Cholesterol Lowering, Cardiovascular Diseases, and the Rosuvastatin-JUPITER Controversy

A Critical Reappraisal

Michel de Lorgeril, MD; Patricia Salen, BSc; John Abramson, MD; Sylvie Dodin, MD; Tomohito Hamazaki, PhD; Willy Kostucki, MD; Harumi Okuyama, PhD; Bruno Pavy, MD; Mikael Rabaeus, MD

Background: Among the recently reported cholesterol-lowering drug trials, the JUPITER (Justification for the Use of Statins in Primary Prevention) trial is unique: it reports a substantial decrease in the risk of cardiovascular diseases among patients without coronary heart disease and with normal or low cholesterol levels.

Methods: Careful review of both results and methods used in the trial and comparison with expected data.

Results: The trial was flawed. It was discontinued (according to prespecified rules) after fewer than 2 years of follow-up, with no differences between the 2 groups on the most objective criteria. Clinical data showed a major discrepancy between significant reduction of nonfatal stroke and myocardial infarction but no effect on mortality from stroke and myocardial infarction. Cardiovascular mortality was surprisingly low compared with total mortality—between 5% and 18%—whereas the expected rate would have been close to 40%. Finally, there was a very low case-fatality rate of myocardial infarction, far from the expected number of close to 50%. The possibility that bias entered the trial is particularly concerning because of the strong commercial interest in the study.

Conclusion: The results of the trial do not support the use of statin treatment for primary prevention of cardiovascular diseases and raise troubling questions concerning the role of commercial sponsors.

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The JUPITER trial tested the effects of rosvuastatin therapy (20 mg/d) in patients without cardiovascular history or established CHD and with normal or low cholesterol levels but relatively high levels of C-reactive protein, a fluctuating biologic marker of inflammation. The authors reported a 50% reduction in low-density lipoprotein cholesterol levels, a 37% reduction in C-reactive protein levels, and a roughly 50% decrease in cardiovascular complications. The publication of the JUPITER trial (in November 2008) was much anticipated since the announcement of the trial's premature discontinuation in March 2008, at a meeting of the American College of Cardiology, following the presentation of the disappointing results of the ENHANCE (Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression) trial. Similarly to ezetimibe (tested in the ENHANCE trial), rosvuastatin was already the subject of aggressive marketing despite the absence of evidence that its use actually decreased CHD complications. Indeed, disregarding open-label studies such as ASTEROID (A Study...
to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden), 21 3 trials with rosuvastatin (CORONA [Controlled Rosu-
vastatin Multinational Trial in Heart Failure], 3 GISSI-HF
[Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico—Heart Failure], 3, and AURORA [A
Study to Evaluate the Use of Rosuvastatin in Subjects on
Regular Haemodialysis: An Assessment of Survival and
Cardiovascular Events]) had been conducted, and all had
failed to provide evidence that rosuvastatin therapy re-
duces CHD complications. The failure of rosuvastatin to
show a significant protective effect was also true for pa-
tients with established CHD, because most patients in the
CORONA and GISSI-HF trials were survivors of a pre-
vious myocardial infarction.

**METHODOLOGICAL PROBLEMS IN THE JUPITER TRIAL**

The JUPITER trial was prematurely terminated. Although
having prespecified early stopping rules is a well-accepted
feature of clinical trials, it is critical that the rules truly be
prespecified. In the case of the JUPITER trial, the prespec-
fied rules were not detailed in the published description of
the study protocol. 22 Indeed, we still do not know which
end point was used to define them, or which level of ben-
efits—unexpected on the basis of the a priori calculated hy-
pothesis—was required to justify early termination. Also,
it was recently shown that truncated trials are associated
with greater effect sizes than trials that are not stopped early,
and this effect is independent of the presence of statistical
stopping rules. 23 In defending the decision to end the trial
early, the JUPITER investigators stated that the decision
was not made by them but by members of an independent
safety-monitoring board. 24 However, the chairman of this
board—an investigator of the Clinical Trial Service Unit of
Oxford University, Oxford, England—has been, and still
is, involved in many other industry-sponsored lipid-
lowering trials, raising issues of conflict of interest. 25,26

Fueling concern about the termination of the study is
that the data are not consistent with a large difference be-
tween treatment and placebo. The primary end point
(Table, line 1) is a composite of cardiovascular complica-
tions, some of which—such as revascularization and hos-
pital admission—are of less relevance because they are not
complications but medical decisions. Taking only the hard
end points of fatal and nonfatal myocardial infarction and
stroke (Table, line 8)—the end points that are less open
to bias and manipulation—the trial was stopped after only
240 events. Furthermore, there was no difference in the
incidence of serious adverse events (total hospitaliza-
tions, prolongations of hospitalizations, cancer, and per-
manent disability) between the 2 groups.

