Circulation

ORIGINAL RESEARCH ARTICLE

# Results of the FUEL Trial

Editorial, see p 652

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**BACKGROUND:** The Fontan operation creates a total cavopulmonary connection, a circulation in which the importance of pulmonary vascular resistance is magnified. Over time, this circulation leads to deterioration of cardiovascular efficiency associated with a decline in exercise performance. Rigorous clinical trials aimed at improving physiology and guiding pharmacotherapy are lacking.

**METHODS:** The FUEL trial (Fontan Udenafil Exercise Longitudinal) was a phase III clinical trial conducted at 30 centers. Participants were randomly assigned udenafil, 87.5 mg twice daily, or placebo in a 1:1 ratio. The primary outcome was the between-group difference in change in oxygen consumption at peak exercise. Secondary outcomes included between-group differences in changes in submaximal exercise at the ventilatory anaerobic threshold, the myocardial performance index, the natural log of the reactive hyperemia index, and serum brain-type natriuretic peptide.

**RESULTS:** Between 2017 and 2019, 30 clinical sites in North America and the Republic of Korea randomly assigned 400 participants with Fontan physiology. The mean age at randomization was 15.5±2 years; 60% of participants were male, and 81% were white. All 400 participants were included in the primary analysis with imputation of the 26-week end point for 21 participants with missing data (11 randomly assigned to udenafil and 10 to placebo). Among randomly assigned participants, peak oxygen consumption increased by 44±245 mL/min (2.8%) in the udenafil group and declined by 3.7±228 mL/min (–0.2%) in the placebo group ($P$=0.071). Analysis at ventilatory anaerobic threshold demonstrated improvements in the udenafil group versus the placebo group in oxygen consumption (+33±185 [3.2%] versus –9±193 [–0.9%] mL/min, $P$=0.012), ventilatory equivalents of carbon dioxide (–0.8 versus –0.06, $P$=0.014), and work rate (+3.8 versus +0.34 W, $P$=0.021). There was an improvement in myocardial performance index (-0.02 vs 0.01, $P$=0.030), but no change in reactive hyperemia index, or serum brain-type natriuretic peptide level.

**CONCLUSIONS:** In the FUEL trial, treatment with udenafil (87.5 mg twice daily) was not associated with an improvement in oxygen consumption at peak exercise but was associated with improvements in multiple measures of exercise performance at the ventilatory anaerobic threshold.

**CLINICAL TRIAL REGISTRATION:** URL: https://www.clinicaltrials.gov. Unique identifier: NCT02741115.

The full author list is available on page 649.

**Key Words:** exercise test ■ Fontan procedure ■ heart defects, congenital ■ phosphodiesterase 5 inhibitor

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## Clinical Perspective

### What Is New?

- Treatment with udenafil did not result in an increase in peak oxygen consumption, but did result in improvements in measures of exercise performance at the anaerobic threshold.
- Udenafil was well tolerated with side effects limited to those previously known to be associated with phosphodiesterase type 5 inhibitors.

### What Are the Clinical Implications?

- Although udenafil was not shown to improve peak oxygen consumption, this study was the first large-scale, phase III clinical trial to demonstrate a positive effect on measures of exercise performance in adolescents after Fontan palliation.
- These findings indicate that therapy with udenafil improves cardiovascular physiology at moderate levels of exercise in the cohort of patients who have undergone a total cavopulmonary connection.
- Ongoing surveillance is needed to determine the effect of chronic treatment with udenafil on the long-term clinical course of those living with single-ventricle congenital heart disease.

Children born with single-ventricle congenital heart disease (SV-CHD) require a series of surgical interventions for long-term survival. The Fontan operation, the final planned palliative procedure in this series, separates the systemic and pulmonary circulations by creating a total cavopulmonary connection.[1,2] In the absence of a subpulmonary pump, however, the resultant Fontan circulation is characterized by passive pulmonary blood flow, chronically elevated central venous pressure, and low cardiac output.[3–6] Although Fontan physiology is often well tolerated during childhood, cardiovascular efficiency deteriorates through adolescence and into adulthood.[7–12] This deterioration correlates with a decline in exercise capacity and an increase in the prevalence of heart failure symptoms, hospitalizations, and mortality.[13–19]

After the Fontan operation, pulmonary blood flow is dependent on the relationship between central venous pressure, pulmonary vascular resistance, and systemic atrial pressure. In this construct, the role of pulmonary vascular resistance as a modulator of pulmonary blood flow and single-ventricular preload is magnified and critical to circulatory efficiency.[3–6] Prior reports have explored the administration of pulmonary vasodilators, including phosphodiesterase type 5 inhibitors, with mixed results.[20–29] A phase I/II study of udenafil (Mezzion Pharma Co Ltd, Seoul, South Korea), a long-acting phosphodiesterase type 5 inhibitor, was previously completed in adolescents with Fontan physiology and demonstrated tolerability at all tested dosing regimens.[30] A dose of 87.5 mg twice daily was associated with the highest average serum concentration and was not associated with dose-limiting adverse events. In the Pediatric Heart Network's FUEL trial (Fontan Udenafil Exercise Longitudinal; ClinicalTrials.org. Unique identifier: NCT02741115), we evaluate the effect of udenafil on exercise performance and other cardiovascular and functional outcomes over a 6-month period in adolescents who have undergone Fontan palliation.

## METHODS

The FUEL trial was an international, multicenter, randomized, double-blind, placebo-controlled trial of udenafil, in addition to standard care, in adolescents with SV-CHD who had undergone Fontan palliation. The trial was supported by the National Heart, Lung, and Blood Institute–funded Pediatric Heart Network in partnership with the regulatory sponsor, Mezzion Pharma Co Ltd, under a Special Protocol Assessment through the US Food and Drug Administration. The FUEL protocol and consent forms and all subsequent amendments were approved by the Data and Safety Monitoring Board, the institution review board or equivalent at each study center, and regulatory agencies from the United States, Canada, and the South Korea. Consent was obtained from the study participant, or the legal guardian for those <18 years of age. Assent was obtained from participants <18 years of age. The trial design has been published previously,[31] and the data that support the findings of this study are available from the corresponding author on reasonable request.

The FUEL protocol was primarily authored by the first and last authors with assistance from the protocol development committee, which consisted of at least one member from each Pediatric Heart Network core institution, and representatives from Mezzion and the Pediatric Heart Network leadership team, as well. The data for this trial were collected by center investigators and analyzed by the data coordinating center (New England Research Institutes). An independent Medical Monitor adjudicated all serious adverse events and an independent Data and Safety Monitoring Board, appointed by National Heart, Lung, and Blood Institute, reviewed interim data, including safety data, at semiannual Data and Safety Monitoring Board meetings. The lead statistician (second author) vouches for the accuracy of the data and analyses, and all the authors vouch for the fidelity of this report to the trial protocol.

### Trial Population

Individuals between the ages of 12 and 18 years (inclusive) who had undergone the Fontan procedure, who were not receiving treatment with a phosphodiesterase type 5 inhibitor, who were ≥40 kg, and who met the minimum height requirement for cycle ergometry (≥132 cm) were eligible for enrollment. To isolate the effect of udenafil on exercise performance, patients with severe ventricular dysfunction, with severe atrioventricular valve insufficiency, or with a prior clinical exercise test in which peak oxygen consumption was <50% of predicted for age and sex, were excluded. The full list of inclusion and exclusion criteria is listed in the study protocol.

