

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

A Critical Reappraisal

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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 mor-

tality 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 RESULTS OF RECENT cholesterol-lowering drug trials on decreasing morbidity and mortality among persons with or without coronary heart disease (CHD) have been consistently negative.¹⁻⁹ However, there is one exception, the JUPITER (Justification for the Use of Statins in Primary Prevention)

See also pages 1007, 1024, and 1073

trial,¹⁰ which showed—in primary prevention—a striking decrease in CHD complications. The JUPITER trial rapidly provoked controversy¹¹⁻¹³ regarding both the results and the methods used in the trial. Although enthusiastic comments have been published,¹⁴⁻¹⁷ and the results have undoubtedly propelled many healthy persons without elevated cholesterol levels onto long-term statin treatment, the clinical relevance of the JUPITER trial remains in question. To understand the rosuvastatin-JUPITER controversy, we critically review several significant issues of that study.

The JUPITER trial tested the effects of rosuvastatin 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.¹⁸ 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.¹⁰ The publication of the JUPITER trial (in November 2008) was much anticipated since the announcement of the trial's premature discontinuation in March 2008,^{19,20} 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.⁹ Similarly to ezetimibe (tested in the ENHANCE trial), rosuvastatin 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 Rosuvastatin Multinational Trial in Heart Failure],¹ GISSI-HF [Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio-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]⁷) had been conducted, and all had failed to provide evidence that rosuvastatin therapy reduces CHD complications. The failure of rosuvastatin to show a significant protective effect was also true for patients with established CHD, because most patients in the CORONA and GISSI-HF trials were survivors of a previous 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 prespecified 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 benefits—unexpected on the basis of the a priori calculated hypothesis²²—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 between treatment and placebo. The primary end point (**Table**, line 1) is a composite of cardiovascular complications, some of which—such as revascularization and hospital 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 hospitalizations, prolongations of hospitalizations, cancer, and permanent disability) between the 2 groups.

Moreover, a close examination of the all-cause mortality curves (Figure 1D in the first JUPITER article¹⁰) 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 article²⁷ 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.

Table. A Summary of the JUPITER Trial Results^a

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

^aAdapted from Ridker et al.¹⁰

^bA combination of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes.

CLINICAL AND EPIDEMIOLOGICAL INCONSISTENCIES IN THE JUPITER TRIAL

In any trial, the consistency of clinical data must be examined to determine whether methodological flaws have increased the risk of bias. For instance, in cardiology, comparison of the rate of hard end points—fatal and nonfatal 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 these differences plausible? Although an “unequivocal reduction 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 myocardial infarctions” and 22 “nonfatal myocardial infarctions”) and 6 (68–62) in the placebo group. Similar calculations for fatal stroke (the difference between “any stroke” and “nonfatal stroke”) show 3 (33–30) in the rosuvastatin group and 6 (64–58) in the placebo group.

Cardiovascular mortality (fatal stroke plus fatal myocardial 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 rosuvastatin and 6 for placebo) to nonfatal myocardial infarction (22 and 62) is incredibly low, especially in the placebo group. Mortality from acute myocardial infarction is a very important issue in cardiology. The data would suggest that the hearts of the JUPITER patients were unexpectedly—and inexplicably—highly resistant to acute ischemia 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.²⁸ 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.²⁸ 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 rosuvastatin 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.²⁸ Another dilemma is raised by this figure as it would imply that the use of rosuvastatin 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 al²⁹ 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 rosuvastatin 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 25 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 Glynn²⁴ 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 rosuvastatin 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 unwitnessed death.³⁰ 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.³¹ As previously underlined,³² 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.^{10,27,33} 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.^{28,34} 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^{1,3,5} involving rosuvastatin 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 rosuvastatin therapy.³⁵⁻³⁸ For example, an entire article was devoted to reporting a significant benefit in 1 secondary end point, reduction of venous thromboembolisms,³⁵ whereas the significant increase in new diagnoses of diabetes among patients taking rosuvastatin—a no less important secondary outcome—was relegated to a short comment.¹⁰ Similarly, secondary analyses of subgroups—women,³⁶ patients with moderate chronic kidney disease,³⁷ or persons 70 years or older³⁸—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 article¹⁰ 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.”¹⁰ 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,^{39,40} gabapentin,⁴¹ and ENHANCE^{9,42-44} 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 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.^{1-9,45-48} None of

