The JUPITER lipid lowering trial and vitamin D

Is there a connection?

William R. Ware

Faculty of Science (Emeritus); University of Western Ontario; London, ON CA

There is growing evidence that vitamin D deficiency significantly increases the risk of adverse cardiovascular events and that a vitamin D status representing sufficiency or optimum is protective. Unfortunately, in clinical trials that address interventions for reducing risk of adverse cardiovascular events, vitamin D status is not generally measured. Failure to do this has now assumed greater importance with the report of a study that found rosuvastatin at doses at the level used in a recent large randomized lipid lowering trial (JUPITER) had a large and significant impact on vitamin D levels as measured by the metabolite 25-hydroxyvitamin D. The statin alone appears to have increased this marker such that the participants on average went from deficient to sufficient in two months. The difference in cardiovascular risk between those deficient and sufficient in vitamin D in observational studies was similar to the risk reduction found in JUPITER. Thus it appears that this pleiotropic effect of rosuvastatin may be responsible for part of its unusual effectiveness in reducing the risk of various cardiovascular endpoints found in JUPITER and calls into question the interpretation based only on LDL cholesterol and CRP changes. In addition, vitamin D status is a cardiovascular risk factor which up until now has not been considered in adjusting study results or in multivariate analysis, and even statistical analysis using only baseline values may be inadequate.

Introduction

The JUPITER primary prevention randomized placebo controlled trial using the HMG-CoA reductase inhibitor rosuvastatin reported in late 2008 with relative risk reductions for adverse vascular events which were considerably larger than in previous statin trials.[1] The trial was terminated about two years into a planned five-year period due to favorable results. By the estimates of the authors, the reduction in vascular risk was double that expected. Furthermore, while not mentioned, this was the first primary prevention statin trial to find benefit for women. Recent meta analyses of previous primary prevention trials gave null results.[2,3] The JUPITER results are particularly interesting since those enrolled had rather low LDL levels (<130 mg/dL, mean 108 mg/dL). More detailed subgroup analyses have regularly appeared subsequent to the original paper, the most recent concerning women[4] and the elderly.[5] The results with a JUPITER subgroup of older individuals found much larger benefits were found for a number of endpoints than were observed in a randomized trial (PROSPER) of pravastatin in elderly individuals in the primary prevention subgroup.[6] It would be surprising if JUPITER fails to have a significant impact on prescribing practices, especially following the FDA approval a new label for rosuvastatin that expands the eligible population dramatically.

The distinguishing feature of the JUPITER study population was elevated C-reactive protein (CRP) with levels greater than 2 mg/L, a mean of 4.2–4.3 and an interquartile range of 2.8 to about 7.2. While described as healthy, asymptomatic adults, about 42% qualified as having the metabolic syndrome and most were overweight and some obese. Large

reductions in LDL and CRP occurred along with the large relative risk reductions in adverse events including nonfatal myocardial infarction (MI), any MI, nonfatal stroke, revascularization, stroke and death from any cause. Absolute risk reductions were small. There is now a debate regarding the merits of CRP screening, especially since CRP is a non-specific marker for inflammation with many potential reasons for small or large elevations.

While the exceptional benefits observed in JUPITER were attributed to the decline in both LDL and CRP,[1,7] this view ignores the potential influence of vitamin D, where deficiency is now recognized as a strong risk factor for cardiovascular disease.[8] In the study population, almost 50% were described as having the metabolic syndrome. Individuals with the metabolic syndrome typically have elevated CRP,[9] and there is some evidence that high levels of CRP correlate with low levels of vitamin D.[10] In addition, studies with large cohorts (e.g., NHANES) indicate that individuals with the metabolic syndrome typically have low levels of vitamin D,[11,12] although smaller studies are inconsistent. It is also widely recognized that the elderly are particularly prone to vitamin D deficiency and JUPITER had a median cohort age of 66 years. JUPITER can be viewed as selecting a study population particularly prone to exhibiting vitamin D deficiency from a population that probably already had a significant number with hypovitaminosis D due to geographic location and widespread deficiency in general. But most importantly, a recent study found that rosuvastatin strongly increases levels of 25-hydroxyvitamin D, a metabolite of vitamin D and marker for vitamin D status, in statin naïve individuals at doses equal to or less than used in JUPITER.[13] The increase was much greater than previously seen with other statins. Since there is strong evidence that low vitamin D status results in enhanced risk of cardiovascular events and high levels are protective, it would appear that baseline levels of vitamin D as well as changes in levels must be considered when comparing treated vs. placebo groups in statin studies, especially those involving rosuvastatin, since for this statin the potential exists for serious confounding arising during the treatment period.

