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TRED-HF: safe to withdraw HF treatment in recovered DCM?

Adil Mahmood MBBS BSc(Hons) MRCP(UK) AFHEA

NIHR Academic Clinical Fellow

Cardiology Specialist Registrar

Queen Mary University of London

Barts Health NHS Trust

Introduction

Dilated cardiomyopathy (DCM) is a disease in which the chambers of the heart enlarge, characterised by left ventricular (LV) dilatation and systolic dysfunction. Many of these patients show an improvement in LV function and clinical outcomes during the course of their disease (1), as has also been observed in other cases of heart failure with reduced ejection fraction (HFrEF) following initial presentation (2-4). Anecdotally, such patients may at times be disinclined to taking medications due to various reasons such as poor compliance, side-effects, hypotension and pregnancy planning. The logical question then arises for those individuals with DCM whose symptoms and LV function have subsequently recovered on pharmacological therapy, is it necessary to continue prognostic medications in the long-term?

Take Home Messages

- Patients with dilated cardiomyopathy (DCM) who are asymptomatic and have recovered left ventricular (LV) function frequently question if they need to continue their heart failure (HF) medications, however little is known about the safety of treatment cessation in this setting.
- The TRED-HF trial examined the effect of withdrawal of HF medications in patients diagnosed with DCM who had recovered their LV function.
- The study found discontinuation of pharmacological therapy in patients with recovered DCM led to relapse of HF.
- Further studies are warranted to delineate predictors of relapse in this patient population which may help to identify those individuals in whom treatment withdrawal can be safely achieved.

TRED-HF trial

The TRED-HF trial was an open-label, randomised clinical trial with a follow-on single-arm crossover phase assessing the effect of withdrawal of heart failure (HF) medications in patients with a prior diagnosis of DCM who had subsequent recovery in LV function (defined as LV ejection fraction (LVEF) >50% and normal LV end-diastolic volume indexed to body surface area (LVEDVi) on cardiovascular magnetic resonance (CMR), N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) <250 ng/L, and New York Heart Association class I symptoms) on treatment with a loop diuretic, mineralocorticoid receptor antagonist (MRA), beta-blocker, angiotensin converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB), or a combination of these drugs (5). Exclusion criteria included at least moderate valvular disease, angina, arrhythmias requiring beta-blockade, uncontrolled hypertension, estimated glomerular filtration rate less than 30 mL/min per 1.73 m^2, pregnancy and age younger than 16 years.

Patients were recruited from identification centres across the UK and underwent comprehensive assessment at the trial centre. 51 patients were randomly assigned to either withdrawal of HF treatment (n = 25) or continuation of medications (n = 26) with a 1:1 allocation. Treatment withdrawal was conducted in a supervised, stepwise manner where patients firstly stopped or reduced the dose of loop diuretic, followed by MRA, beta-blocker, and then ACE inhibitor or ARB. Patients were reviewed every 2 weeks and medication changes were made after each review. Baseline characteristics were generally similar between the two groups (**Table 1**). After 6 months, patients in the continued medication group crossed over to medication withdrawal using the same method. The primary outcome was relapse of HF within a 6-month period (defined as reduction in LVEF of more than 10% to less than 50%, increase in LVEDV by more than 10% to above normal range, two-fold increase in NT-pro-BNP to greater than 400 ng/L, or clinical symptoms of heart failure), at which point medications were recommenced. These cut-offs prioritised patient safety, allowing for the early detection of deterioration and restarting of treatment prior to decompensation.

