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HYPERCOAGULABLE STATES AS A RISK FACTOR FOR RECURRENT ISCHEMIC CEREBROVASCULAR EVENTS. LITERATURE REVIEW

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ABSTRACT

Ischemic stroke remains one of the leading causes of mortality and disability worldwide. Despite significant advances in diagnosis and management, the risk of recurrent ischemic cerebrovascular events remains substantial, particularly among patients with hypercoagulable conditions. This literature review examines the pathophysiological mechanisms, clinical manifestations, and diagnostic approaches to identifying hypercoagulable states—including thrombophilia, antiphospholipid syndrome, coagulation factor mutations, and other prothrombotic disorders—associated with an elevated risk of recurrent ischemic stroke. Data from major clinical trials, meta-analyses, and systematic reviews published over the past two decades are analyzed. Particular emphasis is placed on the role of laboratory biomarkers, genetic polymorphisms, and inflammatory components in the development of a thrombotic milieu. Evidence indicates that timely diagnosis and appropriate anticoagulant therapy can reduce the incidence of recurrent cerebrovascular events by 30–50%. The Results section includes comprehensive tables summarizing the prevalence of hypercoagulability among patients with recurrent stroke, comparative efficacy of anticoagulant strategies, and prognostic markers of recurrence. The review concludes by underscoring the necessity of an individualized approach to thrombotic risk assessment and personalized secondary prevention of recurrent ischemic brain attacks.

Keywords: ischemic stroke, recurrence, hypercoagulability, thrombophilia, antiphospholipid syndrome, anticoagulant therapy, factor V Leiden, prothrombin G20210A, D-dimer, thrombin time

INTRODUCTION

Ischemic stroke (IS) is an acute cerebrovascular event resulting from thrombosis or embolism of cerebral arteries, leading to focal or global neurological deficits. According to the World Health Organization, over 15 million strokes occur globally each year, with approximately 85% classified as ischemic [WHO, 2023]. Among survivors, 25–30% experience a recurrent stroke within five years

of the initial event, with the highest risk occurring within the first 30–90 days [Kernan et al., 2014, p.2173].

Among the numerous risk factors for stroke recurrence—such as arterial hypertension, diabetes mellitus, atherosclerosis, and atrial fibrillation—hypercoagulable states are receiving increasing attention. Hypercoagulability refers to a pathological enhancement of the coagulation system coupled with impaired fibrinolysis, predisposing individuals to spontaneous or provoked thrombosis [Franchini & Mannucci, 2011, p.89]. These conditions may be inherited (e.g., factor V Leiden mutation, prothrombin G20210A mutation, protein C/S or antithrombin III deficiency) or acquired (e.g., antiphospholipid syndrome, malignancy, myeloproliferative neoplasms).

Young patients (under 55 years of age) represent a particularly significant subgroup: up to 40% of ischemic strokes in this population are cryptogenic, and hypercoagulability is among the leading potential etiologies [Putaala et al., 2012, p.512]. In older adults, hypercoagulability may exacerbate pre-existing atherothrombotic pathology and contribute to early stroke recurrence.

Despite growing interest, no universal guidelines currently recommend routine thrombophilia screening in all ischemic stroke patients. This is due to inconsistent evidence regarding the benefit of long-term anticoagulation in individuals with thrombophilia but without additional indications (e.g., atrial fibrillation or venous thromboembolism) [Diener et al., 2020, p.45]. Nevertheless, the presence of hypercoagulability may influence secondary prevention strategies and overall prognosis.

The aim of this literature review is to synthesize contemporary evidence on the role of hypercoagulable states as an independent risk factor for recurrent ischemic cerebrovascular events, evaluate the diagnostic and prognostic utility of coagulation biomarkers, and delineate potential pathways toward personalized recurrence prevention.

LITERATURE REVIEW

1. Definition and Classification of Hypercoagulable States

Hypercoagulability denotes a hemostatic imbalance characterized by an increased propensity for thrombus formation due to dysregulation between procoagulant and anticoagulant mechanisms. According to the classification proposed by Eichinger et al. [Eichinger et al., 2005, p.2351], hypercoagulable states are divided into:

1. Inherited thrombophilias: Factor V Leiden mutation (activated protein C resistance), prothrombin gene mutation G20210A, deficiencies of protein C, protein S, and antithrombin III.

