Acute Non-Cardioembolic Ischemic Stroke: Dual Antiplatelets for Secondary Prevention—Clinical Profile, Timing, Duration, and Outcomes

El-Hady Ahmed Abd El Gawwad, Tarek Abd El Rahman Goda, Eman Mohamed Elewa Mansour, Nancy Abd El Hameed Mohamed

Neurology Department, Faculty of Medicine - Zagazig University
Corresponding Author: Eman Mohamed Elewa Mansour

Received: 28 October 2024, **Accepted:** 17 November 2024, **Published:** 20 November 2024

Abstract

Background: Acute non-cardioembolic ischemic stroke accounts for the majority of ischemic cerebrovascular events and remains a leading cause of long-term disability and mortality worldwide. Early secondary prevention is crucial, as the risk of recurrent ischemic stroke is highest within the first days to weeks following the index event. Antiplatelet therapy represents the cornerstone of management in this population, with aspirin traditionally used as monotherapy. However, residual early recurrence despite single antiplatelet therapy has prompted growing interest in dual antiplatelet therapy (DAPT) as a more effective short-term strategy to reduce ischemic events.

Aim: This review aims to critically evaluate the role of dual antiplatelet therapy compared with single antiplatelet therapy in acute non-cardioembolic ischemic stroke, with a particular focus on patient clinical profiles, optimal timing of initiation, appropriate duration of therapy, functional outcomes, and associated hemorrhagic risks.. Available randomized controlled trials, observational studies, and guideline recommendations are examined to assess the efficacy and safety of DAPT in the acute phase of non-cardioembolic ischemic stroke. Emphasis is placed on patient selection, including minor ischemic stroke and high-risk transient ischemic attack, as well as the impact of early initiation and short-term use of DAPT on stroke recurrence and disability outcomes.

Results: Accumulating evidence indicates that short-term DAPT initiated early after symptom onset significantly reduces the risk of recurrent ischemic stroke compared with antiplatelet monotherapy. The greatest benefit is observed when DAPT is started within the first 24 hours and continued for a limited duration, typically 21–30 days. While dual therapy is associated with an increased risk of bleeding, particularly with prolonged use, short-term regimens demonstrate an overall favorable benefit–risk profile in appropriately selected patients.

Conclusion: Dual antiplatelet therapy represents an effective strategy for early secondary prevention in acute non-cardioembolic ischemic stroke when applied to carefully selected patients and limited to a short treatment window. Individualized assessment of ischemic versus hemorrhagic risk, along with precise timing and duration of therapy, is essential to optimize clinical outcomes.

Keywords: *Acute Non-Cardioembolic Ischemic Stroke, Dual Antiplatelets, Outcomes*

Introduction

Acute ischemic stroke remains one of the leading causes of death and long-term disability worldwide, with non-cardioembolic mechanisms accounting for approximately two-thirds of all ischemic events. These strokes predominantly arise from large artery atherosclerosis or small vessel disease, where platelet activation and aggregation play a central role in thrombus formation. The early period following an ischemic stroke is characterized by a markedly increased risk of recurrence, particularly within the first days to weeks, highlighting the importance of effective early secondary prevention strategies aimed at reducing recurrent cerebral ischemia and improving functional outcomes [1].

Antiplatelet therapy has long been established as the cornerstone of secondary prevention in patients with non-cardioembolic ischemic stroke. Aspirin monotherapy was historically adopted based on its ability to inhibit platelet cyclooxygenase activity and reduce recurrent vascular events. However, despite early aspirin administration, a substantial proportion of patients continue to experience recurrent ischemic strokes, especially during the acute and subacute phases. This residual risk has prompted investigation into more intensive antiplatelet regimens capable of achieving greater platelet inhibition during this vulnerable period [2].

Dual antiplatelet therapy, typically combining aspirin with a P2Y12 receptor inhibitor such as clopidogrel or ticagrelor, offers a pharmacologically rational approach by targeting complementary platelet activation pathways. This strategy has demonstrated substantial benefit in coronary artery disease and acute coronary syndromes, leading to exploration of its role in cerebrovascular disease. In ischemic stroke, however, concerns regarding intracranial hemorrhage and major bleeding initially limited enthusiasm for routine dual therapy, necessitating carefully designed trials to define its safety and efficacy in selected patient populations [3].

Recent large randomized controlled trials have reshaped the therapeutic landscape by demonstrating that short-term dual antiplatelet therapy initiated early after minor ischemic stroke or high-risk transient ischemic attack can significantly reduce recurrent ischemic events without an unacceptable increase in hemorrhagic complications. These findings have influenced international guidelines and clinical practice, although important questions remain regarding optimal patient selection, timing of initiation, choice of antiplatelet agents, and duration of therapy [4].

