

Review

Lipid Metabolism, Statins and Bleeding Risk During Anticoagulant Therapy: Emerging Pharmacological Insights

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Abstract

Lipid metabolism, coagulation, inflammation, and vascular integrity are closely interconnected biological systems. Although statins are primarily prescribed to reduce low-density lipoprotein cholesterol (LDL-C) and prevent atherosclerotic cardiovascular disease, increasing evidence indicates that these agents exert multiple pharmacological effects beyond lipid lowering, including modulation of endothelial function, platelet activation, tissue factor expression, thrombin generation, fibrinolysis, and thrombo-inflammation. These pleiotropic properties have generated growing interest in the potential role of statins as adjunctive modulators of thrombotic risk in patients receiving anticoagulant therapy. Venous thromboembolism, which includes deep vein thrombosis and pulmonary embolism, is a major clinical setting in which anticoagulant treatment reduces recurrence and mortality but exposes patients to bleeding complications. Observational studies and registry-based analyses suggest that statin use may be associated with improved outcomes among anticoagulated patients with venous thromboembolism, particularly for all-cause mortality and early survival after pulmonary embolism. At the same time, emerging evidence suggests that very low LDL-C concentrations may be associated with increased bleeding risk during anticoagulation, raising important questions regarding the relationship between lipid availability, vascular stability, platelet function, and hemostatic balance. This review summarizes current pharmacological and clinical evidence linking lipid metabolism, statin therapy, anticoagulation, thrombosis, and bleeding. Particular attention is devoted to the mechanisms through which statins influence hemostatic pathways, the clinical evidence derived from venous thromboembolism cohorts, and the potential implications of LDL-C levels for personalized bleeding risk assessment. Future strategies that integrate lipid profiles, thrombotic and bleeding risk, and pharmacological modulation of coagulation may contribute to more individualized antithrombotic management.

Keywords: Hydroxymethylglutaryl-CoA reductase inhibitors; cholesterol; venous thromboembolism; pulmonary embolism; venous thrombosis; anticoagulants; hemostasis; hemorrhage; blood coagulation; precision medicine; LDL

1. Introduction

Anticoagulant therapy is the cornerstone of treatment for venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE). Over recent decades, advances in anticoagulant pharmacology have substantially improved the prevention of thrombus extension, recurrence, and VTE-related mortality. Nevertheless, anticoagulant treatment remains intrinsically associated with the risk of bleeding, which represents one of the major determinants of clinical decision-making in both acute and extended treatment phases [1,2]. Consequently, the identification of clinical, biological, and pharmacological factors capable of influencing the balance between thrombotic protection and hemorrhagic risk remains a central priority in contemporary vascular medicine.

Traditionally, lipid metabolism and hemostasis have been considered distinct biological domains. Lipopro-

teins were mainly interpreted within the framework of atherosclerosis and arterial cardiovascular prevention, whereas coagulation pathways were primarily investigated in relation to thrombosis and anticoagulant therapy. However, increasing experimental and clinical evidence indicates that these systems are deeply interconnected. Cholesterol-rich membranes influence platelet activation, endothelial function, coagulation protein expression, and inflammatory signaling. In parallel, lipid-lowering therapies, particularly statins, may modulate hemostatic pathways through mechanisms that extend beyond low-density lipoprotein cholesterol (LDL-C) reduction [3,4].

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of cholesterol biosynthesis, and are among the most widely prescribed drugs worldwide. Their efficacy in reducing major atherosclerotic cardiovascular events is firmly estab-



lished. However, statins also exert so-called pleiotropic effects, including improvement of endothelial nitric oxide bioavailability, reduction of oxidative stress, attenuation of vascular inflammation, modulation of platelet reactivity, and downregulation of tissue factor expression [5,6]. These pharmacological actions provide a plausible biological rationale for investigating whether statins may influence venous thrombosis, anticoagulant outcomes, and bleeding risk.

Several lines of evidence suggest that statins may exert antithrombotic effects relevant to VTE. Experimental studies have shown that statins may reduce thrombin generation, impair tissue factor-mediated coagulation activation, enhance thrombomodulin expression, modulate fibrin clot structure, and improve fibrinolytic potential [7,8]. Clinical and observational data have also suggested possible associations between statin therapy and reduced VTE occurrence or improved outcomes after VTE, although the evidence remains heterogeneous and largely non-randomized [9].

The potential interaction between statin therapy and anticoagulant treatment is particularly important. Patients with VTE frequently have comorbidities such as atherosclerotic cardiovascular disease, diabetes mellitus, chronic kidney disease, obesity, and advanced age, all of which may influence both statin use and clinical outcomes during anticoagulation. In this setting, large international registries have provided valuable real-world information. Analyses from the Registro Informatizado de Enfermedad TromboEmbólica (RIETE) Registry have reported that statin use at baseline was associated with lower mortality in patients receiving anticoagulant therapy for VTE, as well as improved early outcomes in patients with acute symptomatic PE and in those with DVT [10,11,12]. Although these findings do not prove causality, they support the hypothesis that statins may influence prognosis in anticoagulated VTE populations.

A fundamental distinction is required between the biological consequences of low circulating LDL-C and the pleiotropic pharmacological effects of statins. Statin therapy generally reduces LDL-C, but it also inhibits mevalonate-derived isoprenoid synthesis and modulates Rho, Rac, and Ras signaling independently of the achieved lipid concentration. Conversely, very low LDL-C may result from pharmacological treatment, genetic determinants, chronic inflammation, cancer, malnutrition, liver disease, or frailty. Therefore, associations involving statin exposure should not automatically be attributed to LDL-C reduction, and associations involving low LDL-C should not be interpreted as evidence of a statin-specific effect.

A complementary and emerging issue concerns the relationship between LDL-C levels and bleeding risk. The paradigm of cardiovascular prevention has long emphasized that “lower is better” for LDL-C reduction, especially in patients at high or very high atherosclerotic risk. However, the hemostatic implications of very low LDL-C

concentrations remain incompletely understood. Cholesterol contributes to cellular membrane structure, endothelial stability, platelet function, and vascular integrity. Therefore, extremely low LDL-C levels might theoretically alter mechanisms involved in hemostasis or increase susceptibility to bleeding in selected clinical contexts [13,14].

Recent clinical evidence has raised renewed interest in this topic. A large multinational analysis from the RIETE Registry reported an association between low LDL-C concentrations and increased risk of major bleeding in patients receiving anticoagulant therapy for VTE [15]. This observation is clinically relevant because LDL-C is not currently included in conventional bleeding risk scores used for anticoagulated patients. If confirmed by further studies, lipid parameters may represent additional biomarkers for refining bleeding risk stratification, particularly in complex patients requiring long-term antithrombotic treatment.

This review aims to summarize current pharmacological and clinical evidence linking lipid metabolism, statins, coagulation, thrombosis, and bleeding during anticoagulant therapy. First, we discuss the biological relationship between lipoproteins and hemostatic balance. Second, we review the pleiotropic effects of statins on coagulation, platelet function, endothelial biology, inflammation, and fibrinolysis. Third, we summarize clinical evidence regarding statins and outcomes in VTE, with particular attention to real-world registry data. Finally, we discuss emerging evidence on LDL-C levels and bleeding risk during anticoagulation and propose future perspectives for integrating lipid profiles into personalized antithrombotic management.

Literature Search Strategy

This narrative review was developed through a structured literature search of PubMed/MEDLINE, Scopus, and Web of Science. The search included articles published from database inception to June 2026 and used combinations of the following terms: “statins”, “lipid metabolism”, “LDL cholesterol”, “very low LDL cholesterol”, “anticoagulant therapy”, “direct oral anticoagulants”, “venous thromboembolism”, “pulmonary embolism”, “deep vein thrombosis”, “major bleeding”, “intracranial hemorrhage”, “gastrointestinal bleeding”, “platelet function”, “lipid rafts”, “endothelial glycocalyx”, “immunothrombosis”, “neutrophil extracellular traps”, “proteomics”, and “drug–drug interactions”. Priority was given to randomized controlled trials, systematic reviews and meta-analyses, international guidelines, large prospective registries, independent observational cohorts, and experimental studies providing mechanistic information. Articles were selected according to their relevance to the relationship between lipid metabolism, lipid-lowering therapy, coagulation, thrombosis, and bleeding during anticoagulant treatment. Reference lists of the selected publications were also reviewed to identify additional relevant studies. Because this was a narrative rather than a systematic review, no formal risk-of-bias assessment or quantitative evidence synthesis was performed.

