

RESEARCH LETTER

Analysis of the Single Ventricle Reconstruction Trial Using Restricted Mean Survival Time and Shunt Type Received

Stephen J. Dolgner  , MD; Yuen L. Tjoeng, MD, MS; Titus Chan , MD, MS, MPP

The SVR (Single Ventricle Reconstruction) trial was a landmark trial in congenital heart surgery comparing outcomes of infants with single ventricle heart disease randomized to a modified Blalock-Thomas-Taussig shunt (MBTTS) versus a right ventricle-to-pulmonary artery shunt (RVPAS) for pulmonary blood flow.¹ One-year outcomes showed higher survival for the RVPAS group than the MBTTS group. However, subsequent evaluations up to 6 years after surgery have not identified a significant survival difference.² The authors noted nonproportional hazards between groups and used both a Wald test and log-rank test at given times as their primary end point. However, these analyses do not fully account for early differences in mortality, instead prioritizing the final survival rate.³ Other studies evaluating groups with nonproportional hazards have identified survival differences between groups with a similar absolute survival at a given time because of the role of nonproportional hazards.⁴

An alternative approach to analyzing trials with nonproportional hazards is the use of restricted mean survival time (RMST).³ This allows survival analysis without any assumptions on proportional hazards. The output of this method is the difference in average survival time between groups; analogous to comparing the areas under the survival curves.

The National Institutes of Health/National Heart, Lung, and Blood Institute Pediatric Heart Network Single Ventricle Reconstruction Trial and Single

Ventricle Reconstruction Extension Study data sets were used for this study. These data are publicly available and analysis details are available from the corresponding author upon reasonable request. Institutional Review Board approval was not required as the public use data sets contain no personally identifiable information. Data were downloaded from https://www.pediatricheartnetwork.com/pud_login.asp?study_id=SVR on 07/14/2021. We evaluated differences in transplant-free survival (TFS) at 3 and 6 years of follow-up using RMST analysis. Additionally, given significant crossover after randomization, we evaluated differences based on the initial randomized groups and by ultimate shunt type received. Statistical analysis was performed using R version 3.6.1 using the `survRM2` package.

The SVR trial population includes 555 infants, of which 549 are included in the analysis, similar to prior publications; 275 were randomized to MBTTS, and 274 to RVPAS. Comparing randomized groups at 3 years, TFS in the MBTTS group was lower than the RVPAS group (RMST 713 versus 797 days, respectively; $P=0.036$). At 6 years, the difference was no longer significant (RMST 1370 versus 1511 days, respectively; $P=0.091$), a finding similar to previously reported results.

However, 47 patients crossed over between groups after randomization, resulting in 268 patients ultimately receiving the MBTTS and 281 receiving the

Key Words: cardiology ■ congenital heart surgery ■ single ventricle ■ survival analysis ■ nonproportional hazards

Correspondence to: Stephen J. Dolgner, MD, 6651 Main St, Suite E1920, Houston, TX 77030. Email: sjdolgne@texaschildrens.org

For Sources of Funding and Disclosures, see page 3.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

JAHA is available at: www.ahajournals.org/journal/jaha

RVPAS. While clinical trials are typically analyzed using intention-to-treat, given that the shunt type at the end of the procedure is known and may affect the outcome, we evaluated outcomes by ultimate shunt type. At 3 years, the mean TFS was lower for the MBTTS

group than the RVPAS group (703 versus 804 days, respectively; $P=0.012$). At 6 years, the mean TFS also remained lower in the MBTTS group than the RVPAS group (1349 versus 1528 days, respectively; $P=0.033$ [Figure]).

