Questions 17 & 20 evidence tables

# Q17: What lipid-lowering treatments should be used in people who cannot tolerate statins, or in whom statins do not sufficiently lower cholesterol, after stroke or TIA?

# Q20: How low should LDL-C be lowered in secondary vascular prevention after stroke and TIA?

*NB Any discrepancies between reviewers in evidence quality and comment were discussed by the topic group at the evidence review meeting to discuss the question.*

LDL-c = low density lipoprotein-c, MI = myocardial infarction, NNT = number needed to treat, NNH = number needed to harm, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

| Ref ID | Source | Setting, design and subjects | Intervention | Outcomes | Results | Evidence quality (SIGN checklist score) and comment |
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| 485 | P. Amarenco et al. (2020) A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. *New England Journal of Medicine*. 382:9-19 DOI: 10.1056/NEJMoa1910355 | Parallel group RCT in France and South Korea. 2860 patients over 18 with TIA (within 15 days) or ischaemic stroke (imaging-confirmed) together with atherosclerotic disease of the intracranial or extracranial arteries, aortic atheroma or known coronary artery disease.<br>Secondary care-based.<br>Trial terminated early because of lack of finance. | Statin therapy with additional ezetimibe to achieve either LDL-c below 1.8 mmol/L or 2.3-2.8 mmol/L, over a median of 3.5 years.<br>Other risk factors managed according to national guidance.<br>At three years, 99% of the lower-target patients were on moderate or high-intensity statin, and 40% were on Ezetimibe.<br>Discontinuation rates (over 2.7 years) of about 30%. | Composite primary endpoint (ischaemic stroke, myocardial infarction, urgent coronary or carotid vascularisation, cardiovascular death)<br>Secondary outcomes included intracranial haemorrhage and new diabetes. | A statistically significant 2.4% absolute (22% relative) risk reduction in the composite primary endpoint.<br>Mean LDL-c of 1.7 mmol/L in the lower-target group, and 2.5 mmol/L in the higher-target group.<br>Fewer ischemic strokes in the lower-target group (5.7% v. 7.0) – not statistically tested.<br>More intracranial haemorrhages in the lower-target group (18 v. 13, HR 1.38 (0.68-2.82)).<br>More newly diagnosed diabetes in the lower-target group (103 v. 82; HR 1.27 (0.95-1.70)). | **++**<br><br>High quality RCT, despite the early termination before the required number of outcome events.<br>Slow enrollment might suggest some selection bias, but the recruited population appear fairly typical otherwise.<br>Good separation of the groups by achieved LDL-c, maintained for several years on average.<br>Rather young (mean age 66-67 years), recruited within a median of 6 days of qualifying event.<br>Approximately one-third of participants were women.<br>Unusually high proportion of smokers (about 30%).<br>Increased adverse events (ICH or new DM) in lower-target group did not nullify the benefits of more intensive reduction in LDL-c. |

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| 485 | P. Amarenco et al. (2020) A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. New England Journal of Medicine. 382:9-19 DOI: 10.1056/NEJMoa1910355 | Large parallel-group trial conducted in France and South Korea.<br>2,860 patients > 18 with non-disabling, radiographically-proven ischaemic stroke or TIA randomised to low and high LDL treatment arms. | 1,430 assigned to each treatment arm.<br>LDL of 70mg/dl (lower group) versus 110mg/dl (higher group).<br>Investigators asked to treat the LDL cholesterol to achieve the assigned target using any type and dose of statin.<br>Both arms expected to also receive treatment of BP 130/80 in diabetics and 140/90 in others; HBA1C < 7 in diabetics and smoking cessation. | Composite primary end-point events defined as non-fatal cerebral infarction; non-fatal MI; hospitalisation for unstable angina; TIA with carotid intervention or cardiovascular/unexplained sudden death.<br><br>Secondary end points of MI or coronary revascularisation after the onset of new symptoms; cerebral infarction or urgent revascularization of a carotid or cerebral artery after TIA; cerebral infarction or TIA; any revascularization of a coronary, cerebral, or peripheral artery (either urgent or elective); cardiovascular death; death from any cause; cerebral infarction or intracranial hemorrhage; intracranial hemorrhage; newly diagnosed diabetes; and a composite of the primary end point or intracranial hemorrhage. | 121 (8.5%) composite primary end-point events in low-target treatment arm vs. 156 (10.9%) in high-target treatment arm.<br>18 (1.3%) ICHs in lower-target group vs 13 (0.9%) in higher group. New diagnosis of diabetes in 103 (7.2%) in lower target group and 82 (5.7%) in higher group.<br>Significant ($p < 0.05$) reduction in major cardiovascular events with a non-significant different in ICH/diabetes.<br>Trial stopped due to lack of sponsor funding. | High quality RCT.<br>Younger age groups compared to stroke population as a whole (Age 66 +/- 11 yrs IQR). Older patients may demonstrate significant risk:benefit differences.<br>Higher proportion male: 971 (67.9%) and 963 (67.3%) compared to stroke population. |

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| 673 | Lee et al (2022). Association Between Intensity of Low-Density Lipoprotein Cholesterol Reduction With Statin-Based Therapies and Secondary Stroke Prevention<br>A Meta-analysis of Randomized Clinical Trials.<br>*JAMA Neurology.*<br>79 (4).<br>349-358. | Metanalysis of RCTs of more intensive v less intensive LDL-c lowering strategies for patients with ischaemic stroke. 11 RCTs of 20,163 patients, mean FUP 4 years. | More intensive LDL-c lowering – either higher doses of a statin or addition of ezetimibe, or a PCSK-9 inhibitor. | Recurrent stroke, and major CV events and haemorrhagic stroke. | More intensive treatment reduced risk of recurrent stroke by RRR 12% (ARR 1.2%; NNT: 83 over 4 years), independent of the method of LDL-c reduction. Reduced MACE (ARR 2.8%; NNT: 36), and increased ICH (RR 1.46; AR 1.2% v. 0.9%; NNH: 242) and new-onset diabetes (RR 1.26; AR 8.5% v. 6.8%; NNH: 57). No mortality benefit. Risk reduction not seen in trials of patients with no evidence of atherosclerosis. | **++**<br><br>High quality metanalysis, with some heterogeneity between trials (some rather small and without full characterization of the population; limited information on non-Western populations).<br>Broadly supportive of an intensive approach, especially using cheap drugs like statins and ezetimibe, with reasonable NNTs and acceptable NNHs. Principle benefits confined to patients with clinically detectable atherosclerosis, although some uncertainty about precisely how that might be defined. |
| 673 | Lee et al (2022). Association Between Intensity of Low-Density Lipoprotein Cholesterol Reduction With Statin-Based Therapies and Secondary Stroke Prevention<br>A Meta-analysis of Randomized Clinical Trials.<br>*JAMA Neurology.*<br>79 (4).<br>349-358. | Metaanalysis of RCTs (11 trials; 20,163 patients) with stroke. | Statin therapy (vs no statins; statin with ezetimibe vs higher dose statin with ezetimibe; PCSK9 inhibitor with statin vs placebo with statin). | LDL-C measures in lower vs higher intensity groups. | LDL-C, weighted for trial size, was 79mg/dL in groups receiving more intensive therapy vs 119mg/dL in the less intensive group. | LDL-C reduction in patients with ischaemic was not a primary evaluation of some of the trials – 'history of stroke' was used as the subgroup in those studies – presumably includes those with ICH.<br>Risk of recurrent stroke not reduced by LDL-C in RCTs of Asian populations; not known whether the benefit with more intensive LDL-C reduction should be generalised to Asian populations. |