REVIEW ARTICLE

Understanding the molecular mechanisms of statin pleiotropic effects

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Abstract

Statins represent the cornerstone of pharmacotherapy for the prevention of atherosclerotic cardiovascular disease. These medications not only reduce low-density lipoprotein cholesterol (LDL-C) via inhibition of 3-hydroxy-3-methylglutarate attached to CoA reductase, the key rate-limiting step in the cholesterol biosynthetic pathway, but also upregulate expression of the low-density lipoprotein receptor, improving serum clearance. Given LDL-C is a causal risk factor for the development of atherosclerosis, these complementary mechanisms largely explain why statin therapy leads to reductions in major adverse cardiovascular events. However, decades of basic and clinical research have suggested that statins may exert other effects independent of LDL-C lowering, termed pleiotropic effects, which have become a topic of debate among the scientific community. While some literature suggests statins may improve plaque stability, reduce inflammation and thrombosis, decrease oxidative stress, and improve endothelial function and vascular tone, other studies have suggested potential harmful pleiotropic effects related to increased risk of muscle-related side effects, diabetes, hemorrhagic stroke, and cognitive decline. Furthermore, the introduction of newer, non-statin LDL-C lowering therapies, including ezetimibe, proprotein convertase subtilisin/Kexin Type 9, and bempedoic acid, have challenged the statin pleiotropy theory. This review aims to provide a historical background on the development of statins, explore the mechanistic underpinnings of statin pleiotropy, review the available literature, and provide up to date examples that suggest statins may exert effects outside of LDL-C lowering and the cardiovascular system.

Keywords Statin · Cholesterol · LDL · Cardiovascular disease · Atherosclerosis

Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death and disability in the United States, regardless of sex and race/ethnicity (Arnett et al. 2019; Tsao et al. 2022). However, tremendous advances in our understanding and management of atherosclerosis over the prior decades have led to significant improvements in morbidity and mortality from cardiovascular disease, with death rates from ASCVD declining since the early 1980s largely due to risk factor control and implementation of low-density lipoprotein cholesterol (LDL-C) lowering statin therapy (Tsao et al. 2022). However, data from several large studies have uncovered other potential beneficial cardiovascular aspects independent of LDL-C lowering, referred to as statin 'pleiotropic' effects. The purpose of this document is to explore potential pleiotropic effects of statin therapy in the context of the present literature.

Atherogenesis and the fatty streak

The accumulation of atherogenic lipoproteins into the arterial wall initiates a series of specific cell reactions resulting in atherosclerosis. When triggered, activated endothelial cells that line the arterial lumen guide the recruitment of blood leukocytes. When exposed to an atherogenic environment, endothelial cells express leukocyte adhesion molecules and chemokines that facilitate the attachment of monocytes and lymphocytes to the intimal surface. Mononuclear phagocytes can multiply at the site of lesion initiation, and engulf lipids to become foam cells, the trademark of atherosclerotic lesions (Libby 2021). This leads to an inflammatory cascade inducing smooth muscle

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proliferation and migration into the intima, forming the earliest stages of atherosclerotic plaque, which constitutes a Type I lesion (Stary et al. 1994).

Type II lesions consist of layers of lipid-laden foam cells and smooth muscle cells that aggregate forming the first grossly visible sign of atherosclerosis, the fatty streak (Stary et al. 1994). Evidence of aortic fatty streaks dates back to World War I and the Korean War, uncovered from autopsy studies of young men that died in the field. These observations stimulated the medical community and prompted our understanding that atherosclerosis begins in childhood (Berenson et al. 1998; Mönckeberg 1915). The revolutionary Bogalusa Heart Study, which assessed young individuals 2–39 years of age that had an autopsy, found that all individuals studied had evidence of fatty streaks in the aorta, and half of children 2–15 years of age had fatty streaks in their coronary arteries (Berenson et al. 1998).

Total and LDL-cholesterol

The relationship between cholesterol and heart disease was proposed as early as 1938, when Norwegian physician Carl Muller described families with high plasma cholesterol levels that were transmitted in an autosomal dominant fashion, leading to early cardiovascular disease and death (Müller 1938). This disease was named familial hypercholesterolemia (FH). These individuals carried a 20-fold increase in heart attack risk by middle age. Then, in 1951, cardiologists from Massachusetts General Hospital made the observation that heart attacks were more common among individuals with high blood cholesterol, among other now well regarded risk factors (Gertler et al. 1951). A few years later, Ancel Keys launched one of the earliest large epidemiological cohorts called the Seven Countries Study, which demonstrated that serum cholesterol increased in proportion to total dietary fat intake and saturated fatty acid intake, and that heart attack incidence was associated with serum cholesterol levels in a linear fashion (Feinleib 1981; Goldstein and Brown 2015). This concept was then cemented in the landmark Framingham Heart Study, which firmly established the relationship between high serum cholesterol and incident coronary heart disease (Kannel et al. 1961).

The invention of the ultracentrifuge ignited the era of LDL-C, when John Gofman utilized this technology in 1955 to separate lipoproteins according to density (Gofman et al. 2007). LDL-C and high-density lipoprotein cholesterol (HDL-C) were identified, and Gofman went on to discover that heart attacks were more common among individuals with high LDL-C, and less common among individuals with high HDL-C.

Cholesterol biosynthesis and statin therapy

Once the connection between LDL-C and ASCVD was solidified in the 1950s, an intense effort was undertaken by a group of biochemists to understand cholesterol biosynthesis. The identification of the 6-carbon compound 3-hydroxy-3-methylglutarate attached to CoA (HMG CoA) as an important compound committed entirely to the synthesis of cholesterol and other isoprenoids led to the discovery of HMG CoA reductase as the rate-limiting step in the cholesterol pathway (Bucher et al. 1960). Then, in 1972, Michael Brown and Joseph Goldstein began to study mediators of the synthetic cholesterol pathway after meeting young siblings found to have homozygous familial hypercholesterolemia (FH) (Goldstein and Brown 2015). They obtained skin biopsies from patients with homozygous FH and controls and cultured fibroblasts to better understand how these cells utilize cholesterol to maintain the integrity of their cell membranes. In the controls, they discovered that cholesterol was obtained from two sources: endogenous synthesis from the aforementioned biosynthetic pathway, and from receptor mediated uptake and lysosomal hydrolysis of LDL particles. Additionally, these two processes worked in harmony. When cellular levels of cholesterol were high, LDL receptors and HMG CoA reductase levels decreased. When cholesterol levels were low, LDL receptors and HMG CoA reductase levels increased (Brown and Goldstein 1986). This was in sharp contrast to the fibroblasts cultured from homozygous FH patients, which were found to have defective LDL receptors and HMG CoA reductase activity 100-fold above normal (Goldstein and Brown 1973).

