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EDITORIAL

So low. . . so far so good: neurocognitive impact of lowering LDL-C levels with PCSK9 inhibitors

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This editorial refers to 'No evidence of neurocognitive adverse events associated with alirocumab treatment in 3340 patients from 14 randomized Phase 2 and 3 controlled trials: meta-analysis of individual patient data'†, by P.D. Harvey *et al.*, on page 374.

In their meta-analysis in this issue of the journal, Harvey *et al.* report the safety of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition with alirocumab with respect to neurocognitive events based on the pooling of individual participant data from 10 clinical trials and a follow-up of 104 weeks.[1] Outcomes of 3340 patients on maximally tolerated statin treatment receiving 75 or 150 mg of alirocumab every 2 weeks were compared with those of 1276 patients receiving placebo and 618 patients with add-on ezetimibe. Neurocognitive treatment-emergent adverse events were reported in 22 (0.9%) patients treated with alirocumab vs. 9 (0.7%) with placebo; results remained non-significant after pooling corresponding trials [hazard ratio (HR) 1.24; 95% confidence interval (CI) 0.57–2.68]. Similar results were obtained comparing alirocumab vs. ezetimibe (1.3% vs. 1.2%; HR 0.81; 95% CI 0.32–2.08). The rates of neurocognitive adverse events in patients treated with alirocumab were not correlated to the level of LDL-cholesterol (LDL-C) reduction, and did not differ according to age. Therapy discontinuation due to neurocognitive adverse events was low with alirocumab (0.1%) vs. placebo (0.2%) and ezetimibe (0.4%). The findings of this meta-analysis add to the evidence supporting alirocumab as safe in terms of neurocognitive adverse events at 2-year follow-up for patients in whom LDL-C was insufficiently controlled under maximally tolerated statin therapy.

Evaluating the possible impact of lipid-lowering therapy and other cardiovascular risk factors on cognitive function is key in view of the growing ageing population and increasing prevalence of dementia. Cognitive function is affected by several factors, such as age, race, educational levels, literacy level, exercise and healthy lifestyles, psychosocial factors, apolipoprotein E (APOE) ε4 carriers, and the presence of traditional cardiovascular risk factors.[2,3] Epidemiological observational studies have suggested an association between high levels of cholesterol and an increased risk of Alzheimer's disease.[4,5] However, no evidence is available to recommend lipid-lowering therapy for the prevention of dementia. Two meta-analyses regrouping 57 000 and 46 000 participants each did not highlight any relevant positive or negative effects of statin on cognitive outcomes, either for patients with a normal cognitive function or for those with Alzheimer's disease.[6,7] The Food and Drug Administration (FDA) made a critical review on the safety of statin treatment based on published literature and post-marketing surveillance data, concluding that no correlation could be established for increased risk of dementia, mild cognitive impairment, or changes in cognitive performances (http://www.fda.gov/drugs/drugsafety/ucm293101.htm). An important methodological issue is, however, the lack of a standardized definition for neurocognitive side effects, as most of the trials or observational studies reported estimates based on self-reported neurological symptoms, such as memory impairment, rather than a valid and objective tool for testing cognitive function. In addition, the duration of studies is too short to detect any definitive decline of cognitive function or a potential clinically relevant signal over time.[8] Considering the safety of non-statin lipid-lowering therapies in relation to the very low LDL-C levels they can induce when added to statin, there are new data in favour of both ezetimibe and evolocumab. In the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) trial (ezetimibe and simvastatin vs. simvastatin in 18 144 patients with acute coronary syndromes), the addition of ezetimibe was not associated with an increased risk of neurocognitive adverse events, including in patients with very low LDL-C levels (<30 mg/dL).[9] In the FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) study, the pre-specified secondary analysis of 25 982 patients did not highlight any safety concerns even for very low LDL-C achieved over a median of 2.2 years, including subjects with LDL-C values <0.2 mmol/L.[10] Recently, the EBBINGHAUS (Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in high Cardiovascular Risk Subjects) study investigated the effect of low LDL-C levels on