Aim and Research Gap:

The aim of this review is to comprehensively evaluate the role of dual antiplatelet therapy in acute non-cardioembolic ischemic stroke, with emphasis on clinical profile, optimal timing, duration of therapy, functional outcomes, and bleeding risk. Despite growing evidence supporting short-term dual therapy, uncertainties persist regarding its applicability across diverse stroke subtypes, imaging profiles, and comorbid conditions. Addressing these gaps is essential to refine individualized treatment strategies and maximize the benefit–risk balance of antiplatelet therapy in this high-risk population [5].

Pathophysiology of Acute Non-Cardioembolic Ischemic Stroke

Acute non-cardioembolic ischemic stroke primarily results from intrinsic arterial pathology rather than embolism originating from the heart. The two dominant mechanisms are large artery atherosclerosis and small vessel (lacunar) disease. In large artery atherosclerosis, progressive endothelial dysfunction, lipid accumulation, and inflammatory cell infiltration lead to plaque formation within extracranial or intracranial arteries. Plaque rupture or erosion exposes thrombogenic material, triggering platelet adhesion, activation, and aggregation, ultimately resulting in arterial thrombus formation and downstream cerebral ischemia [6].

Small vessel disease represents another major substrate for non-cardioembolic ischemic stroke and is commonly associated with chronic hypertension, diabetes mellitus, and aging. Pathological changes include lipohyalinosis, fibrinoid necrosis, and microatheroma formation in penetrating arteries supplying deep brain structures. These alterations predispose to in situ thrombosis and vessel occlusion, often producing lacunar infarcts. Platelet activation and local thrombus formation remain central mechanisms even in small vessel occlusion, underscoring the relevance of antiplatelet therapy in this

stroke subtype [7].

Platelet activation plays a pivotal role in the acute phase of non-cardioembolic ischemic stroke. Vascular injury and endothelial disruption lead to exposure of collagen and von Willebrand factor, promoting platelet adhesion via glycoprotein receptors. Subsequent platelet activation results in the release of prothrombotic mediators such as thromboxane A_2 and adenosine diphosphate, which amplify platelet aggregation through cyclooxygenase-1 and P2Y12 receptor–dependent pathways. This cascade contributes not only to initial arterial occlusion but also to early stroke progression and recurrence [8].

Inflammation and thromboinflammation further exacerbate ischemic injury in non-cardioembolic stroke. Activated platelets interact with leukocytes and endothelial cells, promoting cytokine release, oxidative stress, and microvascular dysfunction. These processes may extend ischemic damage beyond the primary infarct core and increase the risk of early recurrent events. Enhanced platelet reactivity and systemic inflammatory responses during the acute phase provide a strong biological rationale for intensified antiplatelet inhibition during the early period following stroke onset [9].

The temporal dynamics of thrombosis in non-cardioembolic ischemic stroke are clinically significant. The highest risk of recurrent ischemia occurs within the first hours to days after symptom onset, corresponding to a period of heightened platelet activation and unstable atherosclerotic plaques. This pathophysiological window explains why early initiation of dual antiplatelet therapy may offer superior protection against recurrent stroke compared with delayed or prolonged therapy, while also emphasizing the importance of limiting treatment duration to reduce hemorrhagic complications [10].

Pharmacological Basis of Dual Antiplatelet Therapy in Acute Non-Cardioembolic Ischemic Stroke

Antiplatelet therapy targets platelet activation and aggregation, which are central mechanisms in arterial thrombosis underlying non-cardioembolic ischemic stroke. Aspirin exerts its antithrombotic effect through irreversible inhibition of cyclooxygenase-1, leading to suppression of thromboxane A_2 synthesis and reduced platelet aggregation. While aspirin effectively lowers the risk of recurrent ischemic events, it does not fully inhibit platelet activation mediated through alternative pathways, leaving residual platelet reactivity that may contribute to early stroke recurrence [11].

P2Y12 receptor inhibitors, such as clopidogrel and ticagrelor, provide complementary platelet inhibition by blocking adenosine diphosphate–mediated platelet activation. Clopidogrel is a prodrug requiring hepatic activation via cytochrome P450 enzymes, whereas ticagrelor is a direct-acting, reversible P2Y12 antagonist with more rapid and consistent platelet inhibition. By targeting a distinct signaling pathway from aspirin, P2Y12 inhibitors reduce platelet amplification and stabilize thrombus formation in the arterial circulation [12].

The rationale for dual antiplatelet therapy lies in the synergistic inhibition of multiple platelet activation pathways. Combined blockade of cyclooxygenase-1 and P2Y12 receptors results in more potent and sustained suppression of platelet aggregation than either agent alone. In the acute phase of ischemic stroke, when platelet activation is heightened and atherosclerotic plaques may remain unstable, this intensified inhibition is particularly relevant for preventing early recurrent ischemic events [13].

