ASA Module: Lipid control after stroke

This module reviews the topic of lipid control after stroke.

What is the association between LDL concentration and stroke risk?

A consistent association between lowering LDL concentrations and stroke risk has been seen in both primary and secondary stroke prevention (Amarenco et al. 2009; note figure 4).

What are the non-pharmacological approaches to lipid lowering?

The American Heart Association/American College of Cardiology have described physical activity and dietary recommendations for lipid lowering (AHA/ACC 2014).

The physical activity recommendations are aerobic physical activity lasting on average 40 minutes per session, 3-4 times per week, and involving moderate- to vigorous-intensity activity.

The dietary recommendations include reducing percentage calories from saturated fat to 5-6%, reducing percentage calories from trans fat and consuming a diet that emphasizes vegetables, fruits, whole grains, poultry, fish and nuts rather than sugar and red meat.

The Australian physical activity and sedentary behavior guidelines are hosted on the Australian Department of Health website (www.health.gov.au; updated 2017, full web link in references). For Australians over 65 years of age the Department of Veteran's Affairs and the Department of Health and Ageing have jointly produced a document entitled "Choose Health: Be Active" (www.health.gov.au; update 2005, full web link in references). This focusses on advice for how to achieve at least 30 minutes of exercise per day, but also includes some dietary advice.

The Australian dietary guidelines focus on promoting health and wellbeing and preventing diet-related and chronic disease rather than specifically modifying lipid levels or other risk factors (e.g. blood pressure). (www.eatforhealth.gov.au; updated 2015, full web link in references).

What is the evidence for stroke prevention with statins?

1. **Atorvastatin**

The best evidence we have for prevention of cardiovascular and cerebrovascular events after stroke is from the SPARCL study (Amarenco et al. 2006). Atorvastatin 80 mg given to people who had had a stroke between 1 and 6 months previously and who had an LDL 2.6-4.9 mmol/L had a HR of 0.74 (95% CI 0.66-0.83, p<0.001) of having a cardiovascular or cerebrovascular event after a median follow-up of 4.9 years compared with placebo-treated patients. Cardioembolic stroke was excluded.

The HR for the specific outcome of fatal or nonfatal stroke was 0.84 (95% CI 0.71-0.99, p=0.03).

2. **Other statins**

Rosuvastatin has been assessed in the EUREKA study (Heo et al. 2016). Patients with ischaemic stroke within the previous 48 hours with LDL <4.9 mmol/L (cardioembolic stroke excluded) were randomized to rosuvastatin 20 mg per day or placebo. At 14 days, MRI DWI imaging was used to detect new lesions, and no reduction was seen in the 318 patients randomized. Note that the target enrolment was 520 but this was slow.

What other lipid-lowering medications benefit patients after stroke?

Although several other medications can alter lipid levels, none have been shown to reduce stroke rates in stroke patients in a clinically significant or cost effective way.

There was no strong evidence for stroke prevention after stroke using fibrates in the Cochrane review by Wang (Wang et al. 2015).

There is no strong evidence for stroke prevention after stroke using ezetimibe. Ezetimibe monotherapy lowers LDL (Pandor 2009) but hasn't been shown to affect stroke rates. Adding ezetimibe to statins provided a small improvement in nonfatal stroke (6 fewer nonfatal stroke per 1000 treated, 95% CI 11 fewer to 0 more per 1000; Fei et al. 2017). In a the IMPROVE-IT trial, patients enrolled due to a recent acute coronary syndrome did demonstrate reduced ischaemic stroke rates with the addition of ezetimibe to simvastatin (Cannon et al. 2015), especially in the subgroup with a prior history of stroke (Bohula et al. 2017), but these were not acute stroke patients.

Evolocumab, a PCSK9 inhibitor, was tested in the FOURIER study (Sabatine et al 2017) in patients 40-85 years of age with a history of prior nonhaemorrhagic stroke, MI, PAD and high risk characteristics at a dose of 140 mg s/cut every 2 weeks or 420 mg s/cut every month. There was a 21% reduction in the risk of stroke (HR 0.79, 95% CI 0.66-0.95) but the NNT was 250 for 2 years to prevent one stroke, or 67 for 2 years to prevent one of the primary composite endpoints (cardiovascular death, MI, stroke, hospitalization for unstable angina or coronary revascularization). The cost effectiveness of this approach is therefore quite unclear, and Evolocumab is not currently listed on the PBS except for Familial homozygous hypercholesterolemia (as at Jan 3 2019).