## Randomization and Study Procedures

Enrolled participants were assigned to udenafil or placebo in a 1:1 ratio in a double-blind manner using randomly permuted blocks and stratified by ventricular morphology (left ventricle versus right ventricle or mixed). Randomization assignments were generated by a web-based algorithm after confirmation of trial eligibility and consent.

Baseline clinical testing completed before drug initiation included a blood draw to measure brain-type natriuretic peptide (BNP) level, a cardiopulmonary exercise test using a standardized cycle ergometer ramp protocol (previously described in children and adolescents with Fontan physiology[32]), a standardized echocardiogram, and an assessment of peripheral vascular function using peripheral arterial tonometry (PAT) measured by finger cuff (EndoPAT; Itamar Medical, Israel). Participants who achieved maximal effort, defined as respiratory exchange ratio ≥1.10 at peak exercise during cardiopulmonary exercise test, were eligible for randomization and study drug initiation. Participants who did not achieve maximal effort were given a subsequent opportunity to repeat the exercise test within 2 weeks of the initial attempt. End-of-study clinical testing included repeat measurement of serum BNP, cardiopulmonary exercise test, echocardiogram, and PAT.

## Primary and Secondary End Points

The primary aim was to determine the effect of udenafil on exercise capacity in adolescents with Fontan physiology over a 6-month period. The primary outcome was the between-group difference in the change in oxygen consumption at peak exercise (peak $Vo_2$) from baseline to the 26-week visit. Secondary exercise outcomes included between-group differences in change in additional measures at maximal exertion, and change in measures of submaximal exercise at the ventilatory anaerobic threshold (VAT), as well. All measurement of values for exercise testing was initially made by the exercise physiologists and physicians at the individual participating sites. These were subsequently reviewed for accuracy in a blinded fashion

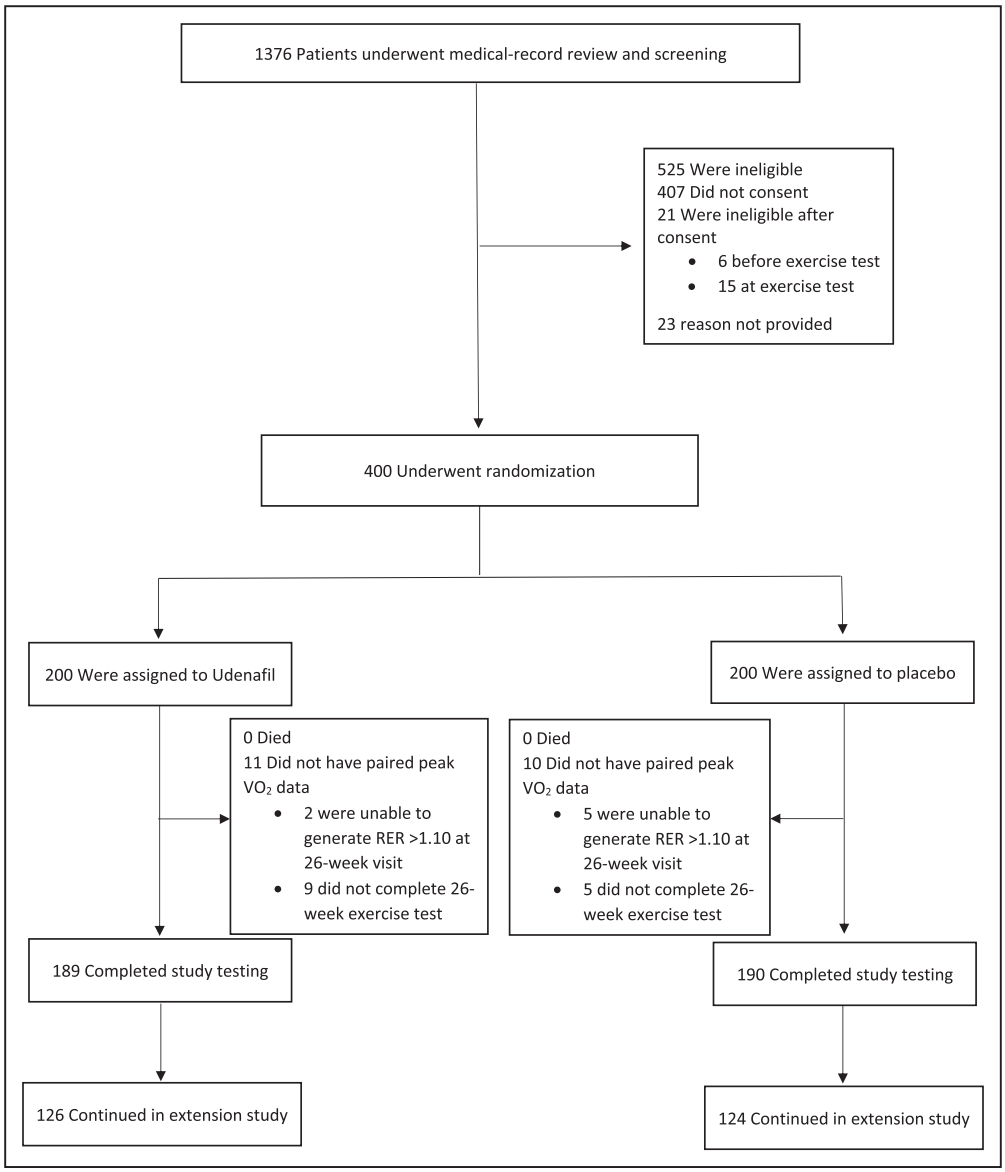


**Figure 1. Random assignment and treatment of FUEL trial (Fontan Udenafil Exercise Longitudinal) participants.**
Peak $Vo_2$ denotes oxygen consumption at peak exercise. RER indicates respiratory exchange ratio.

at each site by one of two trained reviewers (M.G.M., S.M.P.) in conjunction with the sites' exercise teams before finalization. For both peak $Vo_2$ and $Vo_2$ at VAT, unindexed oxygen consumption was evaluated to avoid the introduction of confounding based on short-term change in body habitus. An analysis of oxygen consumption corrected for body weight is included as Table I in the online-only Data Supplement.

The primary outcome for clinical secondary aims included the between-group differences in change in myocardial performance index, an echocardiographically derived measure of systolic and diastolic ventricular function, change in log-transformed reactive hyperemia index, a PAT-derived measure of peripheral vascular function, and change in log-transformed serum BNP level. Measurements for each of these secondary outcomes were performed at core laboratories. Safety was monitored through adverse event reports, which were collected according to a prespecified protocol of study coordinator outreach, and through ad hoc patient and family communication with members of the study team at each site.

