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

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INTRODUCTION

Patients with acute coronary syndrome (ACS) constitute a heterogeneous group regarding the risk of cardiovascular (CV) event recurrence that ranges from very high to extremely high [1, 2]. Despite the advances in ACS treatment, ACS survivors are at high risk of 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 that 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 hypercholesterolemia (HeFH), or diabetes mellitus (DM) with additional risk factors (high-sensitivity C-reactive protein [hs-CRP] ≥3 mg/l, and/or chronic kidney disease with estimated glomerular filtration rate [eGFR] <60 ml/min/1.73 m^2, and/or lipoprotein (a) [Lp(a) >50 mg/dl]. Patients with vascular events within 2 years before admission who did not achieve the LDL-C target (<55 mg/dl) despite maximum tolerated intense statin therapy and ezetimibe are also extremely high-risk. A similar subgroup has also been described by the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias [4]. In particular, an LDL-C target <40 mg/dL was proposed with recommendation class IIb for patients with CV disease (CVD) who experience a second vascular event within 2 years while taking a maximally tolerated statin dose.

This proposal challenged us to estimate the proportion of ACS patients that fulfill the

criteria for the extremely high-risk group and are potential candidates for "extremely" intensive early LLT aiming at the newly proposed stringent 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 adherence to LLT, achievement of LDL-C targets, and frequency of CV events at 6- and 24-months after hospital discharge of ACS patients [5].

During hospitalization, all patients had coronary angiography and lipid measurement 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 participating hospitals, and all subjects gave signed informed consent.

Statistical analysis

Continuous variables were presented as means with standard deviation (SD) while non-normally distributed variables were presented as medians and interquartile ranges. Normal distribution was assessed with the Shapiro-Wilk test. Categorical variables were presented as counts 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 factors among ACS patients is shown in Figure 1. Of 105 HeFH (13.5%) patients, 18 had possible, 65 probable, and 22 definite HeFH. Hs-CRP >3 mg/l was not included in the additional risk factors for DM patients due to the study methodology, i.e., recruitment during the acute phase. Furthermore, none of the patients who had CV events within the previous 2 years (n = 30) was on dual LLT. By excluding the overlap between these conditions, 430 ACS patients (55.1%) had at least one of the characteristics that define extremely high-risk patients (Figure 1).

Before admission, 197 (25.3%) patients were on LLT. All of them were on statins, 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). Calculation of the presumed untreated LDL-C levels in patients under LLT before their admission was done by using correction factors [7]. Subsequently, considering as reference LDL-C levels (1) the pretreatment levels for those using LLT at the time of admission and (2) early hospitalization levels for those LLT naïve, we calculated the expected LDL-C levels that these patients were supposed to reach if

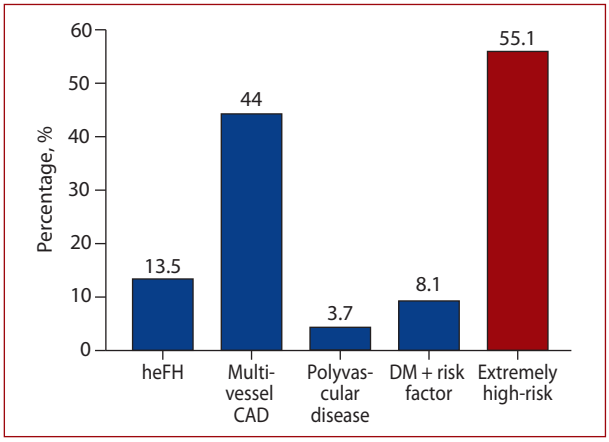

Figure 1. Prevalence of high-risk characteristics among all acute coronary syndrome patients and prevalence of extremely high-risk patients. In the last column, patients with at least one high-risk characteristic were included

Abbreviations: CAD, coronary artery disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia

(1) dual intense LLT (high-intensity statin at high dose plus ezetimibe) had been implemented and (2) LDL-C levels had ideally been reduced by ~65% [4].

The mean age of patients was 60.7 years (SD, 11.1), and a mean LDL-C level was on admission were 117.3 mg/dl (SD, 44.3). Characteristics of patients are shown in Supplementary material, *Table S1*. Presuming a 65% LDL-C reduction compared to the pretreatment levels in the extremely high-risk ACS patients (n = 430) taking intense dual LLT, 312 patients (72.6%) 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 LDL-C levels <40 mg/dl (proposed by the ILEP) with intense dual LLT, which suggests 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, initiated ideally during their hospitalization. The in-hospital addition of PCSK9i has been shown to be well tolerated, with the vast majority of patients 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 for PCSK9i.

The significance of 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 in-hospital addition of PCSK9i in ACS patients on high-intensity statin produces incremental benefits for plaque phenotype in the non-cul-

prit related atherosclerotic lesions that are more likely to cause early recurrent events. The favorable effect comprises a greater reduction in lipid burden and atheroma volume and a 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 given the early clinical benefit produced by in-hospital initiation of intensive statin treatment, it is reasonable 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 LDL-C target <40 mg/dl proposed by the ILEP. Although this strategy has been 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

Conflict of interest: LSR has received research grants and honoraria from Amgen, ELPEN, Sanofi-Aventis, Viatris, Novartis, and Servier, CV has received research grants and honoraria from Amgen, Angelini, Bayer, Boehringer-Ingelheim, ELPEN, Menarini, Merck Sharp & Dohme, Mylan, Novartis, Sanofi-Aventis, Servier, Vianex. Other authors have no relevant conflict of interest to report.

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