HEART FAILURE UPDATE 2022 / HYBRID

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Practically Starting and Stopping GDMT

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Emmanuelle Massie - Conflict of Interest Disclosures

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Learning Objectives

- Review the current paradigm for initiating GDMT in HFrEF
- Identify clinical scenarios which require cessation of GDMT
- Apply TRED-HF clinical trial data for real world practice

Review the current paradigm for initiating GDMT in HFrEF

Question 1

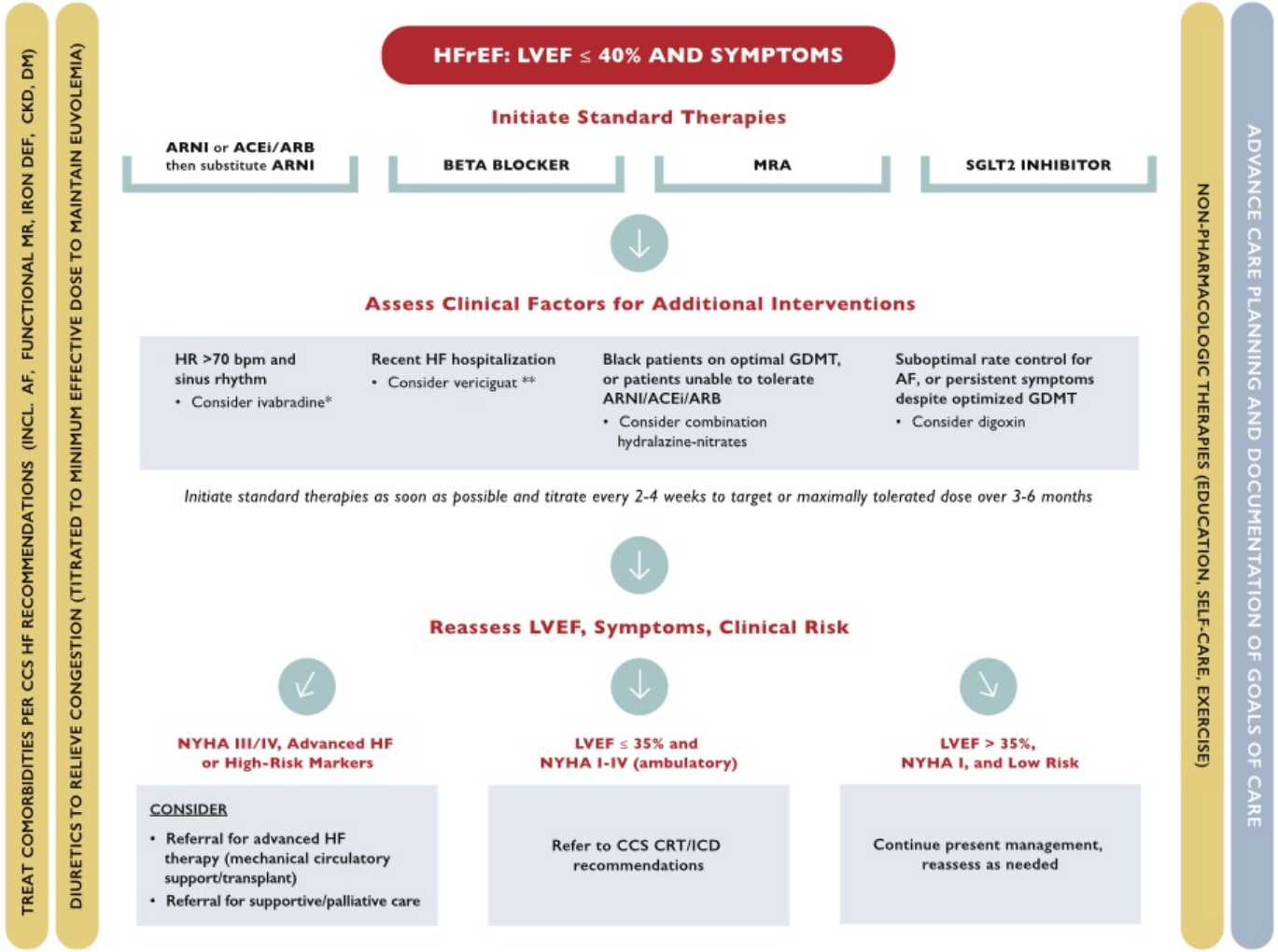
- **38F with no prior medical history, presenting with acute HF secondary to viral myocarditis.**
- **A TTE revealed a moderately dilated LV with diffuse systolic dysfunction (LVEF 15-20%) and moderate RV systolic dysfunction.**
- **Now that her HD status stabilized after a short course of inotropic support, her BP is 102/75 mmHg, HR 75 bpm, and her creatinine level is 73 µmol/l.**
- **Which of the 4 pillars of GDMT do you ideally initiate prior to discharge?**

