Early Use of Statins in Acute Coronary Syndromes

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This review examines the use of statin medications early in the clinical course of acute coronary syndrome (ACS). Available data demonstrate that there are clear clinical benefits to this practice. Numerous previous studies have documented the primary and secondary benefits of statins in the prevention of coronary events. Recent trials show that when statins are used during hospital admissions for ACS, patients experience decreased recurrent myocardial infarction, lower death rates, and fewer repeat hospitalizations for ischemia or revascularization. Several studies suggest that the positive effects of statins on plaque stabilization, inflammation, thrombosis, and endothelial function may be independent of lipid levels. There is also an emerging view that beneficial lipid-lowering with statins in high-risk patients has no lower limit. This information suggests that all patients admitted for ACS should be treated with statins, regardless of cholesterol levels.

Introduction

For patients with non–ST-segment elevation myocardial infarction (MI) or unstable angina (UA), the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend beginning lipid-lowering therapy after discharge from the hospital, and only if low-density lipoprotein (LDL) cholesterol levels are greater than 130 mg/dL [1•]. The more recent recommendations by the third Adult Treatment Panel (ATP) of the National Cholesterol Education Program (NCEP) suggest that therapy be started for LDL cholesterol levels at or above 100 mg/dL in patients with coronary disease, and suggest that the values obtained during admission for acute coronary syndrome (ACS) should guide treatment decisions at or before discharge [2•].

The efficacy of statin medications in preventing adverse outcomes has been repeatedly proven in trials of primary and secondary prevention. Recently, studies have begun to examine whether initiating statin therapy early in the course of an ACS admission improves clinical endpoints. On the basis of this new data, many in the field of cardiology are now calling for a more aggressive approach to lipid lowering in ACS [3,4].

Pathophysiology of Atherosclerosis and Acute Coronary Syndromes: the Role of Statins

In the past it was thought that atherosclerosis was merely a progressive lipid storage disease. Within recent years, a more complicated model has taken shape [5,6]. The endothelium and smooth muscle cells lining the arteries have been identified as crucially important, both in homeostasis and in atheromatous pathogenesis. Inflammation is now believed to be involved in all aspects of atherosclerosis, from the formation of the first fatty streaks to the initiation and propagation of ACS.

The plaque characteristics that are associated with a high risk of rupture leading to ACS are being defined, and from these the concept of the vulnerable plaque has emerged. The cascade of thrombosis and platelet aggregation that may accompany plaque rupture contributes to large and small vessel occlusion and embolization, leading to ischemia and necrosis [6]. All of these elements are closely interrelated, and several have been found to respond favorably to statin therapy (Table 1). These effects of statins are not completely explained by systemic lipid lowering, and have been described as pleiotropic [7•].

Endothelial dysfunction

Endothelial function becomes disordered early in the process of atherosclerosis, and remains so throughout disease progression. Many risk factors for vascular disease (*eg*, smoking, hypertension, diabetes, hypercholesterolemia, hyperhomocysteinemia, aging, a family history of coronary disease) have been linked to dysfunction of the endothelium. The endothelium becomes unable to respond in a normal fashion (*ie*, with vasodilatation) to acetylcholine, responding instead with vasoconstriction [8]. Although endothelial nitric oxide (NO) production is increased in hypercholesterolemia, the NO produced is rapidly inactivated by O_2-, leading to diminished NO levels in the endothelium [9].

Statins preserve coronary endothelial function in hypercholesterolemia [10]. In vitro, statins up-regulate transcriptional activation of the endothelial nitric oxide synthase (eNOS) gene [11]. Statins also inactivate O_2-, and stimulate NO release from endothelial cells [9]. NO-mediated vasodi-

Table 1. Effects of statin use on the pathophysiology of atherosclerosis and acute coronary syndromes

Endothelial function	Upregulate eNOS
	Stimulate NO release
	Inactivate O_2-
	Restore flow-mediated arterial vasodilatation
	Preserve structure of vasa vasorum
Inflammation	Reduce IL-6, TNF-α, CRP
	Reduce matrix metalloproteinases
	Reduce reperfusion injury
	Reduce post-MI remodeling
"Vulnerable plaque"	Reduce macrophage/monocyte burden
	Reduce inflammation (above)
	Increase fibrous cap collagen
	Inhibit endothelial apoptosis
Thrombosis/platelet aggregation	Reduce thrombus formation rate
	Reduce clotting factor activation
	Augment thrombolysis

CRP—C-reactive protein; eNOS—endothelial nitoric oxide synthase; IL—interleukin; MI—myocardial infarction; TNF—tumor necrosis factor.

latation, impaired in patients with elevated cholesterol, is restored with short-term statin therapy [12]. In the Reduction of Cholesterol in Ischemia and Function of the Endothelium (RECIFE) trial [13], patients were randomized to placebo or pravastatin during admission for ACS. In patients who received the statin, endothelium-dependent flow-mediated dilatation was increased by 42% after only 6 weeks of therapy. No correlations were detected between the improvement in dilatation and the fall in total cholesterol (r^2=0.05, P=0.25), or in LDL cholesterol (r^2=0.04, P=0.39), hinting that this effect may be independent of lipid-lowering.