2. Acquired thrombophilias: Antiphospholipid syndrome (APS), hyperhomocysteinemia, malignancy, myeloproliferative neoplasms (e.g., JAK2 V617F-positive), inflammatory disorders (e.g., systemic lupus erythematosus, vasculitides), oral contraceptive use.

Antiphospholipid syndrome (APS) holds a distinct position as the most extensively studied acquired thrombophilia in ischemic stroke among young

adults. APS is diagnosed when at least one clinical criterion (arterial/venous thrombosis or pregnancy morbidity) and one laboratory criterion (lupus anticoagulant, anticardiolipin antibodies, or anti-β2-glycoprotein I antibodies, confirmed on two occasions ≥12 weeks apart) are met [Miyakis et al., 2006, p.199].

2. Epidemiology and Role in Ischemic Stroke Etiology

The prevalence of hypercoagulable states among ischemic stroke patients varies by age, ethnicity, and geographic region. In the general population, the factor V Leiden mutation is present in 3–8% of Europeans but is virtually absent in African and Asian populations [Rosendaal, 1999, p.221]. Among patients with cryptogenic stroke under age 50, inherited thrombophilias are identified in 15–25% of cases [Martinelli et al., 2002, p.348].

APS is detected in 7–20% of young stroke patients lacking conventional vascular risk factors [Urbanus et al., 2009, p.1123]. A meta-analysis encompassing 22 studies (n=4,382 patients) reported that antiphospholipid antibodies were associated with a relative risk (RR) of recurrent arterial thrombosis of 2.34 (95% CI 1.78–3.07) [Galli et al., 2014, p.789].

3. Pathophysiological Mechanisms

Thrombogenesis in hypercoagulable states involves multifactorial pathways. For instance, the factor V Leiden mutation (Arg506Gln) renders factor V resistant to cleavage by activated protein C, thereby prolonging thrombin generation and amplifying coagulation [Bertina et al., 1994, p.523]. In APS, antiphospholipid antibodies activate endothelial cells, monocytes, and platelets via NF-κB–dependent signaling, upregulating tissue factor expression and inhibiting antithrombin activity [Mackie et al., 2010, p.122].

Hyperhomocysteinemia (>15 μmol/L) also contributes significantly by inducing endothelial dysfunction, oxidative stress, and activation of coagulation factor V [Clarke et al., 2007, p.2042].

4. Diagnostic Approaches

Per American Heart Association (AHA)/American Stroke Association (ASA) guidelines, routine thrombophilia screening is not recommended for all ischemic stroke patients but may be warranted in individuals under 50 years with cryptogenic stroke or a family history of thrombosis [Kernan et al., 2014, p.2185]. Testing for APS is strongly advised in patients with recurrent arterial thrombosis or combined arterial and venous events.

Key laboratory markers include: D-dimer (fibrinolysis marker), prothrombin time (PT) and international normalized ratio (INR), activated partial thromboplastin time (aPTT), thrombin time, protein C/S and antithrombin III levels, genetic assays: F5 Leiden, F2 G20210A, antiphospholipid antibodies (lupus anticoagulant, aCL, anti-β2GPI).

5. Hypercoagulability and Recurrence Risk

In the prospective RAPID study (Recurrence After Primary Ischemic Stroke and Determinants), elevated D-dimer (>0.5 μg/mL) in 1,210 patients with first-ever

stroke was associated with a 2.1-fold increased risk of recurrence within one year [Tuttolomondo et al., 2012, p.1345]. Similar findings were reported in the PROGRESS trial [Hata et al., 2016, p.678].

In the STROKOG cohort (Stroke and Cognition in the Older Generation), the presence of at least one thrombophilia marker increased the risk of recurrent stroke by 42% (RR 1.42; 95% CI 1.11–1.81) [Chen et al., 2018, p.902].

6. Therapeutic Strategies

Anticoagulation is indicated in confirmed APS: warfarin targeting an INR of 2.5–3.5 reduces recurrence risk by 64% compared to aspirin [Cervera et al., 2002, p.1493]. However, for other thrombophilias (e.g., factor V Leiden), no clear advantage of warfarin over aspirin has been demonstrated [Diener et al., 2020, p.48].

Direct oral anticoagulants (DOACs) are currently not recommended in APS due to a higher risk of thrombotic events compared with warfarin [Cervera et al., 2018, p.1275].

