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Review Article

Drug therapy in the prevention of failure of the Fontan circulation: a systematic review

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Abstract *Background:* The Fontan circulation is the optimal treatment for patients with univentricular hearts. These patients are at high risk of circulatory failure. There is no consensus on the optimal drug treatment for the prevention of failure of the Fontan circulation. The aim of this systematic review was to provide an overview of evidence for drug therapy used in the prevention of Fontan circulatory failure. *Methods:* We searched the Embase database for articles that reported drug therapy in Fontan patients. Studies published between 1997 and 2014 were included if efficacy or safety of medication was assessed, drug therapy aimed to prevent or treat failure of the Fontan circulation, and if the full text was available. Case reports were excluded. *Results:* A total of nine studies were included with a total of 267 Fontan patients; four studies evaluated the medication sildenafil, one iloprost, three bosentan, and one enalapril. Among all, two sildenafil studies reported improvement in exercise capacity, one in exercise haemodynamics, and one in ventricular performance. In the largest study of bosentan, an increase in exercise capacity was found. Enalapril did not result in improvements. *Conclusion:* The studies analysed in this review suggest that bosentan, sildenafil, and iloprost may improve exercise capacity at the short term. Given the limitations of the studies, more, larger, placebo-controlled studies with longer follow-up periods are needed to better understand which drug therapies are effective in the prevention of failure of the Fontan circulation.

Keywords: Fontan circulation; drug therapy; sildenafil; bosentan; enalapril

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The Fontan circulation is a palliative procedure performed in patients born with a functionally single-ventricular heart. The principle of the Fontan operation is based on redirecting systemic venous return directly through the pulmonary circulation. This means that there is no ventricular chamber that is directly involved in sustaining the pulmonary circulation.[1] It has been well documented that in the long term there is a continuing risk of failure of the Fontan circulation;[2,3] 30% of all Fontan patients have late failure of the Fontan circulation at ~20 years of follow-up.[4]

Problems related to the Fontan operation are impaired ventricular function, increased pulmonary vascular resistance, cardiac arrhythmias, thrombosis, ascites, peripheral oedema, cyanosis, lymphatic dysfunction with protein-losing enteropathy, and plastic bronchitis.[5] For the purposes of this review, the term failing Fontan is used in case of reduced pulmonary blood flow, ventricular dysfunction, protein-losing enteropathy, or plastic bronchitis.

Failing of the Fontan circulation has been associated with a progressive decline in exercise capacity.[6] The inability to increase pre-load and decrease after-load during exercise combined with abnormal ventricular function may lead to reduced cardiac output.[7,8]

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Fontan patients are also at risk for developing plastic bronchitis and protein-losing enteropathy. Plastic bronchitis leads to the formation of fibrinomucoid casts in the airways, caused by high central venous pressure and pulmonary resistance, and low cardiac output.[9] Protein-losing enteropathy is characterised by leakage of proteins into the gastrointestinal tract.[10] The mortality is high in Fontan patients with these complications.[1,10]

Despite these well-known problems, data to guide the use of medication to prevent Fontan circulation failure are few.[11] A recent survey in 546 Fontan patients of seven centres reported a wide variation in the use of medication across the participating centres.[12] This has been confirmed by other studies as well. In addition, the study showed that drug therapy has been used for several clinical indications.

The aim of this systematic review was to provide a systematic overview of studies that have been carried out on drug therapy aimed at prevention of failure of the Fontan circulation.

Methods

This systematic review was carried out according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[13] The Embase database was used to search for relevant articles published up to December, 2014; date of search was 15 January, 2015. We used the following search terms: ("Fontan procedure"/de OR (fontan):ab,ti) AND ("drug therapy"/exp OR "cardiovascular agent"/exp OR (drug* OR pharmac* OR agent* OR medication* OR administration* OR sildenafil* OR bosentan* OR (("dipeptidyl carboxypeptidase" OR ace OR "angiotensin converting enzyme") NEAR/3 inhibitor*) OR diuretic* OR Enalapril*):ab,ti) AND (exercise/exp OR "exercise test"/exp OR "heart output"/exp OR (exercise OR ((heart OR cardiac*) NEAR/3 output)):ab,ti) AND [english]/lim NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Conference Paper]/lim OR [Editorial]/lim). An English language restriction was used. We also screened the references lists of review articles and relevant studies to identify other useful articles, but no relevant articles were found.

