Insuffisance cardiaque : Prise en charge en 2020 et nouveautés

PD Dr Philippe Meyer
Responsable de l'unité d'insuffisance cardiaque et de réadaptation cardiaque
Service de Cardiologie
Philippe.meyer@hcuge.ch

Colloque médecine interne générale – 24.09.2020

Insuffisance cardiaque à FEVG diminuée : Prise en charge en 2020 et nouveautés

PD Dr Philippe Meyer
Responsable de l'unité d'insuffisance cardiaque et de réadaptation cardiaque
Service de Cardiologie
Philippe.meyer@hcuge.ch

Colloque médecine interne générale – 24.09.2020

Disclosure of potential Conflicts of Interest

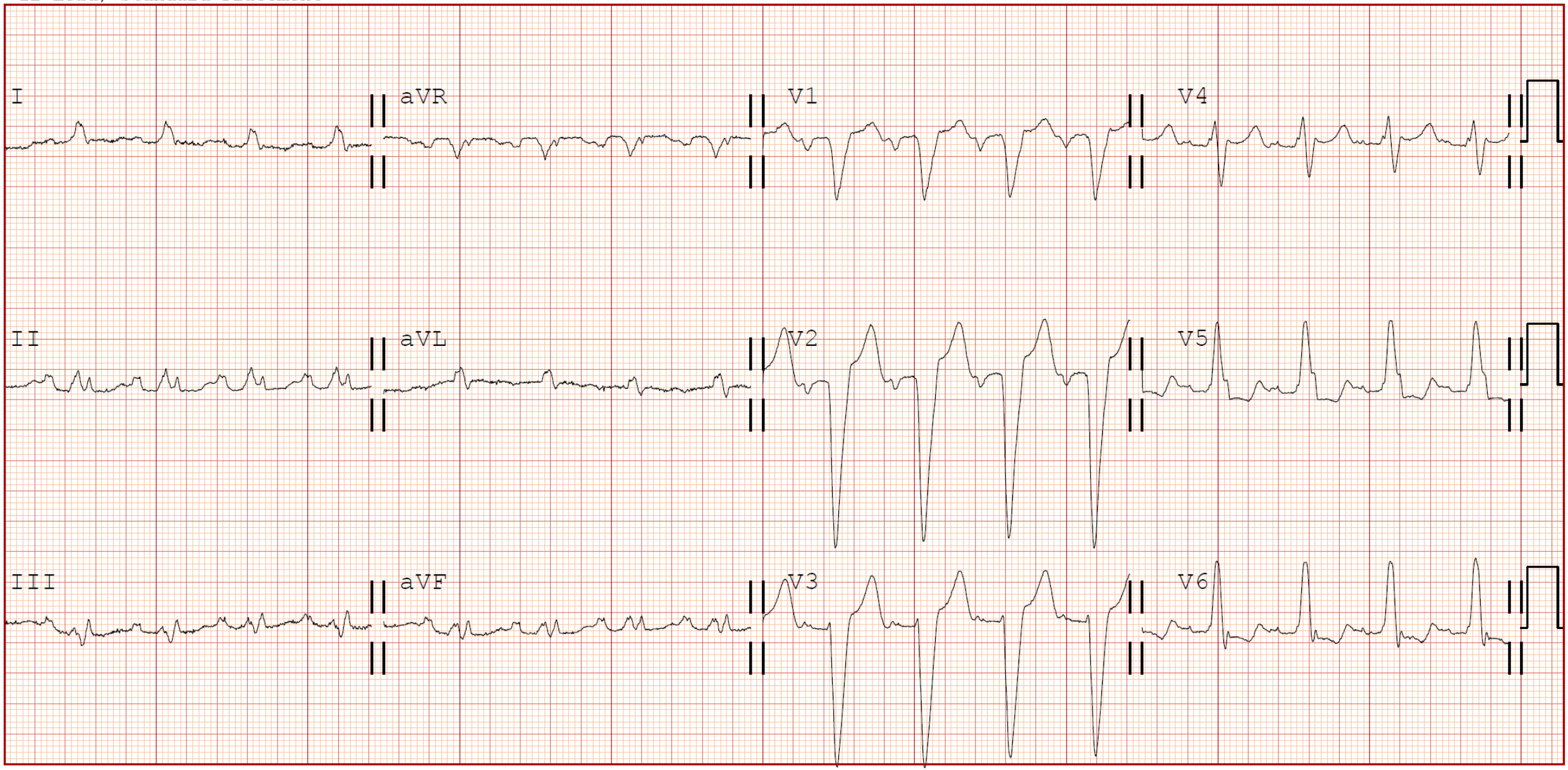
Participation in presentations/advisory boards organized by **Novartis**, **Servier** **Vifor, Bayer, Abbott, Boehringer Ingelheim**

- No personal fee
- All fees paid to a research foundation of the cardiology service (**GEcor**) since 2015

Clinical vignette: Mrs C. N. 1946 – Admission September 2017

Past medical history	• Retired nurse • Influenza infection 01.2017 • Inguinal hernia surgery 08.2017 • Chronic venous insufficiency, varices' surgery
History of present illness	• **Progressive dyspnea** in the last 3 months, currently NYHA class III/IV • **Swollen legs** for 2 weeks
Risk factors	• «Social drinker» (1 glass of wine/day) • Sedentary lifestyle
Medications	• None
Physical exam	• BP 112/81 mmHg. **HR 105** bpm. RR 18/min. **SaO_2: 89%** on room air • **Elevated JVP. Displaced apex beat. Mild pedal oedema. Bibasilar pulmonary rales** • Presence of **S3**, 2/6 apical **holosystolic murmur**

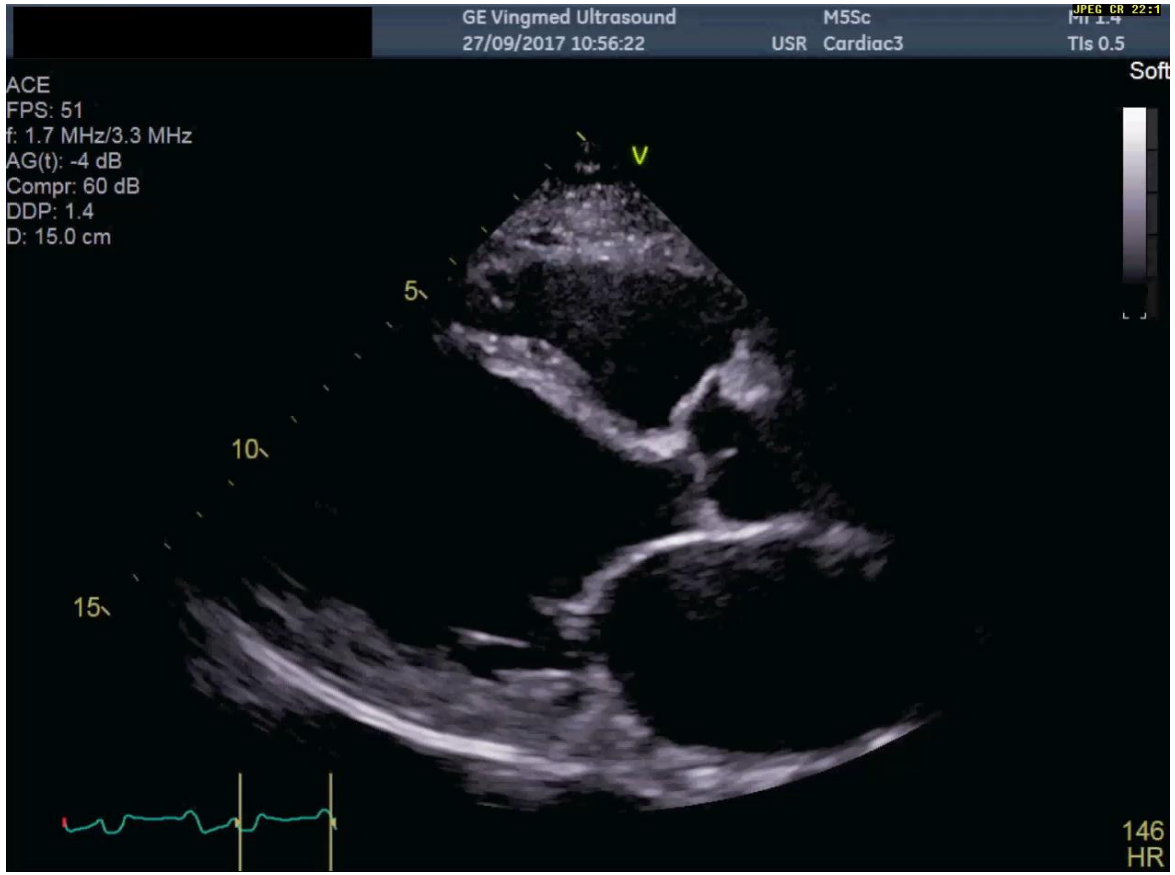
12 Lead; Standard Placement

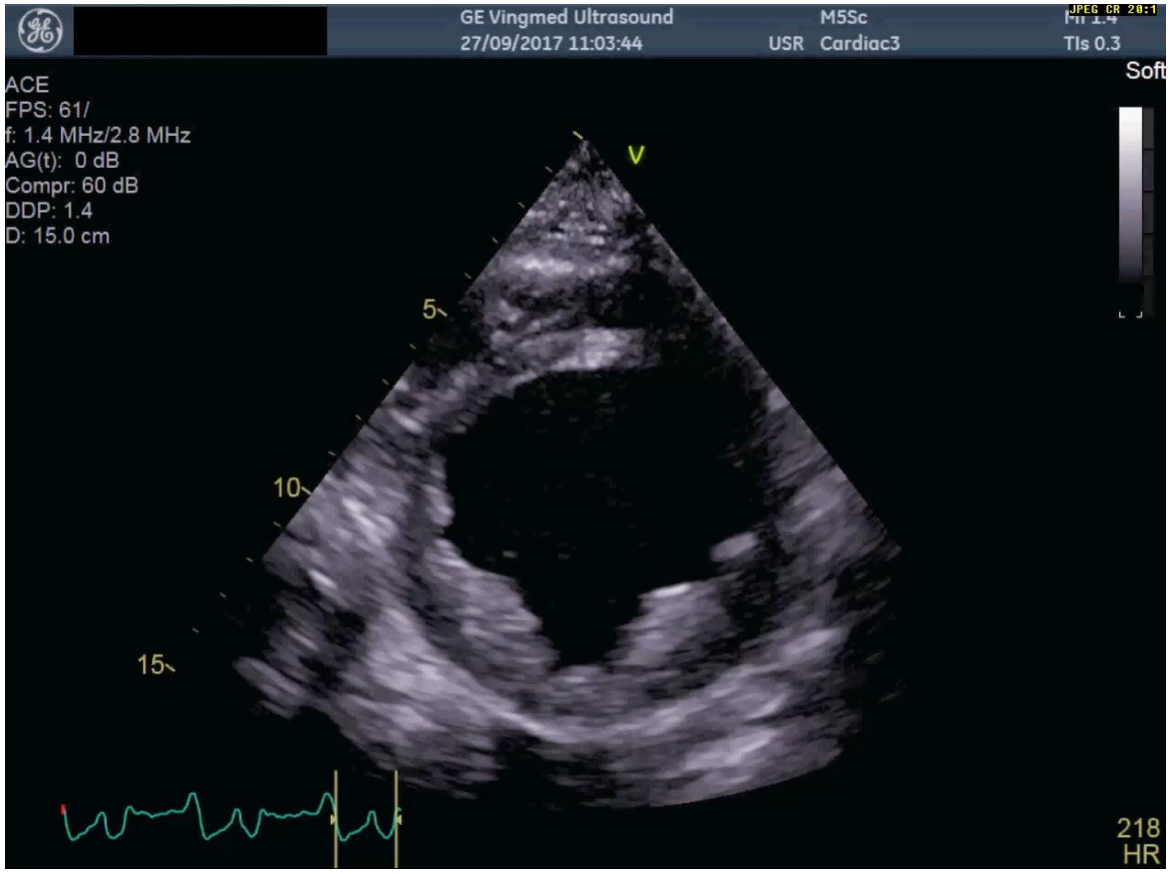


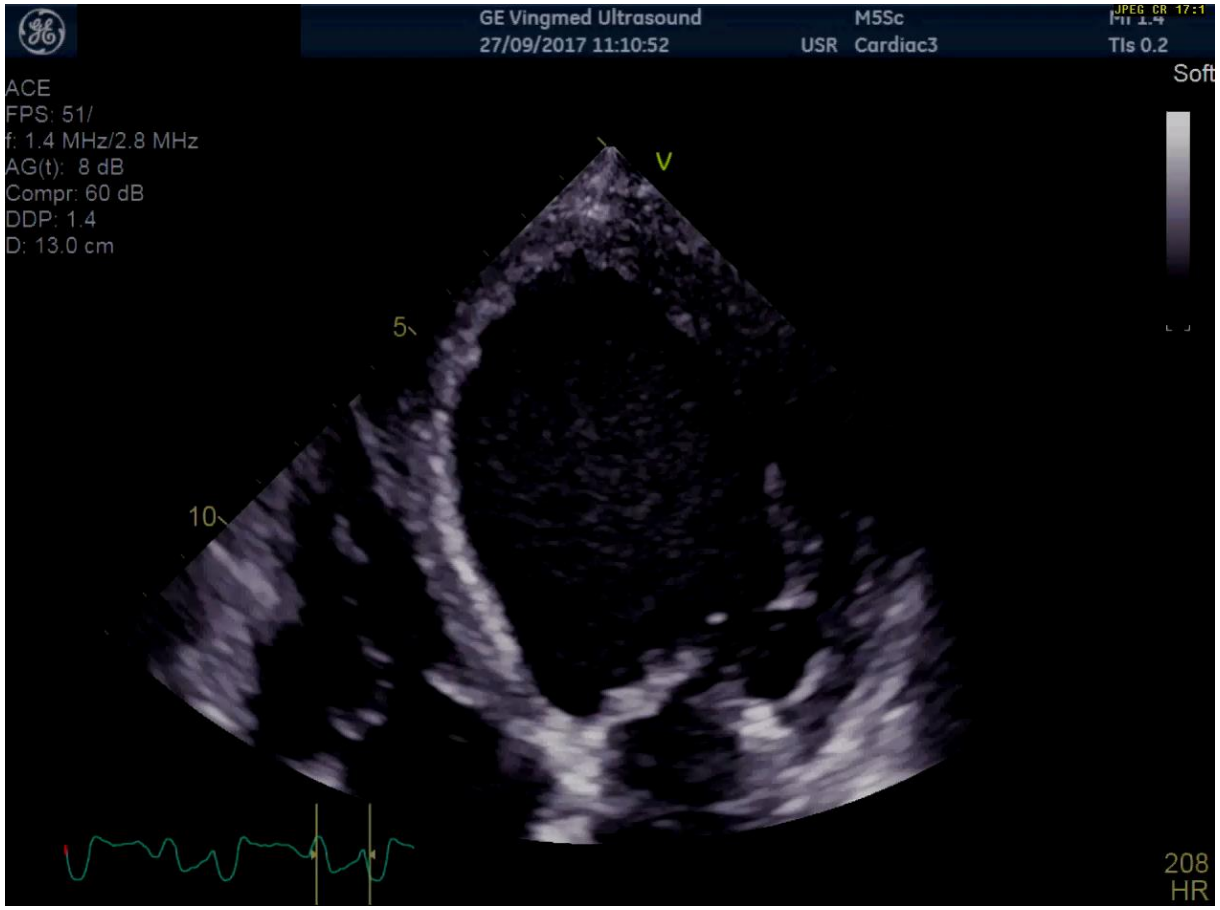
Device: 091739 Speed: 25 mm/sec Limb: 10 mm/mV Chest: 10 mm/mV 50~ 0.5-100 Hz W PH110C CL P?