Do lipid-lowering therapies or does achieving low LDL levels increase the intracerebral haemorrhage risk?

This question first came to prominence after the SPARCL study showed an increase in ICH rates in patients randomized to 80 mg atorvastatin daily vs. placebo (HR 1.66, 95% CI 1.08-2.55; SPARCL investigators 2006). The point estimate was even higher (HR 4.06, 95% CI 0.84-19.57) in the subgroup of 93 patients with a haemorrhagic stroke randomized into this study (Goldstein 2018). The question has been further investigated in a number of ways.

The Cholesterol Treatment Trialists' Collaboration subsequently meta-analysed data from 170 000 patients from 26 trials to further assess this, finding a haemorrhagic stroke rate of 0.34% vs. 0.29% (p=0.2) equating to a number needed to harm of 2052 to cause one haemorrhagic stroke in a broad range of patients (most of whom had not had a prior stroke; Cholesterol Treatment Trialists' collaboration 2010)

The J-STARS study investigated pravastatin 10 mg daily within 1 month of noncardioembolic stroke with total cholesterol 4.6-6.2 mmol/l at baseline (Hosomi 2015). Patients with low baseline LDL (< 2.59 mmol/L) had no increase in intracranial haemorrhage (p=0.30 for trend). Patients who demonstrated larger reductions in LDL (reductions of over 0.65 mmol/L) also had no increase in intracranial haemorrhage (p=0.92 for trend; Hosomi 2018).

Therefore there is one study (SPARCL) suggesting a higher ICH rate with statins without corroboration from other trials. The SPARCL study overall showed lower stroke rates, so a patient with ischaemic stroke derives net benefit from treatment (HR 0.84 for fatal or nonfatal stroke of both types, 95% CI 0.71-0.99, p=0.03; Amarenco 2006). However, if translated to real-world scenarios the SPARCL results would suggest that in most scenarios statins should be with-held after ICH, especially if lobar (Westover 2011). Conversely, the Cholesterol Treatment Trialists' Collaboration meta-analysis and the J-STARS study would suggest that the risk of causing haemorrhagic stroke is low enough to warrant re-starting statins even after a patient has had a haemorrhagic stroke.

What are the muscle-related risks associated with statin use?

The (Australian) National Prescribing Service quotes a statin-related myopathy rate of 1 in 10 000 patient years, and a rhabdomyolysis rate of 1 in 100 000 patient years (https://www.nps.org.au/statin-associated-muscle-symptoms-sams; updated 2017). This is based on a paper by Stroes (Stroes et al. 2015) but the website provides other practical guidance on managing suspected statin intolerance. Interestingly there were numerically similar or fewer episodes of myalgia, myopathy and rhabdomyolysis in the atorvastatin arm of the SPARCL study than the placebo arm (Amarenco 2006) though no differences were statistically significant. Also, Gupta et al. noted a nocebo effect (patients reporting adverse effects based on the expectation of harm from a treatment) in the ASCOT-LLA study (Gupta et al. 2017) which may increase the reported frequency of statin-related muscle symptoms.

Statins can also rarely cause an autoimmune myopathy associated with autoantibodies against HMG-CoA reductase, which often requires immunosuppression (Mammon 2016).

Are there adverse cognitive effects from lipid lowering?

Lipids are an important component of brain tissue and lowering lipid levels may affect brain function though the only supporting evidence is from low level studies (FDA drug safety communication, Feb 28 2012). However low lipid levels were not associated with poor cognition in the EBBINHAUS substudy of the FOURIER trial even when the LDL was reduced to a mean of 0.76mmol/L (vs. 2.32 mmol/L in the control arm) with evolocumab. Neither was this seen in a similar trial of alirocumab (Robinson 2017).

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Australian Guideline for Physical activity overview:

http://www.health.gov.au/internet/main/publishing.nsf/content/health-pubhlth-strateg-phys-act-guidelines, accessed Nov 17 2018

Australian Guideline for Physical activity for adults over 65 years of age:

http://www.health.gov.au/internet/main/publishing.nsf/content/3244D38BBBEBD284CA257BF0001FA1A7/$File/choosehealth-brochure.pdf, accessed Nov 17 2018

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