Extra-Low Cholesterol

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One of cardiology's most debated questions—"*Will pushing cholesterol levels even lower than currently recommended per the present guidelines decrease CVD events even more*?"—will be answered in this *Heartbeat*. Results we have been waiting to see for some time were just presented at the Late-breaking Trials Session at the American College of Cardiology (ACC) Scientific Sessions in New Orleans last month.

Most cardiologists anticipate that the latest results, yielding better outcomes in patients whose LDL-C is aggressively lowered to 62mg/dL, will change current practice as well as the current *National Cholesterol Education Program (NCEP)* guidelines released in May of 2001.[1] The present goal of <100 mg/dL was an approximation based on some very old data. We now have real outcomes data.

Proven: Ultra-low is better

The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial involved 4,162 patients hospitalized for acute coronary syndrome (ACS) within the preceding 10 days.[2] The patients were treated with either 40 mg of pravastatin [Pravachol] daily (standard therapy) or 80 mg of atorvastatin [Lipitor] daily (intensive therapy) before they were discharged, and were followed for an average of 24 months.

In the standard-dose pravastatin group, the median LDL-C level achieved during treatment was 95 mg/dL (meeting present goals) versus 62 mg/dL in the high-dose atorvastatin group (*P*<001).

The study was designed to be a non-inferiority trial of pravastatin, testing the hypothesis that greater lowering of LDL is *not* better. To the surprise of many, the trial did not achieve its primary hypothesis of showing non-inferiority, but rather showed superiority of 80 mg of atorvastatin compared to provastatin. The study's primary end point was a composite of death from any cause, myocardial infarction, documented unstable angina requiring re-hospitalization, re-vascularization (performed at least 30 days after randomization), and stroke—and showed a 16% reduction in atorvastatin patients from 26% to 22%. Interestingly the event curves for the atorvastatin group seemed to separate quite early within the first months of therapy, and appeared to be continuing to separate over time (Figure 1.).

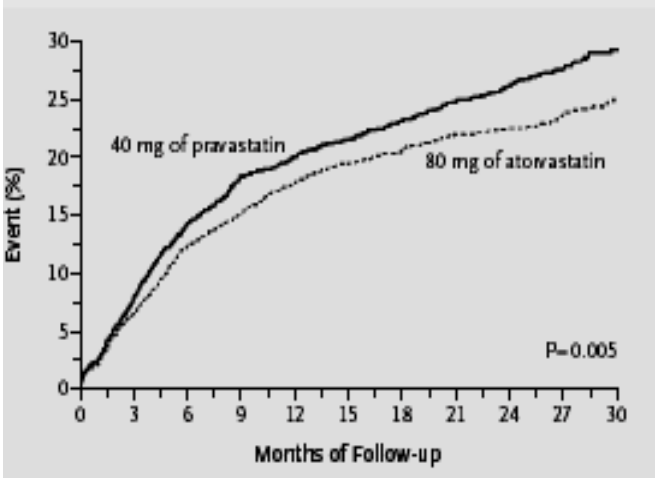

Figure 1. Kaplan-Meier Estimates of Incidence of Primary Endpoint of Death from Any Cause or Major Cardiovascular Event. Atorvastatin reduced the hazard ratio for the event rate by 16% compared to Pravastatin. (Source: *N Engl J Med*)

The death rate among Lipitor patients was 28% lower than among those taking Pravachol, and the death rate from CVD was 30% lower. Dr. Cannon and colleagues conclude that while the study did not meet the pre-specified criterion for equivalence, it did identify the superiority of the more intensive atorvastatin regimen.

"Given the substantially lower LDL cholesterol levels achieved in the group given 80 mg of atorvastatin daily (median, 62 mg/dL), our results suggest that *after an acute coronary syndrome, the target LDL cholesterol level should be lower than that recommended in the current guidelines*".

The study's results, cardiologists say, will greatly change how doctors treat patients with heart disease and will provide impetus to re-evaluate how low cholesterol levels should be, even for people without heart disease.

