

Review Article

The Impact of Statin Administration in Acute Coronary Syndromes

NIKOLAOS PAPAGEORGIOU, DIMITRIS TOUSOULIS, CHARALAMBOS ANTONIADES, ANASTASIOS GIOLIS, ALEXANDROS BRIASOULIS, CHRISTODOULOS STEFANADIS

First Cardiology Department, Athens University Medical School, Hippokraton Hospital, Athens, Greece

Key words:
Myocardial infarction, mortality, pleiotropic effects, statins.

Manuscript received:
September 15, 2008;
Accepted:
December 22, 2009.

Address:
Dimitris Tousoulis

1st Cardiology
Department,
Hippokraton Hospital
Athens University
Medical School
Athens, Greece
e-mail:
drtousoulis@hotmail.com

Acute coronary syndromes (ACS) are often associated with the rupture of vulnerable atherosclerotic plaque, coronary thrombus formation, and abrupt limitation of blood flow, leading to adverse outcomes. The interaction between the vulnerable atherosclerotic plaque and thrombus formation, a process referred to as atherothrombosis, is the cornerstone of ACS. Vulnerable plaque, which is the substrate of this condition, is the target of many therapeutic approaches, including statins.¹

Statin, or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, (HMG-coA inhibitors) form a class of hypolipidemic drugs used to lower cholesterol levels in people with or at risk of cardiovascular disease. They lower cholesterol by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis (Figure 1). Nowadays, statins seem to play a crucial role in modulating cardiovascular disorders such as ACS, not only by affecting lipids, but also by exerting a number of pleiotropic effects beyond lipid lowering, such as plaque stabilization.² Invasive modalities for atherosclerotic plaque examination will further evaluate the beneficial effects of statins on atherosclerotic plaque development, progression and stabilization.³⁻⁴

In the clinical setting statins appear

to have an impact on mortality, which remains the major endpoint following ACS. In this article we review the role of statins in ACS, focusing on mortality as well as other important aspects of their use.

Effects of statins beyond lipid lowering

Statin block the conversion of 3-hydroxy-3-methylglutaryl coenzyme A to mevalonate, leading to decreased cholesterol levels. However the beneficial effects of statins are not only related to lipid-lowering – even if this seems to be beneficial in patients with ACS – but also to direct effects on endothelial function, oxidative stress, inflammation, thrombosis as well as plaque stabilization (Table 1).⁵⁻⁸

Endothelial function

The molecular basis of the association between statins and endothelial function relates to the interaction with nitric oxide (NO) production pathways at the cellular level. Indeed, statins improve endothelial function by upregulating the expression and activity of endothelial nitric oxide synthase (eNOS) as well as through their antioxidant effects. Endothelial nitric oxide synthase expression is upregulated via two different pathways. The first one is by activating protein kinase Akt, which is an important regulator of a number of cellu-

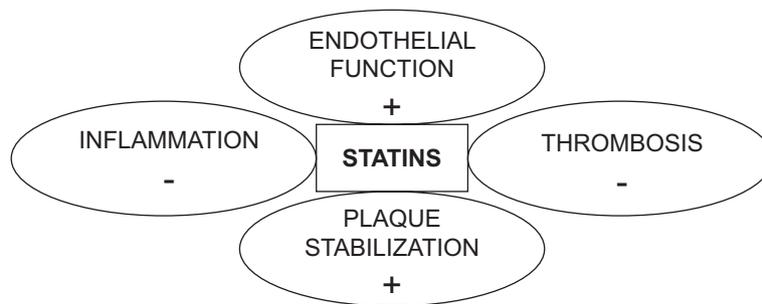
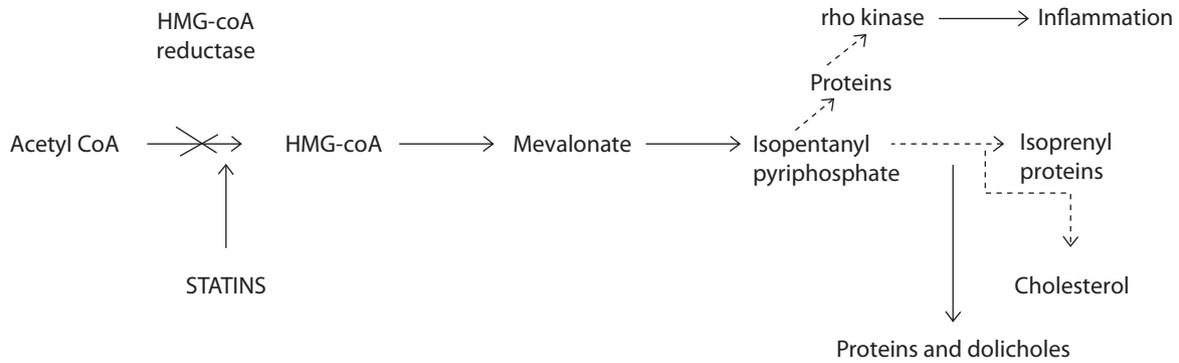


Figure 1. A brief presentation of the mechanism through which statins act. Pleiotropic effects of statins are also presented, focusing on the improvement of endothelial function, plaque stabilization, inhibition of thrombotic process, as well as inhibition of inflammatory process.

Table 1. Pleiotropic effects of statins.

• Endothelial cells	a) + effect on NO b) + effect on endothelial progenitor cells c) - effect on cyclooxygenase-2 d) - effect on endothelin-1 e) - effect on adhesion molecules
• Inflammation	a) - effect on CRP b) - effect on CD40 c) - effect on adhesion molecules d) - effect on pro-inflammatory cytokines
• Thrombosis	a) - effect on fibrinogen b) - effect on platelet aggregation c) - effect on thromboxane-A2 d) - effect on PAI-1 e) + effect on tPA
+ - positive, increase; - - negative, decrease; NO - nitric oxide; CRP - C-reactive protein; PAI-1 - plasminogen activator inhibitor 1; tPA - tissue plasminogen activator.	