Moreover, a close examination of the all-cause mortal-
ity curves (Figure 1D in the first JUPITER article 10) shows
that the curves were actually converging when the trial was
ended, suggesting that the borderline significant differ-
ence between groups may have disappeared in case of a
slightly longer follow-up. Strangely, in a subsequent ar-
ticle 27 that was apparently written to defuse the contro-
versy, the all-cause mortality curves were truncated so that
the previous converging portion was no longer displayed.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Rosuvastatin Group (n=8901)</th>
<th>Placebo Group (n=8901)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end pointb</td>
<td>142</td>
<td>251</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>22</td>
<td>62</td>
</tr>
<tr>
<td>Any myocardial infarction</td>
<td>31</td>
<td>68</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>30</td>
<td>58</td>
</tr>
<tr>
<td>Any stroke</td>
<td>33</td>
<td>64</td>
</tr>
<tr>
<td>Arterial revascularization</td>
<td>71</td>
<td>131</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>Myocardial infarction, stroke, or confirmed</td>
<td>83</td>
<td>157</td>
</tr>
<tr>
<td>deaths from cardiovascular causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause on known date</td>
<td>190</td>
<td>235</td>
</tr>
</tbody>
</table>

Table. A Summary of the JUPITER Trial Resultsa

CLINICAL AND EPIDEMIOLOGICAL INCONSISTENCIES IN THE JUPITER TRIAL

In any trial, the consistency of clinical data must be ex-
amined to determine whether methodological flaws have
increased the risk of bias. For instance, in cardiology, com-
parison of the rate of hard end points—fatal and nonfa-
tal myocardial infarction and stroke, which represent most
cardiovascular complications in any population—to those
expected from a comparable population, at least in the
placebo group, provides such a check on methodology.

At first glance (Table), the difference between the 2
groups in terms of hard end points seems impressive (157
vs 83 for placebo and rosuvastatin, respectively). But are
differences plausible? Although an “unequivocal re-
duction in cardiovascular mortality” was announced in
March 2008 as the main justification for the premature trial
termination, 19,20 the absence of cardiovascular mortality
data in the published article is striking. One may infer from
the Table—although not indicated in the text—that the
total number of fatal myocardial infarctions was 9 in the
rosuvastatin group (the difference between 31 “any myo-
cardial infarctions” and 22 “nonfatal myocardial infar-
ctions”) and 6 (68–62) in the placebo group. Similar cal-
culations for fatal stroke (the difference between “any
stroke” and “nonfatal stroke”) show 3 (33–30) in the ro-
svastatin group and 6 (64–58) in the placebo group.

Cardiovascular mortality (fatal stroke plus fatal myo-
cardial infarction) would therefore be identical in both
groups (12 vs 12). Such a lack of effect on cardiovascular
mortality associated with a strong effect on nonfatal
complications strongly suggests a bias in the data set and
should have led to the continuation of the trial rather than
to its premature ending. Other inconsistencies add to the
confusion.

First, the ratio of fatal myocardial infarction (9 for ro-
suvastatin and 6 for placebo) to nonfatal myocardial in-
farction (22 and 62) is incredibly low, especially in the pla-
cebo group. Mortality from acute myocardial infarction is
a very important issue in cardiology. The data would sug-
gest that the hearts of the JUPITER patients were unex-
pectedly—and inexplicably—highly resistant to acute is-
chemia and infarction. The worst consequence of low
myocardial resistance to ischemia is death, often sudden cardiac death (SCD). Myocardial infarction–related death, the “case-fatality rate” in epidemiological reports, is usually very high and is known, thanks to the World Health Organization’s MONICA study, in many populations with very different risks. Out of 100 patients who have a myocardial infarction, an average of 50 die immediately—usually out of hospital—or within the 3 to 4 weeks that follow, and almost never fewer than 40 out of 100, even in populations with low cardiovascular mortality, for example in Japan and around the Mediterranean sea. In the JUPITER trial, the case-fatality rate in the placebo group was incredibly low: 8.8%, a clinical inconsistency that suggests a major flaw in the study. Moreover, the case-fatality rate in the rosvuvastatin group was 29%. This rate was significantly different from that in the placebo group (Fisher exact test, \( P = .01 \)) and more consistent with (though still lower than) the range reported in the MONICA study. Another dilemma is raised by this figure as it would imply that the use of rosvuvastatin tripled the case-fatality rate. This figure is not credible.

Second, other ways of calculating cardiovascular mortality in the JUPITER trial could be used. For instance, Chan et al used the combined end point “myocardial infarction + stroke + confirmed death from cardiovascular causes” (line 8 of the Table), from which they removed nonfatal myocardial infarction (line 2) and nonfatal stroke (line 4). They calculated that the numbers of deaths from cardiovascular causes were 31 and 37 in the rosvuvastatin and placebo groups, respectively, not a significant difference. Because the total number of fatal myocardial infarction and stroke was 12 in both groups, it would mean that there were 19 and 23 cardiovascular deaths that were not due to myocardial infarction or stroke.

