Mr Abdelhamid 67 ans

- IDM antérieur en 2017 non revascularisé
- Coronarographie : Sténose IVA 60% avec thrombus

- NHYA II
- TA: 116/70 mmhg, Fc 78/mn, saO2: 96%
- Pas de congestion

Examens complémentaires

- ETT = VG 68/56 mm, FEVG en 2D Biplan 35 %, Séquelles nécrose antérieur , PRVG élevé , Im minime .
- ECG: Séquelles nécrose AS, QRS: 98 ms
- Holter rythmique: ESV de morphologie différente, Pas de TV.
- IRM : Absence de viabilité myocardique . FEVG 35%.
- BIOLOGIE
  - Nt pro BNP 6900 pg/ml
  - Créatinine 12 mg/l

Traitement

Ramipril	2,5 mg	1/j
Bisoprolol	2,5 mg	1/j
Acétylsalicylate de Lysine	160 mg	1/j
Atorvastatine	20 mg	1/j
Eplerenone	25 mg	1/j
Furosémide	40 mg	1/j

Evolution

- NHYA II III

- TA: 116/70 mmhg, Fc 78/mn, saO2: 96%
- Pas de congestion

- FE VG 35%

Efficacité et tolérance

	Juillet 2017	Novembre 2017	Décembre 2017	Mars 2018	Janvier 2020
Dose uperio	**0**	**24/26 x2**	**49/51 x2**	**97/103 x2**	**97/103 x2**
PA	**114/60**	**109/80**	**105/70**	**100/63**	**127/70**
Créatinine	**11,3**	**10,9**	**10,8**	**11,1**	**10**
Kaliémie	**4,3**	**4,4**	**4,3**	**4,3**	**4,7**
Nt pro BNP	**6900**			**1450**	**446**

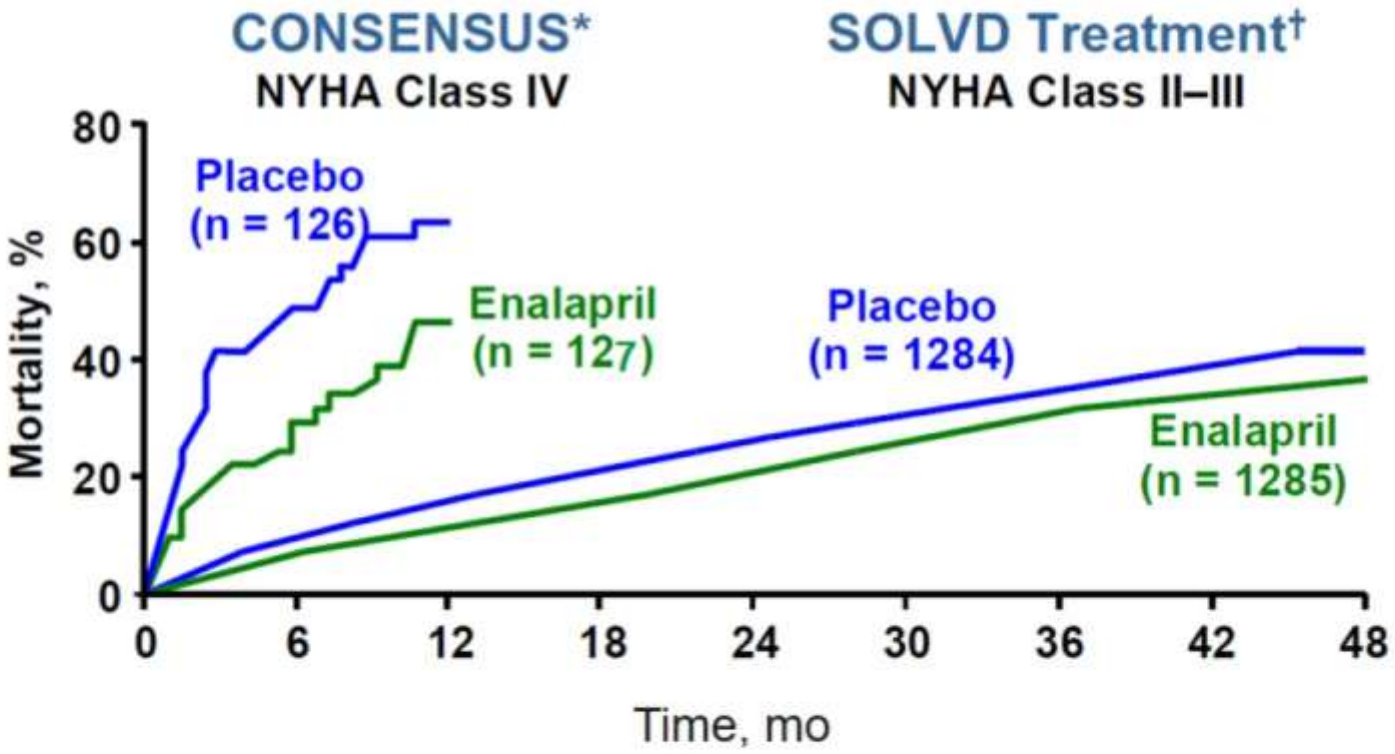
Traitement Janvier 2020

Bisoprolol 10 mg	**1/j**
Eplerenone 50 mg	1/j
Uperio 200 mg	2X/j
Atorvastatine 20 mg	1/j
Forxiga 10 mg	1/j
Acétylsalicylate de Lysine 75 mg	1/j

Status Janvier 2020

- Va bien
- NHYA I
- Marche 1h par jour
- FEVG : 45%
- NT PRO BNP: 446 pg/ml

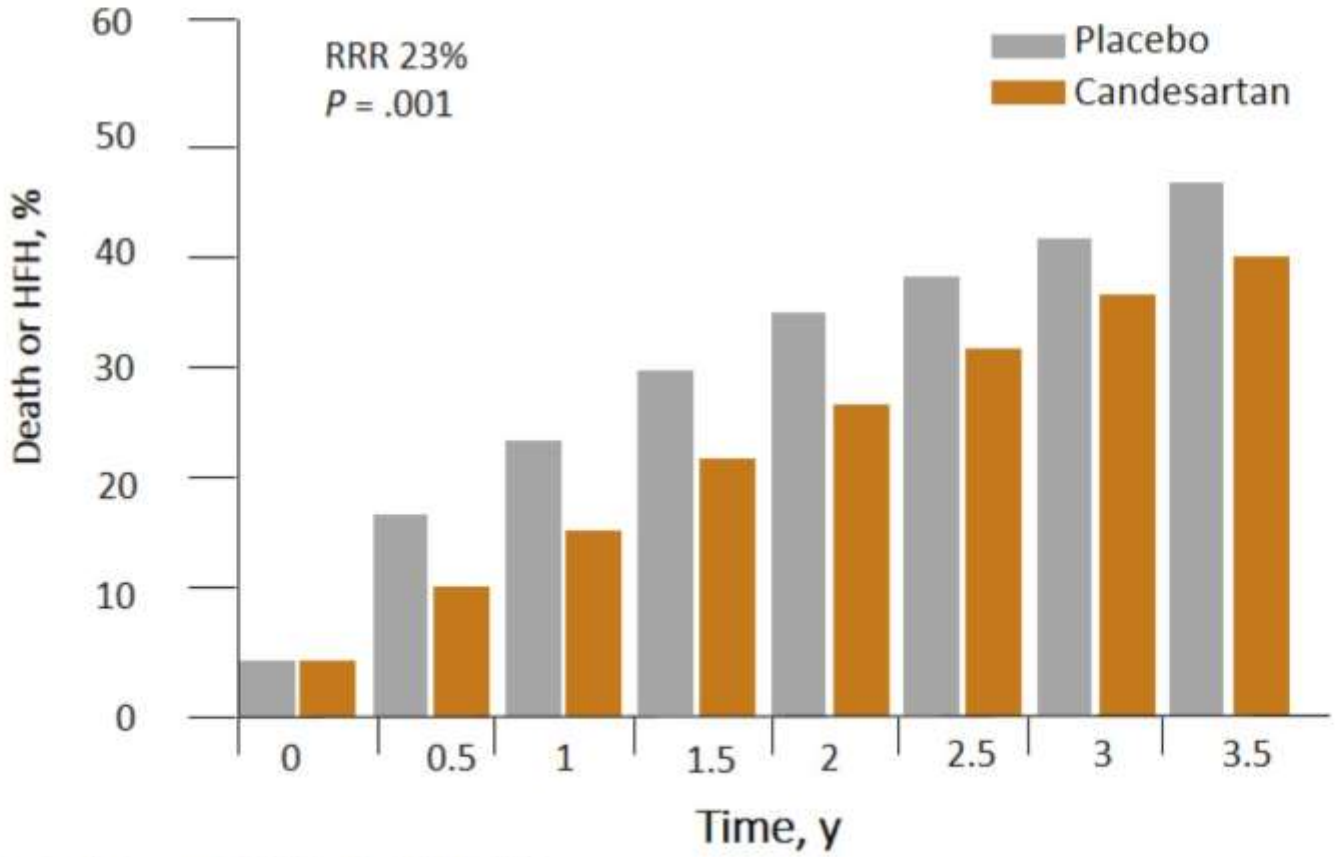
ACE Inhibitors Reduce Mortality, HF Hospitalization, and Improve Symptoms



*Risk reduction 40% (*P*=.002)
†Risk reduction 16 (*P*=.0036)
CONSENSUS Trial Study Group. *N Engl J Med*. 1987;316:1429-1435.
SOLVD Investigators. *N Engl J Med*. 1991;325:293-302.

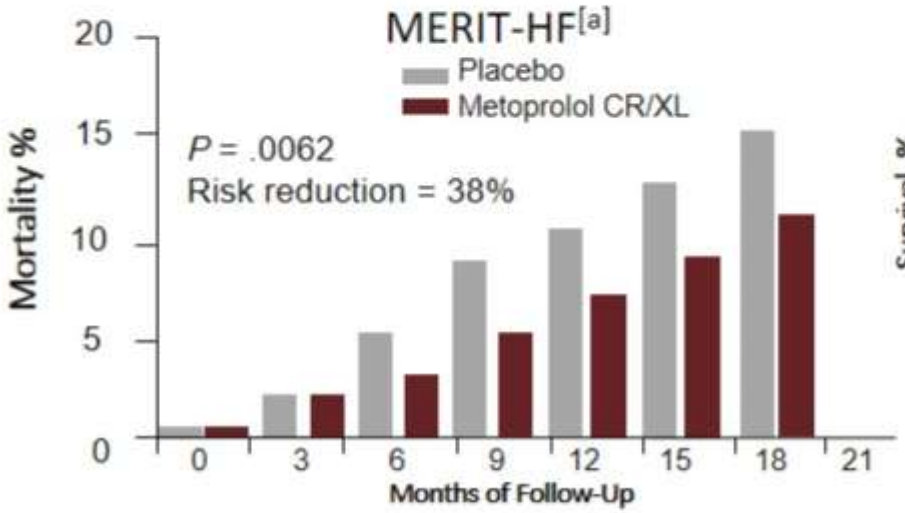
ARBs: Use Only if Intolerant to ACE Inhibitors Due to Cough

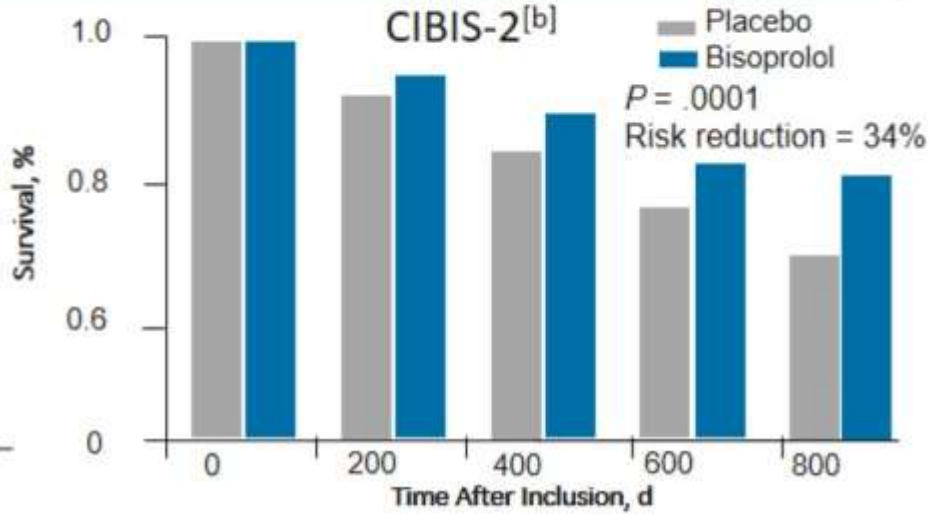
CHARM-Alternative
2028 mainly NYHA class II/III patients
55% beta blocker/24% MRA