Another mechanism through which statins may affect endothelium is through their antioxidant effects. Statins attenuate angiotensin II (Ang II) induced free radical production in vascular smooth muscle cells by inhibiting Rac1-mediated NAD(P)H oxidase activity and down-regulating angiotensin AT₁-receptor expression.¹¹

In line with the hypothesis of endothelial function improvement, the RECIFE study,¹² which included sixty patients with acute myocardial infarction (AMI) and unstable angina (UA), reported that a 40 mg/day dose of pravastatin improved endothelial function in the statin group. Simultaneously with the reduction of total cholesterol levels and low-density lipoprotein cholesterol (LDL) by 23% and 33%, respectively, flow-mediated dilatation (FMD) increased by 42%.

Inflammation

Inhibition of the formation of mevalonate, and thus isoprenoids,¹³ leads to inhibition of critical proteins in the inflammatory cascade (in particular Ras, Rho and

lar processes.⁹ The second pathway is the inhibition of geranylgeranylation of the small G-protein Rho.¹⁰

Rab), which act via nuclear factor- κ B; thus, statins exhibit a powerful anti-inflammatory effect.¹⁴ By inhibiting isoprenylation and preventing the formation of geranylgeranyl pyrophosphate, rosuvastatin has been shown to prevent Rho A translocation to the plasma membrane, increasing the cytosol-to-membrane ratio in the myocardium and achieving infarct size reduction.¹⁵ The inhibition of Rho also prevents its inhibitory action on NO and thus provides a further mechanism of NO upregulation.¹⁶

In the CARE study,¹⁷ patients with high levels of serum amyloid A and C-reactive protein (CRP) had a higher risk of cardiovascular events. Pravastatin reduced cardiovascular events by 54% in patients with persisting inflammation. Moreover, the MIRACL study,¹⁸ which investigated the effect of high dose atorvastatin, demonstrated a reduction in CRP levels by 34% and serum amyloid A by 13%, associated with significant reduction in recurrent ischemic events. In addition, Tousoulis et al¹⁹ showed that even a low dose of atorvastatin is able to reduce the levels of inflammatory markers such as interleukin 6 (IL-6), tumor necrosis factor alpha (TNF- α), soluble vascular cell adhesion molecule 1 (sVCAM-1) and monocyte chemoattractant protein 1 (MCP-1) in patients who received statin treatment compared to those in the placebo group.

Thrombosis

Sanguigni et al²⁰ showed that statins have a beneficial impact on the thrombotic process. This study enrolled 30 hypercholesterolemic patients and 20 controls. A dose of 10 mg/day for a 3-day period significantly decreased platelet factors for thrombin formation, such as CD40 ligand-mediators, thus proving the impact of atorvastatin on thrombosis. Similarly, Tousoulis et al²¹ showed that statins affect thrombosis. The study recruited 45 patients with unstable angina and normal cholesterol levels to receive atorvastatin 10 mg/day for 6 weeks. Patients who did not take the medication were characterized as controls. A low dose of atorvastatin blocked the elevation of von Willebrand factor (vWF) levels during the first week of treatment, while also inhibiting the expression of markers such as factor V, protein C and antithrombin III.

Plaque stabilization

A number of studies have demonstrated that statins

reduce matrix metalloproteinase (MMP) expression and activity when administered to hyperlipidemic animals, and that this is accompanied by changes in plaque morphology consistent with increased stability.²² Moreover, the plaque-stabilizing effects of statins in animal models can apparently be achieved even independently of cholesterol lowering,²² which implies a direct effect of statins on the mechanisms leading to plaque instability. Recent studies reported that statins prevent plaque rupture in animal models of atherosclerosis via decreased expression of MMP-9.²³

Cardioprotection

The direct cardioprotective effect elicited by statin therapy is due to the activation of the reperfusion injury salvage kinase (RISK) pathway, the term given to a group of pro-survival kinases whose activation at the onset of myocardial reperfusion confers powerful cardioprotection on the animal heart.²⁴ In addition, atorvastatin administered at the onset of myocardial reperfusion reduced myocardial infarct size by 50% in isolated perfused murine hearts; this protective effect was mediated through the activation of the PI3K-Akt-eNOS signal transduction pathway, given that the infarct-limiting effects were abrogated in the presence of a PI3K inhibitor and were lost in mice lacking eNOS.²⁵

Effects of statins on mortality and recurrent events

Previous studies have shown that statin treatment in high risk patients significantly reduces the rate of subsequent acute coronary events and thus seems to have a protective role.²⁶⁻²⁸ The majority of clinical studies investigating the effects of statin therapy in patients presenting with ACS have focused on the initiation of statin therapy 1-2 days following admission. Large randomized placebo-controlled studies have already established chronic statin use as effective medical therapy for the primary and secondary prevention of cardiovascular events. Subsequent studies have begun to investigate the effects of acute statin therapy on patients presenting with ACS, but in the majority of these studies statin therapy was initiated 24 h after ACS.

Observational studies

Data from large observational studies, which included patients treated with statins after an acute coronary event, suggest there are important benefits

in terms of the expected survival of these patients (Table 2).

The RIKS-HIA trial²⁹ studied 19,599 patients hospitalized for AMI. Among 14,071 patients not taking a statin at discharge, the unadjusted 1-year mortal-

ity was 9.3%, compared with 4.0% among the 5,528 patients who received statin therapy at discharge. When adjusted for 43 covariates, statin therapy at discharge was associated with a 25% relative risk reduction in 1-year mortality (3.7% vs. 5.0%). Interestingly,

Table 2. Observational studies with statin use in acute coronary syndromes.

