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VIEWPOINT

Synergistic actions between angiotensin-converting enzyme inhibitors and statins in atherosclerosis

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Abstract *Aims:* Hypertension and hypercholesterolemia are independent risk factors for atherosclerotic cardiovascular disease (ASCVD) by acting directly on the endothelium and activating the renin-angiotensin aldosterone system (RAAS) and mevalonate pathways. This review examines how the severity and duration of these risk factors may influence the cardiovascular risk through a reciprocal interplay leading to oxidative stress and pro-inflammatory response.
Data synthesis: The review highlights the clinical evidence supporting the benefits of statins and angiotensin-converting enzyme (ACE) inhibitors for hypertension, lipid disorders and ASCVD management, both individually and combined, at all stages of the cardiovascular continuum.
Conclusion: Drug strategies incorporating an ACE-inhibitor and a statin, and in particular perindopril and atorvastatin, have consistently demonstrated reductions in the rate of ASCVD events in patients with hypertension and lipid disorders, cementing their position as first-line therapies for the management of atherosclerosis complications.

1. Introduction

Atherosclerotic cardiovascular disease (ASCVD) continues to represent the leading cause of mortality in the world, with 2019 World Health Organization estimates indicating that it was responsible for 16% (8.9 million) of total deaths [1]. Furthermore, among the top 10 leading causes of death, ASCVD has seen the largest increase in the past 20 years, rising by more than 2 million from 6.8 million in 2000 [1]. A recent analysis using the Global Burden of Disease dataset indicates that the global prevalence of ASCVD is continuing to rise, and the current prevalence rate of 1655 per 100,000 population is expected to exceed 1845 by the year 2030 [2]. This trend is driven by population aging, and the increased prevalence of obesity, diabetes, and metabolic syndrome as well as some emerging risk factors such as elevated serum uric acid [3].

An early key pathophysiological process leading to ASCVD is endothelial dysfunction. The endothelium is a major regulator of vascular homeostasis, but when chronically activated, for example, under conditions of hypertension and hypercholesterolemia, a cascade of inflammatory mechanisms is initiated that potentiate the pro-atherogenic environment and continued atherosclerotic plaque progression [4]. These risk factors frequently

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coexist, and their interaction amplifies overall ASCVD risk; for example, 5-year cardiovascular risk is doubled in patients with both hypertension and hypercholesterolemia [5].

Angiotensin-converting enzyme (ACE) inhibitors and statins are among the guideline-recommended first-line agents for treatment of hypertension and hypercholesterolemia, which are key risk factors for development of ASCVD. Evidence continues to accumulate to show that these agents have cardiovascular effects beyond blood pressure and cholesterol lowering, leading to additive benefits in terms of mortality and other cardiovascular outcomes [6]. The importance of primary and secondary ASCVD prevention is highlighted by the 2021 ESC guidelines [7]. Moreover, polypill replacement therapy helps to improve patient adherence and compliance. The benefits of switching to a polypill in terms of adherence result in a decrease in cardiovascular risk greater than that obtained with usual treatment with separate molecules. The benefits of switching to a polypill regimen are generally greatest among those who switched from partial or less potent regimens [8].

This article reviews the evidence on the synergistic effects of statins and ACE inhibitors in atherosclerosis and highlights clinical evidence supporting the benefits of statin and ACE inhibitor combinations for ASCVD management.

2. The additive effects of ASCVD risk factors

The endothelium is a key regulator of cardiovascular homeostasis maintaining a balance between relaxing and contracting factors, procoagulant and anticoagulant substances, and between proinflammatory and anti-inflammatory mediators. Factors having an adverse impact on this balance such as hypercholesterolemia, hypertension, diabetes, obesity and smoking, will result in endothelial dysfunction. This will progress with the duration and severity of risk factors but can be halted or attenuated with appropriate treatments. This is important for prevention, since the process of atherosclerosis begins in young adulthood or even earlier when the effects of these risk factors are still modifiable, while the clinical manifestations of ASCVD, such as myocardial infarction (MI) and ischemic stroke, generally appear later in life.

A key point that is not addressed by current ASCVD risk calculators is that not only the level of risk factors may influence risk, but also the duration of individuals' exposure to them. This has been clearly demonstrated for hypertension, the presence of which indirectly correlated to the rate of major cardiovascular disease, but also to the duration of the disease, particularly in the presence of target organ damage [9]. Review of data from longitudinal epidemiological studies covering three decades of follow-up has also demonstrated that individuals with high levels of low-density lipoprotein cholesterol (LDL-C) from early adulthood had a 3.5-fold greater risk (22.6% vs 6.4%) for ASCVD during the next 25 years compared with subjects with consistently low levels [10]. These data have been confirmed by results of Mendelian randomization studies, which have shown that gene variants associated with lower LDL-C levels from birth are associated with a correspondingly lower risk of ASCVD [11,12]. Furthermore, when the effect of each LDL-C variant is plotted against its effect on ASCVD, there is a continuous, dose-dependent, and log-linear causal association between the magnitude of the absolute change in LDL-C and the lifetime risk of ASCVD (Fig. 1) [11,12].

