Revista Portuguesa de Cardiologia 41 (2022) 689–691

Portuguese Society of CARDIOLOGY

Revista Portuguesa de
Cardiologia
Portuguese Journal of Cardiology
www.revportcardiol.org

EDITORIAL COMMENT

Low-density lipoprotein cholesterol lowering in the comfort zone and the benefits of stepping out

Saindo da zona de conforto para obter mais benefícios da redução do colesterol das LDL

Carlos Aguiar

Department of Cardiology, Hospital Santa Cruz, Centro Hospitalar de Lisboa Ocidental, Carnaxide, Portugal

Available online 5 June 2022

Atherosclerosis is the most common pathophysiologic process leading to cardiovascular disease (CVD). In 2016, an estimated 15 123 deaths in mainland Portugal were attributable to ischemic heart disease, ischemic cerebrovascular disease, or peripheral arterial disease, which corresponded to 14.3% of overall mortality. In the same year, disability-adjusted life years attributable to atherosclerosis totaled 260 943, of which 75% were due to premature death (196 438 years of life lost) and 25% due to disability (64 505 years lived with disability).[1]

Plasma lipid abnormalities by themselves may be responsible for as many as 50% of myocardial infarctions and 25% of strokes. Lowering low-density lipoprotein cholesterol (LDL-C), the primary driver of atherogenesis, reduces the risk of major vascular events. Statins, ezetimibe, and PCSK9 inhibitors have biologically equivalent effects on the risk of vascular events per unit change in LDL-C. The clinical benefit of these interventions depends on the absolute magnitude of the achieved LDL-C reduction and the total duration of treatment. In short, lower is better, and so is longer.[2]

Pharmacologic lowering of LDL-C is safe. The risk of serious muscle injury, including rhabdomyolysis, is <0.1%, and the risk of serious hepatotoxicity is about 0.001%. Newly diagnosed diabetes occurs at a rate of about 0.2% per year of treatment, and there is no convincing evidence for a causal relationship between statins and cancer, cataracts, cognitive dysfunction, peripheral neuropathy, erectile dysfunction, or tendonitis.[3]

LDL-C lowering is also cost-effective, even more so with the advent of generic pricing. Accordingly, it has been suggested that eligibility for preventive statin therapy should be expanded to younger individuals and that treating patients at borderline risk regardless of LDL-C level would likely be highly cost-effective.[4,5]

Over the past decade, several observational studies have reported the LDL-C levels of patients receiving lipid-lowering therapy in Portugal (Table 1). These reports indicate that LDL-C levels are above the recommended goals in most patients eligible for pharmacologic LDL-C lowering, and the rates of LDL-C control have not improved over time. An additional reason for concern is the significant number of patients eligible for LDL-C lowering therapy who are not receiving any treatment.

In this issue of the *Journal*, Meireles-Brandão et al. report the results of the ISTO study, which provides further evidence on the control of LDL-C in primary prevention patients living in Portugal.[12] ISTO is a retrospective study of 516 patients managed at a CVD risk outpatient clinic in a university hospital. Study patients had at least two CVD risk factors and were followed for at least two years between 1995 and 2015. At baseline, 75.0% of patients were over-

E-mail address: ctaguiar@gmail.com

https://doi.org/10.1016/j.repc.2022.05.001
0870-2551/© 2022 Sociedade Portuguesa de Cardiologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Table 1 Observational studies reporting total cholesterol and/or low-density lipoprotein cholesterol levels achieved with lipid-lowering therapy in Portugal.

Study	Study population	Results
VALSIM[6]	16 856 patients followed by 719 primary care physicians, 2006-2007	12.8% of statin-treated patients had both total cholesterol ≤175 mg/dl and LDL-C<100 mg/dl
DYSIS-Portugal[7]	916 patients, age ≥45 years, on statin treatment, 2008-2009	37.1% of the (very) high CVD risk subgroup of patients had LDL-C<100 mg/dl
DISGEN-LIPID[8]	368 patients, age ≥40 years, on lipid-lowering therapy, 2014-2015	46.7% of patients with either diabetes or established CVD had LDL-C<70 mg/dl
EUROASPIRE V[9]	295 patients, age <80 years, with history of coronary revascularization or acute coronary syndrome, 2016-2017	30.1% of patients had LDL-C<70 mg/dl
PRECISE[10]	2848 hypertensive patients followed by primary care physicians (1612 on lipid-lowering therapy)	37.7% of patients on lipid-lowering therapy had total cholesterol<190 mg/dl
Araújo et al.[11]	1314 very high CVD risk patients admitted to a cardiology department (871 on lipid-lowering therapy), 2011/2012 and 2016/2017	24.4% of patients had LDL-C<70 mg/dl

CVD: cardiovascular disease; LDL-C: low-density lipoprotein cholesterol.

weight or obese, 71.9% were not regularly physically active, 63.8% had a history of hypertension, 30.6% had diabetes, and 13.0% were current smokers. Moderate-intensity statin therapy was prescribed for 91.5% of patients at baseline and intended to be maintained throughout follow-up. At a median follow-up of 11 years, median LDL-C levels had improved significantly, from 172 mg/dl at baseline to 92 mg/dl at last follow-up. This change was associated with significant reductions in both median carotid intima-media thickness and CVD risk at last follow-up. Nevertheless, since most patients had high CVD risk at baseline (according to the Framingham risk score or the ASCVD risk estimator) and considering the wide range of LDL-C levels at last follow-up, from 37 mg/dl to 211 mg/dl, it seems reasonable to conclude that most patients had not achieved currently recommended LDL-C goals at last follow-up.

