

# Rosuvastatin, inflammation, C-reactive protein, JUPITER, and primary prevention of cardiovascular disease – a perspective

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**Abstract:** The major public health concern worldwide is coronary heart disease, with dyslipidemia as a major risk factor. Statin drugs are recommended by several guidelines for both primary and secondary prevention. Rosuvastatin has been widely accepted because of its efficacy, potency, and superior safety profile. Inflammation is involved in all phases of atherosclerosis, with the process beginning in early youth and advancing relentlessly for decades throughout life. C-reactive protein (CRP) is a well-studied, nonspecific marker of inflammation which may reflect general health risk. Considerable evidence suggests CRP is an independent predictor of future cardiovascular events, but direct involvement in atherosclerosis remains controversial. Rosuvastatin is a synthetic, hydrophilic statin with unique stereochemistry. A large proportion of patients achieve evidence-based lipid targets while using the drug, and it slows progression and induces regression of atherosclerotic coronary lesions. Rosuvastatin lowers CRP levels significantly. The Justification for Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was designed after the observation that when both low density lipoprotein and CRP were reduced, patients fared better than when only LDL was lowered. Advocates and critics alike acknowledge that the benefits of rosuvastatin in JUPITER were real. After a review, the US Food and Drug Administration extended the indications for rosuvastatin to include asymptomatic JUPITER-eligible individuals with one additional risk factor. The American Heart Association and Centers of Disease Control and Prevention had previously recognized the use of CRP in persons with “intermediate risk” as defined by global risk scores. The Canadian Cardiovascular Society guidelines went further and recommended use of statins in persons with low LDL and high CRP levels at intermediate risk. The JUPITER study focused attention on ostensibly healthy individuals with “normal” lipid profiles and high CRP values who benefited from statin therapy. The backdrop to JUPITER during this period was an increasing awareness of a rising cardiovascular risk burden and imperfect methods of risk evaluation, so that a significant number of individuals were being denied beneficial therapies. Other concerns have been a high level of residual risk in those who are treated, poor patient adherence, a need to follow guidelines more closely, a dual global epidemic of obesity and diabetes, and a progressively deteriorating level of physical activity in the population. Calls for new and more effective means of reducing risk for coronary heart disease are intensifying. In view of compelling evidence supporting earlier and aggressive therapy in people with high risk burdens, JUPITER simply offers another choice for stratification and earlier risk reduction in primary prevention patients. When indicated, and in individuals unwilling or unable to change their diet and lifestyles sufficiently, the benefits of statins greatly exceed the risks. Two side effects of interest are myotoxicity and an increase in the incidence of diabetes.

**Keywords:** rosuvastatin, JUPITER study, statin drugs, C-reactive protein, dyslipidemia, cholesterol, primary prevention, cardiovascular risk, coronary heart disease, inflammation, low-density lipoprotein, high-density lipoprotein, diabetes, metabolic syndrome, Framingham risk score, Reynolds risk score, coronary artery calcification, carotid intima-media thickness, hypertension, obesity, HMG CoA reductase, mevalonate, prenylation, statin myopathy, pleiotropic, dolichol

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## Introduction

Cardiovascular disease (CVD) has been the leading cause of death for the past century in the United States (US), except for 1918, the year of an influenza pandemic. Even though

deaths from coronary heart disease (CHD) have fallen during the past 2 decades, the mortality rate from this disease remains the top cause of death in the US, and, by 2020, will attain that status globally as well. An analysis of the fall in CHD death rates from 1980 to 2000 using the IMPACT model of analyzing data from the US National Center for Health Statistics<sup>1,2</sup> revealed that half of this decline was due to improvements in risk factors; 79% was attributable to primary prevention and 21% to secondary prevention.<sup>3</sup> Cholesterol reduction accounted for 42.7% of the death rate reduction in asymptomatic individuals, and for 34% in those with CHD. Use of statin drugs accounted for <20% of the improvement in death rate during those 20 years. Reductions in systolic blood pressure accounted for 38.8% of the fall in asymptomatic individuals and 52.8% in patients with CHD. Decreased use of tobacco accounted for 18.4% of the fall in deaths in asymptomatic individuals, and 12.9% in those with CHD. While the contribution of statins, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGR) inhibitors, was surprisingly small, these results illustrate the power of primary prevention in the management of CHD. Given the lower usage of less potent statins in many of the years surveyed, the data simultaneously suggest that using statin drugs earlier in the disease, for longer periods of time during pathogenesis, and titrated to lower targets, has substantial unrealized potential.

The cardiovascular risk burden in the populations of nearly all countries continues to rise at an alarming rate, and recent analyses show that gains in reducing the death rate from CHD are now being offset by the pressure of increases in reversible factors of obesity,<sup>4</sup> metabolic syndrome, and diabetes, along with the progressive aging of the population.<sup>5–8</sup> Control of risk factors, while impressive thus far, have also fallen short of guideline targets and public health goals. Hence, there is ongoing interest in the best use of all elements of primary prevention in order to improve national heart health. Statin drugs are uniquely effective and prominently recommended in current guidelines. The potency and favorable benefit to risk ratio of rosuvastatin account for its increasing usage in primary and secondary prevention.

Significant and voluminous research concerning the biochemistry, physiology, and clinical potential of measuring C-reactive protein (CRP), has intensified discussions concerning the role CRP monitoring will have in current guidelines for primary prevention. The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, first reported in October 2008, presented evidence that a plasma CRP  $\geq 2$  mg/L reflects higher cardiovascular risk in asymptomatic individuals with low-density

lipoprotein levels (LDL) <130 mg/dL, and that they would benefit from rosuvastatin therapy.<sup>9</sup> Following the JUPITER report, there was lively debate about the data, clinical significance, and how the new information should be incorporated into clinical practice. Many fundamental questions concerning primary prevention have since been revisited, including the early beginnings of CHD and its long incubation period; methods of evaluating risk in the population; how population-based versus individual risk-based approaches may best be employed; role and refinement of global risk factor scores; choice and merits of nontraditional risk factors; assessment of multiple biomarker panels; role of imaging techniques in evaluation and ongoing therapy; value of advanced lipid testing; weights assigned to traditional risk factors, cutoff values, and treatment targets, particularly LDL goals in guidelines; use of statins in primary prevention; reasons for low patient adherence with evidence-based therapies; causes of “clinical inertia” and lack of physician compliance with guidelines; and the etiologies, extent, and minimization of residual risk.

## C-reactive protein

The fundamental role of inflammation in the pathogenesis of atherothrombotic disease is based upon strong evidence and is well-accepted.<sup>11–61</sup> CRP protein is an acute phase reactant discovered by Tillett and Francis at Rockefeller University in 1930 in the blood of patients with pneumonia,<sup>62</sup> was crystallized in 1947, and today, over 60 years later, there is still controversy about its physiology and applications in biomedicine. CRP protein is a pentraxin comprised of 5 subunits (Figure 1) which is primarily synthesized in the liver, and plays an active part in regulating the innate immune system. Since CRP mRNA levels rise in adipose tissue as CRP expression is enhanced in vitro by interleukin-6 (IL-6), adipose cells also have some ability to synthesize CRP. Innate immunity and adaptive immunity significantly modulate atherosclerosis,<sup>13,63,64</sup> with both pro- and anti-atherogenic potential.<sup>64–66</sup>

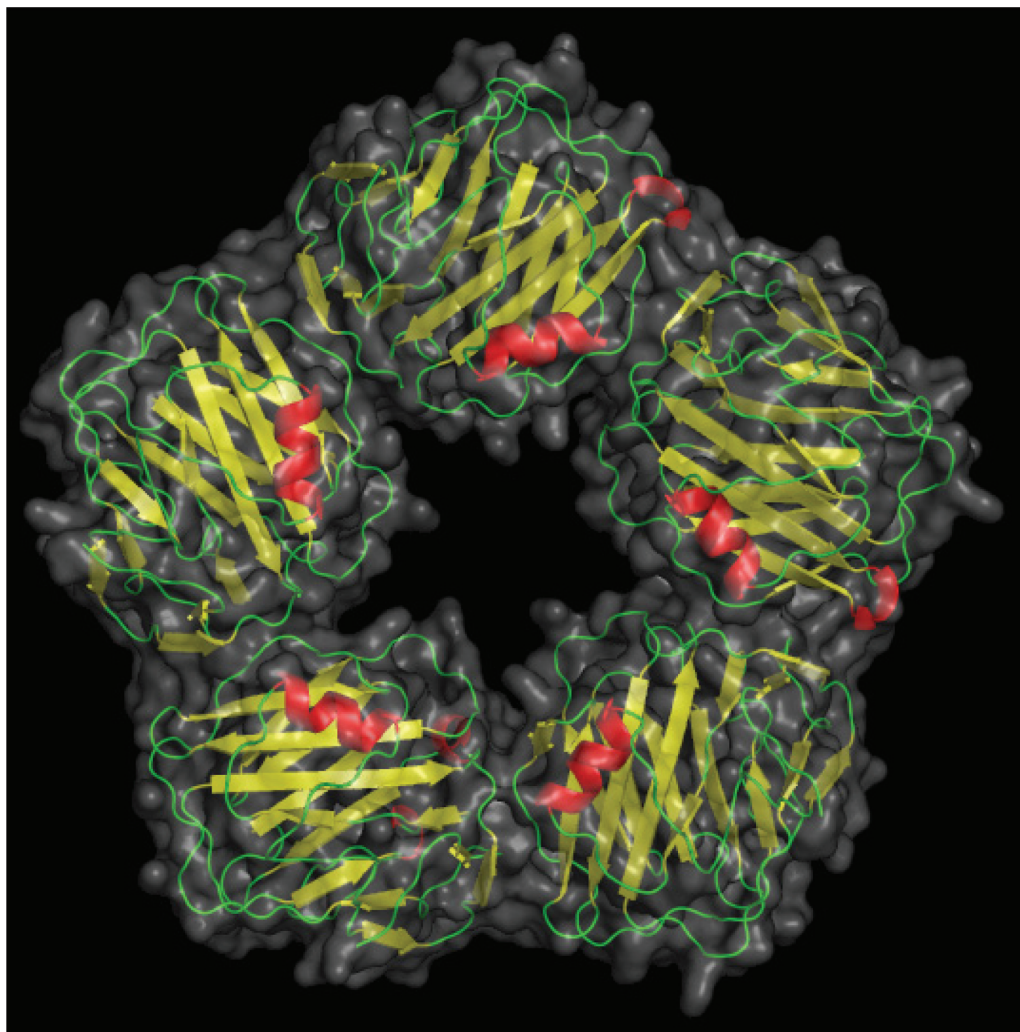
CRP binding offers a glimpse into teleological function. CRP binds to phosphocholine, commonly found in cell membranes as well as in bacterial and fungal polysaccharides. Phosphocholine is used by the placenta and nematodes to cloak them from their host immune system. Binding to complement C1q complex and factor H, CRP assists in human complement activity to promote antigen presentation and phagocytosis,<sup>67</sup> essentially functioning as an innate opsonin. In addition, CRP binds directly with phagocyte Fc $\gamma$  receptors,<sup>68</sup> literally becoming the interface between innate immunity, C1q on complement, and inflammation, Fc $\gamma$  on macrophages. Details of CRP binding to its ligands and their

implications have been recently reviewed.<sup>53</sup> As an acute phase reactant during infections or diffuse tissue destruction, CRP concentrations may increase 50,000-fold quickly.<sup>69</sup> A constant potent stimulus may sustain high circulating CRP concentrations, depending upon synthetic capacity; the half-life of CRP in the circulation is about 19 hours.<sup>70</sup> Hepatic synthesis is driven at the transcriptional level by IL-6, largely expressed by macrophages, T cells, and adipocytes.<sup>11,71</sup> Several upstream cytokines also regulate hepatic CRP release. In part because there is overlap in signaling, plasma CRP values are related to other inflammatory markers. However, despite a plethora of research, the precise role(s) of CRP remain unclear.

