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Saxagliptin and Heart Failure in the SAVOR-TIMI 53 Trial: Reflections on the Bradford Hill Criteria



Saxagliptina e insuficiencia cardiaca en el estudio SAVOR-TIMI 53: bajo la lupa de Bradford Hill

To the Editor,

The association between saxagliptin use and an increased risk of hospitalization for heart failure (HF) has generated considerable controversy.^{1,2} One reason is that the mechanisms of the potential deleterious effect are mainly unknown and speculative. Second, to make the scenario even more complex, we recently pointed out a high risk of type 1 error (chance finding) in the SAVOR-TIMI 53 trial due to an insufficient Bonferroni correction and an apparent deviation from the initial statistical analysis planned by the authors.³

Give the controversy surrounding the relationship between saxagliptin and HF and in an effort to help resolve it, the present article aims to provide a summarized review of the association using the Bradford Hill criteria of causation.

As described by Hill, the criterion *strength of association* attempts to determine whether there is a relationship between the putative causal factor and the effect under study. The more distant the relative risk is from 1, the larger is the strength of the association. With saxagliptin, the hazard ratio (HR) was 1.27 and the 95% confidence interval (95%CI), 1.07–1.51 ($P = .007$).¹ A subsequent analysis including all HF hospitalizations (analysis of recurrent events or Andersen-Gill analysis) showed a slight attenuation of this relationship (HR, 1.26) as well as a reduction in the lower limit of the 95%CI to 1.02, that is, very close to the null hypothesis.¹ This attenuation was produced because the greater risk of HF in saxagliptin-treated patients was only observed in the first 314 days, being virtually neutral thereafter (HR, 1.05; 95%CI, 0.81–1.35).¹ An analysis “excluding the first hospitalization for HF” as part of a sensitivity analysis using another approach, known as the Prentice-Williams-Peterson model, did not find a higher associated risk (HR, 1.06; 95%CI, 0.75–1.50).¹ Thus, different statistical models yielded distinct, even contradictory results. In addition, we should not overlook that HF hospitalization was a secondary endpoint, understood therefore, as exploratory, which would increase the probabilities of chance. Because of all these considerations, the strength of the association is likely to be weak.

Hill considered an association *consistent* if the relationship between the 2 variables were upheld in more than 1 study, in different populations and circumstances. For saxagliptin, the relationship shows little consistency, as it has not been confirmed by recent retrospective observational studies⁴ (although this is not true of all⁵) and there is no robust experimental evidence.

The criterion of *specificity* refers to an effect being attributable to a single cause. With regard to the excess HF risk in the saxagliptin group, one might speculate that it could be due to chance because of the multiplicity of secondary variables (up to 10),³ or to the fact that there were more deaths (nonsignifi-

cantly) in the saxagliptin group, which could lead to a smaller number of patients at risk and therefore, an upward bias in the HF incidence rate.³

Temporality, as related to an association, is essential to ensure that the risk factor appeared before the putative effect, which is verified in the study.¹

The *biological gradient* or dose-response relationship encompasses the concept that increased exposure or dose increases the incidence of a disease. Currently, there is no evidence of a dose-response relationship for the association between saxagliptin and HF.

With regard to *biological plausibility*, the biological context should logically explain the etiology by which a cause produces an effect. This concept is closely related to reproducibility and experimental evidence. In this regard, it should be mentioned that the finding was completely unexpected, as previous studies did not show a greater risk of edema or water retention.¹ Endothelial dysfunction and increased left ventricular volumes have been cited as potential mechanisms,¹ although other studies indicate benefits.⁶

Coherence refers to an association being in line with previous knowledge regarding biological mechanisms. Again, the association was unexpected, in disagreement with later studies⁴ (although not all⁵), and did not have a constant mechanism relating cause and effect.

Lastly, *analogy* is based on established cause-effect relationships, whereby if one risk factor produces an effect, another with similar characteristics should have the same impact. In this line, previous data from the same family of drugs (alogliptin) indicate that there could be a nonsignificant numerical trend toward a higher risk of HF.

In conclusion, on application of the Bradford Hill criteria to evaluate the relationship between saxagliptin use and the risk of HF hospitalization, a robust association was not found. However, as safety is a priority, it is essential to carry out new, specific, prospective studies to confirm or rule out this association.

