American Journal of Biology and Natural Sciences
https://biojournals.us/index.php/AJBNS
ISSN: 2997-7185

Hypercoagulability and Biochemical Markers in Thrombosis and Stroke

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Received: 2025, 15, Jun
Accepted: 2025, 21, Jul
Published: 2025, 18, Aug

Annotation: Hypercoagulability, a state of increased blood clotting potential, plays a critical role in the pathophysiology of thrombotic events, including ischemic stroke. It results from an imbalance between procoagulant and anticoagulant factors, often driven by underlying conditions such as inflammation, malignancy, genetic mutations (e.g., Factor V Leiden), or metabolic disorders. This review aims to highlight the association between hypercoagulability and the development of thrombosis and stroke, with a specific focus on emerging biochemical markers that may aid in early diagnosis, risk stratification, and therapeutic monitoring. Key biomarkers implicated in hypercoagulability include D-dimer, fibrinogen, thrombin-antithrombin complexes, and P-selectin, all of which reflect ongoing coagulation activation and fibrinolysis. Inflammatory mediators such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) have also been shown to contribute to the prothrombotic milieu by activating endothelial cells and platelets. Furthermore,

alterations in lipid profiles, elevated homocysteine levels, and impaired fibrinolytic activity are associated with increased stroke risk in hypercoagulable patients. Understanding the interplay between hypercoagulability and these biomarkers is essential for improving clinical outcomes. Their measurement may enhance early detection of thrombotic risk and support the tailoring of anticoagulant therapies in high-risk individuals. Current research is exploring novel markers and genetic predictors to further refine stroke prediction models. In conclusion, hypercoagulability and its associated biochemical markers are central to the development and progression of thrombosis and stroke. Further studies are needed to validate the clinical utility of these markers in routine practice and to guide personalized therapeutic strategies.

Keywords: Hypercoagulability, Thrombosis, Ischemic Stroke, Biochemical Markers, Inflammatory Cytokines, Risk Stratification.

1. Introduction:

Hypercoagulability denotes an augmented propensity for the conversion of fibrinogen to fibrin, culminating in clot formation that depletes crucial regulatory proteins and precipitates thrombosis or thromboembolic phenomena. This alteration disrupts the intricate hemostatic balance, thereby elevating the risk of both arterial and venous thrombosis [1,2]. A constellation of inherited and acquired factors that amplify prothrombin levels or diminish anticoagulants such as protein C/Z, protein S, or antithrombin III significantly escalates the likelihood of thrombotic occurrences. Recognizing the pivotal influence of hypercoagulability in thrombotic events underscores the imperative for the identification of biochemical markers that may serve to predict thrombosis and cerebrovascular accidents. Thrombosis poses a considerable threat to nearly all organ systems, frequently resulting in acute ischemic conditions. The interplay of thromboembolic events coupled with pervasive atherosclerosis exacerbates the ischemic ramifications. Patients may present as asymptomatic or exhibit a spectrum of symptoms contingent upon organ involvement, manifesting as cerebral strokes, myocardial infarctions, or limb gangrene. The term “stenosis” is aptly employed to describe partial arterial constriction, whereas “thrombosis” signifies complete occlusion. Venous thrombotic events can give rise to pulmonary embolism, orphan lung

syndrome, and subsequent organ infarction [3,4].

2. Understanding Hypercoagulability

Hypercoagulability is a complex condition marked by an imbalance favoring procoagulant factors over anticoagulants, impacting the haemostatic process and vascular microenvironment. A vulnerable balance can occur when pro- and anticoagulants fluctuate within normal ranges but near critical thresholds [5,6]. Changes in various components, including coagulation factors, inhibitors, fibrinolysis systems, and cellular elements like platelets, can create a hypercoagulable state, heightening the risk for thrombosis and stroke. Hypercoagulability is classified as primary, stemming from inherited coagulation factor abnormalities, or secondary, resulting from disease-related changes in coagulation or fibrinolysis factors. Both significantly increase thrombosis and stroke risks [7].