REVERSAL

The *PROVE-IT* results followed the recently published *REVERSAL* (Reversal of Atherosclerosis with Aggressive Lipid-lowering) study, another comparative statin trial, using the same two statins, at the same dosages.[3] Intravascular ultrasound was used at baseline and after 18 months in 502 patients to measure progression of atherosclerosis. This trial attracted considerable attention because it showed that intensive lipid-lowering with atorvastatin 80mg halted the progression of coronary atheroma, whereas pravastatin 40mg was associated with continued coronary atherosclerosis progression.

Both trials demonstrated the superiority of atorvastatin in lowering LDL-C, but they reported a lack of correlation between LDL-C and inflammatory markers (High sensitivity C-reactive protein [*hs*-CRP]) reduction (Table 2).

Table 2. Key findings in Two New Statin Trials.

Variable	REVERSAL	PROVE-IT
Clinical indication for therapy	Stable coronary disease	Acute coronary syndromes
Length of follow-up (mo)	18	24
LDL cholesterol†	150	106‡
Base-line (mg/dl)		
Atorvastatin group (mg/dl)	79	62
Percent decrease	46	42
Pravastatin group (mg/dl)	110	95
Percent decrease	26	10
High-sensitivity CRP		
Base-line (mg/liter)	2.9	12.3
Atorvastatin group (mg/liter)	1.8	1.3
Percent decrease	36	89
Pravastatin group (mg/liter)	2.9	2.1
Percent decrease	5	83

In *REVERSAL* there was a marked reduction in *hs*-CRP—36% with atorvastatin compared to only 5% with pravastatin. In *PROVE-IT*, there was relatively little difference in CRP lowering between the two statin regimens. Clearly, more investigation is necessary to disentangle the independent and interdependent effects of statins on LDL-C and *hs*-CRP. One thing that is for sure is that extra-low cholesterol and LDL-C is good.

ALLIANCE

The results of yet another trial, the Aggressive Lipid Lowering to Alleviate New Cardiovascular Events (ALLIANCE), also presented at the ACC 2004 Scientific Sessions last month, have shown that aggressive lipid-lowering with atorvastatin is superior to usual care in reducing CV events.[4] This study seems to highlight ***a message that seems to be emerging from the ACC convention—"Lower is better".***

The *ALLIANCE* investigators randomized 2,442 CHD patients to aggressive lipid lowering with atorvastatin titrated to a maximum dose of 80mg or to an LDL level of < 80mg.dL vs. usual care—defined as lipid treatment that included cholesterol lowering medications including statins, as well as diet and exercise. LDL-C levels of < 100mg/dL were obtained in 72% of atorvastatin patients and 42% of usual care patients. Treatment with atorvastatin resulted in a 17% reduction in CV complications.

Missed Opportunity

Based on a retrospective analysis of data from patients with ACS, statins are routinely under-dosed in clinical practice—despite the fact that these patients were entered into a clinical study and being followed carefully. Almost a decade after the advent of statins, and after years of emphasizing the importance of statins, many patients remain untreated or under-treated. ***An important opportunity to improve outcomes with aggressive statin therapy is being missed.***

In this study, also presented at the ACC Scientific Sessions last month, the authors analyzed data from 2,220 patients in the TACTICS-TIMI 18 trial.[5] At study entry only 35% were on statins and increased to 51% by 6 months. Only 47% of patients on statins were at goal—LDL-C levels of 100mg/dL or less. It seems as if patients are started at a low dose with the intent of titrating upward to the doses proven beneficial in the studies, but it never happens. Only 17% of patients receiving simvastatin and 36% of patients receiving pravastatin were treated with the 40mg doses shown in clinical trials to be effective in reducing CV events. Thirty-five percent of patients

on statins were on atorvastatin, but only 1% of those were receiving the aggressive 80mg dose.

