



Contents lists available at ScienceDirect

## International Journal of Cardiology

journal homepage: [www.elsevier.com/locate/ijcard](http://www.elsevier.com/locate/ijcard)

## Effect of phosphodiesterase-5 inhibition with Tadalafil on Systolic Right Ventricular size and function – A multi-center, double-blind, randomized, placebo-controlled clinical trial – SERVE trial - Rationale and design

Daniel Tobler <sup>a,\*</sup>, Judith Boucharly <sup>b,c,1</sup>, Engel Reto <sup>d</sup>, Dik Heg <sup>e</sup>, Christian Müller <sup>f</sup>, André Frenk <sup>g</sup>, Harald Gabriel <sup>h</sup>, Jürg Schwitler <sup>b,i</sup>, Tobias Rutz <sup>b,i</sup>, Ronny R. Buechel <sup>j</sup>, Matthias Willhelm <sup>k</sup>, Lukas Trachsel <sup>k</sup>, Michael Freese <sup>f</sup>, Matthias Greutmann <sup>l,1</sup>, Markus Schwerzmann <sup>g,1</sup>, on behalf of the SERVE trial <sup>2</sup>

<sup>a</sup> Department of Cardiology, University Hospital Basel, University of Basel, Basel, Switzerland

<sup>b</sup> Department of Cardiology and Cardiac Surgery (CHUV), Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland

<sup>c</sup> Division of Cardiology, Hôpitaux Universitaires de Genève (HUG), Genève, Switzerland

<sup>d</sup> Cardiology, Kantonsspital St. Gallen, St. Gallen, Switzerland

<sup>e</sup> Department of Clinical Research, Clinical Trials Unit, ISPM, University of Bern, Switzerland

<sup>f</sup> Department of Cardiology and Cardiovascular Research Institute Basel (CRIB), University Hospital Basel, Basel, Switzerland

<sup>g</sup> University Clinic of Cardiology, Center for Congenital Heart Disease, Inselspital, University Hospital, Bern, Switzerland

<sup>h</sup> Department of Cardiology, Vienna General Hospital, Medical University of Vienna, Vienna, Austria

<sup>i</sup> Cardiac MR Center of the University Hospital Lausanne and CMR Corelab (swissCVCORElab, CHUV), Switzerland

<sup>j</sup> Department of Nuclear Medicine, Cardiac Imaging, University Hospital Zurich, Zurich, Switzerland

<sup>k</sup> University Clinic of Cardiology, Preventive Cardiology and Sports Medicine, Inselspital, University Hospital, Bern, Switzerland

<sup>l</sup> University Heart Center, Department of Cardiology, University of Zurich, Switzerland

## ARTICLE INFO

## Article history:

Received 10 April 2017

Received in revised form 9 May 2017

Accepted 20 May 2017

Available online xxx

## ABSTRACT

**Background:** Patients with a systemic right ventricle (RV) have a compromised late outcome caused by ventricular dysfunction. Standard medical heart failure therapy has not been shown to improve RV function and survival in these patients. Phosphodiesterase (PDE)-5 inhibition increases contractility in experimental models of RV hypertrophy, but not in the normal RV. In clinical practice, the effects of PDE-5 inhibition on systemic RV function and exercise capacity in adults with a systemic RV have not been tested.

**Methods:** The SERVE protocol is a double-blind, randomized placebo-controlled multicenter superiority trial to study the effect of PDE-5 inhibition with Tadalafil on RV volumes and function in patients with either D-transposition of the great arteries repaired with an atrial switch procedure or with congenitally corrected transposition of the great arteries. Tadalafil 20 mg or placebo will be given over a study period of 3 years. The primary endpoint is the change in mean end-systolic RV volumes from baseline to study end at 3 years of follow-up (or at the time of permanent discontinuation of the randomized treatment if stopped before 3- years of follow-up), and will be measured by cardiovascular magnetic resonance imaging (CMR) or by cardiac computed tomography in patients with contraindications for CMR. Secondary endpoints are changes in RV ejection fraction, VO<sub>2</sub>max and NT-proBNP.

**Conclusion:** The objective of this study is to assess the effect of PDE-5 inhibition with Tadalafil on RV size and function, exercise capacity and neurohumoral activation in adults with a systemic RV over a 3-year follow-up period.

© 2017 Elsevier B.V. All rights reserved.

## 1. Introduction

The number of adults with congenital heart disease (CHD) continues to increase [1]. Residual lesions and sequelae of previous interventions predispose to higher morbidity and increased mortality rates [2]. Adult patients with prior atrial switch operations (i.e. Senning or Mustard procedures) for complete transposition of the great arteries

\* Corresponding author.

E-mail address: [daniel.tobler@hin.ch](mailto:daniel.tobler@hin.ch) (D. Tobler).

<sup>1</sup> These authors contributed equally to the study design, data interpretation, and manuscript preparation.

<sup>2</sup> See Appendix 1 for a complete list of participating Centers and Investigators.

