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EDITORIAL

JUPITER and satellites: Clinical implications of the JUPITER study and its secondary analyses

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Abstract

The justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER) study was a real breakthrough in primary cardiovascular disease prevention with statins, since it was conducted in apparently healthy individuals with normal levels of low-density lipoprotein cholesterol (LDL-C < 130 mg/dL) and increased inflammatory state, reflected by a high concentration of high-sensitivity C-reactive protein (hs-CRP ⩾ 2 mg/L). These individuals would not have qualified for statin treatment according to current treatment guidelines. In JUPITER, rosuvastatin was associated with significant reductions in cardiovascular outcomes as well as in overall mortality compared with placebo. In this paper the most important secondary analyses of the JUPITER trial are discussed, by focusing on their novel findings regarding the role of statins in primary prevention. Also, the characteristics of otherwise healthy normocholesterolemic subjects who are anticipated to benefit more from statin treatment in the clinical setting are discussed. Subjects at "intermediate" or "high" 10-year risk according to the Framingham score, those who exhibit low post-treatment levels of both LDL-C (< 70 mg/dL) and hs-CRP (< 1 mg/L), who are 70 years of age or older, as well as those with moderate chronic kidney disease (estimated glomerular filtration rate < 60 mL/min every 1.73 m^2) are anticipated to benefit more from statin treatment. Unlikely other statin primary prevention trials, JUPITER added to our knowledge that statins may be effective drugs in the primary prevention of cardiovascular disease in normocholesterolemic individuals at moderate-to-high risk. Also, statin treatment may reduce the risk of venous thromboembolism and preserve renal function. An increase in physician-reported diabetes represents a major safety concern associated with the use of the most potent statins.

Key words: Rosuvastatin; Primary prevention; Justification for the use of statins in prevention: An intervention trial evaluating rosuvastatin; Cardiovascular events; Mortality

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INTRODUCTION

Statins are still the cornerstone in the management of

dyslipidemia. Clinical trials demonstrated that statin therapy is associated with a significant reduction in cardiovascular morbidity and mortality when used for either primary or secondary prevention of cardiovascular events[1-3]. Interestingly, this benefit was so firmly confirmed in primary prevention studies involving patients with hypercholesterolemia, hypertension or diabetes mellitus, that the use of placebo in forthcoming statin trials has been considered as unethical[3].

The justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER) study made a step forward. This trial involved 17 802 apparently healthy individuals with normal low-density lipoprotein cholesterol (LDL-C) (< 130 mg/dL) and increased levels of high-sensitivity C-reactive protein (hs-CRP ⩾ 2 mg/L). The hypothesis whether rosuvastatin may decrease cardiovascular morbidity and mortality as compared with placebo in these subjects was tested[4]. JUPITER participants would not have qualified for statin therapy according to the existing guidelines for the management of dyslipidemia[5].

JUPITER revealed that rosuvastatin 20 mg/d decreased LDL-C levels by 50% and hs-CRP levels by 37%[4]. Also, rosuvastatin was associated with a significant decrease in the combined primary endpoint of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from cardiovascular causes by 44% compared with placebo, after a median follow-up of 1.9 years[4]. Apart from this benefit in the primary endpoint, impressive reductions in the incidence of separate cardiovascular outcomes, including myocardial infarction (by 54%), stroke (by 48%) and revascularization for unstable angina (by 47%) compared with placebo were noted in the rosuvastatin-treated arm[4]. A reduction by 47% was also observed in the secondary combined endpoint of myocardial infarction, stroke, or death from cardiovascular causes[4].

Since the first release of JUPITER, many secondary analyses of this study have come to the light with regard to the results of the study into separate subgroups of the study population. Also, the effect of rosuvastatin treatment on outcomes not assessed in the initial part of the study was examined. In this paper, the most important *post hoc* analyses of the JUPITER study are reviewed by discussing major clinical implications derived from their results.

