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LDL at the Vascular Wall:

New insights, new relevance

Editor-in-Chief

Carl J. Pepine, MD
University of Florida
College of Medicine

Contributing Editor

Andrew P. Selwyn, MD
Harvard Medical School

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Educational Goals

On successful completion of this program, you should have a clearer understanding of the following topics:

- Evidence implicating oxidized LDL and inflammation in the acute coronary syndromes (ACS)
- Effects of aggressive lipid lowering on coronary events in patients following percutaneous coronary intervention (PCI)
- Effects of statins on stroke risk

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Update on mechanisms

Recent clinical trials as well as experimental data on inflammatory and oxidative processes in atherosclerosis highlight the very different pathophysiologies underlying stable coronary artery disease (CAD) and unstable CAD. Lipid-lowering trials in patients with stable CAD show that event reduction is in proportion to the degree of LDL-C reduction; however, in these trials, clinical benefit was evident only after many months of therapy.[1] In contrast, the emerging data with statins in unstable CAD suggest that benefit may begin much earlier. There is evidence that aggressive lipid lowering may reduce inflammation and the lipid content of plaques in as brief a time as 3 months.[2] In addition, several other potential contributing mechanisms of benefit of aggressive lipid lowering in unstable CAD have also been identified. Following are discussions of recent data on the role of oxidation and inflammation in the transition from stable to unstable CAD, and of the rapid effects statins can have on these processes.

Lipid oxidation present at all stages of atherosclerosis

Data now implicate oxidized LDL (ox-LDL) and its receptor LOX-1 in all stages of atherosclerosis—from disease initiation to development of thrombotic complications.

Modulates expression of ACE: Singh et al incubated human coronary artery endothelial cells with ox-LDL (modified) and observed increased expression of angiotensin-converting enzyme (ACE) mRNA in a concentration-dependent fashion.[3] Unmodified LDL had no effect. Pretreatment of cells with blocking antibody to LOX-1 prevented expression of ACE mRNA. These findings suggest an interaction between the renin-angiotensin system (RAS) and ox-LDL that is mediated by LOX-1.

Present in unstable plaques: Plasma levels of ox-LDL are higher in patients with acute myocardial infarction (MI) or unstable angina than in patients with stable angina, suggesting that ox-LDL may contribute to plaque destabilization (Figure 1).[4] In an extension of this work, Sakanoue et al studied expression of LOX-1 in normal coronary artery segments and in atherosclerotic plaques.[5] LOX-1 was

absent in normal arterial segments but was present in both early and advanced plaques. In early lesions, LOX-1 was located in endothelial cells and smooth muscle cells. In advanced lesions it was also present in macrophages and platelet thrombi.

Li et al provided further evidence suggesting involvement of ox-LDL in unstable CAD.[6] Incubation of human coronary artery endothelial cells with ox-LDL increased expression of genes for matrix metalloproteinases 1 and 3, proteolytic enzymes implicated in weakening of the fibrous cap.[7] Pretreatment with blocking antibody to LOX-1 prevented metalloproteinase expression. Unmodified LDL had no effect on metalloproteinase expression.

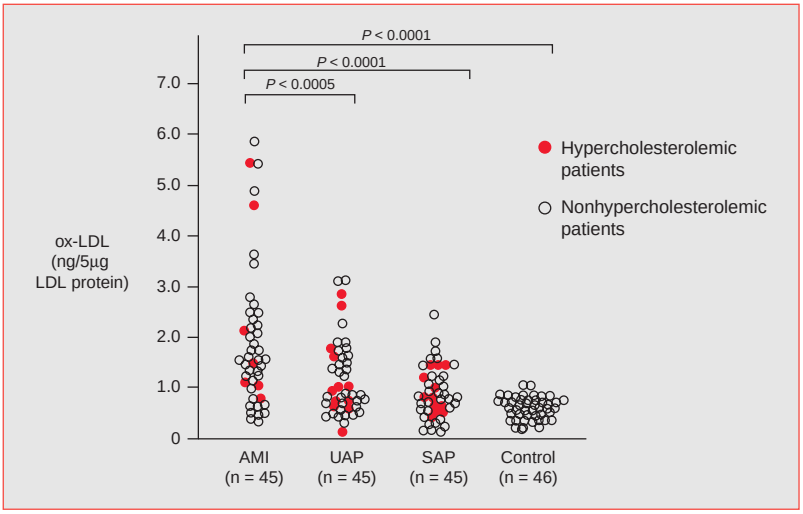

Figure 1. Ox-LDL levels parallel severity of coronary syndrome. As shown, blood levels of ox-LDL are significantly higher in patients with acute MI (AMI) than in patients with unstable angina (UAP, $P < 0.0005$) or stable angina (SAP, $P < 0.0001$).[4]

