

Use of clinical, surrogate, and intermediate endpoints in randomized controlled Fontan trials

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Objectives. Randomized controlled trials (RCT) are pivotal for directing evidence-based clinical care. Selection of meaningful endpoints is an essential part of the study design of an RCT. However, no study has systematically examined endpoint selection in Fontan RCTs. In the present study we sought to examine trends in endpoint selection in contemporary Fontan RCTs.

Methods. A search of the PubMed database was conducted using the keywords 'Fontan circulation', 'Fontan' AND 'randomized controlled trial' OR 'randomized prospective study' to identify all Fontan RCTs published from 2002 to 2017. The following data were extracted from each identified trial: (1) journal, (2) year of publication, (3) study design, (4) intervention, (5) number of patients, (6) number of participating sites and countries, (7) endpoints (primary and secondary), (8) whether the trial met its intended endpoints, and (9) funding sources. Endpoints were categorized as clinical, intermediate or surrogate.

Results. Twenty-two RCT's were found eligible for inclusion. A total of 979 Fontan patients were included in the final analysis. Forty-six primary endpoints were identified. A median of 1 primary endpoint (range 1 - 9) was used per RCT. Eight (17.4%) endpoints were clinical. The majority of these endpoints were categorized as intermediate (n = 25, 54.3%). Change in peak VO₂ was most commonly used (n=8). A total of 100 secondary endpoints were identified, mainly categorized as intermediate (n = 47, 47.0%). Change in heart rate (n = 4) was the most frequently used secondary endpoint. Only nine trials (40.9%) met their intended endpoints. Of the 7 RCT's using clinical endpoints, none were able to reject the null hypothesis. Surrogate and intermediate endpoints were frequently combined in the RCTs (n = 15, 68.2%).

Conclusions. This study is the first to demonstrate the heterogeneity and the frequent use of intermediate and surrogate endpoints in contemporary Fontan RCTs. There is a great need to develop validated and standardized endpoints in Fontan research.