JUPITER IN SUBPOPULATIONS

Unlike other statin trials of primary prevention, JUPITER involved a quite different population, especially in terms of lipid profile and inflammation. Indeed, the population of JUPITER consisted of normocholesterolemic (LDL-C levels < 130 mg/dL), middle-aged (⩾ 50 years for men and ⩾ 60 years for women) subjects who exhibited increased hs-CRP levels (⩾ 2 mg/L)[4]. All individuals were statin-naïve and suitable for statin use in terms of safety parameters, while none had a history of serious medical conditions that could affect morbidity and mortality rates in the study period, including diabetes, uncontrolled hypertension or cancer[4].

From a total of 89 890 people screened, only 17 802 (19.8%) were eligible and finally enrolled in this study. Of the screening failures, more than half (i.e. 52.2%) were due to increased LDL-C levels > 130 mg/dL, while approximately one third (i.e. 36.1%) were due to low hs-CRP levels < 2 mg/L[4]. After 12 mo of treatment with rosuvastatin, LDL-C levels were decreased to the lowest level ever achieved in a primary prevention trial with the use of statins (i.e. 55 mg/dL).

JUPITER results according to cardiovascular risk classification

Several subanalyses explored the efficacy of rosuvastatin in reducing cardiovascular outcomes in different risk groups according to the Framingham or the Reynolds 10-year risk scores or the European systematic coronary risk (SCORE). In contrast to JUPITER participants who exhibited a 10-year risk of < 5%, those with a 10-year risk of ⩾ 5% experienced significant decreases in the relative risk for the primary endpoint associated with rosuvastatin treatment[6]. Rosuvastatin-associated benefits in all subgroups according to the Framingham or Reynolds 10-year risk classification (5%-10%, 11%-20% or > 20%) were comparable with the overall treatment effect observed in this study[6].

Among JUPITER participants, 6091 and 7340 subjects had a baseline estimated 10-year Framingham risk of 5%-10% and 11%-20%, respectively[6]. According to current guidelines these subjects are considered as a population of "intermediate" risk. JUPITER participants with a 10-year risk of 5%-10% or 11%-20% experienced significant absolute risk reductions[6]. Interestingly, absolute risk reductions increased with increasing level of global risk as assessed by either Framingham or the Reynolds risk scores[6]. For example, the estimated 5-year number needed to treat (NNT) of participants with a 5%-10% Framingham risk score was 40 (95% CI: 22-206), whereas in subjects with a Framingham risk score of 11%-20%, NNT was 18 (95% CI: 12-32)[6].

In another subanalysis, the results of JUPITER were evaluated in groups of participants who exhibited high global risk as defined by a 10-year Framingham risk score > 20% or SCORE ⩾ 5%[7]. Rosuvastatin treatment was associated with a relative risk reduction for the combined endpoint of myocardial infarction, stroke and cardiovascular death as compared with placebo in "high" risk subjects defined by either a Framingham score > 20% [hazard ratio (HR), 0.50; 95% CI: 0.27-0.93] or SCORE ⩾ 5% (HR, 0.57; 95% CI: 0.43-0.78)[7]. No differential change in the same endpoint was detected between subjects with a Framingham score above or below 20% as well as between individuals with a SCORE above or below 5%[7]. This benefit of rosuvastatin was also evident for the

primary endpoint among subjects with SCORE ≥ 5%[7]. In high-risk subjects, no heterogeneity for the combined endpoint of myocardial infarction, stroke and cardiovascular death was noted in subgroups by gender, age, race/ethnicity, the presence of hypertension or family history of cardiovascular disease, smoking status, baseline levels of high-density lipoprotein cholesterol (HDL-C) and hs-CRP[7]. Of interest, among high-risk patients, those who were obese at baseline, as defined by body mass index ≥ 30 kg/m^2, had less benefit from rosuvastatin treatment[7].