The purpose of this communication is to suggest that the large relative beneficial effects of rosuvastatin in JUPITER were in part due to the a pleiotropic effect, especially remarkable with this particular statin, whereby vitamin D status was strongly elevated by the intervention in a population where vitamin D deficiency was probably prevalent.

Vitamin D and Statins

Very recently Yavuz et al.[13] reported a study of 91 hyperlipidemic patients who had not been treated with lipid-lowering medications. Vitamin D status was measured by 25-hydroxyvitamin D (25(OH)D) serum levels at baseline and after 8 weeks of rosuvastatin treatment. Rosuvastatin was given in doses of 10–20 mg/day and mean LDL levels decreased from 174 to 100 mg/dL. At baseline the group had a mean level of 25(OH)D of 14 ng/mL which after 8 weeks of treatment increased to 36.3 ng/mL. These changes correspond to going from seriously deficient to what is generally considered sufficient but not optimal. A second study from this same research group[14] compared the vitamin D elevation of rosuvastatin and fluvastatin and confirmed the earlier study as well as studies that found other statins only slightly elevate 25(OH)D levels if at all.[15,16] In the case of fluvastatin there was no significant effect on vitamin D levels. In this second study, the median 25(OH)D levels went from 11.8 to 35.2 ng/mL in the rosuvastatin group. The mechanism for the association between statins and vitamin D metabolism is unknown. The authors cited examples showing that this increase in vitamin D status should provide enhanced protection against MI and all-cause mortality and that the clinical benefit of statins might be mediated through vitamin D increases, but they did not connect this pleiotropic effect with JUPITER.

Vitamin D and the JUPITER Endpoints

The evidence of the importance of vitamin D status in connection with the risk of cardiovascular events is strong and growing.[8,17] Those who doubt there is a

connection may cite the Woman's Health Initiative trial which yielded null results, but that trial did not include measurements of 25(OH)D and the level of supplementation used was considered even by the investigators to have been in retrospect too low.[18] Thus the interesting question involves to what extent the risk reduction in JUPITER can be accounted for by significant vitamin D level elevation. Relevant information is available from a number of studies.

Myocardial infraction. Giovannucci et al.[19] in a prospective study of over 18,000 men in the Health Professionals Follow-up Study, found there was an increased relative risk of 2.42 for MI when those with 25(OH)D ≤15 ng/mL at baseline were compared with those with levels ≥30 ng/mL. Follow-up was for 10 years. Adjustment for a number of confounding variables reduced the relative risk only to 2.09. Both numbers were statistically significant. These risk increases are consistent with the observed risk reductions of the JUPITER trial for essentially the same mean 25(OH)D level differences as measured in the observational study or predicted from the results of Yavuz et al.[13]

First cardiovascular event. Wang et al.[20] in a study of over 1,700 individuals, found that those with 25(OH)D <15 ng/mL had a significant multivariable-adjusted hazard ratio for developing a first cardiovascular event of 1.63 compared to those with this marker ≥15 ng/mL. Adjustment for C-reactive protein did not change the result. The somewhat smaller effect than found in the study of Giovannucci et al. may be related to the difference in the way the comparison was made. Although JUPITER did not have this specific endpoint, the reduction in risk associated with elevated vitamin D levels was similar to that found for combined MI, stroke or cardiovascular related mortality (47%).

Stroke. JUPITER found an approximate 50% reduction in both nonfatal or any stroke. For comparison, three intervention studies (WOSCOP, ASCOT and ALLHAT-LLT) with somewhat similar populations, aside from elevated CRP, found stroke risk reductions of 11, 27 and 9% respectively with statins other than rosuvastatin.[21] The much greater risk reduction found in JUPITER may be

due to the large effect of rosuvastatin on 25(OH)D levels. In an observational study Pilz et al. found low vitamin D levels were associated with increased risk of stroke.[22] For an approximate 20 ng/mL increase in 25(OH)D there was a 33% decrease in the risk of fatal stroke. While JUPITER did not stratify by fatal stroke, the high vitamin D status appears to conferred risk reductions comparable to JUPITER. Lee and Greenfield[23] comment on the work of Pilz et al. by pointing out that statins might have been a confounding factor. They cite a study which found that atorvastatin raised 25(OH)D levels from 16.4 to 18 ng/mL but this appears too small to explain the above discrepancy.

