

Re: Statins again.

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- *From:* berniebagelbear@xxxxxxxx
 - *Date:* 20 May 2007 19:46:36 -0700
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On May 6, 1:22 pm, David Rind <d...@xxxxxxxxxxxxxxxxxxxxxxxx> wrote:

Jason wrote:

In article <f1179j\$dq...@xxxxxxxxxxxxxxxxxxxxxxxx>, David Rind <d...@xxxxxxxxxxxxxxxxxxxxxxxx> wrote:

tonyzs...@xxxxxxxx wrote:

Thank you David for taking the trouble to post details of this meta analysis. I am sorry not to have acknowledged this sooner. One slight difficulty: I have tried to unerth the actual number of deaths and cardiac events, so that a comparison can be made with relative reductions and absolute ones. As I cannot gain access to these data on the internet is it possible for you to provide me with this information?

You generally can't look at absolute rates in a meta-analysis, because the baseline rates vary so much across different populations. Typically a meta-analysis tests for, and then assumes, that the relative reductions are stable across the different studies but that the absolute rates differ.

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If you are trying to figure out how much benefit a statin might have in a given individual, calculate the 10-year-risk of an event (cardiac event or death) using a risk score such as the Framingham score, and then use the relative risk reductions posted earlier to calculate an absolute risk reduction. The absolute reductions even in secondary prevention are typically small (5 to 10 percent) but in a range that most people would find clinically important if it were them.

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David,

One of the problems is that many doctors do not seem to realize that high dose statins (eg 80 mg Lipitor) are more likely to cause serious side effects (eg major muscle pain, memory problems) than low dose statins (eg 5 mg Lipitor). It may take longer for a patient's chol. levels to come down to normal but in the long run—it would be much less likely that patients would develop serious side effects. I was shocked when one of my neighbors was started off on a 80 mg dose of Lipitor. His chol. levels were only slightly above the reference range. I doubt that his doctor realized that he could have caused my neighbor to develop serious side effects. Do you agree or disagree?

jason

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I don't know what your neighbor was being treated for, so it's hard to have a firm opinion.

If we're talking about someone with known stable CHD, the TNT and IDEAL trials suggest that using atorvastatin 80 mg will, in fact, decrease cardiac events by a small additional amount compared with lower intensity statin therapy. Whether that small benefit is worth a higher cost and probably higher rate of side effects with more intensive therapy depends on the patient's preferences.

If we're talking about someone without known CHD, whose only indication for a statin is lipid lowering, I would not normally favor treatment with high dose atorvastatin.

I don't agree with the implication that the difference between higher intensity and lower intensity statin therapy is how quickly lipids will

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return to normal. Statins aren't known to have some cumulative effect that will continue to reduce lipid levels further and further over time.

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David Rind

d...@xxxxxxxxxxxxxxxxxxxxxxxx

Results of recent statin studies as compiled by Dr. Mary Enig, PhD*:

"Most doctors are convinced—and seek to convince their patients—that the benefits of statin drugs far outweigh the side effects. They can cite a number of studies in which statin use has lowered the number of coronary deaths compared to controls. But as Dr. Ravnskov has pointed out in his book *The Cholesterol Myths*,³¹ the results of the major studies up to the year 2000—the 4S, WOSCOPS, CARE, AFCAPS and LIPID studies—generally showed only small differences and these differences were often statistically insignificant and independent of the amount of cholesterol lowering achieved. In two studies, EXCEL, and FACAPT/TexCAPS, more deaths occurred in the treatment group compared to controls. Dr. Ravnskov's 1992 meta-analysis of 26 controlled cholesterol-lowering trials found an equal number of cardiovascular deaths in the treatment and control groups and a greater number of total deaths in the treatment groups.³² An analysis of all the big controlled trials reported before 2000 found that long-term use of statins for primary prevention of heart disease produced a 1 percent greater risk of death over 10 years compared to a placebo.³³

Recently published studies do not provide any more justification for the current campaign to put as many people as possible on statin drugs.