Resulting publications were assessed independently by two reviewers (N.O. and A.M.). Of the articles found in Embase, titles and abstracts were screened and selected based on the following pre-defined criteria: the study population had to consist of patients with a Fontan circulation, there had to be any kind of drug intervention, efficacy or safety of the medication had to be measured, the drug therapy had to be aimed at decreasing pulmonary resistance, improving exercise performance or ventricular function, or at reducing protein-losing enteropathy, and the article had to be published between 1997 and 2014. As patients who develop plastic bronchitis are generally considered to have developed a failing Fontan circulation and as the primary focus of this article was the prevention of failure of the Fontan circulation, we did not include studies on treatment of plastic bronchitis. If titles and abstracts met the inclusion criteria, the full-text articles were studied. Full-text articles of the selected studies were included if the article still matched the first inclusion criterion, was not a case report, and if the full text was available. In case of disagreement, an agreement was negotiated. The risk of bias within each study was assessed using the Cochrane risk of bias tool.[14] If the risk of all types of bias was high – selection bias, detection bias, performance bias, attrition bias, and reporting bias – quality was considered insufficient and the article was not included in this review.

The following data were extracted: publication year, study design, medication and dosage, number of included patients, type of Fontan procedure, age at inclusion, and follow-up duration. Outcome measures of interest were as follows: ventricular performance – myocardial performance index, velocity time integral, and heart rate – exercise capacity – respiratory rate, minute ventilation, ratio of ventilator effort over carbon dioxide production, peak oxygen uptake (VO_2), pulmonary blood flow index, cardiac index, systemic oxygen saturation, and heart rate – exercise haemodynamics – cardiac index, stroke volume indexed to body surface area, ejection fraction, end-systolic volume indexed to body surface area, systemic vascular resistance index, total pulmonary resistance index, end-systolic volume indexed to body surface area, VO_2, and O_2 saturation.

Results

The search method as described above produced 162 articles in Embase. Of these articles, 26 met the inclusion criteria, and after screening of the full text a total of 10 articles were included in this review. In these articles, nine study populations were described; one of the populations had been described in two articles, using different outcome measures.[15,16] The flowchart of the literature search is given in Figure 1. The study by Tunks et al[17] was not included in this review (figure: quality of article was not sufficient), due to lack of randomisation (selection bias), knowledge of the allocated interventions by outcome assessors, patients, and personnel (detection and performance bias), and there was incomplete outcome data and selective outcome reporting (attrition and reporting bias). The study characteristics and populations are described in Table 1.