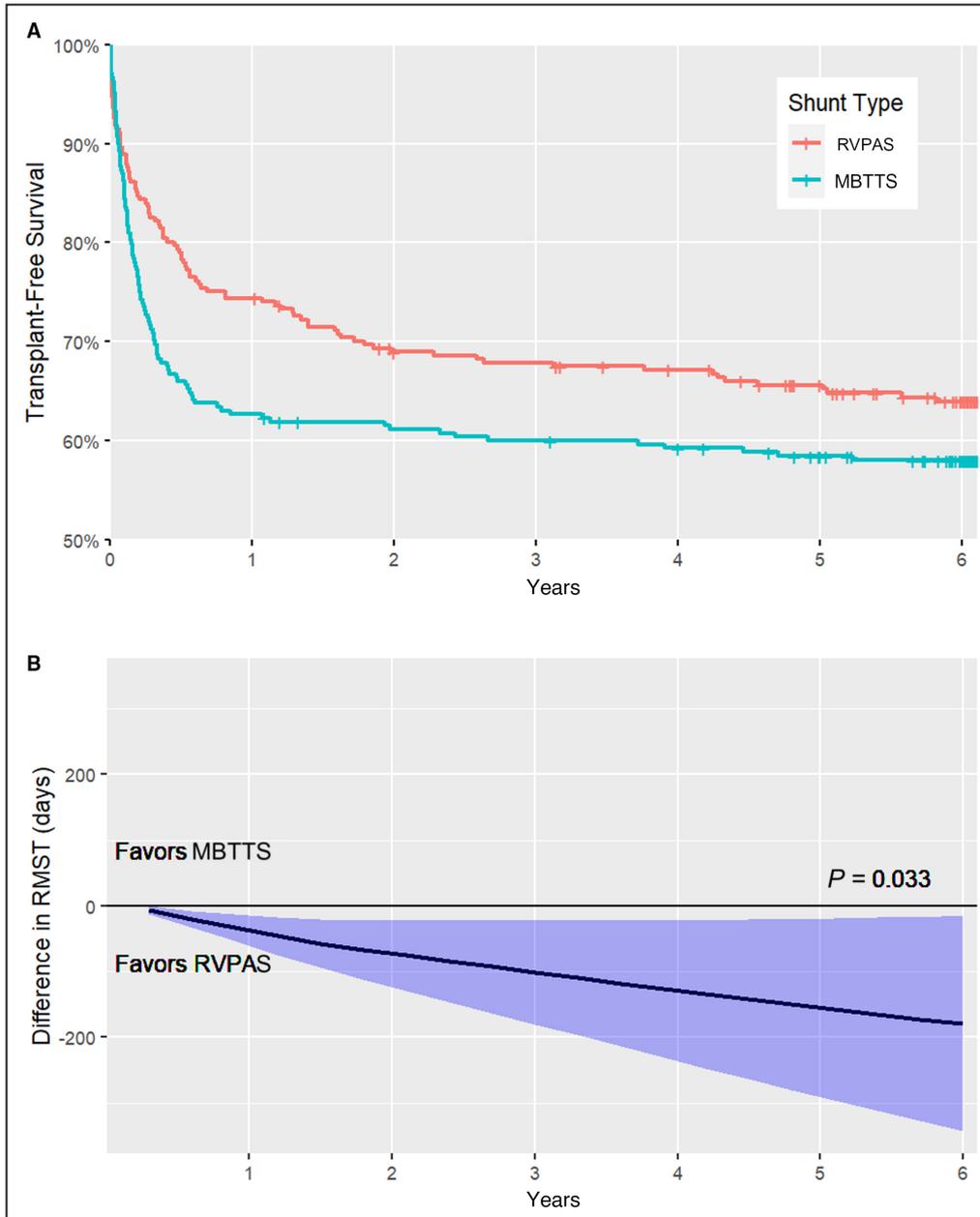


Figure. Restricted mean survival time analysis by shunt type received.

This figure shows superior 6-year outcomes for infants with single ventricle heart disease who received right ventricle-to-pulmonary artery shunt for initial pulmonary blood flow in comparison with those who received modified Blalock-Thomas-Taussig shunt. **A**, Survival estimates for patients who received right ventricle-to-pulmonary artery shunt and modified Blalock-Thomas-Taussig shunt for initial pulmonary blood flow. **B**, Difference in restricted mean survival time between groups by time since initial surgery. Estimates below the horizontal black line favor better survival in the right ventricle-to-pulmonary artery shunt group. *P* value represents the restricted mean survival time difference between groups at 6 years of follow-up. MBTTS indicates modified Blalock-Thomas-Taussig shunt; RMST, restricted mean survival time; and RVPAS, right ventricle-to-pulmonary artery shunt.

