Ongoing clinical trials of the pleiotropic effects of statins

Jean Davignon[1]
Lawrence A Leiter[2]

[1]Clinical Research Institute of Montreal, Montreal, QC, Canada; [2]Division of Endocrinology and Metabolism, St Michael's Hospital, Toronto, ON, Canada

Background: The multiple effects (ie, pleiotropic effects of statins) have received increasing recognition and may have clinical applicability across a broad range of cardiovascular and noncardiovascular conditions.

Objective: To determine the relevance and significance of ongoing clinical trials of the pleiotropic effects of statins, focusing on nonlipid effects.

Method: Ongoing trials were identified through personal communication, reports presented at scientific meetings (2000–2004), and queries made to AstraZeneca, Bristol-Myers Squibb Co, Merck & Co, Novartis, and Pfizer, manufacturers of the currently marketed statins. Published trials and other source material were identified through electronic searches on MEDLINE (1990–2003), abstract books, and references identified from bibliographies of pertinent articles. Eligible studies were the clinical trials of statins currently under way in which primary or secondary outcomes included the statins' nonlipid (ie, pleiotropic) effect(s). Data were extracted and trial quality was assessed by the authors.

Results: Of the 22 ongoing trials of the nonlipid effects of statins identified, 10 assessed inflammatory markers and plaque stabilization, 4 assessed oxidized low density lipoprotein/vascular oxidant stress, 3 assessed end-stage renal disease, 3 assessed fibrinogen/viscosity, 2 assessed endothelial function, 2 assessed acute coronary syndrome, 2 assessed aortic stenosis progression, and 1 each assessed hypertension, osteoporosis, ischemic burden, Alzheimer's disease, multiple sclerosis, and stroke (outcomes often overlapped).

Conclusion: Given the excellent safety and tolerability of statins as a class, full exploration of their pleiotropic effects has the potential to provide additional benefits to many patients.

Keywords: atherosclerosis, cholesterol, clinical trials, endothelium, lipoproteins, metabolism, myocardial infarction, pharmacology, vasculature

Introduction

Most biologically active molecules have "multiple actions", which are referred to as pleiotropic effects. There has been a major shift of interest in recent years towards the pleiotropic effects of statins (Davignon 2004a). Those identified in humans encompass effects on specific biochemical/physiological pathways or have impacts on specific disease entities. The former include the ability to correct endothelial dysfunction (Egashira et al 1994; Anderson et al 1995; Eichstädt et al 1995; Marchesi et al 2000) and antioxidant (Giroux et al 1993; Anderson et al 1996; Aviram, Hussein, et al 1998; Aviram, Rosenblat, et al 1998), antiinflammatory (Albert et al 2001; Jialal et al 2001; Ridker, Rifai, et al 1998), and plaque-stabilizing effects (Corti et al 2001, 2002; Crisby et al 2001). These effects may result from inhibition of isoprenoid synthesis, as illustrated in Figure 1. Some, or a combination of these properties result in beneficial modification of various clinical entities. Statins have the ability to improve survival in heart transplant recipients (Kobashigawa et al 1995; Wenke et al 1997) and decrease mortality in end-stage renal disease (Seliger et al 2002) and following

Correspondence: Jean Davignon
Clinical Research Institute of Montreal,
110 Pine Avenue West, Montreal, QC,
Canada H2W 1R7
Tel +1 514 987 5626
Fax +1 514 987 5700
Email davignj@ircm.qc.ca

percutaneous coronary interventions (Chan et al 2002, 2003). They may have a modest antihypertensive effect (Abetel et al 1998; Borghi et al 2000), promote coronary collateral circulation (Nishikawa et al 2002), improve survival in heart failure (Horwich et al 2004), and may have favorable effects on glucose metabolism and insulin sensitivity (McFarlane et al 2002). These effects extend beyond the cardiovascular realm to include clinical conditions such as Alzheimer's disease, dementia, multiple sclerosis, and osteoporosis (see below). However, the clinical relevance of many other pleiotropic effects is not clear. Some fascinating emergent properties that were first shown in experimental studies, such as the protective effect against myocardial hypertrophy (Takemoto et al 2001), are now being reported in humans (Lee et al 2002). Indeed, there is growing evidence that statins are cardioprotective (for review, see Davignon 2004).

