Withdrawal of pharmacological therapy for heart failure in recovered dilated cardiomyopathy – a randomised trial

TRED-HF

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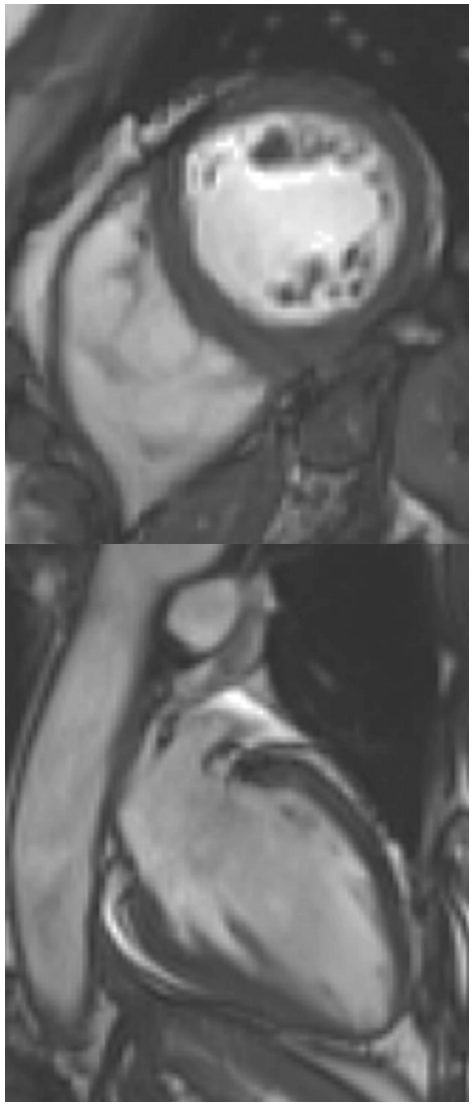
Royal Brompton & Harefield NHS Trust

Imperial College London

British Heart Foundation

Dilated Cardiomyopathy: From Failure to ‘Success’

Remission or cure?



‘Do I need to take the medications forever?’

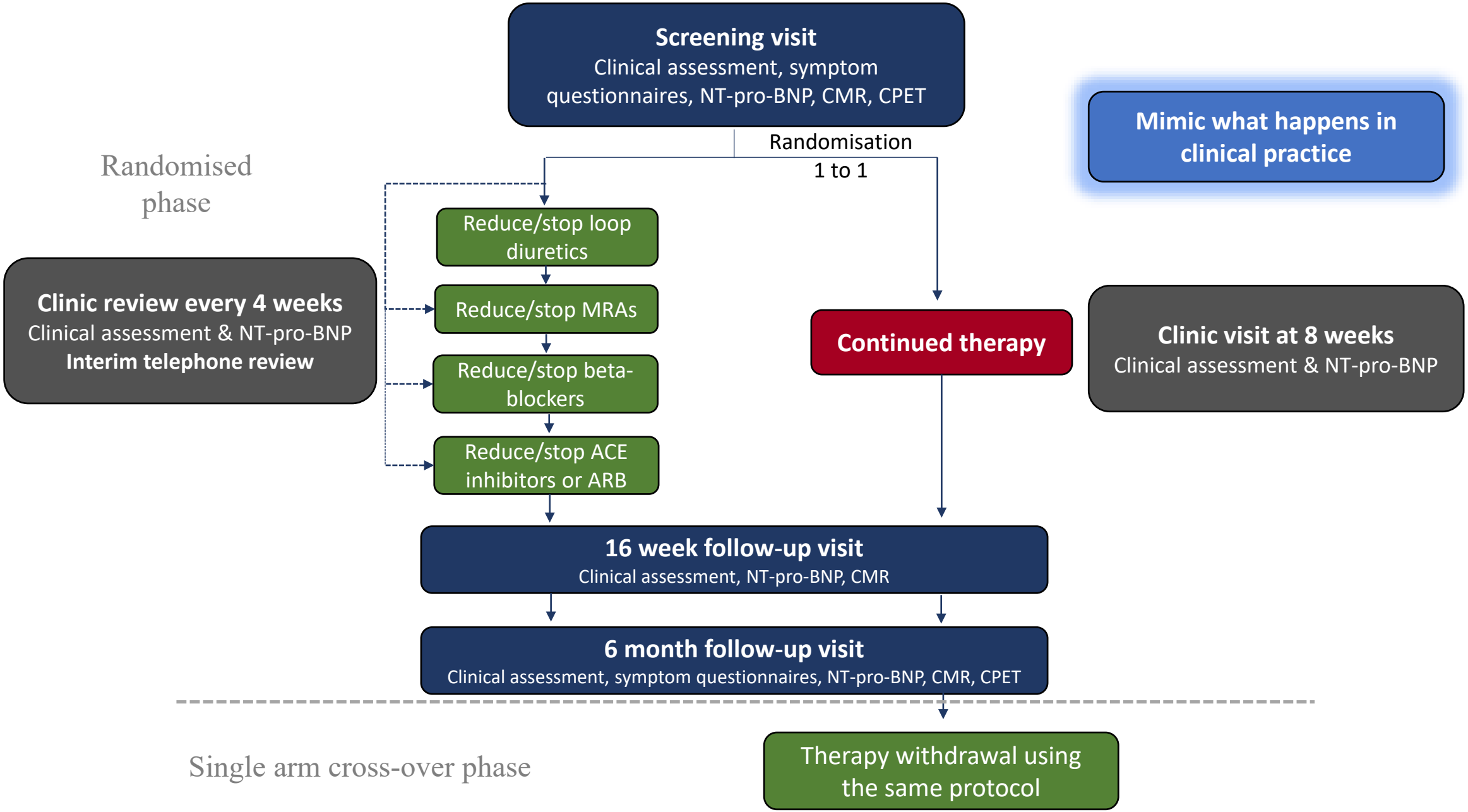
- *Side effects*
- *Pregnancy*
- *Costs*

