ARNI or ARB Treats Residual Left Ventricular Remodelling after Surgery for Valvular Regurgitation: ReReRe study protocol

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Abstract

Aims Patients with persistent or de novo left ventricular (LV) dilation and/or reduced ejection fraction (EF) after correction for primary aortic (AR) or mitral (MR) regurgitation (i.e. residual LV remodelling) have not been well studied with regard to guideline-directed medical therapy after successful aetiology-reversing surgery. We aim to (i) compare the effectiveness of sacubitril/valsartan vs. valsartan in promoting LV reverse remodelling and (ii) explore the safety of medication withdrawal after LV recovery.

Methods and results The ReReRe study is a multicentre, randomized, open-label, parallel trial that consists of two consecutive parts. A total of 371 patients with an LV end-diastolic diameter (LVEDD) > 60 mm or LVEF < 50%, assessed by transthoracic echocardiography (TTE) 7–14 days after valve surgery for significant AR or primary MR will be enrolled. The 1st randomization into the sacubitril/valsartan or valsartan groups and structured follow-up (1, 3, 6, 9, and 12 months after randomization) will be conducted to observe the primary objective as the rate of complete recovery of LV remodelling (i.e. LVEDD < 55 mm and LVEF ≥ 60% by TTE at two consecutive visits). Those who have complete recovery of LV remodelling will be enrolled in Study Part 2; consequently, they will receive the 2nd randomization into the medication withdrawal or maintenance group and 6-monthly visits for the observation of the primary objective as the rate of LV remodelling relapse (LVEDD > 60 mm or LVEF < 50%). The secondary objectives include the rate of composite clinical outcomes and the degree of change in 6-min walk distance and Kansas City Cardiomyopathy Questionnaire scores.

Conclusions The ReReRe study will provide new evidence for the treatment of patients with residual LV remodelling after curable unloaded surgery, as well as the duration of treatment. The study results will fill the gap in identifying an appropriate medical therapy regimen for this group of patients and perhaps for those with reversible aetiologies of heart failure.

Keywords Aortic regurgitation; Mitral regurgitation; Left ventricular remodelling; Sacubitril/valsartan; Medication withdrawal

Introduction

Primary aortic regurgitation (AR) and mitral regurgitation (MR) are common valvular diseases, with a prevalence of 4.9 and 10.0% in the general population, respectively.1–3 Valve interventions are strongly recommended for patients with severe regurgitation, in whom long-standing volume overload leads to left ventricle (LV) remodelling, systolic dysfunction, and symptomatic heart failure (HF).4 However, patients with postoperative persistent or de novo LV dilation...
and/or dysfunction (named ‘residual LV remodelling’ in the current study) are no longer uncommon in real-world studies and have worse outcomes than patients without LV remodelling after surgery.

Despite the lack of solid clinical evidence in this group of patients, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) are recommended if patients present with heart failure with reduced ejection fraction (HFrEF) before or after valve interventions. In recent years, the superiority of the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan over ACEI or ARB in HFrEF has been recognized, but it is uncertain whether this also applies to residual LV remodelling after AR or MR surgery.

Correction of volume overload by surgery at an appropriate time should be curable for HF and LV remodelling, although it might be achieved after a certain period of medical therapy in the targeted study population. It appears sensible to suspend medication in patients who demonstrate complete LV recovery. Indeed, the consequences of medication withdrawal remain unknown as they have never been attempted and reported in this group. Therefore, we designed the ARNI or ARB Treats Residual Left Ventricular Remodelling after Surgery for Valvular Regurgitation (ReReRe) study, which aims to (i) compare the effectiveness of sacubitril/valsartan versus valsartan in promoting LV reverse remodelling and (ii) explore the safety of medication withdrawal after LV recovery.

Methods

Study design

ReReRe is a multicentre, pragmatic, randomized, open-label, parallel trial. Eligible patients will be recruited from six to eight centres in China, where the study will be approved by local ethics committees. This study has been registered at ChiCTR.org.cn (ChiCTR2000038895).