(d-TGA) or adults with congenitally corrected transposition of the great arteries (ccTGA) and no switch procedure have the right ventricle (RV) in subaortic (systemic) position [3]. Although midterm survival is favorable, late outcome is compromised by ventricular dysfunction of the systemic RV often leading to end-stage heart failure and premature death [4–8].

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 ventricular function and survival in patients with left ventricular (LV) failure from acquired heart disease [9]. However, several studies failed to show a similar clinical benefit of these drugs in adults with a failing systemic RV [10–21]. Currently, the only established therapy for end-stage heart failure in patients with a systemic RV is heart transplantation [22]. Ventricular assist devices can be used as bridge to transplant [23,24]. Given the ubiquitous shortage of donor organs and the number of adults at risk, medical options to improve the fate of a systemic RV are urgently needed.

To the best of our knowledge, the effects of PDE-5 inhibition on RV function and exercise capacity have not yet been tested in adults with a systemic RV. The aim of the present study is to assess in a double-blind, randomized, placebo-controlled trial the effect of PDE-5 inhibition with Tadalafil on RV size and function, exercise capacity and neurohumoral activation in adults with a systemic RV over a 3-year follow-up.

## 2. Study design and setting of the study

This study will use a parallel group, double-blind, randomized, placebo-controlled, multi-center, superiority trial design. Patients meeting the inclusion and exclusion criteria will be allocated randomly to Tadalafil vs. placebo treatment in a 1:1 ratio at the screening visit, using a web-based randomization system. Randomization will be stratified by pacemaker implant at screening. The study is registered at [ClinicalTrials.gov](http://ClinicalTrials.gov) (Identifier: NCT03049540).

The primary objective is to assess the effects of Tadalafil on systemic RV endsystolic volume (ESV) measured by cardiovascular magnetic resonance imaging (CMR) or cardiac multirow detector computed tomography (CMDCT) – in patients with contraindications for cardiac MRI – after 3 years of therapy. As our aim is to study the effect of Tadalafil in an unselected group of patients with systemic right ventricles, only few criteria for exclusion were defined and all eligible patients are asked for participation. Our main goal is to define the effect of Tadalafil on long-term outcome and thus a study-duration of three years was chosen. However, to secure the primary endpoint we opted to add an additional MRI-study at one year of follow-up.

The secondary objective of this study is to assess the effects of Tadalafil on systemic RV ejection fraction (EF) measured by CMR or CMDCT at 3 years of follow-up. Another secondary objective of this study is to assess the effects of PDE-5 inhibition on exercise capacity and on serum neurohormonal activation in these patients at 3 years of follow-up. The long-term safety of Tadalafil and its tolerability will be studied in terms of incidence of the following adverse events (AE): headache (reported >10%), epipharyngitis (reported >10%), nausea and dyspepsia (reported >10%) and symptomatic arterial hypotension (reported 1–10%) and in terms of serious adverse event (SAE) such as hospitalization for heart failure or death.

The inclusion and exclusion criteria are detailed in Table 1. All participants will be started on Tadalafil 20 mg or placebo OD without any titration period.

### 2.1. Follow-up

After the baseline inclusion visit and a first follow-up visit after four weeks, further follow-up will consist of yearly outpatient visits and phone calls after 3, 6, 9, 18 and 30 months to control the adherence to the study drug, and to assess the concomitant medication and record

**Table 1**  
Inclusion and exclusion criteria of the SERVE trial.

Inclusion
<ul style="list-style-type: none"> <li>Adults (<math>\geq 18</math> years) with a systemic RV due to D-TGA repaired with an atrial switch procedure or due to ccTGA</li> <li>Signed informed consent</li> </ul>
Exclusion
<ul style="list-style-type: none"> <li>Incapability of giving informed consent</li> <li>Myocardial infarction, stroke, or open heart surgery within the 3 months prior to baseline visit</li> <li>Expected heart transplant within the next 6 months starting from baseline</li> <li>Pregnant or nursing women (a pregnancy test is mandatory prior to randomization; women of childbearing potential must agree to use reliable contraception from randomization to end of study treatment)</li> <li>Severe renal insufficiency (Creatinine clearance <math>\leq 30</math> ml/min)</li> <li>Severe hepatic insufficiency (Child-Pugh-Class C)</li> <li>Hypotension with blood pressures <math>&lt; 90/50</math> mm Hg at the baseline visit</li> <li>Hypersensitivity to Tadalafil</li> <li>Allergy to iodinated (in patients undergoing CMDCT) or gadolinium-based (in patients undergoing CMR) contrast agents</li> <li>Co-medication with nitrates</li> <li>Regular use of "poppers", i.e. alkyl nitrites, that are inhaled for recreational purposes, including as club drugs used at dance clubs</li> <li>Chronic co-medication with potent CYP3A4 inhibitors: Ketoconazol, Ritonavir, Rifampicin</li> <li>Co-medication with other PDE-5 inhibitors for erectile dysfunction during the last four weeks prior to baseline visit</li> <li>Medical history of non-arteritic anterior ischemic optic neuropathy</li> <li>Hereditary galactose intolerance, lactase deficiency or glucose-galactose-malabsorption</li> <li>Participation at another clinical trial in which the primary endpoint has not been reached</li> </ul>

ccTGA = congenitally corrected transposition of the great arteries; CMDCT = cardiac multirow detector computed tomography; CMR = cardiovascular magnetic resonance imaging; D-TGA = D-transposition of the great arteries; PDE = phosphodiesterase.

and document AE and SAE. The rationale to follow participants at yearly intervals after the first year of the study follows requirements of standards of care, defined by the Swiss Working Group for Adults with Congenital heart disease [25].

