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Maximum Low-density Lipoprotein Cholesterol Lowering Capacity Achievable With Drug Combinations. When 50 Plus 20 Equals 60

Máxima reducción de colesterol unido a lipoproteínas de baja densidad alcanzable con combinaciones farmacológicas. Cuando 50 más 20 suma 60

To the Editor,

The results from the IMPROVE-IT trial and data from Mendelian randomization studies reinforce the causal role of low-density lipoprotein (LDL) cholesterol in atheromatous cardiovascular disease.[1,2] The "lower is best" concept has robust evidence-based support, and high-intensity cholesterol-lowering strategies ought to be implemented instead of high-intensity statin therapy.[3]

A clinically relevant question is "What is the maximum LDL-lowering capacity that will be achieved by combination therapy after the introduction of the new proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors?"

Statins have accumulated the most scientific evidence in cardiovascular prevention. Their average cholesterol-lowering effect ranges from 30% to 50%. By adding ezetimibe, their LDL-lowering capacity increased by 20% (22% in the IMPROVE-IT trial).[1] New PCSK9 inhibitors add an LDL reduction capacity of approximately 60%.[4,5] It must be taken into account that these reduction percentages are average values that may vary due to individual response. In addition, these percentages are achieved from the starting LDL values. Therefore, when calculating the overall impact of drug combinations, the effect of previous drugs must be taken into account. The absolute effect of adding drugs is lower than the addition of their relative effects.

For example, in a patient with LDL levels of 200 mg/dL, a high potency statin will decrease LDL cholesterol by 50% to 100 mg/dL.

By adding ezetimibe, we expect a 20% incremental LDL reduction; therefore, LDL concentrations of 100 mg/dL will decrease to 80 mg/dL (20% less). Thus, this patient will have a final reduction of 120 mg/dL, which is a 60% reduction from the starting point (200 mg/dL). Therefore, by adding a drug that reduces LDL by 50% and another that reduces it by 20%, we will have a final absolute reduction of 60% instead of 70%. The same principle can be applied to PCSK9 inhibitors. In this patient, we can expect an incremental LDL reduction of 60%, so the LDL cholesterol level of 80 mg/dL will decrease to 32 mg/dL. This is exactly an 84% reduction, 24% more from the baseline value. This is indeed the maximum LDL-lowering capacity according to available drugs.

The efficacy of different drug combinations can be calculated by the formula in the Figure.

Several points should be stressed. The maximum LDL-lowering capacity obtained with a statin plus ezetimibe was 60%. The maximum LDL-lowering capacity when combining the more potent statin plus a PCSK9 inhibitor was 80%. The maximum LDL-lowering capacity using the 3 drugs in combination was 84% (Table).

This theoretical exercise has implications for clinical decision-making and should also be taken into account in clinical guidelines.

For example, when statins are used as monotherapy (a maximum LDL lowering effect of 50%), only patients with LDL levels below 140 mg/dL will reach secondary prevention targets (LDL < 70 mg/dL). With a statin plus ezetimibe (maximum LDL lowering capacity of 60%), only patients with LDL below 175 mg/dL will reach secondary prevention targets.

With triple therapy (LDL lowering capacity of 84%), almost anyone with LDL levels up to 437 mg/dL could achieve secondary prevention LDL targets.

It seems reasonable to adapt clinical guidelines and recommendations to clinical feasibility.

$$\%A + \%B\,(1-\%A) + \%C\,[1-(\%A + \%B\,(1-\%A))]\ldots$$

Where %A is the theoretical low-density lipoprotein reduction induced by drug A, %B by drug B and %C by drug C.

Application of the formula to the text example:

$$0.5 + 0.2\,(1-0.5) + 0.6\,[1-(0.5 + 0.2\,(1-0.5))] =$$
$$0.5 + 0.2\,(0.5) + 0.6\,[1-(0.5 + 0.2\,(0.5))] =$$
$$0.5 + 0.1 + 0.24 = 0.84$$

Figure. Formula to calculate the percentage of low-density lipoprotein lowering efficacy of drug combinations.