Figure 1 depicts an overview of the study design, and Table 1 describes the eligibility criteria. Eligible patients will receive the 1st randomization into the sacubitril/valsartan or valsartan groups, followed by five scheduled visits (at 1, 3, 6, 9, and 12 months after randomization, Study Part 1). Clinical, laboratory, and imaging assessments will be performed at every visit (Table 2). During this period, patients who have complete recovery of LV remodelling (definitions as in ‘Participants and recruitment’) on two consecutive transthoracic echocardiographies (TTEs) will be labelled as eligible for Study Part 2. The eligible patients will receive a 2nd randomization into the medication withdrawal or maintenance...
Table 1  Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|--------------------|-------------------|
| • Clinically significant AR or/and MR indicated for surgery | • Secondary MR |
| • Aged ≥ 18 years | • Moderate or more severe AS |
| • LVEDD > 60 mm or LVEF < 50% by TTE 7–14 days after valve surgery | • Moderate or more severe MS |
| • Prior history of cardiac surgery or transcatheter interventions (e.g. ICD or CRT implantation) | • Prior history of cardiac surgery or transcatheter interventions (e.g. valve surgery) |
| • Known cardiomyopathies | • Prior history of heart failure admissions |
| • Severe CAD (defined as a history of prior myocardial infarction, coronary revascularization, or significant angiographic coronary stenosis as epicardial artery with ≥ 70% diameter stenosis or left main ≥ 50%) | • Severe systemic disease |
| • Severe MR | • Untreated, uncontrolled, or resistant hypertension (defined as ≥ 3 BP-lowering drugs) |
| • Secondary or more severe AS | • Expected survival < 1 year |
| • Moderate or more severe MS | • Contraindicated to ACEI/ARB/ARNI use |
| • Primary valvular disease and aortic lesions, whereas MR refers to primary valvular lesions. | • ACEI/ARB/ARNI use not suspendable or replaceable |
| • Prior history of CABG, CAD, or valve surgery | • No more than mild paravalvular leakage by TTE 7–14 days after valve surgery |
| • Any condition which the clinicians regard as inappropriate for enrolment (e.g. shock, re-exploration, aborted cardiac arrest, dialysis, disturbance of consciousness, and thromboembolic event after surgery) | • Any condition which the clinicians regard as inappropriate for enrolment (e.g. shock, re-exploration, aborted cardiac arrest, dialysis, disturbance of consciousness, and thromboembolic event after surgery) |
| • Informed consent not obtained | • Informed consent not obtained |

ACEI, angiotensin-converting enzyme inhibitor; AR, aortic regurgitation; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; AS, aortic stenosis; BP, blood pressure; CABG, coronary artery bypass graft; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter deibrillator; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MS, mitral stenosis; TTE, transthoracic echocardiography.

Table 2  Schedule of Study Part 1

| Screen phase | Trial phase: Part 1 |
|--------------|---------------------|
| 1st visit | 3rd visit |
| Within 48 h after admission | 1-M |
| 2nd visit | 4th visit |
| 7–14 days after surgery | 3-M |
| 3rd visit | 5th visit |
| 1-M | 5-M |
| 4th visit | 6th visit |
| 3-M | 6-M |
| 5th visit | 7th visit |
| 5-M | 7-M |
| 6th visit | 8th visit |
| 6-M | 8-M |
| 7th visit | 8-M |
| 7-M | 9-M |
| 8th visit | 9-M |
| 8-M | 10-M |
| 9th visit | 10-M |
| 9-M | 11-M |
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| 13th visit | 14-M |
| 13-M | 15-M |
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| 18-M | 20-M |
| 19th visit | 20-M |
| 19-M | 21-M |
| 20th visit | 21-M |
| 20-M | 22-M |
| 21th visit | 22-M |
| 21-M | 23-M |
| 22th visit | 23-M |
| 22-M | 24-M |
| 23th visit | 24-M |

ECG, electrocardiogram; NT-proBNP, N-terminal pro-brain natriuretic peptide; TTE, transthoracic echocardiography.  
1-M, 3-M, 6-M, 9-M, 12-M, and 24-M; 1, 3, 6, 9, 12, and 24 months after the 1st randomization.

Participants and recruitment

As shown in Table 1, the ReReRe study will enrol patients who have residual LV remodelling [defined as LV end-diastolic diameter (LVEDD) > 60 mm or LVEF < 50% assessed by TTE 7–14 days after valve surgery for significant AR and/or MR], regardless of their LVEF prior to surgery. AR comprises primary valvular diseases and aortic lesions, whereas MR refers to primary valvular lesions. Based on the purposes and two-part design of the study, patients in three major categories will be excluded: (i) those with aetiologies other than primary AR and/or MR, which may also contribute to LV remodelling; (ii) those who are contraindicated to ACEI/ARB/ARNI use or cannot be weaned off ACEI/ARB/ARNI (in the second part); and (iii) patients with severe comorbidities or complications that will significantly affect the prognosis. The detailed exclusion criteria are listed in Table 1. The types of surgery include open-heart valve repair or replacement, the Bentall operation, and transapical aortic valve replacement, which will be recorded as covariates for further analysis. During the scheduled 12-month follow-up of Study Part 1, if the patients are identified as having complete recovery of LV remodelling on two consecutive visits, that is, LVEDD < 55 mm and LVEF > 50% assessed by TTE 3–6 months after valve surgery for significant AR and/or MR, they will stay in Study Part 1 and receive follow-up until 24 months after the 1st randomization.
LVEF $\geq 60\%$ by TTE, they will fulfill the inclusion criterion of Study Part 2 and receive the 2nd randomization.