JUPITER results according to the lowering of lipids and hs-CRP

In another subanalysis, the effect of reductions in LDL-C and hs-CRP levels on trial event rates was assessed, by using pre-defined study cut-offs for both parameters[8]. No significant interaction between the overall efficacy of rosuvastatin and baseline concentrations of hs-CRP above or below 5 mg/dL and LDL-C above or below 100 mg/dL was noted in the JUPITER study[8]. Rosuvastatin-treated subjects who did not reach post-treatment levels of LDL-C < 70 mg/dL experienced no significant benefits as compared with placebo. In contrast, in individuals who attained LDL-C levels < 70 mg/dL a significant reduction in vascular event rates of 55% was noted[8]. A reduction in hs-CRP levels was also associated with clinical benefit. Thus, in patients with hs-CRP levels < 2 mg/L at the end of the study a significant decrease of 62% in cardiovascular events was observed[8]. This decrease was also significant, but modest (i.e. 31%) among individuals who did not achieve hs-CRP levels < 2 mg/L. All of the above variations were independent of the baseline levels of both LDL-C and hs-CRP[8]. Interestingly, subjects who achieved low concentrations of both LDL-C and hs-CRP (< 1 mg/L) after rosuvastatin treatment were at the lowest risk of cardiovascular events, shown by a decrease of 79% in risk[8].

There were similar findings in analogous assessments when other lipid parameters related to residual cardiovascular risk, including non-HDL-C levels above or below 100 mg/dL, apolipoprotein (apo)B target level above or below 80 mg/dL, or apoB to apoA1 ratio above or below 0.5, were put in the analysis as a substitute for LDL-C levels[8]. In all these analyses, participants achieving low concentrations of hs-CRP and low values of each lipid variable had a better clinical outcome compared with those who did not achieve the respective target[8].

To assess whether the rosuvastatin-associated clinical benefit for the primary endpoint was associated with HDL-C and apoA1 levels, study participants were divided into quartiles according to these parameters[9]. In the placebo group, LDL-C levels remained high and there was an inverse association of vascular risk with HDL-C and apoA1 levels. In contrast, this was not the case in the rosuvastatin-treated group in which LDL-C levels were decreased up to 55 mg/dL[9]. Therefore, HDL-C concentrations may not be predictive of residual cardiovascular risk among patients treated with potent statins who attain very low concentrations of LDL-C.

JUPITER results according to age

Compared with other statin trials, the JUPITER study involved a relatively older population (mean age, 66 years)[4]. In older populations there is a weaker association between total cholesterol levels and cardiovascular outcomes, possibly due to the existence of age-related comorbid conditions[10]. To date, there are limited data from randomized clinical trials regarding the efficacy of statins in the primary prevention of cardiovascular disease in the elderly[11]. A *post hoc* analysis of the JUPITER study focused on the efficacy of rosuvastatin to prevent cardiovascular events in study participants who were 70 years or older at recruitment[12]. Of 17 802 participants in the study, 5695 belonged to this age group. Despite being in a minority, older subjects accounted for 49% of the 393 confirmed primary endpoints in the trial[12]. Compared with younger participants, the older subjects exhibited a quite different risk profile, with female gender and hypertension being more prevalent among older persons than in younger ones. On the other hand, a lower percentage of subjects 70 years or older were obese or current smokers compared with younger subjects[12].

No differential effect between older and younger participants was detected with regard to post-treatment reductions of LDL-C and hs-CRP levels[12]. The analysis revealed that subjects 70 years or older may benefit more from rosuvastatin treatment, since the absolute risk reduction of the primary endpoint in this subpopulation was 48% greater than that observed in younger subjects[12]. Likewise, the NNT to prevent one primary endpoint was 24 for older individuals *vs* 36 for younger ones[12]. This difference was also evident for the composite endpoint of the primary endpoint, any death and venous thromboembolism (NNT 17 in older persons *vs* 27 in younger ones)[12]. No serious safety concerns from rosuvastatin use were raised in the older subpopulation compared with the younger one[12].

