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LETTER

Benefits of Rosuvastatin in Cardiovascular Protection Remain Unclear After HOPE-3

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To the Editor

The use of commercialized statins in the prevention of cardiovascular diseases (CVD) has commonly been accepted based on the informative results of the Cholesterol Treatment Trialists (CTT) reports [1] As an additional effort in the prevention of CVD, professional societies have issued practical recommendations for healthcare providers on the effective use of statins in lowering low-density-lipoprotein cholesterol (LDL-C) [2]. Among these statins, atorvastatin and rosuvastatin are regarded as the most effective as they can reduce more than 30% of LDL-C, even at low doses (i.e. atorvastatin 10 mg; rosuvastatin 5 mg) [2]. The results of the recent HOPE-3 study [3], in which 10 mg rosuvastatin was found to reduce the development of CVD by 24% in intermediate-risk persons, may reinforce the role of rosuvastatin in CVD prevention. However, there are some concerns regarding the use of rosuvastatin.

Based on the CTT report [1] and our recent literature review [4], 6 atorvastatin and 4 rosuvastatin studies, characterized by their rigorous double-blind, randomized, placebo-controlled study designs, have been published in the past two decades. A meta-analysis using a random effect model showed that atorvastatin significantly reduced the risk of CVD, with an odds ratio (OR) of 0.82 (95% CI: 0.75-0.90, p <0.001, **Figure 1**). In contrast, the results of a meta-analysis including the 4 rosuvastatin trials failed to detect a significant reduction in CVD risk, with an OR of 0.86 (0.69-1.07, p = 0.163). Surprisingly, the effect of rosuvastatin in CVD risk prevention remained controversial, even after inclusion of the encouraging HOPE-3 study [3] in the analysis, which then yielded an overall OR of 0.84 (0.70-1.01, p = 0.063, **Figure 1**).

While it is believed that CVD is significantly driven by LDL-C, and thereby the "class effect" of statins in lowering LDL-C has been viewed as essential in CVD prevention, the inconsistency in the atorvastatin and rosuvastatin results suggests that the "class effect" of statins in CVD protection

Abbreviations:

4D	Deutsche Diabetes Dialyse Studie
AURORA	A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events
CI	confidence interval
CORONA	Controlled Rosuvastatin Multinational Trial in Heart Failure
CTT	Cholesterol Treatment Trialists
CVD	cardiovascular diseases
GISSI-HF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico - Heart Failure
HOPE-3	Heart Outcomes Prevention Evaluation 3 trial
JUPITER	Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
LDL-C	low-density-lipoprotein cholesterol
OR	odds ratio
TNT	Treating to New Targets

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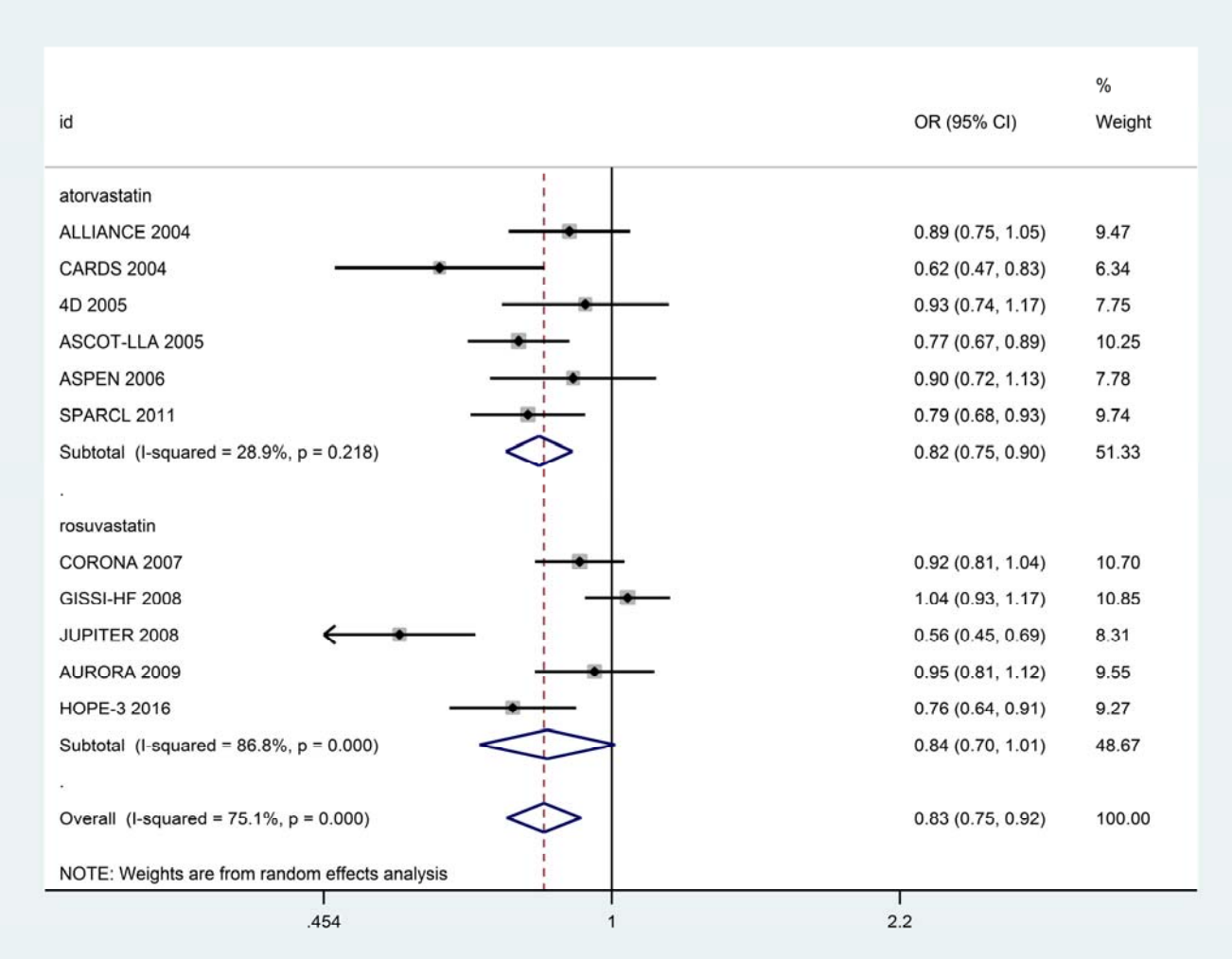

