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INVITED ARTICLE
Miscellaneous

Low levels of low-density lipoprotein cholesterol, intracerebral haemorrhage, and other safety issues: is there still a matter of debate?

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Although some observational studies suggest a potential association of low levels of low-density lipoprotein cholesterol (LDL-C) with intracerebral haemorrhage (ICH), these analyses have issues of confounding where other factors (e.g. older age, frailty) that likely explain the findings, and the number of events was very low. More recent results from randomized clinical trials have not found an increased risk in ICH, most notably trials using PCSK9 inhibitors that achieve very low levels of LDL-C, but also in the long-term follow-up of the IMPROVE-IT trial. Also, other statin-associated safety issues, including new onset diabetes and the cancer risk should not be the reason of statin discontinuation, especially for the former, the benefits highly outweigh the risk (even 5×), and for the latter, there is no confirmed link suggesting any increased risk, in opposite, data exist suggesting benefits of statin therapy in cancer prevention. Furthermore, use of intensive lipid-lowering strategies with statins and non-statin drugs leads to decrease of ischaemic major adverse cardiac events, without safety concern, in a large population of patients with atherosclerotic cardiovascular disease (ASCVD). These data should promote the concept 'the earlier, the lower, the longer, the better' for the lipid management of patients with ASCVD. While few uncertainties remain in several populations that have been underrepresented in clinical trials (African American and Asian patients, low weight individuals), the most recent data with intensive LDL-C lowering with PCSK9 inhibitors are reassuring that the benefit outweighs any possible risk.

Keywords Intracerebral haemorrhage • Lipid-lowering therapy • Low-density lipoprotein cholesterol • Risk • Statins

Current opinion

The debate on low low-density lipoprotein cholesterol and intracerebral haemorrhage

The relationship between low-density lipoprotein cholesterol (LDL-C) level and safety remains a matter of debate.[1] Indeed, statin therapy is associated with improvements in different kinds of cardiovascular (CV) events and also other potential side effects (e.g. cognitive function), and a lower risk of cerebrovascular ischaemic events in the setting of large artery atherothrombosis, but no benefit has been demonstrated either for small vascular disease or for cardioembolic stroke (e.g. atrial fibrillation).[2] Furthermore, some warning signals for harm have been reported notably a higher risk of intracerebral haemorrhage (ICH) in patients with a low (<1.4–1.8 mmol/L/<55–70 mg/dL) and extremely low (<1 mmol/L/<40 mg/dL) level of LDL-C.[2] However, whether this is causal or confounded by poorer health status has been intensely debated.

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The controversy was initiated in 1989 with the Multiple Risk Factor Intervention Trial data.[3] In this observational study including 353 340 men for a 12-year mean follow-up, the absolute number was low, 0.0006% for ICH ($n = 277$) and 0.0004% for subarachnoid haemorrhage ($n = 139$) despite being increased among men with total cholesterol levels below 4.1 mmol/L (160 mg/dL) when compared with the group with a total cholesterol above 4.1 mmol/L (160 mg/dL). Nevertheless, the limits of this observational study are well documented, with many unmeasured confounding factors that can contribute to both low cholesterol and ICH (i.e. alcohol use, poor nutrition, etc.).[3] Furthermore, this study was not designed to evaluate either the stroke risk or the description of the stroke subtypes (based on death certificates), the different fractions of cholesterol components were not evaluated, the excess risk was observed only for a diastolic blood pressure above 90 mmHg and as previously mentioned, the number of patients with ICH was very low.[3]

The next warning sign came in 2008 with the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) randomized trial of high-dose atorvastatin vs. placebo in 4731 patients with a recent stroke.[4] The authors found that although overall CV/myocardial infarction/stroke was reduced, ICH was observed in 55 patients for atorvastatin 80 mg vs. 33 in the placebo group [0.011 vs. 0.006%; hazard ratio (HR) 1.66, $P = 0.02$]. Despite this very low absolute number, this raised the question of whether in a vulnerable population of recent stroke intensive lowering of LDL was harmful.[4] A post hoc analysis of SPARCL showed that ICH was more frequent in patients with a history of haemorrhagic stroke at entry, but the small number of individuals did not allow definitive conclusions. On note, risk of ICH was neither related to the LDL-C levels at entry nor during follow-up.[5]

