

Editorial

Primary prevention. The cornerstone to reduce the burden of cardiovascular disease

Prevención primaria. La piedra angular para reducir la carga de la enfermedad cardiovascular

Vivencio Barrios,^{a,*} Carlos Escobar,^b and Maciej Banach^{c,d}^a Servicio de Cardiología, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Madrid, Spain^b Servicio de Cardiología, Hospital Universitario La Paz, Madrid, Spain^c Department of Hypertension, Medical University of Lodz (MUL), Lodz, Poland^d Department of Medicine, University of Zielona Góra, Zielona Góra, Poland

Article history:

Available online 1 June 2021

Hypercholesterolemia is not only a major, independent cardiovascular (CV) risk factor, but is also the underlying cause of atherosclerosis.¹ Atherosclerosis is a progressive vascular process that usually starts in childhood. It is related to many factors of different etiology, such as genetics, environment, lifestyle habits, metabolic alterations, risk factors, and underlying conditions. Therefore, the occurrence of CV disease outcomes depends not only on lifestyle, or the concomitance of other risk factors, but importantly, on exposure to high cholesterol levels throughout life.^{2,3} Since the atherosclerotic process slows or even regresses when low-density lipoprotein cholesterol (LDLc) levels are below 55 mg/dL,⁴ early intervention seems mandatory for all risk groups to reduce CV burden through LDLc reduction with lipid-lowering therapy.² Based on this evidence, we should now follow not only the approach of “the lower, the better”, and “the longer, the better”, but additionally “the earlier [on LDLc target], the better”.⁵ Notably, in primary prevention patients, this is true not only for the middle-aged population, but also for younger people and elderly persons.^{2,6,7}

For patients with no established atherosclerotic CV disease, current European guidelines recommend lifestyle intervention and considering the addition of lipid-lowering drugs if LDLc is ≥ 116 mg/dL, ≥ 100 mg/dL, ≥ 70 mg/dL, and ≥ 55 mg/dL, for low, moderate, high, and very high-risk patients, respectively. However, immediate lipid-lowering therapy in addition to lifestyle intervention is recommended if LDLc ≥ 190 mg/dL (at least moderate-risk patients), ≥ 100 mg/dL (high-risk patients), ≥ 70 mg/dL (primary prevention very high-risk patients), and ≥ 55 mg/dL (secondary prevention very high-risk patients).¹ In addition, when lipid lowering drugs are required, the European guidelines recommend a stepwise approach, starting with statins up to the highest tolerated dose to reach the goals established for the specific CV risk (IA). If LDLc targets are not attained, a combination with ezetimibe is recommended (IB). With regard to proprotein convertase subtilisin/kexane 9 (PCSK9) inhibitors, these drugs may be considered if targets are not attained for primary prevention patients at very high risk, but without familial hypercholesterolemia (IIBc), and are recommended in very high-risk familial hypercholesterolemia patients (IC).¹ Compared

with the 2016 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines, the application of current guidelines could even double the number of persons eligible for primary prevention with statins, due to the lower LDLc goals and population aging, leading to an improvement of atherosclerotic CV disease prevention.⁸ This is especially important, because in many European countries most of these patients still have LDLc levels above the recommended targets.⁹ Unfortunately, many patients in primary prevention do not achieve LDLc goals.⁹ This is clinically very relevant, as real-life data have recently shown that even in patients at high risk of CV disease, a substantial proportion do not receive the appropriate lipid-lowering therapies for primary prevention, leading to the development of CV events.¹⁰ Therefore, it is important not only to improve medical education for both physicians and patients, in order to reduce the gap between guideline recommendations and clinical practice, but also to provide simple tools that aid the implementation of guidelines.^{1,2} Nevertheless, one of the reasons for the insufficient implementation of lipid-lowering therapies for primary prevention is that guideline recommendations look too rigid and may not be very pragmatic in some circumstances when time could be crucial (the earlier, the better!).² As a result, a more practical and easy approach is warranted to complement guideline recommendations and facilitate rapid and efficient achievement of goals. The first attempt at this was presented last year by members of the International Lipid Expert Panel.⁵ Interestingly, in secondary prevention, it has been observed that application of specific algorithms for patients admitted for an acute coronary syndrome (ACS) improved the proportion of patients who achieved LDLc goals in France.¹¹ The new algorithms, recommending the need for immediate combination therapy for ACS patients, have also recently been proposed by the International Lipid Expert Panel within the ACS EuroPath Central & South European Countries Project.⁵ Similarly, in Spain, the Spanish Society of Cardiology has proposed 3 simple and feasible decision-making algorithms that include most clinical scenarios among patients with ischemic heart disease (ie, acute and chronic patients), with the aim of achieving therapeutic LDLc goals as soon as possible.¹² In addition, a web application has been created to aid their implementation.¹³ Moreover, the usefulness of the application of these algorithms in daily clinical practice is currently being validated in a study.

