

**Cholesterol Lowering, Cardiovascular Diseases, and the Rosuvastatin-
JUPITER Controversy:
A Critical Reappraisal**

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FROM ABSTRACT:

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 pre-specified 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.

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.

BACKGROUND FROM DAN MURPHY

Most (maybe 80-90%) of the cholesterol in the blood is made by one's own liver. The liver makes cholesterol from glucose (sugar). The number of separate enzymatic steps required to convert sugar into cholesterol is 32 (my count from a biochemistry text). Statin drugs block the process by inhibiting the enzyme between the third and fourth steps. Consequently, statin drugs have become the most popular drug for lowering blood cholesterol levels.

C-reactive protein is an enzyme found in the blood. It is a non-specific marker for inflammation. Elevated levels of C-reactive protein have been have been linked to

increased risk of heart disease. Dr. Paul Ridker has been the leading advocate of having one's C-reactive protein checked.

The JUPITER (Justification for the Use of Statins in Primary Prevention) study was published in the New England Journal of Medicine in November 2008. In this study, patients with high C-reactive protein levels but with no heart disease and with normal levels of cholesterol showed a substantial decrease in the risk of cardiovascular disease if they took the statin drug Rosuvastatin [Crestor].

Because of the JUPITER study, physicians have been putting thousands of patients on statin drugs when they have normal cholesterol levels but high levels of C-reactive protein.

Paul Ridker, MD, is the primary author of the JUPITER study. Paul Ridker is also the co-holder of the patent on the test for C-reactive protein, apparently making money each time the test is performed.

Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008;359(21):2195-2207.

These authors critically review the JUPITER study and its controversies.

THESE AUTHORS ALSO NOTE:

- 1) Nine recent studies do NOT show that taking statin drugs reduce morbidity or mortality from coronary heart disease.
- 2) The JUPITER (Justification for the Use of Statins in Primary Prevention) study is the one exception study that shows that taking a statin drug will reduce cardiovascular disease, even if cholesterol levels are normal.
- 3) The JUPITER study has "undoubtedly propelled many healthy persons without elevated cholesterol levels onto long-term statin treatment."
- 4) In the March 2008, meeting of the American College of Cardiology, the JUPITER study authors announced that they were prematurely discontinuing the study because of its excellent results. The drug companies immediately began a marketing blitz of the JUPITER outcomes to enhance sales. (AstraZeneca is the drug company that makes Crestor).
- 5) The JUPITER trial was inappropriately prematurely terminated because the authors did not follow the well-accepted early stopping rules for clinical trials.
- 6) The chairman of the board for the early termination of the JUPITER study is heavily financially supported by the statin drug industry, "raising issues of conflict of interest."

- 7) There was no difference in the incidence of serious adverse events (total hospitalizations, prolongations of hospitalizations, cancer, and permanent disability) between the 2 groups. (JUPITER group and placebo group)
- 8) "A close examination of the all-cause mortality curves shows that the curves were actually converging when the trial was ended, suggesting that the borderline significant difference between groups may have disappeared in case of a slightly longer follow-up. Strangely, in a subsequent article [written solely by Paul Ridker] that was apparently written to defuse the controversy, the all-cause mortality curves were truncated so that the previous converging portion was no longer displayed."
- 9) The "unequivocal reduction in cardiovascular mortality" was announced in March 2008 as the main justification for the premature trial termination, the "absence of cardiovascular mortality data in the published article is striking."
- 10) Numerous clinical inconsistencies in JUPITER "suggests a major flaw in the study."
- 11) One figure in JUPITER implies that the use of rosuvastatin [Crestor] tripled the case-fatality rate.
- 12) Sudden cardiac death (death occurring within 1 hour after the first symptoms of heart attack) is the simplest and most reliable diagnosis in cardiology; it usually represents about 65% to 70% of total cardiac mortality. Yet, the JUPITER trial did not report on sudden cardiac death. "The way sudden cardiac death is reported—or not reported—may be a good indicator of the quality of the methods used in a trial."
- 13) "There is no significant difference in cardiovascular mortality between the 2 groups in the JUPITER trial."
- 14) The JUPITER data appears to be biased; three other trials involving rosuvastatin (Crestor) therapy in high-risk patients did not show any cardiac protection. "The authors of the JUPITER study fail to comment on these negative trials."
- 15) The significant increase in new diagnoses of diabetes among patients taking rosuvastatin was barely mentioned by the JUPITER authors.
- 16) "The JUPITER trial involved multiple conflicts of interest. It was conducted by a sponsor with obvious commercial interests."
- 17) Nine of 14 authors of the JUPITER article have financial ties to the sponsor (AstraZeneca).

- 18) The principal investigator of the JUPITER study has a personal conflict of interest as a co-holder of the patent for the C-reactive protein test.
- 19) The JUPITER study sponsor's [AstraZeneca] own investigators controlled and managed the raw data, which is suspect and inappropriate.
- 20) "The results of the JUPITER trial are clinically inconsistent and therefore should not change medical practice or clinical guidelines."
- 21) "The results of the JUPITER trial support concerns that commercially sponsored clinical trials are at risk of poor quality and bias."
- 22) "Documentation of the failure of the JUPITER trial to demonstrate a protective effect of rosuvastatin 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. None of these trials provided significant evidence of protection against CHD complications—especially fatal complications—by cholesterol lowering." "These failures strongly suggest that the presumed preventive effects of cholesterol lowering drugs have been considerably exaggerated."
- 23) "The time has come for a critical reappraisal of cholesterol-lowering and statin treatments for the prevention of CHD complications."
- 24) "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."
- 25) These authors conclude that JUPITER is "flawed" as it was discontinued after fewer than 2 years of follow-up, and there was no difference between the 2 groups on the most objective criteria. Clinical data showed no effect on mortality from stroke and myocardial infarction between the 2 groups.
- 26) "The possibility that bias entered the trial is particularly concerning because of the strong commercial interest in the study."
- 27) "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."