Figure 1. Forest plot of atorvastatin and rosuvastatin treatment results in CVD prevention studies. The meta-analysis of atorvastatin vs. placebo in CVD prevention studies showed that atorvastatin benefited CVD prevention with an odds ratio of 0.82 (95% CI: 0.75-0.90). In contrast, the meta-analysis of rosuvastatin vs. placebo found no significant benefit of rosuvastatin in CVD prevention, with an odds ratio of 0.84 (95% CI: 0.70-1.01).

should be carefully re-examined. It should be recalled here that well-known controversies about the role of the thiazolidinediones, pioglitazone, and rosiglitazone in CVD protection [5, 6] initiated the requirement for CV outcome trials to be conducted during the development of new anti-diabetic drugs [7]. Similarly, in contrast to the results for sitagliptin [8], the recent heart failure concerns associated with saxagliptin and alogliptin, as announced by the Food and Drug Administration (FDA) [9], suggest that there are clinical differences between dipeptidyl peptidase-4 inhibitors. These facts suggest that drugs in the same class do not always share the same clinical outcomes, and this may explain the contradicting results from the meta-analyses.

Nevertheless, the lack of a significant effect of rosuvastatin may have been biased by studies that included patients with heart failure (i.e. the CORONA [10] and GISSI-HF [11] studies) and end-stage renal disease (ESRD) (i.e. the AURORA study [12]), who were at a particularly high risk of CVD. In this regard, it is interesting that exclusion of the GISSI-HF study [11], which had an OR >1, from the meta-analysis resulted in a significant effect of rosuvastatin, with an OR of 0.79 (0.64-0.98, p = 0.028). It is striking that the ORs of atorvastatin and rosuvastatin in the separate studies

were very similar, and the effects were non-significant, but close to significance. The non-significant result of rosuvastatin in the meta-analysis may be due to a bias based on methodological deviations or variation in populations.

Unlike the ambiguous rosuvastatin results, the overall results of the atorvastatin meta-analysis showed that it consistently protected against CVD, even with the inclusion of an ESRD population (from the 4D study [13]). Moreover, in spite of the lack of double-blind, randomized controlled trials with atorvastatin in advanced heart failure patients, in the TNT study, high-dose atorvastatin reduced the need for hospitalization of heart failure patients without advanced heart failure in a subgroup analysis [14]. It should also be considered that the rosuvastatin results may be weakened by some potential flaws in the JUPITER study, including early study termination, discrepancy in CV outcomes, and the controversial use of high sensitivity C-reactive protein as a predictor of CV risk [15, 16]. In the scenario described above, rosuvastatin may not be beneficial in the prevention of CVD. In the spirit of evidence-based medicine, it would be necessary to clarify the "class effect" of statins in CVD prevention, in particular that of rosuvastatin.

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