Effect of phosphodiesterase-5 inhibition on SystEmic Right VEntricular size and function – a multi-center, double-blind, randomized, placebo-controlled clinical trial – SERVE

Matthias Greutmann, MD[1*], Daniel Tobler, MD[2*], Reto Engel, MD[3], Dik Heg, MD[4], Christian Mueller, MD[5], André Frenk, PhD[6], Harald Gabriel, MD[7], Tobias Rutz, MD[8,9], Ronny R. Buechel, MD[10], Matthias Willhelm, MD[11], Lukas Trachsel, MD[11], Michael Freese, SN[5], Javier Ruperti, MD[2], Emanuela Valsangiacomo Buechel, MD[12], Dietrich Beitzke, MD[13], Philip Haaf, MD[2], Kerstin Wustmann, MD[9], Fabienne Schwitz, MD[6], Mathias Possner, MD[1], Juerg Schwitter, MD[8,9,14] , Judith Bouchardy, MD[8,15*], Markus Schwerzmann, MD[6*], on behalf of the SERVE Investigators[16]

Affiliations

[1] University Heart Center, Department of cardiology, University of Zurich, Switzerland
[2] Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland
[3] Department of Cardiology, Kantonsspital St. Gallen, St. Gallen, Switzerland
[4] CTU Bern, University of Bern, Switzerland
[5] Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, University of Basel, Basel, Switzerland
[6] Department of Cardiology, Center for Congenital Heart Disease, Bern University Hospital, University of Bern, Bern, Switzerland
[7] Department of Cardiology, Vienna General Hospital, Medical University of Vienna, Vienna, Austria
[8] Service of Cardiology, Lausanne University Hospital and University of Lausanne, Lausanne Switzerland
[9] Cardiac MR center of the University Hospital Lausanne and CMR corelab (swissCVIcorelab, CHUV), Switzerland
[10] Department of Nuclear Medicine, Cardiac Imaging, University Hospital Zurich, Zurich, Switzerland
[11] University Clinic of Cardiology, Preventive Cardiology and Sports Medicine, Inselspital, University Hospital, University of Bern, Bern, Switzerland
[12] Department of cardiology, university children's hospital, University of Zurich, Zurich, Switzerland
[13] Department of Biomedical Imaging and Image-guided Therapy, Vienna General Hospital, Medical University of Vienna, Vienna, Austria
[14] Faculty of Biology and Medicine, Lausanne University (UniL), Lausanne, Switzerland
[15] Division of Cardiology, Hôpitaux Universitaires de Genève (HUG), Genève, Switzerland

[16] See Appendix for a complete list of participating Centers and Investigators.

* These authors contributed equally to the study design, data interpretation, and manuscript preparation.

Address for correspondence

Matthias Greutmann, MD, Head Congenital Heart Disease, University Heart Center, University Hospital Zurich, Raemistrasse 100, 8091 Zurich, Switzerland.
E-Mail: Matthias.greutmann@usz.ch; phone: ++41 44 255 3883

Summary

Background
Progressive right ventricular (RV) systolic dysfunction in adults with congenital heart disease and systemic (subaortic) RVs is common and is associated with adverse outcomes. Phosphodiesterase (PDE)-5 inhibition has shown benefits on RV function in animal models. Our aim was to investigate the impact of tadalafil on RV systolic function in adults with systemic RVs.

Methods
We conducted a double-blind, randomized, placebo-controlled, multi-center superiority trial comparing the PDE-5 inhibitor tadalafil 20mg once daily versus placebo (1:1-ratio) in adults with systemic RV. Primary endpoint was the change in RV endsystolic volume (RV-ESV) measured by cardiac magnetic resonance or computed tomography after three years of therapy or earlier in case of permanent discontinuation of study drug. Secondary endpoints were changes in RV ejection fraction, exercise capacity and NT-proBNP-concentration as quantitative markers of cardiac hemodynamic stress at study end compared to baseline. This study is registered at ClinicalTrials.gov (Identifier: NCT03049540).

Findings
A total of 100 adults (33 women, mean age: 40·7 years, SD 10·7) were enrolled. Primary endpoint assessment by intention to treat analysis at one and three years of follow up was possible in 91 and 83 patients respectively (45 and 42 patients in the tadalafil group and 46 and 41 patients in the placebo group). No significant changes over time in RV-ESV were observed in the tadalafil and the placebo-group, and no significant differences between treatment groups (3·4ml, CI -4·3 to 11·0, p=0·39). No significant changes over time were observed for the pre-specified secondary endpoints for the entire study population, without differences between the tadalafil and the placebo-group.

Interpretation
In this trial in adults with systemic RV, right ventricular systolic function, exercise capacity and neuro-hormonal activation remained stable over a three-year follow-up period. No significant treatment effect of tadalafil was observed.

Funding
The SERVE trial was funded by the Swiss National Foundation.

Research in context

Evidence before this study

Adults with systemic right ventricles comprise a large group of adults with complex congenital heart defects. These patients are at high risk of progressive systemic right ventricular dysfunction and clinical heart failure. Previous studies failed to demonstrate a benefit from treatment with conventional heart failure medication, and thus, alternative treatment concepts are urgently needed.

Added value of this study

Promising effects of phosphodiesterase 5-inhibition on function of hypertrophied right ventricles in experimental and animal models did not translate into a clinical benefit in this randomized, placebo-controlled trial in adults with systemic right ventricles. Tadalafil had no impact on right ventricular function, exercise capacity or neuro-hormonal activation.

Implications of all available evidence

Results of studies in patients with heart failure from acquired heart disease cannot be extrapolated to patients with systemic right ventricles. Prospective studies on the effectivity of novel treatment options for adults with failing systemic right ventricles are urgently needed.