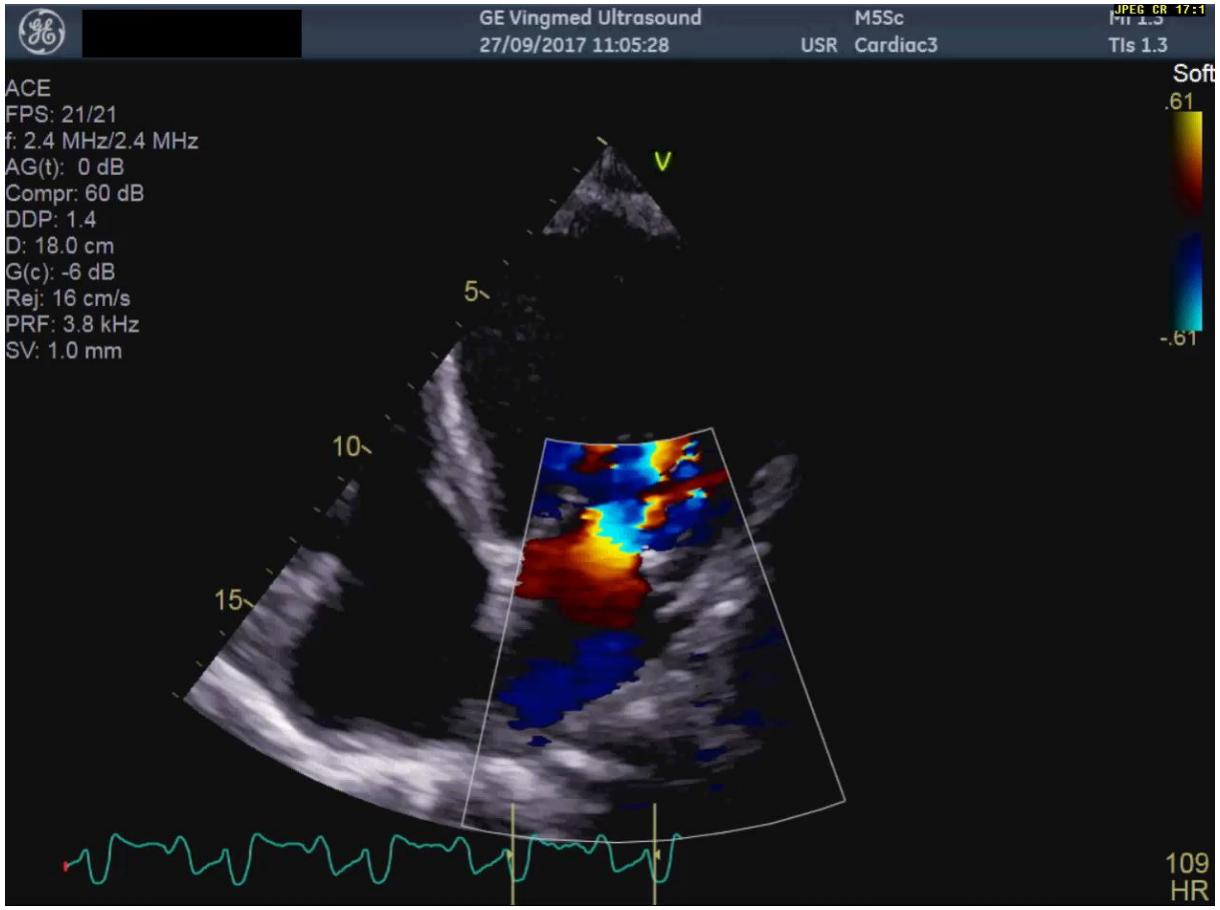
Mrs C. N. 1946 : laboratory tests

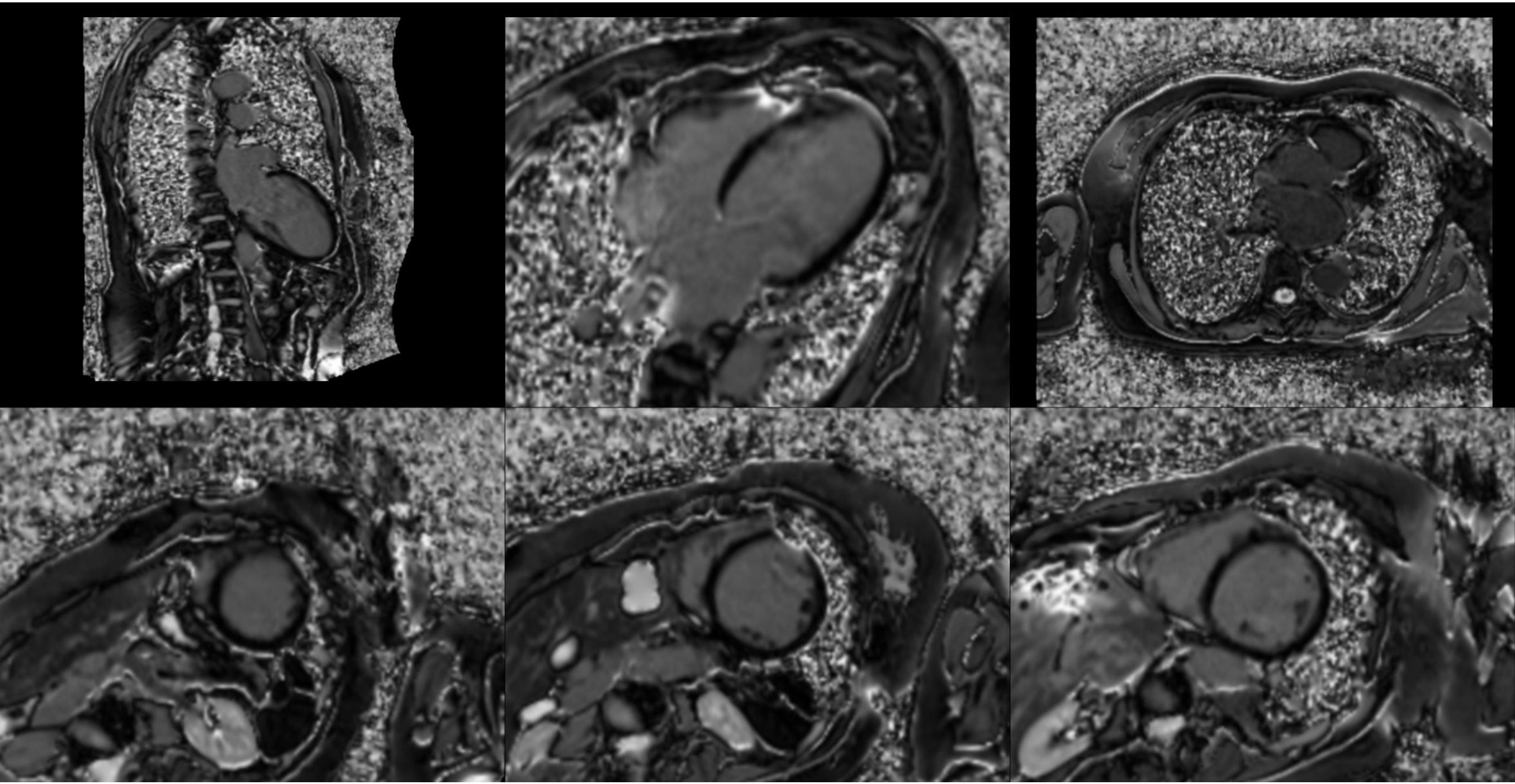
- Normal blood count
- Na 142 mmol/l. K 3.6 mmol/l
- Creatinine: 81 µmol/l, GFR (CKD-EPI) 64 ml/min/1.73 m^2
- Normal thyroid function tests, normal iron work-up
- **NT-proBNP: 8801 ng/mL**


GE Vingmed Ultrasound
27/09/2017 10:56:22
M5Sc
USR Cardiac3
JPEG CR 22:1
TIs 0.5
Soft
ACE
FPS: 51
f: 1.7 MHz/3.3 MHz
AG(t): -4 dB
Compr: 60 dB
DDP: 1.4
D: 15.0 cm
5
10
15
146
HR


GE Vingmed Ultrasound
27/09/2017 11:03:44
M5Sc
USR Cardiac3
JPEG CR 20:1
TIs 0.3
Soft
ACE
FPS: 61/
f: 1.4 MHz/2.8 MHz
AG(t): 0 dB
Compr: 60 dB
DDP: 1.4
D: 15.0 cm
5
10
15
218
HR


GE Vingmed Ultrasound
27/09/2017 11:10:52
M5Sc
USR Cardiac3
TIs 0.2
Soft
ACE
FPS: 51/
f: 1.4 MHz/2.8 MHz
AG(t): 8 dB
Compr: 60 dB
DDP: 1.4
D: 13.0 cm
V
5
10
208
HR


GE Vingmed Ultrasound
27/09/2017 11:05:28
M5Sc
USR Cardiac3
TIs 1.3
Soft
.61
-.61
ACE
FPS: 21/21
f: 2.4 MHz/2.4 MHz
AG(t): 0 dB
Compr: 60 dB
DDP: 1.4
D: 18.0 cm
G(c): -6 dB
Rej: 16 cm/s
PRF: 3.8 kHz
SV: 1.0 mm
V
5
10
15
109
HR



How should this patient be treated in 2020?

European Heart Journal Advance Access published May 20, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw128

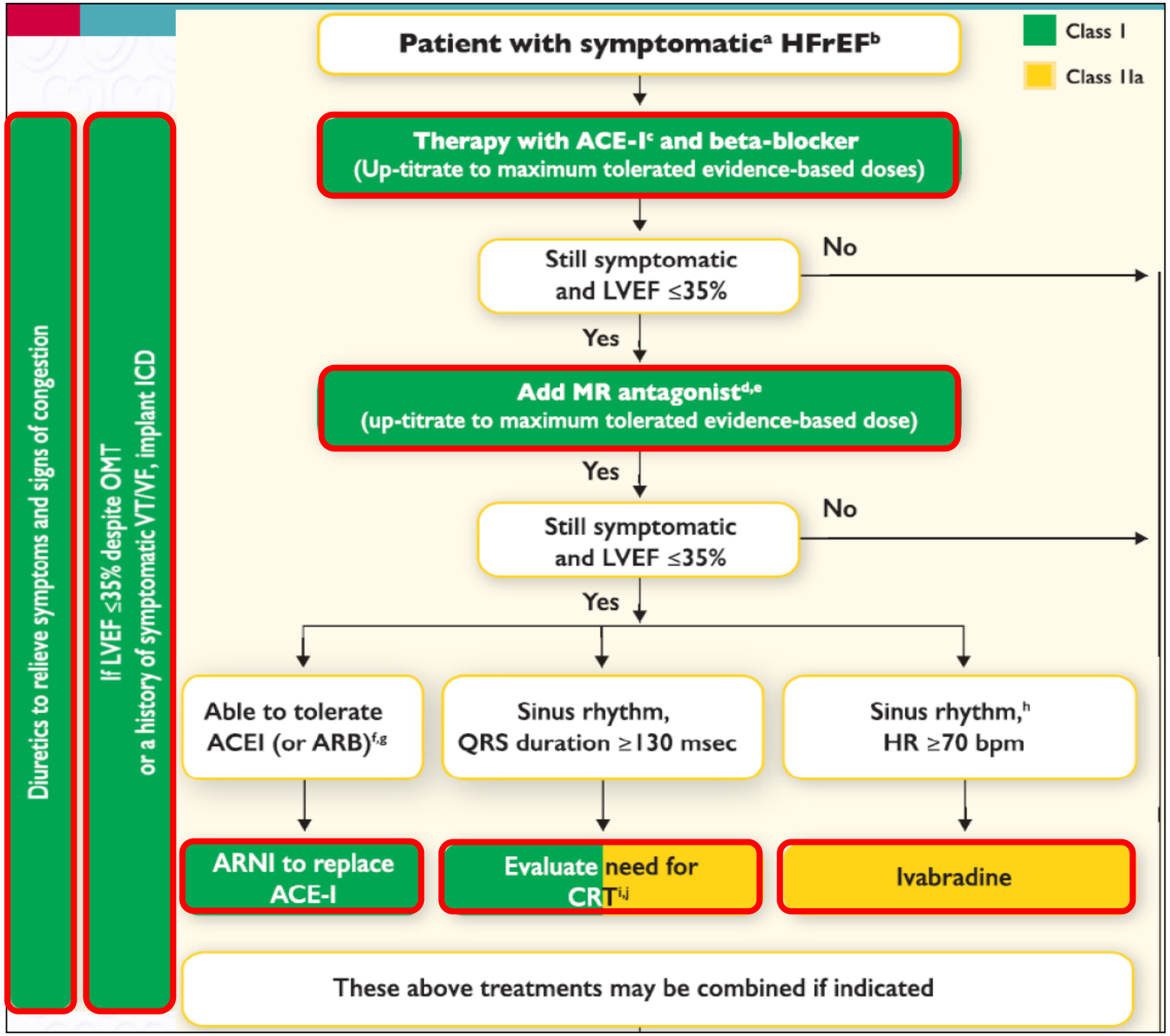
ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

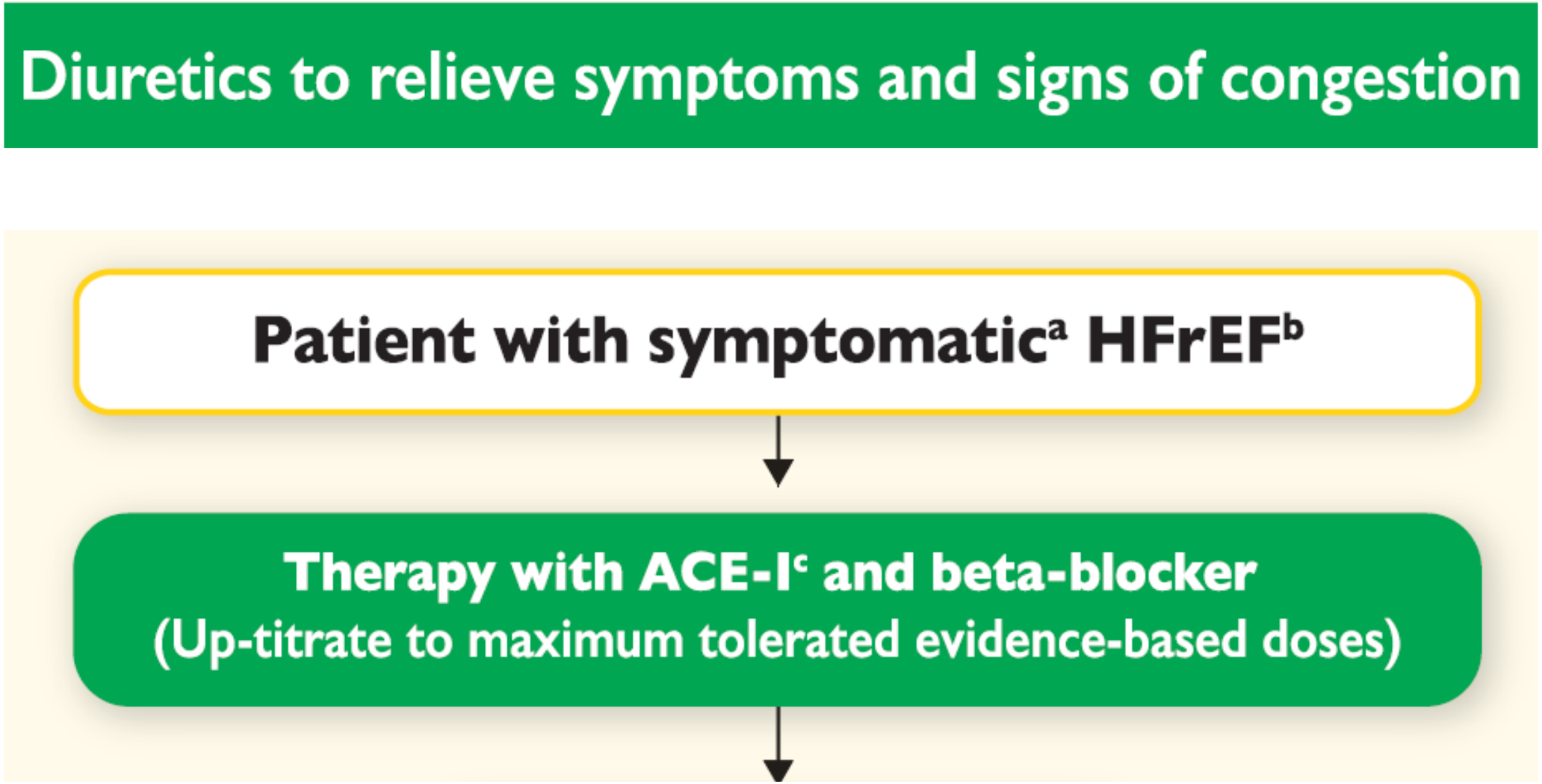
Authors/Task Force Members: Piotr Ponikowski* (Chairperson) (Poland), Adriaan A. Voors* (Co-Chairperson) (The Netherlands), Stefan D. Anker (Germany), Héctor Bueno (Spain), John G. F. Cleland (UK), Andrew J. S. Coats (UK), Volkmar Falk (Germany), José Ramón González-Juanatey (Spain), Veli-Pekka Harjola (Finland), Ewa A. Jankowska (Poland), Mariell Jessup (USA), Cecilia Linde (Sweden), Petros Nihoyannopoulos (UK), John T. Parissis (Greece), Burkert Pieske (Germany), Jillian P. Riley (UK), Giuseppe M. C. Rosano (UK/Italy), Luis M. Ruilope (Spain), Frank Ruschitzka (Switzerland), Frans H. Rutten (The Netherlands), Peter van der Meer (The Netherlands)



- **First step:** ACEi, BB, diuretics
- **Second step:** MRA
- **Third step:**
  - Switch ACEi to ARNI *and/or*
  - Consider CRT *and/or*
  - Consider ivabradine

Ponikowski P et al. Eur Heart J 2016;37:2129–2200.