## Statistical Analysis

A sample size of 200 participants per arm was chosen to allow for 90% power to detect a mean treatment difference in change from baseline to 26-week testing in peak $Vo_2$ of 10% with a type 1 error of 0.05. We assumed a baseline SD of 7.235 mL·kg$^{-1}$·min$^{-1}$, a correlation between peak $Vo_2$ measurements of 0.33, a dropout and incomplete testing rate of 10%, and failure to reach maximal effort at the 26-week exercise testing in 15% of participants. These assumptions were based on historical data and reflect a conservative approach to assessing within-participant correlations and failure to reach maximal effort, and the analysis was performed using a 2-sample, independent means *t* test. The primary analysis used the intention-to-treat population to evaluate the difference in the change in the primary outcome between treatment arms. This difference was assessed with an analysis of covariance with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group, with a continuous covariate of baseline peak $Vo_2$. For

**Table 1. Demographic and Clinical Baseline Characteristics for the 400 Participants Randomly Assigned to a Treatment Arm**

| Demographics | Total (n=400) | Udenafil (n=200) | Placebo (n=200) |
|---|---|---|---|
| Age, y | 15.5 (2.0) | 15.4 (2.0) | 15.6 (2.0) |
| Female, n (%) | 161 (40.3) | 89 (44.5) | 72 (36.0) |
| Race, n (%) | | | |
| White | 324 (81.0) | 169 (84.5) | 155 (77.5) |
| Asian | 38 (9.5) | 17 (8.5) | 21 (10.5) |
| Black | 23 (5.8) | 10 (5.0) | 13 (6.5) |
| Other | 15 (3.8) | 4 (2.0) | 11 (5.5) |
| Predominant ventricular morphology, n (%) | | | |
| Right | 176 (44.0) | 89 (44.5) | 87 (43.5) |
| Left | 189 (47.3) | 94 (47.0) | 95 (47.5) |
| Other (indeterminant and biventricular) | 35 (8.8) | 17 (8.5) | 18 (9.0) |
| Participants with a patent fenestration, n (%) | 131 (32.8) | 73 (36.5) | 58 (29.0) |
| Height, cm | 163.6 (9.6) | 162.5 (10.4) | 164.7 (8.7) |
| Weight, kg | 58.1 (13.6) | 57.1 (13.9) | 59.0 (13.2) |
| Body mass index, kg/m$^2$ | 21.6 (4.1) | 21.5 (3.9) | 21.7 (4.2) |

Values presented are mean (SD) or n (%).

**Table 2. Resting Data and Measures of Exercise Performance With Comparison Based on Treatment Arm**

| Resting Data and Performance Measures | Udenafil | | | Placebo | | | *P* Value |
|---|---|---|---|---|---|---|---|
| | Baseline | 26-Week | Change | Baseline | 26-Week | Change | |
| Resting data | | | | | | | |
| Heart rate, bpm | 87.5±15.3 (200) | 86.6±15.4 (191) | –0.9±12.7 (191) | 88.1±14.1 (200) | 87.4±16.1 (195) | –0.6±12.7 (195) | 0.78 |
| Systolic blood pressure, mm Hg | 112.3±12.1 (200) | 110.5±12.0 (191) | –1.8±12.2 (191) | 113.2±12.9 (200) | 112.8±11.6 (195) | –0.2±12.2 (195) | 0.18 |
| Diastolic blood pressure, mm Hg | 68.4±9.5 (200) | 65.3±9.9 (191) | –2.9±9.7 (191) | 69.3±10.1 (200) | 69.4±9.1 (195) | 0.2±10.7 (195) | 0.003 |
| Oxygen saturation, % | 92.8±3.9 (200) | 93.3±3.5 (191) | 0.5±2.4 (191) | 93.2±3.8 (200) | 92.9±3.7 (195) | –0.3±2.8 (195) | 0.002 |
| Peak exercise | | | | | | | |
| Oxygen consumption (mL/min)* | 1562±437 (200) | 1606±452 (200) | 44±245 (200) | 1627±414 (200) | 1623±432 (200) | –3.7±228 (200) | 0.071 |
| Work rate, W | 120±32 (198) | 124±32 (187) | 3.2±14 (186) | 123±32 (199) | 127±32 (189) | 2.6±14 (188) | 0.85 |
| Heart rate, bpm | 165±20 (200) | 165±20 (189) | –1.4±11 (189) | 168±22 (199) | 166±21 (190) | –2.5±13 (189) | 0.56 |
| Respiratory rate, breaths/min | 51±11 (199) | 50±12 (188) | –1.1±10 (187) | 51±13 (200) | 50±12 (189) | –1.5±10 (189) | 0.72 |
| Minute ventilation, L/min | 71±21 (199) | 73±22 (189) | 1.2±14 (188) | 76±22 (200) | 76±21 (190) | –0.1±14 (190) | 0.84 |
| Oxygen saturation, % | 89.2±5.3 (195) | 89.6±4.9 (190) | 0.4±3.4 (186) | 89.8±5.0 (197) | 89.7±5.0 (192) | –0.1±3.4 (190) | 0.21 |
| Anaerobic threshold | | | | | | | |
| Oxygen consumption, mL/min | 1039±301 (170) | 1073±297 (170) | 33±185 (155) | 1021±280 (181) | 1009±276 (172) | –9.0±193 (162) | 0.012 |
| Work, W | 66.2±26 (167) | 70.3±27 (166) | 3.8±16 (152) | 66.1±23 (177) | 66.7±22 (166) | 0.34±14 (157) | 0.021 |
| $VE/Vco_2$ | 34.3±4.9 (170) | 33.5±4.7 (170) | –0.8±3.7 (155) | 34.8±5.2 (181) | 34.5±4.7 (172) | –0.06±3.1 (162) | 0.014 |

Summaries presented as mean±SD (n).

*For analysis of the primary outcome, missing data at the 26-week visit were imputed as equal to the baseline value (no change). *P* value determined for difference in change, comparing udenafil to placebo, using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and a continuous covariate of baseline peak $Vo_2$.

those without data at the 26-week visit, this value was imputed as equal to the baseline value (no change). The α-level was set at 0.05 with 2-sided testing. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc). Secondary analyses included participants who successfully completed the protocol with measurable values at each of the secondary end points. Secondary outcomes of continuous data points were analyzed in the manner described for the primary outcome. To assess the generalizability of findings at the VAT, demographic and clinical characteristics were compared between participants without paired $Vo_2$ at VAT data and those comprising the remainder of the cohort using the Student *t* test and Fisher exact test. The Fisher exact test was used to compare adverse events between the udenafil and placebo cohorts.

# RESULTS

## Participants

From July 2016 to May 2018, 1376 patients at 30 centers were screened (Figure 1). Of these, 200 were randomly assigned to udenafil and 200 to placebo. Mean age at randomization was 15.5 years, mean height was 163.6 cm, and mean weight was 58.1 kg. Sixty percent of participants were male and 81% described their racial identity as white. Those in the placebo group were taller than those in the udenafil group, but baseline characteristics were otherwise similar between groups (Table 1).