This has led to the concept of 'cholesterol years,' which represents the cumulative exposure (both magnitude and duration) of the arterial wall to LDL over a lifetime (Fig. 1) [11,13]. To determine whether this model also applies to nongenetic models of hypercholesterolemia and ASCVD, Domanski et al. performed an analysis of the CARDIA (Coronary Artery Risk Development in Young Adults) dataset [14]. They examined the relationship between area under the LDL-C versus age curve and incident ASCVD risk and showed that the risk of a future incident ASCVD event at a given age increased with total accumulated area under the LDL-C versus age curve. Thus, even mild LDL-C elevations at a young age elevate ASCVD risk and, because of the greater cumulative exposure, are associated with a greater risk of future disease than similar elevations in older individuals. The data also suggested that early accumulation of area under the LDL-C versus age curve conferred greater risk than when the same area was accumulated later, highlighting the importance of achieving and maintaining optimal LDL-C early in life.

3. Statins and atherosclerotic disease

Statins are inhibitors of HMG-CoA reductase, the enzyme that catalyses the reduction of HMG-CoA and promotes upregulation of hepatic LDL receptor expression, thereby decreasing plasma levels of LDL-C as well as other ApoB-containing lipoproteins [15]. It is hypothesized that maintaining low concentrations of circulating LDL-C and other lipoproteins minimizes the number of particles that become retained in the arterial wall and thereby the rate of atherosclerotic plaque progression [13].

Findings from in vitro and in vivo research as well as indirect evidence from clinical trials suggest that statins can modulate the atherosclerotic process, through mechanisms additive to their actions on blood cholesterol [16]. Statins have a variety of such pleiotropic effects, of which their anti-inflammatory and antioxidant properties may be most relevant for the prevention of ASCVD, although their clinical importance still remains unproven [17,18].

Statins can interfere with the pro-inflammatory pathways at all stages of atherosclerosis including leukocyte/endothelial interactions, adhesion, migration, proliferation, endothelial function, matrix degradation, apoptosis and thrombosis [19]. Inhibition of the mevalonate pathway by atorvastatin results in inactive Rho and Rac, which reduce the endothelial inflammatory response and preserve endothelial junction integrity [20]. Inactive Rho leads to increased expression of eNOS and enhanced production of endothelial NO. Statins also directly increase eNOS expression via activation of the phosphatidylinositol

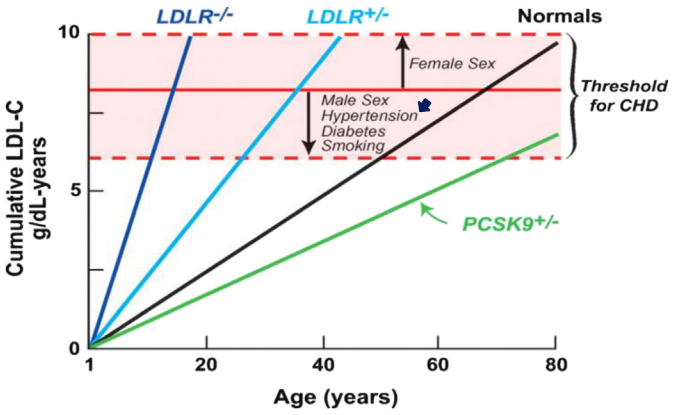

Fig. 1 Relationship between cumulative LDL-C exposure, age and additional risk factors on cardiovascular disease (CVD) development [11]. The figure compares the cumulative LDL-C exposure over a lifetime in homozygotic familial hypercholesterolemia (FH) patients (LDLR−/−), heterozygotic FH patients (LDLR+/−), PCSK9 heterozygotes and normal individuals. The horizontal red line represents a theoretical threshold of the cumulative LDL-C exposure required for development of CVD. The height of the red line will be lower in the presence of additional CVD risk factors (e.g. male sex, smoking, diabetes, and hypertension) (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article). **Reproduced from Horton et al 2009** [11] **(published under CC-BY license)**.

kinase 3/protein kinase Akt pathway, thereby phosphorylating eNOS and increasing activity [21].

Early in atherosclerosis, statins can interfere with the proinflammatory pathway of adhesion of leukocytes to endothelial cells and migration to subendothelial sites [22]. The proliferation and migration of monocytes/macrophages and endothelial and smooth muscle cells leading to the progression of atherosclerotic lesions depends on the activity of the matrix metalloproteinases (MMPs), which are regulated by proinflammatory cytokines such as IL-1, TNF-α, and CD40L, all of which are reduced by statins [23,24]. At later stages of atherosclerosis, the matrix degrading MMPs are also involved in the weakening of the fibrous cap increasing the likelihood of plaque rupture [25]. Statins reduce the expression and function of a broad range of MMPs in most cell types involved in atherogenesis [26]. Atorvastatin at a dose of 20 mg/day for 12 months has been associated with visible fibrous cap thickening in patients with coronary plaques, whereas there was little change in patients receiving the 5 mg/day dose [27]. The increase in fibrous cap thickness correlated with the decrease in serum levels of LDL-C. Further evidence for improved plaque stability has been provided by data from patients who continued or discontinued rosuvastatin after a 2-year study ended [28]. Among patients who continued therapy for a further 2 years, there was a significant decrease in composition and volume of the lipid-rich necrotic core compared with patients who did not continue statin therapy.

