Article published online: 2025-05-19

Pharmacological Profile and Mechanisms of Cardiovascular Protective Effects of Statins: An Update

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Libyan Int Medical Univ J 2025;10:18–28.

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Abstract

This review article highlights recent developments in the clinical pharmacology of statins. A thorough literature search was performed using PubMed Central, Scopus, and Google Scholar, focusing on keywords related to statin kinetics, mechanisms, cardiovascular protection, side effects, and variations in individual responses. Understanding the pharmacokinetics of statins is essential for maximizing their therapeutic effects while reducing side effects and potential drug interactions. Statins have varying degrees of lipophilicity, resulting in different kinetic profiles that affect their bioavailability, elimination, and interactions with other drugs.

The main mechanism by which statins lower cholesterol in blood is by inhibiting liver 3-hydroxy-3-methylglutaryl-CoA reductase, thereby increasing low-density lipoprotein receptor expression on hepatocytes and decreasing its plasma levels. This will ultimately reduce the risk of cardiovascular events. Statins also have antithrombotic and anti-inflammatory effects by increasing the availability of nitric oxide, inhibiting procoagulant proteins, and inhibiting platelet activation, all of which contribute to cardiovascular protection. Several clinical evidences support the effectiveness of statins in preventing venous thromboembolism and acute coronary syndrome. However, statins are associated with an increased risk of new-onset diabetes, particularly with high-intensity statins, necessitating careful monitoring in high-risk patients. Additionally, there is variability in patient responses to statin therapy, influenced by genetic polymorphisms and biological differences, highlighting the need for personalized treatment strategies. As clinical guidelines continue to evolve, incorporating genetic and biological factors will be vital for optimizing statin therapy and managing cardiovascular risks. In conclusion, there is substantial evidence that statins still play a vital role in preventing cardiovascular disease, necessitating a comprehensive approach that combines pharmacological interventions with lifestyle modifications to enhance patient outcomes.

Keywords

- cardiovascular protective effects
- personalized treatment of statins
- statin kinetics
- statin side effects
- statins

received
January 1, 2025
accepted after revision
April 6, 2025
article published online
May 19, 2025

DOI https://doi.org/10.1055/s-0045-1809043.
ISSN 2519-139X.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

المقالة باللغة العربية

الخصائص الدوائية وآليات الحماية القلبية الوعائية للستاتين: مراجعة حديثة

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هذه المقالة المرجعية تسلط الضوء على التطورات الحديثة في علم الأدوية السريري لمجموعة الستاتين الدوائية. تم إجراء بحث شامل باستخدام قواعد البيانات (PubMed Central و Scopus و Google Scholar)، مع التركيز على الكلمات المفتاحية المتعلقة بحركيات الستاتين، وآليات التأثير، والحماية القلبية الوعائية، والآثار الجانبية، والتباين في الاستجابات الفردية.

إن فهم الحركية الدوائية لمجموعة الستاتين أمر ضروري لتعزيز آثارها العلاجية مع تقليل الآثار الجانبية والتفاعلات المحتملة مع الأدوية الأخرى. تتمتع هذه المجموعة بدرجات متفاوتة من الذوبانية في دهون الجسم، مما يؤثر على حركتها في الجسم وبالتالي توافرها الحيوي وإطراحها.

تعمل الستاتينات بشكل رئيسي على خفض الكوليسترول في الدم عن طريق تثبيط إنزيم 3-هيدروكسي-3-ميثيل غلوتاريل-كوانزيم أ (HMG-CoA) ريدوكتاز في الكبد. هذا يزيد من عدد مستقبلات البروتين الدهني منخفض الكثافة (LDL) على الخلايا الكبدية، مما يقلل مستوياته في البلازما ويقلل من خطر الإصابة بالأمراض القلبية الوعائية. بالإضافة إلى ما سبق، تتمتع الستاتينات بتأثيرات مضادة للتخثر ومضادة للالتهاب عن طريق زيادة توافر أكسيد النيتريك، وتثبيط البروتينات المسببة للتخثر، وتقليل تنشيط الصفائح الدموية، مما يسهم في تعزيز الحماية القلبية الوعائية.

توجد أدلة سريرية عديدة تدعم فعالية مجموعة الستاتين في الوقاية من الانصمام الخثاري الوريدي ومتلازمة الشريان التاجي الحادة. ومع ذلك، قد يرتبط استخدامها بزيادة خطر الإصابة بمرض السكري حديث الظهور، خاصة عند استخدام الجرعات العالية، مما يتطلب متابعة دقيقة للمرضى المعرضين لهذا الخطر. علاوة على ذلك، يظهر تفاوت في استجابة المرضى لعلاج الستاتين، وهو ما يتأثر بالتباينات الجينية والاختلافات البيولوجية، مما يبرز أهمية استراتيجيات العلاج الشخصية.

مع استمرار تطور إرشادات العلاج، ستكون مراعاة العوامل الجينية والبيولوجية أمرًا بالغ الأهمية لتحسين العلاج بالستاتين وإدارة المخاطر القلبية الوعائية. في الختام، تشير الأدلة إلى أن مجموعة الستاتين لا تزال تلعب دورًا حيويًا في الوقاية من الأمراض القلبية الوعائية، مما يستدعي اتباع نهج شامل يجمع بين التدخلات الدوائية وتعديلات نمط الحياة لتعزيز نتائج المرضى.