## Exercise Measures

Resting, submaximal, and maximal exercise measures are presented in Table 2. Maximal exercise data were available for all participants at baseline testing, and for 379 participants at 26-week testing (189 in the udenafil group and 190 in the placebo group). Reasons for the absence of data at 26-week testing included patient dropout or errors in data capture (n=14) and participant inability to generate a respiratory exchange ratio≥1.10

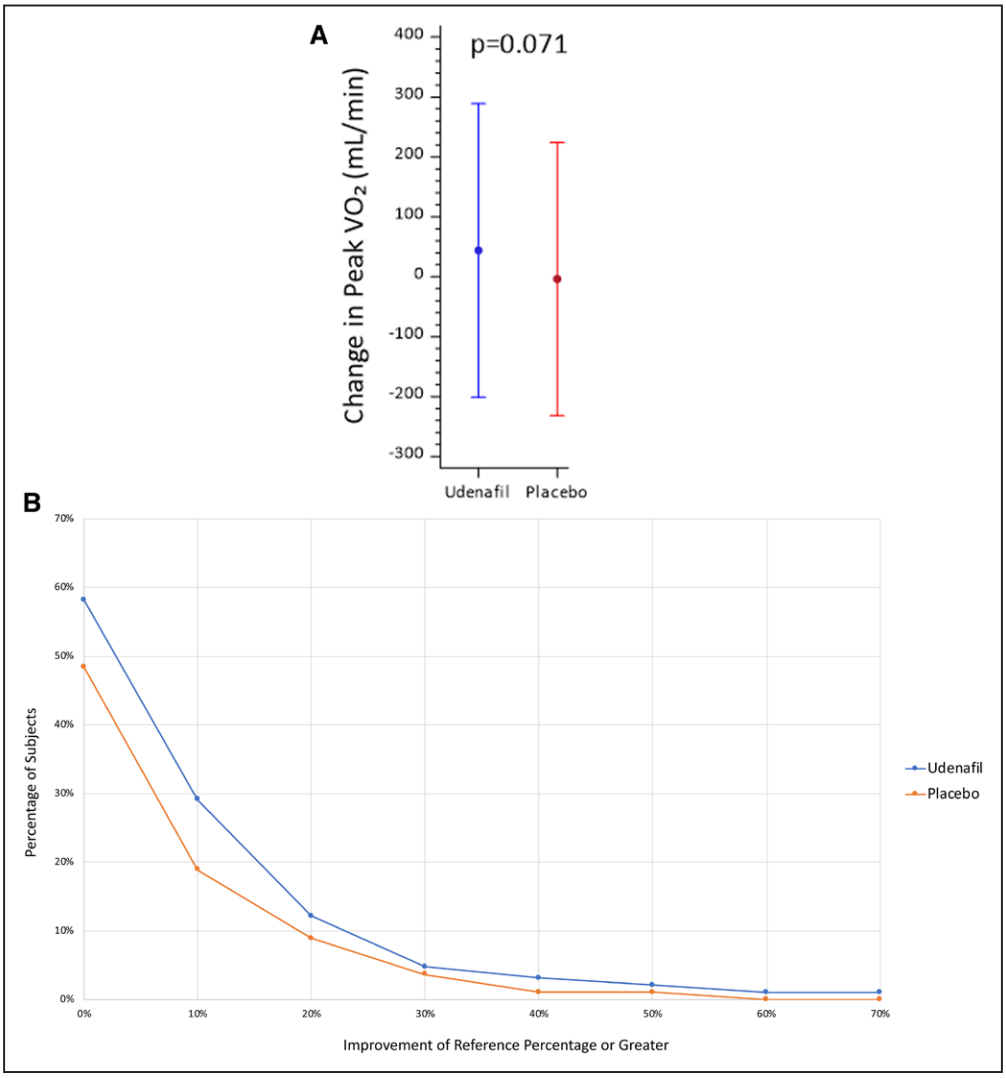


**Figure 2. Oxygen consumption at peak exercise.**
**A**, Demonstration of the difference in the change in mean peak $Vo_2$ from baseline to week 26 along with the SD for each treatment arm. **B**, Demonstration the percentage of participants (*y* axis) who demonstrated improvement in peak $Vo_2$ by the reference percentage or greater (*x* axis).

(n=7). There was no difference in the change from baseline to 26-week testing in resting heart rate, respiratory rate, or systolic blood pressure between the udenafil and placebo groups. Peak minute ventilation at baseline (predrug exposure) was higher in the placebo group, but there was no difference in the change in minute ventilation between groups. There was a small but statistically significant increase in resting oxygen saturation and a small but statistically significant decrease in diastolic blood pressure in the udenafil group.

Analysis at maximal exercise demonstrated an increase in peak $Vo_2$ of 44 mL/min (2.8%) in the udenafil group in comparison with a decline of 3.7 mL/min (–0.2%) in the placebo group, although the difference did not reach statistical significance (Figure 2, *P*=0.071). Metabolic data for the calculation of $Vo_2$ at VAT were available for 317 participants: 155 in the udenafil group and 162 in the placebo group. There was no difference in the baseline demographic or clinical characteristics of this subgroup in comparison with the larger cohort (Table II in the online-only Data Supplement). For those with paired $Vo_2$ at VAT data, there was a statistically significant improvement of 33 mL/min (3.2%) in the udenafil group in comparison with a decrease of 9 mL/min (–0.9%) in the placebo group (Figure 3, *P*=0.012). Ventilatory equivalents of carbon dioxide measured at VAT ($VE/Vco_2$) significantly decreased (improved ventilatory efficiency) by 0.8 in the udenafil group in comparison with 0.06 in the placebo group (*P*=0.014), whereas the work rate significantly improved by 3.8 W (5.7%) in the udenafil group in comparison with 0.34 W (0.5%) in the placebo group (Figure 4, *P*=0.021).

## Secondary Aims

Paired echocardiographic data for the measure of myocardial performance index were available in 250 participants (63%): 122 in the udenafil group and 128 in the placebo group (Table 3). These data demonstrate small improvement in myocardial performance index in