2. Lipid Metabolism and Hemostatic Balance

2.1 Lipoproteins and Coagulation Pathways

The relationship between lipid metabolism and coagulation has attracted increasing scientific interest over the last two decades. Although lipoproteins are traditionally regarded as mediators of atherosclerosis and cardiovascular disease, growing evidence indicates that they also participate in the regulation of hemostatic processes. Both experimental and clinical studies have demonstrated that cholesterol metabolism influences coagulation activation, fibrinolysis, endothelial function, and platelet behavior, suggesting that lipid homeostasis contributes to the maintenance of thrombohemorrhagic balance [16,17].

Low-density lipoproteins (LDL) can directly interact with vascular and circulating cells involved in coagulation. Oxidized LDL particles stimulate tissue factor expression on monocytes and endothelial cells, thereby promoting activation of the extrinsic coagulation pathway and thrombin generation [18]. In addition, LDL particles may enhance the expression of adhesion molecules, increase oxidative stress, and contribute to endothelial dysfunction, creating a prothrombotic vascular environment [19].

Several epidemiological studies have reported associations between lipid abnormalities and thrombotic disorders. Elevated LDL-C concentrations have been linked to increased levels of coagulation factors, including factor VII, factor VIII, and fibrinogen, all of which are known determinants of thrombotic risk [20]. Conversely, lipid-lowering interventions have been associated with reductions in coagulation activation markers, suggesting a potential mechanistic connection between cholesterol metabolism and thrombogenesis [21].

The interaction between lipoproteins and coagulation appears particularly relevant in venous thromboembolism. Unlike arterial thrombosis, which is primarily driven by atherosclerotic plaque rupture and platelet activation, venous thrombosis is characterized by a greater contribution of coagulation activation and fibrin formation. Nevertheless, increasing evidence suggests that inflammatory and metabolic factors common to both arterial and venous diseases may partially explain the overlap between cardiovascular risk factors and VTE occurrence [22].

Experimental models have demonstrated that hypercholesterolemia may increase thrombin generation and alter fibrin clot structure, resulting in denser fibrin networks that are more resistant to fibrinolysis [23]. Such modifications may favor clot persistence and thrombus propagation. These observations provide a biological rationale for investigating whether therapies targeting cholesterol metabolism could influence thrombotic outcomes beyond their traditional cardiovascular indications.

2.2 LDL-Cholesterol and Platelet Function

Platelets play a central role in hemostasis and thrombosis, and accumulating evidence suggests that lipid

metabolism substantially influences platelet biology. Cellular membranes are highly enriched in cholesterol, which regulates membrane fluidity, receptor organization, intracellular signaling, and platelet responsiveness to agonists [24].

A substantial proportion of membrane cholesterol is organized within cholesterol- and sphingolipid-rich microdomains known as lipid rafts. These structures act as dynamic signaling platforms that spatially organize platelet receptors and downstream signaling molecules. Platelet glycoprotein VI, glycoprotein Ib-IX-V, integrin $\alpha\text{IIb}\beta 3$, Fc gamma receptor IIA (Fc γ RIIA), Src-family kinases, and phosphoinositide signaling components may cluster within or interact with these domains during platelet activation. Cholesterol depletion can disrupt receptor colocalization and attenuate signaling, whereas cholesterol enrichment may increase membrane order and facilitate platelet responsiveness [24].

This mechanism provides a plausible, although not yet clinically proven, link between very low cholesterol availability and impaired primary hemostasis. Excessive disruption of cholesterol-rich membrane microdomains could theoretically alter receptor clustering, calcium mobilization, granule secretion, integrin activation, and procoagulant membrane exposure. However, circulating LDL-C is not a direct measure of platelet membrane cholesterol, and the relationship between plasma LDL-C concentrations, membrane composition, and clinically relevant bleeding remains incompletely defined. This distinction should be emphasized to avoid interpreting associative clinical findings as evidence of a direct causal membrane effect.

Elevated LDL-C levels have been associated with increased platelet activation and aggregation. Oxidized LDL particles interact with platelet scavenger receptors, enhancing platelet reactivity and promoting thrombus formation [25]. Hypercholesterolemia has also been linked to increased expression of platelet surface receptors involved in adhesion and aggregation, including glycoprotein IIb/IIIa and P-selectin [26].

Conversely, lipid-lowering therapies may attenuate platelet activation through multiple mechanisms. Statin treatment has been associated with reduced platelet aggregation, lower thromboxane production, and diminished platelet-leukocyte interactions [27]. These effects may occur independently of LDL-C reduction, further supporting the concept of pleiotropic pharmacological actions.

The relationship between LDL-C levels and platelet function may also have implications for bleeding risk. Extremely low cholesterol availability could theoretically modify platelet membrane organization and receptor-dependent signaling involved in primary hemostasis. However, this hypothesis is based predominantly on experimental models, and plasma LDL-C levels should not be considered a direct surrogate for platelet membrane cholesterol content. Although evidence remains limited, several obser-

vational studies have suggested that very low LDL-C levels may be associated with an increased incidence of hemorrhagic events in selected populations, particularly among patients receiving antithrombotic therapy [28].

These observations highlight the complexity of lipid-hemostasis interactions. Whereas elevated LDL-C levels may contribute to thrombosis through enhanced platelet activation and coagulation, excessively low LDL-C concentrations could potentially impair physiological hemostatic mechanisms, emphasizing the importance of achieving an optimal balance rather than focusing exclusively on maximal cholesterol reduction.

2.3 Endothelial Function, Immunothrombosis, and Metabolic Regulation of Hemostasis

The vascular endothelium serves as a critical interface between lipid metabolism and hemostatic regulation. Under physiological conditions, endothelial cells maintain an antithrombotic surface through the production of nitric oxide, prostacyclin, thrombomodulin, and tissue plasminogen activator. Endothelial dysfunction disrupts these protective mechanisms and promotes thrombosis [29].

Dyslipidemia contributes substantially to endothelial injury. LDL particles, particularly when oxidized, induce oxidative stress, reduce nitric oxide bioavailability, and stimulate inflammatory signaling pathways within the vascular wall [30]. These effects increase leukocyte recruitment, endothelial activation, and expression of procoagulant mediators, ultimately favoring thrombus formation.

Recent research has emphasized the concept of thromboinflammation, a bidirectional process linking inflammation and coagulation. Contemporary understanding of this interaction has evolved toward the broader concept of immunothrombosis, in which innate immune mechanisms, platelets, endothelial cells, and coagulation proteins cooperate to contain tissue injury or infection but may also promote pathological thrombus formation. Neutrophil extracellular traps (NETs), composed of extracellular DNA, histones, neutrophil elastase, and myeloperoxidase, provide a scaffold for platelet adhesion, concentrate tissue factor and coagulation proteins, and may impair endogenous fibrinolysis [31,32]. NET formation is therefore increasingly recognized as a mechanistic bridge between inflammation, venous thrombosis, and altered fibrin clot properties.

Recent evidence also suggests that statins may modulate this pathway independently of their LDL-C-lowering effect. In patients with coronary artery disease, intensive atorvastatin or rosuvastatin treatment reduced circulating NET-related proteins, including citrullinated histone H3, myeloperoxidase, and neutrophil elastase. These changes were associated with reduced inflammation and more favorable fibrin clot properties but were not directly correlated with the magnitude of LDL-C reduction [31]. Although these findings were not obtained in anticoagulated VTE populations, they provide a contemporary pharmacological

mechanism that warrants investigation in venous thrombosis.

The endothelial glycocalyx represents another emerging component of thrombo-inflammatory regulation. This carbohydrate-rich luminal layer contributes to vascular permeability control, mechanotransduction, nitric oxide signaling, and the inhibition of leukocyte and platelet adhesion. Glycocalyx degradation exposes endothelial adhesion molecules, promotes vascular permeability, and may facilitate coagulation activation and microvascular injury [33]. Whether statins or other lipid-lowering interventions preserve glycocalyx integrity sufficiently to influence bleeding or thrombotic outcomes remains uncertain.

Platelets are also metabolically active immune-effector cells. Their activation requires rapid reprogramming of glycolysis, oxidative phosphorylation, fatty-acid utilization, and mitochondrial function. This platelet immunometabolism influences granule secretion, integrin activation, procoagulant phosphatidylserine exposure, and platelet-leukocyte interactions [34]. Consequently, changes in membrane lipid composition or intracellular metabolic signaling may modify both thrombotic responsiveness and the efficacy of physiological hemostasis.

Finally, high-throughput proteomic approaches are expanding the characterization of coagulation and thrombo-inflammatory phenotypes. Proteomic signatures may identify coordinated changes in coagulation factors, complement proteins, inflammatory mediators, endothelial proteins, and fibrinolytic pathways that are not captured by conventional coagulation tests. However, these approaches remain primarily investigational and require prospective validation before integration into bleeding or thrombosis prediction models.

