

REVIEW ARTICLE

The Evolving Role of Statins in the Management of Atherosclerosis

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Significant advances in the management of cardiovascular disease have been made possible by the development of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors—"statins." Initial studies explored the impact of statin therapy on coronary artery disease (CAD) progression and regression. Although the angiographic changes were small, associated clinical responses appeared significant. Subsequent large prospective placebo-controlled clinical trials with statins demonstrated benefit in the secondary and primary prevention of CAD in subjects with elevated cholesterol levels. More recently, the efficacy of statins has been extended to the primary prevention of CAD in subjects with average cholesterol levels. Recent studies also suggest that statins have benefits beyond the coronary vascular bed and are capable of reducing ischemic stroke risk by approximately one-third in patients with evidence of vascular disease. In addition to lowering low-density lipoprotein (LDL) cholesterol, statin therapy appears to exhibit pleiotropic effects on many components of atherosclerosis including plaque thrombogenicity, cellular migration, endothelial function and thrombotic tendency. Growing clinical and experimental evidence indicates that the beneficial actions of statins occur rapidly and yield potentially clinically important anti-ischemic effects as early as one month after commencement of therapy. Future investigations are warranted to determine threshold LDL values in primary prevention studies, and to elucidate effects of statins other than LDL lowering. Finally, given the rapid and protean effects of statins on determinants of platelet reactivity, coagulation, and endothelial function, further research may establish a role for statin therapy in acute coronary syndromes. (*J Am Coll Cardiol* 2000;35:1-10) © 1999 by the American College of Cardiology

Recent advances in the management of hypercholesterolemia are primarily due to the development of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors or "statins." The discovery of statins led to important improvements in the primary and secondary prevention of coronary artery disease (CAD). Initial studies explored the impact of statin therapy on CAD progression and regression. Although angiographic changes in response to therapy were modest, accompanying clinical benefit appeared significant. Subsequent large prospective clinical trials have provided unequivocal evidence that cholesterol-lowering therapy with this class of compounds not only reduces the major coronary event rate in primary and secondary prevention, but also reduces all-cause mortality in secondary prevention. This review describes the evolving impact of this class of compounds from their debut in angiographic trials to their subsequent prominence in large primary and secondary prevention studies. Additionally, we explore the

pleiotropic actions of statins in reducing atherosclerosis and its complications.

MECHANISM OF ACTION AND PHARMACOLOGY OF STATINS

HMG CoA reductase is the rate-limiting enzyme for cholesterol formation in the liver and other tissues; HMG CoA reductase responds to negative feedback regulation by both sterol and nonsterol products of mevalonate metabolism through decreased reductase gene expression (1). By inhibiting HMG CoA reductase, statins reduce the hepatocyte cholesterol content and increase expression of low-density lipoprotein (LDL) receptors, responsible for LDL cholesterol uptake via receptor-mediated endocytosis (Fig. 1). Additionally, a second mechanism of LDL reduction may relate to LDL and very-low-density lipoprotein (VLDL) interactions. However, increases in HMG CoA reductase synthesis shortly after statin therapy restore cellular VLDL levels, and the ultimate effect of reductase inhibition is enhanced LDL receptor expression and lower plasma LDL in the setting of normal cellular cholesterol content.

Statins differ in absorption, plasma protein binding, excretion and solubility (Table 1) and exhibit variable

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Manuscript received February 23, 1999; revised manuscript received August 3, 1999, accepted October 5, 1999.

Abbreviations and Acronyms

AFCAPS/TexCAPS	= Air Force/Texas Coronary Atherosclerosis Prevention Study
CAD	= coronary artery disease
CARE	= Cholesterol and Recurrent Events trial
HDL	= high-density lipoprotein cholesterol
HMG CoA	= 3-hydroxy-3-methylglutaryl coenzyme A
LDL	= low-density lipoprotein cholesterol
LIPID	= Long-term Intervention with Pravastatin in Ischemic Disease study
MI	= myocardial infarction
NCEP	= National Cholesterol Education Program
4S	= Scandinavian Simvastatin Survival Study
WOSCOPS	= West of Scotland Coronary Prevention Study

dose-related efficacy in reducing LDL. In addition to lowering LDL, statins cause relatively small reductions in triglyceride levels (5% to 10%) in conjunction with minor increases in high-density lipoprotein (HDL) cholesterol (5% to 10%), and statin therapy does not reduce lipoprotein (a) (2). Most common adverse effects associated with statin therapy are mild, transient, reversible, and include dyspepsia, abdominal pain and flatulence. However, the most important adverse reactions are elevations in serum transaminases and the development of myositis. The risk of myositis increases in patients receiving statins in conjunction with gemfibrozil, nicotinic acid or macrolides, and there is an appreciable risk of myositis in patients also receiving cyclosporine (3). Administration of drugs that inhibit cytochrome P450, such as azole antifungals, cimetidine and methotrexate, also increases the likelihood of adverse effects.

REGRESSION OF ATHEROSCLEROSIS

Although vascular remodeling occurs naturally in the evolution of atherosclerosis (4), it was hypothesized that the introduction of cholesterol-lowering therapy would promote regression and/or retard the progression of atheroma. Trials with nonstatin compounds such as the Lipid Research Clinics Coronary Primary Prevention Trial using cholestyramine (5), and the Helsinki Heart Study (6) using gemfibrozil, supported this hypothesis and demonstrated significant reductions in coronary events. Thus, a number of trials (7-14) were conceived to explore the impact of statin therapy on the progression of coronary atherosclerosis using both quantitative and nonquantitative coronary angiography (Table 2). Although these angiographic trials were not

powered to examine clinical outcomes, the relatively small angiographic changes reported were accompanied by an unexpected clinical benefit. More recently, the beneficial effects of statin treatment on vein graft atherosclerosis were addressed in the Post Coronary Artery Bypass Graft (Post CABG) Trial (15); aggressive LDL reduction to a mean of 95 mg/dl led to a 31% reduction in the likelihood of progression of graft atherosclerosis and a 29% reduction in the rate of revascularization.

Although these angiographic studies used different patient-selection criteria, different baseline cholesterol levels and variable doses and duration of therapy, they demonstrated that plaque progression is common without therapy (40% to 50% of patients) and is reduced by more than one-third with statin therapy. Although clear plaque regression is uncommon (~10% of patients) without therapy, the frequency of regression more than doubles with statins. Because these trials were designed to explore the anatomic impact of statin therapy they were not powered to assess clinical outcome. Nonetheless, small anatomic changes were accompanied by a greater reduction in clinical events than expected based on the angiographic measures, suggesting that statin therapy may cause regression of lipid-rich lesions prone to rupture (16) and/or that statin therapy modulates atherosclerosis through mechanisms independent of anatomic regression (17). These trials provided an important foundation for subsequent large outcome studies.