The relative importance of each pleiotropic effect in determining the clinical benefits of statin therapy remains to be determined in clinical trials designed a priori to study these properties. Such studies are particularly needed in view of preliminary data suggesting that there may be serious consequences of not initiating statin therapy in patients with acute coronary syndromes (ACS) (Walter et al 2002). Furthermore, observational studies suggesting that statin administration may decrease the prevalence of Alzheimer's disease (Jick et al 2000; Wolozin et al 2000), the risk of fracture (Meier et al 2000; Wang et al 2000), and delay the onset of diabetes mellitus (Freeman et al 2001) have important long-term clinical implications. This review summarizes ongoing trials aimed at clarifying the role of cardiovascular and noncardiovascular pleiotropic effects of statins in humans (Table 1). Since pleiotropic effect is defined here, as it should, as "multiple effects" of a drug, there is no attempt in this review at dissociating effects attributable to low-density lipoprotein cholesterol (LDL-C) lowering from those that are not. In fact, this dissociation, in most situations, is difficult to make for the simple reason that inhibiting cholesterol synthesis at the level of mevalonate formation will also inhibit the isoprene pathway, which is responsible for small G-protein prenylation and most of the pleiotropic effect of statins. In other words, it is to be expected that in many instances inhibition of the two effects should be correlated, although some, such as the C-reactive protein (CRP) effect and the LDL-C reduction are not and contribute independently to the risk of coronary artery disease (CAD) (for reviews, see Liao 2002; Davignon 2004a).

Cardiovascular studies

Endothelial function

Impaired endothelial function has been associated with increased risk of coronary events in patients with atherosclerosis (Al Suwaidi et al 2000; Schächinger et al 2000; Heitzer et al 2001; Perticone et al 2001). Effects of statins largely unrelated to cholesterol lowering have been shown to improve endothelial function, increase myocardial perfusion, and enhance the availability of nitric oxide (Egashira et al 1994; Eichstädt et al 1995; Endres et al 1998;

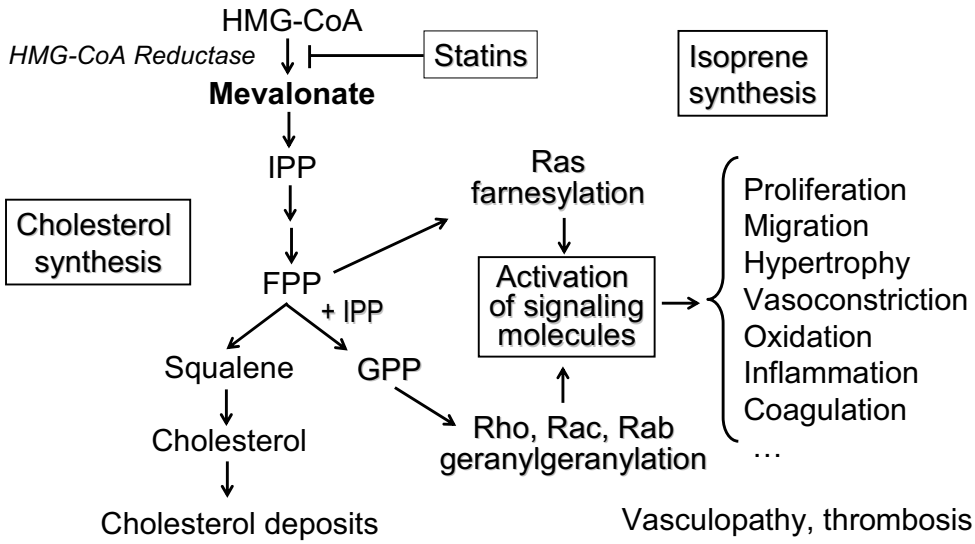

Figure 1 The mevalonate pathway. By inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, statins interfere with the synthesis not only of cholesterol but also of isoprenoid intermediates, such as geranylgeranyl pyrophosphate (PP), which contribute to oxidative stress and cellular proliferation and migration. Inhibition of these isoprenoid intermediates may contribute to the pleiotropic effects of statin therapy. **Abbreviations:** FFP, farnesyl pyrophosphate; GPP, geranylgeranyl pyrophosphate; IPP, isopentenyl pyrophosphate.

Table 1 Ongoing trials of the pleiotropic effects of statins

Trial[a]	Effect(s) under investigation	Statin(s)
ADCLT	Alzheimer's disease	Atorvastatin
ASTRONOMER	Aortic stenosis progression	Rosuvastatin, placebo
A-to-Z	Inflammatory markers	Simvastatin, short placebo arm before low dose statin
AURORA	Oxidized LDL, CRP	Rosuvastatin
AVALON	Arterial compliance	Atorvastatin
BART	Endothelial function	Atorvastatin, pravastatin
BONES	Bone mineral density	Atorvastatin
CAP	Inflammatory markers plus prothrombotic proapoptotic microparticles, type III procollagen propeptide, $F_{2\alpha}$-isoprostane, interferon gamma/interleukin-10 ratio	Atorvastatin
CORONA	Congestive heart failure	Rosuvastatin
GISSI HF	Congestive heart failure	Rosuvastatin
JUPITER	High CRP levels	Rosuvastatin
LEADe	Alzheimer's disease	Atorvastatin
LUNAR	Inflammatory and thrombotic markers	Rosuvastatin
MIRACL Substudy	Oxidized LDL, endothelial function, and inflammatory markers	Atorvastatin
Simvastatin MS Study	Multiple sclerosis	Simvastatin
ORION	Plaque stabilization and inflammatory markers	Rosuvastatin
PROVE IT	Role of inflammatory markers in ACS; fibrinogen	Pravastatin, atorvastatin
PROXI	Vascular oxidant stress; CRP, other inflammatory cytokines	Pravastatin, atorvastatin
SAGE	Plaque stabilization	Atorvastatin, pravastatin
SEAS	Aortic stenosis progression	Simvastatin, ezetimibe
SHARP	Chronic renal disease	Ezetimibe + simvastatin Ezetimibe + placebo
SPARCL	Stroke	Atorvastatin, placebo
STIM	Inflammatory markers plus fibrinogen, oxidized LDL, platelet reactivity, viscosity	Pravastatin, simvastatin
4D	Diabetes on hemodialysis	Atorvastatin, placebo

