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Review article

Multifactorial Determinants of Recurrent Ischemic Stroke and the Role of Antiplatelet Resistance: A Narrative Review

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Abstract: Recurrent ischemic stroke remains a major cause of long-term disability and mortality despite advances in secondary prevention. Although traditional vascular risk factors, including hypertension, diabetes mellitus, dyslipidemia, smoking, and atrial fibrillation, are well-established determinants of recurrence, growing evidence suggests that interindividual variability in antiplatelet responsiveness may contribute to persistent residual thrombotic risk. High on-treatment platelet reactivity (HTPR), traditionally referred to as antiplatelet resistance, has emerged as a potential mechanism underlying recurrent ischemic events despite guideline-directed therapy. This narrative review aimed to synthesize contemporary evidence regarding the multifactorial determinants of recurrent ischemic stroke, with particular emphasis on antiplatelet resistance and HTPR. A comprehensive literature search was performed using PubMed/MEDLINE, Scopus, and Web of Science and was supplemented by manual screening of relevant references. International clinical practice guidelines, randomized controlled trials, observational studies, systematic reviews, and meta-analyses were reviewed and integrated using a thematic narrative approach. Recurrent ischemic stroke results from a complex interplay among traditional vascular risk factors, vascular pathology, systemic inflammation, endothelial dysfunction, and individual variability in antiplatelet responsiveness. Emerging evidence indicates that HTPR is associated with an increased risk of recurrent cerebrovascular events and may represent a clinically relevant marker of residual thrombotic risk. Platelet function testing, particularly through assays such as VerifyNow, offers a potential means of identifying patients with inadequate platelet inhibition. Furthermore, pharmacogenomic determinants, including CYP2C19 polymorphisms, may influence responsiveness to antiplatelet therapy and contribute to interindividual differences in treatment outcomes. Future approaches integrating platelet function assessment, pharmacogenomic profiling, and precision medicine strategies may facilitate more individualized secondary prevention. Recurrent ischemic stroke should be regarded as a multifactorial condition influenced by both established vascular risk factors and biological variability in treatment response. Although routine platelet function testing cannot currently be recommended for all patients, growing evidence supports its potential role in selected high-risk populations. Integrating individualized secondary prevention strategies into comprehensive stroke care may contribute to improved long-term cerebrovascular outcomes, preservation of functional independence, and optimization of rehabilitation outcomes

Keywords: recurrent ischemic stroke; secondary stroke prevention; antiplatelet resistance; high on-treatment platelet reactivity; platelet function testing; VerifyNow; pharmacogenomics; personalized medicine

1. Introduction

Ischemic stroke remains a leading cause of mortality and long-term disability worldwide, and stroke survivors continue to face a substantial risk of recurrent cerebrovascular events despite contemporary secondary prevention strategies. The burden of

recurrence is disproportionate, as recurrent strokes are frequently associated with greater disability, higher mortality, prolonged hospitalization, and increased healthcare costs compared with first-ever events. Importantly, the risk of recurrence is not constant over time. It is highest during the early period following the index event and subsequently stabilizes at a lower but persistent rate, suggesting that early mechanistic drivers, such as unstable atherosclerotic plaques, untreated cardioembolic sources, and gaps in secondary prevention, differ from later mechanisms related to progressive vascular disease, inadequate long-term risk factor control, and persistent prothrombotic states. Recognizing this temporal and mechanistic heterogeneity is essential for optimizing secondary prevention strategies and improving long-term cerebrovascular outcomes [1].

Current guidelines advocate a comprehensive approach to secondary stroke prevention, including antithrombotic therapy in the absence of contraindications, intensive management of blood pressure and lipid levels, smoking cessation, optimization of diabetes control, lifestyle interventions, and thorough etiological investigation, particularly for occult atrial fibrillation in patients without an identified stroke mechanism [1]. Nevertheless, recurrent ischemic events continue to occur in a considerable proportion of patients, highlighting the existence of residual risk that cannot be fully explained by traditional vascular risk factors alone. Increasing evidence suggests that this residual risk is influenced by a broader spectrum of determinants, including atrial cardiopathy, systemic inflammation, endothelial dysfunction, cerebral small vessel disease, and interindividual variability in pharmacological responsiveness, particularly to antiplatelet agents [1,2].

Antiplatelet therapy represents a cornerstone of secondary prevention in patients with non-cardioembolic ischemic stroke and transient ischemic attack. In selected clinical scenarios, particularly minor ischemic stroke and high-risk transient ischemic attack, randomized clinical trials have demonstrated that short-term dual antiplatelet therapy reduces the risk of early recurrence compared with monotherapy, whereas prolonged treatment is associated with an increased risk of bleeding and is generally not recommended for long-term prevention [1,2]. In parallel, accumulating evidence indicates that a considerable proportion of patients exhibit inadequate platelet inhibition despite standard antiplatelet regimens. This phenomenon, traditionally referred to as antiplatelet resistance and more accurately described as high on-treatment platelet reactivity (HTPR), reflects persistent platelet activation despite ongoing therapy. Meta-analyses conducted in patients with ischemic stroke and transient ischemic attack have consistently demonstrated an association between HTPR and an increased risk of recurrent vascular events, although reported prevalence rates vary substantially owing to differences in platelet function assays, diagnostic thresholds, timing of assessment, and patient characteristics [3,4].

The potential clinical relevance of HTPR is twofold. First, it may serve as a marker of residual thrombotic risk, allowing the identification of patients who remain vulnerable to recurrent ischemic events despite adherence to guideline-directed antiplatelet therapy. Second, HTPR provides a mechanistic link between traditional vascular risk factors and therapeutic failure, as conditions such as diabetes mellitus, chronic kidney disease, and systemic inflammation may enhance platelet activation and attenuate pharmacodynamic responsiveness. Nevertheless, the role of routine platelet function testing in cerebrovascular practice remains controversial. Uncertainty persists regarding patient selection, optimal timing of testing, assay choice, threshold values, and, most importantly, the evidence-based therapeutic implications of abnormal results. Moreover, the heterogeneity of currently available methods, including VerifyNow, light transmission aggregometry, multiple electrode aggregometry, and thromboxane metabolite assays, contributes to variability in the classification of HTPR across studies and clinical settings. Consequently, current guidelines continue

to prioritize established population-based secondary prevention strategies over platelet function-guided treatment escalation in unselected populations [1,2,4].

The present narrative review aims to synthesize current evidence regarding the multifactorial determinants of recurrent ischemic stroke, integrating both traditional and emerging pathogenic mechanisms, with particular emphasis on antiplatelet resistance and high on-treatment platelet reactivity. In addition, we summarize the clinical utility and limitations of platelet function testing, including VerifyNow as one of the most widely used point-of-care platforms, within the broader context of personalized secondary prevention. By positioning HTPR within a multifactorial model of stroke recurrence, this review seeks to support more refined risk stratification and to highlight future directions for individualized therapeutic strategies. Ultimately, integrating vascular, inflammatory, pharmacological, and genetic determinants may facilitate the development of precision medicine approaches aimed at reducing residual thrombotic risk and improving long-term cerebrovascular outcomes.

2. Materials and Methods

2.1 Review Design

This study was conducted as a narrative review aimed at synthesizing contemporary evidence regarding the multifactorial determinants of recurrent ischemic stroke, with particular emphasis on antiplatelet resistance, high on-treatment platelet reactivity (HTPR), platelet function testing, and emerging individualized secondary prevention strategies. Given the complex and multifactorial nature of recurrent stroke pathophysiology, a narrative approach was considered appropriate for integrating evidence derived from diverse sources, including clinical practice guidelines, randomized controlled trials, observational studies, systematic reviews, meta-analyses, and translational research focusing on platelet biology and vascular risk.