Inflammatory cytokines such as interleukin-6 and tumor necrosis factor- α stimulate tissue factor expression and thrombin generation, while coagulation proteases amplify inflammatory responses through activation of protease-activated receptors [35]. Lipid abnormalities may contribute to this vicious cycle by promoting both inflammatory and procoagulant pathways.

These lipid-sensitive endothelial and inflammatory pathways provide a biological substrate on which lipid-lowering treatments may act. Their pharmacological modulation by statins is discussed separately in Section 3. Experimental and clinical studies have demonstrated reductions in C-reactive protein levels, improvement in endothelial-dependent vasodilation, attenuation of oxidative stress, and modulation of inflammatory signaling pathways during statin therapy [36,37]. These mechanisms may contribute to the beneficial effects observed in patients with thrombotic disorders.

The emerging concept that lipid metabolism, inflammation, endothelial biology, and coagulation are tightly interconnected has important clinical implications. It suggests that pharmacological interventions targeting lipid

pathways may influence thrombotic and hemorrhagic outcomes through mechanisms that are not entirely captured by conventional lipid measurements. Understanding these interactions is therefore essential for the development of more personalized antithrombotic strategies, particularly in patients requiring long-term anticoagulant therapy [38].

3. Pharmacological Effects of Statins Beyond Lipid Lowering

Statins influence hemostatic pathways through both LDL-C-dependent and LDL-C-independent mechanisms. The following sections focus specifically on their pharmacological actions, avoiding repetition of the general lipid-hemostasis relationships described in Section 2 [39,40].

Many of these pharmacological actions are mediated through inhibition of isoprenoid synthesis, leading to reduced activation of intracellular signaling proteins such as Rho, Rac, and Ras GTPases. Consequently, statins influence numerous cellular pathways involved in vascular homeostasis and thrombosis independently of LDL-C reduction [41]. These observations have generated considerable interest regarding the potential role of statins as modulators of thrombotic and bleeding risk in patients receiving anticoagulant therapy.

3.1 LDL-C Reduction and Statin Pleiotropy as Distinct Biological Exposures

LDL-C lowering and statin pleiotropy represent related but biologically distinct exposures. The lipid-lowering effect of statins is mediated primarily by hepatic HMG-CoA reductase inhibition, increased LDL-receptor expression, and enhanced clearance of circulating apoB-containing (ApoB) particles. In contrast, several non-lipid effects derive from reduced synthesis of isoprenoid intermediates and subsequent modulation of small GTP-binding proteins, endothelial nitric oxide synthase, oxidative signaling, inflammatory transcription, tissue factor expression, and platelet activation.

This distinction has important implications for interpretation of the clinical literature. A patient with very low LDL-C who is not receiving a statin may not share the same thrombo-inflammatory phenotype as a statin-treated patient with an identical LDL-C concentration. Similarly, statin-associated reductions in inflammation, NET-related proteins, or coagulation activation may occur without a direct correlation with the magnitude of LDL-C reduction [31]. Future studies should therefore analyze statin exposure, statin intensity, treatment duration, baseline LDL-C, and achieved LDL-C as separate variables rather than treating them as interchangeable markers.

3.2 Pharmacological Heterogeneity Among Statins

Statins should not be considered a pharmacologically homogeneous class. Lipophilic agents, including simvastatin, atorvastatin, lovastatin, and fluvastatin, generally ex-

hibit greater passive diffusion across extrahepatic cell membranes. Hydrophilic agents, particularly pravastatin and rosuvastatin, show greater hepatoselectivity and depend more extensively on transporter-mediated uptake. Pitavastatin has intermediate physicochemical characteristics and limited Cytochrome P450 (CYP)-mediated metabolism [42].

These differences may influence tissue penetration, extrahepatic anti-inflammatory effects, platelet and endothelial actions, and susceptibility to pharmacokinetic drug interactions. Simvastatin, lovastatin, and atorvastatin are substantially metabolized through cytochrome P450 3A4 (CYP3A4), whereas rosuvastatin undergoes limited metabolism through cytochrome P450 2C9 (CYP2C9) and cytochrome P450 2C19 (CYP2C19), and pravastatin is largely cleared through non-CYP pathways. Fluvastatin is mainly metabolized by CYP2C9.

The clinical relevance of these differences for bleeding during anticoagulant therapy remains uncertain. Lipophilic statins might theoretically exert stronger extrahepatic effects, but they may also be more susceptible to interactions with CYP3A4 inhibitors. Conversely, hydrophilic statins may have lower tissue penetration but are not devoid of anti-inflammatory or antithrombotic effects. Current observational VTE studies are generally underpowered to evaluate individual agents, doses, or lipophilicity, and class-wide conclusions should therefore be interpreted cautiously.

3.3 Anti-Inflammatory Effects

Inflammation represents a fundamental link between atherosclerosis, thrombosis, and vascular dysfunction. Chronic inflammatory activation contributes to endothelial injury, coagulation activation, platelet aggregation, and thrombus formation. Statins have consistently demonstrated anti-inflammatory properties in both experimental and clinical settings [43].

Several studies have shown that statin therapy reduces circulating concentrations of inflammatory biomarkers, including high-sensitivity C-reactive protein (hs-CRP), interleukin-6, and tumor necrosis factor- α [44]. These effects appear partially independent of lipid reduction and may contribute significantly to the observed cardiovascular benefits of statin treatment.

The JUPITER trial provided compelling clinical evidence supporting the relevance of inflammation reduction. In this study, rosuvastatin significantly reduced cardiovascular events among apparently healthy individuals with elevated hs-CRP levels despite relatively normal LDL-C concentrations, suggesting that anti-inflammatory mechanisms contribute substantially to clinical outcomes [37].

Inflammation also plays a critical role in venous thrombosis. Activation of leukocytes, endothelial cells, and inflammatory cytokines promotes tissue factor expression and thrombin generation. Consequently, the anti-inflammatory properties of statins may represent one mech-

anism through which these agents influence thrombotic outcomes in VTE patients [45].

3.4 Endothelial Protection and Vascular Homeostasis

The vascular endothelium is a major target of statin therapy. Endothelial dysfunction is characterized by reduced nitric oxide bioavailability, increased oxidative stress, enhanced leukocyte adhesion, and impaired antithrombotic activity. These alterations contribute to both arterial and venous thrombosis [46].

Statins improve endothelial function through several complementary mechanisms. They enhance endothelial nitric oxide synthase expression, increase nitric oxide production, reduce oxidative stress, and inhibit the generation of reactive oxygen species [47]. Furthermore, statins attenuate endothelial activation by reducing the expression of adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin [48].

Improved endothelial homeostasis may directly influence coagulation and fibrinolysis. Endothelial cells regulate thrombomodulin expression, tissue factor pathway inhibitor activity, and plasminogen activator release. By restoring endothelial function, statins contribute to the maintenance of a less thrombogenic vascular environment [49].

These vascular effects are particularly relevant in patients receiving anticoagulant therapy because endothelial dysfunction is increasingly recognized as an important determinant of recurrent thrombosis and adverse clinical outcomes.

3.5 Effects on Coagulation Pathways

Among the most intriguing pleiotropic effects of statins are their direct interactions with coagulation pathways. Experimental studies have demonstrated that statins may reduce tissue factor expression on monocytes, macrophages, and endothelial cells, thereby attenuating activation of the extrinsic coagulation cascade [50].

Statin therapy has also been associated with reductions in thrombin generation markers, including prothrombin fragment 1 + 2 and thrombin-antithrombin complexes [51]. These findings suggest that statins may decrease the intensity of coagulation activation even in the absence of changes in anticoagulant treatment.

Additional studies have reported favorable effects on coagulation factor concentrations. Reductions in factor VII activity, factor VIII levels, and fibrinogen concentrations have been observed during statin therapy, although results remain somewhat heterogeneous across studies [52]. Nevertheless, the overall evidence supports a modest but consistent antithrombotic effect.

A comprehensive review by Siniscalchi and colleagues [53] summarized the available evidence regarding the effects of statins on blood clotting, highlighting multiple

mechanisms through which statins may influence thrombin generation, fibrin clot architecture, endothelial function, and platelet activity. The authors emphasized that the cumulative impact of these biological effects may contribute to the favorable clinical outcomes observed in thrombotic disorders.

3.6 Effects on Fibrinolysis

Fibrinolysis represents a crucial component of hemostatic balance because it regulates clot dissolution and prevents excessive thrombus persistence. Several studies suggest that statins may enhance endogenous fibrinolytic activity [54].

Statin therapy has been associated with increased tissue plasminogen activator (tPA) activity and reduced concentrations of plasminogen activator inhibitor-1 (PAI-1), the principal inhibitor of fibrinolysis [55]. Through these mechanisms, statins may promote clot resolution and reduce thrombus burden.

