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PLEIOTROPIC EFFECTS OF STATINS IN HEPATOLOGY AND VENOUS THROMBOEMBOLISM: REAL-WORLD EVIDENCE ANALYSIS (2016–2025)

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Background. Statins, as inhibitors of HMG-CoA reductase, exert pleiotropic effects beyond lipid lowering, including endothelial-protective, anti-inflammatory, and antifibrotic properties relevant to liver diseases and venous thromboembolism (VTE).

Objective. To summarize real-world evidence on the pleiotropic effects of statins in hepatology, define the "therapeutic window" in cirrhosis, and evaluate their role in VTE prevention.

Materials and Methods. A structured literature search was performed in PubMed for the period 2016–2025 using predefined keywords related to statins, cirrhosis, hepatocellular carcinoma, portal hypertension, and VTE. A total of 261 publications were identified, of which 35 met the inclusion criteria. To minimize bias, studies employing modern pharmacoepidemiological approaches were prioritized, including propensity score matching, time-lag analysis, and sensitivity analyses.

Results. Statin therapy is associated with improved intrahepatic hemodynamics through KLF2 signaling and nitric oxide pathways, as well as antifibrotic effects mediated by Rho-kinase inhibition. In real-world cohort studies, statin use has been linked to reduced risks of cirrhosis decompensation, hepatocellular carcinoma, and mortality, particularly in patients with compensated disease. The concept of a "therapeutic window" suggests the most favorable benefit-risk balance in patients with Child–Pugh class A cirrhosis. In the context of VTE, statins demonstrate modest effects in primary prevention but a more consistent reduction in recurrence risk. Observational data support a favorable safety profile and challenge the concept of "statin phobia."

Conclusions. Statins may be considered as adjunctive therapy in selected patients with chronic liver disease and increased thrombotic risk. The greatest benefit appears to be observed in compensated stages of disease, while further randomized controlled trials are needed to establish causality and refine clinical indications.

Keywords: statins; pleiotropic effects; liver cirrhosis; venous thromboembolism; real-world evidence.

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ПЛЕЙОТРОПНІ ЕФЕКТИ СТАТИНІВ У ГЕПАТОЛОГІЇ ТА ЗА НАЯВНОСТІ ВЕНОЗНИХ ТРОМБОЕМБОЛІЙ: АНАЛІЗ РЕАЛЬНОЇ ПРАКТИКИ (2016–2025)

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Анотація. У статті представлено аналіз плейотропних ефектів статинів у гепатології та за наявності венозних тромбоемболій (ВТЕ), що базується на даних PubMed за період 2016–2025 рр. Розглянуто молекулярні механізми гепатопротекції. Наведено докази ефективності статинів у зниженні ризику декомпенсації цирозу печінки та профілактиці гепатоцелюлярної карциноми у пацієнтів із вірусними гепатитами. Окрему увагу приділено зниженню частоти первинних та рецидивуючих ВТЕ в умовах реальної практики.

Ключові слова: статини; плейотропні ефекти; цироз печінки; венозна тромбоемболія; реальна практика.

Introduction

Statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) have remained the cornerstone of cardioprotection over the past decades. However, accumulating evidence from the last decade indicates that their biological role extends far beyond their lipid-lowering effect. The pleiotropic effects of statins, primarily endothelial-protective, anti-inflammatory, and antifibrotic, open new perspectives for the treatment of liver diseases and vascular complications, particularly venous thromboembolism (VTE).

According to the systematic analysis by Abdulrazzak et al. (2025), statins demonstrate a unique ability to modulate intrahepatic hemodynamics, making them potential candidates for the treatment of portal hypertension, in contrast to many other non-cardiological applications where the evidence base remains controversial [1]. Of particular importance is their effect on the Rho-kinase signaling pathway and the expression of the transcription factor KLF2, which ensures restoration of sinusoidal endothelial function through activation of nitric oxide synthesis.

In the cohort study by Simon et al. (2019), therapy with lipophilic statins was shown to be associated with a statistically significant reduction in the risk of hepatocellular carcinoma (HCC) and mortality among patients with chronic viral hepatitis, without direct assessment of the effect on fibrosis progression [2]. This correlates with findings from large real-world cohort studies demonstrating a significant

reduction in liver-related mortality among patients with comorbid conditions.

The meta-analysis by Kunutsor et al. (2017), which included randomized and observational studies, showed that statin use was associated with a moderate reduction in the risk of a first episode of VTE, particularly deep vein thrombosis; the authors suggest that this effect may be partially explained by the pleiotropic anti-inflammatory and antithrombotic properties of statins, although the results characterized by heterogeneity [3].