- A – ACEI + BB
- B – ARNI + BB + MRA
- C – ACEI + BB + MRA + SGLT2i
- D – ARNI + BB + MRA + SGLT2i

Question 2

- **69M known for ischemic CMP with systolic dysfunction (LVEF 35-40%), CRT-D implanted 6 months ago. His current medical regimen for HF has been optimized in the last 4 weeks and include:**
- **Bisoprolol 2.5 mg PO daily**
- **Sacubitril-valsartan 51mg/49mg PO BID**
- **Eplerenone 25 mg PO daily**
- **Presents to the HF clinic for his regular follow-up visit with a function NYHA class II, BP 130/82 mmHg, HR 78 bpm, eGFR 39 mL/min/1.73 m2.**
- **What is the next best course of action to optimize his HF therapy?**

- A – Titrate bisoprolol, sacubitril-valsartan, eplerenone, and initiate an SGLT2i
- B – Titrate bisoprolol and initiate an SGLT2i
- C – Titrate bisoprolol, sacubitril-valsartan, and initiate SGLT2i
- D – Initiate an SGLT2i



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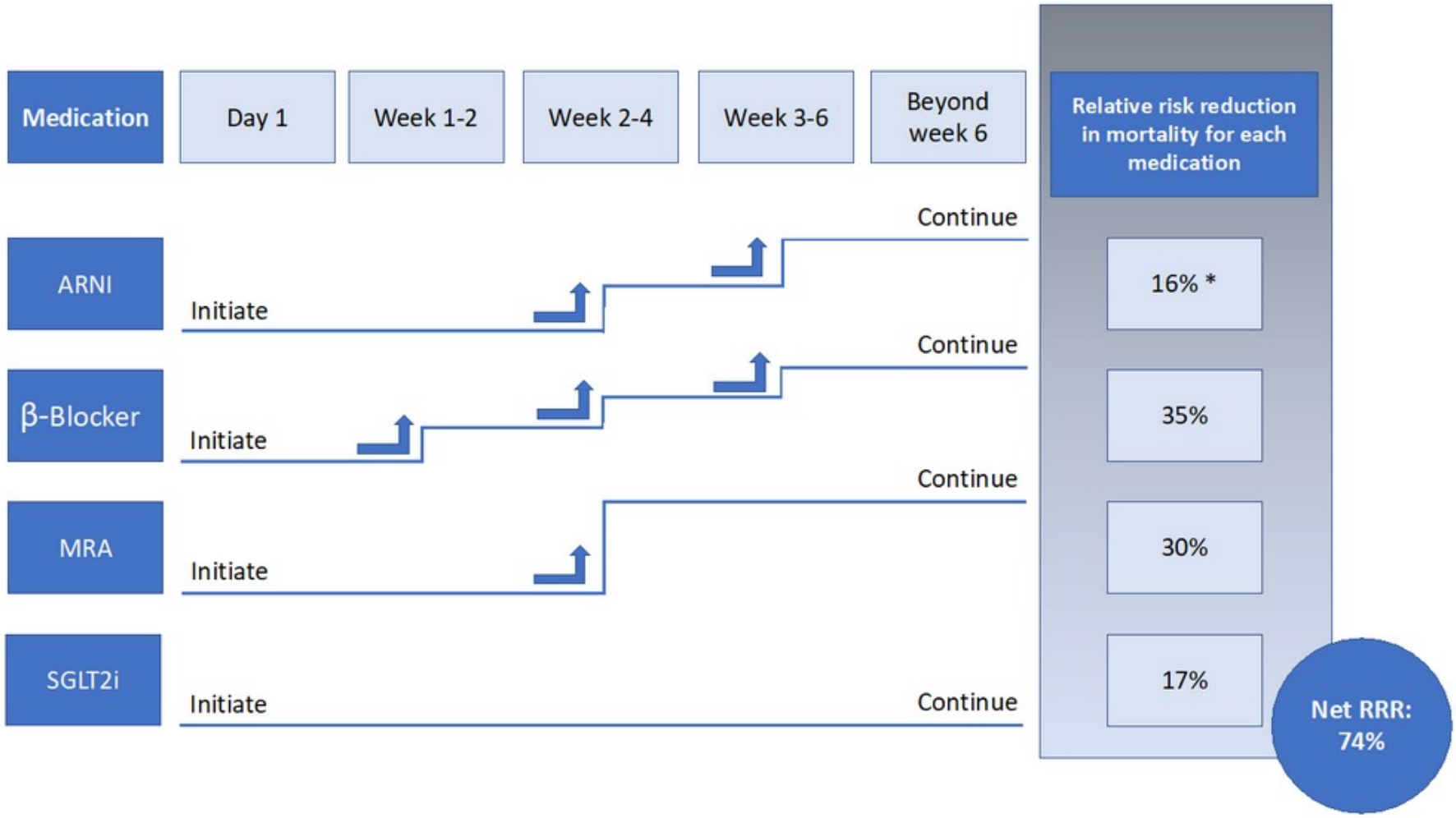