Experimental investigations have also demonstrated that statins can modify fibrin clot structure, resulting in less compact fibrin networks that are more susceptible to fibrinolytic degradation [54]. Such alterations may be particularly relevant in venous thrombosis, where fibrin-rich clots constitute the predominant pathological substrate.

Although the magnitude of these effects remains difficult to quantify in clinical practice, enhancement of fibrinolytic potential likely contributes to the overall antithrombotic profile of statin therapy.

3.7 Effects on Platelet Activation

Platelet activation represents another important target of statin therapy. Beyond their lipid-lowering actions, statins appear capable of reducing platelet reactivity through multiple mechanisms involving membrane cholesterol composition, oxidative stress reduction, and modulation of intracellular signaling pathways [56].

Clinical studies have reported reductions in platelet aggregation, platelet-leukocyte interactions, and expression of platelet activation markers among statin-treated individuals [57]. Furthermore, statins may decrease thromboxane A₂ synthesis and improve responsiveness to endogenous antiplatelet mediators such as nitric oxide and prostacyclin [58].

The clinical significance of these observations remains incompletely understood, particularly in patients already receiving anticoagulant therapy. Nevertheless, attenuation of platelet activation may represent an additional mechanism contributing to the favorable outcomes associated with statin use in thrombotic disorders.

Overall, the available evidence supports the concept that statins exert a broad spectrum of biological effects affecting multiple components of hemostasis. These pleiotropic properties provide a compelling pharmacological rationale for investigating their potential role as ad-

Table 1. Pleiotropic effects of statins on hemostatic pathways.

Hemostatic component	Mechanism of statin action	Potential clinical implications
Endothelial function	Increased nitric oxide bioavailability; reduced oxidative stress	Improved vascular homeostasis and reduced thrombogenicity
Inflammation	Reduction of CRP, IL-6, TNF- α and inflammatory signaling pathways	Attenuation of thromboinflammation and vascular injury
Tissue factor expression	Downregulation of tissue factor on monocytes and endothelial cells	Reduced activation of the extrinsic coagulation pathway
Thrombin generation	Decreased coagulation activation and thrombin formation	Potential reduction in thrombotic risk
Coagulation factors	Reduction in factor VII, factor VIII and fibrinogen activity	Lower procoagulant potential
Fibrinolysis	Increased tissue plasminogen activator activity and reduced PAI-1 levels	Enhanced clot resolution
Fibrin clot structure	Formation of less compact and more fibrinolysis-sensitive fibrin networks	Improved endogenous thrombus degradation
Platelet activation	Reduced platelet aggregation, thromboxane synthesis and platelet-leukocyte interactions	Decreased platelet-mediated thrombosis
Endothelial adhesion molecules	Reduced VCAM-1, ICAM-1 and E-selectin expression	Lower leukocyte recruitment and vascular inflammation
Thromboinflammation	Modulation of inflammatory-coagulation crosstalk	Reduced thrombotic propagation and vascular injury

Legend: Summary of the principal biological mechanisms through which statins may influence coagulation, fibrinolysis, platelet activation, endothelial function, inflammation, and thromboinflammatory processes. These effects extend beyond LDL-cholesterol reduction and may contribute to the modulation of thrombotic and hemorrhagic risk in patients receiving anticoagulant therapy. CRP, C-reactive protein; IL-6, interleukin-6; TNF- α , tumor necrosis factor- α ; PAI-1, plasminogen activator inhibitor-1; VCAM-1, vascular cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; LDL, low-density lipoprotein.

junctive modulators of thrombosis, bleeding, and clinical outcomes in anticoagulated patients. The following section reviews the clinical evidence supporting this hypothesis, with particular attention to patients with venous thromboembolism.

The pleiotropic effects of statins on the various components of hemostasis are summarized in Table 1.

4. Clinical Evidence Linking Statins to Outcomes in Venous Thromboembolism

The biological effects of statins on coagulation, inflammation, endothelial function, and fibrinolysis have stimulated considerable interest regarding their potential impact on clinical outcomes in patients with VTE. While randomized controlled trials specifically designed to evaluate statins as adjunctive therapies in VTE are lacking, a growing body of observational evidence, registry-based analyses, and meta-analyses suggests that statin therapy may confer clinically meaningful benefits in this population [59,60].

Evidence regarding statins and VTE is not limited to registry-based analyses. Randomized evidence from the JUPITER trial suggested a reduction in incident symptomatic VTE with rosuvastatin, while population-based cohorts and meta-analyses have evaluated both first and recurrent VTE across different healthcare systems. These studies generally suggest a possible protective association, but effect estimates vary according to study design, statin ex-

posure definition, VTE phenotype, follow-up duration, and adjustment for cardiovascular comorbidities. Importantly, evidence concerning incident or recurrent VTE should be distinguished from evidence concerning mortality after an established VTE event [61].

The hypothesis that statins could influence VTE outcomes emerged from observations indicating lower rates of thrombotic events among statin users. Subsequent epidemiological studies and post hoc analyses of cardiovascular trials suggested a potential reduction in incident VTE among patients receiving statin therapy, particularly with more intensive lipid-lowering regimens [9,62]. These findings prompted further investigation into the relationship between statin treatment and outcomes among patients with established VTE.

4.1 Statins and Mortality in Anticoagulated VTE Patients

One of the most clinically relevant questions concerns whether statin therapy influences survival among patients receiving anticoagulants for VTE. Mortality remains an important outcome despite advances in anticoagulant treatment, particularly among elderly patients and those with multiple comorbidities.

A large analysis from the RIETE Registry evaluated the association between statin use and all-cause mortality among patients receiving anticoagulant therapy for VTE [10]. This international registry-based study included thousands of patients with objectively confirmed VTE and

demonstrated that baseline statin therapy was associated with significantly lower mortality compared with non-use. Importantly, the association persisted after adjustment for multiple confounding variables, suggesting that the observed benefit could not be fully explained by differences in baseline cardiovascular risk profiles.

These findings attracted considerable attention because they supported the hypothesis that the pleiotropic effects of statins may extend beyond prevention of arterial cardiovascular events. Although causality cannot be established from observational data, the magnitude and consistency of the association suggested that statins might favorably influence outcomes through mechanisms involving coagulation, endothelial function, inflammation, or thromboinflammatory pathways [63].

Population-based cohorts and meta-analyses conducted independently of RIETE have reported associations between statin exposure and lower first or recurrent VTE risk, although the magnitude and consistency of these associations have varied. These external data partly support the biological plausibility of the RIETE findings but do not directly confirm a survival benefit after acute VTE because they frequently evaluated incident or recurrent thrombosis rather than mortality [64].

4.2 Statins and Outcomes in Acute Pulmonary Embolism

The potential role of statins in acute PE has been investigated using data from the RIETE Registry. In a multinational cohort study including patients with symptomatic PE, Siniscalchi and colleagues [11] evaluated the relationship between baseline statin use and 30-day mortality. The investigators found that patients receiving statins at the time of PE diagnosis experienced lower short-term mortality compared with non-users.

These observations are biologically plausible. Acute PE is characterized not only by mechanical obstruction of the pulmonary vasculature but also by inflammatory activation, endothelial dysfunction, platelet activation, and thrombin generation. Statins may attenuate several of these processes simultaneously, thereby reducing disease severity and improving clinical outcomes [65].

Importantly, current evidence is insufficient to recommend statins specifically for the treatment of acute PE. Nevertheless, available data suggest that ongoing statin therapy may represent a favorable prognostic marker and warrant further investigation in prospective studies.

4.3 Statins and Outcomes in Deep Vein Thrombosis

Deep vein thrombosis represents the most common presentation of VTE and remains associated with recurrent thrombosis, post-thrombotic syndrome, and long-term mortality. Given the central role of coagulation activation and inflammation in DVT pathophysiology, statins have been proposed as potential adjunctive modulators of disease progression and prognosis.

Recent RIETE data have provided important insights into this issue. In a multinational analysis focused specifically on patients with DVT, statin use was associated with lower mortality during follow-up [12]. The findings were consistent with previous observations in broader VTE populations and suggested that the potential benefits of statins are not restricted to PE.

These findings are biologically compatible with the pharmacological mechanisms discussed in Section 3; however, mechanistic plausibility does not establish causality in observational cohorts. Furthermore, they may influence clot composition and thrombus resolution, thereby reducing long-term complications associated with venous thrombosis [66].

Meta-analyses evaluating statins and VTE recurrence have produced heterogeneous findings. While some studies reported reductions in recurrent thrombotic events, others found more modest effects. Differences in study design, patient characteristics, statin type, treatment intensity, and duration of follow-up likely contribute to these inconsistencies [61]. Nevertheless, the overall direction of evidence generally favors a protective effect.

