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# Right vEntricular Dysfunction in tEtralogy of Fallot: INhibition of the rEnin-angiotensin-aldosterone system (REDEFINE) trial: Rationale and design of a randomized, double-blind, placebo-controlled clinical trial

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**Background** Renin-angiotensin-aldosterone system (RAAS) inhibition with angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors is beneficial in patients with acquired left ventricular dysfunction. Adult patients with tetralogy of Fallot (TOF) with right ventricular (RV) dysfunction are at high risk for heart failure, arrhythmias, and sudden cardiac death. However, the efficacy of RAAS inhibition has not been established in these patients.

**Methods** The REDEFINE is an investigator-initiated, multicenter, prospective, randomized, double-blind, placebo-controlled trial to study the effects of the angiotensin II receptor blocker losartan (target dosage of 150 mg once daily) in adult patients with TOF. Patients with RV dysfunction in the absence of severe valvular dysfunction are eligible for inclusion. The primary end point is the change in RV ejection fraction after 18 to 24 months, as measured by cardiovascular magnetic resonance imaging. In addition, laboratory measurements, echocardiography, and cardiopulmonary exercise testing are performed.

**Conclusion** The REDEFINE trial will study the effects of RAAS inhibition with losartan in TOF patients with RV dysfunction. (Am Heart J 2017;186:83-90.)

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In contrast to adult patients with acquired heart failure due to left ventricular (LV) dysfunction, adults with congenital heart disease (ACHD) often present with right ventricular (RV) dysfunction. In these patients, RV dysfunction often precedes arrhythmias, decreasing exercise capacity, and sudden cardiac death and plays a key role in the rising mortality in aging patients.[1-3] In patients with acquired LV dysfunction, pharmaceutical inhibition of the renin-angiotensin-aldosterone system (RAAS) is considered the cornerstone of medical treatment.[4] There are only limited and inconclusive data on pharmaceutical treatment of heart failure in ACHD, and current guidelines do not offer specific recommendations to treat RV dysfunction.[5] Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart defect, and 95% of patients now reach adulthood.[6,7] Adult patients with TOF are at risk for RV dysfunction because of residual RV pressure and volume overload after childhood surgery. Pulmonary valve replacement (PVR) is frequently performed in these patients to reduce

**Table I.** Inclusion and exclusion criteria for the REDEFINE trial

| |
|---|
| Inclusion criteria |
| A potential participant must meet all of the following criteria for inclusion: |
| Repaired TOF or close anatomic variants (eg, pulmonary atresia/stenosis with VSD) |
| Age >18 years |
| Exclusion criteria |
| A potential participant who meets any of the following criteria is excluded from participation: |
| Incapable of giving informed consent |
| RV EF >50% on CMR |
| More than moderate tricuspid or pulmonary regurgitation or pulmonary stenosis |
| Hypersensitivity to losartan or any of its help substances |
| Contraindication for CMR |
| Previous angioedema whether or not in relation to the use of an ACE-I or ARB |
| Known bilateral renal artery stenosis |
| Current symptomatic hypotension |
| Estimated glomerular filtration rate of 30 mL/min or lower |
| Plasma potassium level >5.5 mmol/L |
| Moderate-to-severe liver disease: Child-Pugh class B or C |
| Raised plasma transaminases level >3 times upper normal limit |
| Current treatment with an ACE-I or ARB, which cannot be discontinued |
| Treatment with potassium chloride, trimethoprim, tacrolimus, or cyclosporine, which cannot be discontinued |
| Pregnant or nursing women |
| Women with desire to have children within the study period |

Abbreviation: *VSD*, Ventricular septal defect.

volume overload but is not recommended in patients with RV dysfunction in the absence of severe pulmonary valve dysfunction.[3,5,8] Cumulative event-free survival was only 25% after 40 years in a recent prospective cohort study of TOF patients with surgical correction before 1980.[9] Progressive RV heart failure is the cause of death in about 40%.[10] These findings warrant close surveillance of RV function and adequate evidence-based pharmacologic therapy to reduce both morbidity and mortality. Losartan, an angiotensin II receptor blocker (ARB), has fewer adverse effects, such as cough, and was associated with less drug discontinuation compared with an angiotensin-converting enzyme inhibitor (ACE-I).[11] Therefore, we set up the REDEFINE trial to determine the effects of losartan on RV dysfunction in TOF patients without severe valvular dysfunction.