Statins can also modulate the lesion procoagulant activity and platelet function [29]. They also promote fibrinolytic activity via reduced expression of plasminogen activator inhibitor 1 and enhanced expression of tissue-plasminogen activator in endothelial and smooth muscle cells [30,31], and reduce platelet aggregation and deposition in diseased vessels in vivo [32,33].

The above represents a brief summary of some of the mechanisms involved in the so-called “pleiotropic” effects of statins and many in-depth reviews are available on this topic providing much greater detail about the mechanisms involved [34,35].

The cumulative effect of statins results in a significant regression of atherosclerotic disease. Meta-analyses of statin trials have shown to be linearly associated with the absolute level of LDL-C achieved [12]. In addition, intravascular ultrasound studies of atherosclerotic plaques in statin-treated patients demonstrate that progression can be halted at LDL-C levels around 1.8 mmol/L (70 mg dL) (Fig. 2) [12].

These findings highlight the importance of controlling LDL-C levels as the key mechanism of statin benefit and support the achievement of correct targets in patients treated with lipid-lowering drugs. The preventive benefits can be significantly increased when combined with blood pressure control. Greater regression and lesser progression of atheroma burden has been demonstrated in patients achieving guideline-recommended LDL-C and blood pressure targets (Fig. 3) [36].

4. Evidence from statin trials

The benefits of lipid-lowering with statins for the primary and secondary prevention of ASCVD have been demonstrated in numerous large randomized clinical studies. These benefits have been observed irrespective of gender, age, baseline lipid levels, diabetes, metabolic syndrome or hypertension, CHD, unstable angina, post-MI and previous stroke. The trials have demonstrated statistically significant and clinically important reductions in MI, stroke, and CVD death as well as total mortality, and support the continued use of statins as a first-line therapy for decreasing LDL-C and reducing the risk of ASCVD events [37].

Meta-analyses of statin trials have confirmed the relationship between statin-induced LDL-C reduction and vascular events. The Cholesterol Treatment Trialists’ Collaboration (CTTC) meta-analysis included 170,000

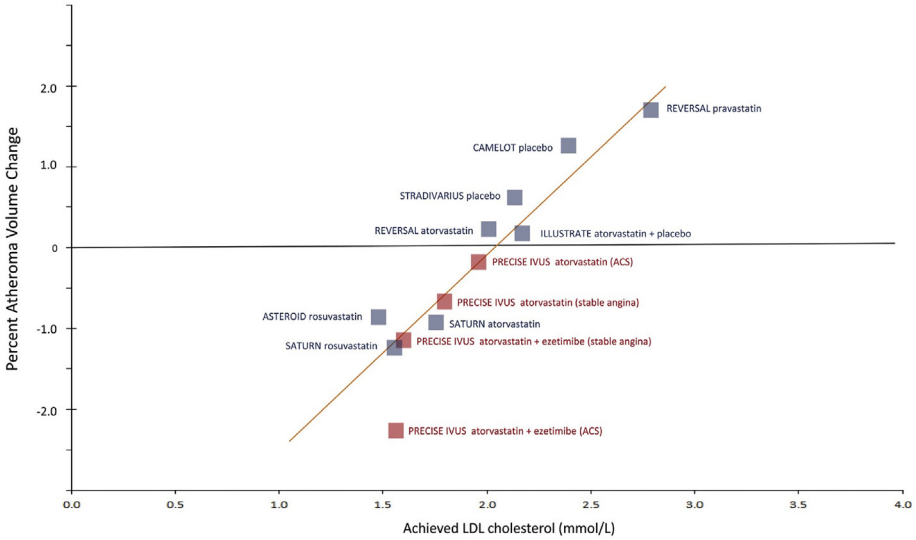

Fig. 2 Linear association between achieved low-density lipoprotein cholesterol (LDL-C) level and progression of atherosclerosis as measured by intravascular ultrasound. **Reproduced from Ference et al, 2017** [12] **(published under CC-BY-NC license).**

patients from 26 randomized trials and showed that statins reduced the relative risk of major vascular events by 22% (95% CI 20–24; P < 0.0001) for every 1.0 mmol/L [39 mg/dL] reduction in LDL-C [38]. All-cause mortality was reduced by 10% per 1·0 mmol/L LDL-C reduction (95% CI 7–13; P < 0·0001). A number of these trials were selected to evaluate whether more intensive LDL-C-lowering would result in a larger benefit in terms of reduction in ASCVD events. This was achieved by comparing standard statin therapy with more intensive therapy, either with a more effective statin or a higher statin dose and includes studies as: A to Z simvastatin 40 mg vs 80 mg [39]; PROVE-IT atorvastatin 80 mg vs pravastatin 40 mg [40]; TNT atorvastatin 10 mg vs 80 mg [41]; IDEAL atorvastatin 40–80 mg vs simvastatin 20–40 mg [42]; and SEARCH simvastatin 20 mg vs 80 mg [43]. A CTTC meta-analysis of these trials, involving 39,612 subjects and 8253 ASCVD events confirmed that more intensive regimens were associated with stronger LDL-c reduction and a significant reduction in ASCVD events of 15% (95% CI 11–18; P < 0·0001) [38]. Importantly, these further reductions in vascular risk can be achieved safely even in individuals with low LDL cholesterol concentrations. A further CTTC meta-analysis confirmed the benefits of statins as primary prevention in individuals without previous ASCVD [44].