In dyslipidemic animals, statins also preserve the structure of the vasa vasorum within the walls of coronary arteries and prevent neovascularization. These effects are independent of lipid lowering, and are probably related to attenuation of expression of vascular endothelial growth factor, hypoxia-inducible factor, and matrix metalloproteinases [14].

Inflammation

Inflammation appears to be a crucial element in the initiation and amplification of ACS. Plasma levels of inflammatory markers, such as soluble intercellular adhesion molecule-1, C-reactive protein (CRP), and interleukin-6 (IL-6), have been shown to reflect the risk of coronary events [15,16]. IL-6 stimulates inflammation and coagulation, is found to be elevated in UA and acute MI, and correlates with adverse outcomes. Statins reduce circulating levels of IL-6 and another inflammatory marker, tumor necrosis factor-α [17].

C-reactive protein in particular seems to independently predict cardiac risk, and may be involved in atherogenesis and plaque rupture [5]. In the Cholesterol and Recurrent Events Trial (CARE) trial [18], patients with a history of MI and an elevated CRP were shown to be at increased risk of future coronary events. This risk was reduced when treatment with pravastatin was initiated, in association with a decrease in CRP [18]. Both effects were independent of lipid levels [19]. Other studies have confirmed that statin drugs reduce levels of CRP independent of lipid lowering, and have correlated this reduction with effective primary prevention in the absence of hypercholesterolemia [20–22].

When acute MI does occur, the resultant myocardial inflammation may cause further tissue injury. Reperfusion injury may occur, and the activation of matrix metalloproteinases appears to play an important role in heart remodeling after infarction [23]. Statins may prevent myocardial ischemia-reperfusion injury in the presence of normal cholesterol levels [24]. In animal studies, statin therapy attenuates increases in metalloproteinase activity after MI, and also prevents left ventricular remodeling and failure [25].

The vulnerable plaque

The early lesions of atherosclerosis consist of inflammatory cells. Over time, a large lipid core may develop, covered by a thin fibrous cap. These lesions are thought to be vulnerable to rupture, and contain more macrophages and monocytes than more stable plaques. The immune cells produce metalloproteinases, which weaken the fibrous cap. Local angiotensin-converting enzyme may also contribute to this process. Subsequent plaque rupture then initiates a cycle of vasoconstriction and platelet aggregation [7•].

In human and animal studies, statins stabilize vulnerable plaques by reducing the macrophage burden present in atheromas, decreasing the levels of local matrix metalloproteinases, decreasing local inflammation, and increasing interstitial collagen in the fibrous cap. They also inhibit endothelial apoptosis, preventing plaque erosion. These effects appear to be independent of lipid levels [26–28].

Thrombosis and platelet aggregation

Hypercholesterolemia enhances platelet activity, increases thromboxane A_2 biosynthesis, and accelerates thrombus formation on injured arteries. With statin treatment, thrombus formation rates decrease. Additionally, statins decrease levels of plasminogen activator inhibitor-1 and tissue plasminogen activator (tPA) antigen [29,30]. Although some data indicate that statins increase levels of tPA, an in vivo study showed no such increase [31]. However, a small patient-based study did show that statins inhibit prothrombin activation, fibrinogen cleavage, factor XIII activation, and factor V formation, while accelerating factor Va inactivation. These effects are unrelated to cholesterol lowering [32].

Statin therapy also dramatically decreases the generation and concentration of thrombin, and inhibits the formation of thromboxane A_2 [33,34]. Further, statin use in tissue culture decreases tissue factor, another major thrombotic mediator in plaque rupture [35].

Table 2. Studies of primary and secondary coronary heart disease prevention with statins

	Period after event	Results: significant decreases in outcomes
Primary		31% coronary events
WOSCOPS		37% coronary events
AFCAPS/TexCAPS		
Secondary	>6 months	34% coronary events
4S		30% all-cause mortality
		42% coronary death
		37% need for revascularization
CARE	3–20 months	24% coronary events
		27% need for revascularization
LIPID	3–36 months	24% coronary death
		28% MI
		22% all-cause mortality
		22% need for coronary bypass
Both		
HPS	Not specified	26% coronary events
		18% coronary death
		12% all cause mortality
		22% need for revascularization

4S—Scandinavian Simvastatin Survival Study; AFACPS/TexCAPS—The Airforce/Texas Coronary Atherosclerosis Prevention Study; CARE—Cholesterol and Recurrent Events Trial; HPS—Heart Protection Study; LIPID—The Long-Term Intervention with Pravastatin in Ischaemic Disease Study; MI—myocardial infarction; WOSCOPS—West of Scotland Coronary Prevention Study.

Statins: Primary and Secondary Prevention

Many trials have evaluated the effectiveness of statins in preventing primary and secondary coronary events. The data obtained have demonstrated significant benefit from statin therapy in a variety of populations and clinical scenarios (Table 2).