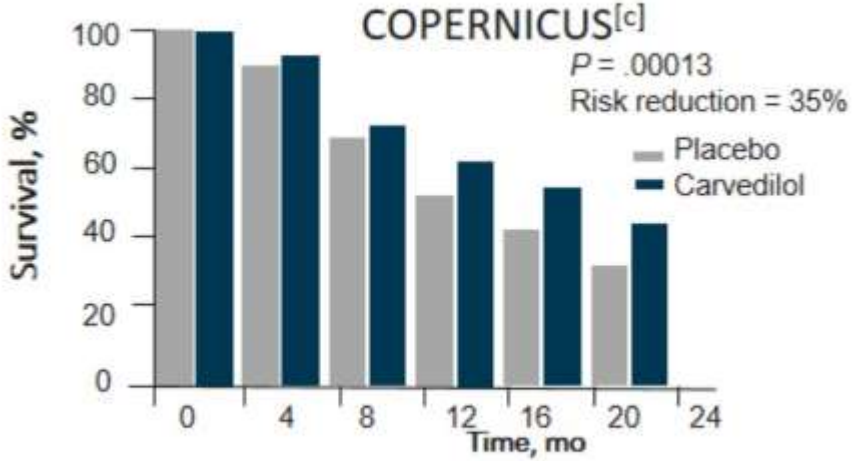


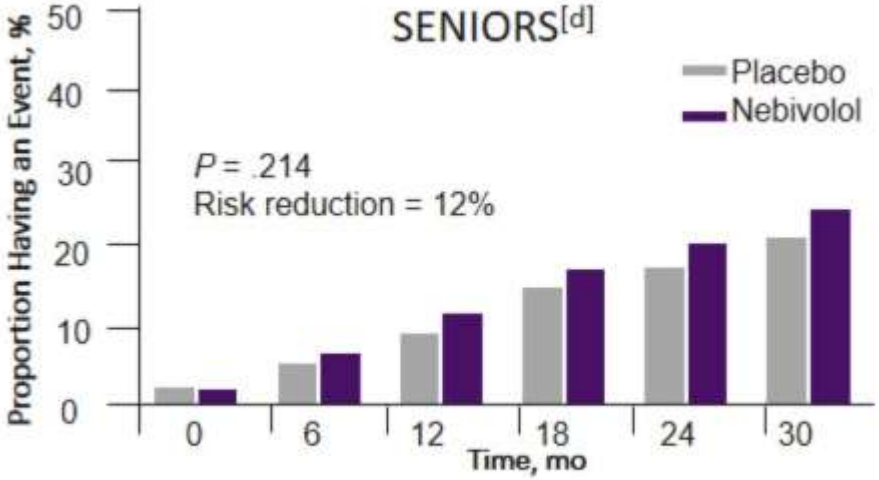
Granger CB, et al. *Lancet*. 2003; 362:772-776.

Beta Blockers Reduce All-Cause Mortality and Hospitalization in HFrEF







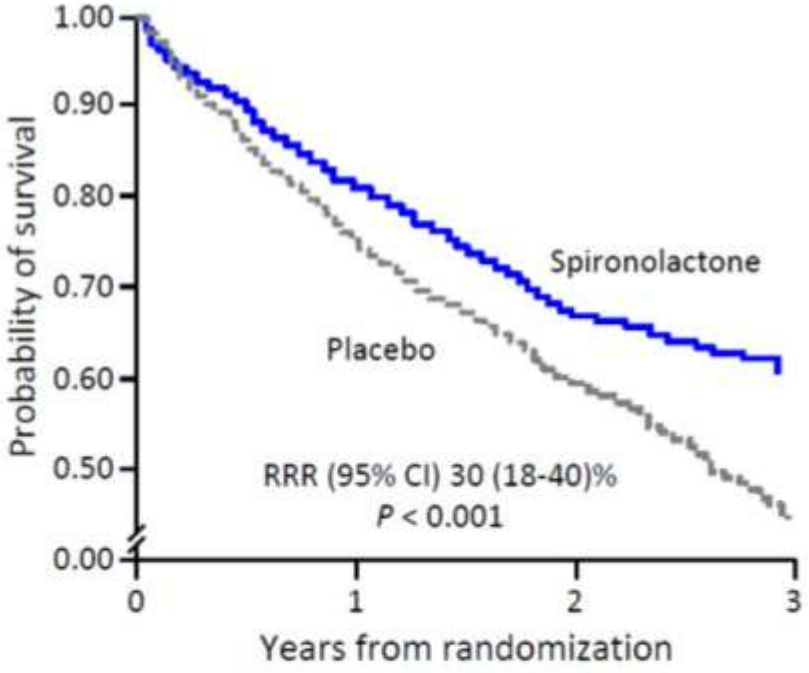


a. MERIT-HF Study Group. *Lancet*. 1999;353:2001-2007; b. CIBIS II Investigators. *Lancet*. 1999;353:9-13; c. Packer M, et al. *Circulation*. 2002;106:2194-2199; d. Flather MD, et al. *Eur Heart J*. 2005;26:215-225.

Benefit of MRAs in HFrEF

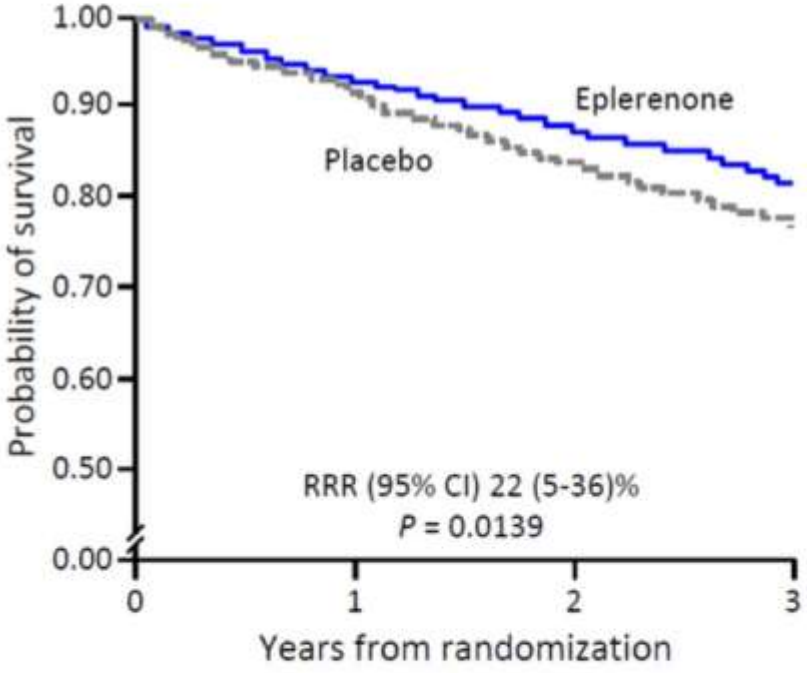
RALES [a]

1663 NYHA class III/IV patients
95% ACE-I/10% β-blocker



EMPHASIS-HF [b]

2737 NYHA class II patients
93% ACE-I or ARB/87% β-blocker



Slide courtesy of Lars Lund, MD.

a. Pitt B, et al. *N Engl J Med.* 1999;341:709-717; b. Zannad F, et al. *N Engl J Med.* 2011;364:11-21.

Treating HFrEF: Where Do We Start?

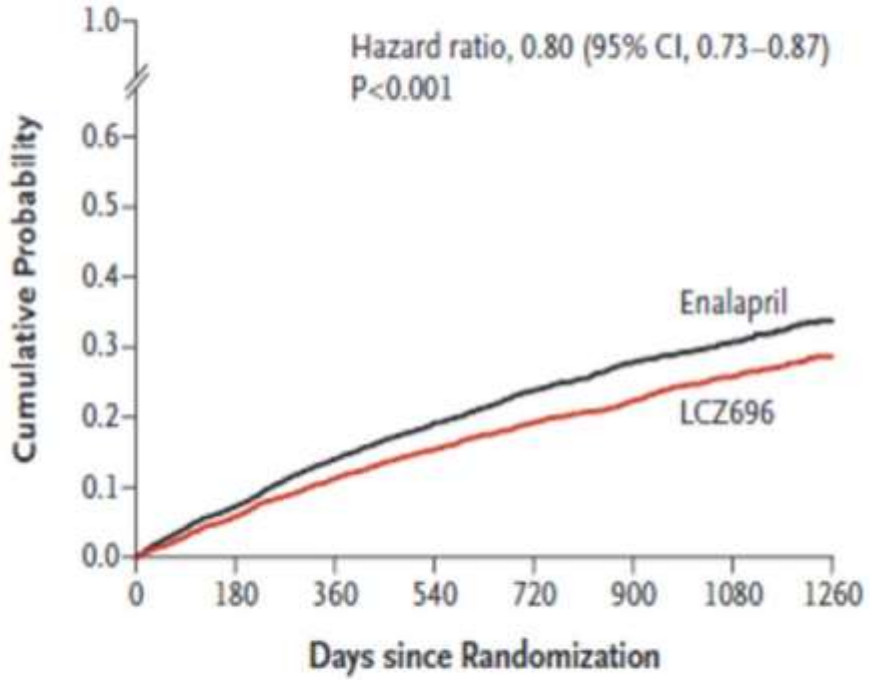
- Patient education is important
  - Inform the patient that even though the condition does not have a very good prognosis, there are very effective therapies
- Treatment benefits include:
  - Decreased mortality
  - Decreased hospitalizations
  - Improved QoL
- Uptitration of therapies toward target dose is important
- Inertia in clinical practices and busy schedules limiting time with patients contribute to delays in treatment uptitration
- Patient's first office visit is often the longest due to review of treatment plan and drug therapies
- It is important that patients understand the necessity for uptitration even if the patient's symptoms are stable

ARNI: Expanding the Treatment Foundation

- PARADIGM-HF[a]: active comparator trial comparing enalapril to sacubitril/valsartan in symptomatic HF patients with LVEF of $\leq$ 40% in the outpatient setting
  - Large global trial - NYHA II-IV
  - Run-in period, then randomized to enalapril or sacubitril/valsartan
- Treatment with sacubitril/valsartan in the hospital setting
  - PIONEER-HF[b]
  - TRANSITION[c]

a. McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004; b. Velazquez EJ, et al. *New Engl J Med*. 2019;380:539-548; c. Wachter R, et al. *Eur J Heart Fail*. 2019;21:998-1007.

PARADIGM-HF: Benefit of ARNI in HFrEF



No. at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

Primary Endpoint: Composite endpoint of death from CV causes or first hospitalization for HF

McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004.