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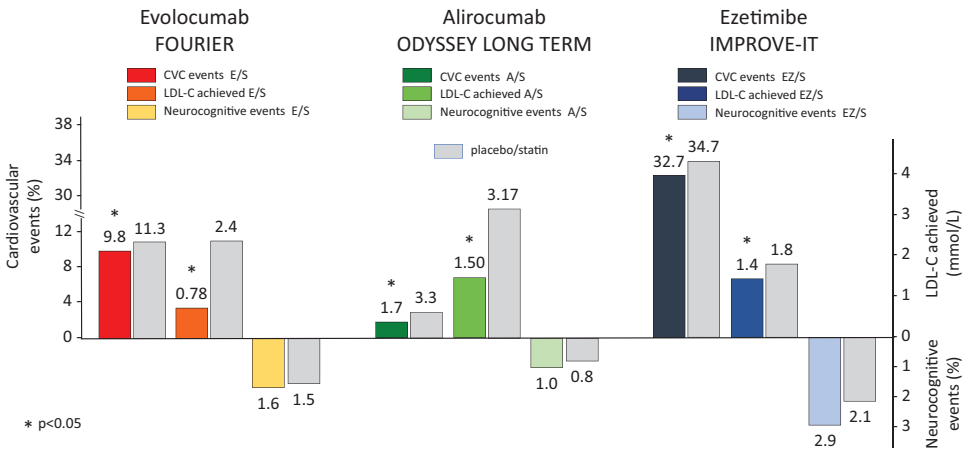

Take home figure Cardiovascular events (%), LDL-C achieved (mmol/L) and neurocognitive events (%) from the FOURIER, the IMPROVE-IT, and the ODYSSEY LONG TERM trials. No head to head comparison. ODYSSSEY LONG TERM cardiovascular outcomes are based on a post-hoc analysis.[16] ODYSSSEY LONG TERM neurocognitive treatment-emergent adverse events were evaluated by the FDA CMQ.[1] E/S, evolocumab/statin; A/S, alirocumab/statin; EZ/S, ezetimibe/statin.

cognitive function in a sample of 1204 patients enrolled in the FOURIER study over a median follow-up of 20 months.[11] The study used the Cambridge Neuropsychological Test Automated Battery (CANTAB, http://www.cambridgecognition.com), a computerized assessment tool that assesses cognitive functions in the context of episodic and working memory, executive function, psychomotor speed, and attention. No clinically relevant or statistically significant changes were observed with the addition of evolocumab to statin therapy.[11] The findings from the EBBINGHAUS study lean strongly toward supporting the safety of lowering LDL-C levels below the current recommended target. In addition to the apparent neutral effect of lipid-lowering therapies on cognitive function in clinical trials, large prospective observational studies have not reported any increased risk of Alzheimer's disease, vascular dementia, or Parkinson's disease for patients with inherent low LDL-C levels resulting from mutations on both the *PCSK9* and *HMGCR* genes.[12]

Growing evidence is strongly weighing in favour of the safety of novel lipid-lowering therapies and their combinations to achieve LDL-C levels below the currently recommended target. The long-term effect of lipid-lowering therapies on neurocognitive functions must, however, continue to be monitored as the reported adverse event rates of 0.1–1.0% are a reminder that they are not so uncommon from a pharmacovigilance point of view. In particular, the occurrence of such adverse events in the elderly/older population could have a strong impact on their quality of life, and also on the economic burden of such treatments. Furthermore, from the patient's perspective, possible treatment side effects on cognition could affect adherence to therapy and autonomy. In addition, biases in the reports of adverse events cannot be excluded, following possible 'over-reporting' of outcomes otherwise 'under-reported' in real life. One way to deal with this issue could be to perform subanalyses according to stroke status or assess the impact of a reduction of stroke events on cognitive functions. Furthermore, subanalyses according to educational and literacy levels, as well as lifestyle habits and control of cardiovascular risk factors could improve our current understanding of the specific characteristics of patients at high risk of neurocognitive side effects.

Neurocognitive function decline is a natural process associated with ageing; any additional positive or negative causal inference of lipid-lowering therapies remains to be proven.[8,13] In the meantime, PCSK9 therapies continue to demonstrate remarkable LDL-C-lowering effects associated with positive clinical outcomes. While the debate for stakeholders such as clinicians will continue to revolve around the relative safety of PCSK9 inhibitors, policy makers will need to address the cost that such therapies could incur when accepted for reimbursement. In the USA, adding this treatment to statin therapy would, on average, incur additional treatment costs of US$337729 per patient for one additional quality-adjusted life year; this is well above conventional accepted cost-effectiveness standards.[14] In Switzerland, applying ESC/EAS consensus criteria to the largest high-risk population that might benefit from PCSK9 inhibitor add-on therapy, we calculated that 5–10% of post-acute coronary syndrome patients could be eligible for treatment.[15] Future perspectives should continue to monitor the impact of PCSK9 inhibitors on neurocognitive function, while at the same time providing more precise eligibility criteria based on subgroup analyses in order to optimize treatment outcomes.

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Conflict of interest: F.M. has received honoraria for advisory boards and conferences on dyslipidaemia from Amgen, AstraZeneca, BMS, Eli Lilly, MSD, Sanofi, and Pfizer, and was a Principal Investigator for the FOURIER, ODYSSEY OUTOCOMES, and IMPROVE-IT trials. B.G. has no conflicts to declare.

