Pleiotropic effects of pitavastatin

Jean Davignon

Hyperlipidemia and Atherosclerosis Research Group, Clinical Research Institute of Montréal (IRCM) and University of Montréal, Montréal, Canada

Correspondence
Professor Jean Davignon OC GOQ MD MSc FRCP(C) FACP FAHA FRSC, Hyperlipidemia and Atherosclerosis Research Group, Clinical Research Institute of Montréal (IRCM), Montréal H2W 1R7, Canada.
Tel.: +1 51 4987 5625
Fax: +1 51 4987 5700
E-mail: Jean.Davignon@ircm.qc.ca

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are established first line treatments for hypercholesterolaemia. In addition to the direct effects of statins in reducing concentrations of atherogenic low density lipoprotein cholesterol (LDL-C), several studies have indicated that the beneficial effects of statins may be due to some of their cholesterol-independent, multiple (pleiotropic) effects which may differ between different members of the class. Pitavastatin is a novel synthetic lipophilic statin that has a number of pharmacodynamic and pharmacokinetic properties distinct from those of other statins, which may underlie its potential pleiotropic benefits in reducing cardiovascular risk factors. This review examines the principal pleiotropic effects of pitavastatin on endothelial function, vascular inflammation, oxidative stress and thrombosis. The article is based on a systematic literature search carried out in December 2010, together with more recent relevant publications where appropriate. The available data from clinical trials and *in vitro* and animal studies suggest that pitavastatin is not only effective in reducing LDL-C and triglycerides, but also has a range of other effects. These include increasing high density lipoprotein cholesterol, decreasing markers of platelet activation, improving cardiac, renal and endothelial function, and reducing endothelial stress, lipoprotein oxidation and, ultimately, improving the signs and symptoms of atherosclerosis. It is concluded that the diverse pleiotropic actions of pitavastatin may contribute to reducing cardiovascular morbidity and mortality beyond that achieved through LDL-C reduction.

Introduction

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) inhibit the biosynthesis of cholesterol. Statins have therefore become established in the treatment of hypercholesterolaemia and attained a central place in cardiovascular medicine because of their proven benefits in both primary and secondary prevention of cardiovascular events (for review see [1]).

Analyses of major trials, coupled with animal experimentation and studies *in vitro*, have suggested that some of the benefits of statins may be due to multiple, pleiotropic effects independent of direct reductions in low density lipoprotein cholesterol (LDL-C). Such effects can include improvements in endothelial function, decreases in smooth muscle proliferation and vascular inflammation

and antiplatelet actions (Table 1), as well as effects on other lipids and lipoproteins [2–4]. Pleiotropic effects may play an important part in reducing cardiovascular mortality and morbidity [3], and differences in the spectrum of such effects between members of the class could be relevant when formulating management plans for individual patients. Furthermore, different enzymes are involved in the metabolism of different statins, leading to unique drug–drug interaction profiles. Such differences are particularly important for patients at high risk of developing atherosclerosis, who are frequently polymedicated.

In an era in which clinicians are increasingly aware of the need to tailor therapeutic approaches to individual patients [5], insight into the potential benefits of statins on factors other than LDL-C reduction is particularly important. Recent research, for example, has highlighted the

Table 1

Pleiotropic effects of statins. Adapted from Sadowitz *et al.* [2]

Cell type	Pleiotropic effect	Atorvastatin	Fluvastatin	Lovastatin	Pitavastatin	Pravastatin	Rosuvastatin	Simvastatin
Platelets	Decreased activation	Yes	Yes		Yes [94]		Yes [75]	
	Decreased aggregation		Yes		Yes [95]			
Endothelial cells	Increased eNOS expression/activity			Yes	Yes [100]		Yes [127]	Yes
	Decreased ROS		Yes		Yes [54]			
	Increased endothelial progenitor cell activity/production	Yes						Yes
Vascular smooth muscle cells	Decreased proliferation				Yes [54]		Yes [129]	Yes
	Decreased migration						Yes [129]	Yes
	Increased apoptosis	Yes	Yes	Yes	Yes [128]			Yes
Macrophages/ monocytes	Decreased proliferation						Yes [130]	Yes
	Decreased MMP expression					Yes	Yes [131]	
	Decreased oxidized LDL uptake			Yes	Yes [72]			
Vascular inflammation	Decreased MHC-II expression	Yes [132]		Yes [132]	Yes [58]	Yes [132]		
	Decreased hs-CRP concentrations			Yes	Yes [61]	Yes	Yes [133]	

eNOS, endothelial nitric oxide synthase; hs-CRP, high sensitivity C-reactive protein; LDL, low density lipoprotein; MHC, major histocompatibility complex; MMP, matrix metallo-proteinase; ROS, reactive oxygen species.

potential of novel statin derivatives to improve the anti-inflammatory [6] and antithrombotic [7] effects of available statins.

Pitavastatin is a novel synthetic lipophilic statin shown to reduce serum concentrations of LDL-C and triglycerides, and increase high density lipoprotein cholesterol (HDL-C), in dyslipidaemic patients [8, 9]. At doses of 2–4 mg daily, pitavastatin has been shown to have a similar effect on LDL-C as atorvastatin 10–20 mg [10], with greater effects on HDL-C [11, 12].

This paper reviews the main pleiotropic effects of pitavastatin on endothelial function, vascular inflammation, oxidative stress and thrombosis. Together with the direct effects of pitavastatin on serum LDL-C concentrations, pleiotropic effects not directly related to cholesterol synthesis may help to explain the unique pharmacological profile of this statin.

Literature search

Publications included in this review were based mainly on a search of the PubMed and EMBASE databases carried out in December 2010. The strategy used was to search for English language publications on pitavastatin in 'all fields' on PubMed or in the 'title/abstract' field in EMBASE. This global search yielded a total of 756 articles (PubMed 329, EMBASE 427). After exclusion of foreign language references and duplicate entries, a total of 431 non-duplicate individual references were screened for relevance to the pleiotropic effects of pitavastatin. Screening removed all conference abstracts, review articles or correspondence (editorials and letters) and articles not relevant to the pleiotropic effects of pitavastatin, yielding a total of 134 relevant articles for further assessment. Relevant papers published after December 2010 were also included as appropriate. References were then grouped under cat-

egory headings (endothelial function, inflammation and immunomodulation, oxidative stress and lipoprotein oxidation, effects of pitavastatin on lipids other than LDL-C, thrombosis and fibrinolysis, cardiovascular and organ-protective effects).

Statin pharmacokinetics and metabolism

Statins may be broadly divided into two categories, according to their solubility (Figure 1). Pravastatin and rosuvastatin possess polar side groups attached to hydrophobic ring structures, rendering them hydrophilic, while pitavastatin, atorvastatin, fluvastatin, lovastatin and simvastatin do not, and are consequently classed as lipophilic [2]. Furthermore, the differing chemical structures of individual statins substantially alter the way these molecules are taken up by the liver and catabolized or excreted. Lovastatin and simvastatin, for example, circulate as an inactive, lactone prodrug [13], while atorvastatin and rosuvastatin are biologically active as calcium salts [14, 15]. Rates of biliary excretion, involving a number of transporters, such as breast cancer resistance protein and multidrug resistance-associated protein 2 [16], and hepatic uptake by various transporting polypeptides, are likely to influence the observed pharmacokinetic differences between statins [17].

