$  microbleeds had greater ICH risk, underscoring the importance of imaging-guided stratification [58].

Meta-analyses integrating RCT and registry data suggest that, for minor-to-moderate infarcts without HT, initiating DOACs between days 2–7 provides the best balance between ischemic prevention and

hemorrhagic safety. Conversely, major infarcts or PH2 hemorrhagic transformation warrant deferral beyond 14 days [59].

Collectively, these findings shift practice from rigid time-based thresholds toward evidence-calibrated, imaging-informed timing, aligning therapy with infarct biology and patient-specific risk rather than fixed chronology [60].

### From Rules to Algorithms

For decades, clinicians have relied on simplified heuristics—most notably the “1-3-6-12 day rule”—to determine when to restart anticoagulation after ischemic stroke. While pragmatic, these linear frameworks were developed in the pre-thrombolysis era and fail to reflect the contemporary landscape shaped by advanced imaging, reperfusion therapies, and the widespread use of DOACs [61]. The rule’s rigidity—initiating anticoagulation 1 day after transient ischemic attack (TIA), 3 days after minor stroke, 6 after moderate, and 12 after severe—ignores the biological heterogeneity between patients with similar NIHSS scores but vastly different infarct morphologies or microvascular integrity [62]. Emerging evidence supports transitioning from time-based to risk-adaptive algorithms, where initiation is determined by objective markers of infarct stability rather than calendar days. These precision algorithms integrate clinical severity, imaging parameters, and hemorrhagic biomarkers to dynamically calibrate the timing of therapy. For instance, one proposed framework stratifies patients into three tiers:

- **Low-risk (small infarct <25 mL, no HT):** Start NOAC within 2–4 days.
- **Intermediate-risk (moderate infarct 25–60 mL or HI1/HI2 on imaging):** Initiate between 5–10 days.
- **High-risk (large infarct >60 mL, PH1/PH2, mass effect, or extensive microbleeds):** Delay beyond 14 days, reassessing with repeat imaging [63].

Such algorithms derive from post hoc analyses of ELAN, RAF-NOAC, and TIMING studies, which consistently show that infarct size and hemorrhagic subtype predict outcomes more accurately than arbitrary time windows [64]. Moreover, integrating imaging biomarkers—such as DWI lesion volume, microbleed count, and perfusion mismatch ratios—further refines safety margins and enables nuanced, data-driven timing decisions [65].

Clinical workflow tools are now being designed to operationalize these concepts. Digital decision-support platforms linked to stroke unit imaging systems can auto-populate key metrics (e.g., infarct volume, presence of HT) to suggest optimal initiation windows [66]. By anchoring anticoagulation decisions to quantifiable imaging and clinical data, such algorithms transform anticoagulation timing from an empirical art into a reproducible precision process [67].

The shift from rules to algorithms embodies the evolution of stroke medicine: replacing uniformity with personalization, and time-based heuristics with biologically rational decision-making tailored to each patient's cerebrovascular recovery state [68].

### Special Populations

Certain patient subgroups exhibit unique pathophysiological and clinical characteristics that significantly modify the risk–benefit profile of anticoagulation timing after AF-related ischemic stroke. These special populations require tailored strategies beyond conventional algorithms, as standard timing may be either unsafe or insufficiently protective [69].

Large territorial infarcts, particularly involving the middle cerebral artery (MCA) or anterior circulation, carry a high risk of hemorrhagic transformation and malignant edema. In such cases, anticoagulation is typically deferred for at least 14 days, pending follow-up imaging to confirm infarct stability and absence of PH-type hemorrhage [70]. Conversely, small deep (lacunar) infarcts generally present with limited blood–brain barrier disruption, allowing earlier initiation—often within 2–4 days—if imaging is reassuring [71].

Posterior circulation strokes pose a different challenge. While brainstem and cerebellar infarcts tend to have lower hemorrhagic risk, the confined anatomic space makes any secondary bleed potentially catastrophic. Clinicians therefore adopt a conservative approach, starting anticoagulation around 7–10 days post-event, contingent upon imaging stability and absence of hydrocephalus or mass effect [72]. Patients with a history of intracerebral hemorrhage (ICH) or probable cerebral amyloid angiopathy (CAA) represent another high-risk cohort. MRI detection of multiple lobar microbleeds or cortical superficial siderosis implies underlying microangiopathy, conferring an elevated risk of recurrent ICH once anticoagulated [73]. In such cases, clinicians often favor delayed initiation, lower-intensity NOAC regimens, or even alternative strategies such as left atrial appendage occlusion (LAAO) when hemorrhagic risk outweighs ischemic benefit [74].