Introduction

Many believe that the discovery of statins in the last century was one of the most important drug discoveries. The first statin, lovastatin, was approved by the U.S. Food and Drug Administration (FDA) in 1987.[1] Since then, several other statins have been introduced into clinical practice. Statins were initially developed and introduced as a therapeutic intervention aimed at preventing cardiovascular (CV) events through the effective reduction of low-density lipoprotein (LDL) cholesterol levels.[2] However, subsequent research has unveiled a broader spectrum of benefits associated with these medications, revealing their pleiotropic effects. Beyond their primary role in cholesterol management, statins have been shown to exert significant antithrombotic and anti-inflammatory properties, improve endothelial functions, and stabilize atherosclerotic plaques. This multifaceted impact underscores the importance of statins not only in lowering cholesterol but also in enhancing CV health through various biological pathways.[3]

This review provides a comprehensive overview of the various mechanisms through which statins exert their CV protective effects, highlighting both well-established and emerging clinical applications. In this context, a search was performed using PubMed, PubMed Central (PMC), Scopus, and Google Scholar, using the following keywords: statin kinetics, statin mechanisms of action, statin antithrombotic effects, statin clinical evidence, statin CV protective effects, statin side effects, and statin clinical guidelines. A total of 123 articles were consulted, of which 63 were included in this review.

The Kinetics of Statins

Studying the kinetics of statins is important for optimizing their therapeutic efficacy, minimizing side effects, and avoiding drug–drug interactions.[4] Some statins are lipophilic in nature, while others are hydrophilic; this difference in lipophilicity affects the kinetic parameters of the statins (►**Table 1**).

Statins are generally administered orally, with varying bioavailability ranging from 5 to 50%. The first-pass effect after oral administration is the main cause of the differences in bioavailability, especially for the lipophilic statins. The lipophilic statins (e.g., lovastatin, simvastatin, and atorvastatin) undergo high first-pass metabolism (FPM) by cytochrome P450 (CYP) enzymes and, thus, have relatively low bioavailability, whereas hydrophilic statins (e.g., pravastatin and rosuvastatin) have little FPM and higher bioavailability. The time to reach peak plasma concentration (PPC) varies as well, with most statins reaching PPC within 5 hours after oral administration. Statins like lovastatin and atorvastatin are primarily metabolized by cytochrome P450 3A4 (CYP3A4), leading to significant drug interactions.[5] Drugs that enhance the activity of CYP3A4, such as rifampicin, troglitazone, carbamazepine, and phenytoin, usually increase the elimination of these statins. On the other hand, inhibitors of CYP3A4, such as ketoconazole, ritonavir, clarithromycin,

Table 1 Statins pharmacokinetics

	Drugs	Introduced	Absorption PPC (h)	Bioavailability (%)	$T_{1/2}$ (h)	Metabolism	Active metabolite	Excretion
Lipophilic statins	Lovastatin	1987	2–4	5 (FPM)	1–3	Liver CYP3A4	β-Hydroxy acid forms	Mainly in bile
	Atorvastatin	1996	1–2	14 (FPM)	14	Liver CYP3A4	Ortho-hydroxy atorvastatin	Mainly in bile
	Fluvastatin	1994	1–3	24	0.5–2.5	Liver CYP2C9	Fluvastatin acid	Mainly in bile
	Simvastatin	1991	1.5–4.	5 (FPM)	2–3	Liver CYP3A4 and microsomal carboxylesterases	Simvastatin hydroxy acid	Mostly in bile
Hydrophilic Statins	Rosuvastatin	2003	3–5	20 (formulation dependent)	9–20	Glucuronidation mostly by UGT2B7	None	Feces (90%), urine (10%)
	Pravastatin	1991	1–1.5	17	1.5–2	Sulfation and glucuronidation	None	Feces (70%), urine (20%)
More lipophilic, less hydrophilic	Pitavastatin	2009	1–4	51	12	Glucuronidation mostly by UGT1A3 and UGT1A7	None	Feces (70%), urine (10%)

Abbreviations: FPM, first-pass metabolism; PPC, peak plasma concentration; T1/2, elimination half-life time; UGT, uridine diphospho-glucuronosyltransferase.

and omeprazole, delay the elimination of the statins and may increase their side effects. This is an important consideration, especially with multiple drug therapy. In contrast, rosuvastatin and pravastatin have a lower dependency on CYP enzymes, reducing their drug interaction potential when taken with drugs metabolized by CYP enzymes.[6] Moreover, the dependency on CYP enzymes affects statin elimination half-life; for example, rosuvastatin, which is metabolized by glucuronidation, has a longer half-life (an average of ~20 hours) compared with lovastatin, which is metabolized by CYP3A4 (with a half-life of 1–3 hours).[4,7]

Most of the lipophilic statins are metabolized into active metabolites (►**Table 1**). For example, simvastatin is converted to its active form, simvastatin acid, while atorvastatin is metabolized into several active metabolites, primarily ortho- and para-hydroxy atorvastatin. These active metabolites prolong the pharmacological duration of action of the drug. In contrast, pravastatin, rosuvastatin, and pitavastatin do not have significant active metabolites; they are primarily excreted unchanged or through glucuronidation.

