Revista Portuguesa de Cardiologia 40 (2021) 649–651

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

EDITORIAL COMMENT

Heaven can wait. . . for lipid control in very high cardiovascular risk patients

O céu pode esperar. . . pelo controlo lipídico nos doentes de muito alto risco cardiovascular

Alberto Mello e Silva [a,b]

[a] *Sociedade Portuguesa de Aterosclerose, Portugal*
[b] *Grupo Luz Saúde, Portugal*

Available online 4 June 2021

Despite efforts to prevent cardiovascular disease (CVD), it remains a leading cause of mortality worldwide, and Portugal is no exception.[1,2] Atherosclerosis is the most common underlying pathophysiological process in CVD. More than half of the reduction in cardiovascular (CV) mortality in the last three decades has been attributed to population-level changes in CV risk factors, primarily reductions in cholesterol and blood pressure levels and smoking.

The burden of atherosclerosis, using the Global Burden of Disease methodology to quantify the economic impact of atherosclerosis in Portugal by estimating disease-related costs, concludes that atherosclerosis has a major economic impact, being responsible for health expenditure equivalent to 1% of Portuguese gross domestic product and 11% of current health expenditure in 2016, which demonstrates the persistent burden of this disease.[3]

There is a large evidence base, supported by clinical trials,[4] for the use of statins as lipid-lowering therapy (LLT) for the prevention of further cardiovascular events, and guidance is available regarding the use of cholesterol targets in long-term follow-up for secondary prevention.

In this issue of the *Journal*, Araújo et al.[5] report rates of low-density lipoprotein cholesterol (LDL-C) control according to the 2011 European Society of Cardiology guidelines for the management of dyslipidemias in patients at very high cardiovascular risk (CVR) admitted to a single cardiology center in two time periods – 2011/2012 and 2016/2017.

The study is well designed and has a representative sample. A total of 1314 patients were reviewed, of whom 443 patients (33.7%) were not under LLT. Regarding drug intensity in patients under LLT, the majority (77.6%) received medium-intensity therapy (atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg, lovastatin 40 mg, fluvastatin 80 mg or pitavastatin 2-4 mg) and only 15.8% received high-intensity therapy (atorvastatin 40-80 mg, rosuvastatin 20-40 mg or any moderate-intensity statin plus ezetimibe), although the use of high-intensity LLT increased significantly in the later years (6.4% vs. 24.0%; $p<0.001$). Overall, atorvastatin (33.5%), simvastatin (30.3%) and rosuvastatin (20.7%) were the most frequently prescribed drugs. Ezetimibe was only prescribed in a small minority of patients (1.8%) in both

E-mail address: amelloesilva@gmail.com

https://doi.org/10.1016/j.repc.2021.05.004

periods (p=0.496). In conclusion, the temporal trends of lipid control in very high CVR patients admitted to this single cardiology center in two time periods – 2011/2012 and 2016/2017 – confirm that LLT prescription only improved slightly, while attainment of adequate lipid control rates remained unchanged and achievement of LDL-C goals was unsatisfactory. Additionally, the prescription rates of dual therapy with a statin and ezetimibe in this study was only marginal, even in the more recent period, and were considerably lower than in other studies.

As acknowledged by the authors, it is a reason for considerable concern that a third of patients were not under LLT, despite recognition that this group of patients at very high CVR derive the most benefit from LLT in the prevention of CV events and considering that the majority (68.3%) had prior documented CVD.

Similar studies in Portugal and other European countries[6–8] have also shown comparably poor lipid control in patients at very high CVR. The recent publication of the EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care (DA VINCI) study,[9] designed to provide contemporary information regarding LDL-C goal attainment for patients across Europe in diverse healthcare settings and previously understudied patient groups, demonstrated that among patients receiving LLT, fewer than half of high/very high-risk primary and secondary prevention patients achieved the 2016 LDL-C goals, with approximately one-fifth achieving the lower 2019 goals.

The availability of generic statins led to reductions in the cost of statin therapy during the course of the study, which were far more significant than the corresponding increase in statin use, and the same phenomenon has been noted with generic ezetimibe.[10]

Secondary non-adherence (stopping or taking a medication differently than prescribed) is a recognized problem.[11,12]

How can evidence-based CV risk prevention be improved, removing barriers to implementation of the national and European cardiovascular disease prevention guidelines?