The review was designed to provide a clinically relevant and mechanistically integrated perspective on recurrent stroke risk, emphasizing the interplay among traditional vascular risk factors, platelet dysfunction, systemic inflammation, endothelial injury, and pharmacogenomic variability.

2.2 Literature Search Strategy

A comprehensive literature search was performed using the PubMed/MEDLINE, Scopus, and Web of Science databases. Additional relevant publications were identified through manual screening of reference lists from major clinical guidelines, review articles, and landmark clinical trials. The search strategy incorporated combinations of Medical Subject Headings (MeSH) terms and free-text keywords related to recurrent ischemic stroke and antiplatelet responsiveness. The principal search terms included “recurrent ischemic stroke”, “stroke recurrence”, “secondary stroke prevention”, “antiplatelet resistance”, “high on-treatment platelet reactivity”, “HTPR”, “platelet function testing”, “VerifyNow”, “aspirin resistance”, “clopidogrel resistance”, “CYP2C19 polymorphism”, “pharmacogenomics”, and “personalized medicine”.

Priority was given to peer-reviewed studies published in English and indexed in major biomedical databases. Particular emphasis was placed on publications from the last fifteen years to ensure relevance to contemporary cerebrovascular practice, while earlier landmark studies were included when considered essential for understanding the evolution of current concepts.

2.3 Selection of Evidence

Eligible sources included international clinical practice guidelines, randomized controlled trials, prospective and retrospective cohort studies, case-control studies, systematic reviews, and meta-analyses addressing recurrent ischemic stroke, antiplatelet therapy, platelet reactivity, and individualized prevention strategies. Studies were selected on the basis of methodological quality, scientific relevance, and their contribution to the current understanding of recurrent stroke pathophysiology, antiplatelet responsiveness, and personalized prevention strategies.

Particular attention was given to evidence addressing the epidemiology and temporal patterns of recurrent ischemic stroke, traditional vascular risk factors associated with recurrence, the mechanisms and clinical implications of antiplatelet resistance, platelet function testing methodologies, pharmacogenomic determinants of antiplatelet responsiveness, and individualized therapeutic approaches aimed at reducing residual thrombotic risk. Publications focusing exclusively on acute stroke management without direct implications for secondary prevention were generally not prioritized unless they provided important mechanistic insights relevant to recurrent cerebrovascular events.

2.4 Data Analysis and Narrative Synthesis

The selected literature was reviewed qualitatively and synthesized using a thematic narrative approach. Evidence was integrated across several interrelated domains, including the epidemiology and temporal patterns of recurrent ischemic stroke, traditional vascular risk factors, antiplatelet therapy, mechanisms of high on-treatment platelet reactivity, platelet function testing, and emerging personalized therapeutic strategies.

The primary objective of this synthesis was to provide a clinically oriented framework integrating vascular, inflammatory, pharmacological, and pharmacogenomic determinants of recurrent ischemic stroke while highlighting potential opportunities for precision-based secondary prevention and future research directions in cerebrovascular medicine.

3. Results

The evidence identified through the literature review was synthesized into several thematic domains reflecting the multifactorial nature of recurrent ischemic stroke. These domains encompass the epidemiology and temporal patterns of recurrence, traditional vascular risk factors, antiplatelet therapy, mechanisms underlying high on-treatment platelet reactivity, platelet function testing, and emerging personalized prevention strategies. The following sections summarize the principal findings derived from the reviewed literature.

3.1 Epidemiology and Timing of Recurrent Ischemic Stroke

3.1.1 Overall Risk and Incidence of Recurrence

Recurrent ischemic stroke represents a major contributor to the overall burden of cerebrovascular disease and is associated with disproportionately worse clinical outcomes than first-ever stroke. Population-based cohort studies and registry analyses consistently report annual recurrence rates ranging from approximately 4% to 12%, depending on patient characteristics, stroke subtype, and the intensity of secondary prevention measures. [5,6] These estimates translate into a substantial cumulative risk over time, with recurrence rates approaching 20–30% at five years in certain high-risk populations. [6]

Importantly, recurrent strokes are frequently associated with more severe neurological deficits than index events. Several mechanisms may account for this observation, including cumulative neuronal injury, reduced cerebral reserve, and progression of the underlying vascular pathology. Moreover, recurrent events are associated with

higher mortality and disability-adjusted life years (DALYs), further emphasizing the importance of effective secondary prevention strategies. [5]

Stroke subtype significantly influences recurrence risk. Patients with large artery atherosclerosis and cardioembolic stroke generally exhibit higher recurrence rates than those with small vessel disease. Large artery atherosclerosis predisposes patients to recurrent artery-to-artery embolism, whereas cardioembolic stroke is characterized by persistent embolic sources, particularly in individuals with untreated or inadequately treated atrial fibrillation. [7]

3.1.2 Temporal Pattern of Recurrence: Early versus Late Recurrence

The risk of recurrent stroke is not constant over time. The early period following the index event, particularly the first 7 to 90 days, represents a phase of heightened vulnerability. Observational studies and randomized clinical trials consistently demonstrate that a substantial proportion of recurrent events occur during this critical window. [8]

Data from the CHANCE and POINT trials showed that most recurrent ischemic events occur within the first three months after minor ischemic stroke or high-risk transient ischemic attack, highlighting the importance of early implementation of effective secondary prevention strategies. [9,10]

The elevated risk of early recurrence is driven by multiple pathophysiological mechanisms, including plaque instability, persistent embolic sources, delayed or suboptimal initiation of secondary prevention measures, and ongoing hypercoagulable or prothrombotic states. Beyond the acute phase, recurrence risk gradually declines but remains persistently elevated compared with that of the general population. Late recurrence is more closely related to chronic vascular risk factors, progressive atherosclerosis, and inadequate long-term risk factor control. [6]

3.1.3 Etiology-Specific Recurrence Risk

Stroke etiology plays a central role in determining the risk of recurrence. According to the TOAST classification, substantial differences exist among the various etiological subtypes.

Large Artery Atherosclerosis

Large artery atherosclerosis is associated with one of the highest risks of recurrent stroke, particularly in patients with significant extracranial or intracranial stenosis. Plaque instability, endothelial injury, and increased local thrombogenic activity contribute to recurrent embolization and subsequent ischemic events. [7]

Cardioembolic Stroke

Cardioembolic stroke, most commonly related to atrial fibrillation, carries a substantial risk of recurrence in the absence of adequate anticoagulation. Even brief episodes of atrial fibrillation may generate emboli capable of causing recurrent cerebral ischemia. [11]

Small Vessel Disease

Small vessel disease is generally associated with a lower risk of early recurrence compared with other etiological subtypes. Nevertheless, it contributes significantly to cumulative long-term cerebrovascular risk. Chronic endothelial dysfunction, microangiopathy, and progressive white matter injury represent characteristic features of this subtype. [12]

Cryptogenic Stroke and Atrial Cardiopathy

A considerable proportion of ischemic strokes remain cryptogenic despite extensive diagnostic evaluation. Emerging evidence suggests that atrial cardiopathy, characterized by structural and functional atrial abnormalities in the absence of overt atrial fibrillation, may represent an important source of embolic risk in these patients. [13]