Table

Theoretical Low-density Lipoprotein Reduction in Percentage Induced by Drugs in Monotherapy or in Combination

Drugs in monotherapy or in combination	Theoretical LDL cholesterol reduction, %
Low intensity statin	30
Moderate intensity statin	40
High intensity statin	50
Ezetimibe	20
PCSK9 inhibitor	60
Low intensity statin + ezetimibe	44
Moderate intensity statin + ezetimibe	52
High intensity statin + ezetimibe	60
Low intensity statin + PCSK9 inhibitor	72
Moderate intensity statin + PCSK9 inhibitor	76
High intensity statin + PCSK9 inhibitor	80
Low intensity statin + ezetimibe + PCSK9 inhibitor	78
Moderate intensity statin + ezetimibe + PCSK9 inhibitor	80
High intensity statin + ezetimibe + PCSK9 inhibitor	84

Low, moderate and high intensity statins are defined according to Stone et al.[6]
LDL, low-density lipoprotein.

CONFLICTS OF INTEREST

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Subcutaneous Defibrillator: Role in the Prevention of Sudden Cardiac Death in the Setting of Mechanical Tricuspid Prosthesis

Desfibrilador subcutáneo: papel en la prevención de la muerte súbita en presencia de una prótesis mecánica tricúspide

To the Editor,

Adequate cardiac defibrillation with a conventional transvenous defibrillation system requires a defibrillation coil to be positioned in the right ventricle. However, this is contraindicated in patients with mechanical tricuspid prostheses. In these patients, implantation of defibrillation systems with epicardial patches via thoracotomy is a valid alternative, although it carries considerable morbidity and mortality. In the literature, isolated cases have been described of alternative techniques using the coronary sinus, which could allow a completely transvenous implantation.[1] The entirely subcutaneous implantable cardioverter-defibrillator (S-ICD) could represent a simple, effective, and safe alternative in many patients with a tricuspid mechanical prosthesis.

We present the case of a 58-year-old man who had an episode of ventricular tachycardia at 190 bpm, which was electrically cardioverted. He had documented ischemic heart disease, with a chronic anterior infarct of unknown duration, chronic occlusion of the mid-left anterior descending artery, and severe left ventricular systolic dysfunction. As secondary prevention, a single-chamber transvenous ICD was implanted without complication (Figure 1), and he was started on treatment with antiplatelet agents, statins, bisoprolol, ramipril, and amiodarone. Sinus rhythm was maintained at 70 bpm, with right bundle branch block. Seven months later, having had no complications, the patient was admitted to hospital with a clinical picture of septic shock with symptoms of lumbar spondylodiscitis. Investigations included an echocardiogram, which revealed the presence of a large vegetation involving the defibrillation lead and the anterolateral leaflet of the tricuspid valve (Figure 1). Blood cultures were positive for methicillin-sensitive *Staphylococcus aureus.* Intravenous antibiotic therapy was started and cardiac surgery was performed via sternotomy for complete removal of the defibrillation system. Due to intraoperative findings, it was necessary to replace the tricuspid valve with a mechanical prosthesis. A deactivated epicardial permanent pacing lead was also placed, in case it was needed at follow-up. The patient progressed satisfactorily, and 6 weeks later, once stable, on anticoagulation with acenocoumarol, and with no residual sequelae, he underwent electrocardiographic screening for S-ICD implantation: all 3 vectors were positive. As permanent pacing was not required (Figure 1), an S-ICD (SQ-RX 1010, Boston Scientific) was implanted at the level of the left lateral thoracic wall, with a single-coil defibrillation lead (Q-Trak 3010, Boston Scientific S-ICD) at the left parasternal level, using a 2-incision technique (Figure 2). Acenocoumarol was continued throughout, with an international normalized ration (INR) of 3. A defibrillation