2.1. Definition and Mechanisms

The phenomenon of hypercoagulability represents an abnormal tendency to form blood clots, influenced by systemic changes in plasma that predispose individuals to thrombotic events. This concept distinguishes cases where blood plasma biochemistry shifts toward clotting without immediate clot formation. Hypercoagulation can be categorized into two main causes. First, circulating materials in plasma can activate thrombin generation [7,8]. Examples include tissue factor (TF) from cancer or diabetic cells, factor XIa, or circulating bacteria initiating systemic clotting upon contact. Second, certain changes don't directly trigger clotting but facilitate its propagation after initiation. These changes include: a) increased levels or activity of procoagulant factors (congenital anomalies, pregnancy, oral contraceptives, G20210A prothrombin mutation, factor V Leiden mutation, and elevated factor VIII, IX, or XI), b) decreased anticoagulant molecule function (deficiencies in antithrombin, protein S, protein C, or dysfibrinogenemias), c) diminished fibrinolysis, and d) increased von Willebrand factor. When hypercoagulation is present, diagnosis should involve detecting systemic prothrombotic changes and specific causes such as altered coagulation factor levels, presence of active factors, or abnormalities in fibrinolysis [8]. Measuring individual factors often yields inconclusive results, as their normal ranges can remain within typical limits despite underlying disease or inflammatory states. Mechanisms explaining hypercoagulation involve the previously mentioned changes, contributing to increased venous and arterial thrombosis prevalent in pathological conditions such as cancer, pregnancy, oral contraceptives, and diabetes mellitus [9].

2.2. Types of Hypercoagulability

Several classification schemes for hypercoagulability exist, primarily divided into primary and secondary types, as outlined in Virchow’s triad. Primary hypercoagulability, or congenital thrombophilia, affects around 3-8% of the population, resulting from hereditary factors leading to increased coagulation. In contrast, secondary hypercoagulability is acquired and can stem from conditions such as cancer or atherosclerosis, often occurring alongside primary hypercoagulability due to other risk factors. The driving mechanisms of procoagulants are often unmeasurable, and most inflammatory markers are not direct coagulation activators, with none exceeding 0.5 [10]. Consequently, secondary hypercoagulability may not involve known initiation processes, yet systemic enhancements can prolong coagulation. Severe sepsis and extreme inflammation may lead to disseminated intravascular coagulation and hypocoagulation [11,12].

3. Thrombosis: An Overview

Thrombosis refers to blood clotting within a blood vessel, leading to various diseases and disorders. Its pathophysiology involves molecular and cellular processes occurring during blood vessel cleansing. Key predisposing factors include blood flow stasis, endothelial lesions, and blood hypercoagulability. Unlike bleeding, which has a smooth surface with fibrin fibers, thrombotic clots have uneven surfaces with strands of fibrin. Clots vary in morphology, cellular composition, and growth patterns [13,14]. Arterial clots mainly consist of platelets and a small

number of erythrocytes, growing by platelet accumulation in the blood flow direction. Venous clots comprise mostly fibrin and erythrocytes, trapping platelets and propagating toward the heart. Thrombosis is significant in stroke development, assessed through biochemical markers like D-dimer, CRP, prothrombin time, NT-ProBNP, S100B protein, and fibrinogen [15].