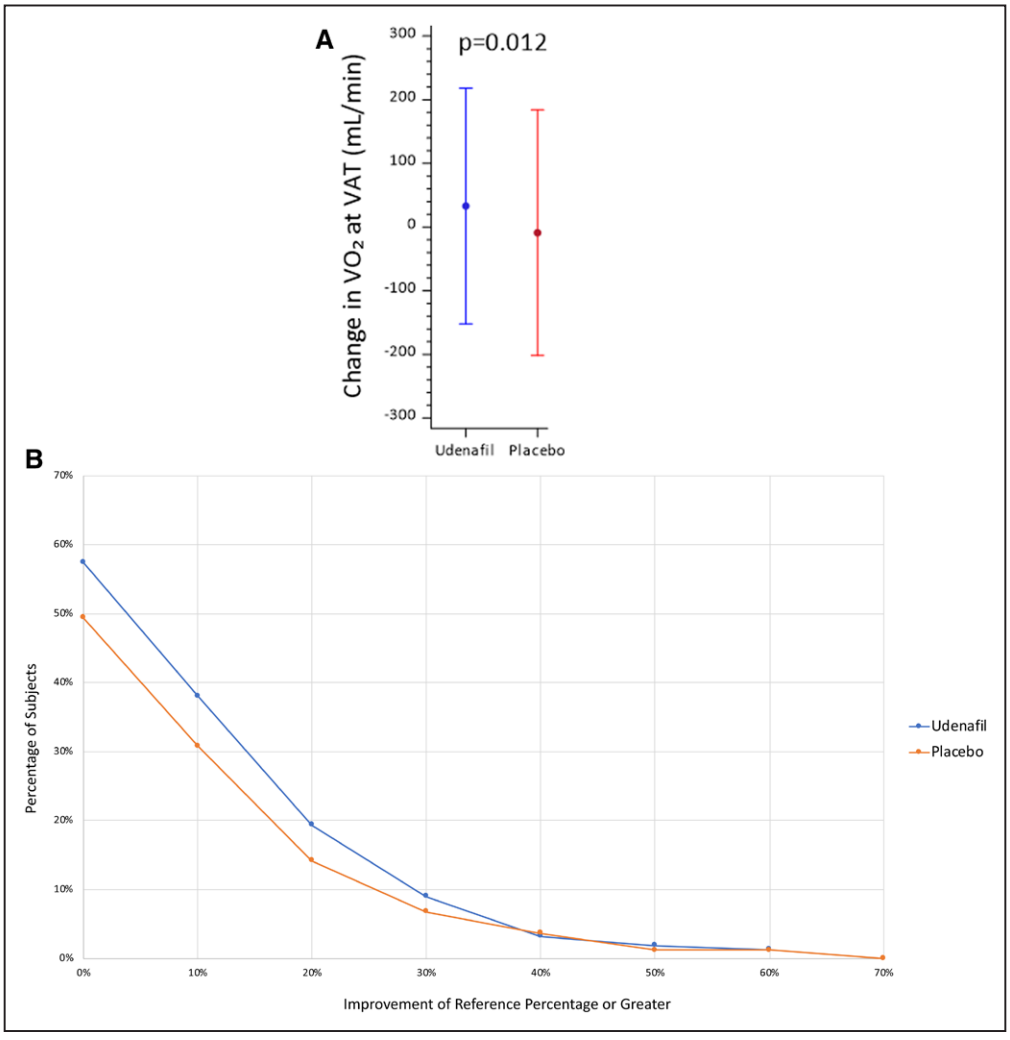


**Figure 3. Oxygen consumption at the ventilatory anaerobic threshold.**
**A**, Demonstration of the difference in the change in mean $Vo_2$ at ventilatory anaerobic threshold (VAT) from baseline to week 26 along with the SD for each treatment arm. **B**, Demonstration of the percentage of participants (*y* axis) who demonstrated improvement in $Vo_2$ at VAT by the reference percentage or greater (*x* axis).

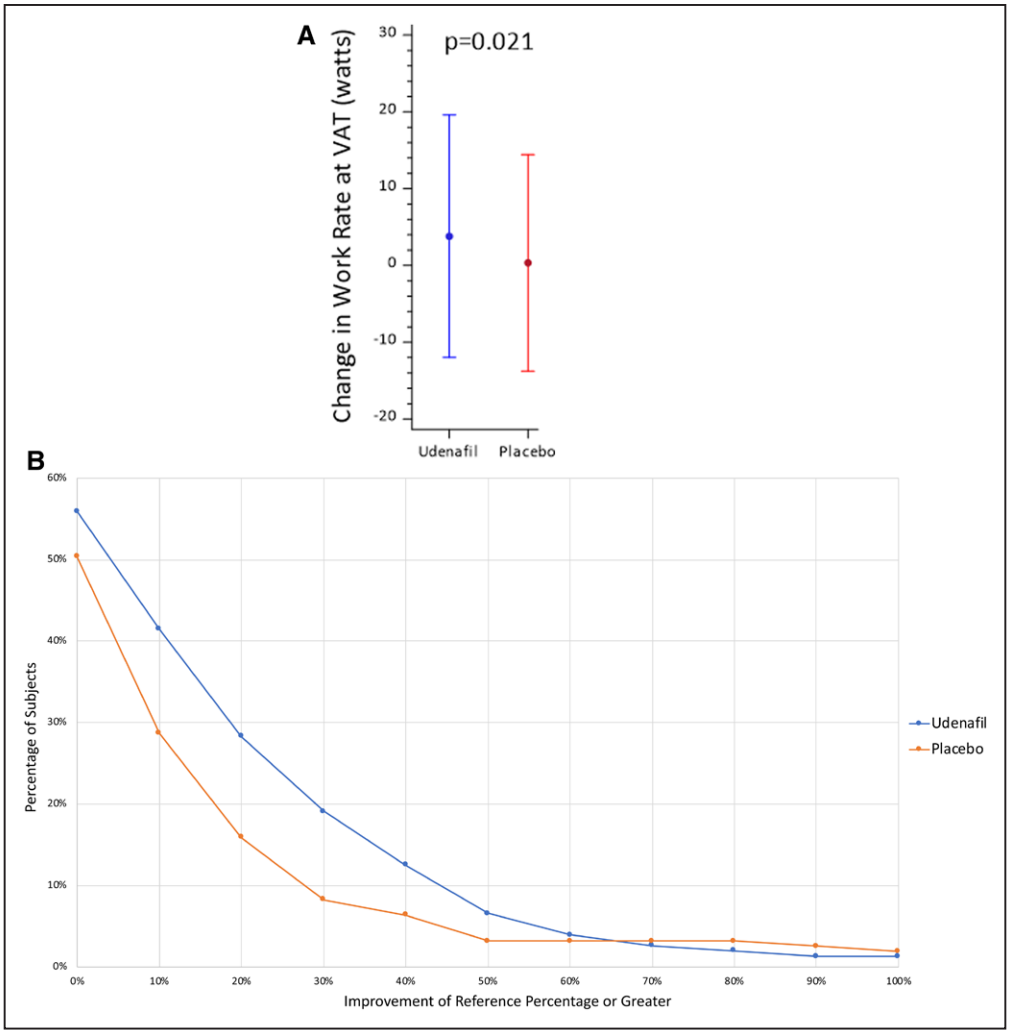


**Figure 4. Work at the ventilatory anaerobic threshold.**
**A**, Demonstration of the difference in the change in mean work rate at ventilatory anaerobic threshold (VAT) from baseline to week 26 along with the SD for each treatment arm. **B**, Demonstration of the percentage of participants (*y* axis) who demonstrated improvement in work rate by the reference percentage or greater (*x* axis).

the udenafil group relative to the placebo group (-0.02 vs 0.01, *P*=0.03). Paired PAT-derived vascular function data were available in 328 participants (81%): 163 in the udenafil group and 165 in the placebo group. There were nonsignificant improvements in log-transformed reactive hyperemia index in both the udenafil and placebo groups (0.07 versus 0.05, *P*=0.59). Paired measures of serum BNP level were available in 378 participants (95%): 187 in the udenafil group and 191 in the placebo group. The change in log serum BNP level was not different between groups (*P*=0.18).

## Safety and Tolerability

Udenafil and placebo were well tolerated by study participants. There were no deaths in the study cohort. A total of 24 participants (6%) experienced a serious adverse event: 14 in the udenafil group and 10 in the placebo group. There were 3 events in the udenafil group and 2 events in the placebo group that were thought to have a possible, probable, or definite relationship to the study drug. Those that occurred in the udenafil group included unilateral retinal artery and vein thrombosis, transient lower extremity diplegia, and transient dyspnea. Frequent nonserious adverse events thought to have a possible, probable, or definite relationship to the study drug are listed in Table 4. Headache, facial flushing, abdominal pain, epistaxis, and erection (male participants) were more common in the udenafil group. There were no reported episodes of priapism. All other adverse events occurred with similar frequency between the groups.

# DISCUSSION

We report the results of the FUEL trial, a phase III clinical trial of udenafil in children with SV-CHD who have undergone the Fontan operation. Although the relative

**Table 3. Secondary Nonexercise Outcomes With Comparison Based on Treatment Arm**

| Outcomes | Udenafil | | | Placebo | | | *P* Value |
|---|---|---|---|---|---|---|---|
| | Baseline | 26-Week | Change | Baseline | 26-Week | Change | |
| Echocardiography | | | | | | | |
| Myocardial performance index | 0.45±0.21 (150) | 0.42±0.15 (146) | –0.02±0.11 (122) | 0.46±0.18 (155) | 0.45±0.21 (148) | 0.01±0.13 (128) | 0.03 |
| EndoPAT | | | | | | | |
| Natural log reactive hyperemia index | 0.46±0.24 (184) | 0.52±0.30 (174) | 0.07±0.30 (163) | 0.47±0.33 (186) | 0.51±0.30 (170) | 0.05±0.37 (165) | 0.59 |
| Biomarker | | | | | | | |
| Log serum brain-type natriuretic peptide* | 2.46±1.00 (200) | 2.53±1.01 (187) | 0.08±0.90 (187) | 2.27±1.14 (199) | 2.30±1.19 (192) | 0.03±1.13 (191) | 0.18 |

Values presented are mean±SD (n).

