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November 13, 2008

P R E S S R E L E A S E **Recent Results on Statins**

A recent article in the *New England Journal of Medicine*¹ has been reported in the media widely as heralding a new use for statin drugs. However, the reporting has largely been shoddy boosterism for the pharmaceutical industry rather than a careful and balanced analysis of the results.² This is shameful and dangerous.

The study included 8901 individuals in each of the treatment (rosuvastatin, brand name Crestor) and the placebo arms, a total of 17,802 individuals. Men over age 50 and women over age 60 were enrolled who had an LDL level under 130 mg/dl. The treatment arm received 20 mg daily of rosuvastatin. The first glaring oversight that the media failed to recognize was that 89,890 people were screened for the study, of whom 72,088 were ineligible, due to their inclusion/exclusion criteria. The notion of *generalizability* of the study's findings is called into serious question.

Yet this important issue was ignored. And it is important as it suggests a very narrow proportion of the population may benefit.

Indeed, these individuals were not “healthy” as has been widely disseminated but had what is widely accepted as a pathologically high level of C-Reactive Protein (where less than 1 mg/L is low risk, 1-3 mg/L moderate and above 3 mg/L high risk). The “baseline” level (the amount in the blood seen at the beginning of the study) among all the participants was 4.2 mg/L in the drug arm and 4.3 mg/L in the placebo arm.

Study Results: They're Relative...

The results of the statin study have been spread widely across the media and represent the most dangerous and disingenuous misinformation campaign. This is the very example of the pharmaceutical industry using science as a marketing tool decried by the media³ and yet, when an egregious example presents itself, the media act like an Advertising Agent and spread the “news” far and wide!

What do the data show? According to gushing media reports, we hear that **50% are less likely to have a stroke and 20% are less likely to die!** (Belluck, *op. cit.*) How impressive! Shouldn't everyone rush to their physician and demand a test and some Crestor? Some more nuanced, if superficial, discussion occurs later in the articles, but only after the misleading headlines and the first few gushing paragraphs.

But if one reads the original paper, one sees this “benefit” is a *relative risk*.⁴ But what is the *absolute*

¹ Ridker, PM, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. *NEJM*, 9 Nov 2008(): <http://content.nejm.org/cgi/content/full/NEJMoa0807646>

² E.g., Belluck P. Cholesterol-Fighting Drugs Show Wider Benefit, *NY Times*, 9 Nov 2008. <http://www.nytimes.com/2008/11/10/health/10heart.html?em>

³ See, e.g., Warner J. Diagnosis Greed. *New York Times*, 9 Oct 2008; <http://warner.blogs.nytimes.com/2008/10/09/diagnosis-greed/?scp=40&sq=pharmaceutical%20fraud&st=cse> (accessed November 11, 2008).

⁴ For a good discussion, see <http://www.cmaj.ca/cgi/content/full/171/4/353>.

risk? Even the study authors cannot hide from their own data. Out of the 8,901 patients in each arm, 251 individuals developed a “primary endpoint” (including, but not limited to, nonfatal or fatal myocardial infarction, stroke, unstable angina, etc.) That is about 2.8% of the placebo recipients. In the treatment arm? 142 primary events or about 1.6%. What does this mean? In terms of an absolute benefit, only 1.2% of those receiving therapy will receive the reduced risk of a “primary event” as defined in the study. That IF only at-risk individuals, as determined by a lucrative CRP test, are provided a drug, **fully 97% will achieve no benefit whatsoever.**

Yet based on a study stopped early, individuals may face life long treatment with a costly, toxic drug from which they are more than likely not to achieve any benefit. And that’s from a very select population. If rampant testing and prescribing are the outcome of the media blitz, an even higher number of individuals, possibly millions, will probably be placed on a toxic, costly drug for no good reason except to boost Astra Zeneca’s profits.

As they note in <http://www.physorg.com/news145450584.html>

Looked at another way, there were 136 heart-related problems per year for every 10,000 people taking dummy pills versus 77 for those on Crestor.

Again, by this analysis, of 10,000 people fitting the narrow criteria used in the study who took the drug, 9,923 would not be expected to experience a primary event. Of 10,000 people taking a placebo, 9,864 people would not expect a difference. Thus, well over 9,800 people would be taking an (artificially) expensive drug for no benefit, and a higher risk of developing diabetes or other side effects. This, again, is absolute risk vs. relative risk.

Put yet another way, the *proportion of participants with hard cardiac events in JUPITER was reduced from 1.8% (157 of 8901 subjects) in the placebo group to 0.9% (83 of the 8901 subjects) in the rosuvastatin group; thus, 120 participants were treated for 1.9 years to prevent one event.*⁵ Here, Hlatky is referring to one of the outcomes nested in the “primary outcome.” This means that 8,901 participants were given placebo, 8,884 had no risk. Meanwhile, out of 8,901 given the drug, 8,781 had no benefit.

Others have noted that the U.S. costs to prevent just ONE event would be about \$300,000: just for the drug. How does that figure if it is only \$1200 a year? Based on the absolute benefit of 1 event for 120 patients treated (again 119 people receiving a drug for no benefit) over 1.9 years at \$1,259/year, the math is straightforward. $\$1259 \times 120 \times 1.9 = \$287,052.$ ⁶ This, of course, does NOT include costs of the testing, other lab tests, doctor visits, treatment for the side effects, etc.

