Editorial

Lipid-lowering therapy in patients with peripheral artery disease – a call for action

Comment on M. Sagris et al., pp. 198–211

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In 1986 Michael Brown and Joseph L. Goldstein were awarded the Nobel Prize in Medicine for their seminal discovery of the LDL-receptor [1, 2]. In their Nobel Prize Lecture in Stockholm the laureates reported that low-density cholesterol (LDL-C) binds optimally to the LDL-receptor when the lipoprotein is present at cholesterol concentrations of 2.5 mg/dl. In view of the 10-to-1 gradient between concentrations of LDL in plasma and interstitial fluid, a level of 25 mg/dl would be sufficient to nourish body cells with cholesterol. Interestingly, this is the level of a newborn human being, and this is roughly one fifth of the level usually seen in Western societies later in life [3].

The Cholesterol Treatment Trialists' Collaboration meta-analysis of statin trials demonstrated that LDL-C lowering with statins by 1 mmol/L (38.7 mg/dl) reduces cardiovascular risk by 23% [4]. IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) demonstrated that lipid-lowering to LDL-C levels of 1.4 mmol/L (55 mg/dl) is superior to 1.8 mmol/L (70 mg/dl) and reduces hard cardiovascular outcomes [5]. The IMPROVE-IT trial was one of the reasons to lower target LDL-C levels for high-risk patients in the revised version of the ESC/EAS-dyslipidemia guidelines to 1.4 mmol/L (55 mg/dl) [6]. Recently reported data in a "real-world setting" reiterated the importance of LDL-C levels in high-risk patients. In a nationwide study of myocardial infarction (MI) patients in Sweden, early LDL-C reduction after MI was associated with lower incidence and reduced adjusted hazard ratios of major cardiovascular outcomes (MACE), all-cause mortality, cardiovascular mortality, MI, ischemic stroke, hospitalization for heart failure, and coronary revascularization. These findings were most evident in patients with the greatest LDL-C reduction, whereas patients that did not have a reduction, or had an increase in LDL-C, had the highest risk. These "real-world data" clearly demonstrate that an LDL-C reduction of 2.0 mmol/L (80 mg/dl) during a 4-year follow-up period reduced all-cause mortality dramatically by almost 70%, hospitalization for heart failure by 65% and incidence of myocardial infarctions by 60% [7]. The relationship between LDL-C reduction and event rate decline was linear and comparable to the Cholesterol Treatment Trialists' Collaboration meta-analysis of statin treatment trials [4]. These data demonstrate the importance of LDL-C reduction in high-risk patients.

In the revised version of the ESC/EAS dyslipidemia guidelines patients with peripheral artery disease (PAD) are defined as "very high risk" [8]. FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) exemplifies the importance of lipid-lowering in PAD patients [9]. The placebo-group of FOURIER revealed that patients with documented PAD had a higher risk for cardiovascular events than patients with prior myocardial infarction or those with prior ischaemic stroke (13% versus 7.6%). Patients with peripheral artery disease and prior MI or ischemic stroke were characterized by the highest risk (14.9%). More importantly, treatment with the proprotein convertase subtilisin/kexin type 9 monoclonal antibody (PCSK9-mab) evolocumab reduced LDL-C and cardiovascular risk in all patients. However, the reduction was much more effective in patients with PAD compared to those without PAD (absolute risk reduction; 3.5% vs. 1.4%). The number needed to treat (NNT) in patients with PAD in FOURIER was 29 and in those without PAD only 72. Similar data have been obtained in ODYSSEY outcomes with alirocumab [10] and in IMPROVE-IT with ezetimibe [11]. By the way, the same holds true for patients with coronary artery bypass-grafts: the higher the cardiovascular risk – the greater the benefit of lipid-lowering [12].

In the current edition of Vasa, Sagris and colleagues performed a meta-analysis of statin trials to explore the impact of statin treatment and treatment intensity on all-cause mortality, cardiovascular mortality, MACE, risk for amputation or loss of patency [13]. This meta-analysis included 39 studies and 275,670 patients. Almost half of them

received statin therapy (49.3%). Statin treatment reduced all-cause mortality by 42% and cardiovascular mortality by 43%. Moreover, statins reduced MACE by 35% and risk of amputation by 35%. High-intensity statin treatment led to a greater reduction in all-cause mortality compared to low-intensity statin therapy.

The findings of this meta-analysis highlight the importance of LDL-C lowering in PAD patients, once again. Despite obvious benefits, secondary prevention and lipid-lowering treatment in particular, in PAD patients is often neglected [14]. Growing evidence suggests that PAD patients have the worst prognosis and benefit most from lipid lowering treatment. Therefore, effective "treat-to-target" lipid-lowering therapy (1.4 mmol/L, 55 mg/dl) with statins as first-line drugs is necessary to reduce cardiovascular outcomes in this high-risk patient population [15]. Unfortunately, the DA VINCI Study has demonstrated only recently that we are far away from reaching these targets in high risk patients [16]. In particular in Germany, where we are "world champions" in interventional cardiology and angiology, only 16% of very-high risk secondary prevention patients reach LDL-C target levels [17]. Eighty-four percent are treated ineffectively. What a shame!

In an effort to do better, the Deutsche Gesellschaft für Fettstoffwechselstörungen und Ihre Folgeerkrankungen (DGFF) started their campaign „auf Ziel" ("on target"). In Jena, all patients with an ST-elevation myocardial infarction (STEMI) were started on the day of admission with a high intensity statin (atorvastatin 80 mg) and the cholesterol absorption inhibitor ezetimibe (10 mg) [18]. During follow-up, all patients who failed to reach the LDL-C target of 1.4 mmol/L (55 mg/dl) were escalated with either bempedoic acid or a PCSK9-mab (evolocumab or alirocumab). Only 2 weeks prior to writing this editorial we presented the data of „Jena auf Ziel - JaZ" in the Hotline Session "Late Breaking Clinical Trials" of the 88th Annual Meeting of the German Society of Cardiology in Mannheim, Germany. Using the entire armamentarium of lipid lowering drugs, LDL-C targets could be reached in all patients with ST-elevation myocardial infarction [19]. This can also be achieved in PAD patients. Let's get the job done!

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