Guide to Drug Withdrawal in HFrecEF

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HF Update

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Disclosures

- AHA Strategically Focused Research Network
- ESC Young Investigator Research Grant
- Bayer-Vascular Canadian Cardiovascular Society grant
- Roche Diagnostics
- Takeda
- BMS-Pfizer
- B.I-CVCT Fellow
- Boeringer-Ingelhiem
- Novartis

Agenda

- Define HF with recovered EF
- Objectives for drug withdrawl
- Indications to withdraw HF therapies
- Strategies and followup
- Q + A

Summary

- Very limited data on therapy withdrawl
- In general, even with HFimpEF with GDMT, there is high risk of relapse
- Current evidence suggests high risk of relapse in people with stable HFimpEF with HF therapies are withdrawn
- If need to withdraw (pregnancy, side-effects), can consider a step-wise approach with serial imaging and follow-up

HF With “Recovered” EF

Consensus Statement

Universal Definition and Classification of Heart Failure

A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

Endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association

JCF; P387-413, APRIL 01, 2021

HF With “Recovered” EF

- Guideline directed medical and device (CRT) therapy may improve LVEF and possibly induce reverse remodeling in patients with HFrEF
- Possibly there may be improvements in LVEF when the stimuli inducing the HFrEF has been removed
  - Tachycardia
  - ETOH/Toxin
  - Peripartum

HF With “Recovered” EF

- No consensus definition for patients with HFrEF whose LVEF ‘improves’
- Variety of terms: “improved” LVEF, HFpEF (borderline), HFpEF, and HF with recovered EF (HFrecEF)

HF With “Recovered” EF

- HFrecEF: baseline LVEF of ≤40%, a ≥10% increase from baseline LVEF, and a second measurement in the LVEF of >40%.

- Recovered HF: persistent resolution of HF symptoms and signs, *normalization of cardiac structure, function, and biomarker profile* after resolution and treatment of a fully reversible cause

JACC; 11 August 2020, Pages 719-734

HF with ‘Improved’ EF

- As we will see, in many cases, withdrawl of therapy in people with “recovered” EF leads to clinical deterioration, hence the underlying cardiomyopathy has not “recovered”
- **HF with improved EF (HFimpEF):** HF with a baseline LVEF of ≤40%, a ≥10-point increase from baseline LVEF, and a second measurement of LVEF of >40%.
- LVEF of 41% to 49% who have an improved LVEF to ≥50% may be categorized as HF with “improved” EF

HFimpEF – Evidence for Therapy Withdrawl

- Not a ton of data out there!
- With improved (or recovered), there is both improvement of ejection fraction AND reverse remodeling of the LV -> implies movement of LV volume from abnormal range to normal range
- Improved EF does not mean that the underlying cardiomyopathy is in ‘remission’ or is ‘cured’