The findings of the ISTO study, like previous studies performed in Portugal, are not surprising. Most of the patients receiving lipid-lowering therapy in these studies were on moderate-intensity statin therapy and very few were taking ezetimibe. Taking a statin is certainly not enough to prevent avoidable atherosclerotic CVD. Optimal lowering of LDL-C is not achieved in most patients initiated on statin monotherapy, and these patients will experience significantly increased risk of future CVD, whether or not established CVD is present at baseline.[13,14]

Now is the time to step out of the comfort zone, to fight treatment inertia and realize the full potential of the benefits of LDL-C reduction in patients at high or very high CVD risk, by combining statin therapy with ezetimibe and/or other LDL-C lowering therapies such as bempedoic acid and PCSK9 inhibitors as needed to achieve the recommended LDL-C goal.

''Great things never came from comfort zones.'' (Neil Strauss)

Conflicts of interest

The author declares having received honoraria for consultancy and/or lectures from Amgen, Daiichi-Sankyo, Medinfar, Novartis, Tecnimede, and Viatris.

References

1. Costa J, Alarcão J, Araújo F, et al. The burden of atherosclerosis in Portugal. Eur Heart J Qual Care Clin Outcomes. 2021;7:154–62.
2. Ference BA, Cannon CP, Landmesser U, et al. Reduction of low density lipoprotein-cholesterol and cardiovascular events with proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors and statins: an analysis of FOURIER, SPIRE, and the Cholesterol Treatment Trialists Collaboration. Eur Heart J. 2018;39:2540–5.
3. Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2019;39:e38–81.
4. Kohli-Lynch CN, Bellows BK, Zhang Y, et al. Cost-effectiveness of lipid-lowering treatments in young adults. J Am Coll Cardiol. 2021;78:1954–64.
5. Kohli-Lynch CN, Bellows BK, Thanassoulis G, et al. Cost-effectiveness of low-density lipoprotein cholesterol level-guided statin treatment in patients with borderline cardiovascular risk. JAMA Cardiol. 2019;4:969–77.
6. Cortez-Dias N, Martins SR, Belo A, et al., on behalf of the VALSIM Study Investigators. Characterization of lipid profile in primary health care users in Portugal. Rev Port Cardiol. 2013;32:987–96.
7. Silva PM, Cardoso SM, on behalf of the DYSIS-Portugal Study Investigators. Persistent lipid abnormalities in patients treated with statins: Portuguese results of the Dyslipidemia International Study (DYSIS). Rev Port Cardiol. 2011;30:47–63.
8. Silva PM, Aguiar C, Morais J, for the DISGEN-LIPID Study Investigators. Suboptimal lipid levels in clinical practice among Portuguese adults with dyslipidemia under lipid-lowering

therapy: data from the DISGEN-LIPID study. Rev Port Cardiol. 2019;38:559–69.
9. Kotseva K, De Backer G, De Bacquer D, et al., on behalf of the EUROASPIRE Investigators. Lifestyle and impact on cardiovascular risk factor control in coronary patients across 27 countries: Results from the European Society of Cardiology ESC-EORP EUROASPIRE V registry. Eur J Prev Cardiol. 2019;26:824–35.
10. Silva PM, Lima MJ, Neves PM, et al. Prevalence of cardiovascular risk factors and other comorbidities in patients with hypertension in Portuguese primary health care populations: the PRECISE study. Rev Port Cardiol. 2019;38:427–37.
11. Araújo PM, Nunes A, Torres S, et al. Temporal trends of lipid control in very high cardiovascular risk patients. Rev Port Cardiol. 2021;40:641–8.
12. Meireles-Brandão JA, Meireles-Brandão LR, Coelho R, et al. Long-term outcomes of primary cardiovascular prevention: a retrospective study at a referral center in Portugal. Rev Port Cardiol. 2022;41.
13. Schleyer T, Hui S, Wang J, et al. Quantifying unmet need in statin-treated hyperlipidemia patients and the potential benefit of further LDL-C reduction through an EHR-based retrospective cohort study. J Manag Care Spec Pharm. 2019;25:544–54.
14. Weng SF, Akyea RK, Man KK, et al. Determining propensity for sub-optimal low-density lipoprotein cholesterol response to statins and future risk of cardiovascular disease. PLoS One. 2021;16:e0260839.