The key role of inflammation in all stages of the atherosclerotic process has led to the use of the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) as a marker of high vascular risk, particularly in primary prevention settings. It was first demonstrated by a number of trials (CARE, AFCAPS/TexCAPS, REVERSAL, PROVE-IT, A to Z) that statins can reduce hsCRP and that their cardiovascular benefit was greater among those with elevated hsCRP levels [45–49]. The effects of statin in patients with elevated hsCRP were then formally tested in the JUPITER trial [50]. The study enrolled 17,802 primary prevention patients deemed to be at increased cardiovascular risk with LDL-C levels <3.37 mmol/L (<130 mg/dL) and hsCRP levels ≥2 mg/L and randomized to rosuvastatin

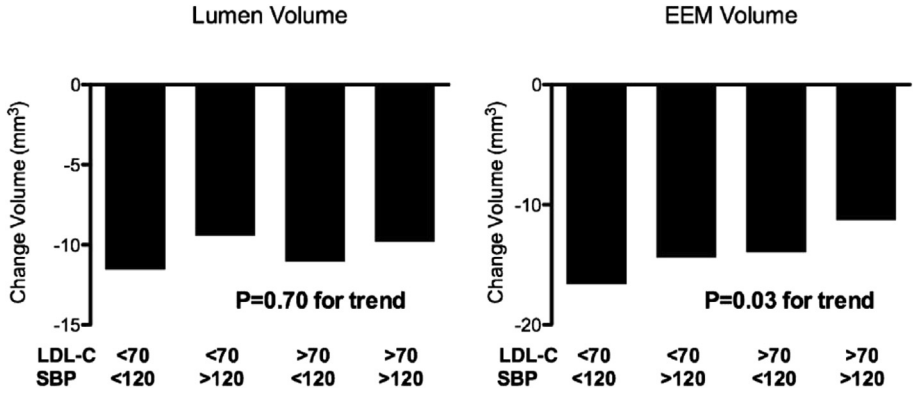

Fig. 3 Serial Changes in vessel wall volumes. Change in lumen and external elastic membrane (EEM) volumes, stratified according to on-treatment LDL-C and systolic blood pressure. **Reproduced with permission from Chhatriwalla et al, 2009** [36].

20 mg/day or placebo [50]. Statin treatment was associated with a 54% reduction in the incidence of MI, a 48% reduction in stroke, a 47% reduction in the need for angioplasty or bypass surgery, a 43% reduction in venous thrombosis, and a 20% reduction in all-cause mortality.

Further information on the benefits of statins in patients has been provided by the CORONA trial, a secondary prevention trial in patients with congestive heart failure (CHF), in which elevated hsCRP levels were associated with a worse prognosis [51]. A post-hoc analysis of the CORONA trial, which stratified patients by baseline hsCRP level found that rosuvastatin was associated with a significant improvement in clinical outcomes among patients with hsCRP values $\geq$ 2 mg/L at study entry. In this group, there was an 11% reduction in total mortality ($P = 0.05$), whereas no such benefit was observed among those in the lower-hsCRP group despite similar LDL-C levels and left ventricular ejection fraction in both groups at baseline and similar reductions in LDL-C over in response to treatment [51,52]. These results further support the anti-inflammatory role of the statins.

Statins are generally anti-inflammatory. However, statin therapy increased the risk of diabetes by 9%–12% in two meta-analyses of statin trials and by 18%–99% in five population-based studies [53]. Statins impair insulin sensitivity and insulin secretion by multiple mechanisms; they can promote inflammasome-mediated adipose tissue inflammation and insulin resistance. One of the possible mechanisms is the lowering of prenylation isoprenoids which activates caspase-1/IL-1β inflammasome responses by statins, resulting in the impairment of endocrine control of adipocyte lipogenesis [54].

There have been conflicting reports about the effects of ACE inhibitors on insulin sensitivity and glycemic control. A number of studies, mainly with captopril and with enalapril, have shown small increases in insulin sensitivity, and there is evidence that this is due to enhanced glucose uptake into skeletal muscle [55]. Conversely, in diabetic mice, temocapril improved insulin resistance and glucose intolerance through increased glucose uptake, especially in skeletal muscle, mediated at least in part through the enhancement of the bradykinin-NO system and consequently GLUT4 translocation [56].