### Variation and significance of CRP levels

Baseline values of CRP are influenced by genetics.<sup>72,73</sup> Even after correction for age, CRP polymorphisms, and

smoking, ancestry affects CRP levels, the highest values being found in blacks, with an average of 2.6 mg/L, followed by Hispanics, 2.51 mg/L, South Asians, 2.34 mg/L, whites, 2.03 mg/L, and East Asians with the lowest level at 1.01 mg/L.<sup>74</sup> CRP levels also vary with the environment, eg, pollutant burdens;<sup>75</sup> fiber intake,<sup>76–79</sup> coffee ingestion,<sup>80</sup> and other dietary factors;<sup>26,29,81–84</sup> smoking;<sup>85</sup> body mass index;<sup>86,87</sup> alcohol consumption;<sup>88,89</sup> drugs, including contraceptives<sup>90</sup> and hormone replacement therapy;<sup>91</sup> chronic infections,<sup>92,93</sup> and noninfectious inflammatory conditions, such as the autoimmune diseases,<sup>94–97</sup> cancer,<sup>98</sup> and polycystic ovary syndrome;<sup>99–102</sup> as well as multiple risk factors for atherosclerosis, including obesity, diabetes, metabolic syndrome, and hypertension. Triage of patients according to CRP levels generally control, correct for, and consider these variations.



**Figure 1** A picture of C-reactive protein (CRP) from 1B09.pdb made using pymol.<sup>10</sup> CRP is a pentameric molecule containing a recognition face that binds phosphocholine and calcium ions, and on the opposite side, an effector face that contains a C1q-binding site. Function depends upon Ca<sup>2+</sup>-dependent ligand binding. See text for details. Reproduced by permission of Skolstoe through Wikipedia commons.

Since CRP binds to LDL and can be identified within atherosclerotic plaque,<sup>103,104</sup> is involved with inflammatory atherogenic processes,<sup>105–116</sup> is elevated in patients with acute (ACS) and chronic coronary syndromes<sup>117–120</sup> with unfavorable plaque compositions in these syndromes,<sup>55</sup> and is associated with complications of heart failure<sup>121</sup> a causal role in atherothrombotic disease has long been suspected. At this time, causality remains unproven.<sup>107,122,123</sup> One intriguing property of CRP is the associated inhibition of endothelial nitric oxide synthase *in vitro*<sup>124</sup> and the relationship to impaired vasoreactivity and hypertension in such models.<sup>125</sup> Overall, the evidence for a role of CRP in endothelial cell dysfunction and monocyte activation in metabolic syndrome is impressive and difficult to ignore.<sup>126</sup> The prevalence of this syndrome is approaching 53% in some populations (excluding those with diabetes)<sup>127</sup> and the importance of endothelial dysfunction in pathogenesis is now unassailable.<sup>128</sup>

It is generally appreciated that a high CRP level (hereafter meaning hs-CRP [hs, highly sensitive] measurements) usually portends a poorer prognosis in patients with CHD, diabetes, hypertension, pre- or postoperative surgery, and vascular comorbidities. A high prevalence of elevated circulating CRP levels in the general population has been known for some time. At the 53rd Annual Scientific Session of the American College of Cardiology, data were presented from the 1999–2000 National Health and Nutrition Examination Survey (NHANES) indicating that 47.1% of respondents aged 20 years or over had high CRP values.<sup>129,130</sup> Levels were higher in females, the obese, and in the elderly, aged 55 to 74. About one-third of the population has CRP levels above 3 mg/L.<sup>131</sup> However, smaller elevations in CRP are even more common, and over half of the population has a CRP  $\geq$  2 mg/L.<sup>132</sup> Such “minor” elevations in CRP also imply a poorer prognosis compared with lower values, both in the ill and the apparently healthy.<sup>133</sup> Raised values of CRP strongly suggest clinical attention is necessary. Common associations of CRP elevations may reflect not only inflammation but widespread tissue distress, degeneration, and/or destruction, much of which may be age-related. At the other end of the continuum, a low CRP has been considered a measure of wellness,<sup>134</sup> and as lifestyle becomes progressively unhealthy in a population, CRP rises. As shown in the Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg Study, negative behaviors and factors, such as a poor quality “Western” diet with low intake of vegetables, fruits, and fiber, high consumption of saturated fats, poor physical fitness, and overfeeding and obesity, are all associated with higher CRP levels.<sup>135</sup> In a global sense, when

no overt disease is evident, the CRP level roughly follows the level of self-inflicted abuse. In these instances CRP elevations reflect poor lifestyle choices that lead to deranged metabolic signaling, inflammation, and the appearance and worsening of traditional risk factors during the early incubation period of atherosclerosis. As such, elevations tend to cluster with conventional risk factors, and teasing apart the significance has been difficult,<sup>136</sup> but studies confirm that the properties of CRP and significance of changes are different. Lifestyle has a greater influence on CRP than does genetics.<sup>137</sup> Conversely, sustained improvement in lifestyle, particularly weight loss with exercise, and measures that relieve the risk burden, including statins, all reduce plasma CRP levels.

In a review of hospital records of 22,962 patients in a large urban population, an analysis of change in CRP status – normal ( $\leq$ 3 mg/L) to elevated ( $>$ 3 mg/L) and vice versa – and mortality, revealed a significant graded association between CRP levels and mortality.<sup>138</sup> The patients were not healthy or chosen at random, but rather a cohort selected by physicians who believed their patients needed a CRP level performed. A change from normal to elevated CRP levels within a year was associated with a 6.7-fold hazard ratio (HR) for all-cause mortality during the following 4 years, compared to subjects whose CRP remained normal. When CRP levels changed from elevated to normal, the HR halved to 3.5. In the hospital setting as well, CRP levels reflect risk and subsequent survival, with a strong relationship to all-cause mortality, particularly in vascular diseases and cancer.<sup>139</sup>

In the elderly, high CRP values are associated with greater risk of all-cause mortality, especially in apolipoprotein E4 carriers, as well as with cognitive decline.<sup>140</sup> The Rancho Bernardo Study reported that the lower the circulating CRP level in elderly men, the greater their longevity, and plasma concentrations of IL-6 were inversely related to survival time in elderly women who did not use estrogen.<sup>141</sup> Finally, the classic paper that showed CRP was a stronger predictor of cardiovascular events than LDL, and measuring both together provided better prognostic information than screening for either alone, firmly established the potential clinical significance of following circulating CRP concentrations.<sup>142</sup> This study also demonstrated the inverse relationship between CRP levels and the probability of event-free survival.

The work cited above supports the significance of circulating CRP levels in “ordinary” individuals as a sensitive but nonspecific index of quality of lifestyle prior to the diagnosis of disease, as a screen for risk refinement beyond traditional risk factors, and as an index that reflects the intensity of either the amount of inflammation or volume of cell distress.<sup>133</sup>



When CRP was compared to other inflammatory markers as a predictor of relative risk of hard coronary events (postmenopausal women, highest versus lowest quartile) relative risk scores were CRP, 4.4, serum amyloid A, 3.0, soluble intercellular adhesion molecule type 1, 2.6, IL-6, 2.2, total cholesterol, 2.4, LDL, 2.4, apolipoprotein B-100, 3.4, high-density lipoprotein (HDL), 0.3, and for the ratio total cholesterol/HDL, 3.4.<sup>35</sup> The predictive power of CRP remained significant for LDL values <130 mg/dL. Of all nontraditional risk factors, CRP is the most studied, with over 34,000 general PubMed results, and 12,500 in connection with CVD, authored by investigators around the world over an extended period of time. CRP is involved in basic pathophysiology, and/or reflects additional risk and/or has predictive power in a number of CVDs, equivalents, or comorbidities, which include hypertension,<sup>143–151</sup> hypertension and blood pressure variability,<sup>152</sup> percutaneous coronary intervention,<sup>153,154</sup> re-endothelialization,<sup>110</sup> stent implantation,<sup>155</sup> coronary artery bypass surgery,<sup>156–158</sup> heart failure,<sup>159–167</sup> peripheral arterial disease,<sup>168,169</sup> carotid artery disease,<sup>170</sup> sudden cardiac death (SCD),<sup>171–173</sup> atrial fibrillation,<sup>174–176</sup> ventricular tachycardia after myocardial infarction (MI) and implantable cardioverter-defibrillator implantation,<sup>177</sup> calcific aortic valve disease,<sup>178</sup> venous thromboembolism,<sup>179,180</sup> pulmonary arterial hypertension,<sup>181</sup> diabetes,<sup>116,182–186</sup> metabolic syndrome,<sup>87,93,168,180,185,187–199</sup> rheumatic mitral stenosis,<sup>200</sup> chronic lung disease and asthma,<sup>201–203</sup> chronic kidney disease,<sup>154,204–206</sup> obstructive sleep apnea,<sup>207–208</sup> air pollution vis-à-vis inflammation and cardiac risk,<sup>75,209,210</sup> obesity,<sup>137,197,211–223</sup> eclampsia,<sup>224</sup> blood concentrations of reactive oxygen species,<sup>225</sup> depression in the obese,<sup>211</sup> depression associated with coronary artery disease,<sup>226</sup> and HIV disease progression.<sup>225</sup> Statins have been found useful in many of these clinical situations. The preponderance of the evidence, from many diverse sources, indicates that CRP measurement has significant broad-based value and is also uniquely related to vascular disease.

## CRP and genetic studies

CRP genetic (pentraxin-related) polymorphisms exist, which, together with diet and other lifestyle factors, contribute to significant interindividual variation in plasma CRP levels, as well as differences in responses to therapeutic agents.<sup>227</sup> Such variants in the CRP locus may account for 30% to 50% of the phenotypic variation in CRP levels,<sup>228</sup> and may also explain some ethnic differences.<sup>229</sup> CRP concentrations are 16% lower, for instance, in Asians, but 26% higher in black people than in whites.<sup>230</sup> In addition, other genetic loci that encode for upstream cytokines (IL-6, IL-1, tumor necrosis

factor  $\alpha$ ) that affect CRP synthesis influence CRP levels, as well as genes related to obesity and insulin resistance.<sup>187</sup>

Mendelian randomization, the random assortment of genes that occurs during reproduction, provides a method for assessing cause and effect that is not influenced by reverse causation.<sup>231–233</sup> By comparing natural variation in known genes and phenotype, strengths of environmental influences may be inferred.<sup>234</sup> A large genome-wide association ( $n = 17,967$ ) and replication study ( $n = 13,615$ ) examined the association of genetic loci with plasma CRP concentrations and risk of CHD.<sup>235</sup> The authors found that genetic variants expected to lower the CRP expression by about 20% did not reduce CHD risk by the predicted amount of 6%. The discordance between anticipated versus actual CRP phenotype argued that, in genetic variants, high CRP levels throughout life do not cause increased risk for ischemic heart disease. Several limitations to the study, and in the use of Mendelian randomization generally, were identified.<sup>236</sup> Another Mendelian randomization study of 47,000 individuals from the general population revealed a comparable situation elsewhere: high plasma CRP values were robustly associated with higher risk of atrial fibrillation, but not with genetically elevated CRP levels.<sup>176</sup>

## Causation versus predictive utility

The Emerging Risk Factors Collaboration (ERFC) reported a meta-analysis of records of 160,309 people with medical histories of vascular disease, associating  $\log_e$  CRP concentrations with conventional risk factors and inflammatory markers.<sup>237</sup> Their data confirmed that downstream markers of inflammation, especially fibrinogen levels, but also the leukocyte count, plasma albumin concentration, and erythrocyte sedimentation rate, were associated with CRP levels. As the investigators adjusted for conventional risk factors, the associations of CRP levels with risk of CHD weakened, but the most significant adjustment was for fibrinogen perturbations during inflammation. Hepatic synthesis of this protein is also regulated by IL-6. Hence, the ERFC concluded that most of the association of CRP with coronary artery disease depends upon conventional risk factors and fibrinogen levels.<sup>18,238–240</sup> Their views are consistent with findings using Mendelian randomization discussed above, noting a disparity between CRP-related phenotypes, coronary risk, and subsequent coronary events.

Interestingly, after adjusting for conventional risk factors, the relative risks for CHD in this meta-analysis were CRP, 1.37, non-HDL cholesterol, 1.28, and systolic blood pressure, 1.35. Therefore, despite the conclusion, their data

actually confirmed that CRP concentrations have a significant predictive association with risk of CHD, stroke, and vascular and nonvascular mortality.

