

## A Game of Unknowns

A. Ross Naylor

Tsivgoulis et al<sup>1</sup> previously reported that acute ischemic stroke (AIS) patients with large artery atherosclerosis (LAA) who took statins before stroke onset had fewer recurrent strokes and better functional outcomes than statin-naïve patients. In this issue of *ATVB*, the same group reports that AIS patients with LAA taking statins before stroke onset had a significant, dose-dependent reduction in spontaneous cerebral embolization compared with statin-naïve individuals.<sup>2</sup> The authors attributed better outcomes and reduced embolization to statin's pleiotropic, anti-inflammatory effects in promoting rapid healing of disrupted atherosclerotic plaques, concluding that randomized controlled trials (RCT) were required to prove that early statin therapy was beneficial in all AIS patients with LAA.

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These findings are identical (in principle) to another multi-centre study, where patients with AIS were stratified according to whether they took aspirin before stroke onset.<sup>3</sup> Pre-existing aspirin users had reduced stroke severity at presentation and better functional outcomes at discharge, despite aspirin failing to prevent their stroke in the first-place (as had pre-treatment with statins in Tsivgoulis's study). Aspirin's beneficial effect was, however, limited to patients with LAA.<sup>3</sup> In Tsivgoulis's study, 67% of statin pre-treated patients with LAA were taking antiplatelet agents before stroke onset (versus 30% of statin-naïve patients;  $P < 0.001$ ), whereas half of statin pre-treated patients experienced a herald transient ischemic attack (TIA; versus 22% of statin-naïve patients;  $P = 0.004$ ),<sup>1</sup> suggesting that statin pre-treated patients were likely to be receiving better medical therapy at stroke onset than statin-naïve patients.

So what is the status of statin prescribing after AIS or acute TIA? A 2011 Cochrane Review (8 RCTs, 625 patients) concluded that there was insufficient evidence to recommend early statin therapy. The problem was an absence of statistically meaningful analyses (other than early mortality) because other outcome data were infrequently reported in the constituent RCTs.<sup>4</sup> An updated 2015 meta-analysis of 70 studies (8 RCTs) concluded that pre-stroke statin therapy was associated with milder initial stroke severity, better functional outcome, and lower 90-day mortality.<sup>5</sup> In-hospital statin treatment was associated with good functional outcomes and lower mortality,

whereas in AIS patients undergoing thrombolysis, statins were associated with better functional outcomes, despite an increased risk of hemorrhagic transformation. Statin withdrawal was, however, associated with poorer functional outcomes. Given there were still only 8 RCTs, it is not surprising that the meta-analysis concluded that there was no evidence that early statin therapy conferred significant benefit.<sup>5</sup>

It would, however, appear that contemporary guidelines and clinical practice are changing (especially in AIS or TIA patients with extra cranial internal carotid artery stenoses), irrespective of calls for further RCTs. Guidelines consistently advise that patients already taking statins should not have these withdrawn.<sup>6-8</sup> The 2013 American Heart Association guidelines provide no specific recommendation about starting statins early, other than advising that there was no proven role as a neuroprotective agent.<sup>8</sup> In the United Kingdom in 2016, the National Institute for Health and Care Excellence advised that statins should be withheld for 48 hours in statin-naïve patients with AIS (based on expert consensus rather than specific RCT data)<sup>6</sup> while the 2016 Intercollegiate Stroke Working Party advised that statins should be started once patients with AIS could swallow.<sup>7</sup>

Of practical relevance to vascular surgeons (at least), the National Institute for Health and Care Excellence and the Intercollegiate Stroke Working Party advise that symptomatic patients under consideration for carotid endarterectomy should be started on statins as soon as possible.<sup>6,7</sup> This would include any acute TIA or nondisabling AIS patient with 50% to 99% internal carotid artery stenoses. In addition to potentially reducing recurrent stroke between index symptom and carotid endarterectomy, statin pre-treatment may also be associated with reduced perioperative stroke rates.<sup>9</sup> In my home area, the doctor referring a patient with suspected TIA (or nondisabling AIS) will start the patient on aspirin and a statin before urgent review at a daily cerebrovascular clinic. Interestingly, it required the addition of dual antiplatelet therapy in the TIA clinic (once hemorrhage was excluded on computed tomographic scan or MRI) to significantly reduce recurrent events (and spontaneous embolization) in the short time period before urgent carotid endarterectomy.<sup>10</sup>

In their discussion, Safouris et al<sup>2</sup> mentions that another RCT (ASSORT [Administration of Statin on Acute Ischemic Stroke Patient Trial], NCT02549846) failed to provide evidence that early statin therapy in AIS patients with LAA conferred significant benefit although there might have been a beneficial trend. However, neither the ClinicalTrials.gov website nor media reports of the trial findings (presented to the 2017 International Stroke Conference) specifically mention analyses in patients with LAA.<sup>11</sup> Accordingly, given changes in practice, it seems unlikely that future RCTs can include patients with nondisabling AIS or acute TIA in the presence of an ipsilateral 50% to 99% internal carotid artery

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stenosis. Most will benefit from urgent carotid endarterectomy, within days of symptom onset. It, therefore, remains for RCTs to determine whether early statin therapy confers significant benefit in patients with disabling AIS (of any vascular territory) or AIS secondary to cardioembolic or lacunar infarction.

### Disclosures

None.

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