4.4 Beyond Mortality: Additional Prognostic Insights From VTE Registries

Independent population-based cohorts and meta-analyses have explored the relationship between statin therapy and the incidence or recurrence of VTE. Although several analyses reported a lower risk among statin users, heterogeneity in exposure ascertainment, adherence, statin intensity, comparator selection, and confounder adjustment limits direct comparison across studies. Moreover, a reduction in VTE incidence or recurrence cannot automatically be extrapolated to a reduction in short-term mortality after PE or DVT.

Taken together, RIETE analyses provide clinically relevant real-world evidence regarding outcomes after established VTE, whereas independent cohorts and meta-analyses provide complementary evidence regarding incident and recurrent events [67].

The convergence of these findings supports further research but remains insufficient to recommend initiation of statin therapy specifically for VTE prevention or treatment.

4.5 Current Limitations of Clinical Evidence

Despite encouraging observational findings, several limitations must be acknowledged. Most available studies evaluating statins in VTE populations are observational and therefore susceptible to residual confounding. Statin users frequently differ from non-users with respect to cardiovascular comorbidities, healthcare utilization, socioeconomic factors, and concomitant medications.

Furthermore, important questions remain unresolved. It is currently unclear whether the observed benefits differ according to statin potency, achieved LDL-C levels, dura-

tion of therapy, or concomitant use of direct oral anticoagulants versus vitamin K antagonists (VKAs). Similarly, the optimal patient subgroups most likely to benefit from statin therapy remain undefined.

An additional concern is the possibility of substantial baseline imbalance between statin users and non-users. Statin-treated patients may have greater cardiovascular comorbidity but may also differ in access to medical care, medication adherence, preventive behavior, functional status, nutritional condition, and intensity of clinical monitoring. Conversely, patients with cancer, advanced frailty, chronic inflammatory disease, liver dysfunction, malnutrition, or other wasting conditions may present with both lower LDL-C concentrations and a higher risk of mortality or bleeding. In such settings, low LDL-C may act as a marker of underlying disease severity rather than a direct determinant of hemorrhagic vulnerability.

Medication adherence is another potential source of bias because baseline prescriptions do not necessarily reflect continued exposure during follow-up. Healthy-adherer and healthy-user effects may therefore contribute to the apparent survival advantage observed among statin users. Although multivariable adjustment and sensitivity analyses reduce some measured confounding, they cannot eliminate unmeasured or time-dependent confounding. Accordingly, the associations reported in registry studies should be interpreted as hypothesis-generating statistical correlations and not as evidence that statins directly improve survival or that low LDL-C directly causes bleeding.

Randomized controlled trials specifically designed to investigate statins as adjunctive treatments in VTE are still lacking. Such studies would be necessary to establish causality and determine whether the favorable associations observed in registries can be translated into therapeutic recommendations [68].

Nevertheless, the available evidence suggests potentially clinically relevant associations between statin exposure and outcomes in anticoagulated VTE patients; however, their causal nature remains unproven. These observations provide the foundation for the next major question addressed in this review: whether lipid levels themselves, particularly LDL-C concentrations, influence bleeding risk during anticoagulant therapy.

4.6 Pharmacokinetic Interactions Between Statins and Direct Oral Anticoagulants

The concomitant use of statins and direct oral anticoagulants (DOACs) is common because cardiovascular disease, atrial fibrillation, and VTE frequently coexist. Potential drug–drug interactions depend mainly on shared CYP3A4 and P-glycoprotein pathways. Apixaban and rivaroxaban are substrates of P-glycoprotein and undergo variable CYP3A4 metabolism, whereas dabigatran is primarily a P-glycoprotein substrate and edoxaban has limited CYP3A4 involvement.

Simvastatin, lovastatin, and atorvastatin are CYP3A4 substrates, but they are not generally strong CYP3A4 or P-glycoprotein inhibitors. Therefore, statins alone are not expected to produce the marked increases in DOAC exposure observed with potent inhibitors such as azole antifungals, HIV protease inhibitors, or certain macrolides. Nevertheless, clinically relevant interactions may arise in the setting of polypharmacy, particularly when a statin and a DOAC are combined with an additional CYP3A4 or P-glycoprotein inhibitor.

Real-world evidence indicates that the concomitant use of rivaroxaban or apixaban with drugs exerting combined P-glycoprotein and moderate CYP3A4 inhibition may increase bleeding risk [69]. These findings do not establish that statins independently increase DOAC concentrations, but they emphasize the importance of evaluating the entire pharmacological regimen, renal function, age, and cumulative interaction burden rather than considering individual drug pairs in isolation.

From a practical perspective, pravastatin and rosuvastatin may be preferred when a lower potential for CYP3A4-mediated interaction is desirable. However, treatment decisions should remain individualized, and current evidence does not support routine statin discontinuation or DOAC dose modification solely because the two drug classes are prescribed together.

4.7 Clinical Heterogeneity and Relevant Patient Subgroups

4.7.1 DOACs Versus Vitamin K Antagonists

The potential relationship among statin exposure, LDL-C levels, and bleeding may differ according to the anticoagulant used. Vitamin K antagonists are influenced by dietary vitamin K intake, hepatic function, genetic variability, international normalized ratio control, and numerous drug interactions [70]. In contrast, DOAC exposure is more dependent on renal function, P-glycoprotein activity, CYP3A4 metabolism for selected agents, and adherence because of their shorter half-lives. Therefore, associations observed in mixed anticoagulant cohorts may not be homogeneous across treatment classes. Current evidence is insufficient to determine whether very low LDL-C has a stronger association with bleeding during DOAC or VKA therapy, and future analyses should include formal treatment-by-LDL-C interaction testing [71].

4.7.2 Statin Intensity

Statin intensity may influence both achieved LDL-C and the magnitude of non-lipid pharmacological effects [61]. However, observational comparisons of low-, moderate-, and high-intensity treatment remain vulnerable to confounding by indication.

4.7.3 East Asian Populations

East Asian populations deserve specific consideration because baseline rates and anatomical patterns of intracra-

nial hemorrhage, average body size, pharmacogenetic determinants, dietary factors, and anticoagulant exposure may differ from those observed in Western cohorts [72]. Some lipid-lowering and cerebrovascular studies have suggested population-related heterogeneity in hemorrhagic risk [73]. However, VTE-specific evidence examining the interaction between LDL-C, statins, and anticoagulant-related bleeding in East Asian patients remains limited. Generalization from predominantly European and North American cohorts should therefore be cautious.

4.7.4 Cancer-Associated Venous Thromboembolism

Cancer-associated VTE represents a particularly complex setting because malignancy simultaneously increases thrombosis, bleeding, inflammation, malnutrition, and mortality. Low LDL-C in patients with active cancer may reflect tumor-related inflammation, cachexia, reduced hepatic synthesis, or poor nutritional status rather than a direct hemostatic effect. Anticancer treatments may also modify CYP and P-glycoprotein activity and interact with DOACs or statins. Consequently, cancer may act both as a confounder and an effect modifier, and dedicated analyses should distinguish cancer type, disease stage, treatment status, and gastrointestinal or genitourinary tumor location [74,75].

4.7.5 Chronic Kidney Disease

Chronic kidney disease is associated with simultaneous prothrombotic and hemorrhagic tendencies resulting from platelet dysfunction, uremic toxins, endothelial abnormalities, anemia, altered drug clearance, and frequent polypharmacy. Renal impairment may increase DOAC exposure and modify the pharmacokinetics of selected statins. Moreover, low cholesterol in advanced kidney disease may represent inflammation and protein-energy wasting, creating a potential reverse-causality pathway. Therefore, the association between low LDL-C and bleeding should be assessed separately across renal-function categories [76,77].

5. Low LDL-Cholesterol Levels and Bleeding Risk During Anticoagulant Therapy

The concept that lower LDL-C levels invariably translate into improved clinical outcomes has become a cornerstone of contemporary cardiovascular prevention. Large randomized trials evaluating intensive statin therapy, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have consistently demonstrated progressive reductions in major cardiovascular events with increasingly lower LDL-C concentrations [78,79,80]. Consequently, current international guidelines advocate aggressive LDL-C lowering in patients at high and very high cardiovascular risk.

However, accumulating evidence suggests that the relationship between LDL-C and clinical outcomes may be more complex in patients receiving anticoagulant therapy.

While lower LDL-C concentrations appear beneficial for the prevention of atherosclerotic events, extremely low lipid levels may influence biological pathways involved in vascular integrity, endothelial homeostasis, platelet function, and hemostatic balance. These observations have raised growing interest in the possibility that LDL-C may also affect bleeding risk [81].

