ADVANCES IN HEART FAILURE

3rd Porto HF Meeting

In what sequence should we add SGLT-2i to neurohormonal modulation in HF?

Pedro Morais Sarmento

Setembro 2020

LUZ SAÚDE

EUROPEAN SOCIETY OF CARDIOLOGY®

European Heart
doi:10.1093/eur

CME

2016 ESC
treatment

The Task Fore
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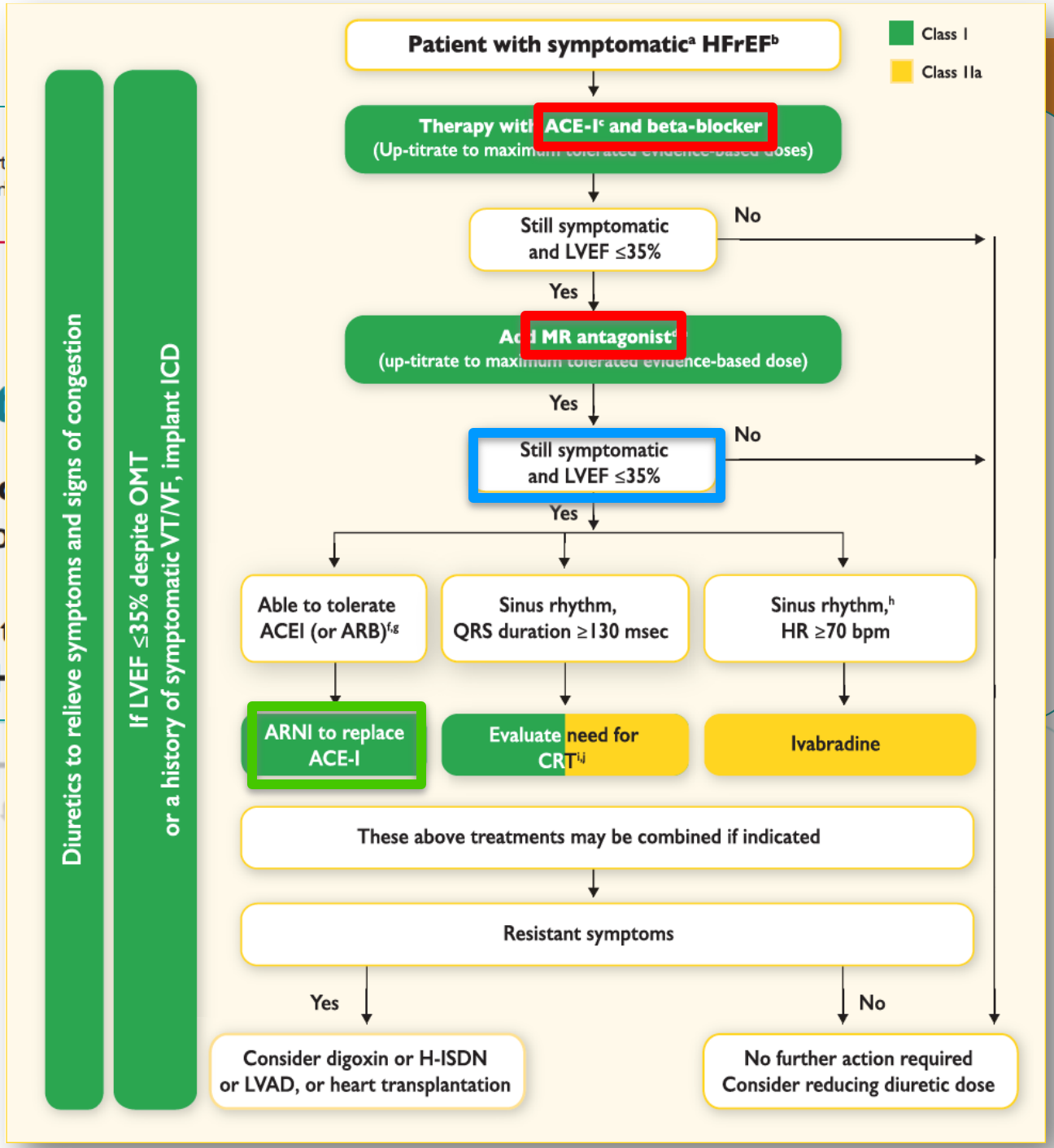
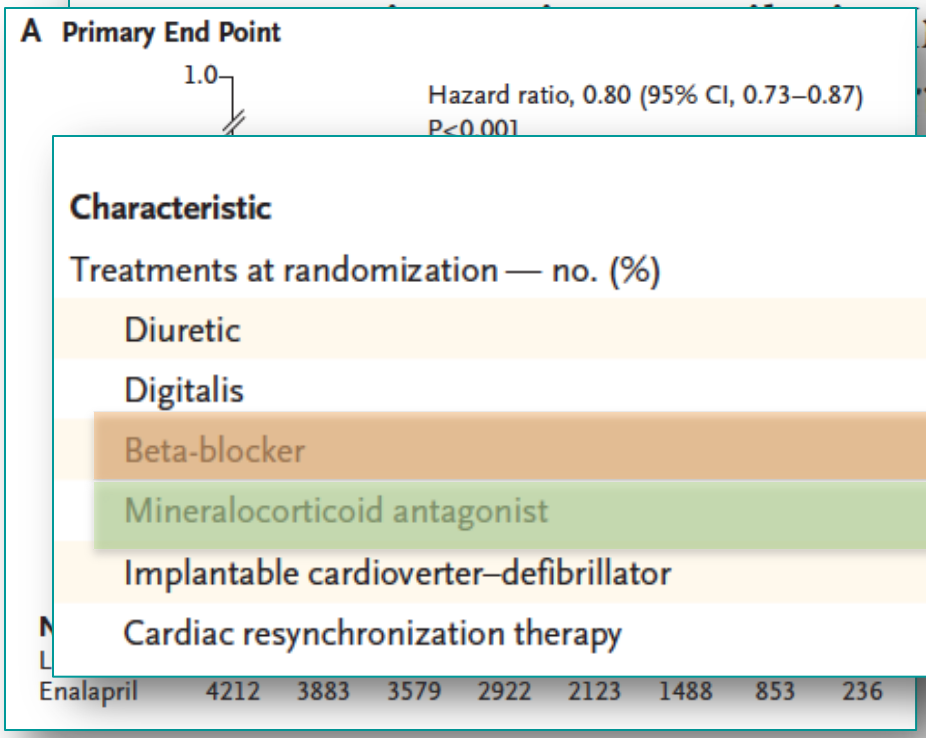
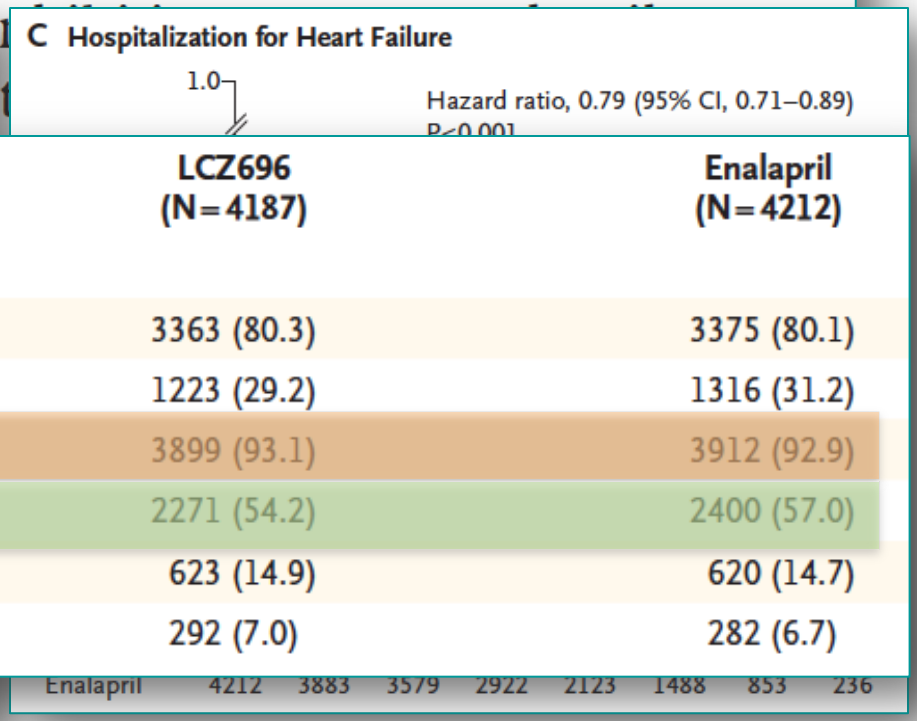