Hepatic uptake of pitavastatin is mediated by organic anion transporting protein 2 (OATP2 or OATP1B1) [18]. The potential impact of OATPs on statin pharmacokinetics is illustrated by the findings that variants of OATP1B1 alleles are associated with decreased hepatic uptake of pitavastatin [19] and that OAT1B1 388A>G polymorphisms are associated with alterations in pitavastatin disposition and
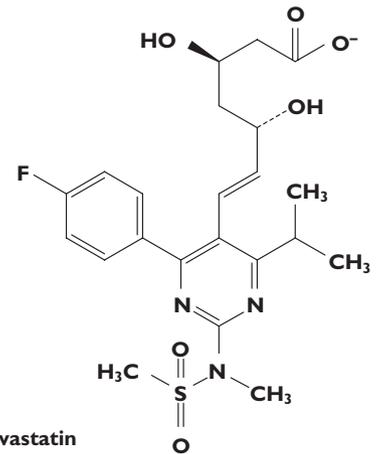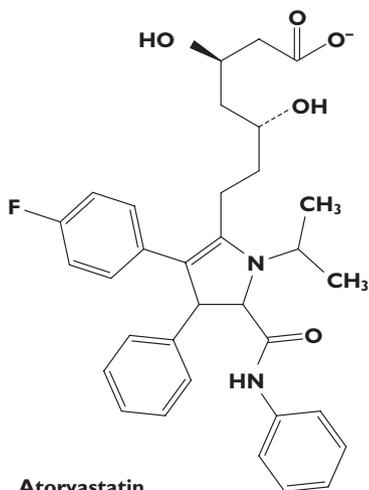
A   HMG-CoA
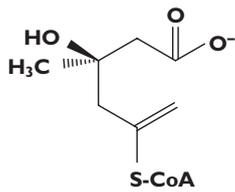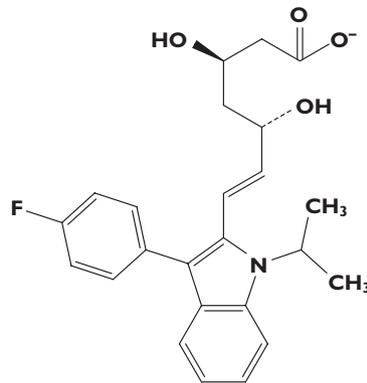
B   Hydrophilic statins
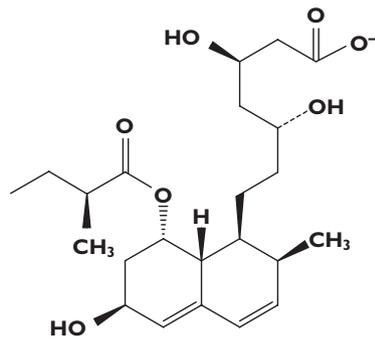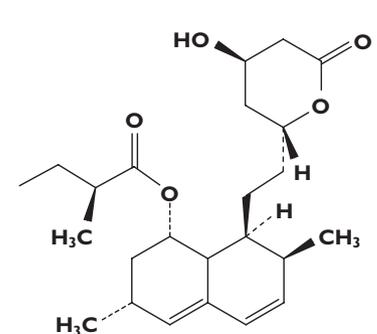
Pravastatin

Rosuvastatin
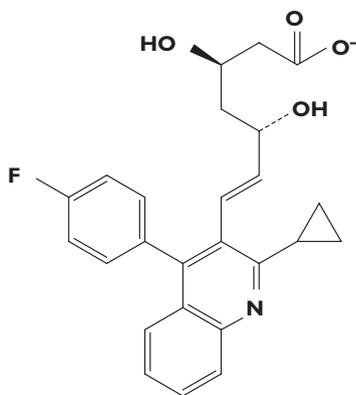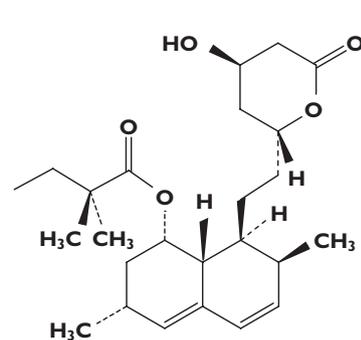
C   Lipophilic statins

Atorvastatin

Fluvastatin

Lovastatin

Pitavastatin

Simvastatin

Figure 1

Molecular structures of (A) HMG-CoA and (B) hydrophilic and (C) lipophilic currently available statins. Adapted from Shitara *et al*. [126]

pharmacokinetics [20]. Indeed, a number of factors can influence hepatic uptake of statins, including substrate–transporter affinity, itself highly dependent on the chemical structure of individual statins, the degree of dose dependency between substrate and transporter, the presence of genetic variation in the transporter and competition among transporters. The effect of genetic variation of transporters on the cellular accumulation of statins was demonstrated recently in a comparison of six statins and two transporters [21]. In oocytes, genetic variation in OATP1B1 (OATP1B1*15) reduced cellular uptake of pravastatin, pitavastatin, rosuvastatin and atorvastatin, but not of fluvastatin or simvastatin, whereas variation in the Na$^+$/taurocholate cotransporting polypeptide (NTCP*2) reduced transport of atorvastatin and rosuvastatin but not of pitavastatin.

Pitavastatin has a number of pharmacodynamic and pharmacokinetic properties that are distinct from those of other statins, and may contribute to (or modulate) its lipid lowering and pleiotropic properties. In contrast to other lipophilic statins, pitavastatin undergoes limited metabolism by, and consequently has a limited risk of interaction with drugs metabolized by, cytochrome P450 (CYP) enzymes, particularly CYP3A4 [22, 23].

Statin safety and tolerability

Although the benefits of statins have been shown to outweigh substantially their potential negative effects [24], co-administration of drugs that can interact with the CYP enzymes responsible for metabolizing statins can markedly increase the risk of developing myotoxicity due to reduced statin clearance [25, 26]. Cerivastatin was withdrawn after it emerged that patients exhibited an unacceptably high incidence of rhabdomyolysis, a condition in which severe muscle degradation may lead to kidney function impairment [27].

Almost all statins undergo extensive hepatic metabolism by the CYP isoenzyme systems; lovastatin, simvastatin and atorvastatin are all catabolized primarily by CYP3A4 [17]. The exception is pravastatin, the major metabolites of which are produced by chemical degradation in the stomach [28]. Co-administration of other drugs that interact with CYP3A4, such as the calcium channel antagonist mibefradil or lipid lowering drugs such as gemfibrozil, can substantially increase the risk of patients experiencing severe adverse events [17].

Although statins such as pitavastatin, fluvastatin and rosuvastatin, which are not extensively metabolized by CYP3A4, may be co-administered with such drugs, these statins have their own unique drug–drug interaction profiles. Fluvastatin and rosuvastatin are primarily metabolized by CYP2C9, which interacts with drugs such as diclofenac and phenytoin [17], while pitavastatin is only marginally metabolized by CYP isoenzymes [26].

Although all statins, to a greater or lesser degree, have the potential to cause adverse events if administered in sufficiently high doses, or in combination with other medications that alter their pharmacokinetics [29], multiple long-term safety studies have shown that these drugs are well tolerated by the majority of patients. For example, comparisons between pitavastatin and atorvastatin [11, 12, 30], pravastatin [31], rosuvastatin [31] and simvastatin [32] have shown that these statins have similarly low treatment emergent adverse event profiles when administered in isolation. Furthermore, a 2 year prospective study of over 20 000 patients treated with pitavastatin revealed no unexpected negative side effects of treatment [33], confirming the general long-term safety and tolerability of statins, as observed for atorvastatin [34], simvastatin [34] and rosuvastatin [35] administered for extended periods in previous studies.