3.1.4 Impact of secondary prevention strategies on recurrence risk

Over the past two decades, the widespread implementation of evidence-based secondary prevention strategies has substantially reduced the risk of recurrent ischemic stroke. These measures include antiplatelet therapy, anticoagulation for atrial fibrillation, intensive blood pressure control, statin therapy, and targeted lifestyle interventions. Antiplatelet therapy reduces recurrence risk by approximately 20–25% in non-cardioembolic stroke. [14] Short-term dual antiplatelet therapy has demonstrated additional benefit in selected high-risk populations, particularly during the early post-stroke period. [9,10] However, despite optimal treatment, residual recurrence risk persists, suggesting that additional mechanisms—including antiplatelet resistance, inflammation, and endothelial dysfunction—contribute to recurrent events. [3,4]

3.1.5 Clinical implications

Understanding the temporal and etiologic patterns of stroke recurrence is essential for optimizing prevention strategies. Early recurrence risk underscores the importance of rapid etiologic evaluation and timely initiation of secondary prevention. Long-term recurrence highlights the need for sustained risk factor control and individualized therapeutic approaches. Emerging concepts such as high on-treatment platelet reactivity and pharmacogenomic variability offer potential opportunities for improved risk stratification and personalized therapy, which will be discussed in subsequent sections.

3.2. Traditional Risk Factors

Recurrent ischemic stroke results from a complex interaction between persistent vascular pathology and inadequately controlled systemic risk factors. Traditional vascular risk factors—including hypertension, diabetes mellitus, dyslipidemia, smoking, and atrial fibrillation—remain the most important contributors to both first-ever and recurrent stroke. These factors promote endothelial dysfunction, accelerate atherosclerosis, and increase thrombogenicity, thereby sustaining long-term recurrence risk despite secondary prevention strategies. [1,5] Effective management of these risk factors remains the cornerstone of secondary prevention. However, even with optimal control, a substantial proportion of patients continue to experience recurrent events, suggesting that traditional factors interact with additional biological and pharmacological determinants, including platelet reactivity and inflammatory activation. [4,6]

3.2.1 Hypertension

Hypertension is the single most important modifiable risk factor for recurrent ischemic stroke. Chronic elevation of blood pressure promotes structural and functional alterations within both large and small cerebral arteries, including endothelial dysfunction, vascular remodeling, arterial stiffness, and accelerated atherosclerosis. These changes increase susceptibility to thromboembolic events and impair cerebral autoregulation. [15] Numerous randomized clinical trials have demonstrated that blood pressure reduction significantly reduces stroke recurrence risk. The PROGRESS trial showed that antihypertensive therapy reduced the risk of recurrent stroke by approximately 28%, highlighting the importance of aggressive blood pressure control in secondary prevention. [16] Hypertension also contributes to cerebral small vessel disease, which represents an important mechanism of recurrent ischemic stroke. Chronic microvascular injury leads to lacunar infarction, white matter damage, and impaired cerebral perfusion, all of which increase recurrence risk over time.

[12] Importantly, hypertension may also contribute indirectly to antiplatelet resistance. Elevated blood pressure is associated with increased platelet activation, enhanced thromboxane production, and endothelial dysfunction, all of which may reduce the effectiveness of antiplatelet therapy. [17]

3.2.2 Diabetes Mellitus

Diabetes mellitus is another major determinant of recurrent ischemic stroke. Diabetic patients have a twofold increased risk of stroke recurrence compared with non-diabetic individuals. [18] This increased risk is mediated by several interrelated pathophysiological mechanisms, including accelerated atherosclerosis, endothelial dysfunction, chronic inflammatory activation, oxidative stress, and heightened platelet reactivity. Hyperglycemia promotes glycation of vascular proteins and impairs endothelial nitric oxide production, resulting in reduced vasodilation and increased vascular stiffness. Additionally, diabetes is associated with enhanced platelet aggregation and reduced responsiveness to antiplatelet therapy, contributing to residual thrombotic risk. [19] Insulin resistance and hyperinsulinemia further promote prothrombotic states by increasing levels of fibrinogen and plasminogen activator inhibitor-1, thereby impairing fibrinolysis. [18] These mechanisms collectively contribute to increased recurrence risk and may partially explain the higher prevalence of antiplatelet resistance observed in diabetic patients. [4]

3.2.3 Dyslipidemia

Dyslipidemia plays a central role in atherosclerotic plaque formation and progression. Elevated levels of low-density lipoprotein cholesterol [LDL-C] promote lipid accumulation within the arterial wall, leading to plaque formation, inflammation, and eventual plaque rupture. Statin therapy has been shown to significantly reduce recurrent stroke risk. The SPARCL trial demonstrated that intensive lipid-lowering therapy with atorvastatin reduced recurrent stroke risk by approximately 16%. [20] In addition to their lipid-lowering properties, statins exert multiple pleiotropic effects, including improvement of endothelial function, reduction of vascular inflammation, stabilization of atherosclerotic plaques, and modulation of platelet activation, thereby contributing to their protective role in secondary stroke prevention.

3.2.4 Atrial Fibrillation

Atrial fibrillation represents one of the strongest predictors of recurrent ischemic stroke. Cardioembolic stroke associated with atrial fibrillation carries a particularly high recurrence risk in the absence of appropriate anticoagulation. [11] Atrial fibrillation promotes thrombus formation through mechanisms consistent with Virchow's triad, including blood stasis, endothelial dysfunction, and a hypercoagulable state. Importantly, atrial fibrillation may be paroxysmal and asymptomatic, leading to underdiagnosis. Prolonged cardiac monitoring has revealed previously undetected atrial fibrillation in a significant proportion of patients with cryptogenic stroke. [11] Appropriate anticoagulation significantly reduces recurrence risk in atrial fibrillation patients, highlighting the importance of accurate diagnosis and targeted therapy. [1]

3.2.5 Smoking

Smoking is a well-established risk factor for both initial and recurrent stroke. Tobacco exposure promotes endothelial dysfunction, oxidative stress, inflammation, and platelet activation. [22] Nicotine and other toxic components of cigarette smoke increase platelet aggregation and impair endothelial nitric oxide production, resulting in a prothrombotic vascular environment. Smoking cessation significantly reduces recurrence risk and remains a key component of secondary prevention strategies. [1]

3.2.6 Chronic Kidney Disease

Chronic kidney disease is increasingly recognized as an independent risk factor for recurrent stroke. Renal dysfunction is associated with endothelial dysfunction, inflammation, oxidative stress, and accelerated atherosclerosis. [23] Patients with chronic kidney disease also exhibit increased platelet reactivity and reduced responsiveness to antiplatelet therapy, contributing to residual thrombotic risk. [23]

3.2.7 Interaction between traditional risk factors and antiplatelet resistance

Traditional vascular risk factors rarely act independently; instead, they converge through overlapping biological pathways that amplify platelet activation, endothelial dysfunction, and thrombotic propensity. Clinical conditions such as diabetes mellitus, chronic kidney disease, hypertension, and systemic inflammatory states are consistently associated with heightened platelet reactivity and diminished response to antiplatelet therapy. [4,17,19] These interrelated mechanisms establish a pathophysiological bridge between established vascular risk factors and antiplatelet resistance, reinforcing the inherently multifactorial nature of recurrent ischemic stroke. To facilitate a comprehensive understanding of these multifactorial interactions, Table 1 summarizes the principal determinants of recurrent ischemic stroke, their underlying pathophysiological mechanisms, and their implications for individualized secondary prevention.