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

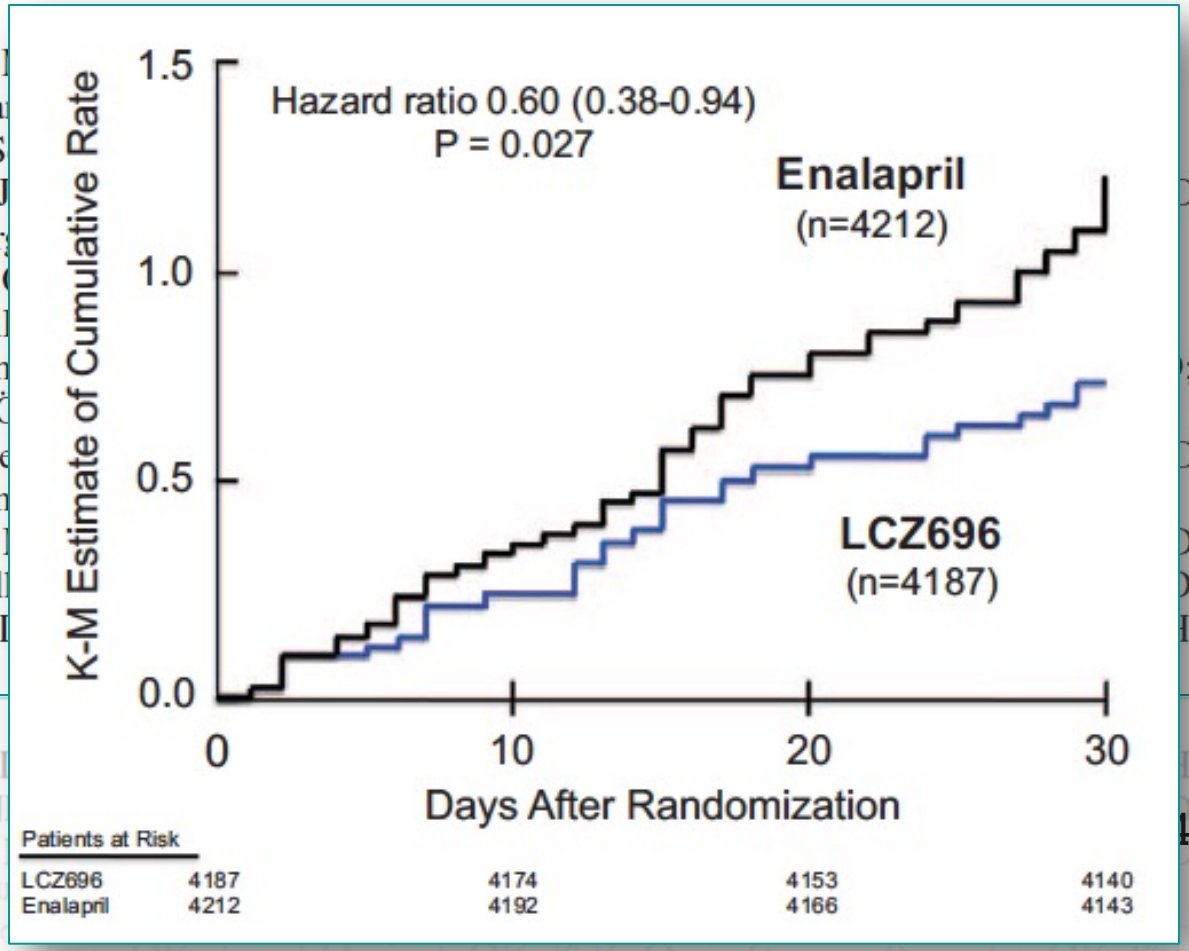




Characteristic	LCZ696 (N=4187)	Enalapril (N=4212)
Treatments at randomization — no. (%)		
Diuretic	3363 (80.3)	3375 (80.1)
Digitalis	1223 (29.2)	1316 (31.2)
Beta-blocker	3899 (93.1)	3912 (92.9)
Mineralocorticoid antagonist	2271 (54.2)	2400 (57.0)
Implantable cardioverter–defibrillator	623 (14.9)	620 (14.7)
Cardiac resynchronization therapy	292 (7.0)	282 (6.7)

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

Milton Packer, M
Jianjian Gong, PhD; Mar
Victor C. Shi, MD; S
Karl Andersen, MD, PhD; J
Michael Böhm, MD; Serg
Carlos Calvo, MD; C
Andrejs Erglis, MD, PhD
Albert A. Hagège, MD, PhD
Kee-Sik Kim, MD, PhD; C
Bela Merkely, MD; Iván Me
Keijo Peuhkurinen
Arvo Rosenthal, MD, PhD; I
Iain B. Squire, MD; Randall
Dragos Vinereanu, MD, PhD