The elderly population and those with comorbidities—such as chronic kidney disease (CKD), hepatic dysfunction, or uncontrolled hypertension—further complicate anticoagulation decisions. Impaired renal clearance increases drug exposure and bleeding risk, particularly with certain DOACs. Dose adjustment, careful monitoring, and repeat neuroimaging are thus essential before early initiation [75]. Finally, patients undergoing dual antithrombotic therapy (e.g., post-stent or post-thrombectomy with stenting) require balancing ischemic and hemorrhagic priorities. In these cases, anticoagulation timing is individualized, often delaying DOAC initiation until the DAPT (dual antiplatelet therapy) course is safely shortened [76].

Understanding the nuances of these populations underscores that “one-size-fits-all” strategies are obsolete. Instead, integrating comorbid, anatomical, and imaging-specific factors allows for a

precision-based timing approach that maximizes safety without compromising secondary prevention efficacy [77].

### **Choice of Agent and Dosing**

The advent of direct oral anticoagulants (DOACs) has transformed the management of atrial fibrillation–related ischemic stroke by providing safer and more predictable anticoagulation compared with vitamin K antagonists (VKAs). Their rapid onset, fewer drug–food interactions, and reduced intracranial bleeding risk make them the preferred agents for most post-stroke patients [78]. However, optimal selection and dosing depend on renal function, hepatic profile, patient frailty, and the timing of initiation relative to stroke severity and imaging findings.

DOACs—including dabigatran, rivaroxaban, apixaban, and edoxaban—demonstrate consistent efficacy in stroke prevention with approximately 50–70% lower rates of intracranial hemorrhage compared to warfarin in AF populations [79]. Among them, apixaban and edoxaban are often favored for elderly or high-bleeding-risk patients because of their lower relative risk of ICH and favorable renal pharmacokinetics [80]. In the context of early post-stroke initiation, reduced or standard dosing remains an area of active investigation. Evidence from ELAN and TIMING suggests that standard therapeutic doses are generally safe when infarct volume is small and no hemorrhagic transformation exists; dose reduction should be reserved for renal impairment or elevated bleeding risk rather than timing alone [81].

Warfarin, while effective, has largely been replaced in this setting due to its delayed onset, variable therapeutic levels, and higher propensity for cerebral bleeding during early recovery. When VKAs must be used (e.g., mechanical heart valves), careful bridging protocols with close INR monitoring are essential, typically delaying initiation until at least 10–14 days post-stroke, and only after imaging excludes HT [82].

Renal and hepatic dysfunction mandate dose adjustments or even avoidance of certain agents. For instance, dabigatran is contraindicated in severe renal impairment (eGFR <30 mL/min), while rivaroxaban and apixaban may be used with caution at adjusted doses [83]. Additionally, drug–drug interactions—particularly with antiplatelets, antifungals, or anticonvulsants—should be reviewed before initiation, as they can significantly alter DOAC plasma levels [84].

Ultimately, agent selection should align with the individual’s imaging-defined bleeding risk, renal and hepatic status, and pharmacologic profile. This personalized approach ensures maximal secondary prevention efficacy while minimizing the hazards of early anticoagulation during the critical post-stroke recovery window [85].

### **Bridging, Antiplatelets, and Left Atrial Appendage Occlusion (LAAO)**

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Bridging and adjunctive antithrombotic strategies in the early post-stroke period represent a delicate balance between preventing recurrent embolism and minimizing bleeding risk. Historically, clinicians employed low-molecular-weight heparin (LMWH) or unfractionated heparin as bridging therapies before achieving therapeutic anticoagulation with warfarin. However, accumulating evidence indicates that this practice significantly increases the risk of intracranial hemorrhage (ICH) and hemorrhagic transformation (HT) without a corresponding reduction in recurrent ischemia [86]. Consequently, major guidelines—including those from the European Stroke Organisation (ESO) and AHA/ASA—now advise against bridging with heparin in the acute post-stroke setting, especially within the first 7 days [87].