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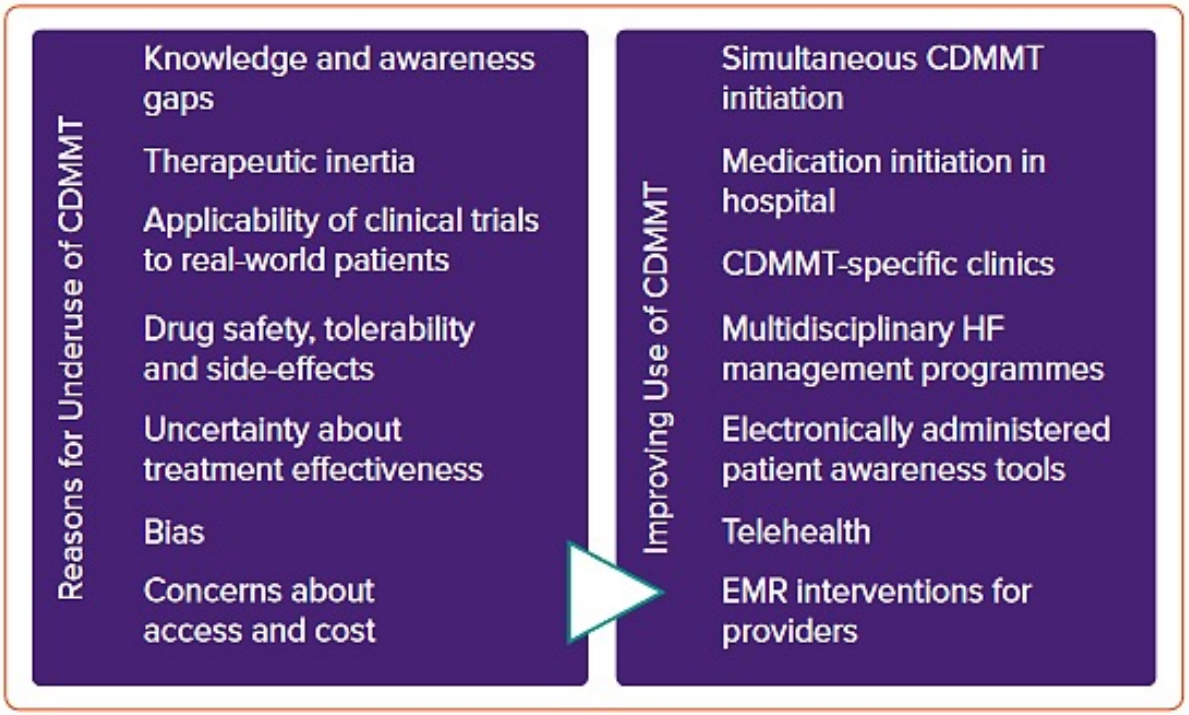