First step: loop diuretics + ACE-inhibitors + Betablockers



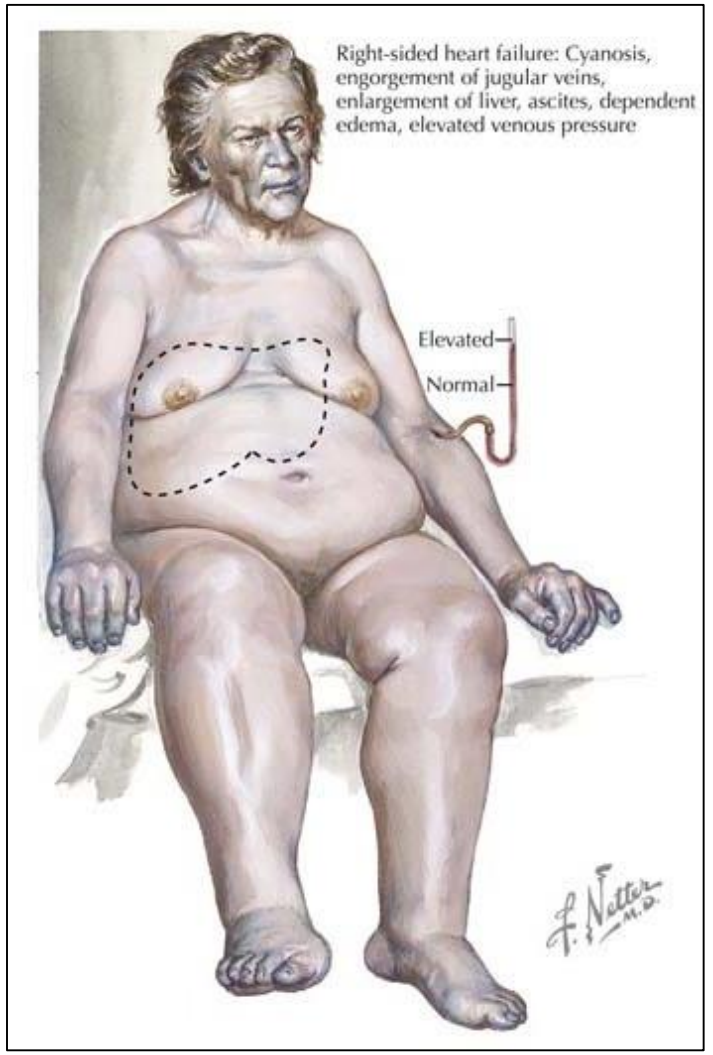
Diuretics in clinical practice

Persisting volume overload

=

Persisting symptoms +

Uneffectiveness of all other medications



ACE-inhibitors and betablockers in clinical practice

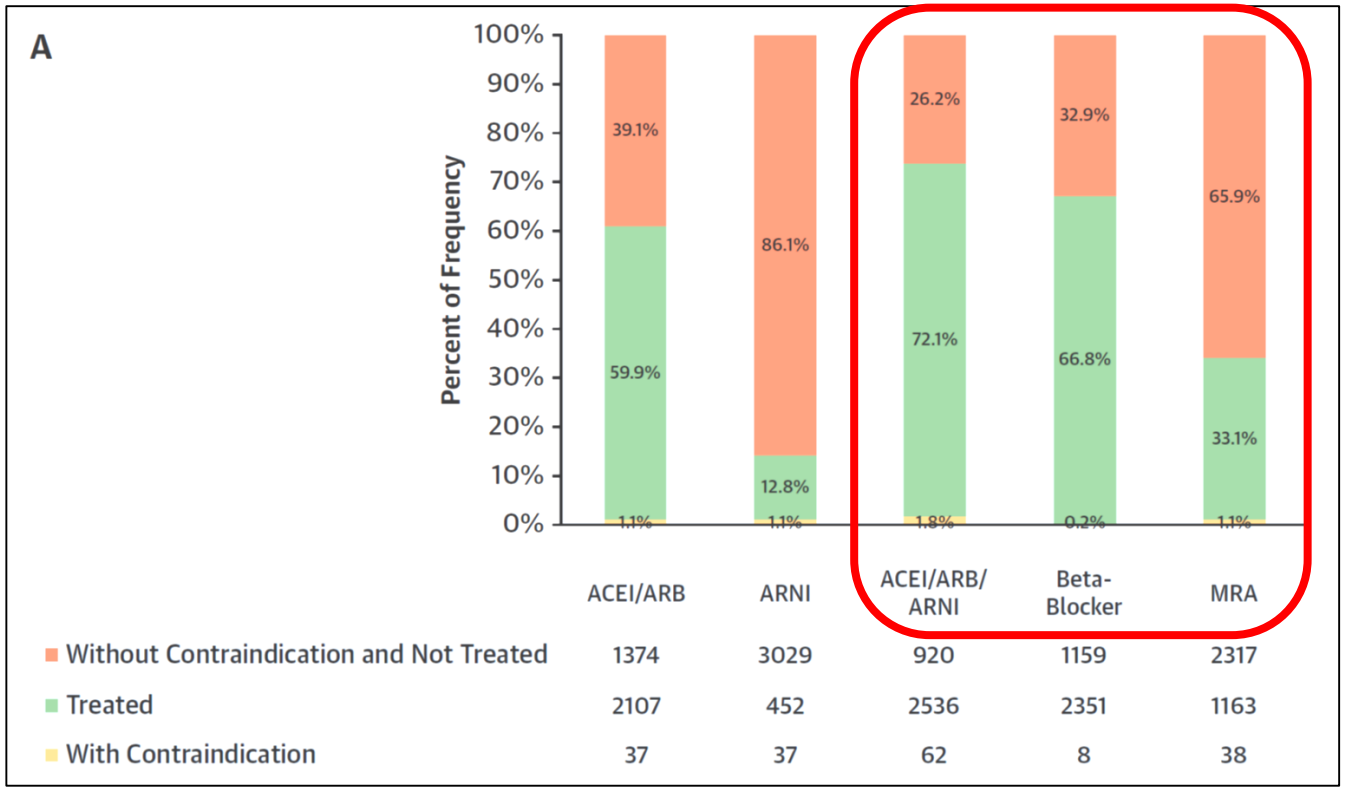
« Start low, go slow, AIM HIGH »

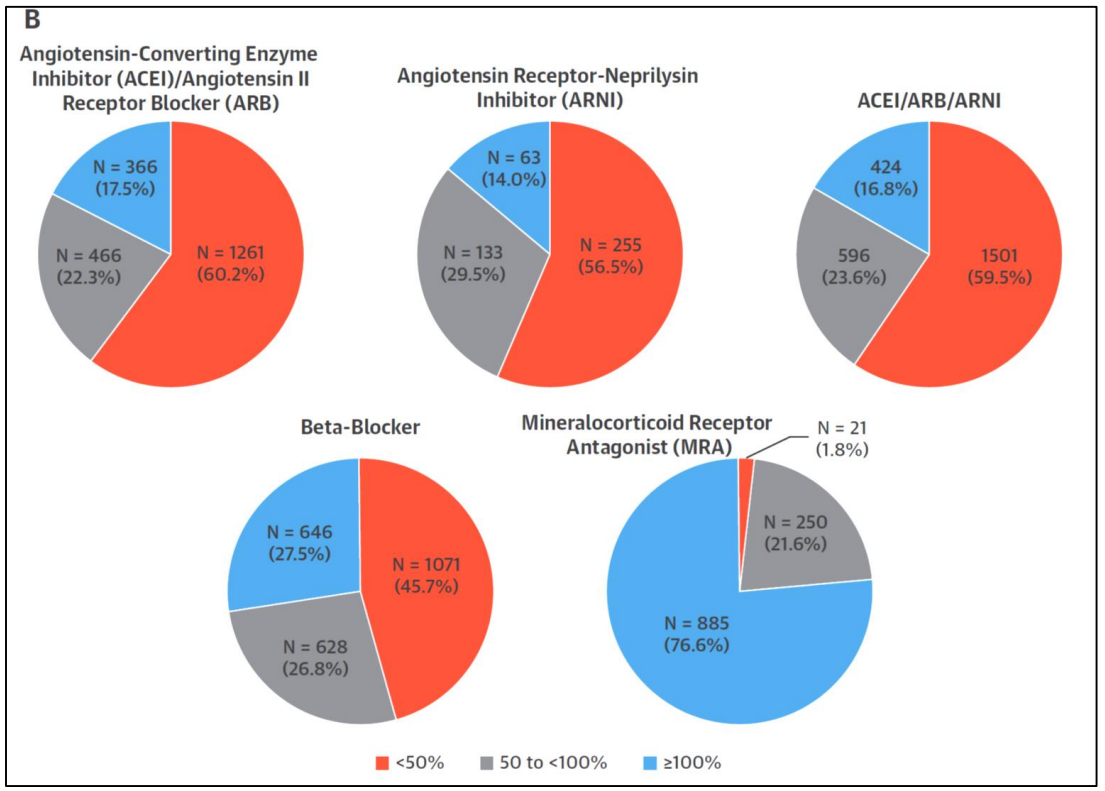
Validated ACE inhibitors, Beta-blockers, and ARBs in HF

	Starting dose (mg)	Target dose (mg)
ACE inhibitor		
Captopril[a]	6.25 t.i.d.	50 t.i.d.
Enalapril	2.5 b.i.d.	10–20 b.i.d.
Lisinopril[b]	2.5–5.0 o.d.	20–35 o.d.
Ramipril	2.5 o.d.	5 b.i.d.
Trandolapril[a]	0.5 o.d.	4 o.d.
Beta-blocker		
Bisoprolol	1.25 o.d.	10 o.d.
Carvedilol	3.125 b.i.d.	25–50 b.i.d.
Metoprolol succinate (CR/XL)	12.5/25 o.d.	200 o.d.
Nebivolol[c]	1.25 o.d.	10 o.d.
ARB		
Candesartan	4 or 8 o.d.	32 o.d.
Valsartan	40 b.i.d.	160 b.i.d.
Losartan[b,c]	50 o.d.	150 o.d.

Medical Therapy for Heart Failure With Reduced Ejection Fraction

The CHAMP-HF Registry





Greene, S.J. et al. J Am Coll Cardiol. 2018;72:351–66.

Why are we so bad?

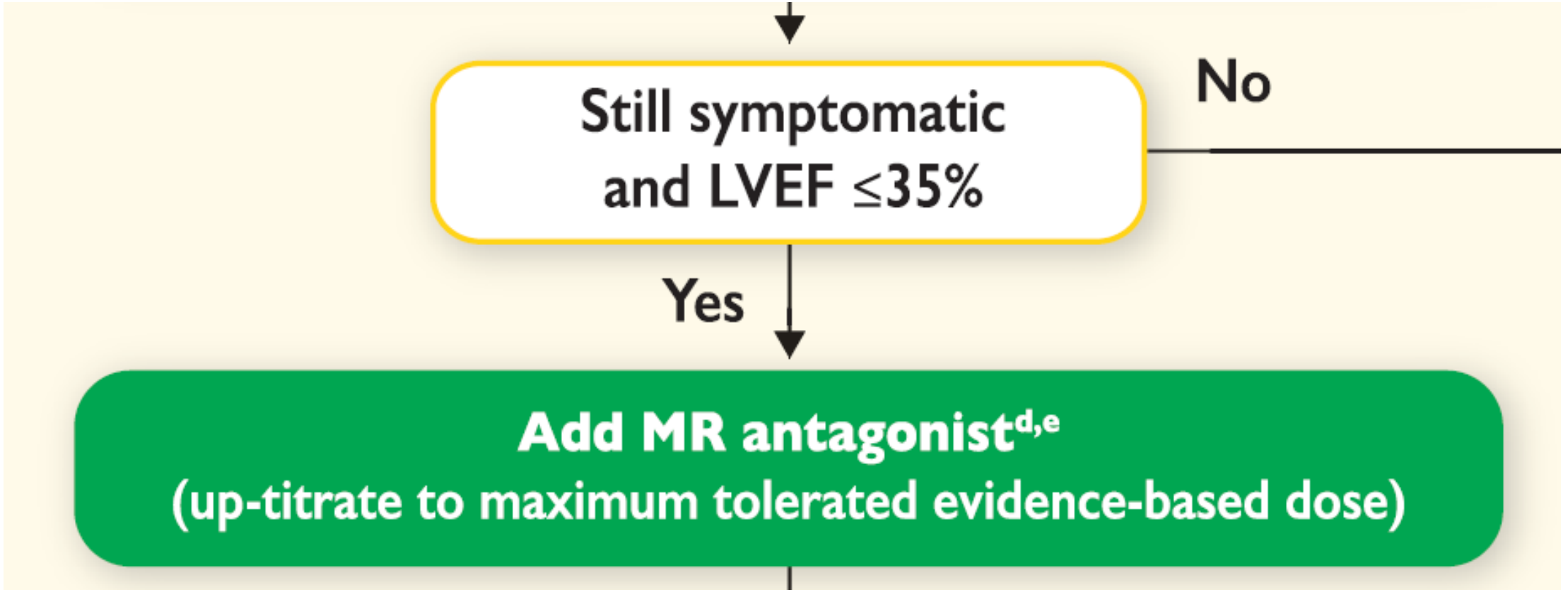
- **The patient's perspective**
  - If they feel better they wish to stop the medication, not to increase the dose!
  - Do not generally feel so good (fatigue, dizziness, increased dyspnea) after each change

Why are we so bad?

- **The patient's perspective**
  - If they feel better they wish to stop the medication, not to increase the dose!
  - Do not generally feel not so good (fatigue, dizziness, increased dyspnea) after each change

- **The doctors' perspective**
  - Doctors are often not proactive if patients have no real complains
  - GPs are afraid of low blood pressure and hyperkaliemia
  - Cardiologists usually have no time to see patients every 2 weeks during 3 months to optimize HF therapy

2nd step: mineralocorticoid receptor antagonists



MRAs in clinical practice

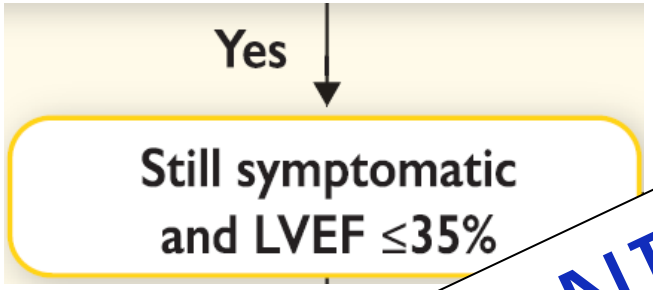
Check K^+ / creatinine regularly

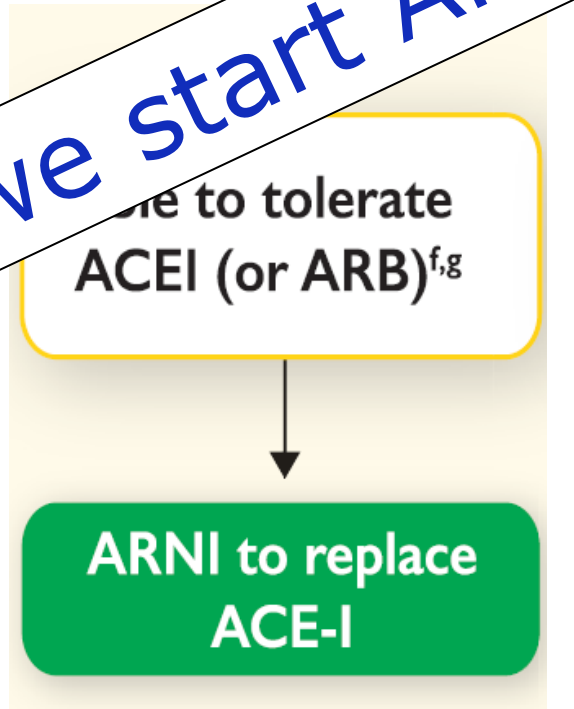
- Do not start if K+ **>5.0** mmol/l and/or eGFR **<30**
- If K+ **>5.5** mmol/l and/or eGFR **<30** => ↓ 25 mg 1/2d
- If K+ **>6.0** mmol/l and/or eGFR **<20** => **STOP**

Back to Mrs C. N. 1946 – December 2017 (3 months later)

History of present illness	• Dyspnea NYHA class II
Physical exam	• BP 129/63 mmHg. HR 70 bpm. SaO_2: 98% on room air • Normal JVP. No oedema. Normal pulmonary auscultation • No S3, 2/6 apical holosystolic murmur
Lab tests	• Na 143, K 5.0, creatinine 75 (eGFR 69), NT-proBNP 2183
Medications	• Metoprolol 50 mg 1-0-0 • Enalapril 10 mg 1-0-1 • Torasemide 5 mg 1-0-0 • Spironolactone 12.5 mg 1-0-0
TTE	• LVEF calculated at 31%

3rd step: switch ACEI to ARNI





Should we start ARNI earlier?

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*

881 patients hospitalized for acute decompensated HF

Randomized after a mean of 2.8 days to enalapril or sacubitril/valsartan

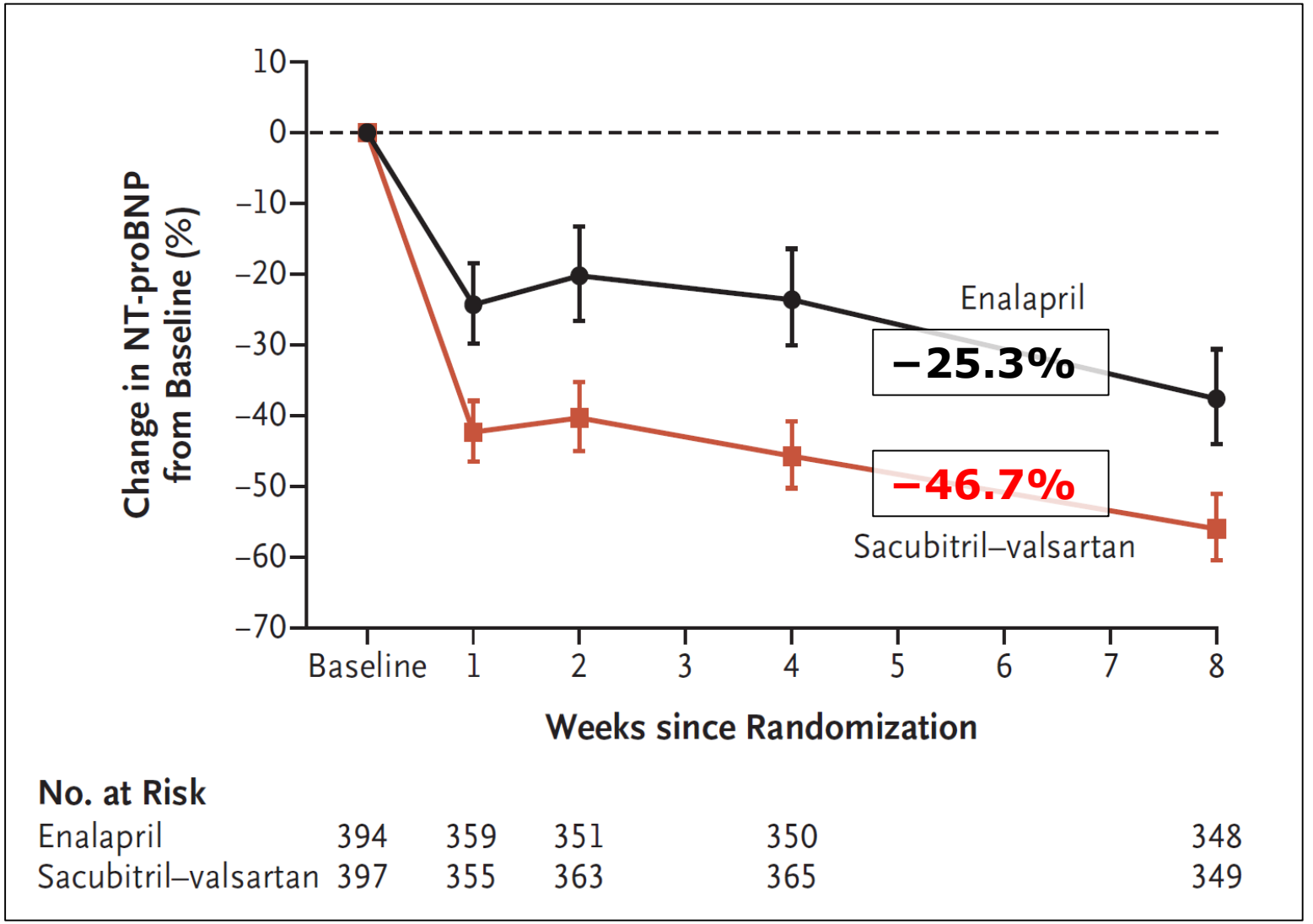
Median LVEF 25%

Median NT-proBNP: 2700 pg/mL

Stabilized (SBP ≥100 mmHg, no recent increase in iv diuretics, no iv vasodilators/inotropes)

N Engl J Med. 2018 Nov 11. doi: 10.1056/NEJMoa1812851. [Epub ahead of print]