Table 2 summarizes the assessment schedule.

## 3. Methods

### 3.1. CMR and CMDCT

CMR will be performed in all patients at baseline, at 1 year and at 3-year follow-up. Image acquisition will be performed with a 1.5-T scanner using a standardized protocol to diminish inter-study variability between the different centers. A position paper of the group of Swiss pediatric and adult cardiologists and radiologists performing CMR in congenital heart disease at university hospitals in Switzerland has been published. The recommendations for imaging a systemic RV as outlined in this paper will be followed for this trial [26].

In patients with contraindication for CMR, CMDCT will be performed at baseline, at 1 year and at 3-year follow-up to establish the primary endpoint. Images will be obtained by contrast-enhanced, electrocardiogram (ECG) gated cardiac MDCT in cranio-caudal direction during inspiratory breath hold. Axial images of 10 cardiac phases are acquired in steps of 10% of the R-R interval. To depict the whole heart, 60–80 slices are made each with 2 mm thickness and no interslice gap. From these, 12–15 short-axis reconstructions will be created for functional analysis.

In both imaging methods, cine loops will be used to define end diastole (largest RV volume) and end systole (smallest RV volume). Trabeculations and papillary muscles will be considered part of the ventricular cavity. The sum of traced contours in end diastole and end systole will be used to calculate end-diastolic and end-systolic volumes using a disc summation method [26].

To minimize bias in image analysis, measurements of ventricular volumes and function will be performed in a blinded fashion by experienced observers in a core lab for CMR data ("swissCVIcorelab" at the Centre Hospitalier Universitaire Vaudois, CHUV, Switzerland) and for CMDCT data (University Hospital Zurich, Switzerland). To decrease the variability in RV ESV, every measurement will be performed twice, by 2 different readers, and the mean volume will be used for study purposes.

### 3.2. Cardiopulmonary exercise testing (CPET)

Cardiopulmonary exercise testing (CPET) will be performed in all patients at baseline and at study end. Before exercise, respiratory flow loops will be acquired and maximal

**Table 2**  
Assessment schedule.

Visit	BL*	Visit 1	PC1**	PC2**	PC3**	Visit 2	PC4**	Visit 3	PC5**	Visit 4	Safety FU
Time (months from BL)	0	1	3	6	9	12	18	24	32	36	37
Window (weeks)	0	± 2	± 2	± 2	± 2	± 4	± 2	± 4	± 2	± 4	± 1
Informed Consent	X										
Eligibility criteria	X										
Demography	X										
Medical history	X										
QoL	X					X				X	
Randomization	X										
Clinical examination	X	X				X		X		X	
IMP delivery	X					X		X			
IMP accountability		X				X		X		X	
ECG	X					X		X		X	
Holter	X									X	
CMR/CMDCT	X					X				X	
CPET	X									X	
Blood analysis	X	X				X		X		X	
Neurohormones	X					X				X	
TTE	X					X		X		X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X
Adherence			X	X	X		X		X		
AE/SAE		X	X	X	X	X	X	X	X	X	X

AE = adverse event; BL = baseline; CMR = cardiovascular magnetic resonance imaging CMDCT = cardiac multirow detector computed tomograph; CPET = cardiopulmonary exercise study; FU = follow-up; IMP = investigational medicinal product; PC = phone call; QoL = quality of life; SAE = serious adverse event.

breathing capacity determined. Patients will be placed on a cycle ergometer to perform continuous measurements of minute ventilation, oxygen consumption, carbon dioxide production, heart rate, blood pressure and electrocardiography. Workload will be increased by 5 to 15 W in a stepwise manner, depending on the individually predicted maximum exercise capacity, in such a way that maximal possible effort can be attained in 10–15 min. Peak VO<sub>2</sub> is defined as the highest value of oxygen consumption during the last 30 s of peak exercise. A 12-lead ECG will be continuously recorded and a finger pulse oxymeter is used for continuous measurement of arterial oxygen saturation. The following additional parameters will be assessed: VE/VCO<sub>2</sub> Slope, PETCO<sub>2</sub>, O<sub>2</sub> pulse trajectory, delta VO<sub>2</sub>/delta W trajectory, heart rate kinetics and heart rate recovery (HRR). Measurements and reporting of these data will follow the recommendations of the European Association for Cardiovascular Prevention and Rehabilitation [27]. The analysis of CPET data will be performed at a single core-lab, located at the University Hospital Inselspital.