In patients who cannot yet be anticoagulated due to recent large infarction or hemorrhagic conversion, temporary antiplatelet therapy (typically aspirin monotherapy) may serve as an interim measure. Studies suggest that short-term aspirin (75–100 mg daily) can reduce early embolic recurrence risk modestly without markedly increasing hemorrhagic events, although it does not offer full cardioembolic protection [88]. Once oral anticoagulation is initiated, antiplatelet therapy should generally be discontinued unless a compelling secondary indication exists (e.g., recent coronary stenting or large-artery atherosclerosis) [89].

The dual antithrombotic state—anticoagulant plus antiplatelet—poses one of the highest ICH risks, particularly within the first two weeks post-stroke. For patients requiring both due to coronary or intracranial stenting, current consensus recommends minimizing overlap duration and selecting the lowest effective antiplatelet burden (e.g., monotherapy with clopidogrel rather than dual antiplatelet therapy) [90].

For individuals with contraindications to long-term anticoagulation—such as those with recurrent HT, high microbleed burden, or probable cerebral amyloid angiopathy—left atrial appendage occlusion (LAAO) has emerged as a viable alternative. Devices such as Watchman and Amplatzer Amulet effectively reduce stroke risk by mechanically excluding the primary thrombus source in AF. Post-procedure, short-term dual antiplatelet therapy is typically employed, followed by single antiplatelet maintenance [91].

In summary, the post-stroke antithrombotic strategy should avoid early heparin bridging, limit unnecessary antiplatelet overlap, and consider mechanical solutions like LAAO in select high-risk individuals. The overarching goal is to achieve embolic protection while respecting the biological vulnerability of recently infarcted brain tissue [92].

### **Monitoring After Initiation**

Once oral anticoagulation is initiated following AF-related ischemic stroke, rigorous clinical and imaging surveillance becomes essential to ensure both efficacy and safety. The early post-initiation phase—particularly the first 7 to 14 days—represents a period of heightened vulnerability, during

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which vigilance for hemorrhagic transformation (HT), recurrent ischemia, and systemic bleeding complications is paramount [93].

**Neurological monitoring** should be performed at least every 4–6 hours during the initial 48 hours of anticoagulation, with particular attention to any sudden neurological decline, which mandates urgent neuroimaging. Early repeat CT or MRI (typically at 24–72 hours post-initiation) is recommended in moderate-to-severe strokes to confirm infarct stability and absence of new bleeding, especially in patients who underwent reperfusion therapy or exhibit early mass effect [94].

Systemic parameters such as blood pressure, renal function, and hepatic enzymes should be closely monitored, as fluctuations in these can alter drug pharmacokinetics and bleeding risk. Strict blood pressure control (<140/90 mmHg) reduces the likelihood of secondary ICH without compromising cerebral perfusion [95]. For patients on DOACs, routine coagulation testing is not required, but in cases of renal impairment, periodic monitoring of estimated glomerular filtration rate (eGFR) is critical to prevent drug accumulation and toxicity [96].

Clinicians should remain alert to drug–drug interactions, particularly with antiplatelet agents, nonsteroidal anti-inflammatory drugs (NSAIDs), or selective serotonin reuptake inhibitors (SSRIs), all of which can heighten bleeding propensity [97]. Additionally, patient education regarding adherence, signs of bleeding, and avoidance of over-the-counter antithrombotics forms a cornerstone of outpatient safety.

In some centers, stroke-anticoagulation clinics or multidisciplinary follow-up programs have been established to coordinate post-stroke monitoring, ensuring standardized imaging, renal testing, and adherence assessments. These structured pathways have been shown to reduce adverse events and improve functional outcomes [98].

Ultimately, vigilant post-initiation monitoring transforms anticoagulation from a high-risk intervention into a controlled and safe secondary prevention strategy. By aligning clinical observation with imaging confirmation and metabolic surveillance, clinicians can mitigate complications and maintain the delicate equilibrium between thromboembolic protection and hemorrhagic safety [99].