5.1 Biological Rationale Linking Low LDL-C Levels and Bleeding

Several mechanisms have been proposed to explain a potential association between very low LDL-C concentrations and hemorrhagic complications. Cholesterol is an essential structural component of cellular membranes and contributes to membrane stability, receptor organization, signal transduction, and cellular integrity. Marked reductions in circulating cholesterol levels may theoretically alter vascular and platelet function in ways that affect physiological hemostasis [82].

Experimental studies suggest that cholesterol depletion may influence platelet membrane composition and receptor clustering, potentially modifying platelet responsiveness to activating stimuli [83]. In addition, cholesterol contributes to endothelial stability and vascular wall integrity. Extremely low cholesterol concentrations have therefore been hypothesized to increase susceptibility to vascular fragility, particularly in the microcirculation [28].

Another potential mechanism involves the interaction between lipid metabolism and coagulation factor activity. Lipoproteins participate in several aspects of coagulation biology, including thrombin generation, phospholipid-dependent coagulation reactions, and fibrin clot formation. Alterations in lipid availability may therefore influence the efficiency of physiological clot formation under certain conditions [84].

The relationship between LDL-C and bleeding is likely multifactorial and may vary according to patient characteristics, concomitant therapies, and underlying disease states. Importantly, the mechanisms potentially linking low LDL-C levels and bleeding remain incompletely understood and require further investigation.

5.2 Human, Genetic, and Congenital Evidence

Direct human evidence linking progressively lower LDL-C concentrations to impaired platelet function or increased endothelial permeability remains limited. Available platelet studies have mainly evaluated hypercholesterolemia, lipid-lowering interventions, or membrane cholesterol manipulation rather than prospectively comparing platelet aggregation, secretion, receptor organization, and procoagulant activity across predefined very-low LDL-C strata. Similarly, clinical studies directly relating LDL-C gradients to validated measures of endothelial permeability or glycocalyx integrity are scarce. This lack of direct human phenotyping represents an important gap between experimental plausibility and clinical association.

Genetic evidence may help distinguish lifelong exposure to lower LDL-C from short-term pharmacological lowering. Mendelian randomization studies using variants in lipid-related genes can approximate the consequences of genetically determined LDL-C reduction while reducing conventional confounding. However, such analyses have primarily focused on cardiovascular and cerebrovascular outcomes rather than major bleeding during anticoagulation. Moreover, genetic instruments affecting HMGCR, PCSK9, NPC1L1, or other lipid pathways may not be biologically equivalent because they reproduce different pharmacological mechanisms.

Individuals with congenital hypobetalipoproteinemia, PCSK9 loss-of-function variants, or other inherited causes of lifelong low LDL-C provide an additional natural model. Most do not appear to exhibit a consistent spontaneous major bleeding phenotype, although severe genetic lipid disorders may be accompanied by hepatic, nutritional, or fat-soluble vitamin abnormalities that independently influence hemostasis. This contrasts with acquired very low LDL-C occurring in cancer, malnutrition, chronic inflammation, liver disease, or frailty, in which LDL-C may primarily reflect systemic illness.

Therefore, congenital, genetically mediated, pharmacologically induced, and disease-related low LDL-C should not be considered interchangeable exposures. Future studies should combine lipid measurements with platelet-function testing, endothelial and glycocalyx biomarkers, nutritional assessment, inflammatory profiling, and longitudinal bleeding adjudication.

5.3 Evidence From Cardiovascular Studies

Interest in the relationship between cholesterol levels and bleeding initially emerged from studies evaluating hemorrhagic stroke. Several epidemiological investigations reported inverse associations between total cholesterol concentrations and intracranial bleeding risk, suggesting that lower lipid levels may be linked to greater susceptibility to hemorrhagic events [85,86].

Subsequent analyses of intensive lipid-lowering trials produced mixed results. While most studies demonstrated substantial cardiovascular benefit without major safety concerns, some observations suggested a slight increase in hemorrhagic stroke among selected high-risk populations achieving extremely low cholesterol concentrations [87]. Nevertheless, the absolute magnitude of this risk appeared small and generally outweighed by the reduction in ischemic cardiovascular events.

More recently, attention has shifted toward broader bleeding outcomes beyond intracranial hemorrhage, particularly among patients exposed to antithrombotic therapies. This issue is clinically important because the coexistence of aggressive lipid lowering and long-term anticoagulant treatment is increasingly common in contemporary practice.

5.4 Evidence in Patients Receiving Anticoagulant Therapy

Despite the clinical relevance of this topic, relatively few studies have specifically evaluated the relationship between LDL-C levels and bleeding risk among anticoagulated patients. Traditional bleeding risk scores incorporate factors such as age, renal function, anemia, cancer, and previous bleeding history, but lipid parameters are generally not considered [88].

Recent evidence from the RIETE Registry has provided novel insights into this issue. In a large multinational cohort of patients receiving anticoagulant therapy for VTE, Siniscalchi and colleagues [15] investigated the association between LDL-C levels and major bleeding events during follow-up. The study demonstrated that lower LDL-C concentrations were associated with an increased risk of major bleeding, even after adjustment for multiple confounding variables.

These findings are particularly relevant because they suggest that LDL-C may represent a previously underrecognized biomarker of hemorrhagic risk in anticoagulated populations. Importantly, the observed association was identified in a large real-world cohort reflecting contemporary clinical practice across multiple countries and healthcare systems.

The biological plausibility of these observations is supported by the mechanistic considerations discussed above. However, the observational nature of the study precludes definitive conclusions regarding causality. Residual confounding remains possible, and low LDL-C levels may also reflect underlying frailty, malnutrition, chronic illness, systemic inflammation, or other factors associated with bleeding susceptibility [89].

Nevertheless, the findings have generated substantial interest because they challenge the traditional assumption that lipid levels are largely irrelevant to bleeding risk assessment.

5.5 Heterogeneity of Bleeding Phenotypes

Major bleeding is a clinically and biologically heterogeneous outcome. Intracranial hemorrhage, gastrointestinal bleeding, retroperitoneal bleeding, genitourinary bleeding, and other extracranial events differ in their underlying mechanisms, baseline risk factors, prognosis, and potential relationship with lipid metabolism.

Intracranial hemorrhage may be influenced by cerebral small-vessel disease, hypertension, cerebral amyloid angiopathy, vascular fragility, and previous cerebrovascular injury. Observational studies have reported inverse associations between cholesterol levels and intracranial hemorrhage, but randomized evidence has been inconsistent. A recent meta-analysis of randomized lipid-lowering trials identified a small overall increase in hemorrhagic stroke, particularly in secondary-prevention populations, while estimates for non-statin agents remained imprecise [90]. Conversely, an American Heart Association scientific statement

concluded that the totality of randomized evidence does not support an increased hemorrhagic stroke risk from achieving very low LDL-C in patients without a previous intracranial hemorrhage [91].

Gastrointestinal bleeding is more strongly influenced by mucosal disease, malignancy, age, renal dysfunction, concomitant antiplatelet or nonsteroidal anti-inflammatory therapy, and local drug exposure. The relationship between intensive LDL-C lowering and intracranial hemorrhage remains controversial. While observational studies have suggested an inverse association between cholesterol concentrations and hemorrhagic stroke, recent randomized evidence indicates that any potential increase in risk is small and largely confined to selected high-risk populations. A recent meta-analysis of randomized lipid-lowering trials reported a modest increase in hemorrhagic stroke overall, although class-specific analyses for non-statin therapies remained inconclusive [90].

Future studies should therefore report bleeding according to standardized definitions and anatomical sites. Analyses restricted to composite major bleeding may obscure potentially different associations between lipid levels and intracranial, gastrointestinal, or other extracranial events.

5.6 Non-Statin LDL-C-Lowering Therapies and Bleeding

The availability of ezetimibe and PCSK9 inhibitors provides an opportunity to distinguish the biological consequences of profound LDL-C reduction from statin-specific pleiotropic effects. Ezetimibe lowers LDL-C by inhibiting intestinal cholesterol absorption, whereas monoclonal antibodies targeting PCSK9 markedly increase hepatic LDL-receptor recycling. Neither mechanism reproduces the complete spectrum of mevalonate-dependent statin effects.

Randomized trials of ezetimibe and PCSK9 inhibitors have generally not demonstrated a clear increase in overall major bleeding. Evidence regarding hemorrhagic stroke is also reassuring overall, although estimates are limited by the low number of events. A 2024 meta-analysis found no statistically conclusive class-specific increase for PCSK9 inhibitors or ezetimibe, while identifying a small overall signal across lipid-lowering trials that appeared more evident in secondary-prevention populations [90]. An American Heart Association scientific statement similarly concluded that achieving very low LDL-C with contemporary lipid-lowering therapy has not been shown to increase hemorrhagic stroke risk in patients without a previous cerebral hemorrhage [91].