*BNP measurements reported by the laboratory as <2.0 were imputed as 1.0. *P* value determined for difference in change using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and a continuous covariate of baseline peak $Vo_2$.

improvement in peak $Vo_2$ in the udenafil group did not reach statistical significance in comparison between treatment arms, treatment with udenafil did lead to statistically significant improvements in prespecified secondary outcome measures of submaximal exercise. Participants randomly assigned to udenafil had superior gains in oxygen consumption, work rate, and ventilatory efficiency at the anaerobic threshold. The data likewise demonstrate an improvement in the myocardial performance index, but not in the PAT-derived reactive hyperemia index or BNP. Overall, udenafil was well tolerated with few serious adverse events, and the side effects were limited to those known to be associated with phosphodiesterase type 5 inhibitor therapy.[21,33,34]

Although the Fontan operation and its modifications have led to the survival of a generation of patients with otherwise terminal SV-CHD, the circulation created by that procedure suffers from inherent physiological flaws: central venous pressure is chronically elevated and cardiac output is chronically diminished.[3–5] Fundamental limitations to cardiovascular efficiency in the Fontan circulation are many, and commonly include abnormalities in pulmonary vascular resistance, single ventricular diastolic function, systemic and pulmonary vascular endothelial dysfunction, pathological vascular remodeling, and others.[4,35–40] Although each pathological feature of the circulation may represent a potential therapeutic target, pharmacotherapy with agents designed to lower pulmonary vascular resistance make intuitive sense given their broad tolerability, their efficacy for the treatment of pulmonary hypertension, and the unique role of pulmonary vascular resistance as a modulator of cardiac output after Fontan.[4]

Despite the inherent appeal of pulmonary vasodilators, prior studies in those with the Fontan circulation have been equivocal.[20–29] Several small, single-site studies across a range of classes of pulmonary vasodilators have demonstrated an acute improvement after a single dose, but these did not look at sustained effect or chronic usage.[24,26,27,29] Two moderate-sized studies have evaluated the use of endothelin-receptor antagonists in adolescents and adults after Fontan palliation, but these 2 trials demonstrated conflicting results and did not undergo phase I testing in this cohort.[22,25] Furthermore, in the study that was suggestive of a benefit, this benefit was associated with a drop in hemoglobin level, a side effect that is likely to offset the presumed benefit of the drug.[22] The FUEL trial is the first large-scale, multi-institutional study to suggest a physiological benefit associated with the use of a specific pulmonary vasodilator at a dose determined by phase I clinical testing in adolescents with SV-CHD after Fontan palliation.

The challenges of living with Fontan physiology are well demonstrated by evaluations of exercise performance. Adolescents with Fontan physiology have diminished exercise capacity relative to healthy peers, a difference that is accentuated over time and associated with an increased rate of hospitalization and heart failure symptoms.[8–14,18,19] Exercise capacity <50% predicted for age and sex is the approximate threshold beyond which circulation-associated morbidities become common and typically occurs during the third decade of life, but may occur earlier.[14] The ability to improve exercise capacity,

**Table 4. Adverse Events Possibly, Probably, or Definitively Related to Study Drug That Occurred in at Least 5% of Participants in Either Treatment Group**

| Adverse Event | No. of Participants | Udenafil | Placebo | *P* Value* |
|---|---|---|---|---|
| Headache/migraine | 119 (29.8) | 69 (34.5) | 50 (25.0) | 0.049 |
| Flushing | 44 (11.0) | 32 (16.0) | 12 (6.0) | 0.002 |
| Abdominal pain/discomfort | 26 (6.5) | 13 (6.5) | 13 (6.5) | 1.0 |
| Dizziness | 24 (6.0) | 9 (4.5) | 15 (7.5) | 0.29 |
| Nausea/vomiting | 21 (5.3) | 10 (5.0) | 11 (5.5) | 1.0 |
| Increased erection† | 15 (6.3) | 13 (11.7) | 2 (1.6) | 0.002 |
| Epistaxis | 14 (3.5) | 11 (5.5) | 3 (1.5) | 0.053 |

Values shown are n (%).

*Fisher exact test.

†Percentage of male participants.

as a marker of improved circulatory function more generally, is likely to be critical to the long-term health of those who have undergone the Fontan procedure. This trial suggests that udenafil may help to improve key measures of exercise capacity after pharmacological intervention in patients undergoing the Fontan operation.

The FUEL trial was powered to detect a change in peak $Vo_2$ because it is relatively easy to measure and because it has been used in previous trials as an accepted surrogate for cardiac events.[41–44] However, although peak $Vo_2$ may be useful as a surrogate for many cardiovascular disease states, it may not be as relevant an end point after the Fontan operation. In this unique physiology, central venous pressure rather than right ventricular contraction is the primary driver of transpulmonary blood flow and, therefore, cardiac output.[3–6] Because the demand for cardiac output increases with exertion, central venous pressure in the Fontan circulation must rise to meet that demand, but eventually reaches a critical ceiling beyond which it can rise no further.[45] At submaximal exertion, the elevation in central venous pressure does not reach the physiological ceiling, and, thus, outcomes at this level of exercise may be more sensitive to pharmacological manipulation of the pulmonary vasculature. This is demonstrated by the relatively high ratio of both oxygen consumption and work rate at the anaerobic threshold in comparison with peak exercise, and is different from the physiology for those with a subpulmonary ventricle in whom central venous pressure changes very little during exercise and for whom trends in improvement or decline in $Vo_2$ at VAT and peak $Vo_2$ are usually equivalent.

Despite the importance of the findings reported here, there are limitations to this trial. First, to minimize the burden to participants, the study design did not include detailed measures of hemodynamics such as might be obtained with cardiac magnetic resonance imaging or an invasive catheterization study. Also, evaluation of the primary PAT outcome did not reveal a benefit to udenafil over placebo. Further interrogation of the multiple measures provided by PAT testing was not performed in this initial analysis but will be the subject of future analyses. Last, the duration of the FUEL trial precluded a long-term assessment of safety, although this is being addressed by the ongoing FUEL open-label extension study.

In conclusion, treatment with udenafil (87.5 mg twice daily), in addition to standard therapy, was not associated with a statistically significant improvement in oxygen consumption at peak exercise but did demonstrate statistically significant improvements in multiple measures of exercise performance at the VAT and in myocardial performance index. As the first large, multicenter, placebo-controlled, randomized trial to demonstrate a measurable physiological benefit for patients undergoing the Fontan operation, the FUEL trial represents a milestone in the nearly 50-year experience with the Fontan circulation and serves as a model of how public-private partnership can advance science in congenital heart disease. Further study is warranted to determine if udenafil is selectively beneficial for subpopulations within the larger cohort with SV-CHD, and to evaluate the long-term tolerability and safety of treatment.

