What are the right numbers for JUPITER?

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Results of clinical trials can sometimes not only change our understanding of the condition studied, but may also affect the way we practice medicine. The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) is such a study.

JUPITER was investigating the prevention of major cardiovascular events (myocardial infarction, stroke, hospitalization for unstable angina, arterial revascularization, death from cardiovascular causes) by treatment with rosuvastatin compared to placebo. Many clinical trials before have looked at the reduction of cardiovascular events by statin treatment in people with elevated cholesterol levels. But in the JUPITER trial, 17,802 apparently healthy men and women with normal levels of LDL cholesterol (< 130 mg/dl) were included based on age (> 50 years for men, > 60 years for women) and elevated levels of high-sensitivity C-reactive protein ($> 2{,}0$ mg/l), a marker for inflammation. The trial was stopped early in March of this year (after a median follow-up of 1.9 years instead of the planned 4 years) because treatment with rosuvastatin significantly reduced the number of cardiovascular events: 0.77 per 100 person-years compared to 1.36 per 100 person-years for placebo. In other words, treating 120 people for 1.9 years with rosuvastatin (at a cost of about $287.000) would prevent one cardiovascular event.

The JUPITER trial is important not only because it shows that a statin can have a beneficial effect in people with normal LDL cholesterol. Which complicates our understanding on how statins work. More importantly, we now have to reconsider who should be treated with statins. What do we do with a small but significant effect in a large group of apparently healthy people? The treatment is expensive (cardiovascular events can probably be prevented for less than $287.000 by other means, e.g. changes in diet and exercise) and can have side effects (e.g. an increase in newly diagnosed diabetes in the JUPITER trial). And, like most important studies, the JUPITER trial raises a number of important new questions. But instead of discussing some of these questions I rather want to look at how we can obtain information about the JUPITER trial.

Clinical Trial Databases

Since 2005 all clinical trials have to be registered in publicly available databases, and information about JUPITER is available.[1] Since September 2008, newly registered trials also have to report their main outcomes.[2] This will become important in the future, as the main outcomes of unpublished trials (most likely trials with negative results) will become publicly available no later than 12 months after data for the last subject were received.

Press Releases

JUPITER was stopped early in March 2008 and AstraZeneca (the sponsor of the trial and manufacturer of rosuvastatin) issued a press release.[3] Another press release was issued on November 9 when the JUPITER results were first presented publicly.[4] As can be expected from press releases, there is selective reporting of the trial results. No absolute numbers for risk reductions were reported, and emphasis was put on relative risk reductions. Instead of the actual number needed to treat (NNT, 120 patients treated for 1.9 years), a projected NNT (25 patients treated for 5 years) was reported. And a significant increase in newly diagnosed diabetes (3.0% vs. 2.4%, p=0.01) was reported as "there was a small increase in physician reported diabetes consistent with data from other large placebo controlled statin trials."

Presentation at a Meeting

The JUPITER results were presented on November 9 at the annual meeting of the American Heart Association (AHA) in New Orleans. More than 6,000 people were listening to this presentation according to James Butcher on the Nature in the Field blog5. The abstract of the presentation is available here.6 The abstract also lists the potential conflicts of interest of the study authors (the senior author Paul Ridger Ridker is co-inventor of patents on CRP testing in cardiovascular disease). The AHA issued a press release on that day7 and commented primarily on the role of CRP testing in the trial.

Journal Paper

The JUPITER study was published in the New England Journal of Medicine (NEJM) on November 20[8], but the paper was preleased on the day of the presentation at the AHA meeting. The full-text PDF of the paper is available without subscription. The full paper is of course the best source to all the primary data. As is typical for many medical journals, it contains a structured abstract, which is a nice summary of the paper. Interestingly, the NEJM is conducting a poll and asks the readers two questions on how the JUPITER results changed their clinical practice.[9] And there are over 400 reader comments as of today.

Editorials

The full paper is discussed in an editorial in the same issue[10], and is also discussed in an editorial in the British Medical Journal[11]. Only the editorial in the NEJM is available without subscription, but both critically discuss the paper and put it in perspective.