Mortality. The association of vitamin D status and mortality was examined in a study using a national database (NHANES III) and eight years of follow-up. The increase in risk of mortality when those with 25(OH)D levels in the lowest quartile (<17.8 ng/mL) were compared to the highest quartile (>32.1 ng/mL) was 26%.[24] A recent study of the same database revealed similar results in older US adults.[25] Also, Dobnig et al.[26] in a prospective cohort study, found that when patients in the highest quartile of 25(OH)D (median 28.4 ng/mL) were used for comparison, all cause mortality for the lowest two quartiles with median levels of 7.6 and 13.3 ng/mL had significant hazard ratios of 2.08 and 1.53. A recent report from the prospective Hoorn Study[27] of older men and women found that when the lowest quartile 12.2 ng/mL 25(OH)D was compared with the three upper quartiles, the highest of which had a mean 25(OH)D of 31.5 ng/mL, the hazard ratio was 1.97. Also a recent study found that as 25(OH)D levels fell below 30 ng/mL risk of sudden cardiac death increased and reached a factor of 5 for levels below 10 ng/mL in an adjusted model.[28] Similar results were found by Semba et al.[29] and in a recent systematic review and meta-analysis.[30] Taken together, these results are similar and perhaps somewhat stronger than those found in JUPITER where a 20% decrease in the risk of all cause mortality was found when treated patients were compared to those on a placebo. There have been a number of randomized intervention trials with

vitamin D that examined overall mortality, but the statistical power was highly variable as were on-treatment 25(OH)D levels. For 12 placebo controlled trials[31] the risk reduction was about 10%, but final 25(OH)D levels were lower than estimated for JUPITER on the basis of the study of Yavuz et al. These randomized trials also appear consistent with JUPITER if one considers that the risk reduction appears proportional to the increase in vitamin D status.

Thus similar risk reductions are found for various endpoints obtained by JUPITER and in observational studies and randomized trials for roughly the same change in vitamin D status, measured in the observational and randomized trials studies and estimated for JUPITER.

Implications and Testing the Hypothesis

The strong association between rosuvastatin and vitamin D status needs to be independently confirmed and the mechanism whereby statins and in particular rosuvastatin increase 25(OH)D levels needs to be investigated. In addition, it remains to be demonstrated that this is a durable effect with continued rosuvastatin use. Furthermore, aside from trials mentioned above with mortality as an endpoint there appear to be only two randomized controlled vitamin D trials with cardiovascular endpoints[18,32] and as Giovannucci points out,[8] both employed doses of vitamin D that may have been too low and in the study where 25(OH)D was measured, the change was rather small. It found a non-significant decrease in cardiovascular disease incidence of 10%. Thus there is an acute need for randomized controlled trials to examine the implications of observational studies and determine if increasing 25(OH)D levels from deficiency to sufficiency through supplementation significantly decreases the risk of adverse cardiovascular events. Such a trial would require supplemental levels of vitamin D sufficient to raise 25(OH)D levels to at least 35–40 ng/mL in individuals not taking statins and monitoring the levels along with some or all of the outcomes examined in JUPITER. These outcomes could possibly be introduced as secondary

in other vitamin D studies or 25(OH)D measurements could be included in future statin comparison trials that included rosuvastatin. A trial like JUPITER but comparing rosuvastatin with vitamin D supplementation rather than a placebo with measured 25(OH)D levels at baseline and during the study would also obviously be informative but will probably never take place. If there are stored serum samples from JUPITER then data might be obtained which would enable one to determine the impact of elevated vitamin D levels.

JUPITER was a short term study and thus the mechanisms whereby benefits which were derived from elevating 25(OHD) levels would have to become effective over this period to have relevance to the hypothesis being advanced. Giovannucci[8] discusses a number of mechanisms for the interaction of vitamin D levels and cardiovascular disease risk mechanisms, some of which of might operate over a two-year period to influence event rates.