[a] See text for trial abbreviations. LDL, low-density lipoprotein; CRP, C-reactive protein; ACS, acute coronary syndromes.

Laufs et al 1998). In patients with hypercholesterolemia and coronary heart disease, the endothelium-dependent vasodilatory response may be improved by a statin and also by an angiotensin-converting enzyme inhibitor; the combination of these drugs is more effective than either agent alone (Esper et al 2000).

BART

The Brachial Artery Vasoreactivity Trial (BART) is a substudy of the Reversal of Atherosclerosis with Lipitor (REVERSAL) trial. The BART substudy will evaluate the comparative effects of the two statins on endothelial function, assessed by high-frequency ultrasound measurements of changes in arterial diameter, in a subset of 200 patients.

MIRACL substudy

A substudy of the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (Schwartz et al 2001) will assess the effect of intensive therapy with atorvastatin 80 mg/d on oxidized LDL and endothelial function in ACS patients. Additional MIRACL substudies will evaluate the effect of statin therapy on a number of inflammatory and endothelial markers, including serum amyloid A, interleukin-6, P selectin, E selectin, soluble vascular cell adhesion molecule, CD 40, and intercellular adhesion molecule-1. The first of these substudies, which demonstrates that the decline in inflammatory markers following an acute coronary syndrome is potentiated by atorvastatin (34% in 16 weeks), has been published (Kinlay et al 2003). More recently, another substudy of MIRACL showed that this statin had only a modest effect on the plasma levels of the proinflammatory, prothrombotic cytokine soluble CD40 ligand (sCD40L), but it abrogated the increased risk of recurrent cardiovascular events associated with high levels of sCD40L (Kinlay et al 2004). Finally, results of the effect of atorvastatin in MIRACL on oxidized LDL in ACS was also published, showing that atorvastatin reduced the risk associated with elevated proinflammatory oxidized phospholipids (OxPL) on apolipoprotein B and promoted their mobilization and clearance (Tsimikas et al 2004).

Antiinflammatory effects, plaque stabilization, antioxidant, and anticoagulant activity

Inflammatory markers, particularly high-sensitivity C-reactive protein (hsCRP), have received increasing recognition as important risk markers for atherosclerosis and coronary events (Ridker, Glynn, et al 1998; Ridker, Rifai, et al 1998; Ridker et al 2000, 2002; Romano et al 2000; Blankenberg et al 2001). Indeed, hsCRP has been shown to predict risk of a first myocardial infarction and other cardiovascular events among apparently healthy middle-aged men and women (Ridker, Buring, et al 1998; Ridker, Glynn, et al 1998). Statins appear to have antiinflammatory effects that decrease the risk of cardiovascular events (Ridker, Rifai, et al 1998; Ridker et al 1999; Jialal et al 2001; Van Wissen et al 2002). Initial results from the Pravastatin Inflammation CRP Evaluation (PRINCE) indicate that pravastatin treatment significantly lowered median CRP levels by 14% ($p < 0.001$) (Albert et al 2001). In the Diabetes Atorvastatin Lipid Intervention (DALI) trial (Berkplanken et al 2001), atorvastatin 10 mg and 80 mg significantly reduced CRP levels by 15% ($p = 0.012$) and 47% ($p < 0.001$), respectively, in patients with type 2 diabetes mellitus but without manifest cardiovascular disease (Van de Ree et al 2003). In a prospective substudy of the effects of statins on CRP in the Effects of Atorvastatin vs Simvastatin on Atherosclerosis Progression (ASAP) trial, greater reductions in hsCRP with atorvastatin (34%) vs simvastatin (9%) ($p < 0.02$, between groups) after 2 years were associated with significantly greater decreases in carotid intima-media thickness, respectively –40.1% on atorvastastin 80 mg/d and –19.7% on simvastatin 40 mg/d (Van Wissen et al 2002). This is some of the first evidence that the change in this inflammatory marker relates to a change in atherosclerosis progression ($r = 0.13$, $p = 0.03$).

