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EVOLVING PARADIGMS IN SECONDARY STROKE PREVENTION: A COMPREHENSIVE REVIEW OF DUAL ANTIPLATELET THERAPY, INTENSIVE LIPID-LOWERING, AND BIOMARKER-DRIVEN STRATIFICATION

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Abstract:

In order to develop optimal, customized procedures for secondary stroke prevention, this study aims to critically assess and synthesize recent developments in clinical trials, mechanistic evidence, and subgroup studies in acute-phase pharmacology. In order to accomplish this, the review systematically examines the safety thresholds, optimal therapeutic windows, and clinical efficacy of combination antithrombotic and high-intensity lipid-lowering regimens. It also discusses how these treatments interact with various patient comorbidities and newly discovered pathophysiological biomarkers to improve risk stratification. By combining data from multicentred registries, secondary subgroup studies, and recent clinical trials published between 2005 and 2026, a thorough literature synthesis was carried out. The Intensive Statin and Antiplatelet Therapy for High-Risk Intracranial or Extracranial Atherosclerosis (INSPIRES) study and short-term intensive statin and dual antiplatelet therapy (DAPT) protocols were the main focus of the systematic evaluation of data from thirty significant studies. Therapeutic initiation latency, recurrent ischemic stroke occurrences, bleeding events, non-traditional metabolic indices, particularly oxidized low-density lipoprotein (ox-LDL) and the stress hyperglycaemia ratio (SHR), and structural healthcare inequities were among the variables that were retrieved. The obtained data shows that extending the treatment window for DAPT initiation to 72 hours after the ictus considerably reduces the probability of a 90-day ischemia recurrence without increasing the risk of serious haemorrhagic consequences. Early micro emboli suppression and endothelial stabilization are provided concurrently by hyper-acute intensive statin regimens, especially in branch atheromatous disease and carotid stenosis. In the end, the successful mitigation of residual ischemic risk is made possible by incorporating patient-specific metabolic profiles and physiological biomarkers like SHR, ox-LDL, and the BUN/Cr ratio. This demonstrates that tailored secondary prevention that strikes a balance between aggressive pharmacology and individual comorbidity profiles is crucial to optimizing stroke care worldwide.

Keywords: *Acute Ischemic Stroke; Transient Ischemic Attack; Dual Antiplatelet Therapy; HMG-CoA Reductase Inhibitors; INSPIRES Trial; Biomarkers; Secondary Prevention.*

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INTRODUCTION:

Acute ischemic stroke (AIS) and transient ischemic attack (TIA) continue to be the world's top causes of mortality and long-term impairment. Patients who present with minor AIS or high-risk TIA have an exceptionally high risk of early recurrent ischemic stroke or early neurological deterioration (END) within the first few days to weeks after the index event [3, 4, 11, 26, 30]. The immediate post-ischemic phase is a time of extreme physiological vulnerability. The delayed introduction of single antiplatelet treatment (SAPT) in conjunction with conventional, reactive lipid-lowering objectives has historically been a major component of secondary preventive regimens [7, 10].

But a significant paradigm change has occurred throughout the last ten years. Stroke neurology has undergone a revolution with the shift from delayed monotherapy to hyper-acute, intensive combination regimens [1, 3]. By investigating longer time frames and synergistic biochemical pathways, historic multi-centre clinical trials—most notably the INSPIRES experiment described in "Randomized Controlled Trial N Engl J Med.docx"—have pushed the frontiers of the past [1, 2, 3, 4]. In order to analyse the effectiveness, safety, and subtle patient selection techniques that define contemporary, precision-guided secondary stroke prevention, this thorough analysis synthesizes current clinical evidence.

THE DAPT PARADIGM: EXPANDING THE THERAPEUTIC WINDOW

For many years, the clinical consensus was that in order to obtain significant plaque stabilization and anti-thromboembolic activity, dual antiplatelet treatment (DAPT) with clopidogrel and aspirin must be started within a precise 24-hour window post-symptom onset. These temporal bounds have been radically modified by recent INSPIRES trial results [1]. The combination of clopidogrel and aspirin started up to 72 hours after an ischemic stroke considerably reduces the absolute risk of recurrent stroke when compared to aspirin alone, according to this extensive, randomized controlled trial [1]. Mechanistically, this prolonged effectiveness is caused by the long-term suppression of two different platelet activation pathways: aspirin-induced thromboxane A2 suppression and clopidogrel-induced adenosine diphosphate (ADP) P2Y12 receptor antagonism, which stops microthrombi from spreading over an unstable atheromatous core [1].

