EBioMedicine 2 (2015) 1008–1009

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

The Japan Statin Treatment Against Recurrent Stroke (J-STARS) Trial: Where to Now?

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ARTICLE INFO

Article history:
Received 1 August 2015
Accepted 4 August 2015
Available online 6 August 2015

In this issue of *EBioMedicine*, Naohisa Hosomi and colleagues report the eagerly awaited results of the Japan Statin Treatment Against Recurrent Stroke (J-STARS) trial (Hosomi et al., in press). A total of 1578 Japanese men and women aged 45 to 80 years with previous non-cardioembolic ischaemic stroke and total cholesterol concentration between 4.65 and 6.21 mmol/l were randomly assigned to open-label pravastatin 10 mg per day or to control (no statin, but non-statin drugs were allowed) and followed for a mean of 4.9 years (Hosomi et al., in press). Allocation to pravastatin was associated with a reduction in mean total cholesterol concentration by 0.57 mmol/l and low-density lipoprotein (LDL) cholesterol by 0.55 mmol/l compared to control, but no difference in the primary endpoint of stroke or TIA (2.56% vs 2.65% per year, adjusted hazard ratio [HR] 0.97, 95% confidence interval [CI]: 0.73 to 1.29) (Hosomi et al., in press). Allocation to pravastatin was however associated with a lower incidence of ischaemic stroke due to atherothrombosis compared to control (0.21% vs 0.64% per year, adjusted HR 0.33, 0.15 to 0.74) without increasing intracranial haemorrhage (0.29% vs 0.31% per year, adjusted HR 1.00, 0.45 to 2.22) or mortality (1.11% vs 0.90% per year, adjusted HR 1.23, 0.79 to 1.93) (Hosomi et al., in press).

The J-STARS trial provides novel data about the safety and efficacy of statins in preventing recurrent stroke in Japanese (Hosomi et al., in press). Although statins have been shown conclusively to reduce the risk of stroke by one sixth (risk ratio [RR]: 0.85, 95% CI: 0.80–0.89) for every 1.0 mmol/l reduction in LDL cholesterol in 174,000 participants enrolled in 27 randomised trials (Cholesterol Treatment Trialists' (CTT) Collaboration, 2015), it has been uncertain whether these results can be generalised to individuals with a history of prior stroke. There have been only 5 randomised controlled trials of statins in patients with prior stroke or TIA (total n = 9224) and the estimate of efficacy in preventing recurrent stroke is marginal (10.8% statin vs 12.1% control; odds ratio [OR]: 0.88, 95% CI: 0.77 to 1.00) (Manktelow and Potter, 2009). In the two trials that recorded the pathological subtype of stroke outcome events, allocation to statins (simvastatin 40 mg daily (Heart Protection Study Collaborative Group, 2004) or atorvastatin 80 mg daily (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators, 2006)) was associated with a significant reduction in ischaemic stroke (7.9% statin vs 9.9% control; OR 0.78, 0.67 to 0.92) but also a significant increase in haemorrhagic stroke (1.9% statin vs 1.1%; OR 1.72, 1.20 to 2.46) (Manktelow and Potter, 2009). As the incidence of haemorrhagic stroke in Japan is twice that observed in Western countries (Suzuki and Izumi, 2015), where previous trials in stroke patients were undertaken (Heart Protection Study Collaborative Group, 2004; The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators, 2006), another uncertainty and concern have been whether statins are safe in Japanese with a history of prior stroke. The only previous randomised controlled trial of a statin in Japanese was the Management of Elevated cholesterol in the primary prevention Group of Adult Japanese (MEGA) trial in 7832 Japanese men and women with hypercholesterolaemia (total cholesterol 5.69–6.98 mmol/l) and no history of stroke (Nakamura et al., 2006). Pravastatin 10–20 mg daily reduced the risk of coronary heart disease (primary outcome) by one third (HR 0.67, 95% CI 0.49 to 0.9) compared to control but did not have a significant effect on any first-ever stroke (2.5% vs 3.0%, HR 0.83, 95% CI: 0.57 to 1.21). There was however, a trend toward a reduction in ischaemic stroke (1.7% vs 2.2%; HR 0.76, 95% CI: 0.49 to 1.18) and increase in intracranial haemorrhage (0.8% vs 0.7%; HR: 1.8, 0.58 to 2.42) with pravastatin compared to control, as observed in the two previous trials of statins in patients with prior stroke (Heart Protection Study Collaborative Group, 2004; The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators, 2006; Suzuki and Izumi, 2015).

The results of the J-STARS trial will reassure clinicians about the safety of pravastatin 10 mg per day in Japanese patients with prior ischaemic stroke. However, they raise questions about the efficacy of pravastatin 10 mg daily in preventing stroke or TIA (HR 0.97, 0.73 to

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2015.08.006
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http://dx.doi.org/10.1016/j.ebiom.2015.08.007

1.29) and any stroke (2.35% vs 2.47% per year, adjusted HR 0.95, 0.71 to 1.28). The failure to prove the efficacy of pravastatin may have several explanations. First, the study was underpowered to reliably identify or exclude a modest but clinically significant effect of pravastatin because it only recruited about half (n = 1578) of the initial target sample size of 3000 and the outcome event rate was lower than expected. Hence, the estimates are prone to substantial random error as indicated by their wide 95% confidence intervals. Second, the dose of pravastatin (10 mg per day) and degree of reduction in LDL cholesterol compared to control (0.55 mmol/l) may have been too small to generate a detectable treatment effect, given that higher doses of pravastatin (40 mg per day) and greater reductions in LDL cholesterol (≥1.0 mmol/l) have been associated with efficacy (White et al., 2000; Cholesterol Treatment Trialists' (CTT) Collaboration, 2010). Third, pravastatin may only be effective in preventing one aetiological subtype of ischaemic stroke — atherothrombotic, as suggested by a subgroup analysis of the J-STARS results (Hosomi et al., in press). However, although this subgroup analysis was pre-specified, the results are only hypothesis-generating. It now behoves researchers to explore the hypothesis that more intense reductions in LDL-cholesterol by higher doses of statins (and other lipid-lowering interventions, such as anti-PCSK9 antibodies (Zhang et al., 2015)) may be safe and effective in preventing recurrent ischaemic stroke due to atherothrombosis, and recurrent stroke of any type, in Japanese patients with recent non-cardioembolic ischaemic stroke and a wide range of LDL cholesterol concentrations.

Disclosures

None.

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