STATINS AND CARDIOVASCULAR EVENTS

Landmark clinical trials have demonstrated that HMG CoA reductase inhibitors not only reduce CAD morbidity and mortality but also increase survival in the setting of both hypercholesterolemia or normocholesterolemia (Table 3). The Scandinavian Simvastatin Survival Study (4S) provided the first evidence that cholesterol-lowering therapy can reduce all-cause mortality in subjects with a history of angina pectoris or myocardial infarction (MI) (18). This study of 4,444 men and women with total cholesterol levels of 212 to 310 mg/dl (5.5 to 8.0 mmol/liter) initially used simvastatin at 20 mg/day and then titrated the drug to 10 or 40 mg/day. At five years, all-cause mortality was reduced by 30%, major coronary event rate by 34% and the coronary death rate by 42%. The dramatic results of the 4S study were extended in the West of Scotland Coronary Prevention Study (WOSCOPS), which was a primary-prevention trial of pravastatin 40 mg daily in 6,595 men with mean total cholesterol levels of 272 mg/dl (7.0 mmol/liter) but without documented CAD (19). After an average of 4.9 years of follow-up, all-cause mortality was nonsignificantly reduced by 22% ($p = 0.051$), but nonfatal MI or death from CAD was significantly reduced by 31% and the CAD death rate reduced by 28%. The need for coronary angiography and revascularization was also significantly lower in the treated group. The Cholesterol and Recurrent Events (CARE) trial was a secondary prevention trial of pravastatin 40 mg daily

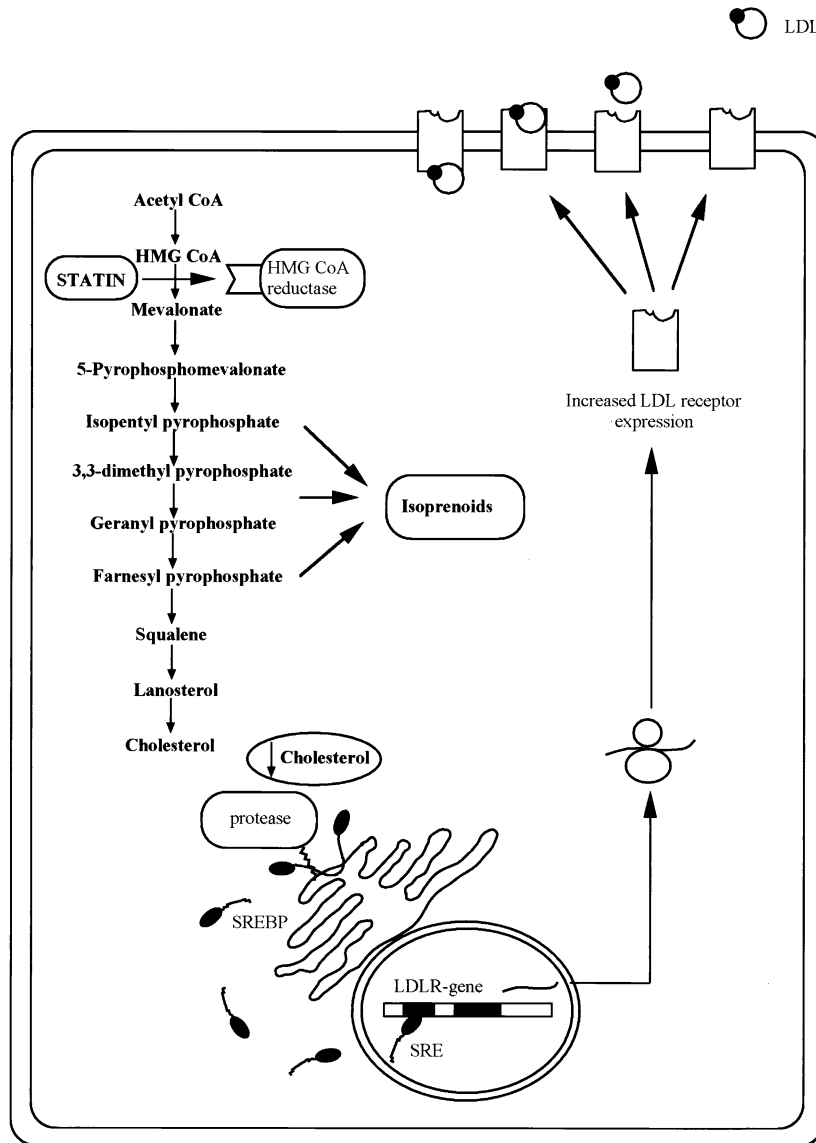


Figure 1. Regulation of cholesterol synthesis. Inhibition of HMG CoA reductase reduces intracellular cholesterol levels, thus activating a protease, which in turn cleaves sterol regulatory element-binding proteins (SREBPs) from the endoplasmic reticulum. The SREBPs translocate to the nucleus where they upregulate expression of the LDL receptor gene. Enhanced LDL receptor expression increases receptor-mediated endocytosis of LDL and thus lowers serum LDL. Inhibition of HMG CoA reductase also reduces intracellular levels of isoprenoids, which are intermediates in cholesterol biosynthesis.

in 4,159 men and women who had an acute MI between 3 and 20 months before randomization and in whom the total cholesterol level was <240 mg/dl (6.2 mmol/liter) with an LDL level of 115 to 174 mg/dl (3.0 to 4.5 mmol/liter) (20). The primary end point of fatal coronary event or nonfatal MI was reduced by 24%, and the need for coronary artery bypass surgery was reduced by 26%. Finally, the CARE study also demonstrated that women experienced a major reduction in risk for coronary events and stroke, with benefit evident beginning at one year (21). It is noteworthy that statins not only reduce overall cardiovascular mortality but also reduce sudden death by a similar order of magnitude as

other cardiovascular events (18). The observed reduction in sudden death may be due to reduced plaque rupture and reduced acute ischemia.