## Methods

The REDEFINE trial (clinicaltrials.gov identifier NCT02010905) is a prospective, multicenter, double-blind, randomized, placebo-controlled trial with 18- to 24-month follow-up. The trial is performed in 6 major centers in the Netherlands and has been approved by all local ethics committees. The primary hypothesis of this trial is that losartan improves RV ejection fraction (EF), as measured by cardiovascular magnetic resonance (CMR) imaging, compared with placebo. The secondary hypotheses are that losartan improves maximal exercise capacity, LV EF, echocardiographic diastolic and systolic function parameters, and quality of life and decreases RV volumes, RV mass, the incidence of (supra)ventricular arrhythmias, and serum N-terminal pro–B-type natriuretic peptide (NT-proBNP). The inclusion of patients was completed in 2015, and the final results are expected late 2017.

### Study population

Patients at least 18 years after surgical repair of TOF, with RV function below normal limits (RV EF <50% as determined with CMR[12]) and without severe valvular lesions, were eligible to participate in the trial. Inclusion and exclusion criteria are detailed in Table I. Potential candidates were identified via the CONCOR database, a national database and DNA bank of patients with ACHD.[13] In addition, patients under care in participating centers who were not yet included in the CONCOR database were identified by treating cardiologists. Eligible patients were sent information letters and, if interested, invited to the outpatient clinics for a detailed explanation of the study and asked for written informed consent. Patients were not obliged to provide a reason for declining participation.

### Randomization

Patients were randomized 1:1 to losartan (active treatment) or matching placebo by block randomization. Each block consisted of 4 patients. The randomization was stratified by site.

Randomization was performed by a randomization list by the hospital pharmacy, which acted as an unblinded third party. Patients, study personnel, and treating cardiologist were blinded to the treatment. All participants were followed up by their own cardiologist according to the same predefined study protocol (Table II).

**Table II.** Investigations as scheduled for each patient

| | V0 baseline | V1 + 2 wk | V2 + 4 wk | V3 + 2 m | V4 + 12 m | V5 + 18-24 m |
|---|---|---|---|---|---|---|
| Start of medication (mg once daily*) | 50 | 100 | 150 | | Continued | |
| Visit outpatient clinic | x | | | | x | x |
| History/events | x | x | x | x | x | x |
| Physical examination | x | | | | x | x |
| Electrocardiography | x | | | | x | x |
| Blood analysis | | | | | | |
| Routine laboratory† | x | x | x | x | x | x |
| NT-proBNP | x | | | | | x |
| Echocardiography | x | | | | x | x |
| Quality of life questionnaires | x | | | | | x |
| CMR | x | | | | | x |
| Cardiovascular exercise testing | x | | | | | x |

V0: first visit to outpatient clinic + investigations and so on. V4: outpatient visit + echocardiography only in patients when clinically indicated by their treating physician.
X indicates which investigations are performed at which visits.
*Trial medication may be reduced for several reasons as described in the Methods section.
† Routine laboratory tests consist of hemoglobin, hematocrit, leukocyte, thrombocytes, sodium, potassium, creatinine, urea, alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, and alkaline phosphatase.

## Study medication

Patients received tablets of 50 mg losartan or placebo tablets matching the 50-mg losartan tablets. Patients started at a dosage of 50 mg once daily. After 2 weeks, the dosage was increased to 100 mg losartan or placebo (2 tablets once daily), and after 4 weeks, it was increased to 150 mg losartan or placebo (3 tablets once daily), if there were no adverse effects, and renal function, liver function parameters, and electrolytes remained within predefined limits.

Patients who previously used ACE-I or ARBs discontinued these at least 4 weeks before baseline CMR and commencing trial medication. All other medications were continued. The appropriate dose of losartan in the treatment of RV dysfunction in patients with TOF is unknown. Consequently, the dose was chosen for its reported effects in LV systolic heart failure.[14]

During the course of the present study, adverse effects are evaluated. If a patient experience adverse effects (such as dizziness due to hypotension, nausea, and abdominal discomfort), trial medication dosage is decreased to 100 mg (two 50-mg tablets) once daily. When adverse effects persist after lowering of trial medication dosage, trial medication is further decreased to 50 mg once daily. When adverse effects persist at the minimum dosage of 50 mg once daily, trial medication is ceased.