Considering that in primary prevention, most patients do not achieve recommended targets and the difficulties of applying

* Corresponding author: Servicio de Cardiología, Hospital Universitario Ramón y Cajal, Ctra. Colmenar Km 9,100, 28034 Madrid, Spain.

E-mail address: vivenciobarrios@gmail.com (V. Barrios).

guidelines in routine practice, in a recent consensus document published in *REC CardioClinics*¹⁴ the Spanish Society of Cardiology has proposed 4 simple and feasible decision-making algorithms according to CV risk (low, moderate, high, and very high), with the aim of achieving LDLc goals in most primary prevention patients rapidly and efficiently.

This consensus document contains important novelties and some substantial differences compared with the European guidelines. Thus, although in this consensus 4 CV risk strata are included, as in the European guidelines, new clinical profiles have been introduced, such as moderate chronic kidney disease with albuminuria (high CV risk), significant subclinical vascular disease in coronary and carotid territories (high CV risk), hypertension with target organ damage (high CV risk), lipoprotein (a) \geq 180 mg/dL and at least 1 CV risk factor (high CV risk), and men > 55 years or women > 60 years without other CV risk factors (moderate CV risk). In addition, the document includes a number of factors that modulate risk, which should be considered in low to high CV risk, such as up-titrating CV risk in persons with 1 or more of these factors.¹⁴

As in the secondary prevention consensus of the Spanish Society of Cardiology, the document includes a table with the different lipid-lowering drugs in monotherapy or in combination and their ability to reduce LDLc levels. Of note, in addition to statins, ezetimibe and PCSK9 inhibitors, alone or in combination, nutraceuticals with demonstrated efficacy in clinical trials¹⁵ and bempedoic acid¹⁶ have also been added as they could represent a good choice for some patients.¹⁴

Finally, 4 simple algorithms according to CV risk were created. In this consensus document, LDLc goals are the same as those proposed by the European guidelines (< 55 mg/dL, < 70 mg/dL, < 100 mg/dL and < 116 mg/dL for very high, high, moderate, and low CV risk, respectively). In the very high-risk and high-risk algorithms, the prior use of statins and if they are prescribed at maximal tolerated doses should be considered. Of note, in contrast to the step-by-step approach, in some cases, the combination of a high-intensity statin plus ezetimibe is recommended as a first therapeutic choice. With regard to PCSK9 inhibitors, although the ESC/EAS guidelines do not recommend treatment with these drugs in high CV risk primary prevention patients,¹ the authors of the document considered that some patients could potentially benefit from this therapy, although economic considerations should be taken into account. In the moderate- and low-risk algorithms, lifestyle changes and their impact on LDLc levels should be strongly recommended.¹⁴

In summary, the consensus document of the Spanish Society of Cardiology to improve lipid management in primary prevention patients seems to be a good alternative that complements the recommendations of the European guidelines and may be very helpful to reduce the gap between guidelines and clinical practice and avoid clinical inertia.

FUNDING

The authors received no funding for the preparation of this editorial; however, the original consensus document by Barrios

et al.¹⁴ referred to in the present editorial was drafted with an unconditional grant from Almirall and Mylan (now Viatris).