Treatment With Sacubitril/Valsartan

- Data are now available to support safely starting sacubitril/valsartan in de novo patients, along with beta blocker and MRA
- Reasonably rapid titration is also possible; observe for hypotension and/or hyperkalemia and treat accordingly
- Shared decision making is important; include the patient in planning the treatment regimen

PIONEER-HF Is Complementary With Other Sacubitril/Valsartan Studies in Patients With HFrEF

Patients at Baseline	Hospitalized Post-ADHF		Ambulatory Chronic HF	
Study	PIONEER-HF[a]	TRANSITION[b]	PARADIGM-HF[c]	TITRATION[d]
Number of patients	N = 887	N = 1002	N = 8442	N = 498
Primary endpoint	Effects of sacubitril/valsartan vs enalapril on changes in NT-proBNP levels	% of patients achieving target dose in pre- vs post-discharge	Morbidity and mortality vs enalapril	Safety and tolerability- 3-wk vs 6-wk uptitration of sacubitril/valsartan
Treatment duration	12 wk	10 wk + 16 wk follow-up	27 mo	11 wk
Outpatients, n (%)	0	0	8442 (100%)	442 (89%)
Inpatients, n (%)	887 (100%)	1002 (100%)	0	56 (11%)
ACE inhibitor/ ARB naive, n (%)	459 (52%)	241 (24%)	0	33 (7%)
De novo, n (%)	303 (34%)	286 (29%)	0	0

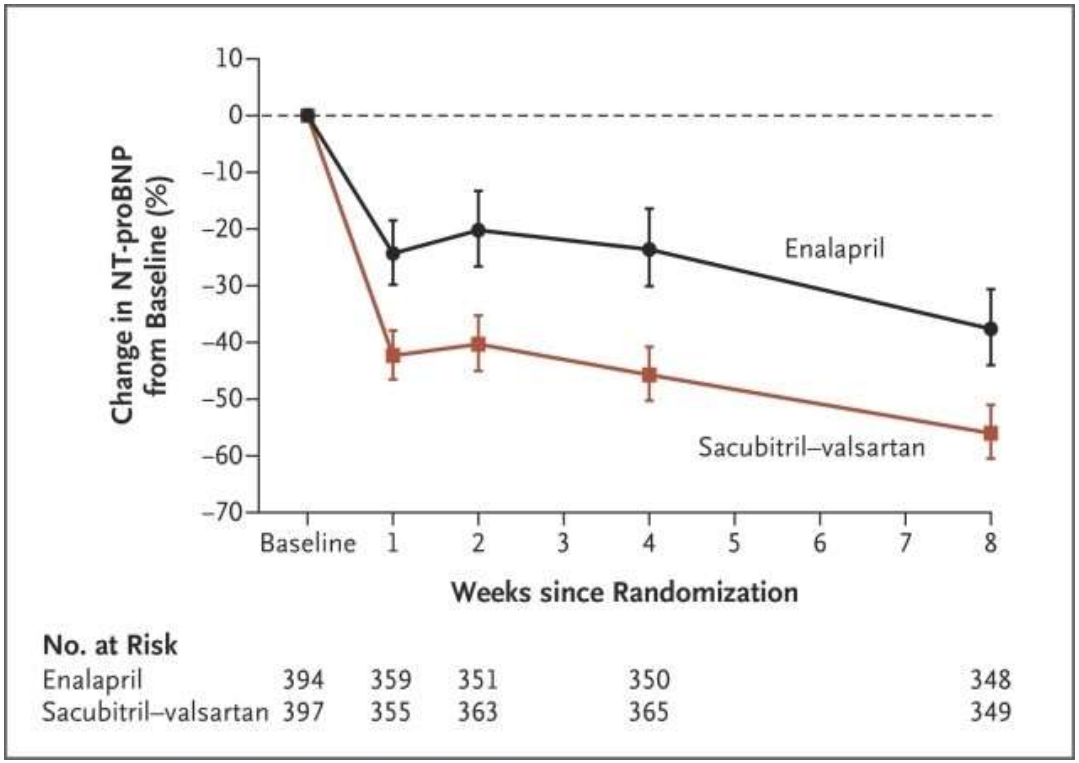
a. Velazquez EJ, et al. *New Engl J Med*. 2019;380:539-548; b. Wachter R, et al. *Eur J Heart Fail*. 2019;21:998-1007; c. McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004; d. Senni M, et al. *Eur J Heart Fail*. 2016;18:1193-1202.

PIONEER-HF

881 patients , 121 US centres

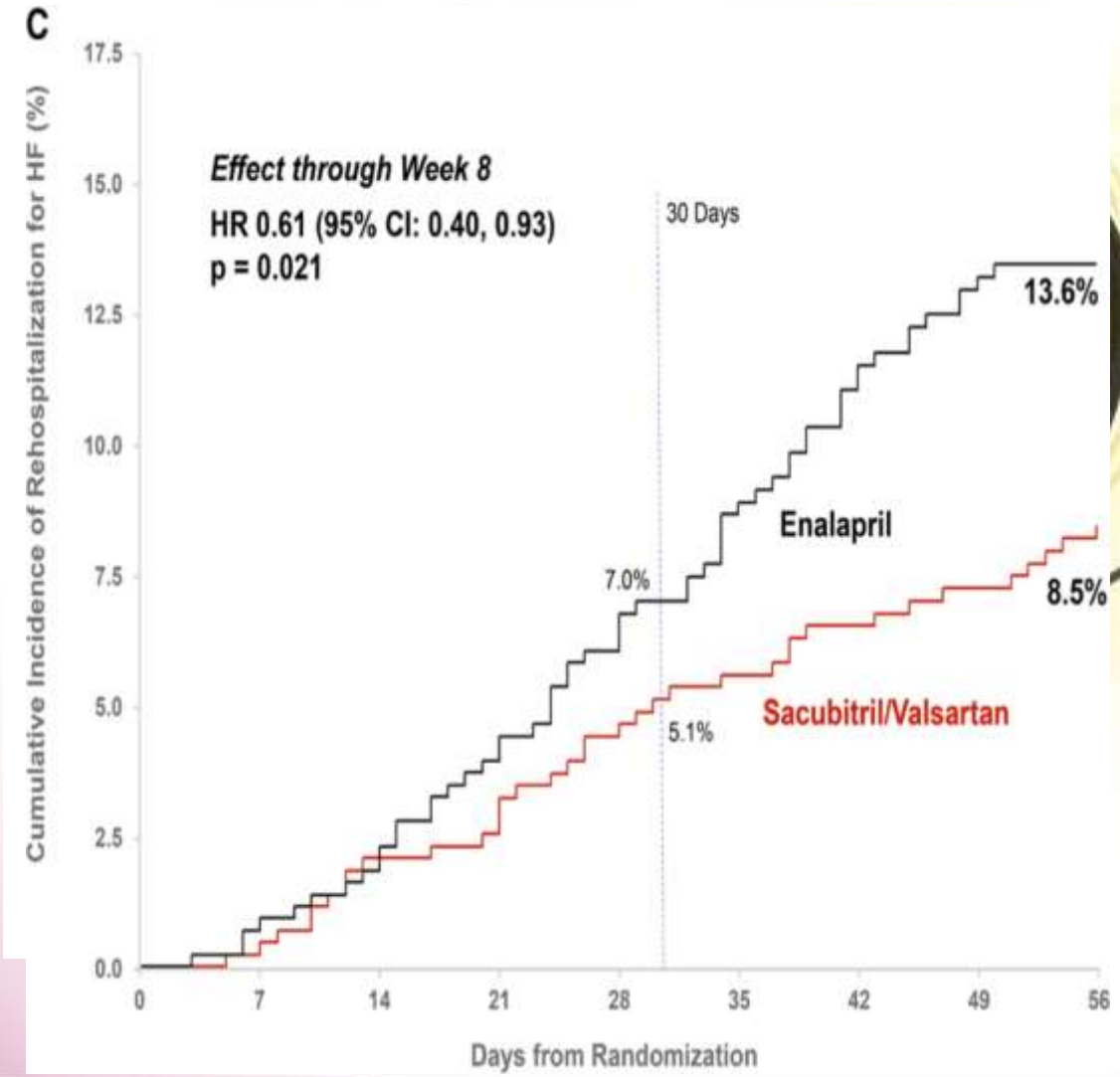
Sacubitril Valsartan (200mg b.d./Enalalpril 10mg b.d)

Rates of worsening renal function, hyperkalemia, symptomatic hypotension, similar



Velazquez E et al NEJM 2019:380;539

In Hospital Sacubitril/Valsartan reduces re-hospitalization for HF

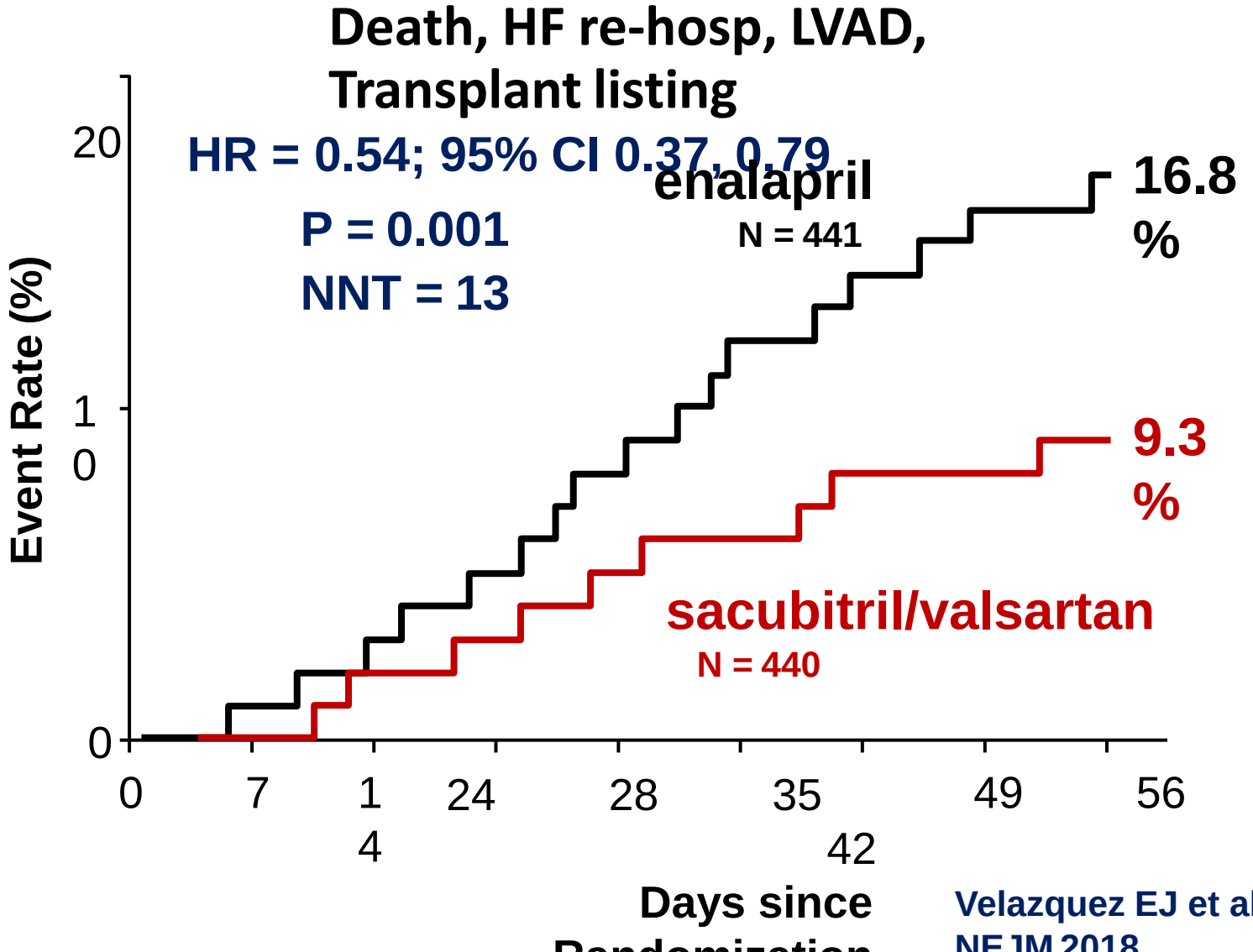


ARR5.1%

Morrow D et al. Circulation. 2019

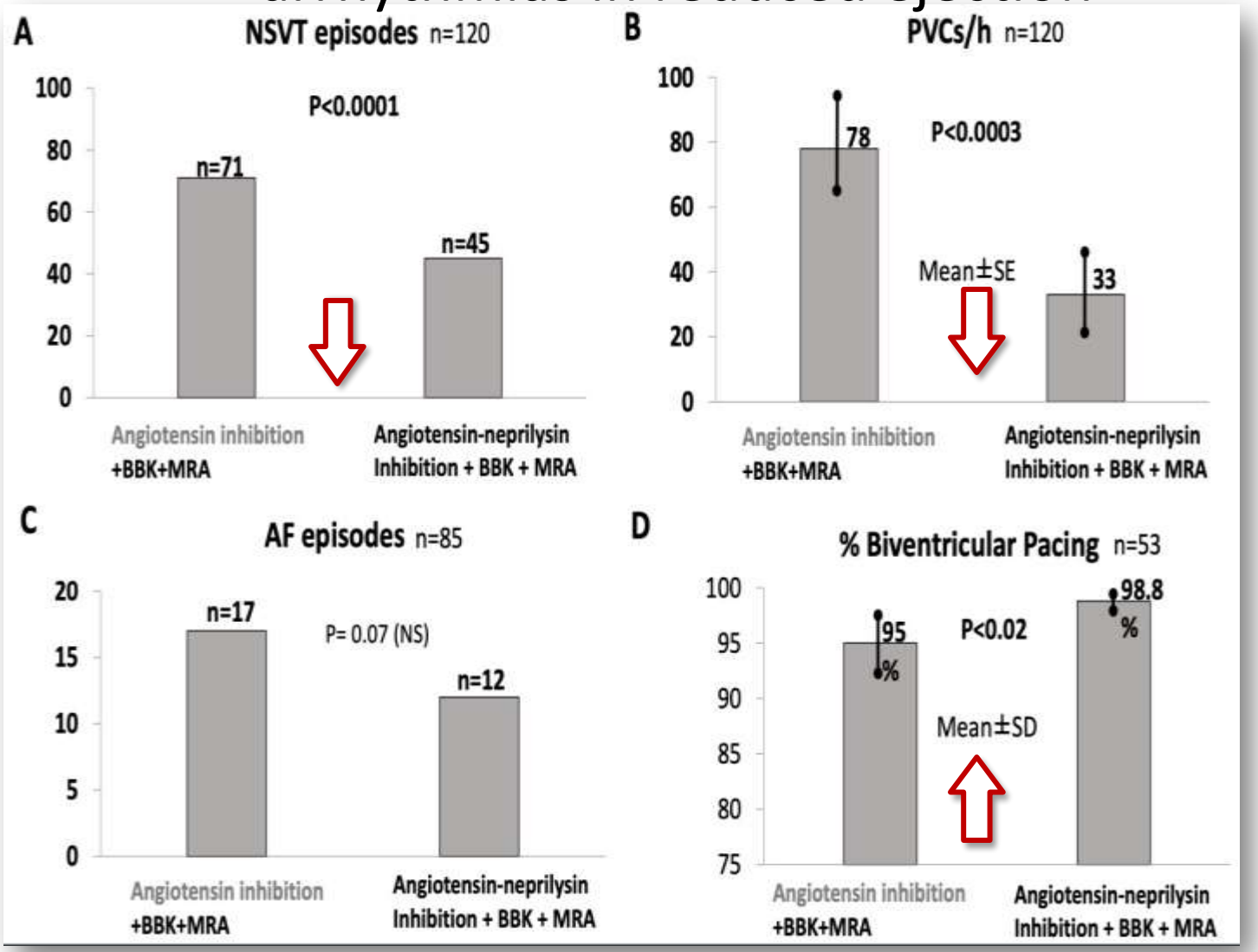
Sacubitril/valsartan in AHF

Serious Composite Clinical Endpoint



Velazquez EJ et al. NEJM 2018

Effects of angiotensin neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection



De Diego C et al. Heart Rhythm.

