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EDITORIAL

Cost-effectiveness evaluation of the use of PCSK9 inhibitors☆

Evaluación del coste-efectividad de la utilización de los inhibidores de PCSK9

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The information accumulated over recent decades thanks to multiple studies in the fields of epidemiology, genetics, cell biology and research in animal models has shown cholesterol transported in low-density lipoproteins (LDL-C) to be one of the main aetiological agents of atherosclerotic cardiovascular disease (ACVD).[1] The large randomised clinical trials (RCTs) with statins in primary and secondary prevention and the more recent IMPROVE-IT with ezetimibe[2] and FOURIER,[3] SPIRE[4] and ODYSSEY OUTCOMES[5] trials with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have provided us with enormous amounts of information on the possibilities, but also on the limitations, of lipid-lowering treatment in cardiovascular prevention. The consistency of the results makes the reduction of LDL-C in large groups of the population at risk of developing ACVD essential, and clear guidelines are indispensable for supporting healthcare professionals when it comes to defining who, when and how to treat.

The interpretation of the RCT results is relatively straightforward. However, their practical application is more difficult, as demonstrated by the differences in criteria of the recommendations of the main national and international scientific societies and, especially, in the indications of PCSK9 inhibitors (PCSK9i).[6,7]

We believe the way we use lipid-lowering drugs today must be changed. Most recommendations are based on the achievement of LDL-C goals, which overlooks the fact that any figure is arbitrary and that the therapeutic effort required to obtain a certain goal is a key factor when indicating a treatment.

The indication of any treatment, and especially of those treatments for prevalent risk factors, aimed at prevention and in many cases in asymptomatic patients, should be based on three factors: benefit obtained from the intervention; adverse effects of the intervention; and the financial, social and personal effort involved in the intervention. An intervention such as low-priced moderately potent statins, for example simvastatin, meets all the requirements: it is effective, with few side effects, it is very cost-effective due to the low price of the medication, it is easy to implement in most health systems with their current structures without additional costs, and it promises easy compliance by a well-informed population. However, not all effective treatments

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have this profile. Sometimes due to price, side effects or extra effort not taken on by the system or by the individual, an effective treatment, such as a change in lifestyle in the treatment of obesity and dyslipidaemia, has very poor success due to the therapeutic effort it requires.[8]

For this reason, interventions should be stratified according to much more pragmatic criteria, making a shift regarding two key concepts: the NNT (the number of patients needed to treat to avoid an event); and whether the effort required to achieve it is worth it from a financial standpoint.

In the treatment of hypercholesterolaemia in cardiovascular prevention, the following evidence is currently available:

- The benefit is primarily dependent on the reduction of LDL-C.[1]
- The benefit is not dependent on the type of drug or the mechanism that drug uses to reduce LDL-C.[9]
- The magnitude of the benefit at five years can be calculated precisely thanks to the work of the collaboration known as CTT (Cholesterol Treatment Trialists), as we know that every 38.7 mg/dl decrease in LDL-C gives rise to a 21% reduction in cardiovascular events.[10]
- The relative benefit in reduction of events is independent of baseline cardiovascular risk and LDL-C concentration if it is greater than 50-70 mg/dl.[10]
- There is no threshold where the benefit of lowering LDL-C to at least 25 mg/dl disappears.[3–5] The lower the LDL-C, the greater the clinical benefit.
- The three pharmacological groups with strong evidence in reducing events – statins, ezetimibe and anti-PCSK9 monoclonal antibodies – are well tolerated by most patients and the frequency of side effects is not substantially different from placebo. The safety information is very strong in the long term for statins, sufficient for ezetimibe and limited to five years for PCSK9i.
- Treatment compliance in the three groups is similar, with drug withdrawals in clinical trials of less than 5% per year.
- The NNT for each drug depends on the absolute risk of the patient to be treated, the absolute decrease in LDL-C achieved by the drug and the baseline LDL-C concentration prior to treatment.
- The effort of an intervention depends on the NNT of the intervention to avoid an event and the cost of its application.
- Each health system must decide on the resources it wants or can afford in order to avoid an event.