3.1. Pathophysiology of Thrombosis

Thrombosis involves blood clot formation within vessels, causing partial or complete blood flow blockage. Key factors include local blood flow disruptions and vessel wall changes. Virchow's triad highlights hypercoagulability, stasis, and endothelial injury in thrombus formation, relevant to both venous and arterial cases [16]. Atherosclerosis, driven by chronic inflammation and lipid exposure, affects the endothelium and coagulation pathways. Platelets facilitate atherogenesis through adhesion and recruiting leukocytes; plaque rupture reveals prothrombotic proteins that trigger thrombus formation. Tissue factor exposure at injury sites activates coagulation, leading to thrombin production, enhancing platelet aggregation and affecting cellular processes via protease-activated receptors [17]. Localized coagulation and fibrin formation are resultant from arterial damage. Thrombogenic initiators are categorized into direct activation materials like microparticles and tissue factor, and factors promoting propagation by shifting coagulation balance, including elevated pro-coagulant factors and reduced anticoagulant molecules. Identifying hypercoagulability involves systemic pro-thrombotic changes, with challenges in isolating specific factors; distinctive states are seen in cancer, pregnancy, oral contraceptive use, and diabetes, each linked to unique thrombosis mechanisms [18,19].

3.2. Risk Factors for Thrombosis

Thrombosis occurs in the arterial or venous systems due to disruptions in Virchow's triad: stasis, vessel wall injury, and altered blood constituents. Stasis leads to thrombus formation by reducing coagulation factor clearance through adhesion molecules. Vessel wall injury exposes collagen and tissue factor, activating platelets. Hypercoagulability, caused by elevated coagulation factors or reduced anticoagulants, triggers thrombosis. Risk factors include hypertension, hyperlipidemia, and smoking, which can damage the endothelium and increase coagulation protein adhesiveness. Cancer may induce thrombosis through stasis, elevated procoagulants, or coagulation abnormalities. Septicemia may cause disseminated intravascular coagulation, leading to microthrombi. Chronic inflammatory diseases, anabolic steroids, varicose veins, and leg immobilization are also risk factors [20,21]. Elevated levels of coagulation factors affect thrombotic events like myocardial infarction (MI) and ischemic stroke (IS). Factors VIII, fibrinogen, plasminogen, von Willebrand factor, X, and XIII raise the risk for MI and IS, while factors XI and XII increase IS risk significantly. Hypercoagulability is particularly associated with IS in women under 50. However, differentiating causative mechanisms is complex, as most research focuses on individual arterial thrombosis manifestations. Patients often present with pain, tenderness, swelling, and redness, with about 30% remaining asymptomatic. Approximately 10% of superficial vein thrombosis cases progress to DVT, which can lead to serious complications like pulmonary embolism (PE) and pulmonary infarction. Symptoms of PE include dyspnea, chest pain, syncope, tachycardia, tachypnea, and swollen legs [23,24]. Stroke can be hemorrhagic or ischemic, each presenting suddenly and influenced by type and causes [25].

4. Stroke: An Overview

Stroke ranks among the most critical health challenges globally, accounting for high mortality and morbidity rates each year [26]. It encompasses a spectrum of debilitating diseases characterized by an acute onset of neurological deficits resulting from cerebral injury. Multiple pathophysiological mechanisms contribute to stroke occurrence: acute coronary syndromes linked to atherosclerotic plaques, cerebral and systemic atherosclerosis, systemic thrombosis affecting cerebral vessels, and underlying microvascular dysfunction. The principal forms of stroke include ischemic stroke, transient ischemic attack (TIA), intracerebral hemorrhagic stroke, and subarachnoid hemorrhagic stroke. Understanding these distinct types, their risk factors, and clinical presentations is pivotal

for effective prevention and management, especially given their overlaps and distinctions relative to thrombosis [27].

4.1. Types of Stroke

Four different types of stroke are commonly recognized: ischemic, hemorrhagic, transient ischemic attack (TIA), and cryptogenic (cryptogenic means without a known cause). Ischemic strokes account for 80% of all strokes, hemorrhagic for 15%, TIAs approximately 10%, and cryptogenic strokes constitute the remaining 25–30% [28,29]. Risk factors for ischemic stroke include older age, diabetes mellitus, male sex, hyperlipidemia, hypertension, heart failure, and smoking; hemorrhagic stroke is more common in younger persons. Because of a combination of high morbidity and risk for recurrence, stroke is a leading cause of long-term disability worldwide [30].