Primary prevention

West of Scotland Coronary Prevention Study

In the West of Scotland Coronary Prevention Study (WOSCOPS), 6595 men with moderate hypercholesterolemia (mean LDL cholesterol=192 mg/dL) received 40 mg/d of pravastatin or a placebo for up to 4.9 years [36,37]. Statin use was associated with a 31% decrease in coronary events. The study authors also concluded that coronary heart disease (CHD) risk reduction occurred only when LDL cholesterol levels were reduced by at least 24%. Risk reduction was independent of baseline lipid levels. However, more profound cholesterol lowering did not correlate with greater benefits.

Air Force/Texas Coronary Atherosclerosis Prevention Study

The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) used 20 to 40 mg/d of lovastatin for up to 5.2 years to treat 6605 healthy men and women with elevated LDL cholesterol levels (mean=150 mg/d) and low high-density lipoprotein (HDL) cholesterol (men: <36 mg/dL, women: <40 mg/dL) [38]. Treatment reduced LDL cholesterol levels by 25%, and decreased major coronary events by 37%.

Secondary prevention

Scandinavian Simvastatin Survival Study

The Scandinavian Simvastatin Survival Study (4S) trial evaluated 4444 high-risk patients with either stable angina or history of an MI more than 6 months prior to enrollment [39]. Patients aged 35 to 70 years were treated with 20 to 40 mg/d of simvastatin or placebo and followed for a median period of 5.4 years. Statin treatment significantly decreased all-cause mortality by 30%, coronary deaths by 42%, major coronary events by 34%, and revascularization procedures by 37%.

Cholesterol and Recurrent Events

Investigators for the Cholesterol and Recurrent Events (CARE) trial [40] recruited a somewhat lower-risk population than 4S. Baseline cholesterol levels were more consistent with national averages (mean: total cholesterol=209, LDL Cholesterol and Recurrent Events=139). In a 5-year trial, patients with an MI in the preceding 3 to 20 months were randomized to placebo (n=2078), or pravastatin 40 mg/d (n=2081). The primary endpoint was death from a coronary event, or nonfatal MI. The study was not powered to evaluate total mortality. Major coronary events declined significantly in the statin group (24%), as did stroke (32%). The need for revascularization was also reduced with statin therapy (27%).

Long-Term Intervention with Pravastatin in Ischemic Disease

Results from the Long-Term Intervention with Pravastatin in Ischemic Disease (LIPID) trial [41] were consistent with

Table 3. Studies of statins in acute coronary syndromes

Study	Results: significant decreases in outcomes
RIKS-HIA	25% all-cause mortality
GUSTO IIb/PURSUIT	50% all-cause mortality, 30-day 51% all-cause mortality, 6-month 33% adjusted all-cause mortality, 6-month
Mayo CCU	75% in-hospital death and reinfarction
FLORIDA	Decreases not significant
L-CAD	29% combined: all-cause death, CV death, MI, need for intervention, stroke, new onset peripheral vascular disease
In TIME II	20%–36% all-cause mortality, 1-year
OPUS-TIMI 16	69% all-cause mortality, 30-day 50% all-cause mortality, 10-month
Lucore *et al.* [56]	65%–72% all-cause mortality
MIRACL	16% combined: death, MI, cardiac arrest, recurrent ischemia

CV—cardiovascular; FLORIDA—Fluvastatin on Risk Diminishing After Acute Myocardial Infarction; GUSTO—Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; In TIME—Intravenous nPA Treatment of Infarcting Myocardium Early II; L-CAD—Lipid-Coronary Artery Disease; MI—myocardial infarction; MIRACL—Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering; OPUS-TIMI—Orbofiban in Patients with Unstable Syndromes-Thrombolysis In Myocardial Infarction; PURSUIT—Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; RIKS-HIA—Register of Information and Knowledge About Swedish Heart Intensive Care Admissions.

those seen in CARE. Enrolled patients had a wide range of initial cholesterol levels and had been admitted with UA or acute MI 3 to 36 months prior. They were treated with placebo (n=4502) or pravastatin 40 mg/d (n=4512) over a mean of 6 years. Occurrence of the primary endpoint, death from a coronary event, was lowered by 24% in the statin group. Other benefits of statin treatment included decreases in all-cause mortality (22%), any MI (28%), and need for coronary bypass surgery (22%). Risk reduction was similar for those enrolled with UA (26%), and those with MI (20%) [42].

One area of controversy in the use of cholesterol-lowering medications has been whether to treat normal or low LDL cholesterol levels in the presence of other risk factors. A large meta-analysis in 1992 did not reveal a significant relationship between serum cholesterol and death from coronary disease in the lowest quartile (<170–180 mg/dL) [43]. Furthermore, the CARE trial did not show overall secondary prevention benefit in the lowest quartile of LDL cholesterol levels (<125 mg/dL) [44]. However, in a subgroup analysis of the LIPID and CARE trials, pravastatin treatment of diabetic participants with low LDL cholesterol decreased CHD events from 34% to 22% (P=0.004), producing minimal effect in nondiabetic participants with low LDL cholesterol. There were also trends observed toward risk reduction in smokers, and in those with low HDL cholesterol (<40 mg/dL) [45].

A subanalysis of the 4S trial showed a linear decrease in subsequent major coronary events with decreasing LDL cholesterol levels, down to the lowest mean levels encountered (77 mg/dL). A 1% decrease in LDL cholesterol was associated with a 1.7% decrease in coronary events [46].