Mechanisms of atherosclerosis: the significance of pleiotropic effects of statins

Atherosclerosis is the result of a complex interaction between dyslipidaemia, lipoprotein oxidation, blood flow, endothelial dysfunction, vascular inflammation and platelet activation and aggregation. Although the vascular endothelium is the major regulator of vascular homeostasis and endothelial dysfunction is recognized as an early marker of atherosclerosis, the molecular mechanisms underlying these interactions have only recently begun to emerge. Nitric oxide (NO), a potent vasodilator, is central to the regulation and maintenance of vascular function and is known to inhibit atherogenic LDL oxidation [36]. In addition, hyperlipidaemia is associated with endothelial disturbance, migration of inflammatory cells to sites of endothelial injury and a prolonged inflammatory response [37]. Endothelial damage also promotes platelet aggregation and activation, leading to thrombosis [36].

The pleiotropic effects of statins may act at multiple points in the complex cascade of events leading to atherosclerosis. Decreases in mortality and morbidity seen in the major trials of statins may therefore reflect multi-faceted actions on the atherosclerotic process. Figure 2 illustrates the cellular mechanisms by which statin-induced reductions in serum mevalonate, the direct reaction product of HMG-CoA reductase and HMG-CoA, may influence vascular function. Reductions in protein prenylation (the addition of an isoprene chain such as farnesol, 15 carbon atoms, or geranylgeraniol, 20 carbon atoms) have diverse, multiple effects on atherosclerotic processes including vasodilation, oxidative stress, inflammation and thrombosis. The evidence for the effects of statins, particularly pitavastatin, on reducing the pathophysiological processes that lead to atherosclerosis is described below.
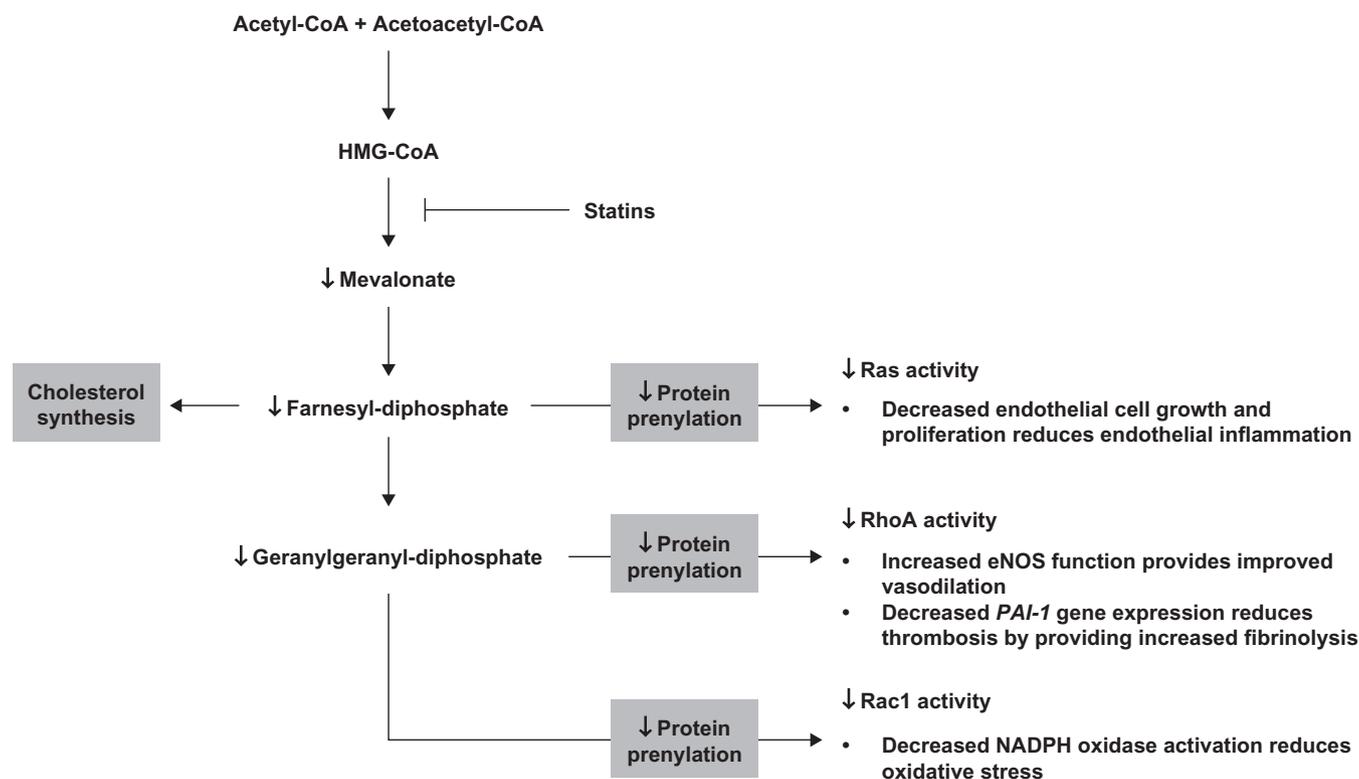
Figure 2

Isoprene synthesis, separate from cholesterol synthesis, modulates cellular function by activating GTPases and G-proteins, such as Ras, Rac1 and RhoA, via addition of an isoprene chain (farnesol or geranylgeraniol). Statin-induced decreases in HMG-CoA reductase activity reduce downstream protein prenylation and have the potential to improve vascular function through multiple pathways. GTP, guanosine triphosphate; PAI-1, plasminogen activator inhibitor-1; Ras, rat sarcoma subfamily; Rac1, Ras-related C3 botulinum toxin substrate 1; RhoA, Ras homologue gene family, A

Endothelial function

Many statin-induced improvements in endothelial function are mediated by transcriptional control of multiple genes, including integrin β4 and thrombomodulin, which affect cell–cell and cell–extracellular matrix interactions and reduce the procoagulant effect of thrombin [38, 39]. Statins have further been shown to promote endothelial progenitor cell proliferation and to modulate the induction of endothelial NO synthase (eNOS), thereby increasing NO production [2].

Animal models have shown that pitavastatin decreases the progression of atherosclerosis, augmenting capillary formation and blood flow recovery and increasing eNOS expression via the Akt (also known as protein kinase B, a serine/threonine-specific protein kinase family) pathway after induction of hind limb ischaemia [40, 41]. Statin therapy also reduces vasoconstriction by inhibiting NADPH oxidase activity and eNOS-dependent production of uncoupled superoxide anion ($O_2^{\cdot-}$) in a rat model of insulin resistance [42]. Furthermore, an *in vitro* study in human umbilical vein endothelial cells, has shown that pitavastatin increases eNOS production [43, 44] and increases the migration and proliferation of endothelial cells [45].

The cellular mechanisms underlying improvements in endothelial function, and how these interact with the mevalonate pathway downstream of HMG-CoA reductase, have recently begun to emerge. Angiogenesis in response to pitavastatin therapy in a murine hind limb ischaemia model was shown to be mediated by Notch-1, a protein regulating the interactions between adjacent cells [46]. This study further demonstrated that angiogenesis was not dependent on vascular endothelial growth factor, suggesting that growth of new blood vessels was not responsible for the observed recovery of blood flow. Pitavastatin treatment further induced endothelial ephrinB2, a selective marker of neovascularization sites on endothelial and smooth muscle cells, downstream of Notch-1, increasing the density of both capillaries and arterioles in the ischaemic limbs of control mice, while animals without Notch-1 were unaffected [46]. Furthermore, in moderately hypercholesterolaemic rabbits, pitavastatin was found to suppress atherosclerosis via inhibition of macrophage accumulation and foam cell formation [47].