Before enrolment, two screening visits will be conducted by the study coordinators. The 1st visit is to screen for patients awaiting AR and/or MR surgery who will be potential candidates for the study according to the criteria listed in Table 1. Surgeons will be contacted and reminded to request a TTE examination 7–14 days after surgery. If they fulfill the study criteria, the 2nd visit (soon after the TTE of 7–14 days) will be conducted in those patients, including informed consent, study case number assignment, the 1st randomization, and baseline assessment. Eligible patients who agree to participate will be enrolled and the process is estimated to last from October 2020 to September 2023.

Randomization and blinding

The 1st or 2nd randomization is performed at a 1:1 ratio using a simple randomization method with a random number generator. Physicians, physician assistants, and patients themselves will be informed of the assigned study group. However, doctors who analyse TTE or cardiac magnetic resonance images will be blinded to the randomization results and clinical assessment.

Procedures

Sacubitril/valsartan or valsartan initiation and up-titration

In patients who have no prior ACEI/ARB/ARNI treatment, ARNI or valsartan will be immediately initiated on the day of the 1st randomization if no contraindications are encountered. In patients with prior use of ARNI or ARB, ARNI or valsartan will be immediately initiated. In patients who have received prior treatment with ACEI, a washout period of 36 h is required if assigned to the ARNI group, whereas a direct switch to valsartan is practical if assigned to the valsartan group. The initial dose of ARNI or valsartan and dose up-titration will depend on the attending physician’s discretion based on the current HF guidelines. The medication is up-titrated to a double dose every 4 weeks; however, the titration process will be tailored to the needs of each individual, and the maximum tolerated dose should be achieved within 12 weeks. At the 6-month follow-up, patients in the valsartan arm who have an LVEF $< 40\%$ will be transferred to the ARNI arm. At the 12-month follow-up, patients who are not eligible for Part 2 of the study will be allowed to change the assigned medication, for example, from sacubitril/valsartan to any ACEI/ARB or from valsartan to sacubitril/valsartan or any ACEI/ARB.

Other guideline-directed medical therapy and device therapy

The β-blockers and mineralocorticoid receptor (MRA) will be initiated in both the sacubitril/valsartan and valsartan arms on the day of 1st randomization if no contraindications are encountered. Similarly, double-dose titration is performed every 4 weeks for β-blockers until the maximum tolerated dose is achieved, whereas no further dose up-titration is planned for MRA. In patients with congestion, loop diuretics will be used as appropriate.

Clinically significant arrhythmias, including atrial flutter or fibrillation, frequent ventricular premature beats (>10,000 beats per day), and haemodynamically unstable ventricular tachycardia or fibrillation, will be treated according to current guidelines. Anticoagulation is indicated in patients with atrial flutter or fibrillation if their CHA2DS2-Vasc score is $\geq 2$.

In addition, patients will be allowed to receive any device therapy (including right ventricular (RV) pacing, implantable cardioverter defibrillator, and cardiac resynchronization therapy) during follow-up if they meet the indications as per the guidelines.

Medication withdrawal

In patients assigned to the medication withdrawal arm of Study Part 2, sacubitril/valsartan or valsartan will be stopped on the day of the 2nd randomization. At the next visit, a
β-blocker and/or MRA will be weaned off if the patients do not have relapse of LV remodelling (defined as the recurrence of LVEDD > 60 mm or LVEF < 50%). Calcium channel blockers will be initiated for blood pressure control to replace ARNI or valsartan in patients with hypertension. In addition to monthly visits, an interim telephone review will be conducted every 2 weeks between follow-up visits to ensure that the patients remain asymptomatic. These patients also have 24-h access to medical advice and the arrangement of unplanned visits if needed. The results of each planned and unplanned visit will be reported weekly to the study steering committee via the registered online meeting platform. HF treatment will be re-established immediately in patients with relapsed LV remodelling or symptomatic HF. However, in patients with consistent LV recovery, but with adverse events other than HF, their management will be discussed by the study steering committee. None of the HF medications will be suspended in the medication maintenance group. The medical therapy of the two groups at the end of Study Part 2 will also be ascertained by the study steering committee.