Primary endpoint: % change in NT-proBNP

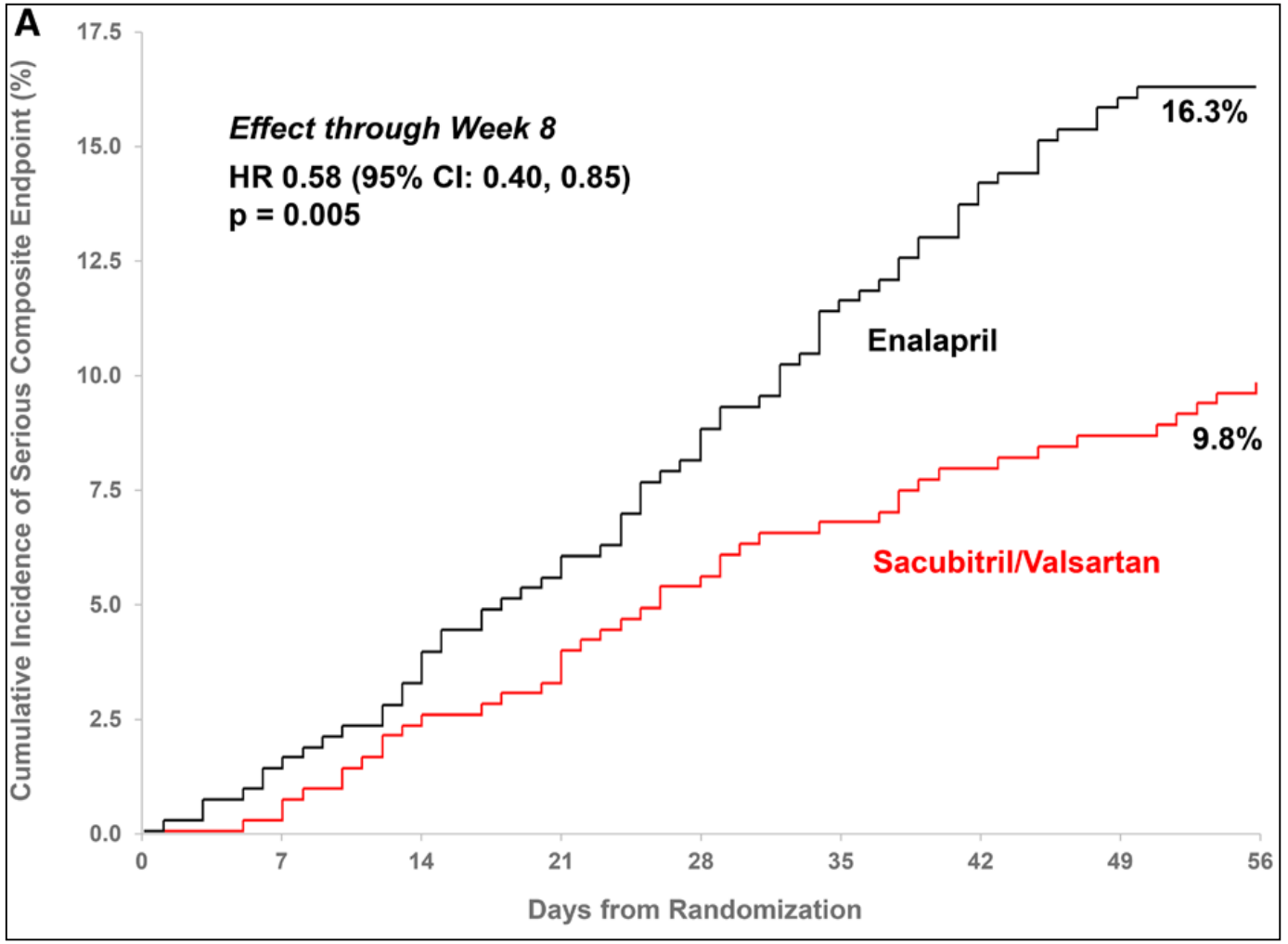


(P<0.001)

Safety events

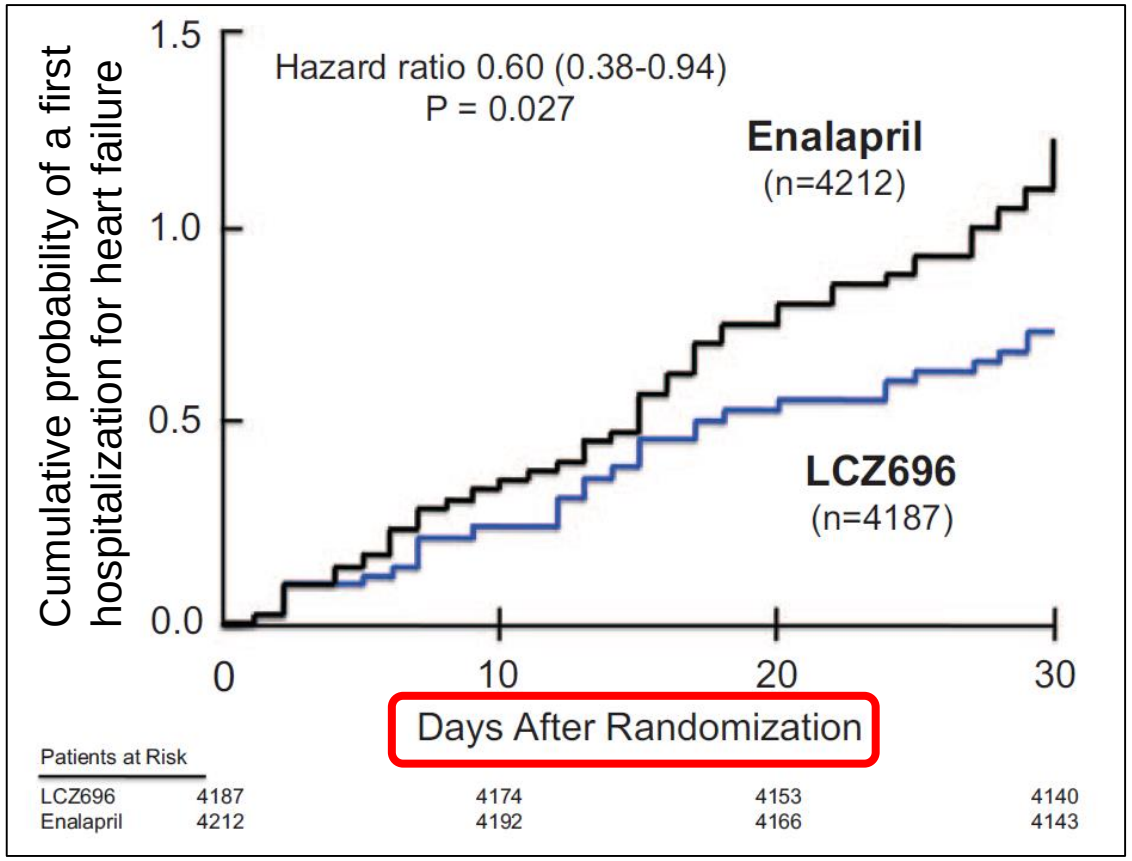
Safety Events (%)	Sacubitril/ Valsartan (n=440) (%)	Enalapril (n=441) (%)	RR (95% CI)
Worsening renal function[a]	13.6	14.7	0.93 (0.67-1.28)
hyperkalaemia	11.6	9.3	1.25 (0.84-1.84)
Symptomatic hypotension	15.0	12.7	1.18 (0.85-1.64)
Angioedema events[b]	0.2	1.4	0.17 (0.02-1.38)

Clinical composite of death from any cause, rehospitalization for HF, LVAD implantation, or listing for cardiac transplant



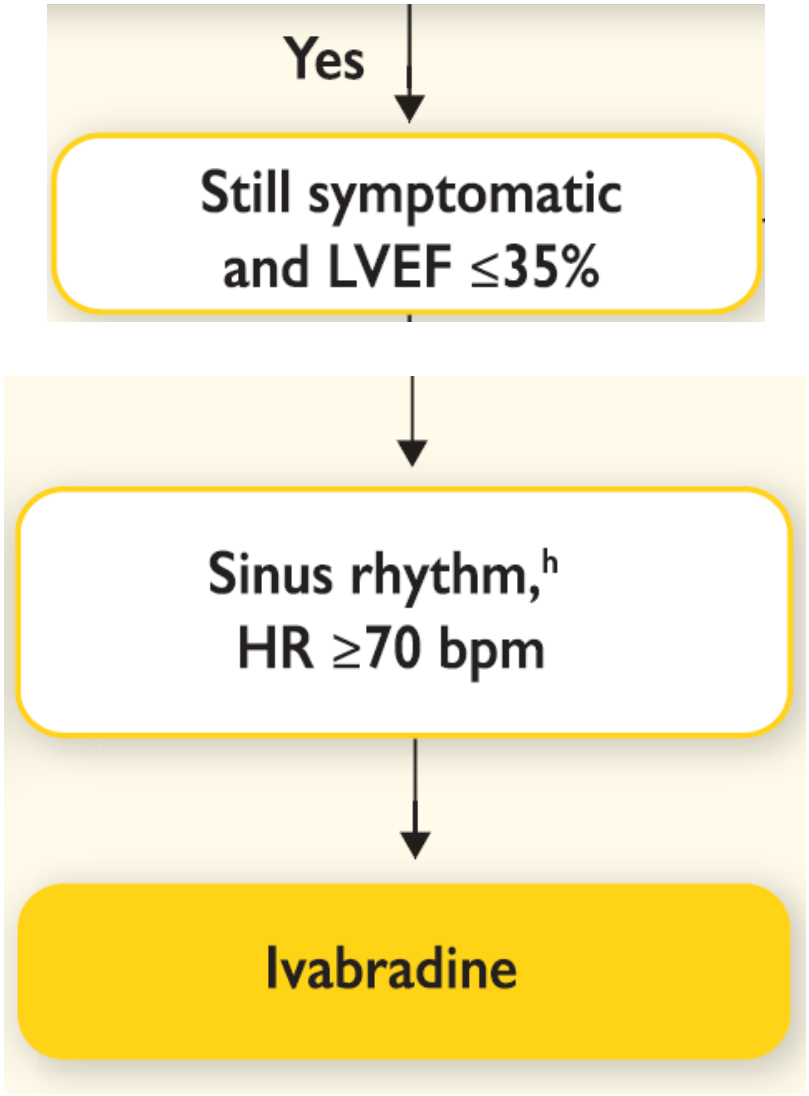
Morrow DA et al. Circulation. 2019;139:2285–2288.

Angiotensin Receptor Neprilysin Inhibition Compared With Enalapril on the Risk of Clinical Progression in Surviving Patients With Heart Failure



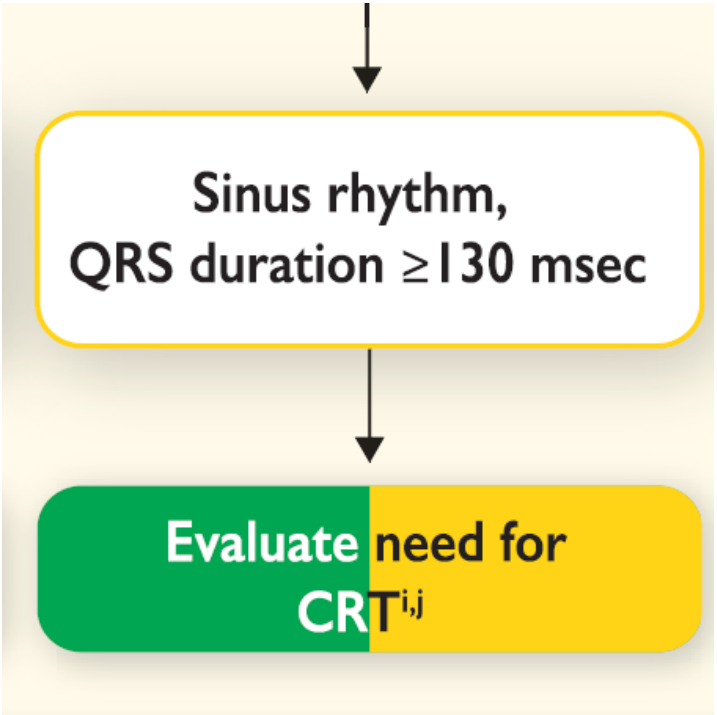
Packer M et al. Circulation. 2015;131:54–61 et al.

3rd step: consider ivabradine

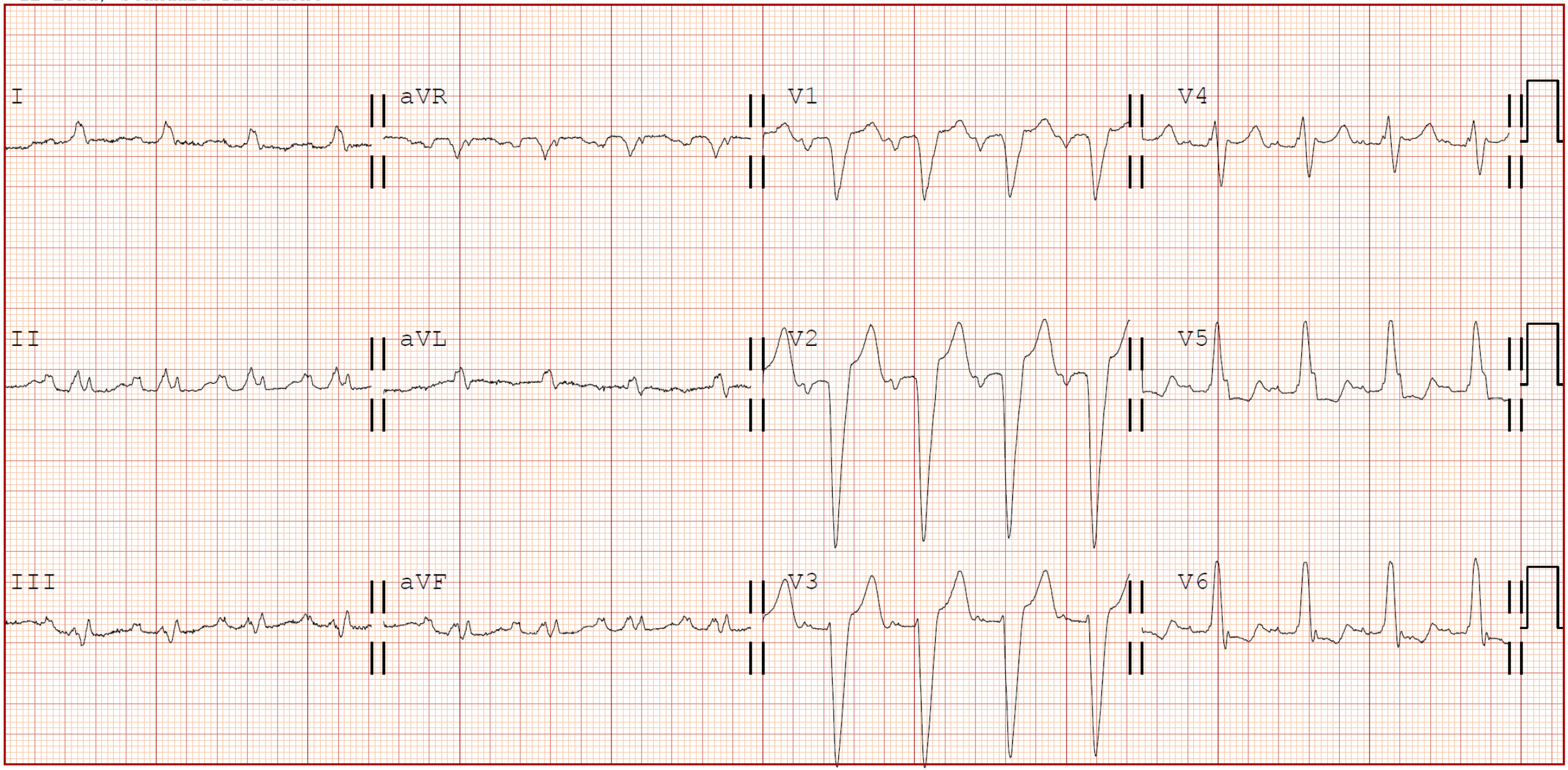


3rd step: consider CRT and/or ICD

If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

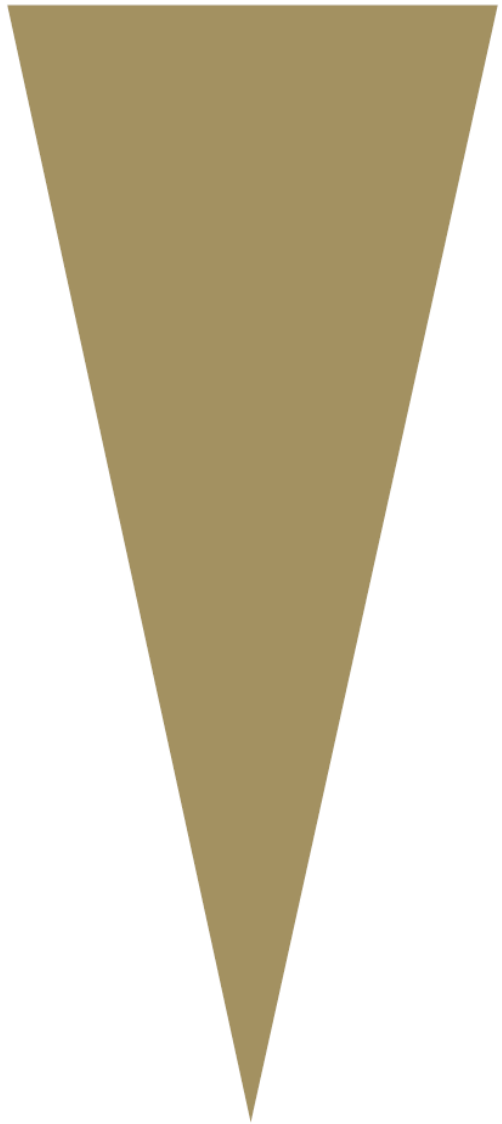


12 Lead; Standard Placement



Device: 091739 Speed: 25 mm/sec Limb: 10 mm/mV Chest: 10 mm/mV 50~ 0.5-100 Hz W PH110C CL P?