Recent studies have confirmed and extended these results. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (22) investigated 6,605 men and women without clinical evidence of CAD, with an average LDL level (130 to 190 mg/dl) with below average HDL cholesterol level (<50 mg/dl), and who were treated with placebo or lovastatin titrated up to 40 mg daily to achieve an LDL level less than 110 mg/dl. After 4.8 years of follow-up, the incidence of first major acute coronary event

Table 1. Pharmacologic Characteristics of Different HMG CoA Reductase Inhibitors

Drug	Daily Dose (mg)	Absorption (%)	Plasma Protein Binding (%)	Renal Excretion (%)	Half-life (h)	Solubility
Lovastatin	20-80	31	95	30	2-3	Lipophilic
Simvastatin	5-80	60-85	98	13	2-3	Lipophilic
Pravastatin	10-40	35	40-50	60	1-3	Hydrophilic
Fluvastatin	20-80	98	99	6	0.5-1	Hydrophilic
Atorvastatin	10-80	NA	98	2	13-16	Lipophilic
Cerivastatin	0.2-0.3	NA	99	24	2-3	NA

NA = not available.

was reduced by 37% in the treated group. The Long-term Intervention with Pravastatin in Ischemic Disease study (LIPID) (23) was a secondary prevention study to compare pravastatin 40 mg daily to placebo in 9,014 men and women with prior MI or unstable angina and total cholesterol levels between 155 and 271 mg/dl. After a mean follow-up of 6.1 years, all-cause mortality was reduced by 22%, mortality due to CAD by 24%, and stroke by 19%.

These trials have unequivocally shown that lowering LDL increases survival by both secondary and primary prevention of CAD not only in individuals with elevated LDL levels, but also in those with average LDL levels. The evidence to date suggests that statin therapy should reduce the clinical consequences of atherosclerosis in a large proportion of the population at risk. These studies have raised questions regarding the relative appropriate pretreatment LDL levels in both primary and secondary CAD prevention and the degree to which LDL should be lowered. The relative reduction in LDL achieved in these trials is depicted in Figure 2.

The results of 4S, CARE and LIPID indicate that statin therapy is highly beneficial in CAD secondary prevention

for patients with both elevated and average LDL levels. Thus, most patients with CAD will benefit from statin therapy. Although CARE suggested that no further risk reduction occurs by lowering LDL below 125 mg/dl, this lower threshold remains controversial. The Post CABG trial demonstrated reduced saphenous vein graft atherosclerosis and reduced need for revascularization in patients in whom LDL was aggressively lowered to a mean of 95 mg/dl (15). The National Cholesterol Education Program (NCEP) has established guidelines for cholesterol management (24) in patients with CAD or peripheral atherosclerotic disease; the recommended goal is an LDL of ≤ 100 mg/dl. Recently published subgroup analyses from 4S and CARE indicate that these NCEP guidelines for secondary prevention of CAD are generally appropriate (25,26). It will be important to determine whether further aggressive LDL lowering will yield additional benefit, especially in subgroups of patients with advanced atherosclerosis.

The WOSCOPS trial (19,27) provides strong evidence that cholesterol-lowering therapy is effective in primary prevention in patients with high LDL. However, WOSCOPS did not give a clear indication of the optimal

Table 2. Summary of Major Angiographic Trials of the Effects of Statins on Coronary Artery Disease

Study (Reference)	Study Description	Duration (yrs)	% Red LDL-C	Control	Treatment	Clinical Events
FATS (7)	146 pts Lovastatin 40-80 mg/d (+colestipol)	2.5	46	46% Prog 11% Regr	21% Prog 32% Regr	Decreased
MARS (8)	270 pts Lovastatin 40 mg bid	2.2	38	41% Prog 12% Regr	29% Prog 23% Regr	NS reduction
CCAIT (9)	331 pts Lovastatin 20-80 mg/d	2	29	50% Prog 7% Regr	33% Prog 10% Regr	NS reduction
MASS (10)	381 pts Simvastatin 20 mg/d	4	31.4	32% Prog 12% Regr	23% Prog 18% Regr	NS reduction
REGRESS (11)	885 pts Pravastatin 40 mg/d	2	29	NA	NA	Decreased
PLAC-I (12)	408 pts Pravastatin 40 mg/d	3	28	50% Prog 15% Regr	37% Prog 21% Regr	Decreased
CIS (13)	254 pts Simvastatin 40 mg/d	2.3	35	53.5 Prog 12.9% Regr	34.6 Prog 18.3 Regr	No difference
LCAS (14)	340 pts Fluvastatin 20 mg bid	2.5	23.9	39.1% Prog 8.3% Regr	28.7% Prog 14.6% Regr	NS reduction

Prog = progression; Regr = regression; NS = nonsignificant; NA = not available.

Table 3. Summary of Major Clinical Intervention Trials of the Effects of Statins on Coronary Events and Stroke

Trial (Reference)	Study Description	Duration (yrs)	Reduction			
			LDL-C (%)	Mortality (%)	CAD Death (%)	Stroke (%)
4S (18)	4,444 pts, HC, CAD, Simvastatin 10–40 mg/d	5.0	35	30	42	30
WOSCOPS (19)	6,595 pts, HC, No CAD Pravastatin 40 mg/d	4.9	26	22 (NS)	33	11 (NS)
CARE (20)	4,159 pts, NC, CAD Pravastatin 40 mg/d	5.0	28	8 (NS)	19	31
AFCAPS/TexCAPS (22)	6,605 pts, NC, No CAD Lovastatin 20–40 mg/d	5.2	25	NA	36	NA
LIPID (23)	9,014 pts, NC, CAD Pravastatin 40 mg/d	6.1	25	22	24	19

HC = hypercholesterolemia; NC = normocholesterolemia; CAD = coronary artery disease; NS = not significant; NA = not available.

LDL cholesterol for the initiation of statin therapy in this setting. The AFCAPS/TexCAPS study revealed that men and women with average LDL and without evidence of vascular disease also derived benefit from statin therapy. Although the NCEP recommends for primary prevention a minimal goal of LDL <160 mg/dl, and in patients with a high burden of risk factors a goal <130 mg/dl, AFCAPS/TexCAPS data support benefit of statin therapy at LDL levels below those currently targeted by the NCEP guidelines. Based on these findings, it would now seem, at minimum, prudent to apply aggressively the NCEP guidelines in the primary prevention of vascular disease. However, given the absence of reduction in overall mortality with statin therapy in AFCAPS/TexCAPS, further studies are warranted to explore the benefit of achieving target cholesterol levels as outlined by the NCEP. It is possible that in high-risk patients it may be appropriate to lower LDL even further. Aggressive LDL lowering may be achieved through

combination therapy of statins with other lipid-lowering drugs. Additional studies are warranted to address these important questions.

