Environmental and genetic risk factors for myopathy in Chinese participants from HPS2-THRIVE

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Purpose: Myopathy is a rare but potentially serious dose-dependent side-effect of statin therapy. For a given dose of a statin, people of Asian origin have been found to have higher blood levels than Caucasians. However, there is limited information on environmental risk factors and genetic susceptibility in this ethnic group.

Methods: HPS2-THRIVE is an ongoing trial in participants with prior vascular disease recruited in China, Scandinavia and the UK. All participants received simvastatin 40 mg daily (with/without ezetimibe 10 mg daily) and 8 weeks on active ER niacin/laropiprant before being randomised to either ER niacin/laropiprant 2g or placebo for a median of 4 years. The effects of environmental factors on the risk of myopathy (definite or incipient) were assessed in 15,551 individuals of Chinese ethnicity entering the pre-randomisation phase (10,909 of whom were later randomised). The effects of common genetic variants on myopathy were examined in a genome-wide study (Illumina 610k panel) in 205 Chinese myopathy cases and 451 matched controls.

Results: The age and sex adjusted risk of myopathy was 7-fold greater in Chinese than Caucasian participants. Among the Chinese individuals, early safety analyses showed that the risk of myopathy post-randomisation was over 4-fold greater in niacin versus placebo-allocated individuals, and about two-thirds of myopathy events occurred within one year of starting the study treatments. Age and sex were strongly associated with myopathy; for example, women over 65 years were at a 5-fold greater risk than men under 65 years (p<0.001). Diabetes and 5kg/m² lower body mass index were each independently associated with a 1.6-fold greater myopathy risk (both p<0.002). In contrast, calcium channel blocker use at the start of the study (mainly nifedipine and amlodipine, in 12% and 6% of Chinese individuals respectively) was not a significant predictor of myopathy (p=0.2). The nonsynonymous rs4149056 variant in SLCO1B1 that has previously been associated with myopathy in Caucasians was associated with a 2.1 greater odds of myopathy (per C allele) in this Chinese population (p=7x10⁻⁶). The genome-wide study did not identify any novel genetic associations.

Conclusions: There are strong environmental and genetic risk factors for myopathy in Chinese individuals, but no novel genetic variants were found that account for their excess risk. Whole genome sequencing to identify variants not represented in genome-wide panels and further studies of environmental factors may identify important new predictors of myopathy in this population.