Table 1. Multifactorial determinants of recurrent ischemic stroke and their clinical implications

Determinant	Pathophysiological mechanism	Impact on recurrence risk	Clinical implications
Hypertension	Endothelial dysfunction, vascular remodeling, arterial stiffness	Major independent predictor of recurrence	Aggressive blood pressure control reduces recurrence risk
Diabetes mellitus	Increased platelet activation, inflammation, endothelial dysfunction	Increased recurrence and antiplatelet resistance	Strict glycemic control and individualized therapy
Dyslipidemia	Atherosclerotic plaque formation and instability	Increased risk of thromboembolic events	Statin therapy reduces recurrence risk
Atrial fibrillation	Cardioembolic thrombus formation	High recurrence risk without anticoagulation	Anticoagulation significantly reduces recurrence
Smoking	Platelet activation, oxidative stress, endothelial injury	Increased thrombotic risk	Smoking cessation reduces recurrence
Chronic kidney disease	Inflammation, endothelial dysfunction, platelet activation	Increased recurrence risk	Close monitoring and risk factor control
Genetic polymorphisms [CYP2C19]	Impaired clopidogrel metabolism	Reduced antiplatelet effectiveness	Consider alternative agents [e.g., ticagrelor]
Inflammation	Enhanced platelet activation, endothelial dysfunction	Increased thrombotic risk	Target underlying inflammatory conditions
Antiplatelet resistance [HTPR]	Persistent platelet activation despite therapy	Increased recurrence risk	Platelet function testing may guide therapy
Atrial cardiopathy	Increased embolic potential	Increased recurrence risk	Prolonged cardiac monitoring and individualized therapy

3.2.8 Clinical Implications

Although traditional vascular risk factors remain central determinants of stroke recurrence, their interaction with platelet biology, inflammation, and vascular dysfunction underscores the need for more individualized prevention strategies. Identifying patients who remain at elevated thrombotic risk despite optimal control of conventional risk factors may facilitate personalized therapeutic approaches, including optimization of antiplatelet therapy and the selective use of platelet function testing.

3.3 Antiplatelet Therapy in Secondary Stroke Prevention

Antiplatelet therapy represents a cornerstone of secondary prevention in patients with non-cardioembolic ischemic stroke and transient ischemic attack. Platelet activation plays a pivotal role in thrombus formation following endothelial injury and atherosclerotic plaque disruption. By inhibiting platelet aggregation, antiplatelet agents reduce thrombus formation and consequently decrease the risk of recurrent ischemic events. [14,24]

The efficacy of antiplatelet therapy in reducing recurrent stroke risk has been consistently demonstrated in randomized clinical trials and meta-analyses. Overall, antiplatelet therapy reduces the relative risk of recurrent stroke by approximately 20–25% in patients with previous ischemic stroke or transient ischemic attack. [14] Nevertheless, recurrent ischemic events continue to occur in a substantial proportion of patients despite widespread use of antiplatelet agents, emphasizing the importance of optimizing antiplatelet strategies and identifying individuals with inadequate therapeutic response.

3.3.1 Aspirin in Secondary Stroke Prevention

Aspirin remains the most widely prescribed antiplatelet agent for secondary stroke prevention. Its antithrombotic effect is mediated through irreversible inhibition of cyclooxygenase-1 (COX-1), thereby suppressing thromboxane A_2 synthesis and reducing platelet aggregation. [25]

Multiple randomized trials and meta-analyses have demonstrated that aspirin significantly reduces the risk of recurrent stroke and other major vascular events. The Antithrombotic Trialists' Collaboration showed that aspirin reduces the incidence of serious vascular events by approximately 22% among high-risk patients. [14]

Aspirin is generally well tolerated, widely available, and cost-effective. However, its effectiveness may be limited by interindividual variability in platelet responsiveness, with some patients exhibiting aspirin resistance or high on-treatment platelet reactivity. [3,4]

3.3.2 Clopidogrel in Secondary Stroke Prevention

Clopidogrel is a P2Y12 receptor inhibitor that suppresses ADP-mediated platelet activation. Unlike aspirin, clopidogrel requires hepatic biotransformation through the cytochrome P450 system to generate its active metabolite. [26]

The CAPRIE trial demonstrated that clopidogrel is modestly more effective than aspirin in reducing vascular events among patients with previous ischemic stroke, myocardial infarction, or peripheral arterial disease. [27] Consequently, clopidogrel is frequently used as an alternative in patients who are intolerant to aspirin or considered to be at increased risk of recurrent vascular events.

However, substantial interindividual variability exists in clopidogrel metabolism, largely owing to CYP2C19 genetic polymorphisms. [26] Carriers of CYP2C19 loss-of-function alleles exhibit impaired conversion of clopidogrel into its active metabolite, resulting in reduced platelet inhibition and an increased risk of recurrent ischemic events. [28]

3.3.3 Dual antiplatelet therapy in early secondary prevention

Dual antiplatelet therapy [DAPT], typically consisting of aspirin and clopidogrel, has been extensively studied in the early period following minor ischemic stroke or high-risk TIA. The CHANCE trial demonstrated that short-term DAPT initiated within 24 hours of symptom onset significantly reduced recurrent stroke risk compared with aspirin monotherapy, without increasing major bleeding risk. [9] Similarly, the POINT trial demonstrated that DAPT reduced the risk of major ischemic events but was associated with a modest increase in major hemorrhage risk. [10] These findings suggest that the benefits of DAPT are greatest during the early post-stroke period,

when recurrence risk is highest. However, prolonged use of DAPT beyond 90 days is associated with increased bleeding risk and is generally not recommended for long-term secondary prevention. [1,24]

3.3.4 Ticagrelor and alternative antiplatelet strategies

Ticagrelor is a direct-acting P2Y12 inhibitor that does not require metabolic activation. Unlike clopidogrel, ticagrelor provides more consistent platelet inhibition and is not affected by CYP2C19 polymorphisms. [29] The THALES trial demonstrated that ticagrelor combined with aspirin reduced recurrent stroke risk compared with aspirin alone in patients with minor stroke or high-risk TIA, although bleeding risk was increased. [30] More recently, the CHANCE-2 trial demonstrated that ticagrelor was superior to clopidogrel in patients with CYP2C19 loss-of-function alleles, further supporting the importance of pharmacogenomic variability in antiplatelet response. [31] These findings highlight the potential value of individualized antiplatelet therapy based on genetic and functional platelet testing.

3.3.5 Limitations of standard antiplatelet therapy

Despite the established efficacy of antiplatelet therapy in secondary stroke prevention, recurrent ischemic events remain frequent in clinical practice. This therapeutic variability is driven by multiple mechanisms, including interindividual differences in drug metabolism, genetic polymorphisms affecting antiplatelet drug activation, increased platelet turnover, systemic inflammatory activation, and comorbid conditions such as diabetes mellitus and chronic kidney disease. Collectively, these factors contribute to high on-treatment platelet reactivity, which represents a major contributor to residual thrombotic risk and recurrent ischemic stroke. [3,4,26]

3.3.6 Clinical implications

Antiplatelet therapy remains the foundation of secondary prevention in non-cardioembolic ischemic stroke. However, variability in treatment response represents an important limitation. Recognition of antiplatelet resistance and individualized therapeutic strategies may improve secondary prevention outcomes. Platelet function testing and pharmacogenomic profiling represent potential tools for identifying patients at increased risk of recurrence. These concepts will be discussed in detail in the following section.

