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RESEARCH LETTER
Hypertension

Sotatercept for the treatment of pulmonary arterial hypertension: a meta-analysis of randomized controlled trials

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Pulmonary arterial hypertension (PAH) is a rare and life-threatening disease due to vasoconstriction, vascular remodelling, and thrombosis *in situ* within the pulmonary vasculature, leading to right heart failure with attendant high morbidity and mortality. Despite the advances in PAH-specific therapies, there remains a significant need for treatments that target the underlying cause of the disease. Sotatercept, a fusion protein that targets the transforming growth factor-β (TGF-β) superfamily signalling pathway, has gained interest as a potential therapeutic option. In this meta-analysis, we sought to examine the available evidence from clinical trials to determine precise estimates of the effect size of sotatercept on key clinical outcomes, such as pulmonary vascular resistance (PVR), pulmonary arterial pressure (PAP), right atrial pressure (RAP), and N-terminal pro-brain natriuretic peptide (NT-proBNP), and provide insight into its potential as a treatment for PAH.

This meta-analysis was conducted in accordance with established methodologies[1] and adhered to a pre-specified study protocol that was registered with PROSPERO (CRD42023410804). A comprehensive systematic literature search was conducted in PubMed, Embase, and Scopus utilizing predefined MeSH terms, coupled with Boolean operators 'AND' and 'OR'. The search strategy included the terms 'Pulmonary artery hypertension' and 'Sotatercept'. Our meta-analysis aimed to include all the multicentre, double-blind, randomized controlled trials (RCTs) published till March 2023, which compared the effects of sotatercept with placebo on patients with PAH. Baseline continuous variables were summarized as mean ± standard deviation, while dichotomous variables were described in frequencies or percentages. For each study, outcomes were pooled by calculating the difference in means and their corresponding 95% confidence intervals (CIs). To measure the degree of heterogeneity between studies, the Q test along with I^2 (%) test was used. All the analyses were conducted using STATA version 17.1 (StataCorp, College Station, TX, USA).

We identified two RCTs with a total of 429 patients with PAH.[2,3] The experimental arm included 237 patients with a mean age of 48.55 ± 0.95 years, of whom 82.28% were female. Furthermore, in the experimental arm, 52.74% had idiopathic PAH, and 18.99% had hereditary PAH. In contrast, the placebo arm included 192 patients with a mean age of 46.95 ± 1.35, of whom 79.69% were female. The majority of patients in the placebo arm had idiopathic PAH (65.10%), while 16.15% had hereditary PAH. The pooled analysis showed that sotatercept significantly reduced PVR [standardized mean difference (SMD) = −1.00, 95% CI = (−1.2, −0.79), $P < 0.001$, $I^2 = 0.00\%$], PAP [SMD = −1.34, 95% CI = (−1.6, −1.08), $P < 0.001$, $I^2 = 20.79\%$], RAP [SMD = −0.66, 95% CI = (−0.93, −0.39), $P < 0.001$, $I^2 = 31.62\%$], and the levels of NT-proBNP [SMD = −0.64, 95% CI = (−1.01, −0.27), $P < 0.001$, $I^2 = 59.91\%$] at 24 weeks from baseline (*Figure 1*). Sotatercept also demonstrated a favourable safety profile, with a lower incidence of adverse events compared with placebo (84.8 vs. 87.5%), including a lower frequency of adverse events leading to death (0.4 vs. 3.1%). However, it is worth noting that thrombocytopenia was more commonly reported with sotatercept (71.7 vs. 20.8%), which warrants further attention.

The significant reduction in PVR suggests that sotatercept may exert a beneficial effect on the remodelling of pulmonary vessels, which is a key pathophysiological feature of PAH. Pulmonary arterial hypertension is associated with down-regulation of the BMPR-II-Smad1/5/8 pathway, which leads to increased production of activin ligands.[2,4] This, in turn, contributes to the up-regulation of the ActRIIA-Smad2/3 pathway, resulting in a reduction in antiproliferative signalling and an increase in pro-proliferative signalling, leading to pulmonary vascular remodelling.[4] Sotatercept works by restoring the balance between pro-proliferative and antiproliferative signalling,[2] which may help to slow down or even reverse the process of pulmonary vascular remodelling that occurs in PAH. The decline in NT-proBNP levels also suggests that sotatercept can improve cardiac function in PAH patients, which is crucial for long-term outcomes. N-terminal pro-brain natriuretic peptide is a biomarker that reflects the degree of cardiac dysfunction in PAH patients and is commonly used as a surrogate secondary endpoint in clinical trials.

It is important to note that the small sample size in these RCTs can have several implications. First, the findings may have limited generalizability, as the small sample size may not be representative of the