While the ERFC appears to argue against a causative role of CRP in atherosclerosis, the issue is far from settled, since there is much convincing basic science that requires specific refutation.<sup>126</sup> In addition, a significant putative role for the monomeric form of CRP (mCRP) has been proposed.<sup>241</sup> Mediated by activated platelets, formation of mCRP,<sup>242</sup> a conformationally distinct isoform which is prothrombotic<sup>243</sup> and inflammatory,<sup>244</sup> might confound conclusions if monomeric conversion of CRP from the pentameric moiety (pCRP) – commonly measured as hs-CRP – were not considered. Indeed, it has been shown that mCRP localizes monocyte-mediated inflammation in the atherosclerotic plaque, and may be deposited in plaques but not in healthy vessels, whereas pCRP is not found in either healthy or diseased arteries.<sup>244</sup> Moreover, mCRP and pCRP have differing actions on neutrophil migration and thrombus evolution. The various metabolic roles of pCRP and mCRP are expertly reviewed in an editorial accompanying the aforementioned paper.<sup>115</sup> There is further evidence that mCRP inserts into lipid raft microdomains within endothelial cell membranes, rather than binds to surface proteins, as a complex function of membrane cholesterol content. The result of this incorporation is endothelial cell activation, as part of an early inflammatory step in the atherosclerotic process.<sup>245</sup> These data are but a small part of the burgeoning scientific literature that underscores the importance of CRP in atherothrombosis, and the need for further research.

A randomized trial using a drug that targets CRP will be necessary to decide whether or not CRP is causally involved in atherogenesis. However, even if proof of CRP participation in the atherothrombotic process is incomplete, separate evidence indicates that measurement of CRP levels is useful in predicting and monitoring particular groups of patients. For instance, AFCAPS-TexCAPS found that patients with higher CRP may anticipate a better response to statins,<sup>246</sup> and selection of patients with high CRP levels in different circumstances adds to absolute risk assessment.<sup>142,247,248</sup> As mentioned above, the ERFC, a large meta-analysis, reported a consistent 1.6-fold rise in vascular risk for each 1-SD rise in CRP levels.<sup>237</sup>

After de Beer reported that elevations in CRP levels predicted a poor outcome after MI,<sup>249</sup> baseline levels were found to predict future cardiac events in stable and unstable angina.<sup>250,251</sup> These observations were extended to people without heart disease in whom baseline CRP measurements

also correlated with future cardiac prognosis.<sup>135,252</sup> Lowering CRP concentrations in patients without elevations in LDL following statin administration improved prognosis.<sup>248,253</sup> Reporting bias, with multiple ways of comparing CRP values, together with publication bias in CRP studies, may hamper full evaluation of prognostic capability.<sup>254</sup> Several studies confirm that patients with higher CRP levels are at greater risk than those with lower values.<sup>118,255</sup> These data support the view that measurement of CRP improves prediction of risk.<sup>118,256</sup> Another approach, as suggested by the American Heart Association, the CDC, and the Canadian Cardiovascular Society, is that patients with heart disease falling in the “intermediate risk” category – with a Framingham Risk Score (FRS) of 10% to 20% – have increased CHD risk if CRP levels are elevated, and may be considered for statin therapy. The Canadian Cardiovascular Society recommends prophylactic statins for men >50 years and women >60 years with a CRP level >2 mg/L, and who are otherwise considered “intermediate risk”.<sup>257</sup> Prior to the JUPITER study,<sup>9</sup> considerable data showed that CRP levels  $\geq 2$  mg/L significantly raised risk, but currently laboratory reports continue to mention that CRP levels 2 to 3 mg/L reflect an average risk, and levels >3 mg/L reflect greater than average risk.<sup>258</sup> Large prospective cohort studies reported age-adjusted relative risks for coronary artery disease from about 2.0 to 3.0 for the highest versus the lowest levels of CRP, again documenting a consistent association with heart disease that has predictive power.<sup>12,86,259</sup>

Some studies report that CRP does not discriminate sufficiently,<sup>260,261</sup> adds little to traditional risk factors,<sup>86</sup> in particular the FRS, and hence may lack cost-effectiveness. On the other hand, investigators have reported remarkable discrimination in a number of clinical settings,<sup>255</sup> have found that when CRP is added to existing risk evaluation systems predictive power is enhanced,<sup>256,262–268</sup> and reported that cost-effectiveness is indeed significant.<sup>269–271</sup> All things considered, CRP is admittedly imperfect, as are all risk factors. However, it is much better than other nontraditional risk factors when used to refine risk, particularly when used along with traditional risk factors. In conclusion, CRP is an acknowledged sensitive marker of systemic inflammation,<sup>11</sup> and in primary prevention, over 40 reports from prospective studies and 2 meta-analyses report a consistent association of CRP with subsequent CHD events.<sup>86,272,273</sup> One evolving view is that traditional risk factors and scores should be used initially, and CRP measured in patients at intermediate risk or in complex patients. If elevated, a more aggressive therapeutic stance may be warranted.

Although lifestyle measures and some pharmacological agents do reduce CRP levels, statins are most frequently employed, and lower CRP levels about 15% to 35%.<sup>274,275</sup> Rosuvastatin and atorvastatin in higher doses have the most significant CRP-lowering properties.<sup>274</sup>

## Rosuvastatin

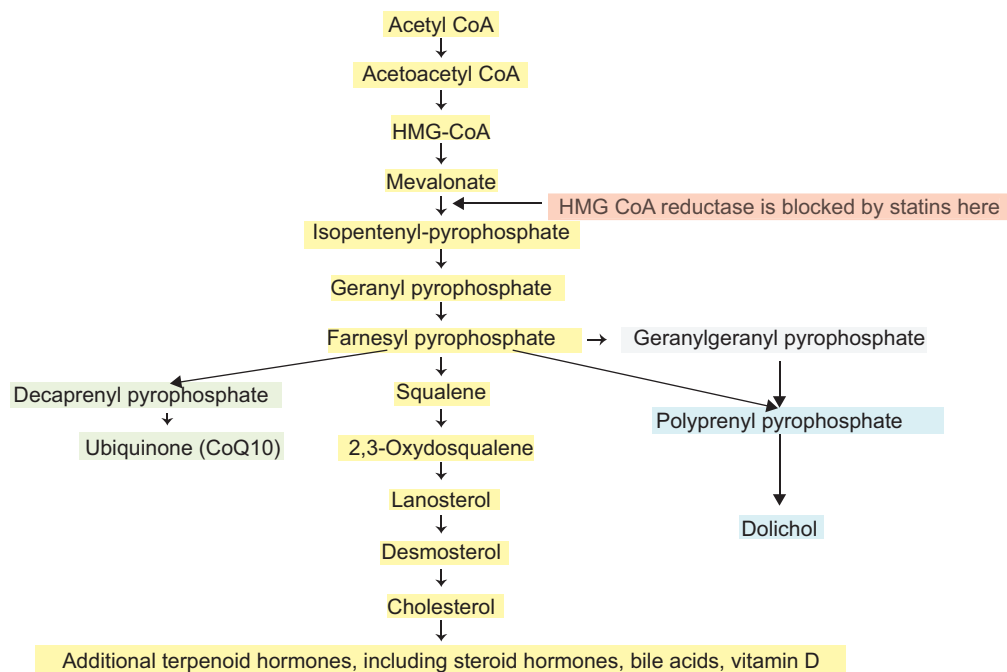
The word cholesterol derives from the Greek *chole-* (bile), *stereos* (solid), and *-ol*, the chemical suffix for alcohol. First identified in gallstones in 1769, the modern name was begun by chemist Eugène Chevreul in 1815. By 1971 Japanese biochemist Akira Endo began seeking compounds to lower cholesterol, and in 1987 Merck began marketing lovastatin isolated from *Aspergillus terreus*.

The endogenous biosynthesis of cholesterol occurs through the mevalonate pathway (Figure 1). HMGR is a highly regulated enzyme which catalyzes the rate-limiting step in cholesterol synthesis. Although HMGR is located within membranes of the endoplasmic reticulum, its catalytic domain remains active after it is cleaved from the transmembrane portion of the enzyme. The reduction of HMG to mevalonic acid involves the transfer of 4 electrons, using 2 molecules of nicotinamide adenine dinucleotide (NADPH) as a reductant in 2 steps. The carboxyl moiety of

hydroxymethylglutarate esterified to the thiol of CoA is first reduced to an aldehyde, and then to an alcohol. Statin drugs are highly efficient competitive inhibitors of HMGR.

## Clinical pharmacology

Rosuvastatin (Figure 3) is a sulfur-containing, hydrophilic statin with multiple sites that form a strong interaction with HMGR and therefore provide more potent enzyme inhibition than other statins. Stereochemical details of the molecular binding between rosuvastatin and HMGR have been detailed elsewhere.<sup>276,277</sup> Rosuvastatin, like other statins, is a competitive antagonist of HMGR, competing directly with the endogenous substrate for the active site cavity of the enzyme. Rosuvastatin employs a modified hydroxyglutaric acid moiety that mimics the 3-hydroxyglutaryl unit of the substrate, HMG CoA, and the mevaldyl CoA transition state intermediate. The pyrimidine ring in rosuvastatin binds tightly to the HMGR enzyme in the same area that normally binds the CoA component of the endogenous substrate HMG CoA. As a synthetic, “type 2”, or second-generation statin, rosuvastatin contains a fluorophenyl group which provides additional polar interactions that strengthen binding to HMGR. All told, rosuvastatin has an affinity for



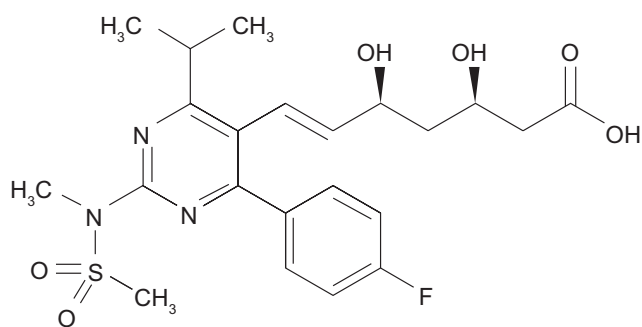
**Figure 2** Cholesterol is synthesized via the mevalonate pathway. Acetyl-CoA forms 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) in several steps. The conversion of 3-hydroxy-3-methylglutaryl (HMG)-CoA to mevalonate, the rate-limiting step in cholesterol synthesis, is catalyzed by HMG-CoA reductase (HMGR), an enzyme within the endoplasmic reticulum. Rosuvastatin is an efficient competitive inhibitor of HMGR, reducing not only mevalonate levels, but also prenylated downstream products. The post-translational process of prenylation is needed for the function of small G proteins, including geranylgeranylation of Rho, Ras, and Rab, necessary for cellular signaling, transduction, and intermembrane translocation. As beneficial as statins are, there are obligatory molecular consequences inherent in their use, some related to their beneficial pleiotropic actions, but also to their side effects. Many steps and enzymes are omitted for clarity.

the HMGR active site that is  $>10^4$ -fold higher than that of HMG CoA.

Rosuvastatin is administered in its active acid form, meaning that the pharmacophore binding to the HMGR needs no transformation for activity compared with simvastatin or lovastatin, which are administered as lactones, a portion of which is hydrolyzed to the active acid form. Rosuvastatin is a hydrophilic statin, with relatively greater hepatoselectivity due to a unidirectional carrier-mediated active transport system. Hydrophilic statins tend to be retained in the liver, in part because they cannot passively diffuse out, whereas lipophilic statins concentrate in nonhepatic tissues. This property of hydrophilic statins is believed to account for fewer adverse events.<sup>278,279</sup> As a result, rosuvastatin joins fluvastatin and pravastatin among statins least likely to produce myotoxicity.

Peak plasma concentration ( $C_{max}$ ) is reached 3 to 5 hours after oral administration,<sup>280</sup> and both  $C_{max}$  and the area under the plasma concentration-time curve (AUC) increase almost linearly with the dose. Absolute bioavailability is about 20%. Rosuvastatin is 88% bound to plasma proteins, chiefly albumin. Mean volume of distribution under steady-state conditions is  $\approx 134$  L. The half-life of rosuvastatin is 19 hours, the longest of the available statins. While pharmacokinetics do not differ meaningfully among white, Hispanic, or black individuals, Asians have about double the median exposure ( $C_{max}$  and AUC) than whites. As a result, lower starting doses are advised in Asian-Americans.