3.4 Antiplatelet Resistance and High On-Treatment Platelet Reactivity

3.4.1 Definition and Clinical Relevance

Antiplatelet resistance refers to an inadequate biological response to antiplatelet therapy, resulting in persistent platelet activation despite appropriate treatment. The preferred mechanistic term is high on-treatment platelet reactivity (HTPR), which describes objectively measured platelet activity during ongoing antiplatelet therapy. [3,32] HTPR has emerged as a clinically relevant contributor to residual ischemic risk in patients with ischemic stroke and transient ischemic attack. Multiple studies and meta-analyses have demonstrated that patients with HTPR exhibit a significantly higher risk of recurrent ischemic events than those with adequate platelet inhibition. [3,4] In cerebrovascular populations, HTPR has been most extensively described among patients receiving aspirin or clopidogrel, although variability in response has been reported with virtually all antiplatelet agents. High on-treatment platelet reactivity has important clinical implications, as it is consistently associated with an increased risk of recurrent ischemic stroke, transient ischemic attack, major adverse cardiovascular events, and treatment failure despite adherence to guideline-directed antiplatelet therapy. These observations suggest that HTPR represents a key mechanistic link between platelet biology and recurrent ischemic events.

3.4.2 Prevalence of HTPR in Patients with Ischemic Stroke

The prevalence of high on-treatment platelet reactivity varies considerably according to the antiplatelet agent used, patient characteristics, and the platelet function assay employed. Meta-analytic data indicate that approximately 5–45% of patients exhibit aspirin resistance, whereas 20–40% demonstrate clopidogrel resistance among ischemic stroke and transient ischemic attack populations. [3,4] This marked heterogeneity is attributable to multiple factors, including methodological differences among platelet function assays, variability in the timing of assessment, underlying genetic polymorphisms, and the influence of comorbid conditions. Importantly, patients with diabetes mellitus, chronic kidney disease, and systemic inflammatory states exhibit disproportionately higher rates of high on-treatment platelet reactivity. [19,23,33]

3.4.3 Mechanisms of Antiplatelet Resistance

HTPR is a multifactorial phenomenon influenced by genetic, biological, pharmacological, and clinical determinants.

3.4.3.1 Genetic Mechanisms

Genetic polymorphisms affecting drug metabolism represent one of the principal causes of clopidogrel resistance. Clopidogrel requires hepatic activation through cytochrome P450 enzymes, particularly CYP2C19. Loss-of-function polymorphisms in CYP2C19 impair the conversion of clopidogrel into its active metabolite, resulting in reduced platelet inhibition. [26,28] CYP2C19 loss-of-function alleles are present in approximately 25–30% of Caucasian individuals and up to 50–60% of Asian populations and are associated with impaired clopidogrel metabolism, diminished platelet inhibition, and an increased risk of recurrent ischemic events. [31] The CHANCE-2 trial demonstrated the superiority of ticagrelor over clopidogrel in CYP2C19 loss-of-function carriers, thereby highlighting the clinical relevance of pharmacogenomic variability in antiplatelet responsiveness. [31]

3.4.3.2 Increased Platelet Turnover

Platelets have a lifespan of approximately 7–10 days. Conditions characterized by accelerated platelet turnover result in a greater proportion of newly formed platelets that have not been exposed to antiplatelet agents. These immature platelets remain fully functional and contribute to persistent platelet reactivity. Enhanced platelet turnover has been described in several clinical settings, including diabetes mellitus, systemic inflammatory states, and acute ischemic stroke, and represents an important mechanism underlying high on-treatment platelet reactivity. [33]

3.4.3.3 Inflammation and Endothelial Dysfunction

Inflammation plays a pivotal role in platelet activation and thrombosis. Pro-inflammatory cytokines, including interleukin-6 and tumor necrosis factor-alpha, enhance platelet activation and promote prothrombotic states. [34] Inflammatory processes also impair endothelial function by reducing nitric oxide bioavailability and promoting platelet adhesion and aggregation. Collectively, these mechanisms may attenuate the effectiveness of antiplatelet therapy and contribute to persistent platelet reactivity.

3.4.3.4 Drug Interactions and Pharmacological Factors

Drug interactions represent another important contributor to antiplatelet resistance. Medications that inhibit cytochrome P450 enzymes, including proton pump inhibitors, may impair clopidogrel activation and consequently reduce its antiplatelet efficacy. [35] In addition, poor medication adherence represents an important but frequently underrecognized cause of apparent antiplatelet resistance.

3.4.3.5 Clinical Predictors of HTPR

Several clinical characteristics have been consistently associated with an increased risk of antiplatelet resistance, including diabetes mellitus, chronic kidney disease, advanced age, obesity, systemic inflammatory states, genetic polymorphisms, and acute ischemic stroke. These factors contribute to heightened platelet reactivity and diminished responsiveness to antiplatelet therapy. [4,19,23,33] Recognition of these predictors may facilitate more accurate risk stratification and enable the identification of patients at increased risk of recurrent ischemic events.

3.4.3.6 Clinical Impact of HTPR on Recurrent Stroke Risk

Accumulating evidence has demonstrated a strong association between high on-treatment platelet reactivity and recurrent ischemic stroke. Meta-analytic data indicate that patients with HTPR have an approximately two- to threefold higher risk of recurrent ischemic events than those achieving adequate platelet inhibition. [3,4] Furthermore, HTPR has been associated with an increased risk of recurrent stroke, major adverse cardiovascular events, and poorer functional outcomes. Collectively, these findings support the role of HTPR as a clinically meaningful biomarker of residual thrombotic risk and treatment failure.

3.4.3.7 HTPR as a Marker of Individualized Risk

High on-treatment platelet reactivity represents a clinically relevant biomarker for identifying patients at increased risk of recurrent ischemic events. Recognition of HTPR may facilitate improved risk stratification, optimization of antiplatelet therapy, and implementation of individualized secondary prevention strategies. Nevertheless, the optimal therapeutic approach for managing high on-treatment platelet reactivity remains an area of ongoing investigation.

3.4.3.8 Clinical Implications

Antiplatelet resistance represents an important contributor to recurrent ischemic stroke risk. Recognition of HTPR underscores the importance of individualized therapeutic approaches and supports the potential role of platelet function testing in carefully selected high-risk patients. The following section discusses currently available platelet function testing methods, including VerifyNow, and their potential clinical applications.

3.5 Platelet Function Testing

3.5.1 Rationale for Platelet Function Testing

Interindividual variability in response to antiplatelet therapy represents a major limitation of current secondary prevention strategies. Although antiplatelet agents such as aspirin and clopidogrel effectively reduce recurrent stroke risk at the population level, a considerable proportion of patients exhibit persistent platelet reactivity despite treatment. This phenomenon contributes to residual thrombotic risk and recurrent ischemic events. [3,4,32] Platelet function testing provides an objective approach for assessing the degree of platelet inhibition during antiplatelet therapy. By directly measuring platelet reactivity, these tests enable the identification of patients with HTPR, who may be at increased risk of recurrent ischemic stroke. [36] The rationale for platelet function testing is based on the premise that individualized antiplatelet strategies guided by platelet reactivity assessment may improve clinical outcomes in carefully selected high-risk patients.

3.5.2 Methods of Platelet Function Testing

Several laboratory-based and point-of-care techniques have been developed to assess platelet function. These methods differ with respect to complexity, reproducibility, standardization, and clinical applicability.

