Myocardial remodelling after withdrawing therapy for heart failure in patients with recovered dilated cardiomyopathy – insights from TRED-HF

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Abstract

Aims: To characterise adverse ventricular remodelling after withdrawing therapy in recovered dilated cardiomyopathy (DCM).

Methods: TRED-HF was a randomised controlled trial with a follow-on single arm cross-over phase that examined the safety and feasibility of therapy withdrawal in patients with recovered DCM over 6 months. The primary end-point was relapse of heart failure defined by 1) a reduction in LVEF >10% and to <50%, 2) >10% increase in LV end-diastolic volume and to above the normal range, 3) a two-fold rise in NT-pro-BNP and to >400ng/l, or 4) evidence of heart failure. Left ventricular (LV) mass, LV and right ventricular (RV) global longitudinal strain (GLS) and extracellular volume were measured using cardiovascular magnetic resonance at baseline and follow-up (6 months or relapse) for 48 patients. LV cell and extracellular matrix masses were derived. The effect of withdrawing therapy, stratified by relapse and genotype, was investigated in the randomised and follow-on phases.

Results: In the randomised comparison, withdrawing therapy led to an increase in mean LV mass (5.4g/m^2; 95%CI 1.3-9.5) and cell mass (4.2g/m^2; 95%CI 0.5-8.0) and a reduction in LV (3.5; 95%CI 1.5-5.4) and RV (2.3; 95%CI 0.1-4.6) GLS. In a non-randomised comparison of all patients (n=47) who had therapy withdrawn in either phase, there was an increase in LV mass (6.2g/m^2; 95%CI 3.6-8.9; p=0.0001), cell mass (4.0g/m^2; 95%CI 1.8-6.2; p=0.0007) and matrix mass (1.7g/m^2; 95%CI 0.7-2.6; p=0.001) and a reduction in LV GLS (2.7; 95%CI 1.5-2.4; p=0.0001). Amongst those who had therapy withdrawn and did not relapse, similar changes were observed (n=28; LV mass: 4.8g/m^2, 95%CI 0.9-8.7, p=0.02; cell mass: 3.7g/m^2, 95%CI 0.3-7.0, p=0.03; matrix mass: 1.7g/m^2, 95%CI 0.4-3.0, p=0.01; LV GLS: 1.7, 95%CI 0.1-3.2, p=0.04). Patients with *TTN* variants (n=10) who had therapy withdrawn had a greater increase in LV matrix mass (mean effect of *TTN* – 2.6 g/m^2; 95%CI 0.4-4.8, p=0.02).

Conclusion: In TRED-HF, withdrawing therapy caused rapid remodelling, with early tissue and functional changes, even amongst patients who did not relapse.

Keywords and Abbreviations

DCM: Dilated cardiomyopathy

ECV: extracellular volume

GLS: global longitudinal strain

LV: left ventricular

RV: right ventricular

TRED-HF: therapy withdrawal in recovered DCM

TTNtv: truncating variants in the gene encoding titin

Translational Perspective

Early adverse remodelling following therapy withdrawal in patients with recovered dilated cardiomyopathy taking part in TRED-HF was characterised by diminished LV and RV longitudinal deformation, LV hypertrophy and an increase in LV cell mass and extracellular matrix mass. These changes were observed even amongst patients who did not meet the primary relapse end-point.

Therapy withdrawal leads to rapid tissue and mechanical remodelling, even before the development of symptoms.

Introduction

Dilated cardiomyopathy (DCM) is characterised by eccentric hypertrophy associated with an increase in myocyte size and extracellular matrix expansion due to interstitial and focal replacement fibrosis (1,2). Left ventricular (LV) reverse remodelling is characterised by reduction in LV size, regression of hypertrophy and fibrosis and an improvement in systolic function. It may be observed in as many as 40-60% of cases and is associated with resolution of symptoms and an excellent outcome (3,4).

Recent work from our group has demonstrated that many asymptomatic patients with DCM and improved LV function relapse after withdrawing heart failure therapy (5). This confirms that these patients have remission of heart failure rather than sustained recovery or cure (5). Amongst these patients, relapse is characterised by LV dilatation and deterioration in systolic function.

Knowledge of the features that accompany early adverse remodelling should lead to improved understanding of disease pathophysiology and may guide the use of treatments that target cellular and interstitial components of the disease. Previous work has demonstrated important sex and genotype differences in remodelling amongst patients with DCM (6,7). Knowledge of disease characteristics that influence the type and degree of remodelling might enable personalised treatment (2,8).

Cardiovascular magnetic resonance (CMR) enables comprehensive characterisation of ventricular remodelling. This includes the assessment of ventricular function and myocardial deformation as well the quantification of LV mass and its cellular and extracellular components, using parametric mapping (9).

In this study, serial CMR assessment was used to characterise changes in myocardial tissue composition and myocardial mechanics after withdrawing therapy, with or without relapse, amongst patients taking part in TRED-HF (Therapy withdrawal in Recovered DCM) (5).

Methods

TRED-HF was an open-label, randomised trial with a follow-on single-arm cross-over phase examining the safety and feasibility of withdrawing treatments for heart failure in patients with recovered DCM. A full description of the methods is provided elsewhere (5). The trial was registered on ClinicalTrials.gov (NCT02859311).

The study was approved by the National Research Ethics Committee and authorised by the Medicine and Healthcare Products Regulatory Agency. All participants provided written, informed consent. At inclusion, all participants were asymptomatic and had a diagnosis of recovered DCM, with a previous LVEF <40% that subsequently improved to ≥50%, with normal left ventricular end diastolic volume (LVEDV), a NT-pro-BNP level <250ng/L and who were still taking at least one heart failure therapy (loop diuretic, beta-blocker, angiotensin converting enzyme [ACE] inhibitor, angiotensin receptor blocker [ARB] or mineralocorticoid receptor antagonist [MRA]). Patients were randomised 1:1 to phased withdrawal of pharmacological heart failure therapy or to continue therapy, over 6 months. Patients had CMR assessment at baseline, 16 weeks and 6 months.