Image acquisition and analysis

Before enrolment, TTE will be performed at least twice with a full dataset recorded, that is, prior to surgery and 7–14 days after surgery. The images can be analysed at local sites but will not be sent to the core lab. The biplane Simpson’s method is required to assess the LVEF.

After enrolment, TTE images will be acquired at the 2nd visit (used as baseline) and at every visit during follow-up for serial monitoring of LV size and function. Image acquisition will follow a standard protocol, which include LV systolic and diastolic volumes, LV diastolic function, RV function, and left atrial (LA) function (see Data S1). The acquired digital images will be stored as DICOM and transferred via the web to the core laboratory for offline analysis. Experienced echocardiologists will measure the LVEDD and LVEF (biplane Simpson’s method) and provide feedback to the corresponding sites on the results used for the enrolment into the study and entry into Study Part 2.

Cardiac magnetic resonance examination will be performed according to the physicians’ discretion and patients’ willingness at baseline and at the 6-month follow-up. Image acquisition will follow a standard protocol, and the images will be saved as DICOM and transferred via the web to the core laboratory. The analysis will use Medis Suite 3.2 (Leiden, Netherlands) following the post-processing guidelines of the Society of Cardiovascular Magnetic Resonance to evaluate late gadolinium enhancement and extracellular volume.

Objectives and outcomes

The primary objectives include (i) the rate of complete recovery of residual LV remodelling during the 12-month follow-up (Study Part 1) and (ii) the rate of relapse of LV remodelling within the 6-month follow-up (Study Part 2).

The secondary objectives are (i) the degree of change in 6-min walk distance and the Kansas City Cardiomyopathy Questionnaire scores and (ii) the composite clinical outcome of all-cause mortality, HF hospitalization, new-onset atrial fibrillation, stroke, or acute myocardial infarction.

Safety monitoring

All patients will be assessed at each study visit for side effects of medical therapy, including symptomatic hypotension or systolic blood pressure <90 mmHg, hyperkalaemia (K + ≥ 5.5 mmol/L), a decrease in the estimated glomerular filtration rate of >35% from Visit 2, or angioneurotic oedema. The composite clinical outcome of the secondary objectives will also be regarded as safety monitoring after medication withdrawal in Study Part 2.

Sample size

Sample size calculations were based on the difference in the rate of the primary endpoint between the study and control groups and were performed using Power Analysis and Sample Size (PASS) software (NCSS Statistical Software, Kaysville, UT, USA). The data from previous studies were used to estimate the expected effect size. As 56–85.7% of patients with primary AR or MR and a prior LVEF < 50% had an LVEF improvement ≥50% during follow-up after surgery, we expected that 50% of the patients in the valsartan arm would achieve the primary endpoint of LVEF recovery. Although no data could be found for ARNI in a similar situation, we expected that 15% more patients in the ARNI arm could achieve the primary endpoint according to a recent report on the rate of LVEF improvement in HFrEF treated with ARNI (61% patients had an LVEF ≥ 45%) or ARB (49% had an LVEF ≥ 40%).

Given the expected 15% difference in the rate of complete LV recovery between the two groups in Study Part 1, a sample size of 334 patients (167 in either group) is needed, assuming a two-tailed α of 5% and 80% power. Consequently, approximately 167 patients will be eligible for Part 2 of the study. Given the assumed 20% relapse rate of LV remodelling in the medication withdrawal group and no relapse in the medication maintenance group, a sample size of 64 patients (32 in each group) is needed for Study Part 2, assuming a two-tailed α of 5% and 80% power. Therefore, 371 patients will meet the needs of both parts when the assumed dropout rate is 10%.
Statistics

The baseline characteristics and clinical outcomes are reported according to the assignment. Continuous variables are presented as the mean ± standard deviation and will be compared by an independent t-test in the case of normality assumption and by the Mann–Whitney U test otherwise. Categorical variables are presented as percentages and will be compared using the chi-square test. Analysis of the primary endpoint will follow the intention-to-treat principle for all randomized subjects. Cox proportional hazards models and fixed baseline confounders will be used to compare the possibility of complete recovery between the sacubitril/valsartan and valsartan groups or relapse between the medication withdrawal and maintenance groups. Comparisons of changes in the 6-min walk distance and Kansas City Cardiomyopathy Questionnaire scores will be performed using ANCOVA with the baseline characteristics as covariates. Post hoc analyses will be performed to compare the primary or secondary endpoints in patients with MR vs. AR, LVEF ≥ 40% vs. <40%, sinus rhythm vs. atrial fibrillation, and normal vs. abnormal RV function. Statistical significance was set at a P value < 0.05, and all tests will be two-sided.