The recently reported Heart Protection Study (HPS) addressed this question directly [47•]. This prospective, placebo-controlled study considered a cohort of over 20,000 patients who were considered high risk for coronary disease, and specifically examined outcomes in those for whom the benefits of statin therapy had not previously been established. This included people with diabetes, with noncoronary vascular disease, normal/low LDL cholesterol levels, those over age 70, and women. Irrespective of age, sex, or lipid levels, simvastatin therapy in this study lowered the risk of MI, stroke, and the need for revascularization by at least one third. The beneficial effects of statin therapy increased with duration of treatment, and no lower limit of LDL cholesterol was identified beyond which these benefits were lost.

Studies of statin therapy in acute coronary syndrome

Several studies have investigated early statin treatment in patients admitted with ACS, and more are ongoing (see Table 3). Statins have been found to be well tolerated, even with high-dose therapy [48•]. Also, despite the variety of trials involving statin treatment, no data have suggested that statins may negate the benefits of other cardiovascular therapies.

Register of Information and Knowledge About Swedish Heart Intensive Care Admissions

The Register of Information and Knowledge About Swedish Heart Intensive Care Admissions (RIKS-HIA) study was a nonrandomized, observational study that examined patients under age 80 admitted with a first-recorded acute MI and successfully discharged [49]. Of these, 5528 received statin treatment at or before discharge, and 14,071 did not. At 1 year, when adjusted for 43 covariates, all-cause mortality showed a 25% risk reduction with early statin therapy (P=0.001). The strongest effect was seen in patients aged 60 to 69 (50% risk reduction).

Global Use of Streptokinase or tPA for Occluded Coronary Arteries IIb/ Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin

The results of another pair of observational trials were combined to evaluate lipid-lowering in ACS [50]. Global Use of Streptokinase or tPA for Occluded Coronary Arteries (GUSTO IIb) enrolled patients with chest pain and ischemic changes in the electrocardiogram (ECG) within the previous 12 hours. These patients received unfractionated heparin or hirudin, with thrombolytic therapy at the physician's

discretion. In the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin (PURSUIT) trial the patients had chest pain in the previous 24 hours, ischemic ECG changes with 12 hours of symptoms, or an elevated creatine kinase-MB. Enrolled patients received placebo or eptifibatide.

A total of 3653 of the combined study populations (20,809) received lipid-lowering therapy. This therapy was associated with a hazard ratio of 0.44 for 30-day all-cause mortality (P=0.0001), and a hazard ratio of 0.48 for 6-month all-cause mortality (P<0.0001). After adjusting for potential confounders, the 6-month relative risk (RR) was still decreased by 33% (P=0.023).

Mayo Clinic Study

Patients admitted for the first time to the Mayo Clinic CCU for acute MI were retrospectively analyzed for the effects of statin therapy [51]. Sixty-six consecutive patients were enrolled who were either already taking a statin, or received a statin within 24 hours of admission. A control group of 198 patients were matched three to one. In-hospital mortality was nonsignificantly reduced by 83% in statin treated patients (P=0.051). In-hospital death combined with reinfarction was reduced by 75% (P<0.05) with statin therapy. There was also a trend toward fewer ischemic complications in the statin group (16.7% vs 26.3%, P=0.11).

FLORIDA

Preliminary results of the Fluvastatin on Risk Diminishing After Acute Myocardial Infarction (FLORIDA) trial have been presented [52]. Patients admitted with acute MI were randomized to receive fluvastatin 40 mg twice daily (n=265) or placebo (n=275) within 8 days of hospital admission. The study was not powered to detect a mortality benefit, but a trend toward fewer deaths was noted with fluvastatin in patients with severe ischemia (P=0.08). For the combined endpoint of reduction in residual ischemia, cardiovascular death, noncardiovascular death, recurrent MI, recurrent ischemia requiring hospitalization, or need for revascularization the statin group showed a trend toward benefit of 17% (P=NS). No differences in ischemia were detected on 48-hour ambulatory ECG at 6 weeks or 1 year. Of note, the mean changes in lipid profiles from baseline with fluvastatin were -13% total cholesterol, -21% LDL cholesterol, and +22% triglycerides.

Lipid-Coronary Artery Disease

The Lipid-Coronary Artery Disease (L-CAD) study [53] was a prospective trial of patients admitted with acute MI and/or primary percutaneous intervention (PCI) for UA. Within 6 days, patients were randomized to receive either pravastatin ± cholestyramine and/or niacin as needed to achieve LDL cholesterol less than or equal to 130 mg/dL (n=70), or other antilipidemic therapy determined by their family physicians (n=56). All patients underwent coronary angiography at inclusion. A combined clinical endpoint was used: total mortality, cardiovascular death, nonfatal MI, need for coronary intervention, stroke, and new onset of peripheral vascular disease. The patients treated with pravastatin experienced a 29% reduction in the endpoint (P=0.005). Also, minimal lumen diameter as determined by angiography remained larger with statin therapy (P=0.004 6-months, P<0.001 at 24 months).

