PIONEERing the initiation of sacubitril-valsartan in hospital

Marie-France Gauthier, BSc, PharmD, ACPR

Clinical Pharmacist at Montfort Hospital

Disclosures

- I have no current or past relationships with commercial entities

Abbreviations

ACEi: Angiotensin-converting enzyme inhibitor

ARB: Angiotensin receptor blocker

ARNI: Angiotensin receptor-neprilysin inhibitor

BB: Beta blocker

BNP: B-type natriuretic peptide

CrCl: Creatinine clearance

CV: Cardiovascular

GDMT: Guideline-directed medical therapy

HF: Heart failure

HFrEF: Heart failure with reduced ejection fraction

LVEF: Left ventricular ejection fraction

MRA: Mineralocorticoid receptor antagonist

NT-proBNP: N-terminal propeptide BNP

NYHA: New York Heart Association

SBP: Systolic blood pressure

SR: Sinus rhythm

Learning objectives

- Critically appraise the PIONEER-HF trial
- Reflect on implications to current practice
- *Critically appraise the DAPA-HF trial*

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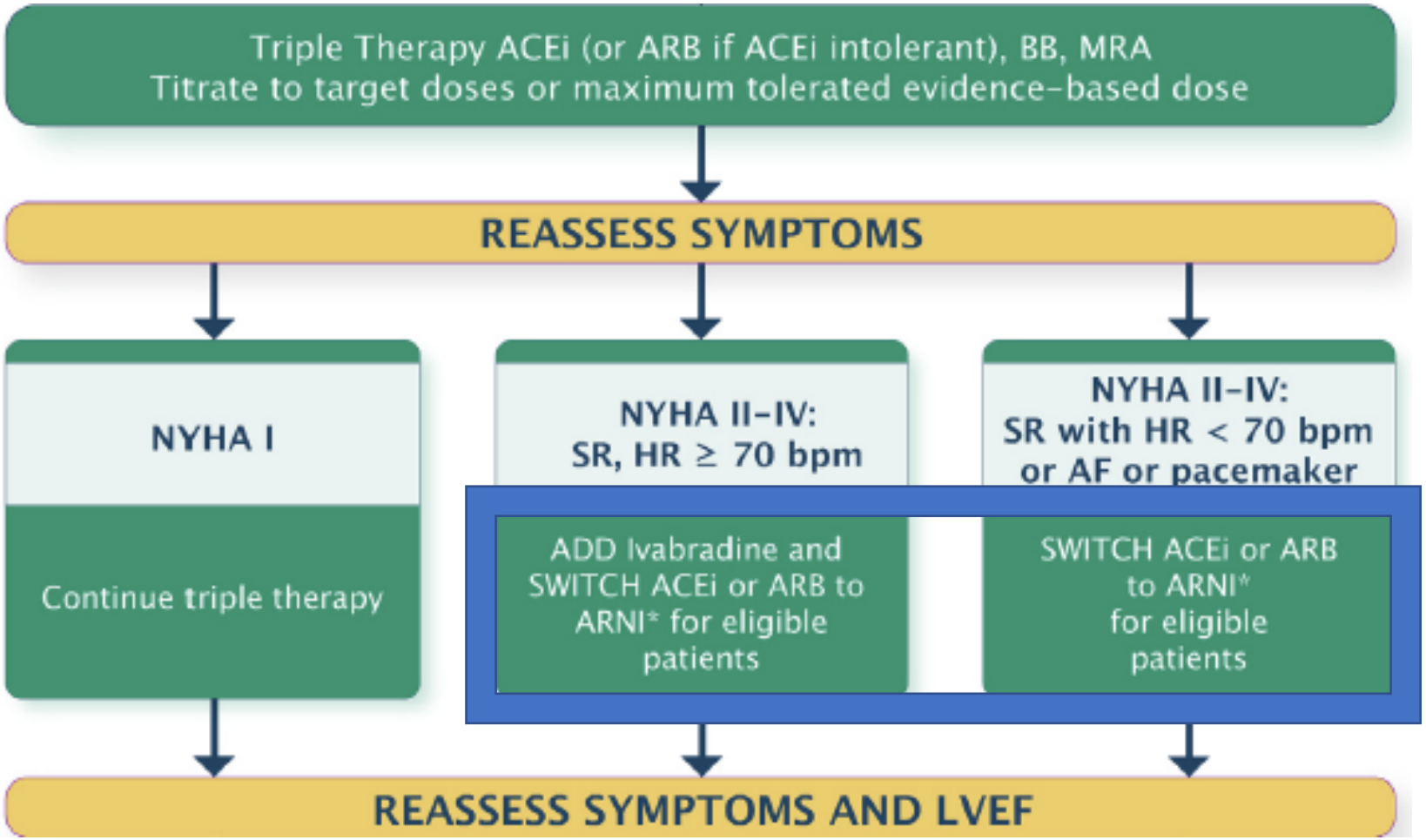
Society Guidelines