Introduction

Patients with systemic (subaortic) right ventricles (RV) in a biventricular circulation comprise up to 10% of adults with complex congenital heart disease, followed at specialized centers. [1] These include patients with complete transposition of the great arteries (d-TGA) after atrial switch operations and patients with congenitally corrected transposition of the great arteries (ccTGA). Although midterm outcome is favorable, systemic ventricular dysfunction is common during long-term follow-up. It is associated with clinical heart failure, arrhythmias and premature death. [2-6] The optimal management of patients with systemic RVs is unknown. Medical heart failure therapy with angiotensin-converting-enzyme inhibitors (ACE-I), angiotensin II receptor blockers (ARBs), beta-blockers, and aldosterone antagonists has been shown to improve left ventricular function and survival in patients with acquired heart disease.[7] However, several studies failed to show a similar clinical benefit of these drugs in adults with a failing systemic RV. [8-17]

Previous studies found that in RV facing an increased afterload, as present in an RV in systemic position, hypertrophic myocardial cells express a fetal gene pattern with an increase in phosphodiesterase-5 (PDE-5) expression, which is not seen in the normal RV. [18] PDE-5 inhibitors have been shown to increase contractility in experimental models of RV hypertrophy, but not in the normal RV. [18] In a rat model of fix RV pressure load after pulmonary artery banding, PDE-5 inhibition with sildenafil had a positive effect on RV diastolic function and attenuated interstitial fibrosis in animals with established RV dysfunction, independent from afterload. [19]

The aim of our investigator-initiated study was, therefore, to assess the effect of the PDE-5 inhibition on systolic RV function in adults with systemic right ventricles.

Methods

Trial Design

Details of the study design have been published previously. [20] In brief, we conducted a parallel group, double-blind, randomized, placebo-controlled, multi-center superiority trial comparing tadalafil versus placebo in a 1:1 ratio. Both, tadalafil and the placebo were manufactured by TEVA/MEPHA Schweiz AG. Tadalafil was chosen over sildenafil for its higher selectivity for PDE-5 receptors and its longer half-live, allowing a single daily dose. The study complies with the Declaration of Helsinki, the resonsible ethics committees and the competent authorities approved the protocol. All participants gave written informed consent prior to participation in the study. The study is registered at ClinicalTrials.gov (Identifier: NCT03049540).

Study Population

Eligible participants were recruited from participating study centers. We included clinically stable adults (≥ 18 years) with d-transposition of the great arteries after atrial switch operation (d-TGA) or adults with congenitally corrected transposition of the great arteries (ccTGA). Patients with a life-expectancy <6 months, severe renal dysfunction (creatinine clearance ≤ 30ml/m^2), severe hepatic insufficiency and known contraindications to the study drug were excluded. Sample size calculation was based on the expected change in RV endsystolic volume (RV-ESV) between study groups. A sample size of 78 patients at three-year follow-up was determined to obtain an 80% power to detect the expected difference in RV-ESV between the two treatment groups. Considering a possible dropout of 20%, the goal was to recruit 98 study participants (49 patients for each group).

Interventions

At baseline, all patients underwent clinical examination, standardized transthoracic echocardiography, cardiovascular magnetic resonance imaging (CMR) or cardiac multirow detector computed tomography (CMDCT) in patients with contraindications for CMR, symptom-limited cardio-pulmonary exercise testing (CPET) and blood sampling for analysis of neuro-hormonal activity. After completion of baseline examinations, participants were started on tadalafil 20 mg or placebo once daily without any titration period.

Randomization and masking

At present, no drug has shown in randomized clinical trials to prevent progressive RV failure in adults with a systemic RV. Therefore, tadalafil was compared against placebo. The randomized allocation lists (tadalafil versus Placebo in 1:1 ratio) were generated by an independent statistician using a random seed with the help of a computer program, and lists were generated stratified according to the presence or absence of a pacemaker (PM) or automated implantable defibrillator (AICD) at baseline (with randomly varying block sizes of 2, 4 or 6 patients). Lists were deposited password protected in a dedicated folder on a central GCP-compliant server. The randomized allocation lists were implemented in the electronic data capturing system and were concealed from all study personnel. As soon

as the patient fulfilled the inclusion and exclusion criteria, the patient was randomized according to the concealed list, the list appropriate to the site and presence/absence of pacemaker at baseline. All study personnel, including CMR or CMDCT assessors, trial statisticians and central data monitors remained blinded after the assignment of the treatments. Packages containing the drugs (tadalafil pills or similarly looking placebo pills) contained identifiers to allow emergency unblinding.

Outcome Measurements

The primary objective was to assess the effect of tadalafil on systemic RV endsystolic volume (RV-ESV) after three years of therapy or earlier, in case of permanent discontinuation of the study drug, measured by cardiovascular magnetic resonance imaging (CMR) or by cardiac multirow detector computed tomography (CMDCT) in patients with contraindications for CMR. Measurement of RV-ESV was chosen as the primary endpoint over RVEF, as it is likely more sensitive to detect changes in RV systolic function. This is based on the notion that in patients with pulmonary artery hypertenstion the RV adapts to its chronically increased afterload first by myocardial remodelling with hypertrophy and increased contractility. If these compensatory mechanisms fail, the RV begins to dilate, followed by a decrease in RVEF. Accordingly, an increase in RV volumes precedes the decrease in RVEF. We assumed that the RV in systemic position may behave similarly. With progressive RV failure and RV dilatation, there is also an increase in secondary tricuspid regurgitation. The increased amount of tricuspid regurgitation may falsely improve RVEF, whereas RV-ESV will nevertheless be increased as sign of progressive RV failure.
Pre-specified secondary objectives were the effects of tadalafil on systemic RV ejection fraction (RVEF) measured by CMR or CMDCT at 3 years of follow-up, its impact on exercise capacity, quality of life and serum neuro-hormonal activation at 3 years of follow-up.