### 3.3. Neurohumoral activation

Neurohumoral activation will be measured in all patients at baseline, at 1 year and at study end. Concentrations of the neurohormones B-type natriuretic peptides (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP), high-sensitive cardiac troponin (hs-cTn), A-type natriuretic peptide (MR-proANP), Pro-adrenomedullin, Copeptin and Pro-endothelin-1 will be measured at a single core-lab with expertise in biomarkers (Cardiovascular Research Institute Basel, CRIB).

Specific patients sets with plastic tubes and barcodes corresponding to the individual patient numbers and time points in the study will be used. Samples will be collected locally, followed by centrifugation, aliquoting and initial storage at  $-80^{\circ}$  at every center. Regular pick up of samples at the individual hospitals and transport to the dedicated biobank at the CRIB will be provided by the core-lab.

## 4. Statistical considerations and sample size

### 4.1. Hypothesis

All primary and secondary endpoints will be analysed by intention-to-treat, tested using two-sided superiority testing with alpha set at 5%. The primary hypothesis tested is that patients randomized to treatment with Tadalafil will improve systemic RV ESV compared to the patients randomized to treatment with placebo. In patients who have to discontinue the study medication prematurely, RV ESV will be re-measured within 4 weeks of the study drug withdrawal and this measurement will then be used for the primary endpoint analyses, unless the treatment period was <3 months. The difference in RV ESV between baseline and the last CMR/CMDCT measurement will serve as primary endpoint.

Secondary endpoints are change in RV EF measured by CMR or CMDCT, change in exercise capacity measured as peak VO<sub>2</sub> during cardiopulmonary exercise testing and change in serum neurohormonal activation (seven biomarkers: BNP, NT-pro BNP, hs-cTn, MR-proANP,

Pro-adrenomedullin, Copeptin and Pro-endothelin-1) from baseline to study end at 3 years of follow-up or at the time of permanent discontinuation of the randomized treatment if stopped before 3 years of follow-up. Again, in patients who have to discontinue the study medication prematurely, RV EF, exercise capacity and neurohumoral activation will be re-measured within 4 weeks of the study drug withdrawal, unless the treatment period was <3 months.

### 4.2. Sample size

The sample size calculation is based on the primary endpoint - the change in RV ESV. In a representative sample of  $n = 79$  TGA patients with a systemic RV from Bern and Zurich with CMR data, the RV end-systolic volume was  $122 \pm 34$  ml [28]. Assuming that RV ESV improve or remain stable in the Tadalafil group and increase by 20% in the Placebo group to  $146 \pm 39$  ml, 78 patients are required to obtain an 80% power to detect this difference in RV end-systolic volumes between the 2 treatment groups. Considering a possible dropout of 20%, 98 patients will be required (49 patients for each group). Assuming that not all RV may respond similarly to Tadalafil, we elected to account for this phenomenon by increasing the standard deviation in the follow-up exam from 34 ml to 39 ml.

### 4.3. Primary analysis

The primary endpoint will be analysed using ANCOVA (Analysis of Covariance), with RV ESV (in ml) at 3 years (or earlier if drug withdrawal) as the response variable, randomized treatment as main independent variable, baseline RV ESV (ml) and time between baseline and follow-up RV volume measurement (in months since baseline) as covariates.

### 4.4. Secondary analyses

Secondary endpoints will be analysed using ANCOVA (Analysis of Covariance) or Tobit regression or Multiple Imputation ANCOVA, with the secondary endpoint (RV EF, peak VO<sub>2</sub>, BNP, NT-pro BNP, hs-cTn, MR-proANP, Pro-adrenomedullin, Copeptin or Pro-endothelin-1) at 3 years (or earlier if drug withdrawal) as the response variable, randomized treatment as main variable, baseline measurement (RV EF, peak VO<sub>2</sub>, BNP, NT-pro BNP, hs-cTn, MR-proANP, Pro-adrenomedullin, Copeptin or Pro-endothelin-1; respectively) and time between baseline

and follow-up measurement time (in months since baseline) as covariates.

## 5. Ethical considerations

The study will be carried out according to the ICH GCP Guidelines. It will be submitted to the responsible ethics committee and to the competent authorities. The clinical study can only begin once approval from all required authorities has been received. Any additional requirements imposed by the authorities will be implemented. Serious Adverse Events and adherence to the study drug will be carefully monitored and reviewed during the study by an independent Data Safety Monitoring Board.

This is a first clinical trial within this patient population with this study drug and the success of the treatment cannot be predicted. The safety profile of the drug and the lack of treatment for these specific patients justify the conduct of the study from an ethical point of view.

## 6. Discussion

We present a double-blind, randomized placebo controlled multi-center superiority trial to study the effect of PDE-5 inhibition with Tadalafil on RV volumes and function in patients with either D-transposition of the great arteries repaired with an atrial switch procedure or with congenitally corrected transposition of the great arteries. The rationale to conduct this study is the fact that currently available medical heart failure therapy, proven to work for heart failure in acquired heart disease, failed in trials that sought preventing RV dysfunction and heart failure with these agents in patients with a systemic RV.

### 6.1. Explanation for choice of the drug and its dose

Considering the negative trials with conventional left heart failure medication, one can argue that in the setting of a failing systemic RV the pursuance of therapies developed for treatment of LV failure has to be abandoned and novel approaches have to be investigated [10].