Elimination is primarily in the liver, with  $\approx 10\%$  through the action of cytochrome CYP2C9, producing a metabolite, N-desmethyl rosuvastatin, having up to half the potency of rosuvastatin. After oral administration, 90% of rosuvastatin and its metabolites are excreted in the feces. Following an intravenous dose, about 72% of total body clearance is via the hepatic route, and 28% through the kidneys. Lipophilic



**Figure 3** The structure of rosuvastatin, uniquely containing sulfur, a fluorophenyl group, and a modified hydroxyglutaric acid moiety. The IUPAC name of rosuvastatin is (E,3R,5R)-7-[4-(4-fluorophenyl)-2-[methyl(methylsulfonyl)amino]-6-propan-2-ylpyrimidin-5-yl]-3,5-dihydroxyhept-6-enoic acid.

statins must be metabolized to water-soluble forms for renal excretion, reactions that depend upon CYP450 isoenzymes. Compared to atorvastatin and some other statins, rosuvastatin has an advantage, since it is not metabolized predominantly through CYP3A4, eliminating many potential drug and food interactions. There are, however, other variables affecting pharmacokinetics and potential dose-related toxicity. P-glycoprotein (P-gp, also called ABCB1), an intestinal ATP-dependent drug efflux pump located in epithelial plasma membranes, prevents cellular uptake of xenobiotic foreign substances. P-gp also transports a number of endogenous biochemicals and drugs across cell membranes, notably digoxin, and is inhibited by several statins. Available data do not indicate that rosuvastatin inhibits P-gp significantly, and therefore interactions with P-gp substrates and inhibitors, many of which are also CYP3A4 interactants, are not clinically relevant. Another potential interaction involves a hepatic uptake transporter, organic anion transporting polypeptide 1B1 (OATP1B1).<sup>281</sup> Cyclosporine and gemfibrozil are OATP1B1 inhibitors, which may explain coadministration interactions.<sup>282</sup> (See further discussion below under Side effects).

For each 39 mg/dL (1 mmol/L) fall in LDL, there is a 21% reduction in major cardiovascular events.<sup>283</sup> Atorvastatin lowers LDL up to 60% at a maximal dose of 80 mg. Rosuvastatin lowers LDL by 45% to 63% (5 mg, 38%; 10 mg, 43%; 20 mg, 48%; 40 mg, 53%; 80 mg, 58%), reduces triglyceride levels by 10% to 35%, and raises HDL by 8% to 14%.<sup>179,284</sup> The rise in HDL is believed to be due to a combination of a lower apolipoprotein A-1 (apoA-1) catabolism, raised hepatic apoA-1 synthesis, peroxisome proliferator-activated receptor- $\alpha$  activation and inhibition of cholesteryl ester transfer protein.<sup>280</sup> Of all the statins, rosuvastatin has the lowest half maximum inhibitory concentration for cholesterol synthesis in the liver. The milligram-equivalent reductions in LDL and elevations in HDL are superior to those of other statins,<sup>179</sup> thereby achieving evidence-based LDL targets in a higher portion of patients and greater success during intensive LDL reduction (Table 1). Rosuvastatin also lowers small, dense LDL concentrations. Although the reductions in LDL are dose-related, increasing the dose beyond 10 mg generally produces progressively smaller absolute reductions in LDL levels per unit.

## Clinical studies with rosuvastatin

The Galaxy Program<sup>285</sup> is a long-term, multi-trial research initiative sponsored by AstraZeneca, a planned portfolio of studies to investigate and support use of rosuvastatin to



improve cardiovascular events and outcomes. The JUPITER study is one component, among others such as ASTEROID, METEOR, and CORONA. JUPITER sought to determine whether 20 mg of rosuvastatin could lower the number of major cardiovascular events in patients with acceptable LDL (under current guidelines) and elevated CRP levels, using a combined end point of death, MI, stroke, unstable angina or revascularization, and is further described below.

The Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) trial randomized 984 asymptomatic participants with a mean age of 57 years, FRS < 10%, modest carotid intima-media thickness (CIMT) thickening (1.2 to <3.5), and elevated LDL (mean, 154 mg/dL) to either rosuvastatin 40 mg or placebo.<sup>286,287</sup> The primary end point was the annualized rate of change in maximum CIMT at 12 sites during the 2-year study period. The rate of progression of maximum CIMT was significantly reduced by rosuvastatin therapy, but actual lesion regression was not achieved.

The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) was conducted from 2003 to 2005 in 371 sites in 21 countries.<sup>288</sup> The study randomized 5011 patients  $\geq 60$  years of age with chronic New York Heart Association (NYHA) class II, III, or IV ischemic systolic heart failure and an ejection fraction less than 40% to either rosuvastatin 10 mg or placebo. Median follow up was 32.8 months. There was a sharp fall in mean LDL (137 mg/dL) and CRP (3.1 mg/dL) at baseline to 3-month values of 76 and 2.1 respectively. The primary end point of the study was a composite of cardiovascular-related death, nonfatal MI, and nonfatal stroke. Secondary outcomes were total and cardiovascular mortality, time to first coronary event, and number of hospitalizations. By the end of the follow-up period, almost one-third of the participants sustained one end point event. There was no significant effect of rosuvastatin on primary or secondary end points, but a subsequent analysis suggested that those with CRP  $\geq 2.0$  had a 13% relative risk reduction and better outcomes.<sup>289</sup> The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure (GISSI-HF) trial, which took place at 357 medical facilities

in Italy, also prospectively randomized 4574 patients with NYHA class II-IV heart failure to rosuvastatin 10 mg or placebo, without an improvement in the primary end point.<sup>290</sup> In GISSI-HF the event rate was similarly high, with over half the patients sustaining a cardiovascular death or hospitalization, reporting a 29% all-cause mortality during a follow-up of over 4 years. Although no explanation was forthcoming, it is apparent that these patients were quite ill with well advanced structural changes and pathophysiology. A recent commentary hypothesized that progression beyond a critical threshold in the pathogenesis of heart failure may have precluded any beneficial effect, citing the need for additional trials.<sup>291</sup>

Likewise, in A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA), 2776 patients with end-stage chronic renal disease (ESRD) at 284 dialysis facilities in 25 countries were randomized to rosuvastatin 10 mg or placebo, and there was no significant difference between groups in a primary end point of time to a major cardiovascular event, even though LDL and CRP levels were substantially reduced in the treatment group.<sup>292</sup> In this population the event rate of MI, stroke and cardiovascular death was >35%, again reflecting complex, advanced disease and extremely high absolute risk. One author proposed that in both ESRD and calcific aortic stenosis, once disease has progressed sufficiently, particularly with anatomical changes, statins may become unable to help achieve the end points chosen.<sup>293</sup> When begun earlier during aortic sclerosis or mild stenosis, improvement is more likely than when stenosis is advanced. In ESRD, since cardiovascular mortality rises sharply by the time a patient requires dialysis, the threshold for benefit may have been passed prior to enrolling in the study.

The results of the A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) study offer insight into the effects of rosuvastatin on the atherosclerotic process using two different, complementary techniques. First, monotherapy with 40 mg rosuvastatin for 24 months, which lowered LDL and raised HDL by about 53% and 15% respectively,

**Table I** Rough equivalent doses of rosuvastatin

% Reduction in LDL	Rosuvastatin	Atorvastatin	Simvastatin	Fluvastatin	Lovastatin	Pravastatin
30–40	5 mg	10 mg	20 mg	80 mg	40 mg	40 mg
40–45	5–10 mg	20 mg	40 mg	N/A	80 mg	80 mg
46–50	10–20 mg	40 mg	80 mg	N/A	N/A	N/A
50–55	20 mg	80 mg	N/A	N/A	N/A	N/A
56–60	40 mg	N/A	N/A	N/A	N/A	N/A

**Abbreviation:** LDL, low-density lipoprotein.

significantly reduced atheroma volume in major coronary arteries that were angiographically normal or were stenosed, as assessed with intravascular ultrasound.<sup>294</sup> Second, using quantitative coronary angiography (QCA), rosuvastatin decreased percentage diameter of coronary stenoses and improved minimum lumen diameter.<sup>295</sup> Intravascular ultrasound images the coronary artery wall in proximal areas with minimal lumen stenosis, and QCA examines luminal narrowing in different segments of the coronary tree. Concordance of the findings strongly suggests rosuvastatin causes both slowing of progression of atherosclerosis and lesion regression in concert with LDL levels  $\leq 70$  mg/L (1.81 mmol/L). Reduction of luminal diameter, as detected by QCA, correlates with lower risk of future coronary events<sup>296</sup> and subsequent mortality.<sup>297</sup> Interestingly, changes in atheroma volume, when stratified above or below a median change of  $-37.1\%$  in LDL and  $-21.4\%$  in CRP levels, was greatest in those with reductions in both LDL and CRP ( $-2$  mm<sup>3</sup>), less when CRP fell but not LDL ( $-1$  mm<sup>3</sup>), progressed when LDL fell but CRP was high ( $+2$  mm<sup>3</sup>), and progressed the most when both LDL and CRP were high ( $+8$  mm<sup>3</sup>).<sup>294</sup>

## The JUPITER study

Based upon (a) the ability of CRP to predict future vascular events,<sup>142,299-301</sup> and (b) of statins to lower CRP,<sup>301</sup> together with (c) additional evidence that the benefits of statins were greater when both LDL and CRP levels were lowered,<sup>249,253</sup> and (d) a post-hoc analysis of the AFCAPS/TExCAPS study that indicated that healthy individuals with elevated CRP levels and normal LDL values could benefit from statin therapy,<sup>246</sup> the global, multicenter JUPITER study was designed.<sup>9,302,303</sup> After screening some 90,000 prospects, JUPITER enrolled 17,802 men ( $\geq 50$  years) and women ( $\geq 60$  years). The study population was not diagnosed with either CHD or diabetes, and had “normal” LDL levels (LDL  $< 130$  mg/dL), but high hs-CRP levels ( $\geq 2.0$  mg/L, median, 4.2 mg/L).

Participants were randomized to either treatment with rosuvastatin 20 mg daily or placebo. Participants' median age was 66 years, and they comprised 62% men, 38% women, 71% Caucasians, 12.5% blacks, and 12.7% Hispanics (Table 2). Although free from clinical illness, the JUPITER population was not healthy, with 41% qualifying for the metabolic syndrome cluster of risk factors, 16% using tobacco, and 11.5% with a family history of premature heart disease. The cohort was fairly representative of the general population, with as-yet undetected, but substantial risk burden. This is an important point, since sometimes the

term “healthy” may automatically be interpreted to mean “no treatment is necessary”.

The primary end point composite included a nonfatal MI, nonfatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or confirmed death from a cardiovascular cause. The secondary end points included the individual components of the primary end point and all-cause mortality.

Although planned as a 5-year study, when patients in the rosuvastatin group had significantly fewer events and deaths than the controls, an independent data and safety monitoring board performed an interim efficacy analysis, and the trial was stopped after a median follow-up time of 1.9 years. About 75% of the treated participants were still taking rosuvastatin when the trial was ended. At that time there were 142 first major cardiovascular events in the rosu-

**Table 2** Baseline clinical data in the JUPITER trial

Characteristic	Treated group	Placebo group
Age, years (%)	66 (median)	66
Female sex, number (%)	3426 (38.5)	3375 (37.9)
Ethnicity		
White, number (%)	6358 (71.4)	6325 (71.1)
Black, number (%)	1100 (12.4)	1124 (12.6)
Hispanic, number (%)	1121 (12.6)	1140 (12.8)
Body mass index, kg/m <sup>2</sup>	28.3 (median)	28.4
Family history, number (%)	997 (11.2)	1048 (11.8)
Tobacco use number (%)	1400 (15.7)	1420 (16.0)
Systolic blood pressure, mm Hg	134 (median)	134
Diastolic blood pressure, mm Hg	80	80
CRP		
mg/L	4.2 (2.8–7.1) <sup>a</sup>	4.3 (2.8–7.2)
nmol/L	40.0 (median)	40.9
Triglycerides		
mg/dL	118 (median)	118
mmol/L	1.33	1.33
Total cholesterol		
mg/dL	186	185
mmol/L	4.82	4.79
LDL cholesterol		
mg/dL	108	108
mmol/L	2.8	2.8
HDL cholesterol		
mg/dL	49	49
mol/L	1.27	1.27
Glucose		
mg/dL	94	94
mol/L	5.22	5.22
HbA <sub>1c</sub> %	5.7 (5.4–5.9)	5.7 (5.5–5.9)
Metabolic syndrome (%) <sup>b</sup>	3652 (41.0)	3723 (41.8)

**Notes:** <sup>a</sup>Interquartile range; <sup>b</sup>Metabolic syndrome was defined according to the National Heart, Lung, and Blood Institute definition or American Heart Association consensus criteria.