CMR and CMDCT

Imaging studies followed a pre-specified protocol and were performed at baseline, after one and three years of follow-up. In patients who had to discontinue the study medication prematurely, RV-ESV was re-measured within 4 weeks of the study drug withdrawal and this measurement was then used for the primary endpoint analysis unless the treatment period was < 3 months. Analyses were performed in core labs by experienced observers, blinded to the sequence of imaging studies and blinded to treatment groups (for CMR: “swissCVIcorelab” at the Centre Hospitalier Universitaire Vaudois, CHUV, Switzerland; for CMDCT: University Hospital Zurich, Switzerland).

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was performed at baseline and at three years of follow-up or earlier in case of permanent discontinuation of the study drug. Data analysis was performed at a core-lab (University Hospital Inselspital Bern) and measurements were reported following the recommendations of the European Association for Preventive Cardiology. [21] Reported measurements included maximum workload in Watt, peak oxygen consumption (peak VO2), both in absolute and relative values based on Jones and Wasserman references, VE/VCO2 Slope, PETCO2, O2 pulse trajectory, delta VO2/delta Watt trajectory, heart rate kinetics and heart rate recovery (HRR).

Neurohormonal activation

Neurohormonal activation was measured in all participants at baseline, at one year and at study end. All samples were analyzed in a single core-lab with expertise in biomarker-research (Cardiovascular Research Institute Basel, CRIB). Measurements included concentrations of the neurohormones B-type natriuretic peptides (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and high-sensitivity cardiac troponin T (hs-cTnT).

Quality of life

Quality of life was assessed by the use of three self-administered questionnaires or scales at baseline, at 12 months, and at study end. These include a linear analog scale (LAS), the Satisfaction with Life Scale (SWL) and the General Self-Efficacy Scale (GSE). [22-24]

Adverse events and safety endpoints

Adverse events were continuously reported as required by medical authorities. As pre-specified per protocol, serious adverse events were reviewed by an independent Data Safety Monitoring board in March 2019 (after inclusion of all patients) and in March 2020.

Subgroup analysis
Subgroup analyses for assessment of differences in treatment effects were performed for gender, d-TGA versus ccTGA, symptomatic versus asymptomatic patients, patients with or without PM / AICD and patient groups stratified for NT-proBNP and hs-Troponin T-levels.

Statistical Analysis
The primary endpoint was analysed using ANCOVA (Analysis of Covariance), with RV-ESV as the response variable, randomized treatment as main independent variable, baseline RV-ESV and time between baseline and follow-up RV volume measurement (in months since baseline) as covariates.
Secondary endpoints were analysed using ANCOVA (Analysis of Covariance), with the secondary endpoint (RVEF, peak VO2, NT-proBNP, hs-cTnT) as the response variable, randomized treatment as main variable, baseline measurement (RVEF, peak VO2, NT-pro BNP, hs-cTnT, respectively) and time between baseline and follow-up measurement time (in months since baseline) as covariates.
All primary and secondary endpoints were analysed by intention-to-treat, using two-sided superiority testing with alpha set at 5%.

Role of the funding source
The funding body (Swiss National Science Foundation) granted the costs of the trial but had no role in study design, data collection, data analysis and data interpretation.

Results

Study Population
From the seven participating study centers, a total of 100 consecutive patients were enrolled, 75 (75%) with d-transposition of the great arteries after atrial switch operations and 25 (25%) with congenitally corrected transposition of the great arteries. Of these patients, 51 were randomly assigned to the tadalafil group and 49 to the placebo group. Baseline characteristics of study participants are displayed in table 1. As illustrated in the study flowchart (figure 1), primary endpoint assessment by intention to treat analysis at one and three years of follow-up was possible in 91 and 83 patients respectively (45 and 42 patients in the tadalafil group and 46 and 41 patients in the placebo group).