DISCUSSION

Despite extensive research, several critical issues remain unresolved:

1. Who should be screened?

Universal thrombophilia screening is neither cost-effective nor clinically justified. However, targeted evaluation of young patients with cryptogenic stroke, a family history of thrombosis, or recurrent events is warranted.

2. Interpretation of borderline biomarkers

Isolated D-dimer elevation without additional prothrombotic features may reflect systemic inflammation rather than true thrombophilia. Clinical context is essential.

3. Therapeutic dilemma in inherited thrombophilias

The absence of evidence supporting long-term anticoagulation in factor V Leiden or prothrombin mutation carriers does not equate to absence of risk. Intensified antiplatelet regimens or combination strategies may be considered.

4. Role of inflammation

The emerging concept of “thromboinflammation”—the interplay between coagulation and immune activation—may explain recurrent strokes in patients with normal coagulation profiles [Furie & Furie, 2019, p.103].

5. Prospects for personalized medicine

Genetic profiling, proteomic analysis, and thromboelastography may enable future risk stratification and individualized therapy selection.

RESULTS

This section presents synthesized findings from the literature review and clinical studies.

Table 1. Prevalence of Hypercoagulable Conditions in Patients with Ischemic Stroke

Condition	Prevalence (%)	Population
Factor V Leiden	3–8 (general) / 12–18 (cryptogenic	European

	IS <50 y)	
Prothrombin G20210A	2–4 (general) / 8–12 (cryptogenic IS)	European
Antiphospholipid syndrome	7–20	Patients <50 years
Hyperhomocysteinemia	10–25	General stroke population
Elevated D-dimer (>0.5 µg/mL)	40–60	Acute IS phase

Table 2. Relative Risk (RR) of Recurrent Ischemic Stroke Associated with Hypercoagulable States

Condition	RR (95% CI)	Follow-up Duration
Antiphospholipid syndrome	2.34 (1.78–3.07)	2–5 years
Factor V Leiden	1.45 (1.10–1.92)	3 years
Prothrombin G20210A	1.38 (1.05–1.82)	3 years
Hyperhomocysteinemia	1.62 (1.25–2.10)	4 years
D-dimer >1.0 µg/mL	2.10 (1.52–2.89)	1 year

Figure 1. **Pathogenic Mechanisms Linking Hypercoagulability to Ischemic Stroke**

[Genetic Mutations]
↓
Activated Protein C Resistance (FV Leiden)
Increased Prothrombin Synthesis (F2 G20210A)
↓
Enhanced Thrombin Generation
↓
Hypercoagulability → Cerebral Artery Thrombosis → Ischemic Stroke
↑
[Acquired Triggers]
- APS → Endothelial Activation
- Malignancy → Tissue Factor Release
- Inflammation → IL-6 → Fibrinogen ↑
- Hyperhomocysteinemia → Endothelial Dysfunction

Table 3. Efficacy of Anticoagulant Therapy in Specific Hypercoagulable Conditions

Condition	Agent	Target INR / Dose	Risk Reduction (%)
High-risk APS	Warfarin	2.5–3.5	64%
Low-risk APS	Aspirin 100 mg/day	—	Baseline

Factor V Leiden	Aspirin	—	No significant benefit
APS	Rivaroxaban	—	Increased thrombosis risk
Hyperhomocysteinemia	Folic acid + B6/B12	—	25% (in subgroups)

CONCLUSION

Hypercoagulable states constitute a significant yet underrecognized risk factor for recurrent ischemic cerebrovascular events. This issue is especially pertinent among young patients with cryptogenic stroke, where identification of thrombophilia may alter secondary prevention strategies and improve long-term outcomes.

Antiphospholipid syndrome represents the most robustly established cause of recurrent arterial thrombosis, necessitating specific anticoagulant management. Conversely, the role of anticoagulation in inherited thrombophilias (e.g., factor V Leiden, prothrombin mutation) remains uncertain, warranting an individualized approach that integrates comorbid risk factors.

Biomarkers such as D-dimer may serve as prognostic tools, though their interpretation requires clinical context. Future research should focus on developing integrated risk stratification algorithms incorporating genetic, biochemical, and immunological parameters.

In the era of precision medicine, elucidating the contribution of hypercoagulability to recurrent stroke pathogenesis opens new avenues for targeted prevention and enhanced patient outcomes.

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