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EDITORIAL

JUPITER: major implications for vascular risk assessment

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ABSTRACT

This Editorial comments on the recently published JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), the further evidence it provides for supporting the role of statins in primary prevention and the major implications this may hold for vascular risk assessment and clinical practice guidelines.

There is convincing evidence that statins reduce vascular morbidity and mortality in patients with established vascular disease or diabetes mellitus (DM)[1,2]. However, the evidence regarding the efficacy of statins in the primary prevention setting is more limited[3–7]. In subjects without established vascular disease, lovastatin and atorvastatin significantly reduced coronary heart disease (CHD) morbidity[3,4]. Pravastatin significantly reduced CHD morbidity in one study[7] and both CHD morbidity and mortality in another[5], but did not improve outcomes in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[6]. The recently published Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) further supports the role of statins in primary prevention[8].

JUPITER included 17 802 subjects (11 001 men older than 50 years of age and 6801 women older than 60 years of age) with low density lipoprotein cholesterol (LDL-C) levels <130 mg/dl [3.4 mmol/l; median levels 108 mg/dl (2.8 mmol/l)], high sensitivity C-reactive protein (hsCRP) levels >2 mg/l and without established vascular disease[8]. Subjects were randomly allocated to rosuvastatin 20 mg/day or placebo. The trial was stopped early after a median follow up of 1.9 years because of a significant reduction in the primary endpoint (myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina or cardiovascular mortality) by 44% [hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.46–0.69; $p<0.00001$][8]. There was also a significant reduction in non-fatal and any myocardial infarction, non-fatal and any stroke, as well as in arterial revascularization (all, $p \leq 0.003$). JUPITER is also the first statin trial to show a reduction in all-cause mortality ($p = 0.02$) in subjects without vascular disease or DM. Moreover, JUPITER showed a significant reduction in vascular events in women without established vascular disease. Previous primary prevention studies either did not enrol women[5] or were not powered to show risk reduction in women[3,4,7].

The findings of JUPITER might mandate a modification of the existing guidelines for lipid-lowering treatment in subjects without CHD or CHD equivalents. According to current guidelines, drug

therapy is optional when LDL-C levels are between 100 and 130 mg/dl (2.6–3.4 mmol/l) and 10-year risk is 10–20%[9]. In JUPITER, rosuvastatin equally reduced the primary endpoint regardless of the baseline Framingham score ($\leq$ or $>10\%$)[8]. These findings suggest that men older than 50 years and women older than 60 years with LDL-C levels <130 mg/dl (3.4 mmol/l) but with hsCRP levels >2 mg/l (i.e., the JUPITER population) could benefit from statin treatment regardless of the Framingham calculated score.

The JUPITER trial also has implications regarding the role of hsCRP testing in risk stratification. In prospective studies, hsCRP levels were independently associated with increased vascular morbidity and mortality[10–12]. Previous studies showed that considering hsCRP levels improves the predictive accuracy of the Framingham risk engine[11,13]. In JUPITER, rosuvastatin improved the outcome (HR 0.63, 95% CI 0.44–0.92; $p = 0.01$) of patients with hsCRP levels >2 mg/l and no other risk factors except increased age[8]. Current guidelines state that measuring hsCRP levels in patients with estimated 10-year risk between 10 and 20% may help risk evaluation[14]. However, the benefits of treatment based on this strategy were uncertain until now[14]. The results of JUPITER suggest that hsCRP testing might be a useful tool in selecting subjects without established vascular disease who will benefit from statin treatment. However, some limitations of hsCRP testing should be mentioned. Several hsCRP assays are currently in use[14]. Moreover, hsCRP testing is not widely available and is costly. In JUPITER, 36.1% of the screened population did not have hsCRP levels >2 mg/l[8]. Moreover, 52.2% of the screened population had LDL-C levels >130 mg/dl (3.4 mmol/l) and the hsCRP levels in these patients were not reported[8]. In the Framingham study, mean hsCRP levels were 2.67 and 2.23 mg/l in men and women, respectively[15]. Therefore, a significant number of subjects will need to be tested in order to identify those with elevated hsCRP levels. In addition, due to the intraindividual variability of hsCRP measurements, it is recommended that hsCRP levels should be measured twice, at least 2 weeks apart[14]. These limitations will further increase the direct and indirect cost of hsCRP testing.