2017 Comprehensive Update of the Canadian Cardiovascular Society Guidelines for the Management of Heart Failure

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

Société canadienne de cardiologie
Communauté. Connaissances. Leadership.

Treatment of HF with reduced ejection fraction

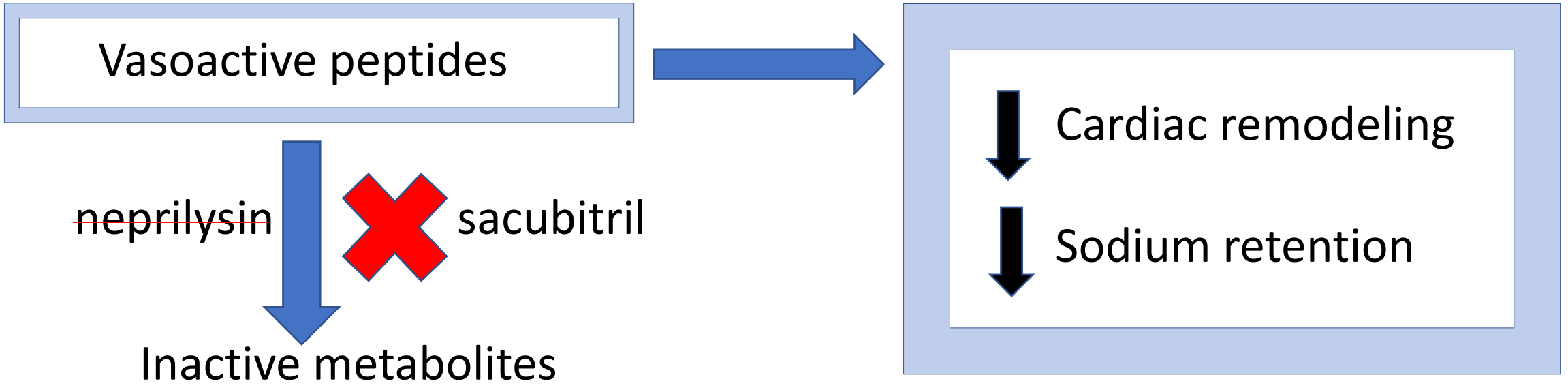


*** Do not combine ACEi + ARB**

NYHA: New York heart association, ARNI: angiotensin receptor-neprilysin inhibitor

Treatment of HF with reduced ejection fraction

- Sacubitril-valsartan (Entresto®)
- Dose: 50 mg bid, 100 mg bid, 200 mg bid
  - Double the dose q2-4 weeks until target
- Mechanism of action:



Treatment of HF with reduced ejection fraction

- PARADIGM-HF (2014)
  - CHFrEF (EF ≤ 40%)
  - Clinically stable (NYHA II-IV) on an ACEi or an ARB at baseline

Sacubitril-Valsartan

Enalapril

CV death, hospitalization for HF
HR 0.80, p < 0.001

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H., Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D., Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D., for the PIONEER-HF Investigators*

