High-dose statin therapy and the risk of haemorrhagic stroke in Asian patients with stable coronary artery disease: insights from the REAL-CAD study

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Background/Introduction: The REAL-CAD study identified that aggressive lipid lowering with high-dose statin reduced cardiovascular events also in Japanese patients with coronary artery disease (CAD). However, data from the SPARCL trial found that the benefits of high-dose atorvastatin treatment were partially offset by an increase in haemorrhagic stroke (HS). Although meta-analysis showed statin does not increase HS in Western countries, the evidence about the relation between statin and HS in Asian countries is still conflicting. In addition, the CREDO-Kyoto score is one of the prediction scorings for bleeding after coronary revascularization and might be a useful tool for the prediction of HS in this cohort. Recognizing the risk of HS and predicting of HS in the Asian cohort is clinically important.

Purpose: This study examined the factors associated with HS using the REAL-CAD cohort. Furthermore, we evaluated the performance of the CREDO-Kyoto bleeding risk score to predict HS in this cohort. We also performed the corresponding analysis of ischaemic stroke for reference purposes.

Methods: We sub-analysed the REAL-CAD study, prospective, multicentre, randomized, open-label, blinded endpoint study, in which 13,054 Japanese patients with stable CAD were randomized to high-dose (4 mg/day) or low-dose (1 mg/day) pitavastatin. Associations for stroke were determined using competing risk models: the Fine and Gray subdistribution hazards model accounting for the competing risk of death in models of haemorrhagic and ischaemic stroke in REAL-CAD trial. Patients were categorized to low (score 0), moderate (score 1–2), and high (score>3) according to CREDO-Kyoto bleeding score for predicting of HS.

Results: The HS events in high-dose group tended to be higher than low-dose group (4mg vs. 1mg: 43 (0.7%) vs. 30 (0.5%)). The associated factors of HS on univariate analysis were non-prior myocardial (hazard ratio (HR): 0.62, 95% CI: 0.39–0.99) and non-prior cerebral (HR: 0.25, 95% CI: 0.09–0.70) infarction, atrial fibrillation (HR: 2.4, 95% CI: 1.2–4.7), prior HS (HR: 4.2, 95% CI: 1.5–11.8), anaemia (HR: 2.4, 95% CI: 1.4–4.1), and non-statins use before run-in period (HR: 0.52, 95% CI: 0.28–0.99). High-dose pitavastatin was not a correlate with HS. The multivariate analysis revealed anaemia might have a relation with HS (HR: 4.3, 95% CI: 0.90–20.6). The number of HS was the highest in the high CREDO-Kyoto bleeding score group (Figure 1, HR: 2.4, 95% CI: 1.3–4.6), whereas there was no significant difference in the number of HS between the moderate- and low-risk groups (HR: 1.4, 95% CI: 0.84–2.3).

Conclusions: High-dose pitavastatin was not associated with the incidence of HS in this large Japanese cohort with stable CAD. High CREDO-Kyoto bleeding score was associated with HS as compared with low or moderate scores, even each of the variables consisting of CREDO-Kyoto score was not associated with HS.

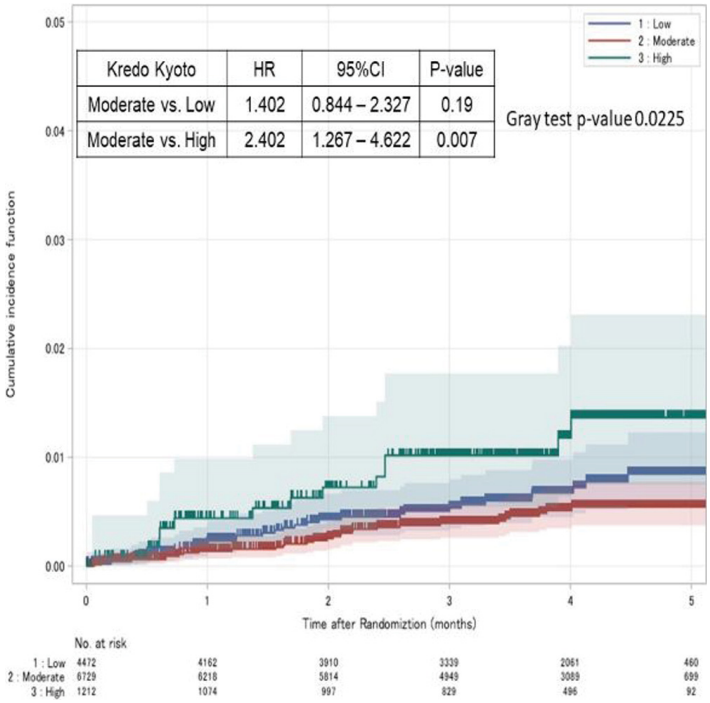

Figure 1