Akira Endo, a Japanese biochemist working at the Sankyo Company in Tokyo, was the first to identify an inhibitor of HMG CoA reductase. This compound, named compactin, was isolated from *Penicillium citrinum* mold, and is widely regarded as the first statin (Endo 2010). Soon afterwards, Alfred Alberts and colleagues discovered mevinolin (later named Mevacor or lovastatin) (Alberts et al. 1980), another fungal HMG CoA reductase inhibitor, which was shown to increase LDL receptor activity and decrease plasma LDL in dogs treated with this compound (Kovanen et al. 1981). Human studies demonstrating similar LDL-C lowering followed (Vega and Grundy 1991), which led to the commercialization of the first statin approved for human use in 1987, lovastatin, produced by Merck. Finally, in 1994, Merck's second-generation statin, simvastatin, was studied in the Scandinavian Simvastatin Survival Study (4S), which established that this medication reduced heart attacks and prolonged life in a population at high risk of ASCVD, when compared with placebo (Group 1994).

Table 1 Randomized-controlled trials demonstrating potential pleiotropic effects

Name of trial	Year	Statin	Control	Total (n)	Primary outcome	Potential pleiotropic effect
4S	1994	Simvastatin 20–40 mg	Placebo	4444	Mortality, 11.5% versus 8.2%. $p < 0.01$	↓ Stroke
AFCAPS/TEXCAPS	1995	Lovastatin 20-40 mg	Placebo	6605	Fatal or nonfatal MI, UA, or sudden cardiac death, 6.8% versus 10.9%, $p < 0.01$	↓ Incident melanoma
CARE	1996	Pravastatin 40 mg	Placebo	4159	Fatal or nonfatal MI, 13.2% versus 10.2%, $p < 0.01$	↓ Stroke
LIPID	1998	Pravastatin 40 mg	Placebo	9014	CHD death, 6.4% versus 8.3%, $p < 0.01$	↓ Stroke
WOSCOPS	1998	Pravastatin 40 mg	Placebo	6595	Nonfatal MI and CHD death, 5.5% versus 7.9%, $p < 0.01$	↑ Time to benefit
MIRACL	2001	Atorvastatin 80 mg	Placebo	3086	Mortality, nonfatal MI, cardiac arrest, or ACS rehospitalization, 14.8% versus 17.4%, $p = 0.048$ ↑	Time to benefit
HPS	2002	Simvastatin 40 mg	Placebo	20,536	Mortality, 12.9% versus 14.7%, $p < 0.01$	↓Overall stroke, ↑ Hemorrhagic stroke*
PROVE IT-TIMI 22	2004	Atorvastatin 80 mg	Pravastatin 40 mg	4162	Mortality, MI, UA rehospitalization, revascularization in 30 days, or stroke, 22.4% versus 26.3%, $p < 0.01$**	↑ Time to benefit
TNT	2005	Atorvastatin 80 mg	Atorvastatin 10 mg	10,001	CAD mortality, nonfatal MI, cardiac arrest, or fatal or nonfatal stroke, 10.9% versus 8.7%, $p < 0.01$	↓ Stroke
SPARCL	2006	Atorvastatin 80 mg	Placebo	4731	Fatal or nonfatal stroke, 11.2% versus 13.1%, $p = 0.03$	↓ Overall stroke, ↑ Hemorrhagic stroke
ARMYDA-3	2006	Atorvastatin 40 mg	Placebo	200	Postoperative AF, 35% versus 57%, $p = < 0.01$	↓ Atrial fibrillation
CORONA	2007	Rosuvastatin 10 mg	Placebo	5011	CV death, nonfatal MI, or nonfatal stroke, 12.3% versus 11.4%, $p = 0.12$	↑ Diabetes***
JUPITER	2008	Rosuvastatin 20 mg	Placebo	17,802	Nonfatal MI, stroke, UA hospitalization, arterial revascularization, or CV death, 0.77 and 1.36 per 100 person-years, $p < 0.01$	↓ Cancer mortality, VTE, hsCRP, ↑ Diabetes
IMPROVE-IT	2015	Simvastatin 40-80 mg	Simvastatin 40 mg	18,144	CV death, major CV event, or nonfatal stroke, 34.7% versus 32.7%, $p = 0.02$	↓ Ischemic Stroke
HOPE-3	2016	Rosuvastatin 10 mg	Placebo	12,705	CV death, MI, stroke, cardiac arrest, HF, revascularization, 4.8% versus 6.2%, $p < 0.01$	↑ Cataract surgery
STICS	2016	Rosuvastatin 20 mg	Placebo	1922	Post-op AF and peri-op MI, 21% versus 20%, $p = 0.72$, between-group difference 1%, $p = 0.08$	↑ Acute Kidney Injury

*Among participants with a history of cerebrovascular disease

**p not significant for equivalence; p 0.005 for superiority

***nonsignificant trend towards incident diabetes

Randomized control trial evidence for statin pleiotropy

Several randomized-controlled trials have offered credence to the statin pleiotropy hypothesis, as summarized in Table 1. As mentioned, the 4S program was one of the first large trials to demonstrate a linear relationship between LDL-C reduction and cardiovascular event rates (Group 1994) This relationship was further promoted in the Cholesterol Treatment Trialists meta-analysis, which suggests that a 1 mmol/L reduction in LDL-C (roughly equivalent to 39 mg/dL) is associated with a 21% decrease in 5-year incidence of major adverse cardiovascular events (Baigent et al. 2005). Several other large studies, including cholesterol and recurrent events (CARE) (Sacks et al. 1996), heart progression study (HPS) (Heart Protection Study Collaborative Group 2002), long-term intervention with pravastatin in ischemic disease (LIPID) (Tonkin et al. 1998), and treating to new targets (TNT) (LaRosa et al. 2005), helped firmly establish the widely held notion that the magnitude of clinical benefit observed with statin therapy is proportional to the absolute reduction in LDL-C.

