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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, CANADA

Scientific Update™

Treating Beyond Current Guidelines: Can Aggressive Lipid Lowering Result in Atherosclerosis Regression? Late-breaking results from the REVERSAL Study

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A Report on Presentations at the Late-Breaking Clinical Trial Sessions and a Satellite Symposium at the 76th Annual Scientific Session of The American Heart Association

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Reported and discussed by:
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Numerous randomized trials of lipid-lowering therapy have demonstrated that 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, or statins, reduce the risk of cardiovascular death, myocardial infarction (MI), stroke, and other cardiovascular events among individuals with established coronary artery disease (CAD) and overt hypercholesterolemia. While standard treatment guidelines have recommended a target low-density lipoprotein cholesterol (LDL-C) of < 2.6 mmol/L for secondary prevention of cardiovascular events, growing evidence suggests that aggressive lipid-lowering by statin therapy may result in clinical benefits even at LDL-C concentrations far below target levels. Specifically, it has been postulated that newer synthetic statins, which have more potent lipid-lowering effects than first generation natural statins, may lead to greater cardiovascular protective effects due to more aggressive LDL-C reduction. In this issue of *Cardiology Scientific Update* clinical data supporting more aggressive LDL-C lowering for secondary prevention in patients with established cardiovascular disease, including late-breaking results of the Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study, will be reviewed.

Guidelines and evidence for the use of statins for cardiovascular protection

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in Canada and in most industrialized countries. Elevated total and low-density lipoprotein cholesterol (LDL-C) are well-recognized risk factors for CVD, and their reduction is associated with important clinical sequelae.[1] Evidence from numerous large-scale, randomized, placebo-controlled, clinical trials has firmly established the benefit of lipid-lowering using HMG-CoA reductase inhibitors (statins) for primary and secondary prevention of atherosclerotic cardiovascular and cerebrovascular disease.[2] Largely on the basis of these lipid-lowering trials, the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines have recommended that high-risk individuals with a 10-year risk >20% (eg, established CAD, or other CAD risk equivalents such as type II diabetes) should be treated to a target LDL-C concentration of <2.6 mmol/L (secondary prevention).[3] However, when baseline LDL-C is below target, the NCEP ATP III guidelines suggest that pharmacologic treatment may not be necessary, based on the lack of clinical trial evidence. Thus, whether cholesterol reduction to levels well below 2.6 mmol/L would further reduce cardiovascular risk remains controversial and raises an important therapeutic question regarding optimal target concentrations of LDL-C.

Observational studies have shown a continuous and positive relationship between plasma cholesterol concentrations and cardiovascular risk, with no obvious lower threshold concentration.[4] These studies suggest a linear relationship between cholesterol levels and cardiovascular risk, implying that the relative risk reduction by lipid-lowering may be similar throughout the range of cholesterol concentrations. In comparison, post hoc analyses of several secondary prevention trials suggest that risk

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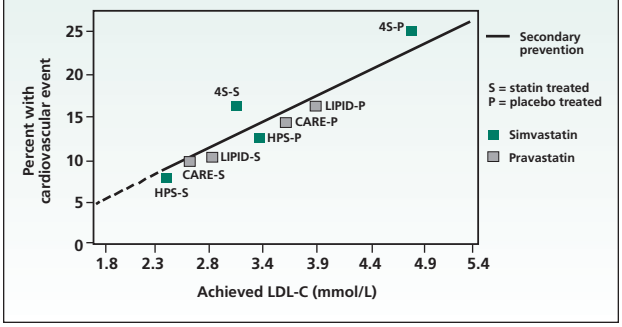
Figure 1: Pooled data from landmark secondary prevention trials of statin therapy – relationship between cardiovascular events and achieved LDL-C levels



reduction is less at lower LDL-C concentrations, implying a curvi-linear relationship. In the 4S trial,[5] the absolute risk reduction was less in patients with lower baseline LDL-C concentrations. Subset analysis from the CARE trial[6] suggested that the absolute LDL-C achieved with statin use is less important, with reduction to <3.2 mmol/L less likely to yield substantial benefit. These data would seem to support the theory that there is a threshold LDL-C level below which additional benefit is minimal. However, when data from CARE and WOSCOPS[7] were pooled with that from the LIPID trial,[8] there appeared to be a benefit for statin therapy in the group with baseline LDL-C <3.5 mmol/L.[9]

