EDITORIAL

Triluminate pivotal trial: Another brick in the wall?

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Key words: Tricuspid valve; Tricuspid valve regurgitation; Transcatheter edge-to-edge tricuspid repair.

Palabras clave: Válvula tricúspide; Insufiiencia de la válvula tricúspide; Reparación transcatéter borde-a-borde.

Cir Card Mex 2024; 9(1): 1-2.

The Triluminate Pivotal (NCT03904147) is a trial comparing the effectiveness of using transcatheter edge-to-edge therapy in tricuspid valve regurgitation (T-TEER) versus isolated medical treatment. Recently, Sorajja et al [1] have published the results after one year of follow-up. In this study, a total of 350 patients were included; out of them, 175 were assigned to the device arm (T-TEER), and 175 to the medical treatment arm. Although 153 (87%) in the T-TEER group had preoperative atrial fibrillation, the authors do not mention whether any cases were due to atrial functional tricuspid regurgitation. Therefore, we assumed that 100% of the cases were due to secondary or functional tricuspid regurgitation due to right ventricular (RV) dysfunction, elevated pulmonary pressures, or both as predominant factors.

The primary endpoint was composed of three items; namely, a) all-cause death or tricuspid-valve operation, b) hospitalization for heart failure, and c) improvement in quality of life (QoL) as measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ-12). The authors conclude that the results of the primary composite endpoint were favorable to the T-TEER group. However, it is important to mention that both death from any cause (8.8% vs 7.7%) and the hospitalization for heart failure (14.9% vs 12.1%) were unchanged in favor of either group. The favorable result for the device, according to this trial, is based exclusively on the fact that the QoL measured by KCCQ-12 was favorable for T-TEER ($p<0.001$). However, it is quite striking that the 6-minute walk test did not present changes in favor of T-TEER ($p=0.25$).

With all of the above, and given the ambiguous of the situation, we must take the results of this trial with all necessary reservations. At the same time, it is necessary to carry out a rough analysis of this trial, as well as the narrative, which can be confusing for the readers.

Primary composite endpoint by three items

A composite endpoint is one that is composed by several different criteria. Although the use of these primary composites may have advantages for researchers, some requirements must be met when using composite outcomes in decision making [2]. There are some criteria to be met. Otherwise, there is a high risk that clinical decisions will become difficult or impossible. When interpreting the results, it is evident that the frequency of occurrence of the different components is not the same, and that the effect of the intervention (T-TEER) on the different components is not the same. Thus, deciding based on a primary composite endpoint may be difficult or impossible. At the same time, in order to evaluate this primary composite endpoint, it is essential that researchers clearly report the results of each component separately. In this trial, the results are not reported individually in the main article, but only in a loose way in the supplementary material [3].

Therefore, in the Triluminate trial, the effectiveness of using T-TEER is based exclusively on the fact of a better QoL measured through the KCCQ-12. Contrariwise, it should be highlighted that the 6-minute walk test was not favorable for T-TEER. The implications derived from the above have a lot to do with the objectivity of the test, given that while the 6-minute walk is a totally objective test, the KKCQ-12 is a test based on 8 questions resulting in a test totally subjective [4]. Although clinical trials have increasingly used it to evaluate the cutting-edge catheter-based techniques, the level of objectivity of KCCQ-12 can be considered ambiguous. In summary, it would appear that the primary composite endpoint by three items in the Triluminate pivotal trial was created "ad hoc" to justify and ensure the results in favor of T-TEER.

What is the level of objectivity of the KCCQ-12?

As formerly explained, The KCCQ-12 is the short version of the original questionnaire [4]. It is composed of 8 questions, which are answered through an "option to choose" from, but always based on "only appreciative" ranges, that is, "qualitative". There is no value in such evidence that can be measured tangibly and objectively. The above becomes particularly important when the results of T-TEER are compared through the 6-minute walk test, which in turn, unlike the KCCQ-12, is a completely objective test.Thus, there was no significant difference between the T-TEER arm and the medical treatment arm ($p=0.25$). In conclusion, Triluminate pivotal trial failed to demonstrate with objective data any benefit after T-TEER.

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Placebo effect of T-TEER

To rule out any placebo effect ofT-TEER, it is necessary a double-blind trial, where neither the researchers nor the patients know the treatment applied in the various comparative groups. In the case of Triluminate pivotal trial, due to the characteristics of the trial, it was an open label trial, in which the patient is perfectly aware that an invasive procedure (placement of the clip) has been performed to improve their cardiovascular and health status. As a result, the approach of this trial is totally deficient. In order to eliminate any placebo effect, it would have to be a comparator arm in which the patient underwent a groin puncture or catheterization (without clip installation), in order to have realistic and objective comparisons.Therefore, in the Triluminate pivotal trial, the placebo effect in favor of T-TEER arm cannot be ruled out.

No improvement in death from any cause and hospitalization for heart failure

Commonly, secondary or functional tricuspid regurgitation is due to an alteration in the function or three-dimensional geometry of the RV. In this sense, it is understandable that simply applying the clip to the regurgitant tricuspid valve cannot solve the underlying RV contractile muscle problem. The negative implication on the final outcome of the patient in terms of survival or rehospitalization for heart failure is more than evident in this study [death from any cause (8.8% vs 7.7%), the rate of hospitalization for heart failure (14.9% vs 12.1 %) for T-TEER arm and isolated medical treatment arm, respectively] [1]. Thus, it remains to be defined in which specific group of patients T-TEER would have any usefulness.

Echocardiographic parameters of irreversibility of right ventricular function

As stated by the authors in Triluminate trial, "The majority of participants in this trial had secondary tricuspid regurgitation" [2]. In cardiac surgery, irreversible RV dysfunction in patients with severe tricuspid regurgitation undergoing left-sided valvular surgery is of paramount importance. At present, we know some parameters related to right ventricular (RV) dysfunction. Tricuspid annular plane systolic excursion (TAPSE) (<15 mm), tricuspid annulus systolic velocity (<11 cm/s), and RV end-systolic area (>20 cm2) have been identified as such [5]. Surprisingly, none of the above is included into the exclusion criteria in Triluminate pivotal trial [3].

In conclusion, the Triluminate pivotal turns out to be a poorly objective trial in terms of the real usefulness of T-TEER in patients with isolated tricuspid regurgitation. At one-year follow-up, it failed to prove any utility of T-TEER on patient survival and heart failure rehospitalization rate. The only parameter in favor of T-TEER was QoL. The improvement in QoL measured only by the KCCQ-12 is controversial, as it does not have sufficient objectivity. In contrast, the 6-minute walk test (objective) failed to demonstrate any benefit for T-TEER. The weakness in the exclusion criteria, from the point of view of RV dysfunction, makes the applicability of this trial extremely limited when it comes to moving from theory to practice.

FUNDING: None

DISCLOSURE: The author has no conflicts of interest to disclose.

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