REVIEW

The JUPITER and AURORA clinical trials for rosuvastatin in special primary prevention populations: perspectives, outcomes, and consequences

Venkata Narla
Michael J Blaha
Roger S Blumenthal
Erin D Michos

The Ciccarone Preventive Cardiology Center, Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Abstract: Statins have emerged at the forefront of preventive cardiology and have significantly reduced cardiovascular events and mortality. Nonetheless, cardiovascular disease remains the leading cause of death in the United States and in other developed countries, as well as the etiology of significant morbidity and health-care expenditure. In an attempt to reduce potentially missed opportunities for instituting preventive therapy, the JUPITER study (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) and the AURORA study (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) examined the effect of statins in two specific patient populations who currently do not meet the guidelines for statin treatment, but nonetheless, are at high cardiovascular risk. This review outlines the JUPITER and AURORA trials, interprets the data and significance of the results, analyses the drawbacks and impact of both trials and delineates the potential for further clinical trials.

Keywords: JUPITER, AURORA, rosuvastatin, cardiovascular disease

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the United States and other industrialized countries and in addition leads to substantial health-care expenditures and morbidity.[1] The American Heart Association projects that 80 million American adults experience one or more forms of cardiovascular disease (CVD), of whom 73 million have hypertension, 16.8 million have coronary heart disease (including 7.9 million with history of myocardial infarction), 6.5 million have experienced a stroke and 5.7 million have heart failure.[1] The estimated cost to treat CVD in the United States in 2008 was US$475.3 billion.[1] Over the last several decades, efforts to treat or prevent risk factors for CVD have substantially lowered rates of CVD-related mortality. HMG-CoA reductase inhibitors, or "statins", have emerged as the predominant therapeutic strategy for preventing and treating CVD.

Several landmark trials from the 1990s established the beneficial effects of statins in reducing cardiovascular events in secondary prevention[2–4] as well as for primary prevention among those with elevated levels of low-density lipoprotein-cholesterol (LDL-C)[5] or with below average levels of high-density lipoprotein-cholesterol (HDL-C).[6] However, lipid screening alone incompletely identifies individuals likely to benefit from statin therapy.[7] Among statin-treated patients with established coronary heart disease, recent data suggest even lower LDL-C targets (such as <70 mg/dL) are associated with more favorable outcomes.[8,9]

Correspondence: Erin D Michos
Assistant Professor of Medicine, Division of Cardiology, Johns Hopkins University, School of Medicine, Carnegie 568, 600 N. Wolfe Street, Baltimore, MD 21287, USA
Tel +1 410-502-6813
Fax +1 410-502-0231
Email edonnell@jhmi.edu

1033

The beneficial effects of statins are usually attributed to their ability to reduce endogenous cholesterol synthesis; however, statins may have pleiotropic effects including reduction of inflammation, improvement of endothelial function, anti-oxidant properties and increased stability of atherosclerotic plaques.[10] These other mechanisms could also contribute to the significant reduction in cardiovascular morbidity and mortality achieved with statins.

Rosuvastatin pharmacology

Statins competitively inhibit hydroxy-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), the principal enzyme involved in cholesterol biosynthesis. Mevalonate, the product of HMG-CoA reductase reaction, is the precursor not only for cholesterol but also for many isoprenoid compounds vital for cellular growth and differentiation. Inhibition of HMG-CoA reductase and the resultant inhibition of these important pathways, appears to explain the pleiotropic effects of statins.

As reviewed by Kapur,[11] there are several pharmacologic properties that differentiate rosuvastatin from other statins. Rosuvastatin displays enhanced binding of HMG-CoA reductase, leading to more potent inhibition of the enzyme. In addition, rosuvastatin is not entirely dependent on cytochrome P450 3A4 for metabolism, which may lead to improved clinical safety profile when used with other medications.

Rosuvastatin is currently approved for the treatment of high LDL-C, high total cholesterol and/or high triglyceride levels. The recommended starting dose ranges from 5 to 20 mg individualized to patient factors and baseline LDL-C, with titration up to 40 mg for individuals who have not achieved LDL-C goal with 20 mg.

Early rosuvastatin efficacy trials

Rosuvastatin appears to be the most potent of the available statins, leading to both the greatest LDL-C lowering and HDL-C raising effects in the MERCURY I and II trials[12,13] and the STELLAR trial.[14] In these studies, rosuvastatin also produced greater reductions in total cholesterol and nonHDL-C and produced similar or greater reductions in triglycerides compared to other statins in patients both with and without the metabolic syndrome. Like other statins, rosuvastatin has beneficial effects on advanced lipid biomarkers such as LDL particle size and number.

High-dose statins have been shown to demonstrate a slowing or halting of progression of atherosclerosis as measured by carotid ultrasound, quantitative coronary angiography, or intravascular ultrasound.[15–18] In the METEOR study, rosuvastatin led to a significant reduction in the rate of progression of maximum carotid intima-media thickness over 2 years, even among "low-risk" middle-aged individuals with a low Framingham Risk Score.[19] The ASTEROID study, which used rosuvastatin, was the first study to show that intensive statin therapy can induce regression of atherosclerotic plaque in the coronary arteries at prespecified intravascular ultrasound locations.[20]

The above studies established rosuvastatin as a potent and effective statin and piqued interest in larger randomized clinical trials with hard clinical endpoints.