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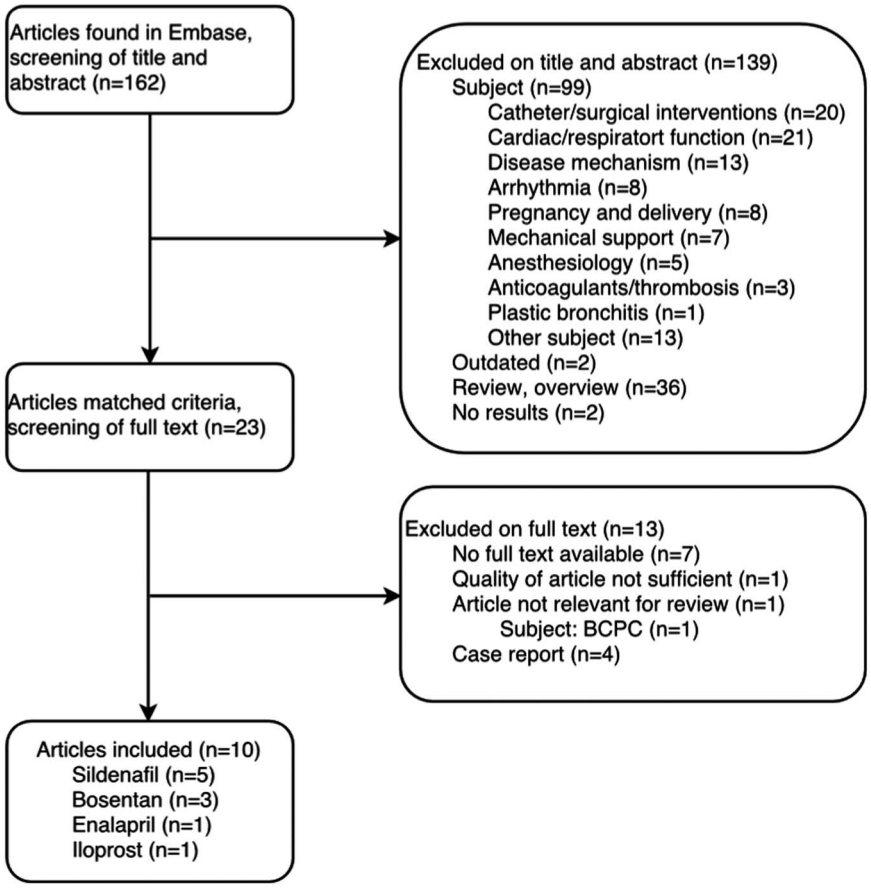

Figure 1.
Flow chart of article selection process.

Of the included studies, four were cross-over, randomised controlled trials,[15,16,18–20] two open-label randomised controlled trials,[21,22] and three were uncontrolled open-label trials.[23–25] Moreover, two articles by Goldberg et al[15,16] on the use of sildenafil were on the same single trial; one of the articles focussed on the exercise test findings[15] and a separate paper evaluated echo findings on ventricular performance.[16] Ventricular performance was a secondary end point of the original trial.[15,16]

Most articles used exercise capacity as the primary outcome measure (n = 8).[15,18–23,25] The other articles reported ventricular performance[16] or clinical state/O_2 saturation[24] as the primary outcome measure.

Follow-up duration varied between 1 day and 6 months. Of the nine studies, only four measured short-term effects of medication before and during exercise tests, and the follow-up duration was 1–2 days.[19,21,23,25] The rest of the studies reported a longer follow-up duration, varying between 6 weeks and 6 months.[15,16,18,20,22,24]

In eight articles, children and young adults were studied,[15,16,18–21,24,25] and in two articles only adults were studied.[22,23] The age of patients in the studies ranged from 1.2 to 55 years. A total of 267 Fontan patients participated in the studies. The number of patients per study ranged from 10 to 75, with a median of 27. After correction for dropouts, 244 patients completed the studies. Most patients included in the studies reviewed had been operated according to current surgical strategies – that is, intralateral tunnel or extracardiac conduit type of Fontan operation (n = 153).[19–25] Of the studies included in this review, five also reported older techniques such as an atriopulmonary connection or atrioventricular connection.[19–23] Only one study included patients with an atriopulmonary connection or atrioventricular connection,[18] and in another study the type of Fontan connection was not mentioned.[15,16]

All the articles reported dropout rates. In three studies, all of the included patients completed the study.[21,23,25] Overall, the dropout range was 0–10 patients with a median of two patients.

The results and conclusions of all nine studies (10 articles) are also shown in Table 1. Of these nine studies (10 articles), four studies evaluated the effect of sildenafil. The effect was assessed by changes in exercise capacity,[15,21,23] exercise haemodynamics,[25] or changes in ventricular function as measured by myocardial performance index.[16] In three studies,

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Table 1. Overview of included studies.

