Journal club

PCSK9 inhibition in PAD patients – a rising star in secondary prevention?

Secondary prevention in PAD patients, e.g. consistent monitoring of dyslipidaemia is a major factor of disease control according to current guideline recommendations. The recently updated ESC/EAS Guidelines on the Management of Dyslipidaemias stratify PAD patients as very high-risk subjects for cardiovascular (CV) events and recommend lifestyle modifications and concomitant drug intervention starting at a low-density lipoprotein cholesterol (LDL-C) level ≥70 mg/dl [1]. However, it has been shown in subjects with cardiovascular disease that LDL-C target achievement is still far from being satisfactory.

The emerging class of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors provides a chance to put target levels into effect, independent from the currently widely used statin medication. Statins have been proven to be beneficial for CV event prevention but also show negative side effects, which often result in unreached LDL-C reduction targets. Furthermore, randomized trials including exclusively PAD patients to prove benefits of LDL-C lowering for cardiovascular event prevention are still scarce.

The FOURIER trial is an endpoint driven, placebo-controlled, double-blind study of the PCSK9 inhibitor evolocumab with more than 27,000 subjects including 3,642 PAD patients [2]. Subjects had to be on stable moderate to high-intensity statin therapy before randomization. In the subgroup analysis of an exclusive PAD patient population, recently published by Bonaca et al., baseline characteristics included a median age of 64, female sex (28%), hypertension (85%), current nicotine use (36%), diabetes mellitus (43%), history of stroke/TIA (19%), and myocardial infarction (MI; 50%) [3].

Evolocumab use in PAD patients led to an absolute risk reduction (ARR) of 3.5% in both primary composite and key secondary endpoint (primary: CV death, MI, stroke, unstable angina, and coronary revascularization; key secondary: CV death, MI, and stroke), resulting in a number needed to treat of 29 over a period of 2.5 years. The effect of evolocumab on LDL-C lowering was sustained throughout the entire duration of the trial leading to a median of 31 mg/dl LDL-C from a baseline level of 94 mg/dl LDL-C.

Moreover, evolocumab reduced major adverse limb events (acute limb ischaemia, major amputation or urgent peripheral revascularization, MALE) by 37%, even though this condition was rare during the 2.2-year clinical trial duration. However, there was a roughly linear association with lower risk of both MALE and major adverse cardiac events (MACE) as well as lower achieved LDL-C down to values of 10 mg/dl. Furthermore, MALE reduction was consistent with all of its components, irrespective of intensity of background statin therapy. The absolute risk reduction of MACE and MALE in PAD patients was 4.1% with evolocumab application, resulting in a number needed to treat of 25 over 2.5 years.

However, the most striking results from this subgroup analysis concerned the number of MACE in placebo patients treated with moderate or high-intensity statin therapy. The risk of MACE in patients with lower extremity symptomatic PAD without prior MI or stroke (n = 1,505) was significantly higher than in those with prior MI or stroke and so far unknown PAD (10.3 vs. 7.6%). This suggests that this population is at an especially high risk of experiencing CV events even before atherosclerosis has become evident in beds other than the peripheral vasculature. Thus, in PAD patients without prior MI or stroke, the effect of evolocumab was consistent with an absolute risk reduction of primary endpoint (ARR 4.9%) and key secondary endpoint (ARR 4.8%) as well as in a reduction of MALE (ARR 1.3%), and a composite of MALE and MACE (ARR 6.3%, all $p < 0.05$).

In summary, the evidence from this subgroup analysis should result in an early detection of PAD before cardiovascular and cerebrovascular beds are affected, in order to provide this very high-risk patient population with the most benefits from durable and profound LDL-C lowering, which can most likely be accomplished by statin titration and, if necessary, with additional PCSK9 application to reach LDL-C target levels <70 mg/dl.

References

1. Catapano et al. Eur Heart J. 2016;37:2999–3058.
2. Sabatine et al. N Engl J Med. 2017;376:1713–22.
3. Bonaca et al. Circulation. 2017 Nov 13. [Epub ahead of print].

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