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Is the novel LDL-cholesterol goal <1.4 mmol/L achievable without a PCSK9 inhibitor in a chronic coronary population from clinical practice?

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The treatment recommendations for low-density lipoprotein cholesterol (LDL-C) have been intensified in the 2019 European guidelines for the management of dyslipidemias.[1] In very high-risk patients, including those with established cardiovascular disease (CVD), a LDL-C reduction of ≥50% from baseline and a LDL-C goal of <1.4 mmol/L received a class 1A recommendation.[1] The guidelines recommend starting proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in patients with an acute coronary syndrome who do not reach LDL-C <1.4 mmol/L after 4–6 weeks of maximum-tolerated statin and ezetimibe therapy.[1] These recommendations are based on the results from two PCSK9 trials: FOURIER[2] and ODYSSEY Outcomes.[3] In FOURIER,[2] which includes 27,564 patients with CVD, adding evolocumab to statin therapy reduced the occurrence of the primary composite major adverse cardiovascular event (MACE) endpoint from 11.3% to 9.8% (number needed-to-treat (NNT) 67) during a 2.2-year period. Only 69% were on high-intensity statin therapy and 5% used ezetimibe at baseline. In ODYSSEY Outcomes,[3] which included 18,924 patients with an acute coronary syndrome median 2.6 months prior to enrollment, alirocumab added to statin therapy also resulted in a similar risk reduction (NNT 63) in MACE. During a run-in period, intensive atorvastatin treatment was initiated to obtain maximum-tolerated doses. At the time of randomization, 88.8% used high-intensity treatment with atorvastatin 40–80 mg daily or rosuvastatin 20–40 mg daily, while 3% used ezetimibe. The absolute benefit of PCSK9 with respect to the primary outcome was most pronounced among patients with a baseline LDL-C level >2.6 mmol/L.[3] In FOURIER,[2] beneficial effects were also observed among patients with the lowest baseline LDL-C quartile of 1.9 mmol/L. The additional effect of a PSCK9-inhibitor on top of treatment with statin plus ezetimibe and the effect of reducing LDL-C from 1.8 to 1.4 mmol/L was not specifically tested in these trials. The important question arises, to what extent the new LDL-C target is achievable in daily clinical practice through optimized conventional lipid-lowering treatment, and, thus, the proportion of patients that would be eligible for treatment with a PSCK9 inhibitor.

To answer these questions, we analyzed data from the cross-sectional NOR-COR study, which included 1095 patients (83% participation rate) who were hospitalized with a coronary event median 16 months earlier.[4] Data on statin doses were missing in 77 patients; thus, 1018 patients were included in this study. Mean LDL-C was 2.10 (standard deviation 0.78) mmol/L and 142 patients (13%) had LDL-C <1.4 mmol/L. Mean LDL-C and the proportion with LDL-C <1.4 mmol/L by intensity of statin therapy and level of adherence is shown in Table 1. Only 4.6%

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Table 1. Low-density lipoprotein cholesterol <1.4 mmol/L by intensity of statin therapy and level of adherence.

	N (%)	Mean LDL-C (SD)	LDL-C <1.4 mmol/L, *N* (%)
No statin treatment or low adherence[a]	132 (13.0)	2.89 (1.22)	8 (6.1)
Low-intensity statin therapy[b]	380 (37.3)	2.13 (0.69)	42 (11.1)
High-intensity statin therapy[b]	506 (49.7)	1.89 (0.60)	83 (16.4)

[a]No statin treatment or statin adherence <7/7 days last week vs statin adherence 7/7 days last week.
[b]High-intensity statin therapy defined as drugs known to lower LDL-C by ~50%: ≥40 mg atorvastatin/day or ≥20 mg rosuvastatin/day. Other drug regimens were considered as low- or moderate-intensity therapy.
LDL-C: low-density lipoprotein cholesterol; SD: standard deviation.

($n = 47$), all taking low- or moderate-intensity statin treatment, used additional treatment with ezetimibe.

In this observational study reflecting daily practice, only 50% ($n = 506$) were highly adherent to high-intensity statin treatment. Among these, 28% ($n = 142$) used atorvastatin 80 mg/day, 0.6% ($n = 3$) used rosuvastatin, which is the most potent statin, and none were treated with ezetimibe. In line with our data, mean daily dosage normalized to atorvastatin potency was 27 ± 20 mg for chronic coronary heart disease (CHD) patients in a recent European study.[5] Thus, intensified statin treatment and strategies to ensure high drug adherence are the first crucial steps to improve LDL-C control.

In the IMPROVE-IT trial, median LDL-C was reduced by 24% when ezetimibe was added to simvastatin.[6] If we extrapolate this additional effect, mean LDL-C in our coronary population treated with high-intensity statin could potentially have been 1.44 mmol/L. These data are by no means representative of a randomized comparison, but give an indication of the effect that may be obtained from optimizing conventional lipid-lowering therapy with statin plus ezetimibe. Nevertheless, even if all chronic coronary outpatients were adherent to maximal lipid-lowering therapy, a large number of patients would be in need of a PCSK9 inhibitor to achieve the novel LDL-C target. In view of the current costs related to these drugs, our study results might be of importance in the ongoing debate regarding implementation of the novel lipid guidelines in clinical practice and in selecting patients for treatment with PCSK9 inhibitors. Last but not least, healthy lifestyle changes including physical activity and dietary modifications with a potential to lower LDL-C, are strongly recommended.[1] Moreover, the beneficial effect of cardiac rehabilitation on LDL-C target achievement was recently demonstrated in a German registry study with significantly higher use of both high-dose atorvastatin and ezetimibe among CHD patients who attended an early and short-term in-patient programme.[7]

LDL-C at the time of the coronary event remains unknown. The additional effect of ezetimibe on LDL-C remains uncertain due to extrapolation from IMPROVE-IT. The routine clinical practice and the participation rate (83%) are strengths of the study.

In summary, there is a vast potential for improving LDL-C levels in coronary outpatients through optimal treatment with conventional lipid-lowering therapy. Still, a large number of patients would be in need of treatment with a PCSK9 inhibitor to reach the treatment target of <1.4 mmol/L.

Author contribution

JM contributed to the conception or design of the work, acquisition, analysis, and interpretation of data for the work, and drafted the manuscript. ES contributed to acquisition and analysis of data. All authors contributed to the interpretation of data, critically revised the manuscript, and gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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