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LETTER

Variable effects of statins on glucose homeostasis parameters and their diabetogenic role. Reply to Kostapanos MS, Agouridis AP and Elisaf MS [letter]

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Abbreviations

HMG-CoA	Hydroxy-methyl-glutaryl coenzyme A
METSIM	Metabolic Syndrome in Men

We thank Dr Kostapanos and collaborators for their comments on our article [1, 2]. The authors refer to their previous small study, which included 72 hyperlipidaemic participants with impaired fasting glucose and which showed that rosuvastatin dose-dependently decreased insulin sensitivity and increased insulin secretion [3]. The authors speculated that compensatory hyperinsulinaemia induced by rosuvastatin prevented the conversion to diabetes. However, insulin secretion was not adjusted for insulin sensitivity, and therefore their study is inconclusive with respect to the interpretation of hyperinsulinaemia.

We analysed insulin sensitivity among Metabolic Syndrome in Men (METSIM) participants on rosuvastatin treatment (n=181) compared with participants who were not on statin therapy (n=6,569) [2]. We found that rosuvastatin decreased insulin sensitivity, evaluated with the Matsuda Index of Insulin Sensitivity (Matsuda ISI), by 22.2%, which is of similar magnitude to simvastatin (21.9%) and atorvastatin (24.4%) [Table 3, reference 2]. Our results do not support the conclusion of Dr Kostapanos and collaborators that insulin resistance is particularly prominent in individuals on rosuvastatin treatment [3]. In addition, we evaluated insulin secretion by the Disposition Index (DI), which is a marker of insulin secretion adjusted for Matsuda ISI [2]. Rosuvastatin treatment decreased insulin secretion by 7.1%, which is very similar to decreases of insulin secretion by simvastatin (7.6%) and atorvastatin (7.4%) [2]. Therefore, our study indicates that rosuvastatin treatment, indeed, impairs insulin secretion, and the hyperinsulinaemia observed in the study by Kostapanos and collaborators [3] is very likely to be caused by the lack of adjustment for prevailing insulin sensitivity.

We also compared the changes in insulin sensitivity and insulin secretion according to different doses of rosuvastatin, simvastatin and atorvastatin. Rosuvastatin dose of 5 or 10 mg/day (only three participants had the lowest dose of 5 mg/day) decreased insulin sensitivity by 19.6%, a very similar decrease to that of low dose (10 or 20 mg/day) simvastatin (20.8%) and low dose (10 mg/day) atorvastatin (16.6%). A high dose rosuvastatin (20 or 40 mg/day) decreased insulin sensitivity by 28.6%, a high dose simvastatin (40 or 80 mg/day) by 25.4%, and a high dose atorvastatin (20 or 40 mg/day) by 30.2%. Insulin secretion decreased on low and high dose rosuvastatin treatments by 4.7% and 13.6%, respectively. The corresponding decreases for low and high dose simvastatin treatments were 6.6% and 9.8%, respectively, and for low and high dose atorvastatin treatments were 3.4% and 10.5%, respectively. These results show that rosuvastatin decreased both insulin sensitivity and insulin secretion in a dose–response manner similarly to simvastatin and atorvastatin. Thus, our

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study does not support the conclusion by Kostapanos and collaborators that statins reduce insulin sensitivity but improve insulin secretion [3].

Rosuvastatin is hydrophilic, in contrast to simvastatin and atorvastatin, which are lipophilic. Dr Kostapanos and collaborators have speculated that this property of statins is essential in the development of statin-induced diabetes [4]. A recent meta-analysis [5] and a cohort study including 239,628 individuals [6] showed that rosuvastatin increased the risk of diabetes by 17% and 42%, respectively, whereas simvastatin increased the risk of diabetes by 10% and 14%, respectively, and atorvastatin by 30% and 25%, respectively. Pravastatin increased the risk of diabetes in these two studies by only 3% and 2%, respectively [5, 6]. In addition, a recent study demonstrated that the risk of incident diabetes was increased with atorvastatin by 22%, rosuvastatin by 18% and simvastatin by 10%, compared with pravastatin treatment [7]. Thus, the risk of diabetes is considerably different between the two hydrophilic statins, pravastatin and rosuvastatin, and it is unlikely that properties of different statins (hydrophilic/lipophilic) could explain differences in the risk of diabetes among the users of statin therapy. However, hydroxy-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibition could at least in part explain the differences between the statins. A recent study including 223,463 individuals demonstrated that a single nucleotide polymorphism of the *HMGCR* gene, encoding HMG-CoA reductase, was associated with a 2% increased risk for type 2 diabetes [8].

Finally, we compared the effects of all hydrophilic (pravastatin, rosuvastatin, $n=209$) and all lipophilic statins (atorvastatin, simvastatin, lovastatin, fluvastatin, $n=1,916$) on insulin sensitivity and insulin secretion in the METSIM Study. Insulin sensitivity did not differ between participants on hydrophilic (5.54 ± 3.09, mean$\pm$SD) and lipophilic statins (5.68 ± 3.42, $p=0.989$). Similarly, insulin secretion was not different between METSIM participants who were on hydrophilic statins (152.56 ± 59.61) and lipophilic statins (154.32 ± 67.21, $p=0.911$). Therefore, our study does not support the view that hydrophilic and lipophilic statins differ in their effects on insulin sensitivity and insulin secretion [2].

In conclusion, our findings from the METSIM Study show that rosuvastatin does not essentially differ from other statins with respect to its effects on insulin sensitivity and insulin secretion.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement All authors were responsible for drafting the article and revising it critically for important intellectual content. All authors approved the version to be published.

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