Intravenous nPA Treatment of Infarcting Myocardium Early-II

The Intravenous nPA Treatment of Infarcting Myocardium Early II (In TIME II) study [54] of 14,124 patients compared tPA and nPA in patients admitted with acute MI. Lipid-lowering therapy started in the hospital was evaluated in this population in a multivariate analysis, and the results have been released in abstract form. In-hospital lipid-lowering was associated with a 20% to 36% lower 1-year post-discharge mortality.

Orbifiban in Patients with Unstable Coronary Syndromes-Thrombolysis in Myocardial Infarction 16

The Orbifiban in Patients with Unstable Coronary Syndromes (OPUS-TIMI 16) trial of 10,288 patients compared an oral GP IIb/IIIa inhibitor and placebo in ACS [55]. Preliminary results included an analysis of lipid-lowering therapy. In all, 38% of patients received lipid-lowering therapy in the hospital (94% statins). Adjusted risk of mortality was decreased by 69% at 30 days and 50% at 10 months in the lipid-lowering group (P<0.0001 for both).

Lucore et al. [*56*]

A group of diabetic patients (n=376) admitted with ACS and followed for more than 6 months were retrospectively divided into those who received statin therapy at discharge, those who took statins prior to admission and at discharge, and those that did not receive a statin. In comparison with the no-statin group, the statin groups had significantly fewer deaths (discharge statin: 65% reduction, pre- and postdischarge statin: 72% reduction).

Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering

The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study [48•] was a prospective, randomized trial designed to evaluate intense, early lowering of LDL cholesterol after an acute coronary event. Patients were enrolled within 24 to 96 hours of an admission for UA or non–Q-wave MI, and randomized to 80 mg/d of atorvastatin (n=1538) or placebo (n=1548). There was no lower limit imposed on LDL cholesterol for enrollment. The primary endpoint was a composite of death, nonfatal MI, cardiac arrest with resuscitation, or recurrent symptomatic ischemia requiring emergent re-hospitalization. The rate of serious side effects was similar (<1% in both groups), although statin users had an increased incidence of liver enzyme elevations (2.5% vs 0.6%). No episodes of myositis occurred. Among patients using atorvastatin the changes in mean lipid

levels were: total cholesterol -27%, LDL cholesterol -40%, HDL cholesterol +5%, triglycerides -16%. At 16 weeks there was a relative 16% decrease in the primary combined endpoint in the statin group (14.8% vs 17.4%, RR=0.84, *P*=0.048). Each of the components of the primary endpoint occurred less often in the statin group, but only recurrent ischemia was significantly decreased (6.2% vs 8.4%, *P*=0.02). Statin use was also associated with a 50% decrease in the number of strokes (*P*=0.05).

Platelet Receptor Inhibition in Ischemic Syndrome Management
Not only do statins appear to be beneficial in ACS, the withdrawal of statins appears to increase coronary event rates in patients with ACS. A review of 1616 patients from the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study [57] who had coronary artery disease and chest pain in the previous 24 hours revealed that statin therapy was associated with a 50% reduction in 30-day event rate compared with patients not treated with statins (*P*=0.004). Additionally, if the statin therapy was withdrawn after admission, cardiac risk increased threefold compared with patients who continued to receive statins (*P*=0.005). This effect was independent of cholesterol levels.

Walter et al. [58]
Another area being investigated is the role of statin therapy in patients undergoing urgent PCI for ACS. These patients were excluded from MIRACL and many other trials, but will be evaluated in A-Z [59]. Walter *et al.* [58] studied whether 704 patients undergoing stent placement for stable angina (n=335), UA (n=224), or Q-wave acute MI (n=145) would obtain short-term benefit from starting a statin at the time of the procedure. Statin therapy was initiated if the patient's LDL cholesterol level was over the 75th percentile. The primary combined endpoint was cardiac death and recurrent MI. In comparison with the lowest-risk group (stable angina patients receiving a statin), placebo-treated USA patients had an RR of 6.9 of reaching the endpoint (*P*=0.004), and Q-wave MI patients had an RR of 7.6 (*P*=0.004). In the UA group, statin therapy decreased the risk to the level of the stable statin group (RR 1.5, *P*=0.7, NS). Notably, the stable angina patients also benefited from statin therapy (*P*<0.05). In contrast, no significant effect was seen in the Q-wave MI group over the 6-month follow-up period.

Ongoing trials of statins in acute coronary syndromes

A to Z
The A to Z trial [59] is an ongoing, randomized, two-phase study, with a 24- to 30-month follow-up. The A-phase is designed to test the relative efficacy of enoxaparin versus unfractionated heparin, in combination with the GP IIb/IIIa inhibitor tirofiban and aspirin, in patients presenting with non–ST-elevation ACS. The Z-phase will test early aggressive simvastatin therapy (40 mg/d for 30 days, followed by 80 mg/d) irrespective of starting LDL cholesterol level, versus an accepted regimen of placebo for 4 months followed by simvastatin 20 mg/d. The primary composite endpoint for the Z-phase includes cardiovascular death, MI, readmission for ACS, and ischemic stroke. This study will include patients who have undergone PCI.