Honolulu Hearth Program (2001)

This report, part of an ongoing study, looked at cholesterol lowering in the elderly. Researchers compared changes in cholesterol concentrations over 20 years with all-cause mortality.³⁴ To quote: "Our data accords with previous findings of increased mortality in elderly people with low serum cholesterol, and show that long-term persistence of low cholesterol concentration actually increases risk of death. Thus, the earlier that patients start to have lower cholesterol concentrations, the greater the risk of death. . . The most striking findings were related to changes in cholesterol between examination three (1971–74) and examination four (1991–93). There are few studies that have cholesterol concentrations from the same patients at both middle age and old age. Although our results lend support to previous findings that low serum cholesterol imparts a poor outlook when compared with higher concentrations of cholesterol in elderly people, our data also suggest that those individuals with a low serum cholesterol maintained over a 20-year period will have the worst outlook for all-cause mortality [emphasis ours]."

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MIRACL (2001)

The MIRACL study looked at the effects of a high dose of Lipitor on 3086 patients in the hospital after angina or nonfatal MI and followed them for 16 weeks.³⁵ According to the abstract: "For patients with acute coronary syndrome, lipid-lowering therapy with atorvastatin, 80 mg/day, reduced recurrent ischemic events in the first 16 weeks, mostly recurrent symptomatic ischemia requiring rehospitalization." What the abstract did not mention was that there was no change in death rate compared to controls and no significant change in re-infarction rate or need for resuscitation from cardiac arrest. The only change was a significant drop in chest pain requiring rehospitalization.

ALLHAT (2002)

ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), the largest North American cholesterol-lowering trial ever and the largest trial in the world using Lipitor, showed mortality of the treatment group and controls after 3 or 6 years was identical.³⁶ Researchers used data from more than 10,000 participants and followed them over a period of four years, comparing the use of a statin drug to "usual care," namely maintaining proper body weight, no smoking, regular exercise, etc., in treating subjects with moderately high levels of LDL cholesterol. Of the 5170 subjects in the group that received statin drugs, 28 percent lowered their LDL cholesterol significantly. And of the 5185 usual-care subjects, about 11 percent had a similar drop in LDL. But both groups showed the same rates of death, heart attack and heart disease.

Heart Protection Study (2002)

Carried out at Oxford University,³⁷ this study received widespread press coverage; researchers claimed "massive benefits" from cholesterol-lowering,³⁸ leading one commentator to predict that statin drugs were "the new aspirin."³⁹ But as Dr. Ravnskov points out,⁴⁰ the benefits were far from massive. Those who took simvastatin had an 87.1 percent survival rate after five years compared to an 85.4 percent survival rate for the controls and these results were independent of the amount of cholesterol lowering. The authors of the Heart Protection Study never published cumulative mortality data, even though they received many requests to do so and even though they received funding and carried out a study to look at cumulative data. According to the authors, providing year-by-year mortality data would be an "inappropriate" way of publishing their study results.⁴¹

PROSPER (2002)

PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) studied the effect of pravastatin compared to placebo in two older

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populations of patients of which 56 percent were primary prevention cases (no past or symptomatic cardiovascular disease) and 44 percent were secondary prevention cases (past or symptomatic cardiovascular disease).⁴² Pravastatin did not reduce total myocardial infarction or total stroke in the primary prevention population but did so in the secondary. However, measures of overall health impact in the combined populations, total mortality and total serious adverse events were unchanged by pravastatin as compared to the placebo and those in the treatment group had increased cancer. In other words: not one life saved.

J-LIT (2002)

Japanese Lipid Intervention Trial was a 6-year study of 47,294 patients treated with the same dose of simvastatin.⁴³ Patients were grouped by the amount of cholesterol lowering. Some patient had no reduction in LDL levels, some had a moderate fall in LDL and some had very large LDL reductions. The results: no correlation between the amount of LDL lowering and death rate at five years. Those with LDL cholesterol lower than 80 had a death rate of just over 3.5 at five years; those whose LDL was over 200 had a death rate of just over 3.5 at five years.

Meta-Analysis (2003)

In a meta-analysis of 44 trials involving almost 10,000 patients, the death rate was identical at 1 percent of patients in each of the three groups—those taking atorvastatin (Lipitor), those taking other statins and those taking nothing.⁴⁴ Furthermore, 65 percent of those on treatment versus 45 percent of the controls experienced an adverse event. Researchers claimed that the incidence of adverse effects was the same in all three groups, but 3 percent of the atorvastatin-treated patients and 4 percent of those receiving other statins withdrew due to treatment-associated adverse events, compared with 1 percent of patients on the placebo.