Study	Population (number)	Duration	Type of study	Comments on survival
RIKS-HIA ²⁹	AMI (19,599)	12 months	Prospective	9.3% mortality in the non statin group 4.0% mortality in the statin group RR: 0.75
PURSUIT & GUSTO II B ³⁰	ACS (20,809)	1 month	Meta-analysis	↓ of risk to death: 3.72% → 1.92% in those who survived in 6 days 1.0% mortality in the non statin group 0.5% mortality in the statin group
		6 months		3.5% mortality in the non statin group 1.7% mortality in the statin group
OPUS-TIMI 16 ³¹	ACS (10,288)	1 month	Meta-analysis	↓Mortality 0.7% mortality in the statin group 2.4% mortality in the non statin group
		10 months		3.1% mortality in the statin group 5.3% mortality in the non statin group Adjusted RR: 0.31 in the statin group and 0.50 in the non statin group
InTIME-II ³²	AMI (14,124)	12 months	Meta-analysis	Unadjusted: 33% lower mortality in the statin group 3.0% mortality in the statin group 4.5 mortality in the non statin group Multivariate adjustment: 20-36% lower mortality in the statin group
PRISM ³³	ACS (1,616)	48 hours or 1 month	Retrospective	↓in the primary endpoint (adjusted hazard ratio, RR: 0.49) ↓ recurrent ischaemia at 48 h in the statin group (RR: 0.35) but not at 1 month. ↓ rate of revascularisation (RR: 0.60) in the statin group ↓hospitalization in the statin group 11.5 days in the non statin group 9.2 days in the statin group
Meta-analysis of SYMPHONY & 2nd SYMPHONY ³⁴	ACS (12,365)	3 months	Meta-analysis	No significant differences between the statin group and nonstatin group at either 90 days or 1 year. The 90-day adjusted HR for death 1.08 HR for death or MI 1.08 HR for death, MI or severe recurrent ischemia 1.15
		1 year		1-year adjusted mortality 0.99 No significant differences between the two groups for any of the secondary endpoints In the statin group lower adjusted risk of stroke alone (HR: 0.54)

↓ – reduction; ACS – acute coronary syndromes; AMI – acute myocardial infarction; HR – hazard ratio; RR – relative risk; UA – unstable angina.

this reduction in mortality following statin therapy was independent of factors such as sex, diabetes mellitus, and prior myocardial infarction. Similar results were found by a meta-analysis of the data from the PURSUIT study and the GUSTO IIB study.³⁰ In 3,653 patients with ACS who were treated with statins after discharge, there was a significant reduction in mortality risk compared to the placebo group (17,156 patients), not only after the first month (0.5% vs. 1.0%), but also six months later (1.7% vs. 3.5%). The OPUS-TIMI 16 study,³¹ which recruited patients presenting with ACS who were treated with statins, also showed that statin treatment resulted in a decrease in mortality (0.7% vs. 2.4%) one month after the event. The mortality difference also persisted at 10 months (3.1 vs. 5.3%). In addition, in the InTIME-II study,³² which enrolled 14,124 patients, the unadjusted 1-year mortality was 33% lower after statin treatment (3.0 vs. 4.5%), while after a multivariate adjustment mortality was 20-36% lower during the same period. Another observational study, PRISM,³³ retrospectively investigated the effects of statin therapy in 1,616 patients hospitalized for ACS. Most patients in the statin group received an intermediate dose. The primary endpoint was death or nonfatal myocardial infarction during the 30-day follow up. Patients receiving statin therapy had a significantly lower incidence of the primary endpoint compared to patients who did not receive statins (adjusted hazard ratio, 0.49). Statin therapy was associated with a significant reduction in recurrent ischemia at 48 hours but not at 30 days (adjusted hazard ratio, 0.79), a lower rate of revascularization procedures, and a shorter duration of hospitalization (11.5 vs. 9.2 days). In contrast, a meta-analysis of the SYMPHONY and 2nd SYMPHONY studies,³⁴ which included 12,365 patients with or without ST-segment elevation or UA, who were not taking statins prior to the index ACS, found no benefit to early statin therapy. The primary assessment looked at the association of early statin therapy with 90-day death, death or myocardial infarction, death, myocardial infarction, or severe recurrent ischemia, and with 1-year death. There were no significant differences between the statin and non-statin groups at either 90 days or 1 year. The 90-day adjusted hazard ratio was 1.08 for death, 1.08 for death or myocardial infarction, and 1.15 for death, myocardial infarction, or severe recurrent ischemia.

Prospective studies

MIRACL was the first large scale trial¹⁸ that aimed to investigate the effects of statins after ACS. The trial

enrolled 3,806 patients with ACS who were treated with atorvastatin 80 mg/day or placebo, 24-96 hours after hospitalization, with a follow up of 4 months. The results of this trial were a 42% reduction in LDL, 24% in triglycerides and 40% in CRP levels in the atorvastatin group, while an increase was observed in the placebo group. Over the period of 4 months, the proportion of patients with recurrent events was 6.2% in the atorvastatin group versus 8.4% in the non statin treated group. The L-CAD study,³⁵ a smaller study comparing intensive pravastatin treatment with a combination of niacin and cholestyramine initiated immediately after ACS, reported a 24% incidence of recurrent events in the pravastatin group and increased minimal lumen diameter after 2 years, versus a 52% incidence of recurrent events and decreased minimal lumen diameter in the niacin and cholestyramine group.

Further studies to clarify these issues became more difficult, as justifying placebo control is ethically difficult. Similarly results to the above were obtained from the PACT study.³⁶ Patients with ACS (3,048) were randomized to receive pravastatin 40 mg/day or placebo, beginning the first 24 hours after event onset. After a 30-day period the reduction in risk of recurrent events was 0.8%, while a relative risk reduction of 6.4% was observed. In the double-blind, randomized LIPID trial,³⁷ the effects of pravastatin (40 mg/day) were compared with those of a placebo for a follow-up period of 6.1 years in 9,014 patients admitted for ACS. The primary study outcome was mortality from coronary heart disease. Death from coronary heart disease occurred in 8.3% of the patients in the placebo group and 6.4% of those in the pravastatin group, while there was a relative risk reduction by 24%. Overall mortality was 14.1% in the placebo group and 11.0% in the pravastatin group. The incidence of all cardiovascular outcomes was consistently lower among patients assigned to receive pravastatin, such as myocardial infarction (risk reduction by 29%), death from coronary heart disease or nonfatal myocardial infarction (risk reduction by 24%), stroke (risk reduction by 19%), and coronary revascularization (risk reduction by 20%).