Data Analysis

This is presuming the data analysis can be fully trusted. It is difficult to evaluate the methods they used as, for example, in Table 2, the follow-up period, does not indicate how many patients were in each arm at the specified time. For example, was there the same number of individuals represented at 12 months in each of the drug and placebo arms as there was at 48 months? The paper is vague on this point. Indeed, the statistical shenanigans appear chock-a-block in the paper, starting with a “primary endpoint” that is nothing of the sort but rather a collection of possible outcomes.

Other anomalies and inadequacies in the paper were disturbing. The randomization procedure appears bizarre, utilizing a voice-response system. No evidence for appropriate blinding at any of the 1,315 sites in 26 countries was presented.

⁵ Hlatky MA. Expanding the Orbit of Primary Prevention — Moving beyond JUPITER. *NEJM*, 11 Nov 2008;359(21):2280-2282.

⁶ McDougall Wellness Center, see <http://www.drmcDougall.com/misc/2008other/news081110crestor.html>

A BBC article noted "Most nations have a finite pot and if you're going to treat everyone with a 10% risk, that's billions of pounds extra and somewhere along the line someone else is going to miss out."

That's for the cost of the drug. In Britain. Where they have price controls. In the United States, it is a free-for-all of rape (resulting in a significant percentage of home foreclosures due to unpayable, outrageous healthcare costs).

Rushing the Data

From the very name of the study, Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER), there is a concern that the intent is to justify selling more drug to more people. Funded by Astra Zeneca, only two of the fifteen listed authors did not declare some significant level of funding from the sponsor. This should raise an immediate red flag, as news reports,⁷ books⁸ and journal articles⁹ have repeatedly warned.

Another question the media failed to address was why did they stop the trial early? Were they afraid the benefit would wane after 2 years? Or that evidence of increased toxicity risks would manifest?

You stop a trial because you see evidence of risk or danger. The placebo group was at no particularly greater risk to justify stopping the trial. Their claim that the O'Brien-Fleming stopping boundaries determined by the Lan-DeMets approach served in some Bayesian way as the rationale to end the study is vague and lacks detail. As some have noted, "The Lan-DeMets, O'Brien-Fleming type boundary is popular because it is not too aggressive."¹⁰ In other words, it was deemed desirable to stop the study earlier using a non-aggressive basis for making the decision.

In his important but largely ignored editorial in the same edition of *NEJM*, Dr. Hlatky (*op. cit.*) notes that [m]eta-regression is not a reliable technique, however, and the early termination of JUPITER owing to the efficacy data probably exaggerated the results to some degree. However, these and other observations were largely overlooked, ignored and nearly scoffed at in a shocking and egregious interview conducted by Ray Suarez on *The News Hour*.¹¹ Virtually the entire interview was devoted to comments of Harlan Krumholtz,¹² simply indicated as a cardiologist from Yale, but clearly a booster for the data. Comments regarding the use of CRP testing, the numbers enrolled and relative risk reduction results were given no argument and Hlatky was reduced to a scholarly but brief and rather opaque set of responses.

While rates of adverse events were strikingly high and similar between arms, the full effect of long-term use remains unclear. The study authors sought to diminish clinical findings of a greater incidence of diabetes among drug recipients. Which is worse? And why did so many clinicians diagnose diabetes despite the study findings of no elevated glucose? Does this suggest some weakness in data collection?

⁷ Warner J. Diagnosis: Greed. *New York Times*, 9 Oct 2008. <http://warner.blogs.nytimes.com/2008/10/09/diagnosis-greed/?scp=40&sq=pharmaceutical%20fraud&st=cse>

⁸ Among others, Angell, MD. *The Truth About the Drug Companies*. Former senior editor, *New England Journal of Medicine*, Random House, New York, NY: 2004.

⁹ Lee K, Bacchetti P, Sim I. Publication of Clinical Trials Supporting Successful New Drug Applications: A Literature Analysis. *PLoS Medicine*, Vol. 5, No. 9, e191 doi:10.1371/journal.pmed.0050191. <http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0050191>

¹⁰ Mehta CR. Efficacy, Safety and Futility: Stopping Boundaries, ExL Pharma Workshop, Philadelphia, PA, Feb 25-26, 2007.

¹¹ See http://www.pbs.org/newshour/bb/health/july-dec08/statins_11-10.html.

¹² It is interesting to note that Krumholtz warned in 1994 that old people with low cholesterol died twice as often from a heart attack as did old people with a high cholesterol. In this study, some patients dropped below a level of 55 mg/dl, which over time may result in increased rates of myopathy, hepatic injury or cancer...perhaps another reason they stopped the study early! http://www.newmediaexplorer.org/sepp/2003/10/17/cholesterol_what_a_business_plan.htm

Curiously, in the data, they note that 198 people died in the rosuvastatin arm (a number higher than the claimed 142 reaching a primary endpoint event). Why is the number greater than the number of individuals “achieving” a primary endpoint? No one in the media asked this question. It would appear that those charged in the media with covering this beat either failed to read the original article, did not understand its contents or were disinclined to evaluate it critically. Perhaps their parent companies receive too much pharmaceutical money for them to be too critical?