The Reversal of Atherosclerosis with Lipitor (REVERSAL) trial has demonstrated the effects of aggressive (atorvastatin 80 mg/d) vs moderate (pravastatin 40 mg/d) lipid-lowering therapy on coronary atherosclerosis regression or progression using intravascular ultrasound technology (Nissen 2000). Intensive therapy was associated with no progression in atheroma volume whereas progresssion persisted with moderate therapy (Nissen et al 2004). A multivariate analysis is being carried out to determine if the difference between the two regimens can be accounted for by the significant difference ($p < 0.0001$, Wilcoxon signed rank test) in hsCRP reduction (and changes in other inflammatory markers) between the pravastatin (5.2%) and atorvastatin (34.6%) groups. Furthermore, it was recently reported that the best clinical outcomes were obtained among statin-treated patients who achieved both an LDL cholesterol < 70 mg/dL as well as a CRP levels < 2.0 mg/dL (Ridker et al 2004). There is recent evidence that the effect of aspirin is additive to that of pravastatin on cardiovascular risk in a meta-analysis of the CARE and the LIPID trials, implying that different antiinflammatory pathways may be involved (Hennekens et al 2004).

In addition to antiinflammatory effects, statins may reduce the risk of coronary events by contributing to plaque stabilization through effects on matrix metalloproteinases, macrophages, T cells, and vascular remodeling (Paoletti et al 1997; Bellosta et al 1998; Corti et al 2001; Crisby et al 2001). There is now evidence from carotid artery specimens obtained from patients pretreated or not with pravastatin (Crisby et al 2001), simvastatin (Cipollone et al 2003), or any statin (Molloy et al 2004) that these agents inhibit markers of plaque destabilization in human carotids. Statins attenuate activation of fibrinogen, factor V, factor XIII, and prothrombin (Undas et al 2001), in addition to inhibiting platelet aggregation (Aviram, Hussein, et al 1998). Findings from the Atorvastatin and Thrombogenicity of the Carotid Atherosclerotic Plaque (ATROCAP) study (Cortellaro et al 2002) assessed the thrombogenicity of atherosclerotic carotid plaques from specimen obtained from 59 patients scheduled for two-step bilateral endarterectomy and randomly assigned placebo or atorvastatin before surgery. Atorvastatin treatment 20 mg/d for 133 ± 63 days resulted in significant reduction of macrophage content, tissue factor antigen, tissue factor pathway inhibitor antigens, and tissue factor activity demonstrating the reduction of the inflammatory and thrombogenic phenotype of carotid plaques by statin treatment.

Oxidative processes may be involved in the development of plaque instability. Indeed, oxidized LDL was associated with markers of plaque instability (increased number of macrophages) in human carotid endarterectomy specimens (Nishi et al 2002). Similarly, the severity of ACS has been shown to correlate with plasma oxidized LDL (Ehara et al 2001). Statins have well known antioxidant properties (Anderson et al 1996; Aviram, Hussein, et al 1998; Aviram, Rosenblat, et al 1998), which are being evaluated in ongoing trials (for reviews, see Davignon et al 2004; Mason et al 2004). Only recently was evidence obtained in humans that statins can lower markers of oxidation. Simvastatin, for instance, lowers urinary 8-Iso-$PGF_{2\alpha}$ in hypercholesterolemic

individuals, an effect that is not enhanced by vitamin E supplementation (De Caterina et al 2002). They also reduce plasma nitrotyrosine (Shishebor, Aviles, et al 2003), chlorotyrosine, and dityrosine (Shishebor, Brennan, et al 2003), which are other oxidative risk markers of atherosclerosis.

There are a number of ongoing clinical trials using different statins, which will provide us important information as to whether the antiinflammatory and other effects discussed above will translate into cardiovascular event reduction.

AURORA

A study to evaluate the Use of Rosuvastatin in subjects On Regular hemodialysis: an Assessment of survival and cardiovascular events (AURORA) is a prospective, randomized, double-blind, placebo-controlled study investigating whether statin therapy can reduce all-cause mortality and incidence of major cardiovascular events in patients with end-stage renal disease who are on chronic hemodialysis, irrespective of their baseline lipid status. AURORA will randomize approximately 2700 men and women aged 50–80 years who have been undergoing hemodialysis for ≥3 months to rosuvastatin 10 mg/d or placebo. The primary end points are time from randomization to death from any cause and time to major cardiovascular event (earliest occurrence of nonfatal stroke, nonfatal myocardial infarction, or cardiovascular death). The study will also evaluate the effects of rosuvastatin on oxidized LDL and CRP at 3 and 12 months post-randomization. Enrollment of patients from Europe, Canada, and Australia began in January 2003; follow-up is expected to continue for 4 years. The design was presented at the World Congress of Nephrology in 2003 (Fellström et al 2003).