Figure 1: Trial profile

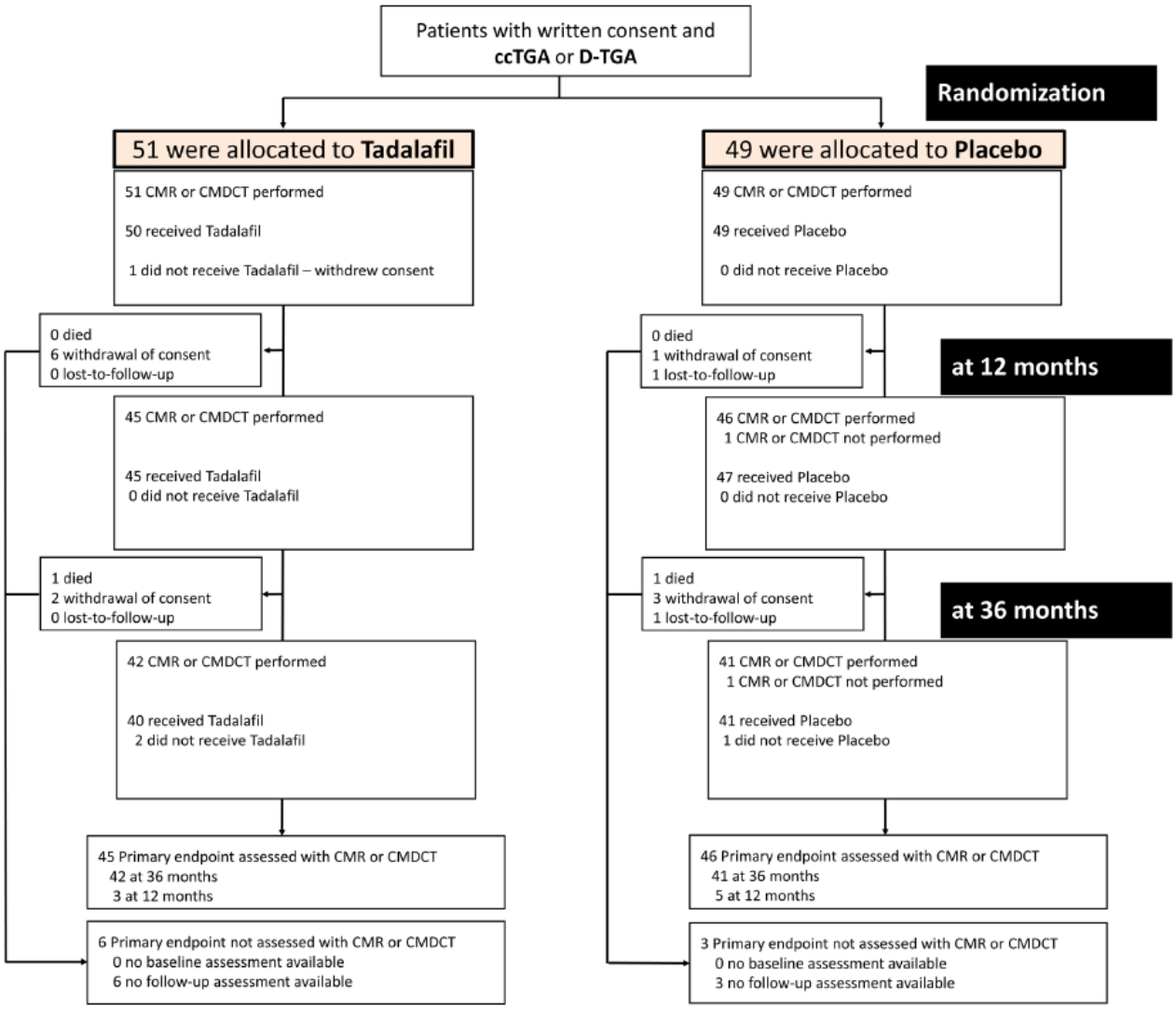

Table 1 Baseline Characteristics

	Tadalafil (n = 51)	**Placebo** (n = 49)
Age, years (SD)	41·3 (10·2)	40·1 (11·4)
Male gender	37 (73%)	30 (61%)
Female gender	14 (27%)	19 (39%)
Cardiac anatomy		
ccTGA	13 (25%)	12 (24%)
d-TGA after Mustard-operation	7 (14%)	16 (33%)
d-TGA after Senning-operation	31 (61%)	21 (43%)
Additional lesions	22 (43%)	18 (37%)
Ventricular septal defect	8 (16%)	3 (6%)
Pulmonary stenosis	4 (8%)	4 (8%)
Ventricular septal defect and pulmonary stenosis	4 (8%)	6 (12%)
Other	6 (12%)	5 (10%)
Previous pacemaker or AICD implantation	11 (22%)	10 (20%)
History of atrial tachy-arrhythmias	19 (37%)	15 (31%)
NYHA class ≥ II	8 (16%)	9 (18%)
Regular cardiac medication		
Beta-blocker	20 (39%)	14 (29%)
ACE inhibitor or ARB	26 (51%)	20 (41%)
Diuretics	10 (20%)	5 (10%)
Antiarrhythmic drugs	4 (8%)	2 (4%)

Data expressed as n (%), means (SD). ccTGA: congenitally corrected transposition of the great arteries; d-TGA: complete transposition of the great arteries after atrial switch operation (Senning or Mustard operation); AICD: Automated Implantable Cardioverter-Defibrillator; NYHA: New York Heart Association; ACE: angiotensin-converting-enzyme; ARB: angiotensin II receptor blockers

Primary endpoint

As outlined in ***table 2***, mean RV-ESV did not change during follow-up in the tadalafil group (145, SD: 57 versus 148, SD: 56, p = 0·27) or in the placebo-group (123, SD: 49 versus 121·2, SD 46, p = 0·67). There was no statistically significant difference between the tadalafil- and the placebo-group (3·37, confidence interval: -4·29 to 11·03, p = 0·39).

Table 2: Treatment Response (Intention-to-Treat Analysis)