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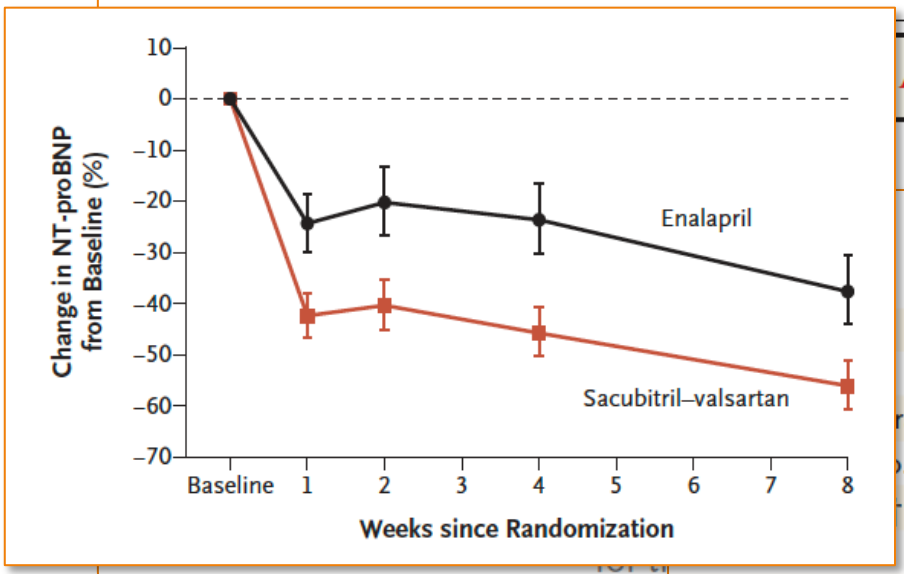
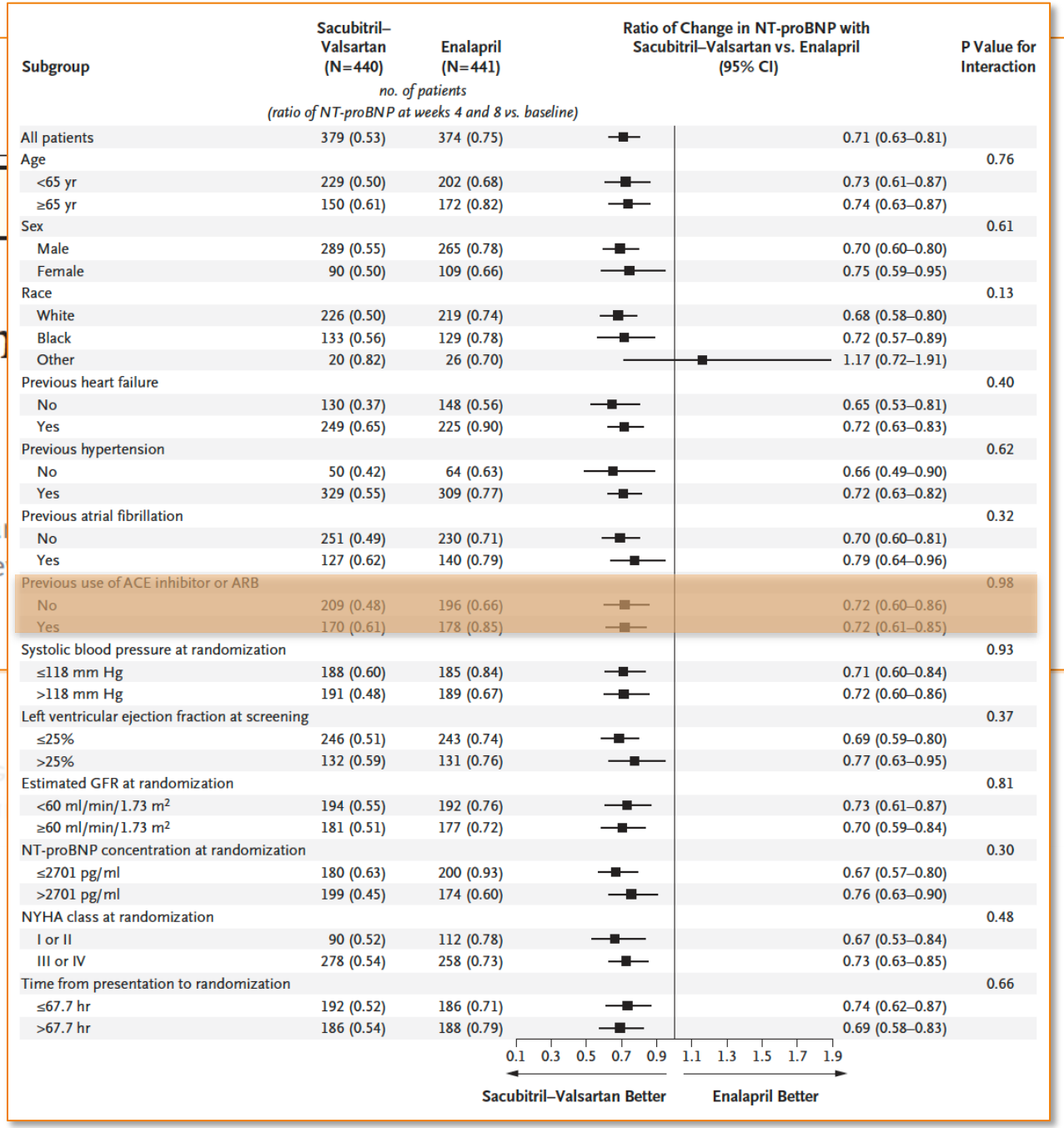


	Sacubitril–Valsartan (N=440)	Enalapril (N=441)
	61	63
range	51–71	54–72
. (%)	113 (25.7)	133 (30.2)
	158 (35.9)	158 (35.8)
White	261 (59.3)	254 (57.6)
Hydralazine	30 (6.8)	33 (7.5)
Nitrate	43 (9.8)	40 (9.1)
Digoxin	41 (9.3)	35 (7.9)

Exploratory clinical outcomes — no. (%)			Hazard ratio (95% CI)§
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)


Subgroup
Sacubitril–Valsartan (N=440)
Enalapril (N=441)
no. of patients (ratio of NT-proBNP at weeks 4 and 8 vs. baseline)
Ratio of Change in NT-proBNP with Sacubitril–Valsartan vs. Enalapril (95% CI)
P Value for Interaction
All patients 379 (0.53) 374 (0.75) 0.71 (0.63–0.81)
Age 0.76
<65 yr 229 (0.50) 202 (0.68) 0.73 (0.61–0.87)
≥65 yr 150 (0.61) 172 (0.82) 0.74 (0.63–0.87)
Sex 0.61
Male 289 (0.55) 265 (0.78) 0.70 (0.60–0.80)
Female 90 (0.50) 109 (0.66) 0.75 (0.59–0.95)
Race 0.13
White 226 (0.50) 219 (0.74) 0.68 (0.58–0.80)
Black 133 (0.56) 129 (0.78) 0.72 (0.57–0.89)
Other 20 (0.82) 26 (0.70) 1.17 (0.72–1.91)
Previous heart failure 0.40
No 130 (0.37) 148 (0.56) 0.65 (0.53–0.81)
Yes 249 (0.65) 225 (0.90) 0.72 (0.63–0.83)
Previous hypertension 0.62
No 50 (0.42) 64 (0.63) 0.66 (0.49–0.90)
Yes 329 (0.55) 309 (0.77) 0.72 (0.63–0.82)
Previous atrial fibrillation 0.32
No 251 (0.49) 230 (0.71) 0.70 (0.60–0.81)
Yes 127 (0.62) 140 (0.79) 0.79 (0.64–0.96)
Previous use of ACE inhibitor or ARB 0.98
No 209 (0.48) 196 (0.66) 0.72 (0.60–0.86)
Yes 170 (0.61) 178 (0.85) 0.72 (0.61–0.85)
Systolic blood pressure at randomization 0.93
≤118 mm Hg 188 (0.60) 185 (0.84) 0.71 (0.60–0.84)
>118 mm Hg 191 (0.48) 189 (0.67) 0.72 (0.60–0.86)
Left ventricular ejection fraction at screening 0.37
≤25% 246 (0.51) 243 (0.74) 0.69 (0.59–0.80)
>25% 132 (0.59) 131 (0.76) 0.77 (0.63–0.95)
Estimated GFR at randomization 0.81
<60 ml/min/1.73 m² 194 (0.55) 192 (0.76) 0.73 (0.61–0.87)
≥60 ml/min/1.73 m² 181 (0.51) 177 (0.72) 0.70 (0.59–0.84)
NT-proBNP concentration at randomization 0.30
≤2701 pg/ml 180 (0.63) 200 (0.93) 0.67 (0.57–0.80)
>2701 pg/ml 199 (0.45) 174 (0.60) 0.76 (0.63–0.90)
NYHA class at randomization 0.48
I or II 90 (0.52) 112 (0.78) 0.67 (0.53–0.84)
III or IV 278 (0.54) 258 (0.73) 0.73 (0.63–0.85)
Time from presentation to randomization 0.66
≤67.7 hr 192 (0.52) 186 (0.71) 0.74 (0.62–0.87)
>67.7 hr 186 (0.54) 188 (0.79) 0.69 (0.58–0.83)
0.1 0.3 0.5 0.7 0.9 1.1 1.3 1.5 1.7 1.9
Sacubitril–Valsartan Better
Enalapril Better