**Abbreviations:** HbA<sub>1c</sub>, glycated hemoglobin; LDL, low-density lipoprotein.

vastatin group, and 251 events in the placebo group, for a 44% reduction in first major cardiovascular events (HR 0.56, 95% confidence interval [CI] 0.46 to 0.69;  $P < 0.00001$ ). There was also a 54% drop in nonfatal MI, a 48% reduction in nonfatal stroke, and a 47% fall in the cumulative incidence of hard end points of MI, stroke, or cardiovascular death in the rosuvastatin group (Table 3). In addition, there was a significant reduction in all-cause mortality of 20% in the treatment group, comparatively greater than in previous statin trials considering the duration. Rosuvastatin lowered CRP levels by 37%, with a 12 month mean of 2.2 mg/L, and lowered LDL by 50%, with a mean treated value of 55 mg/dL. Without a control group with normal CRP levels, whether CRP reduction was responsible for the observed benefits could not be answered.

The number needed to treat to prevent a first major primary end point event in 2 years was 95, falling to 31 in 4 years, and 25 for 5 years of treatment with rosuvastatin. The cardiovascular event rate in the rosuvastatin group was about 1 in 100, compared to approximately 2 in 100 in the placebo group, an absolute risk reduction of  $\approx 1.2\%$  for the 1.9-month study. Hence 25 individuals would require treatment for 5 years to prevent a single event, an absolute risk reduction of about 4%. Note that in primary prevention the baseline risk and event rate is low, so there is relatively less benefit in absolute risk anticipated. It is also instructive to compare the improvement in absolute risk achieved using the Mediterranean diet as the intervention, which may exceed 5% in some situations.<sup>304,305</sup>

JUPITER recorded 270 new cases of diabetes in the treatment group compared to 216 in the control group, and a rise in median glycated hemoglobin ( $\text{HbA}_{1c}$ ) levels, also noted in prior statin studies, amounting to a 25% increase

in physician-reported incidence of diabetes over a 1.9-year period. There were 10 cases of myopathy in the rosuvastatin group versus 9 in the control group, with only 1 instance of rhabdomyolysis associated with rosuvastatin, numbers that are consistent with previous rosuvastatin trials.

Given prior data that CRP values improved prediction of risk, JUPITER suggested that a seemingly healthy patient population at high risk, previously ineligible for statin therapy, may benefit from rosuvastatin treatment, guided by the CRP level.<sup>306</sup> Attention was focused on the large body of research that points to inflammation as a common denominator in atherothrombosis, ie, that inflammation matters at a clinical level.<sup>57</sup> JUPITER, called a landmark study immediately after presentation, has since been the subject of many editorials, discussions, and intense debate. An online poll conducted by the *New England Journal of Medicine* followed publication, with 2553 votes cast over 18 days.<sup>307</sup> Half of the respondents believed JUPITER data should change screening in the general population, with the remainder voting against any change. Similarly, the votes for and against a change in the therapeutic use of statins based upon JUPITER results were about evenly divided.

## Subsequent analyses pertaining to JUPITER

Using data from 1999–2004 NHANES and applying NCEP ATP III 2004 Update (ATP III) criteria, Spatz et al<sup>308</sup> calculated that 57.9% of older adults (men  $\geq 60$  years, women  $\geq 50$  years) are either taking a statin (24.4%) or eligible for a statin (33.5%). If one includes individuals satisfying strict JUPITER criteria – no history of cardiovascular disease, LDL  $< 130$  mg/dL, and CRP  $\geq 2$  mg/L – an additional 13.9% of the age group mentioned above, or nearly 8 million people,

**Table 3** JUPITER trial: comparison of outcomes between treated and nontreated patients

End point	Patients in subgroup rosuvastatin (n = 8901)	Patients in subgroup placebo (n = 8901)	Hazard ratio (95% CI)
Primary end point <sup>a</sup>	142	251	0.56 (0.46–0.69)
Any MI	31	68	0.46 (0.30–0.70)
Nonfatal MI	22	62	0.35 (0.22–0.58)
Any stroke	33	64	0.52 (0.34–0.79)
Nonfatal stroke	30	58	0.52 (0.33–0.80)
Revascularization	71	131	0.54 (0.41–0.72)
Hospitalization for unstable angina	16	27	0.59 (0.32–1.10)
Revascularization or hospitalization for unstable angina	76	143	0.53 (0.40–0.70)
MI, stroke, or death from cardiovascular causes	83	157	0.53 (0.40–0.69)
Any death	198	247	0.80 (0.67–0.97)

**Notes:** <sup>a</sup>Primary end point: composite of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, revascularization, and death from cardiovascular causes.

**Abbreviations:** CI, confidence interval; MI, myocardial infarction.

would become eligible for rosuvastatin therapy. If expanded JUPITER criteria were used – LDL between 130 and 160 mg/dL and CRP  $\geq$  2 mg/L – another 5.3%, or 3 million individuals, would become statin-eligible. Hence a grand total of just under 80% of the older population would have an indication for statin therapy. Compared to the remaining 20%, the “JUPITER group” was composed of more females, was older with a higher body mass index, and tended to have hypertension and metabolic syndrome. They also shared many characteristics with ATP III subjects, particularly the use of tobacco, visceral obesity, and hypertension. Interestingly, the investigators<sup>308</sup> noted that in the Women’s Health Study, about 20% of the women with low and intermediate FRS were reclassified by using the Reynolds risk score, which incorporates CRP values.<sup>35,256,263</sup> These findings support the growing realization that risk is greater than generally believed, and the validity of CRP-guided risk reduction.

Michos and Blumenthal<sup>309</sup> also estimated the prevalence of JUPITER-eligible individuals in the US population using NHANES 1999–2004 data. They found about 6.5 million individuals would be added if strict JUPITER criteria were followed. Based upon the number needed to treat (NNT) of 25 at 5 years, they estimated about 260,000 cardiovascular events could be prevented with rosuvastatin therapy. A subsequent recalculation, after adding the number of venous thromboses that would be avoided, raised the number to about 500,000 per annum.

Ridker<sup>310</sup> clarified aspects of the JUPITER study in mid-2009, observing that all prespecified subgroups benefited by rosuvastatin therapy, including those participants considered at low risk. The decision to terminate the study early was based on rigorous pre-agreed principles. It was noted that the NNT to prevent 1 event for 5 years was comparable to that reported in AFCAPS/TexCAPS, and less than those accepted for the use of diuretics or beta-blockers in treating hypertension for primary prevention. Another point emphasized was that 80% of individuals who developed diabetes occurred among those participants who had impaired glucose tolerance at baseline, but those patients also benefited from treatment in terms of end points. Last, reduction of both LDL and CRP levels was especially successful, and dual targeting may simplify decisions to treat. Another detailed analysis of absolute risk reductions and consequent NNT within the JUPITER trial, including alternative statin regimens, concluded that NNT values are acceptable.<sup>311</sup>

Yang et al,<sup>312</sup> using a JUPITER-eligible cohort from the Atherosclerosis Risk in Communities (ARIC) Study (men  $\geq$  50, women  $\geq$  60, CRP  $\geq$  2 mg/L, LDL  $<$  130 mg/dL), sought to

determine if the absolute event rates and risk reduction seen in JUPITER would persist for a period longer than the 1.9 year follow-up. Of their JUPITER-eligible participants, there was an absolute CVD risk of  $\approx$ 10.9% over a mean follow-up of 6.9 years, or 1.57% per year. Applying JUPITER HRs to this group generated an NNT of 38 over 5 years and 26 over 6.9 years. They concluded that the use of age and CRP level was a convenient method of identifying higher risk individuals.

Vaccarino and coworkers<sup>313</sup> noted the absolute risk reduction of 0.59% per year for the primary end point required 169 persons to be treated for 1 year to prevent a single combination of events. To prevent a major coronary event, such as an MI, 500 patients needed to be treated for 1 year for a single event. An estimate of a drug cost for rosuvastatin of US\$638,750 per year was made to prevent 1 event, and for a generic statin, US\$24,000 per year. In their view, adding CRP screening costs of US\$62,500, and then for additional liver function, glucose, and HbA<sub>1c</sub> monitoring, a total of over US\$137,000 was reached per year for each event prevented. These authors suggested that the funds instead be invested in effective, proven population-based strategies to lower risk, as discussed elsewhere.<sup>314–316</sup> In general, the costs per life year for lifetime treatment using simvastatin vary from US\$2500 to US\$10,990, depending on age and risk.<sup>317</sup> Accad and Fred<sup>318</sup> also opined that, according to their calculations, treatment of 95 individuals for 2 years to avoid 1 event is not a sufficient reward for the person with a high CRP level, but may be acceptable on a population level. On the other hand, Slejko et al<sup>269</sup> maintained that statin therapy in JUPITER patients is cost-effective, at a cost of US\$40,457 per quality adjusted life-year, below the customary threshold of US\$50,000. MacDonald<sup>271</sup> estimated that treating JUPITER-eligible individuals with rosuvastatin is highly cost-effective, but is a function of the initial FRS.

Kappagoda and Amsterdam<sup>319</sup> reviewed treatment in the JUPITER study according to traditional risk factors and guidelines, and their calculations showed the following. Baseline characteristics of the participants revealed 2225 in each group with systolic blood pressures over 145 mm Hg. Treating these elevations would have lowered the number of strokes by 12 over the duration of the study. Similarly, by treating those individuals with LDL  $>$  119 mg/dL and HDL  $<$  40 mg/dL (about 25% of the subjects), and overweight individuals ( $>$ 50%) with weight loss, and eliminating tobacco use in the 16% who smoked, along with administering evidence-based aspirin prophylaxis in men for CHD prevention, and in women for stroke prevention, meaningful



benefits would have changed outcomes. Aspirin alone could potentially have prevented 72 of the 99 MIs that occurred during the course of the JUPITER trial. Finally, since the baseline median HbA<sub>1c</sub> was 5.7% (reference range 4.8% to 5.9%), 2225 individuals in each group had levels >5.9%, suggesting that close to 25% of the entire JUPITER population met this criterion for diabetes. These authors suggested that because guidelines for care were not strictly followed, a spuriously high event rate may have caused an appearance of higher benefit from statin therapy. The event rate, however, was similar in the ARIC profile cohort that was JUPITER-eligible,<sup>312</sup> although smaller, which would argue against this view.

A most significant dual target analysis of the JUPITER study evaluated the effects of rosuvastatin 20 mg versus placebo on the prespecified end points according to on-treatment values of LDL (<70 or ≥70 mg/dL) and CRP (<2 mg/L, or <1 mg/L).<sup>320</sup> Compared to placebo, those in the treatment group who achieved an LDL < 70 mg/dL had a 55% reduction in vascular events per 100-person years (Table 4). Those who achieved CRP < 2 mg/L had a 62% reduction in events. Among those who reached dual reductions, there was a 65% reduction in events compared to a 33% reduction in those who achieved one or neither target. Those who reached an LDL < 70 mg/dL and a CRP < 1 mg/L enjoyed a 79% reduction in events (Table 5). Treatment CRP levels predicted the event rate no matter what lipid end point was used, including the ratio of aopB/aopA-1. Therefore, regardless of the lipid profile, the lower the CRP, the better was the prognosis. An editorial concluded that JUPITER provided “key experimental data” that inflammation mediated the benefits of rosuvastatin, but mused at the prospect of comparing the absolute risk reduction of statins with the effects of weight loss and regular exercise, remarking that such a study is unlikely,<sup>321</sup> both for lack of funding and interest. Many of the pleiotropic effects of rosuvastatin are anti-inflammatory, and a catalog of those actions – significant improvement in endothelial function, immune responses, plaque stabilization, vascular remodeling, and oxidative stress – and antithrombotic actions<sup>322</sup> further underpins the observation that targeting CRP is worthwhile and clinically rewarding.