### **Implementation and Workflow**

The successful adoption of a precision-based anticoagulation timing strategy requires structured, multidisciplinary implementation that translates evolving evidence into consistent bedside practice. This integration depends not only on clinical expertise but also on standardized workflows, protocol-driven decision-making, and seamless communication among stroke neurologists, cardiologists, radiologists, and rehabilitation teams [100].

Modern stroke units have begun employing algorithmic care pathways that embed imaging, clinical severity, and comorbidity parameters into electronic health record (EHR) decision tools. For example, integrating automated ASPECTS scoring or MRI lesion volumetry within EHR alerts allows clinicians

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to categorize patients into low-, intermediate-, or high-risk timing brackets for oral anticoagulation initiation. These digital pathways facilitate consistency, reduce interphysician variability, and shorten decision-to-initiation time while maintaining safety standards [101].

Multidisciplinary stroke rounds are essential for individualized decision-making. Radiologists contribute to lesion characterization and HT classification; cardiologists guide anticoagulant selection and dose adjustment; and stroke nurses monitor adherence, side effects, and hemodynamic parameters. Structured team discussions ensure that timing decisions consider both neurological and systemic perspectives [102].

Protocolized reimaging schedules—for example, CT or MRI at 24 hours, day 5, and before anticoagulation—are increasingly embedded into workflows, ensuring objective confirmation of infarct stabilization before therapy. Parallel BP optimization protocols, glycemic control, and early rehabilitation planning further reduce the risk of hemorrhagic complications [103].

At a systems level, hospital networks should develop stroke-anticoagulation registries to audit timing decisions, outcomes, and complication rates. Continuous feedback loops allow iterative refinement of protocols and benchmarking against evidence-based standards. Moreover, incorporating AI-assisted decision support can enhance risk prediction by integrating lesion topography, patient demographics, and laboratory data into dynamic anticoagulation-timing models [104].

Finally, clinician education remains central. Regular interdisciplinary workshops, protocol refreshers, and simulation-based training promote familiarity with current evidence (e.g., ELAN, TIMING, SoSTART) and ensure protocol adherence. Implementation success hinges not merely on data but on culture—embedding precision and safety as co-equal priorities in every post-stroke anticoagulation decision [105].

## Conclusions

The decision of when to initiate oral anticoagulation after atrial fibrillation-related ischemic stroke represents one of the most nuanced challenges in modern stroke medicine. The historical reliance on fixed, time-based rules such as the “1-3-6-12 day” framework has increasingly given way to precision-guided strategies that incorporate infarct topography, hemorrhagic transformation subtype, and advanced imaging biomarkers. Contemporary evidence demonstrates that individualized assessment—

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anchored in objective imaging and clinical severity—can achieve optimal balance between preventing recurrent embolic events and minimizing intracranial bleeding.

Advances in MRI and CT technology now permit detailed evaluation of lesion volume, blood–brain barrier integrity, and microbleed burden, allowing clinicians to calibrate anticoagulation timing according to biological readiness rather than arbitrary chronology. Trials such as ELAN, TIMING, and SoSTART have validated the safety of earlier initiation in patients with minor or moderate infarcts who lack hemorrhagic transformation, while supporting delayed initiation in those with large territorial infarcts, parenchymal hematoma, or ongoing edema. The synthesis of these data underscores that there is no universal “safe day”—only a patient-specific, evidence-informed window defined by the interplay between tissue recovery and vascular stability.

Precision medicine in post-stroke anticoagulation thus demands a paradigm shift: from prescriptive timelines toward dynamic, imaging-driven algorithms that integrate clinical, radiological, and procedural variables. Incorporating multidisciplinary decision-making, structured imaging follow-up, and electronic workflow support ensures that each anticoagulation decision is both scientifically grounded and individualized.

Ultimately, the future of anticoagulation timing lies in the union of technology and clinical insight—where imaging biomarkers, artificial intelligence, and patient-specific risk modeling converge to guide the neurologist’s judgment. By adopting this biologically rational and patient-centered approach, clinicians can significantly improve functional outcomes, reduce recurrent embolic risk, and ensure that every anticoagulation decision after stroke is made with precision, safety, and confidence.

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