4.2. Risk Factors for Stroke

Prevention and management of ischemic stroke are critically dependent on an accurate understanding of risk factors. Age plays a central role, with additional stratification based on underlying causation [31]. Essential hypertension, characterized by elevated blood pressure unused to maintain homeostasis, and smoking are recurring precipitants of stroke. Details of stroke risk in this context are extensive and, for reasons of space, will not be restated here. The influence of sex and race on stroke rates is also well documented at a broad population level. Young women constitute an important subpopulation, and pregnancy, contraception, and hormone replacement therapy are major contributors to stroke risk [32,33].

4.3. Clinical Manifestations

Thrombosis manifests as pain, redness, swelling, and discoloration, indicative of impaired venous return. Large veins are susceptible to thrombus formation and consequent occlusion [2]. Pulmonary embolism may develop within a week following the onset of venous thrombosis. Arterial thrombosis specifically compromises the blood supply of the involved organ, precipitating ischemia and infarction. Cardiac thrombosis can produce symptoms ranging from angina to myocardial infarction [34]. Cerebral artery thrombosis often results in stroke, characterized by neural dysfunction and paralysis. Thrombosis occurs post-catheterization, involving the jugular or femoral veins, and frequently associates with infection, psychiatric disorders, hypoproteinemia, nephrotic syndrome, or systemic diseases [35,36].

5. Biochemical Markers in Thrombosis

Systemic prothrombotic changes, termed hypercoagulation, are linked to global alterations in blood composition [37]. Detection of hypercoagulable states includes measurement of coagulation factors and inhibitors, circulating active factors, microparticles, and fibrinolysis markers. Several mechanisms contribute to hypercoagulability; for instance, increased levels of procoagulant zymogens or decreased amounts of anticoagulant molecules promote thrombotic processes. Conditions such as cancer, pregnancy, oral contraceptive use, and diabetes mellitus induce specific procoagulant factors coupled with inhibition of anticoagulant systems, predisposing to venous and arterial thrombosis. In acute coronary syndromes and atherosclerosis, the critical role of thrombosis is mediated by thrombin and protease-activated receptors (PARs), while tissue factor signaling modulates cell migration and apoptosis relevant to thrombus formation [38]. The frequent occurrence of total coronary occlusion during early myocardial infarction underscores the necessity of timely intervention. Quantification of circulating procoagulant phospholipids and evaluation of thrombomodulin activity aid in stratifying myocardial infarction risk. Biochemical markers such as D-dimer, fibrinogen, and prothrombin time are thus fundamental to the diagnosis and prognosis of thrombosis in clinical practice [39].

5.1. D-dimer

Plasma D-dimer levels indicate blood clot turnover, with elevated values linked to thrombotic

events. They are independently associated with a 2-fold increase in mortality risk in ST-elevation myocardial infarction patients, suggesting hypercoagulability as a key prognostic factor in arterial thrombosis [40,41]. Secondary haemostasis involves activating plasma proteins and forming a fibrin mesh, initiated by tissue factor complex formation at vascular injury sites, leading to thrombin generation and conversion of fibrinogen to insoluble fibrin polymers. Crosslinking by factor XIIIa traps erythrocytes, stabilising the platelet plug. Thrombus breakdown produces D-dimer, a fibrin degradation product containing two cross-linked D fragments of fibrin. Activated factor XIII creates stable fibrin clots, which are later lysed by plasmin, releasing fibrin degradation products (FDPs) into circulation. D-dimer, a distinct class of FDPs, is specific to cross-linked fibrin lysis but may not be elevated in hypofibrinolysis, where levels often remain normal [42,43].