To better understand these differences, we evaluated the 6-year TFS of patients stratified into 4 groups: randomized to and received RVPAS (n=254: 65% [95% CI, 59%–71%]), randomized to RVPAS and received MBTTS (n=20: 45% [95% CI, 28%–73%]), randomized to and received MBTTS (n=248: 59% [95% CI, 53%–66%]), and randomized to MBTTS and received RVPAS (n=27: 55% [95% CI, 39%–78%]). Patients who received RVPAS after MBTTS randomization had similar TFS to those who were randomized to and received the MBTTS (6-year RMST difference, $P=0.795$). However, TFS for those who received an MBTTS after being assigned an RVPAS was inferior to those who were assigned and received an RVPAS (6-year RMST 1023 versus 1550 days, respectively; $P=0.031$). When analyzed by intention-to-treat, infants assigned to receive an RVPAS are analyzed together, with patients who ultimately received an MBTTS decreasing the average survival time of patients randomized to an RVPAS. Similarly, when the analysis is limited to only those patients who received the shunt to which they were randomized, the differences between groups persist (6-year RMST 1375 days [MBTTS] versus 1550 days [RVPAS]; $P=0.044$).

Thus, when analyzed by ultimate shunt received, patients with an RVPAS had superior TFS at 6-year follow-up in comparison with those who received an MBTTS; there is an early survival advantage that persists to 6-year follow-up. This is similar to results from a propensity-matched cohort of the Congenital Heart Surgeons' Society, which found improved 6-year survival among infants with critical left ventricular outflow tract obstruction who received an RVPAS in comparison with those who received an MBTTS.⁵ Overall, these results suggest that there is a difference in survival between groups at 6 years when accounting for nonproportional hazards and ultimate shunt received at initial surgery. Furthermore, this analysis suggests

that the RVPAS may be the preferable source of pulmonary blood flow for infants undergoing a Norwood palliation.

ARTICLE INFORMATION

Received March 28, 2022; accepted July 25, 2022.

Registration

URL: <https://clinicaltrials.gov/ct2/show/NCT00115934>; Unique identifier: NCT00115934.

URL: <https://clinicaltrials.gov/ct2/show/NCT02110823>; Unique identifier: NCT02110823.

Affiliations

Pediatric Cardiology, Heart Center, Texas Children's Hospital, Baylor College of Medicine, Houston, TX (S.J.D.); and The Heart Center, Seattle Children's Hospital, University of Washington, Seattle, WA (Y.L.T., T.C.).

Sources of Funding

None.

Disclosures

None.

REFERENCES

- Ohye RG, Sleeper LA, Mahony L, Newburger JW, Pearson GD, Lu M, Goldberg CS, Tabbutt S, Frommelt PC, Ghanayem NS, et al. Comparison of shunt types in the Norwood procedure for single-ventricle lesions. *N Engl J Med*. 2010;362:1980–1992. doi: 10.1056/NEJMoa0912461
- Newburger JW, Sleeper LA, Gaynor JW, Hollenbeck-Pringle D, Frommelt PC, Li JS, Mahle WT, Williams IA, Atz AM, Burns KM, et al. Transplant-free survival and interventions at 6 years in the SVR trial. *Circulation*. 2018;137:2246–2253. doi: 10.1161/CIRCULATIONAHA.117.029375
- Gregson J, Sharples L, Stone GW, Burman CF, Ohn F, Pocock S. Nonproportional hazards for time-to-event outcomes in clinical trials: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74:2102–2112. doi: 10.1016/j.jacc.2019.08.1034
- Dolgner SJ, Nguyen VP, Krieger EV, Stempien-Otero A, Dardas TF. Long-term adult congenital heart disease survival after heart transplantation: a restricted mean survival time analysis. *J Heart Lung Transplant*. 2021;40:698–706. doi: 10.1016/j.healun.2021.02.019
- Wilder TJ, McCrindle BW, Phillips AB, Blackstone EH, Rajeswaran J, Williams WG, DeCampi WM, Jacobs JP, Jacobs ML, Karamlou T, et al. Survival and right ventricular performance for matched children after stage-1 Norwood: Modified Blalock-Taussig shunt versus right-ventricle-to-pulmonary-artery conduit. *J Thorac Cardiovasc Surg*. 2015;150:1440–50, 1452 e1–8; discussion 1450–1452. doi: 10.1016/j.jtcvs.2015.06.069