JUPITER results according to gender

Unlike secondary prevention trials, in primary prevention trials the reductions in coronary events associated with statin treatment were significant only in men, and not in women[13]. In the JUPITER study there was a predominance of the male gender over female (11 001 men *vs* 6801 women)[4]. Compared with male participants, female participants were older[14]. The different age-specific inclusion criterion (≥ 60 years in women and ≥ 50 years in men) could have accounted for this difference. Also, the prevalence of obesity, hypertension and metabolic syndrome was higher among women than men[14]. At baseline, women exhibited higher levels of hs-CRP than men (4.6 mg/dL *vs* 4.1 mg/dL), whereas no variation was observed in baseline LDL-C levels[14].

No gender-related variation with regard to post-treat-

ment changes in lipid parameters and hs-CRP levels was noted[14]. Also, the relative risk reduction for the primary endpoint with rosuvastatin was similar and statistically significant in both men and women[14]. Likewise, the reduction in overall mortality was quite similar between men and women (23% and 18%, respectively)[14]. Several differences were detected between men and women with regard to separate cardiovascular outcomes. For example, women experienced a greater risk reduction for revascularization/unstable angina than men (HR, 0.24; 95% CI: 0.11-0.51 for women *vs* HR, 0.63; 95% CI: 0.46-0.85 for men, $P = 0.01$ for heterogenicity)[14]. Nevertheless, unlike in men, no benefit for women was proved for several components of the primary endpoint, including myocardial infarction, stroke or death from cardiovascular causes. Of interest, in women a smaller reduction in nonfatal stroke was observed than in men ($P = 0.04$ for heterogeneity)[14].

Relative risk reductions in events were similar in women with either a Framingham risk score of 5%-10% or > 10% (HR, 0.44; 95% CI: 0.22-0.89 and HR, 0.57; 95% CI: 0.34-0.97, respectively)[14]. The results were also similar for men stratified by Framingham risk scores. However, event rates were low in women and men with a Framingham risk score < 5% as well as in those younger than 65 years[14]. Subgroup analysis revealed that women with a family history of premature coronary heart disease may benefit more from rosuvastatin treatment than those without. This variation was not evident for men[14].

From these findings, the JUPITER study was the first primary prevention study which demonstrated that men and women with elevated hs-CRP levels could experience similar benefits from statin treatment in the prevention of cardiovascular outcomes.

JUPITER results in patients with chronic kidney disease

Patients with chronic kidney disease (CKD) exhibit increased cardiovascular morbidity and mortality compared with individuals with more preserved renal function[15]. Evidence from randomized clinical trials failed to show any benefit of statin treatment in high-risk patients with severe renal failure undergoing maintenance hemodialysis[15]. In the primary prevention basis, the WOSCOPS (West of Scotland Coronary Prevention Study) reported no significant benefit from pravastatin treatment among subjects with moderate CKD[16]. Pravastatin-associated benefits were obvious only in individuals with estimated glomerular filtration rate (eGFR) ⩾ 60 mL/min every 1.73 m^2[16].

The JUPITER study included 3267 patients with CKD, as defined by eGFR < 60 mL/min every 1.73 m^2[17]. From those, the vast majority (3253 subjects) had stage 3 impairment (eGFR 30-59 mL/min every 1.73 m^2) while only 14 had stage 4 renal impairment (eGFR 15-29 mL/min every 1.73 m^2)[17]. Subjects with renal impairment were older, more likely to be female and have a family history of premature cardiovascular disease, and exhibited a worse lipid profile as well as increased hs-CRP levels compared with those with normal renal function[17]. Also, those subjects were at increased risk of developing the primary endpoint of the study (HR, 1.54; 95% CI: 1.23-1.92, $P = 0.0002$) as well as arterial revascularization (HR, 1.53; 95% CI: 1.13-2.08, $P = 0.008$) and the combined endpoint of myocardial, infarction, stroke and cardiovascular death (HR, 1.44; 95% CI: 1.08-1.92, $P = 0.02$) compared with subjects with preserved renal function[17]. The two groups did not differ with regard to all-cause mortality and rates of venous thromboembolism[17].