More active role emerges for CRP

Studies have documented an association between elevated serum levels of C-reactive protein (CRP) and short-term prognosis in patients with unstable disease.[8] Circulating CRP is likely an integrated measure of the intensity of inflammation within atherosclerotic plaques. Data now suggest that CRP may be more than a passive marker of inflammation.

Participation in early lesion development: The liver produces CRP in response to the arrival of cytokines (particularly interleukin-1β, interleukin-6, and tumor necrosis factor α), which have been released into the circulation by inflammatory cells.[8] CRP binds to damaged membranes and protein in the affected tissues, binds complement, and opsonizes the damaged tissue in preparation for clearance by the reticuloendothelial system.[9,10] CRP is deposited in the arterial intima at sites of atherogenesis and mediates monocyte uptake of LDL via a nonoxidative mechanism.[10,11] CRP also increases expression of monocyte chemoattractant protein-1 by human endothelial cells.[12] These data suggest involvement of CRP in early lesion development.

Implicated in plaque destabilization: Bauriedel et al obtained coronary atherectomy samples from target lesions of patients with unstable angina (n = 32) or stable angina (n = 16).[13] CRP was detected in 72% of coronary lesions from the unstable-angina group and in 27% of lesions from the stable-angina group ($P < 0.01$).

Bickel et al reported findings from a 2.9-year follow-up of 1246 patients with angiographically diagnosed CAD enrolled in the AtheroGene registry.[14] CRP, fibrinogen, von Willebrand factor, and leukocyte count were measured. On Cox regression analysis, only CRP remained a significant predictor of CAD mortality. In those patients not taking statins, the probability of cardiac death was highest in those in the top-quartile CRP compared with the lower three quartiles. However, in patients receiving statins, CRP levels lost the association with death, as risk reduction appeared to be independent of LDL levels. These findings provide support for the hypothesis that reduction in inflammatory activity by statins may be a contributing mechanism of early benefit.

"There is evidence that aggressive lipid lowering may reduce inflammation and the lipid content of plaques in as brief a time as 3 months."

Reduction of CRP levels: The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study enrolled 3086 patients hospitalized for ACS.[15] Subjects were randomized immediately after admission to atorvastatin 80 mg/day (n = 1538) or placebo (n = 1548). After 16 weeks, there was a 16% reduction in recurrent ischemic events (relative risk, 0.84; 95% CI, 0.70 to 1.00; $P = 0.048$). A substudy that included 2322 patients found a significant reduction in CRP from baseline in the statin group (–7.5 mg/L compared with –6.0 mg/L in the placebo group; $P < 0.001$).[16] Significant reduction in CRP with atorvastatin was observed in patients with either unstable angina or non–Q-wave MI (Figure 2).