The effects of statins on endothelial cells are associated with significant reductions in coronary artery disease (CAD), cerebrovascular disease and peripheral artery

Figure 3

Control subjects

CAD patients

Maximum forearm blood flow (min^{-1} 100 ml^{-1} ml tissue)
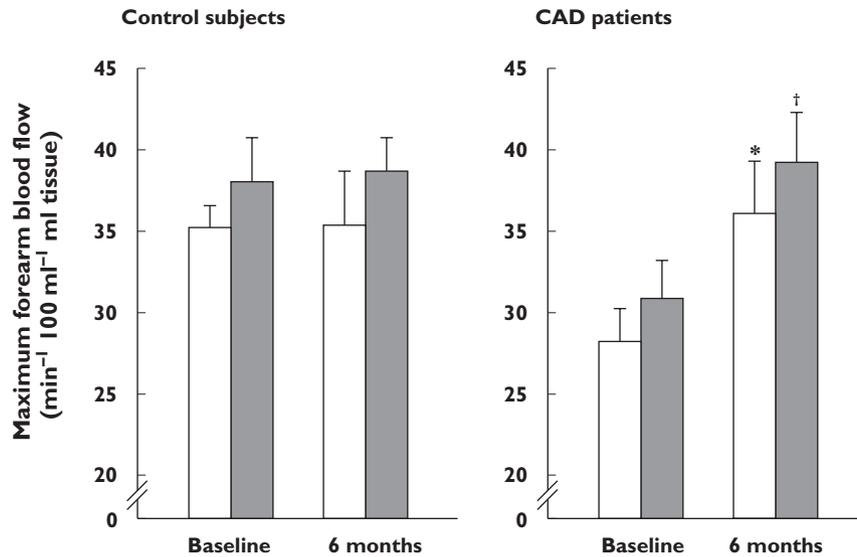
Baseline 6 months

Baseline 6 months

Figure 3

Effects of pitavastatin on forearm blood flow during reactive hyperaemia in patients with coronary artery disease and controls after 6 months' treatment. Blood flow was measured using strain-gauge plethysmography directly before and 2 h after, patients consumed a modified standard test meal (Japan Diabetes Society) after an overnight fast. *$P < 0.05$ *vs.* baseline preprandial data, †$P < 0.05$ *vs.* baseline postprandial data. Reproduced with permission from Arao *et al*. [48]. CAD, coronary artery disease. Before meal (□); After meal (■)

disease [3], and improvements in markers of endothelial function are observed during clinical use of pitavastatin. Fasting and postprandial forearm blood flow increased significantly ($P < 0.05$) during post ischaemic reactive hyperaemia in patients with CAD following 6 months of treatment with pitavastatin, but not in controls (Figure 3) [48]. Vasodilatation of the brachial artery was also increased after short term (2 weeks) treatment with pitavastatin in patients with primary hypercholesterolaemia. This increase was significantly greater in patients treated with pitavastatin ($n = 37$) than in those treated with atorvastatin ($n = 34$) after only 2 weeks of treatment ($P < 0.05$) and remained higher, although not significantly, in patients treated with pitavastatin for 3 months [30]. Furthermore, improvements in endothelium-dependent flow-mediated vasodilatation have been shown following pitavastatin treatment in people who smoke (Figure 4), an effect likely to reflect protection of endothelial cells against oxidative stress [49].

Inflammation and immunomodulation

Vascular inflammation is known to play a central role in the development of atherosclerosis [50, 51]. Statins exert a variety of anti-inflammatory effects, including a decrease in T-cell recruitment and activation, reduction in expression of inflammatory cytokines and chemokines, attenuation of expression of cluster of differentiation 40 (CD40, a member of the tumour necrosis factor [TNF] family of proteins) in T-cells and lymphocytes and inhibition of smooth muscle cell proliferation [2].

Change in endothelial functions (%)
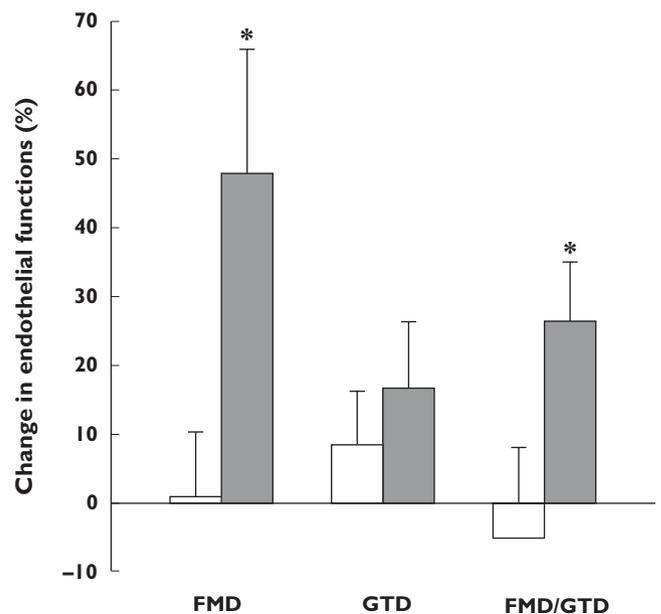
FMD GTD FMD/GTD

Figure 4

Increase in endothelial-dependent vasodilation following 1 month of treatment with 2 mg pitavastatin daily in chronic smokers. Endothelial function was assessed noninvasively, using high-resolution ultrasound, by measuring endothelium-dependent and -independent dilation of the brachial artery by reactive hyperaemia and glycerol trinitrate, respectively. *$P < 0.05$ *vs.* patients not treated with pitavastatin. Reproduced with permission from Yoshida *et al*. [49]. FMD, endothelium-dependent flow-mediated dilatation; GTD, endotheliumindependent glycerol trinitrate-induced vasodilatation. Controls (□); Pitavastatin (■)

By inhibiting mevalonate synthesis, statins can further modulate vascular inflammatory responses by reducing leucocyte migration via a mechanism involving the monocyte chemoattractant protein-1 (MCP-1) [52]. Resistance to plaque formation has been demonstrated in mice deficient in MCP-1, or its receptor (C-C motif chemokine receptor 2 or CCR2) [52]. Similarly, pitavastatin has been shown to have effects on inflammation and immunomodulation that may be mediated, in part, by dose-dependent inhibition of monocyte proliferation through down-regulation of the chemokine receptors CCR2 and CCR5 [53], inhibition of lysophosphatidic acid-induced aortic smooth muscle cell proliferation and expression of MCP-1 [54]. Such effects are mediated by suppression of Rac-1 (rat sarcoma [Ras]-related C3 botulinum toxin substrate 1)-induced generation of reactive oxygen species [54], a finding of interest as statins have been shown to down-regulate chemokine receptors in patients with CAD [55]. In retinal ganglion cells, pitavastatin suppresses N-methyl-D-aspartic acid-induced leucocyte recruitment and up-regulation of endothelial adhesion molecules [56]. In a rat model of cerebral aneurysm, pitavastatin decreased expression of nuclear factor (NF)-κB and other pro-inflammatory mediators, effects that were associated with reduced progression of aneurysms [57]. Other anti-inflammatory and anti-stress responses may be modulated by corticotropin-releasing factor type 1 receptors (CRF-1) via mechanisms including CRF signalling, endogenous CRF receptor agonists and urocortin and its associated polypeptides [58].

In terms of its immunomodulatory effects, pitavastatin has been shown to inhibit the production of interferon-α and TNF-α by human plasmacytoid dendritic cells, which are key molecular and cellular pathogenic components in autoimmune diseases. Specifically, statins have suppressive effects on the multiple signal transduction pathways that mediate interferon responses [59].