STATINS AND CEREBROVASCULAR DISEASE

Despite the established role of cholesterol in the pathogenesis of CAD, current evidence does not demonstrate a clear relationship between the risk of stroke and plasma cholesterol level (28,29). Despite a paucity of clear epidemiologic evidence of a relationship between plasma cholesterol and stroke risk, recent studies indicate that statins have beneficial effects that extend beyond the coronary vascular bed (30,31). Clinical benefit of statins is also supported by imaging studies showing reversal of carotid intimal-medial thickening by statins (32–34). In the CARE study, pravastatin significantly reduced the specified end point stroke by 31%, without increased hemorrhagic stroke (20). Post hoc

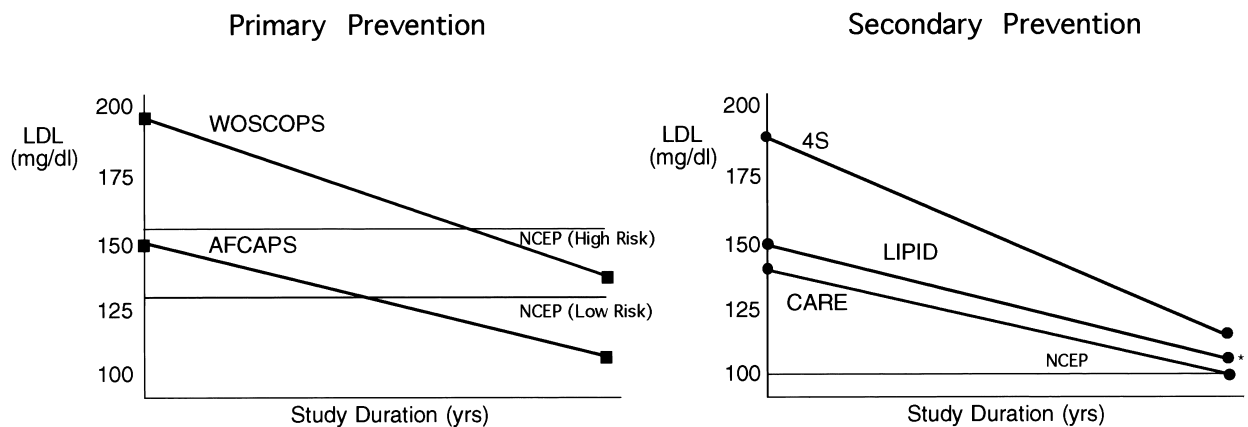


Figure 2. LDL lowering in primary and secondary prevention trials of statin therapy. The mean LDL enrollment levels are depicted for major trials testing statin utility in primary prevention (WOSCOPS, AFCAPS) and secondary prevention (4S, CARE, LIPID) of coronary artery disease. Mean LDL levels achieved after statin therapy in each trial are also depicted. The NCEP-recommended goals for LDL lowering are depicted for both primary and secondary CAD prevention. Note that mean LDL levels achieved with statins in the AFCAPS primary prevention trial to determine drug efficacy are lower than the NCEP goals. (*Absolute value extrapolated from a reported 25% reduction in LDL [23]).

analysis of the 4S trial (18) showed a similarly significant reduction in stroke. In the WOSCOPS primary prevention trial, a nonsignificant 11% reduction in stroke was noted during five-year follow-up (19). Furthermore, two meta-analyses indicate that statin therapy lowers stroke risk by about 30%, an extent comparable to aspirin (31,35).

ANTI-ISCHEMIC PROPERTIES OF STATINS

In addition to angiographic and clinical outcome studies, several investigators have explored the impact of statin therapy on the endothelial control of vasomotor tone in hypercholesterolemic patients (36-38). Improvement in coronary vasomotor function may be seen after as little as six months of therapy (36). Decreased vasospasm is also suggested by improved forearm blood flow in hypercholesterolemic patients treated with statins for only four weeks (39). The relationship between LDL reduction and amelioration of endothelial dysfunction in hypercholesterolemia is supported by the observation that single-session LDL apheresis improves forearm blood flow (40). Improvement in myocardial perfusion, reported to occur after only three months of statin therapy, may relate to decreased vasospasm (41,42). Electron-beam-computed tomography has recently shown that statins reduce the volume of calcified plaque in coronary arteries in 12 months (43). This radiographic surrogate suggests that statins may alter the constituents and behavior of plaque, rendering it more stable. Ultimately, the anti-ischemic effect of statin therapy can also be directly shown with quantitative ST-segment monitoring during 24-h ambulatory electrocardiography (44,45).

PLAQUE STABILIZATION

Atherogenesis is initiated by accumulation of LDL in the subendothelial space, where it becomes oxidized to minimally modified LDL (46), which induces local production of monocyte chemoattractant protein 1 (MCP1) as well as other chemotactic factors that recruit additional leukocytes to the arterial wall (47). Oxidized LDL attracts macrophages directly (48) and stimulates their binding to the endothelium through induction of adhesion molecules such as P-selectin (49) and vascular cell adhesion molecule 1 (VCAM-1) (50). The HMG-CoA reductase inhibitors prevent the oxidation of LDL (51) possibly through preservation of the activity of the endogenous antioxidant system, superoxide dismutase (52). Statins also alter macrophage handling and uptake of LDL. Lovastatin not only inhibits oxidation of LDL, but also reduces the avidity with which macrophages ingest oxidized LDL (51). Reduced LDL oxidation and uptake by macrophages may be due to direct effects of statins on LDL, which change its propensity for oxidation (51). Statins also reduce vascular expression of adhesion molecules (53,54). In humans, both simvastatin and lovastatin reduce monocyte CD11b expression and *ex vivo* CD11b-dependent monocyte adhesion to endothelium in patients with hypercholesterolemia (55).

The monocyte/macrophage is not only a promiscuous initiator of atherosclerosis but also a central orchestrator of plaque rupture, the event which heralds most acute coronary syndromes (56). Modified LDL induces macrophage transformation into foam cells and also promotes macrophage activation, which leads to plaque instability (57). Macrophages have been implicated in the pathophysiology of acute coronary syndromes by producing enzymes, including members of the metalloproteinase family (interstitial collagenase, gelatinase, and stromelysin) that digest and weaken the plaque cap, making disruption more likely (58,59). In addition, macrophages elaborate tissue factor, a membrane-bound glycoprotein that plays an integral role in blood coagulation, and is an important determinant of plaque thrombogenicity (60). Statin therapy inhibits tissue factor expression by cultured human macrophages, and this may reduce thrombotic events (61). In addition to effects on LDL, macrophage activation, and adhesion molecule expression, statins may also attenuate atherogenesis through the inhibition of vascular smooth muscle cell proliferation and migration (62,63) and thus attenuate plaque growth and new lesion formation. Interestingly, pravastatin, a hydrophilic statin, may not share this antiproliferative effect (64), and yet it shows clinical benefit in angiographic and event trials. Experimental/clinical disparities such as this raise questions about the clinical applicability of isolated *in vitro* studies of statins.