3.5.2.1 Light Transmission Aggregometry (LTA)

Light transmission aggregometry has traditionally been regarded as the gold standard for platelet function assessment, as it directly measures platelet aggregation in response to agonists such as adenosine diphosphate and arachidonic acid. However, despite its high analytical accuracy, its widespread clinical application is limited by the requirement for specialized laboratory facilities, labor-intensive procedures, technical complexity, and limited practicality in routine clinical settings. Consequently, light transmission aggregometry remains predominantly a research tool rather than a method routinely used in clinical practice. [37]

3.5.2.2 Multiple Electrode Aggregometry (MEA)

Multiple electrode aggregometry evaluates platelet aggregation in whole blood and provides more rapid results compared with light transmission aggregometry. Although easier to perform, MEA still requires dedicated equipment and trained personnel, limiting its widespread implementation in routine clinical practice. [38]

3.5.2.3 Thromboelastography (TEG)

Thromboelastography assesses clot formation dynamics and provides indirect information regarding platelet function. Although useful in specific clinical scenarios, TEG is less specific for evaluating responsiveness to antiplatelet therapy. [39]

3.5.2.4 VerifyNow Platelet Function Assay

VerifyNow is one of the most widely used platelet function assays in clinical practice. This point-of-care platform provides rapid assessment of platelet reactivity in response to specific agonists and offers several practical advantages, including short turnaround time, operational simplicity, minimal technical requirements, and high reproducibility. [36] These characteristics make VerifyNow particularly suitable for routine clinical use. The assay reports results as P2Y12 reaction units (PRU), reflecting platelet responsiveness to P2Y12 inhibitors such as clopidogrel, and aspirin reaction units (ARU), which evaluate platelet inhibition in response to aspirin.

3.5.3 Clinical Thresholds for HTPR

Several thresholds have been proposed to define high on-treatment platelet reactivity. In patients receiving clopidogrel, a P2Y12 reaction unit value exceeding 208 is widely used to indicate inadequate platelet inhibition and clopidogrel resistance. [40] Similarly, an aspirin reaction unit value of 550 or greater is generally considered indicative of insufficient response to aspirin therapy. [36] Although these cut-off values were initially validated in cardiovascular populations, they are increasingly being applied in cerebrovascular disease. Importantly, elevated PRU values have been consistently associated with an increased risk of thrombotic complications, including recurrent ischemic stroke. [40]

3.5.4 Prevalence of HTPR Assessed by VerifyNow

Studies using the VerifyNow assay have shown that approximately 20–40% of patients with ischemic stroke exhibit clopidogrel resistance, whereas 5–30% demonstrate inadequate platelet inhibition in response to aspirin, depending on patient characteristics and the timing of testing. [3,4,36] Importantly, individuals with diabetes mellitus, chronic kidney disease, and systemic inflammatory conditions exhibit significantly higher PRU values and an increased prevalence of high on-treatment platelet reactivity. [19,23]

3.5.5 Clinical Relevance of VerifyNow in Stroke Populations

Accumulating evidence has demonstrated a strong association between elevated P2Y12 reaction unit values and an increased risk of recurrent ischemic stroke. Patients with high on-treatment platelet reactivity identified using the VerifyNow assay have consistently been shown to experience significantly higher rates of recurrent ischemic events than those achieving adequate platelet inhibition. [40,41]

These findings support the potential role of VerifyNow as a clinically valuable tool for identifying patients at increased risk of therapeutic failure. Furthermore, platelet function testing may facilitate individualized therapeutic decision-making by identifying patients who may benefit from alternative antiplatelet strategies, including switching from clopidogrel to ticagrelor or implementing more personalized secondary prevention approaches. Importantly, the CHANCE-2 trial demonstrated that ticagrelor significantly reduced stroke recurrence compared with clopidogrel among carriers of CYP2C19 loss-of-function alleles, further underscoring the clinical relevance of individualized antiplatelet therapy. [31]

3.5.6 Limitations of Platelet Function Testing

Despite its potential advantages, platelet function testing has several important limitations. First, variability among platelet function assays limits comparability across studies, as different methods may yield discordant results and complicate clinical interpretation. [36] Second, platelet reactivity is dynamic and may vary over time, particularly during the acute phase following ischemic stroke. Third, standardized treatment algorithms based on platelet function testing have not yet been universally established. Consequently, current guidelines do not recommend routine platelet function testing for all patients with ischemic stroke, although testing may be considered in carefully selected high-risk individuals. [1]

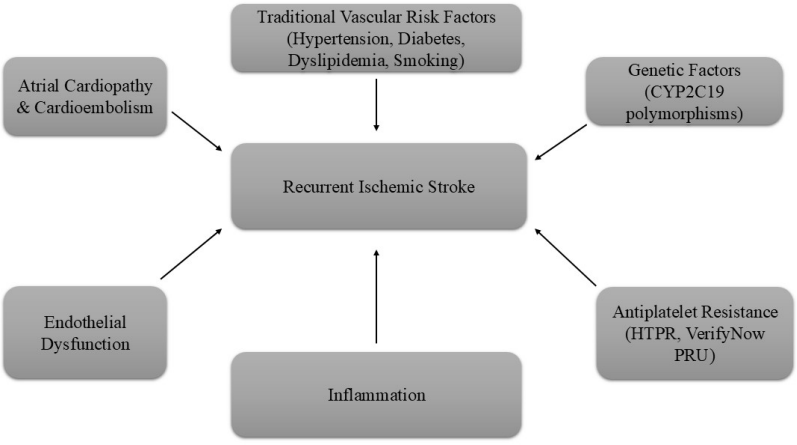
3.5.7 Clinical Implications

Platelet function testing, particularly through the use of VerifyNow, represents a promising approach for identifying patients with antiplatelet resistance and persistent residual thrombotic risk. Although routine implementation cannot currently be recommended for all patients, platelet function testing may play an important role within individualized secondary prevention strategies. Identification of high on-treatment platelet reactivity may facilitate optimization of antiplatelet therapy and potentially contribute to reducing the risk of recurrent ischemic events in selected high-risk populations.

3.6. Personalized Antiplatelet Therapy and Future Perspectives

The multifactorial interactions contributing to recurrent ischemic stroke are illustrated in Figure 1.

Figure 1. Multifactorial model of recurrent ischemic stroke illustrating the interaction between vascular risk factors, inflammation, endothelial dysfunction, and antiplatelet resistance.



3.6.1 Rationale for Personalized Antiplatelet Therapy

Despite the well-established efficacy of antiplatelet therapy in reducing the risk of recurrent ischemic stroke, substantial interindividual variability in treatment response limits its effectiveness in certain patients. High on-treatment platelet reactivity (HTPR), genetic polymorphisms affecting drug metabolism, and multiple clinical comorbidities contribute to persistent residual thrombotic risk despite standard therapy. [3,4,26] These limitations underscore the need for individualized therapeutic strategies tailored to patient-specific characteristics. Personalized antiplatelet therapy aims to optimize treatment efficacy while minimizing adverse events through the integration of clinical, genetic, and laboratory information into therapeutic decision-making. The concept of precision medicine has gained increasing attention in both cardiovascular and cerebrovascular disease management, offering the potential to improve clinical outcomes through individualized treatment approaches. [42]

3.6.2 Role of Pharmacogenomics in Antiplatelet Therapy

Genetic polymorphisms, particularly those involving CYP2C19, represent one of the principal determinants of clopidogrel responsiveness. CYP2C19 loss-of-function alleles impair the conversion of clopidogrel into its active metabolite, resulting in diminished platelet inhibition and an increased risk of recurrent ischemic events. [26,28] The prevalence of CYP2C19 loss-of-function alleles varies across populations, affecting approximately 30% of Caucasian individuals and more than 50% of Asian populations. [31]

The CHANCE-2 trial demonstrated the superiority of ticagrelor over clopidogrel in patients carrying CYP2C19 loss-of-function alleles, reducing recurrent stroke risk without significantly increasing severe bleeding. [31] These findings support the potential clinical utility of pharmacogenomic testing in guiding the selection of antiplatelet therapy.

