JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
EDITORIAL

Low-density lipoprotein cholesterol and stroke: How low should we go?

Diabetes is a well-established risk factor for both ischemic and hemorrhagic stroke. Individuals with diabetes not only have a higher risk of stroke, they also have worse clinical outcomes after stroke, including poorer neurological recovery, higher rates of stroke recurrence and mortality. In addition to optimizing glycemia, control of cardiovascular risk factors, such as hypertension and dyslipidemia, is crucial in stroke prevention in individuals with diabetes. For the management of dyslipidemia, current guidelines from the USA recommend to intensify maximally tolerated statin therapy with ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in high-risk individuals using a low-density lipoprotein cholesterol (LDL-C) threshold >1.8 mmol/L[1]. The latest European guidelines recommend a LDL-C target <1.8 mmol/L in individuals with high cardiovascular risk, and <1.4 mmol/L in those with very high risk[2]. Individuals with diabetes and ischemic stroke fall within this high- to very high-risk category.

Aggressive low-density lipoprotein cholesterol (LDL-C) lowering has been shown to reduce atherosclerotic cardiovascular disease. The recommendation for intensive lipid-lowering therapy with statins to prevent recurrent stroke after transient ischemic attack and ischemic stroke is based on the results of the Stroke Prevention by Aggressive Reduction in Cholesterol Level trial[3]. Patients with previous stroke or transient ischemic attack and a LDL-C level between 2.6 and 4.9 mmol/L were randomized to 80 mg atorvastatin or placebo. At 5 years, statin-treated patients had a significant 2.2% absolute risk reduction in subsequent stroke and 3.5% reduction in major cardiovascular events compared with the placebo group, and there was a non-significantly higher number of hemorrhagic strokes (Table 1). A post-hoc subgroup analysis suggested that individuals who achieved lower levels of LDL-C derived a greater benefit. Patients who reached a level of LDL-C <1.8 mmol/L had a 28% lower relative risk of stroke than those with a LDL-C level >2.6 mmol/L. It has been estimated that the risk of stroke was 20% lower for every 1.0 mmol/L reduction in LDL-C level. A subsequent secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Level trial showed that the benefit of statin treatment in reducing events was similar in individuals with or without type 2 diabetes.

Despite the efficacy of LDL-C lowering on reducing the risk of recurrent stroke, there has been concern that aggressively lowering LDL-C might contribute to an increased risk of hemorrhagic stroke. The relationship between very low cholesterol levels and cerebral hemorrhage has remained controversial. Several epidemiological studies have reported an association between low serum cholesterol level and increased risk of hemorrhagic stroke. In Asia, hemorrhagic stroke is more common than in Western countries. In a recent observational study of Chinese adults aged 35–60 years followed up for 20 years, 22% of total strokes were hemorrhagic[4]. The incidence of hemorrhagic stroke was higher for individuals with LDL-C <1.8 mmol/L than those with LDL-C between 1.8 and 2.6 mmol/L (hazard ratio 1.56; 95% confidence interval 1.04–2.33). The impact of blood pressure was also clearly shown in the study and the risk of hemorrhagic stroke was substantially increased if hypertension was inadequately treated. In individuals with uncontrolled hypertension and LDL-C <1.8 mmol/L, there was a sixfold increase in the risk of hemorrhagic stroke, and almost fourfold increase in those with LDL-C ≥1.8 mmol/L. On the contrary, level of LDL-C <1.8 versus ≥1.8 mmol/L was not associated with a higher risk of hemorrhagic stroke among individuals with normotension or controlled hypertension. Another large prospective study from China also reported a significant association between lower LDL-C and higher risk of intracerebral hemorrhage when the LDL-C level was <1.8 mmol/L after adjusting for confounding factors, including hypertension, and the relationship was no longer significant when the LDL-C level was ≥1.8 mmol/L[5]. As associations reported in observational studies do not necessarily imply causations, the risk of hemorrhagic stroke has been examined in statin trials. A small increase in the incidence of hemorrhagic stroke has been observed in the Stroke Prevention by Aggressive Reduction in Cholesterol Level trial[3]. Several meta-analyses of statin trials have been carried out, and results have not been consistent, with some reporting an association between statin treatment and risk of hemorrhagic stroke or intracranial hemorrhage, whereas others did not. However, all meta-analyses have shown a net benefit of lowering LDL-C with statins in reducing atherosclerotic cardiovascular disease (including ischemic stroke), which far outweighs the small risk of hemorrhagic strokes.