The use of statins in women, particularly for primary prevention, has been heavily debated.<sup>323–325</sup> Mora and coworkers<sup>326</sup> performed a specific gender-specific analysis from JUPITER using rosuvastatin 20 mg or placebo employing the criteria mentioned above. Focusing only on 6801 female participants in JUPITER, treatment significantly lowered the relative risk of the primary end point, composite of MI,

**Table 4** Cardiovascular events fell based on LDL cholesterol and on hs-CRP levels <2 mg/L

LDL cholesterol (mg/dL) and hs-CRP (mg/L) values	Event rate	Hazard ratio (95% CI)
≥70 and ≥2	1.11	1.06 (0.72–1.55)
≥70 and <2	0.54	0.42 (0.18–0.94)
<70 and ≥2	0.62	0.53 (0.38–0.74)
<70 and <2	0.38	0.35 (0.23–0.54)
≥70 or ≥2	0.38	0.64 (0.49–0.84)

**Abbreviations:** CI, confidence interval; LDL, low-density lipoprotein; hs-CRP, high CRP.

**Table 5** Cardiovascular events fell based on LDL cholesterol and on hs-CRP levels <1 mg/L

LDL cholesterol (mg/dL) and hs-CRP (mg/L) values	Event rate	Hazard ratio (95% CI)
≥70 and ≥1	0.95	0.89 (0.62–1.28)
≥70 and <1	0.64	0.46 (0.11–1.85)
<70 and ≥1	0.56	0.49 (0.37–0.66)
<70 and <1	0.24	0.21 (0.09–0.51)
≥70 or ≥1	0.67	0.59 (0.46–0.75)

**Abbreviations:** CI, confidence interval; LDL, low-density lipoprotein; hs-CRP, high CRP.

stroke, revascularization, hospitalization for unstable angina, and death from cardiovascular causes, by 46%. The greatest benefit was seen for revascularization, associated with a treatment-related reduction of 76% compared to placebo. A meta-analysis of 5 studies reporting sex-specific outcomes was also undertaken. Absolute CVD rates per 100 person-years in JUPITER women were lower than for men, with similar relative risk reductions between the sexes. A total of 13,154 women were included from primary prevention trials, and a significant reduction in primary CVD events with statins by one-third was found (relative risk 0.63; 95% CI 0.49 to 0.82;  $P < 0.001$ ). These results were similar to prior results in men, and also to findings for secondary prevention in women. It was postulated that the greater numbers enrolled allowed JUPITER to demonstrate the benefit.<sup>327</sup> CRP was noted as a tighter predictor of events in women than in men, along with the correlation between the degrees of CRP lowering and associated clinical benefit. These authors concluded that while CRP level as an independent predictor of events remains controversial, CRP is accepted as a marker which may be involved in the atherogenic process.<sup>237</sup>

The FDA approved rosuvastatin for primary prevention on February 9, 2010, following a 12-4 vote in a panel 2 months before, which only seemed to flare the ongoing controversy about its use in “healthy” individuals.<sup>328</sup> The new indication was for men ≥ 50 years and women ≥ 60 years with fasting LDL

$\leq 130$  mg/dL, CRP  $\geq 2.0$  mg/L, triglycerides  $\leq 500$  mg/dL, no diagnosed CVD, and at least 1 additional CVD risk factor.

## Summary of articles in the Archives of Internal Medicine

Kaul and collaborators<sup>329</sup> challenged 3 aspects of the JUPITER study, asking (a) does CRP predict risk and treatment response? (b) did early stoppage of JUPITER unduly raise the benefit? and (c) what about guideline recommendations? First, they believed that the predictive value of 1.35%, although positive in JUPITER (241 events in 17,802 patients), was weak, and basically that treatment decisions should not be stratified using CRP values because there was no low-CRP, low-LDL control arm for comparison. This arm was excluded in the design of JUPITER because of the prior post-hoc analysis of AFCAPS/TexCAPS showing no benefit in a group with low CRP.<sup>246,330</sup> The JUPITER authors hypothesized, with considerable supporting evidence from other investigators and studies outlined above, that high CRP levels reflected increased risk, and treatment with rosuvastatin addressed that component over and above any LDL lowering.<sup>310</sup> A fair consensus from the many commentaries and blogs would be that a high level of CRP does have clinical utility, portends an otherwise poorer prognosis, but a normal CRP value does not assure low risk.

Second, the early termination of JUPITER may have led to a somewhat higher benefit than would have been observed from a longer study period. Compared to other statin studies in primary prevention, JUPITER reported unexpectedly larger reductions in ischemic end points including mortality. Studies terminated prematurely in other trials are known to exaggerate benefits, which regress to the mean when follow-up is longer.<sup>331–334</sup> A large systematic review reported that for interventions showing a 20% improvement in completed trials, stopping them early might double the apparent benefit.<sup>332</sup> It is true that other studies used less potent statins, but a rapid mortality benefit within this period is exceptional. Details provided subsequent to JUPITER concerning the circumstances of the early termination did not reflect any intent to exaggerate the positive results. Kaul agreed that rosuvastatin benefits did occur in JUPITER, although perhaps were increased by the early stoppage of the study.<sup>330</sup> The pathology in the CORONA and AURORA populations was sufficiently different from JUPITER to make a comparison of results difficult.

Third, Kaul et al<sup>329</sup> question the conclusion that high CRP levels predict preferential improved response in JUPITER, based on an FDA analysis showing, essentially, that treatment effect of statins was not proportional to the degree of elevation

in CRP.<sup>335</sup> This conclusion was based on a stratification of FRS risk scores according to the CRP level. In addition, however, data presented in Tables 4 and 5 show a clear relationship between low CRP values and good prognosis.<sup>321</sup> Kaul et al concluded that 44% risk reductions in JUPITER-eligible patients in the population will not be typically attained if CRP-guided rosuvastatin therapy is used. Their second conclusion, with which everyone agrees, is that control of risk factors with lifestyle modification trumps pharmacologic intervention in primary prevention. The third conclusion advises that if patients do not change their lifestyle, then statins may be used. In practice, since  $\approx 95\%$  of individuals will fall into this category, ultimately most patients will receive statins, simply because there are no comparable alternatives.

De Lorgeril et al<sup>336,337</sup> maintained that a) there was a discrepancy between the reduction in mortality between end point subgroups; b) cardiovascular mortality was 5% to 18% compared with total mortality and the expected rate is about 40%; c) the case-fatality rate of MI was low compared to an expected figure of 50%; the case mortality rate in the placebo group was 8.8% compared to 29% in the rosuvastatin group; d) no sudden cardiac death was reported in JUPITER; and e) bias may have been introduced because of conflicts of interest and commercial sponsorship. These analysts believed that there was no significant difference in cardiovascular mortality between the two groups in JUPITER. Last, they lamented the secondary end point and subgroup analyses published concerning benefit in preventing venous thromboembolic disease,<sup>338</sup> efficacy in women,<sup>326</sup> lower stages of chronic renal disease,<sup>339</sup> and in the elderly<sup>340</sup> because they shared the limitations of the original study.

Several of the earnest concerns summarized in the papers by Kaul<sup>329</sup> and de Lorgeril<sup>336</sup> have been addressed by investigators other than JUPITER, and have also been answered in part by subanalyses and refinements presented by the JUPITER authors during the past 2 years. For instance, the association of high levels of CRP with vascular risk has considerable supportive evidence from multiple sources, and the recent meta-analysis of 54 prospective studies by the Emerging Risk Factors Collaboration confirmed this relationship.<sup>237</sup> Specifically, the adjusted risk associated with a 1-standard deviation increase in CRP (HR 1.4; 95% CI 1.3 to 1.5) compared quite favorably with that associated with a similar increase in cholesterol (HR 1.2; 95% CI 1.1 to 1.3).

A closer evaluation of the relationship between baseline CRP measurements and cardiovascular risk is also available.<sup>268</sup> Treating CRP as a continuous variable, an

ordinal variable and as a threshold variable, relative risk reduction after rosuvastatin therapy was similar maintained across the entry levels of CRP. Absolute risk reductions therefore were greatest in the patients with the highest entry levels of CRP. Independent corroboration of these data is found in the ARIC study<sup>312</sup> in which groups with similar FRS and LDL levels had higher vascular risk when the CRP was elevated, compared to counterparts with low CRP values.

## JUPITER findings incorporated into the Canadian Cardiovascular Society guidelines

The Canadian Cardiovascular Society acknowledged JUPITER findings in their guidelines and recommended measurement of CRP in JUPITER-eligible individuals at “intermediate risk” as a step toward prophylactic statin treatment.<sup>257</sup> The Society extended recommendations from the CDC in which CRP levels were considered an adjunct to risk assessment in healthy persons with an FRS between 5%–20%, ie, at intermediate risk.<sup>341</sup> In JUPITER, the event rate in the placebo group was greater than in AFCAPS/TexCAPS study, and most individuals had an FRS between 5% and 20%. Analysis of JUPITER trial data stratified according to both the Framingham and Reynolds 10-year risk scores confirmed that treatment of JUPITER-eligible men and women in the “intermediate” categories (5% to 10% and 10% to 20% 10-year risk) significantly reduced cardiovascular events.<sup>342</sup> In the 5% to 10% FRS category who were treated, HR was 0.55 (95% CI 0.36 to 0.84;

5-year NNT = 40,  $P = 0.005$ ) (Table 6). In the 11% to 20% risk category, HR was 0.51 (95% CI 0.39 to 0.68, 5-year NNT = 18;  $P < 0.0001$ ).

Using the FRS, no significant benefit occurred in the groups with either low or very high risk. The Reynolds risk score reclassified more individuals into these two categories, low (<5%) and high (>20%), and rosuvastatin did produce a benefit in those at highest risk. Since the FRS underestimates risk in women, and frequently women do not have FRS > 10%, they may not be considered for treatment under current guidelines. Using CRP  $\geq 2$  mg/L as part of JUPITER criteria would include almost 7000 of such women who could potentially benefit from rosuvastatin therapy. This number becomes considerable in view of the growing awareness of serious gender disparities in CHD treatment.<sup>343</sup>

## Summary of response of JUPITER authors

Ridker and Glynn<sup>330,344</sup> and Ridker<sup>345</sup> responded to the four major issues raised by De Lorgeril et al,<sup>336</sup> namely a potential deficiency in trial design and execution; early termination of the study was inappropriate and/or favored to exaggerate benefit; inconsistencies existed concerning mortality, statin treatment and CRP; and pharmaceutical company sponsorship played a significant part in the positive outcomes, as summarized below.

## JUPITER study design

The study was logically designed, participant follow-up was careful and full, end point adjudication was rigorous, and followed a pre-specified analysis plan.

**Table 6** Event rates and hazard ratios for the primary end point correlated with estimated 10-year Framingham and Reynolds risk scores at baseline

Risk level	Event rate/100-person years, rosuvastatin 20 mg group	Event rate/100-person years, placebo group	Hazard ratio (95% CI)
<b>Framingham 10-year risk score</b>			
<5% (n = 2791, 173 men, 2618 women)	0.22	0.34	0.64 (0.23–1.81)
5%–10% (n = 6091, 2525 women, 3566 men)	0.50	0.92	0.55 (0.36–0.84) 5-year NNT = 40 <sup>a</sup>
11%–20% (n = 7340, 1404 women, 5936 men)	0.95	1.84	0.51 (0.39–0.68) 5-year NNT = 18 <sup>b</sup>
>20% (n = 1555, 242 women, 1313 men)	1.72	2.41	0.70 (0.43–1.14)
<b>Reynolds 10-year risk score</b>			
<5% (n = 3583, 944 men, 2639 women)	0.26	0.41	0.62 (0.27–1.43)
5%–10% (n = 6436, 2651 women, 3785 men)	0.44	1.00	0.45 (0.29–0.68)
11%–20% (n = 5040, 1151 women, 3889 men)	1.07	1.65	0.65 (0.47–0.90)
>20% (n = 2651, 327 women, 2324 men)	1.55	2.84	0.55 (0.38–0.80)

**Notes:** <sup>a</sup>Corresponds to estimated absolute risk difference between treated and placebo groups at 5 year of  $\approx 2.5$  events/100 person-years; <sup>b</sup>Corresponds to estimated absolute risk difference between treated and placebo groups at 5 year of  $\approx 5.7$  events/100 person-years.