However, enhanced antiplatelet potency is intrinsically associated with an increased risk of bleeding, especially intracranial hemorrhage. The cerebral vasculature is uniquely vulnerable due to ischemia-related blood–brain barrier disruption and reperfusion injury. As a result, the pharmacological advantage of dual antiplatelet therapy must be carefully balanced against hemorrhagic risk, emphasizing the importance of short-term use and precise patient selection rather than prolonged or indiscriminate application [14].

Interindividual variability in antiplatelet response further influences the effectiveness and safety of dual therapy. Genetic polymorphisms affecting clopidogrel metabolism, drug–drug interactions, and comorbid conditions such as renal or hepatic dysfunction may alter platelet inhibition and clinical outcomes. These pharmacological considerations highlight the need for tailored antiplatelet strategies in acute non-cardioembolic ischemic stroke, rather than a uniform approach for all patients [15].

Clinical Profile of Patients Eligible for Dual Antiplatelet Therapy

Dual antiplatelet therapy is not universally indicated for all patients with acute non-cardioembolic ischemic stroke, and careful clinical profiling is essential to identify those most likely to benefit. Evidence consistently supports the use of dual therapy in patients presenting with **minor ischemic stroke**, most commonly defined by a National Institutes of Health Stroke Scale (NIHSS) score of ≤3. These patients have a relatively low risk of hemorrhagic transformation but a disproportionately high risk of early recurrent ischemic events, making them ideal candidates for short-term intensified antiplatelet therapy [16].

Patients with **high-risk transient ischemic attack (TIA)** represent another key subgroup in whom dual antiplatelet therapy has demonstrated benefit. High-risk TIA is typically characterized by an $ABCD^2$ score of ≥4 or the presence of symptomatic large artery atherosclerosis. Although neurological deficits resolve completely, these patients share a similar early recurrence risk with minor stroke patients, particularly within the first 48–72 hours, justifying aggressive early secondary prevention with dual antiplatelet agents [17].

Neuroimaging findings play an increasingly important role in defining the clinical profile suitable for dual antiplatelet therapy. Small infarct volumes on diffusion-weighted magnetic resonance imaging and the absence of hemorrhagic transformation on baseline computed tomography are associated with a lower bleeding risk. Additionally, evidence of intracranial or extracranial arterial stenosis on vascular imaging identifies patients with an atherosclerotic substrate who are more likely to benefit from enhanced platelet inhibition [18].

Patient-specific vascular risk factors further influence eligibility for dual antiplatelet therapy. Individuals with diabetes mellitus, hypertension, dyslipidemia, and active smoking have heightened platelet reactivity and systemic inflammation, which may increase the risk of early stroke recurrence. In such patients, the ischemic benefit of short-term dual therapy may outweigh the bleeding risk when initiated promptly and discontinued within the recommended duration [19].

Conversely, patients with more severe ischemic strokes, extensive infarction, or a history of intracranial hemorrhage are generally poor candidates for dual antiplatelet therapy due to an elevated risk of bleeding complications. Advanced age, renal impairment, and concurrent use of anticoagulants or nonsteroidal anti-inflammatory drugs further increase hemorrhagic risk. These factors underscore the importance of individualized clinical assessment rather than routine application of dual therapy in all cases of non-cardioembolic ischemic stroke [20].

Timing of Dual Antiplatelet Therapy Initiation

The timing of dual antiplatelet therapy initiation is a critical determinant of its efficacy in acute non-cardioembolic ischemic stroke. Clinical and epidemiological studies consistently demonstrate that the risk of recurrent ischemic events is highest within the first hours to days following the index stroke or high-risk transient ischemic attack. This early vulnerability is driven by heightened platelet activation, unstable atherosclerotic plaques, and ongoing thromboinflammatory processes, providing a strong rationale for initiating antiplatelet therapy as early as possible after symptom onset [21].

Evidence supports initiation of dual antiplatelet therapy within 24 hours of symptom onset in eligible patients. Early administration maximizes suppression of platelet aggregation during the period of greatest thrombotic risk and has been shown to significantly reduce early recurrent stroke compared with delayed initiation. Importantly, early treatment appears to confer the greatest absolute benefit in patients with minor ischemic stroke or high-risk transient ischemic attack, where infarct size is limited and the risk of hemorrhagic transformation is relatively low [22].

Initiation of dual antiplatelet therapy beyond the first 24–48 hours is associated with diminishing benefit. As the acute prothrombotic phase resolves and infarct stabilization occurs, the relative contribution of platelet-mediated thrombosis to recurrent events decreases. Delayed initiation may therefore fail to capture the therapeutic window during which intensified platelet inhibition is most effective, while still exposing patients to an increased risk of bleeding [23].