Pravastatin or Atorvastatin Evaluation and Infection Therapy / Australian Pravastatin Acute Coronary Treatment
The 2-year Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT) trial will examine over 4000 patients with ACS, and compare the abilities of atorvastatin and pravastatin to prevent subsequent coronary events. It will also evaluate the effect of an antibiotic (gatifloxacin) in preventing coronary events. The Australian Pravastatin Acute Coronary Treatment (PACT) trial will prospectively compare outcomes in patients admitted with ST-elevation MI/ACS, and treated with placebo or pravastatin.

Statin Utilization

Although the secondary prevention benefits accruing from statin therapy appear unequivocal, these medications are still under-prescribed. Mortality curve separation in the secondary prevention trials typically took from 6 months to 2 years to occur, whereas many ACS statin trials demonstrated benefit in 30 days. It is unclear what this may imply about the early initiation of statins. However, starting a statin in the hospital during an ACS admission may have the added benefit of improving utilization and long-term compliance. Fonarow *et al.* [60•] evaluated treatment rates and outcomes before (1992–1993, n=256) and after (1994–1995, n=302) the initiation of a hospital-based, secondary prevention optimization program (CHAMP) for patients admitted with acute MI. Several medications, including statins, were assessed. Statin usage dramatically increased after the program was initiated (pre-CHAMP: 6% at discharge, 10% at 1-year; post-CHAMP: 86% at discharge, 91% at 1-year). Some of this favorable impact may be attributable to a contemporaneous increase in the dissemination of knowledge about the benefits of statin use.

Recommendations

Given the currently available evidence, we feel that statin therapy should play a central role in the treatment of ACS. There are clinical and pathophysiologic data that support the initiation of statin therapy within 24 hours of an admission for ACS, regardless of lipid levels. However, definitive clinical trial data for those with an LDL cholesterol level less than 80 mg/dL are less clear cut. If a statin is already part of the outpatient regimen, it should be continued in the hospital and at discharge. We would also recommend that all patients admitted with ACS have a lipid panel performed within 12 hours of admission (lipid levels may fall precipitously by 24 hours after an acute admission), primarily to identify extraordinarily low or high

values. Low values might suggest the presence of other etiologic risk factors for acute coronary thrombosis (either metabolic, coagulopathic, or environmental) requiring evaluation. Particularly high lipid values might dictate more aggressive follow up of the initial response to statin therapy, in terms of dosing, dietary manipulation, and consideration of additional pharmacologic agents. The choice of statin drug and dose should be from among those that have so far demonstrated efficacy in secondary prevention and statin ACS trials.

Conclusions

Multiple trials have documented one quarter to one third primary and secondary coronary event reduction in at-risk patients treated with statins. ACS consists of a thrombotic and inflammatory cascade, brought on by the rupture of a vulnerable plaque, in the context of endothelial dysfunction. Statin medications reduce inflammation, stabilize plaques, inhibit thrombosis, and restore endothelial function, and produce many of these effects independent of lipid lowering.

Recent trial data show that treatment with statins early in the course of ACS improves outcomes. A policy of early initiation for statins is likely to increase utilization, and unlikely to be associated with significant complications.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1.• Braunwald E, Antman EM, Beasley JW, *et al.*: **ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association task force on practice guidelines.** *Circulation* 2000, **102:**1193–1209.

The recent revision of the treatment guidelines for these conditions provides a current and comprehensive summary of standard care, and the evidence base behind it.

2.• **Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III).** *JAMA* 2001, **285:**2486–2497.

These guidelines for the diagnosis and therapy for high cholesterol constitute a major advance in risk assessment, and are the first revisions in 13 years.

3. Fonarow GC, Ballantyne CM: **In-hospital initiation of lipid lowering therapy for patients with coronary heart disease: the time is now.** *Circulation* 2001, **103:**2768.

4. Acevedo M, Sprecher DL: **Statins in acute coronary syndromes: start them in the hospital.** *Cleveland Clin J Med* 2002, **69:**25–37.

5. Libby P, Ridker PM, Maseri A: **Inflammation and atherosclerosis.** *Circulation* 2002, **105:**1135–1143.

6. Yamada DM, Topol EJ: **Importance of microembolization and inflammation in atherosclerotic heart disease.** *Am Heart J* 2000, **140:**S90–102.

7.• Libby P: **Current concepts of the pathogenesis of the acute coronary syndromes.** *Circulation* 2001, **104:**365–372.

This article is a concise perspective that provides an insightful summary of this evolving topic.

8. Kinlay S, Ganz P: **Relation between endothelial dysfunction and the acute coronary syndrome: implications for therapy.** *Am J Cardiol* 2000, **86S:**10J–14J.

9. Kalinowski L, Dobrucki L, Brovkovych V, *et al.*: **Increased nitric oxide bioavailability in endothelial cells contributes to the pleiotropic effect of cerivastatin.** *Circulation* 2002, **105:**933–938.

10. Wilson SH, Simari RD, Best PJM, *et al.*: **Simvastatin preserves coronary endothelial function in hypercholesterolemia in the absence of lipid lowering.** *Arterioscler Thromb Vasc Biol* 2001, **21:**122–128.

11. Laufs U, Fata VL, Plutzky J, *et al.*: **Upregulation of endothelial nitric oxide synthase by HMG CoA reductase inhibitors.** *Circulation* 1998, **97:**1129–1135.