Importantly, individuals who started treatment within the later 24- to 72-hour window were a major focus of secondary subgroup analysis from the INSPIRES study [2]. The findings demonstrated that clopidogrel-aspirin combination therapy, when started during this prolonged window for high-risk TIA or mild ischemic stroke, is still very effective in reducing ischemic event rates without statistically significantly increasing the risk of moderate-to-severe bleeding complications [2]. In real-world clinical practice, where pre-hospital delays frequently prevent patients from arriving within the conventional 24-hour timeframe, this extended window offers crucial flexibility [2]. DAPT provides better vascular protection than mono-antiplatelet regimens during acute hospitalization for mild-to-moderate strokes, successfully establishing early neurological stabilization, according to real-world hospital-based cohorts [5].

SYNERGISTIC INTENSIVE LIPID-LOWERING THERAPIES

The acute-phase introduction of high-intensity statin therapy has evolved from an unproven approach to a fundamental therapeutic pillar, surpassing aggressive antiaggregating [3, 4]. During the acute phase of AIS, co-administration of short-term DAPT with intensive statins (such as intensive rosuvastatin) had a potent synergistic impact [3, 4]. Statins work quickly through "pleiotropic effects" that go much beyond their ability to decrease low-density lipoprotein cholesterol (LDL-C) over the long term. Statins reduce rapid leukocyte adhesion, enhance nitric oxide bioavailability, control

endothelial inflammation, and downregulate matrix metalloproteinases in the acute context.

A complete decrease in the quantity of circulating micro emboli has been shown by clinical data assessing the hyper-acute administration of high-dose statins [25]. A lower risk of END and stroke recurrence results directly from this quick reduction of micro emboli [3, 4]. In some stroke subtypes, like the following, this hyper-acute stabilization is very important:

• **BRANCH ATHEROMATOUS DISEASE (BAD):** This condition is characterized by a high risk of early, dynamic occlusion due to micro-atheroma at penetrating artery orifices [8, 26]. In individuals with BAD, early intensive statin therapy combined with DAPT offers a powerful protection against increasing neurological impairment [8, 26].

• CAROTID STENOSIS WITH TIA:

In this condition, micro emboli are constantly lost from unstable, ulcerated large-vessel plaques [27]. A safer transition to definitive surgical or endovascular treatments is ensured by early intensive statin therapy in these patients, which is linked to a significant decrease in early stroke risk [27].

COMORBIDITIES AND TAILORED PATIENT SUBGROUPS

A severe "one-size-fits-all" strategy for secondary prevention is fundamentally problematic since real-world stroke populations have complicated medical histories [7, 30]. Recent subgroup analyses have shed light on how particular comorbidities affect the risk-benefit calculation of intense lipid-lowering and antithrombotic treatments:

- **METABOLIC SYNDROME**

Individuals with metabolic syndrome exhibit a highly unstable phenotype marked by rapid atherogenesis and systemic, low-grade vascular inflammation [6]. These patients nonetheless have a high prevalence of residual metabolic risk even though acute DAPT dramatically lowers recurrent ischemia events in this population [6]. This emphasizes the necessity of intensive, multi-targeted therapies that address both platelet reactivity and insulin resistance [6].

- **HYPERTENSION**

Severe arteriolosclerosis is brought on by chronic hypertension, which also modifies baseline vascular autoregulation [15]. Fortunately, thorough evaluations show that the clinical effectiveness of the clopidogrel-aspirin combination is unaffected by a history of hypertension [15]. Clinicians are reassured that the regimen's anti-ischemic advantages outweigh potential haemorrhagic concerns in hypertensive patients because the relative risk reduction for stroke recurrence remains robust across a range of baseline blood pressure profiles [15].

- **ADVANCED AGE**

Due to changed medication clearance, senescent organ function, and age-related vascular fragility, geriatric stroke patients pose a difficult therapeutic challenge [19, 20]. Advanced age can alter the safety profile of intensive statins, but it does not abolish their ischemia advantages, according to subgroup analysis from the INSPIRES study [20]. Due to their high natural baseline of ischemia and systemic fragility, older persons need close clinical monitoring for statin-induced side effects [19, 20].