5. Renin angiotensin aldosterone system as a therapeutic target in managing atherosclerosis

Beside the effects of lipids, the endothelium is also an important target for the renin-angiotensin aldosterone system (RAAS), and thus for the actions of ACE inhibitors and ARBs. The activation of the RAAS increases blood volume by stimulating sodium and water reabsorption, and systemic vascular resistance by enhancing peripheral vascular tone. Angiotensin II (Ang II) is the key product of the RAAS system responsible for the activation of the Ang II type 1 receptor (AT_1) and its downstream signalling cascade [57,58].

Through activation of the AT_1 receptor, Ang II has a number of adverse effects on the vasculature independent of its vasoconstrictive actions, including endothelial dysfunction, inflammation, growth, and cardiovascular remodelling [59]. When not sufficiently counteracted by the actions of bradykinin and NO, both having anti-proliferative, vasodilating and anti-inflammatory effects, Ang II is involved in the pathophysiology of a number of chronic diseases including hypertension, atherosclerosis, and chronic kidney disease [58,60].

Ang II contributes to endothelial dysfunction via its proinflammatory effects, which include recruitment of monocytes into the vascular intima, and facilitating the transformation of macrophages and smooth muscle cells into foam cells by stimulation of the production of reactive oxygen species (ROS). The oxidative stress produced by Ang II also leads to enhanced LDL oxidation and degradation of NO, thus depriving the system of the anti-inflammatory effects of NO. Ang II contributes to plaque growth and destabilisation via its profibrotic (increased production of TGF β, collagen and SMC growth) and prothrombotic effects (increased production of PAI-1 leading to platelet aggregation). Ang II also acts directly on the myocardium to stimulate left ventricular hypertrophy, and upregulates the sympathetic nervous system, which stimulates release of aldosterone and antidiuretic hormone leading to increased levels of sodium reabsorption and increased water reabsorption, respectively, both of which act to increase blood volume.

Although Ang II binds to both type I (AT_1) and type II (AT_2) receptor subtypes, the AT_1 receptor (AT_1R) mediates most of the cardiovascular effects of Ang II, including oxidative stress, vasoconstriction, aldosterone secretion, renal sodium resorption, sympathetic stimulation, vasopressin release, cardiac and vascular cell hypertrophy, and cell proliferation [61]. However, AT_1R represents only one of multiple routes of action of Ang II and of other RAS products. Several peptides, including Ang III, Ang IV, Ang A, Ang (1–7), Ang (1–9) and alamandine, and their respective binding receptors have been identified, albeit mostly in cellular and experimental models [62–64].

Although ACE inhibitors and ARBs target the RAAS by distinct mechanisms, both prevent the action of Ang II, ACE inhibitors by preventing its formation and ARBs by blocking the actions of Ang II at AT1R on bloods vessels and other target organs such as the heart [65].

By targeting ACE, ACE inhibitors not only enhance the availability of NO by inhibiting the conversion of Ang I to Ang II, but mostly by increasing the availability and preventing the degradation of bradykinin. ARBs do not have direct effect on the bradykinin level. The effect of ACE inhibitors on the tissue and plasma levels of bradykinin and on the nitric oxide production and bioavailability is specific to the mechanism of action of ACE inhibitors; it could account for the different effects of ACE inhibitors and ARBs on endothelial function, atherogenesis and fibrinolysis. A consequence of AT1R blockade is uncoupling of a negative-feedback loop and increased levels of circulating Ang II and stimulation of non-AT1 receptors. Blockade of AT1R by ARBs induces a significant and permanent increase in plasma angiotensin II and an over-stimulation of its still

available receptors. In animal models, AT4R has vasoconstrictive, proliferative and inflammatory effects [57]. Moreover, in murine models with kidney damage, atherosclerosis, and/or senescence, AT2R could have deleterious fibrotic, vasoconstrictive and hypertrophic effects [57].

In this respect it is noteworthy that ACE inhibitors, but not ARBs, have consistently demonstrated reduced cardiovascular mortality and all-cause death compared with placebo in a broad range of hypertensive patients [66–68]. Further examination of the all-cause and cardiovascular mortality reduction with ACE inhibitors in these meta-analyses found that perindopril trials had a considerable power in the achievement of these results [60,67].

The larger benefit of ACE-inhibitors in the prevention of cardiovascular mortality may be related to the effects of these drugs on endothelium-dependent vasodilatation with some differences across the class of ACE-inhibitors. Several lines of evidence are offering insights into potential mechanisms that could contribute to the observed greater benefits of ACE inhibitors over ARBs, and perindopril in particular. In the PERTINENT [69] substudy of EUROPA [70], the influence of perindopril versus placebo on a number of inflammatory markers and processes was evaluated in patients with CAD [69]. The endothelial apoptosis observed in placebo-treated patients was accompanied by excess angiotensin II and TNF-alpha, and a reduction in bradykinin, but was reduced by 31% in perindopril-treated patients ($P < 0.05$). The effects of RAAS inhibitors on endothelial apoptosis has also been studied at the cellular level, by cultivating human umbilical vein endothelial cells with serum taken from post-MI patients treated with perindopril or valsartan [71]. Perindopril, but not valsartan, reduced the proapoptotic effect of serum on the endothelium and increased endothelial renewal.