In addition to the *in vitro* demonstration of the anti-inflammatory effects of pitavastatin, there is now evidence, as for other statins, of anti-inflammatory effects in humans. Elevated concentrations of high sensitivity C-reactive protein (hs-CRP), a member of the pentraxin family and an inflammatory marker, are associated with high cardiovascular risk [60], and decreased concentrations of hs-CRP have been found in pitavastatin-treated patients with diabetes [61]. Plasma hs-CRP concentrations decreased significantly from a median value of 0.49 mg l^{-1} at baseline (interquartile range, 0.26–0.87) to 0.37 mg l^{-1} (0.23–0.79) at 6 months ($P < 0.05$), an effect that was independent of changes in serum lipids [61]. Furthermore, plasma concentrations of another pentraxin (PTX-3), also a marker of vascular inflammation and atherosclerosis, were reduced after pitavastatin treatment in patients with hypercholesterolaemia [62]. Decreases in PTX-3 concentrations during 6 months of treatment with pitavastatin correlated with decreases in plaque severity score in the carotid artery. This was particularly the case in patients who had high PTX-3

concentrations at baseline, indicating an effect of pitavastatin on asymptomatic atherosclerosis in these patients.

Oxidative stress and lipoprotein oxidation

Oxidative stress Oxidative stress plays an important role in plaque formation and may be a strong predictor of atherosclerosis, via mechanisms involving oxidized lipoproteins that can trigger inflammation and disrupt normal vascular function [63]. Recent data suggest that leucocyte activation by triglyceride-rich apolipoprotein B (ApoB)-containing lipoproteins can lead to oxidative stress, the production of cytokines and, ultimately, acute endothelial dysfunction. ApoB-containing lipoproteins, however, may also bind to erythrocytes, which may potentially have an anti-atherogenic effect by removing lipoproteins from sites of vascular inflammation [64].

Pitavastatin has been shown to reduce oxidative stress in hypercholesterolaemic rabbits [65] and to reduce elevated levels of reactive oxygen species and NADPH oxidase activity in genetically obese rats [66]. In addition, a reduction in angiotensin II-induced atrial remodelling can be attributed to decreased atrial production of $O_2^{-\cdot}$ in pitavastatin-treated mice [67]. Pitavastatin also increases the plasma concentrations of urocortin, which is produced in endothelial cells and inhibits the formation of reactive oxygen species (Figure 5) [68]. This pleiotropic effect, which has not been reported for other statins, is of interest because urocortin is a potent vasodilator that may lower blood pressure and increase K$^+$ATP channel gene expression. Urocortin may also have inotropic and
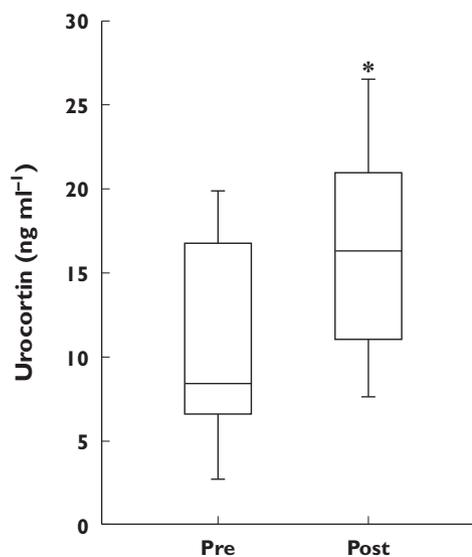

Figure 5
Treatment with pitavastatin (2 mg day^{-1}) for 4 weeks increased serum urocortin concentrations, measured using an enzyme-linked immunosorbent assay, in 15 healthy male volunteers. *$P < 0.01$ *vs.* before pitavastatin treatment. Reproduced with permission from Honjo *et al.* [68]
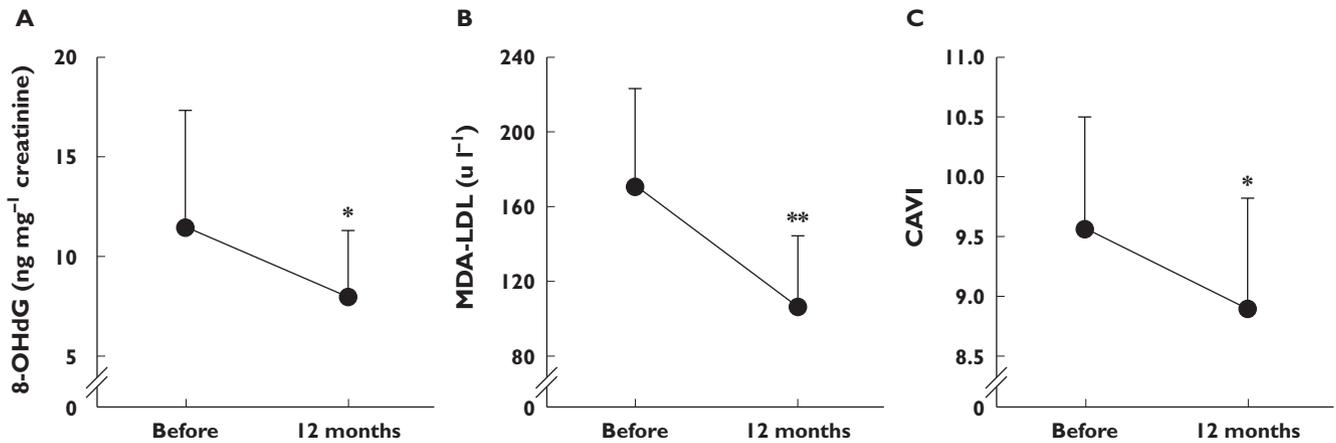
Figure 6

Changes in (A) urinary 8-hydroxy-2'-deoxyguanosine (a marker of oxidative stress), (B) malondialdehyde-LDL (a form of oxidized LDL) and (C) cardio-ankle vascular index in 45 patients with type 2 diabetes mellitus treated with pitavastatin 2 mg day^{-1} for 12 months (mean $\pm$ SD). Urinary 8-hydroxy-2'-deoxyguanosine and malondialdehyde-LDL were measured using enzyme-linked immunosorbent assays. The results for the former were adjusted for serum creatinine concentrations. The cardio-ankle vascular index reflects the stiffness of the aorta and femoral and tibial arteries, independent of blood pressure, and was measured using blood pressure cuffs attached to the biceps and ankles with patients in a supine position. *$P < 0.05$; **$P < 0.01$ vs. before treatment, paired t-test. Adapted from Miyashita et al. [74]. 8-OHdG, 8-hydroxy-2'-deoxyguanosine; CAVI, cardio-ankle vascular index; MDA-LDL, malondialdehyde-low-density lipoprotein

cardio-protective effects in ischaemia–reperfusion injury and beneficial cardiovascular effects in heart failure in humans [69].

Lipoprotein oxidation Statins have been shown to reduce the pro-atherogenic effects of oxidized LDL [2]. Specifically, statin-induced activation of the paraoxonase 1 (PON1) gene (mediated by p44/42 mitogen-activated protein kinase signalling) results in inhibition of LDL oxidation [70, 71], and pitavastatin inhibits the uptake of oxidized LDL by macrophages by down-regulating expression of the type B scavenger receptor CD36 [72]. Pitavastatin reduced lectin-like oxidized LDL receptor 1 (LOX-1) in patients with hyper-cholesterolaemia, but this was not correlated with a reduction in LDL-C [73]. In another study, decreased measures of oxidative stress and lower cardio-ankle vascular index were seen in patients with type 2 diabetes treated with pitavastatin (Figure 6) [74]. These results are clinically important, as oxidative stress is a key pathogenic factor in diabetes. Patients with diabetes often have dysfunctional HDL, and anti-inflammatory, anti-oxidant and cholesterol efflux mechanisms are impaired [75, 76].