TRED-HF

- Open-label, pilot randomised trial
- Examine safety and feasibility of *phased withdrawal of therapy*
- Recruitment from network of hospitals; enrolment in single centre

Prior diagnosis of DCM
    Dilated LV & LVEF <40% at diagnosis
Subsequent recovery
    LVEF >50%
    Normal LVEDVi } CMR
    NT-pro-BNP <250ng/L
    NYHA 1

- Arrhythmia requiring beta-blocker
- Uncontrolled hypertension
- Valvular disease (moderate or greater)
- eGFR <30mls/min
- Pregnancy
- Angina
- Age <16 years


Screening visit
Clinical assessment, symptom questionnaires, NT-pro-BNP, CMR, CPET
Randomisation
1 to 1
Mimic what happens in clinical practice
Randomised phase
Clinic review every 4 weeks
Clinical assessment & NT-pro-BNP
Interim telephone review
Reduce/stop loop diuretics
Reduce/stop MRAs
Reduce/stop beta-blockers
Reduce/stop ACE inhibitors or ARB
Continued therapy
Clinic visit at 8 weeks
Clinical assessment & NT-pro-BNP
16 week follow-up visit
Clinical assessment, NT-pro-BNP, CMR
6 month follow-up visit
Clinical assessment, symptom questionnaires, NT-pro-BNP, CMR, CPET
Single arm cross-over phase
Therapy withdrawal using the same protocol

Pre-specified end-points

- Primary end-point
  - Relapse of DCM defined by *any* ***ONE*** of:

1. Reduction in LVEF by >10% and to <50%
2. Increase in LVEDV by >10% and to above normal range
3. Two-fold rise in NT-pro-BNP and to >400ng/L
4. Clinical evidence of heart failure