Etiolo

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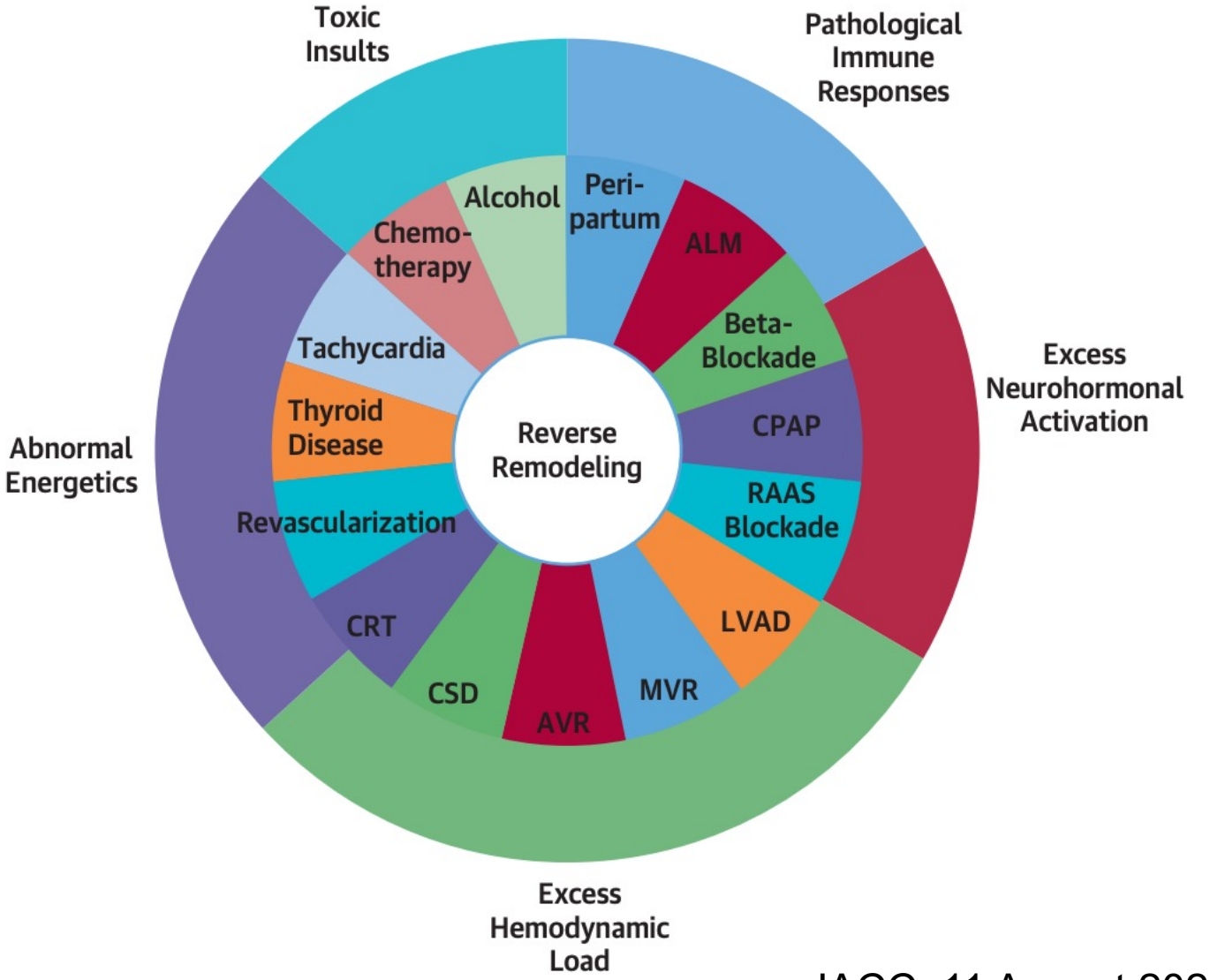

JACC; 11 August 2020, Pages 719-734

Etiology Matters

- Highest rates of recovery of LV function: amelioration of adverse metabolic or energetic circumstances
  - chronic tachycardia, hyperthyroidism, and hypothyroidism

Etiology Matters

- The 2nd recovery of LV function: have been associated with dilated cardiomyopathies - immune responses
  - Peripartum cardiomyopathy, acute lymphocytic myocarditis, and the systemic inflammatory response syndrome.

Etiology Matters

- Recovery of LV function has also been associated with the discontinuation of cardiotoxins:
  - ethanol and cancer chemotherapies - anthracyclines, tyrosine kinase inhibitors, and monoclonal antibodies

Factors with EF Improvement

TABLE 2 Predicting Reverse LV Remodeling Among Patients With HFrEF

	Predictors of Reverse LV Remodeling
Clinical parameters	Nonischemic etiology Lower duration of HF Female No LBBB LBBB in CRT
Genetic factors	Pathogenic gene variants not involving structural cytoskeletal proteins or Z-disk proteins
Echocardiography/CMR imaging	Lower LVEF, greater contractility on strain imaging Greater LV diameters LGE absence
Biomarkers	Lower NT-proBNP Lower troponin Lower sST2 Galectin-3, emerging biomarkers (mimecan, microRNAs, orexin)

Modified with permission from Aimo et al. (58).

CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with a reduced ejection fraction; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sST2 = soluble ST (suppression of tumorigenicity) 2.