COGNITIVE IMPAIRMENT AND DEMENTIA

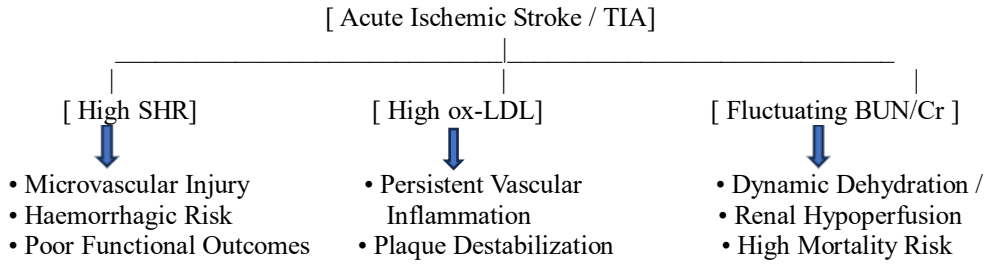
It takes careful clinical balancing to manage secondary prevention in individuals with pre-existing Alzheimer's disease or associated dementia illnesses [17]. Guideline-directed antiplatelet and lipid-lowering regimens clearly improve ischemia in these patients, but they also have a higher risk of haemorrhagic changes and fall-related trauma [17]. In order to reduce polypharmacy and guarantee patient safety, a multidisciplinary strategy combining internists, general practitioners, and caretakers is necessary because significant cognitive decline makes drug adherence more difficult [7, 17].

CROSS-DISCIPLINARY INSIGHTS FROM ADJACENT VASCULAR PATHOLOGIES

Examining treatment results in nearby vascular fields sheds more light on the systemic aspect of endothelial dysfunction [16, 22]. The RIETE study's registry data shows that statin treatment is independently linked to lower overall mortality in patients with deep vein thrombosis (DVT), supporting the drugs' systemic anti-inflammatory and antithrombotic properties [22]. On the other hand, long-term monitoring highlights that, although intense medicinal optimization is essential in complex arterial disorders like ischemic cardiomyopathy, it must be carefully balanced with or without surgical revascularization techniques to obtain optimal survival [16].

BIOMARKERS, METABOLIC INDEXES, AND RESIDUAL RISK

Even with rigorous adherence to severe statin regimens and routine DAPT, a considerable percentage of patients still have recurrent ischemic episodes [30]. New metabolic, inflammatory, and renal indicators are crucial for detecting and reducing this "residual risk" [24, 28, 29, 30].



STRESS HYPERGLYCEMIA RATIO (SHR)

The stress hyperglycaemia ratio (SHR) is a real indicator of acute, stress-induced metabolic dysfunction, in contrast to absolute admission glucose, which might only represent a patient's baseline glycaemic control [24]. A high SHR, which is determined by adjusting admission blood glucose against estimated background haemoglobin A1c (HbA1c), indicates a significant increase in inflammatory cytokines and counter-regulatory hormones [24]. Elevated SHR is a strong, independent predictor of poor functional outcomes, END, and recurrent ischemia episodes, according to secondary analyses of the INSPIRES trial [24]. SHR is an essential tool for early risk stratification because high acute glucose availability increases the formation of free radicals, exacerbates disruption of the blood-brain barrier, and encourages microvascular thrombosis [24].

OXIDIZED LOW-DENSITY LIPOPROTEIN (OX-LDL)

Standard lipid panels measure the amount of LDL in circulation, but they are unable to detect the qualitative changes that cause atherogenesis [28]. Macrophages eagerly absorb oxidized low-density lipoprotein (ox-LDL), a highly atherogenic modified lipid particle, to create foam cells in the vascular intima [28]. Elevated baseline ox-LDL levels are highly linked to poor clinical outcomes and recurrent stroke, regardless of absolute LDL-C levels, according to secondary analyses from the INSPIRES trial [28]. Patients who need sophisticated, non-traditional plaque-stabilizing treatments are identified by high ox-LDL, which indicates active, continuous lipid peroxidation and arterial wall inflammation [28].