A post-hoc analysis of the PERSPECTIVE trial, compared the effects of perindopril versus placebo on progression/regression of atherosclerosis among 118 patients with available coronary ultrasound data [72]. Coronary plaques with no or little calcium (0–25%) regressed on perindopril and did not change on placebo (-0.33 ± 1.74 vs. -0.03 ± 1.66, respectively; $P = 0.04$). Plaques containing moderate calcium (group 25–50%) did not change and plaques with severe amounts of calcification (group 50–100%) equally progressed, suggesting noncalcified plaques may be amenable to regression with ACE inhibitor treatment.

A comparison of different antihypertensive drug classes on conduit artery endothelial function in patients with hypertension, found that while all treatments similarly reduced blood pressure, only the ACE-inhibitor in the form of perindopril increased flow mediated dilation [73].

In a study in normotensive patients with coronary artery disease the pleiotropic effects of enalapril and perindopril were compared. Neither ACE inhibitor had an effect on blood pressure in these normotensive patients, but perindopril was associated with a significantly more pronounced reduction in plasma levels of oxidized LDLs, CRP, MCP-1, fibrinogen and PAI-1, and increased interleukin-10 compared with enalapril [74]. RAAS activity is exerted by both circulating, and local RAAS systems that act at the tissue level, especially in the heart, kidneys, and vasculature. Tissue-bound activity, which increases local Ang II levels is thought to represent the majority of RAAS effects (approximately 90%). The use of agents that have high affinity for tissue ACE such as perindopril [75] may therefore explain why certain ACE-inhibitors produce marked and consistent reductions in MI and cardiovascular death across diverse populations and potentially enhanced pleiotropic effects.

6. Synergy between statins and inhibitors of the renin angiotensin aldosterone system

Hypercholesterolemia and hypertension are often associated and their association significantly increases the cardiovascular risk [76,77]. The epidemiological link between hypercholesterolemia and hypertension has been evaluated in the general population [78] and in hypertensive patients. In a large study including more than 194,000 participants [79], the prevalence of hypercholesterolemia in men was 46.3% in hypertensive patients, whereas it was only 21.7% in normotensive patients. In hypertensive women, the prevalence of hypercholesterolemia was more than three times that of normotensive controls. Similar data were observed in two Italian studies [80,81] and in the Third National Health and Nutrition Examination Survey (NHANES-III) [82].

The association between hypercholesterolemia and hypertension involves activation of the renin-angiotensin system, mainly at the tissue level. LDL, and more specifically oxidized LDL, activates the angiotensin II type 1 receptor by binding to the lectin-like oxLDL receptor [83]. In parallel, circulating LDL-C/ApoB particles increase the stability of the AT1 mRNA resulting in the overexpression of AT1 receptors for angiotensin II and, thus, in an exaggerated structural and functional response to angiotensin II infusion [84]. In addition, angiotensin II directly influences serum cholesterol levels. The stimulation of the macrophage AT1 receptors activates 3- hydroxy-3-methylglutaryl coenzyme A reductase gene expression, finally resulting in cholesterol synthesis, leading to cholesterol accumulation in the macrophages and formation of foam cells [85].

Clinical and experimental evidences suggest a remarkable overlap among the pathways by which hypercholesterolemia and hypertension lead to ASCVD, in particular for those leading to endothelial dysfunction mediated by oxidized LDL and Ang II.

Several animal studies have shown that concomitant statin and RAAS inhibitor administration has a synergistic effect on oxidative stress and inflammatory markers, independent of blood pressure or cholesterol-related effects, and greater than the effects observed with either agent alone [86–88]. Furthermore, in hyperlipidemic hamsters, dual statin/ACE-inhibitor therapy produced an additive reduction in fatty streak area compared with either drug alone [89]. Statins have also been shown to counteract Ang II-induced oxidative stress by reducing LDL and by blocking the isoprenylation and activation of members of the

Rho family, which are a major source of ROS in the vasculature [90,91].

Treatment with statins has been shown to reverse LDL-induced upregulation of AT_1R expression on thrombocytes and to attenuate the blood pressure response to Ang II infusion in hypercholesterolemic men [92]. The same effect of statin on AT_1R was thought to be responsible for the significant reduction in residual albuminuria/proteinuria and enhanced nephroprotection observed in patients with hypertensive renal damage [93].

The synergistic actions between ACE is and statins in atherosclerosis are summarized in Fig. 4.

7. Clinical evidence supporting the benefit of a statin and ACE inhibitor combination

There are several clinical studies reporting the effects of a combination of statins and ACE inhibitors treatment in humans showing a more beneficial effect on mortality and other health-related outcomes compared with either agent alone. Most of these studies have shown that ACE inhibitors or ARBs alone, statins alone, and combined therapy significantly improve flow-mediated dilatation in response to arterial occlusion and decrease plasma oxidative stress and inflammation [94–97]. However, in all the studies the effects of combination strategy were significantly more evident when compared to statin or ACE inhibitor/ARB alone.