The statin-cholesterol-vitamin D biochemistry may be complex. A recent study added supplemental D2 and D3 to atorvastatin already being used by a small group of patients. There was reason to expect that increasing vitamin D metabolites might enhance the clearance of the statin and its active metabolites and reduce the time-integrated statin concentration, which is what appears to have happened. However, total and LDL cholesterol unexpectedly also decreased for reasons that are not clear.[33] Furthermore, in JUPITER, a small increase in type 2 diabetes was seen, but there is strong evidence supporting the role of vitamin D deficiency in promoting the pathogenesis of this disease.[34] Finally, it has been suggested that statins may be analogues of vitamin D,[35] and although rosuvastatin does not appear to significantly bind to the vitamin D receptor, it does bind to the glucocorticoid receptor and the thyroid β1 receptor, both of which strongly bind both 25(OH)D and the active form of this vitamin, 1,25-dihydroxyvitamin D.[36] This active form is also elevated by rosuvastatin.[13]

If the elevation of vitamin D levels by rosuvastatin turns out to play a significant

or perhaps dominant role in the overall benefits of the intervention in JUPITER, then this will impact the current view concerning the significance of lowering CRP in the context of JUPITER and the suggestion of using CRP as an indicator for statin treatment in asymptomatic individuals with low LDL having one or more risk factors. If it turns out that similar cardiovascular benefits can be obtained by bringing individuals up to the upper end of sufficiency or even into the optimum range of 25(OH)D by just using supplements, this becomes an attractive option for a number of reasons including cost, negligible side effects, and especially, benefits related to a number of other disorders.[37] Oral doses of vitamin D3 sufficient to put one in the optimum category (≥50 ng/mL) appear to be completely safe.[38]

Conclusion

Changes in vitamin D status may confound some statin studies finding cardiovascular risk reduction. This possibility appears very likely in JUPITER because of the apparently unusual ability of rosuvastatin to strongly elevate 25(OH)D levels. The similar risk reductions for various endpoints obtained by JUPITER and in observational studies for roughly the same change in vitamin D status, measured in the observational studies and estimated for JUPITER, suggests that this confounding may be significant. Also, it would seem that since vitamin D deficiency now qualifies as a significant risk factor for cardiovascular disease, it should be included in the statistical analysis of results from statin trials and even considering just baseline values may be insufficient for proper interpretation.

Given the results of observational studies regarding the importance of vitamin D status in cardiovascular disease and the impact JUPITER may have on indications for lifelong treatment with statins, relevant and adequately powered studies which address the issues raised above appear to be very important and urgently needed. Finally, it seems that in future clinical and observational studies that are concerned with cardiovascular risk, failure to consider vitamin D status as well as the effect of statins on vitamin D levels represents ignoring an important confounder.