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	Tadalafil						Placebo						Tadalafil vs Placebo	
	n	Baseline	n	Follow-up	Change	p	n	Baseline	n	Follow-up	Change	p	Mean difference of the change* (95% CI)	p
CMR/CMDCT**														
RV-ESV, ml ¶	51	145 (57)	45	148 (56)	3·2 (19·5)	0·27	49	123 (49)	46	121 (46)	1·2 (16·7)	0·67	3·37 (-4·29 to 11·03)	0·39
RV-EDV, ml	51	253 (65)	45	258 (65)	5·0 (23·1)	0·14	49	224 (61)	46	222 (58)	1·3 (26·1	0·80	6·08 (-4·38 to 16·54)	0·26
RVEF, % §	51	44 (8)	45	44 (8)	0·1 (3·5)	0·64	49	46 (8)	46	46 (7)	-0·2 (3·3)	0·67	-0·21 (-1·53 to 1·11)	0·76
RV mass, g	38	94 (21)	34	97 (21)	3·5 (12·0)	0·09	40	87 (22)	37	88 (22)	2·7 (5·8)	0.005	1·25 (-3·2 to 5·7)	0.58
LVEF, %	51	62 (8)	45	63 (7)	0·1 (3·5)	0·74	49	63 (9)	46	64 (7)	0·3 (3·9)	0·56	-0·43 (-1·83 to 0·97)	0·55
LV mass, g	38	74 (13)	34	77 (16)	3·0 (7·4)	0·02	40	71 (16)	37	72 (18)	1·7 (6·4)	0·11	1·13 (-2·16 to 4·43)	0·50
CPET														
Maximum load, W	50	154 (50)	38	159 (56)	3·3 (23·4)	0·35	49	155 (58)	39	156 (54)	-1·5 (22·7)	0·72	4·60 (-5·65 to 14·85)	0·38
Maximum load % predicted, %	50	77 (19	38	79 (22)	2·5 (12·3)	0·22	49	83 (21)	39	84 (19)	2·9 (12·9)	0·21	-1·05 (-6·68 to 4·57)	0·71
Peak VO_2, ml/min/kg	50	23·7 (6·8)	38	23·3 (6·5)	-1·2 (3·7)	0·07	49	25·0 (8·0)	41	23·8 (7·7)	-1·1 (4·7)	0·13	-0·13 (-1·89 to 1·64)	0·89
Peak VO_2 % predicted, %	50	75 (16)	38	75 (16)	-0·1 (12·9)	0·78	49	77 (18)	41	76 (14)	0·7 (12·6)	0·97	-1·21 (-6·37 to 3·95)	0·65
VO_2 workload slope	50	9·6 (1·6)	38	9·1 (2·0)	-0·5 (2·0)	0·11	49	9·2 (1·9)	37	9·1 (1·7)	-0·4 (1·5)	0·28	-0·09 (-0·86 to 0·67)	0·81
O_2 / heart rate, ml/beat)	50	12·9 (4·4)	38	13·0 (4·2)	-0·3 (1·8)	0·43	49	12·2 (4·2)	40	12·4 (3·6)	-0·1 (2·4)	0·96	0·03 (-0·78 to 0·84)	0·94
VE/VCO_2 workload slope	50	28·5 (6·2)	38	30·1 (5·4)	0·5 (5·6)	0·23	49	28·9 (6·2)	41	30·9 (8·3)	1·9 (5·3)	0·02	-1·32 (-3·67 to 1·04)	0·27
Neurohormones														
NT-proBNP, pg/ml	50	497 (852)	38	496 (621)	-45 (653)	0·77	48	398 (584)	39	342 (336)	43 (182)	0·19	42·42 (-114·83 to 199·68)	0·60
hs Troponin T, ng/l	50	9·2 (6·4)	38	10·4 (5·7)	1·9 (2·5)	<0·001	48	7·8 (6·1)	39	8·4 (4·3)	1·9 (2·9)	<0·001	0·34 (-0·81 to 1·49)	0·57
Quality of Life														
LAS scale	51	75 (15)	41	76 (17)	0·6 (12·4)	0·89	49	83 (11)	42	83 (12)	-1·9 (13·7)	0·73	-0·80 (-6·50 to 4·89)	0·78
Satisfaction scale	51	27 (6	41	28 (5)	1·3 (4·2)	0·06	49	29 (4)	42	29 (4)	-0·9 (3·4)	0·14	0·98 (-0·56 to 2·52)	0·21
General self-efficacy	51	31 (5)	41	32 (4)	0·4 (2·7	0·27	49	33 (4)	42	32 (5)	-1·1 (4·6)	0·18	1·04 (-0·55 to 2·64)	0·20

Data expressed as n (%), means (SD) or median (25% to 75% interquartile range IQR).

*Estimates from ANCOVA with the follow-up assessment as response, baseline assessment and time between follow-up assessment and baseline assessment (months) as covariates.

**36 months CMR/CMDCT measurements used, except if not available (e.g. patient died or withdrew consent or discontinued investigational medical product), in which case the 12 months CMR/CMDCT study was used (n = 3 in the tadalafil group, n = 5 in the placebo group).

¶Primary outcome as change 36 months or last assessment versus baseline. § Secondary endpoint as change 36 months or last assessment versus baseline.

Abbreviations: Peak VO2: Peak oxygen consumption; VE/VCO2 slope: minute ventilation carbon dioxide production relationship; NT-proBNP: NT-proB-type natriuretic peptide; hs Troponin: high sensitivity Troponin T

Secondary endpoints

Analyses of secondary endpoints are summarized in table 2. There were no significant changes in enddiastolic volumes and right and leftventricular ejection fraction within the tadalafil and the placebo-group and no statistically significant differences between the tadalafil- and the placebo-group. A small change was observed for RV mass in the placebo-group but no statistically significant differences between the tadalafil- and the placebo-group.

Measures of exercise capacity remained stable over the three-year follow-up period, both within the tadalafil and the placebo-group, without differences between groups.

Among neurohormones, no significant change in NT-proBNP-levels were observed during the three-year follow-up period or between the tadalafil and the placebo-groups. In contrast, a significant increase of hs-Troponin T, was observed, both within the tadalafil- and the placebo-group ($p < 0{\cdot}001$ for both comparisons) without significant differences between the tadalafil- and the placebo-group ($p = 0{\cdot}57$).

Measures of quality of life remained stable during follow-up, without differences between the tadalafil- and the placebo group.

Subgroup analyses

No treatment effect of tadalafil versus placebo was found, when analysis was specified for symptomatic patients (functional class NYHA ≥ 2, n = 17) versus asymptomatic patients (functional class NYHA I, n = 83). Change of RV-ESV among asymptomatic patients was 3·75ml (95% CI: -4·39ml to 11·89ml, p = 0·37) versus 1·39ml (95% CI: -11·13ml to 13·91ml, p = 0·83) in symptomatic patients. No significant treatment effects were found when patients were stratified for previous PM / AICD implantation, ccTGA versus d-TGA, endpoint assessment with CMDCT versus CMR, male versus female, NT-proBNP ≥ 233pg/ml or < 233pg/ml (median of NT-proBNP-measurements) and hs-Troponin ≥7ng/l versus < 7ng/l (see ***supplemental table 1***).