References

1. Harvey PD, Sabbagh MN, Harrison JE, Ginsberg HN, Chapman MJ, Manvelian G, Moryusef A, Mandel J, Farnier M. No evidence of neurocognitive adverse events associated with alirocumab treatment in 3340 patients from 14 randomized Phase 2 and 3 controlled trials: meta-analysis of individual patient data. *Eur Heart J* 2018;**39**:374–381.
2. Yaffe K, Fiocco AJ, Lindquist K, Vittinghoff E, Simonsick EM, Newman AB, Satterfield S, Rosano C, Rubin SM, Ayonayon HN, Harris TB; Health ABC Study. Predictors of maintaining cognitive function in older adults: the Health ABC study. *Neurology* 2009;**72**:2029–2035.
3. Kaup AR, Nettiksimmons J, Harris TB, Sink KM, Satterfield S, Metti AL, Ayonayon HN, Yaffe K; Health, Aging, and Body Composition (Health ABC) Study. Cognitive resilience to apolipoprotein E epsilon4: contributing factors in black and white older adults. *JAMA Neurol* 2015;**72**:340–348.
4. Simons M, Keller P, Dichgans J, Schulz JB. Cholesterol and Alzheimer's disease: is there a link? *Neurology* 2001;**57**:1089–1093.
5. Farrer LA, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* 1997;**278**:1349–1356.
6. Booker A, Jacob LE, Rapp M, Bohlken J, Kostev K. Risk factors for dementia diagnosis in German primary care practices. *Int Psychogeriatr* 2016;**28**:1059–1065.
7. Ott BR, Daiello LA, Dahabreh IJ, Springate BA, Bixby K, Murali M, Trikalinos TA. Do statins impair cognition? A systematic review and meta-analysis of randomized controlled trials. *J Gen Intern Med* 2015;**30**:348–358.
8. Richardson K, Schoen M, French B, Umscheid CA, Mitchell MD, Arnold SE, Heidenreich PA, Rader DJ, deGoma EM. Statins and cognitive function: a systematic review. *Ann Intern Med* 2013;**159**:688–697.
9. Giugliano RP, Wiviott SD, Blazing MA, De Ferrari GM, Park JG, Murphy SA, White JA, Tershakovec AM, Cannon CP, Braunwald E. Long-term safety and efficacy of achieving very low levels of low-density lipoprotein cholesterol: a prespecified analysis of the IMPROVE-IT trial. *JAMA Cardiol* 2017;**2**:547–555.
10. Giugliano RP, Pedersen TR, Park JG, De Ferrari GM, Park JG, Murphy SA, White JA, Tershakovec AM, Cannon CP, Braunwald E. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a prespecified secondary analysis of the FOURIER trial. *Lancet* 2017;**390**:1962–1971.
11. Giugliano RP, Mach F, Zavitz K, Kurtz C, Im K, Kanevsky E, Schneider J, Wang H, Keech A, Pedersen TR, Sabatine MS, Sever PS, Robinson JG, Honarpour N, Wasserman SM, Ott BR; EBBINGHAUS Investigators. Cognitive function in a randomized trial of evolocumab. *N Engl J Med* 2017;**377**:633–643.
12. Benn M, Nordestgaard BG, Frikke-Schmidt R, Tybjaerg-Hansen A. Low LDL cholesterol, PCSK9 and HMGCR genetic variation, and risk of Alzheimer's disease and Parkinson's disease: Mendelian randomisation study. *BMJ* 2017;**357**:j1648.
13. McGuinness B, Craig D, Bullock R, Malouf R, Passmore P. Statins for the treatment of dementia. *Cochrane Database Syst Rev* 2014:CD007514.
14. Arrieta A, Hong JC, Khera R, Virani SS, Krumholz HM, Nasir K. Updated cost-effectiveness assessments of PCSK9 inhibitors from the perspectives of the health system and private payers: insights derived from the FOURIER trial. *JAMA Cardiol* 2017;**2**:1369–1374.
15. Gencer B, Koskinas KC, Räber L, Karagiannis A, Nanchen D, Auer R, Carballo D, Carballo S, Klingenberg R, Heg D, Matter CM, Lüscher TF, Rodondi N, Mach F, Windecker S. Eligibility for PCSK9 inhibitors according to American College of Cardiology (ACC) and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines after acute coronary syndromes. *J Am Heart Assoc* 2017;**6**:e006537.
16. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G, Averna M, Stroes ES, Langslet G, Raal FJ, El Shahawy M, Koren MJ, Lepor NE, Lorenzato C, Pordy R, Chaudhari U, Kastelein JJ. Efficacy and safety of alirocumab in reducinglipids and cardiovascular events. *N Engl J Med* 2015;**372**:1489–1499.