Magnitude of benefit from CRT



Highest (responders)

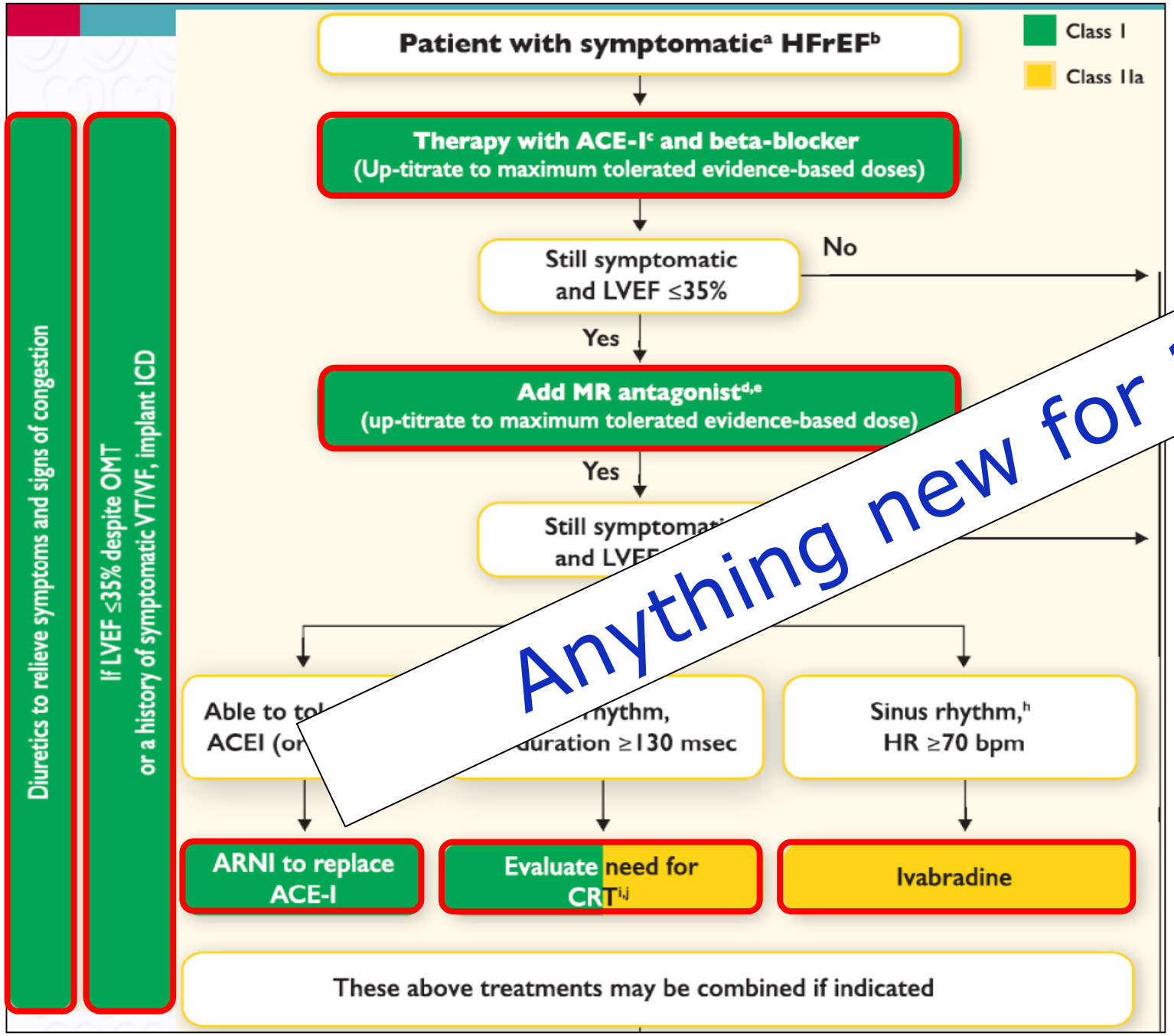
Wider QRS, left bundle branch block, females, non-ischaemic cardiomyopathy

Males, ischaemic cardiomyopathy

Lowest (non-responders)

Narrower QRS, non-left bundle branch block

Brignole M et al. Eur Heart J 2013;34: 2281–2329



Anything new for 2020?

- **First step:** A… BB, diuretics
- **Second step:** MRA
- **Third step:**
  - Switch ACEi to ARNI *and/or*
  - Consider CRT *and/or*
  - Consider ivabradine

Ponikowski P et al. Eur Heart J 2016;37:2129–2200.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

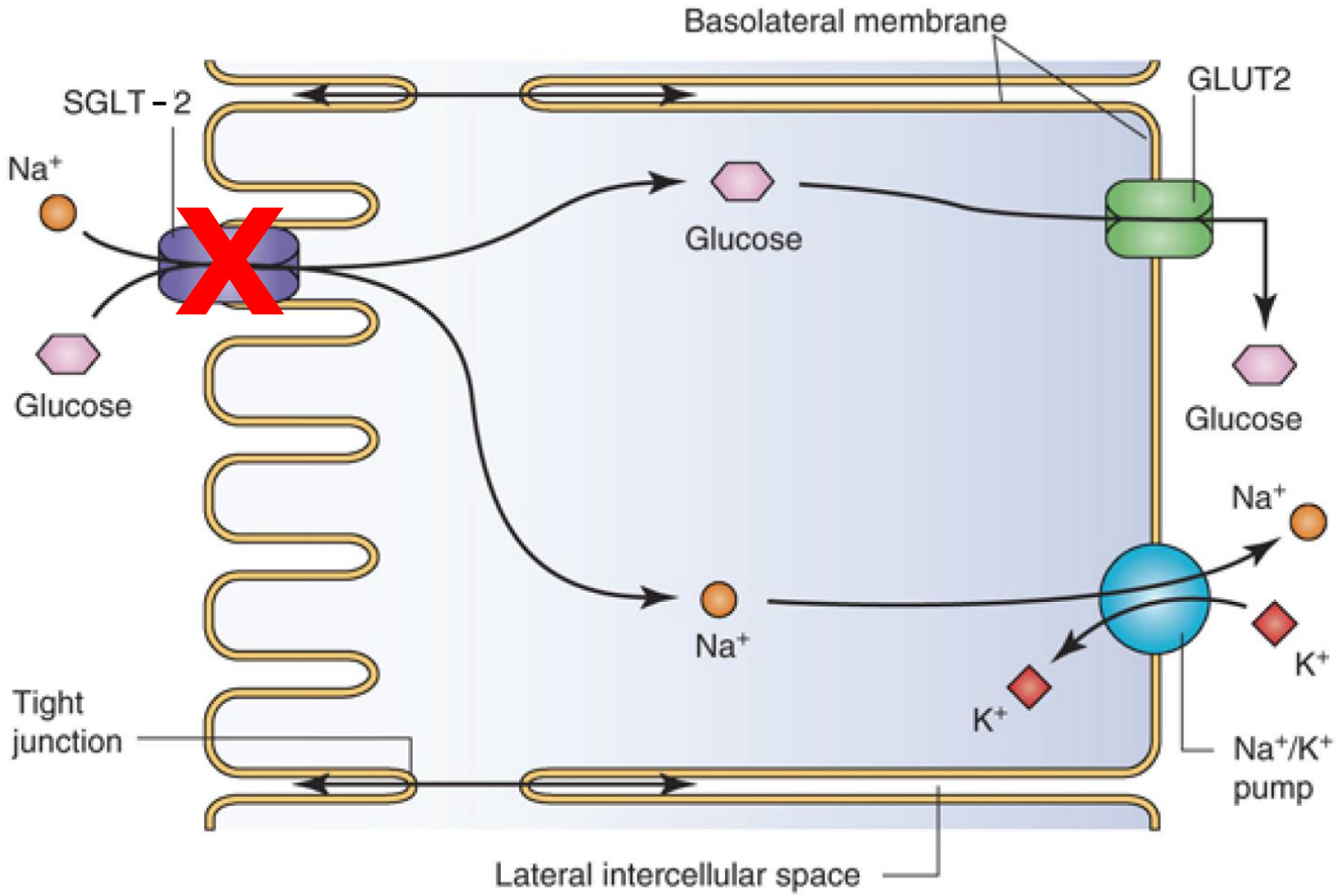
Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

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*

N Engl J Med 2019 Sep 19. doi: 10.1056/NEJMoa1911303. [Epub ahead of print]

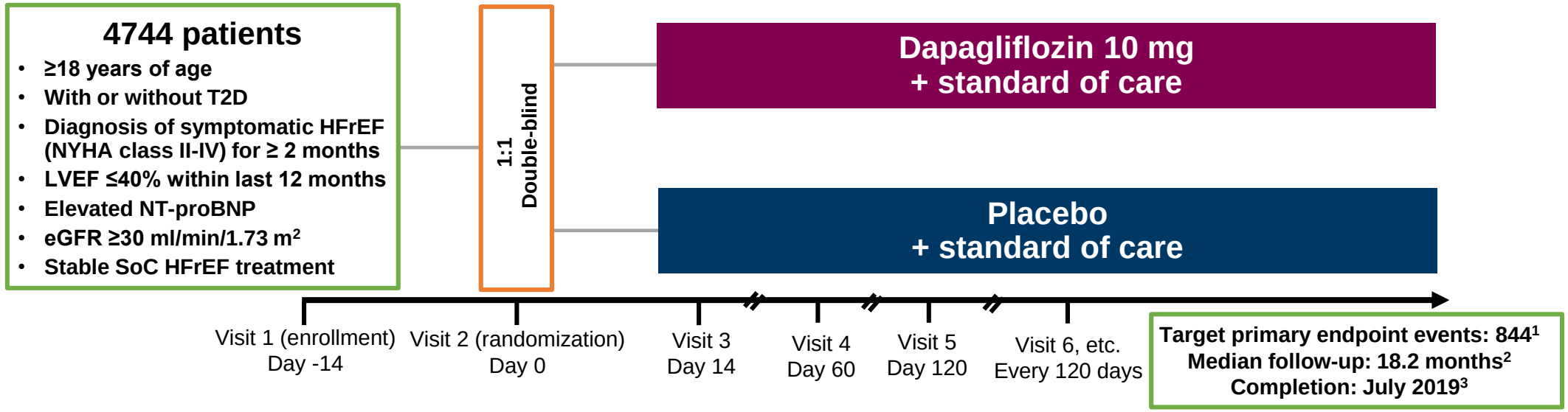
Sodium-glucose co-transporter 2 inhibition in the proximal tubule

Lumen



Interstitial fluid

Study design



Primary Endpoint

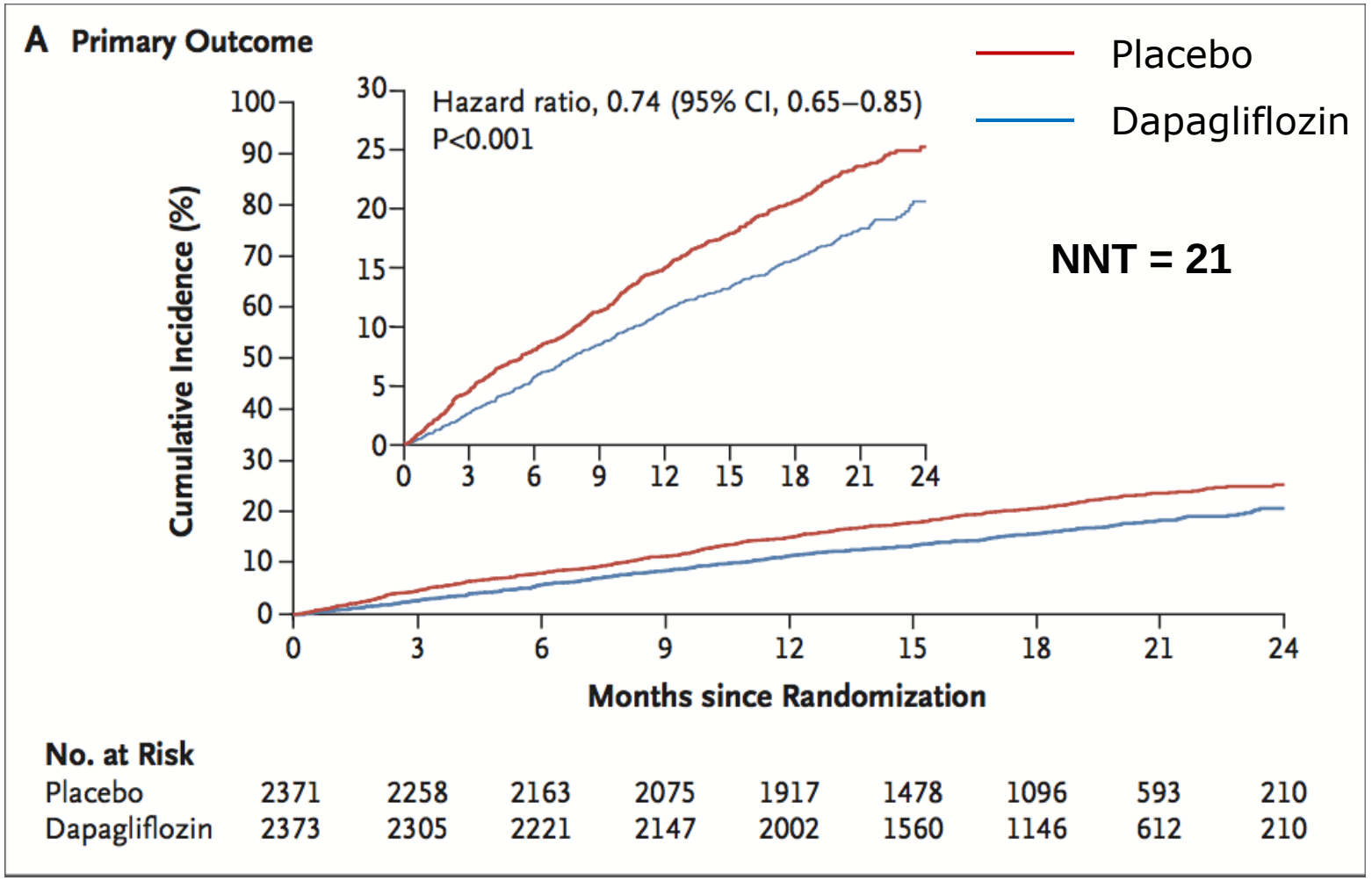
- Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit

Secondary Endpoints

- Time to first occurrence of either of the components of the composite: CV death or hHF
- Total number of (first and recurrent) hHF and CV death
- Change from baseline measured at 8 months in the total symptom score of the KCCQ
- Time to first occurrence of any of the components of the composite: ≥50% sustained decline in eGFR or reaching ESRD or renal death
- Time to death from any cause

McMurray JJV et al. Eur J Heart Fail. 2019;21:665-675.

Primary outcome: CV Death or hHF or an urgent HF Visit



Safety

Variable	Dapagliflozin (N=2373)		Placebo (N=2371)		Hazard or Rate Ratio or Difference (95% CI)	P Value
		events/100 patient-yr		*events/100 patient-yr*		
Safety outcomes						
Discontinuation due to adverse event — no./total no. (%)	111/2368 (4.7)	—	116/2368 (4.9)	—	—	0.79
Adverse events of interest — no./total no. (%)						
Volume depletion	178/2368 (7.5)	—	162/2368 (6.8)	—	—	0.40
Renal adverse event	153/2368 (6.5)	—	170/2368 (7.2)	—	—	0.36
Fracture	49/2368 (2.1)		50/2368 (2.1)	—	—	1.00
Amputation	13/2368 (0.5)	—	12/2368 (0.5)	—	—	1.00
Major hypoglycemia**	4/2368 (0.2)	—	4/2368 (0.2)	—	—	NA
Diabetic ketoacidosis††	3/2368 (0.1)	—	0	—	—	NA
Fournier's gangrene	0	—	1/2368 (<0.1)	—	—	NA

The NEW ENGLAND JOURNAL of MEDICINE

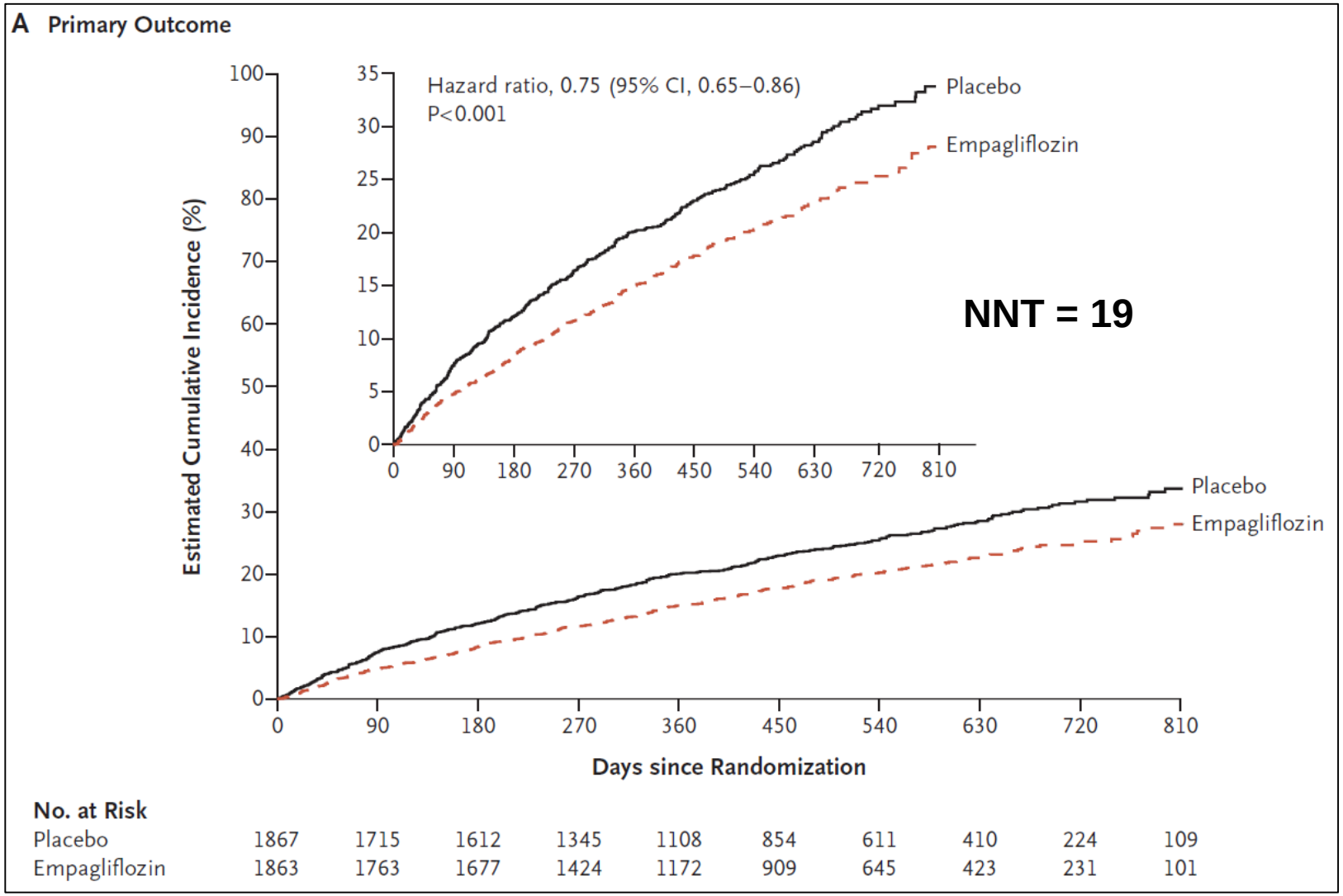
ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

M. Packer, S.D. Anker, J. Butler, G. Filippatos, S.J. Pocock, P. Carson, J. Januzzi, S. Verma, H. Tsutsui, M. Brueckmann, W. Jamal, K. Kimura, J. Schnee, C. Zeller, D. Cotton, E. Bocchi, M. Böhm, D.-J. Choi, V. Chopra, E. Chuquiure, N. Giannetti, S. Janssens, J. Zhang, J.R. Gonzalez Juanatey, S. Kaul, H.-P. Brunner-La Rocca, B. Merkely, S.J. Nicholls, S. Perrone, I. Pina, P. Ponikowski, N. Sattar, M. Senni, M.-F. Seronde, J. Spinar, I. Squire, S. Taddei, C. Wanner, and F. Zannad, for the EMPEROR-Reduced Trial Investigators*

N Engl J Med. 2020 Aug 29. doi: 10.1056/NEJMoa2022190.