Traditional News

The JUPITER trial was of course discussed in many traditional news media such as newspapers, radio and television. The New York Times had a long article[12] where the author had interviewed not only the study authors but also several experts in the field. The article discusses several issues surrounding the study, but failed to report the absolute risk reduction or the number needed to treat (important numbers for the reasons discussed above). National Public Radio discussed the story with two cardiologists, including the author of the editorial in the NEJM (available as transcript and audio file).[13] The interview is again short on actual numbers, but puts JUPITER in perspective for the typical radio listener. The Nature News article[14] also didn't mention the number needed to treat. Stopping a trial early can be controversial, because the numbers for risks and benefits might look different at the planned end of the trial. Nature News should have talked to someone that was not involved in that decision in the JUPITER trial.

Blogs

Scintilla has aggregated the blog posts on this study[15]. Harriet Hall on the Science-Based Medicine Blog not only has the story with the best title (Statins Are Better on JUPITER), but gives a detailed analysis of the study results. Ben Goldacre on Bad Science has a shorter blog post that is more of a discussion of absolute risk, relative risk and number needed to treat (as the title of the blog post suggests).[16]

Conclusions

There are many ways we can learn more about the JUPITER trial, and most of this information is freely available, including the full-text of the paper. It is not the access to the primary data that is the problem, but rather the many different ways the results can be put into perspective. And for that we need not only a basic understanding of cardiovascular risks, but also clinical trials. And we should not forget the financial and other interests that are always connected to large trial like this. I didn't do a systematic analysis of the newspaper articles and blog posts about the study, but it is clear to me that science blogs can add an important perspective.

fn1. JUPITER – Crestor 20mg Versus Placebo in Prevention of Cardiovascular (CV) Events. ClinicalTrials.gov NCT00239681 October 13, 2005

fn2. FDAAA: Push to open data in clinical medicine

fn3. Crestor Outcomes Study JUPITER Closes Early Due To Unequivocal Evidence Of Benefit. AstraZeneca Press Release March 31, 2008

fn4. CRESTOR Demonstrates Dramatic CV Risk Reduction in a Large Statin Outcomes Study. AstraZeneca Press Release November 9, 2008

fn5. AHA 2008: Should statins be put in the water? James Butcher. In the Field November 11, 2008

fn6. Late-breaking abstracts. News Conference November 9, 2008

fn7. American Heart Association Comment on JUPITER trial. AHA Press Release November 9, 2008

fn8. P. M Ridker, E. Danielson, F. A.H. Fonseca, J. Genest, A. M. Gotto, J. J.P. Kastelein, W. Koenig, P. Libby, A. J. Lorenzatti, J. G. MacFadyen, B. G. Nordestgaard, J. Shepherd, J. T. Willerson, R. J. Glynn (2008). Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein *New England Journal of Medicine, 359* (21), 2195-2207 DOI: 10.1056/NEJMoa0807646

fn9. The JUPITER Trial: Will You Change Your Practice? Clinical Directions

fn10. M. A. Hlatky (2008). Expanding the Orbit of Primary Prevention — Moving beyond JUPITER *New England Journal of Medicine, 359* (21), 2280-2282 DOI: 10.1056/NEJMe0808320

fn11. N. Donner-Banzhoff, A. Sonnichsen (2008). Statins and primary prevention of cardiovascular events *BMJ, 337* (nov14 2) DOI: 10.1136/bmj.a2576

fn12. Cholesterol-Fighting Drugs Show Wider Benefit. Pam Belluck. New York Times November 10, 2008

fn13. Study Finds Statins Benefit Patients With no History of Heart Problems. PBS Newshour November 10, 2008

fn14. Should healthy people take statins too? Katharine Sanderson. Nature News November 10, 2008

fn15. Search for term rosuvastatin. Scintilla

fn16. Statins Are Better on JUPITER. Harriet Hall. Science-Based Medicine November 11, 2008

fn17. You are 80% less likely to die from a meteor landing on your head if you wear a bicycle helmet all day. Ben Goldacre. Bad Science November 15, 2008