

## Heart rate as a marker of relapse during withdrawal of heart failure therapy in patients with recovered dilated cardiomyopathy: an analysis from TRED-HF

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**Introduction:** In TRED-HF, 40% of patients with recovered dilated cardiomyopathy (DCM) relapsed in the short-term during phased withdrawal of drug therapy. Non-invasive markers of relapse may be used to monitor patients who wish a trial of therapy withdrawal and provide insights into the pathophysiological drivers of relapse.

**Purpose:** To investigate the relationship between changes in heart rate (HR) and relapse amongst patients with recovered DCM undergoing therapy withdrawal in TRED-HF.

**Methods:** Patients with recovered DCM were randomised to phased withdrawal of therapy or to continue therapy for 6 months. After 6 months of continued therapy, those in the control arm underwent withdrawal of therapy in a single arm crossover phase. HR was measured at each study visit. Mean HR and 95% confidence intervals (CI) were calculated at baseline, 45 days after baseline, 45 days prior to the end of the study or relapse and at the end of the study or relapse. Patients were stratified by treatment arm and the occurrence of the primary relapse end-point. Heart rate at follow-up was compared amongst patients who had therapy withdrawn and relapsed versus those who had therapy withdrawn and did not. ANCOVA was used to adjust for differences in HR at baseline between the two groups.

**Results:** Of 51 patients randomised, 26 were assigned to continue therapy and 25 to withdraw therapy. In the randomised and cross-over phases,

20 patients met the primary relapse end-point; one patient withdrew from the study and one patient completed follow-up in the control arm but did not enter the cross-over phase. Mean HR (standard deviation) at baseline and follow-up for (i) patients in the control arm was 69.9 (9.8) & 65.9 (9.1) respectively; (ii) for those who had therapy withdrawn and did not relapse was 64.6 (10.7) & 74.7 (10.4) respectively; and (iii) for those who had therapy withdrawn and relapsed was 68.3 (11.3) & 86.1 (11.8) respectively [all beats per minute]. The mean change in HR between the penultimate visit and the final visit for those who had therapy withdrawn and did not relapse was -2.4 (9.7) compared to 3.1 (15.5) for those who relapsed. After adjusting for differences in HR at baseline, the mean difference in HR measured at follow-up between patients who underwent therapy withdrawal and did, and did not relapse was 10.4bpm (95% CI 4.0–16.8; p=0.002) (Figure 1 & Table 1).

**Conclusion(s):** A larger increase in HR may be a simple and effective marker of relapse for patients with recovered DCM who have insisted on a trial of therapy withdrawal. Whether HR control is crucial to the maintenance of remission amongst patients with improved cardiac function, or is simply a marker of deteriorating cardiac function, warrants further investigation.

Figure 1: Mean heart rate and 95% CI over follow-up by group

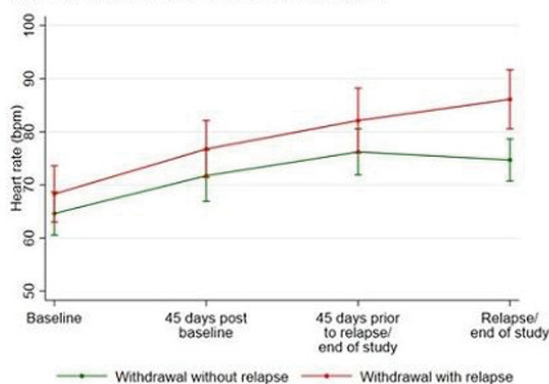


Table 1: Mean heart rate and mean change in heart rate from baseline over follow-up for withdrawal patients by relapse status

	Withdrawal without relapse		Withdrawal with relapse		Mean difference between groups	P <sup>1</sup>
	N	Mean heart rate (95% CI)	Change from baseline	Mean heart rate (95% CI)		
Baseline	49	64.6 (60.5, 68.7)		68.3 (63.0, 73.6)		
45 days post baseline	47 <sup>2</sup>	71.7 (66.9, 76.5)	7.1 (2.9, 11.3)	76.8 (71.4, 82.1)	6.2 (1.8, 10.5)	
45 days prior to relapse/end of study	47 <sup>2</sup>	76.2 (71.9, 80.5)	11.6 (7.8, 15.3)	82.1 (76.0, 88.2)	12.3 (6.9, 17.8)	
Relapse/end of study	49	74.7 (70.7, 78.7)	10.1 (5.6, 14.5)	86.1 (80.6, 91.6)	10.4 (4.0, 16.8)	0.002

<sup>1</sup> Using ANCOVA adjusting for baseline heart rate

<sup>2</sup> Two patients relapsed prior to 45 days