In 2019, the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) published their recommendations for the treatment of dyslipidaemia with two main threads: understanding the cardiovascular risk of the patient to be treated; and establishing an LDL-C target for each individual patient according to their calculated risk.[7] The document classifies a significant group of patients as very high risk, which includes: the entire population with clinical or subclinical ACVD; any patient with familial hypercholesterolaemia and ACVD or with a cardiovascular risk factor; subjects with a 10-year SCORE risk >10%; patients with GFR < 30 ml/min; or patients with diabetes with target organ involvement, or >2 risk factors, or type 1 diabetes lasting >20 years. This means that in those subjects in whom the risk must be precisely stratified in order to be efficient, the document integrates them into a single group, assigns them an LDL-C target <55 mg/dl and recommends using PCSK9i when it is not achieved with high potency statins and ezetimibe. The ESC/EAS recommendations leave out essential aspects such as the cost of the intervention and the NNT, which may make them unaffordable with current drug prices and the structure of health systems in most countries.[11,12]

In 2018, recommendations from different US societies involved in cardiovascular risk were published,[6] which included a much more moderate indication of PCSK9i. In primary prevention, they are only considered to have a IIb recommendation (may be considered), in subjects with heterozygous familial hypercholesterolaemia between 40–75 years of age with LDL-C concentrations >100 mg/dl after the maximum tolerated dose of potent statins and ezetimibe. In secondary prevention, they have a IIa recommendation (should be considered), and are indicated in very high-risk subjects, with LDL-C >70 mg/dl after the maximum tolerated dose of a potent statin and ezetimibe. But the definition of very high risk limits them to subjects with recurrent ACVD, or those with a single episode but with multiple cardiovascular risk factors.

At the Sociedad Española de Arteriosclerosis [Spanish Society of Arteriosclerosis], we have recently proposed some prescription indications for PCSK9i based on evaluating the NNT and therefore the absolute risk of the patient to be treated, the absolute decrease in LDL-C that we are going to achieve, the type of intervention that we are considering and the baseline LDL-C concentration prior to treatment intensification.[13] According to the cost of other accepted interventions in Spain, we established all those NNT for five years below 25 as cost-effective and, therefore, eligible for indication. This implies a figure <100,000 euros per quality-adjusted life year [QALY] gained and an incremental cost-effectiveness ratio (ICER) <3 times the Spanish per capita income. To calculate the NNT, we used the benefit in absolute terms of the data from the ODYSSEY OUTCOMES, FOURIER and SPIRE clinical trials, as well as the sub-analyses of the results of these studies in the different subgroups that have been published, extrapolating the results to five years. It is evident that the strategy proposed by the American scientific societies is close to this NNT but the European guidelines are hard to afford with the current price of PCSK9i and have been demonstrated not to be cost-effective. According to this analysis, PCSK9i would be cost-effective in secondary prevention in subjects with stable disease if their LDL-C remains >130 mg/dl; in the presence of diabetes with any risk factor, or subjects without diabetes with >2 risk factors, or after acute coronary syndrome of less than one year of evolution if LDL-C >100 mg/dl; and above 70 mg/dl in recurrent or multivessel disease, elevated lipoprotein(a) (>50 mg/dl), acute coronary syndrome of less than one year of evolution with diabetes, or chronic kidney disease with any additional risk factor.[14–16] In subjects with familial hypercholesterolaemia, PCSK9i would be cost-effective with LDL-C >160 mg/dl in the absence of significant risk factors, >130 mg/dl in the presence of multiple risk factors; >100 mg/dl with associated diabetes; or >70 mg/dl if in secondary prevention. Our analysis also demonstrated that PCSK9i would be cost-effective in sub-

jects in primary prevention with diabetes and chronic kidney disease (glomerular filtration rate (GFR) <60 ml/min) with LDL-C >130 mg/dl, although this assumption is not included in the funding requirements of the Spanish National Health System.

The lower the LDL-C, the better the cardiovascular prevention, but not at any cost. PCSK9 inhibition is a very powerful, efficient, effective and safe lipid-lowering tool, with hardly any side effects and it is very well accepted by patients, so it is unfortunate, at least for the moment, that we cannot use it in every patient who could benefit from it in order to be efficient. It is only patients with a higher cardiovascular risk and with unacceptable LDL-C concentrations who are currently eligible for to these drugs, but we have no doubt that they have a promising future and that their indications will be expanded in the coming years.

Conflicts of interest

FC and JP-B declare that they have received fees for scientific advice and conferences from Sanofi and Amgen.

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