These findings argue against a simple causal model in which any pharmacologically induced very low LDL-C necessarily causes bleeding. They also reinforce the need to distinguish achieved LDL-C concentration, drug class, previous intracranial hemorrhage, baseline cerebrovascular vulnerability, and concomitant anticoagulant or antiplatelet therapy.

5.7 Clinical Implications for Personalized Anticoagulant Therapy

If confirmed by future investigations, LDL-C levels could become an additional component of individualized bleeding risk assessment. Current anticoagulant management relies heavily on balancing thrombotic and hemorrhagic risks. Incorporating biological markers capable of improving risk prediction remains a major objective of precision medicine approaches.

The potential role of LDL-C is particularly intriguing because lipid measurements are routinely available in clinical practice and involve minimal additional cost. Furthermore, LDL-C levels may capture biological information not reflected by conventional bleeding risk factors.

Patients presenting with very low LDL-C concentrations could potentially benefit from closer clinical monitoring during anticoagulant therapy, especially when additional bleeding risk factors are present. However, current evidence is insufficient to justify modifications of lipid-lowering treatment solely on the basis of bleeding concerns.

It is important to emphasize that the cardiovascular benefits of statin therapy remain well established and should not be questioned by the emerging observations regarding bleeding risk. Rather, the challenge for clinicians lies in understanding how lipid metabolism influences overall hemostatic balance and integrating this information into individualized therapeutic strategies.

5.8 A New Paradigm Linking Lipid Biology and Hemostasis

The growing evidence connecting LDL-C levels, thrombosis, and bleeding suggests that lipid metabolism may play a broader role in hemostatic regulation than previously recognized. Traditionally, cholesterol has been viewed almost exclusively through the lens of atherosclerotic disease. However, contemporary research increasingly supports the concept that lipid biology influences multiple aspects of coagulation, fibrinolysis, platelet function, endothelial homeostasis, and vascular integrity.

This evolving paradigm may have important implications for future research. The integration of lipid biomarkers, inflammatory markers, genetic determinants, and clinical risk factors could facilitate more precise stratification of patients receiving anticoagulant therapy. Such approaches may ultimately improve both efficacy and safety by identifying individuals at increased risk of thrombosis, bleeding, or both.

The potential interaction between lipid metabolism and anticoagulant therapy therefore represents an emerging field at the intersection of pharmacology, vascular medicine, and precision therapeutics. Future studies will be required to determine whether LDL-C should be incorporated into formal bleeding risk prediction models and whether targeted interventions can modify outcomes in high-risk patients [92].

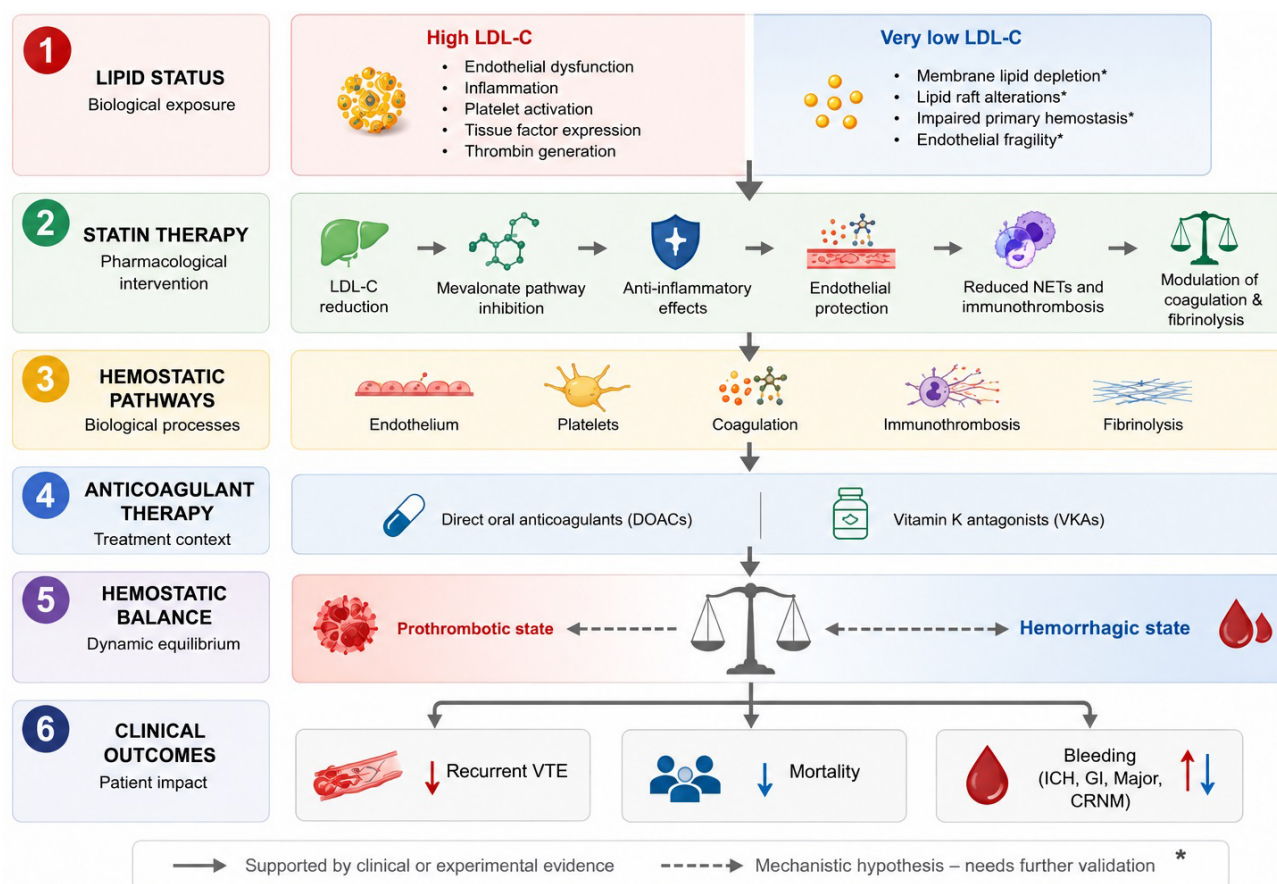


Fig. 1. Proposed model of the interplay between lipid metabolism, statin pleiotropy and hemostatic balance during anticoagulant therapy. Legend: Schematic overview of the biological pathways linking lipid metabolism, statin pleiotropic effects and anticoagulant therapy with thrombotic and hemorrhagic outcomes. High LDL-C promotes thrombosis through endothelial dysfunction, platelet activation and coagulation activation, whereas statins exert both LDL-C-dependent and LDL-C-independent effects that modulate inflammation, immunothrombosis, endothelial function and fibrinolysis. The potential contribution of very low LDL-C to bleeding remains hypothetical and requires further validation. Red denotes a shift toward a prothrombotic state or increased clinical risk, whereas blue denotes a shift toward a hemorrhagic state or decreased clinical risk. NETs, neutrophil extracellular traps; ICH, intracranial hemorrhage; GI, gastrointestinal; CRNM, clinically relevant non-major bleeding.

The complex interplay among lipid metabolism, statin therapy, thrombosis, and bleeding risk is illustrated in Fig. 1.

6. Future Perspectives and Personalized Antithrombotic Management

The growing recognition that lipid metabolism influences both thrombotic and hemorrhagic pathways opens new perspectives for individualized antithrombotic management. Current therapeutic strategies primarily rely on clinical characteristics and conventional laboratory parameters to estimate the risks of thrombosis recurrence and bleeding. However, these approaches remain imperfect, and a substantial proportion of adverse events occur in patients classified as having intermediate risk according to existing prediction models [93].

Precision medicine aims to overcome these limitations by integrating clinical, biological, imaging, genetic, and pharmacological information to guide therapeutic decision-making. Within this framework, lipid biomarkers may represent an emerging source of prognostic information capable of refining current risk stratification approaches. The observation that LDL-C levels may influence both thrombosis and bleeding suggests that lipid metabolism occupies a unique position at the intersection of competing clinical risks.

Future bleeding risk prediction models may incorporate lipid-related variables alongside established predictors such as age, renal function, cancer, anemia, previous bleeding history, and concomitant antithrombotic therapies. Such multidimensional approaches could improve identification of patients most likely to benefit from intensified monitoring or individualized anticoagulant regimens [94].