In JUPITER, LDL-C and hsCRP levels at 12 months were lower (50 and 37%, respectively) in the rosuvastatin group than in the placebo group[8]. These differences were sustained during the study[8]. It is not clear whether rosuvastatin reduced risk due to a fall in LDL-C levels, hsCRP levels or other actions. Previous statin trials in patients with established CHD suggested that a decrease in hsCRP levels is associated with a delay in the progression of coronary atherosclerosis[16] and a reduced risk for vascular events[17]. This decrease in risk was independent of LDL-C lowering[16,17]. It is also not clear whether hsCRP plays a direct role in atherogenesis or is just a marker of the inflammatory process[18–20]. Polymorphisms in the CRP-encoding gene that result in increased hsCRP levels were associated with increased vascular risk in some studies[21] but not in others[22–24].

Besides LDL-C and hsCRP lowering, other actions of rosuvastatin might have contributed to the improved outcome in JUPITER. Triglyceride (TG) levels decreased from 118 to 99 mg/dl (1.3–1.1 mmol/l) at 12 months in the rosuvastatin group (17% lower than TG levels in the placebo group; $p<0.001$) and this effect persisted at 48 months[8]. Elevated TG levels appear to be associated with increased vascular risk[25]. In some statin trials in patients with CHD, the reduction in TG levels correlated with a lower event rate[26–28]. However, this association was not observed in other secondary prevention studies or in subjects without vascular disease[29–33]. Rosuvastatin did not modify HDL-C levels significantly; this might be due to the 'satisfactory' baseline HDL-C levels [49 mg/dl (1.3 mmol/l)]. It would therefore be of interest to report if there was a rosuvastatin-associated increase in HDL-C levels in the participants of JUPITER who had low baseline values of this protective lipoprotein. In other statin trials, the HDL-C levels were relevant to outcome[34]. Interestingly, there was also a very small but significant difference in estimated glomerular filtration rate (eGFR) at 12 months in the rosuvastatin group (66.8 vs. 66.6 ml/min/1.73 m^2 in the placebo group; $p = 0.02$)[8]. Previous statin trials in high risk patients with or without vascular disease reported similar findings[35–41]. This preservation of renal function might play a role in vascular risk reduction during statin treatment[38,39] and might have contributed to the reduced risk of events in JUPITER. Statins also reduced vascular risk in patients with chronic kidney disease[4,42–45]. Patients with serum creatinine levels >2.0 mg/dl (176.8 μmol/l) were excluded from JUPITER but it would be interesting to evaluate the effects of rosuvastatin on renal function and vascular events in a subgroup of patients with the highest baseline creatinine levels (or lowest eGFR). This subgroup might show greater changes in renal function[39].

There was a significantly increased risk for developing type 2 DM in the rosuvastatin group (270 vs. 216 reports; $p = 0.01$)[8]. This difference was observed within 24 months[8]. Median glycated haemoglobin (HbA_{1c}) levels were also marginally but significantly higher at 24 months in patients allocated to rosuvastatin (5.9 vs. 5.8%; $p = 0.001$)[8]. However, fasting blood glucose levels [98 mg/dl (5.4 mmol/l) in both groups] at 24 months and the risk of newly diagnosed glycosuria

at 12 months were similar in the two groups[8]. Type 2 DM in JUPITER was physician-reported and was not adjudicated by the endpoint committee[8]. In the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA; 5011 patients with heart failure treated with rosuvastatin 10 mg/day or placebo for 32.8 months), there was no significant increase in newly diagnosed type 2 DM (100 vs. 88 cases, respectively; $p = 0.40$)[46]. Other long-term studies of rosuvastatin did not specifically report the effects of rosuvastatin on glucose levels or the incidence of newly diagnosed type 2 DM[47–49]. However, this information must be available because glucose was measured. Similar trends were observed in other statin trials as discussed by the authors of the JUPITER study[8]. In other rosuvastatin trials of shorter duration and smaller size, there was no change in glucose levels or in insulin resistance (expressed as homeostasis model assessment index)[50,51].