The A-Z trial³⁸ focused on the effects of high dose statin treatment. Specifically, simvastatin was administered (40 mg/day), followed by a high dose of simvastatin (80 mg/day) or placebo. High dose statin treatment failed to reduce the number of recurrent events. Moreover, myopathy was observed at a surprising rate. However, over the total of 2 years fol-

low up there was a benefit from the more intensive, earlier initiated regime with a modest non-significant reduction in all-cause mortality and cardiovascular death from 6.7 to 5.5% ($p=0.08$) and from 5.4 to 4.1% ($p=0.05$), respectively. In contrast, in the PROVE IT study,³⁹ which included 4,612 patients with ACS, the effects of an 80 mg/day dose of atorvastatin were compared to those of a 40 mg/day dose of pravastatin for 6 months. The atorvastatin group exhibited a 16% lower incidence of recurrent events. All-cause mortality was also reduced by 28% in the high dose statin group. The risk of the secondary endpoint of death due to coronary artery disease (CAD), revascularization, or myocardial infarction was reduced by 14% in patients randomized to atorvastatin. Patients in the high dose statin group had a 25% risk reduction for death, myocardial infarction, or revascularization. Thus, these results demonstrated that high dose statin treatment may be more beneficial than low dose statin treatment while still being safe for patients. Finally, the FLORIDA study,⁴⁰ in which 540 patients with AMI were randomized to receive fluvastatin 80 mg/day or placebo within 14 days following an ACS for one year, failed to corroborate the findings of the MIRACL study. In this trial, there was no significant change in ischemic events at 6 and 12 months. However, a tendency to a reduction in mortality of patients with severe ischemia was observed in the fluvastatin group (low statistical power). Overall, the mortality rate for the fluvastatin group was 2.6% in one year compared to 4.0% observed for the placebo group. The failure of this study to show significant benefit from statin therapy could be attributed to the dose of fluvastatin and to the starting point of the treatment. Data from randomized studies are given in Table 3.

A *post hoc* comparison⁴¹ of the studies suggests that the differences in outcome can be explained by slightly different cohort characteristics (in terms of baseline inflammatory status, LDL-cholesterol levels, intensity of statin therapy) and by a higher rate of pre-randomization revascularization in the PROVE-IT study. The overall conclusion of the comparison, however, remains that early initiation of statin therapy, with or without appropriate revascularization, following an admission for ACS brings a mortality benefit. Patients not amenable to any revascularization procedure also benefit from the early use of statins.⁴²

Forthcoming trials

The FACS-trial⁴³ is a multicenter, randomized, dou-

ble-blind, placebo-controlled study evaluating the effects of fluvastatin therapy initiated at the time of hospital admission. The study will enroll 1,000 participants admitted to hospital for ACS. The primary endpoint of the study will be the impact of fluvastatin therapy on levels of inflammatory markers. A combined secondary endpoint will be 30-day and one-year occurrence of death, nonfatal myocardial infarction, recurrent symptomatic ischemia, urgent revascularization, and cardiac arrest. In addition, another trial still in process, which is designed to end by 2012, is the IMPROVE IT trial.⁴⁴ This is a randomized, double-blind study of subjects with stabilized ACS. The primary objective is to evaluate the clinical benefit of an ezetimibe+simvastatin combination compared with simvastatin 40 mg/day. The clinical benefit will be defined as the reduction in the risk of the occurrence of the composite endpoint of cardiovascular death, major coronary events, and stroke.

Effects of statin treatment on lipid profile in patients presenting with ACS

Despite the non-lipid beneficial effects of statins in patients with ACS, it is very important to mention the critical role of lipid levels in these patients. Several trials have confirmed the benefit of cholesterol-lowering therapy in patients at high risk and support the adult treatment panel III (ATPIII) treatment goal of LDL < 100 mg/dL. The major recommendations for LDL modifications according to the ATPIII⁴⁵ are: a) for individuals at high risk, the recommended goal for LDL levels is < 100 mg/dL (moreover, when a high risk patient has high triglycerides or low high-density lipoprotein cholesterol (HDL) levels, combined treatment of a fibrate or nicotinic acid with an LDL-lowering drug such as statins should be considered); b) for moderately high risk persons the recommended LDL goal is < 130 mg/dL. Additionally, a more aggressive approach, such as that proposed by the PROVE IT-TIMI 22 trial,³⁹ demonstrated that LDL < 70 mg/dl was associated with a greater reduction in coronary heart disease events than LDL < 100 mg/dl after ACS. Generally, according to the ATPIII, when LDL-lowering therapy is performed in high risk or moderately high risk persons, it is advised that the intensity of therapy be sufficient to achieve at least a 30% to 40% reduction in LDL levels. Furthermore, apart from drug administration for achieving low LDL levels, people with risk factors associated with

Table 3. Prospective trials with the use of statins in acute coronary syndromes.

Study	Population (number)	Duration	Statin (mg/day)	Comments on survival
MIRACL ¹⁸	UA, non-Q AMI (3,806)	4 months	Atorvastatin (80 mg/day) vs. Placebo	16% RR reduction (statin group) in the primary endpoint 26% RR reduction (statin group) in rehospitalization for AMI ↓risk for recurrent events by 48% RR for ischemic event: 0,83
L-CAD ³⁵	ACS (126)	6 months and 24 months	Pravastatin or cholestyramine and niacin (20-40 mg/day) vs. Placebo	23% of the patients in the statin group presented a recurrent event 50% of the patients in the non statin group presented a recurrent event ↑MLD in the statin group at 6 and 24 months ↓MLD in the non statin group at 6 and 24 months
PACT ³⁶	ACS (3,408)	1 month	Pravastatin (20-40mg/day) vs. Placebo	11.6% of the patients in the statin group presented a recurrent event 12.4% of the patients in the non statin group presented a recurrent event 6.4% RR reduction No other significant differences in the two groups
LIPID ³⁷	ACS (9,014)	73.2 months	Pravastatin (40 mg/day) vs. Placebo	8.3% death in the non statin group 6.4% death in the statin group 24% RR reduction 14.1% mortality in the non statin group 11.0% mortality in the statin group (RR reduction 22%) 29% RR reduction for AMI in the statin group 19% RR reduction for stroke 20% RR reduction for coronary revascularization
A-Z (2nd phase) ³⁸	STEMI, NSTEMI (4,497)	3-6 months	Simvastatin (40 mg/day) followed by Simvastatin (80 mg/day) vs. Placebo Simvastatin (20 mg/day)	16.7% of patients in the non statin group had a recurrent event 14.4 % of patients in the statin group had a recurrent event 25% reduction in mortality (statin group) 28% reduction in CHF (statin group) No significant difference in secondary endpoints of MI and readmission for ACS,
PROVE IT ³⁹	ACS (4,162)	6 months	Atorvastatin (80mg/day) vs. Pravastatin (40mg/day)	16% RR in the hazard ratio of death, MI, stroke, UA and revascularization in the statin group 28% reduction in all-cause mortality in the aggressive statin therapy group 14% risk reduction of the secondary endpoint of death due to CAD, revascularization, or MI with atorvastatin
FLORIDA ⁴⁰	AMI (540)	12 months	Fluvastatin (80mg/day) vs. Placebo	No significant reduction in recurrent events Tendency to reduce mortality in 1 year period in the statin group (4% → 2.6%)