Study, reference number	Year of publication	Study design	Medication (dose)	Number of patients	Type of Fontan	Age at inclusion: Mean	Age at inclusion: Median	Primary outcome measure	Follow-up	Results	Conclusions
Goldberg[15,16]	2012, 2011	RCT (cross-over, double-blinded, placebo-controlled)	Sildenafil (20 mg 3× daily)	28*	Not mentioned	14.9 ± 5.1		2012: ventricular performance**	6 weeks***	• ↓MPI (95% CI −0.095 to −0.0077) • ↑VTI × HR (95% CI 7.5 to 220) • No change in myocardial velocities on echocardiography • No change in VTI and HR separately	Sildenafil improved ventricular function, but the mechanism and the clinical significance are not clear yet
								2011: exercise capacity	6 weeks***	• ↓Respiratory rate (95% CI −5.37 to −0.01) • ↓Minute ventilation (95% CI −9.02 to −0.16) • ↓VE/VCO_2 (95% CI −4.00 to −0.17) • No significant change in VO_2 max or HR Side-effects: flushing, headache	Sildenafil did not cause an improvement in VO_2 max (primary outcome measure), but there was an increase in ventilatory efficiency and a suggestion of improved oxygen consumption in two subgroups
Giardini[21]	2008	RCT (open-label)	Sildenafil (0.7 mg/kg (range 25–50 mg))	27****	21 TCPC, 6 APC	22.8 ± 4.9 (16–32)		Exercise capacity*****	1 day******	• ↑Peak VO_2 (treatment effect 9.1%) • ↑PBFi and CI in rest (+/−27%) and at peak exercise (+/−10%) • SaO_2 was similar in both groups Side-effects: one mild headache	A single oral dose of sildenafil might acutely improve exercise capacity and increase PBF and CI; however, the benefit was not uniform across this cohort and might be greater in patients with increased pulmonary resistances
Van de Bruaene[25]	2014	Open-label uncontrolled trial	Sildenafil (1 × 50 mg)	10	5 ICC, 5 ECC	19.6 ± 4.0		Exercise haemodynamics**********	1 day******	• ↑CI, SVi, and EF (+5 ± 3%) • ↓ESVi, SVRi, and TPRi (mean effect 1.6 ± 0.4 mmHg × minute × m^2/L) • No change in EDVi	Sildenafil improves exercise haemodynamics, but the precise mechanism is unclear (no enhanced pre-load but enhanced chronotropic response)
Hager[23]	2014	Open-label uncontrolled trial	Sildenafil (1 × 50 mg)	36	16 AVC, 13 APC, 5 ECC, 2 LT	29.8 ± 6.2 (16–42)		Exercise capacity*****	1 day******	• ↑Peak VO_2 (5.1 ± 8.0% baseline) • ↓Resting SBP (not significant)	Acute increase in exercise capacity, mostly in patients with poorer baseline exercise capacity and with NT-proBNP > 1000 pg/ml
Rhodes[19]	2013	RCT (cross-over, double-blinded, placebo-controlled)	Iloprost (1 × 0.5 µg, inhaled)	18*	13 LT**, 4 APC, 1 ECC		16.7 (11.86 IQR)	Exercise c apacity*****	2 days******	• ↑O_2 pulse at peak exercise (1,2 ml/beat) • ↑Peak VO_2 (in all patients with baseline peak VO_2 <30 ml/kg/min) Side-effects: mild throat/chest discomfort (10/18 patients)	Iloprost acutely increases exercise capacity, mostly in patients with depressed exercise function at baseline. Increased O_2 pulse is due to increased forward stroke volume, and thus an increase in pulmonary blood flow, due to lower PVR