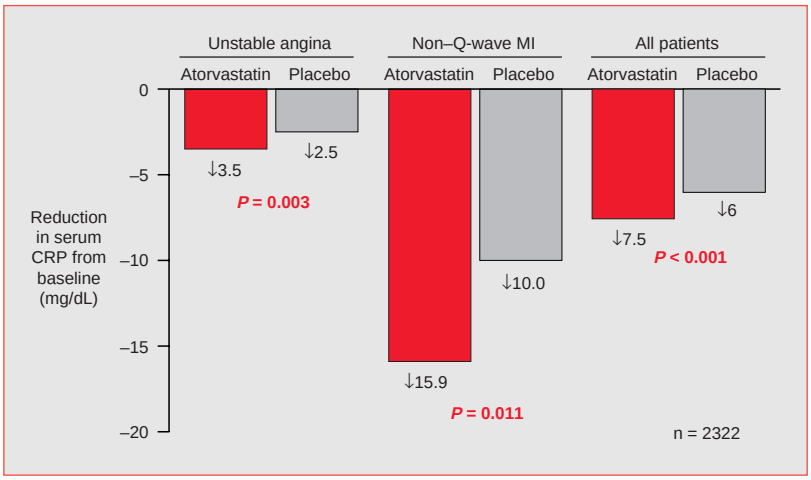

Figure 2. Early statin treatment reduces CRP levels in patients with ACS. Results of a MIRACL substudy, in which subjects were randomized to atorvastatin 80 mg or placebo within 24 to 96 hours after admission for unstable angina or non–Q-wave MI.[16] Data were obtained from 2322 of the original 3086 subjects.

Kinlay et al studied the effects of lipid-lowering intensity on CRP levels in 110 patients with stable angina.[17] Patients were randomized to treatment with atorvastatin 10 to 80 mg daily (with and without vitamins C and E), to an LDL goal of <80 mg/dL, or lovastatin 5 to 10 mg daily, to a goal of <130 mg/dL. In both groups, CRP levels began to decline within the first 4 weeks of therapy, with a more rapid decline noted in the intensive lipid-lowering group (Figure 3). The data show that CRP levels can be rapidly lowered with statins.

Bickel et al measured CRP levels in patients enrolled in the AtheroGene Group cardiovascular registry.[18] A cohort of 255 patients with angiographically diagnosed CAD who were receiving statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, or simvastatin) were matched with 255 patients also with angiographic CAD but who were not receiving statins. The same percentage of patients in each group (30.6%) had unstable CAD. The median CRP level was 4.7 mg/L in the statin group and 7.6 mg/L in the control group ($P = 0.02$).

The Pravastatin Inflammation/CRP Evaluation (PRINCE) study included a cohort of 1375 patients with a history of MI, stroke, or revascularization who received open-label pravastatin 40 mg/day for 24 weeks.[19] At study end, there was a 13.1% reduction in CRP from baseline ($P = 0.003$).

Finally, CRP levels in coronary atherectomy samples representing stable and unstable CAD were significantly lower in patients treated with statins than in patients not treated with statins.[13]

"Data now suggest that CRP may be more than a passive marker of inflammation."

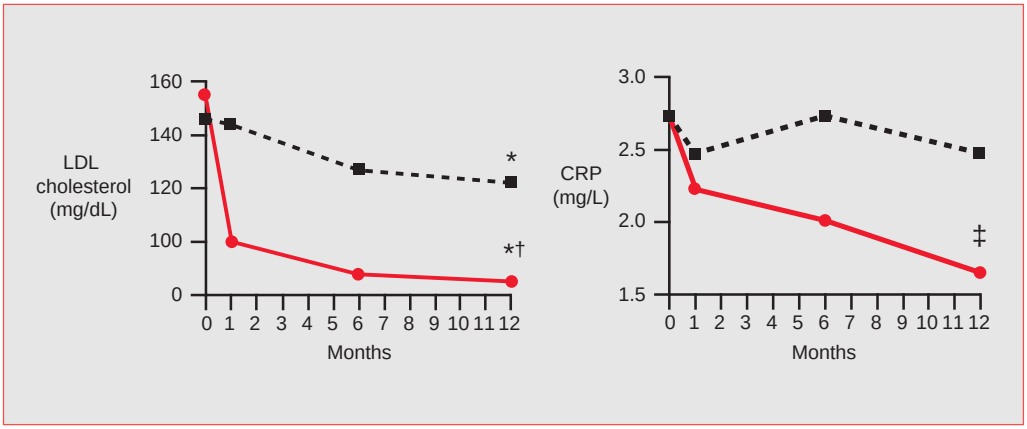

Figure 3. Effects of intensive (atorvastatin 10 to 80 mg, solid line) and modest (lovastatin 5 to 10 mg, dotted line) lipid-lowering regimens on LDL and CRP levels. *$P < 0.01$ vs baseline. †$P < 0.001$ for intensive vs modest lipid lowering. ‡$P = 0.09$ for intensive vs modest lipid lowering.[17]

Inhibition of CRP effects: CRP-mediated increase in expression of monocyte chemoattractant protein-1 is blunted by a statin (simvastatin) and by fenofibrate, an inhibitor of peroxisome proliferator-activated receptor (PPAR)-α.[12]

Reduction in oxidative stress: Production of reactive oxygen species in the aorta of spontaneously hypertensive rats is significantly reduced ($P < 0.05$) by treatment with a statin (atorvastatin) for 30 days.[20] This effect was mediated by decreased expression of NAD(P)H oxidase subunits and increased expression of catalase, an endogenous free-radical scavenger.