Another important difference between the statins is their method of excretion. Some statins that are processed by the liver (the lipophilic statins) are excreted mostly in the bile and may undergo enterohepatic recirculation, potentially prolonging their effects. In contrast, drugs excreted in feces may indicate poor absorption or direct intestinal elimination, with less influence from liver metabolism.[4]

The Mechanism of Action of Statins

Statins have been reported to act beneficially through different mechanisms, resulting in protection against CV events. These mechanisms include inhibition of cholesterol synthesis, antithrombotic properties, and anti-inflammatory effects.

Cholesterol Synthesis Inhibition

Humans need a certain amount of cholesterol because the body uses it to build the structure of cell membranes and to make important hormones like sex hormones, adrenal hormones, and vitamin D. Cholesterol levels in the body come from two sources: dietary intake and biosynthesis. The majority of cholesterol utilized by healthy adults is synthesized in the liver, which produces ~70% of the total daily cholesterol requirement.

Biosynthesis of cholesterol generally takes place in the endoplasmic reticulum of hepatic cells and begins with acetyl-CoA, mainly derived from an oxidation reaction in the mitochondria. Acetyl-CoA and acetoacetyl-CoA are converted to 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) by HMG-CoA synthase. Then, HMG-CoA is converted to mevalonate under the effect of HMG-CoA reductase, the rate-limiting enzyme for de novo cholesterol synthesis in the mevalonate pathway (►**Fig. 1**).[8]

Cholesterol synthesized in the liver is transferred to other body tissues by very low-density lipoprotein (VLDL). In the blood, VLDL is converted to LDL, which is known as "bad

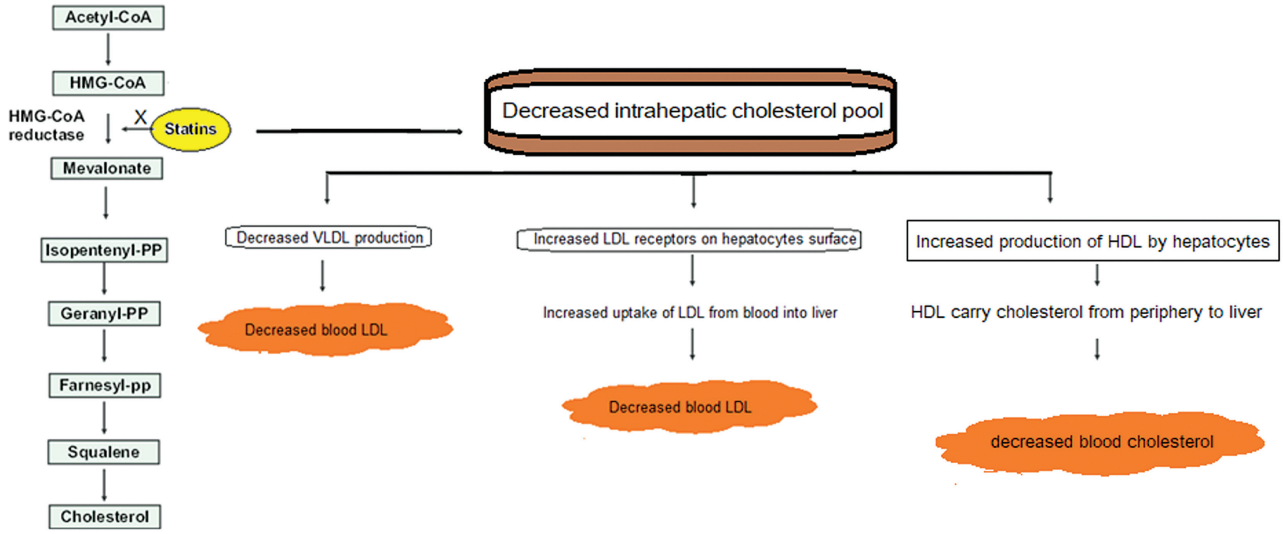

Fig. 1 Mechanisms by which statins decrease cholesterol blood levels. HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

cholesterol" because it is the form of lipoprotein responsible for the formation of atherosclerosis.

Statins decrease blood cholesterol by competitively inhibiting HMG-CoA reductase. They have a structural similarity to HMG-CoA, allowing them to fit into the enzyme's active site and prevent the conversion of HMG-CoA to mevalonate, thus inhibiting cholesterol synthesis.[9] The reduced production of cholesterol in hepatocytes lowers the liver's cholesterol pool. When the liver cannot produce sufficient cholesterol, it compensates by increasing the transcription of LDL receptors (upregulation) on the surface of liver cells (►**Fig. 1**). This increase in LDL receptors allows hepatocytes to uptake cholesterol-rich LDL particles from the bloodstream, thereby lowering overall LDL cholesterol levels. Additionally, there is a decrease in VLDL production from hepatocytes and its subsequent conversion to LDL in the blood. Consequently, the overall effect is a reduction in total LDL levels in the bloodstream.[9] To obtain more cholesterol, the liver increases the production of high-density lipoproteins (HDLs), which transport cholesterol from peripheral tissues back to the liver.[10] Thus, by inhibiting HMG-CoA reductase, statins not only reduce the liver's cholesterol production but also enhance the clearance of LDL from the bloodstream, with a moderate increase in HDL levels. Additionally, statins contribute to a moderate decrease in VLDL levels, further improving lipid profiles. This reduction in LDL cholesterol (LDL-C) is associated with significant decreases in CV events; for instance, every 1 mmol/L reduction in LDL-C correlates with a 22% reduction in CV events.[11]