Conclusions for PIONEER-HF

- PIONEER-HF reconfirms the superiority of sacubitril/valsartan over ACE inhibitors as shown in PARADIGM-HF, now demonstrated in the hospital setting in a wide range of patients with HFrEF who have been hemodynamically stabilized after an ADHF event, including ACE inhibitor/ARB-naive and newly diagnosed (de novo) patients
- In-hospital initiation of sacubitril/valsartan compared with enalapril leads to:
  - Significantly greater and more rapid reduction in NT-proBNP, an established biomarker for HF severity and prognosis
  - Significantly greater reduction of the risk of serious clinical outcomes soon after discharge: in a prespecified, exploratory, serious clinical composite endpoint, risk of death, HF rehospitalization, LVAD implantation, or listing for cardiac transplant was reduced by 46% compared with enalapril over 8 weeks. The risk reduction was driven by the reduction of risk of death and HF rehospitalizations
- PIONEER-HF reconfirms that in-hospital initiation of sacubitril/valsartan shortly after hemodynamic stabilization has safety comparable to enalapril

Velazquez EJ, et al. *New Engl J Med*. 2019;380:539-548.

Extended Indications
In Patient Use of Sacubitril Valsartan-TRANSITION Study

Table. Top Reported Adverse Events by Timing of Sacubitril/Valsartan Initiation*

Adverse Event	Predischarge Initiation (%)	Postdischarge Initiation (%)
Hyperkalemia	11.1	11.3
Hypotension	12.3	9.1
Cardiac failure	6.8	8.5
Dizziness	5.6	4.2
Renal impairment	5.0	3.0

*all differences nonsignificant

1000 patients randomised to up titration of sacubitril/valsartan to target twice-daily dosages of either 100 mg or 200 mg was achieved and maintained in about 62% of patients who started before discharge, compared with 68% for those starting the drug after discharge.

Wacter R et al EJHF (2019) 21, 998–1007

PIONEER-HF and TRANSITION

	PIONEER-HF[a] Sacubitril/Valsartan vs Enalapril (n = 887) Predischarge Initiation	TRANSITION[b] Sacubitril/Valsartan Open Label (n = 1002) Pre- vs postdischarge Initiation
Primary endpoint	Change from baseline in NT-proBNP at 4 and 8 weeks	% patients achieving the target dose 200 mg twice daily 10 weeks after randomization
Key secondary endpoints	Proportional change in NT-proBNP; change in biomarkers of myocardial stress, cardiac fibrosis/remodeling, and tissue perfusion/injury; safety	% patients achieving the 2 highest doses of sacubitril/valsartan; % patients permanently discontinued due to AE during 10 weeks of treatment
Predefined exploratory endpoints	Serious clinical composite endpoint	
Trial results	Significantly greater and more rapid reduction in NT-proBNP. Significantly greater reduction of the risk of serious clinical outcomes soon after discharge: in a prespecified, exploratory, serious clinical composite endpoint, risk of death, HF rehospitalization, LVAD implantation, or listing for cardiac transplant was reduced by 46% compared with enalapril over 8 weeks	Approximately 50% of patients with HFrEF stabilized after an ADHF event achieved the target dose of 200 mg sacubitril/valsartan twice daily within 10 weeks. At week 10, more than 86% of patients in both groups were receiving any dose for 2 weeks or longer without interruption

a. Velazquez EJ, et al. *New Engl J Med*. 2019;380:539-548; b. Wachter R, et al. *Eur J Heart Fail*. 2019;21:998-1007.

Effect of Sacubitril/Valsartan on NT-proBNP in PARADIGM-HF

- In the PARADIGM-HF study, sacubitril/valsartan improved outcomes[a]
- Remodeling of the myocardium is central to the progression of HFrEF and is associated with risk for cardiovascular events[b]
  - Effect of sacubitril/valsartan on cardiac remodeling is not known
- In PARADIGM-HF, benefits of sacubitril/valsartan were associated with a reduction in NT-proBNP concentrations[c]
  - Reduction in NT-proBNP during GDMT for HFrEF is associated with reverse cardiac remodeling[d]
- The association of the change in NT-proBNP after initiation of sacubitril/valsartan with long-term changes in measures of cardiac remodeling was examined in the PROVE-HF trial[e]

a. McMurray JJV, et al. *N Engl J Med*. 2014;371:993-1004; b. Kramer DG, et al. *J Am Coll Cardiol.* 2010;56:392-406; c. Zile MR, et al. *J Am Coll Cardiol.* 2016;68:2425-2436; d. Daubert MA, et al. *JACC Heart Fail.* 2019;7:158-168. e. Januzzi JL, et al. *JAMA*. 2019;322:1085-1095.

PROVE-HF: Goals of the Study

Primary endpoint:

- Correlation between change in NT-proBNP and remodeling at 12 months:
  - LVEF
  - LVEDVi
  - LVESVi
  - LAVi
  - E/e'

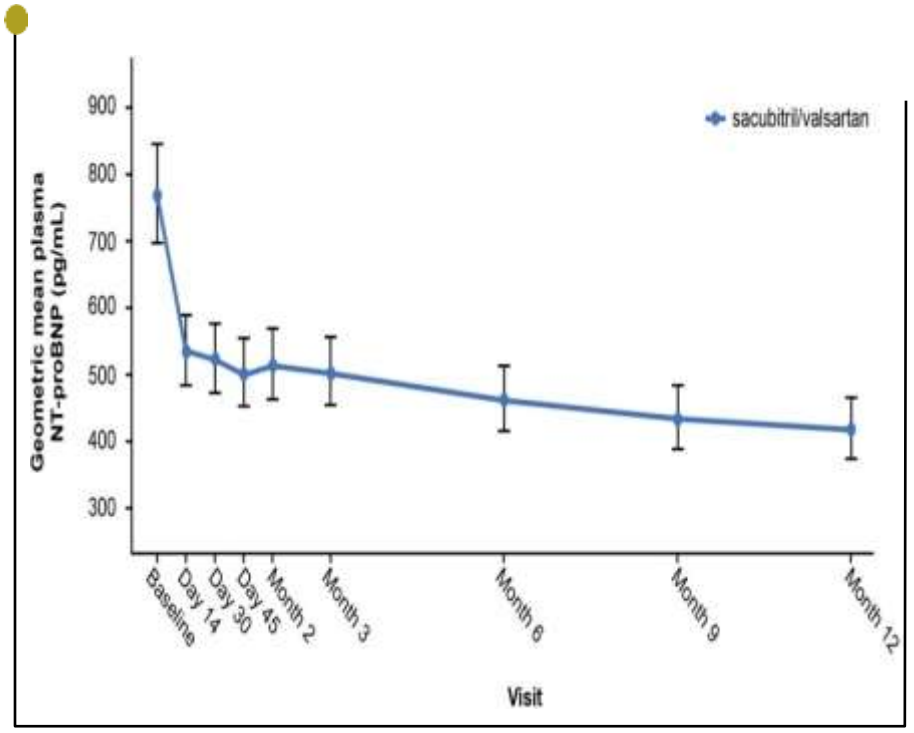
Secondary endpoints:

- Association between change in NT-proBNP and remodeling at 6 months
- Effect of sacubitril/valsartan on cardiac remodeling in specific patient subgroups not represented in the PARADIGM-HF trial:
  - New-onset HF and/or ACE inhibitor/ARB naive
  - Those with BNP or NT-proBNP concentrations below PARADIGM-HF inclusion criteria
  - Patients not reaching target doses of sacubitril/valsartan (97/103 mg twice daily)

Januzzi JL, et al. *Am Heart J.* 2018;199:130-136.

NT-proBNP concentrations

- Rapid and significant reduction of NT-proBNP was observed, with majority of reduction within the first 2 weeks



Primary endpoint

- From baseline to 12 months, weak yet significant correlations were observed between the change in Log_2-NT-proBNP concentration and cardiac remodeling parameters
- Parallel latent growth curve analyses suggested strong association between early NT-proBNP and subsequent reverse cardiac remodeling
- Similar correlations among 3 prespecified subgroups not represented in PARADIGM-HF*

Conclusion

- The degree of reverse remodeling demonstrated may help to explain how sacubitril/valsartan reduces morbidity and mortality in HFrEF

*(1) New-onset HF and/or patients not taking an ACEi/ARB at enrolment; (2) Patients with NT-proBNP lower than inclusion criteria for PARADIGM; (3)Patients not achieving target dose

Januzzi JL, Late Breaking Science in Heart Failure 1, FP 3007

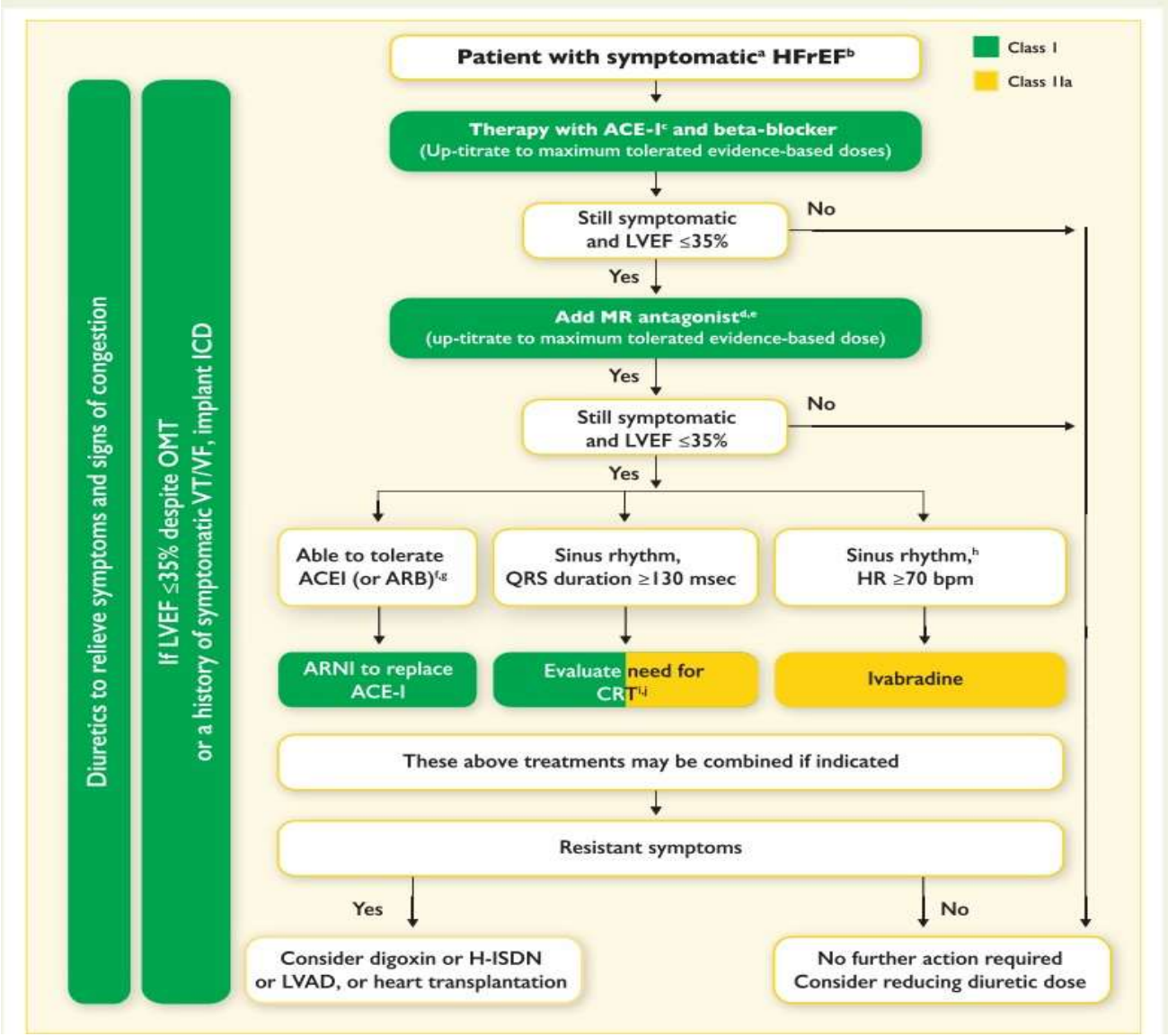
PROVE-HF: Primary Endpoint

- There was a 37% reduction in NT-proBNP at 12 months from baseline in patients treated with sacubitril/valsartan
- From baseline to 12 months, significant correlations were observed between the change in NT-proBNP concentration and cardiac remodeling parameters
- Parallel latent growth curve analyses demonstrated strong association between early NT-proBNP change and subsequent reverse cardiac remodeling