The reduction in the primary endpoint by rosuvastatin treatment compared with placebo was significant (HR, 0.55; 95% CI: 0.38-0.82, $P = 0.002$) in the group of individuals with moderate CKD and was comparable to that observed in subjects with preserved renal function[17]. Likewise, the efficacy of rosuvastatin to reduce the risk of all vascular events was similar between the two groups. All-cause mortality was the only exception, which was reduced more by rosuvastatin in moderate CKD subjects compared with subjects with normal renal function (44% *vs* 12%, P for interaction = 0.048)[17]. Of interest, patients with moderate CKD experienced a greater absolute risk reduction in the primary endpoint than subjects with preserved renal function (NNT 14 and 35, respectively)[17]. No differential effect of rosuvastatin was noted in the two groups with regard to decreases in LDL-C and hs-CRP levels. There was no difference between the two groups regarding safety[17].

JUPITER AND ALTERNATIVE OUTCOMES

Stroke

In primary prevention trials with the use of statins there were no significant decreases in the risk of stroke[18]. Therefore, this outcome was assessed separately in a secondary analysis of the JUPITER study[19]. Rosuvastatin was associated with a decrease in the risk of stroke by 48% compared with placebo, a rate which was similar also for nonfatal strokes[19]. A decrease by 51% associated with rosuvastatin treatment was noted for ischemic strokes, which accounted for the majority of all strokes[19]. Nevertheless, no effect of rosuvastatin treatment was noted with regard to the risk of hemorrhagic stroke or transient ischemic attacks[19].

Rosuvastatin-related benefits in the risk of stroke were similar in different groups according to age, sex, ethnicity, the presence of traditional risk factors for stroke, including age > 70 years, smoking, hypertension and a family history of premature stroke or a Framingham risk score > 10%[19]. As with other vascular outcomes, the greatest reduction in stroke risk was noted among those who achieved LDL-C levels < 70 mg/dL and hs-CRP < 2 mg/L[19].

Venous thromboembolism

There is still controversy with regard to the nature and

the shared pathways of venous and arterial thrombosis[20]. Also, it has not yet been defined whether treatment proven efficacious in the prevention of one condition may have consistent benefits for the other[20]. Statins exhibit many lipid-independent antithrombotic and anticoagulant effects[21]. To date, there are conflicting data from observational studies as to the effect of statin treatment on the risk of venous thrombosis[20]. In the JUPITER study, rosuvastatin treatment was associated with a significant decrease in the risk of pulmonary embolism or deep vein thrombosis by 43% compared with placebo[22]. Similar benefits of rosuvastatin were found when provoked (in patients with cancer, recent trauma, hospitalization or surgery) and unprovoked events of venous thromboembolism were examined separately[22]. Also, subjects at high risk for venous thromboembolism, including those aged > 70 years, body mass index > 30 kg/m^2 and increased waist circumference, exhibited a similar benefit associated with rosuvastatin treatment as in lower risk individuals[22]. No association between the risk of venous thromboembolism and baseline lipid levels was noticed[22].

Renal function

There is evidence that statins, through either their lipid-lowering properties or their pleiotropic effects, may preserve renal function and reduce proteinuria[15]. The effect of rosuvastatin on renal function was also assessed in the JUPITER study. After 12 mo of treatment with rosuvastatin, eGFR was marginally improved compared with placebo (66.8 mL/min every 1.73 m^2 *vs* 66.6 mL/min every 1.73 m^2, $P = 0.02$)[17]. This benefit was not evident in subjects with eGFR < 60 mL/min every 1.73 m^2, while it was more profound in individuals with eGFR ⩾ 60 mL/min every 1.73 m^2 at baseline[17].

