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POINT OF VIEW

Results of the REVEAL study. Why should we not welcome a new lipid-lowering agent?☆

Resultados del estudio REVEAL. ¿Por qué no debemos dar la bienvenida a un nuevo agente hipolipemiante?

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The 'Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification study' (REVEAL)[1] has shown that anacetrapib, administered in combination with statins in patients with cardiovascular disease and very well controlled low-density lipoprotein (LDL) cholesterol levels according to standard parameters, helps to significantly reduce new cardiovascular episodes in this population. Moreover, the reduction in events coincides with the regression line of the Cholesterol treatment trialists' (CTT) collaboration. The study was conducted according to all the principles of good clinical practice and the scientific evidence. Why then, given this good news, should we have misgivings about incorporating a new tool into the arsenal of lipid-lowering drugs now available?

The answer to this question has several elements. The past history of other cholesteryl ester transfer protein (CETP) inhibitors weighs heavily on the minds of clinicians. Neither torcetrapib, nor dalcetrapib, nor evacetrapib, in the Illuminate, Dal-outcomes and Accelerate trials, respectively, achieved significant reductions in cardiovascular events.[2–4] Furthermore, although the effects of dalcetrapib and evacetrapib were neutral, torcetrapib increased mortality by 25%, which was attributed to effects associated solely with the molecular structure of the drug. Given that anacetrapib seems to be the only molecule in this class associated with a beneficial cardiovascular impact, we need to ask: Is anacetrapib a safe drug? What are its ultimate mechanisms of action?

The REVEAL study shows that, yes, anacetrapib is a drug with a good safety profile, and that, unlike its class predecessors, it reduces cardiovascular events. However, the mechanisms of action that determine its effect on cardiovascular disease prevention are not at all clear.

It should be remembered that CETP inhibitors were developed in order to increase the levels of high-density lipoprotein (HDL) cholesterol, the ''protective'' lipoprotein fraction and, in fact, in the REVEAL trial, anacetrapib led to a 104% increase in HDL cholesterol. The authors, however, ignored this effect, and concluded that the entire effect

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in reducing events was attributable to the variation in LDL levels and, in any case, non-HDL cholesterol levels. In fact, this conclusion is reinforced by the correlation between the decrease in non-HDL cholesterol (18%) and the reduction in cardiovascular events, which, as we mentioned, is in line with the CTT data. We must draw attention to the fact that this is the first time that the Oxford researchers (CTT) have used non-HDL cholesterol, instead of LDL, to analyse the association with the reduction in relative risk. Why?

If we analyse the metabolic effects of CETP and, therefore, of its inhibition, we might realise that CETP inhibitors are not strictly speaking lipid-lowering drugs, unlike those that we currently use, like statins, ezetimibe or PCSK9 inhibitors.

Inhibition of CETP blocks the exchange of lipids between lipoproteins; specifically, cholesterol from the HDLs is not transferred to the LDLs or very-low-density lipoproteins (VLDLs). Theoretically, this effect should be highly beneficial, by preventing the atherogenic lipoproteins from cholesterol loading and, in exchange, increasing its content in HDLs, which are responsible for eliminating it via the liver. However, lipid metabolism is more complex. By loading the HDLs with cholesterol, the HDLs lose their capacity for recycling into more basic forms with greater capacity for removal of cholesterol from tissues. Furthermore, LDLs with a lower cholesterol content—and therefore small—can become more damaging. In short, the final result is not a reduction in atherogenic particles, but a transfer of cholesterol between particles.

This effect is reflected in the results of studies such as the Accelerate and Illuminate trials, conducted with CETP inhibitors. Although they found some effect on LDL cholesterol levels, the impact on the ApoB levels was much lower, generally around 50%. This suggests that instead of reducing the number of particles, it tends to decrease their cholesterol content. The results of the REVEAL study are very confusing with respect to the impact of the drug on LDLs. LDL cholesterol was reduced by 41% using a direct analytical method. In accordance with the qualitative changes that we have mentioned, these methods, as well as the Friedewald formula, are known to be inaccurate when measuring LDL cholesterol following treatment with CETP inhibitors, maximising the reduction in LDL cholesterol.[5] For this reason, the investigators analysed a subgroup of 2000 post-treatment samples (no pre-treatment samples) using a combination of ultracentrifugation and precipitation of ApoB-containing lipoproteins (beta quantification),[5] and the results were extrapolated to the population set. The variation obtained is surprising: from a 41% decrease in LDL it fell to only 17% (a 58% lower effect) which, although it agrees with the changes in non-HDL cholesterol (18%), does not fit with what we know with respect to the impact on ApoB (18%) which, as we said, is usually much lower than the LDL cholesterol reduction.

That is, it creates serious doubts about the effects of anacetrapib on LDLs and we have to ignore the major effect on HDL. Nonetheless, as clinicians, we depend on scientific evidence and, therefore, it comes down to the fact that we have a drug that significantly reduces LDL and cardiovascular events. Welcome to the family!

But if we delve into the scientific bases, what a tortuous path we have ahead of us!

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