Parameter	Pearson r (IQR)	*P* Value
NT-proBNP (pg/mL) / LVEF (%)	-0.381 (-0.448, -0.310)	<.001
NT-proBNP (pg/mL) / LVEDVi (mL/m^2)	0.320 (0.246, 0.391)	<.001
NT-proBNP (pg/mL) / LVESVi (mL/m^2)	0.405 (0.335, 0.470)	<.001
NT-proBNP (pg/mL) / LAVi (mL/m^2)	0.263 (0.186, 0.338)	<.001
NT-proBNP (pg/mL) / E/E'	0.269 (0.182, 0.353)	<.001

Januzzi JL, et al. *JAMA*. 2019;322:1085-1095.

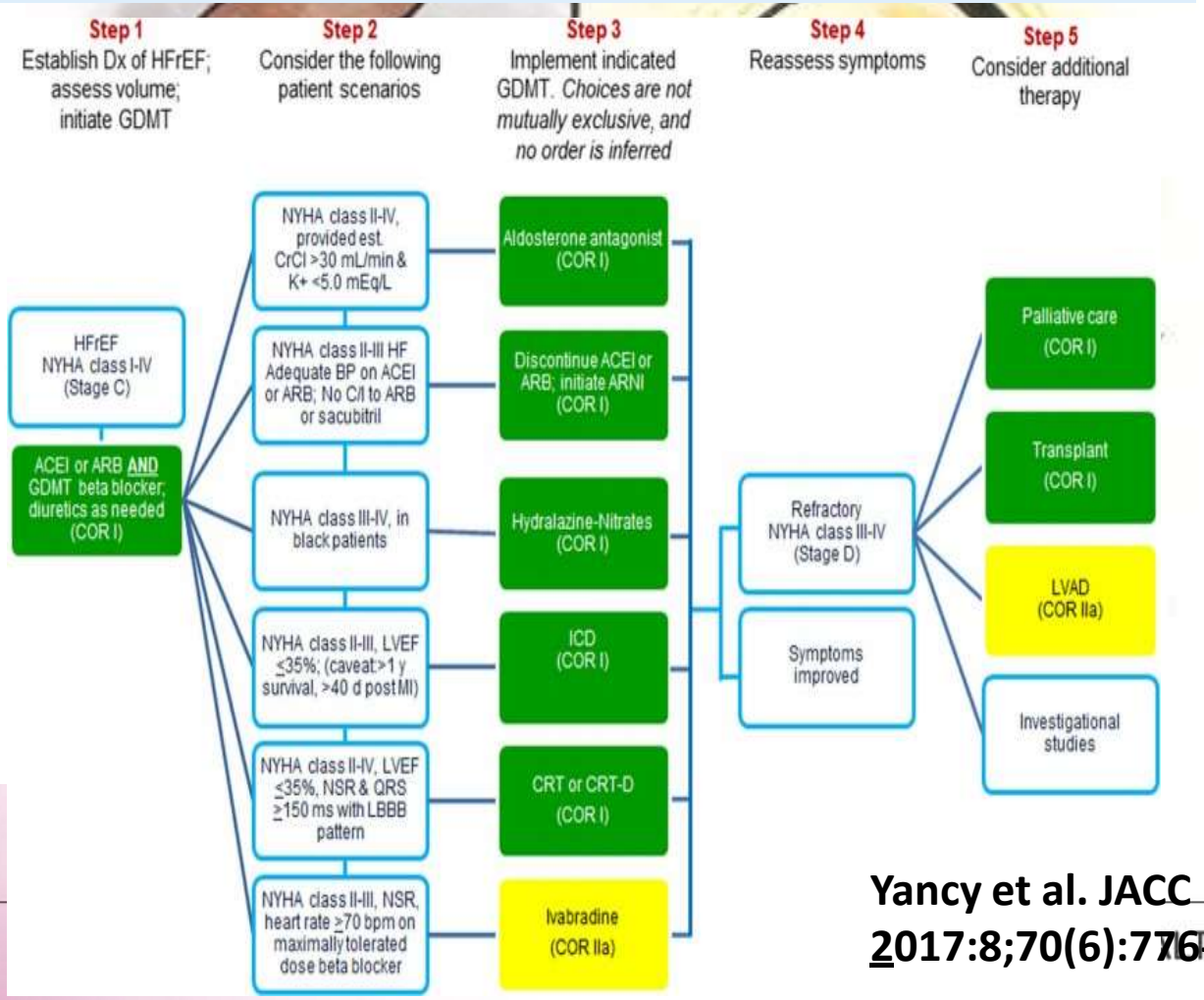
Therapeutic algorithm for a patient with symptomatic heart failure with reduced



2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure , Eur J Heart Fail. 2016

CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE

2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure



Yancy et al. JACC 2017:8;70(6):776-803

ESC HFA 2019 Clinical Practice Update Highlights SGLT2 Inhibitors, Sacubitril/Valsartan, K^+ Binders...

SGLT2 inhibitors[a]

- Canagliflozin, dapagliflozin, empagliflozin should be considered in patients with T2D with/at risk of CVD (and prioritized over metformin) to prevent onset of HFH
- No specific recommendations can be made for established HF... yet

Sacubitril/Valsartan[b]

- May be considered in place of ACE inhibitor/ARB for patients hospitalized with new-onset or decompensated chronic HF to reduce the short-term risk of AEs and avoid ACE inhibitor titration/switching

Potassium binders[b]

- Patiromer and ZS-9 may be considered to manage hyperkalemia in HF with or without CKD, or in such patients to enable uptitration of MRAs while avoiding hyperkalemia

Canakinumab[b]

- Evidence not sufficient in HF

HFmrEF[b]

- Beta blockers, candesartan, and spironolactone *may be considered* for symptomatic patients

Rivaroxaban[b]

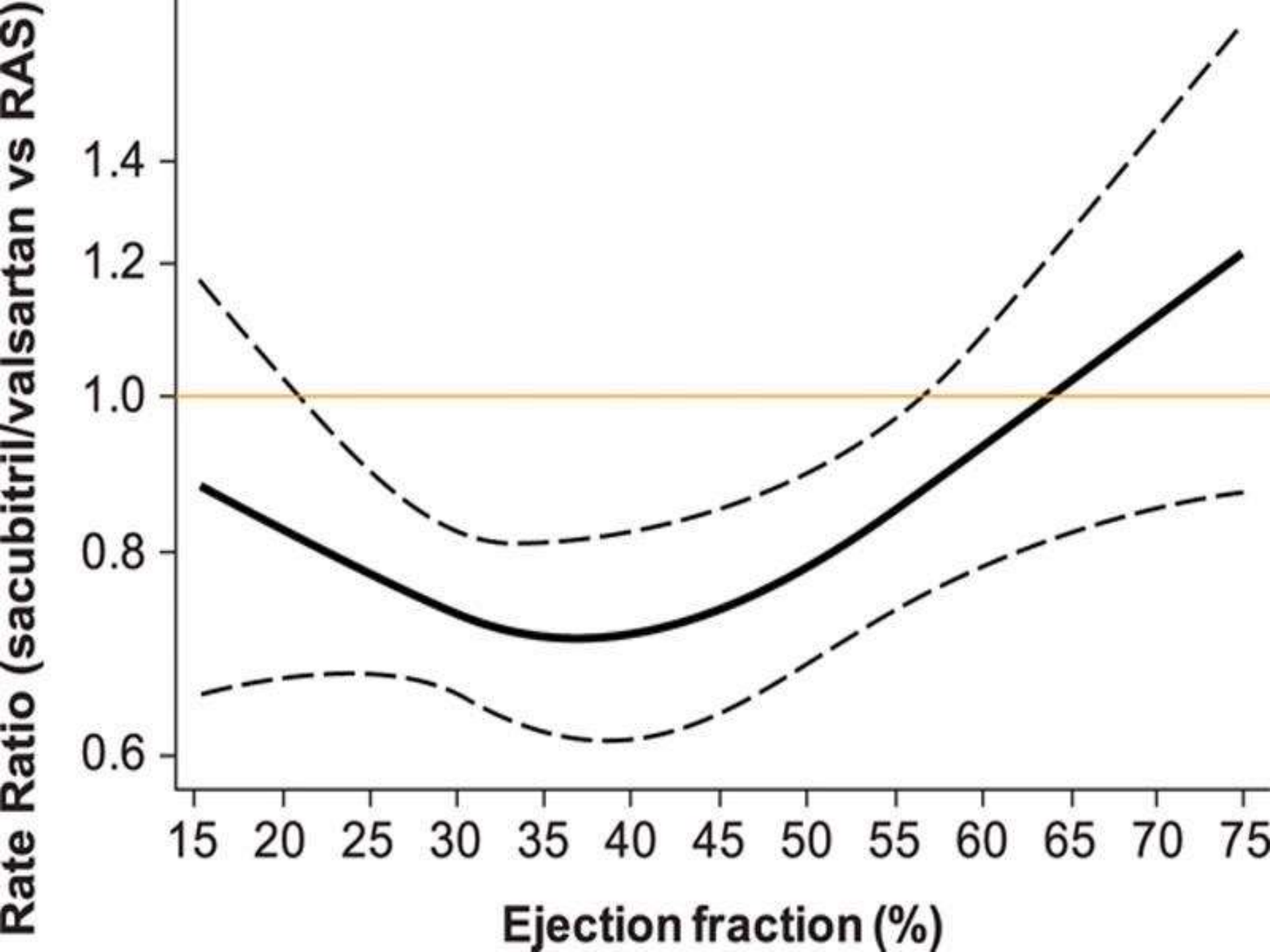
- Low dose with aspirin may be considered to reduce stroke and CV death in ambulatory patients with CAD and HF in NYHA I/II with EF > 30%
- Cannot be recommended in recent HrEF hospitalization or persistent NYHA III/IV

a. Cosentino F, et al. *Eur Heart J.* 2019;00:1-69; b. Seferovic PM, et al. *Eur J Heart Fail.* 2019;21:1169-1186.

HFmrEF: Effective Therapies

- Meta-analysis of beta blockers demonstrated benefit of therapy up to LVEF of 50%[a]
- TOPCAT trial with spironolactone demonstrated benefit of MRAs in patients at the lower end of the LV spectrum[b]
  - Enrollment included patients with LVEF of 44-85%
  - Mean LVEF was 57%; median LVEF was 56%
- CHARM trial demonstrated benefit of candesartan to improve outcomes in HFmrEF to a similar degree as in HFrEF [c]

a. Cleland J, et al. *Eur Heart J.* 2018;39:26-35; b. Solomon S, et al. *Eur Heart J.* 2016;37:455-462; c. Lund L, et al. *Eur J Heart Fail.* 2018;20:1230-1239.