JACC; 11 August 2020, Pages 719-734

Follow-up

TABLE 3 Recommended Interval Follow-Up for HFrecEF

Interval Follow-Up Time Period (After Meeting the HFrecEF Definition)	Clinical Examination and ECG	Holter Monitoring (24 h)	NT-pro BNP	Echocardiography With Mechanics (Strain)	CMR
Every 6 months (until 12–18 months of HFrecEF).	X		X	X	
After ~1 yr of "clinically stable" HFrecEF					X*
Every 6–12 months (at minimum).	X		X		
Optimal interval of echocardiography/imaging is unknown. It is reasonable clinical practice to assess durability every 1–3 yrs after stable recovery depending on etiology.				X	
Every 1–2 yrs for certain genetic cardiomyopathies at risk of atrial dysrhythmias (e.g., *TTN*).		X			

*Consider CMR if one was not performed at de novo diagnosis of HFrEF.

CMR = cardiac magnetic resonance; ECG = electrocardiogram; HFrecEF = heart failure with recovered ejection fraction; other abbreviations as in Table 2.

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Do I Need To Continue Taking All of These Medications?

Therapy Withdrawl

- Reverse LV remodeling and recovery of LV function are associated with improved clinical outcomes

- However: Among patients with HFimpEF with GDMT, 40% will develop recurrent LV dysfunction accompanied by recurrent HF events

Journal of the American Heart Association. ;4:e001504

Therapy Withdrawl

- Majority of clinical examples of spontaneous recovery of LV function associated with *durable clinical stability* occur after transient injury (e.g., energetic defects or myocardial toxins)

- Less likely to be clinically stable with HFimpEF with more “permanent injury” myocardial infarction, genetic abnormalities

Therapy Withdrawl

- Optimal clinical management of HFimpEF, remains unclear due to lack of robust prospective data
- Currently only one published trial of HF therapy withdrawl