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Percutaneous Mitral Repair With MitraClip in Patients Treated With Transcatheter Aortic Valve Implantation



Reparación mitral percutánea con MitraClip en pacientes tratados con implante percutáneo de válvula aórtica

To the Editor,

Up to 40% of patients treated with transcatheter aortic valve implantation (TAVI) have at least moderate mitral regurgitation (severe in 15.9%), and its persistence after prosthesis implantation (7.9% of patients) negatively affects prognosis.¹ In almost half of the patients, mitral regurgitation is reduced, mainly in patients with functional etiology, nondilated annulus, and noncalcified valves.^{1,2} If the regurgitation is not reduced and the patient continues to have limiting symptoms, one option that has been proposed is the use of percutaneous repair techniques with the MitraClip device; there are already published case series of solution in Europe.³ In Spain, the use of the MitraClip has become more widespread since 2011, mainly for patients with functional mitral regurgitation.^{4,5} The technique requires adequate mitral valve anatomy to allow MitraClip implantation, although it has been proposed that the selection criteria be relaxed in centers with experience.⁶ In patients with TAVI, the mitral annulus and/or mitral leaflets are often calcified, which can limit the treatment indication, and therefore the valve must be assessed in detail.

This study combines the experience of the first 5 cases of severe mitral regurgitation after percutaneous treatment with TAVI

performed in 3 hospitals in Spain (2015 to 2016), with particular emphasis on patient selection.

Below we present the characteristics at baseline, those related to the previous TAVI, to MitraClip implantation, and at follow-up. Mitral regurgitation was present prior to TAVI in all 5 patients and persisted without reduction until MitraClip implantation, an average of 16.2 months later.

In patients 1, 2, and 5, and particularly in 5, the valve had abnormalities (degenerative etiology), which the clinician must take into account when deciding whether the procedure is indicated:

- The free edge of the anterior mitral valve must have at least 1 free 7-mm segment⁶ that does not interfere with the TAVI. The presence of a previous dysfunctional bioprosthesis treated with TAVI (valve-in-valve), as in patient 1, did not present anatomical obstacles to treatment with MitraClip. Similarly, patient 3 had a double TAVI valve (both implanted in the same procedure because the first was too deep at 13 mm), although this did not interfere with the MitraClip device. The average depth of the valves was 7.25 mm.
- Calcification and flexibility of leaflets: in patients with calcified degenerative aortic stenosis, the calcification often extends to the posterior mitral annulus and to the “mitral-aortic curtain”, as in patient 5 (Figure). Once again, at least 7 mm of noncalcified tissue is required in each of the valves to allow device implantation. In patient 5, the regurgitation jet originated on either side of the calcified area, and it was possible to implant the devices avoiding

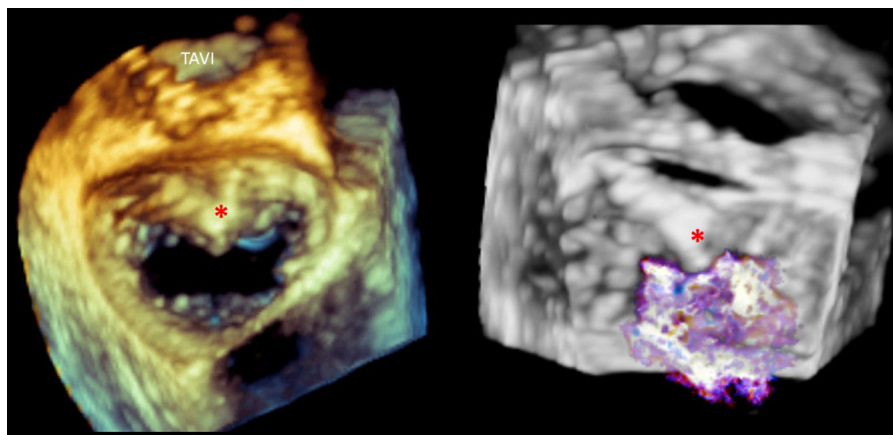


Figure. Three-dimensional transesophageal echocardiogram with a view of the mitral valve from the left atrium in patient 5. The asterisk indicates an area of calcification along the mitral-aortic curtain. The regurgitation originates mainly on either side of the calcified area. TAVI, transcatheter aortic valve implantation.