Rate Ratio (sacubitril/valsartan vs RAS)
1.4
1.2
1.0
0.8
0.6
15
20
25
30
35
40
45
50
55
60
65
70
75
Ejection fraction (%)

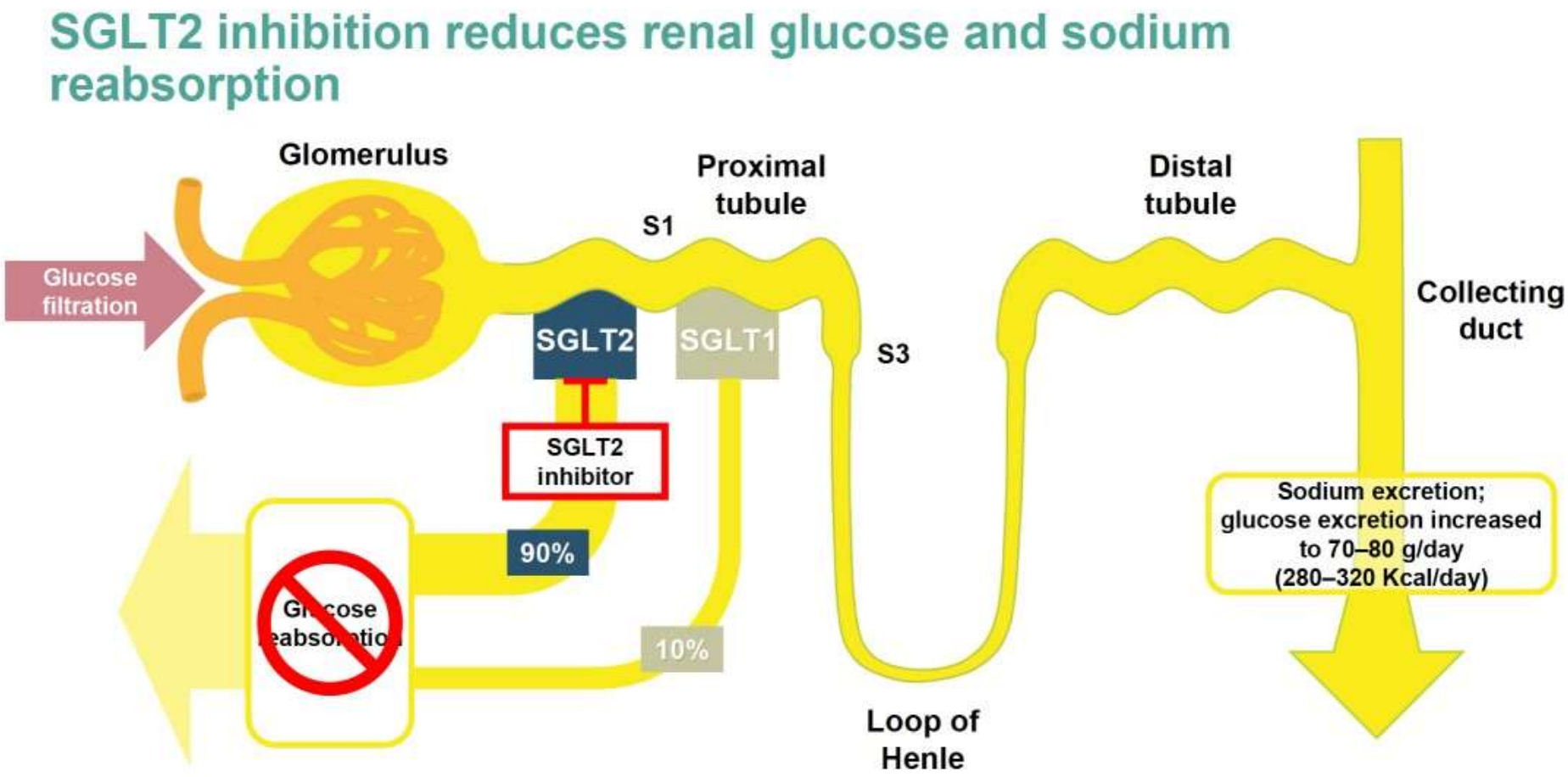
Starting and Target Dosing of HFrEF Therapies

Drug	Starting Dose	Target Dose
Beta Blockers [a]		
Bisoprolol	1.25 mg once daily	10 mg once daily
Carvedilol	3.125 mg twice daily	25 mg twice daily for weight ≤85 kg and 50 mg twice daily for weight > 85 kg
Metroprotol succinate	12.5 - 25 mg daily	200 mg daily
Nebivolol	1.25mg once daily	4 mg once daily
ARNI [b]		
Sacubitril/valsartan	24/26 mg - 49/51 mg twice daily	97/103 mg twice daily
ACE Inhibitors [b]		
Enalapril	2.5 mg twice daily	10 - 20 mg twice daily
Lisinopril	2.5 - 5 mg daily	20 - 40 mg daily
Ramipril	1.25-2.5 mg daily	10 mg daily
Captopril	6.25 mg 3X daily	50 mg 3X daily

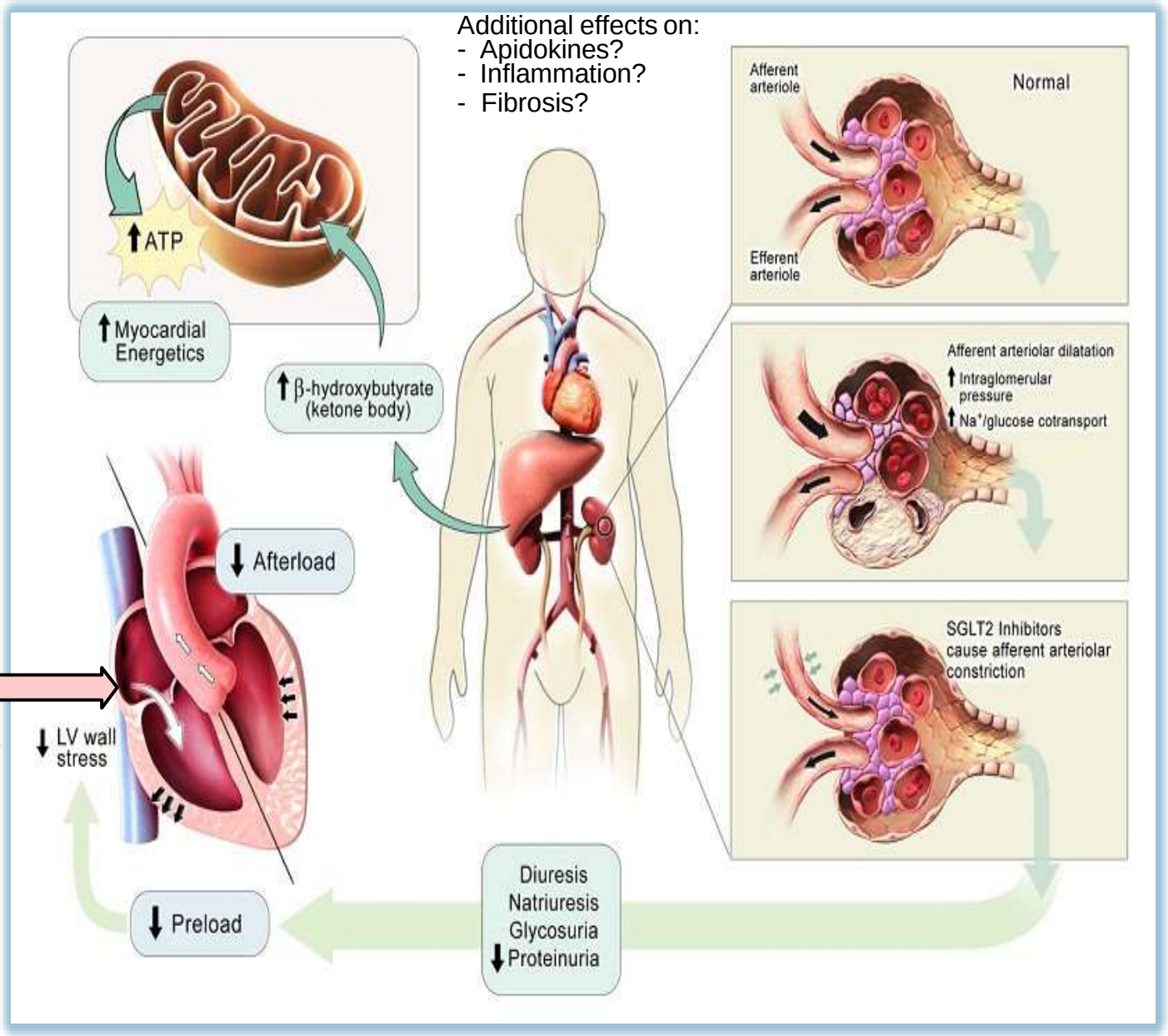
Drug	Starting Dose	Target Dose
ARB [b]		
Candesartan	4 - 8 mg daily	32 mg daily
Losartan	25 - 50 mg daily	50-150 mg daily
Valsartan	20-40 mg twice daily	160 mg twice daily
Aldosterone Antagonists [a]		
Eplerenone	25 mg once daily	50 mg once daily
Spironolactone	25 mg once daily	50 mg once daily
Vasodilators [b]		
Isosorbide dinitrate and hydralazine	20-30 mg isosorbide dinnitrate/25-50 mg hydralagine 3x daily or once daily	40 mg isosorbide dinnitrate/75 mg hydralazine 3x daily
Fixed-dose combination isosorbide dinitrate/hydralazine	20 mg/37.5 mg (1 tablet) 3x daily	2 tablets 3x daily
Ivabradine [a]		
Ivabradine	5 mg twice daily	Maximum dose 7.5 mg twice daily

a. Ponikowski P, et al. Eur Heart J. 2016:18:891-975. b. Yancy C, et al. Circulation. 2017;136:e137-e161

SGLT2i-Prevention of HF in T2DM



SGLT2 inhibitors: How do they work?