Effects of statins on lipids other than LDL-C

The effects of statins on lipids beyond those exerted via LDL-C reduction may play a substantial role in mediating their cardiovascular benefits. The release of pro-inflammatory free cholesterol of erythrocyte membrane (CEM) from red blood cells in atherosclerotic plaques during intraplaque haemorrhage or neoangiogenesis has also been identified as a risk factor for CAD, and a marker of plaque vulnerability, which is independent of serum LDL-C concentrations. A study of 212 patients with acute coronary syndromes undergoing assessment for angina pectoris showed a substantial reduction in CEM in patients receiving statin therapy, which was not associated with changes in serum concentrations of LDL-C, HDL-C or triglycerides [77]. A retrospective database analysis of 105 patients with type III dysbetalipoproteinaemia, a remnant removal disease, has also shown statin-induced regression of lipid deposits in the skin (palmar crease xanthoma) [78].

HDL-C The anti-inflammatory effects of pitavastatin result in increased expression of macrophage scavenger receptor class B type 1, which plays an important role in bidirectional cholesterol interchange between cells and HDL-C [79]. Pitavastatin also induces endothelial sphingosine-1-phosphate type 1 receptors, which are believed to mediate vascular responses to HDL-C [80].

Differences between statins in their effects on HDL-C may be clinically relevant because of the many anti-atherogenic properties of this lipoprotein fraction. Greater increases in HDL-C with pitavastatin than with atorvastatin were seen in Japanese patients with impaired glucose tolerance and elevated LDL-C [11]. Other statins have less consistent effects on HDL-C [81], which may be related to different mechanisms of action. It has been proposed that statins increase HDL-C by inhibiting cholesteryl ester transfer protein and stimulating ApoAI synthesis [81], potentially via a mechanism mediated by RhoA suppression [82,

83]. There is also evidence that pitavastatin may increase HDL-C by increasing expression of ApoAI and ATP-binding cassette transporter A1, key components of reverse cholesterol transport [84–86].

Studies of the effects of statins on dysfunctional HDL species would be of interest because, currently, only niacin [76] and vitamin E in patients with diabetes with the haptoglobulin 2–2 genotype [87] are known to have beneficial effects on HDL dysfunction. Although statins do affect many of the protein components transported by HDL, such as PON1 which is increased by statin treatment [88] and reduced in patients with congestive heart failure [89], there is, to our knowledge, no study that addresses the effect of pitavastatin treatment on serum PON1 concentrations in humans directly, rather than in cultured cells.

Apolipoproteins Decreased secretion of ApoB100 from hepatoma cells has been reported in the presence of pitavastatin [90], and pitavastatin was more potent than simvastatin or atorvastatin in inducing ApoAI secretion [82]. There was also a correlation between decreases in ApoB with pitavastatin and a reduction in small, dense LDL-C [91]. Statin therapy has further been shown to reduce postprandial lipaemia, an independent risk factor for CAD, by inhibiting the production of ApoB-containing lipoproteins, thereby increasing the clearance of triglyceride-rich lipoproteins produced in the liver and intestines [92].

Thrombosis and fibrinolysis

Thrombosis associated with unstable plaques represents a serious risk for individuals with CAD, and statins are now well established as part of the pharmacological approach to reducing the risk of cardiovascular events. Their pleiotropic effects include decreasing platelet activation and aggregation [3] and increasing the expression of multiple genes involved in coagulation and fibrinolysis [39, 93].

Pitavastatin has been shown to decrease markers of platelet activation (platelet-derived microparticles), cell adhesion molecules and chemokines (MCP-1) through a mechanism that appears to involve increasing adiponectin concentrations [94, 95]. Pitavastatin also induces endothelial expression of thrombomodulin via inhibition of Rho family G proteins, resulting in an antithrombotic effect (Figure 2) [96]. In addition, pitavastatin reduces the expression of tissue factor (platelet tissue factor or coagulation factor III) and plasminogen activator inhibitor-1, and increases expression of tissue-type plasminogen activator, thereby promoting a balance in favour of fibrinolysis and reducing the risk of thrombus formation at unstable atherosclerotic plaques [97].

Cardiovascular and organ-protective effects

Heart In an animal model of hypertensive heart failure, pitavastatin inhibits load-induced cardiac hypertrophy and fibrosis through inhibition of RhoA-ERK-serum response factor signalling [98, 99]. Pitavastatin reduces
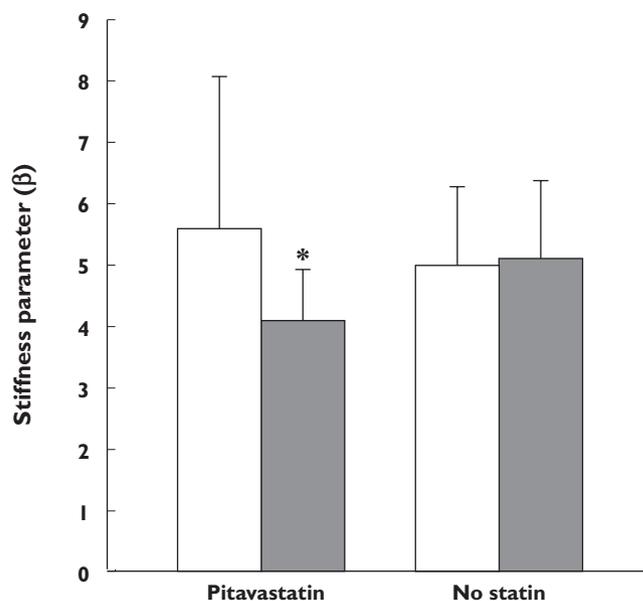

Figure 7

Changes in carotid arterial stiffness in 30 patients with hypercholesterolaemia randomized to receive either pitavastatin (1–2 mg day^{-1}, n = 15) or diet and exercise therapy for 12 months. Carotid ultrasonography was used to reveal end-systolic and end-diastolic diameters of the common carotid artery, Ds and Dd, respectively, and arterial stiffness, β, was calculated using the formula ln(SBP/DBP)/[(Ds − Dd)/Dd], where SBP and DBP are the systolic and diastolic blood pressures, respectively. *P < 0.05 vs. no statin group after treatment. Data from Mizuguchi *et al*. [102]. Baseline (□); 12 months (▦)

remodelling and improves ventricular function in rat hearts through increased eNOS production associated with PI3K signalling and a decrease in oxidative stress [100]. In the absence of eNOS in a mouse model, pitavastatin also reduced cardiac remodelling induced by angiotensin II and renal insufficiency through inhibition of the transforming growth factor-β-Smad signalling pathway by suppression of oxidative stress [67]. Similar results were obtained by Takuwa *et al*. [101], who showed that pitavastatin reduces cardiac remodelling, by inhibition of sphingosine kinase 1, and reduces oxidative stress in juvenile mice. Furthermore, in a 12 month randomized, controlled trial in 30 patients with hypercholesterolaemia and preserved left ventricular ejection fraction, treatment with pitavastatin (1 or 2 mg day^{-1}, n = 15) for 1 year significantly reduced carotid arterial stiffness and significantly improved regional left ventricular systolic and diastolic function (P < 0.05) compared with patients given placebo (Figure 7) [102].