Conflicts of Interest

While a nod was given to the fact this study was sponsored by the drug’s manufacturer, Astra Zeneca, the media also ignored the egregious conflicts of interest of nearly all the study. Indeed, the fact that Dr. Ridker not only reported grant support from Astra, he also “is listed as a co-inventor on patents held by Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease, including the use of high-sensitivity C-reactive protein in the evaluation of patients’ risk of cardiovascular disease. These patents have been licensed to Dade Behring and AstraZeneca” (Ridker, *op. cit.*).

Indeed, Astra Zeneca hardly has a track record that inspires trust. In 2003, the company “pleaded guilty today to a felony charge of health care fraud and agreed to pay \$355 million to settle criminal and civil accusations that it engaged in a nationwide scheme to illegally market a prostate cancer drug.”¹³ The industry as a whole has distorted science frequently for the sake of profit—and this appears to be yet another case.

CRP Testing/Cost

The first premise to be addressed is the extent to which C-Reactive Protein should become a more standardized test. It may well be. But how much does it cost? While the focus remained on the *drug* and its cost (depending on where you live), NONE of the media discussed the cost of the test!

What about the cost of the high-sensitivity CRP test? Each test is approximately \$50 and may not be covered.¹⁴ Dr. Ridker and Astra will be the happy beneficiaries of proceeds of this as yet unproven, overpriced test. One can imagine the cost of the test also soaring in the near future.

In the meantime, as one review noted, *[u]ntil more data regarding CRP and statin use are available, pharmacists must continue to focus on risk factors other than CRP, such as cholesterol levels, medical history, social history, and lifestyle characteristics, when making clinical decisions regarding statin therapy.*¹⁵

Lowering CRP

The second premise to be challenged is whether statins as a class represent the best method for lowering CRP. Even the study authors suggest this, though nowhere was this raised in the media—except to suggest that generic statin drugs could be used.

Are there cheaper and safer alternatives to lowering CRP. Yes! A low-fat diet, for example, can cut CRP in half in 4 weeks.¹⁶

¹³ Peterson M. AstraZeneca Pleads Guilty In Cancer Medicine Scheme *Times* 21 Jun 2003. <http://query.nytimes.com/gst/fullpage.html?res=9C07E7D8163BF932A15755C0A9659C8B63&sc=17&sq=pharmaceutical%20fraud&st=cse> (accessed November 11, 2008).

¹⁴ See <http://www.bcbst.com/learn/treatment-options/crp.shtml>

¹⁵ Gortney JS, Sanders RM. Impact of C-reactive protein on treatment of patients with cardiovascular disease. *Am J Health Syst Pharm.* 2007 Oct 1;64(19):2009-2016.

¹⁶ Rankin JW, Turpyn AD. Low carbohydrate, high fat diet increases C-reactive protein during weight loss. *J Am Coll Nutr.* 2007 Apr;26(2):163-169.

How about just adding some fiber? See <http://www.medscape.com/viewarticle/553590>. They found an 18.1% reduction in CRP using supplemental fiber. While rosuvastatin appears to have done better with a 37% reduction, just using fiber can get one half way there. Also, it is unclear what degree of reduction might be clinically important, although a generally agreed upon level of greater than 1.0 mg/liter CRP is considered problematic.¹⁷

Vitamin C has also shown some benefit. One study reported that [p]articipants who took about 500 milligrams of vitamin C supplements per day saw a 24 percent drop in plasma C-reactive protein (CRP) levels after two months.¹⁸ Another study among healthy non-smokers saw a 25.3% reduction in CRP levels among those with a level greater than 1.0 mg/L at the beginning of the study.¹⁹

Perhaps our new president WILL get us healthcare--that COVERS "alternative" therapies. And these will be studied more vigorously, with an eye toward science based on helping individuals and physicians make the best treatment choices not based on how much a company will profit but rather a fair evaluation of risks and benefits.

The media have yet again failed to INFORM the public but instead have acted despicably as little more than a booster for a wholly untrustworthy, profit-driven industry. As a result, more people will suffer needlessly.

George M. Carter
Director

62 Sterling Pl., Suite 2, Brooklyn, NY 11217
tel: 718-622-0212 / web: <http://www.fiar.us>

¹⁷ Note that even the best that was seen after 48 months was a reduction from a baseline level of 4.8 mg/l to 1.8 mg/l at 48 months; the placebo group also plunged, inexplicably, from 4.3 mg/l to 3.3 mg/l. Remember further that it remains uncertain how many people were being treated at 48 months—the data were not provided—after the study was halted early.

¹⁸ http://www.prohealth.com/library/showarticle.cfm?id=5584&t=CFIDS_FM.

¹⁹ Block G, Jensen CD, Dalvi TB, et al. Vitamin C treatment reduces elevated C-reactive protein. *Free Radic Biol Med*. 2008 Oct 10 [epub ahead of print].