Table 1. *Continued*

Study, reference number	Year of publication	Study design	Medication (dose)	Number of patients	Type of Fontan	Age at inclusion: Mean	Age at inclusion: Median	Primary outcome measure	Follow-up	Results	Conclusions
Hebert[20]	2014	RCT (double-blinded, placebo-controlled)	Bosentan (62.5 mg 2× daily for 2 weeks; 125 mg 2× daily for 12 weeks)	75*******	45 LT, 24 ECC, 6 APC		20 ± 7.4	Peak VO_2*****	14 weeks	• ↑Peak VO_2 2 ml/kg/minute versus 0.6 ml/kg/minute ($p = 0.02$) • ↑Secondary end points: ↑CPET time, ↓BNP Side-effects: flushing (17%)	Bosentan improves exercise capacity and time, and NYHA functional class without serious adverse effects
Schuuring[22]	2013	RCT (open-label)	Bosentan (125 mg 2× daily)	42********	20 APC, 18 ECC, 4 LT		28 (18–55)	Exercise capacity*****	6–9 months*********	• No significant change in peak VO_2, minute ventilation, CO, or other parameters was found Side-effects: three severe headache, one dyspnoea, one anaemia and leucocytopaenia, one peripheral oedema	No significant improvement of bosentan on primary or secondary end points was detected
Ovaert[24]	2009	Multicentre, open-label, uncontrolled trial	Bosentan (half dose for 4 weeks, usual dose for 12 weeks)	10**********	7 ICC, 3 ECC		12.12 (4.41–33.41)	Clinical state, O_2 saturation	16 weeks	• ↑O_2 saturations at rest and during exercise. No significant results as a group. Five patients were considered responders, two continued on bosentan after the study Side-effects: two mild transient fatigue	This study did not show any significant results for the group of patients with failing Fontan circulation, only in individual patients
Kouatli[18]	1997	RCT (cross-over, double-blinded, placebo-controlled)	Enalapril (0.2–0.3 mg/kg daily (max 15 mg))	21**********	20 APC, 1 AVC (only in 11 patients Glenn procedure first)		14.5 ± 6.2 (8–27)	Exercise capacity	20 weeks	• No change in blood pressures, HR, respiratory rates, VO_2 max, or O_2 saturations • ↑CI from rest to exercise decreased with enalapril Side-effects: no difference in enalapril versus placebo	Enalapril did not affect baseline haemodynamics, exercise capacity, or diastolic function

APC = right atrium-to-pulmonary artery connection; AVC = right atrium-to-right ventricular connection; BNP = brain natriuretic peptide; CI = cardiac index; CO = cardiac output; CPET = cardiopulmonary exercise test; ECC = extracardiac conduit; EDVi = end-diastolic volume index; EF = ejection fraction; ESVi = end-systolic volume index; HR = heart rate; ICC = intracardiac conduit; IQR = interquartile range; LT = lateral tunnel; MPI = myocardial performance index; PBFi = pulmonary blood flow index; PVR = pulmonary vascular resistance; RCT = randomised controlled trials; SaO_2 = systemic oxygen saturation; SBP = systolic blood pressure; SVi = stroke volume index; SVRi = systemic vascular resistance index; TCPC = total cavopulmonary connection; TPRi = total pulmonary resistance index; VE/VCO2 = ventilatory equivalents for carbon dioxide; VTI = velocity time integral (of left ventricular outflow tract); VTI × HR = a surrogate of cardiac output

*Dropout of three patients

**Measured by MPI

***Patients received placebo/sildenafil for 6 weeks and were switched after a washout period of another 6 weeks

****Including control group of nine patients

*****Tested by cardiopulmonary exercise test (CPET/CPX)

******Exercise tests only

*******Dropout of six patients

********Dropout of 10 patients due to lack of motivation

*********All patients received 6 months of bosentan, the control group was untreated for the first 3 months

**********Dropout of three patients

***********Tested by exercise cardiac magnetic resonance

************Dropout of one patient

exercise tests were performed 1 day after completion of drug use for the pre-defined amount of time, without further follow-up.[21,23,25] In the other study, a follow-up duration of 6 weeks was obtained.[15,16]

A significant improvement after the use of sildenafil was noted for exercise capacity in two studies, for exercise haemodynamics in one, and for ventricular function in another. The improvements were explained by an increase in cardiac index, maximal oxygen uptake, ejection fraction, and/or pulmonary blood flow.

Goldberg et al did not report an improvement in maximal oxygen uptake, the primary outcome measure of their study; however, there was an increased ventilatory efficiency during peak and submaximal exercise and a suggestion of improved O_2 consumption in two subgroups during submaximal exercise, in those with single left ventricular or mixed ventricular morphology and in those with brain natriuretic peptide levels $\geqslant$100 pg/ml.