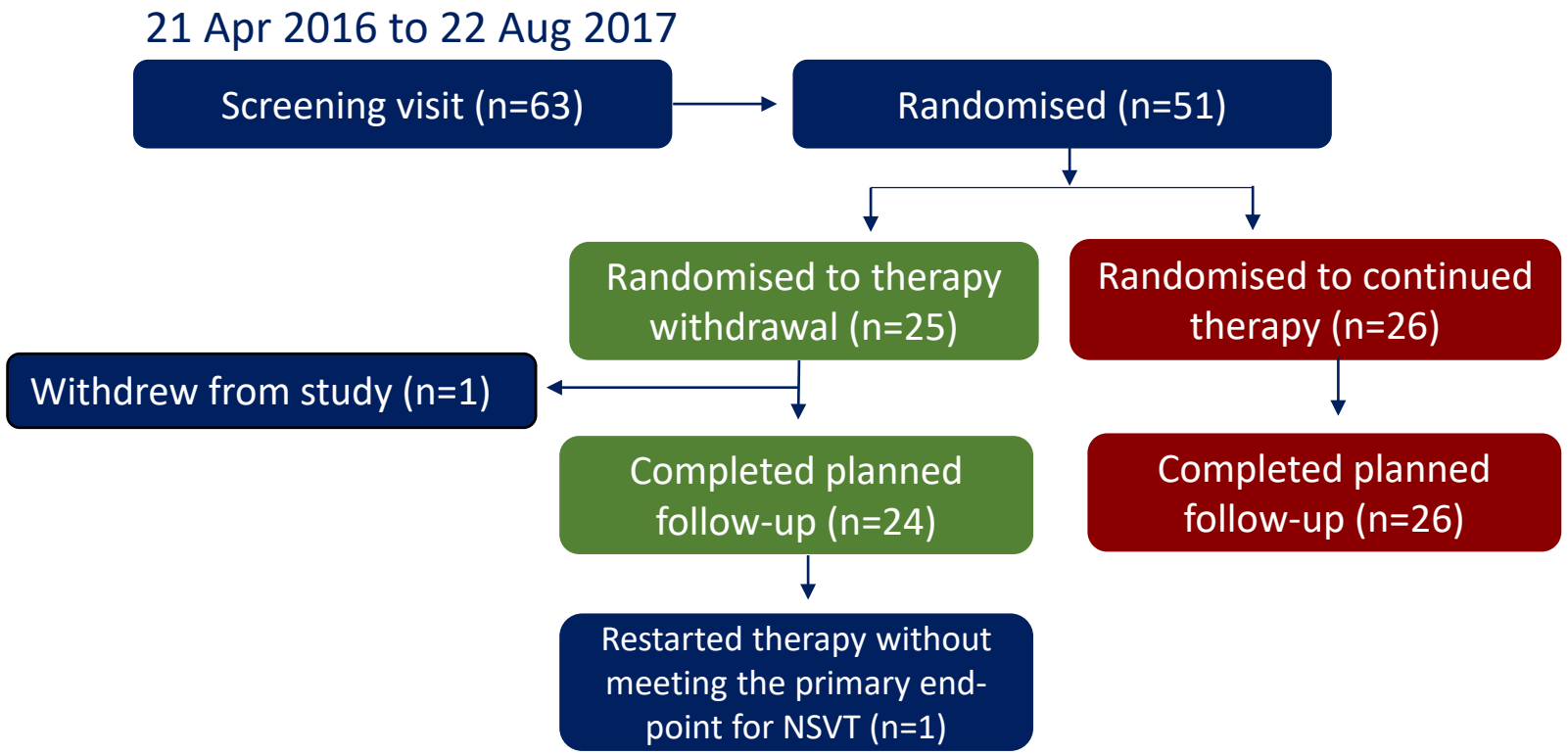
→ Immediate re-introduction of therapy

- Safety end-point
  - (CV mortality, MACE, unplanned CV hospitalisation)
- Arrhythmia (sustained) end-point
- Changes in secondary clinical variables

Patient Safety

- Protocol approved by
  - National Research Ethics Committee
  - Medicines and Healthcare Products Regulatory Agency
  - Institutional Oversight Committee and Patient Advisory Group
  - Funding Body
  - National Patient Organisations
- Doctor available for medical advice 24/7
- General practitioners and physicians kept up-to-date
- All trial data reviewed weekly
  - AEs managed on an individual case basis
- Independent data monitor

Randomised phase



25 pts randomised to therapy withdrawal **vs** 26 pts randomised to continued therapy **ITT Primary analysis**

Baseline

- Median age: 55 years (IQR 45 to 64)
- 34 (67%) men

- At first diagnosis
  - Median LVEF: 25% (IQR 20 to 33)
  - Median time from diagnosis: 4.9 yrs (IQR: 2.1 to 8.3)

- At enrolment
  - All in sinus rhythm
  - Median LVEF: 60% (IQR 55 to 64)
  - Median NT-pro-BNP: 72ng/L (IQR 39 to 135)

- All patients on ACEi/ARB
- 45 (88%) on beta-blocker
- 24 (47%) on MRA
- 6 (12%) on loop diuretic