European Hear
doi:10.1093/eur

2021 ESC treatment

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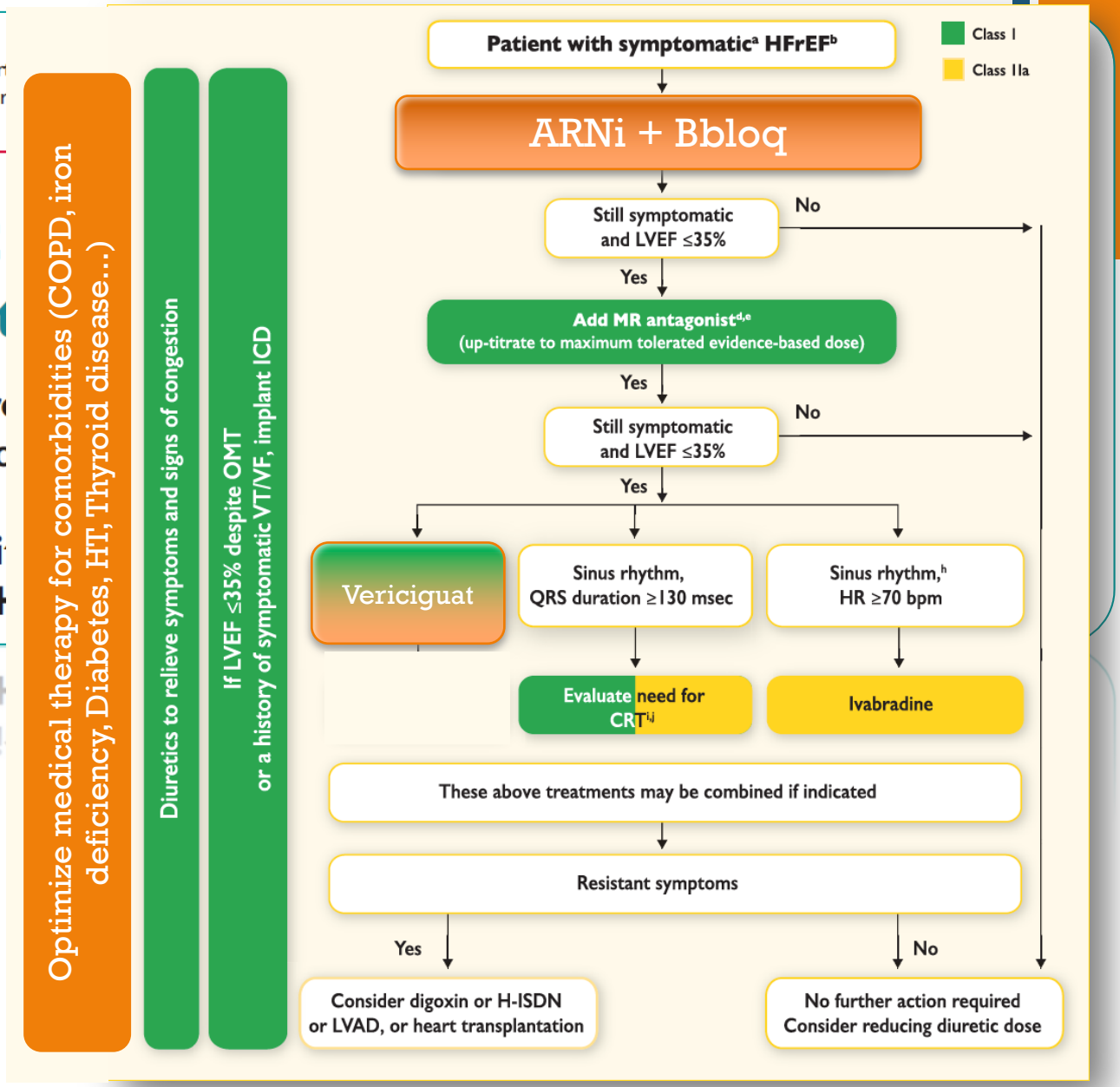

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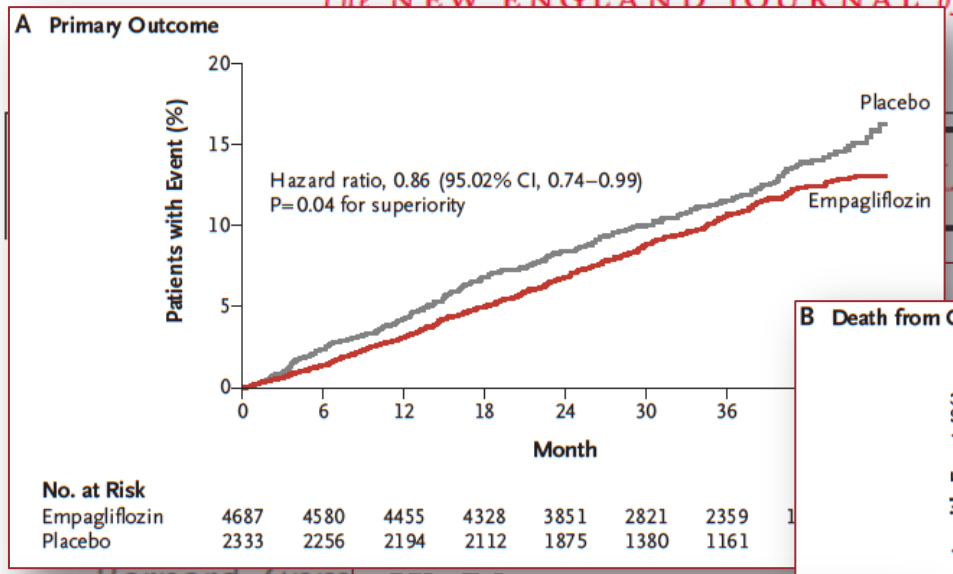

