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The narrow window of TRISCEND II: a step forward but how far?

La estrecha ventana del TRISCEND II: un paso adelante, ¿pero qué tan lejos?

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ABSTRACT

The TRISCEND II trial seemingly demonstrates the superiority of transcatheter tricuspid valve replacement over medical treatment for patients with severe functional tricuspid regurgitation. However, closer examination reveals substantial methodological vulnerabilities, including a contentious 2:1 randomization ratio favoring device allocation and lack of blinding. While improvements in quality of life and NYHA functional classification were reported, no significant differences were observed in hard endpoints such as mortality, heart failure hospitalization, right ventricular device implantation or cardiac transplantation. The subjective nature of quality of life assessments using the Kansas City Cardiomyopathy Questionnaire introduces bias. The use of soft endpoints (e.g. quality of life, symptom severity) may artificially inflate the number of events, thereby compromising the trial reliability. Furthermore, the study's demographic composition, predominantly comprising patients with atrial functional tricuspid regurgitation, limits generalizability. Notably, significant device-related complication rates necessitate thorough risk-benefit analysis. In conclusion, the trial fails to provide generalizable results for the majority of patients with severe functional tricuspid regurgitation and is susceptible to bias. Prolonged follow-up is required to assess hard endpoints and mitigate bias induced by soft endpoints.

RESUMEN

El ensayo clínico TRISCEND II sugiere beneficios del reemplazo valvular tricuspídeo percutáneo sobre el tratamiento médico en pacientes con insuficiencia tricúspide funcional severa. Sin embargo, un análisis más detallado revela vulnerabilidades metodológicas significativas. La relación de randomización 2:1 a favor del dispositivo y la falta de cegamiento (estudio no ciego, abierto) introducen sesgos. Aunque el estudio reportó mejoras en la calidad de vida y clasificación funcional de la NYHA, no hubo diferencias significativas en endpoints duros como mortalidad, hospitalización por falla cardíaca, implante de dispositivos de asistencia ventricular derecha o trasplante cardíaco. La medición de la calidad de vida mediante el cuestionario Kansas City Cardiomyopathy Questionnaire es subjetiva y susceptible a sesgos. La inclusión de endpoints blandos (como calidad de vida o la presencia, ausencia o intensidad de la sintomatología) puede inflar artificialmente el número de eventos, comprometiendo la rigurosidad del estudio. La composición demográfica del estudio, predominantemente pacientes con insuficiencia tricúspide funcional atrial, limita la generalizabilidad de los resultados. Los índices significativos de complicaciones en el grupo del dispositivo requieren una evaluación exhaustiva en el análisis de riesgo-beneficio. En resumen, el estudio no demuestra resultados generalizables para la mayoría de los pacientes con insuficiencia

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Palabras clave: *cateterismo, enfermedad valvular cardíaca, implante de prótesis valvular cardíaca, válvula tricúspide, insuficiencia de la válvula tricúspide.*

An examination of TRISCEND II trial outcomes reveals an apparent advantage of transcatheter tricuspid valve replacement (TTVR) over medical treatment in patients with severe functional tricuspid regurgitation (TR) at two years of follow-up,[1] but closer scrutiny exposes substantial methodological vulnerabilities.

Randomized controlled trials (RCTs) constitute the gold standard for assessing medical interventions, as randomization ensures the equitable distribution of known and unknown confounding variables across treatment arms, mitigating selection bias.[2,3] In TRISCEND II trial, the 2:1 randomization ratio favoring device allocation is particularly contentious, as it may contravene established ethical principles and introduce bias, thereby necessitating rigorous reassessment of the study's implications.

This trial's primary composite outcome showed favorable results for the device plus medical treatment cohort, mainly driven by improvements in quality of life, NYHA functional classification, and 6-minute walking test performance. However, no significant differences were observed in hard endpoints [mortality, heart failure hospitalization (HFH), right ventricular (RV) assistant device implantation, or cardiac transplantation], highlighting the importance of contextualizing these results.