The question raised is obvious: What are the causes of these so many “other” cardiovascular deaths? In the March 5, 2009, issue of the New England Journal of Medicine, Ridker and Glynn explain that the calculations by Chan and colleagues are incorrect “because they do not account for deaths from vascular causes, such as aneurysm rupture.” Would this mean that in the same period of time there were 6 fatal infarctions and 25 fatal aneurysm ruptures in the placebo group? This is highly unlikely and still does not explain why the calculations made by Chan and coauthors are incorrect. Even Ridker and Glynn write that the number of confirmed deaths from cardiovascular causes was 35 in the rosvuvastatin group and 43 in the placebo group (no significant difference), based on “very strict end point classification criteria” that are not clearly described, and surprisingly do not mention SCD.

Sudden cardiac death actually is the simplest and most reliable diagnosis in cardiology because, contrary to myocardial infarction, there is no need for biologic and/or electrocardiographic criteria. It is defined as a death occurring within 1 hour after the first symptoms of heart attack—or as an un witnessed death. It is therefore very surprising that no SCD is reported in the JUPITER trial because SCD usually represents about 65% to 70% of total cardiac mortality. As previously underlined, the way SCD is reported—or not reported—may be a good indicator of the quality of the methods used in a trial.

None of these clinically inconsistent numbers has been explained in the different JUPITER articles. Although it is quite unusual that the burden of calculating cardiovascular mortality is placed on the readers, all methods used, however, lead to the same conclusion: there is no significant difference in cardiovascular mortality between the 2 groups in the JUPITER trial. Moreover, cardiovascular mortality in the JUPITER trial appears to be unexpectedly low compared with total mortality—between 5 and 18%, depending on the means of calculation—whereas the expected rate would have been close to 40% in a non-Japanese and non-Mediterranean population. These mortality data are not epidemiologically consistent, and the early termination of the JUPITER trial likely was, at least partly, responsible for that lack of consistency.

Therefore, the JUPITER data set appears biased. Three other trials involving rosvuvastatin therapy in high-risk patients did not show any protection. The authors of the JUPITER study fail to comment on these negative trials but go on to report secondary end point and subgroup analyses that appear to support the efficacy (and safety) of rosvuvastatin therapy. For example, an entire article was devoted to reporting a significant benefit in secondary end point, reduction of venous thromboembolisms, whereas the significant increase in new diagnoses of diabetes among patients taking rosvuvastatin—a no less important secondary outcome—was relegated to a short comment. Similarly, secondary analyses of subgroups—women, patients with moderate chronic kidney disease, or persons 70 years or older—are subject to all the limitations of the main data set.

THE SPONSOR’S ROLE AND CONFLICTS OF INTEREST IN THE JUPITER TRIAL

The JUPITER trial involved multiple conflicts of interest. It was conducted by a sponsor with obvious commercial interests. Nine of 14 authors of the JUPITER article have financial ties to the sponsor. The principal investigator has a personal conflict of interest as a coholder of the patent for the C-reactive protein test.

The sponsor’s pervasive role is clearly described in the second paragraph of the “Methods” section of the report: “the sponsor collected the trial data and monitored the study sites.” It means that the sponsor’s own investigators controlled and managed the raw data. This does not mean that raw data have been modified before being transmitted to statisticians, but it does increase the chance of bias seeping into the data set, as the misrepresentation of data about rofecoxib, gabapentin, and ENHANCE have shown.

In conclusion, the results of the JUPITER trial are clinically inconsistent and therefore should not change medical practice or clinical guidelines. The results of the JUPITER trial support concerns that commercially sponsored clinical trials are at risk of poor quality and bias. Documentation of the failure of the JUPITER trial to demonstrate a protective effect of rosvuvastatin is all the more important as it occurred in the context of the failure of more than 12 other cholesterol-lowering trials published in recent years and in various clinical settings.
these trials provided significant evidence of protection against CHD complications—especially fatal complications—by cholesterol lowering. Two other cholesterol-lowering studies were either not published49 or abruptly halted50 because of lack of effect. These failures strongly suggest that the presumed preventive effects of cholesterol-lowering drugs have been considerably exaggerated.32,51

Clearly, the time has come for a critical reappraisal of cholesterol-lowering and statin treatments for the prevention of CHD complications. The emphasis on pharmaceuticals for the prevention of CHD diverts individual and public health attention away from the proven efficacy of adopting a healthy lifestyle, including regular physical activity, not smoking, and a Mediterranean-style diet.32,53

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Correspondence: Michel de Lorgeril, MD, Laboratoire Cœur et Nutrition, Faculté de Médecine, TIMC-IMAG, Université Joseph Fourier and Centre National de la Recherche Scientifique, UMR 5523, Domaine de la Merci, 38706 La Tronche, France (michel.delorgeril@ujf-grenoble.fr).

Author Contributions: Study concept and design: de Lorgeril and Rabaeus. Acquisition of data: Hamazaki. Analysis and interpretation of data: de Lorgeril, Salen, Abramson, Dodin, Hamazaki, Kostucki, Okuyama, and Pavy. Drafting of the manuscript: de Lorgeril and Rabaeus. Critical revision of the manuscript for important intellectual content: de Lorgeril, Salen, Abramson, Dodin, Hamazaki, Kostucki, Okuyama, Pavy, and Rabaeus. Statistical analysis: de Lorgeril and Abramson. Administrative, technical, and material support: Abramson. Study supervision: Kostucki and Rabaeus.

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