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.^{52,53}

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REFERENCES

- Kjekshus J, Apetrei E, Barrios V, et al; CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med.* 2007;357(22):2248-2261.
- Barter PJ, Caulfield M, Eriksson M, et al; ILLUMINATE Investigators. Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med.* 2007;357(21):2109-2122.
- Tavazzi L, Maggioni AP, Marchioli R, et al; GISSI-HF Investigators. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomized, double-blind, placebo-controlled trial. *Lancet.* 2008;372(9645):1231-1239.
- Rossebo AB, Pedersen TR, Boman K, et al; SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med.* 2008;359(13):1343-1356.
- Fellström BC, Jardine AG, Schmieder ME, et al; AURORA Study Group. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med.* 2009;360(14):1395-1407.
- Wanner C, Krane V, März W, et al; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med.* 2005;353(3):238-248.
- Knopp RH, d'Emden M, Smilde JG, Pocock SJ. Efficacy and safety of atorvastatin in the prevention of cardiovascular end points in subjects with type 2 diabetes: the Atorvastatin Study for Prevention of Coronary Heart Disease End points in Non-Insulin-Dependent Diabetes Mellitus (ASPEN). *Diabetes Care.* 2006;29(7):1478-1485.
- Cowell SJ, Newby DE, Prescott RJ, et al; Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med.* 2005;352(23):2389-2397.
- Kastelein JJ, Akdim F, Stroes ES, et al; ENHANCE Investigators. Simvastatin with or without ezetimibe in familial hypercholesterolemia. *N Engl J Med.* 2008;358(14):1431-1443.
- 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.
- Donner-Banzhoff N, Sönnichsen A. Statins and primary prevention of cardiovascular events. *BMJ.* 2008;337:a2576.
- Nissen SE. The Jupiter trial: key findings, controversies and implications. *Curr Cardiol Rep.* 2009;11(2):81-82.
- Vaccarino V, Bremner JD, Kelley ME. JUPITER: a few words of caution. *Circ Cardiovasc Qual Outcomes.* 2009;2(3):286-288.
- Hlatky MA. Expanding the orbit of primary prevention: moving beyond JUPITER. *N Engl J Med.* 2008;359(21):2280-2282.
- Spatz ES, Canavan ME, Desai MM. From here to JUPITER: identifying new patients for statin therapy using data from the 1999-2004 National Health and Nutrition Examination Survey. *Circ Cardiovasc Qual Outcomes.* 2009;2(1):41-48.
- Wood S. Eyes trained on JUPITER: cardiologists seek details to understand how statin use may expand. Medscape Web site. <http://www.medscape.com/viewarticle/583040>. Accessed November 6, 2008.
- Normal cholesterol? you may still be at risk. CardioSmart Web site. <http://www.cardiosmart.org/News/Default.aspx?id=2238>. Accessed November 9, 2008.
- Bogaty P, Brophy JM, Boyer L, et al. Fluctuating inflammatory markers in patients with stable ischemic heart disease. *Arch Intern Med.* 2005;165(2):221-226.
- O'Riordan M. Crestor outcomes study JUPITER closes early due to unequivalent evidence of benefit. theheart.org Web site. <http://www.theheart.org/article/852735.do>. Accessed March 31, 2008.
- O'Riordan M. JUPITER halted: rosuvastatin significantly reduces cardiovascular morbidity and mortality. Medscape Web site. <http://medscapemobile.com/viewarticle/572270>. Accessed April 1, 2008.
- Ballantyne CM, Raichlen JS, Nicholls SJ, et al; ASTEROID Investigators. Effect of rosuvastatin therapy on coronary artery stenoses assessed by quantitative coronary angiography: a study to evaluate the effect of rosuvastatin on intravascular ultrasound-derived coronary atheroma burden. *Circulation.* 2008;117(19):2458-2466.
- Ridker PM; JUPITER Study Group. Rosuvastatin in the primary prevention of cardiovascular disease among patients with low levels of low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: rationale and design of the JUPITER trial. *Circulation.* 2003;108(19):2292-2297.
- Bassler D, Briel M, Montori VM, et al; STOPIT-2 Study Group. Stopping randomized trials early for benefit and estimation of treatment effects: systematic review and meta-regression analysis. *JAMA.* 2010;303(12):1180-1187.
- Ridker PM, Glynn RJ. Rosuvastatin in patients with elevated C-reactive protein [reply]. *N Engl J Med.* 2009;360(10):1041-1042.
- Mueller PS, Montori VM, Bassler D, Koenig BA, Guyatt GH. Ethical issues in stopping randomized trials early because of apparent benefit. *Ann Intern Med.* 2007;146(12):878-881.
- Montori VM, Devereaux PJ, Adhikari NK, et al. Randomized trials stopped early for benefit: a systematic review. *JAMA.* 2005;294(17):2203-2209.
- Ridker PM. The JUPITER trial: results, controversies and implications for prevention. *Circ Cardiovasc Qual Outcomes.* 2009;2(3):279-285.
- Tunstall-Pedoe H, Kuulasmaa K, Mähönen M, Tolonen H, Ruokokoski E, Amouyel P. Contribution of trends in survival and coronary-event rates to changes in coronary heart disease mortality: 10-year results from 37 WHO MONICA project populations: monitoring trends and determinants in cardiovascular disease. *Lancet.* 1999;353(9164):1547-1557.
- Chan PS, Nallamothu BK, Hayward RA. Rosuvastatin in patients with elevated C-reactive protein [letter]. *N Engl J Med.* 2009;360(10):1039.
- Zipes DP, Wellens HJ. Sudden cardiac death. *Circulation.* 1998;98(21):2334-2351.
- Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation.* 2001;104(18):2158-2163.
- de Lorgeril M, Salen P. Cholesterol lowering and mortality: time for a new paradigm? *Nutr Metab Cardiovasc Dis.* 2006;16(6):387-390.
- Ridker PM, Danielson E, Fonseca FAH, et al; JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. *Lancet.* 2009;373(9670):1175-1182.
- de Lorgeril M, Salen P, Paillard F, Laporte F, Boucher F, de Leiris J. Mediterranean diet and the French paradox: two distinct biogeographic concepts for one consolidated scientific theory on the role of nutrition in coronary heart disease. *Cardiovasc Res.* 2002;54(3):503-515.
- Glynn RJ, Danielson E, Fonseca FAH, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Engl J Med.* 2009;360(18):1851-1861.
- Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for the

- primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) and meta-analysis of women from primary prevention trials. *Circulation*. 2010;121(9):1069-1077.
37. Ridker PM, Macfadyen J, Cressman M, Glynn RJ. Efficacy of rosuvastatin among men and women with moderate chronic kidney disease and elevated high-sensitivity C-reactive protein: a secondary analysis from the JUPITER (Justification for the Use of Statins in Prevention—an Intervention Trial Evaluating Rosuvastatin) trial. *J Am Coll Cardiol*. 2010;55(12):1266-1273.
 38. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. *Ann Intern Med*. 2010;152(8):488-496, W174.
 39. Ross JS, Hill KP, Egilman DS, Krumholz HM. Guest authorship and ghostwriting in publications related to rofecoxib: a case study of industry documents from rofecoxib litigation. *JAMA*. 2008;299(15):1800-1812.
 40. Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. *JAMA*. 2008;299(15):1813-1817.
 41. Landefeld CS, Steinman MA. The Neurontin legacy: marketing through misinformation and manipulation. *N Engl J Med*. 2009;360(2):103-106.
 42. Mitka M. Controversies surround heart drug study: questions about Vytarin and trial sponsors' conduct. *JAMA*. 2008;299(8):885-887.
 43. Greenland P, Lloyd-Jones D. Critical lessons from ENHANCE trial. *JAMA*. 2008;299(8):953-955.
 44. O'Riordan M. Congress continues to probe Merck and Schering-Plough: angry emails highlight ENHANCE controversy. Medscape Web site. <http://www.medscape.com/viewarticle/572392>. Accessed April 1, 2008.
 45. Asselbergs FW, Diercks GFH, Hillege HL, et al; Prevention of Renal and Vascular Endstage Disease Intervention Trial (PREVEND IT) Investigators. Effect of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. *Circulation*. 2004;110(18):2809-2816.
 46. Pedersen TR, Faergeman O, Kastelein JJ, et al; Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) Study Group. High-dose atorvastatin vs. usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study, a randomized controlled trial. *JAMA*. 2005;294(19):2437-2445.
 47. Bowman L, Armitage J, Bulbulia R, Parish S, Collins R; SEARCH Study Collaborative Group. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH): characteristics of a randomized trial among 12064 myocardial infarction survivors. *Am Heart J*. 2007;154(5):815-823, 823.e1-e6.
 48. Study of the effectiveness of additional reductions in cholesterol and homocysteine (SEARCH). ISRCTN Register Web site. <http://www.controlled-trials.com/ISRCTN74348595/>. Accessed December 12, 2007.
 49. O'Riordan M. CASHMERE: no IMT effect with atorvastatin over 12 months. theheart.org Web site. <http://www.theheart.org/article/880873.do>. Accessed July 9, 2008.
 50. O'Riordan M. ACHIEVE stopped: IMT study with Niacin/Laropiprant halted by Merck & Co. theheart.org Web site. <http://www.theheart.org/article/869153.do>. Accessed May 22, 2008.
 51. de Lorgeril M. Disappointing recent cholesterol-lowering drug trials: is it not time for a full reappraisal of the cholesterol theory? *World Rev Nutr Diet*. 2009;100:80-89.
 52. de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation*. 1999;99(6):779-785.
 53. de Lorgeril M, Salen P, Martin JL, Boucher F, Paillard F, de Leiris J. Wine drinking and risks of cardiovascular complications after recent acute myocardial infarction. *Circulation*. 2002;106(12):1465-1469.

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