The RV and LV have different embryological origins, myocardial architecture and contractile properties [29,30]. In response to increased afterload, as present in an RV in systemic position, the RV expresses a fetal gene pattern with an increase in phosphodiesterase-5 (PDE-5) expression [31]. PDE-5 is not expressed in the normal RV, but is up-regulated in hypertrophied RV myocardium. PDE-5 inhibitors increase contractility in experimental models of RV hypertrophy, but not in the normal RV [31]. 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 [32].

In pulmonary arterial hypertension (PAH) patients, Sildenafil and Tadalafil are the most widely used PDE-5 inhibitors. Tadalafil has a longer half-life (18 h) than Sildenafil (3–4 h) and higher selectivity for PDE-5 [33]. Tadalafil can be taken as a single daily dose. In studies investigating the effects of Tadalafil on cardiac and circulatory function, single Tadalafil doses up to 50 mg have been reported to be safe in terms of an absence of significant systemic vasodilation [33]. In several large PAH trials, Tadalafil therapy was well tolerated through up to 68 weeks of dosing [34,35]. In the large number of patients using PDE-5 inhibitors for treating erectile dysfunction, Tadalafil had an excellent safety profile without significant cardiovascular safety issues [36]. In over 30 trials, > 12,000 men (mean age 55 years) with erectile dysfunction received Tadalafil and 2000 men (mean age 56 years) received placebo. Tadalafil 2 mg to 50 mg was taken as needed, 3 times/week, or once a day. Across all trials, the incidence rate of serious cardiovascular events was similar in Tadalafil-treated men compared to placebo-treated ones [37].

For all these reasons, we decided to use Tadalafil as PDE-5 inhibitor in this clinical study. In the PHIRST trial, a study with PAH patients,

Tadalafil 2.5 mg, 10 mg, 20 mg and 40 mg OD was compared against placebo [38]. There was no significant difference between Tadalafil 20 mg OD vs. 40 mg OD with respect to the hemodynamic measures and changes in 6 min walking distance. In the PHIRST-2 extension trial, patients receiving either 20 mg or 40 mg of Tadalafil, had both a sustained beneficial effect for up to 52 additional weeks of treatment [35]. The most common adverse effect of Tadalafil in this trial was headache, occurring in 14% of patients with the 20 mg dose and 28% of patients with the 40 mg dose. Overall, 20 mg Tadalafil seems to have beneficial cardiovascular effects in PAH patients, but probably less side effects than 40 mg Tadalafil. Therefore, in our study Tadalafil 20 mg OD will be compared to placebo.

### 6.2. Explanation for choice of the RVESV as primary outcome measure

LV dimensions (end-systolic and end-diastolic volumes) and EF have been shown to be one of the most powerful predictors of survival in chronic LV heart failure [39]. Dimensions and EF of the systemic ventricle are also important prognostic factors in adults with a systemic RV [7, 40,41]. We elected to use changes in RV ESV as primary endpoint for our trial for the following reasons:

- In patients with LV systolic dysfunction, short-term therapeutic effects of study drugs or a device on LV dimensions were associated with longer-term effects on mortality [42,43]. We assume that the same prognostic assumptions between systemic ventricular volumes and hard clinical endpoints can be made for a failing RV: in a recent MRI based study with PAH patients and RV failure, RV ESV (but not end-diastolic volumes) at baseline were predictive of late RV failure leading to death or lung transplantation after a follow-up of 8 years [44].
- MRI-based measurements of volumes have the highest reproducibility among all RV measures [45].
- Measurement of RV ESV is likely more sensitive to detect changes in RV function in TGA patients than RV EF because the RV of patients with PAH adapts to its chronically increased afterload first by myocardial remodelling with hypertrophy and increased contractility [46]. If these compensatory mechanisms fail, the RV begins to dilate, followed by a decrease in RV EF. Accordingly, an increase in RV volumes precedes the decrease in RV EF. The systemic RV in patients with TGA may behave similarly. With progressive RV failure and RV dilatation, there is also an increase in secondary tricuspid regurgitation [5]. The increased amount of tricuspid regurgitation may falsely improve RV EF, whereas RV ESV will nevertheless be increased as sign of progressive RV failure.
- Performing a placebo-controlled trial that assesses differences in mortality is not feasible in TGA patients, as it would need to involve too large patient numbers.

## 7. Funding

The SERVE trial is funded by the Swiss National Science Foundation (Schweizerischer Nationalfonds zur Förderung der wissenschaftlichen Forschung, 311C30\_166855).

## 8. Conclusions

The objective of this study is to assess the effect of PDE-5 inhibition with Tadalafil on RV size and function, exercise capacity and neurohumoral activation in adults with a systemic RV over a 3-year follow-up period.

## Conflict of interest

There are no conflicts of interest to disclose.

## Contributors

DT and JB contributed in drafting of the manuscript, in the conception of the research, critical revision of the manuscript for important intellectual content and supervision. MG 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. CM, RB, MW, MF, DH, JS, and TR contributed to the conception of the design and critical revision of the manuscript for important intellectual content. RE and HG contributed in critical revision of the manuscript for important intellectual content.