A more recent warning signal came from an observational post hoc analysis from the Women Health Study, which was initially a randomized trial of aspirin and vitamin E.[6] A total of 27 937 women, aged 45 years or more, were finally enrolled, and had baseline lipids measured and were followed prospectively. During a mean follow-up of 19.3 years, the number of ICH was very low ($n = 137$, 0.0049%). After multivariate adjustment, in comparison with women with LDL-C level between 2.5 and 3.4 mmol/L (100–129.9 mg/dL), which was the referent group, those with LDL-C levels <1.8 mmol/L (<70 mg/dL) had a relative risk (RR) of 2.17 [95% confidence interval (CI) 1.05–4.48] of haemorrhagic stroke. Nevertheless, the absolute number was only nine vs. four patients.[6] No increased risk of ICH was reported for women with LDL-C levels between 3.4 and 4.1 mmol/L (130–159.9 mg/dL; RR 1.14; 95% CI 0.72–1.80) or 1.8 and 2.5 mmol/L (70–99.9 mg/dL; RR 1.25; 95% CI 0.76–2.04).[6] A meta-analysis of observational studies proposed a putative mechanism is that low LDL-C may play a role in promoting arterial medial layer smooth muscle cell necrosis increasing the risk of developing microaneurysms that are the chief pathological finding of intracranial haemorrhagic events.[7] Like in the aforementioned observational studies, the adjustments do not totally prevent the influence of unmeasured confounders that might mitigate the conclusion regarding the link between low lipid levels and ICH incidence. Irrespectively of the limitations of these studies, these results opened the debate on this potential statin related adverse effect which was next monitored in all subsequent trials with statin and non-statin therapies.

The Cholesterol Treatment Trialists (CTT) 2015 analysis of 26 randomized trials showed that an intense decrease of LDL-C provided further reduction in major CV events by 28% (95% CI 22–34; $P < 0.0001$) per 1.0 mmol/L (40 mg/dL), with a risk reduction of stroke by 16% (95% CI 11–21; $P < 0.0001$) for 1.0 mmol/L (40 mg/dL) LDL-C decrease, due to a reduction in ischaemic stroke (1427 vs. 1751; RR 0.79, 95% CI 0.74–0.85; $P < 0.0001$) without significant increase of haemorrhagic stroke (RR 1.12, 95% CI 0.93–1.35; $P = 0.20$); with a very low rate of reported ICH (0.1% in both groups).[8]

The recent data of Treat Stroke to Target randomized trial, investigating more intensive LDL-C reduction in secondary prevention after ischaemic stroke, were also reassuring by reporting no difference in ICH in patients randomized to an LDL target <1.8 mmol/L (70 mg/dL) vs. those with a target <2.5 mmol/L (100 mg/dL), with respective rates of 1.3 and 0.9%, HR = 1.38 (0.68–2.82) P = NS.[9]

The IMPROVE-IT trial looked at further LDL-C lowering and compared statin vs. statin plus ezetimibe [achieving LDL-C levels of 1.8 vs. 1.4 mmol/L (70 vs. 54 mg/dL) respectively].[10] There was no difference in the rate of ICH 0.6 vs. 0.8%, HR 1.38, $P = 0.11$, while there was a significant 21% relative and 0.7% absolute reduction in ischaemic stroke (aRR: 4.1 vs. 3.4%, HR: 0.79, $P = 0.008$). Investigators further analysed achieved low level of LDL-C (<0.8 mmol/L/<30 mg/dL) at 1 month vs. 6-year outcomes of ICH and other safety issues, as well as the long-term clinical efficacy.[10] No significant association between the low-level LDL-C and the nine pre-specified safety endpoints, including ICH, cancers, and new onset of diabetes was reported, whereas a low LDL-C was associated with a further reduction of major adverse cardiac events after a 6-year follow-up.[10]