- 1 pt had CRT-D and 1 pt an ICD in situ

	Therapy Withdrawal (n=25)	Control (n=26)
Demographics		
Median Age (IQR), yrs	54 (46,64)	56 (45,64)
Men, n (%)	16 (64)	18 (69)
Previous cardiovascular history		
Time since initial DCM diagnosis, months	63 (36,112)	41 (20, 91)
LVEF at initial diagnosis, %	28 (20,33)	25 (19,33)
Absolute improvement in LVEF, %	29 (23,36)	30 (25,38)
Time since LVEF >50%, months	28 (8,45)	20 (6,44)
Previous heart failure admission, n (%)	18 (72)	14 (54)
Previous moderate alcohol excess, n (%)	8 (32)	9 (35)
Previous atrial fibrillation, n (%)	8 (32)	4 (15)
Aetiology		
Idiopathic, n (%)	20 (80)	15 (58)
Familial, n (%)	3 (12)	4 (15)
Environmental insult, n (%)	2 (8)	7 (27)
TTNtv, n (%)	7 (28)	4 (15)
Medications at enrolment		
ACE inhibitor /ARB, n (%)	25 (100)	26 (100)
Beta-blocker, n (%)	21 (84)	24 (92)
Mineralocorticoid receptor antagonist, n (%)	12 (48)	12 (46)
Loop diuretic, n (%)	3 (12)	3 (12)
Clinical characteristics at enrolment		
Heart rate, beats per minute	62 (58,74)	70 (60,75)
Systolic blood pressure, mmHg	123 (117,133)	127 (117,134)
Diastolic blood pressure, mmHg	72 (68,80)	76 (70,80)
Left bundle branch block, n (%)	3 (12)	4 (15)
QRS duration, ms	98 (85,108)	94 (88,111)
NT-pro-BNP, ng/l	72 (44,147)	75 (37,133)
CMR variables at enrolment		
LVEDVi, ml/m^2	86 (66, 91)	80 (70,91)
LVEF, %	62 (55, 66)	60 (55,61)

Results

Randomised phase

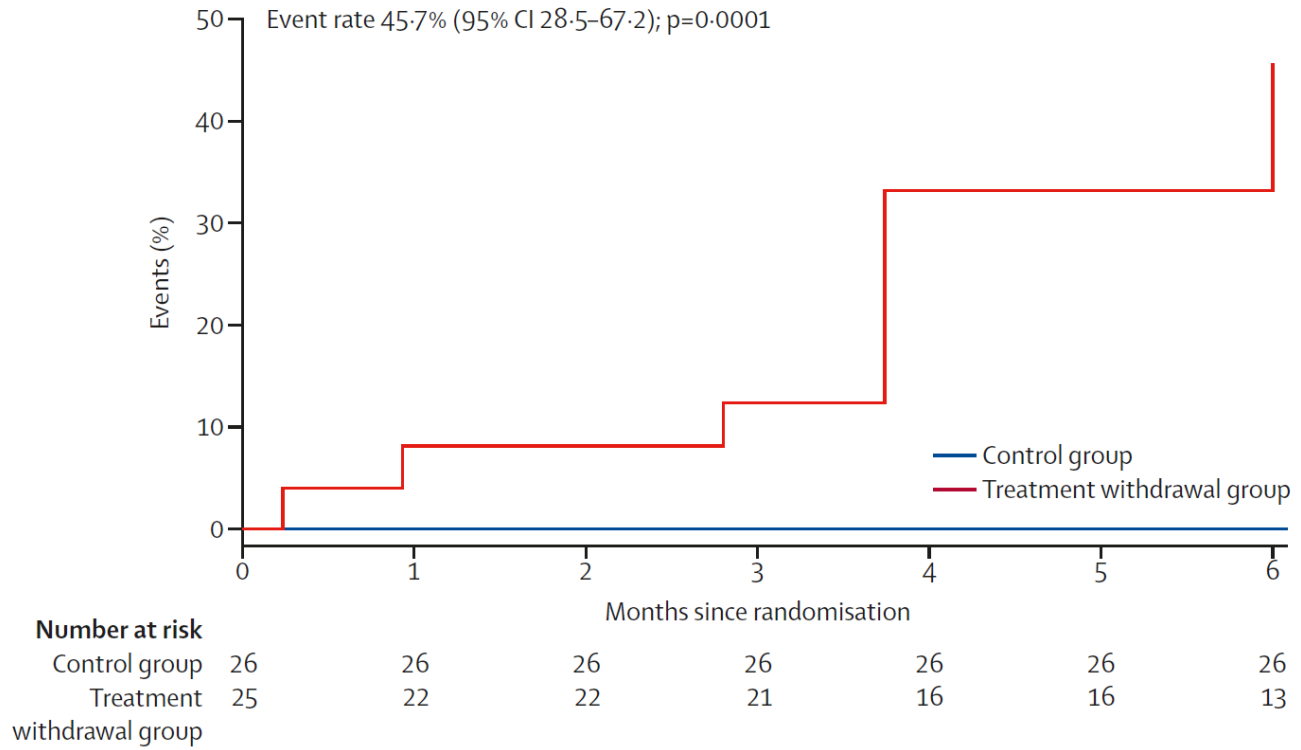
Arm	Pts	Relapse n (%)
Therapy withdrawal	25	11 (44)
Control	26	0 (0)