Primary outcome: CV death or hospitalization for HF



N Engl J Med. 2020 Aug 29. doi: 10.1056/NEJMoa2022190.

The NEW ENGLAND JOURNAL of MEDICINE

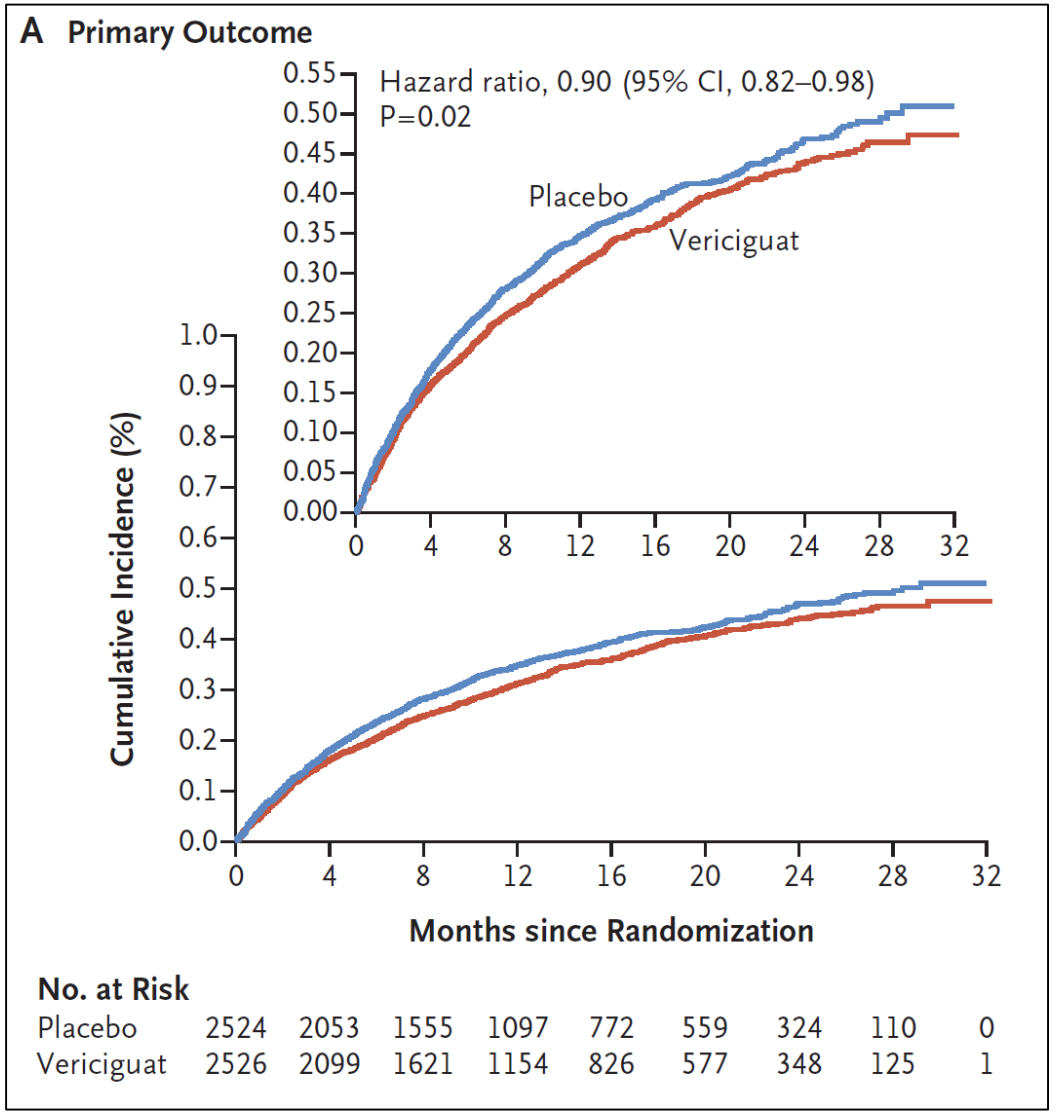
ORIGINAL ARTICLE

Vericiguat in Patients with Heart Failure and Reduced Ejection Fraction

Paul W. Armstrong, M.D., Burkert Pieske, M.D., Kevin J. Anstrom, Ph.D., Justin Ezekowitz, M.B., B.Ch., Adrian F. Hernandez, M.D., M.H.S., Javed Butler, M.D., M.P.H., M.B.A., Carolyn S.P. Lam, M.B., B.S., Ph.D., Piotr Ponikowski, M.D., Adriaan A. Voors, M.D., Ph.D., Gang Jia, Ph.D., Steven E. McNulty, M.S., Mahesh J. Patel, M.D., Lothar Roessig, M.D., Joerg Koglin, M.D., Ph.D., and Christopher M. O'Connor, M.D., for the VICTORIA Study Group*

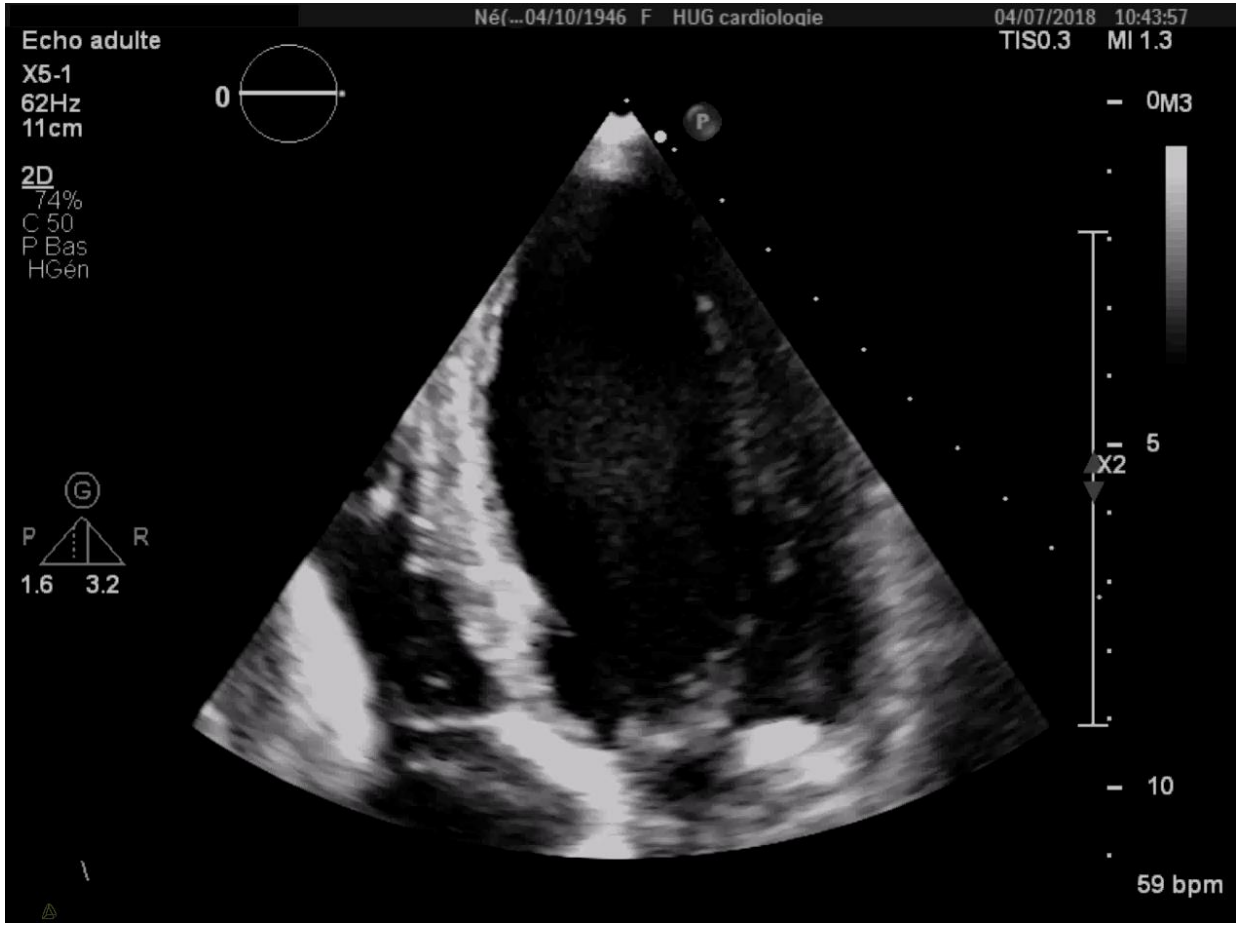
N Engl J Med. 2020 May 14;382(20):1883-1893.

Primary outcome: CV death or hospitalization for HF



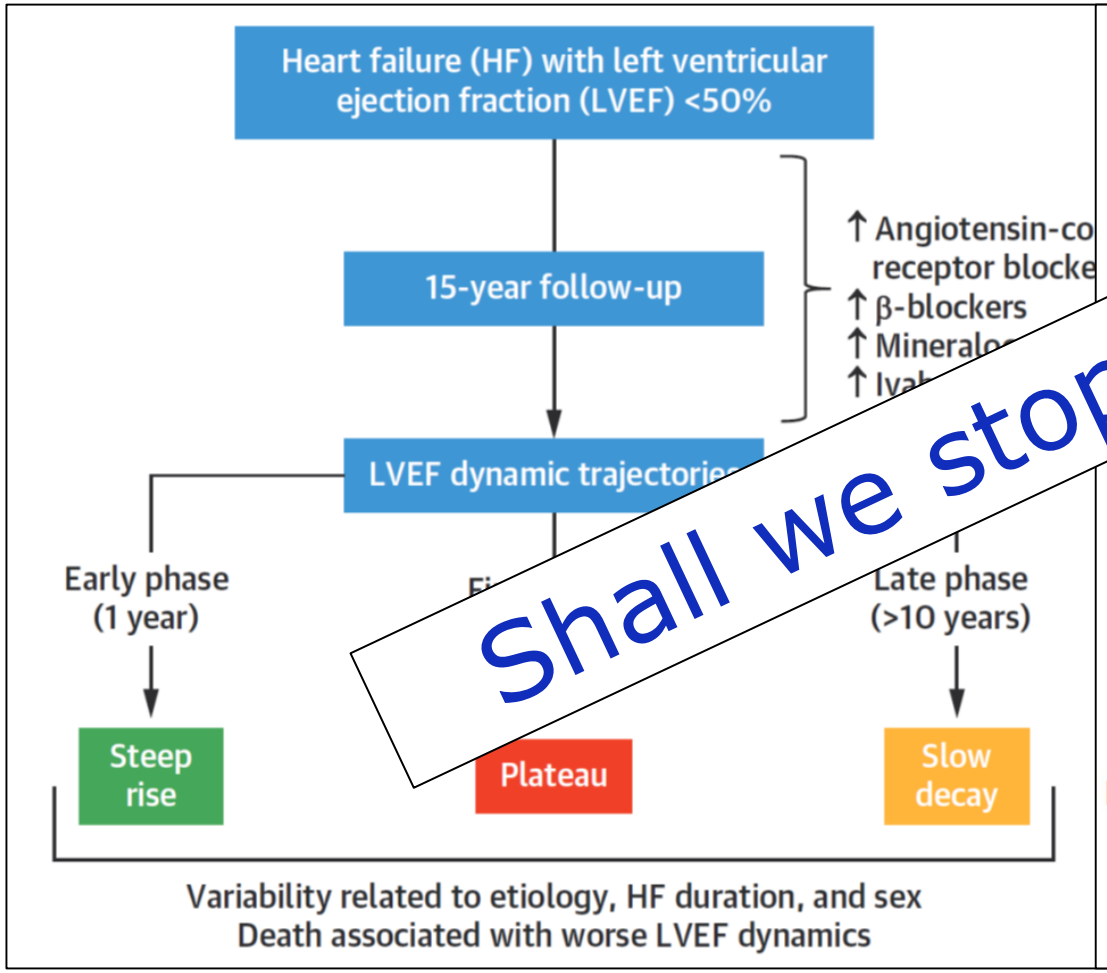
Back to Mrs C. N. 1946 – July 2018 (9 months later)

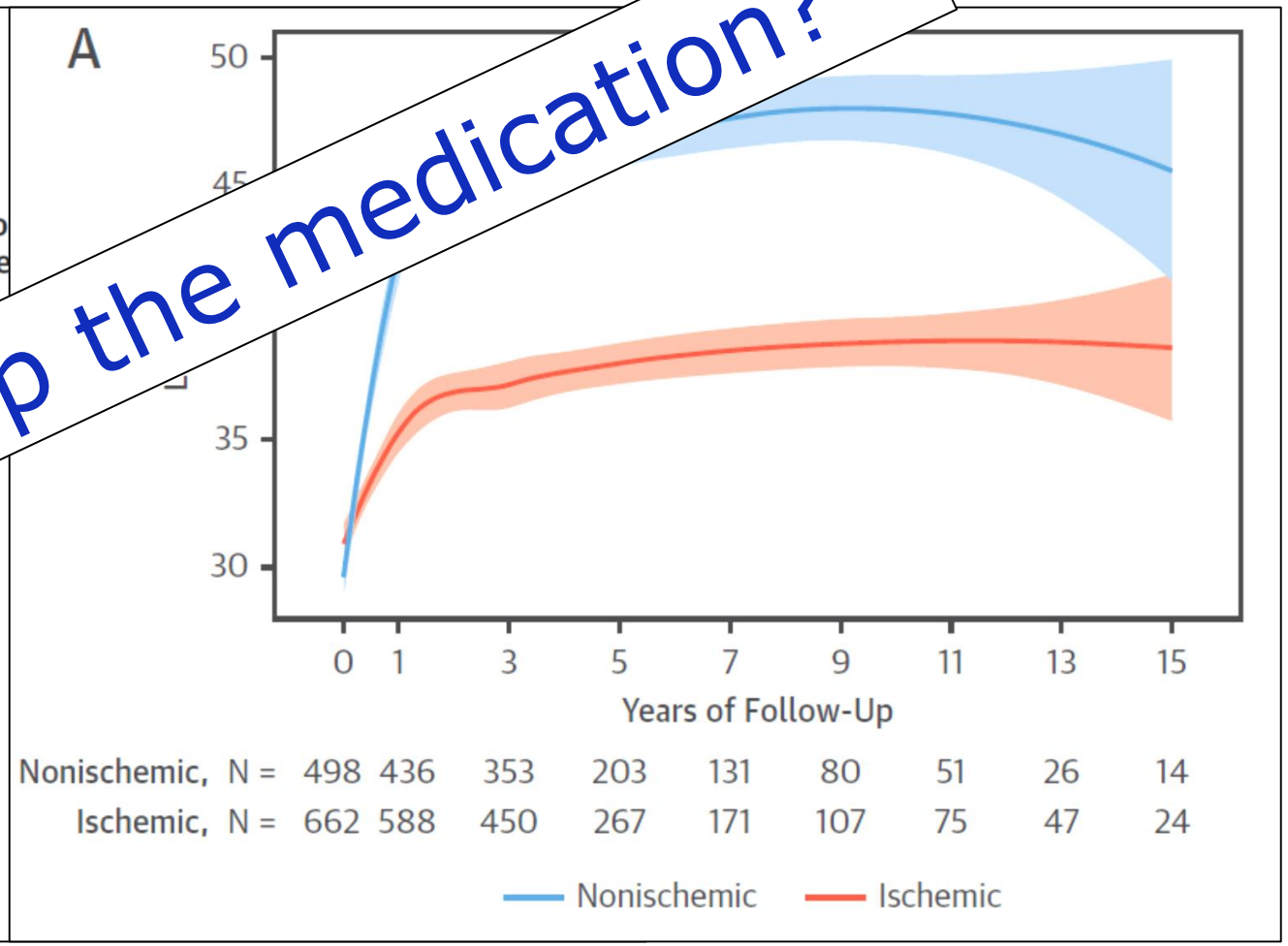
History of present illness	• Asymptomatic
Physical exam	• BP 107/65 mmHg, HR 65 bpm, No HF signs
Lab tests	• NT-proBNP 262 ng/mL
Medications	• Metoprolol 50 mg 1-0-0 • Sacubitril/Valsartan 100 mg 1-0-1 • Spironolactone 25 mg 1-0-0


Né(...04/10/1946 F HUG cardiologie
04/07/2018 10:43:57
Echo adulte
TIS0.3 MI 1.3
X5-1
62Hz
11cm
2D
74%
C 50
P Bas
HGén
0M3
5
X2
10
59 bpm
1.6 3.2


Né(...04/10/1946 F HUG cardiologie
04/07/2018 10:43:45
Echo adulte
TIS0.3 MI 1.3
X5-1
62Hz
11cm
2D
74%
C 50
P Bas
HGén
0M3
5
X2
10
128 bpm
1.6 3.2

Dynamic Trajectories of Left Ventricular Ejection Fraction in Heart Failure





Shall we stop the medication?

