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VIEWPOINT

Unblinded trials of transcatheter interventions with subjective endpoints: what are the implications?

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Recently, two breakthrough transcatheter devices were approved by the U.S. Food and Drug Administration (FDA) for improving health status in patients with symptomatic severe tricuspid regurgitation (TR) despite optimal medical therapy (OMT). The approval of these devices has sparked a debate about whether unblinded trials with bias-/placebo effect-prone outcomes – such as symptom status, functional capacity and quality of life (QoL) – provide valid scientific evidence to establish "reasonable assurance" of a device's safety and effectiveness for approval.

The two devices – EVOQUE (Edwards Lifesciences) for transcatheter tricuspid valve replacement (TTVR)[1] and the TriClip G4 (Abbott) system for tricuspid transcatheter edge-to-edge repair (T-TEER)[2] – were approved based on supportive data from two pivotal trials, TRISCEND II[1] and TRILUMINATE[3], respectively. Both were prospective, open-label, multicentre, randomised controlled trials comparing the TTVR or T-TEER device plus OMT versus OMT alone. Both trials met their primary safety and effectiveness endpoints. In TRISCEND II, the primary effectiveness endpoint was a hierarchical composite of improvements in: Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS) score >10, at least 1 New York Heart Association (NYHA) Functional Class, and 6-minute walk distance (6MWD) of at least 30 m from baseline to 6 months. In TRILUMINATE, the primary effectiveness endpoint was a hierarchical composite of mortality or tricuspid valve (TV) surgery, heart failure hospitalisation, and improvement in KCCQ-OS score >15 from baseline to 1 year. The primary effectiveness endpoint in both trials was driven mainly by improvements in patient-reported QoL and investigator-adjudicated functional status, without any significant impact on clinical outcomes, the biomarker NT-proBNP or the intensity of medical therapy.

The 1-year follow-up results of TRISCEND II were recently published, and the favourable 7-component hierarchical composite effectiveness endpoint was driven primarily by improvements in symptoms and QoL[4]. There were significantly increased risks of bleeding and pacemaker implantation with TTVR, which adversely impacted the overall benefit-risk[4]. A deeper dive into health status revealed that the greatest QoL improvement at 1 year was observed in patients with massive or torrential TR at baseline in whom right ventricular function and functional capacity were less impaired[5]. Unlike in TRISCEND II, the improvement in KCCQ-OS in TRILUMINATE was not related to the baseline severity of TR, and the vast majority of health status improvement was evident within 30 days of intervention. In contrast, there was a moderately large health status benefit compared with OMT at 30 days that continued to increase up to 6 months in TRISCEND II[5]. While the reduction in TR grade was impressive in both trials, whether it represents merely a cosmetic effect or a clinically meaningful benefit that alters the natural history of the disease is not clear, as the health status improvement in both trials was driven by outcomes that are susceptible to a bias/placebo effect in unblinded trials.

Open-label trials, where patients and investigators are aware of assigned therapy, are rarely adequate to support labelling claims based on patient-reported outcomes (PRO). There are several examples of cardiovascular device trials in which a favourable treatment effect on PRO in unblinded trials was not replicated in blinded, sham-controlled trials. For example, the results of two trials assessing haemodynamic monitoring via an implantable device in heart failure provide instructive

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insights. GUIDE-HF (ClincalTrials.gov: NCT03387813; NYHA Class II-III, left ventricular ejection fraction [LVEF] 39%) used a double-blind, implanted control design, whereas a similar trial MONITOR-HF (International Clinical Trials Registry Platform, NTR7673 [NL7430]; NYHA Class III, LVEF 39%) was open-label, unblinded, and had a non-implanted control group. The KCCQ-OS score at 12 months was significantly improved in the unblinded trial (7.05 vs –0.08 [control]; p=0.013) but not in the blinded trial (5.20 vs 4.12 [control]; p=0.48). Another blinded, sham-controlled trial in patients with heart failure (REDUCE LAP-HF TRIAL II; NCT03088033) failed to demonstrate any positive effects of interatrial shunting on the KCCQ-OS score at 12 months (10.2 vs 9.4; p=0.73), despite a prior open-label, single-arm trial yielding sustained improvements in NYHA Class, QoL and 6MWD after interatrial septal shunt device implantation (REDUCE LAP-HF; NCT01913613). In addition, a randomised, double-blind, placebo-controlled trial of interatrial shunting using the Ventura (V-Wave) in patients with heart failure (RELIEVE-HF; NCT03499236) failed to replicate the improvements in QoL and functional outcomes observed in the roll-in cohort of RELIEVE-HF or an earlier open-label feasibility study without placebo control.