4D (Die Deutsche Diabetes Dialyse Studie)

The 4D study is looking at the effects of atorvastatin 20 mg daily vs placebo in 1200 hyperlipidemic patients with diabetes type 2 on hemodialysis treatment for no more than two years with a follow up of at least 2.5 years. The objective is to improve cardiovascular mortality and nonfatal myocardial infarction (MI) (Wanner et al 1999). The results are expected in 2004.

SHARP

In addition, the SHARP (Study of Heart and Renal Protection) trial (Baigent and Landry 2003), comparing simvastatin 20 mg plus ezetimibe 10 mg daily with simvastatin 20 mg plus placebo, is currently enrolling 9000 patients with chronic kidney disease (serum creatinine ≥130 μmol/L in women and ≥150 μmol/L in men) or receiving dialysis. The primary end point is time to a first major vascular event (defined as nonfatal MI or cardiac death, nonfatal or fatal stroke, or revascularization), with the secondary end points including progression of end stage renal disease in the nondialysis patients. This study will answer the question as to whether additional LDL-C lowering through a non-statin mediated mechanism will result in additional clinical benefit with results expected in 2009.

A-to-Z trial

The A (for Aggrastat)-to-Z (for Zocor) Trial is a two-phase, multicenter, randomized, controlled, double-blind trial designed to investigate the clinical efficacy and tolerability of early treatment with simvastatin 40 mg/d for 30 days followed by simvastatin 80 mg/d thereafter in tirofiban-treated ACS patients randomized to receive enoxaparin or unfractionated heparin in conjunction with aspirin (Blazing et al 2001). A substudy of this trial evaluates plasma samples taken at 4 and 8 months to determine whether early aggressive statin therapy reduces the levels of inflammatory markers and if such reductions are associated with decreased cardiovascular event rates. The Z phase of the A-to-Z trial, comparing 40–80 mg/d simvastatin with placebo (4 months) followed by 20 mg/d of simvastatin over two years on cardiovascular event rates in ACS patients, was published recently (De Lemos et al 2004). It failed to achieve the prespecified end point, seemingly because of fewer events than anticipated from power calculation. Several cases of myopathy and rhabdomyolysis were reported at the high doses. CRP levels were measured. A comparison made in an editorial by Nissen (2004) between A-to-Z, MIRACL, and PROVE-IT indicated that another contributing factor might have been the relatively weak effect of simvastatin, as compared with atorvastatin, on CRP reduction, reflecting weaker antiinflammatory properties.

CAP

The Comparative Atorvastatin Pleiotropic effects (CAP) trial is a double-blind, randomized, multicenter (France and Canada) trial comparing atorvastatin 10 and 80 mg/d over a 26-week period in 300 subjects with coronary atherosclerosis, LDL cholesterol levels of ≤150 mg/dL (≤3.87 mmol/L), and plasma hsCRP levels of ≥1.5 mg/L but <15 mg/L. The relative efficacy of these two doses will

be compared for a number of known as well as putative pleiotropic effects, including plasma hsCRP, interleukin-6, interleukin-18, soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, soluble E-selectin, prothrombotic proapoptotic microparticles, type III procollagen propeptide, $F_{2\alpha}$-isoprostane, and interferon gamma/interleukin-10 ratio, a measure of circulating lymphocyte activation.

JUPITER

Primary prevention of cardiovascular events with rosuvastatin 20 mg/d is being assessed in 15 000 patients with low levels of LDL cholesterol (< 130 mg/dL), but elevated levels of CRP (> 2.0 mg/L) in a long-term, randomized, double-blind, placebo-controlled trial entitled: The Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER; see Ridker and JUPITER Study Group 2003).

LUNAR

The LUNAR (Limiting UNdertreatment of lipids in ACS with Rosuvastatin) study (Schuster and Fox 2004) is comparing the effects over 12 weeks of rosuvastatin 20 or 40 mg daily with atorvastatin 80 mg daily on lipoprotein fractions and CRP in 1836 subjects with a baseline LDL > 70 mg/dL. A substudy will compare the effects of these statins on additional inflammatory and thrombotic markers.

ORION

The effect of moderate vs aggressive lipid lowering with rosuvastatin on carotid atheroma volume will be assessed by magnetic resonance imaging in the Outcome of Rosuvastatin treatment on carotid artery atheroma: a magnetic resonance Imaging Observation (ORION), a prospective, randomized, double-blind, parallel-group trial. Approximately 42 men and women aged ≥ 18 years, with LDL-C levels between 100 and 250 mg/dL (2.6 and 6.5 mmol/L) and moderate asymptomatic carotid artery stenosis, will be randomized to receive rosuvastatin 5 mg (n = 21) or 80 mg (n = 21) once daily for 2 years. The primary end point is change in carotid atheroma volume. Secondary end points include changes in lesion composition as determined by magnetic resonance imaging, carotid intima-media thickness by ultrasound, and concentrations of inflammatory markers and atherogenic lipoproteins and apolipoproteins.