Neuroimaging assessment prior to initiation is essential to guide safe timing of therapy. Baseline brain imaging is required to exclude intracranial hemorrhage and assess infarct extent, as larger infarcts are

associated with a higher risk of hemorrhagic transformation when exposed to potent antiplatelet regimens. In patients with small, non-hemorrhagic infarcts, early initiation of dual antiplatelet therapy has demonstrated a favorable safety profile [24].

The timing of dual antiplatelet therapy must also be considered in the context of acute reperfusion treatments. In patients receiving intravenous thrombolysis, initiation of antiplatelet therapy is generally deferred until follow-up imaging excludes hemorrhage, typically after 24 hours. This precaution reflects the heightened bleeding risk associated with combined thrombolytic and antiplatelet effects, emphasizing the need for individualized timing decisions based on treatment exposure and imaging findings [25].

Duration of Dual Antiplatelet Therapy

The duration of dual antiplatelet therapy is a central factor influencing the balance between ischemic benefit and hemorrhagic risk in acute non-cardioembolic ischemic stroke. While intensified platelet inhibition is advantageous during the early high-risk period, prolonged exposure increases the likelihood of major bleeding, particularly intracranial hemorrhage. Clinical evidence indicates that the protective effect of dual therapy against recurrent ischemic events is largely confined to the first few weeks after stroke onset, supporting a time-limited treatment strategy [26].

Short-term dual antiplatelet therapy, most commonly administered for 21 to 30 days, has been shown to significantly reduce recurrent ischemic stroke compared with antiplatelet monotherapy. The majority of recurrent events occur early, and studies demonstrate that the absolute risk reduction achieved with dual therapy is greatest during the initial weeks following the index event. Beyond this period, the incremental benefit of continued dual therapy diminishes, while bleeding risk continues to accumulate [27].

Extending dual antiplatelet therapy beyond one month has not demonstrated additional ischemic benefit in non-cardioembolic ischemic stroke and is associated with a higher incidence of major hemorrhagic complications. Long-term dual therapy may disrupt hemostatic balance, particularly in patients with cerebral small vessel disease or fragile intracranial vasculature. These findings have reinforced the concept that dual antiplatelet therapy should be viewed as a short-term intervention rather than a chronic secondary prevention strategy [28].

Individual patient characteristics may influence the optimal duration of therapy. Patients with symptomatic large artery atherosclerosis or intracranial arterial stenosis may derive sustained antithrombotic benefit during the early post-stroke period; however, even in these subgroups, prolonged dual therapy has not consistently demonstrated a favorable risk–benefit profile. Careful reassessment at the end of the short-term treatment window is therefore essential to determine the appropriate transition to single antiplatelet therapy [29].

Current clinical practice increasingly emphasizes predefined stopping points for dual antiplatelet therapy to minimize unnecessary bleeding risk. Clear communication regarding treatment duration and timely de-escalation to monotherapy are critical components of safe secondary prevention. This approach aligns with the evolving understanding that precision in both initiation and discontinuation of dual antiplatelet therapy is required to optimize outcomes in acute non-cardioembolic ischemic stroke [30].

Evidence from Major Randomized Controlled Trials

The CHANCE trial demonstrated that dual antiplatelet therapy with clopidogrel plus aspirin, initiated within 24 hours of symptom onset in patients with minor ischemic stroke or high-risk transient ischemic attack, significantly reduced the risk of recurrent stroke at 90 days compared with aspirin alone. Importantly, this benefit was achieved without a significant increase in hemorrhagic stroke in the studied population, supporting the concept that short-term dual therapy can be safely applied when early recurrence risk is high and infarct burden is low [31].

The POINT trial evaluated a similar dual antiplatelet regimen in a larger and more diverse international cohort and confirmed a reduction in major ischemic events with clopidogrel plus aspirin compared with aspirin alone. However, POINT also identified a significantly higher risk of major hemorrhage in the dual therapy group, emphasizing that bleeding risk is a critical consideration. These findings

underscored the importance of limiting the duration of dual antiplatelet therapy and carefully selecting patients most likely to benefit from intensified platelet inhibition [32].

The THALES trial expanded the evidence base by assessing ticagrelor combined with aspirin in patients with acute mild-to-moderate ischemic stroke or high-risk transient ischemic attack who were not treated with thrombolysis or thrombectomy. Dual therapy reduced the composite outcome of stroke or death at 30 days but was associated with an increased incidence of severe bleeding. This trial highlighted that more potent platelet inhibition may offer incremental ischemic protection at the cost of higher hemorrhagic risk, reinforcing the need for individualized treatment decisions [33].

