Extreme cardiovascular risk – do we need a new risk category?

Krzysztof Dyrbuś[1,2], Mariusz Gąsior[1,2], Peter E. Penson[3,4], Maciej Banach[5-7]*

[1]3rd Chair and Department of Cardiology, Medical University of Silesia in Katowice, Poland; [2]School of Medicine with the Division of Dentistry in Zabrze, Silesian Center for Heart Diseases, Zabrze, Poland; [3]School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, UK;[4]Liverpool Centre for Cardiovascular Science, Liverpool, UK; [5]Department of Preventive Cardiology and Lipidology, Medical University of Lodz, Lodz, Poland; [6]Department of Cardiology and Adult Congenital Heart Diseases, Polish Mother's Memorial Hospital Research Institute (PMMHRI), Lodz, Poland; [7]Cardiovascular Reseach Centre, University of Zielona Gora, Zielona Gora, Poland

*Corresponding Author:
Prof. Maciej Banach, MD, PhD, FNLA, FAHA, FESC, FASA, President, the International Lipid Expert Panel (ILEP, ilep.eu); Department of Preventive Cardiology and Lipidology, Medical University of Lodz (MUL), Rzgowska 281/289; 93-338 Lodz, Poland. Phone: +48422711124; Email: maciej.banach@umed.lodz.pl

The highest CVD risk patients – heterogenous group at different CVD risk

Cardiovascular disease (CVD) remains the most common cause of death worldwide [1]. Low density lipoprotein cholesterol (LDL-C) is the most important risk factor for atherosclerosis and plays a significant role in the development of atherosclerotic CVD (ASCVD). To estimate the risk of death in patients with established CVD or atherosclerotic risk factors, a range of risk categories have been created. Recent updates to the categories also finally included very old patients and replaced total cholesterol with non-HDL, which is much more predictable [2]. At present, the guidelines of the European Society of Cardiology (ESC) distinguish four categories of CV risk: low, moderate, high, and very-high, and these categories determine the approach to the management of patients [1].

Unfortunately, the population of patients included to the different risk categories is mostly very heterogeneous, what is most apparent in the very-high risk category. The very-high risk category includes both patients without documented CVD but with a very high probability of a cardiovascular event due to existing risk factors, as well as patients with previously diagnosed CVD and/or patients who have had a cardiovascular event [1]. The latter group of patients is also very heterogeneous, as it includes patients with various comorbidities and varying degrees of CVD progression, which are not mentioned in the risk categories. There has always been a question as to whether, after acute coronary syndrome (ACS), patients have the same risk as those with two (cardio)vascular events, or those with ACS and stroke, or even ACS and diabetes or diabetic nephropathy. Recent data seems to clearly confirm that the risk is completely different, as the effect of interventions is greater in the patients with the highest risk [3]. As a result, the category of very high cardiovascular risk could be further divided, in order to identify patients at extremely high cardiovascular risk of CVD who are simply "sicker" than the rest of the group. It is very likely that better outcomes could be achieved in this group of patients if they were treated with intensive and optimally managed therapy, with a special emphasis on adherence to therapy (using maximal doses of statins, immediate combination therapy and therapy with innovative drugs) [4].

Extremely high risk patients – what data and recommendations say?

One of the key elements of CV pharmacotherapy in this group is lipid-lowering treatment. Evidence relating to the association between LDL-C and elevated CV risk is continuously accumulating, as is evidence for the benefits of intensified lipid-lowering therapies. Consequently, lower serum concentrations of LDL-C/non-HDL-C are now recommended as treatment targets [3,4]. Unfortunately, despite the widespread availability of effective and safe cholesterol-lowering drugs, as well as the efforts of the scientific societies to foster the adoption of guideline recommended therapies, LDL-C levels in most populations still exceed recommended levels for >70% of patients [5].

The latest 2019 ESC/European Atherosclerosis Society (EAS) guidelines have brought many innovations into the treatment of lipid disorders in the general population. In particular, the new recommendations have significantly reduced target LDL-C concentrations in all cardiovascular risk categories [1]. In addition, in selected patient groups – defined as those at the extremely high CVD risk (that is, in patients with ASCVD who experienced a second vascular event within two years despite treatment with statins at the maximum tolerated dose), the guidelines allow for even more aggressive treatment and lowering of LDL-C to <1.0 mmol/L (<40 mg/dL) (IIb/B) [2]. Since the release of these guidelines, and in fact, even before, many experts have been convinced that sufficient data exist to allow for an extended definition of patients at extremely high risk of CVD. Therefore, the published recommendations were surprising in this respect [1,3,4].

