Data Alert

Blunting the atherosclerotic process in patients with coronary artery disease

Dear Colleague:

Statin therapy lowers serum levels of atherogenic lipoproteins and reduces cardiovascular (CV) morbidity and mortality in a wide range of patients in clinical trials.1-7 These major trials were placebo-controlled, and provide limited evidence about differences between individual statins, or about target levels for lipid lowering.

The Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial8 has now compared the effects of two different statin treatments in patients with established coronary artery disease (CAD). This is the first major study to measure the progression of coronary atherosclerosis using intravascular ultrasound (IVUS), a technique that can quantify plaque by visualization of the coronary arterial wall.

The results from the REVERSAL trial demonstrate that intensive lipid-lowering treatment with atorvastatin 80 mg halts the progression of atherosclerosis in CAD patients. In contrast, patients treated with moderate lipid lowering using pravastatin 40 mg experience continued atherosclerotic disease progression.

**REVERSAL: Study design**

- Prospective, randomized, double-blind, multicenter trial comparing the effects of atorvastatin 80 mg vs pravastatin 40 mg
- 654 patients with symptomatic CAD, ≥20% stenosis on angiography, LDL-C 125–210 mg/dL
- Primary endpoint = atheroma volume in coronary artery with ≥20% stenosis
- Atheroma volume measured by IVUS at baseline and at 18-month follow-up

IVUS = intravascular ultrasound

Nissen SE et al.8
REVERSAL was a prospective, randomized, double-blind, multicenter trial enrolling 654 patients with symptomatic CAD, as shown by ≥20% stenosis with angiography, and low-density lipoprotein cholesterol (LDL-C) levels of 125 to 210 mg/dL. Patients were randomized to atorvastatin 80 mg or pravastatin 40 mg, and IVUS measurements were taken at baseline and at the 18-month follow-up. The primary outcome was the rate of atherosclerotic progression measured by the percent change in atheroma volume.

LDL-C and the inflammatory marker C-reactive protein (CRP) were reduced significantly more by treatment with atorvastatin compared with pravastatin. CRP reductions were 36.4% versus 5.2%, respectively (P < 0.001). LDL-C was reduced 46.3% with atorvastatin compared with 25.2% with pravastatin (P < 0.001) and mean LDL-C was reduced to 79 mg/dL versus 110 mg/dL, respectively (P < 0.001). Of the patients treated with atorvastatin, 97% achieved LDL-C <100 mg/dL compared with 65% in the pravastatin group.

IVUS provides detailed images of the blood vessel wall by using a miniature ultrasound transducer placed within the coronary artery to make cross-sectional images. Images can be generated along the vessel’s length and in this study were analyzed at 1.0-mm intervals. Atherosclerotic disease progression was quantified by computing atheroma volume and percent atheroma volume along the index artery, as shown in the following figure (see Definitions). The figure also shows the calculations used for the primary outcome (percent change in atheroma volume) as well as the change in percent atheroma volume, one of several pre-specified secondary outcomes.

Patients receiving intensive lipid lowering showed no apparent progression of atheroma measured by the primary outcome (percent change in atheroma volume). In fact, these patients achieved a small regression (−0.4% vs baseline; 95% CI, −2.4% to 1.5%). Significant atheroma progression did occur in patients treated with modest lipid lowering (+2.7% vs baseline; 95% CI, 0.2% to 4.7%) (P = 0.02, atorvastatin vs pravastatin).

Nissen SE et al.8

![Change at 18 months](image-url)
A significant difference in the rate of progression of atheroma was also demonstrated by changes in the percent atheroma volume, a secondary outcome (0.2% change with atorvastatin vs 1.6% change with pravastatin; \( P < 0.001 \), atorvastatin vs pravastatin). Another secondary outcome, atheroma volume in the most severely diseased 10-mm vessel subsegment, was also significantly lower with atorvastatin \( (P = 0.01\), atorvastatin vs pravastatin; data not shown). The absence of atheroma progression versus baseline was consistent across 22 pre-specified subgroups in the atorvastatin-treated patients, while progression occurred in the pravastatin-treated cohort of 15 subgroups. When subgroups that attained the National Cholesterol Education Program (NCEP) guideline level for LDL-C (<100 mg/dL) were compared, there was progression in the pravastatin group \( (P < 0.01) \) and no progression in the atorvastatin-treated patients \( (P = 0.93) \), compared with baseline. Safety data showed that both lipid-lowering regimens were well tolerated and safe.