STATINS AND ENDOTHELIAL DYSFUNCTION

Several lines of evidence indicate that statins biochemically "modify" the paracrine functions of endothelium in hypercholesterolemia, and transform the endothelium from predominantly prothrombotic and vasospastic to thromboresistant and vasodilatory. The mechanisms underlying the benefit of statin therapy on endothelial dysfunction induced by hypercholesterolemia remain unclear, but hypotheses center on nitric oxide (NO)-dependent mechanisms. Direct upregulation of endothelial nitric oxide synthase (eNOS) by HMG CoA reductase inhibitors has recently been reported, and this may represent an important mechanism by which these compounds preserve endothelial NO synthesis (65). Nitric oxide regulates the paracrine antiatherosclerotic functions of the endothelium, which include inhibition of leukocyte and platelet adhesion, control of vascular tone and growth and maintenance of a thromboresistant interface between the bloodstream and the vessel wall. There is a growing body of evidence suggesting that impaired NO synthesis or activity accompanies hypercholesterolemia (66). Increased concentrations of oxidized LDL may directly inhibit NO by excess production of oxygen-derived free radicals and reduced transcription or increased posttranslational destabilization of eNOS mRNA (66). Hypercholesterolemia also reduces eNOS activity through cytokine production (67), or increases in dimethyl arginine, an endogenous inhibitor of eNOS (68).

INHIBITION OF ISOPRENOID BIOSYNTHESIS

In addition to lowering intracellular levels of sterols, HMG CoA reductase inhibitors reduce levels of isoprenoids, which are derived from intermediates of the cholesterol biosynthetic pathway (Fig. 1). Isoprenoids posttranslationally prenylate a variety of cellular proteins that play central roles in both cell growth and in signal transduction pathways such as low-molecular weight guanine nucleotide binding proteins (G-proteins), which have been shown to modulate signal transduction and mitogenic pathways (69). Finally, the putative antioxidant effects attributed to statins (52) may be due to attenuated isoprenylation of NADPH oxidase, which in its isoprenylated state generates superoxide anion (70).

ANTI-THROMBOTIC ACTIONS OF STATINS

Platelets play a fundamental role in atherogenesis and in the pathophysiology of acute coronary syndromes (71,72). Hypercholesterolemia is associated with both hypercoagulability as well as enhanced platelet activation (73). High LDL levels increase platelet reactivity in association with enhanced thromboxane A₂ (TXA₂) biosynthesis, and enhanced TXA₂ production has been demonstrated in the majority of patients with type IIa hypercholesterolemia (74). Hypercholesterolemia has also been associated with increased platelet alpha₂ adrenergic receptor density (75), changes in the composition of platelet membrane phospholipids and cholesterol (76) and increases in platelet cytosolic calcium (77).

Several studies demonstrate reductions in platelet reactivity with statin treatment (74,78,79). Although the precise mechanism responsible for the effects of statins on platelet function is unclear, one mechanism may involve decreased platelet TXA₂ production. The finding that the membrane cholesterol content of both erythrocytes and platelets is reduced in patients treated with pravastatin (80) suggests that certain properties of these membranes are altered in a manner that renders them less prone to participation in thrombosis. Moreover, Nofer and colleagues (81) have recently elucidated a novel mechanism that increases platelet activation in hypercholesterolemia through inhibition of platelet Na⁺/H⁺ antiport by LDL. Statin therapy also ameliorates the enhanced thrombotic and reduced fibrinolytic state that accompanies hypercholesterolemia (82). Although statins do not directly reduce lipoprotein (a) [Lp(a)] levels and may even increase levels of this lipoprotein (2), statins may still modify prothrombotic states related to simultaneously elevated LDL and Lp(a) (83-85). Additionally, platelet-dependent thrombin generation is increased in subjects with hypercholesterolemia, and treatment with pravastatin normalizes thrombin production (86).

These observations add to the growing body of evidence linking hypercholesterolemia and thrombosis and suggest that statins reverse the thrombotic-fibrinolytic imbalance

that accompanies hypercholesterolemia. Given that thrombotic disruption of plaque precipitates most acute coronary syndromes, the impact of statin therapy in reducing both the thrombotic tendency of blood, in addition to the thrombogenicity of plaque, may be particularly important in the overall reduction of clinical events.

SUMMARY

Recent advances in the management of hypercholesterolemia are largely due to the development of HMG CoA reductase inhibitors. Initial studies explored the impact of statin therapy on CAD progression and regression, and although the angiographic changes were unimpressive, the accompanying clinical benefit appeared significant. Subsequent large prospective clinical trials gave clear evidence that statin therapy not only reduces major coronary event rate but also reduces all-cause mortality. For lipid lowering, the NCEP-defined goals provide targets for statin therapy. For patients with CAD or other atherosclerotic disease, the NCEP goal is an LDL of ≤ 100 mg/dl. The NCEP recommends a minimal goal of LDL < 160 mg/dl in primary prevention, and in patients with a high burden of risk factors, the recommended goal is LDL < 130 mg/dl. The anatomic/clinical disparity manifest in clinical trials may best be explained by effects of statins over and above lipid lowering: promotion of plaque stability, improvement of endothelial dysfunction and reversal of coagulation and platelet abnormalities that accompany hypercholesterolemia. Recent studies also suggest that statins have beneficial effects extending beyond the coronary vascular bed and are capable of reducing ischemic stroke risk by approximately one-third in patients with evidence of vascular disease. Burgeoning clinical and experimental evidence indicates that the beneficial action of statins occurs rapidly and may yield clinically important anti-ischemic effects as early as one month after commencement of therapy. Statins exhibit pleiotropic effects on many components of atherosclerosis, including plaque thrombogenicity, cellular migration, endothelial function and thrombotic tendency (Fig. 3). Clinical benefits of these effects in vivo remains to be determined.