5.2. Fibrinogen

Fibrinogen is a 340 kDa glycoprotein made of three polypeptide chain pairs (Aα, Bβ, and γ), mainly produced by hepatocytes. It is crucial for clot formation as it serves as the precursor for fibrin monomers, a ligand for platelet glycoprotein IIb/IIIa, and facilitates platelet aggregation. Fibrinogen's role in thrombus formation is significant [44,45]. Elevated plasma fibrinogen levels correlate with increased blood viscosity, platelet aggregation, and fibrin formation, indicating a higher risk for acute ischemic stroke. These concentrations are particularly linked to cardioembolic stroke risk, especially in Asians. Variations in fibrin structure can affect thrombogenic potential and predisposition to thrombotic diseases [46,47].

5.3. Prothrombin Time

Prothrombin time (PT) measures blood coagulation, evaluating the extrinsic pathway and monitoring anticoagulant therapy. Abnormal PT may indicate clotting disorders, liver disease, or anticoagulant effects. Understanding clinical context and lab standards is essential for interpretation. In ischemic stroke patients, PT was measured at one, seven, and fourteen days post-event [48,49]. Prothrombin-derived molecules increased significantly in atherothrombotic and cardioembolic strokes by 10% and 25%, respectively, compared to controls. Cardioembolic stroke analysis showed prothrombin and degraded forms, including thrombin (~72 and 37 kDa), with thrombin generation confirmed by the N-terminal fragment F1+2 (~40 kDa) [49].

6. Biochemical Markers in Stroke

C-reactive protein (CRP) is a biomarker used to estimate inflammation and is associated with increased severity, recurrence, and poorer prognosis in acute ischemic stroke (AIS). It serves as an effective indicator of stroke progression and other cardiovascular conditions. N-terminal pro B-type natriuretic peptide (NT-proBNP), a cardiac hormone from the ventricles, is elevated in conditions like systolic heart failure. Post-stroke, high NT-proBNP levels indicate worse functional outcomes and higher mortality rates, making it a promising biomarker for cardioembolic stroke source diagnosis, outperforming CRP in discriminative ability. S100B, an intracellular calcium-binding protein, increases with injury or blood-brain barrier (BBB) disruption, correlating with BBB damage severity, infarct size, and outcomes, mainly in the first 96 hours post-ischemic onset. It has shown diagnostic and prognostic value in brain-related diseases, particularly in subacute and recovery phases [50,51].

6.1. C-reactive Protein

C-reactive protein (CRP) was identified in patients infected with Streptococcus pneumoniae and is recognized as a nonspecific inflammatory marker. When brain tissue is damaged, CRP rises rapidly, reflecting tissue damage severity and potentially contributing to further damage in ischemic stroke. Elevated CRP levels are associated with poor prognosis and high mortality in subarachnoid hemorrhage. The introduction of high-sensitivity CRP (hs-CRP) has enhanced its role in clinical medicine by measuring lower CRP levels relevant for preclinical vascular inflammation in cardiovascular disease [52,53]. Inflammation in ischemic stroke can activate atherosclerosis through prooxidants like myeloperoxidase and superoxide anion, which activate

CRP formation via the NF-κB pathway. High CRP levels in stroke patients correlate with high lipoprotein-associated phospholipase A2 (Lp-PLA2) levels, suggesting CRP as a short-term mortality marker and a tool for cardiovascular risk stratification in healthy individuals. As an acute-phase reactant, CRP may rise during inflammatory syndromes, acute myocardial infarction, or atherosclerotic ischemia, serving as a marker for stroke pathogenesis. Proinflammatory cytokines, particularly IL-6, produced by cells like microglia and astrocytes, influence the disease course through cytotoxic effects and leukocyte activation. Elevated IL-6 in ischemic stroke may indicate independent factors or consequences of thrombosis, highlighting potential avenues for new therapies [54].