Recently, the Heart Protection Study[10] demonstrated that statin therapy reduced the incidence of major vascular events in a broad range of high-risk patients regardless of pre-treatment LDL-C. Specifically, statin therapy in patients whose baseline LDL-C was <2.6 mmol/L had benefits that were relatively similar to patients whose initial LDL-C was >3.4 mmol/L. Similarly, the ASCOT-LLA study,[11] reviewed in a recent issue of *Cardiology Scientific Update*, found that in a population at high risk for CVD, the relative risk reduction in cardiovascular endpoints was unrelated to baseline cholesterol levels and consistent across the whole range of cholesterol levels.

When data from large, secondary prevention trials of statin therapy are pooled, the incidence of cardiovascular events over a wide range of achieved LDL-C levels can be further examined (Figure 1). On reviewing the results of these landmark statin trials, a linear relation between cardiovascular events and LDL-C levels is observed, similar to that found in previous observational studies. These results suggest that a threshold LDL-C below which further reduction fails to produce additional benefits in vascular risk reduction has not yet been defined, and may not even exist. If true, the implications are that adherence to current guidelines may potentially lead to inadequate treatment of at-risk patients who may still derive benefit from statin therapy.

While the majority of statin trials have been placebo-controlled studies, the question of whether more aggressive LDL-C lowering (below current guideline recommendations) has additional benefit can be best answered by trials that compare statins. Newer generation synthetic statins (eg, atorvastatin and rosuvastatin), now available, have more potent LDL-C lowering effects than first generation natural statins.[12] Whether these potent statins offer greater vascular protection than the current statins has not been well-studied to date. A limited number of recently completed clinical trials, using mainly surrogate endpoints, have directly compared these newer lipid-lowering agents to established first generation statins.

The ARBITER study

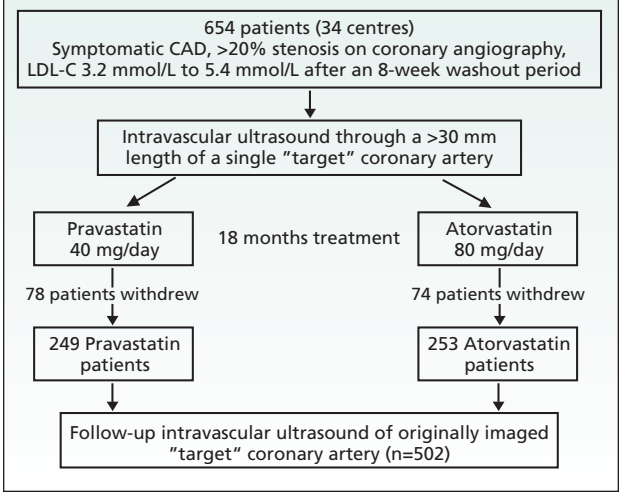
The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trial[13] was a single centre, prospective, randomized, open-label, clinical trial comparing the effects of atorvastatin 80 mg daily and pravastatin 40 mg daily. The primary outcome was carotid intima-media thickness (CIMT), as measured by high-frequency vascular ultrasound of the distal common carotid artery, performed in a blinded fashion. CIMT is a validated and reproducible noninvasive measure of carotid atherosclerosis burden and has been used as a surrogate cardiovascular endpoint in previous lipid-lowering trials.[14] Between December 1999 and February 2001, 161 patients (mean age 60, 71.4% male, 46% with established CAD) that met NCEP II criteria for pharmacologic lipid-lowering, were enrolled in the trial. Patients were randomly assigned to open-label treatment with either atorvastatin 80 mg/day (n=79) or pravastatin 40 mg/day (n=82) for a follow-up period of 12 months. Baseline CIMT and other characteristics were similar between study groups. After 12 months of therapy, atorvastatin treatment resulted in lower LDL-C levels as compared to pravastatin (2.0±0.6 *vs* 2.8±0.8 mmol/L, respectively, p<0.001). Over the same time period, atorvastatin treatment was associated with progressive CIMT regression (change in CIMT, -0.034±0.021mm), while CIMT was unchanged in the pravastatin treated group (change in CIMT, +0.025±0.017 mm; p=0.03 *vs* atorvastatin group). No patient in the study experienced significant elevations (3 times the upper limit of normal) in liver enzymes or had myositis. Treatment with atorvastatin also resulted in continued reduction in C-reactive protein (CRP) levels that were significantly lower than those observed in the pravastatin group at 12 months. This study comparing 2 statins demonstrated a benefit for more aggressive lipid-lowering using a surrogate cardiovascular endpoint (CIMT) and thus adds further evidence to the hypothesis that a threshold LDL-C may not exist.