Therapy Withdrawl

Articles

Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial

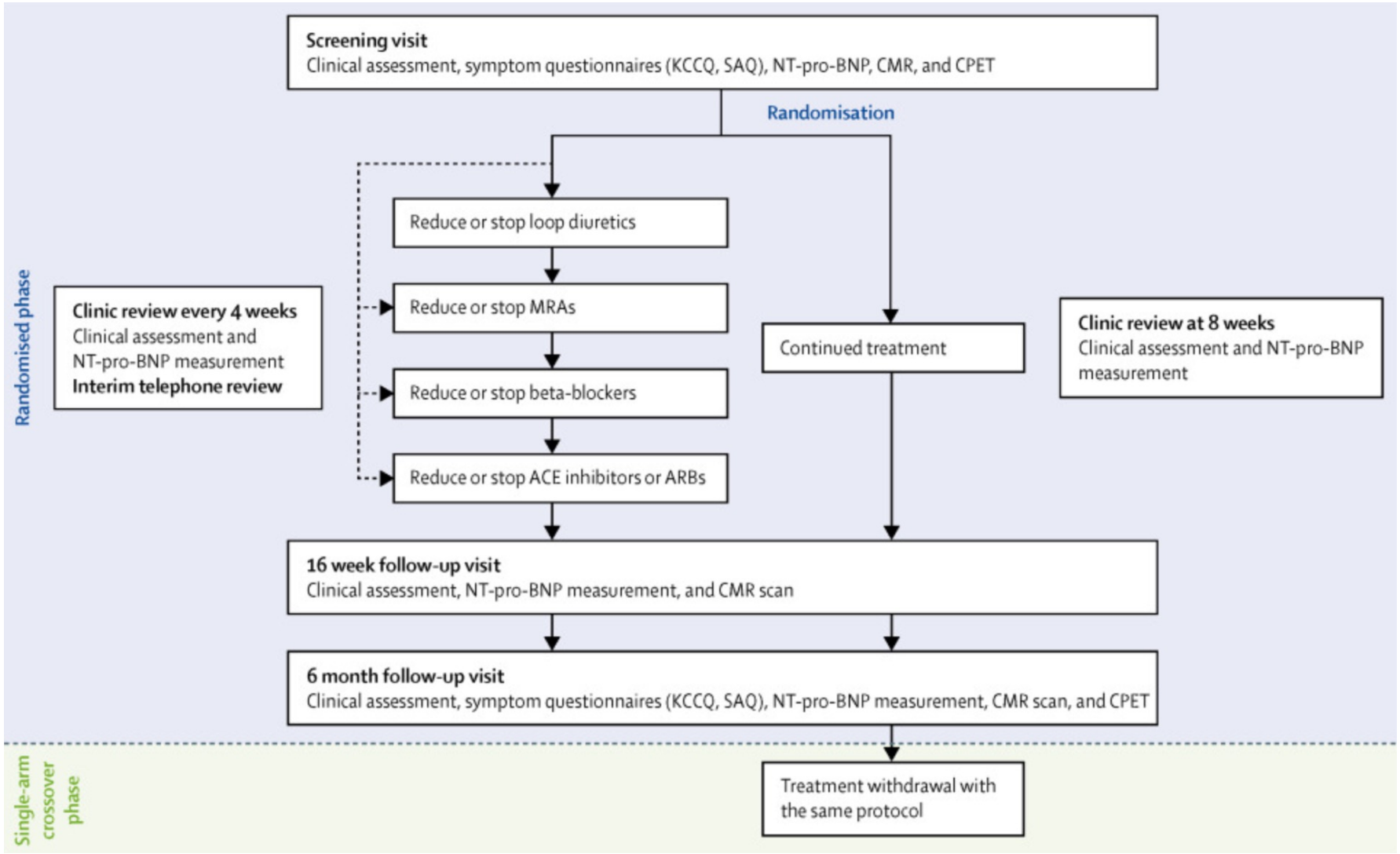
January 2019, Pages 61-73

TRED-HF: Inclusion

- Previous diagnosis of dilated cardiomyopathy with LVEF 40% or lower;
- Absence of current symptoms of heart failure; current treatment with a loop diuretic, ACEI/ARB, BB, MRA
- Current LVEF of 50% or greater and a left ventricular EDV indexed to body surface area (LVEDVi) within the normal range on cardiovascular magnetic resonance (CMR);
- NTproBNP concentration less than 250 ng/L.

TRED-HF: Primary Outcome

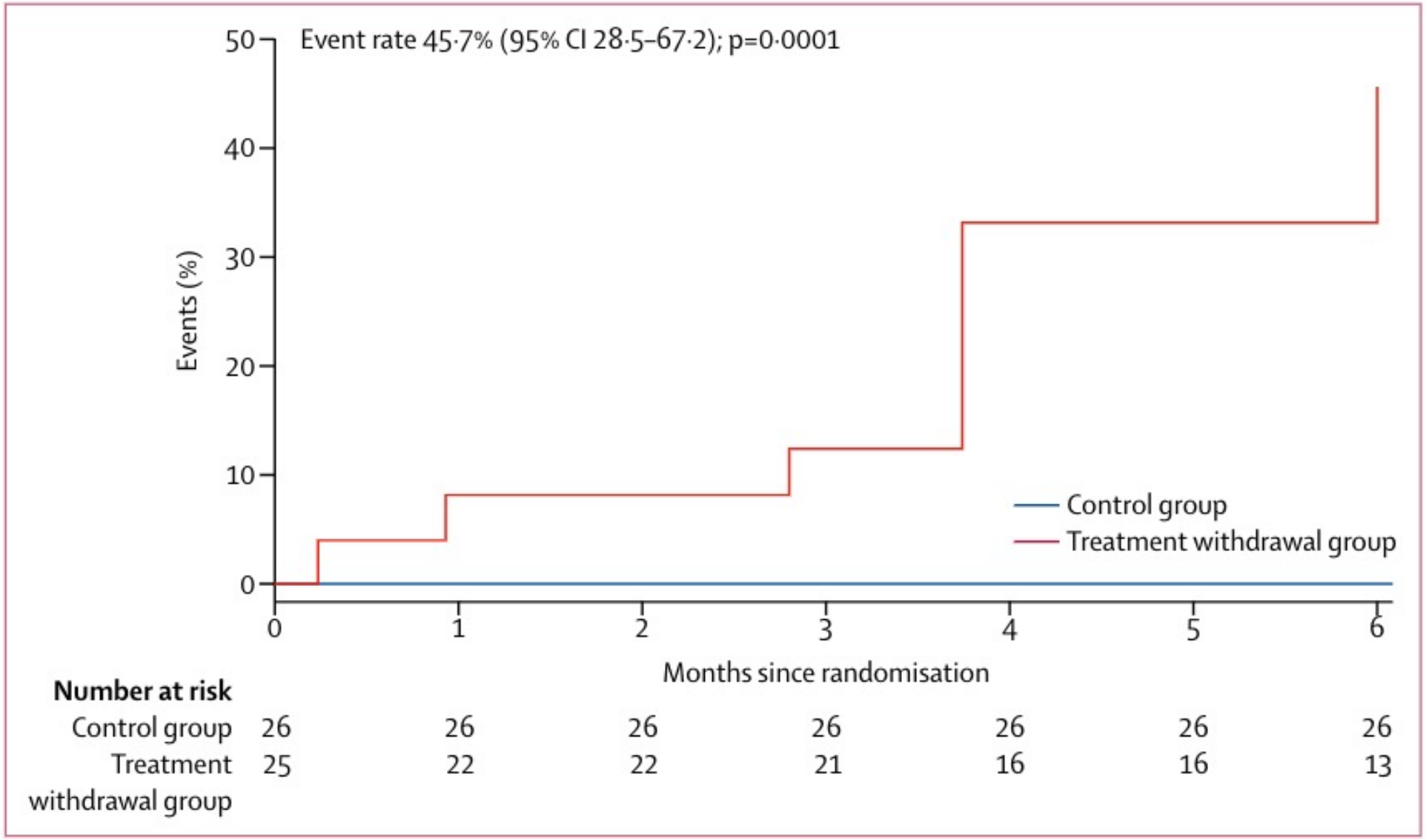
- Relapse of dilated cardiomyopathy within 6 months, defined by at least one of the following:
  - a reduction in LVEF by more than 10% and to less than 50%;
  - an increase in LVEDV by more than 10% and to higher than the normal range;
  - a two-fold rise in baseline NT-pro-BNP concentration and to more than 400 ng/L;
  - clinical evidence of heart failure, based on signs and symptoms as adjudicated by the research team