BLOOD UREA NITROGEN TO CREATININE (BUN/CR) RATIO

Renal and hydration index dynamic fluctuations during the acute stroke period have significant predictive significance [29]. After a stroke, an increasing or continuously increased BUN/Cr ratio usually reflects subclinical renal hypoperfusion and relative intravascular dehydration [29]. Significant increases in the BUN/Cr ratio are a powerful predictor of poor functional recovery and higher death, according to clinical cohort evidence [29]. Maintaining ideal fluid balance during acute antithrombotic optimization is crucial because hemoconcentration brought on by dehydration increases blood viscosity, reduces microcirculatory flow, and encourages thrombus formation [29].

ALTERNATIVE PHARMACOTHERAPIES AND SAFETY SAFEGUARDS

Alternative pharmaceutical approaches offer useful alternatives for some clinical circumstances [18], even though DAPT and statins continue to be the front-line standard of care [1, 3]. One effective treatment for acute ischemic stroke is the direct thrombin inhibitor argatroban [18]. Argatroban offers a consistent anticoagulant response without the possibility of heparin-induced thrombocytopenia (HIT) by directly blocking both clot-bound and soluble thrombin [18]. Argatroban has an acceptable safety profile without appreciably raising the risk of substantial systemic or symptomatic cerebral haemorrhage, and systematic reviews and meta-analyses demonstrate that it has great efficacy in preserving arterial patency and preventing early recurrence [18].

However, a strict approach to safety monitoring is necessary when implementing vigorous, multi-agent regimens [12, 21]. For instance, the radiological characteristics and clinical course of recurrent intracerebral haemorrhages (ICH) may be affected by a history of prior extensive statin medication [21]. Under long-term lipid-lowering medication, clinicians need to be mindful of possible structural alterations in cerebral micro vessels [21].

Additionally, different patient populations need for very specific protocols:

- **CHRONIC KIDNEY DISEASE (CKD):** Patients with chronic kidney disease (CKD) exhibit a challenging clinical dilemma since they have both platelet dysfunction and hypercoagulability [12]. This greatly increases their chances of uremic bleeding and ischemic stroke recurrence [12]. Strict, individualized dosage modifications and close observation are necessary for antiplatelet treatments in CKD [12].
- **MOYAMOYA DISEASE:** Vascular remodelling is distinctive in this progressive, non-atherosclerotic

cerebrovascular illness [13]. Although statins are widely used, national cohort data shows that their long-term stroke prevention patterns and therapeutic processes in Moyamoya are very different from those of classical atherosclerotic stroke, necessitating unique, disease-specific procedures [13].

GLOBAL HEALTHCARE DELIVERY AND DISPARITIES

The effectiveness of secondary stroke prevention in the actual world is largely dependent on the standard, efficiency, and consistency of the local healthcare system [7, 14, 23]. Even within identical healthcare systems, large-scale, real-world registries show significant regional and socioeconomic disparities in acute ischemic stroke medication patterns and subsequent clinical outcomes [14]. Regional differences in clinical expertise, diagnostic imaging availability, and prompt guideline adherence are the main causes of these discrepancies [14]

In developing tertiary care settings, such those in sub-Saharan Africa, this implementation gap is especially noticeable [23]. The real-world effectiveness of advanced antiplatelet and lipid-lowering medicines is significantly undermined by uneven access to continuous diagnostics, extended pre-hospital transport times, and financial obstacles to acquiring high-intensity pharmaceuticals, according to structured quality-of-care audits [23]. Healthcare organizations must fund extensive training programs for internists and general practitioners in order to close this gap between clinical trial data and general practice [7]. In order to identify high-risk TIAs, start rapid, guideline-directed therapy within the proper therapeutic window, and manage long-term adherence and risk factor control, these frontline doctors are crucial [7].

CONCLUSION:

A highly proactive, customized approach to treating acute ischemic stroke and TIA is supported by the available research. When paired with immediate high-intensity statin therapy, starting DAPT within an extended 72-hour window dramatically lowers the risk of early recurrence and microembolization [1, 2, 3, 25]. Clinicians must consider patient-specific characteristics, such as comorbidities like metabolic syndrome and dementia, in addition to biomarkers like SHR, ox-LDL, and BUN/Cr ratio, in order to optimize this technique [6, 17, 24, 28, 29, 30]. In order to enhance real-world clinical results and eradicate structural healthcare disparities, future research should focus on standardizing these harsh regimens universally [7, 23].

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