The REVERSAL Study

Study design

The REVERSing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) study was a prospective, multicentre, double-blind, randomized trial designed to compare the effects of an aggressive lipid-lowering regimen (atorvastatin 80 mg/day)

Figure 2: REVERSAL Study Design[15]



and a moderate lipid-lowering regimen (pravastatin 40 mg/day), on coronary atheroma burden, as measured by intravascular ultrasound (IVUS). The rationale and design of REVERSAL has been published previously,[15] and the study design is summarized in Figure 2. Patients with symptomatic CAD, a 20% or greater stenosis by angiography and LDL-C concentrations between 3.2 mmol/L and 5.4 mmol/L after an 8-week washout period (off statin therapy), were eligible for entry into the study. The main exclusion criteria was the presence of >50% stenosis of the left main coronary artery. A total of 654 patients in 34 hospitals across the United States were enrolled in the study between June 1999 and September 2001. Patients were randomized to receive pravastatin 40 mg daily or atorvastatin 80 mg daily for 18 months. The rationale for using pravastatin 40 mg was:

- it was the highest dose approved for this drug at the start of this trial
- it was proven clinically beneficial for the secondary prevention of CAD
- it was approved in the United States for slowing progression of atherosclerosis.

Atorvastatin was chosen because it was the most potent lipid-lowering agent available, and was effective in reducing LDL-C levels to below existing guidelines. Of the 654 patients enrolled, 502 completed the trial, 249 on pravastatin and 253 on atorvastatin. The main reason for withdrawal was a reluctance to undergo a repeat cardiac catheterization during the follow-up period.

Study endpoints

The primary pre-specified endpoint of the study was percent change in IVUS-determined atheroma volume. Secondary endpoints included absolute change in total coronary atheroma volume, change in percent obstructive volume, and change in CRP levels on treatment. IVUS was performed during baseline

Table 1: Baseline characteristics of patients in REVERSAL

Characteristic	Pravastatin (n=249)	Atorvastatin (n=253)	*p* value
Age (years)	56.6	55.8	0.37
Male	73%	71%	0.69
Caucasian	87%	90%	0.54
Current smoker	27%	26%	0.97
Previous smoker	74%	74%	0.97
History of hypertension	70%	68%	0.70
History of diabetes	18%	20%	0.65
Prior statin use	32%	25%	0.06
Total cholesterol (mmol/L)	6.02±0.88	6.00±0.89	0.80
LDL-cholesterol (mmol/L)	3.89±0.67	3.89±0.72	0.99
HDL-cholesterol (mmol/L)	1.11±0.30	1.10±0.26	0.51
Triglycerides (mmol/L)	5.12±2.74	5.11±2.48	0.96
C-reactive protein	3.0±2.9	2.8±3.0	0.46

cardiac catheterization and at study completion. A core laboratory at The Cleveland Clinic, blinded to treatment assignment, performed all IVUS measurements.

IVUS is a modality used for imaging atherosclerotic plaque, performed via a 1 mm high frequency (30 MHz) ultrasound catheter positioned within the lumen of a vessel.[16] The catheter rotates at 1800 revolutions per minute, allowing real-time imaging of plaques within the wall of the coronary artery. The cross-sectional area of atherosclerotic plaque is then measured in a single slice by planimetry. A motor-drive device performs a standardized pullback of the ultrasound catheter at 0.5 mm per second and, at every mm along the vessel, another cross-sectional slice is obtained. The atheroma volume of the 'target' coronary artery between 2 fixed points is then calculated, based on the plaque area at each mm section of the coronary artery imaged (Simpson's rule). All patients underwent IVUS through a 30 mm or longer length of single 'target' coronary artery.