Discussion

The ReReRe study is designed to test whether ARNI is superior to valsartan in promoting LV recovery after AR and/or MR surgery, and more importantly, whether LV recovery is sustainable after medication withdrawal.

It is well accepted that the extent of LV reverse remodelling after guideline-directed medical therapy (GDMT) represents a very good surrogate marker, as it can predict long-term outcomes in addition to being objective and easily blinded.21 Correction of the volume overload condition in AR or MR by surgery is the major contributor to LV reverse remodelling, as reflected by an abrupt reduction in LV volumes in most patients. However, in patients who have residual LV remodelling shortly after surgery, it remains unknown whether the LV will reverse further naturally without any medication or whether there will be any difference in the degree or speed of recovery by using different medication regimens. This group of patients has been frequently underrepresented in previous HF trials, which might have discouraged clinicians from generalizing GDMT for HF.8 Despite the common practice of implementing neurohumoral blockade therapy for HFrEF, there is a lack of definite recommendations in guidelines with supporting evidence. The post hoc analysis of the PARADIGM-HF study confirmed consistent additional benefits of ARNI over enalapril across different aetiologies of HF, including ischaemic (60.0%), hypertensive (9.5%), idiopathic HF (11.5%), and others (19.0%). Nevertheless, it is difficult to apply the findings to patients with residual LV remodelling because in PARADIGM-HF, valvular diseases only accounted for 1.3% of the study patients.22 Patients with valvular heart disease were not included in most of the other published or ongoing ARNI trials.23 Therefore, the present pragmatic, prospective randomized study will be the first to determine whether ARNI behaves better than ARB in terms of promoting LV recovery after unloaded surgery for AR and/or MR.

Both the standardized regimen of treatment and the issue of weaning medications after complete recovery remain to be clarified. An optimal duration of treatment is uncertain for HF with reversible aetiologies and normalized heart chambers,8,24,25 because few studies have explored the feasibility in small numbers of patients. Amos et al. retrospectively found that no deterioration occurred in five patients with recovered peripartum cardiomyopathy (PPCM) who withdrew HF medications over a follow-up of 29 months.26 Fatt et al. also observed that a sustained recovery occurred in 37/38 (97%) of retrospectively enrolled patients with PPCM who discontinued medications vs. in 35/36 (97%) of those who continued medications.27 Although these findings shed light on the safety of medication withdrawal in this specific group of patients, they only serve as weak evidence owing to the limitations of selection bias, recall bias, and other confounding factors in retrospective studies.28

In contrast, the TRED-HF study by Halliday et al. demonstrated that in patients with recovered dilated cardiomyopathy, the withdrawal of standardised HF medications resulted in a 44% relapse rate within 6 months compared with zero in the group of continued treatment.20 Certainly, these findings might not be extrapolated to patients with HF with corrected aetiologies, as in the current study. However, regarding the safety concerns of medication withdrawal, a similar phased withdrawal followed by a close and comprehensive monitoring strategy was adopted from the TRED-HF study. Moreover, a more rigid criterion of LVEF ≥ 60% to define recovery (other than >50% in the TRED-HF) was implemented to secure the patients from relapse. The TRED-HF study reported a high incidence of LV remodelling relapse after medication withdrawal, but fortunately, no adverse cardiovascular events occurred during follow-up, and 85% of the relapsed patients regained LVEF > 50% 1 month after re-establishment of medication.20 Therefore, it can be confidently stated that the second part of the ReReRe study will explore the feasibility of medication weaning with a guarantee of patient safety.

Study limitations

As patients with MR or AR will be enrolled in the study, group randomization in MR or AR is more appropriate than simple...
randomization. However, given the concerns about the inadequate sample size in each subgroup, simple randomization is finally adopted when its condition of use is fulfilled. Hopefully, the impact of different pathophyslogies of LV remodeling or dysfunction on MR and AR will be answered in post hoc analysis. Similarly, some other factors that might influence the clinical course after surgery, such as LVEF, heart rhythm, or RV function, are not treated in pre-defined but post hoc subgroup analysis.

Conflict of interest

None to declare.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Data S1 SupportIng Information.
ered ejection fraction in patients with dilated cardiomyopathy. Int Heart J 2021; 62: 801–810.
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