Statins and Plaque (2003)

A study published in the American Journal of Cardiology casts serious doubts on the commonly held belief that lowering your LDL-cholesterol, the so-called bad cholesterol, is the most effective way to reduced arterial plaque.⁴⁵ Researchers at Beth Israel Medical Center in New York City examined the coronary plaque buildup in 182 subjects who took statin drugs to lower cholesterol levels. One group of subjects used the drug aggressively (more than 80 mg per day) while the balance of the subjects took less than 80 mg per day. Using electron beam tomography, the researchers measured plaque in all of the subjects before and after a study period of more than one year. The subjects were generally successful in lowering their cholesterol, but in the end there was no statistical difference in the two groups in the progression of arterial calcified plaque. On average, subjects

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in both groups showed a 9.2 percent increase in plaque buildup.

Statins and Women (2003)

No study has shown a significant reduction in mortality in women treated with statins. The University of British Columbia Therapeutics Initiative came to the same conclusion, with the finding that statins offer no benefit to women for prevention of heart disease.⁴⁶ Yet in February of 2004, *Circulation* published an article in which more than 20 organizations endorsed cardiovascular disease prevention guidelines for women with several mentions of "preferably a statin."⁴⁷

ASCOT-LLA (2003)

ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm) was designed to assess the benefits of atorvastatin (Lipitor) versus a placebo in patients who had high blood pressure with average or lower-than-average cholesterol concentrations and at least three other cardiovascular risk factors.⁴⁸ The trial was originally planned for five years but was stopped after a median follow-up of 3.3 years because of a significant reduction in cardiac events. Lipitor did reduce total myocardial infarction and total stroke; however, total mortality was not significantly reduced. In fact, women were worse off with treatment. The trial report stated that total serious adverse events "did not differ between patients assigned atorvastatin or placebo," but did not supply the actual numbers of serious events.

Cholesterol Levels in Dialysis Patients (2004)

In a study of dialysis patients, those with higher cholesterol levels had lower mortality than those with low cholesterol.⁴⁹ Yet the authors claimed that the "inverse association of total cholesterol level with mortality in dialysis patients is likely due to the cholesterol-lowering effect of systemic inflammation and malnutrition, not to a protective effect of high cholesterol concentrations." Keeping an eye on further funding opportunities, the authors concluded: "These findings support treatment of hypercholesterolemia in this population."

PROVE-IT (2004)

PROVE-IT (PRavastatin Or AtorVastatin Evaluation and Infection Study),⁵⁰ led by researchers at Harvard University Medical School, attracted immense media attention. "Study of Two Cholesterol Drugs Finds One Halts Heart Disease," was the headline in the *New York Times*.⁵¹ In an editorial entitled "Extra-Low Cholesterol," the paper predicted that "The findings could certainly presage a significant change in the way heart disease patients are treated. It should also start a careful evaluation of whether normally healthy people could benefit from a sharp drug-induced reduction in their cholesterol levels."⁵²

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The Washington Post was even more effusive, with a headline "Striking Benefits Found in Ultra-Low Cholesterol."⁵³ "Heart patients who achieved ultra-low cholesterol levels in one study were 16 percent less likely to get sicker or to die than those who hit what are usually considered optimal levels. The findings should prompt doctors to give much higher doses of drugs known as statins to hundreds of thousands of patients who already have severe heart problems, experts said. In addition, it will probably encourage physicians to start giving the medications to millions of healthy people who are not yet on them, and to boost dosages for some of those already taking them to lower their cholesterol even more, they said."

The study compared two statin drugs, Lipitor and Pravachol. Although Bristol Myers-Squibb (BMS), makers of Pravachol, sponsored the study, Lipitor (made by Pfizer) outperformed its rival Pravachol in lowering LDL. The "striking benefit" was a 22 percent rate of death or further adverse coronary events in the Lipitor patients compared to 26 percent in the Pravachol patients.