Results

The preliminary results of the REVERSAL study were recently presented. Baseline characteristics were well-matched between the 2 treatment groups (Table 1). The mean age was 56 years, 70% were male, and 20% were diabetic. Baseline LDL-C was 3.9 mmol/L in both treatment groups. Table 2 shows the lipid values at the end of the study period, along with the percent changes in the respective lipid values. After 18 months, patients receiving atorvastatin had significantly lower LDL-C levels compared to those on pravastatin (2.0±0.8 mmol/L vs 2.8±0.7 mmol/L respectively, p<0.0001). Treatment with atorvastatin resulted in a mean LDL-C (2.0 mmol/L) well below the

Table 2: Lipid values after 18 months of statin treatment in REVERSAL

Lipid value (mmol/L)	Pravastatin (n=249) Final value	Change (%)	Atorvastatin (n=253) Final value	Change (%)	p value
Total cholesterol	4.87±0.83	-18.4	3.91±1.01	-34.1	<0.0001
LDL-cholesterol	2.85±0.67	-25.2	2.05±0.78	-46.3	<0.0001
HDL-cholesterol	1.17±0.28	+5.6	1.11±0.28	+2.9	0.06
Triglycerides	4.30±2.38	-6.8	3.83±2.46	-20.0	0.0009

target level set by current guidelines. Atorvastatin treatment also resulted in significantly lower triglyceride levels compared to pravastatin treatment. There was a slight nonsignificant increase in high-density lipoprotein (HDL) cholesterol in the pravastatin-treated group compared to the atorvastatin-treated group.

Results of the primary study endpoint are shown in Figure 3. While percent change in atheroma volume was unchanged by atorvastatin (0.4% decrease), atheroma volume was seen to increase significantly (2.7% increase) in the pravastatin arm. Results of the secondary endpoints are summarized in Figures 4 and 5. Similar to the primary endpoint, there was no significant change in total atheroma volume and percent obstructive volume with atorvastatin treatment, while there was significant progression of both in patients on pravastatin (Figure 4A and 4B). Both treatment arms showed significant reductions in CRP levels, with significantly greater reductions noted in the atorvastatin arm compared to the pravastatin arm (Figure 5). These differences in the primary and secondary IVUS endpoints

Figure 3: REVERSAL primary endpoint — Percent change in atheroma volume

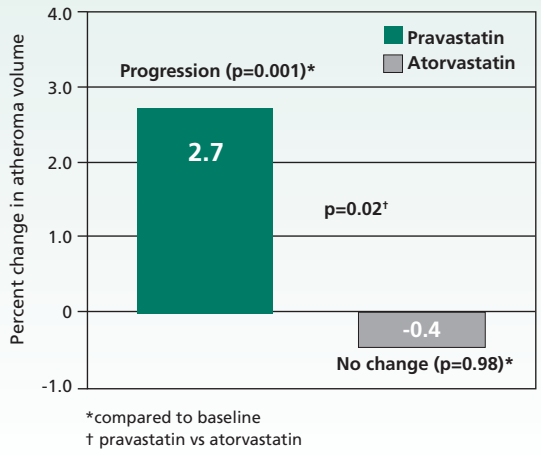
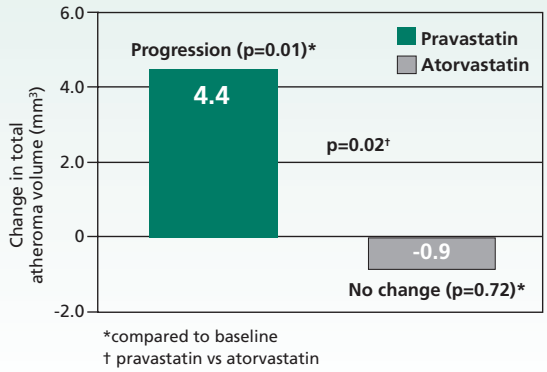


Figure 4A: REVERSAL secondary endpoint — IVUS parameters



between treatment groups were consistent across the 22 prespecified subgroups. The only exception was in patients without hypertension, where little progression was seen in either treatment arm.

