Atherosclerosis 281 (2019) 216–218

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

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Bridging the treatment gap in patients at 'extreme' cardiovascular risk: Evidence from a lipid clinic

ARTICLE INFO

Keywords:
Extreme cardiovascular risk
Cholesterol
Target
Statin

To the Editor,

Rallidis et al. evaluated whether achieving low-density lipoprotein cholesterol (LDL-C) less than 55 mg/dL in patients at 'extreme' cardiovascular disease (CVD) risk is feasible in clinical practice [1]. They showed that more than 50% of all patients with stable coronary artery disease were at 'extreme' CVD risk as proposed by the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) [2]. Of these, 20.3% had LDL-C < 70 mg/dL and 5.3% achieved an LDL-C level < 55 mg/dL [1]. Authors do not provide data on specific lipid-lowering therapy in these individuals. Therefore, it would be of interest to investigate the association between statin intensity ± ezetimibe with LDL-C target attainment in 'extreme' CVD risk patients.

In this context, we performed a similar analysis in a previously published study [3,4]. This was a retrospective study including consecutive adult patients followed for ≥3 years (1999–2015) in the outpatient Lipid Clinic of the University Hospital of Ioannina, Greece. For the purposes of the present analysis, we identified the following groups of patients as 'extreme' CVD risk: (a) patients with established CVD and diabetes (DM), chronic kidney disease (CKD) stages 3–4 or familial hypercholesterolemia (FH), (b) patients with premature CVD and (c) patients with recurrent CVD event despite LDL-C < 70 mg/dL [2]. The intensity of statin therapy was classified as high, moderate and low on the basis of the average expected LDL-C lowering of ≥50, 30–50 or < 30%, respectively.

Among 1334 study participants, 244 patients (18.1%) were diagnosed with CVD and 48.4% of them (n = 118) had features of 'extreme' CVD risk. Their characteristics are depicted in Table 1. Notably, the majority of these patients were diagnosed with DM or CKD and 1 out of 3 was receiving high-intensity statin treatment. One third of the patients were also receiving ezetimibe (Table 1). Fig. 1 shows the distribution of LDL-C levels in relevance to targets. Of the 'extreme' CVD risk patients, 37% achieved LDL-C < 70 mg/dL, while 16% achieved the most stringent goal of < 55 mg/dL. Among those on high-intensity statin monotherapy (n = 30), the rates of target attainment were 48% for LDL-C < 70 mg/dL and 19% for LDL-C < 55 mg/dL. The corresponding rates were lower (30% and 10%, respectively) among those taking a combination therapy of a high-intensity statin with ezetimibe (n = 10). However, the latter group was more likely to be diagnosed with FH (33% vs 7%) and therefore had higher baseline LDL-C levels compared with those on statin monotherapy [224 (187–269) *vs.*

Table 1
Characteristics of study participants at 'extreme' cardiovascular risk.

	Patients at 'extreme cardiovascular risk' (n = 118)
Gender (male), %	37
Age, years	74 (65–79)
Follow-up, years	7 (4–11)
Diabetes mellitus, %	60
Chronic kidney disease stage 3 or 4, %	52
Familial hypercholesterolemia, %	15
Premature coronary artery disease,%	40
Recurrent cardiovascular event despite LDL-C < 70 mg/dL, %	8
Coronary artery disease, %	49
Stroke, %	40
Peripheral artery disease, %	39
Carotid stenosis, %	13
Total cholesterol, mg/dL	152 (135–175)
Triglycerides, mg/dL	117 (87–146)
High-density lipoprotein cholesterol, mg/dL	48 (41–56)
Low-density lipoprotein cholesterol, mg/dL	78 (62–99)
Statin therapy, %	96
High-intensity statins, %	34
Moderate-intensity statins, %	60
Low-intensity statins, %	2
Combination therapy of a statin plus ezetimibe, %	33

Variables are presented as median (interquartile range), unless percentages are shown.

DOI of original article: https://doi.org/10.1016/j.atherosclerosis.2018.06.821

https://doi.org/10.1016/j.atherosclerosis.2018.11.022
Received 28 October 2018; Accepted 9 November 2018
Available online 14 November 2018