12. Stroes ES, Koomans HA, de Bruin TW, *et al.*: **Vascular function in the forearm of hypercholesterolemic patients off and on lipid-lowering medication.** *Lancet* 1995, **346:**467–471.

13. Dupuis J, Tardif J-C, Cernacek P, *et al.*: **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.

14. Wilson SH, Herrmann J, Lerman LO, *et al.*: **Simvastatin preserves the structure of coronary adventitial vasa vasorum in experimental hypercholesterolemia independent of lipid lowering.** *Circulation* 2002, **105:**415–418.

15. Ridker PM, Hennekens CH, Roitman-Johnson B, *et al.*: **Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men.** *Lancet* 1998, **351:**88–92.

16. Biasucci LM, Vitelli A, Liuzzo G, *et al.*: **Elevated levels of interleukin-6 in unstable angina.** *Circulation* 1996, **94:**874–877.

17. Rosenson RS, Tangney CC, Casey LC: **Inhibition of proinflammatory cytokine production by pravastatin.** *Lancet* 1999, **353:**983–984.

18. 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. The Cholesterol and Recurrent Events (CARE) Investigators.** *Circulation* 1999, **98:**839–844.

19. Ridker PM, Rifai N, Pfeffer MA, *et al.*: **Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators.** *Circulation* 1999, **100:**230–235.

20. Jialal I, Stein D, Balis D, *et al.*: **Effect of hydroxymethyl glutaryl coenzyme A reductase inhibitor therapy on high sensitive C-reactive protein levels.** *Circulation* 2001, **103:**1933–1935.

21. Albert MA, Danielson E, Rifai N, *et al.*: **Effect of statin therapy on C-reactive protein levels: the Pravastatin Inflammation/CRP Evaluation (PRINCE): a randomized trial and cohort study.** *JAMA* 2001, **286:**64–71.

22. Ridker PM, Rifai N, Clearfield M, *et al.*: **Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events.** *N Engl J Med* 2001, **344:**1959–1965.

23. Spinale FG, Coker ML, Bond BR, *et al.*: **Myocardial matrix degradation and metalloproteinase activation in the failing heart: a potential therapeutic target.** *Cardiovasc Res* 2000, **46:**225–238.

24. Lefer AM, Campbell B, Shin YK, *et al.*: **Simvastatin preserves the ischemic-reperfused myocardium in normocholesterolemic rat hearts.** *Circulation* 1999, **100:**178–184.

25. Hayashidani S, Tsutsui H, Shiomi T, *et al.*: **Fluvastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, attenuates left ventricular remodeling and failure after experimental myocardial infarction.** *Circulation* 2002, **105:**868–873.

26. Belosta S, Via D, Canavesi M, *et al.*: **HMG-CoA reductase inhibitors reduce MMP-9 secretion by macrophages.** *Arterioscleros Thromb Vasc Biol* 1998, **18:**1671–1678.

27. Fukumoto Y, Libby P, Rabkin E, *et al.*: **Statins alter smooth muscle cell accumulation and collagen content in established atheroma of watanabe heritable hyperlipidemic rabbits.** *Circulation* 2001, **103:**993–999.

28. Crisby M, Nordin-Fredriksson G, Shah PK, *et al.*: **Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization.** *Circulation* 2001, **103:**926–933.
29. Lacoste L, Lam JY, Hung J, *et al.*: **Hyperlipidemia and coronary disease. Correction of the increased thrombogenic potential with cholesterol reduction.** *Circulation* 1995, **92:**3172–3177.
30. Dangas G, Badimon JJ, Smith DA: **Pravastatin therapy in hyperlipidemia: effects on thrombus formation and the systemic hemostatic profile.** *J Am Coll Cardiol* 1999, **33:**1294–1304.
31. Newby DE, Witherow FN, Wright RA, *et al.*: **Hypercholesterolemia and lipid lowering treatment do not affect the acute endogenous fibrinolytic capacity in vivo.** *Heart* 2002, **87:**48–53.
32. Undas A, Brummel KE, Musial J, *et al.*: **Simvastatin depresses blood clotting by inhibiting activation of prothrombin, factor V, and factor VIII, and by enhancing factor Va inactivation.** *Circulation* 2001, **103:**2248–2253.
33. Szczeklik A, Musial J, Undas A, *et al.*: **Inhibition of thrombin generation by simvastatin and lack of additive effects of aspirin in patients with marked hypercholesterolemia.** *J Am Coll Cardiol* 1999, **33:**1286–1293.
34. Notarbartolo A, Davi G, Averna M, *et al.*: **Inhibition of thromboxane biosynthesis and platelet function by simvastatin in type IIa hypercholesterolemia.** *Arterioscleros Thromb Vasc Biol* 1995, **15:**247–251.
35. Colli S, Eligini S, Lalli M, *et al.*: **Vastatins inhibit tissue factor in cultured human macrophages. A novel mechanism of protection against atherothrombosis.** *Arterioscleros Thromb Vasc Biol* 1997, **17:**265–272.
36. 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:**1440–1445.
37. Sheperd J, Cobbe SM, Ford I, *et al.*: **Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group.** *New Engl J Med* 1995, **333:**1301–1307.
38. Downs JR, Clearfield M, Weis S, *et al.*: **Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels.** *JAMA* 1998, **279:**1615–1622.
39. 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:**1383–1389.
40. Sacks FM, Pfeffer MA, Moye LA, *et al.*: **The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels.** *N Engl J Med* 1996, **335:**1001–1009.
41. 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. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group.** *N Engl J Med* 1998, **339:**1349–1357.
42. Tonkin AM, Colquhoun D, Emberson J, *et al.*: **Effects of pravastatin in 3260 patients with unstable angina: results from the LIPID study.** *Lancet* 2000, **356:**1871–1875.
43. Jacobs D, Blackburn H, Higgins M, *et al.*: **Report of the Conference on Low Blood Cholesterol: mortality associations.** *Circulation* 1992, **86:**1046–1060.
44. 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:**1446–1452.
45. Sacks FM, Tonkin AM, Craven T, *et al.*: **Coronary heart disease in patients with low LDL-cholesterol: benefit of pravastatin in diabetics and enhanced role for HDL-cholesterol and triglycerides as risk factors.** *Circulation* 2002, **105:**1424–1428.
46. Pederson TR, Olsson AG, Faergeman O, *et al.*: **Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S).** *Circulation* 1998, **97:**1453–1460.
47.• Collins R, presenting for the MRC/BHF Investigators: **MRC/BHF Heart Protection Study.** *American Heart Association Scientific Sessions;* New Orleans, LA; 2001.