Single-arm cross-over phase

Arm	Pts	Relapse n (%)
Therapy withdrawal	25	9 (36)

Further 3 restarted therapy

- 2 for hypertension, 1 for AF

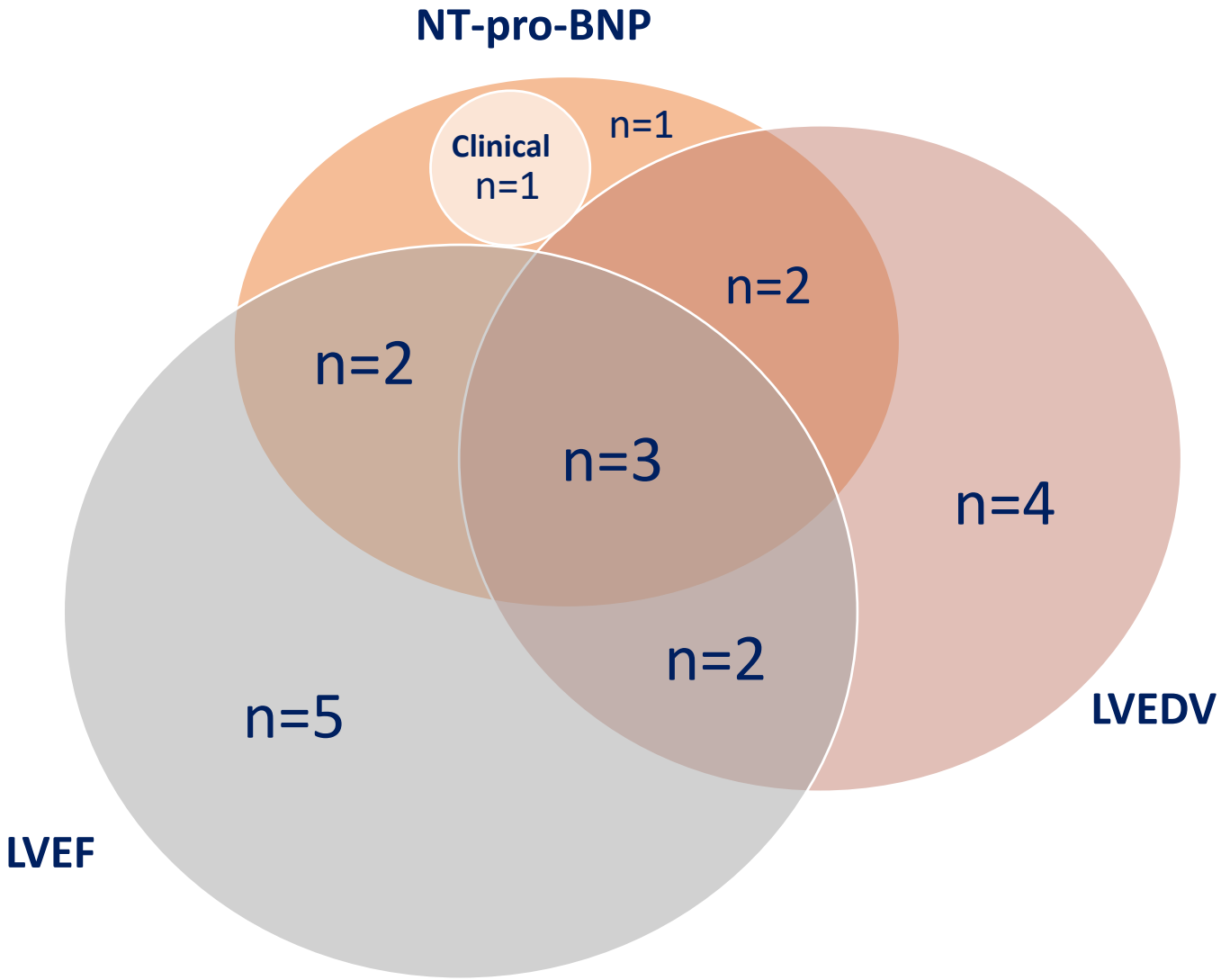


Of 50 pts who began therapy withdrawal, 20 (40%) met primary end-point

25 of 50 (50%) patients completed follow-up without re-initiation of treatment

16 of 50 (32%) completed withdrawal without deterioration in LVEF (>3%)