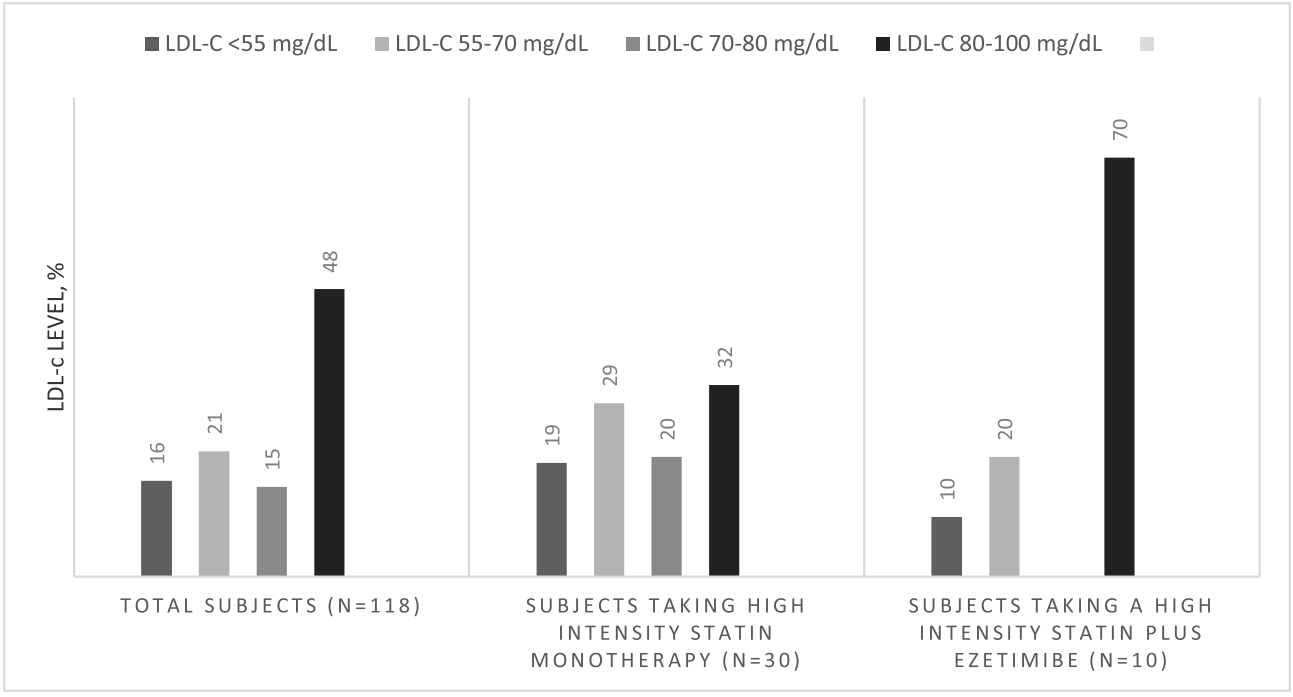

Fig. 1. Distribution of LDL-C levels.
LDL-C: low-density lipoprotein cholesterol.

165(136–181) mg/dL, $p < 0.05$].

In contrast to Rallidis et al., we enrolled patients with coronary artery disease as well as stroke and peripheral arterial disease, currently described as atherosclerotic cardiovascular disease (ASCVD) in all guidelines. Nevertheless, the notion that half of CVD patients belong to 'extreme' CVD risk category is in agreement with Rallidis et al. Although our attainment of the standard LDL-C target < 70 mg/dL in CVD patients was higher compared with Rallidis et al. and previously published studies [1,5], achievement of LDL-C < 55 mg/dL was markedly low (5–15%) in both studies. It should be acknowledged, however, that the AACE/ACE guidelines were not published at the time of patient enrollment.

Furthermore, we show that high-intensity lipid-lowering therapy was prescribed only to half of patients at 'extreme' CVD risk and was associated with increased rates of LDL-C target attainment. However, this was not the case for the most stringent LDL-C goal proposed by AACE/ACE. Despite the fact that more patients at 'extreme' CVD risk achieved LDL-C < 55 mg/dL in this analysis compared with Rallidis et al. (16% *vs*. 5%), which could be attributed to the heterogeneity of either the eligible patients' characteristics or the clinical practice of physicians practicing on different settings (primary-secondary-tertiary hospital/clinic, variety of specialization from cardiologists to general practitioners), the majority remained above this target, even for those on intensive lipid-lowering therapy. Considering the distance to the new target (Fig. 1), novel therapies such as proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors could benefit such patients [6].

In conclusion, we corroborate that 'extreme' CVD risk is quite prevalent in everyday clinical practice. Only a minority of these patients is taking optimal lipid-lowering therapy and even fewer achieve optimal LDL-C levels. Although the combination of high-intensity statins with ezetimibe remains imperative for such patients, it might be inadequate, especially in those with FH. Considering the distance to the new target, PSCK9 inhibitors may be necessary to bridge the therapeutic gap in patients at 'extreme' CVD risk.

Conflicts of interest

The authors report conflicts of interest outside the submitted work. FB has participated in educational and research activities sponsored by Amgen, Pfizer, Sanofi and Boehringer Ingelheim. ME reports honoraria from MSD, Novartis, Chiesi, Bayer, AstraZeneca, Pfizer, Abbott, MYLAN, Sanofi, Amgen, Boehringer Ingelheim, ELI LILLY, GSK and Angelini. EL has participated in educational, research and advisory activities sponsored by AstraZeneca, MSD, Lilly, Bayer, Amgen, Sanofi, Boehringer Ingelheim, Novartis, Novo Nordisk, VALEANT AND SERVIER. ER has participated in educational, research and advisory activities sponsored by AstraZeneca, MSD, Lilly, Bayer, Amgen, Sanofi, Boehringer Ingelheim, Novartis, Novo Nordisk, WINMEDICA, ELPEN.

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