In two of the four studies on sildenafil use, mild side-effects were reported. These included flushing and mild headache.[15,21] Sildenafil was well tolerated in most patients.

A single study looked at the effects of inhaled iloprost.[19] This was a cross-over, randomised controlled trial with 18 patients. The primary outcome measure was exercise capacity, and follow-up was limited to the 1-month period between exercise tests. The results of this study showed that iloprost increased O_2 pulse at peak exercise with 1.2 ml/beat, and that VO_2 max was increased in all patients who had a baseline peak VO_2 of $<$30 ml/kg/minute. Side-effects related to the inhalation of iloprost, including mild throat or chest discomfort, were reported by 10 of the 18 patients.

Bosentan use was evaluated in three studies. Outcome was measured by exercise capacity[20,22] or clinical state.[24] These three studies were randomised controlled trials, in which the treatment group received bosentan for 14 weeks to 6 months, respectively. In the study by Schuuring et al, the control group only received bosentan for 6 months after the first 3 months. All studies used a relatively long follow-up period. The largest number of patients was reported by Hebert et al; 69 of their patients completed the trial. In this treatment with endothelin receptor antagonist in fontan patients, a randomized, placebo-controlled, double-blind study measuring peak oxygen consumption (TEMPO) trial, a small increase in exercise capacity was noted.[20] Schuuring et al and Ovaert et al concluded that bosentan had no significant effect on either outcome measure. Side-effects reported in these three studies included severe headache, flushing, dyspnoea, chest pain, anaemia and leucocytopaenia, peripheral oedema, and mild transient fatigue.

The study by Kouatli et al[18] was the only study that analysed the effects of an angiotensin-converting enzyme inhibitor – enalapril – on exercise capacity in Fontan patients; 10 weeks of enalapril treatment was compared with 10 weeks of treatment with placebo in this cross-over, randomised controlled trial. After 20 weeks, no differences in blood pressures, heart rate, respiratory rate, maximal oxygen uptake, or O_2 saturations were detected. In contrast, a decrease in the cardiac index increase from rest to peak exercise was noted after enalapril therapy (125% after placebo versus 102% after enalapril). From this study, it was concluded that enalapril does not alter exercise capacity, diastolic function, or any of the baseline haemodynamics. There were no differences in reported side-effects between enalapril use and placebo.

The Cochrane risk of bias tool was used to assess the quality of the included studies (Appendix). There was a low risk of bias in two studies.[18,20] There was a substantial risk of performance and detection bias in five studies, due to lack of blinding.[21–25] In two studies, the method used to conceal the allocation was not described.[15,16,19]

Discussion

This systematic review provides an overview of studies that have been carried out on drug therapies to prevent failure of the Fontan circulation. We found that sildenafil and iloprost improve exercise capacity, mainly in short-term studies.[15,16,19,21,23,25] In one study with 14 weeks of follow-up, bosentan showed a significant effect to improve exercise capacity.[20] This is in contrast with other bosentan studies and with enalapril that did not affect exercise capacity.[18,22,24] Exercise capacity has been recognised as a key factor in survival of Fontan patients.[26] In a recent study in 321 Fontan patients, an association between exercise capacity and morbidity in Fontan patients has been reported.[27] Patients with poor exercise capacity had an increased risk of cardiac-related hospitalisation. Therefore, it seems essential to prevent exercise intolerance in Fontan patients. The normal response to exercise in a biventricular circulation includes a decrease of up to 50% of pulmonary vascular resistance compared with the value at rest, an increase of ventricular end-diastolic volume, and a decrease of end-systolic volume, resulting in an increase of cardiac output.[28] Fontan patients are unable to decrease pulmonary vascular resistance and increase ventricular pre-load, which limits the exercise capacity.[8] Furthermore, 47% of the Fontan patients have elevated pulmonary vascular resistance at ~9 years after the Fontan operation.[29] In Fontan patients, pharmacological vasodilators might decrease pulmonary vascular resistance and subsequently increase pulmonary blood flow to sustain cardiac output during exercise.