In the most recent meta-analysis of the observational studies ($n = 355\,591$) and RCTs ($n = 165\,988$), the authors showed that lipid-lowering agents (LLAs = statins + non-statin therapies) decreased the risk of all types of strokes (ischaemic, haemorrhagic strokes, ICH, intraparenchymal haemorrhage, cerebral infarction, and cerebral haemorrhage) for those who achieved LDL-C < 1.8 mmol/L [<70 mg/dL; RR = 0.88, 0.80–0.96, aRR: 0.7%, number needed to treat (NNT): 143].[11] Statin therapy decreased the risk of all strokes (RR = 0.88, 0.80–0.97, aRR: 0.6%, NNT: 167), and with regard to ischaemic stroke only LLAs decreased the risk by 25% for those who achieved LDL-C <1.8 mmol/L (<70 mg/dL; RR = 0.75, 0.67–0.83, aRR: 1.3%, NNT: 77); the same was observed for statins (RR = 0.76, 0.69–0.84, aRR: 1.3%, NNT: 77). No significant link was found between LDL-C levels and ICH events (HR: 0.99, 0.77–1.28, $P = 1.0$). The authors did not also show any significant effect of LLAs regardless of the achieved level of the LDL-C on the risk of haemorrhagic stroke.[11]

Very low-density lipoprotein cholesterol, innovative therapies, and intracerebral haemorrhage?

Two recent well-conducted RCTs using PCSK9i in patients with atherosclerotic CV disease (ASCVD) also report reassuring findings concerning this issue.[12,13] In the FOURIER study, which randomly assigned 27 564 patients with ASCVD between evolocumab and placebo, rare ICH (29 vs. 25) was reported without differences

between groups (HR 1.16, P = NS). When analysed by achieved LDL, authors also found no difference in ICH rate, even at very and extremely low LDL levels: 10% (n = 2669) of patients reached LDL-C level below 0.5 mmol/L (20 mg/dL), 31% of patients (n = 8003) achieved LDL-C between 0.5 and <1.3 mmol/L (20 and <50 mg/dL), whereas 59% had LDL-C above 1.3 mmol/L (50 mg/dL). The very low levels of LDL-C were associated with a lower rate of the primary and secondary ischaemic endpoints, with no association between low LDL-C and any of the pre-specified safety endpoints.[12]

More recently, the pre-specified propensity score-matching analysis of the ODYSSEY OUTCOMES study compared patients according to their LDL-C at 4 months follow-up (the nadir of LDL-C level) that were classified in three groups: LDL-C <0.65, 0.65–1.3, and >1.3 mmol/L (<25, 25–50, and >50 mg/dL).[13] Another analysis was performed for patients with two consecutive LDL-C measurements below 0.4 mmol/L (15 mg/dL) with a 1:3 propensity score (n = 730). Only 33 haemorrhagic strokes were reported, without increasing risk under alirocumab compared with placebo [HR 0.83 (0.42–1.65)], whereas alirocumab by decreasing LDL-C provided a reduction of ischaemic stroke by 27% [HR 0.73 (0.57–0.93)].[13] The authors reported no other safety alert concerning neurocognitive functions, liver function, and new onset of diabetes Type 2. These data are therefore reassuring, especially since patients with a very low LDL-C level have lower body mass index, and more frequently enrolled in Asia, which were two potential risk factors identified in previous studies.[13]

Nevertheless, some points may still be debated.[14] First, the time exposure may matter to identify warning signal, and as mentioned, PCSK9i trials follow-up is relatively short. The ongoing Open Label Extension FOURIER will provide useful information to confirm long-term safety of low LDL-C with PCSK9i.[15] The debate may, however, already be closed in our opinion, in view of the previous studies and the reassuring data of long-term follow-up (median 6 years) for approximately 1000 patients who achieved LDL-C <0.8 mmol/L (<30 mg/dL) in IMPROVE-IT trial.