6.2. N-terminal Pro B-type Natriuretic Peptide

N-terminal pro B-type natriuretic peptide (NT-proBNP) is a key biomarker for cardiac function and stroke risk assessment. N-terminal natriuretic peptide fragments predict stroke and atrial fibrillation. Cardiac function is assessed through bioactive fragments atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) or their N-terminal prohormones: N-terminal proatrial natriuretic peptide (NT-proANP) and NT-proBNP. Elevated levels of these peptides indicate left ventricular systolic dysfunction, particularly in mild cases. Research shows that high NT-proBNP levels correlate with adverse outcomes following acute ischemic stroke, supporting its role in secondary stroke prevention and guiding antithrombotic therapy [55,56]. Additionally, studies explore the relationship between NT-proBNP and stroke subtypes, mortality, and cardioembolic sources. This biomarker, when combined with other cardiovascular indicators, aids in prognosis and treatment strategies. High brain natriuretic peptide levels in atrial fibrillation patients offer insights into cardiovascular events and stroke risk. As an accessible clinical marker, NT-proBNP plays a significant role in stroke prevention and therapy decisions [57].

6.3. S100B Protein

S100B contributes to several aspects of the inflammatory response [58]. In ischemic stroke, S100B serum levels are increased in proportion to infarct size, neurological deficits, and functional outcome. Serum S100B can differentiate brain damage from cerebral abnormalities [59]. S100B is overexpressed in ischemic brain injury [60]. Plasma S100B concentrations have prognostic value after aneurysmal subarachnoid hemorrhage and correlate with health-related quality of life and functional outcome at 1 year. Patients with elevated S100B levels have a higher risk of haemorrhagic transformation than patients with low or normal S100B levels following thrombolytic therapy. Serum S100B improves prediction of symptomatic intracranial haemorrhage and brain oedema after ischemic stroke. S100B functions as an outcome predictor in severe traumatic brain injury. Early CSF and serum concentrations of S100B have prognostic value in traumatic brain injury and subarachnoid haemorrhage. Cerebrospinal fluid S100B levels correlate strongly with brain atrophy in Alzheimer's disease [60].

7. Diagnostic Approaches

Laboratory assays and imaging techniques are crucial for identifying procoagulant states and thrombosis time courses. Assessing hypercoagulability is difficult as current tests fail to capture the relevant pathophysiological processes. Conventional tests like prothrombin time and activated partial thromboplastin time only indicate abnormalities through reduced coagulation factor concentrations, limiting their utility for thrombotic risk assessment since they focus on "clot-formation" rather than "thrombin generation." Detecting hypercoagulability in vitro is best achieved through platelet and plasma factor-driven thrombin generation. Clinically, low plasma clotting times and elevated clotting times dependent on procoagulant phospholipids, along with raised fibrinogen levels, suggest hypercoagulability. The role of D-dimer in diagnosing conditions like deep vein thrombosis and stroke is well recognized, though its prognostic significance is debated. Tracking D-dimer levels and the D-dimer/fibrinogen ratio could mitigate these uncertainties. Imaging techniques provide anatomical insights into thrombotic processes [60,61]. Ultrasound and venography are preferred over contrast venography and angiography for early

venous thromboembolism diagnosis and follow-up, while angiography remains essential for many arterial thrombosis cases despite advancements in computed tomography and magnetic resonance imaging. Increased exposure to thrombin relates to proximal thrombus formation, whereas lower doses can lead to distal embolization, with maximum distal thrombus size unchanging despite additional thrombin exposure, explained by a wedging mechanism that captures micro-emboli [62].

7.1. Laboratory Tests

Hypercoagulability refers to the increased tendency of blood to clot, raising the risk of thrombosis, which can result in stroke by disrupting blood supply to the brain. It can be categorized as primary, due to inherited coagulation disorders, or secondary, arising from illnesses like cancer or inflammation. Various laboratory tests help investigate hypercoagulability, while additional tests and imaging methods are used to detect thrombosis and stroke [62,63].