References

1. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein. N Engl J Med 2008; 359:2195-207.
2. Eisenberg T, Wells M. Statins and Adverse Cardiovascular Events in Moderate-risk Females: A Statistical and Legal Analysis with Implication for FDA Preemption Claims. J Emperical Legal Studies 2008; 5:507-50.
3. Petretta M, Costanzo P, Perrone-Filardi P, Chiariello M. Impact of gender in primary prevention of coronary heart disease with statin therapy: a meta-analysis. Int J Cardiol 2010; 138:25-31.
4. 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; 121:1069-77.
5. 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; 152:488-96.
6. Shepherd J, Blauw GJ, Murphy MB, Bollen EL, Buckley BM, Cobbe SM, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360:1623-30.
7. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. 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; 373:1175-82.
8. Giovannucci E. Vitamin D and cardiovascular disease. Curr Atheroscler Rep 2009; 11:456-61.
9. Ford ES. The metabolic syndrome and C-reactive protein, fibrinogen and leukocyte count: findings from the Third National Health and Nutrition Examination Survey. Atherosclerosis 2003; 168:351-8.
10. Timms PM, Mannan N, Hitman GA, Noonan K, Mills PG, Syndercombe-Court, et al. Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM 2002; 95:787-96.
11. Ford ES, Ajani UA, McGuire LC, Liu S. Concentrations of serum vitamin D and the metabolic syndrome among US adults. Diabetes Care 2005; 28:1228-30.
12. Lee DM, Rutter MK, O'Neill TW, Boonen S, Vanderschueren D, Bouillon R, et al. Vitamin D, parathyroid hormone and the metabolic syndrome in middle-aged and older European men. Eur J Endocrinol 2009; 161:947-54.
13. Yavuz B, Ertugrul DT, Cil H, Ata N, Akin KO, Yalcin AA, et al. Increased levels of 25 hydroxyvitamin D and 1,25-dihydroxyvitamin D after rosuvastatin treatment: a novel pleiotropic effect of statins? Cardiovasc Drugs Ther 2009; 23:295-9.
14. Ertugrul DT, Yavuz B, Cil H, Ata N, Akin KO, Kucukazman M, et al. STATIN-D Study: Comparison of the Influences of Rosuvastatin and Fluvastatin Treatment on the Levels of 25 Hydroxyvitamin D. Cardiovasc Ther 2010.
15. Perez-Castrillon JL, Vega G, Abad L, Sanz A, Chaves J, Hernandez G, et al. Effects of Atorvastatin on vitamin D levels in patients with acute ischemic heart disease. Am J Cardiol 2007; 99:903-5.
16. Aloia JF, Li-Ng M, Pollack S. Statins and vitamin D. Am J Cardiol 2007; 100:1329.
17. Sood A, Arora R. Vitamin D Deficiency and Its Correlations With Increased Cardiovascular Incidences. Am J Ther 2009.
18. Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, et al. Calcium/vitamin D supplementation and cardiovascular events. Circulation 2007; 115:846-54.
19. Giovannucci E, Liu Y, Hollis BW, Rimm EB. 25-hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch Intern Med 2008; 168:1174-80.
20. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation 2008; 117:503-11.
21. Navi BB, Segal AZ. The role of cholesterol and statins in stroke. Curr Cardiol Rep 2009; 11:4-11.
22. Pilz S, Dobnig H, Fischer JE, Wellnitz B, Seelhorst U, Boehm BO, et al. Low vitamin D levels predict stroke in patients referred to coronary angiography. Stroke 2008; 39:2611-3.
23. Lee P, Greenfield JR. 25-Hydroxyvitamin D and risk of stroke: possible mediation by statin therapy? Stroke 2009; 40:35-8.
24. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. Arch Intern Med 2008; 168:1629-37.
25. Ginde AA, Scragg R, Schwartz RS, Camargo CA Jr. Prospective study of serum 25-hydroxyvitamin D level, cardiovascular disease mortality and all-cause mortality in older US Adults. J Am Geriatr Soc 2009; 57:1595-603.
26. Dobnig H, Pilz S, Scharnagl H, Renner W, Seelhorst U, Wellnitz B, et al. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. Arch Intern Med 2008; 168:1340-9.
27. Pilz S, Dobnig H, Nijpels G, Heine RJ, Stehouwer CD, Snijder MB, et al. Vitamin D and mortality in older men and women. Clin Endocrinol (Oxf) 2009; 71:666-72.
28. Pilz S, Marz W, Wellnitz B, Seelhorst U, Fahrleitner-Pammer A, Dimai HP, et al. Association of Vitamin D Deficiency with Heart Failure and Sudden Cardiac Death in a Large Cross-Sectional Study of Patients Referred for Coronary Angiography. J Clin Endocrinol Metab 2008; 93:3927-35.
29. Semba RD, Houston DK, Bandinelli S, Sun K, Cherubini A, Cappola AR, et al. Relationship of 25-hydroxyvitamin D with all-cause and cardiovascular disease mortality in older community-dwelling adults. Eur J Clin Nutr 2010; 64:203-9.
30. Parker J, Hashmi O, Dutton D, Mavrodaris A, Stranges S, Kandala NB, et al. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. Maturitas 2010; 65:225-36.
31. Autier P, Gandini S. Vitamin D Supplementation and Total Mortality: A Meta-analysis of Randomized Controlled Trials. Arch Intern Med 2007; 167:1730-7.
32. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003; 326:469.
33. Schwartz JB. Effects of vitamin D supplementation in atorvastatin-treated patients: a new drug interaction with an unexpected consequence. Clin Pharmacol Ther 2009; 85:198-203.
34. Chowdhury TA, Boucher BJ, Hitman GA. Vitamin D and type 2 diabetes: Is there a link? Prim Care Diabetes 2009; 3:115-6.
35. Grimes DS. Are statins analogues of vitamin D? Lancet 2006; 368:83-6.

36. Marshall TG. Are statins analogues of vitamin D? Lancet 2006; 368:1234.

37. Borradale D, Kimlin M. Vitamin D in health and disease: an insight into traditional functions and new roles for the 'sunshine vitamin'. Nutr Res Rev 2009; 22:118-36.

38. Heaney RP. Vitamin D: criteria for safety and efficacy. Nutr Rev 2008; 66:178-81.