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REVIEW

Key questions resulting from the JUPITER trial assessing cardiovascular disease intervention with rosuvastatin

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Abstract

This paper presents an analysis of the recently published Justification for the Use of statins in Prevention (JUPITER: an intervention trial evaluating rosuvastatin) trial, which tested the statin rosuvastatin in apparently healthy individuals with no prior cardiovascular (CVD) disease and with normal plasma low density lipoprotein (LDL) cholesterol concentrations but with raised plasma high sensitivity C-reactive protein (hsCRP) levels. The rate of the combined primary CVD endpoint was significantly reduced in the treatment arm after a median of under 2 years. The JUPITER trial is distinct from previous studies examining statin use in primary prevention groups because the target group for drug therapy was apparently healthy men and women at low or intermediate risk for developing CVD. On the basis of JUPITER's findings, there are key questions that should be assessed on the therapeutic intervention of CVD regarding: the primary prevention groups that should be targeted for statin therapy, the utility of targets in addition to plasma LDL cholesterol levels, and the need to consider the metabolic state of individuals targeted for therapy (including the presence of obesity and inflammation). The conclusion from the current analysis is that the JUPITER results warrant further LDL cholesterol lowering than is currently targeted in primary prevention groups that have a pre-existing condition or lifestyle that elevates CVD risk but still do not have a high global CVD risk (as assessed with current algorithms). This group is not captured in current widely used CVD risk calculations, however, with the identification of useful biomarkers, such as hsCRP, this group can be better identified and targeted for intervention.

Key words: Statin; C-Reactive Protein; Low density lipoprotein cholesterol; Inflammation; Cardiovascular diseases

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INTRODUCTION

The recently published Justification for the Use of statins in Prevention (JUPITER: an intervention trial evaluating rosuvastatin) trial by Ridker *et al*[1] has been received with much fanfare. The JUPITER trial tested the statin rosuvastatin in 17 802 apparently healthy individuals with no prior cardiovascular (CVD) disease and with normal plasma low density lipoprotein (LDL) cholesterol concentrations but with raised plasma high sensitivity C-reactive protein (hsCRP) levels. The key

findings of the study were that: (1) rosuvastatin reduced LDL cholesterol levels by 50% in the target group; (2) rosuvastatin reduced hsCRP by 37% in the group; and (3) the rate of the combined primary CVD endpoint of myocardial infarction, stroke, arterial revascularization, hospitalization for unstable angina, or death from CVD causes was significantly reduced in the treatment arm after a median of under 2 years.

Currently, the established guidelines, including the most recent Adult Treatment Panel Guidelines (ATP Ⅲ) recommendations[2] and the Canadian Cardiovascular Society position statement on statin treatment[3,4], are based mainly on large randomly controlled clinical studies using statin intervention in the secondary prevention of CVD endpoints after a CVD event has already taken place (including myocardial infarction, ischemic heart disease, and heart failure). The JUPITER trial target group adds to the growing list of primary prevention groups, either proposed or directed (those with diabetes, with hypertension, with elevated LDL cholesterol levels, or at high global risk for CVD) for statin usage by the medical community.

While statins are known to be effective in the secondary prevention of CVD in patients with established CVD, whether the benefits apply to primary prevention have not been definitely shown due to ambiguous results of statin studies in relatively small numbers of primary prevention individuals. A recent meta-analyses by Brugts *et al*[5] was carried out on 10 randomised trials (including the JUPITER trial) that focused on whether statin use in primary prevention is justified to reduce all cause mortality and the incidence of major coronary and cerebrovascular events in people without established CVD but with cardiovascular risk factors. The data from 70 388 individuals showed Statin therapy was associated with significant risk reductions in all cause mortality, in major coronary events, and in major cerebrovascular events[5]. These results are in line with those previously published on the effects of statins in secondary prevention[6]. The efficacy of statins in subgroups of people aged more than 65, women, and those with diabetes mellitus has also been debated; the Brugts *et al*[5] meta-analyses also showed that statins improve survival and the risk of major CVD in these primary prevention groups as well.