Despite encouraging scientific findings, a certain degree of "statinophobia" still persists in clinical practice, driven by concerns regarding the hepatotoxicity of these drugs. This creates a barrier to the use of the pathogenetic potential of statins in patients at high risk of decompensation of liver diseases and vascular catastrophes.

The objective of the study was to summarize current data on the pleiotropic effects of statins in real-world clinical practice, to determine the "therapeutic window" for their safe use in liver cirrhosis, and to assess their role in the prevention of VTE. To achieve this aim, the methodological reasons for discrepancies between the results of observational and randomized controlled trials (RCTs) were analyzed, and the sources of systematic bias in the assessment of non-cardiological effects were identified.

Materials and Methods

The search for scientific publications was conducted in the specialized medical database PubMed for the period from January 2016 to December 2025. The following keywords and their combinations were used: statins, real-world, VTE, cirrhosis, portal hypertension, HCC, HBV, HCV, MASLD/NAFLD.

The initial search in the PubMed database using the specified search terms identified 261 unique publications. The search was performed using combinations of keywords with the filters "humans" and "adults 19+". Based on relevance criteria, 35 articles were selected for full-text analysis. All sources included in the final review were identified in the PubMed database, ensuring their compliance with international standards of biomedical peer review and the transparency of the evidence base.

The studies reviewed employed methods to minimize the "healthy user" effect by balancing patient groups according to age, sex, disease severity, and concomitant comorbidities. The analyzed publications included time-lag analysis to eliminate immortal time bias by establishing a fixed waiting period before the initiation of drug effect assessment. Sensitivity analyses were performed to evaluate the robustness of the results to potential unmeasured confounding factors. Relative risk (RR) and odds ratio (OR) estimates were summarized using 95% confidence intervals. The topic of the scientific study was approved at a meeting of the Department of Internal Medicine No. 2 with Postgraduate Education (Protocol No. 7 dated May 20, 2025).

Research results and their discussion

1. Methodological evolution of real-world practice analysis

One of the most widely discussed topics in modern pharmacoepidemiology is the discrepancy between the results of RCTs and observational studies. In this context, Karim et al. (2016) as well as Suissa et al. (2020) have described in detail the mechanisms of time-related biases, in particular "immortal time bias," which may lead to an overestimation of drug effects in previous studies [4; 5]. This bias occurred when the time from diagnosis to the initiation of statin therapy was incorrectly attributed to the treatment period, which artificially inflated survival.

However, analysis of publications from 2021–2025 demonstrated a shift toward a qualitatively new methodology, namely the use of propensity score–based balancing methods and time-dependent models. In a large observational study, Mahmud et al. (2022) showed that after multivariable adjustment, statin use is associated with a reduced risk of severe complications of cirrhosis, including acute-on-chronic liver failure [6].

Similarly, in contemporary cohort analyses focused on VTE, the use of adjusted models demonstrated that statin therapy may be associated with a reduced risk of VTE recurrence even after accounting for potential confounding factors [7].

Taken together, these data suggest a probable contribution of pleiotropic mechanisms of statins, although a causal relationship requires further confirmation.

2. Molecular pathways of hepatoprotective action

Modern hepatology considers statins not as lipid-lowering agents, but as modulators of hepatic microcirculation through the regulation of endothelial protective signaling pathways, particularly those related to KLF2 signaling. Experimental data suggest that these mechanisms may improve sinusoidal endothelial function and increase nitric oxide bioavailability via eNOS-dependent pathways [8].

In the setting of cirrhosis, which is characterized by sinusoidal endothelial dysfunction and reduced NO-dependent vasodilation, such effects may potentially contribute to a reduction in intrahepatic vascular resistance and a moderate decrease in portal pressure, without significant changes in systemic arterial pressure [1; 9].

The antifibrotic effects of statins are likely partly related to modulation of RhoA/Rho-kinase-dependent signaling pathways, which, according to experimental data, may limit the activation of hepatic stellate cells and their transformation into a myofibroblast-like phenotype. These mechanisms are associated with reduced fibrogenic activity and extracellular matrix production. In the context of portal hypertension, this may potentially contribute to a reduction in the dynamic component of intrahepatic vascular resistance, although a direct causal relationship between these molecular effects and clinical hemodynamic changes in humans has not yet been definitively established [10; 11].