Incidence of physician-reported diabetes

Increasing interest has been focussed on the effect that various statins may exert on glucose metabolism and the risk of diabetes[23]. In WOSCOPS pravastatin was associated with a decrease of 30% in the incidence of diabetes compared with placebo[24]. Nevertheless, JUPITER showed an increase in physician-reported diabetes in rosuvastatin-treated subjects compared with placebo-treated subjects (270 and 216 reports, respectively, $P = 0.01$)[4]. These events were not adjudicated by the endpoint committee of the trial. This result was documented despite no difference being observed between study groups for fasting glucose or newly diagnosed glycosuria[4]. However, a minimal increase in glycosylated hemoglobulin (Hb) was observed in the rosuvastatin group (5.9% *vs* 5.8%, $P < 0.001$)[4]. After this finding we have shown that rosuvastatin may be associated with a dose-dependent increase in insulin resistance among hyperlipidemic patients with impaired fasting glucose[25]. These findings were consistent with those of two recent meta-analyses of large-scale placebo-controlled and standard-care controlled trials, which, respectively, reported a 9% and 13% increased risk for incident diabetes associated with statin therapy[26].

Hb levels in patients with anemia

There is evidence suggesting that anemia of chronic disease may be associated with a functional iron deficiency mediated by immune mechanisms[27]. It has also been hypothesized that statins may contribute to an increase in Hb levels through immunomodulatory properties. In the JUPITER trial, Hb levels were determined at baseline and at the final visit in a secondary analysis which included study participants with anemia, as defined by Hb < 13 g/dL for men and < 12 g/dL for women[28]. A total of 369 women and 433 men met the inclusion criteria for this analysis. No difference between rosuvastatin and placebo was noted with regard to post-treatment changes in Hb levels[28]. Similar results were also found among patients with slightly worse anemia, as defined by Hb < 12.5 g/dL for men and < 11.5 g/dL for women[28].

CLINICAL IMPLICATIONS

Before JUPITER, studies showing a benefit of statins in primary prevention were limited to groups at high risk of cardiovascular disease, currently characterized as individuals with diabetes, hyperlipidemia, a family history of premature cardiovascular disease or those at high global cardiovascular risk. Since JUPITER, the potential efficacy of statins to prevent cardiovascular outcomes has been expanded to include normolipidemic individuals. The JUPITER population consisted of apparently healthy men and women with normal levels of LDL-C and an increased inflammatory state, indicated by high levels of hs-CRP. This disturbance was mainly attributed to obesity, smoking or metabolic syndrome, conditions which were frequent among the subjects. In this population there was no indication for statin treatment according to clinical practice guidelines. Interestingly, in JUPITER, rosuvastatin markedly decreased cardiovascular outcomes and moderately decreased mortality in this cohort.

Almost 20% of population screened in the JUPITER study fulfilled the criteria for inclusion in the study. When the eligibility criteria of JUPITER were analyzed in comparison with other community-based studies, such as the REGARDS (Reasons for Geographic and Racial Differences in Stroke) and the ARIC (Atherosclerosis Risk in Communities) studies, it was found that 21% and 18.2%, respectively, of each study could have been eligible for inclusion in the JUPITER study[29,30]. Another analysis suggested that approximately 6.5 million people in the United States could have been eligible for JUPITER[31]. Therefore, according to the JUPITER results a relatively high proportion of an age-matched population in the community could benefit from statin treatment in terms

of primary prevention. If these data are translated into practice, the current guidelines for statin use in primary prevention may dramatically change, leading to increased use of statin treatment. Furthermore, increasing interest will be applied in measuring hs-CRP in the screening of the normolipidemic population[32].

Secondary analyses of JUPITER highlighted those subjects who could benefit more from rosuvastatin treatment in terms of reduction in clinical outcomes. JUPITER suggested that no such benefit may be evident among individuals at low 10-year risk of < 5%. On the other hand, in subjects considered as of "intermediate risk", including those with a 10-year risk of 5%-10% or 11%-20%, a profound clinical benefit in the primary prevention of cardiovascular disease may be produced by statin treatment. This finding implies that this group of subjects, who were currently outside treatment guidelines according to their baseline LDL-C levels (i.e. < 104 mg/dL), might well be considered for statin therapy. Also, in such populations hs-CRP may comprise a useful tool for the reclassification of risk. In an analysis recently performed by Choudhry *et al*[33], it has been suggested that measuring hs-CRP levels may be valuable in order to identify patients in whom rosuvastatin treatment may be cost-effective in the primary prevention setting. Rosuvastatin treatment was proved cost-effective among JUPITER-eligible patients, especially in those with a Framingham risk score ⩾ 10%[33].