The JUPITER trial is distinct, however, from previous studies examining statin use in primary prevention groups precisely because the target group for drug therapy is apparently healthy men and women at low or intermediate risk (using established factors for risk assessment) for developing CVD. The JUPITER trial results are important in the assessment of CVD risk and the assessment of individuals targeted for statin therapy for three reasons; it demonstrates: (1) the benefit of targeting a population at apparently low or moderate risk for developing CVD for statin use; (2) the potential of hsCRP as a CVD biomarker; and (3) the suitability of targeting individuals with inflammation but no other obvious CVD risks for statin use. On the basis of JUPITER's findings, there are four questions that I, and most likely others in the CVD medical and research community, would like to ask to ascertain the impact of the study.

SHOULD WE BE TARGETING A WIDER PRIMARY PREVENTION POPULATION FOR THERAPEUTIC CVD RISK LOWERING THERAPY

In general, statin therapy in primary prevention has been limited to groups at high risk for CVD, currently characterized as individuals with diabetes, hyperlipidemia, a family history of premature vascular disease, or those at high global risk of developing CVD. However, this group only comprises a small percentage of the population CVD burden (in Canada, it is approximately 10% when combined with the high-risk secondary prevention group)[3-7]. With the high health, social and economic burden of CVD (accounting for approximately 30% of deaths in Canada)[8], approaches to decrease the population CVD burden are urgently required. Targeting a broader proportion of the population could result in a substantial decrease in clinical disease incidence and the population burden of CVD. Both lifestyle modification and, when needed, pharmacological interventions should be included as therapeutic options for such individuals.

The current characterization of high-risk primary prevention groups does not capture all of the individuals without a prior CVD event who are at high risk of CVD. The number of individuals targeted for therapy in the primary prevention group is expected to increase as more reliable CVD biomarkers are identified (which may be plasma hsCRP or normal, Western plasma LDL cholesterol levels, which may be too high in certain primary prevention groups).

Furthermore, as the composition of the population in Canada and globally continues to change, including greater numbers of individuals at higher risk of CVD - particularly, overweight and obese individuals and individuals with metabolic syndrome - risk factors that capture these higher risk metabolic conditions (again these may include hsCRP or normal, Western plasma LDL cholesterol levels, which may be too high in certain primary prevention groups) should be incorporated in calculations of CVD risk and individual physician decisions on whether to treat or not to treat.

DO WE NEED OTHER TREATMENT TARGETS FOR THERAPEUTIC CHOLESTEROL-LOWERING INTERVENTION?

In the JUPITER trial, in the treatment arm, Crestor reduced CRP by 37% and lowered LDL cholesterol by

50% in individuals with normal (a mean of 100 mg/dL) cholesterol, with a subsequent highly significant reduction in myocardial infarction and stroke of approximately half and a 20% reduction in mortality. The question is whether the marked reduction in LDL cholesterol in any targeted group for statin therapy should be the sole focus of therapy. LDL cholesterol reduction with statin therapy alone reduces heart attacks by up to 40% in 5-year statin trials, regardless of the presence of other risk factors[9]. Moreover, analysis of the large-scale, randomized, placebo-controlled statin trials showed that the decrease in coronary events was best predicted by the absolute decrease in plasma LDL cholesterol concentrations[9]. Thus, it is concurred in the medical community that in individuals with either elevated plasma LDL cholesterol levels or at high CVD risk (which were the key cohorts studied in the large statin trials), LDL cholesterol reduction is likely a sufficient target of the therapy, regardless of other measurable biochemical risk factors.

A more debated question is whether individuals with normal plasma LDL cholesterol levels exhibiting adverse metabolic states (e.g. obesity or the metabolic syndrome) or lifestyles (e.g. smoking), in whom hsCRP levels are elevated, should be targeted for cholesterol reduction therapy. The current evidence indicates that this mode of therapy may be warranted. The lifetime CVD risk is quite high in "healthy" men and women by age 40, even with "normal" Western LDL-C levels[4]. This is in contrast to populations with much lower LDL-C levels (less than 70 mg/dL), due to diet and lifestyle, that have an absence of the earlier indications of chronic disease seen in the young and atherosclerosis in older people in Western populations[10,11]. Other evidence of the potentially beneficial effects of lower-than-normal LDL cholesterol concentrations comes from studies in individuals with a functional mutation in the gene for the serine protease *PCSK9*[12]. The resulting inactive protein results in decreased serum LDL cholesterol levels in affected individuals (28% in blacks and 15% in whites) with concomitant very large reductions in CVD risk (88% and 50% reductions in the coronary event rate, respectively)[12]. The resultant large reductions in CVD risk for the relatively modest decreases in LDL cholesterol, below normal, underscores the potentially large reductions in CVD risk achievable in healthy populations if therapy is initiated early enough, before LDL cholesterol levels reach normal, Western levels.