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## REFERENCES

1. Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax.* 1971;26:240–248. doi: 10.1136/thx.26.3.240
2. Kreutzer G, Galíndez E, Bono H, De Palma C, Laura JP. An operation for the correction of tricuspid atresia. *J Thorac Cardiovasc Surg.* 1973;66:613–621.
3. Gewillig M, Goldberg DJ. Failure of the Fontan circulation. *Heart Fail Clin.* 2014;10:105–116. doi: 10.1016/j.hfc.2013.09.010
4. Egbe AC, Connolly HM, Miranda WR, Ammash NM, Hagler DJ, Veldtman GR, Borlaug BA. Hemodynamics of Fontan failure: the role of pulmonary vascular disease. *Circ Heart Fail.* 2017;10:1–8.
5. Gewillig M, Brown SC, Eyskens B, Heying R, Ganame J, Budts W, La Gerche A, Gorenflo M. The Fontan circulation: who controls cardiac output? *Interact Cardiovasc Thorac Surg.* 2010;10:428–433. doi: 10.1510/icvts.2009.218594
6. Goldberg DJ, Avitabile CM, McBride MG, Paridon SM. Exercise capacity in the Fontan circulation. *Cardiol Young.* 2013;23:824–830. doi: 10.1017/S1047951113001649
7. Dennis M, Zannino D, du Plessis K, Bullock A, Disney PJS, Radford DJ, Hornung T, Grigg L, Cordina R, d'Udekem Y, et al. Clinical outcomes in adolescents and adults after the Fontan procedure. *J Am Coll Cardiol.* 2018;71:1009–1017. doi: 10.1016/j.jacc.2017.12.054
8. Fernandes SM, McElhinney DB, Khairy P, Graham DA, Landzberg MJ, Rhodes J. Serial cardiopulmonary exercise testing in patients with previous Fontan surgery. *Pediatr Cardiol.* 2010;31:175–180. doi: 10.1007/s00246-009-9580-5
9. Giardini A, Hager A, Pace Napoleone C, Picchio FM. Natural history of exercise capacity after the Fontan operation: a longitudinal study. *Ann Thorac Surg.* 2008;85:818–821. doi: 10.1016/j.athoracsur.2007.11.009
10. Jenkins PC, Chinnock RE, Jenkins KJ, Mahle WT, Mulla N, Sharkey AM, Flanagan MF. Decreased exercise performance with age in children with hypoplastic left heart syndrome. *J Pediatr.* 2008;152:507–512. doi: 10.1016/j.jpeds.2007.09.050
11. Paridon SM, Mitchell PD, Colan SD, Williams RV, Blaufox A, Li JS, Margossian R, Mital S, Russell J, Rhodes J; Pediatric Heart Network Investigators. A cross-sectional study of exercise performance during the first 2 decades of life after the Fontan operation. *J Am Coll Cardiol.* 2008;52:99–107. doi: 10.1016/j.jacc.2008.02.081
12. Atz AM, Zak V, Mahony L, Uzark K, D'agincourt N, Goldberg DJ, Williams RV, Breitbart RE, Colan SD, Burns KM, et al; Pediatric Heart Network Investigators. Longitudinal outcomes of patients with single ventricle after the Fontan procedure. *J Am Coll Cardiol.* 2017;69:2735–2744. doi: 10.1016/j.jacc.2017.03.582
13. Diller GP, Dimopoulos K, Okonko D, Li W, Babu-Narayan SV, Broberg CS, Johansson B, Bouzas B, Mullen MJ, Poole-Wilson PA, et al. Exercise intolerance in adult congenital heart disease: comparative severity, correlates, and prognostic implication. *Circulation.* 2005;112:828–835. doi: 10.1161/CIRCULATIONAHA.104.529800
14. Diller GP, Giardini A, Dimopoulos K, Gargiulo G, Müller J, Derrick G, Giannakoulas G, Khambadkone S, Lammers AE, Picchio FM, et al. Predictors of morbidity and mortality in contemporary Fontan patients: results from a multicenter study including cardiopulmonary exercise testing in 321 patients. *Eur Heart J.* 2010;31:3073–3083. doi: 10.1093/eurheartj/ehq356
15. Downing TE, Allen KY, Glatz AC, Rogers LS, Ravishankar C, Rychik J, Faerber JA, Fuller S, Montenegro LM, Steven JM, et al. Long-term survival after the Fontan operation: Twenty years of experience at a single center. *J Thorac Cardiovasc Surg.* 2017;154:243–253.e2. doi: 10.1016/j.jtcvs.2017.01.056
16. Khairy P, Fernandes SM, Mayer JE Jr, Triedman JK, Walsh EP, Lock JE, Landzberg MJ. Long-term survival, modes of death, and predictors of mortality in patients with Fontan surgery. *Circulation.* 2008;117:85–92. doi: 10.1161/CIRCULATIONAHA.107.738559
17. Pundi KN, Johnson JN, Dearani JA, Pundi KN, Li Z, Hinck CA, Dahl SH, Cannon BC, O'Leary PW, Driscoll DJ, et al. 40-year follow-up after the Fontan operation: long-term outcomes of 1,052 patients. *J Am Coll Cardiol.* 2015;66:1700–1710. doi: 10.1016/j.jacc.2015.07.065
18. Cunningham JW, Nathan AS, Rhodes J, Shafer K, Landzberg MJ, Opotowsky AR. Decline in peak oxygen consumption over time predicts death or transplantation in adults with a Fontan circulation. *Am Heart J.* 2017;189:184–192. doi: 10.1016/j.ahj.2017.04.009
19. Udholm S, Aldweib N, Hjortdal VE, Veldtman GR. Prognostic power of cardiopulmonary exercise testing in Fontan patients: a systematic review. *Open Heart.* 2018;5:e000812. doi: 10.1136/openhrt-2018-000812
20. Agnoletti G, Gala S, Ferroni F, Bordese R, Appendini L, Pace Napoleone C, Bergamasco L. Endothelin inhibitors lower pulmonary vascular resistance and improve functional capacity in patients with Fontan circulation. *J Thorac Cardiovasc Surg.* 2017;153:1468–1475. doi: 10.1016/j.jtcvs.2017.01.051
21. Goldberg DJ, French B, McBride MG, Marino BS, Mirarchi N, Hanna BD, Wernovsky G, Paridon SM, Rychik J. Impact of oral sildenafil on exercise performance in children and young adults after the fontan operation: a randomized, double-blind, placebo-controlled, crossover trial. *Circulation.* 2011;123:1185–1193. doi: 10.1161/CIRCULATIONAHA.110.981746
22. Hebert A, Mikkelsen UR, Thilen U, Idorn L, Jensen AS, Nagy E, Hanseus K, Sørensen KE, Søndergaard L. Bosentan improves exercise capacity in adolescents and adults after Fontan operation: the TEMPO (Treatment With Endothelin Receptor Antagonist in Fontan Patients, a Randomized, Placebo-Controlled, Double-Blind Study Measuring Peak Oxygen Consumption) study. *Circulation.* 2014;130:2021–2030. doi: 10.1161/CIRCULATIONAHA.113.008441
23. Mori H, Park IS, Yamagishi H, Nakamura M, Ishikawa S, Takigiku K, Yasukochi S, Nakayama T, Saji T, Nakanishi T. Sildenafil reduces pulmonary vascular resistance in single ventricular physiology. *Int J Cardiol.* 2016;221:122–127. doi: 10.1016/j.ijcard.2016.06.322
24. Rhodes J, Ubeda-Tikkanen A, Clair M, Fernandes SM, Graham DA, Milliren CE, Daly KP, Mullen MP, Landzberg MJ. Effect of inhaled iloprost on the exercise function of Fontan patients: a demonstration of concept. *Int J Cardiol.* 2013;168:2435–2440. doi: 10.1016/j.ijcard.2013.03.014
25. Schuuring MJ, Vis JC, van Dijk AP, van Melle JP, Vliegen HW, Pieper PG, Sieswerda GT, de Bruin-Bon RH, Mulder BJ, Bouma BJ. Impact of bosentan on exercise capacity in adults after the Fontan procedure: a randomized controlled trial. *Eur J Heart Fail.* 2013;15:690–698. doi: 10.1093/eurjhf/hft017
26. Tunks RD, Barker PC, Benjamin DK Jr, Cohen-Wolkowiez M, Fleming GA, Laughon M, Li JS, Hill KD. Sildenafil exposure and hemodynamic effect after Fontan surgery. *Pediatr Crit Care Med.* 2014;15:28–34. doi: 10.1097/PCC.0000000000000007
27. Van De Bruaene A, La Gerche A, Claessen G, De Meester P, Devroe S, Gillijns H, Bogaert J, Claus P, Heidbuchel H, Gewillig M, et al. Sildenafil improves exercise hemodynamics in Fontan patients. *Circ Cardiovasc Imaging.* 2014;7:265–73.
28. Goldberg DJ, French B, Szwast AL, McBride MG, Marino BS, Mirarchi N, Hanna BD, Wernovsky G, Paridon SM, Rychik J. Impact of