Our search resulted in the identification of four studies that observed the effect of sildenafil, a phosphodiesterase inhibitor, on exercise capacity, exercise haemodynamics, or ventricular performance.[15,16,21,23,25,30] Of the three studies that measured exercise capacity, two showed an increased exercise capacity.[15,21,23] Van de Bruaene et al[25] demonstrated an improvement in exercise haemodynamics, and Goldberg et al[16] noted improvement in ventricular function. Sildenafil decreases pulmonary vascular resistance, which might improve ventricular pre-load in the Fontan circulation. Furthermore, it may decrease systemic vascular resistance. This might explain the improvement of exercise capacity in the study by Hager et al[23] and Giardini et al;[21] however, these assumptions have not been supported for all aspects by the results of the elegant invasive study by Van de Bruaene et al. They demonstrated a decrease in pre-load with exercise, which was unaffected by sildenafil, despite a decrease in pulmonary resistance.[25] At the same time, sildenafil resulted in a further decrease of end-systolic volume during exercise, resulting in a net increase of exercise stroke volume. This may relate to the decrease of systemic vascular resistance by sildenafil. In contrast to the results of Hager et al[23] and Giardini et al,[21] Goldberg et al[15] observed no effect on exercise capacity after sildenafil treatment. This difference in results could be explained by the differences in baseline conditions of the patients, the dose of sildenafil, and follow-up duration.[23] Hager et al hypothesised that patients with a poor baseline condition profit more from sildenafil. Hager et al and Giardini et al included patients with a poorer baseline condition than Goldberg et al. Furthermore, Goldberg et al used lower doses of sildenafil than Hager et al and Giardini et al. Sildenafil has a short half-life time, which could possibly result in a lower sildenafil serum concentration in the patients of Goldberg et al during the exercise tests. In addition, both the studies by Hager et al and Giardini et al were not blinded, in contrast to the study by Goldberg et al. Finally, Goldberg et al had a longer follow-up duration than Hager et al and Giardini et al.

Further, two smaller studies measured exercise capacity after intake of bosentan, an endothelin receptor antagonist, and found no significant improvement in exercise capacity.[22,24] Ovaert et al[24] only showed an increase in exercise capacity in patients with limited exercise capacity. Therefore, the authors hypothesised that only patients with an elevated pulmonary vascular resistance would benefit from bosentan. This in contrast to the results of Schuuring et al,[22] who reported no increase in exercise capacity, although all patients had limited baseline exercise capacity. These authors suggested that endothelin-1 levels in Fontan patients are not elevated enough to demonstrate improved exercise capacity, in contrast to the situation in patients with pulmonary arterial hypertension, for whom bosentan was originally developed.[31] In the largest study in the field so far, Hebert et al used a randomised controlled design to demonstrate the superiority of bosentan over placebo to improve VO_2, exercise time, and reduce pro-brain natriuretic peptide levels, without serious adverse effects.

The studies analysed in this review suggest that bosentan, sildenafil, and iloprost are vasodilators that improve exercise capacity in Fontan patients.

With regard to angiotensin-converting enzyme inhibitors, commonly used in heart-failure treatment in acquired heart disease, Kouatli et al[18] reported no effect of enalapril in exercise capacity, exercise haemodynamics, and diastolic function. It is possible that the study failed to show an effect because the renin–angiotensin system was not activated in the Fontan patients and may not be the optimal target in Fontan patients.[32] Further explanations were the use of a small number of patients, a low dose of enalapril, and a short follow-up period. In addition, study patients were in relatively good condition at baseline. Further research is clearly needed, particularly as at present a considerable percentage of Fontan patients are on angiotensin-converting enzyme inhibitors, without real evidence supporting their use in these patients.[12]

There are several limitations to this review. Despite the selected time period, well after the introduction of the total cavopulmonary connection, there were six studies that included patients with an atrioventricular or atriopulmonary connection type of Fontan operation,[18–23] as well as one study that did not mention the Fontan type.[15,16] This heterogeneity in the included patients resulted in less comparability of the studies in this review.