With the advent of PCSK9 inhibitors, LDL-C levels can now be lowered to unprecedented levels. The two large cardiovascular outcome trials comparing PCSK9 monoclonal antibodies with placebo (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk [FOURIER] and Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome During Treatment With Alirocumab

Table 1 | Summary of stroke-related outcomes in low-density lipoprotein cholesterol-lowering trials

Trial	Agent(s)	Participants' baseline characteristics	Achieved LDL-C	Follow-up period, median (years)	Stroke-related outcomes
SPARCL[3] *N* = 4,731	Atorvastatin 80 mg/day vs placebo	Recent stroke or TIA LDL-C 2.6–4.9 mmol/L No known coronary heart disease	1.9 mmol/L	4.9	Primary outcome (fatal or non-fatal stroke); HR 0.84 (95% CI 0.71–0.99, $P = 0.03$) Secondary outcome (stroke or TIA): HR 0.77 (95% CI 0.67–0.88, $P < 0.001$)
FOURIER[6] *n* = 27,564	Evolocumab 140 mg every 2 weeks or 420 mg monthly vs placebo	Atherosclerotic cardiovascular disease (~20% had history of non-hemorrhagic stroke) LDL-C ≥ 1.8 mmol/L while on statin therapy	0.78 mmol/L	2.2	Secondary outcome: All stroke: HR 0.79 (95% CI 0.66–0.95, $P = 0.01$) Ischemic stroke: HR 0.75 (95% CI 0.62–0.92) Hemorrhagic stroke: HR 1.16 (95% CI 0.68–1.98)
ODYSSEY Outcomes[7] *n* = 18,924	Alirocumab 75 mg every 2 weeks vs placebo	Recent acute coronary syndrome LDL-C ≥1.8 mmol/L while on statin therapy 5%had history of cerebrovascular disease	1.0 mmol/L	2.8	Prespecified analysis on stroke: All stroke: HR 0.72 (95% CI 0.57–0.91, $P = 0.005$) Ischemic stroke: HR 0.73 (95% CI 0.57–0.93, $P = 0.01$) Hemorrhagic stroke: HR 0.83 (95% CI 0.42–1.65, $P = 0.59$)
Treat stroke to target[8] *n* = 2,860	Statin and/or ezetimibe Higher-target vs lower-target	Recent ischemic stroke or TIA	Higher-target group: 2.5 mmol/L Lower-target group: 1.7 mmol/L	3.5	Primary composite outcome (ischemic stroke, myocardial infarction, urgent coronary or carotid revascularization, or cardiovascular deaths): HR 0.78 (95% CI 0.61–0.98, $P = 0.04$)

CI, confidence interval; FOURIER, Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; ODYSSEY Outcomes, Evaluation of Cardiovascular Outcomes after an Acute Coronary Syndrome During Treatment With Alirocumab; SPARCL, Stroke Prevention by Aggressive Reduction in Cholesterol Level; TIA, transient ischemic attack.

[ODYSSEY Outcomes]) have reported positive results with a significant reduction in major adverse cardiovascular events, and individuals with diabetes in these trials derived greater absolute benefit because of their higher baseline risk. The two trials have also been analyzed to address the potential benefit and harm of aggressively lowering LDL-C in stroke prevention, and to determine whether hemorrhagic stroke is associated with very low LDL-C levels. In the FOURIER trial, evolocumab conferred a significant 25% relative risk reduction in ischemic stroke compared with placebo[6]. The number of hemorrhagic strokes was very small (0.19%) in the study, and was not statistically different between treatment groups (Table 1). Similarly, in a prespecified analysis from the ODYSSEY Outcomes trial, there was a significant 28% relative risk reduction in all-cause stroke, and 27% relative risk reduction in ischemic stroke in the alirocumab-treated arm (Table 1)[7]. The effect of alirocumab on stroke was similar in patients with and without a history of previous cerebrovascular disease. Hemorrhagic stroke occurred in just 0.2% of individuals. When stratified by LDL-C level in the alirocumab-treated group, there was no adverse dose–response signal of hemorrhagic stroke with incrementally lower LDL-C levels down to a level of <0.65 mmol/L.