FUTURE DIRECTIONS

Although statin therapy is established as an integral component in the management of CAD, many questions concerning such therapy remain unanswered. The issue of how far LDL should be lowered is still controversial. The management of patients with CAD and baseline LDL of 100 to 129 mg/dl needs to be addressed in a specific clinical trial as well as a study exploring threshold LDL values in primary prevention. The role of hypertriglyceridemia and its treatment in patients already receiving statin therapy also needs prospective evaluation. Several promising small studies (87,88) should prompt large-scale clinical trials and meta-analyses of current databases to test utility of other lipid-lowering drugs in combination with statins in patients

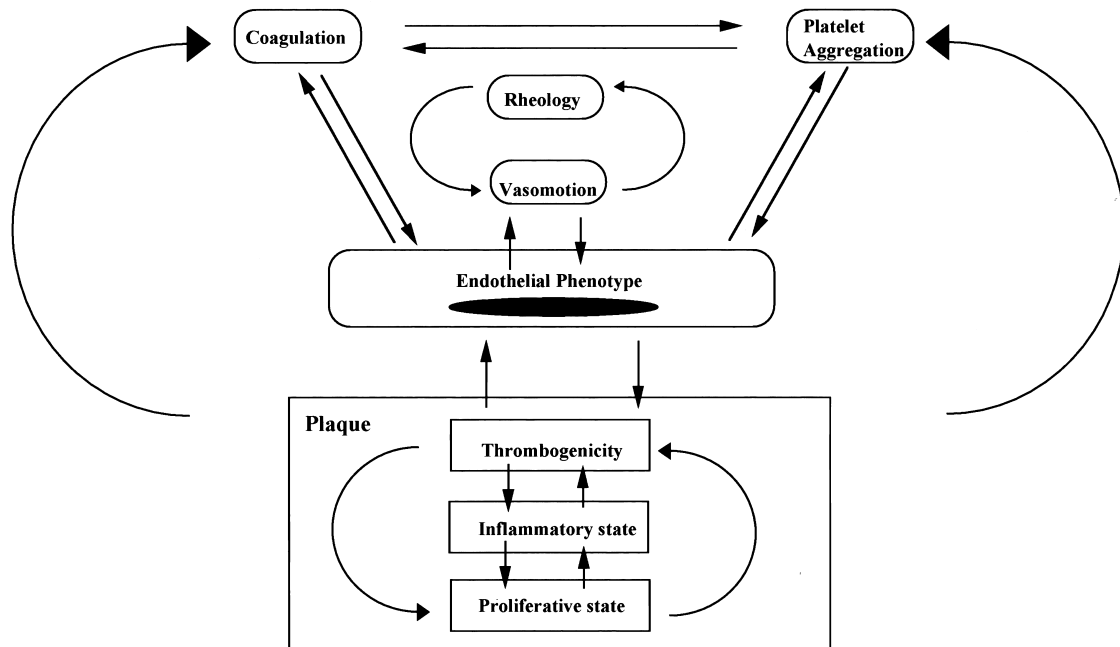


Figure 3. Statins and determinants of acute coronary syndromes. Statins exhibit pleiotropic effects on many components of atherosclerosis that accompany hypercholesterolemia, including platelet coagulation abnormalities, abnormal endothelial function, and determinants of plaque thrombogenicity such as plaque inflammation and proliferation.

with a spectrum of dyslipidemias. Further data are also awaited to support the growing importance of cholesterol as a risk factor for ischemic stroke and the benefit of statin therapy in patients with cerebrovascular disease. Elucidation of statin effects other than LDL lowering will undoubtedly provide an increasing number of therapeutic goals for statin therapy. In addition, the role of immediate statin therapy in patients presenting with acute coronary syndromes is unknown. Given the rapid and protean effects of statins on determinants of platelet reactivity, coagulation and endothelial function, future investigation may address a role for statin therapy in acute coronary syndromes.

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REFERENCES

- Brown MS, Goldstein JL. Multivalent feedback regulation of HMG CoA reductase, a control mechanism coordinating isoprenoid synthesis and cell growth. *J Lipid Res* 1980;21:505-17.
- Kostner GM, Gavish D, Leopold B, et al. HMG CoA reductase inhibitors lower LDL cholesterol without reducing Lp(a) levels. *Circulation* 1989;80:1313-9.
- Regazzi MB, Iacona I, Campana C, et al. Altered disposition of pravastatin following concomitant drug therapy with cyclosporine A in transplant recipients. *Transplant Proc* 1993;25:2732-4.
- Glagov S, Weisenberg E, Zarins CK, et al. Compensatory enlargement of human atherosclerotic arteries. *N Engl J Med* 1987;316:1371-5.
- Lipid Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial results: I. reduction in the incidence of coronary artery disease. *JAMA* 1984;251:351-64.
- Frick MH, Elo O, Haapa K, et al. Helsinki Heart Study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med* 1987;317:1237-45.
- Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;323:1289-98.
- Blankenhorn DH, Azen SP, Krams DM, et al. Coronary angiographic changes with lovastatin therapy. *Ann Intern Med* 1993;119:969-76.
- Waters D, Higginson L, Gladstone P, et al. Effects of monotherapy with an HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography. *Circulation* 1994;89:959-68.
- MAAS Investigators. Effect of simvastatin on coronary atheroma: the Multicentre Anti-Atheroma Study (MAAS). *Lancet* 1994;344:633-8.
- Jukema JW, Bruschke AVG, van Boven AJ, et al. Effects of lipid lowering by pravastatin on progression and regression of coronary artery disease in symptomatic men with normal to moderately elevated serum cholesterol levels. *Circulation* 1995;91:2528-40.
- Pitt B, Mancini JGB, Ellis SG, et al., for the PLAC-I Investigators. Pravastatin limitation of atherosclerosis in the coronary arteries (PLAC-I): reduction in atherosclerosis progression and clinical events. *J Am Coll Cardiol* 1995;26:1133-9.
- Bestehorn HP, Rensing UFE, Roskamm H, et al. The effect of simvastatin on progression of coronary artery disease. *Eur Heart J* 1997;18:226-34.
- Herd JA, Ballantyne CM, Farmer JA, et al. Effects of fluvastatin on coronary atherosclerosis in patients with mild to moderate cholesterol elevations (Lipoprotein and Coronary Atherosclerosis Study [LCAS]). *Am J Cardiol* 1997;80:278-86.
- The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med* 1997;336:153-62.
- Brown BG, Zhao XQ, Sacco DE, Albers JJ. Lipid-lowering and

