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Empaglifozin cardiovascular benefit: can we separate fact from fiction?

Benefício cardiovascular da empaglifozina: podemos separar o fato da ficção?

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After recent repercussion in the scientific medical environment despite of the promising results about the use of empaglifozin, an inhibitor of SGLT-2, several strategies have been implemented for the disclosure of these results with subsequent stimulation of this drug prescription. After the launch of the Brazilian Evidence Based Guideline on Cardiovascular Disease Prevention in Patients with Diabetes sponsored by the Brazilian Society of Cardiology and Endocrinology, recently (August 2018) a new public hearing was held for the implementation of this drug in the Brazil's public health system (SUS) due to the results found with the use of empaglifozin in the EMPA REG Outcomes Trial, a request that was already denied by CONITEC (National Commission for the Incorporation of SUS) in their last decision. Taking this trigger reported above as a moment to discuss this interesting issue, my goal will be to return to questioning: Is the result of reducing cardiovascular mortality in the EMPA REG Trial really confirms what they (investigators) found or are we still in the field of exploratory results, where we need more robust evidence to ensure this benefit for the population? It is worth remembering that the cost of this new medication, empaglifozin, will have a dramatic impact on the SUS budget and the goal of this article will be to go over again in this clinical trial that showed a benefit focusing on the proof of concept.

The EMPA REG trial has important relevance in medicine, because reducing cardiovascular outcomes in high-risk diabetics patients is something that converges in a common interest in the medical practice, empaglifozin reduced (true) cardiovascular mortality, but we must ask ourselves: What is the magnitude of this impact in reducing primary outcomes? Is there really robust evidence leading guidelines about diabetes and cardiovascular risk reduction with empaglifozin? Only with this result have we reached the scientific "certainty" of benefit? Far away from it, we are still in the phase of an exploratory and non-confirmatory study, where we must wait for more results which will strengthen this information or reject it, thus avoiding hasty behavior which might be promising something that can not be fulfilled.

Proof of Concept

When we read a scientific article we should look at it with our investigative reading skills and make sure if the clinical trial proved the concept tested, and the question regarding this would be: Reduce blood glucose prevents atherosclerotic outcomes?

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We know that the main causes of death due to atherosclerotic cardiovascular outcomes are caused by stroke and acute myocardial infarction, then as empaglifozin showed reduction of cardiovascular death, by the principle of reversibility (reducing atherosclerosis reduces stroke and myocardial infarction) it would be expected that both the reduction of myocardial infarction and stroke had an impact at this reduction of cardiovascular mortality, a fact that would demonstrate consistency in the cardiovascular mortality reduction, but this was not the case.

When we look at the cardiovascular death categories in the supplementary appendix of the article (Section - L table), we notice there was no reduction of infarction (8% in both placebo and drug groups) and there was a slight increase in stroke outcomes in the empaglifozin group (12 %). Interestingly, half of the cardiovascular deaths were due to death from worsening heart failure and "other" cardiovascular deaths, which together accounted 53% and 49% of cardiovascular deaths in the placebo and drug groups, respectively.

These "other" cardiovascular deaths were deaths that the authors did not have assured information about the cause of death, but agreed as a cardiovascular death. It is at least curious that almost half of the deaths that occurred classified as cardiovascular deaths were deaths that the authors are unaware of their true cause and if we only look at death from heart failure (HF), empaglifozin reduced this outcome by 54%. In other words, the result of cardiovascular mortality reduction found in the study (veracity) might have been driven by these reductions described above and not as expected as a reduction of stroke and myocardial infarction, since we are testing the concept that reducing blood glucose reduces atherosclerosis.

In summary, it is true the study showed that the drug reduces cardiovascular death, but the myocardial infarction outcome did not contribute at all and the stroke outcome increased discreetly with the treatment. It is almost like this, the treatment does the great (reduce cardiovascular death) without doing the good (reduce stroke and heart attack). It would be something like a soccer player who always scores every time he kicks from the midfield, but loses all penalties attempts. This study failed to prove the concept for which it was designed, to better control blood glucose (surrogate outcome) does not prevent cardiovascular outcomes from atherosclerosis. This result has been pursued for years in several other clinical trials with antidiabetic pills, and they had never proved it even with so many attempts. In fact that demonstrates a low pre-test conditional probability of the study (low positive predictive value), where the result needs to be consistent to raise up this study's posttest probability, increasing its positive predictive value.

However, how to analyze the excellent impact on heart failure of this new antidiabetic drug? This medication has an initial osmotic diuretic effect which in addition to reducing blood pressure just a little, has reduced blood volume, where this volume reduction may have caused a great initial effect on the reduction of hospital admission due to HF, since they are more severe patients and perhaps (uncertainty) is the reason for the early opening of the graph curves (A, B, C and D). It is not because the drug has a fast effect on mortality, but because it reduces outcomes related to heart failure leading by the osmotic diuresis effect, and because it is a hazard ratio analysis, those who used the medication had less worsening heart failure hospitalization. This would be plausible, since we know that increasing the diuresis decreases the heart failure worsening.

Another important issue is, the reduction of blood pressure should have been minimal or irrelevant effect by the empaglifozin, I am mentioning this because we know that from the principle of reversibility already proven in other clinical trials, the main cardiovascular outcome that reduces when we better control blood pressure levels is the stroke outcome, which in this study followed the opposite way, the group that used empaglifozin (increase of 12%) had a higher incidence of stroke.

The EMPA REG study showed a reduction in cardiovascular mortality promoted by em-paglifozin, but this reduction was a tad misunderstood and did not make us comfortable adopting this treatment for this purpose. In other words, the trial failed to prove the concept in which reducing blood glucose prevents atherosclerosis and only showed that by its diuretic effect heart failure worsening hospitalizations were

reduced. Anyways, it seems something like this: the authors aimed one specific target but they ended up hitting another.

Perhaps this is the take home message of this particular study, but does anyone still doubt that increasing diuresis we reduce hospitalizations in heart failure field? Why should we use empaglifozin instead increase the diuretic dose in our heart failure patients? It might be the big picture question. After this discussion we should stay with the null hypothesis at the moment regarding empaglifozin and its cardiovascular mortality reduction promise, because it is still only a uncertain promise so far and with lacked of proof of concept.

Competing interests

No financial, legal or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).