↑ – increase; ↓ – reduction; MLD – minimal lumen diameter UA – unstable angina; ACS – acute coronary syndromes; AMI – acute myocardial infarction; HDL – high density lipoprotein cholesterol; LDL – low density lipoprotein cholesterol; Lp(a) – lipoprotein (a); CRP – C-reactive protein; CAD – coronary artery disease, RR – relative risk; CHF – congestive heart failure; STEMI – ST-elevation myocardial infarction; NSTEMI – non ST-elevation myocardial infarction

lifestyle should also aggressively modify their lifestyle.

Besides the awareness regarding the modification of LDL levels, triglyceride levels are also a potential target for patients with ACS. Interestingly, Miller et al⁴⁶ aimed to evaluate the impact of on-treatment triglycerides on coronary heart disease risk after ACS. The association between on-treatment levels of triglycerides and LDL and the composite endpoint of death, myocardial infarction, and recurrent ACS was assessed 30 days after initial presentation. On-treatment triglyceride levels <150 mg/dl were independently associated with a lower risk of recurrent coronary heart disease events, lending support to the concept that achieving low triglycerides may be an additional consideration beyond low LDL in patients after ACS.

Time point of statin administration and patients' compliance with statin treatment

Since the publication of large scale studies, such as the 4S, the CARE and the LIPID trials, statins have been recognized as an effective treatment for the secondary prevention of cardiovascular events. In those trials, statin therapy was started after a coronary event and the benefit was observed after long-term use. Beyond the favorable effects on lipid levels, statins have been found to stabilize coronary plaques.⁴⁷ Accordingly, in patients with ACS it could be advantageous to start statin treatment early after hospital admission. Two observational studies have confirmed this hypothesis. In the Swedish myocardial infarction registry,⁴⁸ and in the combined data sets of the GUSTO IIb and PURSUIT trials, patients who received statin therapy before hospital discharge had lower mortality compared to those who were not discharged on lipid-lowering agents.⁴⁹

In contrast, in the SYMPHONY studies, statin therapy within 3 days after admission was not associated with an improved outcome.³⁴ Randomized trials that have been conducted so far of early statin therapy compared to controls in ACS patients showed mixed results. The MIRACL trial¹⁸ reported a statistically significant 16% lower rate of death and nonfatal major cardiac events at 4 months follow up in patients receiving 80 mg/day of atorvastatin compared to placebo. In the MIRACL study,¹⁸ medication was initiated within 24-96 h after admission. In the FLORIDA trial,⁴⁰ fluvastatin therapy (80 mg/day) did not affect the incidence of major adverse cardiac events when compared to placebo. The median time to the initia-

tion of study medication after the onset of symptoms was 8 days. The larger A to Z trial³⁸ showed a favorable, but statistically non-significant trend towards reduction of major cardiovascular events during 6-24 months' follow up in patients receiving intensive simvastatin treatment (40 mg/day for 1 month followed by 80 mg/day thereafter) when compared with those receiving a less intensive treatment (placebo for 4 months followed by 20 mg/day of simvastatin). Study medication in the A to Z trial was started after patients were stabilized for at least 12 h. Recently, Lenderink et al,⁴⁸ analyzing data derived from an observational database of patients who were admitted for ACS, suggested that very early statin therapy (within 24 hours after admission) is associated with reduced mortality in patients presenting with myocardial infarction. However, the risk profile of patients receiving statins was more favorable compared with patients not receiving statins on admission.

It is worth mentioning that studies have demonstrated that patients are more likely to continue taking medications after hospital discharge if they are prescribed during the initial inpatient stay. Probably, hospital-based initiation of therapy may also help alleviate patient concerns about monitoring, medication tolerability, and side effects. In one study of medication compliance, 77% of patients who began treatment with statins as inpatients were compliant with their dosage regimens, compared with only 40% of those who began treatment with a statin after hospitalization.⁵⁰ Furthermore, improved drug compliance is associated with improved cholesterol parameters and reduced mortality among cardiovascular patients.⁵¹ Although, there were insufficient data to investigate compliance in this analysis, this is an important consideration for any treatment regimen.