Antithrombotic Properties

Thrombotic disorders are considered one of the most important factors involved in CV events. Conditions that lead to thrombosis, such as deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, can contribute to serious CV issues, including heart attacks and strokes. Therefore, managing thrombotic disorders is crucial in preventing adverse CV outcomes. Most recommended antithrombotic drugs and anticoagulants carry a risk of bleeding as a potential side effect. These medications, which include anticoagulants (e.g., warfarin, rivaroxaban, and apixaban) and antiplatelet agents (e.g., aspirin and clopidogrel), work by inhibiting various aspects of the coagulation process to prevent thrombosis.[12] However, this mechanism also increases the risk of bleeding. A drug that reduces thrombus formation without increasing the risk of major bleeding and mortality is hypothetically the ideal therapy. Several lines of evidence prove that statins can reduce CV events by preventing venous and arterial thrombosis through molecular mechanisms that extend beyond their lipid-lowering capabilities. These mechanisms include the enhancement of endothelial nitric oxide (NO) bioavailability, inhibition of procoagulant proteins, and modulation of platelet activation. The following sections detail these key aspects.

Enhancement of Nitric Oxide Bioavailability

NO is an endothelial hormone that exerts a powerful relaxant effect on the smooth muscle of blood vessels, causing vasodilation. It has been demonstrated that statins can enhance NO production by activating endothelial NO synthase (eNOS).[13] Increasing NO levels in blood vessels provides several significant benefits that promote CV health. First, NO-induced vasodilation reduces blood pressure and improves blood flow. This enhanced circulation facilitates the efficient delivery of oxygen and nutrients to tissues and organs. Additionally, elevated NO levels inhibit platelet aggregation, reducing the risk of thrombosis and promoting smoother blood flow. NO also exhibits anti-inflammatory properties, helping to mitigate vascular inflammation and protect endothelial cells from damage.[13]

Furthermore, the antioxidant effects of NO neutralize reactive oxygen species, further safeguarding vascular health. Moreover, NO plays a critical role in angiogenesis, the formation of new blood vessels, which is essential for healing and tissue regeneration.

Overall, by maintaining adequate NO levels, statins improve endothelial function and contribute to a reduced risk of CV diseases.[13]

Inhibition of Procoagulant Proteins

Statins exert a significant influence on the coagulation system, particularly through the reduction of tissue factor (TF) expression.[14] TF is a transmembrane protein that plays a crucial role in initiating the coagulation cascade. When tissue injury occurs, TF is exposed to circulating blood, where it binds to factor VIIa, forming a complex that activates several downstream coagulation factors, ultimately leading to thrombin generation. Thrombin is a key enzyme in the coagulation process, responsible for converting fibrinogen into fibrin, which forms the structural basis of blood clots. By reducing the expression of TF, statins effectively inhibit this initial step in the coagulation cascade, which in turn reduces the overall tendency for blood clot formation. This is particularly important in preventing thrombotic events, such as heart attacks and strokes, which can occur due to excessive clotting in response to vascular injury or inflammation.[14]

Moreover, the reduction of TF expression by statins can be attributed to their pleiotropic effects, which include anti-inflammatory properties and the modulation of endothelial function. For instance, statins can decrease the production of proinflammatory cytokines that promote TF expression in endothelial cells and other tissues.[15] Furthermore, by enhancing endothelial NO availability, statins also improve endothelial health, further contributing to a less procoagulant environment.[13]

In summary, statins reduce the expression of TF, a critical protein in the coagulation cascade, thereby decreasing thrombin generation and lowering the risk of thrombotic events. This mechanism underscores the broader CV protective effects of statins, highlighting their role in maintaining vascular homeostasis and preventing clot-related complications.

Modulation of Platelet Activation

Statins play a significant role in inhibiting platelet activation, a critical process in thrombus formation. One of the primary mechanisms through which statins achieve this is by inhibiting the prenylation of Ras homolog family member A protein (RhoA[a]). RhoA is a small guanosine triphosphatase (GTPase) that is vital for various cellular functions, including the activation and aggregation of platelets.[16] This results in decreased aggregation and activation of platelets, which are critical components in the formation of a thrombus. By lowering the likelihood of thrombus formation, statins contribute to improved CV outcomes.

Additionally, statins modulate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway. NF-κB is a transcription factor that regulates the expression of proinflammatory cytokines and adhesion molecules involved in platelet activation. By inhibiting NF-κB activation, statins decrease the expression of these mediators, resulting in a lower activation state of platelets and contributing to a less pro-thrombotic environment.[16] Moreover, statins enhance the expression of Kruppel-like factor 2 (KLF2), a transcription factor that promotes an anti-inflammatory and antithrombotic state in endothelial cells. Increased levels of KLF2 help counteract proaggregatory signals that would otherwise lead to heightened platelet activation. The combined effects of inhibiting RhoA prenylation, modulating NF-κB, and enhancing KLF2 expression contribute to a significant reduction in thrombus formation, particularly important in acute coronary syndromes (ACS), where rapid platelet activation can result in severe events such as myocardial infarction.[17]

Therefore, the antiplatelet effects of statins, alongside their lipid-lowering properties, provide a dual mechanism of action that enhances their therapeutic efficacy in preventing CV events. This action contributes to the overall reduction in thrombus formation, particularly in ACS.