SHOULD ALL INDIVIDUALS WITH NORMAL LDL CHOLESTEROL LEVELS BE TARGETED FOR STATIN THERAPY?

The majority of individuals recruited into the JUPITER study and in whom CVD and mortality benefits were demonstrated were either obese, had the metabolic syndrome, or were smokers. Beyond these sets of patients, in whom hsCRP levels are elevated, there is not currently justification for statin use. While the cost-benefit analyses for individuals with normal, Western LDL cholesterol levels and who are neither obese, have the metabolic syndrome nor smoke has not been calculated, it would be expected that the numbers needed to treat to decrease the CVD rate and mortality and the economic cost of drug intervention in such large numbers of individuals would be too high. Furthermore, because of a lower baseline CVD risk, overall mortality benefits, it would be expected, would be more difficult to demonstrate. Finally, there is the issue of adverse effects, which might result in significant numbers of total affected individuals in the clinic, due to the large numbers in this primary prevention group.

By targeting individuals for treatment in the subset of individuals with normal, Western LDL cholesterol levels that are obese, have the metabolic syndrome, smoke or that have elevated hsCRP, we may be targeting individuals with functionally abnormal LDL particles. Elevated hsCRP is associated with increased insulin resistance and dysglycemic conditions[13]. These are conditions in which LDL particles increasingly become oxidized, glycosylated and become small and dense[14,15]. Oxidation of LDL plays a critical role in the early development of atherosclerosis[15], through the recruitment of monocyte-derived macrophages into the arterial wall and by stimulating the incorporation of cholesterol within macrophages, which results in foam cell formation and the resulting fatty streak in the arterial wall. CRP is known to form complexes with oxidized LDL[16] and thus may serve as a biomarker of oxidized LDL. In fact this may be identified by elevated hsCRP plasma levels. In this regard, the Jupiter trial may not have yielded beneficial outcome results of statin preventive intervention if smokers and obese individuals had been excluded. Despite this limitation, the Jupiter trial raises an important issue whether CRP plasma levels could be useful in the primary cardiovascular risk stratification. Rosuvastatin's beneficial CVD effects in the JUPITER trial may thus be explained both by LDL cholesterol lowering and its known pleiotropic effects, including its favourable effects on oxidized LDL and vascular remodelling[17].

SHOULD THE PRESENCE OF AN ELEVATED INFLAMMATORY STATE BE INCORPORATED IN GLOBAL CALCULATIONS OF CVD RISK, OR BE SUFFICIENT TO JUSTIFY ALTERATIONS IN LIFESTYLE OR THERAPEUTIC INTERVENTION?

CRP is a sensitive marker of inflammation and this may also be a reason that declines in CRP levels with rosuvastatin reduced CVD endpoints[1]. There is an increasing consensus that inflammation plays a key role

in advancing the atherosclerotic process in arterial walls. How does this occur? Pro-inflammatory stimulators upregulate vascular cell adhesion molecule expression by cells in the arterial wall[18,19]. This leads to the recruitment of T cells, leukocytes and macrophages to the arterial wall[18,19]. These cells, in turn, play a pathogenic role in atherosclerosis by producing pro-inflammatory cytokines and chemokines[18,19]. In animal studies, the development of atherosclerotic lesions were reduced in *ApoE* knock-out mice when specific cytokines (e.g. TNF-α)[20] and chemokines (*MCP-1* action *via* knockout of its receptor *CCR-2*)[21] were also knocked out. These studies indicated the importance of the above inflammatory cells and their secretory products in the initiation and development of atherosclerosis. The above recruited inflammatory cells also contribute to the formation of vulnerable plaques, which are prone to rupture[22]. This is because the cells contribute to the production of thrombogenic and matrix-degrading substances. Indeed, atherosclerotic plaques from unstable symptomatic patients exhibit significant infiltration by leukocytes[23]. This process results in subsequent clinical events, such as acute coronary syndromes (unstable angina, myocardial infarction and sudden death)[23].