The mechanistic properties of statin therapy may not exclusively explain the outcomes observed in many large randomized-controlled trials. For example, a meta-analysis of 33 trials demonstrated that several non-statin therapies that increase LDL receptor activity have similar LDL-C lowering and cardiovascular benefits when compared with statins (Silverman et al. 2016). Trials with non-statin therapies often require more time to derive cardiovascular benefits. While the time to benefit is largely within 5 years for the majority of statin trials, the lipid research clinic-coronary primary prevention trial (LRC-CPPT; cholestyramine), (The Lipid Metabolism-Atherosclerosis Brach NHLBI 1984) program on the surgical control of hyperlipidemias (POSCH; partial ileal loop bypass surgery) (Buchwald et al. 1990), and ezetimibe added to statin therapy after acute coronary syndromes (IMPROVE-IT; ezetimibe in addition to simvastatin) trial (Cannon et al. 2015) demonstrated benefit within 7.4, 9.7, and 7.0 years, respectively. In fact, the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study demonstrated measurable clinical benefit at 16 weeks (Schwartz et al. 2001), while the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial (Cannon et al. 2004) demonstrated benefit at 30 days. This rapid time to cardiovascular benefit may not be fully explained by the LDL-C lowering properties of statin therapy.

Further pleiotropic effects may be mediated by changes in inflammation of the cardiovascular system. A large body of clinical research indicates that inflammation is a fundamental component of atherogenesis and development of ischemic cardiovascular disease (Libby and Hansson 2019). The inflammatory cytokine C-reactive protein (CRP) is a sensitive biomarker of risk for CVD (Ridker et al. 2018), now serving as a risk enhancer in American College of Cardiology/American Heart Association (ACC/AHA) guidelines (Grundy et al. 2018), and can be modulated by statin therapy. In the Pravastatin Inflammation/CRP Evaluation (PRINCE) trial, pravastatin lowered CRP at 12 and 24 weeks from drug initiation, in a largely LDL-C independent fashion (Albert et al. 2001). These results were consistent with data from the CARE trial (Ridker et al. 1998), and MIRACL trial (Schwartz et al. 2001), which used atorvastatin. Then, the rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein (CRP) (JUPITER) trial found that rosuvastatin reduced LDL-C and high-sensitivity CRP by 50% and 37%, respectively (Ridker et al. 2008). This translated to significant reductions in the primary composite cardiovascular endpoint and all cause-mortality, despite baseline LDL-C levels that were relatively well controlled (mean LDL-C 108 mg/dL in both rosuvastatin and placebo arms) (Ridker et al. 2008). Other large randomized-controlled trials have been undertaken to understand if targeted anti-inflammatory medications reduce CVD, with mixed results. While the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) (Ridker et al. 2017), Low-Dose Colchicine (LoDoCo) trial (Nidorf et al. 2020), and Colchicine Cardiovascular Outcomes (COLCOT) Trial (Tardif et al. 2019) demonstrated reductions in cardiovascular outcomes, the Cardiovascular Inflammation Reduction Trial (CIRT) failed to reduce cardiovascular events among patients treated with methotrexate (Ridker et al. 2019). While some postulate that CIRT was a negative trial, because it failed to show a reduction in CRP, Mendelian randomization studies have shown that CRP may not be a causal factor in the development of CVD (Collaboration et al. 2011). These disparate findings highlight the lack of clarity that remains on the complex relationship between statin therapy, CRP, inflammation, and ASCVD.

Several of the aforementioned large randomized-controlled trials also found that statins reduce the primary incidence of stroke (2002; Group 1994; LaRosa et al. 2005; Sacks et al. 1996), suggesting pleiotropic effects beyond coronary heart disease. This is particularly noteworthy given data from observational studies have not shown an association between LDL-C and stroke (Bots et al. 2002; Leppälä et al. 1999; Shahar et al. 2003). The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial confirmed this relationship in a secondary prevention of stroke population, which demonstrated a 16% reduction in stroke among patients in the atorvastatin arm (Amarenco et al. 2006).

Furthermore, evidence from the Atorvastatin for Reduction of MYocardial Dysrhythmia After cardiac surgery (ARMYDA-3) clinical trial showed that treatment with atorvastatin initiated 7 days prior to surgery lowers the risk of post-operative atrial fibrillation, and subsequently shortens hospital stay when compared with placebo (Patti et al. 2006). However, these results were not substantiated in the Statin Therapy in Cardiac Surgery (STICS) trial, which demonstrated that patients taking perioperative statin therapy did not prevent post-operative atrial fibrillation among those undergoing elective surgery (Zheng et al. 2016). Given these disparate results, one cannot conclude with certainty that statins are beneficial in preventing atrial fibrillation after cardiac surgery, though we cannot exclude the possibility of statin pleiotropy either. Thus, further investigation is warranted.

Possible mechanisms of statin pleiotropy

Given the multitude of clinical trials that suggested health benefits of statins beyond LDL-C lowering, scientists have sought to better understand the mechanistic underpinnings to better explain trial results (Fig. 1).

Improved endothelial function and vascular tone

Endothelial injury, which can occur in the setting of hypercholesterolemia, constitutes one of the earliest step in the development of atherosclerotic cardiovascular disease.

When the endothelium is injured and becomes dysfunctional, endothelium-derived nitric oxide (NO) is released, which mediates not only vasodilation, but also inhibits leukocyte adhesion and platelet aggregation, and decreases vascular smooth muscle proliferation (Janssens et al. 1998). Thus, NO is protective, and low levels of NO predict an increased risk of cardiovascular events (Liao et al. 1991).

Statins upregulate endothelial NO synthase (eNOS) and therefore increase NO bioavailability, through a variety of mechanisms and pathways (Oesterle and Liao 2019). For example, statins increase eNOS expression by prolonging eNOS mRNA half-life. This is mediated by inhibition of RhoA geranylgeranylation, modification of the cytoskeleton, and localization of the eNOS mRNA (Laufs and Liao 1998). Statins also reduce caveolin-1, an integral membrane protein which binds eNOS inhibiting its ability to NO (Plenz et al. 2004). There is also evidence that statin therapy can activate the phosphatidylinositol 3-kinase (PI3K)/protein kinase Akt pathway (Kureishi et al. 2000), which leads to increased eNOS and plays a role in the regulation of cellular survival, growth, and proliferation (Simoncini et al. 2000).