Therapy was withdrawn in a supervised, step-wise fashion over a maximum of 16 weeks. Changes were made every 2 weeks following clinic or telephone review. Loop diuretics, if prescribed, were withdrawn first, followed by MRAs, beta-blockers and ACE inhibitors or ARBs. Those randomised to the control arm continued therapy and had follow-up visits at 8 weeks, 16 weeks and 6 months. After 6 months, these patients entered a single arm cross-over phase and had therapy withdrawn, as described above, between 6-12 months. They were followed-up in the same way as the randomised phase of the trial after entering the cross-over phase.

The primary end-point was a relapse of DCM defined by any one of the following: 1) a reduction in LVEF by >10% and to <50%, or 2) an increase in LVEDV by >10% and to above the normal range, or 3) a two-fold rise in NT-pro-BNP from baseline and to >400ng/L, or 4) clinical evidence of heart failure. Therapy was re-introduced as soon as any of the primary end-point criteria were fulfilled. The management of patients who did not meet the primary end-point, but suffered adverse events was determined by the study team and the participant's usual physicians.

Cardiovascular magnetic resonance

CMR was performed at baseline, 16 weeks and 6 months, in both the randomised and cross-over phases, using a standardised protocol on a single 3 Tesla scanner (*Skyra, Siemens, Erlangen, Germany)*. Long- and short-axis cine images were acquired using breath-hold steady-state free precession images. Measurement of ventricular volumes and mass was carried out using CMR Tools (*Cardiovascular Imaging Solutions, London)* using a thresholding technique that includes papillary muscles and trabeculae as part of the LV mass. LV and right ventricular (RV) global longitudinal strain were measured from the horizontal long axis view by a single expert operator (XC), who was blinded to trial arm and phase, using feature-tracking software (*Medis Suite MR, Medis, Leiden, Netherlands)*.

At baseline and 6 months in the randomised and cross-over phases, native and post-contrast T1 maps were acquired at basal- and mid-ventricular level in identical short-axis planes, using a breath-hold 5-3-3 modified Look-Locker inversion recovery (MOLLI) sequence. Two maps were acquired in each plane. Post-contrast maps were acquired, 15 minutes after the administration of gadobutrol (0.1mmol/kg). A single expert operator (VV) who was blinded to study arm and phase, measured global myocardial and blood pool T1 on short axis slices using dedicated software (*CVI42*, *Circle Cardiovascular Imaging, Calgary, Alberta)*. Endocardial and epicardial borders were contoured and partial volume artefact from blood was minimised by using a 10% automatic offset from each border. The extracellular volume (ECV) fraction was calculated from the mean myocardial and blood pool T1 values using a published formula (9). The haematocrit was taken from blood tests performed immediately before each scan. LV mass was calculated from the LV volume and specific gravity of myocardium (1.05g/ml); LV cell and extracellular matrix mass were derived using the ECV fraction.

Statistical analysis

Characteristics of patients are presented at randomisation. Variables are presented as mean/standard deviation (SD), or median/interquartile range (IQR) if skewed and compared between men and women and carriers and non-carriers of *TTNtv* using Mann-Whitney U test for continuous data and Fisher's Exact test for categorical data. The effect of withdrawing therapy on LV, cell and matrix mass index and LV and RV

GLS was examined by comparing these variables between randomised groups using a regression model in which the value at follow-up was the response variable and the treatment indicator and value at baseline were the explanatory variables (ie. analysis of covariance). It was estimated that a sample size of at least 28 (14 in each group) would have 80% power to detect a 6g/m^2 increase in LV mass, with the hypothesis that this would be driven by cellular rather than interstitial changes in the early phase, assuming a standard deviation of 6 for interstudy change and an alpha of 0.05.

Since the number of patients was small, we also performed a non-randomised comparison of these values before and after therapy was withdrawn in either the randomised (baseline at 0 months) and cross-over phases (baseline at 6 months). Comparisons were made using paired t-tests.

Differences in the change in these values were also compared amongst men and women and amongst carriers and non-carriers of *TTNtv* using analysis of covariance. A p value of <0.05 was taken as significant throughout. Statistical analyses were performed using Stata version 15.1 (*StatCorp, College Station, TX, USA*).

Results

Of the 51 patients randomised, 2 were excluded as echocardiography was performed in place of CMR due to implanted electronic cardiac devices. One patient withdrew from the study shortly after enrolment. Therefore, data from 48 patients were included (*Figure 1)*. One patient randomised to the control arm did not cross-over after 6 months, therefore analyses examining patients who had therapy withdrawn in either phase of the study included 47 patients. Baseline and follow-up parametric mapping data were not available, due to the sequence being unavailable, for 13 of 48 patients in the randomised phase and 11 of 47 patients who had therapy withdrawn in either phase of the study.

At enrolment, the mean age of patients was 53 years (SD 12.1) and 33 of 48 (68.8%) were men. The most common aetiology was idiopathic DCM (n=33, 68.8%) and 10 (20.8%) patients were carriers of *TTNtv.* Mean values for Ventricular volumes, ejection fraction and LV mass were within normal ranges (10,11). The mean (SD) LVEF, LV

GLS, RVEF and RV GLS at enrolment were 60.1% (5.7), -21.3 (3.1), 59.2% (5.7) and -27.3 (4.5) respectively, and the mean LVEF at the time of original diagnosis was 25.7% (9.2). The mean (SD) LV mass, ECV, LV cell mass and LV matrix mass were 67.7g/m^2 (14.8), 26.1% (3.2), 50.1g/m^2 (12.3) and 17.7g/m^2 (4.0), respectively.