Supplemental table 1 – Subgroup analysis

	Tadalafil						Placebo						Tadalafil vs Placebo	
	n	Baseline	n	Follow-up	Change	p	n	Baseline	n	Follow-up	Change	p	Mean difference of the change* (95% CI)	p
NYHA ≥ 2**														
RV-ESV, ml ¶	8	166 (79)	8	177 (92)	11·4 (17·9)	0·05	9	128 (58)	8	131 (59)	2·8 (13·4)	0·53	1·39 (-11·13 to 13·91)	0·83
NYHA 1**														
RV-ESV, ml ¶	43	140 (51)	37	142 (44)	1·4 (19·6)	0·66	40	118 (41)	38	119 (44)	0·9 (17·4)	0·76	3·75 (-4·39 to 11·89)	0·37
Interaction p-value														0·37
With PM / AICD**														
RV-ESV, ml ¶	11	144 (45)	8	144 (45)	-3·1 (12·7)	0·47	10	137 (45)	10	125 (37)	-12·1 (18·8)	0·03	11·42 (-2·36 to 25·20)	0·10
Without PM / AICD**														
RV-ESV, ml ¶	40	145 (60)	37	149 (59)	4·7 (17·6)	0·02	39	115 (44)	36	120 (49)	4·9 (14·2)	0·04	0·14 (-8·41 to 8·70)	0·97
Interaction p-value														0·38
ccTGA**														
RV-ESV, ml ¶	13	140 (52)	10	139 (54)	0·9 (16·1)	0·87	12	151 (70)	9	152 (86)	1·7 (26·2)	0·84	0·99 (-19·11 to 21·08)	0·92
dTGA**														
RV-ESV, ml ¶	38	146 (58)	35	151 (57)	3·8 (20·5)	0·26	37	113 (32)	37	114 (27)	1·1 (14·0)	0·63	7·03 (-1·27 to 15·33)	0·10
Interaction p-value														0·52
CMR**														
RV-ESV, ml ¶	38	138 (48)	35	146 (54)	7·9 (14·4)	<0.001	40	115 (43)	37	119 (49)	4·8 (14·0)	0·04	1·00 (-5·66 to 7·66)	0·77
CMDCT**														
RV-ESV, ml ¶	13	162 (73)	10	156 (65)	-13·4 (26·1)	0·10	9	142 (43)	9	129 (37)	-13·7 (19·2)	0·02	7·56 (-8·54 to 23·66)	0·36
Interaction p-value														0·76
Male**														
RV-ESV, ml ¶	37	156 (55)	33	162 (54)	4·3 (22·1)	0·24	30	131 (44)	29	133 (51)	2·1 (17·4)	0·51	3·64 (-6·75 to 14·02)	0·49
Female**														
RV-ESV, ml ¶	14	111 (48)	12	111 (46)	0·1 (9·2)	0·97	19	101 (38)	17	101 (28)	-0·4 (15·9)	0·93	2·41 (-6·62 to 11·45)	0·60
Interaction p-value														0·66
NT-proBNP ≥ 233pg/ml**														
RV-ESV, ml ¶	28	164 (67)	25	169 (63)	5·1 (19·5)	0·29	25	131 (51)	24	131 (57)	0·0 (17·5)	0·99	6·9 (-5·42 to 19·31)	0·27
NT-proBNP < 233pg/ml **														
RV-ESV, ml ¶	23	123 (31)	20	122 (33)	0·8 (11·2)	0·79	24	108 (31)	22	110 (29)	2·5 (16·1)	0·46	-0·05 (-8·67 to 8·57)	0·99
Interaction p-value														0·28
Hs-Troponin ≥7ng/l**														
RV-ESV, ml ¶	33	161 (59)	29	169 (55)	6·4 (22·9)	0·12	27	138 (48)	25	137 (55)	-1·6 (20·9)	0·70	9·82 (-2·16 to 21·80)	0·11
Hs-Troponin <7ng/l **														
RV-ESV, ml ¶	18	114 (34)	16	111 (35)	-2·7 (8·9)	0·21	22	98 (26)	21	103 (23)	4·5 (8·9)	0·02	-5·82 (-11·76 to 0·12)	0·06
Interaction p-value														0·03

Data expressed, means (SD) or median (25% to 75% interquartile range IQR). NT-proBNP and Troponin T stratified by median value.

*Estimates from ANCOVA with the follow-up assessment as response, baseline assessment and time between follow-up assessment and baseline assessment (months) as covariates. **36 months CMR/CMDCT measurements used, except if not available (e.g. patient died or withdrew consent or discontinued investigational medical product), in which case the 12 months CMR/CMDCT study was used. ¶Change at 36 months or last assessment versus baseline.

Abbreviations: NYHA: New York Heart Association; PM: Pacemaker; AICD: Automated Implantable Cardioverter-Defibrillator; ccTGA: congenitally corrected transposition of the great arteries; d-TGA: complete transposition of the great arteries after atrial switch operation (Senning or Mustard operation); CMR: Cardiac magnetic resonance imaging; CMDCT: Cardiac multirow detector computed tomography; NT-proBNP: NT-proB-type natriuretic peptide; hs Troponin: high sensitivity Troponin T.

Adverse events and safety endpoints

A higher rate of drug specific adverse events (headache, nausea and dyspepsia) was observed in the tadalafil-group but there was no indication of a safety concern. An overview of adverse events in the entire study population is summarized in table 3. Results were unchanged when analysis of adverse events was performed in the safety population (only considering patients while on study drug). In both, the tadalafil and the placebo-group one patient died. Death in the treatment arm was not related to the study drug (post-interventional death after perctuaneous mitral valve repair). There was no significant difference in drug adherence between patients in the tadalalfil and placebo-group (excluding patients with permanent discontinuation of the study drug).

