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EDITORIAL

Warning: a short circuit has been detected in the prescription of PCSK9 inhibitors☆

Peligro: se ha detectado un cortocircuito en la prescripción de los inhibidores de PCSK9

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Pathophysiological awareness of atherosclerosis has been continuously progressing and is increasingly more accurate.[1] The pillars of cardiovascular health include giving up smoking or not smoking at all; having a healthy heart diet; weight control; carrying out regular physical exercise; controlling stress, and having periodical check-ups for blood pressure, glycaemia and cholesterol. These seemingly simple steps are often ignored by the person affected and on no few occasions underestimated by healthcare professionals. This simple fact may explain, at least partially, why we are facing a CVD epidemic in our daily practice. As a result, it is easy to understand the concept of preventative interventions that reduce the risk of cardiovascular disease (CVD) but it is difficult to implement them in clinical practice.

Clinical practice guidelines are a set of recommendations based on the systematic review of evidence and on the evaluation of the risks/benefits of different alternatives for optimising patient healthcare. If we apply this to the control of dyslipidaemias we have to take it for granted that therapeutic objectives in low density lipoprotein (LDL) cholesterol recommended by the joint 2019 guideline of the *European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS)*[2] are obtainable with the available lipid lowering tools for effective cardiovascular disease prevention. However, different national[3] and international[4] studies repeatedly show an unacceptable low rate of achievement of therapeutic objectives in LDL cholesterol, particularly in patients with high/very high cardiovascular risk, making them one of the main goals of cardiovascular medicine.

Regarding control of dyslipidaemia and cardiovascular risk in healthcare practice, there are three clinical situations where this is more difficult or where ultimately a greater therapeutic effort is required to achieve LDL cholesterol targets. These are: patients with intolerance to statins; patients with very high levels of LDL cholesterol, such as cases of familial hypercholesterolaemia syndrome, and those who require extremely major LDL cholesterol reduction, such as patients with very high vascular risk.

Patients with established CVD are considered very high cardiovascular risk, and the 2019 European guideline for control of dyslipidaemias[2] therefore recommends an LDL cholesterol < 55 mg/dL with a ≥ 50% reduction compared with baseline, as its therapeutic objective, supported by the findings from the IMPROVE-IT[5], FOURIER[6] and ODISSEY[7] studies. Furthermore, this evidence points towards changing the terminology of the use of high-intensity statins for high-intensity cholesterol-lowering therapy[8] and later for optimised lipid-lowering therapy, a term coined by the *Spanish Society of Atherosclerosis (SEA for its initials in Spanish)*[9] which theoretically would lead to a reduction of at least 50% LDL cholesterol with an 80% adherence. We know that the main barrier in this clinical setting continues to be the lack of achievement of therapeutic goals in LDL cholesterol, resulting from under-treatment. There are different reasons as to why treatment is insufficient, but ultimately, in very high risk patients we cannot repeat enough times that the physician should plan the lipid-lower therapeutic strategy based on two parameters: the targeted LDL cholesterol according to the patient's cardiovascular risk and the required percentile reduction required for choosing the best pharmacological treatment to ensure the desired objective is reached. It has been reported that prior therapeutic planning through the use of target-oriented cholesterol-lowering therapy tables,[10] or the use of computerised tools incorporated into the medical history[11] or the application of therapeutic algorithms[12] significantly boost the rate of achievement

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of therapeutic objectives, particularly in patients with very high cardiovascular risk.[13]

Furthermore, using any therapeutic strategy in cardiovascular prevention must be based on three elements: the benefit obtained, the adverse effects and the economic, social and personal intervention efforts.[14] On certain occasions, either due to price, side effects or the additional effort not accepted by the system or the individual, including, for example, a change to lifestyle in the treatment of obesity,[15] an effective treatment may have very little success because of the therapeutic effort it requires. In this regard, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are very powerful, efficient, effective, lipid-lowering drugs, with an excellent safety profile and highly accepted by patients, but which for the time being we are only able to use in the higher cardiovascular risk patients with unacceptable LDL cholesterol levels. The SEA has recently proposed several prescription indications for PCSK9 inhibitors, assessing the number of patients needed to treat (NNT) to avoid a cardiovascular episode and therefore the absolute patient risk, the absolute drop in LDL cholesterol to be reached, the type of intervention planned and the baseline LDL cholesterol level prior to the therapeutic intensification.[9] In keeping with the cost of other accepted interventions in Spain, all NNT at 5 years, < 25 was established as cost-effective and therefore indicatable.

The reality is that these new lipid-lowering therapies are underused,[4] and simulation studies are available which show that, for example, within 90 days after an acute coronary syndrome, over a third of patients would be potentially eligible for PCSK9 inhibitors,[16] or that, even with the use of high-intensity statins to the maximum tolerated dose and ezetimibe, around half of the patients with myocardial infarction would be eligible for treatment with PCSK9 inhibitors, in keeping with the 2019 ESC/EAS[17] guidelines.

In Spain, there are major limitations to the prescription of PCSK9 inhibitors from an administrative viewpoint and due to prescription restrictions. The butterfly effect project[18] demonstrated a highly diverse usage profile in the different autonomous communities with the use of PCSK9 inhibitors being most extensive in the hospitals and areas with lipid units accredited by the SEA, and those without specific prescription control commissions. Furthermore, 78% of respondents said they had moderate or severe difficulties in prescribing PCSK9 inhibitors in their hospital centres. This is a relevant fact, given that there is an inverse relationship between difficulty and the number of prescriptions.

In this edition of *Clínica e Investigación en Arteriosclerosis*, Barrios et al.[19] presented an analysis of the PCSK9 inhibitor prescription process in cardiology departments (IKIGAI study). A national representative sample revealed the under-usage of PCSK9 inhibitors, and among the main reasons from participants were that requests were not in keeping with the therapeutic positioning report (TPR) (52%); there was a lack of detection in patients /lack of time (47%); situations in which denial was foreseen (36%), or they were only used in those patients where they were very sure of the diagnosis (27%). Based on these results, the authors are putting forward proposals for improvement, among which are optimisation of the hospital discharge report and simplification of the application/approval forms. Given that the updating of the TPR of PCSK9 inhibitors should be considered a major breakthrough in the rational use of these drugs,[9] it would be positive if there was greater dissemination of the actual recommendations of the Spanish Society of Cardiology[20] among its members to achieve a higher penetration rate.

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