Primary end-point components



Safety end-points

- No deaths, unplanned heart failure hospitalisations or MACE
- 3 serious adverse events in withdrawal arm
  - Hospitalisations: urinary sepsis, non-cardiac chest pain and an elective procedure
- No sustained ventricular arrhythmia or device therapies
- Three pts developed AF in withdrawal arm
- All pts who met primary end-point were NYHA 1 after restarting treatment
  - 17 of 20 pts had LVEF >50%
  - 2 had LVEF 45-50% and 1 had LVEF 43%

Secondary end-points

Randomised comparison of baseline and follow-up variables
Withdrawal vs control in randomised phase

Outcome	Estimated mean effect of therapy withdrawal on 6-month values (95% CI)	P value
LVEF, %	-9·5 (-14·0 to -4·9)	0·0001
LVEDVi, ml/m^2	4·7 (-1·5 to 11·0)	0·14
LAVi, ml/m^2	0·5 (-4·2 to 5·2)	0·82
Heart rate, bpm	15·4 (10·0 to 20·9)	<0·0001
Systolic BP, mmHg	6.6 (-0.1 to 13.4)	0.055
Diastolic BP, mmHg	7·0 (1·9 to 12·1)	0·008
Log NT pro-BNP, ng/L	0·3 (-0·1 to 0·7)	0·11
Peak VO_2 (ml/kg/min)	-1·2 (-3·9 to 1·6)	0·40
Exercise time (secs)	-3·4 (-36·0 to 29·2)	0·83
KCCQ, 0-100	-5·1 (-9·9 to -0·4)	0·035
SAQ, 0-100	0·3 (-0·1 to 0·6)	0·15

ANCOVA

Baseline vs follow-up variables for
all those who had treatment withdrawal

Outcome	Estimated mean change between baseline & 6 months (95% CI)	P value
LVEF, %	-6·9 (-9·6 to -4·3)	<0·0001
LVEDVi, ml/m^2	6·5 (3·1 to 9·8)	0·0003
LAVi, ml/m^2	2·0 (-0·6 to 4·6)	0·12
Heart rate, bpm	13·2 (9·3 to 17·1)	<0·0001
Systolic BP, mmHg	8·7 (4·6 to 12·9)	0·0001
Diastolic BP, mmHg	6·7 (3·2 to 10·1)	0·0003
Log NT pro-BNP, ng/L	0·3 (0·0 to 0·6)	0·025
VO_2 max (ml/kg/min)	-0·7 (-2·1 to 0·7)	0·33
Exercise time (seconds)	-0·6 (-14·9 to 13·8)	0·94
KCCQ, 0-100	-2·2 (-4·7 to 0·3)	0·078
SAQ, 0-100	0·1 (-0·1 to 0·3)	0·38

Paired T test

Exploratory analyses

Association between baseline characteristics and primary end-point

Characteristic		Hazard ratio (per SD change unless specified)	P value
Age (per 10 yrs)		1·6 (1·0 to 2·4)	0·031
MRA		3·9 (1·4 to 10·8)	0·004
Number of HF medications	≤2 agents	1·0 (reference)	
	3 agents	3·7 (1·3 to 10·6)	0.004
	4 agents	4·8 (1·1 to 20·2)	
Log NT-pro-BNP, ng/L		1·8 (1·1 to 2·8)	0·016
Global radial strain		0·55 (0·34 to 0·90)	0·018

Conclusion

- Withdrawal of therapy from patients deemed to have recovered DCM resulted in relapse in ~40% of cases
  - Likely to be even greater in the longer-term
- Currently, patients should generally be advised **not** to withdraw therapy.
- If the patient insists on a trial of treatment-withdrawal, a robust monitoring plan should be in place
- Advice might change if
  - Predictors of (non)relapse are identified – prior to or early after treatment withdrawal
  - Further trials show that some selected therapies can be safely withdrawn or reduced
- Improvement in function represents *remission* rather than *permanent recovery* for many patients

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Patients