HsCRP as a biomarker of CVD risk

Of the nearly 800,000 myocardial infarctions and 700,000 strokes that occur in the United States each year, almost half of these events occur in apparently healthy men and women with levels of LDL-C that are below currently recommended thresholds for treatment with statins. Therefore, a need exists to improve risk assessment in asymptomatic individuals without overt evidence of hyperlipidemia, but who may nonetheless benefit from statin therapy.

Numerous biomarkers have been proposed to improve prediction of cardiovascular risk. One such biomarker, high-sensitivity C-reactive protein (hsCRP), is an inflammatory biomarker that has been shown to independently predict cardiovascular events[21,22] across all Framingham Risk groups[23,24] Therefore, hsCRP has been proposed as a novel screening strategy to detect high vascular risk even in the absence of hyperlipidemia and to improve global risk stratification.[25]

HsCRP is strongly associated with the metabolic syndrome and obesity,[26] and because of the epidemic of obesity and metabolic syndrome in the United States,[27] it is likely that the prevalence of elevated hsCRP will increase as well. Weight loss[28] and physical activity[29] can both lower hsCRP levels and lifestyle changes are first line therapy in primary prevention to lower CVD risk. Statins also lower hsCRP levels providing support for the hypothesis that statins may have anti-inflammatory effects in addition to the lipid-lowering effects.[30]

The JUPITER clinical trial
JUPITER trial design

The JUPITER trial (Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) sought to investigate whether statin therapy would reduce first cardiovascular events in individuals who have low levels of LDL-C (outside of current treatment guidelines

for statin therapy), but are nonetheless at increased risk given hsCRP of ≥ 2.0 mg/L.[31,32] The JUPITER trial was a multicenter, randomized, double-blinded, placebo-controlled trial conducted in 26 countries, the largest contributors of patients being the United States, United Kingdom, South Africa and Canada.

The study population consisted of men ≥50 years of age and women ≥60 years of age, who did not have any pre-existing history of CVD, with LDL-C of <130 mg/dL and an hsCRP level of ≥2.0 mg/L. Excluded from the study were those with previous or current use of lipid-lowering therapy, evidence of hepatic dysfunction (alanine aminotransferase level more than twice the upper limit of normal), creatinine >2.0 mg/dL, current use of postmenopausal hormone therapy, creatine kinase elevated to more than 3 times the upper limit of normal, diabetes, uncontrolled hypertension (either systolic blood pressure >190 mmHg or diastolic blood pressure >100 mmHg), cancer within 5 years of enrollment (except basal cell or squamous cell carcinoma of the skin), uncontrolled hypo-thyroidism (thyroid-stimulating hormone level elevated to more than 1.5 times the upper limit of normal), triglyceride level ≥500 mg/dL, history of inflammatory conditions such as lupus, severe arthritis, inflammatory bowel disease, current use of immunosuppressive medications such as cyclosporine and tacrolimus and long-term use of glucocorticoids. Potentially eligible participants underwent a 4-week run-in phase during which they received the placebo and their compliance was assessed. Only those subjects who took more than 80% of all study tablets were defined as demonstrating good compliance and were subsequently enrolled in the study.

After screening approximately 90,000 adults (of which most were not eligible because of either an elevated LDL-C (52%) or a low hsCRP level [36%]), 17,802 apparently healthy men and women who met the inclusion criteria were ultimately random-ized to receive either 20 mg of rosuvastatin daily or placebo. Follow-up visits were scheduled to occur at 13 weeks and subsequently, at 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months. The primary endpoint investigated in JUPITER was the occur-rence of a first major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure, or death from a cardiovascular cause. Secondary endpoints included the individual components of the primary endpoint as well as all-cause mortality.

JUPITER trial results

Although the study was designed to continue for a total of 5 years, a prespecified interim efficacy analysis was per-formed and the independent data and safety monitoring board voted to terminate the trial given the significantly favorable outcomes in the rosuvastatin treatment arm. At the time of study termination with a median follow-up time of 1.9 years, 142 first major cardiovascular events had occurred in the rosuvastatin group as compared to 251 events in the placebo group. The rates of the primary endpoint were 0.77 and 1.36 per 100 person-years of followup in the rosuvastatin and placebo groups, respectively (with a relative risk reduction of 44%, hazard ratio [HR] of 0.56, 95% confidence interval [CI] 0.46 to 0.69, $P < 0.00001$). The rates of the other endpoints are summarized in Table 1. At 12 months, the rosuvastatin group had a 50% lower median LDL-C, a 37% lower hsCRP, a 17% lower triglyceride level and a 4% higher HDL-C level as compared to the placebo group.

