Safety and tolerability of ER niacin/laropiprant in a randomized trial involving 25,673 people.
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**Background** Extended release niacin (ERN) is an effective lipid-modifying agent but its tolerability is limited by flushing and other side-effects and data about its muscle and liver safety in combination with statins is limited.

**Methods** HPS2-THRIVE is a randomized trial of 2g ERN plus 40 mg laropiprant (ERN/LRPT) daily in 25,673 participants with vascular disease from UK, Scandinavia and China. Participants receive background 40mg simvastatin (S40) plus, if required, 10mg ezetimibe daily. Following an 8-week active ERN/LRPT run-in, they were randomized to receive ERN/LRPT or placebo. At each follow-up muscle and liver symptoms are sought, all serious adverse events recorded, and alanine transaminase (ALT) and, if muscle symptoms are reported or ALT >1.5xULN, of creatine kinase (CK) measured. During 3.4 years’ median follow-up, myopathy (i.e. muscle symptoms and CK >10xULN), rhabdomyolysis (i.e. myopathy with end-organ damage) and presumed drug-induced hepatitis (i.e hepatitis symptoms plus ALT >5xULN or ALT >3xULN with alkaline phosphatase/bilirubin >3xULN and no other probable cause) have been assessed. Interim analyses of the reasons for stopping study treatment, muscle and liver safety during follow-up were pre-specified.

**Results** During 3.4 years median follow-up, 3087 (24.0%) participants allocated ERN/LRPT versus (vs) 1975 (15.4%) allocated placebo had stopped study treatment. Flushing was given as the reason for stopping by only 111 (98 [0.8%] vs 13 [0.1%]) of the participants. Other skin-related reasons, mainly pruritus and rashes (typically maculopapular), were over 4x more common with allocation to ERN/LRPT (659 [5.1%] vs 151 [1.2%]) and gastrointestinal reasons were about twice as common (465 [3.6%] vs 200 [1.6%]). Allocation to ERN/LRPT vs placebo increased the risk of myopathy (69 [0.54%] vs 12 [0.09%]: risk ratio 5.8, 95% CI 3.1-10.7, p<0.001); 7 vs 3 of these were rhabdomyolysis. The excess risk was greater among the 10,932 participants in China (62 [1.13%] vs 10 [0.18%]) than among the 14,741 participants in Europe (7 [0.09%] vs 2 [0.03%]). Consecutive ALT measures >3xULN in 81 (0.63%) vs 31 (0.24%) participants; >10xULN in 42 (0.33%) vs 22 (0.17%); >3x plus bilirubin ≥2xULN in 15 (0.12%) vs 18 (0.14%); and presumed drug-induced hepatitis (all of whom recovered) in 4 (0.03%) vs 2 (0.02%). Of the 112 participants with consecutive ALT >3xULN, 89 (79%) were in China and about half were associated with myopathy.

**Conclusions** Among those tolerating 8 weeks’ treatment, about three-quarters continued taking active ERN/L after 3.5 years follow-up. There was an absolute excess of about 8% participants stopping study treatment among those assigned active treatment. ERN/LRPT increased the risk of myopathy with background S40. Compared with participants in Europe, those in China had a considerably higher rate and excess of myopathy with ERN/LRPT. ERN/L was also associated with an excess of raised ALT, but this was related in part to the excess of myopathy and was not associated with a clear excess of liver damage.