**Abbreviations:** CI, confidence interval; NNT, number needed to treat.

### Early termination of the trial

The details concerning the charter between the investigators and members of the independent Monitoring Board that decided to end the trial early were described. The decision to do so followed that agreement and was just and proper. The investigators reiterated that any overestimate of relative risk reduction involved would have been small, estimated by an FDA statistical analysis at  $\leq 1\%$ .<sup>346</sup> Since the benefit was highly significant at 44% reduction in relative risk for the primary end point, there would be no clinically significant change in outcome interpretation. Simulation studies indicated that stopping the study early under similar circumstances produced valid treatment results.<sup>347,348</sup>

The benefits of rosuvastatin therapy in JUPITER were much larger than those reported in earlier statin trials. However, the relative risk lowering in JUPITER was similar to the analysis of a JUPITER-eligible cohort in the AFCAPS/ TexCAPS study previously reported.<sup>246</sup> In addition, earlier statin trials showed that a 1% fall in LDL level corresponded to a 1% reduction in relative risk. This was approximately the same in JUPITER, since rosuvastatin lowered LDL by 50%, and the resulting fall in relative risk was about the same magnitude.

A sequential review of the benefit of rosuvastatin treatment throughout JUPITER demonstrates that the differences between treatment and placebo groups increased steadily as the study progressed, rather than decreased.<sup>344</sup>

### Inconsistencies in case-fatality rate

Instances of events and deaths required proof to be classified as cardiovascular, and many out-of-hospital deaths were termed “noncardiovascular” in the absence of such proof. There were 35 deaths from CVD in the treated group and 43 in the placebo group. The death rates for SCD were

16 in the rosuvastatin group versus 25 in the placebo group, suggesting a larger beneficial effect in the SCD component than was reported for total and cardiovascular mortality (Table 7).

### Influence of the sponsor-affected outcomes

The sponsor, AstraZeneca, had no access to the data or any role in the analyses or manuscript writing.

### Side effects

Pharmaceuticals nearly always have side effects, but most do not rise to clinical significance. Adverse events associated with statins have been exceptionally well studied. As the most potent member of its class, rosuvastatin is also associated with unwanted events. Molecular mechanisms have yet to be fully characterized. No one study imposes use of drugs on any patient – use is weighed on the ratio of potential benefits with respect to risks, first by the FDA, then subsequently by the prescribing physician. A vast amount of clinical evidence suggests that, for statins in general, and rosuvastatin in particular, this ratio is large.

JUPITER reported a rise in the number of cases of diabetes in the treatment group, amounting to 270 events, or about a 25% increased risk of developing diabetes. In about 1.4% of prescriptions, rosuvastatin has to be discontinued due to adverse reactions, with the Package Insert quoting the incidence of myalgia at 3.1%, abdominal discomfort, 2.6%, asthenia, 2.5%, and nausea at 2.2%. The frequency of overt myotoxicity, with diagnostic elevations in creatine kinase (CK) 10-fold higher than the upper limit of normal and requiring inpatient care, is in the order of 0.4 per 10,000 person-years.<sup>349,350</sup> Less severe myalgia, however, may be responsible for discontinuing statins in 5% to 10% of statin users.<sup>351,352</sup> Both myotoxicity and an increase in the incidence

**Table 7** Components of the primary end point reached in the JUPITER study

End point	Rosuvastatin group	Placebo group	Hazard ratio	95% CI	P value
Primary end point	142	251	0.56	0.46–0.69	<0.00001
Nonfatal MI	22	62	0.35	0.22–0.58	<0.00001
Any MI	31	68	0.46	0.30–0.70	<0.0002
Nonfatal stroke	30	58	0.52	0.33–0.80	0.003
Any stroke	33	64	0.52	0.34–0.79	0.002
Revascularization or Unstable angina	76	143	0.53	0.40–0.70	<0.00001
MI, stroke, CV death	83	157	0.53	0.40–0.69	<0.00001
Total mortality	198	247	0.80	0.67–0.97	0.02
CV death (verified)	35	43	0.82	0.52–1.27	0.37
Sudden death	16	25	0.64	0.34–1.20	0.16

**Abbreviations:** CI, confidence interval; CV, cardiovascular; MI, myocardial infarction.



of diabetes, as noted in JUPITER, are currently of greatest interest.

## Statins raise incidence of diabetes

In a study of 345,417 men, Sukhija et al<sup>353</sup> reported that a decrease in insulin sensitivity was a class effect of statin drugs, and found that the change in fasting plasma glucose level in nondiabetic statin users was 7 mg/dL (versus 5 mg/dL in patients not using statins;  $P < 0.0001$ ), and in diabetic statin users, the rise was 39 mg/dL (versus 32 mg/dL in patients not using statins;  $P < 0.0001$ ). The effect has subsequently been confirmed for atorvastatin<sup>354</sup> and for rosuvastatin,<sup>355</sup> which produced a dose-dependent rise in insulin resistance. Using data from the Cholesterol Treatment Trialists' Collaborators,<sup>356</sup> Sattar and colleagues<sup>357</sup> conducted a meta-analysis of 13 randomized statin trials and studied the incidence of diabetes among 91,140 participants. Statin therapy was associated with a 9% increased risk for diabetes, translating to 1 extra case of diabetes per 255 patients treated over 4 years. Absolute risk was low, at 1 case per 1000 patient-years of treatment. During those 4 years, however, 5.4 MIs or cardiovascular deaths and 5.4 coronary revascularizations and strokes would be prevented, amounting to an overall benefit of 9:1 events. Their analysis also indicated that lowering glucose tolerance was a class effect of statins, in agreement with a review of several statin trials prior to JUPITER.<sup>310</sup> Baker et al<sup>358</sup> systematically reviewed 16 studies and determined there was no class effect of statins upon glucose tolerance in patients without diabetes, and that differences between statins may have accounted for prior findings.

Some side effects of statins are obligatory consequences of HMGR inhibition of the mevalonate pathway used for cholesterol synthesis (Figure 2), and are molecularly unavoidable, extending throughout the metabolome. Among the intermediate products of this pathway are the 15-carbon farnesyl pyrophosphate and 20-carbon geranylgeranyl pyrophosphate molecules, used to add an isoprenoid group to over 100 signaling proteins in a fundamental post-translational modification known as prenylation.<sup>359</sup> This addition of an isoprenoid group is necessary for function of small Rho-family GTPases such as Rac, Rho, and Rab. Some of these GTPases serve as molecular switches, and others are involved in intracellular membrane trafficking, using the lipophilic prenyl group to anchor in membranes.<sup>360</sup> Many desirable pleiotropic actions of statins, such as the antioxidant, anti-inflammatory, and antiproliferative properties<sup>361–363</sup> may be related to decreased ability to prenylate signaling molecules. Inhibition of Rho and its downstream

target Rho kinase (ROCK) function is especially important, since elevated ROCK activity may occur in association with elevated CRP levels<sup>364</sup> and contribute to atherosclerosis.<sup>365,366</sup> Less desirable consequences of HMGR inhibition may arise from deficiencies in downstream metabolites of the mevalonate pathway such as ubiquinone and dolichol, which are, respectively, ignored and largely unknown. Dolichol, a family of linear polyisoprenols containing 16 to 22 isoprene units, are carriers involved in N-glycosylation of nascent polypeptides, and serve as sites for assembly of oligosaccharides during the formation of glycoproteins, ensuring the membrane fluidity and permeability required for glycoprotein maturation and secretion.

There are several signaling steps between the insulin receptor and translocation of the glucose transporter GLUT4 from specialized intracellular compartments to the plasma membrane. Individual statins may have different effects upon these steps, and which of them predominate may account for differences on overall glucose tolerance.<sup>367</sup> Thus, in one preparation, atorvastatin may improve glucose tolerance, possibly by lowering membrane cholesterol content<sup>368</sup> yet in another report atorvastatin appeared to attenuate the expression of GLUT-4 in adipocytes to lower glucose tolerance.<sup>369</sup> In addition, there may be differential effects of statins upon levels of adiponectin, leptin, and other inflammatory mediators that affect glucose intolerance. Differences in lipophilicity among the statins may contribute both to the effects on insulin sensitivity and myotoxicity. Pravastatin, which improves glucose tolerance when compared with atorvastatin, has a relatively favorable effect on beta-cell function.<sup>370,371</sup> It has been suggested that pravastatin, hydrophilic but forming weak steric interactions with HMGR, has limited ability to block the mevalonate pathway in cells outside the liver.<sup>358</sup> Simvastatin, which worsens glucose tolerance, has a greater affinity for cell membranes due to its lipophilicity, and may block L-type calcium channels, interfering with glucose-induced cytosolic calcium signaling and insulin secretion in beta cells.<sup>372</sup> Another possible explanation for statin-induced glucose intolerance includes dysfunctional insulin receptors and/or insulin-like growth factor receptors as a result of impaired glycosylation (see above).<sup>373</sup> Finally, by upregulating hepatic LDL receptors, a greater number of triglyceride-rich particles returning to the liver may induce hepatic insulin resistance.<sup>374</sup>

In view of the large reduction in major vascular events associated with use of statins in diabetics,<sup>356</sup> the small increase in diabetes discussed above has not changed clinical

practice,<sup>375</sup> and further work is needed to delineate its clinical significance.

## Statin-induced myopathy

Statin myotoxicity is a major concern of practitioners; part of the reluctance to titrate LDL levels down to guideline targets is a fear of myopathy. Although this phenomenon has received enormous attention from researchers, clinicians, the lay press, and on the internet, its mechanism and optimal management remain uncertain. The spectrum of myopathy or myotoxicity includes myalgia (muscle ache or weakness without CK elevation), myositis (muscle symptoms with raised CK levels), and rhabdomyolysis (symptoms with CK over the upper limit of normal by a factor of at least 10).<sup>376</sup> Myalgia is noted in randomized statin trials in the order of <3%, compared to the incidence in outpatient lipid clinics, which varies between 5% and 10%.<sup>377</sup> Underreporting is commonly assumed, but individuals with predisposing conditions are carefully screened, and many randomized trials include a run-in period, then fail to randomize candidates with myopathic symptoms.

During vigorous exercise, the phenomenon is accentuated, raising the reported incidence of myalgia up to 25%.<sup>378</sup> Statin intolerance among athletes is well known. Factors that predispose to myopathy are increasing age, female gender, hepatic or renal disease, diabetes, polypharmacy, and any condition that diminishes muscle reserve (small frame, frailty, sarcopenia), or causes muscle pathology, including hypothyroidism or hyperthyroidism, metabolic muscle disease, polymyalgia rheumatica, autoimmune diseases with myositis, postoperative status, hypovitaminosis D, chronic alcohol use, and others.

Some adverse reactions may be minimized by avoiding negative drug–drug interactions. As mentioned above, since rosuvastatin is not eliminated through the CYP3A4 pathway, only minimally metabolized by the CYP2C9 enzyme, and does not interfere with P-gp, drugs that inhibit OATP1B1, a transporter that facilitates rosuvastatin uptake in the liver, may clinically be more important offenders than cytochrome P450 inhibitors or substrates. Common drugs usually mentioned that may raise the likelihood of myotoxicity are cyclosporine, gemfibrozil, itraconazole, ketoconazole, fluconazole, lopinavir/ritonavir, atazanavir/ritonavir, fosamprenavir/ritonavir, warfarin, and amiodarone. Some of the quantitative effects of coadministered drugs are summarized in Tables 8 and 9. As noted in Table 9, digoxin coadministered with rosuvastatin only raises the AUC 4%, reflecting the statin is not a P-gp substrate. Genetic polymorphism

within *SLCO1B1*, the gene that encodes OATP1B1, produces a variant which increases susceptibility to statin-induced myopathy.<sup>379</sup>

Since statins affect many different molecules and signaling systems, the mechanism of statin myopathy also remains uncertain. A relationship to a deficiency of prenylating moieties, farnesyl pyrophosphate and geranylgeranyl pyrophosphate, is again likely. Inability to prenylate selenoproteins, dolichols, and small GTPases Rho, Ras, and Rac is believed to disturb intracellular trafficking of proteins between membranes needed for muscle growth and repair. Statins specifically activate mechanisms that lead to muscle atrophy in a number of circumstances, mediated by overexpression of atrogen-1, a muscle-specific E3 ubiquitin ligase in the ubiquitin proteasome proteolytic pathway.<sup>380–382</sup> Induction of atrogen-1 appears to be significant in the pathogenesis of statin myopathy, but is by no means the only mechanism. Experimental overexpression of peroxisome proliferator-activated receptor-gamma coactivator-1 $\alpha$  (PPAR $\gamma$  coactivator 1 $\alpha$  or PGC-1 $\alpha$ ), coactivator of many transcription factors and a regulator of mitochondrial number and function, attenuates statin-induced atrogen-1 expression, protects against statin myotoxicity, and may lead to a therapeutic target.