Statins also modulate the fibrinolytic system of vascular smooth muscle and endothelial cells (Bourcier and Libby 2000). In a rat model, statin therapy increased the expression of tissue-type plasminogen activator and inhibited the expression of PAI-1 (Essig et al. 1998), an endogenous inhibitor of tissue plasminogen activator, mediated in part through the (PI3K)/protein kinase Akt pathway (Mukai et al. 2007). Statins also inhibit the expression of prepro
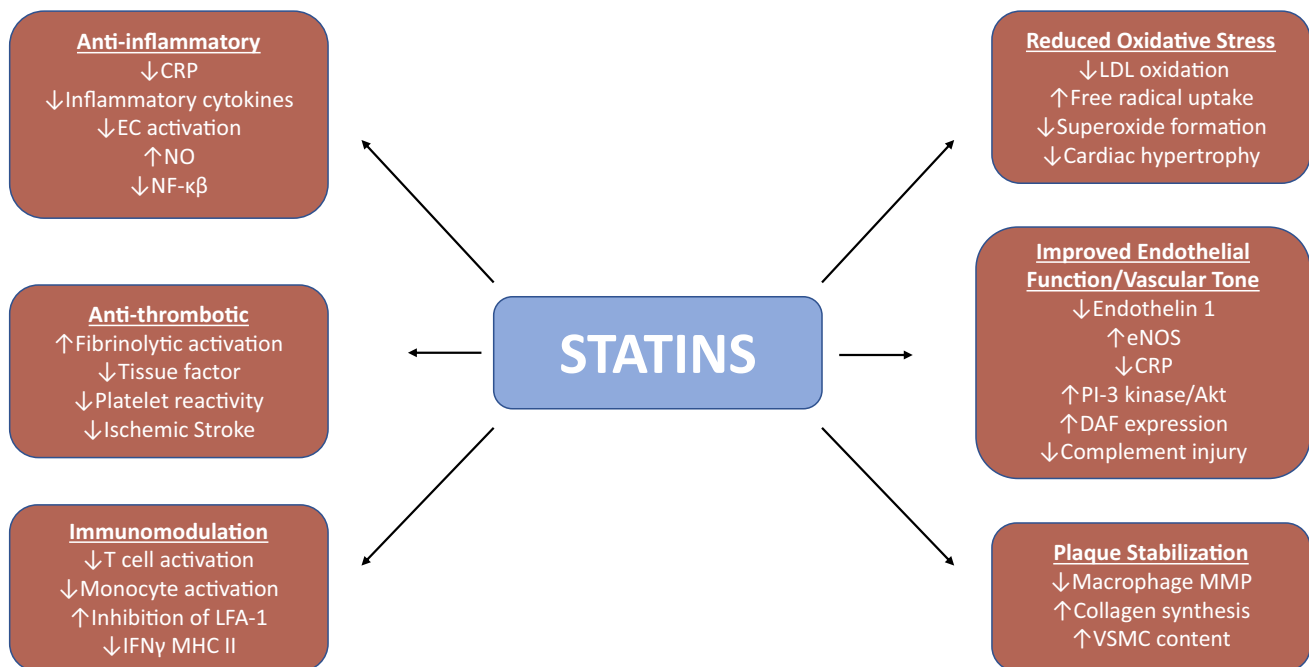

Fig. 1 Mechanisms of statin pleiotropic effects

endothelin-1(Hernández-Perera et al. 2000) and reduce endoethelin and angiotensin subtype I receptor expression (Ichiki et al. 2001; Xu et al. 2002). These vasoconstricting agents, which may be elevated in patients with severe atherosclerosis (Lerman et al. 1991), counteract the vasodilation effects of NO and may contribute towards the development of atherosclerotic plaque.

Plaque stabilization

Several clinical trials using intravascular ultrasound (IVUS) technology helped establish the notion that statin therapy, particularly high-intensity statin therapy, may result in plaque stabilization and regression. In the Reversal of Atherosclerosis with Aggressive Lipid-Lowering (REVEAL) trial published in 2004, Nissen et al. showed that patients with coronary heart disease taking 80 mg of atorvastatin had no progression of atheroma volume at 18 months, though patients taking 40 mg of pravastatin showed progression of atherosclerosis (Nissen et al. 2004). Two years later, A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) showed that 40 mg of rosuvastatin resulted in modest atherosclerotic plaque regression at 24 months of therapy (Nissen et al. 2006). These studies demonstrated the efficacy of high-intensity statin therapy on atheroma volume. Then, in 2011, Nicholls et al. published The Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN) trial, which sought to investigate which high-intensity statin achieved greater plaque stability. After 2 years of therapy, patients taking 40 mg of rosuvastatin had lower LDL-C compared with patients taking 80 mg of atorvastatin (62.6 vs. 70.2 mg/dL, respectively), a similar degree of plaque atheroma regression was observed (Nicholls et al. 2011).

Newer technology, including optical coherence tomography (OCT), has enabled researchers the ability to utilize high resolution imaging for characterization of atherosclerotic plaque. The Effect of Atorvastatin Therapy on Fibrous Cap Thickness in Coronary Atherosclerotic Plaque as Assessed by Optical Coherence Tomography (EASY-FIT) Study utilized OCT to show that atorvastatin 20 mg resulted in a greater increase in fibrous cap thickness compared with atorvastatin 5 mg (Komukai et al. 2014). The Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging (PARADIGM) study used a non-invasive imaging technique, coronary computed tomography angiography, to demonstrate that individuals on statins had a slower rate of percent atheroma volume progression, increased plaque calcification, and reductions in other high-risk plaque features when compared with statin-naïve patients. Importantly, despite increases in calcification,

there was no increase in stenosis severity among patients on statin therapy (Lee et al. 2018).

Anti-inflammatory

In addition to the clinical trial evidence suggesting a possible CRP mediated anti-inflammatory role on the relationship between statins and CVD, observations also align with in vitro and basic science evidence as well. In one study, simvastatin, atorvastatin, and lovastatin were shown to downregulate nuclear factor-kappa B (NF-kappaB), activator protein-1, and hypoxia-inducible factor-1alpha in endothelial and arterial smooth muscle cells, which play a role in downstream activity of pro-inflammatory cytokines, chemokines, adhesion molecules, and growth factors (Dichtl et al. 2003).