Compared to men, women were less likely to have a history of atrial fibrillation (0 vs 36.4%; p=0.009) and late gadolinium enhancement (1.3 vs 51.5%; p=0.02) and had lower systolic blood pressure (118.3 [12.1] vs 127.0 [11.1] mmHg; p=0.02) as well as lower LV mass (53.6 [7.9] vs 74.0 [12.7] g/m^2; p<0.0001) and its components, LV cell mass (38.6 [6.6] vs 55.9 [10.3] g/m^2; p<0.0001) and LV matrix mass (13.7 [2.0] vs 19.4 [3.4] g/m^2; p<0.0001). Carriers of *TTNtv* tended to be younger (46.7 [12.6] vs 54.7 [11.0] years; p=0.29) with lower LV mass (43.2 [8.5] vs 52.4 [12.5] g/m^2; p=0.29) compared to non-carriers.

Effect of withdrawing therapy on remodelling

Comparing remodelling variables amongst the randomised groups, withdrawing therapy led to an increase in LV mass (estimated mean effect: 5.4g/m^2; 95% CI 1.3-9.5; p=0.01) and LV cell mass (4.2g/m^2; 95% CI 0.5-8.0; p=0.03) as well as worsening LV GLS (3.5; 95% CI 1.6-5.5; p=0.001) and RV GLS (2.4; 95% 0.1-4.7; p=0.04) (*Table 2 & Figure 2)*. There was no change in any of the variables between baseline and follow-up amongst patients who continued therapy.

In a non-randomised comparison of variables between baseline and follow-up for patients who had therapy withdrawn in either the randomised or cross-over phases, there was also an increase in LV mass (mean change: 6.2g/m^2; 95% CI 3.6-8.9; p=0.0001), LV cell mass (4.0g/m^2; 95% CI 1.8-6.2; p=0.0007) and LV matrix mass (1.7g/m^2; 95% CI 0.7-2.6; p=0.001) and a reduction in LV GLS (2.7; 95% CI 1.5-4.0; p=0.0001) (*Table 3)*. In a similar non-randomised analysis including only those who had therapy withdrawn and who did not meet the trial criteria for relapse (n=28), there was an increase in LV mass (mean change: 5.1g/m^2; 95% CI 1.5-8.8; p=0.0001), LV cell mass (3.7g/m^2; 95% CI 0.3-7.0; p=0.03) and LV matrix mass (1.7g/m^2; 95% CI 0.4-3.0; p=0.01) and a reduction in LV GLS (1.7; 95% CI 0.1-3.2; p=0.04).

Differences in remodelling by sex and genotype

Women had smaller LV mass before therapy was withdrawn compared to men (mean: 53.2 [standard deviation: 7.8] vs 74.0 [13.4] g/m^2) and greater absolute increase in LV mass (9.3 [7.6] vs 4.8 [9.4] g/m^2) following this. After adjusting for baseline differences in remodelling variables between sexes, the effect of sex on change in LV mass was non-significant (-3.7g/m^2; 95%CI -10.2, 2.8; p=0.26) *(Table 4*). The effect of sex on change in other variables was also not significant *(Table 4*).

Similarly, carriers of *TTNtv* who had therapy withdrawn in either the randomised or cross-over phases of the study, had greater increases in LV matrix mass compared to patients without *TTNtv* (mean effect of *TTNtv* – 2.6 g/m^2; 95%CI 0.4-4.8, p=0.02) *(Table 4*). The effect of genotype on change in other variables was not significant *(Table 4*)

Discussion

This is the first study to investigate the serial changes in tissue characteristics and cardiac mechanics that accompany early adverse remodelling in patients with DCM. By harnessing advanced CMR techniques including parametric mapping and feature-tracking, we demonstrate that withdrawing pharmacological therapy leads to a rapid reduction in LV and RV GLS and an increase in overall LV mass and LV cell mass. Due to the relatively small number of patients, a non-randomised comparison of baseline and follow-up values amongst all patients who had therapy withdrawn was also performed. This suggested there was also an increase in LV extracellular matrix mass after therapy was withdrawn. The absence of a change in remodelling variables over follow-up amongst patients who continued therapy supports the validity of the findings of the non-randomised analyses.

These results are important for several reasons. They emphasise that early adverse remodelling is associated with diminished longitudinal deformation of both the left and right ventricle. This is in-keeping with previous studies which have suggested that DCM is a global myocardial process that involves both ventricles (12,13). The development of changes in RV function within 8 weeks of completing withdrawal of therapy, before the development of symptoms or elevated plasma concentrations of

natriuretic peptides, supports the notion of intrinsic RV disease, rather than simply remodelling related to increasing afterload. Equally, we also recognise the absence of evidence supporting a beneficial effect of heart failure therapy on intrinsic RV disease.

Myocardial relapse occurred rapidly amongst patients in the TRED-HF trial. One might have expected that short-term adverse remodelling would be driven by cellular changes such as abnormal calcium handling, energetic dysfunction or sarcomeric dysfunction. Indeed, a marked increase in LV cell mass was observed after withdrawing therapy in both the randomised and non-randomised comparisons, reflecting myocyte hypertrophy, a pathological hallmark of DCM (1). Non-randomised comparisons, however, also demonstrated an increase in LV extracellular matrix mass between baseline and follow-up after withdrawing therapy. Although this was not borne out in the randomised comparison, possibly due to small patient numbers, this suggests that there might also be rapid extracellular matrix remodelling following therapy withdrawal. Whether this is rapid accumulation of interstitial fibrosis or secondary to interstitial oedema is unclear but deserves further consideration and investigation.