Brain Pitavastatin reduces ischaemia-induced neuronal damage in animal models [103, 104]. In the middle cerebral artery occlusion model in the rat, both pitavastatin and simvastatin significantly reduced infarction volume

relative to that observed in control animals ($P < 0.05$ and $P < 0.01$, respectively), while the reduction attributable to atorvastatin did not reach significance [105]. More recently, a decrease in ischaemia-induced neuronal cell death after treatment with pitavastatin was found to be associated with down-regulation of expression of NF-κB in gerbils [106], and it has been suggested from a study in rats that pitavastatin may strengthen the integrity of the blood–brain barrier through up-regulation of claudin 5 (a functional protein at endothelial tight junctions) [107].

Statins have been shown to augment cerebral blood flow and to confer significant protection against stroke in animal models (for review see [108]). This protective effect in animal models has been replicated in published case studies: two elderly patients (72 and 77 years of age) showed clinically significant increases in cerebral blood flow following 6 months of treatment with pitavastatin 2 mg day^{-1} [109].

Kidney Pitavastatin improves renal function in diabetic mice, increasing the bioavailability of nitric oxide via a mechanism which suppresses eNOS uncoupling, the process by which eNOS activity is inhibited by an oxidative stress-induced deficiency in the NOS cofactor tetrahydrobiopterin (BH$_4$) [110]. In clinical studies, 6 months of treatment with pitavastatin 1 mg day^{-1} significantly ($P < 0.01$) reduced urinary liver-type fatty acid-binding protein (a marker of renal injury), concentrations of 8-hydroxy-2′-deoxyguanosine (a marker of oxidative stress), and proteinuria in 30 non-diabetic patients with chronic kidney disease, independently of any lipid-lowering effects [111]. The beneficial effect on proteinuria was enhanced when co-administered with ezetimibe (Figure 8) [112]. In a 2 year surveillance study, estimated glomerular filtration rate increased significantly ($P < 0.001$) from baseline (< 60 ml min^{-1} 1.73 m^{-2}) in 958 patients with hypercholesterolaemia and chronic kidney disease [113].

Clinical evidence for pleiotropic effects

The potential importance of the pleiotropic effects of pitavastatin is highlighted by the results of clinical trials in patients with atherosclerotic disease.

Stabilization of vulnerable carotid plaques was seen within 1 month of treatment with pitavastatin 4 mg day^{-1} in 33 patients with acute coronary syndrome in a placebo-controlled trial (Figure 9) [114]. In the JAPAN-ACS (Japan assessment of pitavastatin and atorvastatin in acute coronary syndrome) study, a significant ($P < 0.001$) reduction in coronary plaque volume was seen in 111 patients given pitavastatin 4 mg day^{-1} for 8–12 months. The decrease in plaque volume with pitavastatin was similar to that seen in 115 patients treated with atorvastatin 20 mg day^{-1} ($-16.9 \pm 13.9\%$ *vs.* $-18.1 \pm 14.2\%$) [115]. Stabilization of coronary plaques, determined by colour angioscopy, occurred following treatment with pitavastatin 2 mg day^{-1} for 52 weeks in patients with CAD. This stabilization was not

correlated with changes in LDL-C, suggesting a direct contribution of pleiotropic effects unrelated to cholesterol reduction (Figure 10) [116]. Such angioscopic regression has also been reported with atorvastatin in a previous report but, in contrast to the pitavastatin study, a correlation was observed between changes in the mean angioscopic (yellow) score for plaque stabilization and the change in LDL-C concentrations [117]. Furthermore, in another study, reductions in angioscopic score were correlated with subsequent changes in atheroma volume, measured by intravascular ultrasound, considered to reflect an improvement in plaque vulnerability [118].

How changes in these secondary markers of cardiovascular disease correlate with hard clinical outcomes, however, remains unclear. Few studies investigate such correlations, and those that do are unable to disentangle clinical improvements due to pleiotropic effects from those attributable to improvements in serum lipid profiles [119]. Furthermore, patient mortality appears to correlate most significantly with concentrations of serum lipids, such as increased LDL-C [120] or apolipoproteins, such as ApoAI and ApoB [121]. One recent retrospective analysis of 743 patients receiving percutaneous coronary intervention, or angioplasty, revealed a significant reduction in major adverse coronary events, including myocardial infarction and sudden cardiac death, in patients treated with adjunctive statin therapy compared with no statin [122]. Further analysis showed that the incidence of coronary events correlated with reductions in LDL-C and increases in HDL-C. Statin therapy also appears to be significantly more effective in reducing the risk of experiencing a major coronary event in patients who display the atherogenic triad (elevated LDL-C and triglycerides, and low HDL-C) than in those presenting with hypercholesterolaemia alone (relative risk [95% CI]; 0.47 [0.32–0.70] *vs.* 0.91 [0.59–1.41], respectively, $P = 0.03$) [123].

Nevertheless, long-term follow-up studies are clearly necessary to elucidate precisely how the pleiotropic effects exerted by statins might influence mortality and morbidity in patients at high risk of developing atherosclerosis. Recently, the JUPITER trial has indicated that the incidence of cardiovascular events in apparently healthy subjects with elevated concentrations of the inflammatory marker hs-CRP can be reduced with statin therapy [124]. This suggests not only that inflammation plays an important role in mediating the incidence of cardiovascular events, but also that this effect may be independent of changes in serum lipids, as decreases in hs-CRP did not correlate with reductions in LDL-C. The current consensus appears to be that the anti-atherosclerotic effects of statins are likely to be attributable both to their lipid-lowering action (inhibition of HMG-CoA reductase) and to their wide range of additional pleiotropic effects on pro-atherogenic processes, such as correction of endothelial dysfunction, reduction of LDL oxidation and oxidative stress, and decreased vascular inflammation [125].
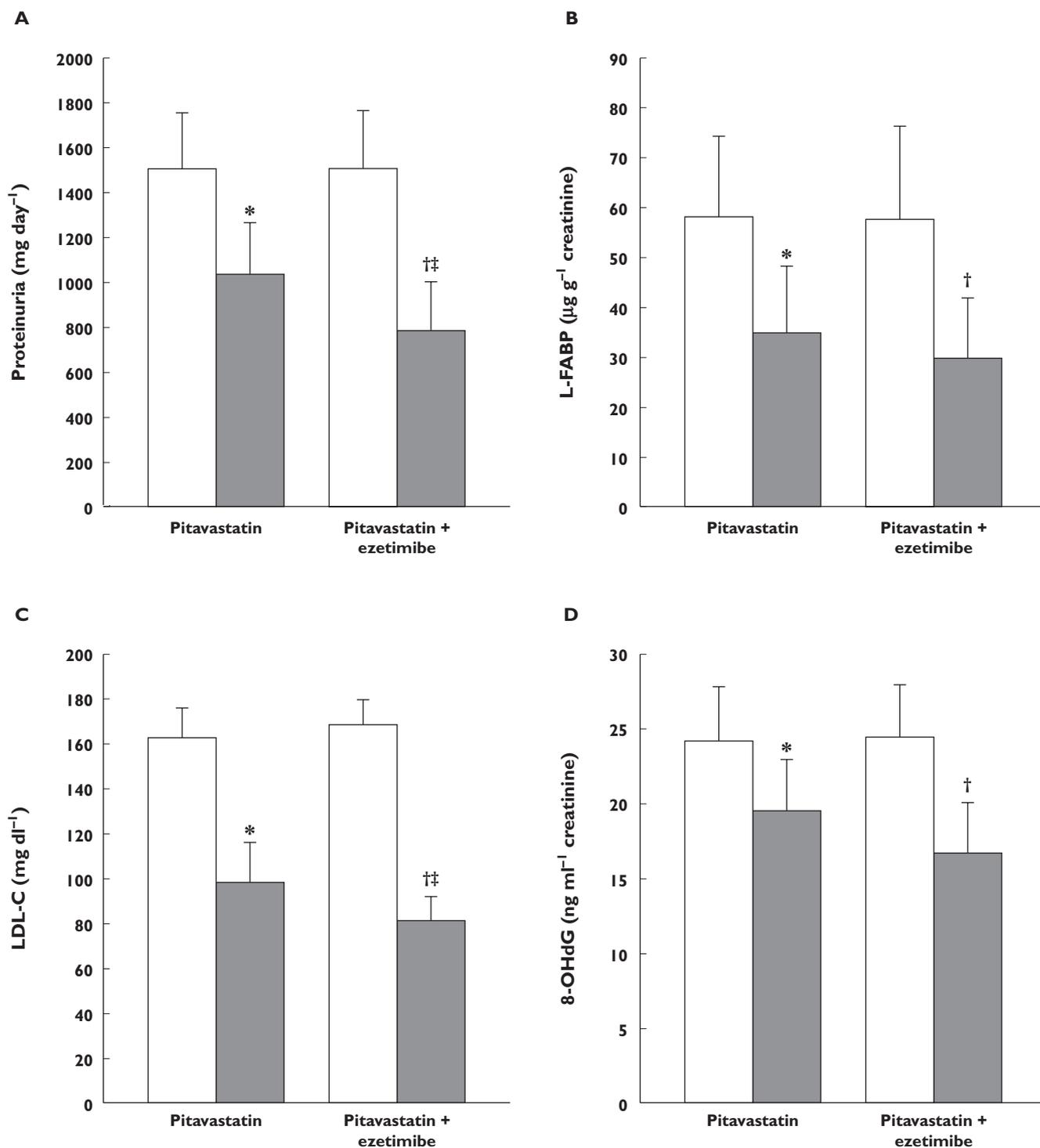
Figure 8