## Study measures

Study measures were obtained in all participating patients at baseline (at least within 1 year before inclusion, at least 1 month after stopping RAAS inhibitors). Study measures are repeated after 18 to 24 months of treatment, with deviation possible due to logistical reasons. Clinical outcomes include a composite of all-cause mortality, increase of heart failure or hospitalization for heart failure, supraventricular tachycardia, and ventricular tachycardia (VT). Safety end points include the rate of any reported adverse events, blood analysis including renal function, hyperkalemia, and liver function abnormalities. Finally, the rate of drug discontinuation and the maximum tolerated dose between both groups are compared. Adherence to trial medication is assessed using returned medication. A list of secondary outcome parameters is provided in Table III.

## Cardiovascular magnetic resonance

Cardiovascular magnetic resonance imaging acquisition is performed with locally available scanners using a standardized protocol.[15] A steady-state free procession sequence with retrospective electrocardiographic triggering is acquired to obtain 2-, 3-, and 4-chamber views. These views are used to obtain contiguous 8-mm short-axis slices perpendicular to the ventricular septum encompassing the total heart throughout the cardiac cycle. The CMR images are acquired during repeated end-expiratory breath holds. MASS Analytical Software System (Medis, Leiden, the Netherlands) is used for CMR image analysis. Image analysis is performed by a single observer, blinded to treatment, for all patients to exclude interobserver variability. Cine loops are used to determine RV and LV volumes (end-diastolic and end-systolic) and mass. *End-diastole* is defined as the phase with the largest RV volume. *End-systole* is defined as the phase with the smallest RV volume. Trabeculations and papillary muscles are considered part of the ventricular cavity.[16] *Stroke volume* is defined as end-diastolic volume minus end-systolic volume. *Ejection fraction* is defined as stroke volume/end-diastolic volume × 100%. All volumes are corrected for body surface area. In a subgroup of patients, regional ventricular fibrosis is assessed on CMR by late gadolinium enhancement with a T1-weighted inversion recovery–prepared fast gradient echocardiogram. Single-slice CMR T1 mapping is performed at the midlevel of the RV body to asses diffuse RV fibrosis by using a modified Look-Locker inversion

**Table III.** Secondary outcome parameters of the REDEFINE trial

1. The RV and LV volumes and mass. LV EF
2. Maximal exercise capacity ($VO_2$ max)
3. Hospitalization for heart failure
4. Death
5. Cardiac fibrosis as determined with T1-mapping/late enhancement on CMR*
6. Prevalence of (supra)ventricular arrhythmias
7. Serum NT-proBNP levels
8. Circulating microRNA's in plasma*
9. Serum galectin-3 levels*
10. NYHA class
11. Quality of life
12. Echocardiographic markers of strain
13. Aortic root diameter

Abbreviation: *NYHA*, New York Heart Association.
*Secondary outcome measures only determined in subgroup of patients from the Academic Medical Center.

recovery sequence. In the first 34 patients with CMR available for analysis, intraobserver variability was assessed for RV and LV volumes and EF with a second measurement >1 year after the first measurement.

## Echocardiography

Parasternal and apical views are obtained according to the recommendations by the European and American guidelines.[17] Echocardiography is performed for qualitative and quantitative assessment of systolic function of the RV and the LV.[17] Tricuspid and mitral annular plane systolic excursions are measured by M-mode; tissue Doppler imaging was obtained to measure peak systolic myocardial velocities at the tricuspid and mitral annuli. Diastolic function of the RV and the LV is determined using an apical 4-chamber view, with transtricuspid and transmitral pulsed-wave Doppler curves and pulsed-wave tissue Doppler imaging curves. *Longitudinal 2-dimensional LV strain* and *longitudinal 2-dimensional RV strain* are defined as the peak negative value on the strain curve during the entire cardiac cycle.[18] Right ventricular and LV myocardial performance index is evaluated by using tissue Doppler imaging method.[19] The eccentricity index is obtained at the end-systole and end-diastole.[20] The severity of tricuspid and pulmonary regurgitation is quantified according to current European guidelines.[21] *Restrictive RV physiology* is defined as the presence of late-diastolic forward flow in the main pulmonary artery.