7.2. Imaging Techniques

Imaging methods play a crucial role in the diagnosis and management of thrombosis and stroke. Doppler ultrasound is an effective technique to confirm venous thrombosis and establish the presence of venous obstruction. Further, CT or MRI of the brain and its vessels can differentiate various types of stroke and identify the territories of cerebral arterial occlusion. Conventional aortography remains the most sensitive technique for detecting aortic atheroma. CT scanning and MRI can also reveal nonvascular abnormalities that may mimic stroke [64,65].

8. Management of Hypercoagulability

Management of hypercoagulability is crucial for preventing thrombosis and related complications like stroke and coronary artery disease. Anticoagulation therapy mainly uses vitamin K antagonists, which suppress the synthesis of vitamin K-dependent coagulation factors and proteins, thereby reducing coagulation potential. If oral anticoagulants are unsuitable, heparins offer an alternative by enhancing antithrombin activity. Management also includes treating underlying disorders like cancer and nephrotic syndrome [66]. Moreover, addressing hypercoagulability involves both pharmacological interventions and lifestyle modifications to reduce thrombophilic conditions. Many cases of venous thrombosis and pulmonary embolism in younger populations underline this need. Substituting high-risk contraceptives, maintaining an active lifestyle, and following a healthy diet with weight control are vital strategies to decrease hypercoagulability-related complications [67].

8.1. Anticoagulation Therapy

Anticoagulants are crucial for treating hypercoagulability, thrombosis, and stroke, with the choice depending on disease severity. Warfarin, a mainstay for hypercoagulability, stands out as it effectively treats various thrombosis, including deep vein thrombosis. This oral anticoagulant inhibits vitamin K, reducing coagulation factors II, VII, IX, and X in the bloodstream. Additionally, it lowers anticoagulant proteins C and S, enhancing its effects. However, warfarin's major drawback is the need for continuous blood monitoring to maintain therapeutic anticoagulation levels [68,69].

8.2. Lifestyle Modifications

Lifestyle changes after stroke are pivotal for reducing the risk of recurrence and enhancing overall well-being. Common recommendations include smoking cessation, moderate-intensity exercise, limited alcohol consumption, adherence to a Mediterranean diet, and maintenance of a healthy body mass index [70]. However, the efficacy of these approaches is contingent upon the stroke subtype, with the largest benefits observed in patients with large artery atherosclerosis. Implementation challenges arise from stroke-related motor and cognitive impairments and post-stroke depression, which hinder participation and diminish quality of life. Long-term adherence remains difficult due to a lack of individualized, comprehensive programs tailored to specific

needs. Despite evidence supporting the importance of lifestyle modifications, many patients exhibit a preference for pharmacological approaches to risk reduction. Clinicians are therefore encouraged to emphasize both medical and lifestyle strategies in secondary stroke prevention, fostering greater patient acceptance and compliance [71-72].

9. Preventive Strategies for Thrombosis and Stroke

Stroke is a significant cause of morbidity and disability globally, stemming from blood flow disruption in cerebral arteries that causes cellular damage and neurological symptoms. It can result from thrombosis or embolism in ischemic strokes, and local bleeding in hemorrhagic strokes. The classification of strokes includes hemorrhagic, ischemic, and cryptogenic types. Transient ischemic attacks (TIAs) are short-lived neurological deficits lasting less than 24 hours, not considered strokes by WHO [72,73]. Hemorrhagic strokes often result in death, while ischemic strokes may improve with treatment. Ischemic strokes account for 87% of cases worldwide, particularly in Asia. A hypercoagulable state increases clot formation, boosting thrombosis risks. Investigating these conditions can lead to better therapeutic targets for prevention and treatment of stroke. Biochemical markers like D-dimers and fibrinogen are crucial for diagnosing and prognosticating thrombotic events. Emerging markers such as C-Reactive Protein, N-terminal pro B-type natriuretic peptide, and S-100B show promise in stroke pathophysiology [74].