As mentioned earlier, the term failing Fontan in this review has been used in case of reduced pulmonary blood flow, ventricular dysfunction, protein-losing enteropathy, or plastic bronchitis. Considering the focus on prevention of Fontan failure, we have excluded one article about plastic bronchitis. We did not include articles about protein-losing enteropathy, as we only found case reports on this patient group. Further randomised controlled studies are needed to evaluate plastic bronchitis and protein-losing enteropathy treatment. In addition, we could identify only one article that studied the effect of angiotensin-converting enzyme inhibitors in Fontan patients.[18] Considering the limitations of that study, further research is needed.

Considering the generally small number of patients, heterogeneity in surgical techniques, and drug types used, we did not perform meta-analysis.

Remarkably, several of the included studies did not use a control group; three studies were uncontrolled.[23–25] Many of the studies that assessed exercise capacity, exercise haemodynamics, or ventricular performance had a short follow-up period.[15,16,18,19,21,23,25] Consequently, the long-term effects of sildenafil, iloprost, and enalapril in Fontan patients are still unknown. Furthermore, some studies did not evaluate safety of the drug under study.[23]

We conclude that, based on the studies analysed in this review, bosentan, sildenafil, and iloprost may improve exercise capacity at the short term in Fontan patients. Given the small number of studies, the small number of patients, the short follow-up duration, and the lack of control groups in several studies, the results need to be interpreted carefully. More, larger, and longer placebo-controlled studies are needed to evaluate efficacy and safety of drug therapies in the prevention and treatment of failure of the Fontan circulation.

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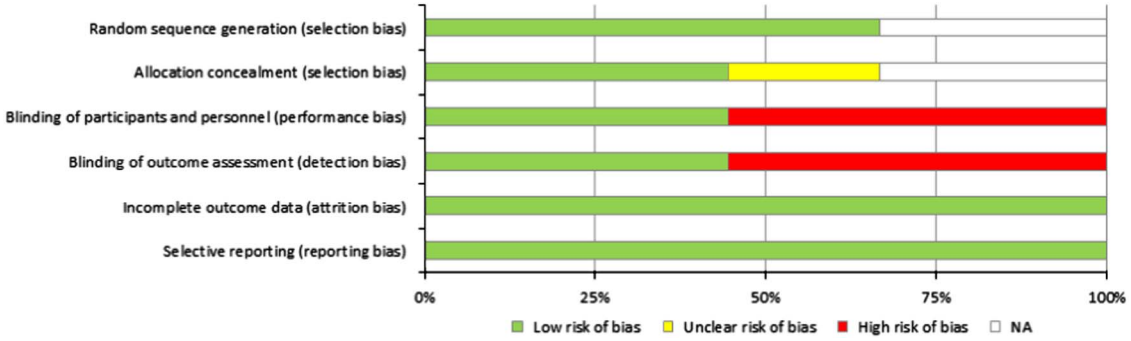
Appendix: Assessment of risk of bias of included studies according to the Cochrane risk of bias tool

A: Risk of bias graph for the studies included in this systematic review



B: Risk of bias summary

1 = random sequence generation; 2 = allocation concealment; 3 = blinding of participants and personnel; 4 = blinding of outcome assessment; 5 = incomplete outcome data; 6 = selective reporting; "+" = low risk of bias; "?" = unclear risk of bias; "–" = high risk of bias.

	1	2	3	4	5	6
Goldberg	+	?	+	+	+	+
Giardini	+	+	-	-	+	+
Rhodes	+	?	+	+	+	+
Hebert	+	+	+	+	+	+
Schuuring	+	+	-	-	+	+
Kouatli	+	+	+	+	+	+
Van de Bruane	NA	NA	-	-	+	+
Hager	NA	NA	-	-	+	+
Ovaert	NA	NA	-	-	+	+

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