Statins also may play a role in the regulation of T-cell phenotype by blunting pro-inflammatory IL-17 helper T-cell differentiation (Kagami et al. 2009), and promoting the expression of FoxP3 regulatory T cells that induce immune tolerance (Kagami et al. 2009). Antigen presenting cells express major histocompatibility complex II, which is propagated in the presence of interferon-γ. Statins have been shown to reduce the expression of major histocompatibility complex II on antigen presenting cells, ultimately leading to decreased activation of T cells (Kavalipati et al. 2015). Moreover, statins also can bind to an allosteric site within β_2-integrin function-associated antigen-1 protein, leading to its inhibition, which then decreases lymphocyte adhesion and impairs T-cell co-stimulation (Weitz-Schmidt et al. 2001).

Anti-thrombotic

During an acute coronary syndrome, intracoronary plaque ruptures leading to platelet aggregation and partial or complete occlusion of the artery, which then leads to ischemia and acute myocardial infarction. Interestingly, hypercholesterolemia is associated with increased platelet reactivity (Opper et al. 1995), potentially mediated by increases in platelet cytosolic calcium (Le Quan Sang et al. 1995), platelet α_2-adrenergic receptor density (Baldassarre et al. 1997), and thromboxane A_2 biosynthesis (Notarbartolo et al. 1995). Therefore, lowering LDL-C via statin therapy may lessen these pro-thrombotic characteristics.

In mice, atorvastatin therapy led to a reduction in platelet factor 4 and β-thromboglobulin, which are upregulated in states of platelet reactivity (Kaplan and Owen 1981; Laufs et al. 2000). Studies of fluvastatin, acting through PPARα and PPAR-γ, have demonstrated reduced platelet aggregation when compared with colestimide (Ali et al. 2009; Haramaki et al. 2007). Similarly, atorvastatin acutely decreases Nox2, Rac1, platelet phospholipase A2, protein kinase C, thromboxane A2, while increasing nitric oxide levels (Pignatelli et al. 2012). Another study utilizing several different

statins demonstrated augmentation of Kruppel-like factor 2 activity, promotion of thrombomodulin expression, and enhancement of the protein C anticoagulation pathway (Sen-Banerjee et al. 2005).

These effects were corroborated clinically in observational studies and randomized-controlled trials. In the Heart and Estrogen/progestin Replacement Study, the risks for thromboembolic events were decreased by 50% among participants taking statins (Grady et al. 2000). Another study showed that statin use was associated with a 22% relative risk reduction in the risk of deep vein thrombosis (Ray et al. 2001). In the JUPITER trial, patients taking rosuvastatin experienced less thromboembolism compared with the control group (Glynn et al. 2009). Given hypercholesterolemia is not a particularly strong risk factor for venous thromboembolism, it remains unlikely this outcome was driven by LDL-C reduction alone (Oesterle et al. 2017).

Decreased oxidative stress

Oxidation of LDL particles in the vascular endothelium constitute one of the key initial drivers of atherosclerotic plaque formation. Both in vitro and ex vivo evidence suggests that statins have direct antioxidant properties (Aviram et al. 1998a; Suzumura et al. 1999). Atorvastatin hydroxy-metabolites, for example, inhibit oxidation of LDL, HDL, and VLDL particles, which suggests an antioxidant effect may also contribute to halt progression of atherosclerosis, independent of LDL-C lowering (Aviram et al. 1998b). These metabolites, which represent roughly 70% of active atorvastatin, accomplish this by scavenging free radicals. Another possible mechanism may be attributable to statins capacity to decrease the ability of macrophages to oxidize lipoproteins (Giroux et al. 1993), via decreasing the activity

of macrophage CD36, a receptor for oxidized LDL (Fuhrman et al. 2002).

Additionally, the ability of statins to inhibit the production L-Mevalonate from 3-hydoxy-3-methylglutaryl-CoA in the cholesterol biosynthetic pathway also leads to inhibition of downstream production of Rac1 (Oesterle et al. 2017). This G protein member of the Rho GTPase subfamily activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and also mediates the production of reactive oxygen species (ROS) (Takemoto et al. 2001), which can contribute to endothelial dysfunction, inflammation, and oxidation of LDL particles, which all contribute towards the development of atherosclerosis (Miller et al. 2010; Nowak et al. 2017). Irrespective of ROS, statins have demonstrated an ability to attenuate downstream deleterious effects of Rac1 and NADPH oxidase activity which may partially explain how these mediates decrease oxidative stress and inhibit atherosclerosis.

Potential negative non-cardiovascular pleiotropic effects

Statin-associated muscle symptoms

Several off-target, negative side effects have commonly been associated with statin therapy, which also contributes to the notion of statin pleiotropy (Fig. 2). Statin intolerance, a clinical syndrome comprising a variety of statin-associated muscle symptoms (SAMS) and signs pertaining to multiple organ systems, is common and can lead to discontinuation in up to 53% of patients (Lin et al. 2016). The most frequent side effects pertain to skeletal muscle-related symptoms (myalgia) which commonly include muscle aches, soreness, and cramping, though myopathy, myositis,
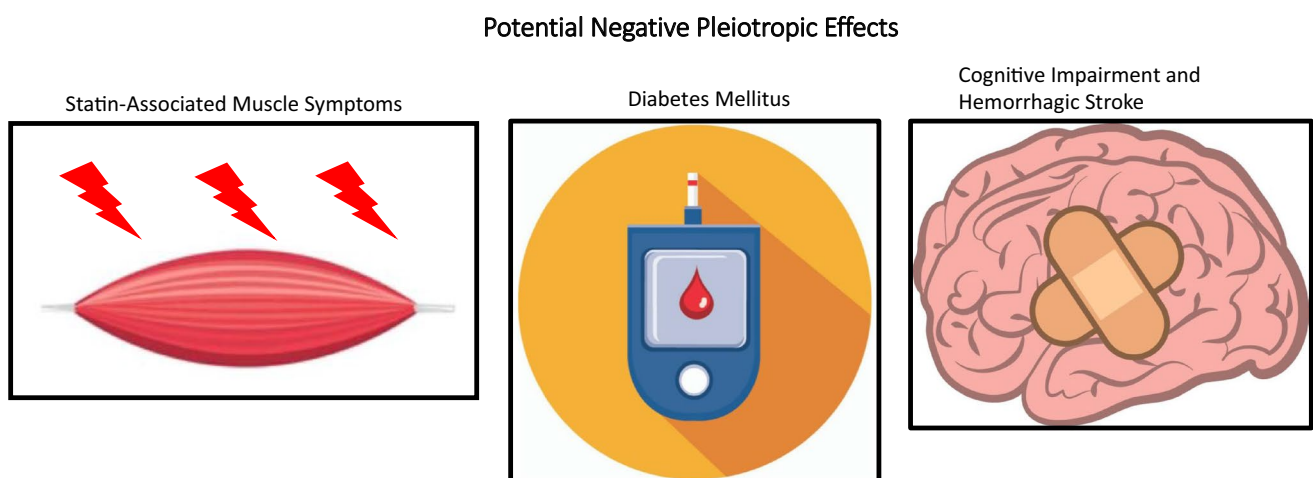
Potential Negative Pleiotropic Effects