To date, there is no clinically proven effect of statins on M1/M2 polarization of Kupffer cells in humans. However, experimental data suggest that statin therapy may induce anti-inflammatory changes in the liver through effects on macrophage-mediated inflammatory pathways. In particular, in a diet-induced mouse model of nonalcoholic steatohepatitis, atorvastatin administration led to suppression of NF-κB-dependent signaling, a reduction in the number of F4/80-positive macrophages, and decreased

severity of hepatic inflammation. This indicates the ability of statins to modify the inflammatory microenvironment of the liver through effects on macrophage functional status [12].

3. Differentiated approach to molecule selection: lipophilicity versus hydrophilicity

The clinical discussion regarding the choice between atorvastatin, simvastatin and rosuvastatin in hepatological practice is based on their physicochemical properties. Given their higher membrane permeability, lipophilic statins may theoretically reach not only hepatocytes but also non-parenchymal liver cells, including stellate cells, which is considered a possible explanation for differences in their pleiotropic effects compared with hydrophilic analogues [13].

Epidemiological data and meta-analyses suggest that the use of lipophilic statins may be associated with a more pronounced reduction in the risk of HCC compared with hydrophilic analogues, although a causal relationship has not been established. Experimental models also demonstrate that atorvastatin may exert a stronger effect on cellular signaling pathways and gene expression related to hepatic carcinogenesis, which may potentially explain these clinical observations [14; 15].

Hydrophilic statins, in particular rosuvastatin and pravastatin, are characterized by minimal metabolism via the CYP3A4 isoform of cytochrome P450, which potentially reduces the risk of interactions with drugs affecting this cytochrome system. At the same time, their transport into hepatocytes largely depends on transporter proteins (primarily OATP1B1 and BCRP); therefore, during combination therapy, particularly with direct-acting antiviral agents or antiretroviral drugs, increased systemic exposure may occur, requiring dose adjustment and assessment of potential drug–drug interactions. Thus, the choice between hydrophilic and lipophilic statins in hepatological practice is determined not only by cytochrome-mediated metabolism but also by the profile of transport interactions and the specific concomitant therapy regimen [16; 17].

4. Clinical efficacy and safety of statins in liver cirrhosis

Analyses of large national cohorts from Taiwan, Sweden, and the United States indicate that statin use in patients with chronic liver diseases is associated with a reduced risk of clinical progression, including cirrhosis decompensation, development of HCC, and overall mortality. Although the magnitude of the effect varies between studies, most real-world data demonstrate a relative risk reduction of approximately 30–50%, supporting the potential clinical benefit of statins in this population [18; 19].

The concept of a "therapeutic window" for statin use in liver cirrhosis suggests the most favorable benefit-risk ratio in patients with compensated disease (Child–Pugh class A), whereas in more advanced stages of cirrhosis (classes B/C), the safety profile of these drugs requires greater caution and an individualized dosing approach. In particular, clinical studies indicate that in patients with decompensated cirrhosis, statin use may be associated with an increased risk of adverse effects, which is dose-dependent and requires careful clinical and laboratory monitoring [20; 21].

With deterioration of liver function (Child–Pugh classes B/C), pharmacokinetic changes in statins occur, including reduced hepatic clearance and increased systemic exposure, which in turn may be associated with an increased risk of myopathy and other adverse events [20].

Of particular interest is the potential effect of statins on the risk of portal vein thrombosis, a common complication of cirrhosis and portal hypertension. Real-world clinical data indicate that statin use is associated with a statistically significant reduction in the incidence of portal vein thrombosis; in a propensity score-matched analysis, the risk was reduced by approximately 76% (HR ≈ 0.24), suggesting a possible protective effect of this drug class [22]. Although the magnitude of the association appears clinically significant, it should be interpreted in light of potential residual confounding and selection bias inherent to real-world cohort studies, which does not allow the observed effect to be unequivocally interpreted as causal.

5. Oncoprevention strategy in relation to hepatocellular carcinoma

Experimental studies in HCC models have shown that inhibition of the mevalonate pathway by statins disrupts the geranylgeranylation processes of small guanosine triphosphate-binding regulatory proteins of the Ras/Rho family, which may suppress oncogenic signaling cascades and tumor cell proliferation [23].

Accumulated clinical data suggest that statin use is associated with a reduced risk of HCC development in populations with chronic liver diseases [24].

The most pronounced cancer-protective signal is observed in patients with chronic hepatitis B or C, including cohorts of patients with cirrhosis, although a causal relationship has not been definitively established [14; 25].