## Appendix 1

### Steering committee

**Coordinating Investigator:** M. Schwerzmann

**Co-Principle Investigators:** J. Bouchardy, M. Greutmann, D. Tobler

**Co-Investigators:** R. Engel, H. Gabriel

**CMR Core Laboratory (“swissCVIcorelab”, CHUV, Lausanne):** J. Schwitler, T. Rutz

**CMDCT Core Laboratory (University Hospital Zurich):** R. Buechel

**CPET Core Laboratory (Inselspital Bern):** M. Wilhelm, L. Trachsel, David Herzig, Prisca Eser

**Biomarker Core Laboratory (University Hospital Basel):** Ch. Mueller

**Echocardiography Core Laboratory (University Hospital Zurich):** M. Greutmann

**Participating centers:** University Hospital Basel, Inselspital Bern, University Hospital Geneva, University Hospital Lausanne, Kantonsspital St. Gallen, University Hospital Vienna (Austria), University Hospital Zurich

**Electronic Data Capture and Statistical analyses (CTU Inselspital Bern):** D. Heg

**Contributors of the SERVE trial (mentioned as 'on behalf of the SERVE study):**

**University Hospital Basel:** D. Tobler, Ph. Haaf, M. Freese, Ch. Mueller; **University Hospital Inselspital:** A. Frenk, K. Mülchi, M. Schwerzmann, F. Schwitz, L. Trachsel, M. Wilhelm, K. Wustmann, D. Heg; **University Hospital Geneva:** Judith Bouchardy, C. Blanche; **University Hospital Lausanne** (Division of Cardiology – Congenital Heart Disease in Adults): J. Bouchardy, T. Rutz; (CMR Center and “swissCVIcorelab”): P.-G. Masci, P. Monney, T. Rutz, G. Vincenti, J. Schwitler; **Kantonsspital St. Gallen:** R. Engel, D. Stambach, N. Ehl, D. Abbühl; **University Hospital Vienna:** Harald Gabriel; Irene M. Lang, Julia Mascherbauer, Matthias Schneider, Rochus Pokan; **University Hospital Zurich:** Matthias Greutmann, Ronny R Buechel, Christine H. Attenhofer Jost, Bruno Santos Lopes, Francesca Bonassin Tempesta, Emanuela Valsangiacomo Büchel