Some patients, especially those for whom very low LDL-C targets are indicated, should be treated even more aggressively based on the principles that '*the lower, the better for longer*' and '*the earlier, the better*' with respect to LDL-C reduction [3,4]. It has long been known that following a first myocardial infarction (MI), patients have a 5- to 7-fold increased risk of subsequent MI and death compared with the general population [1-3]. The risk of MI or death due to ischemic heart disease (CHD) is also exacerbated by the presence of atherosclerosis in other arterial beds, including the aorta, the peripheral arteries (PAD), and the carotid and cerebral arteries [1-3].

Individuals with known PAD or carotid artery disease have a 4- to 6-fold increased risk of symptomatic CHD. In addition, those with known CHD have a 3- to 4-fold increased risk of stroke and TIA over a 10-year follow-up period [1-3]. Additionally, post-stroke patients have a 2- to 3- fold increased risk of MI, symptomatic CHD, and sudden cardiac death (SCD) and as much as a 9- fold increased risk of another stroke [1-3]. Finally, patients with severe and symptomatic PAD have a 15-fold increased risk of CV death [1-3]. At the same time, data from large RCTs on aggressive treatment of lipid disorders with PCSK9 inhibitors showed that combination intensive lipid-lowering therapy is safe for patients and even reverses the atherosclerotic process, thereby improving survival [6,7].

What should be the optimal definition of the extremely high CVD risk group?

In a recent analysis performed using data from the Hyperlipidaemia Therapy in the tERtiary Cardiological cEnTer (TERCET) Registry, we have demonstrated that in post-MI patients, elevated LDL-C levels, presence of anaemia, diabetes, multivessel coronary artery disease, atrial fibrillation,COPD, age >75 years, and LVEF < 35% were associated with significant increased all-cause mortality at 3-years of follow-up (**Figure 1**) [8]. However, most of these factors do not appear in any definition of cardiovascular risk categories. For more than ten years, we have known that a 1.0 mmol/L (38 mg/dL) reduction in LDL-C as a result of statin therapy translates into a significant reduction in the risk of major vascular events (MI, CHD death, stroke from any cause, or need for coronary revascularization) by about 22%, major coronary incidents by 23%, CHD death by 20%, strokes by 17%, and total mortality by 10% [1-3]. In addition, a recent sub-analysis of the FOURIER trial showed that there is strong evidence of additional CV benefit in patients who were able to lower LDL-C < 1 mmol/L (40 mg/dL) with PCSK9 inhibitors [9].

Based on the results of available studies, including ours from the TERCET Registry, and in order to enable the optimal management of ACS patients, we would like to recommend a new extended definition of patients at extremely high cardiovascular risk. US experts have already offered their expert opinion in relation to this group in the 2017 AACE/ACE Lipid Guidelines [4,8]; however they did not have sufficient data from RCTs to confirm and validate these criteria. In our opinion, the European category of extreme cardiovascular risk should include the extended group of patients patients, based on the available EBM, what was presented in **Table 1.**

Table 1. The expert recommendations on the definition of patients at the extremely high CVD risk.

1. In primary prevention with a (Pol)SCORE >20% (e.g., a 60-year-old man with smoking, systolic blood
*pressure >160 mmHg, and total cholesterol 6 mmol/L)**
2. A history of ACS and other vascular events within the last two years
3. After ACS with peripheral vascular disease or polyvascular disease
4. After ACS with concomitant multivessel coronary artery disease
5. After ACS with familial hypercholesterolemia (FH)
6. After ACS with diabetes and at least one additional risk factor (elevated Lp(a) >50 mg/dL or hsCRP >3 mg/L or chronic kidney disease [eGFR <60ml/min/1.73m2]).

*The same risk is recommended based on the SCORE2 [2]; the estimated risk of this concrete example patient is 23-25%.

These recommendations have already been approved and included in the joint guidelines of six Polish scientific societies on the diagnosis and therapy of lipid disorders [10] (**Figure 2**). Some of them were included in the previous expert opinion papers and recommendations in Poland [11] and were summarized and approved in recommendations of the International Lipid Expert Panel (ILEP) in April this year [4]. Based on the available study results, we agree that the target LDL-C concentration in patients at extreme risk should be <1 mmol/l (40 mg/dl). Furthermore, we strongly believe, based on EBM, that broadening the population of patients in whom LDL-C should be lowered

so much will positively influence the effectiveness of therapy and consequently improve the prognosis in this most burdened group of patients.