Therefore, what should the target level of LDL-C be to reduce cardiovascular events after stroke, and how safe is a "low" LDL-C level? These questions have been addressed by the recent Treat Stroke to Target Trial[8]. The study was designed to evaluate the benefit of achieving a target level of LDL-C <1.8 mmol/L (lower-target) versus a target range of 2.3–2.8 mmol/L (higher target) using statin with or without ezetimibe to reduce cardiovascular events in individuals with prior ischemic stroke or transient ischemic attack. The primary end-point was a composite of ischemic stroke, myocardial infarction, urgent coronary or carotid revascularization, or cardiovascular deaths. To achieve the specified LDL-C targets during the trial, 34% of the patients in the lower-target group required a combination of statin and ezetimibe compared with 6% in the higher-target group. At 3 years, the percentage of patients taking high-intensity statin was 23.6% in the lower-

target group and 8.5% in the higher-target group, respectively. After a median follow-up period of 3.5 years, the lower-target group had a significant reduction in primary cardiovascular end-points compared with the higher-target group (8.5% vs 10.9% respectively), with a relative risk reduction of 22% (Table 1). There were no significant differences in the incidence of intracranial hemorrhage (1.3% vs 0.9%, respectively) and new onset diabetes (7.2% vs 5.7%, respectively) between the two groups. The trial was carried out in France and Korea, and approximately 25% of the participants were recruited from Korea. Korean participants had a lower body mass index, and the proportion of Korean participants with diabetes at baseline was higher compared with those from France (37% and 18%, respectively). There was no heterogeneity in the results between these national groups. Unfortunately, the trial had to be terminated earlier than planned due to lack of funding and there was no significant between-group difference for the secondary end-points.

In conclusion, data from randomized placebo-controlled trials of statins, ezetimibe or PCSK9 inhibitors suggest that lowering LDL-C is effective in both primary and secondary prevention of ischemic stroke[3,6,7,8]. The Treat Stroke to Target Trial has shown that patients with ischemic stroke benefit from a lower LDL-C target[8]. What about the controversial connection between low LDL-C levels and hemorrhagic stroke? The data collected so far from more recent trials where very low LDL-C levels have been achieved have been reassuring[6–8]. However, the durations of these trials were short (median follow up ranged from 2.2 to 3.5 years), and longer follow up is required to adequately monitor this safety concern. Participants in most of these trials are predominantly white, and whether the risk-to-benefit ratio is the same in Asia remains to be determined, because of the higher incidence of hemorrhagic stroke in Asians. Nevertheless, patients should not be inadequately treated with cholesterol-lowering therapy because of fear of the perceived side-effect of hemorrhagic stroke. It is important that blood pressure should be adequately controlled to reduce the risk of hemorrhagic stroke, and effective LDL-C-lowering therapy should be part and parcel of other lifestyle and pharmacological strategies in the management and prevention of stroke in people with diabetes.

DISCLOSURE

The authors declare no conflict of interest.

David TW Lui, Kathryn CB Tan*
Department of Medicine, University of Hong Kong, Hong Kong
**E-mail: kcbtan@hku.hk*

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, *et al*. 2018AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2019; 73: 3168–3209.
2. Mach F, Baigent C, Catapano AL, *et al*. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; 41: 111–188.
3. Amarenco P, Bogousslavsky J, Callahan A III, *et al*. High dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006; 355: 549–559.
4. Zhang X, Liu J, Wang M, *et al*. Twenty-year epidemiologic study on LDL-C levels in relation to the risks of atherosclerotic event, hemorrhagic stroke, and cancer death among young and middle-aged population in China. *J Clin Lipidol* 2018; 12: 1179–1189.
5. Ma C, Gurol ME, Huang Z, *et al*. Low-density lipoprotein cholesterol and risk of intracerebral hemorrhage: a prospective study. *Neurology* 2019; 93: e445–e457.
6. Sabatine MS, Giugliano RP, Keech AC, *et al*. FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017; 376: 1713–1722.
7. Jukema JW, Zijlstra LE, Bhatt DL, *et al*. Effect of alirocumab on stroke in ODYSSEY outcomes. *Circulation* 2019; 140: 2054–2062.
8. Amarenco P, Kim JS, Labreuche J, *et al*. A comparison of two LDL cholesterol targets after ischemic stroke. *N Engl J Med* 2020; 382: 9–19.

Doi: 10.1111/jdi.13310