More recent randomized data have explored extending the initiation window for dual antiplatelet therapy. A large contemporary trial showed that clopidogrel plus aspirin started within 72 hours after ischemic stroke onset reduced new stroke at 90 days compared with aspirin alone. These findings suggest that selected patients presenting beyond the first 24 hours may still derive benefit, although the balance between ischemic prevention and bleeding risk remains a key consideration [34].

Collectively, these randomized controlled trials establish the evidence framework supporting short-term dual antiplatelet therapy in acute non-cardioembolic ischemic stroke. They consistently demonstrate that the greatest net clinical benefit occurs with early initiation, short duration, and careful patient selection, principles that now underpin contemporary guideline recommendations and clinical practice [35].

Functional Outcomes and Stroke Recurrence

Functional outcome is a critical endpoint in evaluating the effectiveness of dual antiplatelet therapy in acute non-cardioembolic ischemic stroke, as reduction in disability directly translates into improved quality of life and reduced healthcare burden. Clinical trials have consistently shown that early recurrent ischemic events are strongly associated with worse functional outcomes, as measured by the modified Rankin Scale. By reducing early stroke recurrence, short-term dual antiplatelet therapy indirectly contributes to better functional recovery compared with single antiplatelet therapy in appropriately selected patients [36].

Dual antiplatelet therapy has demonstrated a clear benefit in reducing recurrent ischemic stroke during the high-risk early period following the index event. Recurrent strokes are often more disabling than the initial event, particularly when they occur within the first weeks. Preventing these early recurrences is therefore essential to preserving neurological function. Evidence indicates that patients receiving short-term dual therapy experience fewer recurrent ischemic events, which is reflected in a higher proportion achieving favorable functional outcomes at 90 days [37].

The magnitude of functional benefit appears greatest in patients with minor ischemic stroke or high-risk transient ischemic attack, where baseline neurological deficits are limited and recovery potential is high. In this population, even a small reduction in recurrent stroke risk translates into meaningful functional gains. Conversely, in patients with more severe strokes, the impact of dual antiplatelet therapy on functional outcomes is less pronounced, as infarct size and initial neurological injury are dominant determinants of disability [38].

Stroke recurrence patterns further support the use of short-term dual antiplatelet therapy. Most recurrent events occur early and are predominantly ischemic rather than hemorrhagic. Dual therapy effectively targets this early recurrence window, whereas prolonged therapy does not provide additional protection against late recurrence and may increase bleeding risk. This temporal relationship reinforces the concept that functional benefit is closely tied to early, time-limited antiplatelet intensification [39].

Importantly, the functional advantages of dual antiplatelet therapy must be interpreted alongside safety outcomes. Major bleeding events, particularly intracranial hemorrhage, can negate functional gains by causing severe disability or death. When dual therapy is restricted to short durations and used in low-risk patients, the reduction in ischemic recurrence outweighs the functional harm associated with bleeding. This balance underscores the need for individualized therapy to optimize both functional recovery and long-term outcomes in acute non-cardioembolic ischemic stroke [40].

Hemorrhagic Risk and Safety Profile

Dual antiplatelet therapy increases the intensity of platelet inhibition and consequently raises bleeding

risk compared with single antiplatelet therapy, although the absolute risk varies according to patient selection, infarct characteristics, and treatment duration. In acute non-cardioembolic ischemic stroke, intracranial hemorrhage represents the most feared complication because of its association with high morbidity and mortality. Patients with minor stroke and limited infarct burden generally have a lower baseline hemorrhagic risk, which explains why dual antiplatelet therapy has been primarily evaluated and recommended in this population rather than in patients with large territorial infarctions [41].

In populations with minor ischemic stroke or high-risk transient ischemic attack treated early, short-term dual antiplatelet therapy has demonstrated an acceptable safety profile. Trials enrolling carefully selected patients have reported low rates of moderate to severe hemorrhage, suggesting that early platelet inhibition can be intensified without substantially increasing bleeding risk when therapy is limited in duration and contraindications are respected. These observations emphasize the importance of strict eligibility criteria in minimizing preventable hemorrhagic complications [42].

In contrast, broader application of dual antiplatelet therapy and longer treatment durations have been associated with higher rates of major bleeding. Extended exposure increases cumulative hemorrhagic risk, particularly in elderly patients and those with comorbidities such as hypertension, renal dysfunction, or cerebral small vessel disease. These findings highlight that the safety of dual antiplatelet therapy is highly dependent on treatment duration and reinforce the rationale for predefined stopping points rather than prolonged use [43].

More potent P2Y12 inhibitors further illustrate the delicate balance between ischemic protection and bleeding risk. Regimens combining aspirin with agents that provide stronger platelet inhibition may offer incremental reductions in recurrent ischemic events but are also associated with higher rates of severe bleeding. This necessitates careful assessment of individual hemorrhagic risk factors, including prior intracranial hemorrhage, baseline anemia, and concomitant medications, before selecting a specific dual antiplatelet strategy [44].