Lupon J et al. J Am Coll Cardiol 2018;72:591–601.

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

Brian P Halliday, Rebecca Wassall, Amrit S Lota, Zohya Khalique, John Gregson, Simon Newsome, Robert Jackson, Tsveta Rahneva, Rick Wage, Gillian Smith, Lucia Venneri, Upasana Tayal, Dominique Auger, William Midwinter, Nicola Whiffin, Ronak Rajani, Jason N Dungu, Antonis Pantazis, Stuart A Cook, James S Ware, A John Baksi, Dudley J Pennell, Stuart D Rosen, Martin R Cowie, John G F Cleland, Sanjay K Prasad

51 patients with a **recovered previous dilated cardiomyopathy** with LVEF ≤40%

Current HF treatment (loop diuretic, beta-blocker, ACE-inhibitor, ARB, or MRA)

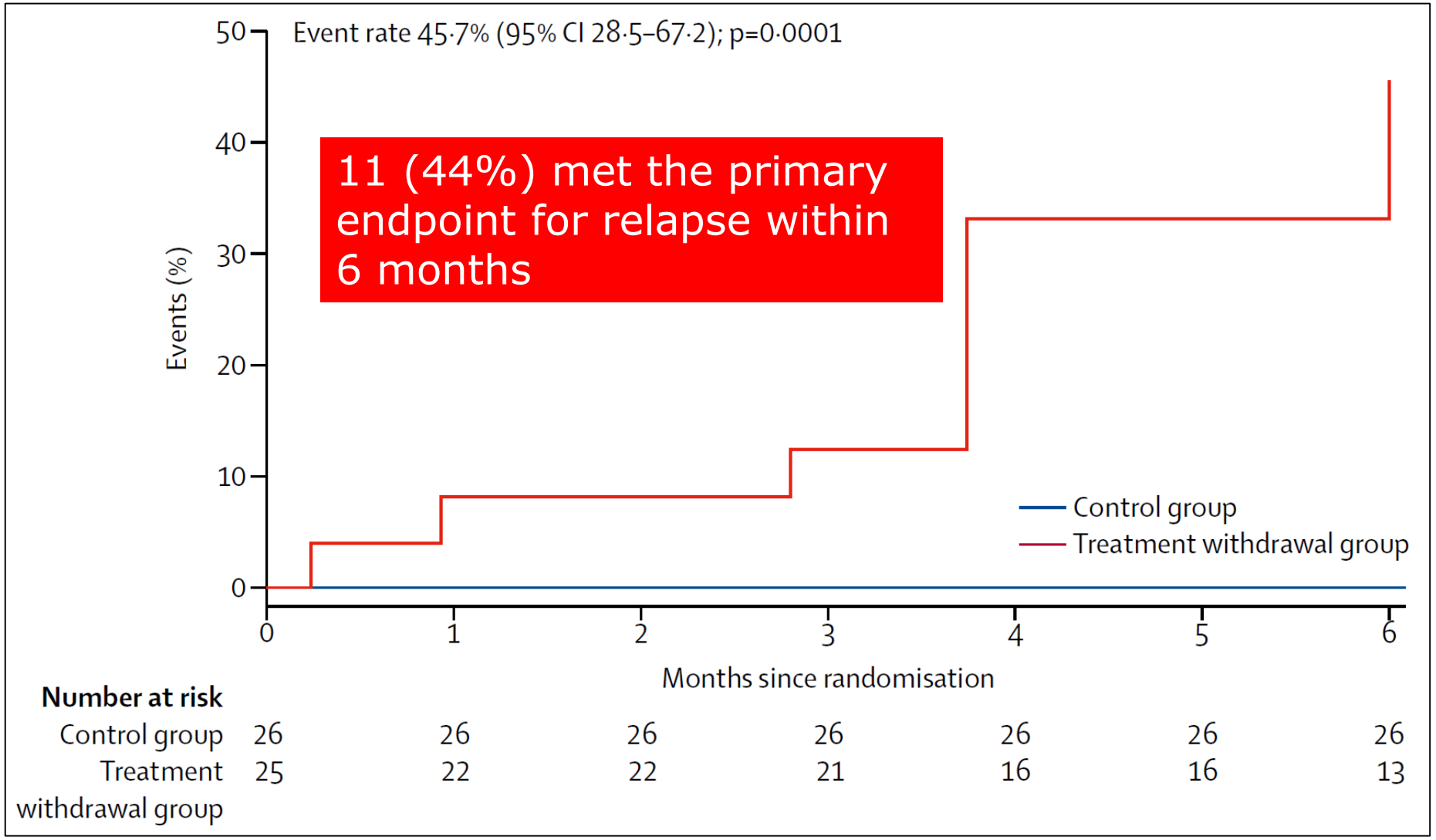
Randomized to **progressive medication withdrawal** versus **continued treatment**

Clinical assessment + NT-proBNP + CMR at 16 weeks and 6 months

Primary endpoint: **relapse** defined as ↘ **LVEF** by >10%, ↗ **LVEDV** by >10%, **2x rise in baseline NT-pro-BNP** or clinical evidence of HF

Lancet 2019;393:61–73.

Kaplan-Meier curve of time to primary endpoint



Messages

- **Treat first congestion**
- **«Start low, go slow, aim high»**
- **Early introduction of Sacubitril/Valsartan? Probably yes!**
- **SGLT2-inhibitors: in the starting blocks for a routine use**
- **Patients with recovered DCM should be considered as «in remission»**

MERCI!

PD Dr Philippe Meyer
Responsable de l'unité d'insuffisance cardiaque et de réadaptation cardiaque
Service de Cardiologie
Philippe.meyer@hcuge.ch

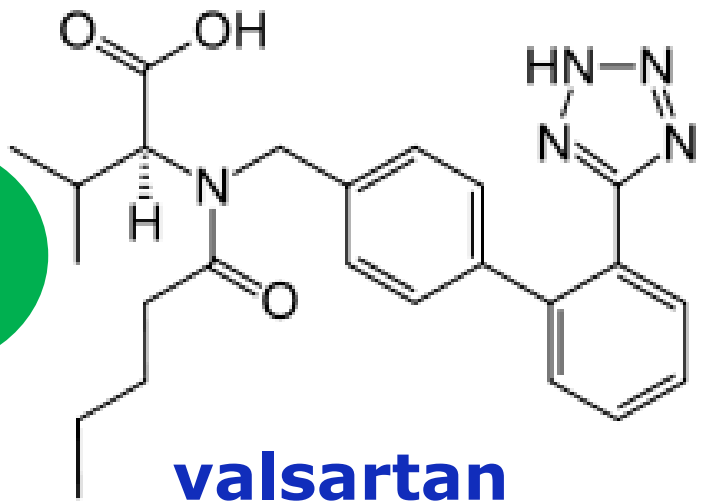
Colloque médecine interne générale – 24.09.2020

Dosage **200 mg 2x/j**
CHF **5.90** par jour
CHF **177.00** par mois

Dosage **10 mg 2x/j**
CHF **0.72** par jour
CHF **22.00** par mois

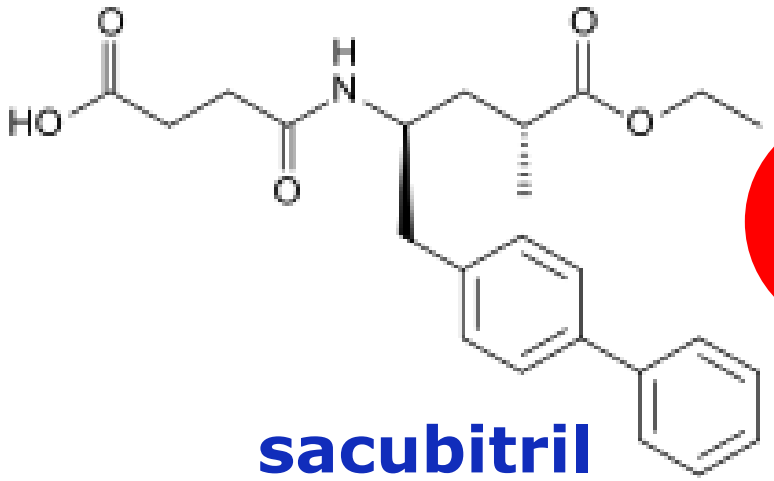
ARNI = Angiotensin receptor-neprilysin inhibitor

AR



valsartan

+



sacubitril

NI

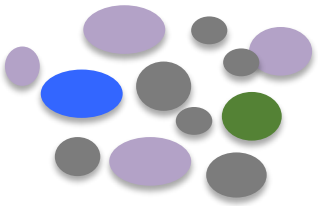
ARB

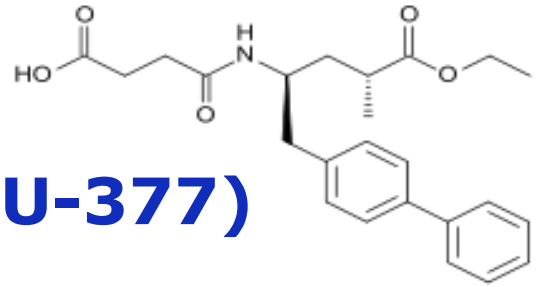
Neprilysin inhibitor

LCZ-696
(Entresto®)

Neprilysin inhibition

Neprilysin



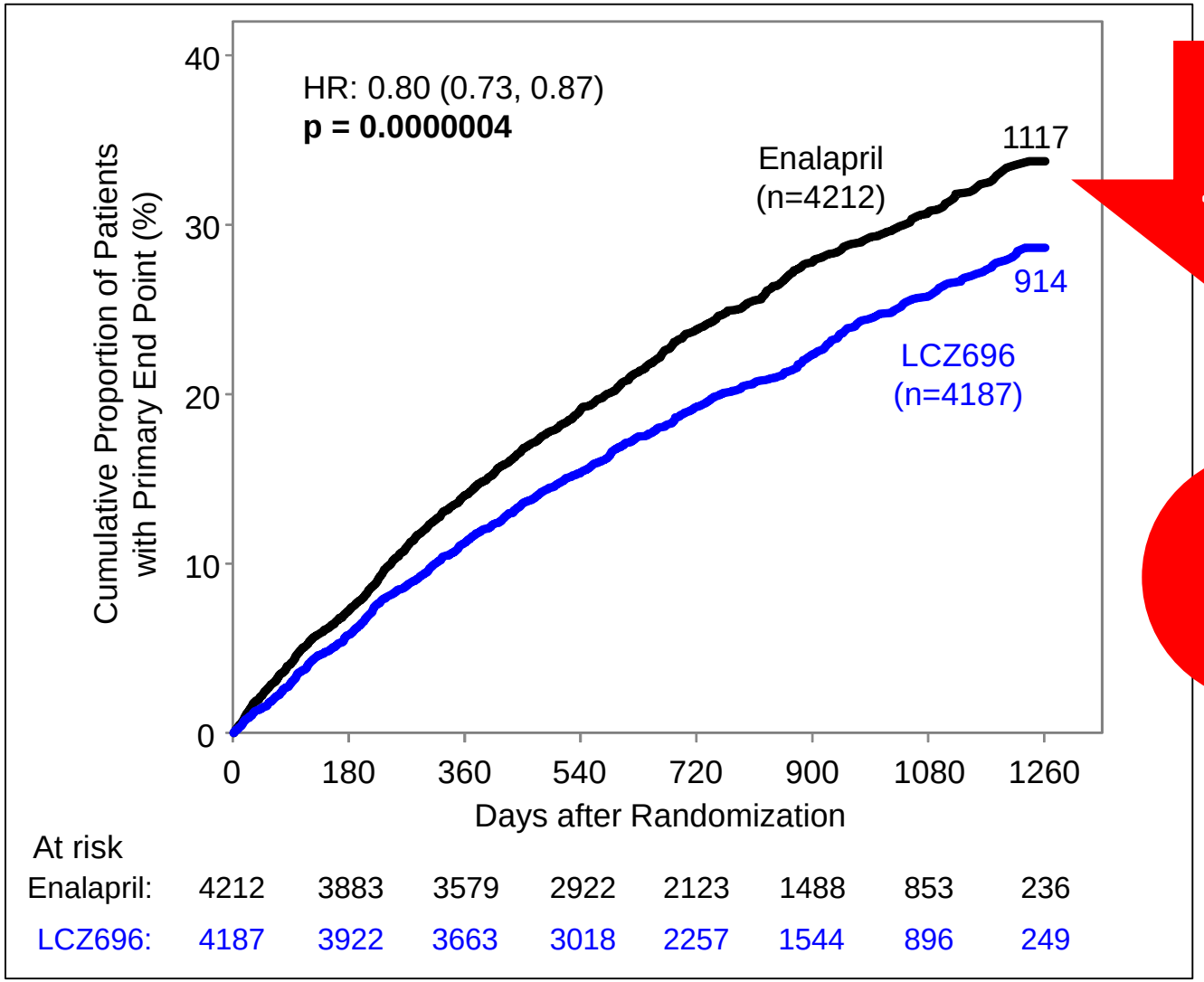


Sacubitril (AHU-377)

Sacubitrilat (LBQ-657)

Primary endpoint: CV mortality + HF hospitalizations

- 8442 patients
- **Ambulatory outpatients with chronic heart failure**
- LVEF ≤40%



RR -20%

NNT 21

McMurray JJ et al. N Engl J Med 2014;371:993-1004.

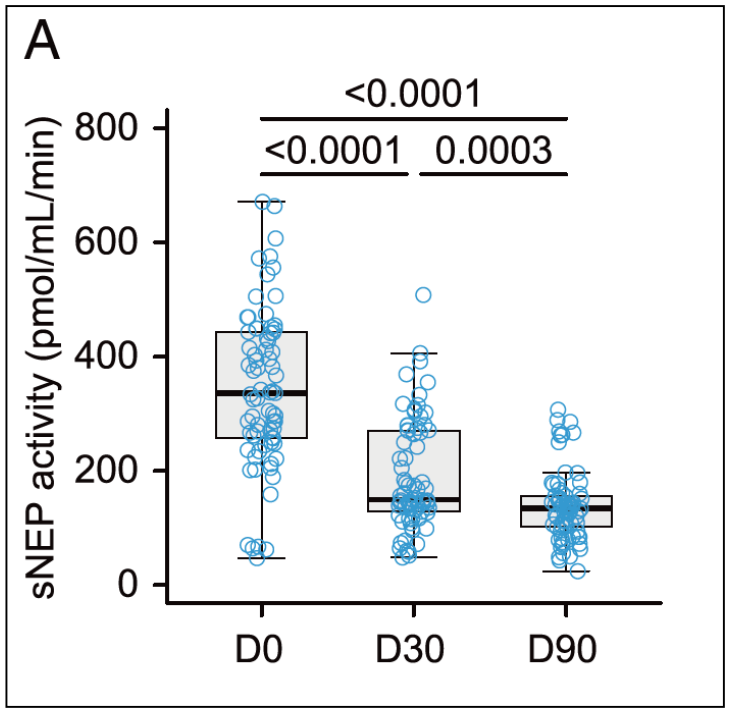
Effects of sacubitril/valsartan on neprilysin targets and the metabolism of natriuretic peptides in chronic heart failure: a mechanistic clinical study

- 73 chronic HF patients switched from ACE-I or ARB to sacubitril/valsartan
- Clinical / echocardiographic assessment
- Plasma biomarkers measured **at baseline, day 30 and day 90**
  - Circulating form of **neprilysin (sNEP)** activity and concentration
  - **NEP substrates** (ANP, BNP, adrenomedullin, substance P, GLP-1,…)
  - **Other cardiovascular biomarkers** (NT-proBNP, hs-troponin I,…)

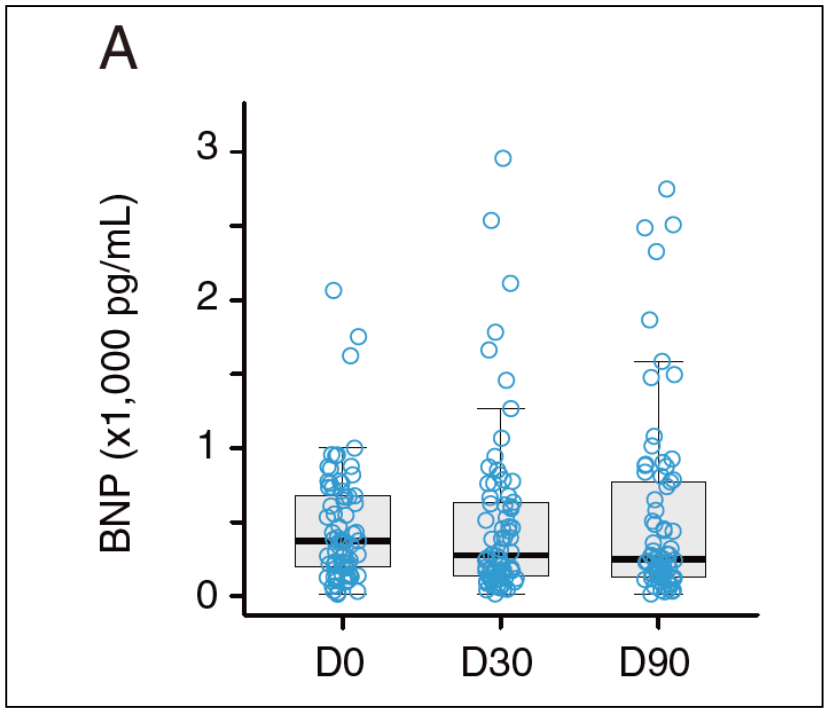
Nougué H et al. Eur J Heart Fail 2019;21:598–605.