10. Future Directions in Research

Advances in the identification of alternative and emerging biomarkers during large vessel occlusion stroke, and in understanding the interaction of the coagulation system with the endothelium and immune responses, emphasize the need for comparative evaluations of established markers in clinical practice. These developments also highlight the potential for novel thrombosis and stroke therapeutics. Large-scale prospective studies of multicenter cooperation are warranted for external validation of hemostatic molecular markers, particularly thrombin-antithrombin complex, plasmin-α2-antiplasmin complex, and soluble thrombomodulin, obtained proximal to the thrombus; such markers may serve as auxiliary factors for stroke risk stratification and therapeutic decision-making [75]. Extensive modeling of diverse prothrombotic genotypes old and new through biochemical and global tests, calibrated plasma clot substrate analysis, and computational systems biology generates an avalanche of candidate molecular triggers, many previously unknown for prothrombotic potential and predictions of influencing thrombotic risk. Global coagulation assays address the need for laboratory techniques capable of detecting hypercoagulation and quantifying risk. Illustration of the pathogenesis of venous thrombosis in vivo guides the qualitative and functional scope for such techniques [76,77].

10.1. Emerging Biomarkers

Biomarkers that are currently under investigation for coronary artery disease (CAD) offer insights into emerging candidate molecules capable of identifying both obstructive and severe CAD [78]. Several multicenter studies, including the Global Registry of Acute Coronary Events (GRACE), the Myocardial Ischemia National Audit Project (MINAP), and the European Society of Cardiology Multi-country Acute Coronary Syndrome Survey (ESC-ACS), reported a range of 10% to 20% in hospital mortality for myocardial infarction (MI) with ST segment elevation (STEMI) and non-ST segment elevation (NSTEMI). Hemostatic molecular markers obtained from blood drawn proximal to intracranial occlusive thrombi during mechanical thrombectomy provide novel information about acute stroke induced by large vessel occlusion (LVO). They are also reported to be relevant for therapeutic decision-making, although confirming their clinical applicability will require clarification through large-scale prospective studies [79].

10.2. Novel Therapeutics

A number of therapeutic approaches have recently been proposed for targeting hypercoagulability and thrombosis. Several anticoagulants (heparin, low-molecular weight heparin [LMWH], fondaparinux and rivaroxaban) and haemodilution could be applied for secondary prevention of

acute coronary syndrome (ACS), by targeting the hypercoagulability detected by a global haemostatic assay [8-]. Biological therapies (‘biologicals’), in which an antibody, a soluble receptor or an analogue of a physiological inhibitor is produced, were approved during the 1990s and have been widely used to treat haematological disorders and cancer [79,80].

11. Conclusion

Thrombosis is an intravascular blood clot formed by activated platelets and the coagulation cascade, which involves the sequential activation of zymogens and needs platelets and phospholipids. Coagulation occurs via intrinsic and extrinsic pathways, converging at factor X activation. The intrinsic pathway starts with negatively charged surfaces, while the extrinsic pathway begins with vessel wall breaks exposing tissue factor. Both produce thrombin, crucial for platelet activation and converting fibrinogen to fibrin. The accumulation of a clot is a hallmark of thrombosis. Stroke occurs when blood supply to the brain is interrupted, leading to cell death in minutes. Ischemic blood markers are important for predicting stroke characteristics. Acute ischemic stroke (AIS) is the most common type, showing symptoms like one-sided paralysis, speech difficulties, fatigue, seizures, or severe headaches. These symptoms often arise suddenly, affecting mobility and daily activities. Prevention focuses on reducing risk factors, surgical interventions, and anticoagulation for atrial fibrillation. Elevated erythrocyte sedimentation rate, C-reactive protein, and fibrinogen levels are nonspecific indicators.

10. Conclusion

Funding

There is no funding

Declaration of Competing Interest

The authors say they don't have any known personal or financial relationships or financial interests that could have seemed to affect the work in this study.

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