Skeletal muscle expresses drug transporters such as OATP2B1, high-affinity uptake transporters for both atorvastatin and rosuvastatin.<sup>383</sup> A number of efflux transporters, multidrug-resistance-associated proteins 1, 4, and 5, are also expressed on the sarcolemmal membrane of skeletal muscle. Susceptibility to myotoxicity may depend not only on the serum concentration of rosuvastatin, but also locally on the balance between activities of muscle fiber uptake and efflux transporters. For example, in one experimental model, probenecid, which inhibits efflux transporter MRP1, raised myocyte rosuvastatin levels and promoted myotoxicity.<sup>384</sup>

Lipophilic statins, such as lovastatin or simvastatin, inhibit protein synthesis in skeletal myotubules to a greater extent than hydrophilic statins, such as pravastatin.<sup>385</sup> Statins in higher doses may decrease the ability of muscle progenitor cells (satellite cells) to repair and regenerate skeletal muscle.<sup>386</sup> Only in part because they severely reduce ubiquinone (coenzyme Q10) levels, statins are associated with multiple defects in muscle mitochondrial anatomy and function.<sup>387</sup> Lower mitochondrial volume, mitochondrial DNA loss, reduction in mitochondrial membrane potential, inefficient oxidative phosphorylation, anatomical fractionation, leakage of pro-apoptotic chemicals through mitochondrial membranes, and apoptosis have all been

**Table 8** Effect of coadministered drugs on rosuvastatin systemic exposure

Coadministered drug and dosing regimen	Rosuvastatin		
	Dose (mg) <sup>a</sup>	Change in AUC <sup>b</sup>	Change in C <sub>max</sub> <sup>b</sup>
Cyclosporine – stable dose required (75–200 mg twice daily)	10 mg daily for 10 days	↑ 7-fold <sup>c</sup>	↑ 11-fold <sup>c</sup>
Gemfibrozil 600 mg twice daily for 7 days	80 mg	↑ 1.9-fold <sup>c</sup>	↑ 2.2-fold <sup>c</sup>
Lopinavir/ritonavir combination 400 mg/100 mg twice daily for 10 days	20 mg daily for 7 days	↑ 2-fold <sup>c</sup>	↑ 5-fold <sup>c</sup>
Atazanavir/ritonavir combination 300 mg/100 mg daily for 7 days	10 mg	↑ 3-fold <sup>c</sup>	↑ 7-fold <sup>c</sup>
Tipranavir/ritonavir combination 500 mg/200 mg twice daily for 11 days	10 mg	↑ 26%	↑ 2-fold
Fosamprenavir/ritonavir 700 mg/100 mg twice daily for 7 days	10 mg	↑ 8%	↑ 45%
Fenofibrate 67 mg 3 times daily for 7 days	10 mg	↑ 7%	↑ 21%
Aluminum and magnesium hydroxide combination antacid, administered simultaneously	40 mg	↓ 54% <sup>c</sup>	↓ 50% <sup>c</sup>
The above, administered 2 hours apart	40 mg	↓ 22%	↓ 16%
Erythromycin 500 mg 4 times daily for 7 days	80 mg	↓ 20%	↓ 31%
Ketoconazole 200 mg twice daily for 7 days	80 mg	↑ 2%	↓ 5%
Itraconazole 200 mg daily for 5 days	10 mg	↑ 39%	↑ 36%
Fluconazole 200 mg daily for 11 days	80 mg	↑ 28%	↑ 15%
	80 mg	↑ 14%	↑ 9%

**Notes:** <sup>a</sup>Single dose unless otherwise noted; <sup>b</sup>Mean ratio (with/without coadministered drug and no change = 1-fold) or % change (with/without coadministered drug and no change = 0%); symbols of ↑ and ↓ indicate the exposure increase and decrease, respectively; <sup>c</sup>Clinically significant.

**Abbreviations:** AUC, area under the plasma concentration-time curve; C<sub>max</sub>, peak plasma concentration.

reported. Apoptosis of muscle cells – direct myotoxicity – has been described after acute statin exposure.<sup>383,388</sup> Intracellular calcium overload and activation of caspase-3 to initiate apoptosis is yet another proposed mechanism.<sup>389</sup> Dolichol is needed for synthesis of  $\alpha$ -dystroglycan, a major protein in the skeletal muscle dystrophin–glycoprotein complex, and deficiencies have been linked to muscle dysfunction. Finally, some evidence also implicates immune involvement, which may persist after statin therapy is discontinued.<sup>390,391</sup> Four detailed, well-referenced recent reviews of statin myotoxicity are available.<sup>392–395</sup>

In summary, it appears that the side effects of statins are just as multimechanistic, or “pleiotropic”, as the beneficial actions. Despite these seemingly complex biochemical

effects, in practice, the incidence of myopathy and glucose intolerance is far outweighed by the overall benefits of statins in general, and rosuvastatin in particular.<sup>396,397</sup> Most serious events may be averted with careful monitoring and avoidance of drug interactions, but individual and genetic susceptibility can unfortunately not yet be predicted clinically. The overwhelming majority of patients tolerate rosuvastatin well. In JUPITER, there were no significant differences in myotoxicity between treatment and control groups.

## Conclusion

The challenge of a rising sea of cardiovascular risk, threatening to reverse improved coronary death rates, is immense. The reality is that few individuals will sustain the necessary

**Table 9** Effect of rosuvastatin coadministration with warfarin, digoxin, and an oral contraceptive

Rosuvastatin dosage regimen	Coadministered drug		
	Name and dose	Change in AUC	Change in C <sub>max</sub>
40 mg daily for 10 days	Warfarin 25 mg, single dose	R-Warfarin ↑ 4%	R-Warfarin ↓ 1%
		S-Warfarin ↑ 6%	S-Warfarin 0%
40 mg daily for 12 days	Digoxin 0.5 mg, single dose	↑ 4%	↑ 4%
40 mg daily for 28 days	Oral contraceptive (EE 0.035 mg and NG 0.180, 0.215, and 0.250 mg) daily for 21 days	EE ↑ 26%	EE ↑ 25%
		NG ↑ 34%	NG ↑ 23%

**Abbreviations:** AUC, area under the plasma concentration-time curve; C<sub>max</sub>, peak plasma concentration; EE, ethinyl estradiol; NG, norgestrel; R-warfarin and S-warfarin, referring to the stereoisomers.

lifestyle and behavioral changes to lower their risk, and this is amply reflected by the dismal success in weight control. Obesity drives the dual epidemics of diabetes and CHD. Primary prevention, sometimes regarded as an illusion, is only effective if it is done early and intensively. When lifestyle modification fails, reduction of elevated risk factors through pharmacological means is imperative, because by the time they are evident, atherosclerotic processes are already advanced. If we are to stem the tide, simply waiting for a cardiovascular event or diagnosis will no longer suffice.

Asymptomatic individuals randomized in the JUPITER study, many similar to those in the general population, bore a considerable cardiovascular burden, even though they were free from a formal diagnosis of heart disease, diabetes and dyslipidemia. Studies other than JUPITER confirm that higher values of CRP are associated with greater cardiovascular risk, which may assist in the decision of whether to treat or not. With the FDA approval for the use of rosuvastatin in JUPITER-eligible patients with at least one additional cardiovascular risk factor, an additional choice became available to clinicians.

The prevalence of metabolic syndrome in JUPITER participants was about the same as in US adults at the present time. JUPITER demonstrated that within this population, those persons with elevations in CRP levels benefited from rosuvastatin therapy. While, as mentioned, some critics, observing that 41% of JUPITER participants had metabolic syndrome, suggested this diminished the value of the study. However, one can argue that the opposite was true, in that JUPITER demonstrated that rosuvastatin therapy in this syndrome, when CRP was elevated, was effective therapy. The prevalence of metabolic syndrome more closely follows the rise in level of visceral adiposity within the population, now averaging 53%.<sup>398</sup> At the moment, the highest prevalence of metabolic syndrome reported in an US subpopulation also stands at 53%.<sup>127</sup> The evidence that inflammation plays a critical role in the pathogenesis of components of metabolic syndrome is of high quality.<sup>198,199</sup> A recent systematic review and meta-analysis of 87 studies involving 951,083 patients found that metabolic syndrome is associated with a 2-fold increase in risk of CVD, cardiovascular mortality, and stroke, and a 1.5-fold rise in all-cause mortality.<sup>399</sup>

DeMazumder et al<sup>400</sup> noted that the use of global risk assessment tools may result in denial of statin therapy to individuals at low risk when current guidelines are employed, while others with a high absolute risk may not benefit from statin therapy. These authors therefore suggested that statin therapy might be better allocated on the basis of randomized trial evidence rather than global risk

scores. Nambi and Ballantyne<sup>401</sup> proposed a formal protocol using the FRS, lifetime risk, and CRP, CIMT, calcium artery calcification burden, or genetic risk markers for progressive refinement of stratification. CRP measurements may be repeated easily, and are less involved than imaging, with no radiation exposure.

The reaction to JUPITER, many physicians will agree, has been most unusual. The rationale and findings are bracketed by many other independent investigations, but the final interpretation of the data presented is up to each physician. A repeat of JUPITER will probably not occur. The study is not perfect, and limitations are clear and well known. Controversies in medicine may endure for years without resolution. In the individual case, certainly other methods for risk stratification, such as CIMT measurement and coronary artery calcium score, are available. Processes bringing about alterations in each risk factor are different but overlap, and the information their changes bring to the physician's desk are complementary, not identical. Eventually a place for each will be found in the clinician's toolbox, but ultimately, the individual practitioner has the choice of where to reach in his armamentarium, the essence of the "art of medicine". It is encouraging to note that in blog comments written by individuals critical of some results and potential applications of JUPITER, when presented with specific cases, rosuvastatin is in fact being prescribed for high-risk individuals with elevated CRP values in primary prevention, indicating that patients' needs are being valued with higher priority than personal views.

Almost all JUPITER-eligible patients who would benefit from rosuvastatin have an alternative. Weight loss, especially in conjunction with exercise and dietary changes, are powerful techniques to lower cardiac risk and CRP levels<sup>197,213-222</sup> and in fact would be preferred. The pervasive condition for which rosuvastatin has been found effective in JUPITER differs significantly from other diseases. This "illness" of unrecognized cardiovascular risk is diffuse, significant, difficult to quantitate, but deadly nonetheless. However, it is also largely self-inflicted, with a common cause in poor personal lifestyle choices. A recurring comment that ostensibly healthy people are being subjected to testing and side effects may be, in part, rooted in erroneously equating "asymptomatic" with *ideal cardiovascular health* – free of risk factors and a likelihood that none will appear in the near future<sup>402</sup> – by the public. Perception of risk by patients is commonly inaccurate, and educational programs have been repeatedly recommended.<sup>403</sup>



The broader message of JUPITER is, first, it reminds us that the level of cardiovascular risk is currently oppressive, and greater than previously recognized when evaluated by LDL and global risk scores. Second, physicians must go on the offensive, delve into the population, and ferret out the risk, rather than wait for the risk to open their office door.

Today the clinician has a much greater amount of information and a wider variety of techniques from which to choose in order to evaluate individuals for primary prevention. Rosuvastatin will lower risk in JUPITER-eligible subpopulations, but also in many others selected differently for risk, even if one uses age for stratification, simply because the current level of risk is so high. Whatever markers or techniques are chosen, a fresh view of preventive care is before us, and action is now imperative. New guidelines in preparation will hopefully provide even greater direction in maximizing returns in primary prevention and improve future outcomes in our patients.

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