Previous studies with laser myocardial revascularisation[6] or intracoronary infusion of vascular endothelial growth factor (VIVA[7]) have underscored the powerful placebo effect that can lead to durable improvements in angina and exercise duration. Moreover, significant improvements in exercise treadmill time (ETT), angina relief, and QoL (all prone to bias/placebo effect in unblinded trials) observed with percutaneous coronary intervention (PCI)+OMT compared with OMT alone in open-label trials was not replicated in the sham-controlled ORBITA trial (NCT02062593). In another sham-controlled trial (ORBITA-2; NCT03742050), there was a modest placebo-resistant treatment effect of PCI observed on the angina symptom score, driven by daily anginal episodes but not daily antianginal medications. The improvement in ETT with PCI was greater in ORBITA-2 compared with ORBITA (60 vs 21 seconds) but less than that observed with PCI in ACME[8], conducted in 1992 without a placebo control (96 seconds at 6 months). Blinded studies of pacemaker implantation for hypertrophic cardiomyopathy show a strong placebo effect similar to the pacemaker implantation for resistant neurocardiogenic syncope in VPS II[9]. These examples illustrate the powerful impact of the placebo effect on subjective endpoints with transcatheter cardiac interventions in unblinded trials.

Without a sham-controlled trial, it is not possible to provide unequivocal proof that TTVR or T-TEER provides health status benefits beyond a placebo effect. The TRISCEND II investigators assert that the magnitude and durability of health status benefit, the emerging pattern of health status benefit over the first 6 months of follow-up, and the relationship between baseline TR severity and the magnitude of health status benefit provide circumstantial evidence of a true biological effect[5]. While these findings might support a biological component, they might still be consistent with a placebo response. Placebo effects are real biological effects based on patient expectations and/or conditioned responses to certain interventions, and they can amplify, mimic or even change the effects of bioactive substances. The placebo effect in unblinded device trials may be augmented by patient expectations of highly specialised and expensive technological interventions, more frequent repeat visits, attentive patient and care provider interactions, and lack of other treatment options, thereby leading to greater magnitude of the placebo effect compared with drug trials. Neither the magnitude, durability or emerging trajectory, nor the dose-response of the placebo effect convincingly argue against its existence.

Unlike drug trials, sham-controlled device trials are challenging to design and conduct. It is debatable whether blinded implanted control trials are feasible in patients with severe TR. Even if it is possible to initiate such a trial, it would nevertheless be challenging to maintain the blind for a long period, i.e., >6 months. One potential solution would be to evaluate bias-prone QoL and functional outcomes during the shorter blinded phase (3 to 6 months) and assess relatively bias-resistant morbidity-mortality outcomes at longer follow-up when maintaining the blind is no longer feasible. This was the trial design mandated by the FDA for the renal denervation (RDN) trials when the profound reduction in office systolic blood pressure in the unblinded Symplicity HTN-2 trial (NCT00888433; –32 RDN vs +1 control, difference –33 mmHg; p<0.0001) was not replicated in the sham-controlled SYMPLICITY HTN-3 trial (NCT01418261; –14.1 RDN vs –11.7 sham control, difference –2.4 mmHg; p=0.26). Based on these trial designs, two breakthrough devices – Paradise Ultrasound RDN system (Recor Medical) and Symplicity Spyral RDN system (Medtronic) – were approved by the FDA in 2023.

In conclusion, while symptom relief, improved daily function and QoL are important treatment goals, these outcomes should be assessed in rigorously designed and conducted trials that minimise bias and disentangle placebo effects, thereby generating valid and credible evidence to reliably inform and guide clinical practice.

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Conflict of interest statement

S. Kaul is a consultant to Abbott, Amgen, Bayer, Edwards Lifesciences, Medtronic, Recor Medical, and Novo Nordisk.

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