Patients who had therapy withdrawn and did not meet the primary relapse end-point also had an increase in LV cell mass and matrix mass and a reduction in GLS. This is in-keeping with the reduction in LVEF reported amongst this group of patients in the primary analysis (5) and confirms evidence of early adverse remodelling even amongst patients who did not meet the trial criteria for relapse. This supports the concept that a greater proportion of patients would have relapsed if therapy had been withdrawn for a greater length of time. It also demonstrates the importance of considering adverse remodelling and relapse as being on a continuous spectrum rather than an all-or-nothing binary phenomenon.

Previous work has demonstrated important differences between men and women with DCM as well as carriers and non-carriers of *TTNtv* (6,7,14). In-keeping with this, at baseline, women had lower total LV, LV cell and LV matrix mass compared to men. After withdrawing therapy, women had a larger absolute increase in LV mass, although after adjustment for differences at baseline, the effect of sex on LV mass was non-significant. The explanation for this is unclear. It is well established that women are more likely to have reverse remodelling in response to treatment compared to men

(15). It is possible that women have more complete reverse remodelling compared to men and that following withdrawal of therapy withdrawal, a greater deterioration. Further investigation of sex differences in remodelling and the effects of specific therapies are required.

Consistent with previous work (7), carriers of *TTNtv* tended to have lower LV mass and cell mass index at baseline (14). Interestingly, they also had greater expansion of extracellular matrix mass during therapy withdrawal. Verdonschot and colleagues previously demonstrated that patients with DCM and *TTNtv* had greater interstitial fibrosis compared to genotype negative patients with DCM (7). Our data supports the concept that *TTNtv* may lead to a more fibrotic phenotype. Sarcomeric variants have been associated with upgregulation of genes involved in extracellular matrix expansion in models of hypertrophic cardiomyopathy (16,17). Other studies have confirmed that interstitial expansion is an early feature of disease (16,17). Whether patients with *TTNtv* may be more likely to benefit from targeted anti-fibrotic agents deserves further attention (2).

Limitations

The small number of patients in this sub-study and the incomplete data on parametric mapping data are important limitations and should be borne in mind when interpreting the results. Correction for multiple testing was not performed due to the exploratory nature of the analysis. The analyses investigating differences in remodelling based on sex and genotype should be viewed as hypothesis-generating and require validation in larger studies, considering the small numbers of patients in these sub-analyses. Nevertheless, these results are consistent with previous data and suggest that important differences exist within these sub-groups. It should also be recognised that changes in LV geometry can affect measures of systolic function, including ejection fraction and strain. Previous data has confirmed that GLS is confounded to a lesser degree than ejection fraction by such changes (18).

Conclusions

In TRED-HF, withdrawing therapy for heart failure led to a deterioration in measures of LV and RV systolic function and LV hypertrophy due to an increase in both LV cell and extracellular matrix mass within 6 months. This suggests that early adverse remodelling is a biventricular process with both cellular and interstitial changes. Such changes were observed amongst patients who had therapy withdrawn even if they did not meet the trial criteria for relapse, suggesting that more patients would have relapsed if therapy had been withdrawn for longer. Sex- and genotype-specific differences in remodelling may exist; greater understanding of these may enable more personalised therapy.

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Figure Legends

Graphical Abstract/Central Figure

Tissue and mechanical changes during early adverse remodelling in patients with recovered dilated cardiomyopathy during therapy withdrawal

(CI – confidence intervals, CMR – cardiovascular magnetic resonance, ECV – extracellular volume, GLS – global longitudinal strain, LV – left ventricular, RV – right ventricular, SD – standard deviation)

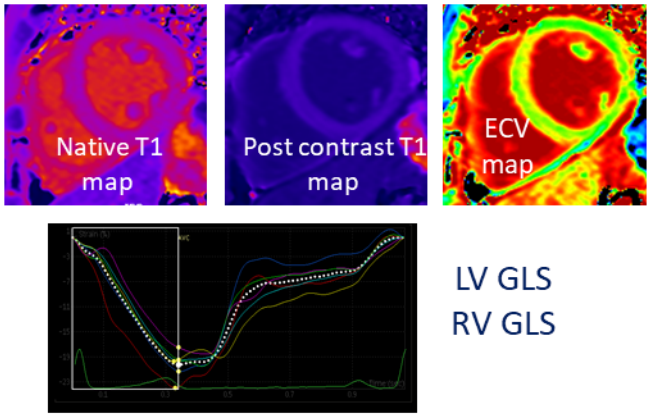
Figure 1. Derivation of the study cohort

(Atrial fibrillation – AF; TTE – transthoracic echocardiography)

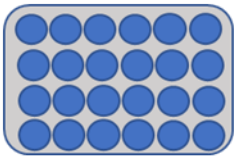
Figure 2. Scatter plots demonstrating changes in remodelling variables between baseline and follow-up for patients in either treatment arm of the randomised phase

(CI – confidence intervals; GLS – global longitudinal strain; LV – left ventricular; RV – right ventricular)