Treatment of HF with reduced ejection fraction

- PIONEER-HF (2019)

Population	EF ≤ 40%, elevated BNP, admitted with exacerbation
Intervention	Sacubitril-valsartan (up to 97/103 mg PO bid)
Comparator	Enalapril (up to 10 mg PO bid)
Outcome	Time-averaged proportional change in NT-proBNP over 8 weeks

- Hemodynamic instability (SBP < 100 mmHg, IV vasodilator, IV inotrope)
- eGFR < 30 mL/min or K > 5.2 mmol/L
- Angioedema related to previous ACEi or ARB

Treatment of HF with reduced ejection fraction

- PIONEER-HF (2019)

Baseline characteristics, N=881	
Age	62 years
Female	28%
Race	White: 58% ; Black: 36%
Systolic blood pressure	118 mmHg
NYHA functional class (%)	II: 25% ; III: 62%
Pretrial use of ACEi or ARB (%)	48%
Pre-trial use of beta blocker (%)	59%

Treatment of HF with reduced ejection fraction

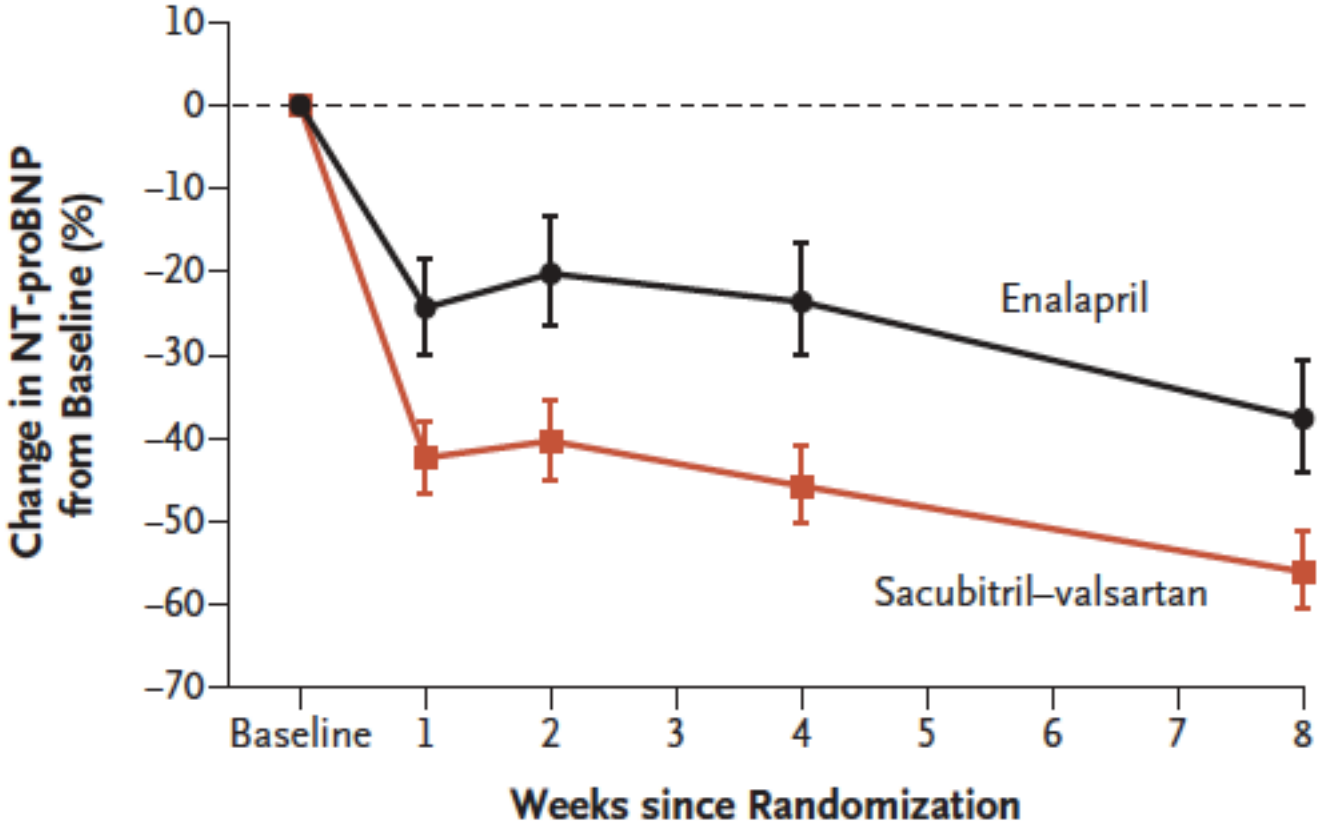
Primary outcome

Change in the NT-proBNP concentration

Ratio of change: 0.71

95% CI, 0.63 to 0.81, P<0.001

Percent change from baseline
sacubitril-valsartan: 46.7%
enalapril: 25.3%

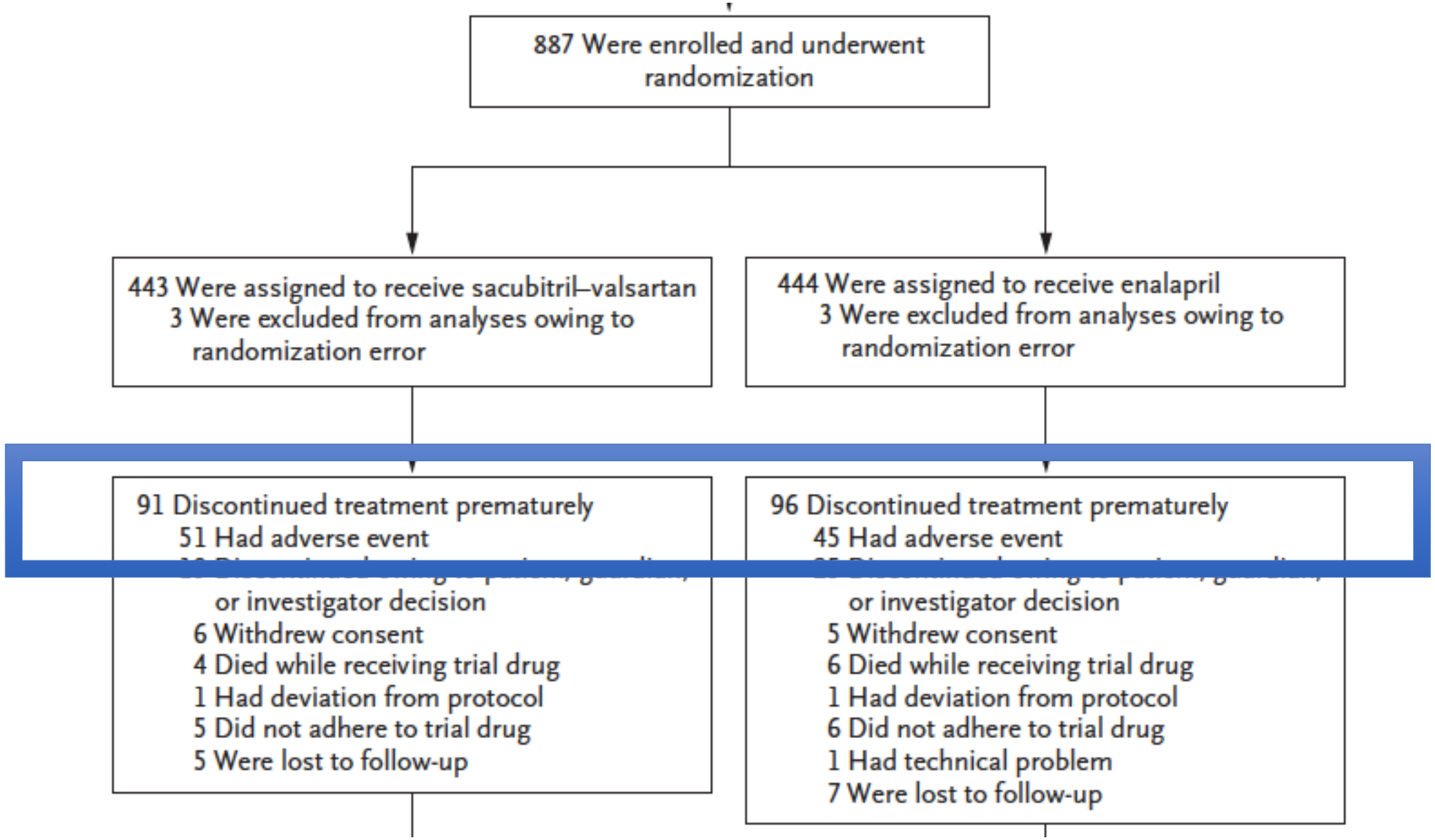