Safety of statin use

Statins not only block the production of mevalonate, an early metabolite in the cholesterol-production pathway, but may also reduce other products of this pathway, including geranylgeranyl pyrophosphate, dolichols and ubiquinone. Statins are extremely well tolerated by the majority of patients, but can produce an unexplained myopathy with symptoms ranging from mild myalgia to fatal rhabdomyolysis.⁵² The reported incidence of statin myalgia in clinical trials is 3-5%,⁵³ but rises to 10% in clinical, observational studies of patients on high dose statins.⁵⁴ Fatal rhabdomyolysis is estimated to occur in only 1.5 patients

per 10 million prescriptions.⁵⁵ The risk of statin myopathy generally increases with the statin dose, so that more patients are likely to be affected with the higher doses currently used to achieve lower LDL goals. The clinical presentation of statin myopathy, other causes of creatine kinase increase, and the medications thought to increase the risk of statin myopathy have been reviewed in detail elsewhere.^{56,57}

The exact mechanism of statin myopathy is unknown, but decreased sarcolemmal, or sarcolemmal reticular cholesterol,⁵⁸ reduced production of ubiquinone or coenzyme Q10,⁵⁹ decreased production of prenylated proteins, changes in fat metabolism,⁶⁰ increased uptake of cholesterol⁶¹ or phytosterols,⁶² failure to replace damaged muscle protein via the ubiquitin pathway,⁶³ disruption of calcium metabolism in the skeletal muscle,⁶⁴ and inhibition of selenoprotein synthesis,⁶⁵ have all been suggested as possible etiologies. Although the exact mechanism by which statins affect muscle is unknown, statins may uncover previously asymptomatic inherited muscle myopathies. Patients with statin-induced myopathy who underwent mutation testing were four times more likely to have mutant alleles for muscle myopathies than asymptomatic patients on statins.⁶⁶ Furthermore, individuals with genetic variants of the *SLCO1B1* gene, which encodes for the organic anion transporter and thereby affects statin hepatic uptake, have an increased incidence of rhabdomyolysis during statin therapy.⁶⁷ In clinical practice, if creatine kinase (CK) is elevated to more than 10 times the upper normal limit (ULN), strong consideration should be given to stopping therapy. Some asymptomatic patients will have moderate (i.e. between 3 and 10 times the ULN) CK elevations at baseline, during treatment, or after a drug holiday. Such patients can usually be treated with a statin without harm. However, particularly careful monitoring of symptoms and more frequent CK measurements are indicated. Importantly, myopathy (usually referring to myalgias without creatine phosphokinase elevation) is not only the main side effect of statins, which varies between 5-10% in daily practice, but also a reason for a long debate. Therefore, data from large scale studies have underestimated this side effect, mainly due to the selection of patients who participated, as many of those studies excluded patients with conditions favoring myopathy.

Elevated hepatic transaminases generally occur in 0.5% to 2.0% of cases and are dose-dependent.^{68,69} Whether transaminase elevation with statin therapy constitutes true hepatotoxicity has not been deter-

mined. Progression to liver failure specifically due to statins is exceedingly rare, if it ever occurs.⁷⁰ Reversal of transaminase elevation is frequently noted with a reduction in dose, and elevations do not often recur with either re-challenge or selection of another statin.^{71,72} Cholestasis and active liver disease are listed as contraindications to statin use; however, no specific evidence exists showing exacerbation of liver disease by statins. Furthermore, statins have not been shown to worsen the outcome in persons with chronic transaminase elevations due to hepatitis B or C, and treatment of hyperlipidemia may actually improve transaminase elevations in individuals with fatty liver.⁷³ Therefore, modest transaminase elevations (less than 3 times the ULN) are not thought to represent a contraindication to initiating, continuing, or advancing statin therapy, as long as patients are carefully monitored.

Regarding the carcinogenic effects of HMG-Co A reductase inhibitors, such evidence should not be generalized or misinterpreted. The majority of studies showed a (significant) lack of association between statin administration and cancer incidence. Thus, in a meta-analysis⁷⁴ of data from 90,056 participants in 14 randomized trials of statins, not only did statin treatment prove its beneficial effects, but also there was no evidence of statin involvement in the increase of the incidence of cancer overall ($p=0.9$) or at any particular site.

Conclusions

It is commonly accepted that HMG-Co A reductase inhibitors represent a useful tool for secondary prevention, especially in patients with ACS. Beyond their cholesterol-lowering effects, it is now well known that they exert anti-inflammatory and anti-thrombotic effects, while stabilizing atheromatous plaque. Moreover, a significant effect on survival of patients with ACS has been reported in the majority of the studies. However, many more randomized controlled trials are required to evaluate the potential role of statins in cardiovascular disease and especially in patients with acute coronary syndromes.

References

1. Dupuis J. Mechanisms of acute coronary syndromes and the potential role of statins. *Atheroscler Suppl.* 2001; 2: 9-14.
2. Van Velzen JE, Schuijff JD, De Graaf FR, et al. Imaging of atherosclerosis: invasive and noninvasive techniques. *Hellenic J Cardiol.* 2009; 50: 245-263.