This represents the largest single statin trial, combining primary and secondary prevention of coronary events. Compared with placebo, simvastatin therapy was associated with significant reductions in death and coronary events. This study presents the strongest evidence so far in support of the view that statins may be beneficial for patients at risk at any level of LDL cholesterol or total cholesterol. Final results are still pending publication.

48.• Schwartz GG, Olsson AG, Ezekowitz MD, *et al.*: **Effects of atorvastatin on early recurrent events in acute coronary syndromes: the MIRACL study: a randomized controlled trial.** *JAMA* 2001, **285:**1711–1718.

The MIRACL trial is the largest completed trial to date to evaluate the early use of statins for ACS. The high doses of atorvastatin in the treatment group were well tolerated, and provided significant benefits within 3 months.

49. Stenestrand U, Wallentin L, for the Swedish Register of Cardiac Intensive Care (RIKS-HIA): **Early statin treatment following acute myocardial infarction and 1-year survival.** *JAMA* 2001, **285:**430–436.
50. 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.
51. Bybee KA, Wright RS, Williams BA, *et al.*: **Effect of concomitant or very early statin administration on in-hospital mortality and reinfarction in patients with acute myocardial infarction.** *Amer J Cardio* 2001, **87:**771–774.
52. **Fluvastatin on Risk Diminishing After Acute Myocardial Infarction (FLORIDA).** *American College of Cardiology annual meeting;* Orlando, FL; 2001.
53. Arntz H-R, Agrawal R, Wunderlich W, *et al.*: **Beneficial effects of pravastatin (± cholestyramine/niacin) initiated immediately after a coronary event (the randomized lipid-coronary artery disease [L-CAD] study).** *Am J Cardiol* 2000, **86:**1293–1298.
54. iugliano RP, Antman EM, Thompson SL, *et al.*: **Lipid lowering drug therapy initiated during hospitalization for acute MI is associated with lower postdischarge 1-year mortality [abstract].** *J Am Coll Cardiol* 2001, **37(Suppl):**A316.
55. Cannon CP, McCabe CH, Bentley J, *et al.*: **Early statin therapy is associated with markedly lower mortality in patients with acute coronary syndromes: observations from OPUS-TIMI 16 [abstract].** *J Am Coll Cardiol* 2001, **37(Suppl):**A334.
56. Lucore CL, Landsman P, Sajjan S, *et al.*: **Statin use associated with reduced risk of death and MI in diabetic patients with acute coronary syndromes [abstract].** *Diabetes* 2001, **50(Suppl 2):**A160.
57. Heeschen C, Hamm CW, Laufs U, *et al.*: **Withdrawal of statins increases event rates in patients with acute coronary syndromes.** *Circulation* 2002, **105:**1446–1452.
58. Walter DH, Fichtlscherer S, Britten MB, *et al.*: **Benefits of immediate initiation of statin therapy following successful coronary stent implantation in patients with stable and unstable angina pectoris and Q-wave acute myocardial infarction.** *Am J Cardiol* 2002, **89:**1–6.
59. Blazing MA, de Lemos JA, Dyke CK, *et al.*: **The A-Z trial: methods and rationale for a single trial investigating combined use of low-molecular-weight heparin with the glycoprotein IIb/IIIa inhibitor tirofiban and defining the efficacy of early aggressive simvastatin therapy.** *Am Heart J* 2001, **142:**211–217.
60.• Fonarow GC, Gawlinski A, Moughrabi S: **Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP).** *Am J Cardiol* 2001, **87:**819–822.

This trial demonstrated vastly improved utilization of numerous secondary prevention therapies after a coronary event when an in-hospital management program was initiated. It also demonstrated that improvements in utilization and compliance may lead to improved outcomes in coronary disease.