No. at Risk

Enalapril	394	359	351	350	348
Sacubitril–valsartan	397	355	363	365	349

Treatment of HF with reduced ejection fraction

Event	Sacubitril-valsartan (%) (N=440)	Enalapril (%) (N=441)	Relative risk
Worsening renal function	13.6	14.7	0.93 (NS)
Hyperkalemia	11.6	9.3	1.25 (NS)
Symptomatic hypotension	15	12.7	1.18 (NS)
Angioedema	0.2	1.4	0.17 (NS)


887 Were enrolled and underwent randomization
443 Were assigned to receive sacubitril–valsartan
3 Were excluded from analyses owing to randomization error
444 Were assigned to receive enalapril
3 Were excluded from analyses owing to randomization error
91 Discontinued treatment prematurely
51 Had adverse event
or investigator decision
6 Withdrew consent
4 Died while receiving trial drug
1 Had deviation from protocol
5 Did not adhere to trial drug
5 Were lost to follow-up
96 Discontinued treatment prematurely
45 Had adverse event
or investigator decision
5 Withdrew consent
6 Died while receiving trial drug
1 Had deviation from protocol
6 Did not adhere to trial drug
1 Had technical problem
7 Were lost to follow-up

Treatment of HF with reduced ejection fraction

- PIONEER-HF authors' conclusions (2019)

"Among patients with HFrEF who were hospitalized for acute decompensated HF, the initiation of sacubitril-valsartan led to a greater reduction in the NT-proBNP concentration than enalapril therapy.

Rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema did not differ significantly between the two groups."

Treatment of HF with reduced ejection fraction

Medication	Cost per tablet	Coverage by ODB
Entresto®	$ 3.70	√ LU 497

For the treatment of patients with CHF and:

- Reduced LVEF (less than 40%)
- NYHA class II-III symptoms despite at **least four weeks of treatment with a stable dose of an ACEi or ARB**
- In combination with a beta blocker and other recommended therapies, including an aldosterone antagonist (if tolerable).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

Treatment of HF with reduced ejection fraction

- DAPA-HF (2019)

Population	EF ≤ 40%, elevated BNP, class II-IV (N=4744)
Intervention	Dapagliflozin 10 mg daily
Comparator	Placebo
Outcome	CV death or worsening HF