The number of patients who would have needed to be treated (NNT) for 2 years to prevent one primary endpoint was 95 and extrapolated to 5 years, the NNT is estimated at 25. These NNT values compare even more favorably with NNT values from other large-scale statin trials. For example, the 5-year NNT value for statin treatment of dyslipidemic individuals enrolled in the WOSCOPS and AFCAPS/TexCAPS primary prevention trials was 44 and 49 respectively.[5,6] This suggests that the strategy of selecting individuals for statin therapy on the basis of an elevated hsCRP is effective. However, the NNT value at 5 years in the JUPITER trial is an extrapolated value as the trial was terminated after a median followup of only 1.9 years, whereas the AFCAPS/TexCAPS and WOSCOPS trials had an average of ~5 years of followup.

JUPITER is also the first large-scale randomized pro-spective study to demonstrate that a statin reduces the risk of venous thromboembolism. Rosuvastatin lowered the risk of deep venous thrombosis or pulmonary embolism by 43% (95% CI, 0.37 to 0.86).[33] Furthermore, there was no increased hemorrhagic stroke risk with rosuvastatin in the JUPITER trial. Therefore, statin therapy may provide a novel approach to preventing deep venous thrombosis and pulmonary embo-lism without a bleeding risk.

All subgroups significantly benefited from rosuvastatin, including those who were previously considered "low-risk" such as women, those without metabolic syndrome, nonsmokers, those with Framingham risk scores of 10% or less, black and Hispanic populations, those with LDL-C level of 100 mg/dL or less and those with body mass indices less than 25 kg/m². JUPITER was the first statin prevention trial to show clear benefits in women (46% risk reduction, 95% CI 0.37 to 0.80), in Blacks and Hispanics (37% risk reduction, 95% CI 0.41 to 0.98) and in the elderly (those above age 70 years, 39% risk reduction, 95% CI 0.46 to 0.82). For those with elevated

Table 1 Summary of JUPITER and AURORA trial results

Endpoint	Rosuvastatin rates per 100 person-year	Placebo rates per 100 person-year	Relative risk reduction %	*P* value
JUPITER results	N = 8901	N = 8901		
Primary endpoint	0.77	1.36	44	<0.00001
Nonfatal MI	0.12	0.33	65	<0.00001
Nonfatal stroke	0.16	0.31	48	0.003
Arterial revasc	0.38	0.71	46	<0.0001
MI, stroke, and CV death	0.45	0.85	47	<0.00001
Death from any cause	1	1.25	20	0.02
AURORA results	N = 1389	N = 1384		
Primary endpoint	9.2	9.5	4	0.59
Nonfatal MI	2.1	2.5	16	0.23
Nonfatal stroke	1.2	1.1	NA	0.42
Death from CV cause	7.2	7.3	0	0.97
Death from any cause	13.5	14	4	0.51
Death from non-CV causes	5.5	6	8	0.34

Abbreviations: MI, myocardial infarction; revasc, revascularizations; CV, cardiovascular.

hsCRP and no other major risk factor except for increased age, the benefit of rosuvastatin was similar to that for higher-risk individuals (39% risk reduction, $P = 0.01$).

There was no significant difference in the incidence of myopathy and newly-diagnosed cancer between the rosuvastatin and placebo groups. There was a small but significant increase in physician-reported diabetes in the rosuvastatin group (270 in rosuvastatin group and 216 in placebo group, $P = 0.01$), as well as a small but significant increase in the median value of glycated hemoglobin (5.9% and 5.8% respectively, $P = 0.001$). However, there was no significant difference between the two groups with respect to fasting blood glucose and glycosuria in the followup period. Therefore, further evaluation must be undertaken to better understand this possible effect. This small increase in diabetes has been observed in previous clinical trials of pravastatin, simvastatin and atorvastatin.

JUPITER unanswered questions
The JUPITER trial demonstrated that in apparently healthy men and women who do not have evidence of hyperlipidemia but who are nonetheless at increased risk given elevated hsCRP, rosuvastatin significantly reduced the risk of first major cardiovascular event and all-cause mortality.

Limitations of the study include the exclusion of individuals with low levels of hsCRP. We cannot know from the JUPITER trial whether individuals with both a low baseline hsCRP and low LDL-C would also have achieved a significant event reduction with statin therapy. The JUPITER trial

investigators made the decision not to include those with low baseline hsCRP based on a posthoc analysis from the AFCAPS/TexCAPS study which found that individuals with low LDL-C (<149.1 mg/dL) and low hsCRP (<1.6 mg/L) had low CVD event rates.[7] Therefore it was felt by the study investigators that the NNT would be too great to enroll individuals with low hsCRP into JUPITER and that it would be unlikely to show a benefit among this subgroup, although the individuals in the AFCAPS/TexCAPS study may have been somewhat younger on average than the JUPITER participants (mean age 58 years in AFCAPS/TexCAPS vs median age of 66 years in JUPITER). It still remains unclear whether all older adults regardless of hsCRP might benefit from statin therapy by virtue of increased baseline risk.