In JUPITER, rates of myopathy, elevated alanine aminotransferase levels >3 times the upper limit of reference range and other adverse events were similar in the rosuvastatin and placebo groups[8]. Rosuvastatin 20 mg/day appears to lower LDL-C levels to a similar degree as atorvastatin 80 mg/day and more than simvastatin 80 mg/day[52]. However, both atorvastatin and simvastatin at these doses are associated with increased risk of side-effects and treatment discontinuation[53–56].

In conclusion, the findings of JUPITER have important implications for clinical practice. This trial suggests that hsCRP testing is a useful tool in identifying subjects without vascular disease who should receive statins despite a low (e.g., Framingham 10-year risk $\leq 10\%$) or intermediate calculated risk. Existing guidelines might need to be revised. For example, the threshold for LDL-C levels for considering statin treatment in primary prevention may need to be evaluated in the light of plasma hsCRP levels. JUPITER also has major cost implications if the benefits observed can not be reproduced by 'generic' statins. The problem is how do you answer this question? Furthermore, can we really estimate true cost in a trial that was prematurely discontinued after only an average follow-up of 1.9 years?

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References

1. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005;366:1267-78
2. Kearney PM, Blackwell L, Collins R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008; 371:117-25
3. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA 1998;279:1615-22
4. Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial– Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149-58
5. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med 1995;333:1301-7
6. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002; 288:2998-3007
7. Nakamura H, Arakawa K, Itakura H, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet 2006;368:1155-63
8. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;39:2195-207
9. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110: 227-39
10. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. N Engl J Med 2004;351:2599-610
11. Ridker PM, Rifai N, Rose L, et al. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002; 347:1557-65
12. Ridker PM, Cook N. Clinical usefulness of very high and very low levels of C-reactive protein across the full range of Framingham Risk Scores. Circulation 2004;109:1955-9
13. Koenig W, Lowel H, Baumert J, et al. C-reactive protein modulates risk prediction based on the Framingham Score: implications for future risk assessment: results from a large cohort study in southern Germany. Circulation 2004;109: 1349-53
14. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107: 499-511