Finally, pretreatment with a statin (simvastatin) attenuated the effect of ox-LDL on ACE expression.[3]

"CRP is deposited in the arterial intima at sites of atherogenesis and mediates monocyte uptake of LDL via a nonoxidative mechanism. CRP also increases expression of monocyte chemo-attractant protein-1 by human endothelial cells."

Benefits of statins in post-intervention

In recent years, management of patients with ACS has been revolutionized. The safety and efficacy of PCI has progressively improved to the point where some propose, on the basis of recent randomized clinical trials, that PCI should be routinely performed in intermediate- and high-risk patients presenting with ACS.[21] The MIRACL study provided impressive clinical evidence of the safety and efficacy of aggressive lipid lowering with statins in patients with ACS for whom coronary revascularization was not planned or anticipated.[15] These two strategies have now converged.

LIPS: Clinical trial of statins plus PCI

The Lescol Intervention Prevention Study (LIPS) enrolled 1677 patients with a broad range of total-C levels (135 to 270 mg/dL) who were scheduled for a first PCI procedure.[22] At an average of 2.7 days following the procedure, subjects were randomized to either statin (fluvastatin 40 mg bid) or placebo. The primary outcome was time to first major adverse cardiac event (MACE: cardiac death, nonfatal MI, or repeat revascularization). Initial results have been reported.[22] Times to first MACE for statin and placebo started to diverge after 1.5 years. At study end (4 years), there was a 22% reduction in risk of MACE for statin versus placebo (P = 0.013). Greater risk reductions were achieved in subjects with multivessel disease (34%, P = 0.011) or diabetes (47%, P = 0.041).

Observational studies of statins plus PCI

Chan et al reported data from an observational study of 5052 patients who underwent PCI at the Cleveland Clinic Foundation from 1993 to 1999.[23] As shown in Figure 4, statin therapy at time of the procedure was associated with 47% reduction in 30-day mortality (0.8% versus 1.5%; odds ratio [OR], 0.53; P = 0.048) and a 33% reduction in 6-month mortality (2.4% versus 3.6%; OR, 0.67; P = 0.046).

Moscucci et al reported data from an observational study of 9084 patients pretreated with statin therapy prior to PCI and 7848 patients who were not.[24] Data represent procedures conducted between July 1997 and September 2000. In-hospital mortality rates were 0.58% in the statin-pretreatment group and 2.8% in the no-statin group (OR, 0.2; 95% CI, 0.14 to 0.24; P < 0.001).

Walter et al reported on 704 consecutive patients who underwent successful PCI between 1997 and 1999.[25] The study population included 335 patients with chronic stable angina, 224 with unstable angina, and 145 with Q-wave MI. Statin therapy (atorvastatin, fluvastatin, lovastatin, or simvastatin) was initiated 24 hours after PCI in all patients in whom LDL-C levels were >75th percentile, adjusted for age and sex. Many patients also received aspirin, beta-blockade, and ACE inhibition. Statin treatment reduced the risk of cardiac death or nonfatal MI in the stable-angina and unstable-angina groups but not in the Q-wave–MI group. For example, compared with patients with stable angina who