Screening visit
Clinical assessment, symptom questionnaires (KCCQ, SAQ), NT-pro-BNP, CMR, and CPET
Randomisation
Reduce or stop loop diuretics
Reduce or stop MRAs
Reduce or stop beta-blockers
Reduce or stop ACE inhibitors or ARBs
Clinic review every 4 weeks
Clinical assessment and
NT-pro-BNP measurement
Interim telephone review
Continued treatment
Clinic review at 8 weeks
Clinical assessment and NT-pro-BNP measurement
16 week follow-up visit
Clinical assessment, NT-pro-BNP measurement, and CMR scan
6 month follow-up visit
Clinical assessment, symptom questionnaires (KCCQ, SAQ), NT-pro-BNP measurement, CMR scan, and CPET
Treatment withdrawal with the same protocol
Randomised phase
Single-arm crossover phase

	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%)

Etiology

- 35 (69%) patients had idiopathic dilated cardio-myopathy
- Seven (14%) had familial dilated cardio-myopathy
- Nine (18%) had dilated cardiomyopathy secondary to a trigger including previous excess alcohol consumption, pregnancy, remote anthracycline administration, hyperthyroidism, and a previous episode of myocarditis.


Event rate 45·7% (95% CI 28·5–67·2); p=0·0001
Events (%)
50
40
30
20
10
0
0
1
2
3
4
5
6
Months since randomisation
Control group
Treatment withdrawal group
Number at risk
Control group 26 26 26 26 26 26 26
Treatment withdrawal group 25 22 22 21 16 16 13

TRED-HF

- Most patients relapsing within 8 weeks of their last medication
- 38% of the people with ”triggers” or ”reversible” causes of HF had relapse
- Improvement in cardiac function following treatment does not reflect full and sustained recovery but rather reflects remission, which requires at least some treatment to be maintained.
- ***Withdrawal of treatment should therefore not be attempted routinely in these patients.***