CONFLICTS OF INTEREST

V. Barrios reports personal fees from Almirall, Amgen, Daiichi-Sankyo, Ferrer, Mylan, MSD, Novartis, Sanofi, and Servier, outside the submitted work. C. Escobar reports personal fees from Amgen, Daiichi-Sbkyi, Ferrer, MSD, Mylan, Novartis, Sanofi, and Servier outside the submitted work. M. Banach reports fees from Amgen, Daiichi-Sankyo, Esperion, Freia Pharmaceuticals, Polfarmex, Her-bapol, Kogen, KRKA, Mylan/Viatris, Novartis, Novo-Nordisk, Polpharma, Sanofi-Aventis, Servier Valeant, and Zentiva outside the submitted work.

REFERENCES

- 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*. 2020;41:111–188.
- Penson PE, Pirro M, Banach M. LDL-C: lower is better for longer—even at low risk. *BMC Med*. 2020;18:320.
- Gidding SS, Allen NB. Cholesterol and Atherosclerotic Cardiovascular Disease: A Lifelong Problem. *J Am Heart Assoc*. 2019;8:e012924.
- Roberts WC. Quantitative Extent of Atherosclerotic Plaque in the Major Epicardial Coronary Arteries in Patients with Fatal Coronary Heart Disease, in Coronary Endarterectomy Specimens, in Aorta-Coronary Saphenous Venous Conduits, and Means to Prevent the Plaques: A Review after Studying the Coronary Arteries for 50 Years. *Am J Cardiol*. 2018;121:1413–1435.
- Banach M, Penson PE, Vrablik M, et al. ACS EuroPath Central & South European Countries Project. Optimal use of lipid-lowering therapy after acute coronary syndromes: A Position Paper endorsed by the International Lipid Expert Panel (ILEP). *Pharmacol Res*. 2021;166:105499.
- Kostis JB, Giakoumis M, Zinonos S, Cabrera J, Kostis WJ. Meta-analysis of Usefulness of Treatment of Hypercholesterolemia with Statins For Primary Prevention in Patients Older Than 75 Years. *Am J Cardiol*. 2020;125:1154–1157.
- Kaneko H, Itoh H, Kiriyama H, et al. Lipid Profile and Subsequent Cardiovascular Disease among Young Adults Aged < 50 Years. *Am J Cardiol*. 2021;142:59–65.
- Mortensen MB, Nordestgaard BG. 2019 vs. 2016 ESC/EAS statin guidelines for primary prevention of atherosclerotic cardiovascular disease. *Eur Heart J*. 2020;41:3005–3015.
- Ray KK, Molemans B, Schoonen WM, et al. 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. zwaa047.
- Gaviria-Mendoza A, Zapata-Carmona JA, Restrepo-Bastidas AA, Betancur-Pulgarín CL, Machado-Alba JE. Prior Use of Medication for Primary Prevention in Patients with Coronary Syndrome. *J Prim Care Community Health*. 2020;11:2150132720946949.
- Buonvino C, Chopard R, Guillon B, et al. An innovative lipid-lowering approach to enhance attainment of low-density lipoprotein cholesterol goals. *Eur Heart J Acute Cardiovasc Care*. 2020;9:879–887.
- Escobar C, Anguita M, Arrarte V, et al. Recommendations to improve lipid control. Consensus document of the Spanish Society of Cardiology. *Rev Esp Cardiol*. 2020;73:161–167.
- Control lipídico* [Computer software]. Version 1.0. Madrid: Sociedad Española de Cardiología; 2020. Available at: <https://control-lipidico.app/>. Accessed 22 Apr 2021.
- Barrios V, Escobar C, Anguita M, et al. Recommendations to improve lipid control in primary prevention patients. A consensus document of the Spanish Society of Cardiology. *REC CardioClinics*. 2021. <http://doi.org/10.1016/j.rcccl.2021.05.002>.
- Cicero AFG, Colletti A, Bajraktari G, et al. Lipid-lowering nutraceuticals in clinical practice: position paper from an International Lipid Expert Panel. *Nutr Rev*. 2017;75:731–767.
- Banach M, Duell PB, Gotto Jr AM et al. Association of Bempedoic Acid Administration With Atherogenic Lipid Levels in Phase 3 Randomized Clinical Trials of Patients With Hypercholesterolemia. *JAMA Cardiol*. 2020;5:1–12.