Anti-inflammatory Effects of Statins

Chronic inflammation significantly contributes to CV diseases through mechanisms such as endothelial dysfunction and atherogenesis. Chronic inflammation disrupts the vascular endothelium, leading to the release of proinflammatory cytokines that increase vascular permeability. This allows lipoproteins, particularly LDL, to infiltrate the vascular wall, promoting the development of atherosclerosis. Additionally, inflammatory conditions recruit immune cells, especially macrophages, which can adopt either proinflammatory or anti-inflammatory roles, influencing plaque stability. The presence of proinflammatory macrophages increases plaque vulnerability, increasing the risk of plaque rupture and acute CV events.[18] Overall, chronic inflammation not only drives atherosclerosis but also contributes to hypertension, underscoring the need for targeted therapies to mitigate its adverse effects on CV health.[19]

Statins exhibit anti-inflammatory effects in CV disease through several molecular mechanisms. These mechanisms involve the modulation of inflammatory pathways, regulation of macrophage function, and alterations in cellular cholesterol levels.

IL-6 Signaling Pathway

Research indicates that statins may influence inflammatory processes independently of the IL-6 signaling pathway. Although statins affect upstream IL-6 levels, their anti-inflammatory effects do not appear to be mediated through this pathway, suggesting the involvement of alternative mechanisms.[20]

[a] Statins, by inhibiting HMG-CoA reductase, will decrease the availability of isoprenoid intermediates, which are necessary for the prenylation of proteins like RhoA (see ►**Fig. 1**).

Macrophage Function and JMJD3

By lowering cholesterol levels in macrophages, statins trigger the upregulation of Jumonji domain-containing protein 3 (JMJD3),[b] an epigenetic demethylase that plays a critical role in promoting anti-inflammatory responses. This upregulation enhances the expression of anti-inflammatory cytokines, particularly IL-10, which helps regulate immune responses and reduce inflammation. Additionally, by modulating macrophage activation states, statins shift the balance away from proinflammatory phenotypes, thereby suppressing inflammatory processes that contribute to coronary artery disease (CAD). This mechanism highlights the dual role of statins not only in managing cholesterol levels but also in exerting significant anti-inflammatory effects that benefit CV health.[21]

In contrast, while statins are generally recognized for their beneficial anti-inflammatory properties, some studies suggest that they may also have adverse effects, such as an increased risk of certain inflammatory responses under specific conditions, underscoring the complexity of their action in CV disease.[22]

Pathogenesis of Atherosclerosis

The pathogenesis of atherosclerosis begins with endothelial injury, often triggered by risk factors such as hypertension, smoking, diabetes, and elevated levels of LDL.[23] This injury increases the permeability of the endothelium and promotes inflammation. As LDL infiltrates the arterial wall, it undergoes oxidation, leading to the recruitment of immune cells, particularly monocytes, which differentiate into macrophages and engulf oxidized LDL, forming foam cells. The accumulation of these foam cells contributes to the development of fatty streaks. Smooth muscle cells migrate to the intima, proliferate, and produce extracellular matrix components, forming a fibrous cap over the lipid core, resulting in the formation of atherosclerotic plaques. Over time, these plaques can become unstable and rupture, exposing thrombogenic material to the bloodstream, which may lead to thrombus formation and obstruct blood flow, causing acute CV events such as heart attacks or strokes. Chronic inflammation and calcification may further exacerbate the condition, making atherosclerosis a multifactorial disease influenced by genetic, environmental, and lifestyle factors.[23]

Clinical Evidence for the Effectiveness of Statins in Cardiovascular Events

Statins have been extensively studied in clinical trials for their CV-protective effects, particularly in high-risk patient populations. These trials have consistently demonstrated that statins significantly reduce the risk of CV events, making them a cornerstone in the management of patients with conditions such as venous thromboembolism (VTE), ACS, and in certain cases of diabetes mellitus. The following sections outline key clinical trials and findings that highlight the efficacy of statins in these conditions.

Statins in Venous Thromboembolism

VTE, which includes DVT and PE, has been shown to be potentially preventable with statin therapy, particularly rosuvastatin. The JUPITER study (2009)[24] was the first randomized trial to demonstrate that rosuvastatin significantly reduced the risk of symptomatic VTE by 43% compared with placebo (hazard ratio [HR] of 0.57). Importantly, this benefit was achieved without an increased risk of bleeding episodes, unlike anticoagulants, which carry a significant risk of bleeding complications.

A 2022 meta-analysis of two randomized controlled trials involving 30,507 patients at intermediate CV risk[25] found that rosuvastatin was associated with a HR of 0.53 for VTE risk, reflecting a 47% reduction compared with placebo. This protective effect was consistent across various subgroups, including age, sex, CV risk factors, and history of cancer, with no significant interactions observed.