Table 3: Adverse events

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	Tadalafil (n = 51)			**Placebo** (n = 49)					**Zero-inflated Poisson regression**	
	Number of patients with event	Total number of events	% of this event IMP (temporarily) stopped	Number of patients with event	Total number of events	% of this event IMP (temporarily) stopped	Rates Tadalafil (95% CI)	Rates Placebo (95% CI)	Rate ratio (95% CI)	p
Person-years at risk							**136·3 person-years**	**138·1 person-years**		
Serious adverse events										
Death	1 (2%)	1	0 (0%)	1 (2%)	1	0 (0%)	0·007 (0·000- 6·2e+07)	0·007 (0·000- 7·2e+07)	0·95 (0·03-30·88)	1·0
Worsening heart failure	2 (4%)	2	0 (0%)	3 (6%)	3	1 (33%)	0·015 (0·000- 1·5e+05)	0·022 (0·000- 1·3e+04)	0·68 (0·11-4·04)	0·67
Vascular event*	0 (0%)	0	0 (0%)	0 (0%)	0					
New or worsening arrhythmias	7 (14%)	9	1 (11%)	6 (12%)	10	1 (10%)	0·066 (0·000-134·763)	0·072 (0·000-105·256)	0·69 (0·23-2·12)	0·35
Renal function impairment	1 (2%)	1	1 (100%)	0 (0%)	0		0·007 (0·000- 6·2e+07)			1·0¶
Other SAE leading to dis-continuation of study drug	0 (0%)	0	0 (0%)	1 (2%)	1	1 (100%)		0·007 (0·000- 7·2e+07)		0·49¶
SAE other then any of the above	7 (14%)	11	2 (18%)	6 (12%)	10	1 (10%)	0·081 (0·000-79·548)	0·072 (0·000-105·256)	1·06 (0·36-3·09)	1·0
Adverse events										
Headache	11 (22%)	13	3 (23%)	4 (8%)	5	1 (20%)	0·096 (0·000-54·089)	0·036 (0·000-1074·746)	2·79 (0·90-8·68)	0·16
Renal function impairment	0 (0%)	0	0 (0%)	1 (2%)	1	0 (0%)		0·007 (0·000- 7·2e+07)		0·49¶
Allergic reaction	1 (2%)	1	0 (0%)	0 (0%)	0		0·007 (0·000- 6·2e+07)			1·0
Epipharyngitis	1 (2%)	1	0 (0%)	0 (0%)	0		0·007 (0·000- 6·2e+07)			1·0
Nausea and dyspepsia	4 (8%)	4	0 (0%)	1 (2%)	1	0 (0%)	0·029 (0·000-2704·737)	0·007 (0·000- 7·2e+07)	4·05 (0·45-36·27)	0·36
Symptomatic arterial hypertension	0 (0%)	0	0 (0%)	1 (2%)	1	0 (0%)		0·007 (0·000- 7·2e+07)		0·49
Other AE leading to discontinuation of study drug	3 (6%)	3	2 (67%)	1 (2%)	1	1 (100%)	0·022 (0·000- 1·2e+04)	0·007 (0·000- 7·2e+07)	6·72 (0·36-127·03)	0·62
New or worsening arrhythmias	6 (12%)	10	0 (0%)	2 (4%)	2	0 (0%)	0·074 (0·000-101·340)	0·014 (0·000- 1·7e+05)	5·26 (0·96-28·65)	0·55
AE other than any of the above	13 (26%)	18	2 (11%)	5 (10%)	5	1 (20%)	0·132 (0·001-28·964)	0·036 (0·000-1074·746)	3·76 (1·31-10·80)	0·12

Data expressed as number of patients with event (% of all patients) and total number of events reported. P-value from Poisson regression comparing the event rates, with time to last assessment as offset (i.e. days between baseline and 3 years follow-up or last contact).

*Stroke, transient ischemic attack, myocardial infarction, peripheral embolism, other vascular events.

Discussion

In this prospective, multi-center, randomized, placebo-controlled trial with long-term follow-up, we investigated a novel pharmacologic treatment concept for improvement of ventricular function in adults with systemic RVs. Promising results from concepts in basic research and animal models did not translate into favourable clinical results. As compared to placebo, tadalafil, a phosphodiesterase-5 inhibitor, did not improve systemic right ventricular function and had no impact on other clinical endpoints, such as exercise capacity, neuro-hormonal activation or quality of life.

Scope of the problem

Patients with systemic RVs include patients with ccTGA and patients with d-TGA after atrial switch operation. Patients with ccTGA and associated lesions often require surgical interventions in childhood. [25] Patients born with d-TGA do not survive childhood without intervention. The introduction of the atrial switch operations in the 1960s changed their fate dramatically and survival to adulthood became the rule for the majority of these patients. However, these patients are not cured and are at high risk for clinical heart failure in adult life due to systemic right ventricular dysfunction. Among all adults with congenital heart disease and end-stage heart failure undergoing orthotopic heart transplantation, those with systemic right ventricles currently comprise about one third of all

patients. [26] Given the evolution and demographical characteristics of these patient cohorts, a further increase in the number of adults with systemic RVs and end-stage heart failure is expected over the upcoming years and decades. [27] This contrasts with the very limited number of donor organs, limiting the availability of timely heart transplantation for all patients in need. [26]
Several studies in adults with systemic right ventricles failed to demonstrate a benefit of conventional medical heart failure therapy, and thus routine use of ACE inhibitors, ARBs, beta-blockers or aldosterone antagonists is not recommended in guidelines. [28,29] There is thus an urgent need for novel treatment alternatives in adults with systemic right ventricles and heart failure. [8]