Fig. 2 Potential negative statin pleiotropic effects

and rhabdomyolysis may also occur in rare cases (Cheeley et al. 2022). The diagnosis of SAMS is subjective; however, organizations like the National Lipid Association have proposed a scoring system based on regional distribution, temporal patterns, and symptoms related to initiation and withdrawal of the medication (Rosenson et al. 2014).

Risk factors for SAMS include female sex, advanced age, lower body mass index, hypothyroidism, vitamin D deficiency, physical disability, and high statin doses (Schech et al. 2007). Roughly 75% of statins are metabolized by the cytochrome P450 (CYP) system in the liver; atorvastatin, simvastatin, and lovastatin use the 3A4 isoenzyme for metabolism (Guengerich 2008). Thus, medications that also use CYP3A4 can increase statin concentrations by competing for catabolism, thereby precipitating SAMS. Grapefruit juice and other tropical juices such as pomegranate and starfruit contain CYP3A4 as well, which may lead to increased systemic statin concentrations (Sorokin et al. 2006). Alternatively, fluvastatin, pitavastatin, and rosuvastatin are metabolized predominantly by CYP2C9, with lesser contributions from CYP3A4 (fluvastatin), CYP2C8 (fluvastatin, pitavastatin), and CYP2C19 (rosuvastatin) (Thompson Paul et al. 2016). Given fewer medications depend on non-CYP3A4 metabolism, there is less risk of drug interactions and subsequent SAMS.

Although the exact pathophysiology SAMS is poorly understood, in vitro studies suggest that reductions in intracellular cholesterol may facilitate cell membrane instability and lysis (Bouitbir et al. 2020). Statins also adversely impact sarcoplasmic reticulum calcium handling (Lotteau et al. 2019), and genetic variants with a missense mutation of leukocyte immunoglobulin-like receptor subfamily B and T521C polymorphism of organic anion transport protein 1B1 can predispose certain individuals to SAMS (Link et al. 2008; Siddiqui et al. 2017). Statin therapy also inhibit the ubiquinone pathway involved in mitochondrial electron transport, thereby decreasing energy production and increasing intracellular levels of reactive oxygen species (Baigent et al. 2010). Interestingly, studies have suggested that supplementation with coenzyme Q10 (i.e., ubiquinone) can reverse mitochondrial dysfunction induced by statins in mice (Muraki et al. 2012). This observation, which has been substantiated in human studies (Qu et al. 2018), led to the notion that coenzyme Q10 may be a viable therapy for SAMS. However, the data have been inconsistent (Banach et al. 2015; Schaefer et al. 2004), and no convincing evidence has emerged on the ability of coenzyme Q10 to mitigate SAMS.

Managing patients with SAMS can be challenging, though several strategies may help facilitate adherence. When symptoms arise, the medication should be stopped until symptom resolution. Measurement of creatinine kinase and liver function tests should be obtained to exclude end organ damage. Patients can then be re-challenged with a lower dose of the same statin, or alternative statins can be trialed. Statins with longer half-lives, such as rosuvastatin, atorvastatin, and pitavastatin, can also be given every other day or less frequently (Keating et al. 2013; Thompson Paul et al. 2016). Data suggest that ≤ 10 mg rosuvastatin given twice weekly reduces LDL-C by 26%. Contributing factors, such as vitamin D deficiency and hypothyroidism, should be excluded and treated, and a thorough medication reconciliation should be done to identify medications with significant statin interactions. Furthermore, it is possible that a considerable proportion of patients that experience SAMS may be due to the "nocebo effect," a phenomenon in which negative expectations about medicine or a treatment manifest as real symptoms, which is associated with early discontinuation (Nielsen and Nordestgaard 2015). The innovative Self-Assessment Method for Statin Side-effects Or Nocebo (SAMPSON) trial was designed to test the nocebo effect of SAMS among statin users, and found that in participants who had discontinued statin therapy because of side effects, 90% of the symptom burden elicited by the statin was also elicited by placebo. With this knowledge in hand, 50% of participants previously diagnosed with SAMS were able to re-start their statin 6 months after the conclusion of the trial (Howard et al. 2021). Thus, similar strategies could be utilized in clinical practice to mitigate SAMS.

Cognitive impairment and hemorrhagic stroke

In 2012, the US Food and Drug Administration issued a black box warning regarding an association between statin use and cognitive impairment, based on several small studies conducted in the 1990s and early 2000s (Schultz et al. 2018). These side effects may have been driven by the ability of some statins (i.e., lipophilic statins) to cross the blood–brain barrier, leading to the potential for neurotoxicity and cognitive impairment. Additionally, genes encoding cytochrome P450 enzymes, mitochondrial enzymes, and influx and efflux transporters may explain differential cognitive side effects among individuals on statins (Canestaro et al. 2014). Conversely, statins also have been shown to reduce neuroinflammation and amyloid β in animal models of Alzheimer's disease, which support the concept that statins may also have beneficial effects on cognitive function.