Table 1. Baseline characteristics of patients

	Treatment withdrawal group (n=25)	**Continued treatment group (n=26)**
Demographics		
Median age, years	54 (46 to 64)	56 (45 to 64)
Men	16 (64%)	18 (69%)
Previous cardiovascular history		
Time since initial DCM diagnosis, months	63 (36 to 112)	41 (20 to 91)
LVEF at initial diagnosis	28% (20 to 33)	25% (19 to 33)
Absolute improvement in LVEF	29% (23 to 36)	30% (25 to 38)
Time since LVEF >50%, months	28 (8 to 45)	20 (6 to 44)
Previous unplanned heart failure admission	18 (72%)	14 (54%)
Previous excess alcohol consumption	8 (32%)	9 (35%)
Previous atrial fibrillation	8 (32%)	4 (15%)
Previous hypertension	3 (12%)	1 (4%)
Diabetes	0 (0%)	1 (4%)
Smoker	0 (0%)	3 (12%)
Cause		
Idiopathic	20 (80%)	15 (58%)
Familial	3 (12%)	4 (15%)
Environmental insult	2 (8%)	7 (27%)
Truncating variant in *TTN*	7 (28%)	4 (15%)
Medications at enrolment		
ACE inhibitor or ARB	25 (100%)	26 (100%)
Beta-blocker	21 (84%)	24 (92%)
Mineralocorticoid receptor antagonist	12 (48%)	12 (46%)
Loop diuretic	3 (12%)	3 (12%)
Clinical characteristics at enrolment		

Table 1. Baseline characteristics of patients		
	Treatment withdrawal group (n=25)	**Continued treatment group (n=26)**
Body surface area, m^2	2·1 (1·7 to 2·3)	2·0 (1·8 to 2·2)
Heart rate, bpm	62 (58 to 74)	70 (60 to 75)
Systolic blood pressure, mmHg	123 (117 to 133)	127 (117 to 134)
Diastolic blood pressure, mmHg	72 (68 to 80)	76 (70 to 80)
Left bundle branch block	3 (12%)	4 (15%)
QRS duration, ms	98 (85 to 108)	94 (88 to 111)
NT-pro-BNP, ng/L	72 (44 to 147)	75 (37 to 133)

Adapted from TRED-HF (5). Data are median (IQR) or n (%). (Abbreviations) ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; bpm, beats per min; DCM, dilated cardiomyopathy; LVEF, left ventricular ejection fraction; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

The study found that the primary outcome of relapse was met by 44% of patients in the treatment discontinuation group vs. 0% of those in the treatment continuation group ([95% confidence interval 28.5–67.2]; p=0.0001). Furthermore, 96% of patients in the treatment continuation group underwent treatment withdrawal following 6 months, of which relapse occurred in 36% [95% confidence interval 20.6-57.8]. There were no deaths in either group and 3 patients developed atrial fibrillation during treatment withdrawal.

Analysis

The authors are to be commended for their research that aimed to address a novel and thought-provoking question. The study explored the safety and efficacy of HF treatment withdrawal in patients with DCM who had recovered LV function, highlighting some key findings. Although a significant number of patients relapsed following treatment withdrawal, there were a proportion who did not. This suggests patients whose ventricular function has restored can be categorised into those with LV dysfunction in remission (i.e. those who relapsed) vs. recovery (i.e. those who did not relapse).

A possible hypothesis is that patients with ventricular dysfunction in "remission" are likely to have abnormal myocardial contractility (e.g. impaired strain metrics) compared to those in "recovery" whose cardiac mechanics may have normalised. Indeed, studies have demonstrated abnormalities in strain measures in patients whose LV function has returned to normal who remain at risk of relapse despite ongoing HF medication use (6). Counterintuitively, when assessed using CMR feature-tracking, the majority of patients in the study had normal strain metrics. A possible explanation for this is the lack of standardisation of strain measurements, with a greater number of values within the normal range being described when using CMR feature-tracking (7). In addition to validating CMR measures of strain, the ability to detect recovery of LV function may improve through a deeper understanding of processes at the molecular level that are implicated in excitation-contraction coupling (8) and T-tubule function (9).

There are some limitations of the TRED-HF trial. These include the small sample size of patients with DCM, its unblinded design and that it was a single-centre study. Moreover, patients were not medically optimised by current standards given both angiotensin receptor-neprilysin inhibitors and sodium-glucose co-transporter 2 inhibitors were not assessed. The results of this

study suggest that HF medications should be continued indefinitely in patients with DCM whose LV function has normalised until predictors of relapse have been identified, which should be a focus of future work in the field.

Conclusions

In conclusion, results from the TRED-HF trial indicate HF medications should not be completely withdrawn in individuals with recovered DCM given almost half of the patients in the study went into relapse. Future research should be aimed at differentiating patients who have permanently recovered from ventricular dysfunction from those with temporary restoration of cardiac function, as this represents a patient population wherein the discontinuation of some or all HF medications may be safely achieved.

Disclosures

No disclosures to declare.

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