Letter to the Editor

Studies With Molecules Within the Same Class, but With Different Designs Yield Different Results. EMPA-REG, CANVAS and DECLARE

Estudios con moléculas de la misma clase pero con diseños distintos ofrecen resultados diferentes: EMPA-REG, CANVAS y DECLARE

Since the publication of the EMPA-REG-OUTCOME trial,[1,2] several hypotheses have emerged in an attempt to clarify the mechanisms underlying the cardiovascular protection profile of sodium-glucose-linked transporter type-2 inhibitors (SGLT2i) in type 2 diabetes.[3] In the context of the previous cardiovascular outcome trials (CVOTs), EMPA-REG-OUTCOME and CANVAS,[4] the results of DECLARE-TIMI-58[5] strongly suggest a hemodynamic basis for SGLT2i cardiovascular protection. Moreover, when the components of major adverse cardiovascular events (MACE) are taken separately, those CVOTs fail to show a significant reduction in the risk of myocardial infarction (MI) and stroke. The EMPA-REG-OUTCOME trial showed a reduction in the risk of cardiovascular death (CVD) but the list of event assignments of this outcome includes several hemodynamic alterations, arrhythmias, and other disorders not specifically related to ischemia. In a low-risk population with a small proportion of patients previously diagnosed with heart failure, DECLARE-TIMI-58 showed a significant reduction in the risk of the dual primary endpoint, CVD or hospitalization for heart failure (CVD/HHF), an interesting finding that helps to understand the favorable cardiovascular effect of dapagliflozin (and therefore of other SGLT2i). Likewise, CANVAS reported a significant reduction in the risk of CVD/HHF. In the substudy of DECLARE-TIMI-58 conducted by Kato et al.,[6] dapagliflozin therapy reduced HHF both in patients with and without heart failure or reduced ejection fraction (EF), and also reduced deaths and all-cause mortality in those patients with reduced EF. The DECLARE-TIMI-58 substudy carried out by Furtado et al.[7] showed that, in patients with a prior MI, indeed at high risk of MACE and CVD/HHF, dapagliflozin appeared to reduce both MACE and CVD/HHF, with greater absolute benefit compared with that in patients without a history of MI; moreover, there was a decrease in type 2 MI caused by a mismatch between myocardial oxygen supply and demand rather than by plaque rupture. Since the decrease in cardiovascular risk induced by dapagliflozin is more pronounced in patients at high risk, it is necessary to emphasize a concept that is usually overlooked when comparative judgments are made between the results of the SGLT2i CVOTs in the clinical care settings, namely "studies carried out with molecules within the same class, but different designs yield different results". Thus, it is inappropriate to compare from the results of EMPA-REG OUTCOME, CANVAS and DECLARE-TIMI-58 from a perspective of equality, because the baseline risk of the populations studied in each of these trials is strikingly different.

In this regard, the "real life" study by Norhammar et al. is of special interest.[8] The study included a cohort matched to the characteristics of the DECLARE-TIMI-58 population. The authors found that the association between the proportion of participants with CV disease at baseline and all-cause mortality rates in the groups not treated with SGLT2i seemed linear, and a similar linearity was also observed when the 3 CVOTs were analyzed in the same way.

Through a similar assessment, we found a statistically significant correlation between the event rates in placebo groups and the CVD relative risk reduction in SGLT2i groups, when the subpopulations with and without previous atherosclerotic events in EMPA-REG-OUTCOME, CANVAS and DECLARE-TIMI-58 were taken separately[9] (figure 1).

In conclusion, we believe that it is reasonable to affirm that the cardiovascular protection induced by SGLT2i is related to patients' intrinsic risk, and also that this protection has a mainly hemodynamic basis.

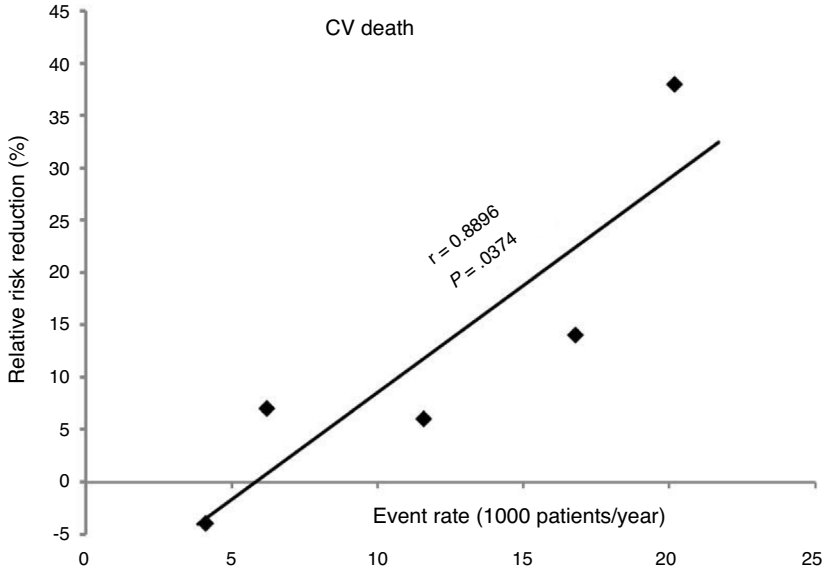

Figure 1. Correlation (Spearman) between event rates in the placebo groups (horizontal axis) and relative risk reductions of cardiovascular deaths in the SGLT2i groups (vertical axis) when the subpopulations with and without atherosclerotic events in EMPA-REG-OUTCOME, CANVAS, and DECLARE-TIMI trials are taken separately. Data from Zeilniker et al.[9] CV, cardiovascular.

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CONFLICTS OF INTEREST

A. Gippini has received fees for presentations and advisory boards from AstraZeneca, Boehringer-Ingelheim, Eli Lilly, Janssen, Novartis, NovoNordisk, and Sanofi. A. Prado works in Cardiovascular Renal and Metabolism (CVRM) Medical Department of AstraZeneca, Spain.

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