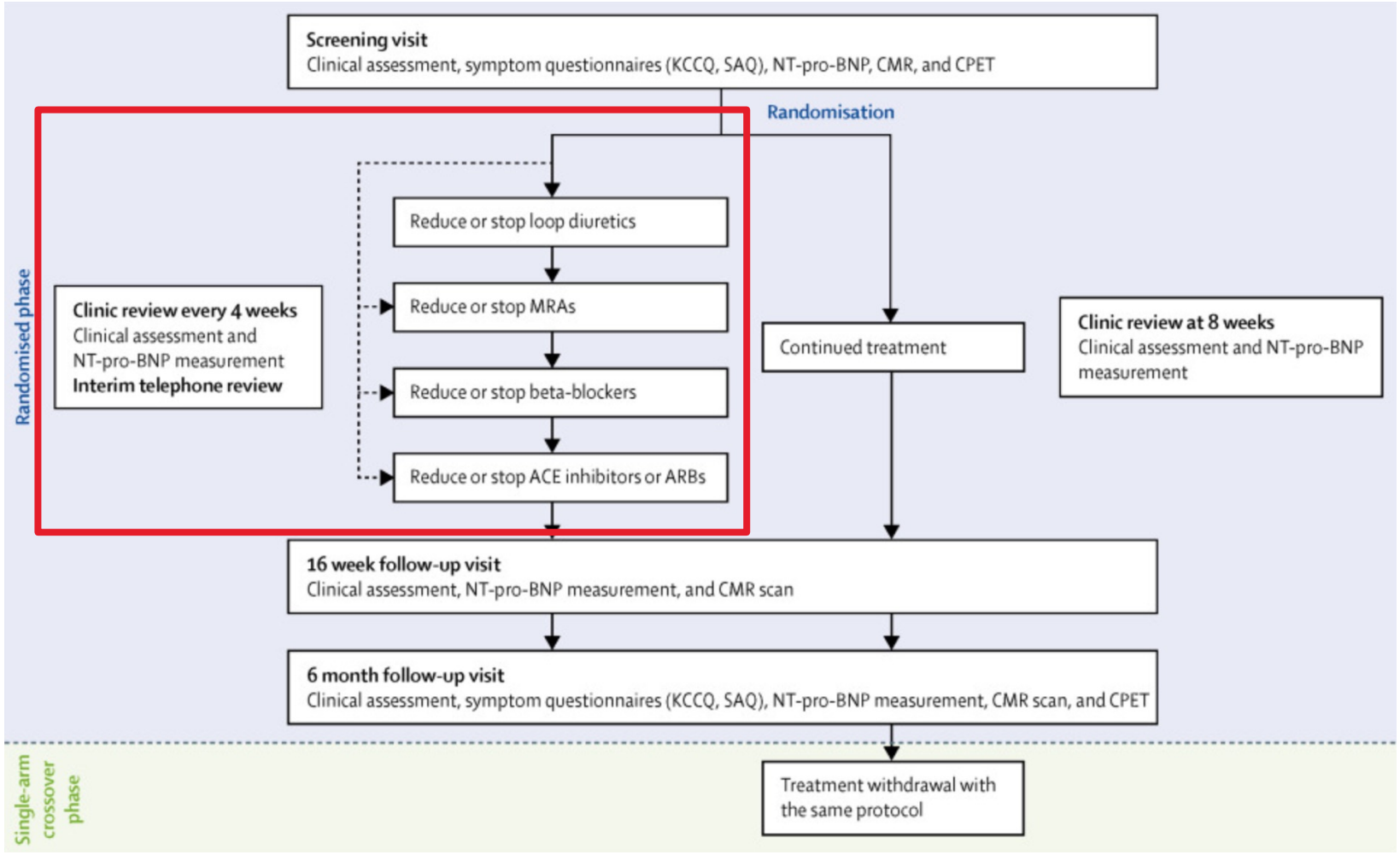
Consensus

- Guideline-directed medical and device therapy for patients with HFrecEF should be continued indefinitely until the biology and clinical epidemiology of HFrecEF is better understood

- HFrecEF patients should have close clinical follow-up due to the high risk of heart failure relapse

JACC; 11 August 2020, Pages 719-734

If You Really Need To….



If You Really Need To….

- Most common need to withdraw pregnancy, personal decision/choice, side-effects
- HF medications should be weaned in a stepwise fashion with frequent clinical assessment and echocardiographic monitoring of LVEF i.e., every 3 to 6 months
- Reassessment of LV function is advised after drug discontinuation followed by annual clinical and echocardiographic assessment.

J Am Coll Cardiol. 2020 Jan, 75 (2) 207–221

Summary

- Very limited data on therapy withdrawl
- In general, even with HFimpEF with GDMT, there is high risk of relapse
- Current evidence suggests high risk of relapse in people with stable HFimpEF with HF therapies are withdrawn
- If need to withdraw (pregnancy, side-effects), can consider a step-wise approach with serial imaging and follow-up

Thanks!