- plaque regression: new insights into prevention of plaque disruption and clinical events in coronary disease. *Circulation* 1993;87:1781-91.
17. Vaughan CJ, Murphy MB, Buckley BM. Statins do more than just lower cholesterol. *Lancet* 1996;348:1079-82.
 18. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
 19. Shepherd J, Cobbe SM, Ford I, et al., for the West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med* 1995;333:1301-7.
 20. Sacks FM, Pfeffer MA, Moye LA, et al., for the Cholesterol and Recurrent Events Trial Investigators. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-9.
 21. Lewis SJ, Sacks FM, Mitchell JS, et al., for the CARE investigators. Effect of pravastatin on cardiovascular events in women after myocardial infarction: the Cholesterol and Recurrent Events (CARE) trial. *J Am Coll Cardiol* 1998;32:40-6.
 22. Downs JR, Clearfield M, Weis S, et al., for the AFCAPS/TextCAPS Research Group. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TextCAPS. *JAMA* 1998;279:1615-22.
 23. The Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med* 1998;339:1349-57.
 24. National Cholesterol Education Program. Second report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994;89:1329-445.
 25. Pedersen TR, Olsson AG, Faergeman O, et al., for the Scandinavian Simvastatin Survival Study Group. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). *Circulation* 1998;97:1453-60.
 26. Sacks FM, Moye LA, Davis BR, et al. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the cholesterol and recurrent events trial. *Circulation* 1998;97:1446-52.
 27. West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). *Circulation* 1998;97:1440-5.
 28. Prospective Studies Collaboration. Cholesterol, diastolic blood pressure, and stroke: 13,000 strokes in 450,000 people in 45 prospective studies. *Lancet* 1995;346:1647-53.
 29. Iso H, Jacobs DR, Wentworth D, et al., for the MRFIT Research Group. Serum cholesterol levels and six-year mortality from stroke in 350,977 men screened for the multiple risk factor intervention trial. *N Engl J Med* 1989;320:904-10.
 30. Delanty N, Vaughan CJ. Vascular effects of statins in stroke. *Stroke* 1997;28:2315-20.
 31. Blauw GJ, Lagaay AM, Smelt AHM, Westendorp RGJ. Stroke, statins, and cholesterol: a meta-analysis of randomized, placebo-controlled, double-blind trials with HMG-CoA reductase inhibitors. *Stroke* 1997;28:946-50.
 32. Furberg CD, Adams HP, Applegate WB, et al., for the Asymptomatic Carotid Artery Progression Study (ACAPS) Research Group. Effect of lovastatin on early carotid atherosclerosis and cardiovascular events. *Circulation* 1994;90:1679-87.
 33. Crouse JR III, Byington RP, Bond MG, et al. Pravastatin, lipids, and atherosclerosis in the carotid arteries (PLAC-II). *Am J Cardiol* 1995;75:455-59.
 34. MacMahon S, Sharpe N, Gamble G, et al. Effects of lowering average or below-average cholesterol levels on the progression of carotid atherosclerosis: results of the LIPID atherosclerosis substudy. *Circulation* 1998;97:1784-90.
 35. Crouse JR III, Byington RP, Hoen HM, Furberg CD. Reductase inhibitor monotherapy and stroke prevention. *Arch Intern Med* 1997;157:1305-10.
 36. Egashira K, Hirooka Y, Kai H, et al. Reduction in serum cholesterol with pravastatin improves endothelium-dependent coronary vasomotion in patients with hypercholesterolemia. *Circulation* 1994;89:2519-24.
 37. Treasure CB, Klein JL, Weintraub WS, et al. Beneficial effects of cholesterol-lowering therapy on the coronary endothelium in patients with coronary artery disease. *N Engl J Med* 1995;332:481-7.
 38. Anderson T, Meredith I, Yeung A, et al. The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vasomotion. *N Engl J Med* 1995;332:488-93.
 39. O'Driscoll G, Green D, Taylor RR. Simvastatin, an HMG-coenzyme A reductase inhibitor, improves endothelial function within 1 month. *Circulation* 1997;95:1126-31.
 40. Tamai O, Matsuoka H, Itabe H, et al. Single LDL apheresis improves endothelium-dependent vasodilation in hypercholesterolemic humans. *Circulation* 1997;95:76-82.
 41. Gould KL, Martucci JP, Goldberg DI, et al. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease. *Circulation* 1994;89:1530-8.
 42. Eichstadt HW, Eskotter H, Hoffman I, et al. Improvement of myocardial perfusion by short-term fluvastatin therapy in coronary artery disease. *Am J Cardiol* 1995;76:122-5A.
 43. Callister TQ, Raggi P, Cooil B, et al. Effect of HMG-CoA reductase inhibitors on coronary artery disease as assessed by electron-beam-computed tomography. *N Engl J Med* 1998;339:1972-8.
 44. Andrews TC, Raby K, Barry J, et al. Effects of cholesterol reduction on myocardial ischemia in patients with coronary artery disease. *Circulation* 1997;95:324-8.
 45. van Boven AJ, Jukema JW, Zwinderman AH, et al. Reduction of transient myocardial ischemia with pravastatin in addition to conventional treatment in patients with angina pectoris. *Circulation* 1996;94:1503-5.
 46. Navab M, Berliner JA, Watson AD, et al. The yin and yang of oxidation in the development of the fatty streak: a review based on the 1994 George Lyman Duff Memorial Lecture. *Arterioscler Thromb Vasc Biol* 1996;16:831-42.
 47. Parhami F, Fang ZT, Fogelman AM, et al. Minimally modified low density lipoprotein-induced inflammatory responses in endothelial cells are mediated by cyclic adenosine monophosphate. *J Clin Invest* 1993;92:471-8.
 48. Quinn MT, Parthasarathy S, Steinberg D. Lysophosphatidylcholine: a chemotactic factor for human monocytes and its potential role in atherogenesis. *Proc Natl Acad Sci* 1988;85:2805-9.
 49. Vora DK, Fang Z-T, Liva SM, et al. Induction of P-selectin by oxidized lipoproteins. *Circ Res* 1997;80:810-8.
 50. O'Brien KD, Allen MD, McDonald TO, et al. Vascular cell adhesion molecule-1 is expressed in human coronary atherosclerotic plaques. *J Clin Invest* 1993;92:945-51.
 51. Aviram M, Dankner G, Cogan U, et al. Lovastatin inhibits LDL oxidation and alters its fluidity and uptake by macrophages: in vitro and in vivo studies. *Metabolism* 1992;41:229-35.
 52. Chen L, Haught WH, Yang B, et al. Preservation of endogenous antioxidant activity and inhibition of lipid peroxidation as common mechanisms of antiatherosclerotic effects of vitamin E, lovastatin and amlodipine. *J Am Coll Cardiol* 1997;30:569-75.
 53. Kimura M, Kurose I, Russell J, Granger DN. Effects of fluvastatin on leukocyte-endothelial cell adhesion in hypercholesterolemic rats. *Arterioscler Thromb Vasc Biol* 1997;17:11521-6.
 54. Lehr HA, Seemuller J, Hubner C, et al. Oxidized LDL-induced leukocyte/endothelium interaction in vivo involves the receptor for platelet activating factor. *Arterioscler Thromb* 1993;13:1013-8.
 55. Weber C, Erl W, Weber KSC, Weber PC. HMG-CoA reductase inhibitors decrease CD11b expression and CD11b-dependent adhesion of monocytes to endothelium and reduce increased adhesiveness of monocytes isolated from patients with hypercholesterolemia. *J Am Coll Cardiol* 1997;30:1212-7.
 56. Davies MJ, Richardson PD, Woolf N, et al. Risk of thrombosis in human atherosclerotic plaques: role of extracellular lipid, macrophage, and smooth muscle cell content. *Br Heart J* 1993;69:377-81.
 57. Libby P. Molecular bases of the acute coronary syndromes. *Circulation* 1995;91:2844-50.
 58. Henney AM, Wakeley PR, Davies MJ, et al. Location of stromelysin gene in atherosclerotic plaques using in situ hybridisation. *Proc Natl Acad Sci USA* 1991;88:8154-8.
 59. Richardson PD, Davies MJ, Born GV. Influence of plaque configura-