## Exercise testing

Cardiopulmonary exercise testing is performed to assess maximal exercise capacity, blood pressure, and heart rate. Patients are placed on a cycle ergometer, or alternatively a treadmill, to perform continuous measurements of minute ventilation, oxygen consumption, heart rate, blood pressure, and electrocardiography. Work load is increased, depending on the individually predicted maximum exercise capacity in such a way to achieve maximal effort in approximately 10 to 15 minutes. All patients exercise to their maximum exercise capability. The test is discontinued prematurely in case of symptoms (severe angina, dizziness, dyspnea, or fatigue), arrhythmia, systolic blood pressure >250 mm Hg and/or diastolic blood pressure >130 mm Hg, blood pressure drop of >10 mm Hg, or a decrease in heart rate during exercise.

## Laboratory testing

Laboratory testing is performed before onset of trial medication and during follow-up according to the trial protocol (Table II) and includes standard biochemical parameters, NT-proBNP, and complete blood count. All scheduled laboratory analyses are shown in Table II. In addition to the standard laboratory parameters, plasma is isolated and frozen for future analysis of specific parameters in a subset of patients.

## Quality of life

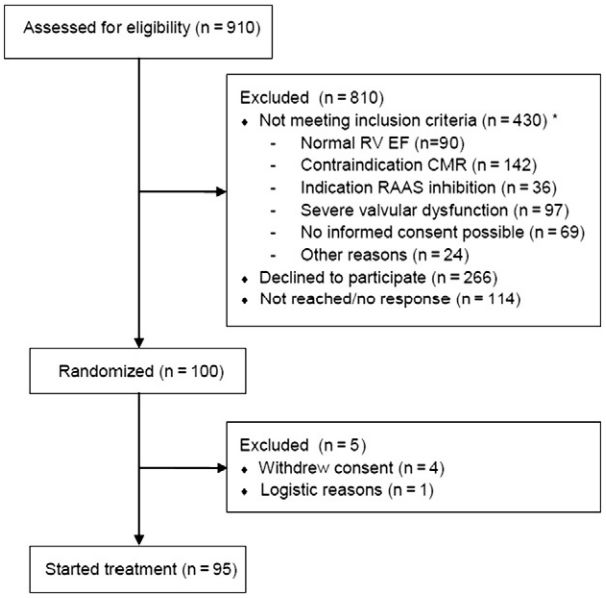
*Quality of life* is defined as the patients' personal perception of their well-being. Quality of life is assessed using the Dutch translation of the Medical Outcomes Study 36-Item Short Form.[22] Patients' habitual physical activity is assessed using the Short Questionnaire to Assess Health-Enhancing Activity.[23]

## Sample size and statistical considerations

Sample size calculation is based on the primary end point change in RV EF in the intention-to-treat analysis. Based on an SD of 5%, we calculated that approximately 90 patients are required to obtain 80% power to detect a difference of 3% between 2 treatment groups after treatment with a 2-sided $\alpha$ of .05. We aimed to include 120 patients, taking into account a 25% dropout of follow-up for various reasons during the study period. A difference of change in RV EF between groups of >3% is considered clinically significant because it could lead to future long-term clinical benefit. In a large multicenter study, a 3% higher baseline RV EF was associated with a ~15% to 20% lower rate of death/VT,[1] roughly similar to the reduced 20% in mortality after treatment with ACE-I in LV heart failure.[4,24] Importantly, a 20% reduction in death/VT due to losartan treatment would equal a low absolute reduction during study follow-up. However, if reduced mortality would extend throughout lifetime, this would be clinically highly relevant in this young population. In the VALHEFT trial, treatment with valsartan led to a ~4% increase of LV EF after 18 to 24 months of treatment in patients not receiving ACE-I.[25]

For statistical analyses, SPSS 23.0 (SPSS Inc, Chicago, IL) for Windows is used. A 2-sided $\alpha$ of <.05 is used as a criterion for statistical significance. Descriptive data will be presented as number with percentage, mean with SD, or median with interquartile range, as appropriate. The effect of losartan on RV EF change will be evaluated by covariance analysis with baseline RV EF as covariate.

**Figure 1**




Flowchart on study inclusion of the REDEFINE trial. * Multiple reasons for not meeting inclusion criteria could be present in 1 patient.