PROVE IT

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial (Cannon et al 2002) compared pravastatin 40 with atorvastatin 80 mg/d for secondary prevention in ACS patients with total cholesterol levels ≤ 240 mg/dL (6.2 mmol/L). Four thousand one hundred and sixty two patients were randomized, and the results showed a greater protection of the more intensive therapy on deaths or major cardiovascular events. A 16% reduction in the hazard ratio for the primary end point favored more aggressive LDL-C lowering with atorvastatin over moderate LDL-C lowering with pravastatin ($p = 0.005$). This supplemental benefit emerged after only 30 days. Substudies of PROVE IT will examine the role of inflammatory markers in precipitating events in ACS patients and the effect of pravastatin treatment on these markers and on fibrinogen levels.

PROXI

The primary objective of the PRavastatin and atorvastatin effects on OXidative stress and Inflammation (PROXI) trial is to compare the effects of pravastatin 40 mg and atorvastatin 10 and 80 mg with placebo on vascular oxidant stress and inflammatory cytokines, including CRP. Urinary isoprostane $F_{2\alpha}$-VI will be measured at baseline and at 4 months. Patients aged 18–80 years with no history of cardiovascular disease and an LDL-C level between 130 mg/dlL (3.36 mmol/L) and 220 mg/dL (5.68 mmol/L) will be enrolled; the enrollment goal is 30 patients per treatment arm. Additional analysis will determine if the effects observed with pravastatin are independent of changes in LDL-C.

STIM

The Statin Therapy & Immunological Mediators (STIM) trial has 4 treatment arms with 18 patients each: pravastatin 40 mg, simvastatin 20 and 80 mg, and placebo. This trial will evaluate the effect of statin therapy on fibrinogen, platelet reactivity, and plasma viscosity as well as on oxidized LDL. In addition, STIM will evaluate inflammatory cytokines, including CRP, interleukins, monocyte chemoattractant protein-1, tumor necrosis factor-α, and the tumor necrosis factor-α receptor.

Hypertension

Recent findings (Abetel et al 1998; Borghi et al 2000) suggest that statins may have antihypertensive effects that

are independent of lipid lowering. The cholesterol-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (Sever et al 2003) was designed to test the hypothesis that combination therapy with a statin (atorvastatin 10 mg) and antihypertensive agents (amlodipine ± perindopril or atenolol ± bendroflumethiazide) provides an incremental benefit to antihypertensive therapy plus placebo in further decreasing the risk of cardiovascular events. The cholesterol-lowering arm was terminated after a median follow-up of 3.3 years because of the significant benefit observed with atorvastatin in reducing the risk of nonfatal MI and fatal coronary heart disease (36%, $p = 0.0005$) (Sever et al 2003). Possible synergistic effects between statins and antihypertensive agents on blood pressure will be assessed when the blood pressure-lowering arm of the trial concludes.

AVALON

AVALON is a randomized, placebo-controlled trial with 3 treatment phases – double-blind, single-blind, and open-label – and an enrollment goal of 1000 hyperlipidemic and hypertensive patients. The objectives are to determine whether combination therapy with atorvastatin and amlodipine is superior to monotherapy with either drug in decreasing the calculated risk of cardiovascular disease, and to assess the effect of dual therapy on arterial compliance. Data are expected in 2004.

Stroke

Evidence suggests that statins may act through a nonlipid-lowering mechanism to reduce the risk of a cerebrovascular accident (Bucher et al 1998; Collins et al 2002). In the recent Heart Protection Study, patients both with and without a prior history of stroke ($n = 20\,536$) who were treated with simvastatin 40 mg/d for 5 years experienced 25% fewer strokes vs placebo ($p < 0.0001$); the reduction was primarily due to a 30% decrease in risk of ischemic stroke (Collins et al 2002). Recent results from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial (Shepherd et al 2002), however, showed no significant effect of pravastatin treatment on stroke prevention in elderly patients, although there was a trend toward reduction in the incidence of transient ischemic attacks (hazard ratio 0.75, $p = 0.051$).

SPARCL

The Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) trial evaluates the benefits of atorvastatin 80 mg in reducing overall stroke in patients free of coronary heart disease but who have experienced a prior minor stroke or transient ischemic attack (Amarenco et al 2003). This prospective, double-blind, randomized, placebo-controlled trial will enroll approximately 4200 patients with LDL-C levels between 100 and 190 mg/dL (2.59 and 4.91 mmol/L). Carotid endarterectomy specimens will be studied in a subset of patients to examine the effect of therapy on plaque composition. Follow-up will be completed when 540 strokes have been recorded (approximately 5 years). Study results are expected in 2005.