Despite early concerns, contemporary data from randomized-controlled trials and meta-analyses found no clear, consistent association between statins and cognitive side effects (Adhikari et al. 2021; Giugliano et al. 2017; Zhou et al. 2021). In fact, the Heart and Estrogen/progestin Replacement Study and Cardiovascular Health Study both showed that statin use was associated with a reduction in cognitive decline among older adults (Bernick et al. 2005; Yaffe et al. 2002). Beneficial cognitive effects were

also observed in a meta-analysis of 7 observational studies, concluding that statin use not only reduced the risk of cognitive decline, but also Alzheimer's disease (Etminan et al. 2003; Sparks et al. 2008). Given significant heterogeneity in study results, the 2013 ACC/AHA Cholesterol Guidelines concluded that the evidence suggests no adverse effect on cognitive changes or risk of dementia among individuals on statin therapy (Stone et al. 2014). At present, 2 large ongoing randomized-controlled trials are underway to assess the cognitive effects of statin use, specifically among older adults. The Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults (PREVENTABLE) trial aims to enroll 20,000 primary prevention patients ≥ 75 years of age, and will be randomized to atorvastatin 40 mg daily or placebo. The primary outcome is incident dementia and physical disability. The Clinical Trial of Statin Therapy for Reducing Events in the Elderly (STAREE) trial will assess the efficacy of atorvastatin 40 mg versus placebo among 18,000 patients ≥ 70 years of age, and will assess incident death or development of dementia as well as cardiovascular events. These trials should help provide clarity to important questions surrounding the cognitive effects related to statin use among older adults.

Another neurological concern was unearthed from the SPARCL trial, mentioned previously. Despite atorvastatin lowering the incidence of overall stroke and cardiovascular events, there was a small increase in incident hemorrhagic stroke (Amarenco et al. 2006). Some hypothesized that this may have been driven by statin's antithrombotic, fibrinolytic pleiotropic effects (Violi et al. 2013). However, a study by Ribe et al. used data from a large Danish registry of > 55,000 individuals found no evidence that statins increase the risk of intracerebral hemorrhage over 10 years of follow-up (Ribe et al. 2020). Current ACC/AHA cholesterol guidelines note that this potential side effect is "unfounded" (Grundy et al. 2018).

Diabetes mellitus

Diabetes mellitus is a potent risk factor for the development of ASCVD, such that guidelines suggest at least a moderate intensity statin among individuals 40–75 years of age, regardless of their 10-year ASCVD risk score (Grundy et al. 2018). However, both clinical trial and observational data have suggested a link between statin use and incident diabetes, causing concern among both clinicians and patients. In the JUPITER trial, glycated hemoglobin concentrations were higher among those on rosuvastatin, and a small increase in incident diabetes mellitus was observed (3.0% vs 2.4%, $p = 0.01$) when compared with placebo (Ridker et al. 2008, 2012). Several other large-scale cardiovascular clinical trials have either demonstrated a null or modest positive association with statin use, with meta-analyses suggesting a

statistically significant increased risk (Rajpathak et al. 2009; Sattar et al. 2010a). These relationships appear to be time and dose dependent, with both cumulative dosing and higher potency statins showing stronger relationships (Ko et al. 2019). Additionally, incident diabetes was also more common among those with other risk factors, including overweight and obesity, impaired fasting glucose, and metabolic syndrome (Waters et al. 2011, 2013). Although mechanisms remain unclear, it is possible that individuals already predisposed to diabetes may cross the threshold to overt disease. However, the annual risk of new onset diabetes among those treated with statins is roughly 0.1% (Sattar et al. 2010b), and the absolute risk reduction in major adverse cardiovascular events is roughly 0.42% annually (Cholesterol Treatment Trialists 2012). Therefore, the cardiovascular benefits far outweigh the risk of incident diabetes, and this concern should not be considered a contraindication to statin therapy and should not lead to statin discontinuation (Grundy et al. 2018).

Challenges to the hypothesis: non-statin lipid lowering therapy

Although statins remain first line in reducing LDL-C and cardiovascular events among those at risk, several non-statin lipid lowering agents have become increasing common in clinical care. The IMPROVE-IT trial helped cement the "lower is better" LDL-C hypothesis, which demonstrated that ezetimibe added to simvastatin further reduced major adverse cardiovascular events compared with simvastatin alone (Cannon et al. 2015). Once the efficacy of ezetimibe was established, investigators sought to compare ezetimibe with statins to evaluate if comparable pleiotropic effects could be uncovered. Landmesser et al. showed that simvastatin improves endothelial function independent of LDL-C lowering, though this benefit was not observed among patients treated with ezetimibe (Landmesser et al. 2005). Several other small studies have also documented similar findings (Fichtlscherer et al. 2006; Liu et al. 2009; Matsue et al. 2013). However, results have not been completely uniform. Pesaro et al. showed no difference in markers of inflammation when comparing individuals on ezetimibe/simvastatin vs simvastatin monotherapy (Pesaro et al. 2012). A similar study showed no difference in endothelial function with the addition of ezetimibe to simvastatin (Westerink et al. 2013). While these two studies suggest that non-LDL-C dependent effects can be achieved with ezetimibe, heterogeneous groups with small sample sizes limit interpretability and comparison.

The discovery of proprotein convertase subtilisin/kexin 9 (PCSK9) and its role in cholesterol metabolism have led to the development of 2 monoclonal antibodies directed against

this protein, with evidence demonstrating these medications not only reduce LDL-C, but also major adverse cardiovascular events with added to statin therapy (Sabatine et al. 2017; Schwartz et al. 2018). PCSK9 inhibitors are now FDA approved to reduce risk among patients with established ASCVD and familial hypercholesterolemia, when added to a maximally tolerated statin. Interestingly, multiple preclinical studies have uncovered a myriad of potential pleiotropic anti-atherosclerotic effects of PCSK9i. Mounting evidence indicates that PCSK9 inhibition blunts pro-inflammatory pathways, attenuates cholesterol plaque oxidative stress and inflammation, and reduces platelet reactivity possibly decreasing thromboses (Karagiannis et al. 2018). When evaluating effects of PCSK9 inhibitors in larger randomized-controlled clinical outcomes trials, features of statin efficacy including time to benefit, plaque regression, and stroke reduction were comparable with the statin trials (Yu and Liao 2022). Thus, the literature suggests that PCSK9 inhibitors may also exhibit pleiotropic effects via multiple pathways outside of LDL-C lowering.