6.1 Direct Oral Anticoagulants and Individualized Risk Assessment

The introduction of DOACs has transformed the management of VTE. Compared with vitamin K antagonists, DOACs offer more predictable pharmacokinetics, fewer drug interactions, and lower rates of major bleeding in several clinical settings. Nevertheless, significant variability in bleeding risk persists among patients receiving these agents [95].

Current treatment algorithms generally focus on clinical characteristics when determining anticoagulant intensity and treatment duration. However, increasing evidence suggests that biological factors may provide complementary information. Biomarkers reflecting coagulation activation, inflammation, endothelial dysfunction, and lipid metabolism may contribute to a more comprehensive assessment of net clinical benefit.

In this context, LDL-C levels may emerge as a novel component of personalized anticoagulant management. While current evidence remains insufficient to support therapeutic decisions based solely on lipid concentrations, future studies may identify clinically relevant thresholds associated with increased hemorrhagic vulnerability during anticoagulant treatment.

6.2 Biomarkers and Integrated Risk Models

The future of anticoagulant management will likely involve integrated risk models combining multiple sources of information. Several biomarkers have already demonstrated prognostic value in VTE, including D-dimer, troponins, natriuretic peptides, inflammatory markers, and indicators of coagulation activation [96].

Among these biomarkers, D-dimer remains one of the most extensively studied. Beyond its diagnostic role, D-dimer contributes to recurrence risk assessment and may help guide treatment duration in selected patients. Recent developments have emphasized the importance of age-adjusted D-dimer thresholds, which improve diagnostic performance among older adults while reducing unnecessary imaging investigations [97].

The incorporation of lipid-related biomarkers into similar predictive frameworks represents an attractive future direction. LDL-C measurements are widely available, inexpensive, standardized, and routinely performed in clinical practice. Therefore, if their prognostic relevance is confirmed, implementation into clinical algorithms could occur relatively easily compared with more complex molecular biomarkers.

Machine-learning approaches may further enhance the utility of these variables by identifying complex interactions among lipid profiles, clinical characteristics, anticoagulant exposure, and bleeding outcomes that are difficult to capture using conventional statistical models [98].

6.3 Pharmacogenomics and Personalized Pharmacology

Another promising field is pharmacogenomics. Genetic determinants influence both lipid metabolism and anticoagulant response, suggesting the possibility of integrated pharmacogenomic strategies for optimizing treatment.

Polymorphisms affecting cholesterol synthesis, lipoprotein metabolism, inflammatory pathways, and coagulation factors may contribute to interindividual variability in both thrombotic and bleeding risk. Similarly, genetic factors influencing anticoagulant pharmacokinetics and pharmacodynamics may affect treatment safety and efficacy [99].

Although pharmacogenomic-guided anticoagulation remains largely investigational, advances in genomic technologies and decreasing sequencing costs may facilitate broader implementation in the coming years. Future models may integrate genetic information with lipid biomarkers and clinical variables to support truly individualized therapeutic decisions.

6.4 Future Research Priorities

Several important questions remain unanswered. First, the causal relationship between LDL-C levels and bleeding risk requires confirmation through prospective studies. Second, the mechanisms linking lipid metabolism to hemorrhagic complications need further clarification. Third, it remains uncertain whether modification of lipid levels can directly influence bleeding outcomes.

Randomized clinical trials specifically designed to investigate the interaction between lipid-lowering therapy and anticoagulant treatment are currently lacking. Such studies would help determine whether the associations observed in observational registries represent true biological effects or merely reflect residual confounding.

In addition, future investigations should evaluate whether specific lipid fractions, including lipoprotein(a), remnant cholesterol, apolipoproteins, or oxidized LDL particles, provide additional prognostic information beyond conventional LDL-C measurements. The increasing availability of advanced lipid profiling techniques may facilitate these analyses [100].

LDL-C quantifies the cholesterol content of LDL particles but does not fully represent the number, composition, oxidation state, or thrombogenic potential of circulating lipoproteins. Apolipoprotein B reflects the total number of atherogenic particles and may provide information that is not captured by LDL-C alone, particularly in patients with metabolic syndrome, diabetes, or hypertriglyceridemia. Non-HDL cholesterol includes cholesterol carried by LDL, intermediate-density lipoproteins, very-low-density lipoproteins, and remnant particles and may therefore better represent total atherogenic cholesterol burden in selected populations.

Remnant cholesterol has been linked to inflammatory and endothelial pathways, whereas oxidized LDL may directly activate endothelial cells, monocytes, and platelets through scavenger receptors. Lipoprotein(a) additionally carries oxidized phospholipids and has potential proinflammatory, antifibrinolytic, and thrombotic properties. However, the relationships of these biomarkers with bleeding during anticoagulant therapy remain largely unexplored.

Future investigations should determine whether the association between low LDL-C and bleeding persists after accounting for apoB, non-HDL cholesterol, triglyceride-rich remnants, nutritional status, systemic inflammation, and lipoprotein(a). Such analyses may help establish whether LDL-C acts as a causal biological determinant, a surrogate of broader lipid metabolism, or a marker of frailty and chronic disease.

Finally, integration of lipid biomarkers into validated bleeding risk scores should be explored. Such efforts could ultimately contribute to more precise therapeutic decision-making and improved patient outcomes.

7. Conclusions

The relationship between lipid metabolism, statin therapy, coagulation, and bleeding represents an emerging area of considerable pharmacological and clinical interest. Although statins remain primarily indicated for cardiovascular prevention, growing evidence demonstrates that these agents exert multiple pleiotropic effects affecting endothelial function, inflammation, platelet activity, coagulation pathways, and fibrinolysis.

Experimental investigations and clinical studies suggest that statins may influence thrombotic outcomes in patients with venous thromboembolism. Observational evidence, including data derived from large international registries, indicates potential associations between statin use and improved survival among anticoagulated patients with pulmonary embolism and deep vein thrombosis. These findings support the hypothesis that the biological effects of statins extend beyond lipid lowering and may contribute to modulation of thromboinflammatory processes.

At the same time, emerging evidence indicates that very low LDL-C concentrations may be associated with increased bleeding risk during anticoagulant therapy. Although the underlying mechanisms remain incompletely understood, these observations challenge the traditional view that lipid metabolism is unrelated to hemorrhagic risk and suggest a more complex interaction between cholesterol homeostasis and hemostatic balance.

Future research should focus on clarifying the causal nature of these associations, identifying the biological pathways involved, and determining whether lipid biomarkers can improve current bleeding risk prediction models. The integration of lipid profiles, clinical characteristics, coagulation biomarkers, and pharmacological variables may ultimately facilitate more personalized antithrombotic management.

As precision medicine continues to evolve, understanding the interplay between lipid metabolism and hemostasis may provide new opportunities for optimizing the safety and efficacy of anticoagulant therapy. The emerging convergence of lipid biology, thrombosis, bleeding, and pharmacology represents a promising field that may influence future therapeutic strategies in patients with venous thromboembolism and other thrombotic disorders.

Abbreviations

ApoB, Apolipoprotein B; CYP2C9, Cytochrome P450 2C9; CYP2C19, Cytochrome P450 2C19; CYP3A4, Cytochrome P450 3A4; DOAC, Direct Oral Anticoagulant; DVT, Deep Vein Thrombosis; HDL-C, High-Density Lipoprotein Cholesterol; HMG-CoA, 3-Hydroxy-3-Methylglutaryl Coenzyme A; LDL-C, Low-Density Lipoprotein Cholesterol; NET, Neutrophil Extracellular Trap; PAI-1, Plasminogen Activator Inhibitor-1; PCSK9, Proprotein Convertase Subtilisin/Kexin Type 9; PE, Pulmonary Embolism; RIETE, Registro Informatizado de Enfermedad TromboEmbólica; tPA, Tissue Plasminogen Activator; VKA, Vitamin K Antagonist; VTE, Venous Thromboembolism.

Author Contributions

CS, PDM, AP, and FFB conceived the study and developed the review framework. CS prepared the original draft of the manuscript and designed the figures and tables. MB, AP, and FFB contributed to the literature review, data interpretation, and figure preparation. PDM contributed to the conceptualization of the study and provided critical guidance on the scientific content and manuscript structure. MB and PDM critically revised the manuscript for important intellectual content. All authors contributed to manuscript revision, have read and approved the final version of the manuscript, participated sufficiently in the work, and agree to be accountable for all aspects of the work.

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The authors declare no conflicts of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used ChatGPT (OpenAI, San Francisco, CA, USA) to assist

with drafting selected sections of the text, language editing, improvement of readability, manuscript organization, and the creation and graphical refinement of figures. All AI-generated content was carefully reviewed, revised, and validated by the authors. The authors take full responsibility for the final content of the manuscript and for all interpretations, analyses, and conclusions presented herein.

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