Strong and rapid reduction of neprilysin activity but…

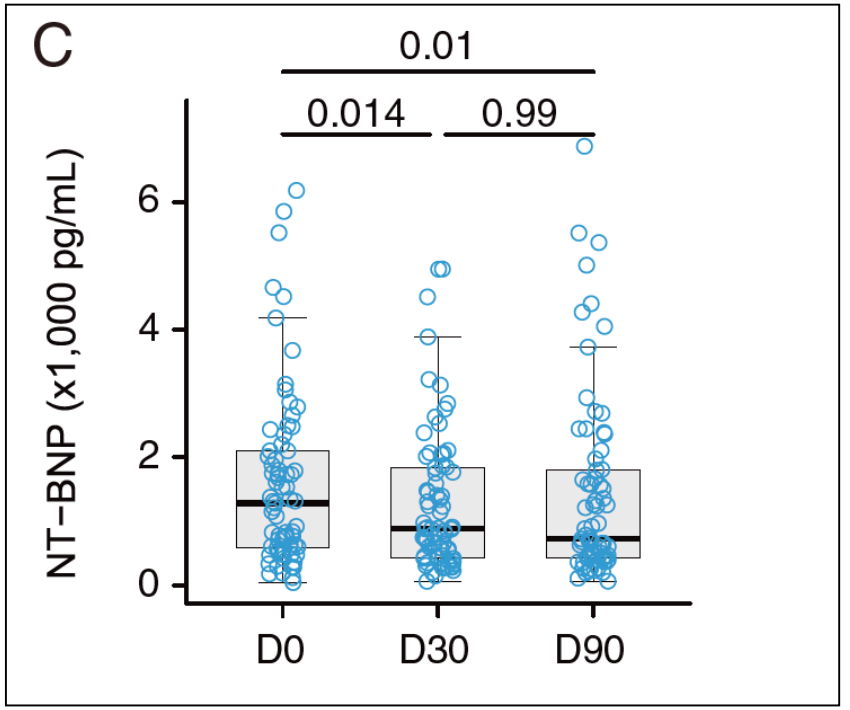
Strong and rapid reduction



No difference

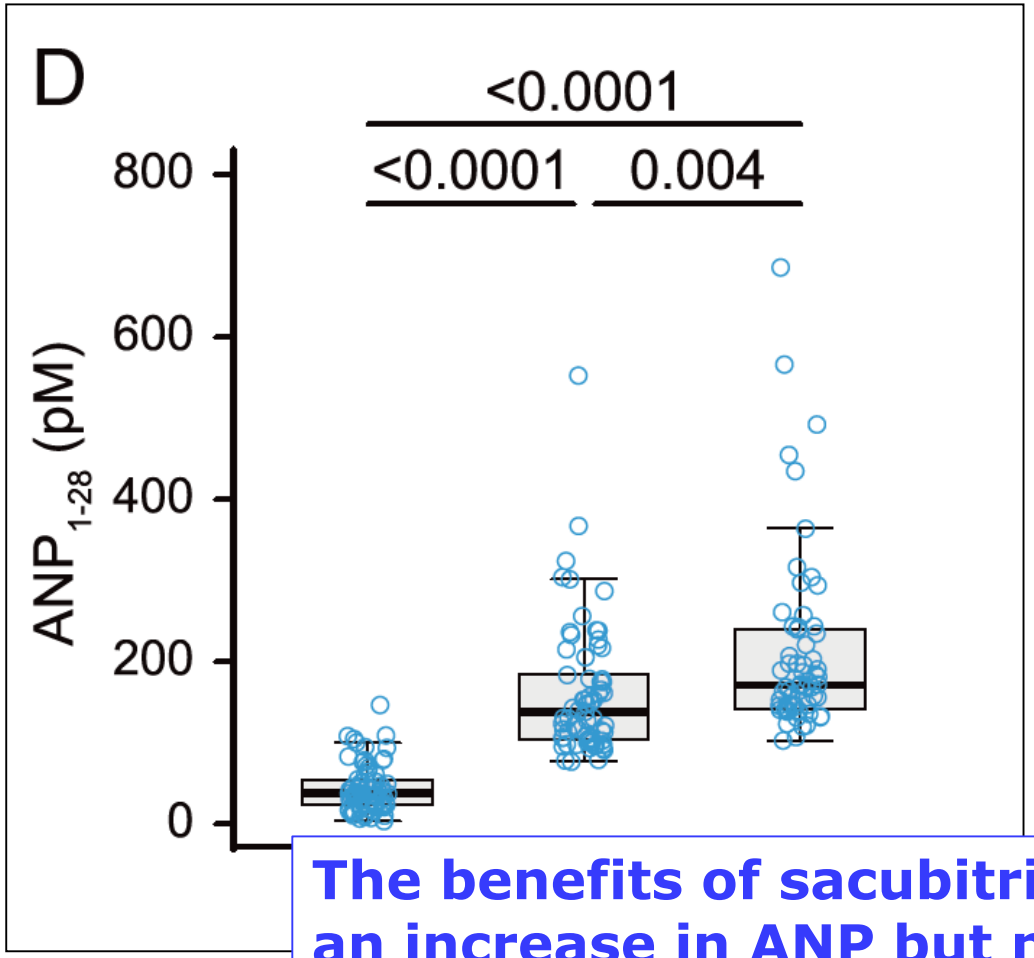


Mild reduction

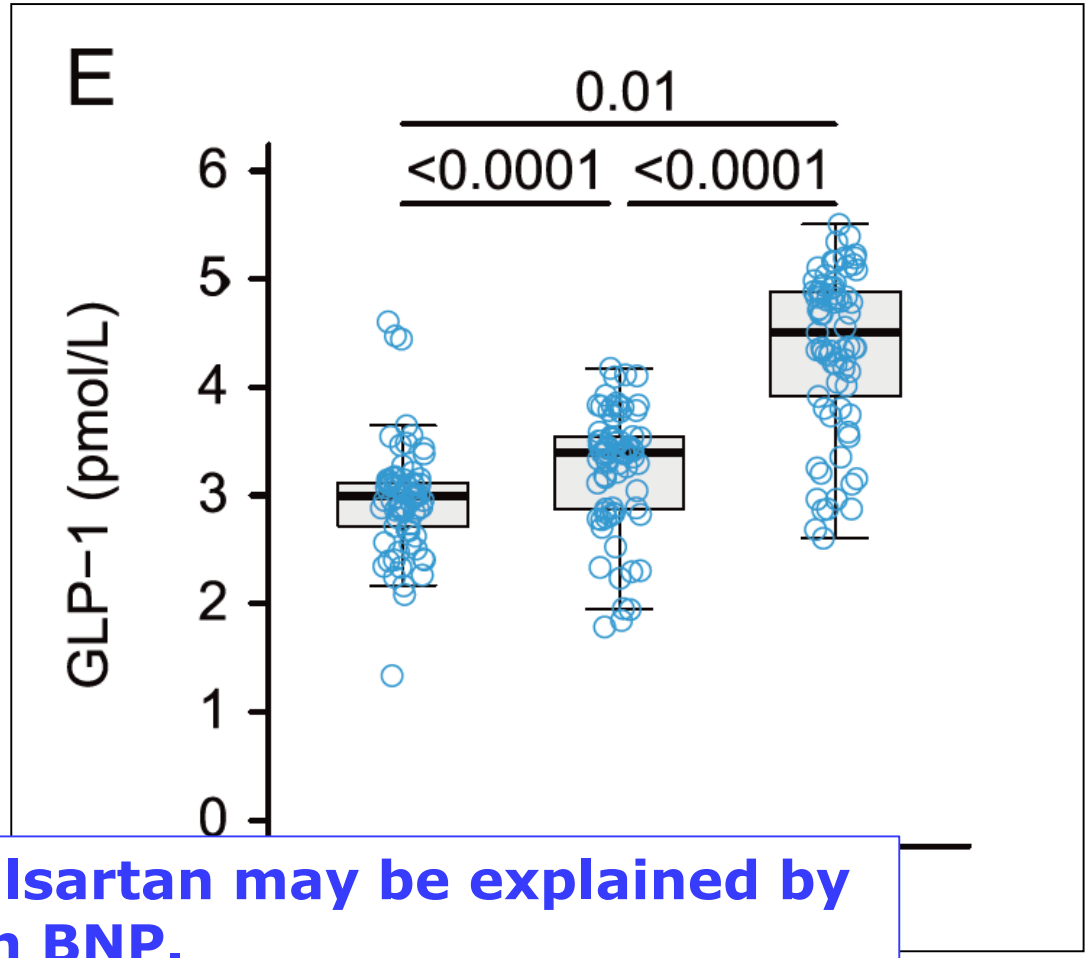


ANP and glucagon-like peptide 1 are strongly increased

4-fold increase

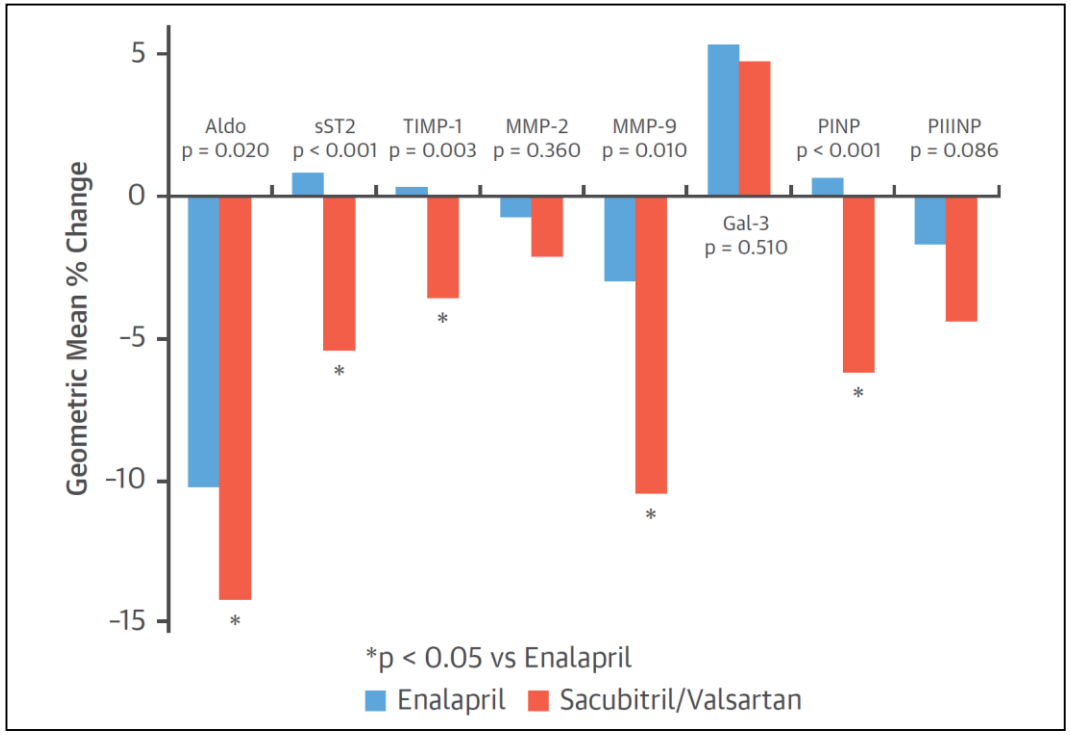


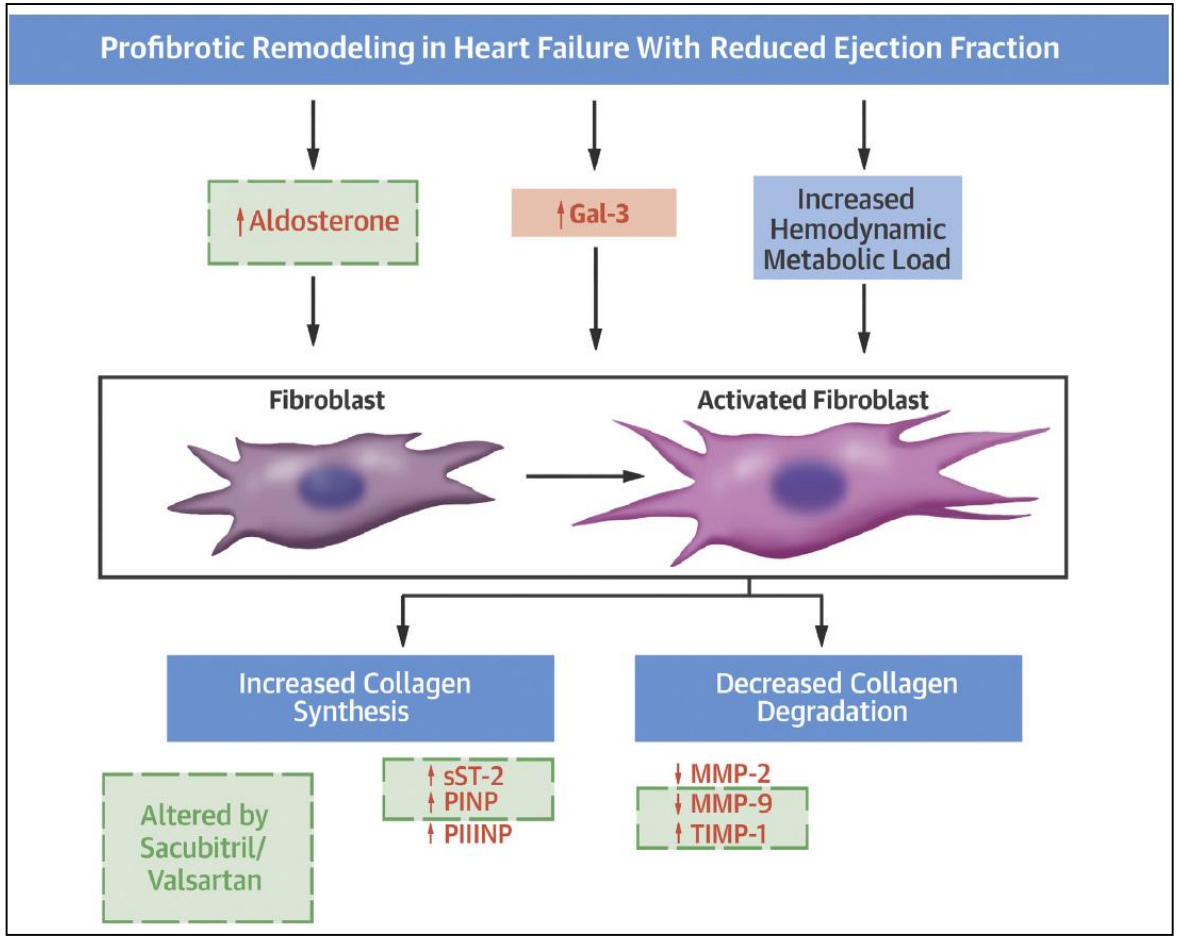
50% increase



The benefits of sacubitril/valsartan may be explained by an increase in ANP but not in BNP.
Other pathways are probably involved…

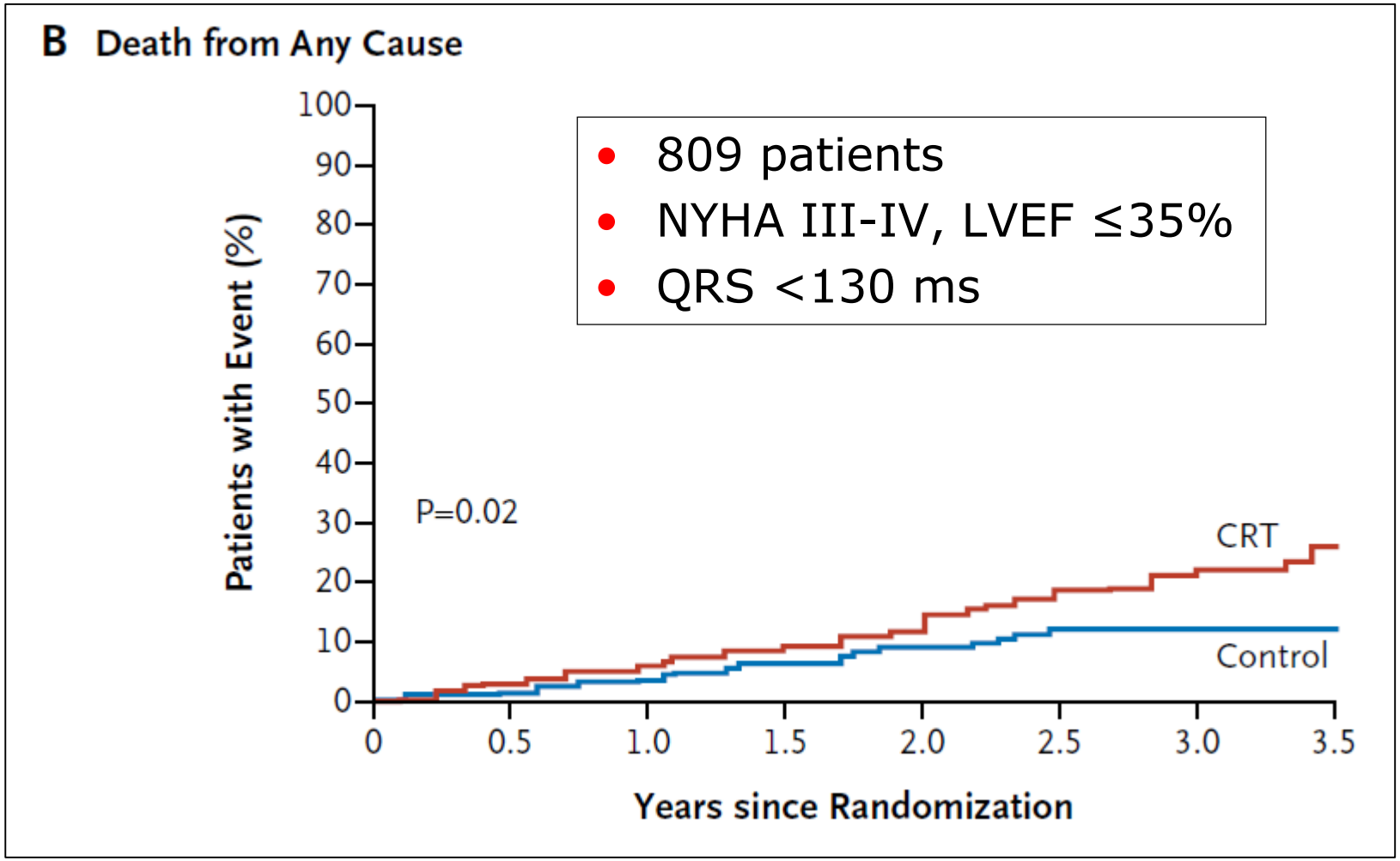
Effects of Sacubitril/Valsartan on Biomarkers of Extracellular Matrix Regulation in Patients With HFrEF





Zile MR et al. J Am Coll Cardiol 2019;73:795–806.

Cardiac-Resynchronization Therapy in Heart Failure with a Narrow QRS Complex



Ruschitzka F et al. N Engl J Med 2013.

Evolution of heart failure: «classical perspective»