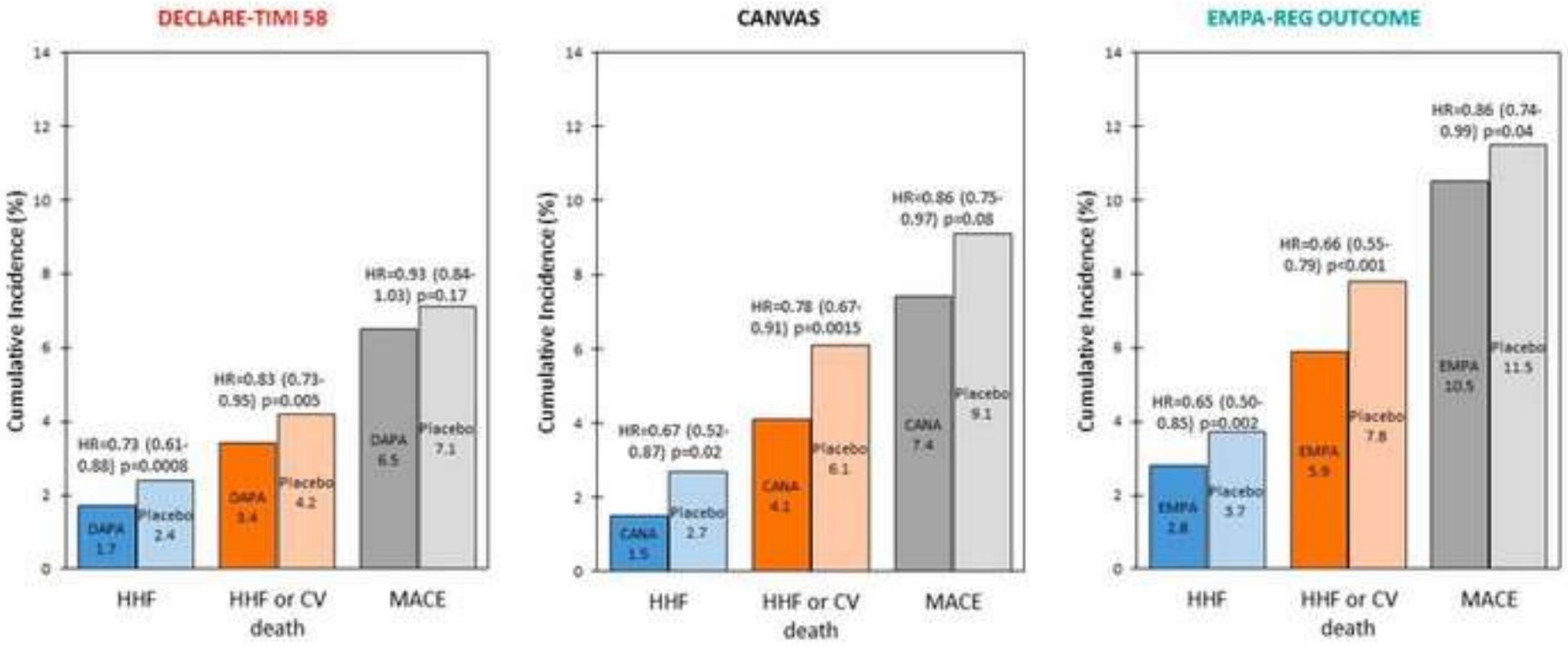


Na+/H+ exchanger

CaMKII/RyR2 activity

Adapted from Verma, McMurray & Cherney JAMA Cardiol. 2017; 2:939-940

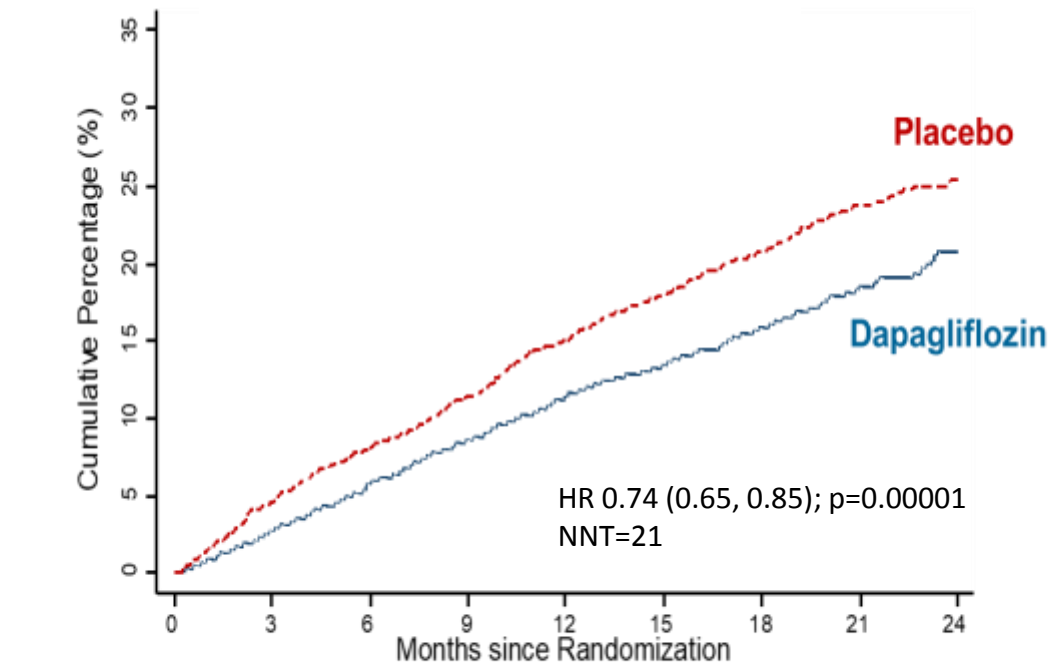
Empaglifosin, Canaglifosin and Dapaglifosin



Cardiorenal Outcomes in the CANVAS, DECLARE-TIMI 58, and EMPA-REG OUTCOME Trials: A Systematic Review -https://www.researchgate.net