Aortic stenosis

Hyperlipidemia is associated with aortic stenosis (Rossebo and Pedersen 2004). There is also evidence that statin therapy may be associated with a reduced risk for progression of aortic stenosis (AS) (Novaro et al 2001; Bellamy et al 2002; Baghdasarian et al 2004). This has been tentatively ascribed to the antiinflammatory properties of statins (Pate et al 2003). This is currently being assessed in two double-blind, randomized controlled studies.

In the ASTRONOMER (Aortic STenosis pROgressioN: Observation Measuring Effect of Rosuvastatin) study, 442 Canadian patients with mild to moderate aortic stenosis are being randomly allocated to 40 mg of rosuvastatin daily vs placebo and followed for a minimum of 3 years. Primary outcomes include increase in AV gradient and decrease in AV area with secondary outcomes including cardiac death and AV replacement. Expected completion is in 2008.

In contrast, the SEAS (Simvastatin and Ezetimibe in Aortic Stenosis) study, (Rossebo and Pedersen 2004) is an event driven 4-year study in which treatment with the combination of simvastatin 40 mg plus ezetimibe 10 mg daily is being compared with placebo in 1870 subjects with moderate, asymptomatic, aortic stenosis. The primary end point is a composite of major cardiovascular events including cardiovascular death, aortic valve replacement surgery, and congestive heart failure as a result of progression of AS, nonfatal MI, coronary artery bypass grafting, percutaneous coronary intervention, hospitalized unstable angina, and nonhemorrhagic stroke. Expected completion is 2008.

Heart failure

CORONA (COntrolled ROsuvastatin multiNAtional trial in heart failure) is comparing the effects of adding rosuvastatin 10 mg or placebo to standard therapy on cardiovascular outcomes in about 4950 elderly patients with

chronic symptomatic systolic heart failure. It is speculated that the effects of statins on neoangiogenesis and inhibition of proinflammatory cytokines, in addition to the known beneficial effects on plaque stabilization and endothelial function, may result in clinical benefit (Schuster and Fox 2004).

In addition, the GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto myocardio Heart Failure) is investigating the effects of rosuvastatin 10 mg or n-3 PUFA (fish oil) on cardiovascular events in 7000 patients with symptomatic heart failure of any etiology already receiving standard treatment (Baldesseroni et al 2003).

Noncardiovascular studies

Dementia

Statin treatment has been reported to reduce the risk of dementia (Jick et al 2000; Wolozin et al 2000), possibly by causing a reduction in amyloid-β peptides in the cerebrospinal fluid and brain (Wolozin et al 2000; Fassbender et al 2001), and by promoting the activity of the neuroprotective alpha-secretase ADAM 10 (A Disintegrin And Metalloprotease) (Kojro et al 2001). Recent results from PROSPER, however, showed no significant effects of pravastatin therapy on slowing cognitive decline (Shepherd et al 2002). Cognitive function was assessed by a telephone questionnaire in the Heart Protection Study, but no effect of simvastatin was observed (Collins et al 2002).

ADCLT

Recently, the results of the Alzheimer's Disease (AD) Cholesterol-Lowering Treatment (ADCLT) trial (Sparks et al 2003) involving 63 patients with AD randomized to 80 mg atorvastatin or placebo (1:1) daily for 12 months were presented at the 8th International Montreal/Springfield Symposium on Advances in Alzheimer's Disease Therapy 2004. Although the study was relatively small (46 subjects completed the trial), the atorvastatin therapy was associated with a significant delay in cognitive deterioration assessed by the Alzheimer's Disease Assessment Scale-Cognition (ADAS-cog) scores. These promising results certainly support the importance of more definitive studies to be carried out in this area.

CLASP

The randomized, double-blind, placebo-controlled, parallel-group Cholesterol Lowering Agent to Slow Progression (CLASP) of Alzheimer's disease study will assess the efficacy and safety of simvastatin in Alzheimer's disease, as measured by the ADAS-Cog and the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) scale. A total of 400 men and women aged ≥ 50 years with mild-to-moderate Alzheimer's disease will be randomized to 20 mg/d simvastatin or placebo for 6 weeks, followed by 40 mg/d simvastatin or placebo for the rest of the 18-month study period. Mental status, functional ability, behavioral disturbances, quality of life, and economic indicators will also be evaluated. Study completion is expected in 2005.

LEADe

The Lipitor's Effect in Alzheimer's Dementia (LEADe) trial is an 80-week, randomized, multicenter, parallel-group, double-blind study of the efficacy and safety of atorvastatin plus an acetylcholinesterase inhibitor (donepezil) for the treatment of mild-to-moderate Alzheimer's disease. The trial will enrol approximately 600 men and women at 60 sites worldwide. Subjects will be randomized to 18 months of treatment with either atorvastatin 80 mg plus donepezil 10 mg or to matching placebo plus donepezil 10 mg. The primary objective of the study is to demonstrate the superiority of the effects of combined treatment with atorvastatin plus an acetylcholinesterase inhibitor compared with acetylcholinesterase inhibitor alone on cognition, as assessed by the ADAS-Cog, and on global functioning, as assessed by the ADCS-CGIC scale. Study completion is expected in 2006.