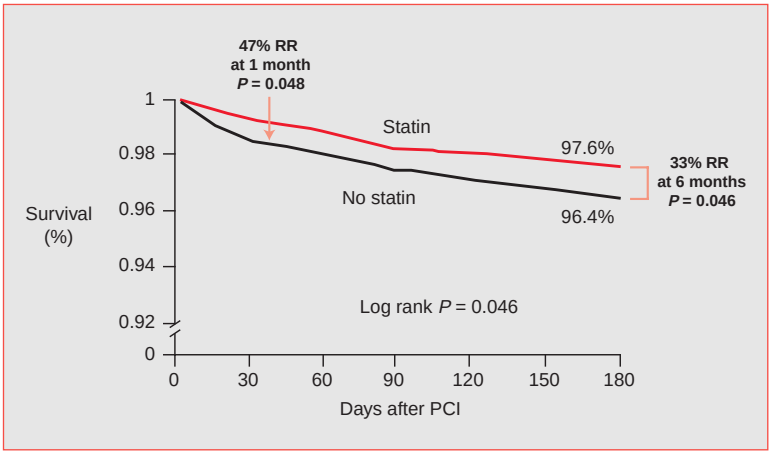

Figure 4. Statins reduce all-cause mortality following PCI. Survival curve data obtained from an observational study of patients who were and were not receiving statin treatment at time of admission for an interventional procedure.[23]

received statins, there was almost a 7-fold increased risk in patients with unstable angina who did not receive statins (OR, 6.9; 95% CI, 1.5 to 31; $P = 0.004$), but this risk was substantially less in patients with unstable angina who received statins (OR, 1.5; 95% CI, 0.2 to 11; $P = 0.7$). The beneficial effects of statin treatment appeared to be most prominent during the first 4 weeks.

The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) study was a comparison of glycoprotein IIb/IIIa inhibition (tirofiban) and unfractionated heparin in 3232 patients with ACS.[26] All patients also received aspirin; angiography was performed in 62% and PCI in 21%. Heeschen et al performed a subgroup analysis of 1616 patients, 465 of whom were taking statins (lovastatin, pravastatin, or simvastatin) before symptom onset.[27] Statin therapy was withdrawn on hospitalization in 86 of these 465 patients (18.5%), and was associated with an approximate tripling in risk of cardiac events at 30 days compared with patients who continued to receive statins (hazard ratio, 2.93; 95% CI, 1.64 to 6.27; $P = 0.005$).

Statins decrease myocardial necrosis following PCI

Aronow et al compared the incidence of myocardial necrosis after elective PCI in patients who were (n = 155) and were not (n = 706) on lipid-lowering therapy prior to their procedure.[28] Overall, 16% had post-PCI necrosis as diagnosed by creatine kinase–MB ≥3 times upper limit of normal. The incidence of necrosis was significantly lower among the lipid-lowering pretreatment group (9% versus 17%; risk ratio, 0.49; 95% CI, 0.28 to 0.82; $P = 0.006$).

Clinical implications: The results of these studies are consistent with the insight that PCI provides effective management of a culprit lesion but has no effect on atherosclerotic plaques distal to that lesion.[29] Lesions with <50% stenosis are much more numerous than more highly stenotic lesions and are an important cause of ischemic events.[30-32] Aggressive lipid lowering with statins will stabilize these lesions, and there is now compelling clinical evidence that statin therapy should begin early regardless of whether or not PCI is planned.

Economic implications: An economic analysis of the MIRACL data calculated the incremental costs of atorvastatin 80 mg over the 16 weeks following admission for unstable angina or non–Q-wave MI.[33] Aggressive lipid lowering with this statin incurred an estimated incremental cost of $339 per patient, which corresponded to $4,337 per event avoided. These findings suggest that in low-risk ACS patients for whom PCI may not be planned, reduction in downstream events with statin therapy may be a cost-effective strategy.

Cholesterol, stroke, and dementia

Currently, approximately 750,000 Americans suffer a first or recurrent stroke.[34] Almost 160,00 of these events are fatal (stroke is the third most frequent cause of death in this country).[35,36] In addition, nonfatal stroke is the leading cause of serious adult disability and a major contributor to dementia in later life.[35,37] The economic cost of stroke for 2002 is projected to total $49.4 billion in combined direct and indirect costs.[37]

Reduction in stroke with statins

Statins appear to have a prominent effect in preventing stroke.

Meta-analysis involving 21,303 patients[38]**:** A variety of designs (2 primary prevention studies, 5 mixed primary/secondary prevention studies, 10 regression studies) and statins (lovastatin, pravastatin, or simvastatin) were represented. The calculated odds ratios were 0.77 for fatal stroke (95% CI, 0.57 to 1.04) and 0.69 for nonfatal stroke (95% CI, 0.54 to 0.88) comparing statin with the control group.