Primary composite outcome

CV death/HF hospitalisation/urgent HF visit

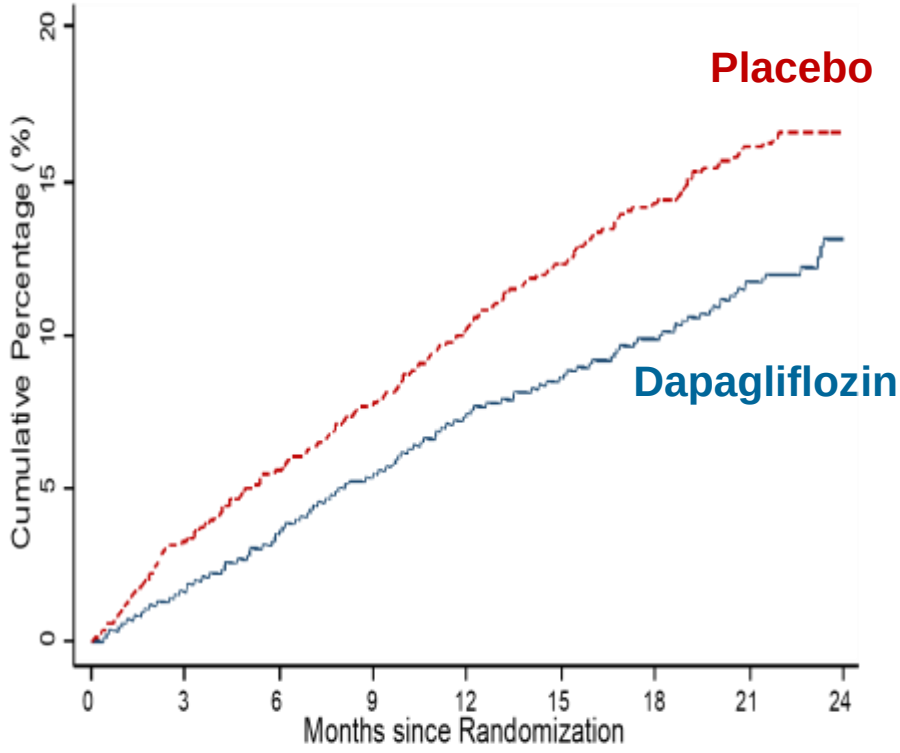


Number at Risk									
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

Components of primary outcome

Worsening HF event

HR 0.70 (0.59, 0.83); p=0.00003

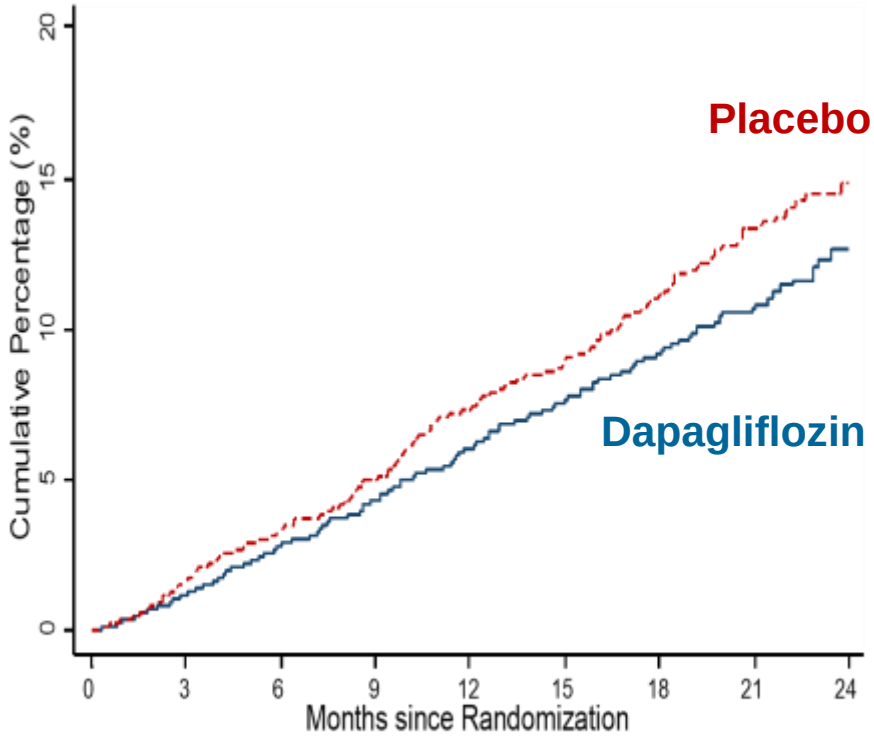


Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

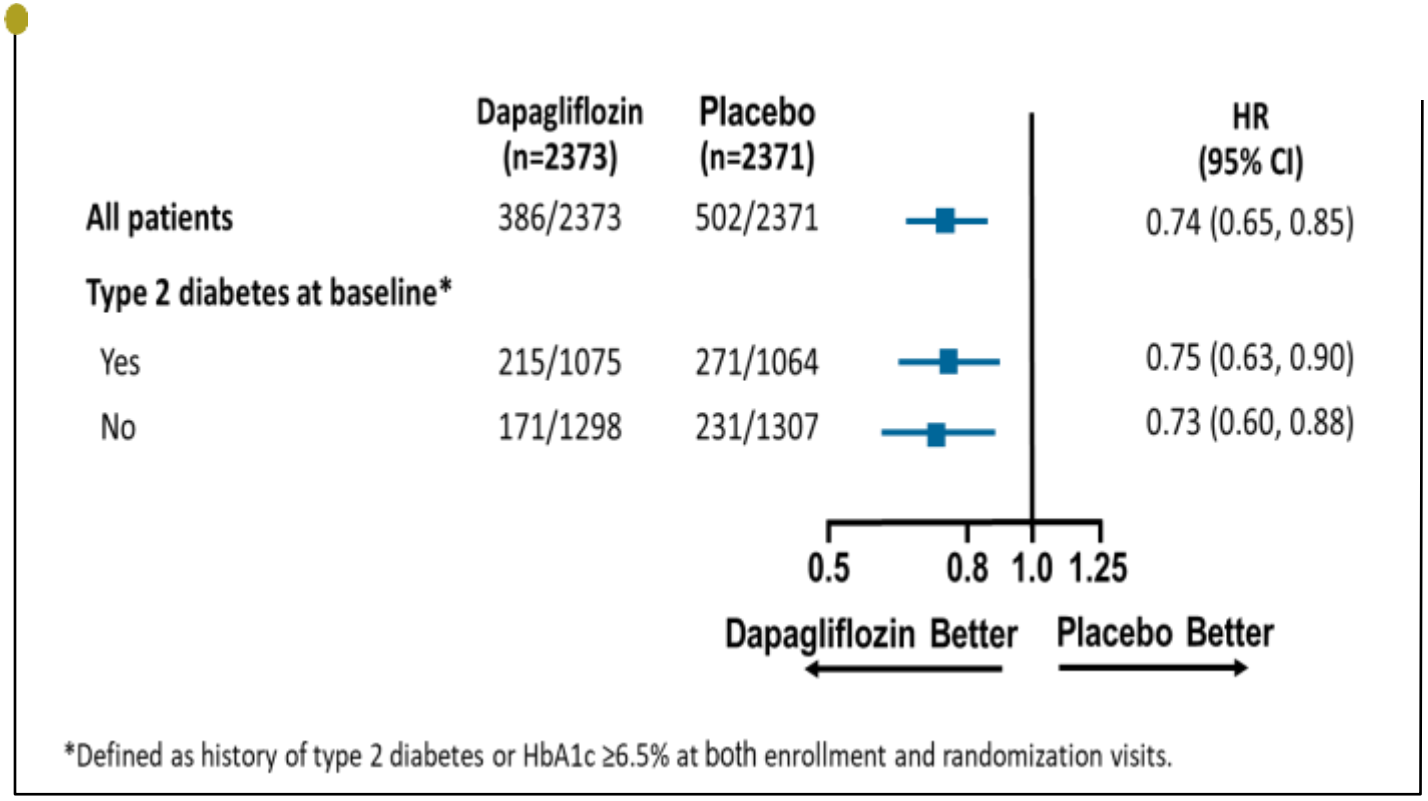
Cardiovascular death

HR 0.82 (0.69, 0.98); p=0.029



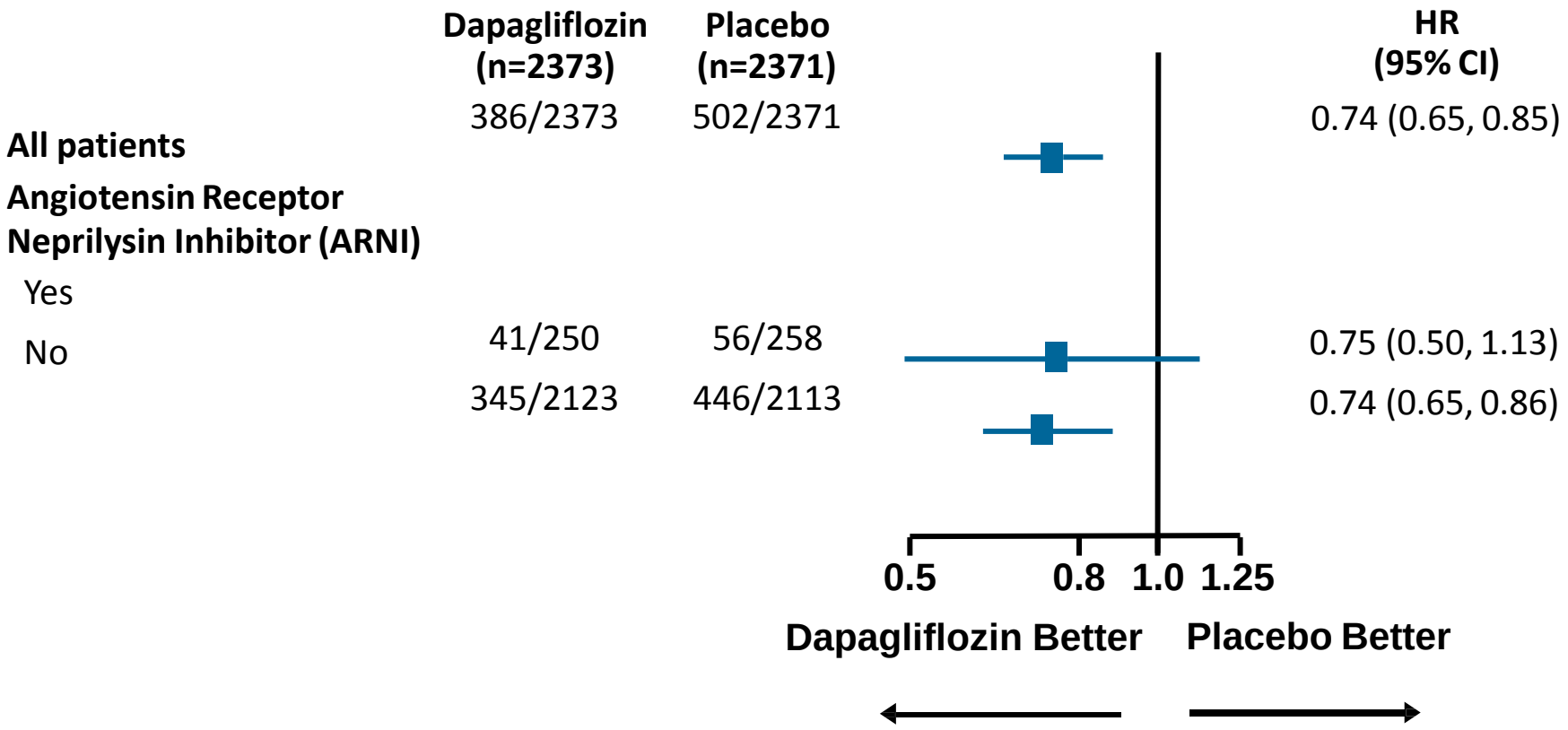
liflozin	2373	2339	2293	2248	2127	1664	1242	671	232
o	2371	2330	2279	2230	2091	1636	1219	664	234

No diabetes/diabetes subgroup: Primary endpoint

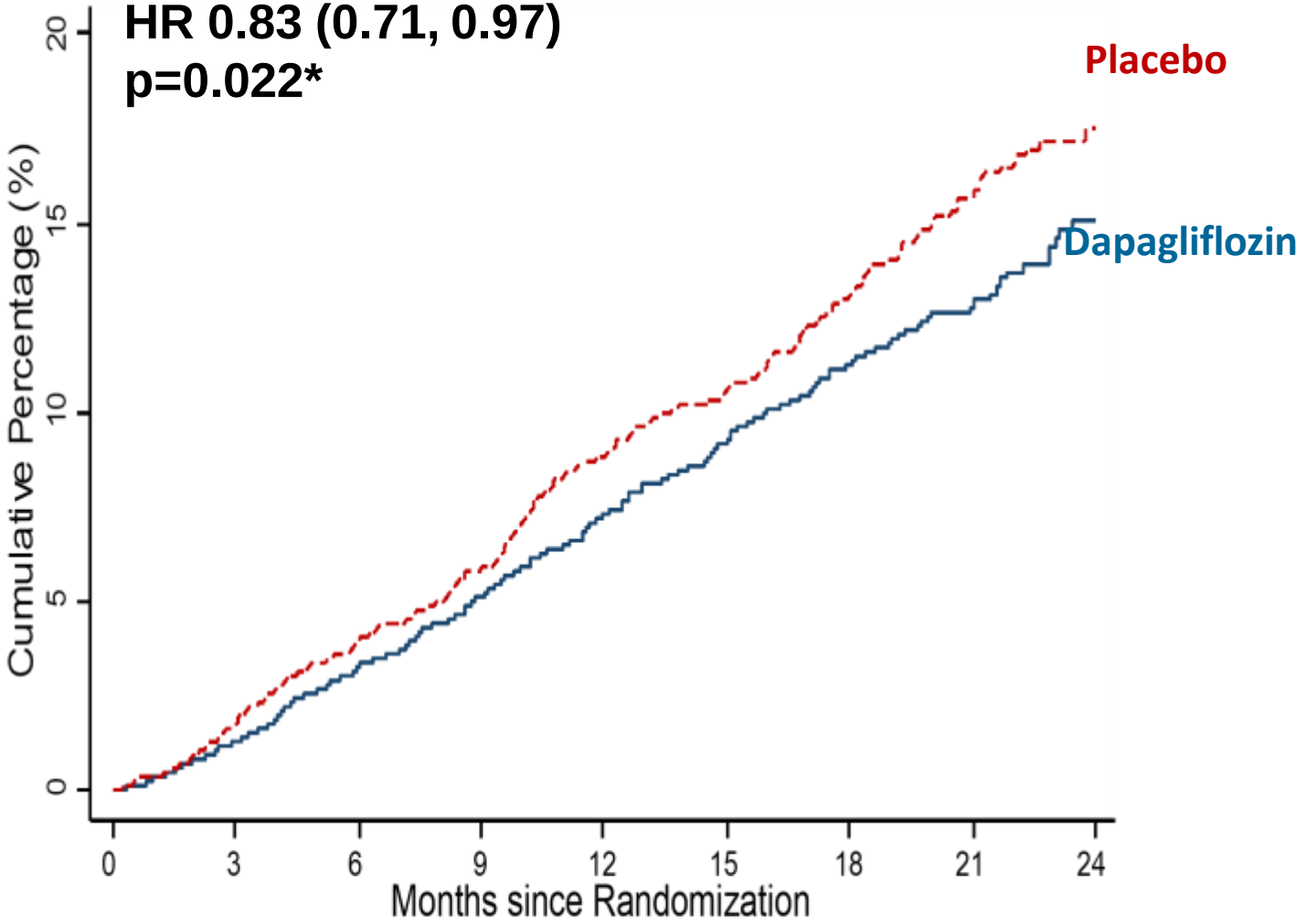


J McMurray, Hot Line Session 1

ARNI/no ARNI *post hoc* subgroup: Primary endpoint



All-cause death



Number at Risk									
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

DAPA-HF: Use of Dapagliflozin in HFrEF

- There was a 26% RR in the primary endpoint of CV death or worsening HF event (HR = 0.74; CI: 0.65, 0.86; *P* = .0001)[a]
- NNT was only 21 to delay 1 of these events[a]
- Approximately 50% of the patients did not have diabetes at the time they were in the trial[a]
- Treatment effect was present whether diabetes was present or not[a]
- Improvements in symptoms, physical function and QoL have also been demonstrated[b]

a. McMurray JJV, et al. *N Engl J Med*. 2019;381:1995-2008.
b. Kosiborod MN, Jhund P, et al. *Circulation*. 2019. Epub ahead of print.

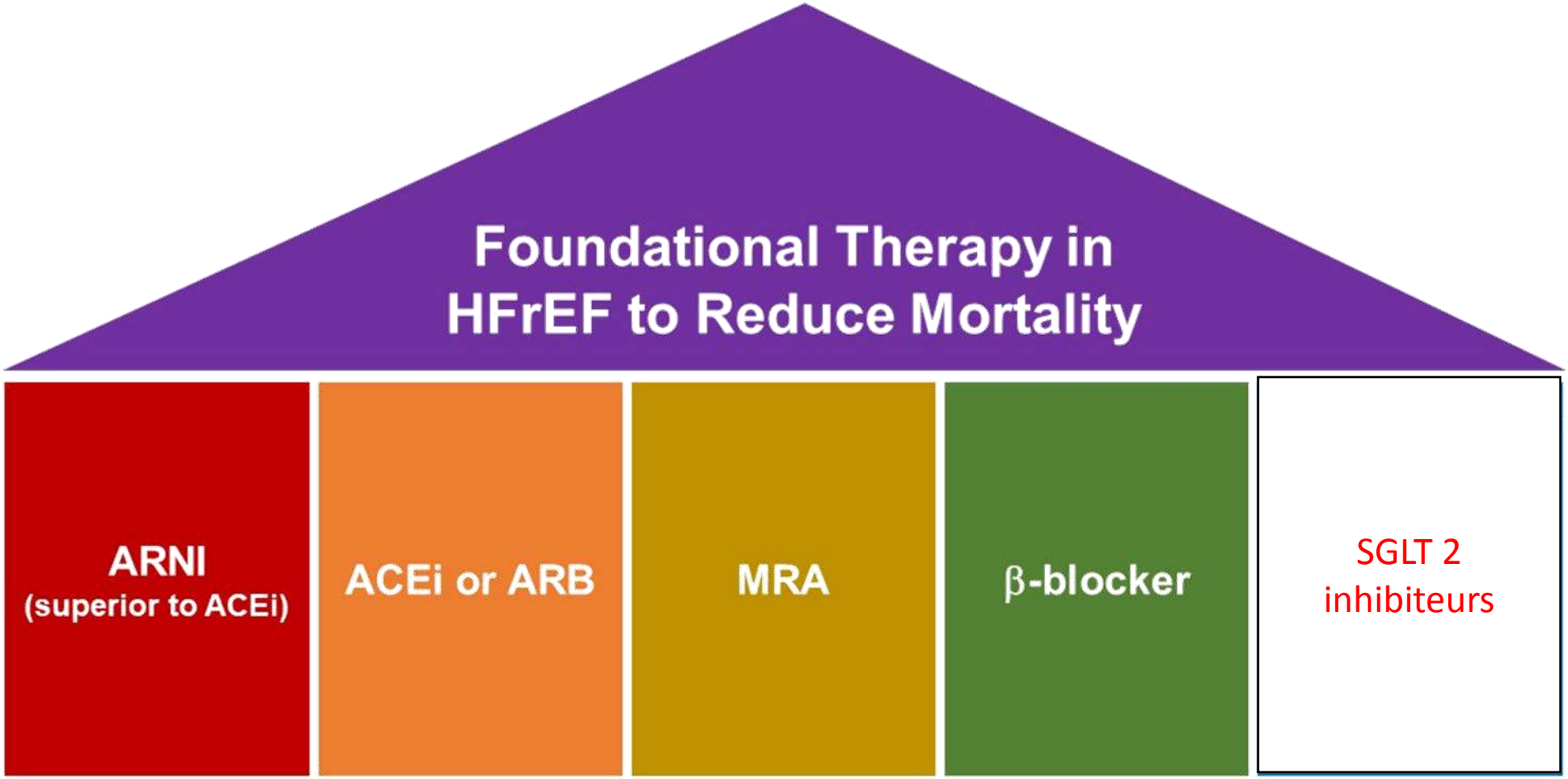
DAPA-HF: SGLT2 Inhibitor Use In Addition to an ARNI In HFrEF

- Post hoc subgroup analysis in DAPA-HF of patients taking sacubitril/valsartan, an ARNI at baseline compared with those not taking sacubitril/valsartan[a]
- The baseline use of sacubitril/valsartan[b], which is more effective than RAAS inhibition alone at reducing the incidence of hospitalization for HF and death from cardiovascular causes, was low[a]
- Small subgroup, involving 508 patients on an ARNI and 4236 not taking an ARNI at baseline. There were similar hazard ratios for the primary outcome (95% CI): 0.75 (0.50,1.13) – on an ARNI and 0.74 (0.65,0.86) - not on an ARNI [a]
- There is no interaction of the use of dapagliflozin with the use of an ARNI[a]
- It is not an either/or concept – dapagliflozin use should be in addition to the ARNI

a. McMurray JJV, et al. *N Engl J Med*. 2019;381:1995-2008. b. McMurray JJV, et al. *N Engl J Med*. 2014; 371: 993-1004.

Conclusions: Take-Home Messages

- Robust evidence generation is really important, but it is only the first step
- It is important to implement use of evidence-based therapies into clinical practice; followed by uptitration to target dosing when possible
- Team approach to patient management is vital
- Novel therapies will likely be used in addition to the foundational therapies
- Keeping the patient in the center of the decision-making process is key to the success of patient management



Bhatt DL, Verma S, Braunwald E. *CELL METABOLISM*. 2019;30:847-849.