**Response variables measured by IVUS**

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Percent change in atheroma volume</th>
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<tr>
<td>Secondary outcome</td>
<td>Change in percent atheroma volume</td>
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Definitions:

- **Atheroma volume** = \( \sum (\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}}) \)
- **Percent atheroma volume** = \( \frac{\sum (\text{EEM}_{\text{CSA}} - \text{LUMEN}_{\text{CSA}})}{\sum \text{EEM}_{\text{CSA}}} \) \times 100

CSA = cross-sectional area; EEM = elastic external membrane; IVUS = intravascular ultrasound

**REVERSAL: Primary and secondary outcomes**

Nissen SE et al.
REVERSAL demonstrates that maximally intensive lipid lowering can halt progression of atherosclerosis, a result not achieved with modest lipid lowering. The differential effects of intensive therapy with atorvastatin were evident even in patients with LDL-C levels below the achieved means (atorvastatin 79 mg/dL, pravastatin 110 mg/dL) and may be, at least partly, related to the greater reduction in CRP levels. Importantly, the results in the more intensive–treatment group were achieved with a safety and tolerability profile similar to the more moderate lipid-lowering regimen.

REVERSAL suggests that intensive treatment with atorvastatin (to lower LDL-C below the currently recommended NCEP guideline level of LDL-C <100 mg/dL) should be considered in secondary prevention.

REVERSAL did not assess clinical outcomes, due to the small number of patients. However, recent results of the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators (PROVE IT–TIMI 22) trial\textsuperscript{10} now confirm the clinical significance of the findings in REVERSAL.

**REVERSAL: Clinical Implications**

- Findings warrant consideration of more intensive treatment with atorvastatin 80 mg for secondary prevention
- Maximally intensive lipid lowering can essentially halt atherosclerotic disease progression
- Differences between atorvastatin and pravastatin in reducing atherosclerotic progression evident, even in pravastatin patients reaching NCEP goal
- No increase in adverse events with intensive treatment

**PROVE IT–TIMI 22: LDL-C levels during study**

Cannon CP et al.\textsuperscript{10}
PROVE IT–TIMI 22 randomized 4162 patients who had been recently hospitalized for acute coronary syndromes (ACS) to atorvastatin 80 mg or pravastatin 40 mg, which had been considered the reference standard dose since it had been shown to prevent death and other adverse outcomes in several large clinical trials. Patients achieved median LDL-C 62 mg/dL with atorvastatin and 95 mg/dL with pravastatin (P < 0.001). The primary outcome (combined all-cause death, myocardial infarction, hospitalization for unstable angina, coronary revascularization, and stroke) occurred in 22.4% of atorvastatin-treated patients and 26.3% of pravastatin-treated patients (16% relative risk reduction in favor of atorvastatin, P = 0.005 at the mean 24-month follow-up).  

Prove It–Timsi 22: Primary outcome

Thus, in patients with a recent ACS, intensive versus moderate statin treatment provides greater protection against death or major CV events. Results from PROVE IT–TIMI 22 also support the idea that the IVUS measurements of atherosclerotic progression used in the REVERSAL study may offer a clinically useful tool for assessing disease burden.

Two other studies that have used an ultrasound method for vessel wall imaging (measurement of carotid intima-media thickness) showed that progression of atherosclerosis was reduced with intensive lipid lowering (atorvastatin 80 mg) versus modest lowering (simvastatin or pravastatin 40 mg).  Earlier studies have indicated that progression of coronary artery disease predicts future clinical coronary events.  These studies demonstrated that small differences in the rate of atherosclerotic progression were associated with significant differences in clinical outcomes.

Potential mechanisms

The REVERSAL investigators point out that the greater benefit seen with intensive lipid lowering may be due to several potential mechanisms.  Levels of LDL-C, total cholesterol, and triglycerides were all reduced to a greater extent with intensive treatment. Other factors may also contribute, including the differential effects of the two treatments on the inflammatory marker CRP. Furthermore, while linear regression analysis indicated an inverse relationship between percent
reduction in LDL-C level and atherosclerosis progression for both statins, LDL-C reduction alone did not explain all of the differences in efficacy. At any level of LDL-C reduction, the rate of atherosclerotic progression was lower with atorvastatin than with pravastatin (equivalent to an additional 20% or 30 mg/dL reduction in LDL-C).

**SUMMARY**

Intensive lipid-lowering treatment with atorvastatin 80 mg halted the progression of coronary atherosclerosis in patients with established CAD, whereas modest lipid lowering with pravastatin 40 mg was associated with significant disease progression. Intensive treatment produced greater reductions in atherogenic lipoproteins and CRP; both lipid lowering and anti-inflammatory effects may explain the improved outcomes.

REVERSAL suggests, and PROVE IT confirms, that more intensive lipid lowering than currently recommended by national and international guidelines may be required for maximal secondary prevention of coronary disease.

Sincerely,

Carl J. Pepine, MD

**REFERENCES**