3. Yilmaz A, Klingel K, Kandolf R, Sechtem U. Imaging in inflammatory heart disease: from the past to current clinical practice. *Hellenic J Cardiol.* 2009; 50: 449-460.
4. Sanidas EA, Vavuranakis M, Papaioannou TG, et al. Study of atheromatous plaque using intravascular ultrasound. *Hellenic J Cardiol.* 2008; 49: 415-421.
5. Vogiatzi G, Tousoulis D, Stefanadis C. The role of oxidative stress in atherosclerosis. *Hellenic J Cardiol.* 2009; 50: 402-409.
6. Li D, Mehta JL. 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors protect against oxidized low-density lipoprotein-induced endothelial dysfunction. *Endothelium.* 2003; 10: 17-21.
7. Wassmann S, Nickenig G. Interrelationship of free oxygen radicals and endothelial dysfunction—modulation by statins. *Endothelium.* 2003; 10: 23-33.
8. Karatzis EN. The role of inflammatory agents in endothelial function and their contribution to atherosclerosis. *Hellenic J Cardiol.* 2005; 46: 232-239.
9. Kureishi Y, Luo Z, Shiojima I, et al. The HMG-CoA reductase inhibitor simvastatin activates the protein kinase Akt and promotes angiogenesis in normocholesterolemic animals. *Nat Med.* 2000; 6: 1004-1010.
10. Laufs U, Marra D, Node K, Liao JK. 3-Hydroxy-3-methylglutaryl-CoA reductase inhibitors attenuate vascular smooth muscle proliferation by preventing rho GTPase-induced down-regulation of p27(Kip1). *J Biol Chem.* 1999; 274: 21926-21931.
11. Wassmann S, Laufs U, Bäumer AT, et al. Inhibition of geranylgeranylation reduces angiotensin II-mediated free radical production in vascular smooth muscle cells: involvement of angiotensin AT1 receptor expression and Rac1 GTPase. *Mol Pharmacol.* 2001; 59: 646-654.
12. Dupuis J, Tardif JC, Cernacek P, Throux P. Cholesterol reduction rapidly improves endothelial function after acute coronary syndromes. The RECIFE (reduction of cholesterol in ischemia and function of the endothelium) trial. *Circulation.* 1999; 99: 3227-3233.
13. Istvan ES. Structural mechanism for statin inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase. *Am Heart J.* 2002; 144: S27-S32.
14. Hernández-Presa MA, Ortego M, Tuñón J, et al. Simvastatin reduces NF-kappaB activity in peripheral mononuclear and in plaque cells of rabbit atheroma more markedly than lipid lowering diet. *Cardiovasc Res.* 2003; 57: 168-177.
15. Bulhak A, Roy J, Hedin U, Sjöquist P-O, Pernow J. Cardio-protective effect of rosuvastatin in vivo is dependent on inhibition of geranylgeranyl pyrophosphate and altered RhoA membrane translocation. *Am J Physiol Heart Circ Physiol.* 2007; 292: H3158-3163.
16. Ni W, Egashira K, Kataoka C, et al. Antiinflammatory and antiarteriosclerotic actions of HMG-CoA reductase inhibitors in a rat model of chronic inhibition of nitric oxide synthesis. *Circ Res.* 2001; 89: 415-421.
17. Ridker PM, Rifai N, Pfeffer MA, et al. Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation.* 1998; 98: 839-844.
18. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA.* 2001; 285: 1711-1718.
19. Tousoulis D, Antoniadis C, Katsi V, et al. The impact of early administration of low-dose atorvastatin treatment on inflammatory process, in patients with unstable angina and low cholesterol level. *Int J Cardiol.* 2006; 109: 48-52.
20. Sanguigni V, Pignatelli P, Lenti L, et al. Short-term treatment with atorvastatin reduces platelet CD40 ligand and thrombin generation in hypercholesterolemic patients. *Circulation.* 2005; 111: 412-419.
21. Tousoulis D, Bosinakou E, Kotsopoulou M, Antoniadis C, Katsi V, Stefanadis C. Effects of early administration of atorvastatin treatment on thrombotic process in normocholesterolemic patients with unstable angina. *Int J Cardiol.* 2006; 106: 333-337.
22. Bea F, Blessing E, Bennett B, Levitz M, Wallace EP, Rosenfeld ME. Simvastatin promotes atherosclerotic plaque stability in apoE-deficient mice independently of lipid lowering. *Arterioscler Thromb Vasc Biol.* 2002; 22: 1832-1837.
23. Nakamura K, Sasaki T, Cheng XW, Iguchi A, Sato K, Kuzuya M. Statin prevents plaque disruption in apoE-knockout mouse model through pleiotropic effect on acute inflammation. *Atherosclerosis.* 2009; 206: 355-361.
24. Hausenloy DJ, Yellon DM. Reperfusion injury salvage kinase signalling: taking a RISK for cardioprotection. *Heart Fail Rev.* 2007; 12: 217-234.
25. Bell RM, Yellon DM. Atorvastatin, administered at the onset of reperfusion, and independent of lipid lowering, protects the myocardium by up-regulating a pro-survival pathway. *J Am Coll Cardiol.* 2003; 41: 508-515.
26. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease. *Lancet.* 1994; 344: 1383-1389.
27. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med.* 1996; 335: 1001-1009.
28. Heart Protection Study Collaborative Group, MRC/BHF. Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals. *Lancet.* 2002; 360: 7-22.
29. Stenestrand U, Wallentin L; Swedish Register of Cardiac Intensive Care (RIKS-HIA). Early statin treatment following acute myocardial infarction and 1-year survival. *JAMA.* 2001; 285: 430-436.
30. Aronow HD, Topol EJ, Roe MT, et al. Effect of lipid-lowering therapy on early mortality after acute coronary syndromes: an observational study. *Lancet.* 2001; 357: 1063-1068.
31. Smith CS, Cannon CP, McCabe CH, Murphy SA, Bentley J, Braunwald E. Early initiation of lipid-lowering therapy for acute coronary syndromes improves compliance with guideline recommendations: observations from the Orbofiban in Patients with Unstable Coronary Syndromes (OPUS-TIMI 16) trial. *Am Heart J.* 2005; 149: 444-450.
32. Llevadot J, Giugliano RP, Antman EM, et al. Availability of on-site catheterization and clinical outcomes in patients receiving fibrinolysis for ST-elevation myocardial infarction. *Eur Heart J.* 2001; 22: 2104-2115.
33. Heeschen C, Hamm CW, Laufs U, Snapinn S, Böhm M, White HD. Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation.* 2002; 105: 1446-1452.
34. Newby LK, Kristinsson A, Bhapkar MV, et al. Early statin initiation and outcomes in patients with acute coronary syndromes. *JAMA.* 2002; 287: 3087-3095.