3.6.3 Platelet Function Testing in Personalized Therapy

Platelet function testing represents an important component of individualized antiplatelet therapy. Point-of-care assays such as VerifyNow enable direct quantification of platelet reactivity and facilitate the identification of patients with suboptimal responsiveness to antiplatelet agents. Detection of high on-treatment platelet reactivity may inform therapeutic decision-making, including switching from clopidogrel to ticagrelor, tailoring antiplatelet regimens, or implementing intensified surveillance strategies. Although robust randomized evidence in stroke populations remains limited, current data suggest that platelet function testing may improve risk stratification in carefully selected high-risk individuals. [36,40] Integration of platelet function testing with clinical assessment and pharmacogenomic profiling represents a promising framework for precision-based secondary stroke prevention.

3.6.4 Alternative Antiplatelet Agents and Therapeutic Strategies

Ticagrelor represents a clinically relevant alternative antiplatelet agent, particularly in patients with clopidogrel resistance or inadequate platelet inhibition. Unlike clopidogrel, ticagrelor does not require metabolic activation and provides more consistent and reliable platelet inhibition. [29] The THALES trial demonstrated that ticagrelor combined with aspirin significantly reduced the risk of recurrent stroke compared with aspirin alone in patients with minor ischemic stroke or high-risk transient ischemic attack. [30] Emerging therapeutic strategies include individualized dual antiplatelet therapy, genotype-guided treatment, and platelet function-guided therapeutic approaches. These precision-based strategies aim to optimize antiplatelet efficacy while minimizing bleeding risk, thereby improving overall secondary prevention outcomes.

3.6.5 Integration of Clinical, Genetic, and Laboratory Data

Effective secondary stroke prevention requires the integration of multiple determinants, including conventional vascular risk factors, underlying stroke etiology, platelet function testing, and pharmacogenomic profiling. Patients exhibiting several predictors of antiplatelet resistance are likely to derive the greatest benefit from individualized therapeutic approaches. A comprehensive precision-based framework integrating clinical assessment with biological and genetic information may improve risk stratification and facilitate more targeted optimization of antiplatelet therapy.

3.6.6 Future Research Directions

Future investigations should focus on several key areas. Large-scale prospective studies are needed to evaluate the clinical utility of platelet function-guided antiplatelet therapy in patients with ischemic stroke. Establishing standardized diagnostic thresholds for antiplatelet resistance will be essential for improving consistency and enhancing clinical applicability across studies. Furthermore, integration of pharmacogenomic testing into routine clinical practice may facilitate more precise therapeutic decision-making and potentially improve patient outcomes. Finally, the development of novel antiplatelet agents and precision-based therapeutic strategies holds considerable promise for further reducing the burden of recurrent ischemic stroke.

3.6.7 Clinical Implications

Personalized antiplatelet therapy represents a promising approach to optimizing secondary stroke prevention. Although routine platelet function testing and pharmacogenomic assessment cannot currently be recommended for all patients, these tools may play an important role in carefully selected high-risk individuals. Integration of individualized therapeutic strategies may contribute to reducing recurrent stroke risk, improving long-term cerebrovascular outcomes, and ultimately supporting better functional recovery and rehabilitation outcomes.

4. Discussion

The present narrative review highlights recurrent ischemic stroke as a multifactorial clinical condition resulting from the interaction of traditional vascular risk factors, platelet biology, inflammation, endothelial dysfunction, and individual variability in antiplatelet responsiveness. The available evidence suggests that residual thrombotic risk cannot be fully explained by conventional risk factors alone and that emerging biological determinants may contribute substantially to recurrent cerebrovascular events despite guideline-directed therapy.

4.1 Recurrent ischemic stroke as a multifactorial clinical entity

The prevention of recurrent ischemic stroke remains one of the greatest challenges in contemporary cerebrovascular medicine. Despite substantial advances in secondary prevention, a considerable proportion of patients continue to experience recurrent ischemic events even when guideline-directed therapies are appropriately implemented. This observation suggests that recurrent stroke should not be viewed solely as the consequence of inadequately controlled traditional vascular risk factors but rather as the result of complex interactions among vascular pathology, systemic inflammation, endothelial dysfunction, cardiac abnormalities, and individual variability in treatment response. The evidence reviewed in this article highlights the heterogeneous nature of recurrent stroke mechanisms. While hypertension, diabetes mellitus, dyslipidemia, smoking, atrial fibrillation, and chronic kidney disease remain major determinants of recurrence, these factors frequently converge through shared biological pathways that promote endothelial injury, platelet activation, and thrombus formation. Consequently, patients with apparently similar clinical profiles may ex-

hibit markedly different risks of recurrence, underscoring the need for more individualized approaches to secondary prevention and more refined risk stratification models incorporating biological and pharmacological variability. [1,4,6]

4.2 High on-treatment platelet reactivity and residual thrombotic risk

Among the emerging determinants of recurrent ischemic stroke, high on-treatment platelet reactivity has attracted increasing attention as a potential marker of residual thrombotic risk. Multiple studies have demonstrated that a substantial proportion of patients exhibit persistent platelet activation despite treatment with aspirin or clopidogrel. This phenomenon appears to result from a combination of genetic, biological, pharmacological, and clinical factors rather than from a single mechanism.

Importantly, HTPR may provide a pathophysiological link between established vascular risk factors and recurrent ischemic events. Conditions such as diabetes mellitus, chronic kidney disease, obesity, and systemic inflammatory states are consistently associated with enhanced platelet reactivity and reduced responsiveness to antiplatelet therapy. As a result, recurrent stroke may occur despite apparent adherence to evidence-based treatment recommendations. The growing body of evidence associating HTPR with recurrent cerebrovascular events supports its potential role as a clinically relevant biomarker capable of identifying patients who remain at elevated residual thrombotic risk despite conventional secondary prevention measures. [3,4,32]

Nevertheless, the relationship between HTPR and clinical outcomes remains complex. Although observational studies and meta-analyses have demonstrated significant associations with recurrent ischemic events, uncertainty persists regarding the optimal therapeutic interventions that should follow identification of HTPR in routine clinical practice. In addition, the absence of universally accepted therapeutic algorithms continues to limit the routine implementation of platelet function-guided strategies. [1,3,4,36]

4.3 Clinical utility and current limitations of platelet function testing

The potential value of platelet function testing lies in its ability to provide individualized information regarding antiplatelet responsiveness. Among currently available assays, VerifyNow has gained particular attention because of its rapid turnaround time, ease of use, and reproducibility. In selected clinical scenarios, platelet function testing may help identify patients with inadequate platelet inhibition and persistent thrombotic risk.