If there are significant baseline differences between groups on parameters that could influence study outcome, we will perform covariate-adjusted comparisons as a secondary analysis. In addition, a secondary on-treatment analysis will be performed. Differences between baseline and follow-up measurements within groups will be assessed using a paired *t* test. Covariate by treatment group interaction tests will be performed to analyze whether there are differences in treatment effects between subgroups. Predefined subgroups are as follows: patients with or without symptoms (New York Heart Association class II), restrictive RV physiology, previous PVR, moderate (<40%) RV dysfunction, and QRS fragmentation.[26]

For this trial design paper, the intraobserver agreement coefficient (AC) of RV and LV end-diastolic volumes and EF between both measurements was calculated as 100 (1−2 |Measurement 1 − Measurement 2|/ Measurement 1 + Measurement 2).[16] In addition, the mean difference between measurements (bias) and SD of difference was calculated. In a subset of 18 consecutive patients in whom the follow-up CMR was performed, SD of RV EF change was also calculated.

### Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) monitors the trial progress. The DSMB focuses on safety of the trial participants and reviews the rates of (serious) adverse events. The DSMB may call for deblinding of the trial when there are concerns regarding a high rate of adverse events. The DSMB does not perform interim analysis for efficacy, as this is not feasible considering the trial design.

### Study participants

Patients were enrolled in the study from May 2014 until December 2015. Of 910 adult patients with TOF who were considered for the study (Figure 1), 430 (47%) did not meet inclusion/exclusion criteria. Of 480 eligible patients, 114 (24%) patients could not be reached or did not give a final response regarding trial participation and 266 (55%) refused participation for various reasons. Reported reasons for not participating included the following: not willing to use any medication, fear of adverse effects, pregnancy wish within 2 years, and lack of time. One hundred (21%) patients provided informed consent and were randomized to receive either losartan or placebo. After randomization, 4 patients withdrew their consent and did not start study medication. In 2 of these patients, baseline investigations were incomplete. Furthermore, 1 patient did not complete baseline examinations and did not start study medication because of logistical problems. Baseline characteristics of the 95 patients who started trial medication are noted in Table IV. A total of 6 patients (6%) withdrew from RAAS inhibition >4 weeks before inclusion in the study. Differences between included and declining patients are also provided in Table IV. Proportionately, more men and older patients provided informed consent and were included.

### Intraobserver agreement

In a subset of 34 patients, intraobserver variability of RV EF was satisfying (AC 94; SD of difference 3.5) and comparable with previous reports (Table V).[16,27] In a subset of 18 in whom follow-up CMR was performed, mean change of RV EF was +1.7% with an SD of 3.1%.

The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the manuscript.

## Discussion

This is a multicenter, randomized, double-blind, placebo-controlled trial that evaluates long-term effects of RAAS inhibition in adult TOF patients with RV dysfunction. To our knowledge, this is the largest randomized controlled trial in adults with TOF. The results of this trial are expected to define the role of RAAS inhibition in these patients.

Inhibition of RAAS by ACE-I or ARB is beneficial in patients with acquired LV dysfunction.[4] Neurohormonal activation is similarly caused by reduced cardiac output in patients with either left- or right-sided systolic ventricular dysfunction.[28] Neurohormonal activation affects collagen turnover, resulting in collagen accumulation and increased myocardial stiffness.[29] In the long term, this

**Table IV.** Patient characteristics at time of start with trial medication are reported for included patients

| Patient characteristics | All patients (n = 95) | Declined (n = 258) | *P* |
|---|---|---|---|
| Included in CONCOR | 79 (83%) | 200 (72%) | .248 |
| Pulmonary atresia and VSD | 8 (8%) | 16 (8%) | .640 |
| Male gender | 66 (70%) | 107 (54%) | .002 |
| Age (y) | 39 ± 12 | 37 ± 11 | .025 |
| Age at initial correction (per year) | 2.9 (1.4-7.0) | 3.0 (1.4-5.9) | .387 |
| Previous shunt procedure | 37 (39%) | 64 (32%) | .178 |
| Age at shunt procedure | 1.2 (0.4-2.3) | 0.6 (0.02-2.6) | .834 |
| Previous supraventricular tachycardia | 22 (23%) | 28 (14%) | .075 |
| Previous VT | 5 (5%) | 5 (3%) | .522 |
| PVR | 60 (63%) | 114 (57%) | .443 |
| QRS duration (ms)* | 147 ± 25 | 143 ± 25 | .239 |
| RV EF (%)* | 42 ± 10 | 44 ± 9 | .211 |
| LV EF (%)* | 52 ± 7 | 53 ± 7 | .300 |

Data are described as number with frequency, mean with SD, or median with interquartile range.
Comparison on all parameters between included and declining patients was feasible for those (n = 279) included in CONCOR.
*QRS duration, and RV EF and LV EF reported from electrocardiogram and CMR at CONCOR inclusion, which was available in CONCOR patients.