Second, although patients with prior stroke were included in FOURIER, the size of this subgroup most vulnerable to further intracranial bleeding was small and thus justifies further research to allow definitive conclusion. Specific data of underrepresented populations in clinical trials are also needed, as African American and Asian individuals represent the most vulnerable populations for stroke, whereas the ODYSSEY OUTCOME trial and FOURIER mainly included white participants (84.5 and 85%, respectively). As accurate data on low LDL-C in African American as well as Asian American individuals are still missing, dedicated studies are also warranted.[15]

Low-density lipoprotein cholesterol and other potential adverse events

Other potential adverse events of low LDL-C should be also briefly discussed at the occasion of this debate. The potential effect of intense LDL lowering therapies on the incidence of cancer has long been questioned. The 2015 CTT analysis showed no effect of lipid-lowering therapies on cancer incidence or on cancer death.[7] One may even consider targeting cholesterol metabolism as a new therapeutic approach in cancer. Indeed, cholesterol is known to play an important role in cancer development. External cholesterol can directly activate the oncogenic Hedgehog pathway, and internal cholesterol can induce mTORC1 signalling. Cholesterol is also a key component of lipid rafts, which are the major platforms for signalling regulation in cancer, and chelating membrane cholesterol is an effective anti-cancer strategy that disrupts the functions of lipid rafts.[1,16] In addition, cholesterol metabolism is often reprogrammed in cancer cells and was shown to reduce apoptosis in breast cancer cells.[17] But current data failed to demonstrate either a protective or a negative impact of low cholesterol in this setting, indicating rather possible predictive role of high-density lipoprotein cholesterol in the cancer patients.[18,19]

Statin induced LDL reduction is also known to increase the risk of new onset diabetes (NOD), but the slight increase observed with high doses of potent statins is overweighed by the major clinical benefits (even 5× higher) in relation with a profound and prolonged decrease of LDL-C levels provided by this lipid-lowering class.[1,20–22] Similar findings have been reported in a post hoc analysis of the JUPITER study, which showed that the CV and mortality benefits of intensive statin therapy exceed the diabetes hazard in primary prevention patients, including among those at higher risk for developing diabetes.[23] A recent cross-sectional study comparing patients with very low and normal LDL-C concluded that low LDL-C concentration occurring independently of statin treatment was associated with a two-fold higher rate of Type 2 diabetes but affecting a low number of patients.[24] In addition Mendelian randomization analysis showed that individuals with PCSK9 or/and HMGCR scores below median had higher odds ratio for diabetes.[25] Several mechanistic hypotheses have been proposed regarding the link between statin treatment and NOD, including changes in calcium channel function in pancreatic beta-cells, inhibition of GLUT4 translocation, decreased cell signalling, and decreased adiponectin levels that may interact with insulin secretion and glucose homeostasis.[26,27] No excess of NOD was observed with PCSK9 inhibitors even if patients in the active group achieved very low LDL-C level.[28] Of notice, opposite to statins, PCSK9 inhibitors only target circulating PCSK9 having limited impact on LDL receptor expression in pancreatic islet that may result in cholesterol accumulation and beta-cell dysfunction. However, long-term clinical trials are needed to confirm PCSK9 inhibitors neutral effect on glucose metabolism, but available data are encouraging.

Conclusion

In conclusion, recent findings confirm that intensive decrease of LDL-C is associated with further CV benefits by reducing ischaemic events, which clearly contrast with the small possible increase in adverse effects, leading to a major net clinical benefit in high to extremely high-risk atherosclerotic patients.[7,29] With large numbers and significant patients/years of follow-up, no warning signal was ever observed regarding low LDL-C and cancer incidence with statins. A significant but moderate increase in NOD was observed with statins (which is largely overweighted by the CV benefit), but not with either ezetimibe or the potent PCSK9 inhibitors. Further research remains nevertheless warranted in some specific vulnerable

populations with longer follow-up and adequate sample size to definitively close the debate.[30,31]

Data availability

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Author contributions

All authors contributed to the development of this manuscript.

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