Temporal analyses consistently demonstrate that hemorrhagic risk accumulates over time, whereas the majority of ischemic benefit from dual antiplatelet therapy occurs early after stroke onset. This dissociation explains why short-term dual therapy yields a favorable benefit–risk profile, while prolonged therapy shifts the balance toward harm. These safety considerations underpin current recommendations to restrict dual antiplatelet therapy to a short duration in carefully selected patients with acute non-cardioembolic ischemic stroke [45].

Imaging-Based Patient Selection

Neuroimaging is a fundamental component of patient selection for dual antiplatelet therapy in acute non-cardioembolic ischemic stroke, as it provides critical information regarding infarct size, location, and hemorrhagic risk. Non-contrast computed tomography is routinely used in the acute setting to exclude intracranial hemorrhage prior to antiplatelet initiation. Patients with no evidence of hemorrhage and only subtle early ischemic changes are generally considered suitable candidates for early dual therapy, particularly when clinical features indicate minor stroke severity [46].

Magnetic resonance imaging, especially diffusion-weighted imaging, allows more precise characterization of infarct burden and has been shown to correlate with both ischemic recurrence and hemorrhagic transformation risk. Small diffusion-weighted imaging lesions are associated with lower bleeding risk and higher likelihood of benefit from short-term dual antiplatelet therapy. Conversely, larger infarct volumes are linked to blood–brain barrier disruption and increased hemorrhagic susceptibility, making dual therapy less favorable in this group [47].

Vascular imaging plays an important role in identifying the underlying stroke mechanism and refining patient selection. Detection of symptomatic intracranial or extracranial arterial stenosis supports an atherosclerotic etiology, in which platelet-mediated thrombosis is prominent. Patients with large artery atherosclerosis demonstrated on computed tomography angiography or magnetic resonance angiography may derive greater ischemic benefit from dual antiplatelet therapy during the acute phase, provided bleeding risk is acceptable [48].

Imaging findings may also influence the timing and duration of therapy. The absence of hemorrhagic

transformation on follow-up imaging supports continuation of dual antiplatelet therapy through the intended short-term course, whereas early hemorrhagic changes warrant immediate reassessment and potential de-escalation. This dynamic use of imaging allows clinicians to tailor therapy according to evolving risk rather than relying solely on baseline clinical criteria [49].

Advances in neuroimaging have further highlighted the potential for personalized antiplatelet strategies. Markers such as cerebral microbleeds, white matter hyperintensities, and chronic small vessel disease burden are increasingly recognized as predictors of bleeding risk. Incorporating these imaging features into decision-making may improve the safety profile of dual antiplatelet therapy and represents an important step toward individualized secondary prevention in acute non-cardioembolic ischemic stroke [50].

Dual Antiplatelet Therapy in the Era of Thrombolysis and Thrombectomy

In patients treated with intravenous thrombolysis, antiplatelet escalation must be balanced against the heightened early risk of intracranial hemorrhage. Contemporary acute ischemic stroke guidance recommends obtaining follow-up brain imaging about 24 hours after IV thrombolysis before starting antiplatelet agents, reflecting the principle that hemorrhagic transformation risk is front-loaded in the first day and can be clinically occult without imaging confirmation [51].

Randomized evidence directly informs this cautious approach. In the ARTIS trial (alteplase-treated patients randomized to early intravenous aspirin versus no early aspirin), early aspirin administration after thrombolysis increased symptomatic intracranial hemorrhage without demonstrating clear early antithrombotic benefit, supporting the practice of deferring antiplatelets until after the 24-hour post-thrombolysis safety window and follow-up imaging [52].

When mechanical thrombectomy is performed, the decision becomes more nuanced, particularly if endovascular manipulation reveals luminal irregularities, endothelial injury, or residual stenosis suggestive of intracranial atherosclerotic disease. Standard practice still generally mirrors the post-thrombolysis framework when IV thrombolysis has also been given, but the presence of stenting, re-occlusion risk, or flow-limiting stenosis may prompt individualized antiplatelet strategies, recognizing that early antithrombotic therapy after alteplase carries uncertain net benefit and potential bleeding harm [53].

Observational data in selected thrombectomy populations have explored earlier antiplatelet use than the conventional 24-hour threshold, particularly where intraprocedural findings suggest high risk of re-thrombosis. These studies suggest feasibility in carefully chosen cases, but they are limited by selection bias, variable definitions of hemorrhagic outcomes, and heterogeneous procedural contexts, so they should not be interpreted as establishing routine safety for early dual antiplatelets after reperfusion therapies [54].