Finally, after the results of JUPITER were disseminated, the Canadian Cardiovascular Society changed its guidelines to include the measurement of hs-CRP, along with LDL-C and HDL-C levels, among otherwise healthy men and women at "intermediate risk"[34]. Of interest, the absolute risk reduction associated with statin treatment in intermediate risk subjects may be in parallel with their 10-year risk for cardiovascular disease. All patients at high risk as defined by a Framingham score of > 20% or SCORE ⩾ 5%, except obese subjects, may experience significant benefits from statin treatment in the reduction of cardiovascular outcomes.

Clinical benefit from statin use may also be associated with post-treatment decreases in LDL-C levels and hs-CRP levels among normocholesterolemic subjects with increased hs-CRP levels. The JUPITER study proposed LDL-C levels 70 mg/dL and hs-CRP 1 mg/L as the cut-off points below which major clinical benefit could be achieved. If alternative lipid parameters are to be assessed instead of LDL-C, the suggested cut-off points are < 100 mg/dL for non-HDL-C, < 80 mg/dL for apoB and < 0.5 for the ratio apoB to apoA1. In contrast, HDL-C levels may not predictive of residual vascular risk in patients treated with a potent statin who attain very low concentrations of LDL-C.

Despite similar reductions in LDL-C and hs-CRP levels, elderly normocholesterolemic individuals with increased inflammation may benefit more by statin treatment compared with younger subjects. Also, there may not be a gender-specific effect of statin treatment on the incidence of cardiovascular outcomes in normocholesterolemic subjects with increased hs-CRP concentrations. Statin-associated reductions in clinical outcomes in primary prevention of normocholesterolemic subjects with hs-CRP > 2 mg/L may be evident either in the clinical setting of moderate CKD. Of interest, mortality rates are more amenable to a reduction after statin treatment in those subjects compared with individuals with preserved renal function.

Furthermore, it has been hypothesized that the carriers of the KIF6 allele are preferentially affected by statin treatment compared with non-carrier subjects. This hypothesis was tested in a recent *post hoc* analysis of the JUPITER study. No significant association of KIF6 polymorphism and the efficacy of rosuvastatin treatment in primary prevention resulted from this study[35].

Stroke incidence may also be reduced by statin treatment in normocholesterolemic subjects with increased inflammation. Both lipid-lowering effects of statins and antiinflammatory properties of these drugs could contribute to this benefit. Furthermore, except for a reduction in the incidence of atherothrombotic events, antithrombotic effects of statins may also be associated with a decrease in the risk of venous thromboembolism. Also, statin treatment could contribute to an improvement in renal function of normocholesterolemic subjects with increased hs-CRP levels.

A potential increase in the incidence of diabetes should be a safety concern with statin treatment, especially when most potent drugs of the class are prescribed. However, this issue is currently under investigation. To this context, aggregation of clinical trials supports the notion that statins modestly increase the risk of diabetes. Because diabetes has been considered as a risk equivalent for vascular disease, these findings create a paradox whereby statin therapy may be withheld to avoid excess risk of diabetes, while representing the strongest cardiovascular risk reduction tool in diabetics[26]. A close monitoring of glucose homeostasis parameters in patients treated with statins is strongly recommended.

A future promising indication for statins, as effective antiinflammatory agents, is suggested by recent studies reporting a role of inflammation, and particularly of CRP, in enhanced atherogenicity among subjects with autoimmune inflammatory disorders, such as rheumatoid arthritis, systemic lupus erythematosus, familial Mediterranean fever and Behcet's disease[36].

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