Similarly, men less than 50 years of age and women less than 60 years of age were excluded from the study. Therefore, conclusions cannot be drawn from JUPITER whether younger individuals with elevated hsCRP and low LDL-C levels would also experience a significant event reduction with rosuvastatin therapy and thus the results of JUPITER should not necessarily be extrapolated to younger individuals. In a younger patient population with low LDL-C levels, the possible reduction in event rate that may be achieved with rosuvastatin therapy must be weighed against the risk of prolonged exposure to statin therapy.

Furthermore, the benefit of further reducing hsCRP level beyond LDL-C reduction is not entirely clear. Although hsCRP was substantially reduced in the rosuvastatin group,

LDL-C was also significantly reduced and the median LDL-C level achieved was 55 mg/dL. However, the reduction in event rate by rosuvastatin appeared to be greater than would have been anticipated by the magnitude of the LDL-C reduction. In posthoc analyses of the JUPITER trial, Ridker et al demonstrated that the lowest event rates were among those who achieved both LDL-C level less than 70 mg/dL and hsCRP level less than 2.0 mg/L; however, those who did not achieve on-treatment hsCRP less than 2.0 mg/L were more likely to have higher baseline levels of hsCRP and were more likely to be smokers and have a higher body-mass index.[34]

In performing this posthoc statistical analyses comparing event rates based on categories of achieved on-treatment hsCRP and LDL-C levels, several such factors were adjusted for, including baseline LDL-C, baseline hsCRP, age, sex, smoking status, body-mass index, blood pressure, baseline HDL-C and parental history of premature coronary artery disease. However, given that this was a nonrandomized posthoc analysis, there may be residual confounding factors including the possibility that those with higher levels of baseline and on-treatment hsCRP may have more sedentary, with less healthier lifestyles. These types of subtle confounding factors differentiating "good health" vs "poorer health" are measured imprecisely and cannot be adequately adjusted for in an observational analysis.

Because rosuvastatin dramatically lowers both LDL-C and hsCRP, the JUPITER trial cannot be used to determine whether hsCRP reduction alone leads to reduced vascular risk. This hypothesis could be tested with agents that have targeted vascular anti-inflammatory effects but do not have proven LDL-C reducing effects. The JUPITER study did not prospectively titrate statin therapy to achieve the dual goals of hsCRP level <2.0 mg/L and LDL-C level <70 mg/dL. Therefore, further evaluation is required to determine whether titrating towards a specific goal hsCRP level is beneficial.

In summary, the JUPITER trial demonstrated that the hsCRP level may be a useful tool in selecting for individuals who could benefit from statin therapy and would otherwise not be candidates for statins under current treatment guidelines. Although lifestyle interventions such as weight loss and exercise can reduce hsCRP and remain critical for prevention, the JUPITER eligibility criteria (in terms of hsCRP screening and indications for statin treatment) are likely to impact future CVD prevention guidelines.

The AURORA clinical trial
AURORA trial design
The AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events) trial was a primary prevention study which examined the potential benefit of statins in another specific patient population at high CVD risk – end-stage renal disease (ESRD) patients on chronic hemodialysis.[35] ESRD patients have previously been excluded from studies on statins because of their numerous comorbidities and issues of safety, leading to a paucity of data on these patients. However, CVD is very common in patients with renal insufficiency and, in particular, the rates of cardiovascular morbidity and mortality are substantially higher among dialysis patients than in those without renal disease.[36] Therefore, there is a crucial need to find an effective method of preventing CVD in this particular patient population.

AURORA was a randomized, double-blinded, placebo-controlled multicenter trial, with patients recruited from 280 centers in 25 countries. The study population included men and women between 50 to 80 years of age with ESRD who had been treated with regular hemodialysis for at least 3 months. Exclusion criteria included: statin therapy within the last 6 months, expected kidney transplantation within 1 year, serious neoplastic, gastrointestinal, hematologic, metabolic (except diabetes), or infectious disease that was predicted to reduce survival to less than 1 year, a history of malignancy, active liver disease (defined as alanine aminotransferase level more than three times the upper limit of normal), unexplained creatine kinase elevation to more than three times upper limit of normal and uncontrolled hypothyroidism (defined by thyroid-stimulating hormone level greater than 1.5 times the upper limit of normal).

There were 2776 patients who met the inclusion criteria who were randomly assigned to rosuvastatin 10 mg or placebo. The two groups of patients were similar with respect to baseline characteristics including age, mean duration of dialysis treatment, sex and race/ethnicity. Followup visits occurred 3 months after randomization and then every 6 months thereafter. Mean length of followup was 3.2 years. No patients were lost to followup.

The primary endpoint investigated in AURORA was time to a major cardiovascular event, defined as nonfatal myocardial infarction, nonfatal stroke, or death from a cardiovascular cause. Secondary endpoints included: all-cause mortality, death from noncardiovascular causes, death from noncardiovascular causes, cardiovascular event-free survival (ie, free from nonfatal myocardial infarction, nonfatal stroke, death from any cause), coronary or peripheral revascularization and procedures performed for stenosis or thrombosis of arteriovenous grafts or fistulas that were being used for hemodialysis.

