Extremely high-risk patients with acute coronary syndrome: how “extreme” should be the lipid-lowering therapy if the LDL-C target <40 mg/dl is considered?

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Extremely high-risk patients with acute coronary syndrome: how “extreme” should be the lipid-lowering therapy if the LDL-C target <40 mg/dl is considered?

Short running head: extremely high-risk patients after acute coronary event

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INTRODUCTION

Patients with acute coronary syndrome (ACS) constitute a heterogeneous group regarding the risk for cardiovascular (CV) events recurrence ranging from very high to extremely high-risk subgroups [1, 2]. Despite the advances in the treatment of ACS, survivors of ACS are at high risk for recurrent CV events, particularly within 12 months after discharge[3]. Furthermore, the lipid-lowering therapy (LLT) algorithm which is based on the step-wise approach is similar for ACS and stable coronary artery disease (CAD) patients despite the higher early CV risk recurrence in ACS patients [4].

A recent position paper [1] endorsed by the International Lipid Expert Panel (ILEP) proposed the criteria which define the extremely high-risk ACS patients for whom a lower LDL-C target (<40 mg/dl) was proposed. This subgroup comprises patients with multivessel CAD (significant stenosis in more than one of the 3 coronary arteries), polyvascular disease (additional involvement of arteries of lower extremities or cerebrovascular arteries or presence of abdominal aneurysm), heterozygous familial hypercholesterolaemia (heFH), or diabetes mellitus (DM) with additional risk factors [high sensitivity-C-reactive protein (hsCRP) ≥3 mg/l and/or chronic kidney disease with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m² and/or lipoprotein(a) [Lp(a)] >50 mg/dl]. Extremely high-risk patients are also patients with vascular event within 2 years prior admission not being on LDL-C target (<55 mg/dl) despite maximally tolerated intense statin therapy and ezetimibe. A similar subgroup has also been described by the ESC/EAS guidelines for the management of dyslipidaemias [4]. In particular, an LDL-C target <40 mg/dL was proposed with a IIb class of recommendation for patients with CV disease (CVD) who experience a second vascular event within 2 years while taking maximally tolerated statin.

This proposal challenged us to estimate the proportion of ACS patients that fulfill the criteria of the extremely high-risk group and are potential candidates for “extremely” intensive early LLT aiming at the new stringent proposed LDL-C target <40 mg/dl.
METHODS
We recruited 780 consecutive patients (608 males) with ACS who were participants of the CALLINICUS-Hellas Registry, a prospective multicenter observational study that explores the adherence to LLT, the achievement of LDL-C targets and the CV events at 6- and 24-months after hospital discharge of patients with ACS [5].

During the hospitalization all patients had coronary angiography and lipids measured within 24 hours from admission. Significant CAD was defined as >70% luminal stenosis of any of the three coronary arteries or their primary branches or >50% luminal stenosis of the left main coronary artery. For the diagnosis of heFH the Dutch Lipid Clinic Network (DLCN) criteria were applied [6].

The study was approved by the ethics committee of all participants hospitals and all subjects gave signed informed consent.

Statistical analysis
Continuous variables are presented as means with standard deviation (SD) while non-normally distributed variables are presented as medians and interquartile ranges. Normal distribution was assessed with the Shapiro–Wilk test. Categorical variables are presented as absolute and relative frequencies. The data were analyzed using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, US).

RESULTS AND DISCUSSION
A previous history of CVD was present in 172 patients (22.1%). The prevalence of high risk components among ACS patients is shown in Figure 1. Of 105 heFH (13.5%) patients, 18 had possible, 65 probable and 22 definite heFH. HsCRP >3 mg/l was not incorporated in the additional risk factors of patients with DM due the methodology of the study, i.e., recruitment during acute phase. Furthermore, none of the patients who had CV event within the previous 2 years (n = 30) was on dual LLT. By excluding the overlapping between these conditions, 430 ACS patients (55.1%) had at least one of the characteristics which define the extremely high-risk patients (Figure 1).

Prior to admission 197 (25.3%) were on LLT. All of them were on statin, either monotherapy (81%) or combination therapy with ezetimibe (19%). The most frequently used statin was atorvastatin (n = 95) and the mean equivalent atorvastatin dose was 28.4 mg (SD 9.8). The calculation of the presumed untreated LDL-C levels in patients under LLT prior their admission was done by using correction factors [7]. Subsequently, considering as reference LDL-C levels
the pretreatment levels for those using LLT at the time of admission and the early hospitalization levels for those naïve to LLT, we calculated the expected LDL-C levels that they were supposed to reach if dual intense LLT (high-intensity statin at high dose plus ezetimibe) had been implemented and LDL-C levels had ideally been reduced by ~65% [4].

Mean age of patients was 60.7 years (SD, 11.1) and mean LDL-C levels at admission were 117.3 mg/dl (SD, 44.3). Characteristics of patients are displayed in Supplementary material, Table S1. Presuming a 65% LDL-C reduction of the pretreatment levels of the extremely high-risk ACS patients (n = 430) by taking intense dual LLT, 312 patients, i.e., 72.6% of them, would fail to achieve LDL-C levels <40 mg/dl. This corresponds to 40% of all initially recruited ACS patients and suggests that these patients might be candidates for triple LLT, i.e., high-intensity statin plus ezetimibe plus proprotein convertase subtilisin/kexin type 9 inhibitor (PCSK9i).

Our hypothetical model shows that 40% of all ACS patients are extremely high-risk and unable to achieve with intense dual LLT the recently proposed by ILEP LDL-C levels <40 mg/dl suggesting that they require more aggressive LLT. Practically, extremely high-risk ACS patients with pretreatment LDL-C >110 mg/dl are potential candidates for triple LLT, i.e., intense dual LLT plus PCSK9i, ideally during their hospitalization. The in-hospital addition of PCSK9i has been shown to be well tolerated with the vast majority of patients being able to achieve rapidly the currently recommended LDL-C goals [8]. However, it should be mentioned that the feasibility of such an approach is questionable in various healthcare systems due to reimbursement barriers of PCSK9i.

The significance of the early “extremely” aggressive LLT has been explored in recent angiographic studies combined with imaging of the arterial wall before treatment and 50-52 weeks later [9–11]. It was shown that the in-hospital addition of PCSK9i in patients with ACS on high-intensity statin produces incremental benefits on plaque phenotype in the non-culprit related atherosclerotic lesions which are more likely to cause early recurrent events. The favourable effect comprises greater reduction in lipid burden and atheroma volume and greater increase in minimal fibrous cap thickness. This stabilizing effect on vulnerable atherosclerotic lesions was noticed at very low LDL-C levels averaging less than 30 mg/dL and in view of the early clinical benefit produced by the in-hospital initiation of intensive statin treatment, it is resonable to hypothesize that early very intensive LLT with the addition of a PCSK9i is likely to be also associated with early clinical benefit [12].

In conclusion, our analysis suggests that almost 1 in 2 patients with ACS have extremely high-risk characteristics and are potential candidates for in-hospital triple LLT aiming at the proposed by the ILEP LDL-C target <40 mg/dl. Although this strategy has shown to improve
plaque stability, it needs to be tested by outcome studies and should be always combined with intensive lifestyle management.

Supplementary material
Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information
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Figure 1. Prevalence of high-risk characteristics among all acute coronary syndrome patients and prevalence of extremely high-risk patients. For the creation of the last column, patients with at least one high-risk characteristic were included and the overlapping of these characteristics was excluded.

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; heFH, heterozygous familial hypercholesterolaemia.