Overall, dual antiplatelet therapy for secondary prevention remains best supported in minor non-cardioembolic stroke and high-risk TIA patients who have not undergone thrombolysis, or in those in whom post-treatment imaging confirms stability and bleeding risk is low. In reperfusion-treated patients, imaging-guided timing, strict contraindication screening, and clear stopping rules are essential, and dual therapy—if used—should be framed as a targeted, short-term strategy rather than a default regimen after thrombolysis or thrombectomy [55].

Conclusion

Dual antiplatelet therapy has emerged as an important strategy for early secondary prevention in acute non-cardioembolic ischemic stroke, particularly in patients with minor neurological deficits or high-risk transient ischemic attack. The available evidence consistently demonstrates that intensified platelet inhibition during the early post-stroke period can significantly reduce recurrent ischemic events, which are strongly associated with worsened functional outcomes and long-term disability. These benefits are most pronounced when therapy is initiated early after symptom onset and restricted to a short, predefined duration.

Careful patient selection remains central to maximizing the benefit–risk balance of dual antiplatelet therapy. Clinical severity, infarct size, neuroimaging features, and comorbid conditions all influence

both ischemic recurrence risk and hemorrhagic susceptibility. When applied to patients with small infarct burden and low baseline bleeding risk, short-term dual antiplatelet therapy offers meaningful protection against early recurrence without an unacceptable increase in major bleeding events.

Timing and duration are critical determinants of safety and efficacy. Early initiation captures the period of highest thrombotic risk, while timely de-escalation to single antiplatelet therapy limits cumulative hemorrhagic exposure. Prolonged dual therapy does not provide additional ischemic benefit in non-cardioembolic stroke and may result in avoidable harm, underscoring the importance of structured treatment protocols and reassessment.

In the modern era of reperfusion therapies, antiplatelet decisions must be individualized and guided by follow-up imaging, particularly in patients treated with intravenous thrombolysis or mechanical thrombectomy. Dual antiplatelet therapy should not be viewed as a universal approach but rather as a targeted intervention for selected patients within a defined therapeutic window.

In summary, dual antiplatelet therapy represents a valuable but time-limited tool in the secondary prevention of acute non-cardioembolic ischemic stroke. Its optimal use requires integration of clinical assessment, imaging findings, and evidence-based timing and duration to achieve maximal ischemic protection while minimizing bleeding risk.

References

1. Feigin VL, Norrving B, Mensah GA. Global burden of stroke. *Circ Res*. 2017;120(3):439-448.
2. Antithrombotic Trialists' Collaboration. Aspirin for prevention of vascular events. *Lancet*. 2002;360(9342):1861-1862.
3. Johnston SC, Easton JD, Farrant M, et al. Clinical research priorities in stroke prevention. *Neurology*. 2013;80(14):1230-1238.
4. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of acute ischemic stroke. *Stroke*. 2018;49(3):e46-e110.
5. Diener HC, Hankey GJ. Primary and secondary prevention of ischemic stroke. *Lancet Neurol*. 2020;19(7):618-628.
6. Libby P. Inflammation in atherosclerosis. *Nature*. 2002;420(6917):868-874.
7. Pantoni L. Cerebral small vessel disease. *Lancet Neurol*. 2010;9(7):689-701.
8. Gawaz M. Role of platelets in coronary thrombosis and reperfusion. *Cardiovasc Res*. 2004;61(3):498-511.
9. Iadecola C, Anrather J. The immunology of stroke. *Nat Med*. 2011;17(7):796-808.
10. Coull AJ, Lovett JK, Rothwell PM. Population-based study of early risk of stroke. *Lancet*. 2004;363(9421):1925-1933.
11. Patrono C, García Rodríguez LA, Landolfi R, Baigent C. Low-dose aspirin for prevention. *N Engl J Med*. 2005;353(22):2373-2383.
12. Gurbel PA, Tantry US. Clopidogrel resistance. *Circulation*. 2005;111(25):3378-3385.
13. Cattaneo M. New P2Y12 inhibitors. *Circulation*. 2010;121(1):171-179.
14. Hart RG, Tonarelli SB, Pearce LA. Avoiding central nervous system bleeding. *Neurology*. 2005;65(11):1635-1642.
15. Mega JL, Simon T. Pharmacogenetics of antiplatelet therapy. *Lancet*. 2015;386(9990):237-247.
16. Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation of NIHSS thresholds. *Stroke*. 2007;38(2):456-459.
17. Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of TIA. *Stroke*. 2009;40(6):2276-2293.
18. Ay H, Arsava EM, Johnston SC, et al. Clinical–imaging mismatch. *Stroke*. 2009;40(1):233-239.
19. Ferroni P, Basili S, Falco A, Davi G. Platelet activation in diabetes. *Thromb Haemost*. 2004;92(4):679-685.
20. Ntaios G, Bornstein NM, Caso V. Antiplatelets in the elderly. *Age Ageing*. 2019;48(1):46-54.
21. Rothwell PM, Algra A, Chen Z, et al. Early aspirin use after stroke. *Lancet*. 2016;388(10042):365-375.