AURORA trial results

A total of 804 patients had a major cardiovascular event during the followup period, of which 396 were in the rosuvastatin group and 408 were in the placebo group (9.2 and 9.5 events per 100 person-years of followup respectively). There was no significant effect of treatment with rosuvastatin on the primary combined endpoint (HR 0.96; 95% CI 0.84 to 1.11; p = 0.59). There was also no significant effect of treatment with rosuvastatin on the individual components of the primary endpoint. A summary of the AURORA trial results can be found in the Table. The lack of effect of rosuvastatin on the primary endpoint was consistent among all subgroups including those with diabetes, high LDL-C level, elevated hsCRP, hypertension and preexisting CVD. The lack of effect of rosuvastatin on the primary endpoint was also not influenced by overall time on hemodialysis.

At 3 months, LDL-C was reduced by 43% by rosuvastatin as compared to only a 1.9% reduction in the placebo group ($P < 0.001$ for comparison). At 3 months, rosuvastatin also reduced total cholesterol by 27% (as compared with a 0.5% in the placebo group, $P < 0.001$) and triglycerides by 16% (as compared to a 0.9% increase in the placebo group, $P < 0.001$). Median hsCRP level was elevated at baseline (4.8 mg/L in rosuvastatin group vs 5.2 mg/L in the placebo group). This was decreased by 12% by rosuvastatin at 3 months (by 0.65 mg/L vs an increase of 0.21 mg/L in the placebo group, $P < 0.001$).

There was no statistically significant increase in the incidence of rhabdomyolysis or liver disease in the rosuvastatin group as compared to the placebo group. There was a small but statistically significant increase in the incidence of hemorrhagic stroke in diabetic patients who received rosuvastatin in the AURORA trial; this is consistent with findings in the 4D study (Die Deutsche diabetes Dialyse Studie).[37] In addition, there was no increased incidence of physician-reported diabetes as seen in the JUPITER study. Only 10 patients in the rosuvastatin group and fourteen patients in the placebo group were reported to have new-onset diabetes mellitus in the AURORA trial ($P = 0.40$).

AURORA trial unanswered questions

The AURORA trial demonstrated no cardiovascular benefit of rosuvastatin in ESRD patients on chronic hemodialysis despite improvement in surrogate biomarkers. These results from AURORA are comparable with the results from the previously published 4D study, which also examined the cardiovascular benefit of statins in hemodialysis patients. The 4D study also showed no significant benefit of statin therapy on the composite primary endpoint of nonfatal myocardial infarction, fatal or nonfatal stroke and death from a cardiovascular cause in type 2 diabetes patients undergoing chronic hemodialysis. The lack of cardiovascular benefit from statins in both the AURORA trial and 4D trial suggests that CVD in hemodialysis patients may be different from that in the population without renal disease or from those with milder forms of chronic kidney disease (CKD) (ie, CKD stages 1 to 3).

The pattern of cardiovascular events in hemodialysis patients also differs from that in the general population. In the general population, a majority of cardiovascular events are coronary events such as myocardial infarctions. In the hemodialysis population, however, only approximately 25% of cardiovascular events are myocardial infarctions.[38] Rather, heart failure, sudden cardiac death and arrhythmias predominate in this population. Therefore, the anti-inflammatory and lipid-lowering effects of statins may not benefit a population in which myocardial infarctions do not predominate. Rosuvastatin was shown to be ineffective in reducing the incidence of cardiovascular events in heart failure patients in the CORONA and the GISSI-HF trials.[39,40] In these patients, myocardial infarctions were also not responsible for most of the deaths.

Many patients with ESRD on chronic dialysis have calcification of the vascular tree, including medial calcification and valvular calcification, which may not be treatable with statins. While medial and intimal (atherosclerotic) calcification may have some shared risk factors, the distinction of the two types of calcification is important because screening, treatment and prognosis may differ.[41] Instead, issues related to hyperphosphatemia and hyperparathyroidism, both of which are not treatable by statins, may have a more significant influence on medial vascular calcification. Indeed, the authors of the AURORA trial stated that a high phosphate level was one of the strongest risk factors for the occurrence of cardiovascular endpoints in their study. Similarly, left ventricular hypertrophy (LVH) is common in ESRD patients and has been shown in previous studies to be a strong predictor of cardiovascular events in dialysis patients.[42] It is unclear whether statins affect LVH and in fact, data on LVH were not demonstrated in AURORA.

An analogy can potentially be drawn between ESRD and calcific aortic stenosis, where statins seem to have little benefit once the disease process is advanced, but may be beneficial in earlier precursor stages. Degenerative aortic stenosis has many similarities to atherosclerotic plaque histologically and has many similar predisposing risk factors. Statin therapy has therefore been proposed as a way

to slow the rate of progression of aortic stenosis given the similarity with atherosclerosis. However, in the SALTIRE study, treatment with atorvastatin 80 mg had no effect on the rate of progression of calcific aortic stenosis over 2 years of follow-up as assessed by Doppler echocardiography and by change in CT calcium score of the valve, despite reducing the LDL-C by more than 50%.[43] This was further confirmed in the SEAS trial which found simvastatin 40 mg plus ezetimibe 10 mg daily was ineffective at reducing overall events compared with placebo among patients without hyperlipidemia that had calcific aortic stenosis,[44] although ischemic events were reduced. These data suggests that statins reduce cardiac events related to atherosclerosis but not cardiac events related to other pathophysiologic mechanisms.