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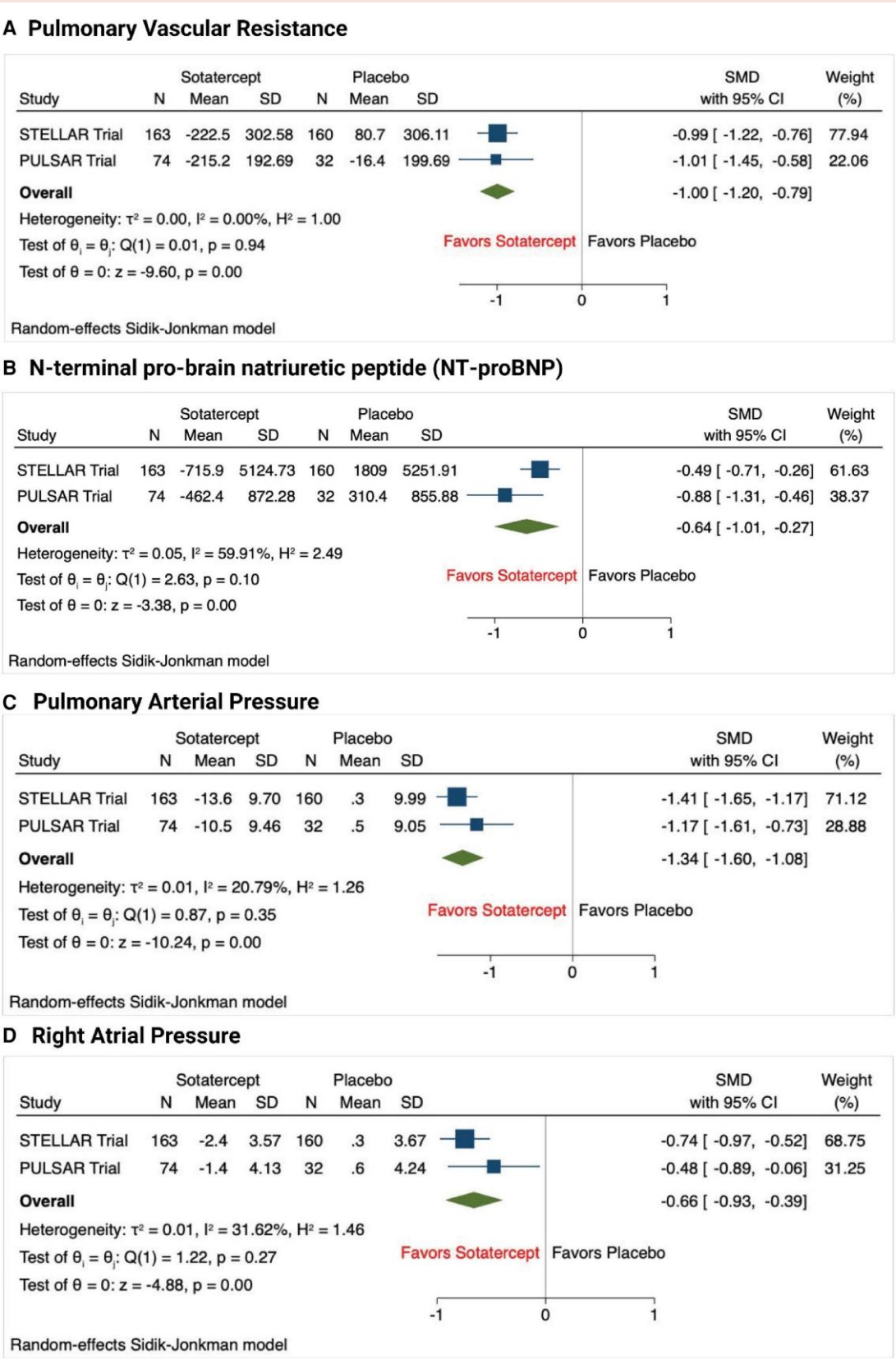

Figure 1 Forest plot of meta-analysis of outcomes: (*A*) pulmonary vascular resistance, (*B*) N-terminal pro-brain natriuretic peptide level, (*C*) pulmonary arterial pressure, and (*D*) right atrial pressure.

broader PAH population. Second, small sample sizes can increase the risk of Type I and Type II errors, and finally, a small sample size may not capture the full range of adverse events associated with sotatercept treatment. Rare adverse events may not be detected, and the safety profile of sotatercept may not be fully understood.

The interpretation of our meta-analysis results should take into consideration several key points. First, the analysis included two trials, each with distinct dosing regimens: one trial featured 0.3 vs. 0.7 mg/kg vs. placebo (PULSAR), while the other had 0.7 mg/kg vs. placebo (STELLAR). Notably, both treatment arms were combined in the analysis. Secondly, it is essential to recognize that the results of our meta-analysis are based on a limited pool of data, with only two trials included in the analysis. Despite these limitations, our findings suggest that sotatercept is an effective treatment option for PAH, with the potential to improve both pulmonary and cardiac function. As such, sotatercept may represent an important addition to the current armamentarium of PAH treatments and may offer new hope for patients who have previously experienced limited treatment options and poor outcomes. However, further studies are needed to determine the optimal dosing and treatment duration, as well as to evaluate the long-term safety and efficacy of sotatercept in diverse patient populations.

Lead author biography

Vikash Jaiswal is a doctor and outcome-based cardiovascular researcher at Larkin Community Hospital, South Miami, FL, USA. Alongside, he runs his own JCCR Cardiology Research Group, which has published quality papers in reputable journals. He is interested in exploring the field of cardio-oncology, preventive cardiology, and racial disparities among cardiovascular outcomes. He won the Prestigious Paul Dudley White International Scholar Award in 2021 and 2022 from American Heart Association for best Cardiovascular Research from the Philippines and Indian region. His father and elder brother Dr Akash Jaiswal keep motivating him to perform his best towards humanity and in the field of medicine.

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Data availability

The data underlying this article are available in the article and rest will made available upon resonable request from from corresponding/lead author.

Author contributions

V.J. contributed to the conception or design of the work. S.P.A. contributed to the acquisition, analysis, or interpretation of data for the work. V.A., V.J., D.B., V.B., A.D., T.D.M., and G.C.F. drafted the manuscript. G.C.F. and T.D.M. critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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