Improvements in markers of (A and B) renal function, (C) serum cholesterol and (D) oxidative stress in patients with chronic kidney disease and dyslipidaemia after treatment with 2 mg pitavastatin daily alone, or in combination with 10 mg ezetimibe, for 6 months. 8-hydroxy-2'-deoxyguanosine and L-fatty acid binding protein were measured enzymatically using enzyme-linked immunosorbent assays, proteinuria was measured using a pyrogallol red method and LDL-C concentrations were calculated using Friedewald's formula. *$P < 0.001$ vs. before pitavastatin treatment, †$P < 0.001$ vs. before pitavastatin + ezetimibe treatment, ‡$P < 0.05$ vs. after pitavastatin treatment alone. Data from Nakamura et al. [112]. Before (□); After (▓). 8-OHdG, 8-hydroxy-2'-deoxyguanosine; LDL-C, low density lipoprotein cholesterol; L-FABP, L-fatty acid binding protein
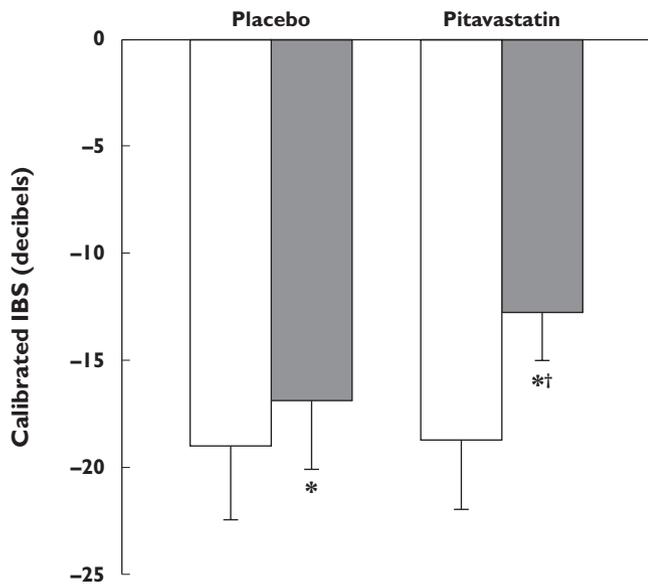
Figure 9

Stabilization of carotid plaques, measured as the change in integrated backscatter (IBS) on carotid ultrasound, following treatment with pitavastatin 4 mg day^{-1} for 1 month in patients with acute coronary syndromes (mean $\pm$ SD). *$P < 0.05$ vs. baseline within treatment group; †$P < 0.05$ vs. placebo at 1 month. Data from Nakamura et al. [114]. Baseline (□); 1 month (■)

Figure 10

Lack of correlation between stabilization of coronary plaques (expressed as reduction in yellow plaque content) and change in LDL-C in patients with coronary artery disease treated with pitavastatin 2 mg day^{-1} for 52 weeks. Intravascular ultrasound and coronary angiography were used to grade yellow atherosclerotic plaques and to assess their regression during treatment. Reproduced with permission from Kodama et al. [116]. LDL-C, low density lipoprotein cholesterol

Conclusions

Many patients do not achieve their lipid targets on current treatment regimens, and discontinuing or modifying statin therapy based on lipid targets alone potentially ignores the potential valuable cardio- and vasculo-protective pleiotropic properties of these compounds and the benefits they may provide to patients in addition to their ability to modulate serum lipid profiles. Statins provide potent lowering of LDL-C and triglycerides, and elevation of HDL-C, together with diverse pleiotropic effects on pro-atherogenic processes, which are likely to contribute to reductions in cardiovascular mortality and morbidity. Differences in pleiotropic effect profiles between statins, such as the up-regulation of urocortin seen with pitavastatin, are likely to become increasingly important in choosing the most appropriate treatment for individual patients.

Statins also differ in the extent to which they interact with drugs metabolized by cytochrome P450. This is important because combination therapy with statins and other agents is likely to become increasingly common, both to achieve lipid targets and to treat comorbidities. Pitavastatin, which has a low risk of interactions with drugs metabolized by cytochrome P450, therefore offers a useful addition in the management of dyslipidaemia and cardiovascular disease.
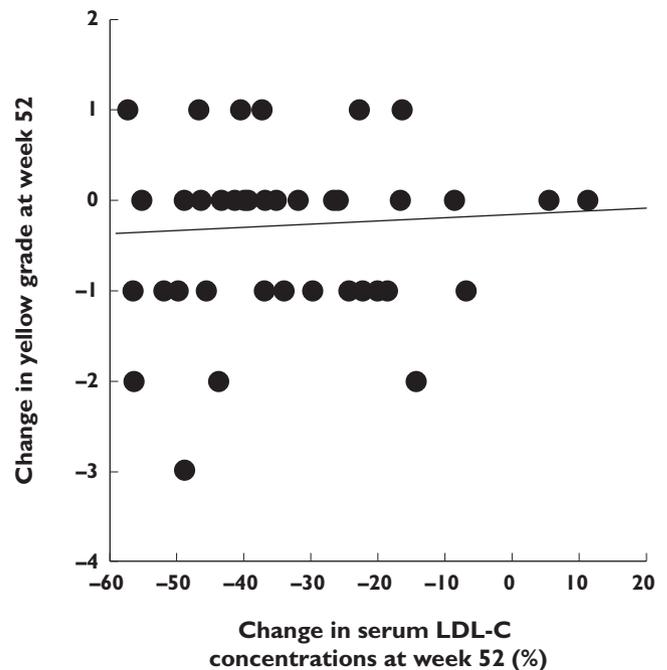
Competing Interests

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