However, statins may be beneficial when given earlier in the disease process. Using observational data from medical records, Antonini-Canterin et al showed that statins reduce progression of aortic sclerosis and mild aortic stenosis, but not moderate aortic stenosis or greater.[45] Analogous to statins reducing progression of aortic sclerosis but not significant aortic stenosis, statins may not benefit dialysis patients based on the fact that cardiovascular mortality increases progressively through the early stages of CKD and becomes exponentially higher in hemodialysis patients (almost 10 to 20 times higher than the general population). Therefore, it may be too late for statins to provide any benefit in dialysis patients, who have already attained such a high cardiovascular risk, in the same way that statins cannot reduce progression of a frankly stenotic valve.

In patients with CKD but perhaps not end-stage, statin therapy may slow the progression of kidney decline.[46] In a posthoc analysis from the CARDS study,[47] diabetics with moderately decreased estimated glomerular filtration rate of 30 to 60 mL/min/1.73 m^2 experienced a 42% reduction in CVD events with atorvastatin treatment including a 61% reduction in stroke. A Cochrane review of CKD patients not receiving dialysis did confirm that statins overall significantly reduce the risk of all-cause and CVD mortality and appear to be safe in this population.[48]

Limitations of the AURORA trial include some of the exclusion criteria. Specifically, those who were already on a statin were excluded from the trial (this consisted of approximately 30% to 40% of patients on hemodialysis). This group, however, likely included those with a history of previous cardiovascular events and therefore could have been the most likely group to benefit from statin treatment.

Another limitation in this study was that only patients above 50 years of age were included in this trial. It is possible that statins could have benefited younger CKD patients who start statin treatment early. This is in contrast to starting a statin in someone over the age of 50 years, who has been chronically ill for several years with multiple comorbidities, who has already been on dialysis for 3 years and has likely suffered the irreversible deleterious vascular effects of dialysis. Futhermore, the increase in cardiovascular risk among hemodialysis patients is disproportionately higher in young patients.

In addition, those who may undergo kidney transplantation within 1 year were excluded from the study. This likely represents a healthier population of ESRD patients on hemodialysis who may have been more likely to benefit from statin therapy. Another limitation of this study is the possibility of insufficient statistical power. Lastly, approximately 50% of patients in AURORA discontinued treatment; this could have biased the effect of rosuvastatin towards a null result.

Clinical perspectives

Half of all cardiovascular events in the United States each year occur among individuals with normal or low LDL-C levels, suggesting that screening lipid levels alone incompletely identifies individuals who are likely to benefit from statin therapy. In an attempt to reduce these potentially missed opportunities for instituting preventive therapy, the JUPITER and AURORA studies examined the effect of statins in two specific primary prevention patient populations who currently do not meet the guidelines for statin treatment, but nonetheless, are at higher cardiovascular risk than would be predicted by LDL-C alone.

The results from JUPITER have the potential to significantly impact public health and prevention of cardiovascular disease, providing a rationale for broader use of statin therapy for primary prevention than currently recommended. A recent meta-analysis of over 10 clinical trials (including WOSCOPS, AFCAPS/TexCAPS, CARDS, JUPITER and others) together enrolling greater than 70,000 individuals without established CVD but with some CVD risk factors showed that treatment with statins over a mean 4.1 years was associated with a significant 22% reduction in all-cause mortality, 30% reduction in the risk of major coronary events, a 19% reduction in the risk of major cerebrovascular events and no evidence of an increased risk of cancer.[49]

The absolute event rate, which in the JUPITER trial was moderate, must be taken into account when considering broader use of statins in the primary prevention population. A critical question is whether rosuvastatin therapy would be cost-effective and we await forthcoming cost-effectiveness analyses. Previous cost-effectiveness analyses for other primary prevention studies (ASCOT, WOSCOPS) have shown

statin use to be cost-effective.[50,51] The cost of expanding the use of statins may be at least partially offset by the potentially significant reduction in the rates of hospitalization and arterial revascularization that would occur with rosuvastatin treatment as demonstrated in the JUPITER study.

Using data from the National Health and Nutrition Examination Survey (NHANES 1999–2004), we estimated that 6.5 million additional adults could be potential candidates for initiating statin therapy according to the JUPITER criteria.[52] Using the JUPITER eligibility strategy, we estimate that 260,000 CVD events could be prevented in the United States over 5 years. Rosuvastatin costs approximately US$1200/year for each individual and therefore, treating this entire subpopulation would cost approximately US$7.8 billion/year.