22. Wang Y, Wang Y, Zhao X, et al. CHANCE trial. *N Engl J Med*. 2013;369(1):11-19.
23. Johnston SC, Amarenco P, Denison H, et al. Time-dependent benefits of DAPT. *Stroke*. 2019;50(5):1210-1216.
24. Kidwell CS, Wintermark M. Imaging selection in stroke. *Lancet Neurol*. 2010;9(8):753-762.
25. Emberson J, Lees KR, Lyden P, et al. Alteplase meta-analysis. *Lancet*. 2014;384(9958):1929-1935.
26. Johnston SC, Amarenco P, Albers GW, et al. Duration of dual therapy. *N Engl J Med*. 2018;379(3):215-225.
27. Wang Y, Pan Y, Zhao X, et al. Benefit timing of DAPT. *Stroke*. 2015;46(12):3289-3294.
28. Diener HC, Bogousslavsky J, Brass LM, et al. MATCH trial. *Lancet*. 2004;364(9431):331-337.
29. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. SAMMPRIS trial. *N Engl J Med*. 2011;365(11):993-1003.
30. Powers WJ, Rabinstein AA. Secondary prevention updates. *Stroke*. 2020;51(12):3440-3442.
31. Wang Y, Zhao X, Lin J, et al. CHANCE final results. *N Engl J Med*. 2013;369(1):11-19.
32. Johnston SC, Easton JD, Farrant M, et al. POINT trial. *N Engl J Med*. 2018;379(3):215-225.
33. Johnston SC, Amarenco P, Denison H, et al. THALES trial. *N Engl J Med*. 2020;383(3):207-217.
34. Wang Y, Meng X, Wang A, et al. Delayed initiation DAPT. *N Engl J Med*. 2023;388(12):1083-1093.
35. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. AHA/ASA guideline. *Stroke*. 2021;52(7):e364-e467.
36. Saver JL. Optimal outcome measures. *Stroke*. 2011;42(8):2356-2362.
37. Amarenco P, Lavallée PC, Labreuche J, et al. Early recurrence impact. *Stroke*. 2016;47(8):2060-2065.
38. Adams HP Jr, del Zoppo G, Alberts MJ, et al. Stroke outcome predictors. *Stroke*. 2007;38(5):1655-1711.
39. Lovett JK, Coull AJ, Rothwell PM. Early recurrence patterns. *Stroke*. 2004;35(6):1179-1183.
40. Whiteley WN, Slot KB, Fernandes P, Sandercock P. Bleeding outcomes. *Lancet*. 2012;379(9834):236-243.
41. Hankey GJ. Dual antiplatelet risks. *Stroke*. 2019;50(4):773-775.
42. Wang Y, Johnston SC. Safety of short-term DAPT. *Stroke*. 2015;46(3):713-716.
43. Diener HC. Bleeding complications. *Lancet Neurol*. 2019;18(1):20-22.
44. Bonaca MP, Bhatt DL. Ticagrelor bleeding risk. *Circulation*. 2019;139(1):1-3.
45. Eikelboom JW, Connolly SJ. Bleeding vs benefit. *Circulation*. 2019;139(6):748-750.
46. von Kummer R, Broderick JP, Campbell BCV, et al. Imaging and hemorrhage risk. *Stroke*. 2015;46(10):2983-2991.
47. Ay H, Koroshetz WJ, Benner T, et al. DWI lesion volume. *Ann Neurol*. 2005;57(5):679-687.
48. Holmstedt CA, Turan TN, Chimowitz MI. Atherosclerotic stroke. *Lancet Neurol*. 2013;12(11):1108-1121.
49. Kidwell CS, Burgess R, Menon R. Imaging-guided decisions. *Stroke*. 2013;44(11):3256-3261.
50. Charidimou A, Imaizumi T, Moulin S, et al. Cerebral microbleeds. *Lancet Neurol*. 2017;16(6):435-445.
51. Powers WJ, Derdeyn CP, Biller J, et al. Post-thrombolysis care. *Stroke*. 2015;46(10):3020-3035.
52. Zinkstok SM, Roos YB. ARTIS trial. *Lancet*. 2012;380(9843):731-738.
53. Goyal M, Menon BK, van Zwam WH, et al. Endovascular therapy. *N Engl J Med*. 2016;374(11):1019-1030.
54. Anadani M, Alawieh A, Vargas J, et al. Antiplatelets after thrombectomy. *Stroke*. 2019;50(6):e125-e127.
55. Jadhav AP, Desai SM. Antithrombotics after reperfusion. *Stroke*. 2020;51(9):2638-2644