Cardiovascular death and HFH are unequivocal, binary events characterized by high objectivity and minimal bias, making them quintessential hard clinical endpoints. Hard endpoints are based upon quantifiable, objective criteria unaffected by personal opinions. On the contrary, soft endpoints, such as quality of life or symptoms, albeit crucial in clinical practice, are prone to unintended bias in unblinded trials due to reliance on physician and patient interpretation and the physician's therapeutic intent. Blinding has long been recognized as the gold-standard solution to mitigate this bias in measuring these endpoints. Unfortunately, this kind of trials is quite difficult to blind.[4]

Considering these factors, what significance do they hold in relation to the TRISCEND II study? Particular mention should be noted about the quality of life in this trial, which was measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ). This tool, the KCCQ-driven quality of life assessment is susceptible to critique due to its inherently subjective character. Although the KCCQ is a widely recognized, validated tool for evaluating health status in heart failure patients,[5] its subjective design inherently limits its objectivity, potentially introducing biases due to patient self-reporting.[6] Likewise, as mentioned above, the symptom-based NYHA functional classification may introduce interpretative biases. As a matter of fact, evidence suggests that unblinded evaluations can skew subjective (soft endpoints) outcomes. Research suggests that simply communicating a treatment plan, such as ruling out surgery, can profoundly impact patient symptoms. Furthermore, the placebo effect associated with invasive procedures, like intracardiac device implantation, can substantially influence patient-reported outcomes, including lifestyle adjustments and symptom alleviation. The problem is that the *power of faith healing* influences scientific research in unblinded trials.[4] Another further potential bias concern emerges in these trials when treatment is compared to a control group where standard treatment is omitted. This phenomenon, known as *subtraction anxiety*, refers to the anxiety that arises when a patient requires routine treatment but does not receive it, generating anxiety for the physician and patient due to unmet treatment expectations. This situation can create a need to alleviate tension through action, triggering urgent interventions, or even urgent hospitalizations. Consequently, this may compromise the objectivity of clinical trials and medical decision-making, particularly in routine procedures where treatment expectations are high. Subtraction anxiety plays a pivotal role in the control arm of unblinded trials. Unblinded trials of proven beneficial interventions are particularly susceptible to subtraction anxiety in the control group.[4]

Conversely, unlike soft endpoints, TRISCEND II revealed no statistically significant differences in objective, hard endpoints, specifically mortality, HFH, reoperation, and RV assistant device implantation or cardiac transplantation). Even reoperation or reintervention fall short of these criteria, due to the multitude of factors that may prevent patients from undergoing repeat procedures, thereby introducing bias. Therefore, the primary composite endpoint must be objective and impervious to bias from unblinded assessment: namely, cardiovascular death, and at a lesser extent, HFH. Perhaps, the same can be said about HFH for non-treated patients by an already known percutaneous treatment. The inclusion of soft endpoints, as occurred in TRISCEND II, may artificially inflate the number of events, undermining the rigor and reliability of this trial.

Another crucial aspect warranting clarification is the TRISCEND II demographic composition, predominantly characterized by atrial functional TR. This is evidenced by the high prevalence of atrial fibrillation (> 90%), only mildly impaired tricuspid annular plane systolic excursion (TAPSE) values (16.3-15.4 mm), mild-to-moderate pulmonary artery systolic pulmonary hypertension (PASP: 38.6-37.6 mmHg), and preserved left ventricular ejection fraction (LVEF) values (54.4 and 54.3%). Notably, fewer than 34 and 31% of patients had undergone prior valvular heart interventions including left-sided valvular heart diseases. Collectively, these characteristics suggest that the study population primarily comprised patients with atrial functional TR, a subgroup known for its relatively favorable long-term prognosis and outcomes. Consequently, TRISCEND II findings may have limited generalizability, applying to a highly specific subset of patients with severe functional TR, potentially comprising less than 25% of all secondary or functional TR cases.[7] To mitigate interpretative biases and ensure translational relevance in clinical practice, it is essential to recognize this critical limitation.

The device arm's significant complication rates up to 10.4% bleeding at 31-days and 17.4% permanent pacemaker implantation at 1-year demand thorough evaluation in the risk-benefit analysis, particularly when balancing these adverse events against enhancements in quality of life and symptom alleviation.

The 1-year site-reported serious adverse event profile reveals a significant disparity, with a 4.2% incidence of RV dysfunction in the device arm versus 0% in the control arm. Preexisting RV dysfunction may contribute to this increased risk, as Laplace's law predicts elevated RV wall stress post-implantation of TTVR.[8] However, subgroup analyses are requisite to confirm this potential association.

In summary, the evidence suggests that, although well-conducted, this trial ultimately fails to demonstrate generalizable results applicable to the vast majority of patients with severe secondary or functional TR. Furthermore, this trial is highly prone to bias, and longer follow-up can enable assessment of hard primary endpoints, while eliminating the risk of bias induced by soft endpoints, such as quality of life and symptoms.

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