Moreover, the addition of a nonstatin cholesterol-lowering drug, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i)[c] to statin therapy, provided more pronounced benefits, as demonstrated by a 2024 study analyzing 45 randomized controlled trials (RCTs) involving 254,933 patients.[26] The combination significantly reduced VTE risk by 41% (risk ratio [RR] of 0.59) compared with placebo. In contrast, high-intensity statins alone in the 2024 study showed only a nonsignificant trend (RR = 0.84), differing from the JUPITER trial,[24] which demonstrated a significant reduction in VTE risk with rosuvastatin (HR = 0.57). While the metrics (RR and HR) are not directly comparable, the findings suggest that the benefit of high-intensity statins alone may be less pronounced than the robust effect observed with rosuvastatin in the JUPITER trial. These findings suggest that combining statins with other lipid-lowering agents, such as PCSK9 inhibitors, enhances VTE risk reduction, with higher-intensity regimens correlating with better outcomes.

Collectively, these studies provide strong evidence that statin therapy, particularly rosuvastatin and high-intensity statins combined with PCSK9 inhibitors, is associated with a significant reduction in VTE risk among individuals at CV risk, highlighting the broader benefits of statins beyond cholesterol management.

Statins in Acute Coronary Syndrome

ACS encompasses conditions like unstable angina and myocardial infarction caused by reduced blood flow to the heart,

[b] JMJD3 (KDM6B) is a histone demethylase that removes repressive H3K27me3 marks, activating genes involved in anti-inflammatory responses, macrophage polarization, and cellular differentiation, and its upregulation by statins contributes to their anti-inflammatory and cardioprotective effects.

[c] Normally, PCSK9 binds to LDL receptors on the surface of liver cells, leading to their degradation. This reduces the liver's ability to remove LDL cholesterol from the blood. By inhibiting PCSK9, these drugs increase the number of LDL receptors on liver cells, enhancing the clearance of LDL cholesterol from the bloodstream.

often due to CAD. A recent 2024 meta-analysis[27] of nine trials involving 38,640 ACS patients found that intensive lipid-lowering therapies, such as high-dose statins, significantly reduced the risk of adverse CV events. The analysis showed significant reductions in several adverse outcomes: a 12% lower risk of major adverse cardiovascular events (MACEs; RR = 0.88), an 18% reduction in recurrent ACS events (RR = 0.82), a 13% lower risk of nonfatal myocardial infarction (RR = 0.87), and a 17% decrease in stroke risk (RR = 0.83). Additionally, hospitalizations for unstable angina were reduced by 43% (RR = 0.57). However, no significant effects were observed for all-cause mortality (RR = 0.94), CV-related mortality (RR = 0.96), or coronary revascularization (RR = 0.89). These findings highlight the benefits of intensive statin therapy in reducing CV events, though their impact on mortality remains unclear.

Another meta-analysis[28] of 11 trials involving 6,291 patients (75.4% undergoing PCI) showed that high-dose statin loading reduced major adverse CV and cerebrovascular events (MACCE) by 43% at 30 days (RR = 0.57). This was driven by a 39% reduction in MI (RR = 0.61). However, no significant reduction in all-cause mortality was observed (RR = 0.92). Subgroup analysis revealed a 33% reduction in MACCE for ST-elevation myocardial infarction (STEMI) patients (RR = 0.67) and a 52% reduction for non-ST-elevation ACS (NSTE-ACS) patients (RR = 0.48), suggesting rosuvastatin may be particularly effective in NSTE-ACS.

In conclusion, while statins effectively reduce CV events in ACS patients, their impact on mortality remains uncertain, warranting further research into their long-term benefits.

The Controversy: Statins in Diabetes Mellitus

The increased risk of CV complications in patients with diabetes mellitus (DM) is primarily attributed to endothelial dysfunction,[29] chronic inflammation,[30] and a heightened risk of thrombosis due to metabolic disturbances.[31] These factors interact to create a pathological environment that promotes vascular damage and thrombotic events.

Statins have been studied for their potential CV benefits in patients with DM. By lowering LDL cholesterol and addressing underlying mechanisms such as endothelial dysfunction and chronic inflammation, statins may reduce the risk of major CV events, including myocardial infarction and stroke.[32] Studies have also shown that diabetic patients not receiving guideline-directed statin therapy face a higher risk of stroke and mortality compared with those who do.[33]

However, the use of statins in DM is not without controversy. Research suggests that statins, particularly high-intensity statins like atorvastatin and rosuvastatin, may be associated with an increased risk of new-onset diabetes.[34] A meta-analysis revealed that high-intensity statin therapy was linked to a 36% proportional increase in new-onset diabetes compared with placebo.[35] This has raised concerns about the long-term metabolic effects of statins, especially in patients with prediabetes or other risk factors for diabetes.

Despite these concerns, the potential CV benefits of statins in DM highlight the need for careful patient selection, individualized treatment plans, and regular monitoring to balance the benefits against the risk of developing diabetes.[32,33]

Statins Safety Profile

The use of statins is associated with potential adverse effects. Three notable concerns associated with statin therapy are muscle related side effects, an increased risk of developing DM and elevations in hepatic transaminases.

Muscle-Related Side Effects

Muscle-related side effects of statins can range from mild discomfort (myalgia) to more severe conditions like rhabdomyolysis, although the latter is rare.