It is generally thought that the significant reduction in CVD events conferred by statins is a "class-effect", as event reduction has been shown with all 6 available statins on the US market, with the amount of benefit being related to the magnitude of LDL-C reduction and the patient's absolute risk. As outlined above, clearly certain statins such as rosuvastatin are more potent in terms of LDL-C reduction and may be preferred in patients who have trouble reaching LDL-C goal; however there is no data yet to support that once an LDL-C goal such as <70 mg/dL is reached, that one statin would be preferred over another one. Thus for cost-effectiveness, one may consider treating with generic statin as first line choice if appropriate LDL-C target can be attained.

In addition to costs, the safety profile of statin therapy needs to be considered before a major expansion in statin use can take place. The JUPITER trial was terminated after a median follow-up of only 1.9 years; therefore, the possible (but unlikely) adverse effects of longer-term statin therapy need to be further evaluated. The marginal but significant increase in possible physician-reported diabetes that was demonstrated in the JUPITER trial and other previous statin trials also need to be further evaluated.

On the other hand, the AURORA trial did not show promising results for expanding the use of statins to dialysis patients. The pathogenesis of cardiovascular disease in hemodialysis patients may differ from that in the general population. Although in both subpopulations, the pathogenesis is multifactorial, consisting of calcification, inflammation and atherothrombosis, the degree to which each of these three components contributes to the process may differ substantially. Therefore, the quest for new interventions to reduce cardiovascular risk in dialysis patients should be based on a more accurate understanding of the causal pathway of cardiovascular disease in dialysis patients.

Disclosures

The authors have no financial disclosures or conflicts of interest.

References

1. American Heart Association. Heart disease and stroke statistics – 2008 update. 2008. www.americanheart.org/downloadable/heart/1200082005246HS_Stats%202008.final.pdf Accessed June 2009.
2. The Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet*. 1994;344:1383–1389.
3. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med*. 1998;339:1349–1357.
4. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial Investigators. *N Engl J Med*. 1996;335:1001–1009.
5. Shepherd J, Cobbe SM, Ford I, et al; for the West of Scotland Coronary Prevention Study Group (WOSCOPS). Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med*. 1995;333:1301–1307.
6. 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;279:1615–1622.
7. Ridker PM, Rifai N, Clearfield M, et al; for the Air Force/Texas Coronary Atherosclerosis Prevention Study Investigators. Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med*. 2001;344:1959–1965.
8. LaRosa JC, Grundy SM, Waters DD, et al; for the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352(14):1425–1435.
9. Ridker PM, Cannon CP, Morrow D, et al; for the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators. C-reactive protein levels and outcomes after statin therapy. *N Eng J Med*. 2005;352:20–28.
10. Bellosta S, Ferri N, Bernini F, Paoletti R, Corsini A. Non-lipid-related effects of statins. *Ann Med*. 2000;32:164–176.
11. Kapur NK. Rosuvastatin: a highly potent statin for the prevention and management of coronary artery disease. *Expert Rev Cardiovasc Ther*. 2007;5:161–175.
12. Schuster H, Barter PJ, Stender S, et al. Effective Reductions in Cholesterol Using Rosuvastatin Therapy I study group. Effects of switching statins on achievement of lipid goals: Measuring Effective Reductions in Cholesterol Using Rosuvastatin Therapy (MERCURY I). *Am Heart J*. 2004;147:705–713.
13. Ballantyne CM, Bertolami M, Hernandez Garcia HR, et al. Achieving LDL cholesterol, nonHDL cholesterol and apolipoprotein B target levels in high-risk patient: Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapy (MERCURY II). *Am Heart J*. 2006;151:975.e1–e9.

14. Jones PH, Davidson MH, Stein EA, et al; STELLAR Study Group. Comparison of the Efficacy and Safety of Rosuvastatin versus Atorvastatin, Simvastatin and Pravastatin Across Doses (STELLAR trial). *Am J Cardiol*. 2003;92:152–160.

15. Nissen SE, Tuzcu EM, Schoenhagen P, et al; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. *JAMA*. 2004;291:1071–1080.

16. De Groot E, Jukema JW, van Boven AJ, et al. Effect of pravastatin on progression and regression of coronary atherosclerosis and vessel wall changes in carotid and femoral arteries: a report from the Regression Growth Evaluation Statin Study (REGRESS). *Am J Cardiol*. 1995;76:40C–46C.

17. Blankenhorn DH, Azen SP, Kramsch DM, et al; MARS Research Group. Coronary angiographic changes with lovastatin therapy: the Monitored Atherosclerosis Regression Study (MARS). *Ann Intern Med*. 1993;119:969–976.

18. Waters D, Higginson L, Gladstone P, et al. Effects of monotherapy with HMG-CoA reductase inhibitor on the progression of coronary atherosclerosis as assessed by serial quantitative arteriography: the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT). *Circulation*. 1994;89:959–968.

19. Crouse JR III, Raichlen JS, Riley WA, et al; METEOR Study Group. Effect of Rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: the METEOR trial. *JAMA*. 2007;297:1344–1353.