Meta-analysis of three major studies with a single statin (pravastatin)[39]**:** The studies were Cholesterol and Recurent Events (CARE), Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), and West of Scotland Coronary Prevention Study (WOSCOPS). The combined CARE, LIPID, and WOSCOPS data showed a significant risk reduction for total fatal/nonfatal stroke (OR, 0.80; 95% CI, 0.68 to 0.93; $P = 0.01$). There was a 24% risk reduction in nonfatal stroke (OR, 0.76; 95% CI, 0.64 to 0.90) and a neutral effect on fatal stroke (OR, 1.02; 95% CI, 0.64 to 1.61). Benefit was primarily due to a reduction in nonhemorrhagic stroke (OR, 0.77; 95% CI, 0.63 to 0.94).

Two recent prospective statin studies—MIRACL and the Heart Protection Study (HPS)—also demonstrated a significant risk reduction in ischemic stroke and a trend towards lower risk of hemorrhagic stroke. As discussed herein, these studies expand the range of patients who may benefit.

MIRACL: Conducted in 3086 patients with ACS who received atorvastatin 80 mg/day or placebo beginning 24 to 36 hours after hospital admission. This study found a significant risk reduction in stroke at 16 weeks.[40] Of 31 nonfatal strokes, 22 occurred in the placebo group and 9 in the atorvastatin group (OR, 0.40; 95% CI, 0.19 to 0.88; $P = 0.02$). Of 36 fatal and nonfatal strokes, 24 occurred in the patients treated with placebo and 12 in the group treated with atorvastatin (OR, 0.49; 95% CI, 0.2 to 0.98; $P = 0.04$). There were three hemorrhagic strokes in the placebo group and none in the atorvastatin group.

Clinical implications: MIRACL shows that aggressive lipid lowering with a statin is effective in preventing cerebral as well as coronary vascular events when given immediately after an acute coronary event, without an increase in risk of myositis, hemorrhage, or liver problems.

HPS: This study compared the effects of simvastatin 40 mg, antioxidant vitamins (vitamin E 600 mg, vitamin C 500 mg, and beta-carotene 20 mg), and placebo in 20,536 patients with confirmed atherosclerotic disease of the cardiovascular, cerebral, or peripheral arteries.[41] Patients with total-C levels >135 mg/dL were eligible; thus, a substantial number of subjects in this study had "normal" cholesterol levels. At baseline, LDL-C levels were <116 mg/dL in 6793 patients, and between 116 mg/dL and 135 mg/dL in 5063 patients.

At study end (5.5 years), the rate of stroke was 4.3% in the statin group and 5.7% in the placebo group, a 25% reduction ($P < 0.0001$). This was driven by a 30% reduction in ischemic stroke (2.8% versus 4%), although there was also a nonsignificant trend toward fewer hemorrhagic strokes in the statin group compared with the placebo group (Figure 5). There was no evidence of a beneficial effect of antioxidant therapy on vascular events.

Clinical implications: HPS extends the benefits of aggressive lipid lowering to high-risk patients with "normal" cholesterol levels.