Estimating statin-associated muscle symptoms (SAMS) is challenging due to inconsistent definitions across studies. The STOMP study found a 9.4% incidence of myalgia in patients taking atorvastatin compared with 4.6% in the placebo group.[36] In contrast, the ASCOT-LLA and JUPITER trials reported no significant differences in muscle-related events between statin and placebo groups.[37,38] The PROSISA study indicated a 9.6% prevalence of SAMS, particularly among women and physically active individuals,[39] while the PRIMO study found that 10.49% of patients on high-dose statins reported muscular symptoms.[40]

The nocebo effect, where patients experience adverse effects due to negative expectations rather than the drug itself, may explain these variations.[41] Meta-analyses have shown no significant difference in muscle symptoms between statin and placebo groups, supporting this theory.[42] Furthermore, "N-of-1" trials, where individual patients serve as their own controls, have provided additional evidence for the nocebo effect. Studies like SAMSON[43] and StatinWISE[44] demonstrated no significant differences in muscle symptoms between statins and placebo.

In summary, assessing SAMS is complicated by inconsistent definitions and the nocebo effect. While some studies report higher myalgia rates with statins, others find no significant differences compared with placebo, highlighting the need for better patient education and adherence strategies.

Risk of Diabetes Mellitus

Studies have shown that statin therapy is associated with a 10% increase in new-onset diabetes for low- to moderate-intensity statins and a 36% increase for high-intensity statins.[35] A meta-analysis indicated that patients on any statin had an RR of 1.09 for developing diabetes, meaning statin users had a 9% higher risk compared with non-users.[45] High-intensity statins showed an RR of 1.11, indicating an 11% higher risk of diabetes compared with non-users.[46] The risk is notably higher in patients with preexisting risk factors for diabetes, such as older age and elevated baseline glycemic levels.[46] However, in patients with transient ischemic attack, statin use was associated with a lower incidence of diabetes compared with non-users, suggesting variability based on patient context.[47]

In conclusion, the relationship between statin therapy and diabetes risk is characterized by a moderate increase in new-

onset diabetes, particularly with high-intensity statins. While the risk is higher in patients with preexisting diabetes risk factors, the effect varies depending on patient context, underscoring the need for individualized treatment approaches.

Hepatic Enzyme Elevations

Statin-induced liver injury has been associated with both hepatocellular and cholestatic patterns of injury. A hepatocellular pattern of liver injury is defined by a predominant rise in aminotransferases, more specifically alanine aminotransferase (ALT), while a cholestatic pattern is associated with a principal rise in alkaline phosphatase and bilirubin.[48]

The prevalence of statin-induced hepatic enzyme elevations in patients with dyslipidemia is a significant concern in clinical practice, as it highlights the balance between the therapeutic benefits of statins and their potential adverse effects.

A study involving 206 patients undergoing atorvastatin therapy revealed that the majority had normal ALT and aspartate aminotransferase (AST) levels throughout the study, averaging 23.3 and 21.8 IU/L, respectively.[49] Importantly, no significant relationship was found between atorvastatin dosage and changes in liver enzyme levels. However, male patients consistently exhibited significantly higher ALT levels compared with female patients at baseline and throughout the treatment period. These findings indicate that atorvastatin therapy generally maintains liver enzyme levels within normal ranges for most patients, with only a small percentage experiencing elevated ALT and AST. Additionally, gender differences in ALT levels highlight the need for individualized monitoring in clinical practice.[49] Overall, the study supports the safety profile of atorvastatin regarding liver function in patients with dyslipidemia.

On the other hand, another study involving 28 dyslipidemic patients aged 28 to 84 years on statin therapy reported different results.[50] Among the participants, 71.42% had normal serum transferases (AST and ALT), while 28.58% exhibited abnormal levels. The patients with abnormal levels were divided into two groups. Group 1, consisting of five patients on atorvastatin, showed mildly elevated AST and ALT. In contrast, Group 2 included three patients on rosuvastatin with significantly higher elevations (>10 times the normal limit). This group primarily comprised older patients (over 60) with prolonged rosuvastatin use, alongside other chronic conditions such as CV disease, type 2 diabetes, acute pancreatitis, and alcohol abuse.[50] The prevalence of these elevations is influenced by several risk factors, including age, sex, and the presence of concurrent health conditions.

Additionally, the dosage of statins plays a crucial role in determining the likelihood of liver enzyme elevations. Higher doses of statins are correlated with increased liver enzyme levels, although it is important to note that these elevations typically remain below twice the upper limit of normal.[51]

In summary, while mild hepatic transaminase elevations are common in patients treated with statins, significant liver injury is rare. Understanding the prevalence and risk factors associated with these elevations can help clinicians better manage and monitor patients undergoing statin therapy, ensuring that the benefits of lipid-lowering treatment are maximized while minimizing potential hepatic risks.

Cognitive Dysfunction

A systematic review analyzed 14 studies with 68,724 participants to assess the effects of statin therapy on cognitive functions in the elderly.[52] It found that while some research showed neutral effects, others indicated potential benefits, ultimately suggesting that statins do not negatively impact cognitive function. This is reassuring for clinicians and patients, given the widespread use of statins among the elderly.