20. Nissen SE, Nicholls SJ, Sipahi I, et al; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. *JAMA*. 2006;295:1556–1565.

21. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Eng J Med*. 2002;347:1557–1565.

22. Pai PK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med*. 2004;351:2599–2610.

23. Koenig W, Löwel H, Baumert J, Meisinger C. C-reactive protein modulates risk prediction based on the Framingham risk score: implications for future risk assessment: results from a large cohort study in southern Germany. *Circulation*. 2004;109:1349–1353.

24. 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;109:1955–1959.

25. Ridker PM. C-reactive protein and prediction of cardiovascular events among those at intermediate risk. *J Am Coll Cardiol*. 2007;49:2129–2138.

26. 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;168:351–358.

27. Mokdad AH, Serdula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The continuing epidemic of obesity in the United States. *JAMA*. 2000;284:1650–1651.

28. Heilbronn LK, Noakes M, Clifton PM. Energy restriction and weight loss on very-low fat diets reduce C-reactive protein concentrations in obese, healthy women. *Arterioscler Thromb Vasc Biol*. 2001;21:881–883.

29. Kadoglou NP, Iliadis F, Angelopoulou N, et al. The anti-inflammatory effects of exercise training in patients with type 2 diabetes mellitus. *Eur J Cardiovasc Prev Rehabil*. 2007;14:837–843.

30. Plenge JK, Hernandez TL, Weil KM, et al. Simvastatin lowers C-reactive protein within 14 days: an effect independent of low-density lipoprotein cholesterol reduction. *Circulation*. 2002;106:1447–1452.

31. Ridker PM; for the 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;108:2292–2297.

32. Ridker PM, Danielson E, Fonseca FA, et al; for the JUPITER study group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Eng J Med*. 2008;359:2195–2207.

33. Glynn RJ, Danielson E, Fonseca FA, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. *N Eng J Med*. 2009;360:1851–1861.

34. Ridker PM, Danielson E, Fonseca FA, 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;373:1175–1182.

35. Fellström BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Eng J Med*. 2009;360:1395–1407.

36. Baigent C, Burbury K, Wheeler D. Premature cardiovascular disease in chronic renal failure. *Lancet*. 2000;356:147–152.

37. Wanner C, Krane V, März W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353:238–248.

38. Foley RN, Murray AM, Li S, et al. Chronic kidney disease and the risk of cardiovascular disease, renal replacement and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol*. 2005;16:489–495.

39. GISSI-HF Investigators, Tavazzi L, Maggioni AP, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomized double-blind, placebo-controlled trial. *Lancet*. 2008;372:1231–1239.

40. Kjekshus J, Apetrei E, Barrios V, et al; for the CORONA Group. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med*. 2007;357:2248–2261.

41. Amann K. Media calcification and intima calcification are distinct entities in chronic kidney disease. *Clin J Am Soc Nephrol*. 2008;3:1599–1605.

42. Zoccali C, Benedetto F, Mallamaci F, et al. Left ventricular mass monitoring in the follow-up of dialysis patients: prognostic value of left ventricular hypertrophy progression. *Kidney Int*. 2004;65:1492–1498.

43. 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 Eng J Med*. 2005;352:2389–2397.

44. Rossebø AB, Pedersen TR, Boman K, et al; SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. *N Engl J Med*. 2008;359:1343–1356.

45. Antonini-Canterin F, Hirsu M, Popescu BA, et al. Stage-related effects of statin treatment on the progression of aortic valve sclerosis and stenosis. *Am J Cardiol*. 2008;102:738–742.

46. Huskey J, Lindenfeld J, Cook T, et al. Effect of simvastatin on kidney function loss in patients with coronary heart disease: findings from the Scandinavian Simvastatin Survival Study (4S). *Atherosclerosis*. 2009;205:202–206.

47. Colhoun HM, Betteridge DJ, Durrington PN, et al; CARDS Investigators. Effects of Atorvastatin on Kidney Outcomes and Cardiovascular Disease in Patients with Diabetes: An Analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). *Am J Kidney Dis*. 2009 Jun 18. [Epub ahead of print].

48. Navaneethan SD, Pansini F, Perkovic V, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev*. 2009 Apr 15;(2):CD007784.

49. Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ*. 2009;338:b2376.

50. Lindgren P, Buxton M, Kahan T, et al. ASCOT investigators. Cost-effectiveness of atorvastatin for the prevention of coronary and stroke events: an economic analysis of the Anglo-Scandinavian Cardiac Outcomes Trial – lipid-lowering arm (ASCOT-LLA). *Eur J Cardiovasc Prev Rehabil*. 2005;12:29–36.

51. Shepherd J. Economics of lipid lowering in primary prevention: lessons from the West of Scotland Coronary Prevention Study. *Am J Cardiol*. 2001;87:19B–22B.

52. Michos ED, Blumenthal RS. Prevalence of Low Low-Density Lipoprotein Cholesterol with elevated high sensitivity C-reactive protein in the US. *J Am Coll Cardiol*. 2009;53:931–935.