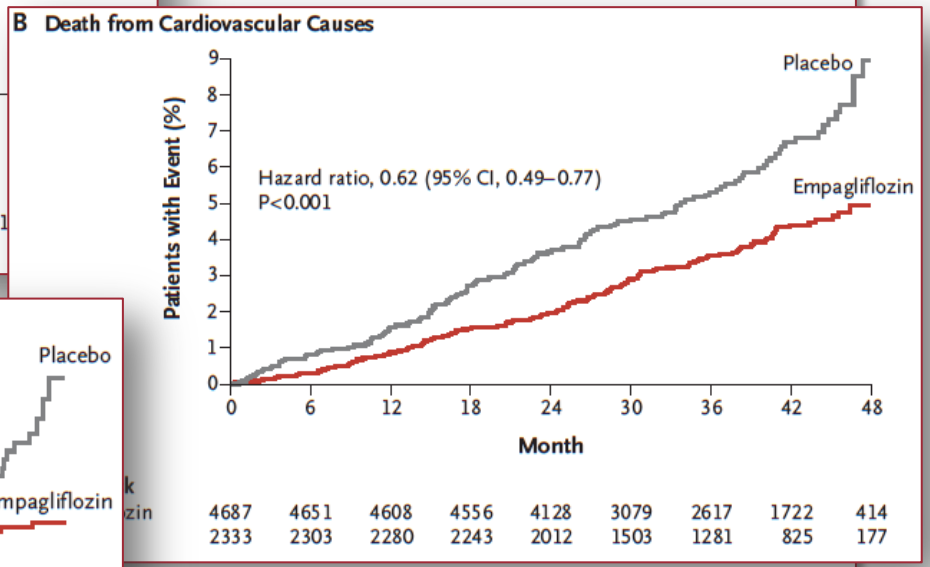

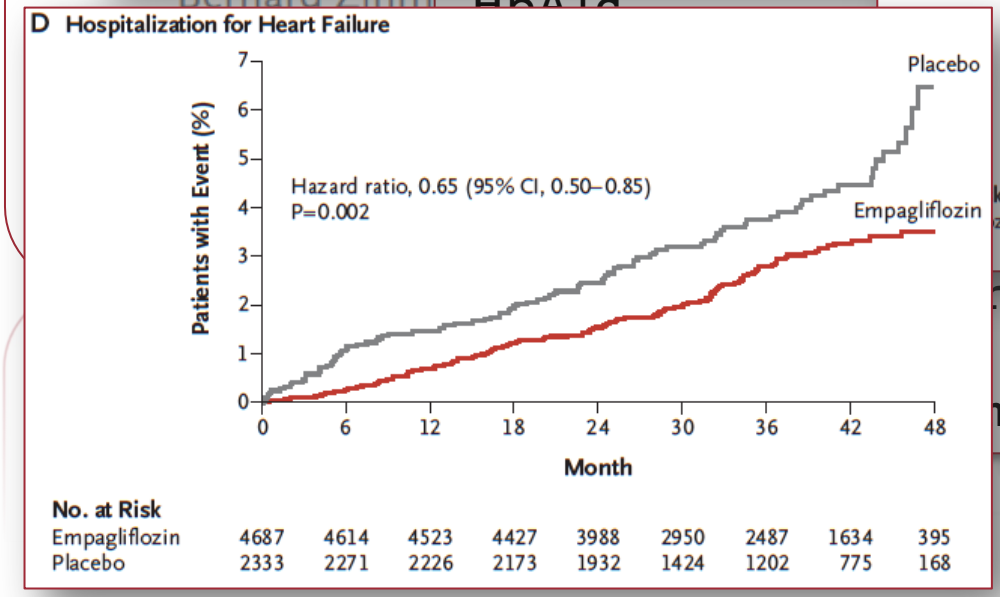

at least 12 weeks before

e: 3.1 years

N Engl J Med. 2015;373:2117-28

European Heart Journal (2016) **37**, 1526–1534
doi:10.1093/eurheartj/ehv728

AHA FASTTRACK
Heart failure/cardiomyopathy

Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high

f the EMPA-REG

Loop diuretics were introduced in a significantly lower proportion of patients in the empagliflozin group than the placebo group [HR: 0.62 (95%CI: 0.53–0.73); P < 0.001]

risk of the composite outcomes of hospitalization for heart failure or introduction of loop diuretics [HR: 0.63 (95% CI: 0.54–0.73); P < 0.001]

			Empagliflozin (*N* = 4687)		HR (95% CI)	*P*-value
			n (%)	Rate/1000 patient-years		
Heart failure hospitalization or cardiovascular death	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001
Hospitalization for or death from heart failure	104 (4.5)	15.8	129 (2.8)	9.6	0.61 (0.47–0.79)	<0.001
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
			204 (4.4)	15.3	0.70 (0.56–0.87)	0.001
			192 (4.1)	14.4	0.69 (0.55–0.86)	0.001
			1725 (36.8)	161.9	0.89 (0.82–0.96)	0.003

line.

Eur Heart J. 2016; 37: 1526–1534

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Dap

S.D. W
T.A
J.P.H.

- 17,160
- median
- > = 40
- type 2 d
- eGFR >
- multiple risk factors for or established ACVD

Characteristic	Dapagliflozin (N=8582)	Placebo (N=8578)
Age — yr	63.9±6.8	64.0±6.8
Female sex — no. (%)	3171 (36.9)	3251 (37.9)
Estimated glomerular filtration rate — ml/min/1.73 m^2	85.4±15.8	85.1±16.0
Established atherosclerotic cardiovascular disease — no. (%)	3474 (40.5)	3500 (40.8)
History of coronary artery disease — no. (%)	2824 (32.9)	2834 (33.0)
History of peripheral artery disease — no. (%)	522 (6.1)	503 (5.9)
History of cerebrovascular disease — no. (%)	653 (7.6)	648 (7.6)
History of heart failure — no. (%)	852 (9.9)	872 (10.2)
North America	2737 (31.9)	2731 (31.8)
Europe	3806 (44.3)	3823 (44.6)
Latin America	946 (11.0)	931 (10.9)
Asia–Pacific	1093 (12.7)	1093 (12.7)
Body-mass index‡	32.1±6.0	32.0±6.1
Median duration of type 2 diabetes (IQR) — yr	11.0 (6.0–16.0)	10.0 (6.0–16.0)
Glycated hemoglobin — %	8.3±1.2	8.3±1.2

N Engl J Med 2019;380:347-57.