PROVE-IT investigators took 4162 patient who had been in the hospital following an MI or unstable angina. Half got Pravachol and half got Lipitor. Those taking Lipitor had the greatest reduction of LDL—cholesterol—LDL in the Pravachol group was 95, in the Lipitor group it was 62—a 32 percent greater reduction in LDL levels and a 16 percent reduction in all-cause mortality. But that 16 percent was a reduction in relative risk. As pointed out by Red Flags Daily columnist Dr. Malcolm Kendrick, the absolute reduction in the rate of the death rate of those taking Lipitor rather than Pravachol, was one percent, a decrease from 3.2 percent to 2.2 percent over 2 years.⁵⁴ Or, to put it another way, a 0.5 percent absolute risk reduction per year—these were the figures that launched the massive campaign for cholesterol-lowering in people with no risk factors for heart disease, not even high cholesterol.

And the study was seriously flawed with what Kendrick calls "the two-variables conundrum." "It is true that those with the greatest LDL lowering were protected against death. However, . . . those who were protected not only had a greater degree of LDL lowering, they were also on a different drug! which is rather important, yet seems to have been swept aside on a wave of hype. If you really want to prove that the more you lower the LDL level, the greater the protection, then you must use the same drug. This achieves the absolutely critical requirement of any scientific experiment, which is to remove all possible uncontrolled variables. . . As this study presently stands, because they used different drugs, anyone can make the case that the benefits seen in the patients on atorvastatin [Lipitor] had nothing to do with greater LDL lowering; they were purely due to the direct drug effects of atorvastatin." Kendrick notes that the carefully constructed J-LIT study, published 2 years earlier, found no correlation whatsoever between the amount of LDL lowering and

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death rate. This study had ten times as many patients, lasted almost three times as long and used the same drug at the same dose in all patients. Not surprisingly, J-LIT attracted virtually no media attention.

PROVE-IT did not look at side effects but Dr. Andrew G. Bodnar, senior vice president for strategy and medical and external affairs at Bristol Meyer Squibb, makers of the losing statin, indicated that liver enzymes were elevated in 3.3 percent of the Lipitor group but only in 1.1 percent of the Pravachol group, noting that when liver enzyme levels rise, patients must be advised to stop taking the drug or reduce the dose.⁵⁵ And withdrawal rates were very high: thirty-three percent of patients discontinued Pravachol and 30 percent discontinued Lipitor after two years due to adverse events or other reasons.⁵⁶

REVERSAL (2004)

In a similar study, carried out at the Cleveland Clinic, patients were given either Lipitor or Pravachol. Those receiving Lipitor achieved much lower LDL-cholesterol levels and a reversal in "the progression of coronary plaque aggregation."⁵⁷ Those who took Lipitor had plaque reduced by 0.4 percent over 18 months, based on intravascular ultrasound (not the more accurate tool of electron beam tomography); Dr. Eric Topol of the Cleveland Clinic claimed these decidedly unspectacular results "Herald a shake-up in the field of cardiovascular prevention. . . the implications of this turning point—that is, of the new era of intensive statin therapy—are profound. Even today, only a fraction of the patients who should be treated with a statin are actually receiving such therapy. . . More than 200 million people worldwide meet the criteria for treatment, but fewer than 25 million take statins."⁵⁸ Not surprisingly, an article in The Wall Street Journal noted "Lipitor Prescriptions Surge in Wake of Big Study."⁵⁹

But as Dr. Ravnskov points out, the investigators looked at change in atheroma volume, not the change in lumen area, "a more important parameter because it determines the amount of blood that can be delivered to the myocardium. Change of atheroma volume cannot be translated to clinical events because adaptive mechanisms try to maintain a normal lumen area during early atherogenesis."⁶⁰

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Dr. Enig has authored numerous journal publications, mainly on fats and oils research and nutrient/drug interactions, and is a well-known invited lecturer at scientific meetings and a popular interviewee on

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TV and radio shows about nutrition. She was an early and articulate critic of the use of trans fatty acids and advocated their inclusion in nutritional labeling; the scientific mainstream is now challenging the food product industry's use of trans-containing partially hydrogenated vegetable oils. She received her Ph.D. in Nutritional Sciences from the University of Maryland, College Park, and is a Fellow of The American College of Nutrition, a member of The American Society for Nutritional Sciences, and President of the Maryland Nutritionists Association