Physicians and patients face numerous barriers when it comes to prescribing and adhering to statin therapy. From the physician's perspective this includes LDL thresholds with failure to titrate, underuse of combination therapy with LLT other than statins, and conflicting clinical guidelines. From the patient's perspective, fear of side effects or negative previous experiences with medication or simply unwillingness to take additional medications, are important issues to deal with. Additional barriers include mistrust of the pharmaceutical industry and inadequate communication skills on the part of both physicians and patients.

Different people need different information. Risk-based intervention strategies as a function of total CV risk and LDL levels need to be explained clearly. The ultimate goal of treatment, including LLT, is not to obtain good numbers in blood tests, but to prevent CV events.

Shared decision-making is important in the management of patients with dyslipidemia in order to optimize LLT and to reduce CV risk, improving patient outcomes.

What matters for CV risk reduction is the absolute reduction in LDL-C and the duration of that reduction, hence the concept of cumulative exposure to time-averaged LDL-C, which is a function of adherence (patients) and the treatment intensity prescribed (physicians).[13]

In this context, changing the paradigm from intensive statin monotherapy toward intensive lipid-lowering regimens using combination therapy with non-statin LLT and individualized care is one important approach to achieve the targets for patients at highest risk.[9,10] In the DA VINCI registry, use of combination therapy with ezetimibe or a PCSK9 inhibitor was low at 9% and 1%, respectively.[9]

The 2019 European guidelines,[14] which lowered the LDL-C target to less than 55 mg/dl (1.4 mmol/l) for very high risk patients, strongly recommended identifying patients at high or very high risk and putting them on more aggressive LLT. Gaps between clinical guidelines and clinical practice for lipid management persist and will be widened by the 2019 guidelines.

The need for risk management in secondary prevention, which encompasses coronary heart disease, stroke and peripheral arterial disease, is clear, and optimal treatment of plasma lipids within the secondary prevention population is key to reducing the increasing burden of CVD in society. Even with optimized statins, greater use of non-statin LLT is likely needed to reduce these gaps for patients at highest risk, but there is still a long way to go to obtain the maximum possible health benefits from LLT.

Last but not least, medications only work if patients take them.

Conflicts of interest

Dr. Alberto Mello e Silva has received consultancy and speaker fees from Bayer, Daiichi-Sankyo, Menarini, Mylan, Novartis, Servier and Tecnimede.

References

1. World Health Organization. The top 10 causes of death; 2018. Available from: https://www.who.int/news-room/fact-sheets/detail/ the top-10-causes-of-death.
2. Pereira M, Azevedo A, Lunet N, et al. Explaining the decline in coronary heart disease mortality in Portugal between 1995 and 2008. Circ Cardiovasc Qual Outcomes. 2013;6:634–42.
3. Costa J, Alarcão J, Araújo F, et al. The burden of atherosclerosis in Portugal. Eur Heart J Qual Care Clin Outcomes. 2020:1–9, http://dx.doi.org/10.1093/ehjqcco/qcaa060.
4. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376:1670.
5. Araújo PM, Nunes A, Torres S, et al. Temporal trends of lipid control in very high cardiovascular risk patients. Rev Port Cardio. 2021;40.
6. Silva PM, Cardoso SM. Anomalias lipídicas persistentes em doentes tratados com estatinas: resultados portugueses do estudo internacional de dislipidemia (DYSIS). Rev Port Cardiol. 2011;30:47–63.
7. Silva PM, Aguiar C, Morais J. 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.
8. Kotseva K, De Backer G, De Bacquer D, et al. 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.
9. Ray KK, Molemans B, Schoonen WM, et al. DA VINCI study EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study. Eur J Prev Cardiol. 2020, http://dx.doi.org/10.1093/eurjpc/zwaa047.
10. Banach M, Penson PE. Statins and LDL-C in secondary prevention—so much progress so far to go. JAMA Netw Open. 2020;3, http://dx.doi.org/10.1001/jamanetworkopen.2020.25675, e2025675.
11. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation. 2009;119:3028–35.
12. Kini V, Ho PM. Interventions to improve medication adherence: a review. JAMA. 2018;320:2461–73.
13. Brandts J, Ray KK. Low density lipoprotein cholesterol-lowering strategies and population health: time to move to a cumulative exposure model. Circulation. 2020;141:873–6.
14. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019:1–78.