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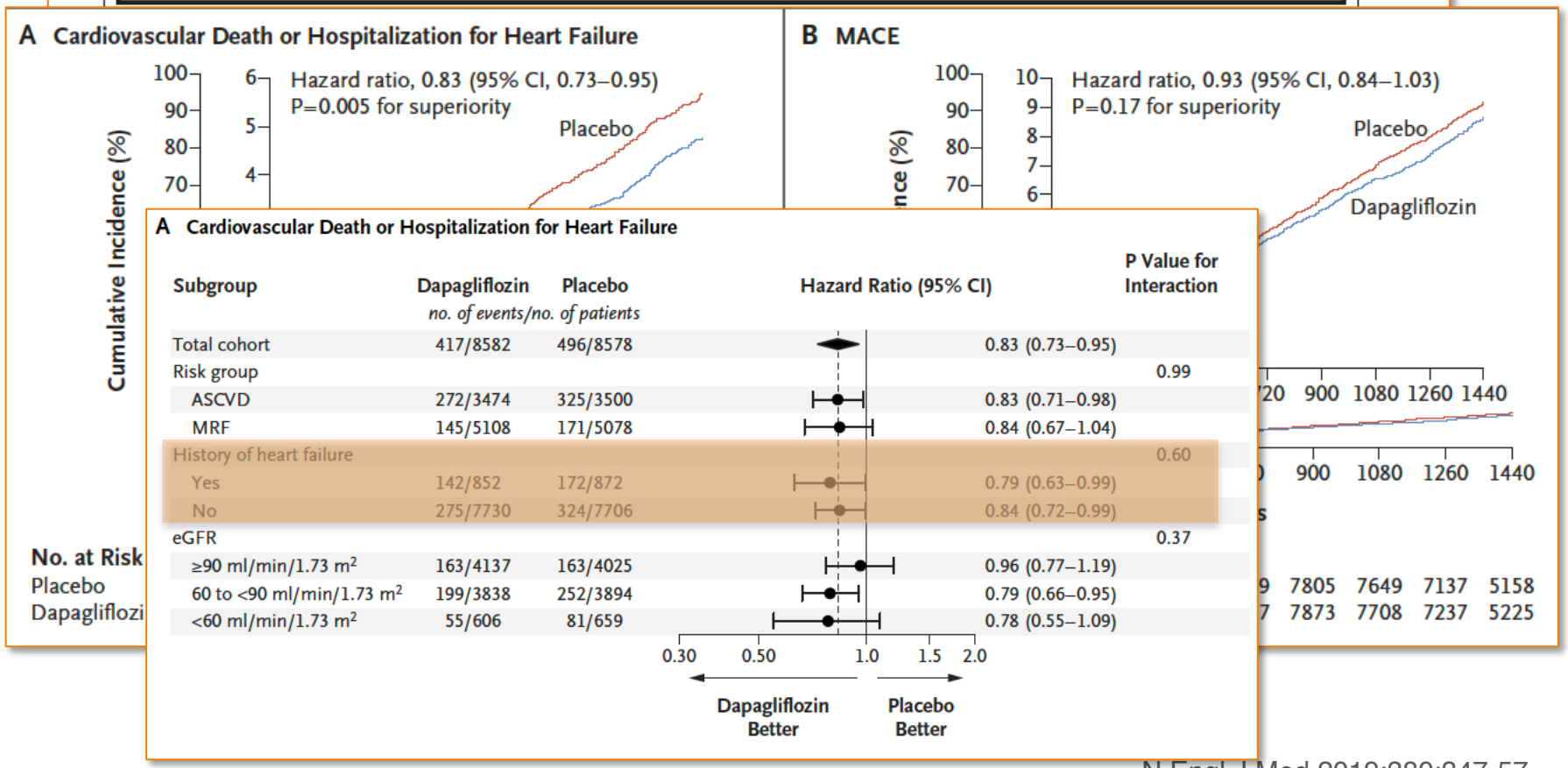
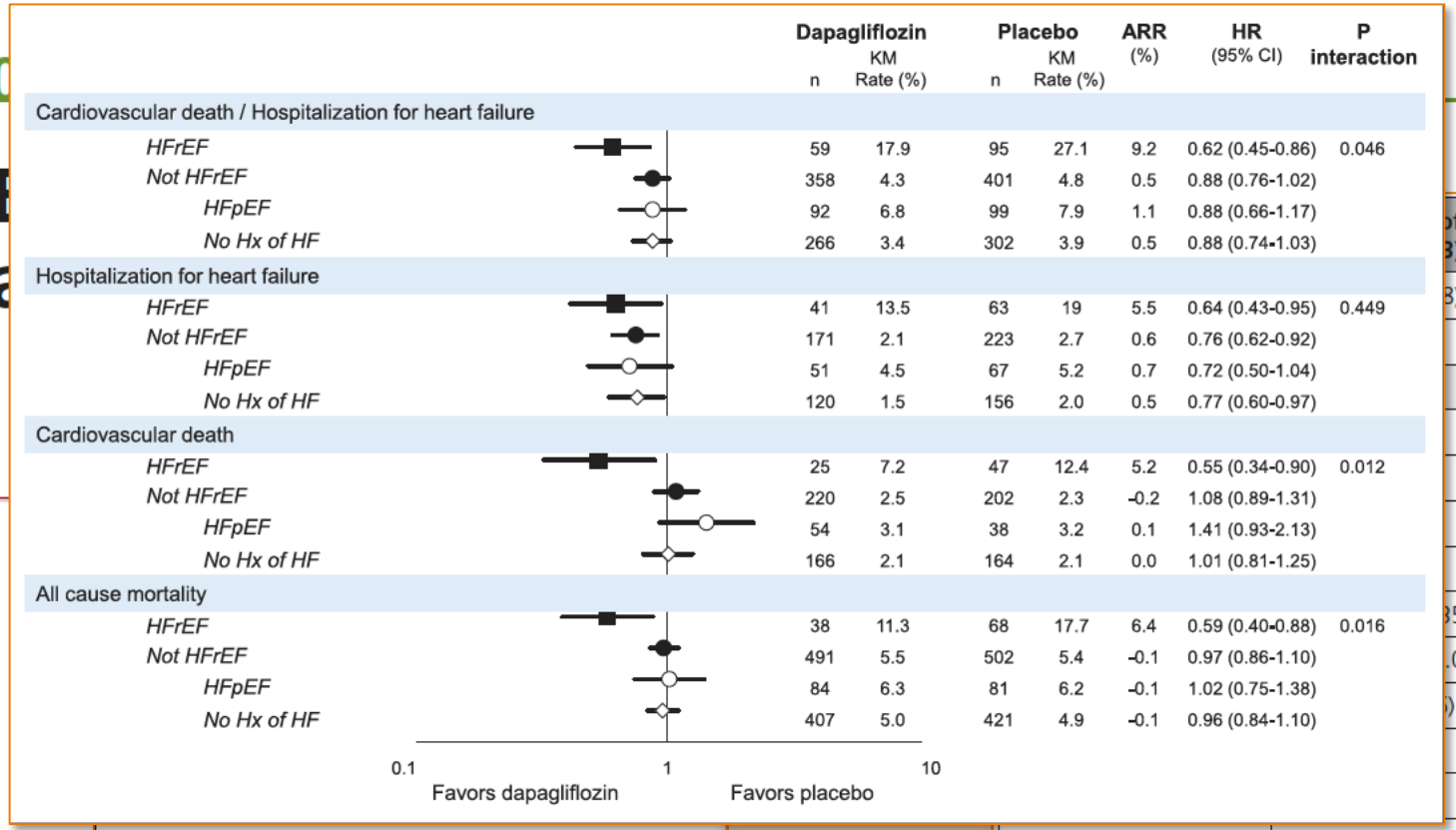
ORIGINAL ARTICLE



N Engl J Med 2019;380:347-57.

Circulation



History of hypertension, %	87.0	95.9	89.5
LVEF, median (IQR), %	38 (30–40)	55 (50–61)	60 (55–65)
eGFR by CKD-EPI equation, median (IQR), mL/min/1.73m²	83 (66–95)	86 (70–96)	89 (76–97)

Circulation. 2019;139:2528–2536.