However, several important limitations currently restrict the widespread implementation of platelet function-guided therapy in stroke populations. Considerable variability exists among available platelet function assays, including differences in methodology, cut-off values, timing of assessment, and interpretation of results. Furthermore, standardized treatment algorithms for patients identified as having HTPR remain insufficiently established. While alternative antiplatelet strategies, including ticagrelor-based regimens and pharmacogenomic-guided approaches, have shown promising results in selected populations, robust evidence demonstrating improved clinical outcomes through routine platelet function testing remains limited. [30,31,36,40]

For these reasons, current international guidelines continue to prioritize proven population-level preventive strategies, including aggressive vascular risk factor control, evidence-based antithrombotic therapy, and comprehensive etiological evaluation. Nevertheless, platelet function testing may have an important role in carefully selected high-risk patients, particularly those with recurrent ischemic events despite apparent adherence to standard therapy. [1,2,36]

An additional challenge is the absence of universally accepted definitions and thresholds for high on-treatment platelet reactivity across cerebrovascular populations. Although cut-off values such as PRU >208 have been widely adopted from cardiovascular studies, their applicability to stroke populations remains incompletely validated. Variability among platelet function assays, differences in testing timing, and heterogeneity of stroke mechanisms complicate the interpretation of platelet reactivity measurements. Consequently, the translation of laboratory findings into standardized therapeutic decisions remains a significant obstacle to the broader implementation of platelet function-guided strategies. [36,40,41]

4.4 Future directions and implications for personalized secondary prevention

The growing recognition of biological heterogeneity among stroke survivors has accelerated interest in precision medicine approaches to secondary prevention. Future strategies are likely to incorporate multiple sources of information, including clinical characteristics, neurovascular imaging findings, platelet function testing, circulating biomarkers, and pharmacogenomic profiling. Such integrated approaches may improve risk stratification and facilitate more individualized therapeutic decision-making. Such multidimensional approaches may facilitate more accurate risk stratification and improve individualized therapeutic decision-making. [31,36,42]

In particular, pharmacogenomic testing has emerged as a promising tool for identifying patients with reduced responsiveness to clopidogrel, especially carriers of CYP2C19 loss-of-function alleles. Findings from recent trials suggest that genotype-guided antiplatelet selection may improve outcomes in selected populations, supporting the concept of tailored antithrombotic therapy. Similarly, advances in biomarker discovery and digital health technologies may contribute to more dynamic assessment of recurrent stroke risk in the future. Importantly, personalized secondary prevention should not be viewed solely through the lens of antiplatelet responsiveness. Future precision-based models will likely require simultaneous consideration of vascular imaging characteristics, inflammatory biomarkers, cardiac monitoring data, genetic susceptibility, and patient-specific clinical factors.

Taken together, the evidence suggests that recurrent ischemic stroke prevention is gradually evolving from a uniform treatment paradigm toward a more individualized model that recognizes the complex interplay between vascular risk factors, platelet biology, inflammation, and genetic variability. Although several challenges remain, the integration of these emerging concepts may ultimately lead to more effective and personalized strategies for reducing recurrent cerebrovascular events. [31,42]

4.5 Implications for Physical and Rehabilitation Medicine

Recurrent ischemic stroke has major implications for Physical and Rehabilitation Medicine, as each recurrent cerebrovascular event may substantially worsen functional outcomes, reduce rehabilitation potential, and increase the long-term burden of disability [43,44]. Stroke recurrence during the recovery period can interrupt rehabilitation programs, delay motor and cognitive recovery, increase dependence in activities of daily living, and reduce the likelihood of regaining functional independence. Therefore, secondary prevention should be considered an integral component of comprehensive stroke rehabilitation rather than a separate vascular intervention [43].

From a rehabilitation perspective, identifying patients at increased risk of recurrent ischemic events is particularly important during the subacute and chronic phases of recovery. Traditional vascular risk factors, atrial cardiopathy, systemic inflammation, endothelial dysfunction, and variability in antiplatelet responsiveness may all influence not only recurrence risk but also the trajectory of functional recovery [1,45]. In this context, high on-treatment platelet reactivity may represent a clinically relevant

marker of residual thrombotic risk in selected patients undergoing long-term rehabilitation and follow-up.

Individualized secondary prevention strategies may support rehabilitation goals by reducing the probability of recurrent events, preserving neurological gains achieved during therapy, and improving long-term participation and quality of life [46]. Preventing recurrent ischemic stroke is therefore essential not only for reducing mortality but also for maximizing rehabilitation outcomes and preserving long-term functional independence. The integration of vascular risk factor management, antiplatelet optimization, pharmacogenomic considerations, and platelet function testing in selected high-risk patients may contribute to more personalized recovery pathways. Consequently, close collaboration between neurologists, rehabilitation physicians, cardiologists, and primary care providers is essential to align secondary prevention with functional recovery planning and long-term disability prevention [45,46].

5. Limitations

Several limitations of the present narrative review should be acknowledged. First, the narrative design inherently carries a risk of selection bias, as study inclusion was not based on a formal systematic review protocol or quantitative meta-analytic methodology. Although the literature search was comprehensive and focused on clinically relevant evidence, the possibility of incomplete study identification cannot be entirely excluded.

Second, substantial heterogeneity exists among studies evaluating antiplatelet resistance and high on-treatment platelet reactivity, including differences in patient populations, platelet function assays, timing of testing, and diagnostic thresholds. This variability complicates direct comparisons across studies and limits the standardization of HTPR assessment in cerebrovascular populations.

Third, although accumulating evidence supports an association between HTPR and recurrent ischemic events, robust randomized data demonstrating improved clinical outcomes through routine platelet function-guided therapeutic adjustment remain limited. Moreover, much of the currently available evidence regarding platelet function testing and pharmacogenomic-guided therapy originates from cardiovascular research, whereas stroke-specific evidence remains comparatively less extensive.

Finally, recurrent ischemic stroke is a highly multifactorial condition influenced by complex interactions among vascular, inflammatory, genetic, pharmacological, and lifestyle-related determinants. Consequently, no single biomarker or diagnostic strategy is likely to fully capture the biological complexity underlying recurrent cerebrovascular risk.

Despite these limitations, the present review provides a clinically oriented synthesis of contemporary evidence regarding recurrent ischemic stroke, antiplatelet resistance, and emerging precision-based secondary prevention strategies. By integrating traditional vascular risk factors with platelet biology, pharmacogenomics, and individualized therapeutic approaches, this review highlights potential directions for future research and supports the development of more personalized strategies aimed at improving long-term cerebrovascular and functional outcomes.

6. Conclusions

Recurrent ischemic stroke should be regarded as a multifactorial clinical entity resulting from the complex interplay among traditional vascular risk factors, vascular pathology, inflammation, endothelial dysfunction, and interindividual variability in antiplatelet responsiveness. Although established secondary prevention strategies have substantially reduced recurrence rates, considerable residual thrombotic risk persists in a subset of patients despite guideline-directed therapy.

Accumulating evidence suggests that high on-treatment platelet reactivity represents an important contributor to recurrent cerebrovascular events and may serve as a clinically relevant marker of residual ischemic risk. Platelet function testing and pharmacogenomic profiling have emerged as promising tools for improving risk stratification and supporting more individualized antiplatelet strategies. Nevertheless, further prospective studies are warranted before these approaches can be routinely implemented in clinical practice.

From the perspective of Physical and Rehabilitation Medicine, prevention of recurrent ischemic stroke extends beyond vascular protection and represents a fundamental prerequisite for preserving neurological recovery, maintaining functional independence, and improving long-term quality of life. Consequently, reducing recurrent stroke risk is essential for optimizing rehabilitation outcomes and minimizing the long-term burden of disability.

Future advances in precision medicine, including the integration of clinical characteristics, platelet function assessment, and pharmacogenomic information, may facilitate more individualized approaches to secondary stroke prevention. Ultimately, multidisciplinary strategies integrating vascular protection with functional recovery may contribute to optimizing both cerebrovascular and rehabilitation outcomes.

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