## References

- [1] A.J. Marelli, R. Ionescu-Ittu, A.S. Mackie, L. Guo, N. Dendukuri, M. Kaouache, Lifetime prevalence of congenital heart disease in the general population from 2000 to 2010, *Circulation* 130 (2014) 749–756.
- [2] D. Mylotte, L. Pilote, R. Ionescu-Ittu, M. Abrahamowicz, P. Khairy, J. Therrien, et al., Specialized adult congenital heart disease care: the impact of policy on mortality, *Circulation* 129 (2014) 1804–1812.
- [3] R.H. Anderson, P.M. Weinberg, The clinical anatomy of transposition, *Cardiol. Young* 15 (Suppl. 1) (2005) 76–87.
- [4] J.W. Roos-Hesselink, F.J. Meijboom, S.E. Spitaels, R. van Domburg, E.H. van Rijen, E.M. Utens, et al., Decline in ventricular function and clinical condition after Mustard repair for transposition of the great arteries (a prospective study of 22–29 years), *Eur. Heart J.* 25 (2004) 1264–1270.
- [5] J.A. Cuypers, J.A. Eindhoven, M.A. Slager, P. Opic, E.M. Utens, W.A. Helbing, et al., The natural and unnatural history of the Mustard procedure: long-term outcome up to 40 years, *Eur. Heart J.* 35 (2014) 1666–1674.
- [6] S. Piran, G. Veldtman, S. Siu, G.D. Webb, P.P. Liu, Heart failure and ventricular dysfunction in patients with single or systemic right ventricles, *Circulation* 105 (2002) 1189–1194.
- [7] M. Schwerzmann, O. Salehian, L. Harris, S.C. Siu, W.G. Williams, G.D. Webb, et al., Ventricular arrhythmias and sudden death in adults after a Mustard operation for transposition of the great arteries, *Eur. Heart J.* 30 (2009) 1873–1879.
- [8] T.P. Graham Jr., Y.D. Bernard, B.G. Mellen, D. Celermajer, H. Baumgartner, F. Cetta, et al., Long-term outcome in congenitally corrected transposition of the great arteries: a multi-institutional study, *J. Am. Coll. Cardiol.* 36 (2000) 255–261.
- [9] J.J. McMurray, S. Adamopoulos, S.D. Anker, A. Auricchio, M. Bohm, K. Dickstein, et al., ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC, *Eur. Heart J.* 33 (2012) 1787–1847.
- [10] S.L. Roche, A.N. Redington, The failing right ventricle in congenital heart disease, *Can. J. Cardiol.* 29 (2013) 768–778.
- [11] T. van der Bom, M.M. Winter, B.J. Bouma, M. Groenink, H.W. Vliegen, P.G. Pieper, et al., Effect of valsartan on systemic right ventricular function: a double-blind, randomized, placebo-controlled pilot trial, *Circulation* 127 (2013) 322–330.
- [12] A. Dore, C. Houde, K.L. Chan, A. Ducharme, P. Khairy, M. Juneau, et al., Angiotensin receptor blockade and exercise capacity in adults with systemic right ventricles: a multicenter, randomized, placebo-controlled clinical trial, *Circulation* 112 (2005) 2411–2416.
- [13] S.J. Lester, D.B. McElhinney, E. Vilorio, G.P. Reddy, E. Ryan, W. Tworetzky, et al., Effects of losartan in patients with a systemically functioning morphologic right ventricle after atrial repair of transposition of the great arteries, *Am. J. Cardiol.* 88 (2001) 1314–1316.
- [14] J. Therrien, Y. Provost, J. Harrison, M. Connelly, H. Kaemmerer, G.D. Webb, Effect of angiotensin receptor blockade on systemic right ventricular function and size: a small, randomized, placebo-controlled study, *Int. J. Cardiol.* 129 (2008) 187–192.
- [15] S.J. Hechter, P.M. Fredriksen, P. Liu, G. Veldtman, N. Merchant, M. Freeman, et al., Angiotensin-converting enzyme inhibitors in adults after the Mustard procedure, *Am. J. Cardiol.* 87 (2001) 660–663 (A11).
- [16] A.R. Doughan, M.E. McConnell, W.M. Book, Effect of beta blockers (carvedilol or metoprolol XL) in patients with transposition of great arteries and dysfunction of the systemic right ventricle, *Am. J. Cardiol.* 99 (2007) 704–706.
- [17] A. Giardini, L. Lovato, A. Danti, R. Formigari, G. Gargiulo, F.M. Picchio, et al., A pilot study on the effects of carvedilol on right ventricular remodeling and exercise tolerance in patients with systemic right ventricle, *Int. J. Cardiol.* 114 (2007) 241–246.
- [18] R.E. Shaddy, M.M. Boucek, D.T. Hsu, R.J. Boucek, C.E. Canter, L. Mahony, et al., Carvedilol for children and adolescents with heart failure: a randomized controlled trial, *JAMA* 298 (2007) 1171–1179.
- [19] L. Dos, S. Pujadas, M. Estruch, A. Mas, I. Ferreira-Gonzalez, A. Pijuan, et al., Eplerenone in systemic right ventricle: double blind randomized clinical trial. The evedes study, *Int. J. Cardiol.* 168 (2013) 5167–5173.
- [20] G.P. Diller, D. Okonko, A. Uebing, S.Y. Ho, M.A. Gatzoulis, Cardiac resynchronization therapy for adult congenital heart disease patients with a systemic right ventricle: analysis of feasibility and review of early experience, *Europace* 8 (2006) 267–272.
- [21] J. Janousek, V. Tomek, V.A. Chaloupecky, O. Reich, R.A. Gebauer, J. Kautzner, et al., Cardiac resynchronization therapy: a novel adjunct to the treatment and prevention of systemic right ventricular failure, *J. Am. Coll. Cardiol.* 44 (2004) 1927–1931.
- [22] T. Carrel, J.P. Pfammatter, Complete transposition of the great arteries: surgical concepts for patients with systemic right ventricular failure following intraatrial repair, *Thorac. Cardiovasc. Surg.* 48 (2000) 224–227.
- [23] E. Peng, J.J. O’Sullivan, M. Griselli, C. Roysam, D. Crossland, M. Chaudhari, et al., Durable ventricular assist device support for failing systemic morphologic right ventricle: early results, *Ann. Thorac. Surg.* 98 (2014) 2122–2129.
- [24] O. Loup, K. Wustmann, M.V. Martinelli, M. Schwerzmann, P. Mohacs, T.P. Carrel, et al., Failing systemic right ventricles with persistent pulmonary hypertension: candidates for ventricular assist devices as destination therapy? *Ann. Thorac. Surg.* 103 (2017) e179–e181.
- [25] J. Bouchardy, M. Greutmann, M. Schwerzmann, C.H. Attenhofer Jost, G. De Pasquale, A. Oxenius, et al., Grown-up congenital heart disease (GUCH) recommendations for standards of care, *Cardiovasc. Med.* 18 (2015) 144–145.
- [26] T. Rutz, K. Wustmann, M. Prsa, J. Vallée, B. Donner, J. Bremerich, et al., Cardiac magnetic resonance imaging in congenital heart disease, *Cardiovasc. Med.* 19 (2016) 176–184.
- [27] M. Guazzi, V. Adams, V. Conraads, M. Halle, A. Mezzani, L. Vanhees, et al., EACPR/AHA joint scientific statement. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations, *Eur. Heart J.* 33 (2012) 2917–2927.
- [28] M. Schwerzmann, A. Stauber, C. Wey, M. Greutmann, D. Tobler, K. Wustmann, et al., Biventricular interactions and their impact on systemic ventricular function and exercise capacity in adults with a subaortic right ventricle (P3738). European Society of Cardiology (ESC). Rom, 30.08.2016, *Eur Heart J* (2016) 762–763.
- [29] M.K. Friedberg, A.N. Redington, Right versus left ventricular failure: differences, similarities, and interactions, *Circulation* 129 (2014) 1033–1044.
- [30] S. Zaffran, R.G. Kelly, S.M. Meilhac, M.E. Buckingham, N.A. Brown, Right ventricular myocardium derives from the anterior heart field, *Circ. Res.* 95 (2004) 261–268.
- [31] J. Nagendran, S.L. Archer, D. Soliman, V. Gurtu, R. Moudgil, A. Haromy, et al., Phosphodiesterase type 5 is highly expressed in the hypertrophied human right ventricle, and acute inhibition of phosphodiesterase type 5 improves contractility, *Circulation* 116 (2007) 238–248.
- [32] M.A. Borgdorff, B. Bartelds, M.G. Dickinson, M.P. van Wiechen, P. Steendijk, M. de Vroomen, et al., Sildenafil treatment in established right ventricular dysfunction