CDMMT = comprehensive disease-modifying medical therapy; EMR = electronic patient record. Source: Fonarow GC. GDMT implementation is challenging. Presented at: HFSA 2021 Annual Scientific Meeting, Denver, CO, US, 11 September 2021. Brownell NK, Ziaeian B, Fonarow GC. The gap to fill: rationale for rapid initiation and optimal titration of comprehensive disease-modifying medical therapy for heart failure with reduced ejection fraction. *Card Fail Rev* 2021;7:e18.

Table 3: Potential Starting Doses and Titration of Comprehensive Disease-modifying Medical Therapy

CDMMT	Starting Dose	Typical Titration Dose(s)	Final Dose	Monitoring Parameters
ACEI or ARB				
Captopril	6.25 mg three-times daily	12.5 mg three-times daily; 25 mg three-times daily	50 mg three-times daily	Monitor blood pressure, electrolytes and renal function Can titrate every 1–2 weeks in outpatients and every 1–2 days in hospitalised patients
Enalapril	2.5 mg twice daily	5 mg twice daily; 10 mg twice daily	10–20 mg twice daily	
Lisinopril	2.5–5 mg daily	10 mg daily; 20 mg daily	20–40 mg daily	
Ramipril	1.25 mg daily	2.5 mg daily; 5 mg daily	10 mg daily	
Candesartan	4-8 mg daily	16 mg daily	32 mg daily	
Losartan	25–50 mg daily	100 mg daily	150 mg daily	
Valsartan	40 mg twice daily	80 mg twice daily	160 mg twice daily	
ARNI				
Sacubitril/valsartan	24/26 mg twice daily	49/51 mg twice daily	97/103 mg twice daily	Monitoring same as ACEI or ARB Starting dose based on daily equivalent of ACEI
β-blocker				
Bisoprolol	1.25 mg daily	2.5 mg daily; 5 mg daily	10 mg daily	Initiate only in stable patients Monitor blood pressure, heart rate and for signs of congestion Can titrate every 2 weeks
Carvedilol	3.125 mg twice daily	6.25 mg twice daily; 12.5 mg twice daily	25 mg twice daily*	
Metoprolol succinate	12.5–25 mg daily	50 mg daily; 100 mg daily	200 mg daily	
MRA				
Eplerenone	25 mg daily	NA	50 mg daily	Monitor electrolytes and renal function. Avoid in eGFR ≥30 ml/min/1.73 m^2 or K^+ >5 mEq/l
Spironolactone	12.5–25 mg daily	NA	25–50 mg daily	
SGLT2i				
Dapagliflozin	10 mg daily	NA	10 mg daily	Dapagliflozin: Only if eGFR ≥30 ml/min/1.73 m^2
Empagliflozin	10 mg daily	NA	10 mg daily	Empagliflozin: Only if eGFR ≥20 ml/min/1.73 m^2

**Maximum dose of carvedilol is 50 mg twice daily for weight ≥85 kg. ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; eGFR = estimated glomerular filtration rate; K+ = potassium; SGLT2i = sodium glucose cotransporter 2 inhibitor. Source: Fonarow et al. 2021*[31,39]

Brownell NK, Ziaeian B, Fonarow GC. The gap to fill: rationale for rapid initiation and optimal titration of comprehensive disease-modifying medical therapy for heart failure with reduced ejection fraction. *Card Fail Rev* 2021;7:e18.