Of note, the results were also consistent among patients with LDL cholesterol and CRP levels above and below mean values. In the pravastatin group, progression of atherosclerosis was still seen even when lower LDL-C levels were achieved. A post hoc analysis was performed on the subset of the 167 patients treated with pravastatin who reached target LDL-C of < 2.6 mmol/L (as per NCEP ATP III guidelines). The results are shown in Figure 6. In this subgroup of the pravastatin arm, there was significant atherosclerosis progression by IVUS, despite LDL-C mean values of 2.2 mmol/L. Regarding safety data of the high-dose statin therapy used in the study, there were no significant differences in adverse events between the 2 treatment groups, with no differences in AST, ALT, or CK levels between treat-

Figure 4B: REVERSAL secondary endpoint — IVUS parameters

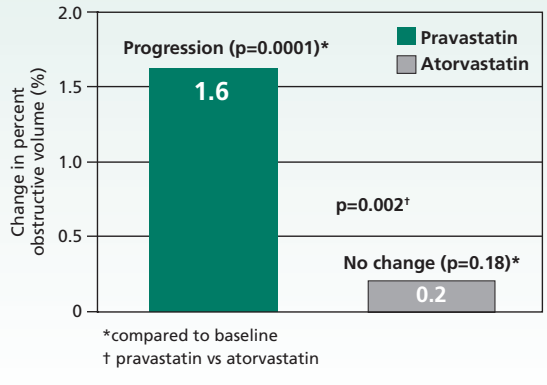
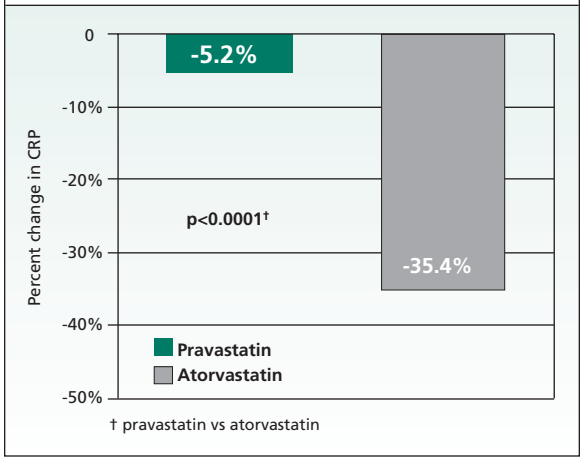


Figure 5: REVERSAL secondary endpoint — C-reactive protein (CRP)



ment groups (Table 3). No patients experienced clinical myositis/myopathy.

Discussion and clinical implications

The principle findings of the REVERSAL study are that a more aggressive lipid-lowering regimen using atorvastatin had greater beneficial effects on IVUS-determined coronary atheroma burden compared to a more modest lipid-lowering regimen with pravastatin. This was achieved without significant increases in adverse events, particularly myositis. The results are consistent with those of the ARBITER study[13] that used identical treatment arms, with similar beneficial effects on carotid atherosclerosis measured by CIMT. While REVERSAL was not powered to assess differences in clinical events, these results using a surrogate endpoint raise the possibility that reduction in LDL-C levels to <2.6 mmol/L may lead to additional cardiovascular benefits in patients with symptomatic CAD. While previous studies have

Figure 6: REVERSAL post hoc analysis — Subgroup of pravastatin treated patients achieving target LDL-C <2.6 mmol/L

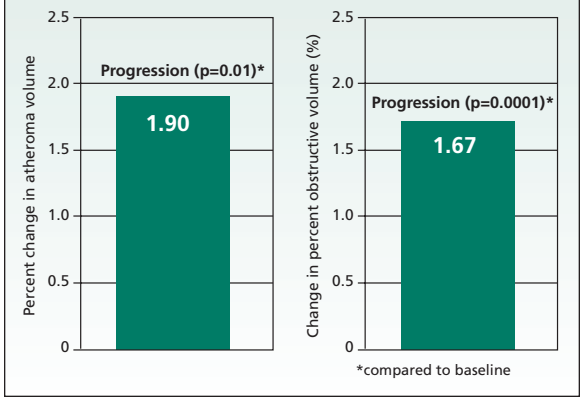


Table 3: Adverse events in REVERSAL

Adverse event	Pravastatin (n=327)	Atorvastatin (n=327)
Death	1 (0.3%)	1 (0.3%)
MI	7 (2.1%)	5 (1.5%)
Stroke	1 (0.3%)	1 (0.3%)
ALT>3×ULN	3/316(0.9%)	4/311(1.3%)
AST>3×ULN	1/316(0.3%)	1/311(0.3%)
CK>10×ULN	0/316(0.0%)	0/311(0.0%)

ULN = upper limit of normal

demonstrated a consistent relationship between atherosclerosis progression rates and major cardiovascular events, the impact of stopping atherosclerosis progression by aggressive lipid-lowering demonstrated in the REVERSAL study needs to be confirmed by similarly designed comparative statin trials with hard clinical endpoints.