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Dapagliflo
and

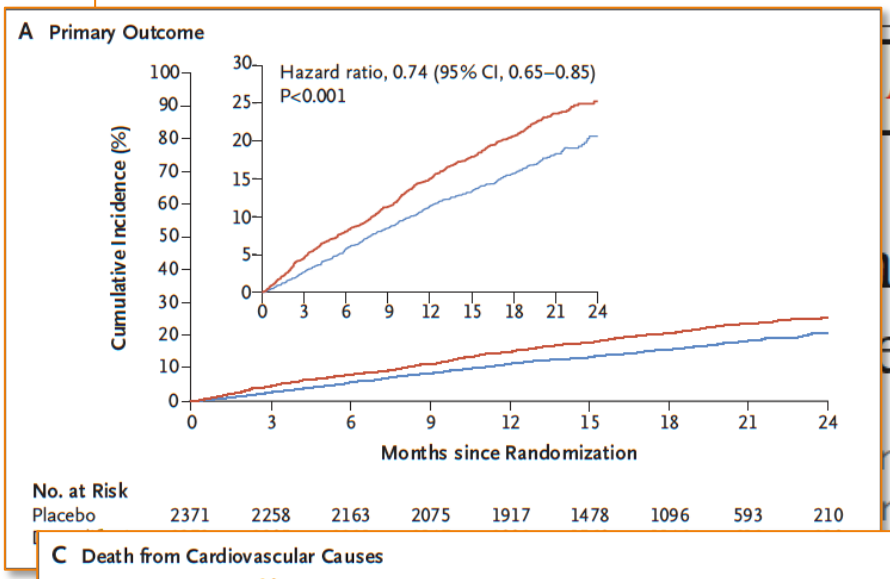
J.J.V. McMurra
F.A. Martinez, P. P
C.-E. Chiang, V.K.
J. Ge, J.G. Howlett,
E. O'Meara, M.

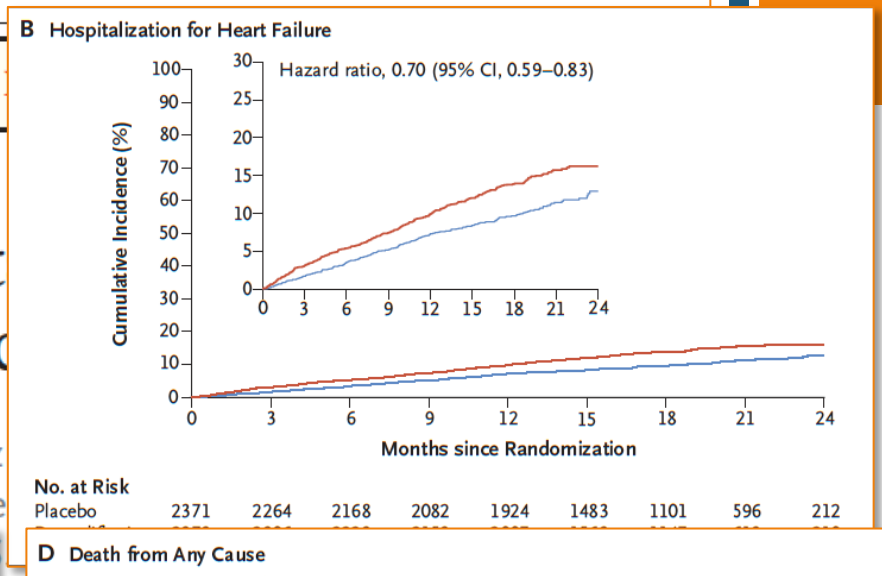
Characteristic	Dapagliflozin (N=2373)	Placebo (N=2371)
Heart failure medication — no. (%)		
Diuretic	2216 (93.4)	2217 (93.5)
ACE inhibitor	1332 (56.1)	1329 (56.1)
ARB	675 (28.4)	632 (26.7)
Sacubitril–valsartan	250 (10.5)	258 (10.9)
Beta-blocker	2278 (96.0)	2280 (96.2)
Mineralocorticoid receptor antagonist	1696 (71.5)	1674 (70.6)
Digitalis	445 (18.8)	442 (18.6)
Glucose-lowering medication — no./total no. (%)**		
Biguanide	504/993 (50.8)	512/990 (51.7)
Sulfonylurea	228/993 (23.0)	210/990 (21.2)
DPP-4 inhibitor	161/993 (16.2)	149/990 (15.1)
GLP-1 receptor agonist	11/993 (1.1)	10/990 (1.0)
Insulin	274/993 (27.6)	266/990 (26.9)
Cardiac resynchronization therapy	190 (8.0)	164 (6.9)

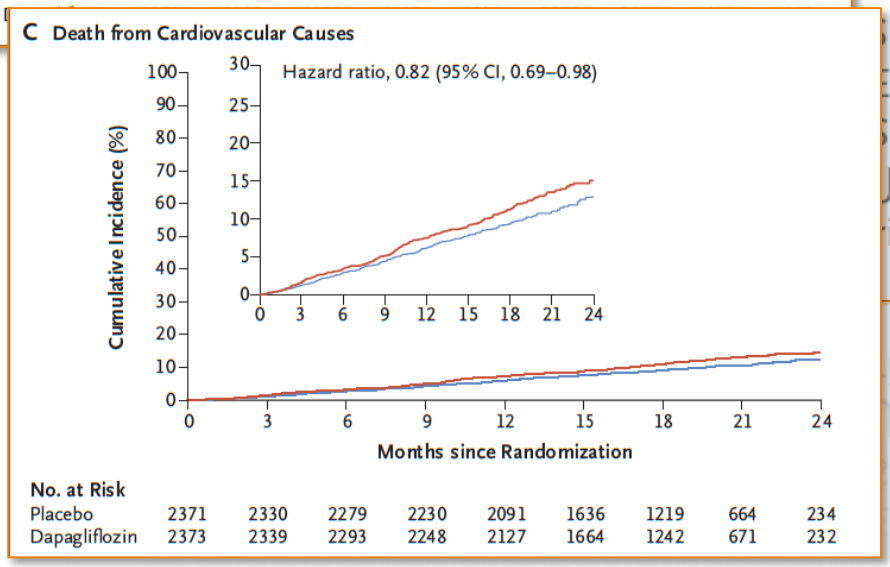
95%

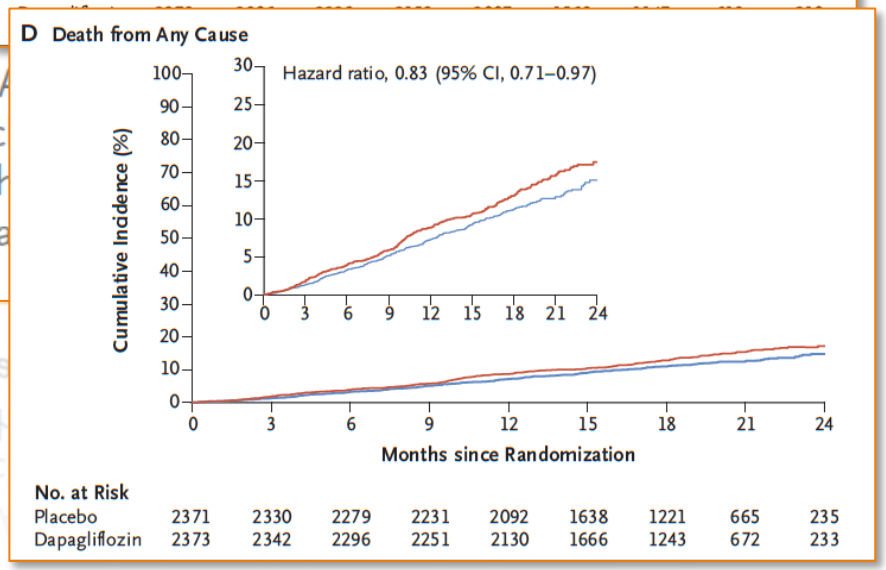
- phase 3, placebo-co
- 4744 patients ; NYH
- ejection fraction <=
- dapagliflozin 10 mg once daily vs placebo, in addition to recommended therapy
- 18.2 months median FU