- Symptomatic hypotension or SBP < 95 mmHg
- eGFR < 30 mL/min
- Type 1 diabetes

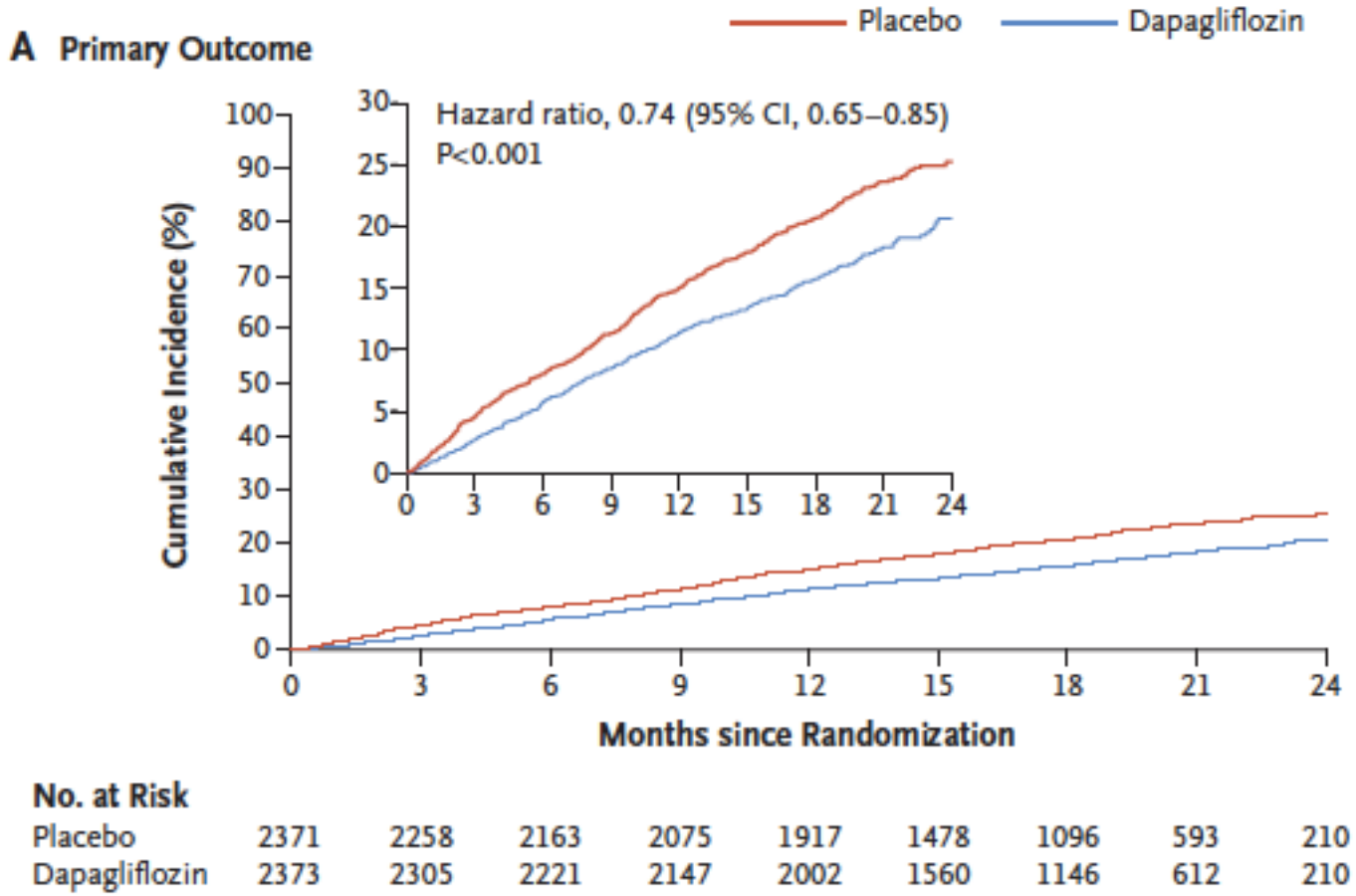
Treatment of HF with reduced ejection fraction

Primary outcome

CV death or worsening HF

Dapagliflozin: 16.3%
Placebo: 21.2%
(0.65-0.85, p < 0.001)

NNT = 21 over 18 months



Treatment of HF with reduced ejection fraction

Event	Dapagliflozin (%) (N=2373)	Placebo (%) (N=2371)	P value
Discontinuation due to adverse event	4.7	4.9	0.79
Volume depletion	7.5	6.8	0.4
Renal adverse event	6.5	7.2	0.36
Diabetic ketoacidosis	0.1	0	NA

Questions?

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