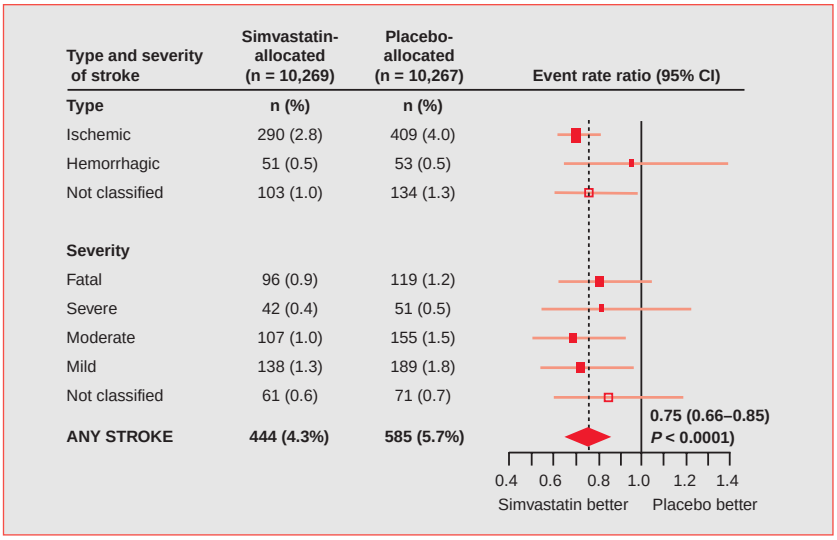

Figure 5. Reduction of stroke in high-risk patients: Effects of statin by stroke subtype. Ischemic stroke risk was reduced by simvastatin 40 mg, with no increase in risk for hemorrhagic stroke. Data are from the Heart Protection Study.[41]

Possible mechanisms of benefit

Many thromboemboli arise from atheromas in the carotid artery or aortic arch. Since development of atherosclerotic disease at these vascular sites parallels the disease process in the coronary arteries, the same antiatherosclerotic effects by which statins prevent coronary ischemic events have been postulated to play a role in prevention of stroke.[42] Of these putative beneficial mechanisms, evidence to date implicates cholesterol lowering, anti-inflammatory effects, and modulation of nitric oxide synthase activity.

Cholesterol lowering: An observational study was conducted in 11,177 patients with documented coronary heart disease.[43] In 6 to 8 years of follow-up, 478 patients had verified ischemic stroke or transient ischemic attack (TIA). Odds ratios for this combined outcome were calculated for lipid levels in the upper versus lower tertile. Odds ratios were: total-C, 1.50 (95% CI, 1.18 to 1.90); LDL-C, 1.43 (95% CI, 1.12 to 1.82); HDL-C, 0.72 (95% CI, 0.56 to 0.93). These data provide the first strong evidence implicating cholesterol as a risk factor for ischemic stroke.

Anti-inflammatory effects: A number of studies implicate CRP as possibly predictive of stroke.[42,44] For example, data from the Framingham Heart Study related plasma CRP levels to incidence of first ischemic stroke or TIA.[44] During 12 to 14 years of follow-up, 196 ischemic strokes and TIAs occurred. Independent of age, men in the highest CRP quartile had 2 times the risk of ischemic stroke/TIA ($P = 0.028$), and women had almost 3 times the risk ($P = 0.0003$) compared with those in the lowest quartile. After adjustment for smoking, total or HDL cholesterol, systolic blood pressure, and diabetes, the increase in risk across CRP quartiles remained statistically significant for both men and women.

Modulation of nitric oxide synthase activity: Endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) appear to have opposing actions in the cerebral vasculature. Following experimental induction of ischemic stroke in mice, animals that lack the eNOS gene experienced larger infarcts than wild-type mice, while those that lack the iNOS gene had smaller infarcts.[45,46] Treatment with statin (simvastatin) prior to induction of ischemic stroke augmented cerebral blood flow and reduced infarct size in wild-type but not in eNOS-knockout mice.[47] The protective effect in wild-type mice was mediated by enhanced eNOS activity.

"Two recent prospective statin studies—MIRACL and the Heart Protection Study (HPS)—also demonstrated a significant risk reduction in ischemic stroke and a trend towards lower risk of hemorrhagic stroke… these studies expand the range of patients who may benefit."

Updated ACC/AHA guidelines on risk factor modification following ACS

The American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines has issued an update to the Guidelines for the Management of Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction (UA/NSTEMI) that were originally published in September 2000.[48] This update reflects the findings of a number of clinical trials and observational studies that have appeared since that time.

The 2002 update guidelines provide new recommendations (highlighted below) on the role of lipid-lowering therapy in a post-discharge risk factor management plan. While recognizing that the evidence from clinical trials of a beneficial effect of predischarge initiation of lipid-lowering therapy is not yet robust or definitive, the Task Force also notes that observational studies support this policy (for example, see the review by Pepine[49]).