In hypertensive hypercholesterolemic patients, dual therapy was associated with greater increases in serum NO and greater reductions in hsCRP [98], and in diabetic patients with critical limb ischemia, life expectancy was improved with combined ACE inhibitor and statin therapy compared with patients treated with either therapy alone [99].

7.1. Hypertension

A number of studies and meta-analyses suggest that patients receiving concomitant antihypertensive and statin therapy experience a reduction in blood pressure that could not be explained solely by the lipid-lowering effect of the statin or the effect of the antihypertensive medication. Treating dyslipidemia may therefore have beneficial effects on blood pressure [100], particularly in patients with diabetes [101] or those with higher blood pressure at baseline [102].

A prespecified objective of the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial Lipid Lowering Arm) was to assess whether there was any synergy between the lipid-lowering and blood-pressure-lowering regimens for the prevention of cardiovascular events [103]. A total of 19,257 patients with hypertension and three or more risk factors for CVD, but no prior history of MI or CHD, were randomized to an amlodipine-based regimen (with perindopril added as required) or atenolol-based regimen (with bendroflumethiazide diuretic added as required). Of these, 10,305 subjects with total cholesterol $\leq$6.5 mmol/L were further randomized to atorvastatin 10 mg daily or placebo. In the blood pressure arm of ASCOT Study (ASCOP-BPLA), the treatment with a combination of Perindopril and Amlodipine was more effective than Atenolol and Bendrofluazide [104] supporting the larger preventive benefit associated with a drug combination addressing the progression of atherosclerosis. The addition of atorvastatin for a mean treatment duration of 2 years, further reduced the cumulative incidence of the primary endpoint (non-fatal MI and fatal CHD) by 53% (HR 0.47, CI 0.32–0.69, $P < 0.0001$) in patients allocated amlodipine–perindopril regimen, and by 16% (HR 0.84, CI 0.60–1.17, NS) among those allocated to atenolol–thiazide diuretic regimen ($P = 0.025$ for heterogeneity).

After 16 years of follow-up of the UK participants in the original ASCOT-LLA trial, significantly fewer cardiovascular deaths have been reported among patients basically assigned to atorvastatin (HR 0·85, 0·72–0·99, $P = 0·0395$) compared with placebo [105].

In a small randomized double-blind, placebo-controlled crossover study, 20 patients with essential hypertension on an ACE inhibitor received fluvastatin 80 mg daily or

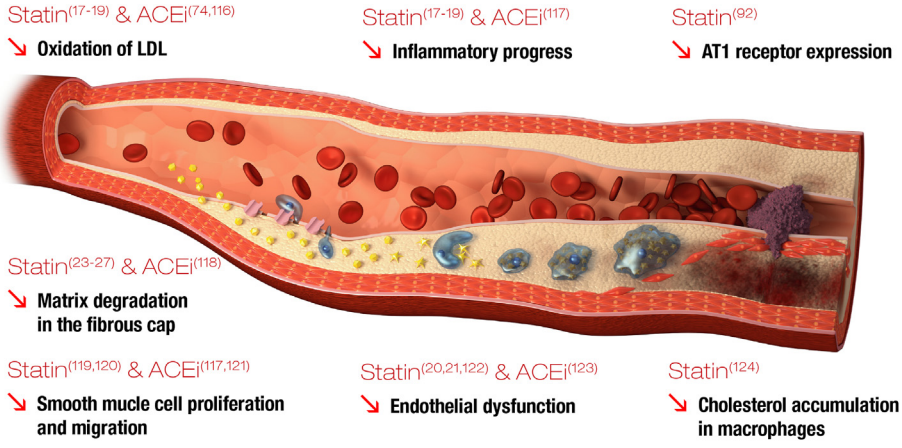

Fig. 4 Effects of ACE inhibitors and statins on atherosclerosis: beyond blood pressure and LDL-C lowering [17–21,23–27,74,92,116–124]. ©**Les Laboratoires Servier, 2021**.

placebo for 6 weeks [106]. The addition of statin therapy resulted in statistically significant reductions in LDL-C, CRP, von Willebrand factor, and vascular endothelial growth factor, and improved flow-mediated vasodilation.

7.2. Coronary artery disease

A post-hoc analysis of the GREACE (GREek Atorvastatin and Coronary heart disease Evaluation) trial divided 1600 patients into four groups according to long-term treatment: statin + ACE inhibitor, statin, ACE inhibitor, and neither statin nor ACE inhibitor. During the 3-year follow-up, patients in the combined treatment experienced significantly fewer ASCVD events than those in either a statin or ACE inhibitor alone [107].

In a post-hoc analysis of the JCAD (Japanese Coronary Artery Disease) study, which followed 13,812 patients with angiographically confirmed CAD for a mean of 2.7 years, there were no statistically significant differences in event rates between patients receiving neither statins nor RAS inhibitors and those receiving monotherapy with either drug. However, in patients receiving dual therapy, Kaplan-Meier analysis showed a statistically significant 22% decrease in the event rate [108].