Bempedoic acid is a non-statin LDL-C lowering therapy that targets cholesterol biosynthesis in hepatocytes. While statins inhibits HMG CoA reductase, bempedoic acid inhibits ATP-citrate lyase, which is two step upstream from HMG CoA reductase in the same pathway. Given bempedoic acid is administered as a prodrug that requires activation by enzymes only found in the liver, as opposed to muscle, this medication does not result in increased muscle-related side effects when compared with placebo (Laufs et al. 2019). This medication lowers LDL-C by up to 29% (Ballantyne et al. 2018; Goldberg et al. 2019; Laufs et al. 2019; Ray et al. 2019), and the ongoing Cholesterol Lowering via Bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) Outcomes trial will elucidate whether bempedoic acid results in reductions in major adverse cardiovascular events (Nicholls et al. 2021). Each of the CLEAR series of trials measured the effect of bempedoic acid on high-sensitivity CRP, and evidence from CLEAR Wisdom (Goldberg et al. 2019), Harmony (Ray et al. 2019), Serenity (Laufs et al. 2019), and Tranquility (Ballantyne et al. 2018) all demonstrating significant reductions in this inflammatory marker. Thus, bempedoic may exhibit anti-inflammatory properties, akin to statin therapy which was observed in the JUPITER trial. Furthermore, a pooled analysis of the aforementioned 4 CLEAR trials showed that new onset and worsening diabetes was less frequent among individuals taking bempedoic acid compared with placebo (Bays et al. 2020), which differs from what has previously been observed with statins.

Recent developments in statin pleiotropy

Gut microbiome

Several recent studies have suggested a link between statins and the gut microbiome. In 2020, Vieira-Silva et al. demonstrated that statin therapy modifies microbiome diversification. In this study, a cohort of statin-naive patients with a microbiome enriched with *Bacteroides*, which is associated with systemic inflammation, was highly prevalent among individuals with obesity and correlates with BMI. Interestingly, matched overweight and obese patients on statin therapy were found to have lower rates of *Bacteroides* predominant gut microbiomes when compared with their statin-naïve counterparts (Vieira-Silva et al. 2020). This led to the speculation that statin therapy may influence the gut microbiome and counteract a downstream pro-inflammatory environment which can be found in individuals with overweight and obesity. Alternatively, statins anti-inflammatory properties may be exerted on the host, which consequently allows the establishment of a more favorable gut microbiome (Reichel and Knauf 2021). Another study published in 2022 found that LDL-C lowering and insulin resistance differed among statin users with different gut microbiomes, suggesting that responses to statin therapy may, in part, be due to differences in metabolism via the microbiome (Wilmanski et al. 2022).

Preeclampsia

Interesting data have recently emerged on a potential beneficial effect of statins in preventing preeclampsia, an important cause of maternal morbidity and mortality. Preeclampsia and ASCVD share similar risk factors, and both are characterized by inflammation and endothelial dysfunction (Roberts and Redman 1993). Mouse models with overexpression of soluble fms-like tyrosine kinase-1 result in preeclampsia like conditions (Bergmann et al. 2010), and elevations in this protein have been observed in women prior to the clinical development of preeclampsia (Levine et al. 2004, 2006). Importantly, lowering soluble fms-like tyrosine kinase-1 reverses pathological features of preeclampsia (Bergmann et al. 2010), and evidence suggests that statins can inhibit cytokine-mediated release of soluble fms-like tyrosine kinase-1 (Cudmore et al. 2007). To test this hypothesis, Döbert et al. randomized women at high risk of term preeclampsia to pravastatin 20 mg versus placebo, and observed no reduction in the incidence of preeclampsia despite good adherence to the medication. Additionally, there was no significant between-group differences in soluble fms-like tyrosine kinase-1 concentrations (Döbert et al. 2021). Although some have postulated that these negative results may have

been due to the low potency or short duration of statin use (Wei et al. 2021), this study suggests that statins may not have pleiotropic beneficial effects among women at risk for preeclampsia.

COVID-19

The coronavirus 2019 (COVID-19) pandemic has ignited a firestorm of research in an attempt to find novel therapies that may mitigate its devastating effects on morbidity and mortality. In severe cases, infection from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV 2) can result in severe acute respiratory distress syndrome (ARDS), due to an exaggerated inflammatory response, which may be fatal (Li and Ma 2020). Furthermore, infection with SARS-CoV 2 can also lead to serious cardiovascular complications (Hansson and Libby 2006), including stroke, venous thromboembolism, myocardial injury, myocarditis, pericarditis, arrhythmias, cardiomyopathy and heart failure, cardiogenic shock, and cardiac arrest (Xie et al. 2022). SARS-CoV 2 binds to angiotensin converting enzyme 2 (ACE2) on the surface of lung cells which mediates entry and subsequent infection (Li et al. 2003; Tai et al. 2020), in addition to serving as a regulatory enzyme in the renin-angiotensin system. Since ACE2 breaks down the pro-inflammatory angiotensin II, it has been postulated that low levels of ACE2 may be associated with at least some of the inflammatory effects induced by SARS-CoV 2 infection (Long et al. 2020). Given statins increase ACE2 levels, some believe that these medications may have a beneficial role in improving outcomes among those with COVID-19. One observational study using data from the AHA's COVID-19 cardiovascular disease registry found that patients taking a statin prior to hospitalization for COVID-19 had a 16% lower odds of death compared with those not on a statin (Daniels et al. 2021). Several meta-analyses have demonstrated similar benefits among statin users, with literature suggesting reductions in the risk of fatal or severe disease (Kow and Hasan 2020), progression to severe illness or death (Onorato et al. 2021), and reductions in hard clinical outcomes (Scheen 2021). Although these welcome pleiotropic effects from statin use seem to benefit COVID-19-related outcomes, these studies are observational in nature and causality cannot be confirmed. However, ongoing randomized-controlled trials will help further elaborate on the role of statins in SARS-CoV 2 infection (Torres-Peña et al. 2021).

Conclusion

While it is clear that the LDL-C lowering properties of statins largely explain the cardiovascular benefits attributable to this life saving class of medications, decades of basic and clinical research have suggested unique off-target pleiotropic effects not fully explained by their principle mechanism of action. While favorable properties on endothelial function, platelets, vascular smooth muscle, and inflammation have been demonstrated in preclinical studies, these effects have not consistently translated in large-scale randomized-controlled trials, while several non-statin therapies have shown similar off-target effects. Although controversy remains regarding the concept of statin pleiotropy, the cardioprotective effects are unequivocal. Several novel lipid lowering medications in the pipeline will help further elucidate if these non-LDL-C lowering properties are unique to statin therapy.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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