- improves diastolic function and attenuates interstitial fibrosis independent from afterload, *Am. J. Physiol. Heart Circ. Physiol.* 307 (2014) H361–H369.
- [33] H.A. Ghofrani, R. Voswinckel, F. Reichenberger, H. Olschewski, P. Haredza, B. Karadas, et al., Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study, *J. Am. Coll. Cardiol.* 44 (2004) 1488–1496.
- [34] N. Galie, J.A. Barbera, A.E. Frost, H.A. Ghofrani, M.M. Hooper, V.V. McLaughlin, et al., Initial use of Ambrisentan plus Tadalafil in pulmonary arterial hypertension, *N. Engl. J. Med.* 373 (2015) 834–844.
- [35] R.J. Oudiz, B.H. Brundage, N. Galie, H.A. Ghofrani, G. Simonneau, F.T. Botros, et al., Tadalafil for the treatment of pulmonary arterial hypertension: a double-blind 52-week uncontrolled extension study, *J. Am. Coll. Cardiol.* 60 (2012) 768–774.
- [36] C.C. Carson III, Cardiac safety in clinical trials of phosphodiesterase 5 inhibitors, *Am. J. Cardiol.* 96 (2005) 37M–41M.
- [37] R.A. Kloner, G. Jackson, A.M. Hutter, M.A. Mittleman, M. Chan, M.R. Warner, et al., Cardiovascular safety update of Tadalafil: retrospective analysis of data from placebo-controlled and open-label clinical trials of Tadalafil with as needed, three times-per-week or once-a-day dosing, *Am. J. Cardiol.* 97 (2006) 1778–1784.
- [38] N. Galie, B.H. Brundage, H.A. Ghofrani, R.J. Oudiz, G. Simonneau, Z. Safdar, et al., Tadalafil therapy for pulmonary arterial hypertension, *Circulation* 119 (2009) 2894–2903.
- [39] I.S. Anand, V.G. Florea, L. Fisher, Surrogate end points in heart failure, *J. Am. Coll. Cardiol.* 39 (2002) 1414–1421.
- [40] P. Moons, M. Gewillig, T. Sluysmans, H. Verhaaren, P. Viart, M. Massin, et al., Long term outcome up to 30 years after the Mustard or Senning operation: a nationwide multicentre study in Belgium, *Heart* 90 (2004) 307–313.
- [41] N. Vejstrup, K. Sorensen, E. Mattsson, U. Thilen, P. Kvidal, B. Johansson, et al., Long-term outcome of Mustard/Senning correction for transposition of the great arteries in Sweden and Denmark, *Circulation* 132 (2015) 633–638.
- [42] M.A. Konstam, D.G. Kramer, A.R. Patel, M.S. Maron, J.E. Udelson, Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment, *JACC Cardiovasc. Imaging* 4 (2011) 98–108.
- [43] D.G. Kramer, T.A. Trikalinos, D.M. Kent, G.V. Antonopoulos, M.A. Konstam, J.E. Udelson, Quantitative evaluation of drug or device effects on ventricular remodeling as predictors of therapeutic effects on mortality in patients with heart failure and reduced ejection fraction: a meta-analytic approach, *J. Am. Coll. Cardiol.* 56 (2010) 392–406.
- [44] M.C. van de Veerdonk, J.T. Marcus, N. Westerhof, F.S. de Man, A. Boonstra, M.W. Heymans, et al., Signs of right ventricular deterioration in clinically stable patients with pulmonary arterial hypertension, *Chest* 147 (2015) 1063–1071.
- [45] C.F. Mooij, C.J. de Wit, D.A. Graham, A.J. Powell, T. Geva, Reproducibility of MRI measurements of right ventricular size and function in patients with normal and dilated ventricles, *J. Magn. Reson. Imaging* 28 (2008) 67–73.
- [46] A. Vonk-Noordegraaf, F. Haddad, K.M. Chin, P.R. Forfia, S.M. Kawut, J. Lumens, et al., Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology, *J. Am. Coll. Cardiol.* 62 (2013) D22–D33.