CMR protocol



Tissue characterisation

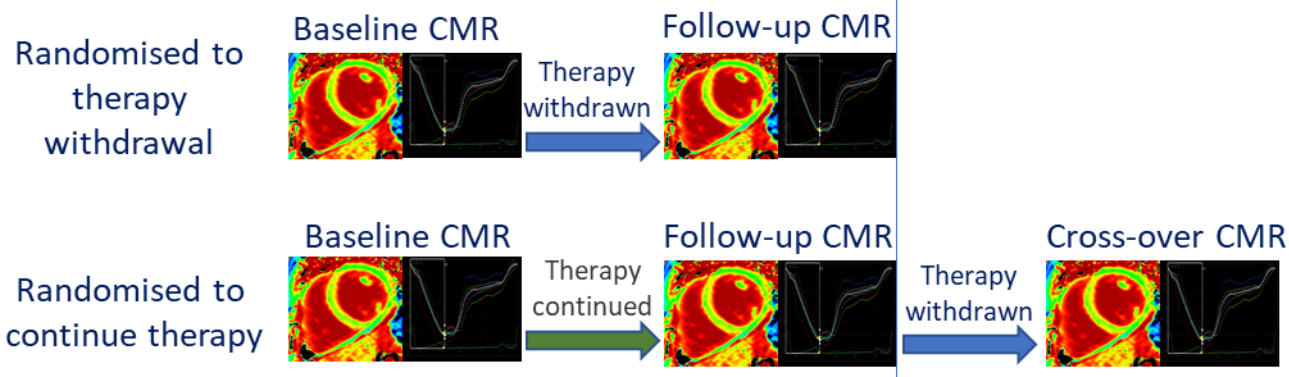


LV cell mass = (1-ECV fraction) x LV mass

LV extracellular matrix mass = ECV fraction x LV mass

Randomised phase

Cross-over phase



Comparison of change in variables between arms in randomised phase (n=48)

	Estimated mean effect of treatment withdrawal (95% CI)	P-value*
LV mass (g/m²)	5.4 (1.3, 9.5)	0.01
Cell volume (g/m²)	4.2 (0.5, 8.0)	0.03
Matrix volume (g/m²)	1.3 (-0.6, 3.2)	0.19
LV GLS	3.5 (1.6, 5.5)	0.001
RV GLS	2.4 (0.1, 4.7)	0.04

*Comparison between groups using ANCOVA

Comparison of baseline vs follow-up variables during therapy withdrawal in either phase (n=47)

	Mean difference (95% CI)	P-value*
LV mass (g/m²)	6.2 (3.6-8.9)	0.0001
Cell volume (g/m²)	4.0 (1.8-6.2)	0.0007
Matrix volume (g/m²)	1.7 (0.7-2.6)	0.001
LV GLS	2.7 (1.5-4.0)	0.0001
RV GLS	0.8 (-1.1 – 2.6)	0.40

*Comparison between baseline and follow-up using paired t-tests

Figure 1

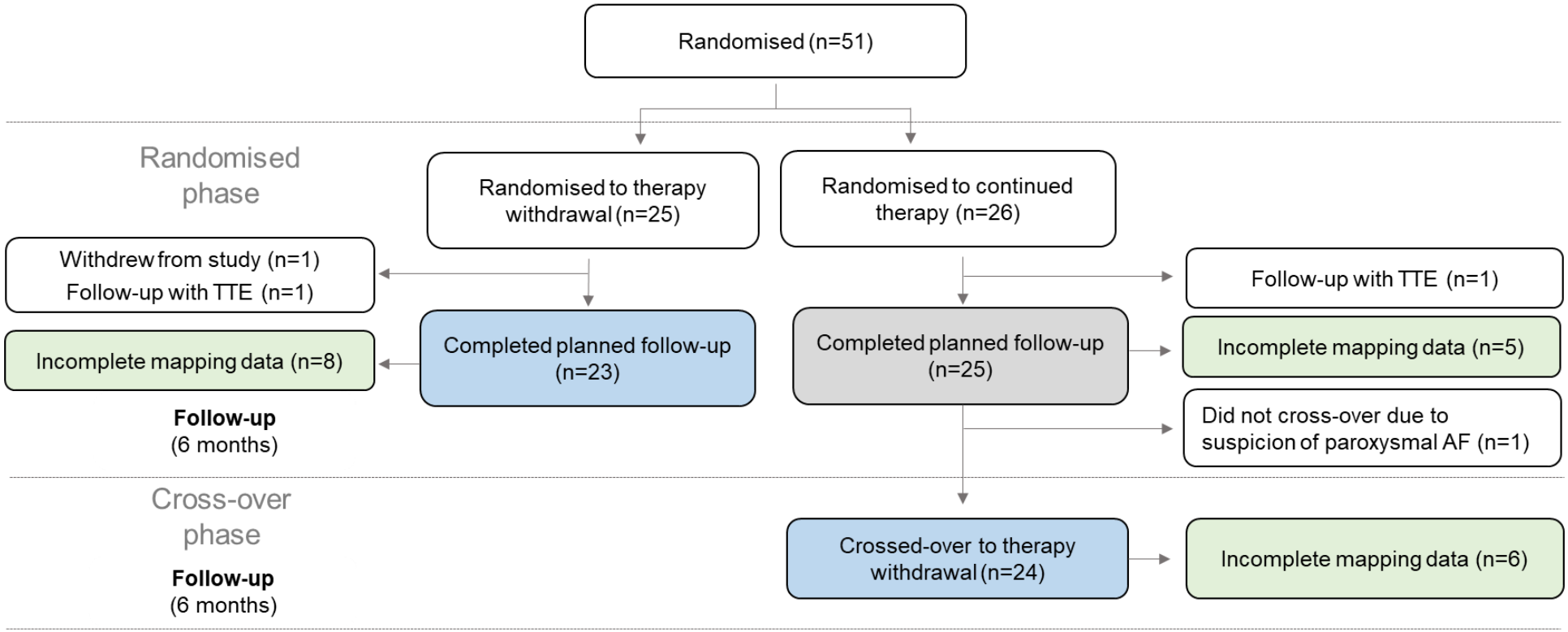

Randomised (n=51)
Randomised phase
Randomised to therapy withdrawal (n=25)
Randomised to continued therapy (n=26)
Withdrew from study (n=1)
Follow-up with TTE (n=1)
Incomplete mapping data (n=8)
Completed planned follow-up (n=23)
Completed planned follow-up (n=25)
Follow-up with TTE (n=1)
Incomplete mapping data (n=5)
Did not cross-over due to suspicion of paroxysmal AF (n=1)
Follow-up
(6 months)
Cross-over phase
Crossed-over to therapy withdrawal (n=24)
Incomplete mapping data (n=6)
Follow-up
(6 months)

