EDITORIAL

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A critical analysis of the RESHAPE-HF2 trial: biases and limitations that should be considered before incorporating it into next clinical guidelines

Análisis crítico del ensayo RESHAPE-HF2: sesgos y limitaciones que deben tenerse en cuenta antes de incorporarlo a las próximas guías clínicas

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The recently published Transcatheter Valve Repair in Heart Failure with Moderate to Severe Mitral Regurgitation (RESHAPE-HF2) trial[1] presents a randomized controlled comparison of guided directed medical therapy (GDMT) with and without transcatheter edge-to-edge repair (TEER) in patients with moderate to severe functional mitral regurgitation (FMR). A total of 505 patients were enrolled in a 1:1 ratio to receive either GDMT alone (n = 255) or GDMT plus TEER (n = 250). The trial featured a novel triple primary endpoint, comprising the combination of cardiovascular mortality and heart failure hospitalization (HFH), and HFH alone, both of them assessed at 24 months. Notably, a third primary endpoint was added once the trial was completed: The Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score at 12 months.

The most compelling results showed a significant reduction in HFH rate at 24 months, favoring TEER plus GDMT, with 26.9 events per 100 patient-years versus 46.6 events per 100 patient-years in the GDMT alone group (RR = 0.59; 95% CI, 0.42 to 0.82; p = 0.002). Additionally, TEER plus GDMT demonstrated a positive effect on the Kansas City Cardiomyopathy Questionnaire-Overall Summary (KCCQ-OS) score, with a mean increase of 21.6 ± 26.9 points versus 8.0 ± 24.5 points in the control group (mean difference, 10.9 points; 95% CI, 6.8 to 15.0; p < 0.001).[1]

At first glance, the results of this trial seem to suggest a clear benefit of combining TEER with GDMT for the treatment of moderate to severe FMR. However, several concerns warrant careful consideration, tempering the initial enthusiasm for this therapeutic approach.

Firstly, notably a triple primary endpoint was used in this trial. Moreover, the primary endpoint was shifted once the trial was completed by adding HFH rate at 24 months, and the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score at 12 months.

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A dual concern arises in this context. On one hand, the modification of endpoints after a trial's initiation (and particularly after its completion) contravenes standard research protocols. On the other hand, the retroactive addition of the KCCQ-OS score at 12 months as a primary endpoint in a concluded trial raises significant ethical and methodological concerns. This circumstance prompts the question of whether this alteration was a deliberate attempt to secure a more readily achievable endpoint within an abbreviated follow-up interval, thereby avoiding potential declines in subjective clinical improvement as assessed by the KCCQ in patients with HF with reduced ejection fraction (HFrEF). Furthermore, the improvement in KCCQ-OS) score at 12 months in the device group is somewhat debatable due to its inherently subjective nature and the trial's non-double-blinded design, which may introduce bias because of the placebo effect in favor of TEER.

The second critical issue emerging from this trial pertains to the inclusion criterion of patients presenting with overt HF symptoms, despite being on GDMT, coupled with moderate to severe functional mitral regurgitation (FMR) (graded 3+ or 4+), as defined by the European Association of Echocardiography. It is essential to note that these echocardiographic recommendations primarily focus on criteria for the imaging assessment of prosthetic heart valves, as reported by the European Association of Cardiovascular Imaging. Specifically, moderate mitral regurgitation (MR) is characterized by the following quantitative parameters: effective regurgitant orifice area (EROA) = 20-39 mm^2, regurgitant volume (RVol) = 30-59 ml, and regurgitant fraction (RF) = 30-50%. In contrast, severe MR is defined by EROA $\geq$ 40 mm^2, RVol $\geq$ 60 ml, and RF > 50%.[2] These severity criteria for MR are also endorsed by the American Society of Echocardiography.[3]

The RESHAPE-HF2 trial revealed a mean EROA of 23 mm^2 (range, 19 mm^2 - 30 mm^2) and a RVol of 35.4 ml (range, 28.2 ml - 43.9 ml), indicating a predominantly moderate degree of FMR. Notably, a mere 14% of patients exhibited an EROA > 40 mm^2, whereas a substantial one-quarter of patients (23%) displayed an EROA < 20 mm^2, suggestive of mild FMR prior to the procedure. This disparity raises important questions regarding patient selection and the potential impact on trial outcomes.

The Mitral Valve Academic Research Consortium (MVARC) defines an "acceptable" outcome following TEER as a reduction in MR by at least two grades or a residual MR of $\leq$ 2+, tantamount to moderate MR. Under these circumstances, it is strikingly discordant that the definition of "acceptable MR" subsequent to TEER serves as the benchmark for the inclusion criteria in the RESHAPE-HF2 trial.

The third pivotal issue arising from this trial pertains to the GDMT employed in patients with HFrEF and FMR. According to the current guideline for HF management, in patients with HFrEF and New York Heart Association (NYHA) class II to III symptoms, the use of angiotensin receptor-neprilysin inhibitors (ARNi) is recommended to reduce morbidity and mortality (Class of Recommendation [COR] 1, Level of Evidence [LOE] A). Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are reserved for cases where ARNi is not feasible. Furthermore, in patients with chronic symptomatic HFrEF (NYHA class II or III) who tolerate ACEI or ARB, replacement with ARNi is recommended to further reduce morbidity and mortality (COR 1, LOE B-R). In patients with symptomatic chronic HFrEF, sodium-glucose cotransporter 2 inhibitors (SGLT2i) are recommended to reduce HFH and cardiovascular mortality (COR 1, LOE A).[4]

A meta-analysis comprising 75 trials, which enrolled 95,444 patients with HFrEF, demonstrated that the maximum benefit was achieved with a quadruple combination therapy consisting of ARNi, beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), SGLT2i, resulting in a significant reduction in all-cause mortality and the composite outcome of cardiovascular death or first HFH.[5] Furthermore, the combination of ARNi/BB/MRA was superior to ACEI/BB/MRA and ARB/BB/MRA in improving LV adverse remodeling and increasing LV ejection fraction in patients with HFrEF.[6] The use of SGLT2 inhibitors has been associated with significant improvements in patient-centered outcomes, as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ).[7] Moreover, regarding the improvement in clinical status measured by KCCQ in the trial, it is noteworthy that a comprehensive meta-analysis of 17 studies, encompassing 23,523 patients, has consistently demonstrated that SGLT2 inhibitor therapy is associated with substantial enhancements in patient-centered outcomes, as quantified by the Kansas City Cardiomyopathy Questionnaire-overall summary score (KCCQ-OSS) (mean difference, 1.90 points; 95% CI, 1.41-2.39 points; $p < 0.001$).[8] Notably, the low usage rates of ARNi (11%) and SGLT2i (8.4%) in the control group at baseline in the RESHAPE-HF2 are striking. Moreover, there is no report available on GDMT across the entire follow-up period. Under these circumstances, it is impossible to establish any comparison between the two groups, where GDMT is a crucial element of utmost importance. Therefore, given the suboptimal quality of GDMT reported at least in baseline in this study, it is difficult to obtain results with sufficient reliability in terms of a comprehensive and up-to-date GDMT based on quadruple therapy (ARNi, SGLT2i, beta-blockers, and mineralocorticoid receptor antagonists).

Confronted with such profound uncertainty, the initial euphoria surrounding the RESHAPE-HF2 trial's outcomes

gives way to disillusionment, compelling us to pursue alternative solutions firmly rooted in pragmatic trials that rigorously uphold the foundational principles of exemplary clinical practice.

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