Identify clinical scenarios which require cessation of GDMT

Question 3

- **32F with prior history of peripartum CMP presents to clinic expressing her desire to get pregnant. Her last TTE showed recovered LVEF and LV volumes. She is NYHA functional class I with normal neurohormone levels. Her current medical regimen includes carvedilol 25 mg PO BID, enalapril 10 mg PO daily, and spironolactone 25 mg PO daily. What would be the best course of action?**

- A – Stop enalapril and spironolactone
- B – Stop carvedilol, enalapril, and spironolactone
- C – Add an SGLT2i
- D – Continue all her medication

Question 4

- **54H with history of alcohol-induced CMP, no alcohol use for the past year, recovered LVEF and LV volumes on his last TTE 1 month ago, normal neurohormones, NYHA functional class I. He is on optimal doses of GDMT. The patient wants to train for the Montreal Marathon and side effects from BB have consequences on his performance.**

  What course of action would you take?

- A – You withdraw BB as per the patient's preference.
- B – You reduce BB dosing to see if the side effects will be tolerable on a lower dose.
- C – You explain the risk of HF recurrence with therapy withdrawal, trying to advocate for GDMT continuation.

HF with “Recovered” EF

- No consensus definition for patients with HFrEF whose LVEF improves

HFrecEF

Persistent resolution of HF symptoms and signs, normalization of cardiac structure, function, and biomarker profile, after resolution and treatment of a fully reversible cause

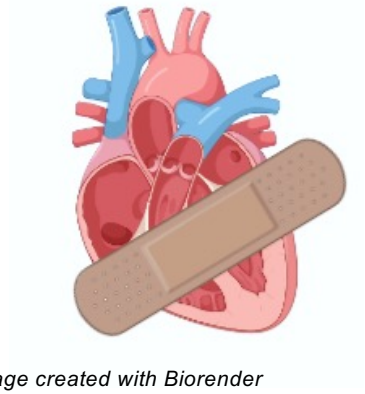

Image created with Biorender

“Reversible” HF

- There are clinical scenarios where improvement in LVEF may occur when the stimuli inducing the HFrEF has been removed

