Circulation

LETTER TO THE EDITOR

Letter by Alkhalil Regarding Article, "Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)"

Mohammad Alkhalil, MD, MRCP

To the Editor:

Bonaca et al[1] reported an important analysis from the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) demonstrating that evolocumab was consistently effective in reducing the primary end point in patients with and without peripheral arterial disease (PAD). The authors highlighted a higher residual risk in patients with PAD compared with those without PAD (16.8% versus 12.1%) and subsequently reasoned that such higher risk would be translated into a larger absolute risk reduction using evolocumab (3.5% versus 1.6%). This reinforced an important concept that treating high-risk patients more aggressively conferred greater benefits. However, this was not borne out in patients with PAD and previous stroke or myocardial infarction within the FOURIER trial. Despite having an absolute residual risk of 19.9%, the absolute risk reduction using evolocumab was 2.7%, which was remarkably lower than patients with PAD with no prior stroke or myocardial infarction. This mismatch between the residual absolute risk and absolute risk reduction in patients with PAD with or without concomitant stroke or myocardial infarction highlights the need for a better mechanistic understanding of the residual risk and how to target this risk. For an effective reduction of any risk to be realized, the applied therapeutic intervention should reflect the nature of the targeted risk.[2] Herein, the risk in patients with polyvascular atherosclerosis is widely heterogeneous and does not allow to delineate the beneficial signal of evolocumab above noise. Complex substrates of thrombosis, inflammation, and atherogenesis are intricately determining the risk in patients with polyvascular disease. Therefore, new strategies that factor disease substrates to match drugs' mechanism should be used in assessing and quantifying patients' risk.[2] In the example of evolocumab, the benefits of low-density lipoprotein cholesterol reduction via PCSK9 inhibition were associated with a decrease in atherosclerosis burden compared with placebo in the GLAGOV trial (Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients)[3]; thereby, patients with a large plaque burden (or large lipid content) at multiple sites would probably benefit maximally.

This finding is important given that the clinical benefit of evolocumab in the overall FOURIER trial was modest, with a hazard ratio of 0.85 and an absolute risk reduction of 1.5% in "all-comers."[4]

ARTICLE INFORMATION

Affiliation

Acute Vascular Imaging Centre, Radcliffe Department of Medicine, University of Oxford, UK.

Sources of Funding

Dr Alkhalil was supported by the National Institute for Health Research Oxford Biomedical Research Center.

Disclosures

None.

REFERENCES

1. Bonaca MP, Nault P, Giugliano RP, Keech AC, Pineda AL, Kanevsky E, Kuder J, Murphy SA, Jukema JW, Lewis BS, Tokgozoglu L, Somaratne R, Sever PS, Pedersen TR, Sabatine MS. Low-density lipoprotein cholesterol lowering with evolocumab and outcomes in patients with peripheral artery disease: insights from the FOURIER trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk). *Circulation*. 2018;137:338–350. doi: 10.1161/CIRCULATIONAHA.117.032235.
2. Alkhalil M, Chai JT, Choudhury RP. Plaque imaging to refine indications for emerging lipid-lowering drugs. *Eur Heart J Cardiovasc Pharmacother*. 2017;3:58–67. doi: 10.1093/ehjcvp/pvw034.
3. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, Cho L, Kastelein JJ, Koenig W, Somaratne R, Kassahun H, Yang J, Wasserman SM, Scott R, Ungi I, Podolec J, Ophuis AO, Cornel JH, Borgman M, Brennan DM, Nissen SE. Effect of evolocumab on progression of coronary disease in statin-treated patients: the GLAGOV randomized clinical trial. *JAMA*. 2016;316:2373–2384. doi: 10.1001/jama.2016.16951.
4. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, Kuder JF, Wang H, Liu T, Wasserman SM, Sever PS, Pedersen TR; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med*. 2017;376:1713–1722. doi: 10.1056/NEJMoa1615664.

Letter by Alkhalil Regarding Article, "Low-Density Lipoprotein Cholesterol Lowering With Evolocumab and Outcomes in Patients With Peripheral Artery Disease: Insights From the FOURIER Trial (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)"

Mohammad Alkhalil

Circulation. 2018;138:220-221
doi: 10.1161/CIRCULATIONAHA.117.033207
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539