Figure 2

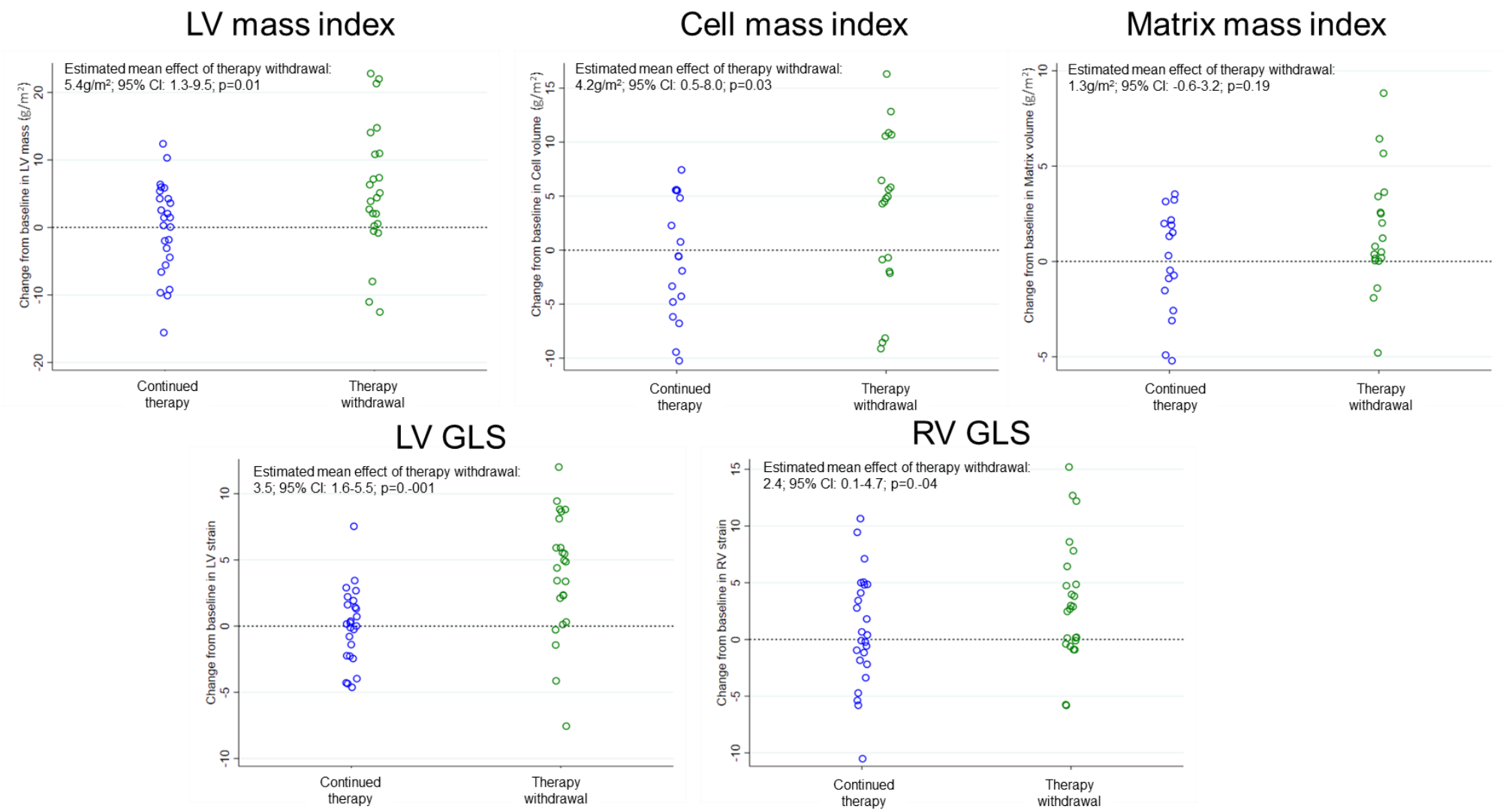

LV mass index
Estimated mean effect of therapy withdrawal:
5.4g/m²; 95% CI: 1.3-9.5; p=0.01
Change from baseline in LV mass (g/m²)
Continued therapy
Therapy withdrawal
Cell mass index
Estimated mean effect of therapy withdrawal:
4.2g/m²; 95% CI: 0.5-8.0; p=0.03
Change from baseline in Cell volume (g/m²)
Continued therapy
Therapy withdrawal
Matrix mass index
Estimated mean effect of therapy withdrawal:
1.3g/m²; 95% CI: -0.6-3.2; p=0.19
Change from baseline in Matrix volume (g/m²)
Continued therapy
Therapy withdrawal
LV GLS
Estimated mean effect of therapy withdrawal:
3.5; 95% CI: 1.6-5.5; p=0.-001
Change from baseline in LV strain
Continued therapy
Therapy withdrawal
RV GLS
Estimated mean effect of therapy withdrawal:
2.4; 95% CI: 0.1-4.7; p=0.-04
Change from baseline in RV strain
Continued therapy
Therapy withdrawal