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Therapy withdrawal

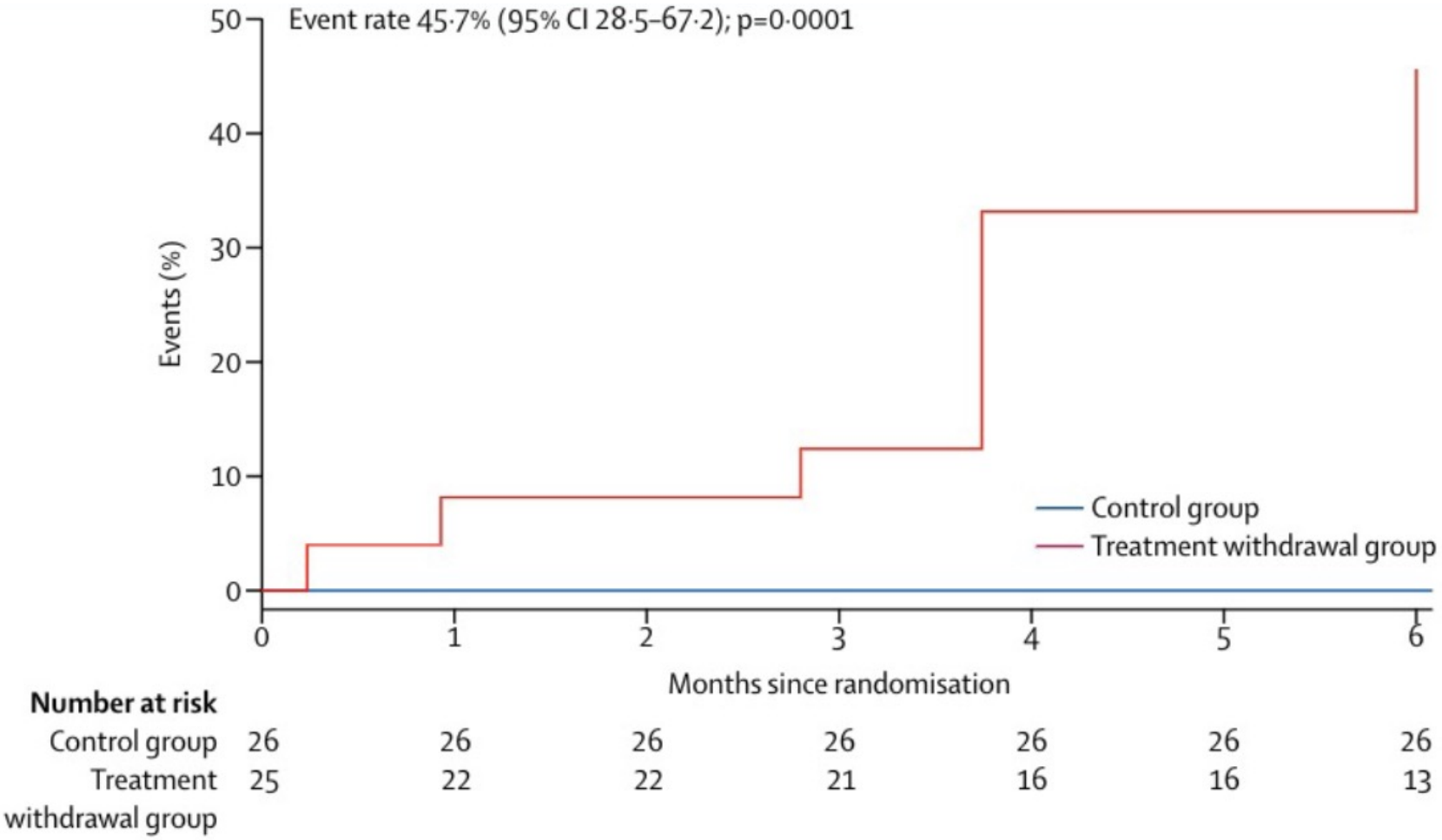
- Recovery of LV function → improved clinical outcomes
- However, among patients with improved LVEF with GDMT, **40% will develop recurrent LV dysfunction and recurrent HF events**
- Optimal clinical management of HFrecEF remains unclear due to lack of robust data

TRED-HF

- Therapy withdrawal in REcovered Dilated cardiomyopathy trial

In patients with dilated CMP whose symptoms and cardiac function recover, does withdrawing medications increase the likelihood for relapse at 6 months?

- Inclusion criteria:
  - Previous diagnosis of dilated CMP with LVEF ≤ 40%
  - Absence of HF symptoms
  - Current treatment with a loop diuretic, ACEI/ARB, BB, MRA
  - Current LVEF of 50% or greater and a LVEDVi within the normal range on CMR
  - NTproBNP < 250 ng/L



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Bottom line

- **Patients with dilated CMP whose function recovers with treatment are at increased risk of relapse at 6 months if treatment is withdrawn**

- Limited by generalizability, given large proportion of idiopathic or familial dilated CMP

Therapy withdrawal

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

- Most common reasons to withdraw:
  - Pregnancy
  - Side-effects
  - Personal decision/choice

- HF medication should be weaned in a stepwise fashion with frequent clinical assessments and echocardiographic monitoring of LVEF

Recommended Follow-Up for HFrecEF

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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Take-home messages

- ✓ Initiation of quadruple therapy should be simultaneous and titrated over a short period of time
- ✓ Very limited data on therapy withdrawal with associated high risk of HF relapse
- ✓ If required, withdrawal of GDMT should be done slowly in a stepwise fashion with close follow-up

Q&A Session

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