The increased inflammation in the vasculature may be reflected in the systemic circulation by factors such as CRP. CRP levels increase in conditions with increased inflammation, including lupus, inflammatory bowel syndrome, smoking, insulin resistance and obesity[24-28]. While a direct role for CRP in mediating inflammation and atherosclerosis progression has not been conclusively established, CRP is a marker for inflammatory factors that may themselves be directly affecting CVD health since they have a known functional/enzymatic role. CRP correlates both with mediators of increased and decreased inflammation which decrease and increase, respectively, as CRP levels are reduced. Factors that are correlated with CRP and stimulate inflammation include secretory phospholipase A2, serum amyloid A (SAA) and oxidized LDL[29]. Those that are inversely correlated with CRP and decrease inflammation include HDL and its components apolipoprotein A-1 (apoA-1) and paraoxonase 1 (PON1)[29]. For example, *in vitro* and animal experiments have found that SAA can enhance inflammation by inducing the expression of proteinases thought to degrade the extracellular matrix[29]. It can also act as a chemoattractant for inflammatory cells such as monocytes, polymorphonuclear leukocytes, and T-lymphocytes[29]. Conversely, PON1 inhibits the oxidation of LDL[29,30], thereby inhibiting the effects of oxidized LDL in forming lipid-filled foam cells from macrophages, (which forms the fatty streak in atherosclerotic lesions) and activating macrophages to secrete cytokines and chemokines. The above factors that have a direct role in inflammation and affect CVD risk should be assessed for their relative utility in predicting CVD events. In the meantime, measurement of plasma hsCRP has been found to be a sensitive and reproducible marker of inflammation. This fact is highlighted in the Reynolds Score, which incorporates CRP in CVD risk calculations, and has been shown to be superior to some other CVD global risk calculations in predicting CVD events[30]. The findings of the utility of hsCRP in the JUPITER trial also suggests that incorporating plasma levels of inflammatory markers when other CVD risk factors are present (e.g. the presence of obesity) can strengthen a case for and further justify therapeutic intervention in an individual. Conversely, a convincing case has not been made for therapeutic intervention in individuals solely on elevated plasma hsCRP or other inflammatory markers. Rosuvastatin does decrease the levels of some of these factors, which have known inflammatory effects (e.g. SAA)[17], and increases others that have known benefits (HDL apoA-1)[31], while others have not been tested (e.g. PON1).

CONCLUSION

The JUPITER trial demonstrated the utility of targeting a larger primary prevention population group for therapeutic intervention than is currently targeted. Although apparently "healthy" individuals were part of the study cohorts, the majority of these individuals had at least one underlying condition or lifestyle habit, in addition to an elevated hsCRP, that is known to elevate CVD risk; e.g. the presence of obesity and smoking. While LDL cholesterol lowering alone, which was substantial in the study cohort that was administered rosuvastatin, is known to decrease CVD risk markedly, regardless of an individual's baseline plasma LDL cholesterol level, the costs for such an approach would likely be too high. Thus, pharmaceutical intervention is not warranted currently for such a broad group. The JUPITER results do indicate, however, that further LDL cholesterol lowering in primary prevention groups that have a pre-existing condition or lifestyle that elevates CVD risk but still do not have a high global CVD risk (as assessed with current algorithms) should be considered for therapeutic intervention. This group is not captured in current widely used CVD risk calculations, however, with the identification of useful biomarkers such as hsCRP, this group can be better identified and targeted for intervention.

Lifestyle changes, including cessation of smoking, exercise intervention, dietary changes and normalisation of body weight should be achieved first before considering preventive statin therapy according to CRP plasma levels.

The aim here is to decrease the high population burden of CVD and to begin therapy in individuals early enough such that their high lifetime burden of disease is lowered. As more of these biomarkers, in addition to hsCRP, are indentified and evaluated for their utility, more primary prevention groups can be rationally targeted. Just as with an elevated hsCRP, inflammation on its own is not a sufficient CVD risk factor for therapeutic intervention, but combined with other risk factors, it can

move an individual over the boundaries of who should and should not be targeted for therapy. Future directions of study on CRP include determining the direct effects of CRP in plaque progression, lesion advancement and unstable plaque formation *via* targeted CRP antisense combined with IVUS and other imaging modalities. This should help in determining the true role of CRP in atherosclerosis. Meanwhile, both lifestyle interventions and pharmaceutical treatments should be considered for individuals with elevated hsCRP that have sufficently elevated CVD risk due to the presence of other CVD risk factors, currently considered insufficient for therapeutic intervention.

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