Recommendations

Class I

1. Specific instruction should be given on the following:
   a) Smoking cessation and achievement or maintenance of optimal weight, daily exercise, and diet (Level of Evidence: B)
   b) Statins for LDL-C >130 mg/dL (Level of Evidence: A)
   c) Lipid-lowering agent if LDL-C after diet >100 mg/dL (Level of Evidence: B)
   d) *A fibrate or niacin if HDL-C <40 mg/dL, occurring as an isolated finding or in combination with other lipid abnormalities (Level of Evidence: B)**
   e) Hypertension control to a blood pressure <130/85 mm Hg (Level of Evidence: A)
   f) Tight control of hyperglycemia in diabetes (Level of Evidence: B)
2. Consider the referral of patients who are smokers to a smoking cessation program or clinical and/or outpatient cardiac rehabilitation program (Level of Evidence: B)

Class IIa

1. *Statins and diet for LDL-C >100 mg/dL begun 24 to 96 hours after admission and continued at hospital discharge (Level of Evidence: B)**
2. Gemfibrozil or niacin for patients with HDL-C <40 mg/dL and triglycerides >200 mg/dL (Level of Evidence: B)

**New recommendations*

Summary

In the original trials of lipid-lowering therapy, statins significantly reduced unstable angina and MI in patients with stable CAD. Patients with unstable angina and recent MI were excluded. Data from more recent trials show that lipid-lowering therapy (particularly with statins) is associated with benefit when given to patients with acute ischemic syndromes. Importantly, (1) clinical benefit is observed regardless of whether or not patients are scheduled for PCI; (2) reductions in cerebrovascular as well as cardiovascular ischemic events have been noted; and (3) clinical benefit may be seen in as short a time as 4 months and extend out to 4 years.

Several possible mechanisms of benefit may exist. Aggressive lipid lowering can have relatively rapid effects on the lipid content of coronary atheromas. In addition, cholesterol has recently been implicated as a risk factor for ischemic stroke. It is also likely that inhibition of inflammatory and oxidative processes occurring in the vascular wall are important.

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Self-assessment questions

Please check the appropriate answer for each question on the Answer Key.
Instructions for obtaining CME credit are provided on the back of the Answer Key.

1. C-reactive protein (CRP) is found in atherosclerotic plaques as well as in the circulation.
   a. True
   b. False

2. Macrophage uptake of lipids does not involve any nonoxidation-mediated mechanisms.
   a. True
   b. False

3. Which effect is not associated with oxidized LDL (ox-LDL)?
   a. Increased expression of ACE
   b. Thrombosis
   c. Decreased expression of matrix metalloproteinases

4. In the Lescol Intervention Prevention Study (LIPS), 4 years of statin therapy post-percutaneous coronary intervention (PCI) reduced the combined outcome of cardiac death, nonfatal MI, or revascularization by how much?
   a. 15% to 20%
   b. 20% to 25%
   c. 25% to 30%

5. An observational study at the Cleveland Clinic found that pretreatment with statins prior to PCI was associated with a reduction in early (30-day) mortality of how much?
   a. 20% to 30%
   b. 30% to 40%
   c. 40% to 50%

6. Data from an observational study by Moscucci et al suggest that pretreatment with statins is not associated with any effect on in-hospital mortality following PCI.
   a. True
   b. False

7. What is the current estimate of stroke prevalence in the USA?
   a. 600,000/year
   b. 650,000/year
   c. 700,000/year
   d. 750,000/year

8. The Heart Protection Study reported a reduction in ischemic stroke of how much?
   a. 10% to 20%
   b. 20% to 30%
   c. 40% to 50%

9. The MIRACL study found a reduction in nonfatal stroke of how much?
   a. 10% to 20%
   b. 20% to 30%
   c. 40% to 50%
   d. 50% to 60%

10. The MIRACL and HPS studies demonstrate a trend towards reduction in hemorrhagic stroke with statins.
    a. True
    b. False

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Answer Key

Please check the correct box for each question. There is only 1 correct response for each question.

1. [A] [B]
2. [A] [B]
3. [A] [B] [C]
4. [A] [B] [C]
5. [A] [B] [C]
6. [A] [B]
7. [A] [B] [C] [D]
8. [A] [B] [C]
9. [A] [B] [C] [D]
10. [A] [B]

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Your input will help us improve our educational activities.
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Readability and presentation	5	4	3	2	1
Usefulness of illustrations	5	4	3	2	1
	Agree				**Disagree**
Importance to physicians	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Did not promote particular product or company	5	4	3	2	1

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