Multiple sclerosis

Cerebrosterol (24S-hydroxycholesterol) is increased in the plasma of subjects with multiple sclerosis (Leoni et al 2002). Simvastatin 80 mg/d was recently found to decrease plasma levels of this sterol in hypercholesterolemic subjects (Locatelli et al 2002). Atorvastatin was shown to prevent or reverse chronic relapsing paralysis in an animal model of autoimmune encephalomyelitis mimicking multiple sclerosis (Youssef et al 2002), and lovastatin had a similar effect in rats (Stanislaus et al 2002), effects that were attributed to the immunomodulatory properties of statins and to their induction of a bias toward Th2 cell antiinflammatory cytokine production (Stanislaus et al 2002; Youssef et al 2002) These findings prompted the undertaking of an exploratory clinical trial.

SIMVASTATIN in multiple sclerosis

This open-label, single-arm study will assess the safety and efficacy of 6 months of simvastatin 80 mg/d in

approximately 45 relapsing-remitting multiple sclerosis patients aged 18–55 years. Treatment will be assessed by magnetic resonance imaging. Eligible patients will have at least one gadolinium-enhanced lesion after a 3-month pretreatment period. Primary outcome is the difference between the mean number of gadolinium-enhanced lesions from the 3 monthly pretreatment cranial scans and the 3 scans performed at months 4, 5, and 6 of treatment. Secondary outcomes include safety, volumes of gadolinium lesions and number of new gadolinium lesions, the change from baseline in neurologic assessments, and cytokine activity. Preliminary analysis of pre- and post-treatment magnetic resonance imaging data showed a decrease in mean number of gadolinium lesions (–44%, $p < 0.0001$) and in mean volume of gadolinium lesions (41%, $p = 0.0018$) (Vollmer et al 2004). The positive results of this exploratory trial warrant further investigation in a larger cohort of patients.

Osteoporosis

Statin therapy may protect against bone fractures and promote increased bone mineral density (Mundy et al 1999; Chung et al 2000; Edwards et al 2000; Meier et al 2000; Wang et al 2000; Pasco et al 2002). Two large case-control studies (Meier et al 2000; Wang et al 2000) demonstrated that use of statins is significantly associated with a decreased risk of fracture. Other reports, however, did not confirm these results (Wada et al 2000; Reid et al 2001). The first prospective randomized study comparing the effect of simvastatin (40 mg/d) to that of a lipid-lowering diet on bone mineral density (BMD) has been published recently (Lupattelli et al 2004). It showed a time-dependent increase in BMD in postmenopausal women in femoral bone and spine over two months, whereas there was a slight decrease on the diet.

BONES

The benefit of atorvastatin 10–80 mg/d on BMD in postmenopausal women at risk for osteoporosis will be evaluated in BONES (not an acronym), a placebo-controlled, randomized, dose-ranging trial. This 12-month trial will enroll approximately 575 postmenopausal women 40–75 years of age with LDL-C levels between 130 mg/dL and 190 mg/dL (3.36 and 4.91 mmol/L). The primary end point will be the change from baseline to week 52 in bone mineral density. Changes in biochemical markers of bone metabolism will also be assessed at 6 and 12 months. The expected study completion date is 2005.

Rheumatoid arthritis and related diseases

Although there are no trials aimed at studying the pleiotropic effects of statins in this disease, recent small successful trials have indirectly tested the immunomodulatory and anti-inflammatory effects of statins in rheumatoid arthritis and related diseases. Atorvastatin (McCarey et al 2004) and simvastatin (Abud-Mendoza et al 2003) reduced clinical manifestations and CRP levels in rheumatoid arthritis. The latter report included cases of systemic lupus erythematosus who responded well to therapy. A patient with a refractory case of systemic juvenile idiopathic arthritis (Still's disease), who was prednisone-dependent, disabled, with a protracted course, entered into remission with normalization of CRP, loss of prednisone dependency, and loss of confinement to a wheelchair with atorvastatin treatment (Ten Cate et al 2004). No doubt these conditions will be studied further and future studies might include a panel of markers of immunity and inflammation.

Conclusion

Available evidence indicates that many of the pleiotropic effects of statins have application to a wide variety of clinical conditions. Promising findings from preliminary investigations have led to initiation of many ongoing clinical trials to evaluate the potential role of statins in a number of cardiovascular and noncardiovascular conditions. Results from the ongoing clinical trials reviewed in this article are anticipated over the next several years, and should help clinicians and their patients make fully informed treatment decisions.

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