Previous clinical trials have attempted to look at regression of coronary atherosclerosis by lipid-lowering using coronary angiography.[17] While the traditional, angiographic-based view of the atherosclerotic process held that plaque accumulation led to progressive luminal narrowing and stenosis development, contemporary views are that early during the atherosclerosis process – as plaque accumulates and the vessel enlarges, or remodels – there is little or no change in lumen area until the lesion occupies approximately 40% of the area within the vessel wall.[18] Because angiography can only assess the vessel lumen, previous angiographic studies of atherosclerosis regression likely lacked the sensitivity to assess these early extraluminal changes. These trials only demonstrated a reduced progression of coronary atherosclerosis with lipid-lowering, as opposed to the absence of progression seen in REVERSAL. While the less sensitive method used to assess coronary atherosclerosis may have been a contributing factor, the results of previous angiographic trials are likely related to less aggressive LDL-C reduction. The REVERSAL study demonstrated for the first time that, in patients with symptomatic CAD, the progression of coronary atherosclerosis can be inhibited by aggressive reduction in LDL-C with atorvastatin therapy.

In the subgroup of pravastatin-treated patients that achieved LDL-C reductions below the target of 2.6 mmol/L, progression of atherosclerosis was still noted. The potential implications are that the benefits on atherosclerosis seen in the atorvastatin-treated group were not due solely to the potent LDL-C lowering effects of atorvastatin. Similar to the results of the ARBITER study, patients on atorvastatin achieved much greater reductions in CRP levels compared to those on pravastatin. Higher levels of this inflammatory biomarker have been associated with a significantly increased risk of cardiovascular events, namely MI, stroke,

and sudden cardiac death, even in apparently healthy patients with low LDL-C levels.[19] Thus, differences in atherosclerosis progression between treatment groups in REVERSAL may potentially be explained by the greater anti-inflammatory effects of atorvastatin, one of the established pleiotropic effects of statin therapy. While these findings are intriguing, it would be premature to attribute them to beneficial non-lipid-lowering effects of atorvastatin and, at this point, are purely hypothesis generating.

Conclusions

While there is overwhelming evidence for the benefit of statin therapy in patients with established CAD, controversy still exists as to the optimal target LDL-C concentration. Based on data from recently completed placebo-controlled statin trials, benefit may exist even at lower LDL-C levels than recommended in current NCEP guidelines. The results of the REVERSAL study presented in this *Cardiology Scientific Update* add further objective evidence for the benefit of more aggressive LDL-C reduction in CAD patients, and highlight the potential role of newer, more potent, statin therapy. While the results of REVERSAL are highly provocative, the hypothesis that aggressive LDL-C reduction (beyond targets set by current guidelines) will yield additional benefit in patients with established CAD still needs to be proven in randomized clinical trials, with cardiovascular mortality and morbidity endpoints. In this regard, a number of comparative statin trials with clinical endpoints are currently underway. The Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE IT-TIMI 22) is comparing the same 2 statins used in the REVERSAL study in 4,000 patients with acute coronary syndromes. The results of PROVE IT should be available for presentation at the annual American College of Cardiology meeting in March, 2004. Similar comparative studies are also in progress. The IDEAL (The Incremental Decrease in Endpoints through Aggressive Lipid Lowering) trial is comparing atorvastatin 80 mg/day and simvastatin 20-40 mg/day in 8,888 patients with acute MI or a history of MI. The TNT (Treating to New Targets) study is comparing 2 doses of atorvastatin, (80 mg/day versus 10 mg/day) in 10,000 patients with clinically established CAD. Results of both are expected in 2005. Only through the results of these large comparative trials will there be a significant impact on existing recommendations for statin use in the secondary prevention of CVD. Thus, their results are eagerly awaited.

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