EASE –Y to Turbo-Charge Statins

Results of a recent study designed to assess the effectiveness of ezetimibe (Zetia) used concomitantly with statin therapy have shown the combination more effective than statin therapy alone even at increased dosages. The study, known as the Ezetimibe Add-on to Statin for Effectiveness (EASE) trial and presented during the late-breaking clinical trials session at the ACC Scientific Sessions, showed that ezetimibe "turbo-charges" statin therapy and provides greater reductions of cholesterol compared to statin therapy alone.[6]

The addition of ezetimibe further reduced LDL-C by 25% compared to the statin alone. This compares favorably with the usual 6-8% reduction seen when the statin is doubled. More patients on the combo reached goal LDL-Cs than those treated with a statin only. There were also improvements in triglycerides and HDL-C favoring the ezetimibe-statin combination. The LDL-C reduction was consistent across the different statin brands and doses with no significant difference in side effects.

Comments:

The Heart Protection Study (HPS) in 2002, the largest statin trial ever, further confirmed the benefits of statins, and raised other questions.[7] This trial showed a one third reduction of MIs and strokes using simvastatin 40mg in a high-risk population—compared to placebo, and these same benefits were sustained even in patients with a baseline serum LDL-C below 100 mg/dL, the present NCEP III Guideline target. This surprising finding raised questions about whether more benefits could be obtained by lowering the LDL-C goal and how low to go. Obviously it means we treat everyone with known disease or high-risk (> 20%/10yr) with a minimum of simvastatin 40mg regardless of their LDL-C level, but to what goal? And how should we treat moderate-risk patients?

Together, the results of all these studies—especially *HPS*, *REVERSAL* and *PROVE-IT*—herald a new paradigm in cholesterol management. Previously, optimal LDL-C was $\leq$ 100mg/dL. We now know that much more aggressive statin therapy, resulting in extra-low cholesterol levels, slows coronary atheroslerosis and improves clinical outcomes. Indeed, the 80mg dose of atorvastatin is the most intensive LDL-C lowering regimen for which data on clinical outcomes are available. The implications of this paradigm shift—*a new era of intensive statin therapy*—are profound. The potential magnitude of benefit from intensive statin therapy compared to usual care would be the same as that seen when statins were first introduced compared to placebo ten years ago..

Unfortunately, one of the primary reasons for under treatment, cost, will also be magnified. The statin drugs already account for the largest prescription drug expenditure in the US at over $12 billion per year. Treatment based on the new data can only escalate costs even further. A year's supply of the weaker drug tested, Pravachol (Bristol-Myers) or the weaker brand of Lipitor 10mg (Pfizer) can cost around $900. A year's supply of the more potent dose of Lipitor used in the studies can cost around $1400. That will make it very expensive for uninsured individuals, and also costly for insurance companies that cover prescription drugs. It will be very important for health plans to negotiate for discounts. A huge demand could increase pressure on the government to rein in drug prices which has long been needed.

Both REVERSAL and PROVE-IT underline the great benefit in comparing the performance of two different prescription drugs. Traditionally, drugs are only tested against placebos. From now on, the value of head to head comparisons should be obvious to everyone.

New Conclusions on Cholesterol

- Patients with ACS should leave the hospital on a high dose statin. Everyone needs to shift up one level in their intensity of cholesterol treatment.

- Aggressive LDL-C lowering compared to lower dose statins or usual care results in slowing of atherosclerosis and improved clinical outcomes without additional safety concerns.

- The vast majority of patients with hypercholesterolemia do not reach NCEP III target levels. Better compliance in obtaining LDL-C goals can be accomplished by starting statins, in the appropriate patients, at a dosage that was proven effective in outcomes studies

and/or will get them to goal—usually no need to titrate. Another way to improve statin dosing is to order labs before the patient's next visit so the results are immediately available during your face-to-face visit and appropriate adjustments can be made at that time to get them to goal. More aggressive lipid lowering with statins and combination therapy with other lipid-lowering agents is warranted.

- The 25% reduction of LDL-C achieved by adding ezetimibe (Merck) to a statin—*EASE*—has implications in clinical practice, especially in light of the anticipated changes with regard to more aggressive LDL-C lowering and the difficulties in getting people to the present goals with statins alone.

- The implication for prevention in people, who have not had a vascular event, is less clear. Although statins may be the next aspirin, further study and evaluation are necessary before everyone starts taking a statin on a daily basis.

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