sildenafil on echocardiographic indices of myocardial performance after the Fontan operation. *Pediatr Cardiol.* 2012;33:689–696. doi: 10.1007/s00246-012-0196-9
29. Giardini A, Balducci A, Specchia S, Gargiulo G, Bonvicini M, Picchio FM. Effect of sildenafil on haemodynamic response to exercise and exercise capacity in Fontan patients. *Eur Heart J.* 2008;29:1681–1687. doi: 10.1093/eurheartj/ehn215
30. Goldberg DJ, Zak V, Goldstein BH, Chen S, Hamstra MS, Radojewski EA, Maunsell E, Mital S, Menon SC, Schumacher KR, et al; Pediatric Heart Network Investigators. Results of a phase I/II multi-center investigation of udenafil in adolescents after Fontan palliation. *Am Heart J.* 2017;188:42–52. doi: 10.1016/j.ahj.2017.02.030
31. Goldberg DJ, Zak V, Goldstein BH, McCrindle BW, Menon SC, Schumacher KR, Payne RM, Rhodes J, McHugh KE, Penny DJ, et al; Pediatric Heart Network Investigators. Design and rationale of the Fontan Udenafil Exercise Longitudinal (FUEL) trial. *Am Heart J.* 2018;201:1–8. doi: 10.1016/j.ahj.2018.03.015
32. Sleeper LA, Anderson P, Hsu DT, Mahony L, McCrindle BW, Roth SJ, Saul JP, Williams RV, Geva T, Colan SD, et al; Pediatric Heart Network Investigators. Design of a large cross-sectional study to facilitate future clinical trials in children with the Fontan palliation. *Am Heart J.* 2006;152:427–433. doi: 10.1016/j.ahj.2006.02.009
33. Barnes H, Brown Z, Burns A, Williams T. Phosphodiesterase 5 inhibitors for pulmonary hypertension. *Cochrane Database Syst Rev.* 2019;1:CD012621. doi: 10.1002/14651858.CD012621.pub2
34. Chang HJ, Song S, Chang SA, Kim HK, Jung HO, Choi JH, Lee JS, Kim KH, Jeong JO, Lee JH, et al. Efficacy and safety of udenafil for the treatment of pulmonary arterial hypertension: a placebo-controlled, double-blind, phase IIb clinical trial. *Clin Ther.* 2019;41:1499–1507. doi: 10.1016/j.clinthera.2019.05.006
35. Averin K, Hirsch R, Seckeler MD, Whiteside W, Beekman RH 3rd, Goldstein BH. Diagnosis of occult diastolic dysfunction late after the Fontan procedure using a rapid volume expansion technique. *Heart.* 2016;102:1109–1114. doi: 10.1136/heartjnl-2015-309042
36. Goldstein BH, Connor CE, Gooding L, Rocchini AP. Relation of systemic venous return, pulmonary vascular resistance, and diastolic dysfunction to exercise capacity in patients with single ventricle receiving fontan palliation. *Am J Cardiol.* 2010;105:1169–1175. doi: 10.1016/j.amjcard.2009.12.020
37. Hays BS, Baker M, Laib A, Tan W, Udholm S, Goldstein BH, Sanders SP, Opotowsky AR, Veldtman GR. Histopathological abnormalities in the central arteries and veins of Fontan subjects. *Heart.* 2018;104:324–331. doi: 10.1136/heartjnl-2017-311838
38. Khambadkone S, Li J, de Leval MR, Cullen S, Deanfield JE, Redington AN. Basal pulmonary vascular resistance and nitric oxide responsiveness late after Fontan-type operation. *Circulation.* 2003;107:3204–3208. doi: 10.1161/01.CIR.0000074210.49434.40
39. Mitchell MB, Campbell DN, Ivy D, Boucek MM, Sondheimer HM, Pietra B, Das BB, Coll JR. Evidence of pulmonary vascular disease after heart transplantation for Fontan circulation failure. *J Thorac Cardiovasc Surg.* 2004;128:693–702. doi: 10.1016/j.jtcvs.2004.07.013
40. Sarkola T, Jaeggi E, Slorach C, Hui W, Bradley T, Redington AN. Assessment of vascular remodeling after the Fontan procedure using a novel very high resolution ultrasound method: arterial wall thinning and venous thickening in late follow-up. *Heart Vessels.* 2013;28:66–75. doi: 10.1007/s00380-011-0217-2
41. Dallaire F, Wald RM, Marelli A. The role of cardiopulmonary exercise testing for decision making in patients with repaired tetralogy of fallot. *Pediatr Cardiol.* 2017;38:1097–1105. doi: 10.1007/s00246-017-1656-z
42. Mancini D, LeJemtel T, Aaronson K. Peak VO(2): a simple yet enduring standard. *Circulation.* 2000;101:1080–1082. doi: 10.1161/01.cir.101.10.1080
43. Okonko DO, Grzeslo A, Witkowski T, Mandal AK, Slater RM, Roughton M, Foldes G, Thum T, Majda J, Banasiak W, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and nonanemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol.* 2008;51:103–112. doi: 10.1016/j.jacc.2007.09.036
44. Redfield MM, Chen HH, Borlaug BA, Semigran MJ, Lee KL, Lewis G, LeWinter MM, Rouleau JL, Bull DA, Mann DL, et al; RELAX Trial. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial. *JAMA.* 2013;309:1268–1277. doi: 10.1001/jama.2013.2024
45. Navaratnam D, Fitzsimmons S, Grocott M, Rossiter HB, Emmanuel Y, Diller GP, Gordon-Walker T, Jack S, Sheron N, Pappachan J, et al. Exercise-induced systemic venous hypertension in the Fontan circulation. *Am J Cardiol.* 2016;117:1667–1671. doi: 10.1016/j.amjcard.2016.02.042