Current evidence and interpretation of study results
So far, most of the treatment recommendations for adults with failing systemic RV are based on data from retrospective studies and expert opinion.[29] Prospective randomized trials are scarce in the field of adult congenital heart disease. To the best of our knowledge, all small prospective trials investigating conventional heart failure medication for patients with systemic right ventricles failed to demonstrate favorable treatment effects.
Our trial indicates that tadalafil does not improve systemic ventricular function in adults with systemic RVs. There is also no signal that it has a beneficial effect on other clinical endpoints, such as exercise capacity or neuro-hormonal activation. At least, treatment with tadalafil was not associated with an increased risk for major adverse events.
Study design and power-calculations of this trial were partially based on results from a previously published, randomized controlled study, assessing the effects of valsartan in adults with systemic RVs. [9] Compared to the patient cohort reported by van der Bom and colleagues, patients within our cohort were on average about seven years older. Still, in the study by van der Bom, more patients were symptomatic at baseline (NYHA class ≥ 2 in 32% versus 17% within our cohort), and fewer were on conventional heart failure medication (Renin-angiotensin-aldosterone system blockers 20% versus 56%, beta blockers 16% versus 34% and diuretics 7% versus 15%). In the study by van der Bom, baseline systemic right ventricular volumes measured by CMR or CT were larger compared to our cohort and RVEF was lower, indicating that the patients included in our study most likely had less advanced heart disease than the cohort from the Netherlands. While a treatment effect of valsartan in the subgroup of symptomatic patients was found in the study by van der Bom, in our study, no significant treatment effect for tadalafil was found when patients were stratified for symptoms at baseline. The frequency of adverse cardiac events over the three-year study period was comparable between the two studies. While in the study by van der Bom et al, a significant increase in RV-ESV over the three years follow-up was found in the placebo-group, this was not observed in our study. Interestingly, a significant decrease in exercise capacity over three years of follow-up was observed in the study by van der Bom and colleagues for the valsartan and for the placebo group, while in our cohort, average exercise capacity remained stable.
There may be several possible explanations why conventional heart failure medication does not work in adults with systemic RVs. First, structure, architecture, and function of a morphological RV differs in many ways from a morphological left ventricle.[8] Second, heart failure in patients with complex congenital heart disease may be promoted by the repair strategy. Stiff venous baffles, redirecting venous blood on atrial level may importantly limit ventricular preload, independent of the actual myocardial function. Extensive scar tissue from previous repair operations, the high prevalence of atrial arrhythmias, sinus node dysfunction and conduction abnormalities may interact with ventricular function and hemodynamics.
Since planning and designing of the current trial, several novel treatment options for patients with heart failure, such as Sacubitril/Valsartan and sodium–glucose cotransporter 2 (SGLT2) inhibitors have been introduced in clinical practice. Based on lack of evidence for similar efficacy of standard heart failure medication in adults with systemic RVs, it remains questionable whether these novel heart failure drugs will be effective in patients with systemic right ventricles. It is thus important that the efficacy of these drugs in adults with systemic right ventricles will be properly investigated in prospective trials. Our trial demonstrates that investigator-initiated prospective multi-center-trials, meeting contemporary quality standards are feasible. We thus hope that our efforts encourage other groups to conduct such trials to enhance the urgently needed evidence base for improved treatment of adults with congenital heart disease.
In a recent study, a substantial proportion of adults with systemic RVs, undergoing cardiac catheterization, was found to have pulmonary hypertension. [30] Almost one third of patients were found to have pre-capillary or combined pre- and post-capillary pulmonary hypertension. Such patients may benefit from specific treatment with PDE-5 inhibitors. In our study, treatment with tadalafil was associated with expected side-effects of treatment with a PDE-5 inhibitor, such as headaches and dyspepsia but showed no signal for an excess in cardiovascular complications.
Within our trial, a large amount of high-quality data was prospectively collected, including data from cardiac imaging, neuro-hormonal activation and exercise testing. Careful analysis of these data by means of pre-specified

sub-analyses and substudies are planned and will likely improve our understanding of the disease trajectory in adults with systemic right ventricles and may help to facilitate prognostication in the future.

Limitations
Although our study was not powered to detect a reduction in hard clinical endpoints, given the results of our analysis, it is rather unlikely that such a benefit was to be expected in larger patient cohorts with longer follow-up duration. Whether the lack of efficacy of tadalafil is a class-effect or specifically related to tadalafil cannot be answered by the current study. Arrhythmic events during follow-up may have had an impact on measures of ventricular volumes and function.

Conclusion
In this trial in adults with systemic RV, right ventricular systolic function, exercise capacity and neuro-hormonal activation remained stable over a three-year follow-up period. No significant treatment effect of tadalafil was observed.

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Contributors
All authors met the International Committee of Medical Journal Editors criteria for authorship for this Article, take responsibility for the integrity of the work as a whole, were involved in drafting and critical review of the manuscript, and approved the final version for submission. All authors agree to be accountable for all aspects of the work and attest to the accuracy and integrity of the work. MG and DT contributed in drafting of the manuscript, in the conception of the research, critical revision of the manuscript for important intellectual content and supervision. JB and MS contributed in the conception and design of the research, critical revision of the manuscript for important intellectual content and supervision. AF contributed in the conception and design of the research, critical revision of the manuscript for important intellectual content and supervision. JS, RB, MW, CM were responsible for the corelabs of CMR, CT, CEPT and neurohormones, respectively. MF, DH, JR, PH, DB, KW, FS, MP, JS, and TR contributed to the conception of the design and critical revision of the manuscript for important intellectual content. RE, EVB and HG contributed in critical revision of the manuscript for important intellectual content.

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Other Investigators and contributors to be listed in PUBMED:
David Herzig, Prisca Eser (CPET Core laboratory University hospital Bern)
Coralie Blanche (University Hospital Geneva)
Dominik Stambach, Niklas Ehl (Kantonsspital St. Gallen)
Irene M. Lang, Julia Mascherbauer, Matthias Schneider, Rochus Pokan (University Hospital Vienna)
Christine H. Attenhofer Jost, Bruno Santos Lopes, Francesca Bonassin Tempesta, Lukas Meier, Daniela Babic, Georgios Benetos (University Hospital Zurich, Switzerland)
David Jean Winkel (University Hospital of Basel, Basel, Switzerland)