Registry-based studies indicate that lipophilic statins (in particular atorvastatin and simvastatin) may be associated with a more pronounced reduction in HCC risk compared with hydrophilic analogues, which is potentially attributed to differences in tissue permeability and intracellular effects [2].

Recent systematic analyses also suggest a possible association between statin use and a lower risk of biliary tract cancer, although these data remain predominantly observational [26].

6. Steatotic liver disease (SLD) and overcoming "statin phobia"

For a long time, elevated transaminase levels were considered a relative contraindication to statin therapy; however, current data show that most such changes are transient, asymptomatic, and often normalize even without drug discontinuation, reflecting hepatic adaptation rather than true injury [27].

Clinical observations demonstrate that moderate increases in ALT/AST during statin therapy are rarely associated with clinically significant drug-induced hepatitis or liver failure [28].

In patients with SLD, statin use is associated with a reduction in fibrosis progression according to vibration-controlled transient elastography data. However, existing studies are mostly observational in nature; therefore, the observed effects should be interpreted as associations rather than proven direct antifibrotic treatment [29].

From the perspective of clinical hepatology, statins are now considered safe in most patients with chronic liver diseases when appropriate clinical monitoring is provided [30]. The current management concept for such patients does not imply avoidance of statins due to moderate transaminase fluctuations, but rather an individualized balance between cardiovascular benefit and the rare risk of hepatotoxicity [31].

7. VTE and the hemostatic system

The pleiotropic effect of statins on the hemostatic system is considered one of the potential mechanisms for reducing venous thrombotic risk; however, current data suggest that this effect is likely mediated through a combination of metabolic and anti-inflammatory mechanisms [32].

Clinical studies have shown that statin therapy may modify the tissue factor pathway of coagulation, in particular through a reduction in factor VII activity and changes in levels of tissue factor inhibitors, thereby creating a less procoagulant profile. At the same time, these changes are not uniformly expressed across all populations and do not allow the effect to be interpreted as a direct inhibition of coagulation in vivo in every patient [32].

In addition to effects on the coagulation cascade, statins have antiplatelet properties: in clinical studies in patients with hypercholesterolemia, simvastatin reduced platelet aggregation and levels of platelet activation markers (in particular sP-selectin and sCD40L), which may potentially contribute to a reduction in thrombotic risk [33].

In a large nationwide Danish population cohort (601,011 individuals initiating statin therapy and 1,803,033 comparison participants), initiation of statin therapy was associated with a small reduction in the risk of a first episode of VTE (adjusted hazard ratio approximately 0.95), indicating a weak but statistically significant preventive effect [34].

In contrast, in a large retrospective real-world cohort from Indiana (United States) including 192,908 patients with prior VTE, statin use was associated with approximately a 25% lower risk of recurrence (OR approximately 0.75), suggesting a more pronounced potential of statins in secondary prevention of thrombotic events [35].

Thus, statin therapy is associated with a small reduction in the risk of a first VTE and a more pronounced effect in secondary prevention; however, the existing evidence base, predominantly derived from observational studies, supports their use as a potential additional pharmacological approach rather than an alternative to anticoagulant prophylaxis.

Conclusions

The pleiotropic effects of statins extend beyond their lipid-lowering action and encompass key pathogenetic mechanisms of liver diseases and vascular complications. The endothelioprotective, anti-inflammatory, and antifibrotic effects provide a biological basis for considering statins as a potential adjuvant therapeutic tool, although most available evidence is currently based on observational studies.

In hepatology, the most consistent clinical associations are observed in patients with compensated forms of chronic liver diseases, where real-world data demonstrate an association between statin therapy and a reduced risk of cirrhosis decompensation, development of HCC, and mortality. This suggests that the potential benefit of statins is most likely realized at stages of preserved liver function, when the benefit-risk ratio is optimal.

Current data revise traditional concepts regarding statin hepatotoxicity in SLD and other chronic liver conditions. Moderate elevations in transaminases are usually transient and rarely associated with clinically significant liver injury, allowing statins to be considered a safe strategy when appropriate clinical monitoring is provided.

In VTE prevention, the effect of statins differs depending on the clinical context: in primary prevention, only a small reduction in the risk of a first VTE episode is observed, whereas in secondary prevention a more consistent association with reduced recurrence risk is seen, which is likely related to their effects on coagulation balance, platelet activation, and systemic inflammation.

Overall, statins should be considered not as an alternative to standard treatment methods, but as a potential multiorgan risk modifier. Their use is most justified as part of combination therapy in selected patients, while the determination of optimal treatment regimens requires further prospective randomized studies.

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