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Figure 1: Factors that stratify cardiovascular risk and significantly increase all-cause mortality in patients after MI within 36 months based on the data from the TERCET Registry [8].

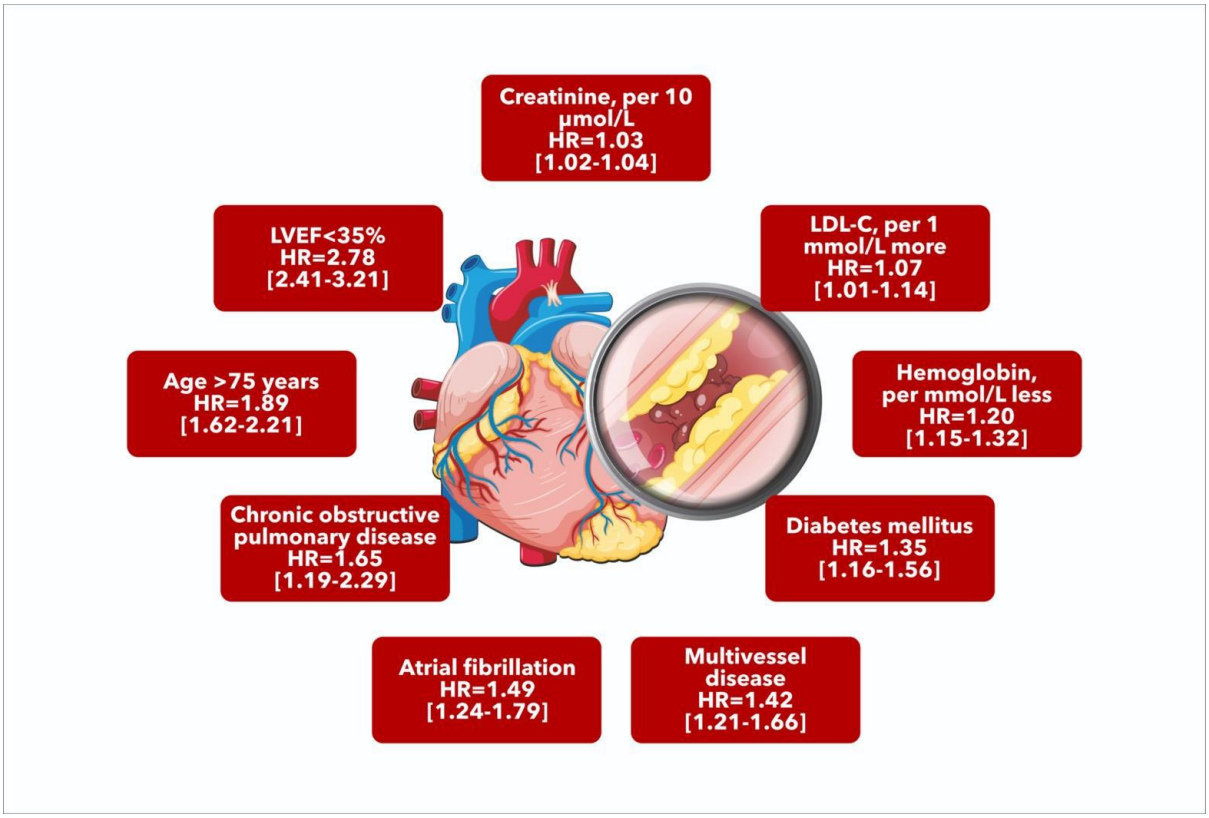

Figure 2: Recommendations for a new definition of the extremely high cardiovascular risk category with a target LDL-C concentration based on new Polish guidelines [11].

In patients in primary prevention with a Pol- SCORE >20% *OR* after an acute coronary syndrome (ACS) and another vascular incident within the past two years *OR* after an ACS, who has the peripheral vascular disease or polyvascular disease *OR* after an ACS with coexisting polyvascular disease OR after an ACS with familial hypercholesterolemia (FH) *OR* after an ACS with diabetes mellitus and at least one additional risk factor (elevated Lp(a) >50 mg/dL or hsCRP >3 mg/L or chronic kidney disease [eGFR <60ml/min/1, 73m2]) may be considered as a target LDL fraction cholesterol <1.0 mmol/L (<40 mg/dL)	IIB	B