**Table V.** Intraobserver coefficients of agreement of CMR volumes and EF by a single observer of the same baseline scan

| | RV EDV (mL) | RV EF (%) | LV EDV (mL) | LV EF (%) |
|---|---|---|---|---|
| Mean ± SD (final measurement) | 200 ± 40 | 45.4 ± 4.5 | 184 ± 48 | 50.8 ± 5.3 |
| Mean difference ± SD | −4.9 ± 16 | −0.3 ± 3.5 | −1.4 ± 11 | 0.3 ± 4.1 |
| Limits of agreement | −33 to 48 | −7.8 to 8.6 | −22 to 38 | −13.8 to 7.5 |
| AC (%) | 93 | 94 | 96 | 94 |

Both measurements were performed with >1-year time interval.
Abbreviation: *EDV*, End-diastolic volume.

leads to unfavorable remodeling by causing hypertrophy, fibrosis, and apoptosis of the cardiomyocyte.[30] By this means, neurohormonal activation contributes to progressive deterioration of myocardial function in both patients with acquired LV dysfunction and TOF patients with RV dysfunction. Indeed, in adult patients with TOF, increased neurohormonal activation[28,31] and diffuse myocardial fibrosis[32] have been reported. In animal models of induced RV dysfunction, RAAS inhibition has shown to attenuate unfavorable RV remodeling.[33,34] In another animal model of pulmonary volume overload, losartan reduced pulmonary vascular resistance, resulting in reduced RV afterload.[35] Furthermore, treatment with RAAS inhibitors decreases adrenergic activity and reverses the reduced heart rate response to exercise in patients with LV dysfunction,[36] suggesting interacting effects between the RAAS and adrenergic systems.

Our study group previously revealed that RAAS inhibition improved systemic RV function in symptomatic adult patients with transposition of the great arteries.[37] Previously, Babu-Narayan et al[38] found that RAAS inhibition with ACE-I treatment improved biventricular longitudinal function but did not significantly improve RV EF in patients with TOF. However, the study included patients with severe pulmonary regurgitation and a preserved RV EF (mean 53%). In addition, this study was limited by small sample size (n = 64) and short-term (6 months) follow-up.

We aim to evaluate the effects of RAAS inhibition in TOF patients with RV dysfunction without severe valvular dysfunction. In these young patients, RV dysfunction causes neurohormonal activation and precedes morbidity and mortality.[1,9,28] By excluding severe valvular disease, heterogeneity of the population is reduced, assessment of RV function is not obscured, and no other treatments such as PVR are available.[3] We also aim to investigate the effects of RAAS inhibition on myocardial fibrosis and several biomarkers, which reflect neurohormonal activation.[28,32,39] These factors are likely to play a role in progressive RV dysfunction.

The target inclusion of this trial was 120 patients, to allow up to 25% dropout during the study period, for instance, patients stopping trial medication and refusing follow-up scans. Only a small percentage of the eligible patients participated in the trial, as these young patients reported many different reasons for not participating in a medication trial. We did not achieve the sample size because 100 patients were randomized to receive trial medication. Of these patients, 5 patients did not start

study medication and will not be included in the intention-to-treat analysis. The statistical power will depend on the number of patients who will complete follow-up examinations and the SD (power calculation 5%) of RV EF change. We are confident that 90 patients, or at least very close, needed in the intention-to-treat analysis will be achieved. In analysis of the first 18 patients with follow-up CMR completed, SD of RV EF change was lower than according to the sample size calculation, which is reassuring.

### Limitations

The trial design comes with limitations. First, both the limited absolute number of patients with TOF and low numbers of serious cardiac events hamper detection of therapeutic effect on serious cardiac events. Second, although we plan to evaluate the primary outcome change in RV EF within several subgroups, statistical power to detect changes in the primary end point within subgroups is limited.

## Summary

This prospective, multicenter, double-blind, randomized, placebo-controlled trial will establish the role of RAAS inhibition with losartan in the treatment for TOF patients with RV dysfunction. There is currently no evidence-based treatment available for these patients, and our results may provide the first long-term and evidence-based treatment option.

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Contributors

All authors contributed to the conception, design, critical revision, and final approval of this manuscript. Jouke P. Bokma analyzed and interpreted the data and drafted the manuscript under supervision of senior authors Barbara J.M. Mulder and Berto J. Bouma.

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