Table 1. Characteristics of patients at randomisation

	Overall population n=48	Control n=25	Therapy withdrawal n=23	p
Demographics				
Mean Age (SD), yrs	53.0 (12.1)	52.4 (13.0)	53.6 (10.3)	0.88
Men, n (%)	33 (68.8)	18 (72.0)	15 (65.2)	0.76
Previous cardiovascular history				
Time since initial DCM diagnosis, months	60.8 (41.2)	55.7 (41.9)	66.4 (40.8)	0.24
LVEF at initial diagnosis, %	25.7 (9.2)	25.4 (8.6)	26.2 (9.9)	0.66
Absolute improvement in LVEF, %	30.9 (10.0)	31.1 (8.4)	30.7 (11.6)	0.59
Time since LVEF>50%, months	24.7 (22.7)	26.8 (24.5)	26.6 (19.8)	0.77
Previous heart failure admission, n (%)	31 (64.6)	14 (56.0)	17 (73.9)	0.24
Previous atrial fibrillation, n (%)	12 (25.0)	4 (16.0)	8 (34.8)	0.19
Previous hypertension, n (%)	4 (8.3)	3 (12.0)	1 (4.3)	0.61
Diabetes mellitus, n (%)	1 (2.1)	1 (4.0)	0 (0)	1
Smoker, n (%)	3 (6.3)	3 (12.0)	0 (0)	0.24
Aetiology				
Idiopathic, n (%)	33 (68.8)	14 (56.0)	19 (82.6)	
Familial, n (%)	6 (12.5)	4 (16.0)	2 (8.7)	0.15
Environmental insult, n (%)	9 (18.8)	7 (28.0)	2 (8.7)	
TTNtv, n (%)	10 (20.8)	4 (16.0)	6 (26.1)	0.49
Medications at enrolment				
ACE inhibitor /ARB, n (%)	48 (100)	25 (100)	23 (100)	N/A
Beta-blocker, n (%)	42 (87.5)	23 (92.0)	19 (82.6)	0.41
Mineralocorticoid receptor antagonist, n (%)	21 (43.8)	11 (44.0)	10 (43.5)	1
Loop diuretic, n (%)	6 (12.5)	3 (12.0)	3 (13.0)	1
Clinical characteristics at enrolment				
Body surface area, m^2	2.0 (0.3)	2.0 (0.3)	2.0 (0.3)	0.75
Heart rate, beats per minute	67.2 (11.0)	69.8 (10.0)	64.3 (11.5)	0.08
Systolic blood pressure, mmHg	124.2 (12.0)	126.0 (11.3)	122.5 (11.5)	0.32
Diastolic blood pressure, mmHg	73.9 (8.9)	75.2 (7.1)	72.6 (10.6)	0.31
Left bundle branch block, n (%)	7 (14.6)	4 (16.0)	3 (13.0)	1
NT-pro-BNP, ng/l	68 (38,129)	68 (37, 132)	64 (43, 96)	0.93
CMR variables at enrolment				
LVEDVi, ml/m^2	80.4 (12.5)	81.0 (11.5)	79.8 (13.8)	0.89
LVEF, %	60.1 (5.7)	59.0 (5.1)	61.4 (6.2)	0.43
LV mass index, g/m^2	67.7 (14.8)	68.5 (12.1)	66.7 (17.6)	0.54
RVEDVi, ml/m^2	77.5 (16.6)	76.6 (16.6)	78.6 (16.9)	0.64
RVEF, %	59.2 (5.7)	58.8 (6.1)	59.6 (5.2)	0.68
Late Gd enhancement, presence	19 (39.6)	10 (40.0)	9 (39.1)	1
Extracellular volume, %	26.0 (2.6)	26.5 (2.8)	25.6 (2.5)	0.38
Cell mass index, g/m2	50.6 (12.3)	51.0 (9.7)	50.3 (14.5)	0.55
Matrix mass index, g/m2	17.7 (4.0)	18.4 (3.8)	17.1 (4.3)	0.4
LV Global longitudinal strain	-21.3 (3.1)	-21.0 (3.1)	-21.5 (3.2)	0.35
RV Global longitudinal strain	-27.3 (4.5)	-27.4 (5.0)	-27.3 (4.1)	0.81

Data presented as mean (SD), median (IQR) or n (%). Characteristics at randomisation.

ACE – angiotensin converting enzyme; ARB: angiotensin receptor blocker; BP: blood pressure; GLS: global longitudinal strain; LV: left ventricular; LVEDVi: left ventricular end diastolic volume indexed to body surface area; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor blocker; NT-pro-BNP – N-terminal propeptide of brain natriuretic peptide; RV: right ventricular; RVEDVi: right ventricular end diastolic volume indexed to BSA; *TTNtv:* truncating variant in the gene encoding titin; VO2: oxygen consumption

Table 2. The effect of therapy withdrawal on myocardial remodelling

	Mean (SD) in continued treatment group	Mean (SD) in treatment withdrawal group	Estimated mean effect of treatment withdrawal (95% CI)	P-value
	(N=25)*	(N=23) †		
LV mass (g/m^2)				
Baseline	68.5 (12.1)	66.7 (17.6)		
Follow-up	68.5 (12.3)	72.7 (13.1)	5.4 (1.3, 9.5)	0.01
Cell volume (g/m^2)				
Baseline	51.0 (9.7)	50.3 (14.5)		
Follow-up	50.1 (10.8)	53.8 (9.9)	4.2 (0.5, 8.0)	0.03
Matrix volume (g/m^2)				
Baseline	18.4 (3.8)	17.1 (4.3)		
Follow-up	18.4 (3.9)	18.7 (4.1)	1.3 (-0.6, 3.2)	0.19
LV GLS				
Baseline	-21.0 (3.1)	-21.5 (3.2)		
Follow-up	-21.0 (3.1)	-17.6 (4.1)	3.5 (1.6, 5.5)	0.001
RV GLS				
Baseline	-27.4 (5.0)	-27.3 (4.1)		
Follow-up	-26.4 (4.2)	-24.0 (4.0)	2.4 (0.1, 4.7)	0.04

Change in variables between baseline and 6 months compared between randomised groups using ANCOVA.