In a post-hoc analysis of the EUROPA trial, which randomized over 12,000 patients with stable CAD to perindopril or placebo and included patients with angina or a previous MI, 7703 patients were already on lipid-lowering therapy; based on prescription data around 31% were taking atorvastatin. In this subgroup, the endpoint of cardiovascular mortality, nonfatal MI, and/or cardiac arrest with successful resuscitation occurred in 4.9% of patients treated with the combination of perindopril and a statin, corresponding to a 22% relative risk reduction [109].

In a small, proof-of-concept study, which compared the inflammatory response after coronary artery bypass grafting in patients treated with high-dose versus standard doses of a statin/ACE inhibitor combination, the intense systemic inflammatory response that is normally observed following CABG was almost completely prevented by early treatment with the high-dose combination [110].

7.3. Myocardial infarction

A large observational study in ST-segment elevation myocardial infarction (STEMI) patients that compared patients treated with statin + ACE inhibitor (n = 8705) and statin + ARB (n = 3001) demonstrated that the rates of major adverse cardiovascular events (MACE), MI, and revascularization were similar between the two groups, while a statin/ACE inhibitor combination was associated with a significantly reduced mortality rate [111].

In a population of 232 consecutive hypertensive diabetic patients admitted with a diagnosis of acute MI, outcomes were compared between patients who were receiving ACE inhibitor for at least 3 months prior to MI (n = 140) and those who were receiving combination statin/ACE inhibitor therapy (n = 92) [112]. Prior combination therapy appeared to be associated with greater protection in that patients had smaller infarct size, and less hospital morbidity and mortality.

7.4. Stroke

In a small study that analyzed data from 210 consecutive patients presenting within 24 h of stroke onset, triple therapy with an antiplatelet agent, ACE inhibitor and a statin was associated with a shorter length of hospitalization and better functional status upon discharge compared with dual or monotherapy [113].

7.5. Diabetes

In patients with type 2 diabetes, the vascular and metabolic effects of a simvastatin/ramipril combination have been compared with either agent alone [96]. The combination resulted in significantly greater improvements in endothelial function (assessed by flow-mediated dilation, reduced oxidative stress, and decreased inflammatory markers) with no adverse metabolic effects.

Evidence suggesting that combined therapy is more effective in reducing the rate of cardiovascular events in high-risk patients with type 2 diabetes and CAD comes from a large US observational study [114]. Compared with patients who had no exposure to fixed doses of a generic statin and ACE inhibitor/ARB combination, the risk of hospitalization for MI or stroke was significantly lowered in patients who received the combination, with higher exposure associated with a greater reduction.

8. Conclusion

Atherosclerosis is foremost a disease of the endothelium, a key regulator of vascular homeostasis and tone. Endothelial dysfunction is involved in all stages of atherosclerotic disease, and predisposes the vessel to vascular lesions, inflammation, vasoconstriction, thrombosis, and finally plaque rupture.

Endothelial dysfunction is closely linked to atherosclerotic risk factors, and is influenced by both their severity and duration. This is supported by the results of interventional studies that have demonstrated regression of endothelial dysfunction and improved outcomes with treatment. The co-existence of risk factors such as hypertension and hypercholesterolemia has more than an additive adverse impact on the endothelium. Evidence continues to accumulate that ACE inhibitors and statins have beneficial effects beyond blood pressure and lipid lowering, and that when combined achieve greater improvements in outcomes than those associated with either as monotherapy.

Ang II and NO are key mediators common to the pleiotropic actions of both ACE inhibitors and statins, affecting both oxidative stress and inflammatory pathways. Current evidence suggests that these agents may reduce ASCVD events via a dual mechanism of action

involving both blood-pressure/lipid-lowering pathways and additional "pleiotropic" effects. Combining an ACE inhibitor with a statin therefore offers a simple strategy to maximise treatment effects on the endothelium and improve outcomes in patients with a range of ASCVD manifestations.

The clinical success of such treatment combinations depends on the choice of agents with strong evidence of cardiovascular protection in large, long-term, randomized clinical trials. ACE-inhibitors, have an advantage over ARBs for their demonstrated efficacy in reducing the incidence of MI, cardiovascular mortality, and all-cause mortality. Perindopril and atorvastatin, in particular, have a larger dataset of favorable evidence for clinical use. A recent post-hoc analysis of four observational studies in patients with mild-to-moderate hypertensive in a real-world setting has confirmed the efficacy and safety of this treatment combination [115]. The prevention of atherosclerotic disease relies on the identification and effective management of both consolidated and emergent cardiovascular risk factors. Hypertension and hypercholesterolemia (high LDL-C) are responsible for a large proportion of ASCVD, particularly when combined in the same patient, and require an aggressive approach to treatment. Appropriate drug strategies should address the most important mechanistic pathways responsible for the vascular disease (HMG-CoA and RAAS). ACE-inhibitors and statins, and in particular perindopril plus atorvastatin with the addition of amlodipine as required, have been designed to address such targets. They have consistently demonstrated reductions in the rate of ASCVD in patients with hypertension and lipid disorders and should be considered the gold standard of treatment for the management of a disease that it is still the leading cause of mortality across the globe.

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