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New prospects for PCSK9 inhibition?

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This commentary refers to '2017 update of ESC/EAS task force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia', by U Landmesser *et al.*, 2018;39: 1131–1143.

In 2017, this Task Force updated practical guidance for clinical use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition following publication of FOURIER.[1] Beyond licenced indications, PCSK9 inhibitors may have application in other high-risk conditions, such as severe hyperlipidaemia with liver failure,[2] supported by pharmacodynamic data,[3] although the lack of trials to date does not allow recommendations.

Recent insights from FOURIER help to define patients at highest risk with elevated low-density lipoprotein cholesterol (LDL-C) levels who benefit most from PCSK9 inhibition. These include those with symptomatic peripheral artery disease (PAD), a group often underrecognized and undertreated, in whom evolocumab reduced major adverse cardiovascular events (MACE) by 27% and major adverse limb events by 37%, with benefits extending to LDL-C levels <0.26 mmol/L.[4] Patients with recent or recurrent myocardial infarction (MI), or multivessel disease, at 34–90% higher risk of a MACE, also derived greater benefit from evolocumab than those without these characteristics (*Sabatine MS, Annual Scientific Sessions, American Heart Association, 13 November 2017*). Thus, irrespective of other vascular disease, symptomatic PAD, the timing and frequency of MI, or multivessel disease, associated with residual LDL-C burden, indicate very high-risk patients who merit consideration of PCSK9 inhibition.

Will results from ODYSSEY OUTCOMES extend use of PCSK9 inhibitors to early post-MI patients? Such findings would align with the MIRACL trial[5] and may imply further stabilization of atherosclerotic plaque from LDL-C lowering with PCSK9 inhibition.

Conflict of interest: Potential conflicts of interest of the authors are denoted in reference 1.

References

1. Landmesser U, Chapman MJ, Stock JK, Amarenco P, Belch JJF, Borén J, Farnier M, Ference BA, Gielen S, Graham I, Grobbee DE, Hovingh GK, Lüscher TF, Piepoli MF, Ray KK, Stroes ES, Wiklund O, Windecker S, Zamorano JL, Pinto F, Tokgözoglu L, Bax JJ, Catapano AL. 2017 update of ESC/EAS task force on practical clinical guidance for proprotein convertase subtilisin/kexin type 9 inhibition in patients with atherosclerotic cardiovascular disease or in familial hypercholesterolaemia. *Eur Heart J* 2018;**39**:1131–1143.

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2. Glowczynska R, Hus A, Raszeja-Wyszomirska J, Opolski G. Are the proprotein convertase subtilisin/kexin type 9 inhibitors new therapeutic chance for patients with familial hypercholesterolaemia and liver failure? *Eur Heart J* 2018; doi: 10.1093/eurheartj/ehy361.
3. Gibbs JP, Slatter JG, Egbuna O, Geller M, Hamilton L, Dias CS, Xu RY, Johnson J, Wasserman SM, Emery MG. Evaluation of evolocumab (AMG 145), a fully human anti-PCSK9 IgG2 monoclonal antibody, in subjects with hepatic impairment. *J Clin Pharmacol* 2017;**57**:513–523.
4. 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.
5. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, Zeiher A, Chaitman BR, Leslie S, Stern T. Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *Jama* 2001;**285**:1711–1718.