Designs and methods for impact evaluation of interventions. Response

Diseños y metodologías para evaluar el impacto de las intervenciones. Respuesta

To the Editor,

We would like to thank Antonio Sarria-Santamera for the interest shown in our article.[1] In his letter, he raises 2 different issues.

First, he mentions limitations in interpreting the hazard ratio. However, these limitations are inherent in the estimator and do not depend on whether the study is experimental or not and, consequently, would not be mitigated by a different study design.[2]

Second, he mentions the causal relationship between implementation of the PROGALIAM program and the decrease in mortality. The ideal context for this kind of inference is a clinical trial, but conducting a trial would not have been ethical in view of the nature of the study. As he points out, the alternative is to find a comparable group around the same timeframe. In the case of the IPHENAMIC program, this was not possible because the PROGALIAM network was established simultaneously throughout the geographical area, which precluded application of some of the methods proposed. Other alternatives, such as propensity score matching, are not desirable because they start with the effect that the intervention could influence the profile of patients arriving at the hospital alive, and this effect should not be cancelled out. The plausibility of causal effects between PROGALIAM implementation and reduced mortality is supported by the survival analysis and by observations such as the fact that 30-day gross mortality before PROGALIAM was almost unchanged and began to decline after implementation, as shown in figure 2 of our article.[1] Likewise, figure 1 of the additional material shows that 30-day mortality in the total population and in each of the areas dropped significantly, particularly in areas where access improved to a greater extent. Although not impossible, it is highly unlikely that there are any variables not included in our study that coincided with PROGA-

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LIAM implementation and had sufficient impact on mortality to explain these findings.

Despite the limitations of observational studies, we believe that they are essential in certain settings and, as expressed by the European Union and by the author himself in his references, are very useful for collecting real-world information, identifying outcomes, and ensuring responsible use of public funds.[3,4]

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116? How much should LDL-C be lowered in the «low risk» population?

¿116? ¿Hasta cuánto hay que bajar el cLDL de la población catalogada como en «bajo riesgo»?

To the Editor,

Although the target values for plasma lipid concentrations have been revised and reduced, there is no consensus as to whether or not low density lipoprotein cholesterol (LDL-C) levels should be treated according to target values.[1,2]

The American Heart Association/American College of Cardiology guidelines published in 2014[3] recommended a "shoot and forget" strategy in which the strength of the statin selected was more in line with the patients' cardiovascular risk (CVR) than with their final target.

In the European Society of Cardiology guidelines published on 31 August 2019, the recommended LDL-C level for the low-risk population (score, <1%) is < 116 mg/dL.[4] This recommendation was already present in the previous guidelines of 2016,[5] but with a huge difference: At that time, the recommendation specified "lifestyle recommendations" (no intervention on lipids) when LDL-C concentration was 155 to 190 mg/dL and the CVR was < 1%, whereas now it indicates "Lifestyle intervention, consider adding drug if uncontrolled" when LDL-C is between 116 and 190 mg/dL at the same CVR (see table 5 in both guidelines).[4,5]

Then I wondered, how many of my patients, regardless of their CVR, had LDL-C values < 116 mg/dL without receiving treatment, and how many had those values with treatment? I reviewed the analysis requests for the past week and found that more than 70%

of patients had values > 116 mg/dL; that is, they would need drug treatment. Looking at a larger database[6] and without taking diabetes or CVR into consideration, a similar percentage of patients would have to be treated.

In light of the possibility of a huge increase in lipid-lowering treatments, I delved more deeply into the recent recommendations (p. 22).[4] The LDL-C value of < 116 in low-risk individuals is based on reference 36, from 2012, by Mihaylova et al.[7] (also an author of the 2019 guidelines[4]). Hence, the current guidelines used an article from 2012 to support recommendations for 2019.

The study by Mihaylova did not propose any LDL-C target goal, much less 116. It was focused on avoidable events in populations with different CVR levels by decreasing LDL-C by 1 mmol (38 mg/dL), which, parenthetically, yielded a nonnegligible number of patients that would have to be treated.[7]

Where did the authors of the current guidelines get this value of 116? Is there a reference for the article from 2012 in the 2016 guidelines by the same authors? Remember, in 2016 the recommendation was not to intervene if the LDL-C concentration was between 155 and 190 mg/dL (p. 13, Table 5).[5] As the article states: "Low-risk people should be given advice to help them maintain this status" (references 61-71). Furthermore, on page 17 the text says: "... the task force accepts that the choice of any given target goal for LDL-C may be open to debate... (references 65 and 66).

As it turns out, reference 66, which contributes to sustaining these 2 statements, is the same as reference 36 in the 2019 guidelines: the study by Mihylova et al.[7]

In summary, the 2019 European guidelines[4] cite a study from 2012[7] to recommend LDL-C target goals for low-risk patients, but in 2016[5] they use the same reference to support very different recommendations.

What does this mean? And if it were really appropriate to attempt a goal of < 116 mg/dL in low-risk patients, which would imply medicating around 70% of the population, could any health system sustain it?

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COVID-19 and treatment guided by biochemical and molecular diagnostic tests to reduce myocardial damage and cardiotoxicity

COVID-19 y tratamiento guiado con tests de diagnóstico bioquímicos y moleculares para reducir el daño cardiaco y la cardiotoxicidad

To the Editor,

Because of the lack of scientific evidence on the effect of cardiovascular treatment on the infectivity of SARS-CoV-2 and on COVID-19 disease progression, the mechanisms that increase the risk of cardiac damage and thrombosis in patients with COVID-19, and the cardiotoxicity of antiviral treatment, we must consider the need for diagnostic tests that help health care professionals when making therapeutic decisions. Important aspects to consider are the following 5 points:

1. Hypertension, diabetes, and cardiovascular disease are the most prevalent comorbidities in patients with COVID-19.[1] Although they do not appear to affect the infectivity of the virus,[2] they do increase disease severity. One of the common mechanisms of this effect is via the renin-angiotensin-aldosterone system. Their treatment reduces levels and activity of angiotensin II, as it contributes to inflammation and endothelial dysfunction. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) and the protease TMPRSS2 to enter the host cell. ACE2 converts angiotensin II into an isoform with anti-inflammatory and vasodilator activity. It has not yet been ascertained whether the overexpression of tissue ACE2, in pathological states or induced by treatment, increases infection with SARS-CoV-2 or makes up for its deficiency to reduce cardiac, pulmonary, and renal inflammation and vasoconstriction. It is also necessary to study the regulation of serum ACE2 levels and its role in reducing the affinity of SARS-CoV-2 for tissue ACE2 and, consequently, infection (figure 1).