

## 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

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Hypercholesterolemia is not only a major, independent cardiovascular (CV) risk factor, but is also the underlying cause of atherosclerosis.<sup>1</sup> 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.<sup>2,3</sup> Since the atherosclerotic process slows or even regresses when low-density lipoprotein cholesterol (LDLc) levels are below 55 mg/dL,<sup>4</sup> early intervention seems mandatory for all risk groups to reduce CV burden through LDLc reduction with lipid-lowering therapy.<sup>2</sup> 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”.<sup>5</sup> Notably, in primary prevention patients, this is true not only for the middle-aged population, but also for younger people and elderly persons.<sup>2,6,7</sup>

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  $\geq 116$  mg/dL,  $\geq 100$  mg/dL,  $\geq 70$  mg/dL, and  $\geq 55$  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  $\geq 190$  mg/dL (at least moderate-risk patients),  $\geq 100$  mg/dL (high-risk patients),  $\geq 70$  mg/dL (primary prevention very high-risk patients), and  $\geq 55$  mg/dL (secondary prevention very high-risk patients).<sup>1</sup> 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).<sup>1</sup> 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.<sup>8</sup> This is especially important, because in many European countries most of these patients still have LDLc levels above the recommended targets.<sup>9</sup> Unfortunately, many patients in primary prevention do not achieve LDLc goals.<sup>9</sup> 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.<sup>10</sup> 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.<sup>1,2</sup> 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!).<sup>2</sup> 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.<sup>5</sup> 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.<sup>11</sup> 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.<sup>5</sup> 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.<sup>12</sup> In addition, a web application has been created to aid their implementation.<sup>13</sup> 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

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guidelines in routine practice, in a recent consensus document published in *REC CardioClinics*<sup>14</sup> 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.<sup>14</sup>

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 trials<sup>15</sup> and bempedoic acid<sup>16</sup> have also been added as they could represent a good choice for some patients.<sup>14</sup>

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,<sup>1</sup> 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.<sup>14</sup>

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.

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