*n=8 and †n=4 patients in the continued treatment arm and withdrawal arm respectively had missing values for cell volume and matrix volume

Table 3. Non-randomised comparison of baseline and follow-up variables amongst patients who had therapy withdrawn in the randomised or cross-over phases

	All patients who had therapy withdrawn (n=47)*				No primary outcome (n=28) †				Primary outcome (n=19) ‡			
	Baseline Mean (SD)	Follow-up Mean (SD)	Mean difference (95% CI)	P	Baseline Mean (SD)	Follow-up Mean (SD)	Mean difference (95% CI)	P	Baseline Mean (SD)	Follow-up Mean (SD)	Mean difference (95% CI)	P
LV mass (g/m^2)	67.5 (15.1)	73.8 (12.8)	6.2 (3.6-8.9)	0.0001	71.2 (15.9)	76.3(14.6)	5.1 (1.5-8.8)	0.0001	62.2 (12.4)	70.1 (9.1)	7.9 (3.8-12.1)	0.0008
Cell vol (g/m^2)	50.5 (12.3)	54.5 (9.8)	4.0 (1.8-6.2)	0.0007	52.2 (13.8)	55.9 (11.6)	3.7 (0.3-7.0)	0.03	47.7 (9.2)	52.2 (5.7)	4.6 (1.9-7.3)	0.003
Matrix vol (g/m^2)	17.6 (4.0)	19.3 (4.3)	1.7 (0.7-2.6)	0.001	17.7 (4.1)	19.4 (4.6)	1.7 (0.4-3.0)	0.02	17.4 (4.0)	19.1 (3.8)	1.6 (0.0-3.2)	0.05
LV GLS (g/m^2)	-21.2 (3.1)	-18.5 (3.4)	2.7 (1.5-4.0)	0.0001	-21.4 (3.3)	-19.7 (2.8)	1.7 (0.1-3.2)	0.04	-20.9 (3.0)	-16.6 (3.5)	4.3 (2.3-6.6)	0.0003
RV GLS (g/m^2)	-26.8 (4.2)	-26.0 (5.1)	0.8 (-1.1 – 2.6)	0.40	-25.8 (3.1)	-26.2 (5.0)	-0.4 (-2.7 – 2.0)	0.75	-28.2 (5.1)	-25.8 (5.3)	2.4 (-0.6 – 5.5)	0.11

Baseline and follow-up variables compared using paired t-tests. For patients in the cross-over phase, baseline and follow-up are 6 and 12 months, respectively.
* n=36, †n=22, ‡n=14 for cell volume and matrix volume

Table 4. The effect of sex and genotype on myocardial remodelling amongst patients who had therapy withdrawn in the randomised or cross-over phases

		Men vs women (n=47)*					
		Men (n=32)		**Women (n=15)**		**Estimated mean effect of male sex (95% CI)**	**P†**
		Mean (SD)	**Mean (SD) change**	**Mean (SD)**	**Mean (SD) change**		
LV mass (g/m^2)	Baseline	74.0 (13.4)		53.2 (7.8)		-3.7 (-10.2, 2.8)	0.26
	Follow-up	78.9 (10.9)	4.8 (9.4)	62.5 (9.4)	9.3 (7.6)		
Cell vol (g/m^2) *	Baseline	55.7 (10.4)		38.6 (6.9)		-0.4 (-5.6, 4.7)	0.87
	Follow-up	58.1 (8.6)	2.4 (6.5)	46.2 (7.3)	7.6 (5.0)		
Matrix vol (g/m^2) *	Baseline	19.1 (3.7)		14.2 (2.2)		0.7 (-1.8, 3.3)	0.56
	Follow-up	20.3 (4.0)	1.2 (2.6)	16.9 (4.0)	2.7 (3.3)		
LV GLS	Baseline	-20.8 (3.0)		-21.9 (3.5)		0.6 (-1.6, 2.8)	0.61
	Follow-up	-18.6 (3.3)	2.4 (4.1)	-18.2 (3.9)	3.4 (4.7)		
RV GLS	Baseline	-26.2 (4.0)		-27.9 (4.3)		-0.9 (-4.3, 2.4)	0.57
	Follow-up	-25.6 (5.0)	0.6 (7.0)	-26.8 (5.3)	1.2 (4.5)		

		***non-TTNtv* vs *TTNtv* (n=47)**					
		Non-*TTNtv* (n=37)		***TTNtv* (n=10)**		**Estimated mean effect of TTNtv (95% CI**	**P†**
		Mean (SD)	**Mean (SD) change**	**Mean (SD)**	**Mean (SD) change**		
LV mass (g/m^2)	Baseline	69.0 (15.8)		62.1 (11.5)		4.0 (-2.0, 9.9)	0.18
	Follow-up	74.1 (13.3)	5.1 (9.3)	72.8 (11.1)	10.8 (7.0)		
Cell vol (g/m^2) *	Baseline	52.2 (12.7)		44.5 (9.0)		1.4 (-3.1, 5.9)	0.53
	Follow-up	55.4 (10.2)	3.2 (6.5)	51.4 (7.9)	6.9 (5.8)		
Matrix vol (g/m^2) *	Baseline	18.0 (4.0)		16.3 (3.9)		2.6 (0.4, 4.8)	0.02
	Follow-up	19.0 (4.3)	1.0 (2.7)	20.2 (4.3)	3.9 (2.5)		
LV GLS	Baseline	-21.7 (3.2)		-19.4 (2.0)		-0.3 (-2.9, 2.3)	0.82
	Follow-up	-18.5 (3.5)	3.2 (4.0)	-18.4 (3.3)	1.1 (5.0)		
RV GLS	Baseline	-27.1 (4.4)		-25.6 (3.1)		0.7 (-3.1, 4.4)	0.71
	Follow-up	-26.2 (5.1)	0.9 (6.4)	-25.3 (5.1)	0.3 (6.1)		

Effect of sex and genotype on change in variables examined using ANCOVA.
*7 male and 4 female patients had missing values for cell volume and matrix volume
† p value calculated using ANCOVA