15. Wilson PWF, Pencina M, Jacques P, et al. C-reactive protein and reclassification of cardiovascular risk in the Framingham Heart Study. Circ Cardiovasc Res Outcomes 2008;1:92-6
16. Nissen SE, Tuzcu EM, Schoenhagen P, et al. Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. N Engl J Med 2005;352:29-38
17. Ridker PM, Cannon CP, Morrow D, et al. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005; 352:20-8
18. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. J Am Coll Cardiol 2007;49:2129-38
19. Athyros VG, Kakafika AI, Karagiannis A, et al. Do we need to consider inflammatory markers when we treat atherosclerotic disease? Atherosclerosis 2008;200:1-12
20. Paraskevas KI, Mikhailidis DP. C-reactive protein (CRP): more than just an innocent bystander? Curr Med Res Opin 2008; 24:75-8
21. Lange LA, Carlson CS, Hindorff LA, et al. Association of polymorphisms in the CRP gene with circulating C-reactive protein levels and cardiovascular events. JAMA 2006;296:2703-11
22. Zacho J, Tybjaerg-Hansen A, Jensen JS, et al. Genetically elevated C-reactive protein and ischemic vascular disease. N Engl J Med 2008;359:1897-908
23. Pai JK, Mukamal KJ, Rexrode KM, et al. C-reactive protein (CRP) gene polymorphisms, CRP levels, and risk of incident coronary heart disease in two nested case-control studies. PLoS ONE 2008;3:1395
24. Lawlor DA, Harbord RM, Timpson NJ, et al. The association of C-reactive protein and CRP genotype with coronary heart disease: findings from five studies with 4,610 cases amongst 18,637 participants. PLoS ONE 2008;3:e3011
25. Sarwar N, Danesh J, Eiriksdottir G, et al. Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 2007;115:450-8
26. Sacks FM, Moye LA, Davis BR, et al. Relationship between plasma LDL concentrations during treatment with pravastatin and recurrent coronary events in the Cholesterol and Recurrent Events trial. Circulation 1998;97:1446-52
27. Miller M, Cannon CP, Murphy SA, et al. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. J Am Coll Cardiol 2008;51:724-30
28. Athyros VG, Kakafika AI, Papageorgiou AA, et al. Atorvastatin decreases triacylglycerol-associated risk of vascular events in coronary heart disease patients. Lipids 2007;42:999-1009
29. Pedersen TR, Olsson AG, Faergeman O, et al. Lipoprotein changes and reduction in the incidence of major coronary heart disease events in the Scandinavian Simvastatin Survival Study (4S). Circulation 1998;97:1453-60
30. Olsson AG, Schwartz GG, Szarek M, et al. High-density lipoprotein, but not low-density lipoprotein cholesterol levels influence short-term prognosis after acute coronary syndrome: results from the MIRACL trial. Eur Heart J 2005;26:890-6
31. Simes RJ, Marschner IC, Hunt D, et al. Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? Circulation 2002;105: 1162-9
32. Gotto AM Jr, Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Circulation 2000;101:477-84
33. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation 1998;97:1440-5
34. Kakafika A, Athyros VG, Tziomalos K, et al. High density lipoprotein cholesterol and statin trials. Curr Med Chem 2008;15:2265-70
35. Shepherd J, Kastelein JJ, Bittner V, et al. Effect of intensive lipid lowering with atorvastatin on renal function in patients with coronary heart disease: the Treating to New Targets (TNT) study. Clin J Am Soc Nephrol 2007;2:1131-9
36. Tonelli M, Isles C, Craven T, et al. Effect of pravastatin on rate of kidney function loss in people with or at risk for coronary disease. Circulation 2005;112:171-8
37. Collins R, Armitage J, Parish S, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005-16
38. Athyros VG, Mikhailidis DP, Liberopoulos EN, et al. Effect of statin treatment on renal function and serum uric acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: a subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. Nephrol Dial Transplant 2007; 22:118-27
39. Athyros VG, Mikhailidis DP, Papageorgiou AA, et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease. A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. J Clin Pathol 2004; 57:728-34
40. Youssef F, Gupta P, Seifalian AM, et al. The effect of short-term treatment with simvastatin on renal function in patients with peripheral arterial disease. Angiology 2004; 55:53-62
41. Alnaeb ME, Youssef F, Mikhailidis DP, et al. Short-term lipid-lowering treatment with atorvastatin improves renal function but not renal blood flow indices in patients with peripheral arterial disease. Angiology 2006;57:65-71
42. Tonelli M, Isles C, Curhan GC, et al. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 2004;110:1557-63
43. Shepherd J, Kastelein JJ, Bittner V, et al. Intensive lipid lowering with atorvastatin in patients with coronary heart disease and chronic kidney disease: the TNT (Treating to New Targets) study. J Am Coll Cardiol 2008;51:1448-54
44. Chonchol M, Cook T, Kjekshus J, et al. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. Am J Kidney Dis 2007;49:373-82
45. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22
46. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med 2007;357: 2248-61
47. Gissi-Hf I. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 2008
48. Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006;295:1556-65
49. Crouse JR III, Raichlen JS, Riley WA, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR Trial. JAMA 2007;297:1344-53
50. Milionis HJ, Rizos E, Kostapanos M, et al. Treating to target patients with primary hyperlipidaemia: comparison of the effects of ATOrvastatin and ROSuvastatin (the ATOROS study). Curr Med Res Opin 2006;22:1123-31
51. Ter Avest E, Abbink EJ, Holewijn S, et al. Effects of rosuvastatin on endothelial function in patients with familial combined hyperlipidaemia (FCH). Curr Med Res Opin 2005; 21:1469-76

52. Jones PH, Davidson MH, Stein EA, et al. Comparison of the efficacy and safety of rosuvastatin versus atorvastatin, simvastatin, and pravastatin across doses (STELLAR* Trial). Am J Cardiol 2003;92:152-60
53. Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005;294: 2437-45
54. de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004;292:1307-16
55. Kiortsis DN, Filippatos TD, Mikhailidis DP, et al. Statin-associated adverse effects beyond muscle and liver toxicity. Atherosclerosis 2007;195:7-16
56. Davidson MH, Robinson JG. Safety of aggressive lipid management. J Am Coll Cardiol 2007;49:1753-62

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