- ration and stress distribution on fissuring of coronary atherosclerotic plaques. *Lancet* 1989;2:941-4.
60. Toschi V, Gallo R, Lettino M, et al. Tissue factor modulates the thrombogenicity of human atherosclerotic plaque. *Circulation* 1997;95:594-9.
 61. Colli S, Eligini S, Lalli M, et al. Vastatins inhibit tissue factor in cultured human macrophages: a novel mechanism of protection against atherosclerosis. *Arterioscler Thromb Vasc Biol* 1997;17:265-72.
 62. Rogler G, Lackner KJ, Schmitz G. Effects of fluvastatin on growth of porcine and human vascular smooth muscle cells in vitro. *Am J Cardiol* 1995;76:114-6A.
 63. Negre-Aminou P, van Vliet AK, van Erck M, et al. Inhibition of proliferation of human smooth muscle cells by various HMG-CoA reductase inhibitors: comparison with other human cell types. *Biochim Biophys Acta* 1997;1345:259-68.
 64. Corsini A, Pazzucconi F, Arnaboldi L, et al. Direct effects of statins on the vascular wall. *J Cardiovasc Pharmacol* 1998;31:773-8.
 65. Laufs U, La Fata V, Plutzky J, Liao JK. Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors. *Circulation* 1998;97:1129-35.
 66. Liao JK, Shin WS, Lee WY, Clark SL. Oxidized low-density lipoprotein decreases the expression of endothelial nitric oxide synthase. *J Biol Chem* 1995;270:319-24.
 67. Rosenkranz-Weiss P, Sessa WC, Milstein S, et al. Regulation of nitric oxide synthesis by proinflammatory cytokines in human umbilical vein endothelial cells: elevations in tetrahydrobiopterin levels enhance endothelial nitric oxide synthase specific activity. *J Clin Invest* 1994;93:2236-43.
 68. Cooke JP, Tsao PS. Arginine: a new therapy for atherosclerosis? *Circulation* 1997;95:311-2.
 69. Hall A. The cellular functions of small GTP-binding proteins. *Science* 1990;249:635-54.
 70. Bokoch GM, Prossnitz V. Isoprenoid metabolism is required for stimulation of the respiratory burst oxidase of HL-60 cells. *J Clin Invest* 1992;89:402-8.
 71. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and acute coronary syndromes. *N Engl J Med* 1992;326:310-8.
 72. Fitzgerald DJ, Roy L, Catella F, Fitzgerald GA. Platelet activation in unstable coronary disease. *N Engl J Med* 1986;315:983-9.
 73. Badimon JJ, Badimon L, Turitto VT, Fuster V. Platelet deposition at high shear rates is enhanced by high plasma cholesterol levels: in vivo study in the rabbit model. *Arterioscler Thromb* 1991;11:395-402.
 74. Notarbartolo A, Davi G, Averna M, et al. Inhibition of thromboxane biosynthesis and platelet function by simvastatin in type IIa hypercholesterolemia. *Arterioscler Thromb Vasc Biol* 1995;15:247-51.
 75. Baldassarre D, Mores N, Colli S, et al. Platelet alpha₂-adrenergic receptors in hypercholesterolemia: relationship between binding studies and epinephrine-induced platelet aggregation. *Clin Pharmacol Ther* 1997;61:684-91.
 76. Mazeaud MM, Driss F, Le Quan Sang KH, et al. Biochemical and functional alterations associated with hypercholesterolemia in platelets from hypertensive patients. *Atherosclerosis* 1992;94:201-11.
 77. Le Quan Sang KH, Levenson J, Megnien JL, et al. Platelet cytosolic Ca²⁺ and membrane dynamics in patients with hypercholesterolemia: effects of pravastatin. *Arterioscler Thromb Vasc Biol* 1995;15:759-64.
 78. Mayer J, Eller T, Brauer P, et al. Effects of long-term treatment with lovastatin on the clotting system and blood platelets. *Ann Hematol* 1992;64:196-201.
 79. Lacoste L, Lam JYT, Hung J, et al. Hyperlipidaemia and coronary disease: correction of the increased thrombogenic potential with cholesterol reduction. *Circulation* 1995;92:3172-7.
 80. Linjen P, Celis H, Fagard R, et al. Influence of cholesterol lowering on plasma membrane lipids and cationic transport systems. *J Hypertens* 1994;12:59-64.
 81. Nofer J-R, Tepel M, Kehrel B, et al. Low-density lipoproteins inhibit the Na⁺/H⁺ antiport in human platelets: a novel mechanism enhancing platelet activity in hypercholesterolemia. *Circulation* 1997;95:1370-7.
 82. Wada H, Mori Y, Kaneko T, et al. Elevated plasma levels of vascular endothelial cell markers in patients with hypercholesterolemia. *Am J Hematol* 1993;44:112-6.
 83. Armstrong VW, Cremer P, Eberle E, et al. The association between serum Lp(a) concentrations and angiographically assessed coronary atherosclerosis: dependence on serum LDL levels. *Atherosclerosis* 1989;62:249-57.
 84. Lundstam U, Hurt-Camejo E, Olsson G, et al. Proteoglycans' contribution to association of Lp(a) and LDL with smooth muscle cell extracellular matrix. *Arterioscler Thromb Vasc Biol* 1999;19:1162-7.
 85. Maher VM, Brown BG, Marcovina SM, et al. Effects of lowering elevated LDL cholesterol on the cardiovascular risk of lipoprotein (a). *JAMA* 1995;274:1771-4.
 86. Aoki I, Aoki N, Kawano K, et al. Platelet-dependent thrombin generation in patients with hyperlipidemia. *J Am Coll Cardiol* 1997;30:91-6.
 87. Brown BG, Zambon A, Poulin D, et al. Use of niacin, statins, and resins in patients with combined hyperlipidemia. *Am J Cardiol* 1998;81:52B-9B.
 88. Pasternak RC, Brown LE, Stone PH, et al. Effect of combination therapy with lipid-reducing drugs in patients with coronary heart disease and "normal" cholesterol levels: a randomized, placebo-controlled trial. Harvard Atherosclerosis Reversibility Project (HARP) study group. *Ann Intern Med* 1996;125:529-40.