Another longitudinal study investigated the effects of statin use on individuals diagnosed with Alzheimer's disease (AD).[53] This study measured cognitive function using the Mini-Mental State Examination (MMSE), a widely used tool for assessing cognitive impairment. Over 3 years, statin users demonstrated an average increase of 0.63 points in their MMSE scores compared with those who did not use statins. This improvement, although seemingly modest, suggests a potential protective effect of statins on cognitive decline in AD patients.

On the other hand, a study involving 510 older adults with mild to moderate AD reported that over one-third (34.9%) of participants were prescribed statins during the 18-month duration.[54] No significant association between statin use and cognitive decline or dementia progression was found. This challenges the previous report about the protective effects of statins in this population. Additionally, statin use in this group of patients was not associated with an increase in adverse events, serious adverse events, unscheduled GP visits, or hospitalizations, suggesting that statin therapy can be safely maintained without exacerbating health risks.[54]

These findings underscore the necessity for personalized treatment approaches and further investigation into the long-term effects of statins on cognitive health in general.

The Clinical Consensus versus Individual Variation

Clinical Guidelines

Clinical guidelines from organizations such as the American College of Cardiology (ACC) and the American Heart Association (AHA) advocate for statin use in high-risk populations, including individuals with established CV disease and those with elevated LDL cholesterol levels.[55] These recommendations are based on extensive research demonstrating the drugs' efficacy in reducing CV events.

Individual Variation in Statin Response

The clinical significance of individual variation in statin response is profound, as it directly impacts treatment efficacy and safety. While consensus guidelines provide a framework for statin therapy, they often overlook the substantial interindividual variability in response, which can lead to

suboptimal outcomes. This variability is influenced by genetic, biological, and lifestyle factors, necessitating a more personalized approach to statin therapy.

Genetic Influences on Statin Response

Genetic polymorphisms significantly influence statin metabolism, particularly variations in genes such as SLCO1B1, ABCG2, and CYP2C9.[56] The SLCO1B1 gene encodes a liver transporter that facilitates the uptake of statins into liver cells.[57] Specific variants can reduce this transport activity, leading to higher plasma concentrations of statins and an increased risk of adverse effects like myopathy and rhabdomyolysis. Similarly, ABCG2 is involved in the efflux of drugs from cells, and polymorphisms in this gene can affect statin elimination,[58] further increasing the likelihood of side effects. Moreover, the CYP2C9 gene encodes an enzyme responsible for metabolizing certain statins; genetic variations can alter enzyme activity, resulting in prolonged drug action and a heightened risk of toxicity in individuals with reduced CYP2C9 function.[59] Given these implications, pharmacogenomic testing can identify patients at risk for poor responses or adverse effects, allowing healthcare providers to tailor treatment plans accordingly. By assessing these genetic variations, clinicians can optimize statin therapy, ensuring that patients receive the most effective and safest treatment based on their genetic profiles.[60]

Biological Variation and Treatment Outcomes

Studies indicate that biological factors, particularly cellular lipid trafficking, significantly contribute to the variability in low-density lipoprotein cholesterol (LDL-C) response to statins. Some individuals may maintain a proatherogenic lipid profile despite being on high-intensity statin therapy, suggesting that standard treatment regimens may not be effective for everyone. Research by Hlushchenko et al.[61] reveals that as much as 25% of the variability in LDL-C levels can be attributed to individual differences in lipid uptake and storage mechanisms. This highlights the complexity of lipid metabolism and the need for a more nuanced approach to statin therapy. Integrating genetic and biological assessments into treatment plans allows for more personalized care.[62] Pharmacogenomics (e.g., SLCO1B1 testing) may enable personalized dosing, while novel formulations could target specific tissues (e.g., nanoparticle statins for plaque targeting). These avenues may expand statins' therapeutic roles while optimizing their safety profile.

By understanding each patient's unique genetic makeup and biological responses, healthcare providers can tailor statin therapy to optimize outcomes and minimize risks.

Future Directions

Emerging research explores statins' potential beyond CV protection, including NLRP3 inflammasome modulation for plaque stabilization,[63] antiaging effects via telomerase activation,[64] gut microbiome-mediated efficacy enhancement,[65] neuroprotective applications in AD and stroke recovery,[66] and cancer chemoprevention through mevalonate pathway inhibition.[67]

Conclusion

Statins remain a cornerstone of CV prevention, effectively lowering LDL cholesterol while reducing inflammation and thrombosis to mitigate atherosclerosis and its complications. Though they demonstrate benefits in preventing VTE and ACS, their potential metabolic effects (e.g., diabetes risk) and hepatotoxicity warrant careful patient selection. For high-risk individuals, alternatives like PCSK9 inhibitors or lifestyle modifications may be considered. As personalized medicine advances, guidelines should integrate genetic and biological factors to optimize therapy. Statins will continue to play a pivotal role in CV protection, complemented by tailored approaches for individual risk profiles.

Conflict of Interest

None declared.

Acknowledgment

The language corrections and improvements in this article were assisted by **DeepSeek-V3**, an AI language model, to ensure clarity, grammatical accuracy, and readability. The AI was used solely for language polishing and did not contribute to scientific content, data analysis, or conclusions. The final content was reviewed and approved by the authors to maintain the integrity and originality of the work.

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