35. Arntz HR, Agrawal R, Wunderlich W, et al. Beneficial effects of pravastatin (+/-colestyramine/niacin) initiated immediately after a coronary event (the randomized Lipid-Coronary Artery Disease [L-CAD] Study). *Am J Cardiol.* 2000; 86: 1293-1298.
36. Thompson PL, Meredith I, Amerena J, Campbell TJ, Sloman JG, Harris PJ; Pravastatin in Acute Coronary Treatment (PACT) Investigators. Effect of pravastatin compared with placebo initiated within 24 hours of onset of acute myocardial infarction or unstable angina: the Pravastatin in Acute Coronary Treatment (PACT) trial. *Am Heart J.* 2004; 148: e2.
37. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med.* 1998; 339: 1349-1357.
38. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. *JAMA.* 2004; 292: 1307-1316.
39. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.* 2004; 350: 1495-1504.
40. Liem AH, van Boven AJ, Veeger NJGM, et al. Effect of fluvastatin on ischaemia following acute myocardial infarction: a randomized trial. *Eur Heart J.* 2002; 23: 1931-1937.
41. Wiviott SD, de Lemos JA, Cannon CP, et al. A tale of two trials: a comparison of the post-acute coronary syndrome lipid-lowering trials A to Z and PROVE IT-TIMI 22. *Circulation.* 2006; 113: 1406-1414.
42. Colivicchi F, Guido V, Tubaro M, et al. Effects of atorvastatin 80 mg daily early after onset of unstable angina pectoris or non-Q-wave myocardial infarction. *Am J Cardiol.* 2002; 90: 872-874.
43. Ostadal P, Alan D, Hajek P, et al. Fluvastatin in the therapy of acute coronary syndrome: Rationale and design of a multicenter, randomized, double-blind, placebo-controlled trial (The FACS Trial)[ISRCTN81331696]. *Curr Control Trials Cardiovasc Med.* 2005; 6: 4.
44. IMPROVE-IT. Examining Outcomes in Subjects with Acute Coronary Syndrome: Vytorin (Ezetimibe/Simvastatin) vs. Simvastatin (Study P04103) ClinicalTrials.gov Identifier: NCT00202878.
45. Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. *J Am Coll Cardiol.* 2004; 44: 720-732.
46. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E; PROVE IT-TIMI 22 Investigators. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. *J Am Coll Cardiol.* 2008; 51: 724-730.
47. Jukema JW, Bruschke AV, 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. The Regression Growth Evaluation Statin Study (REGRESS). *Circulation.* 1995; 91: 2528-2540.
48. Lenderink T, Boersma E, Gitt AK, et al. Patients using statin treatment within 24 h after admission for ST-elevation acute coronary syndromes had lower mortality than non-users: a report from the first Euro Heart Survey on acute coronary syndromes. *Eur Heart J.* 2006; 27: 1799-1804.
49. Muhlestein JB, Horne BD, Bair TL, et al. Usefulness of in-hospital prescription of statin agents after angiographic diagnosis of coronary artery disease in improving continued compliance and reduced mortality. *Am J Cardiol.* 2001; 87: 257-261.
50. Lappé JM, Muhlestein JB, Lappé DL, et al. Improvements in 1-year cardiovascular clinical outcomes associated with a hospital-based discharge medication program. *Ann Intern Med.* 2004; 141: 446-453.
51. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA.* 2004; 291: 1071-1080.
52. Thompson PD, Clarkson PM, Rosenson RS. An assessment of statin safety by muscle experts. *Am J Cardiol.* 2006; 97: 69C-76C.
53. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA.* 2003; 289: 1681-1690.
54. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients-the PRIMO study. *Cardiovasc Drugs Ther.* 2005; 19: 403-414.
55. Libow LS. The acts of terrorism. *N Engl J Med.* 2002; 346: 539.
56. Rosenson RS. Current overview of statin-induced myopathy. *Am J Med.* 2004; 116: 408-416.
57. Venero CV, Thompson PD. Managing statin myopathy. *Endocrinol Metab Clin North Am.* 2009; 38: 121-136.
58. Draeger A, Monastyrskaya K, Mohaupt M, et al. Statin therapy induces ultrastructural damage in skeletal muscle in patients without myalgia. *J Pathol.* 2006; 210: 94-102.
59. Marcoff L, Thompson PD. The role of coenzyme Q10 in statin-associated myopathy: a systematic review. *J Am Coll Cardiol.* 2007; 49: 2231-2237.
60. Phillips PS, Haas RH. Statin myopathy as a metabolic muscle disease. *Expert Rev Cardiovasc Ther.* 2008; 6: 971-978.
61. Yokoyama M, Seo T, Park T, et al. Effects of lipoprotein lipase and statins on cholesterol uptake into heart and skeletal muscle. *J Lipid Res.* 2007; 48: 646-655.
62. Päivä H, Thelen KM, Van Coster R, et al. High-dose statins and skeletal muscle metabolism in humans: a randomized, controlled trial. *Clin Pharmacol Ther.* 2005; 78: 60-68.
63. Urso ML, Clarkson PM, Hittel D, Hoffman EP, Thompson PD. Changes in ubiquitin proteasome pathway gene expression in skeletal muscle with exercise and statins. *Arterioscler Thromb Vasc Biol.* 2005; 25: 2560-2566.
64. Guis S, Figarella-Branger D, Mattei JP, et al. In vivo and in vitro characterization of skeletal muscle metabolism in patients with statin-induced adverse effects. *Arthritis Rheum.* 2006; 55: 551-557.
65. Moosmann B, Behl C. Selenoprotein synthesis and side-effects of statins. *Lancet.* 2004; 363: 892-894.
66. Vladutiu GD, Simmons Z, Isackson PJ, et al. Genetic risk factors associated with lipid-lowering drug-induced myopathies. *Muscle Nerve.* 2006; 34: 153-162.
67. Link E, Parish S, Armitage J, et al. SLC10B1 variants and statin-induced myopathy—a genome-wide study. *N Engl J Med.* 2008; 359: 789-799.
68. Hsu I, Spinler SA, Johnson NE. Comparative evaluation of the safety and efficacy of HMG-CoA reductase inhibitor monotherapy in the treatment of primary hypercholesterolemia. *Ann Pharmacother.* 1995; 29: 743-759.
69. Bradford RH, Shear CL, Chremos AN, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results. I. Efficacy in modifying plasma lipoproteins and adverse event

- profile in 8245 patients with moderate hypercholesterolemia. *Arch Intern Med.* 1991; 151: 43-49.
70. Pedersen TR, Tobert JA. Benefits and risks of HMG-CoA reductase inhibitors in the prevention of coronary heart disease: a reappraisal. *Drug Saf.* 1996; 14: 11-24.
 71. Cressman MD, Hoogwerf BJ, Moodie DS, Olin JW, Weinstein CE. HMG-CoA reductase inhibitors. A new approach to the management of hypercholesterolemia. *Cleve Clin J Med.* 1988; 55: 93-100.
 72. Hunninghake DB. Drug treatment of dyslipoproteinemia. *Endocrinol Metab Clin North Am.* 1990; 19: 345-360.
 73. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med.* 2002; 346: 1221-1231.
 74. Baigent C, Keech A, Kearney PM, et al; Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005; 366: 1267-1278.