DOI: 10.1056/NEJMoa1911303

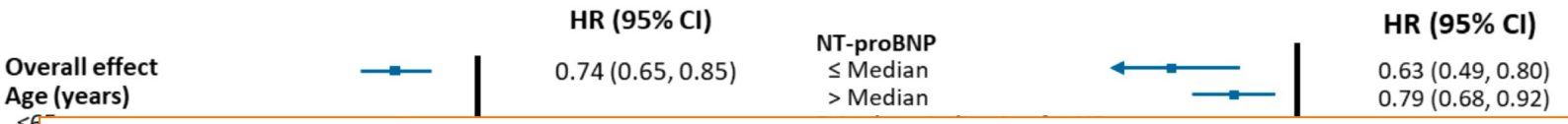

A Primary Outcome
Hazard ratio, 0.74 (95% CI, 0.65–0.85)
P<0.001
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2258 2163 2075 1917 1478 1096 593 210


B Hospitalization for Heart Failure
Hazard ratio, 0.70 (95% CI, 0.59–0.83)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2264 2168 2082 1924 1483 1101 596 212


C Death from Cardiovascular Causes
Hazard ratio, 0.82 (95% CI, 0.69–0.98)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2330 2279 2230 2091 1636 1219 664 234
Dapagliflozin 2373 2339 2293 2248 2127 1664 1242 671 232

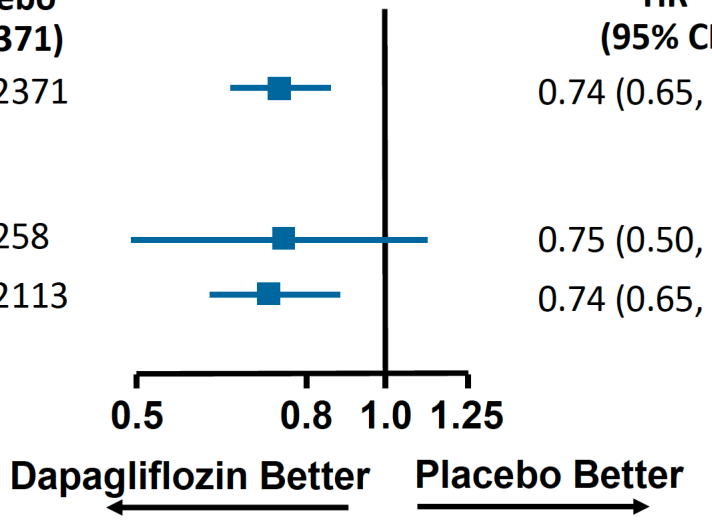

D Death from Any Cause
Hazard ratio, 0.83 (95% CI, 0.71–0.97)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2330 2279 2231 2092 1638 1221 665 235
Dapagliflozin 2373 2342 2296 2251 2130 1666 1243 672 233

Primary Endpoint: Prespecified subgroups



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

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Angiotensin Receptor Neprilysin Inhibitor (ARNI)			
Yes	41/250	56/258	0.75 (0.50, 1.13)
No	345/2123	446/2113	0.74 (0.65, 0.86)



iECA 1332

ARB 675

no RAASi 116 (5%)

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Ca
wi

M. Packer,
S. Verma, H
D. Cotton, E
S. Janssen

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Heart rate — beats/min	71.0±11.7	71.5±11.8
Systolic blood pressure — mm Hg	122.6±15.9	121.4±15.4
Left ventricular ejection fraction		
Mean value	27.7±6.0	27.2±6.1
Value of ≤30% — no. (%)	1337 (71.8)	1392 (74.6)

Characteristic	Empagliflozin (N=1863)	Placebo (N=1867)
Heart failure medication — no. (%)		
Renin–angiotensin inhibitor§		
Without neprilysin inhibitor	1314 (70.5)	1286 (68.9)
With neprilysin inhibitor	340 (18.3)	387 (20.7)
Mineralocorticoid receptor antagonist	1306 (70.1)	1355 (72.6)
Beta-blocker	1765 (94.7)	1768 (94.7)
Device therapy — no. (%)		
Implantable cardioverter–defibrillator¶	578 (31.0)	593 (31.8)
Cardiac resynchronization therapy‖	220 (11.8)	222 (11.9)

88,8%

Estimated glomerular filtration rate		
Mean value — ml/min/1.73 m^2	61.8±21.7	62.2±21.5
Value of <60 ml/min/1.73 m^2 — no./total no. (%)	893/1862 (48.0)	906/1866 (48.6)

- 3730 HF patie
- EF <=40%; N
- eGFR EPI > 2
- Empagliflozir
  or placebo + r
  therapy
- Median FU: 16 months

DOI: 10.1056/NEJMoa2022190

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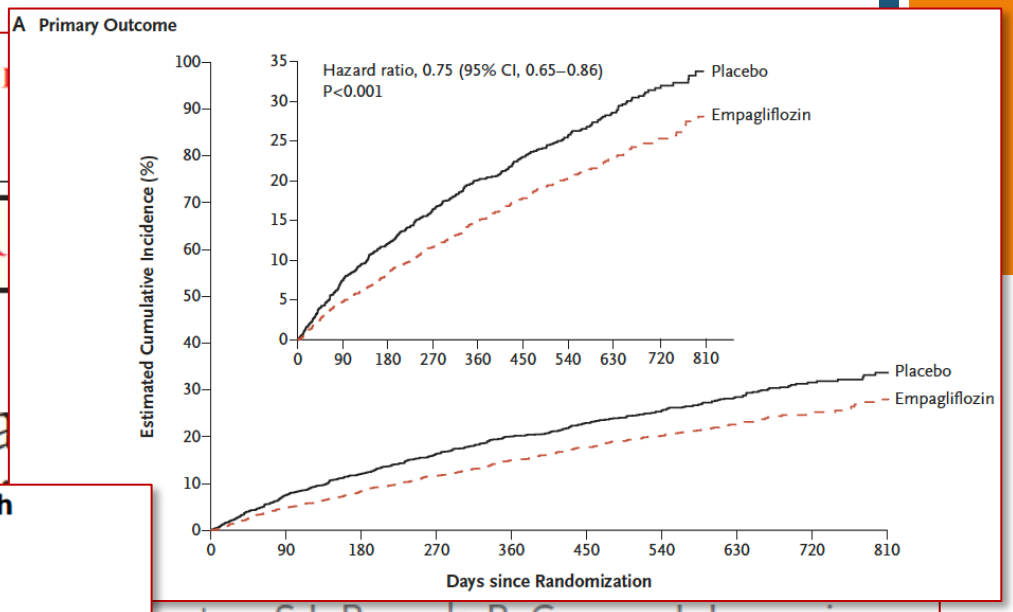

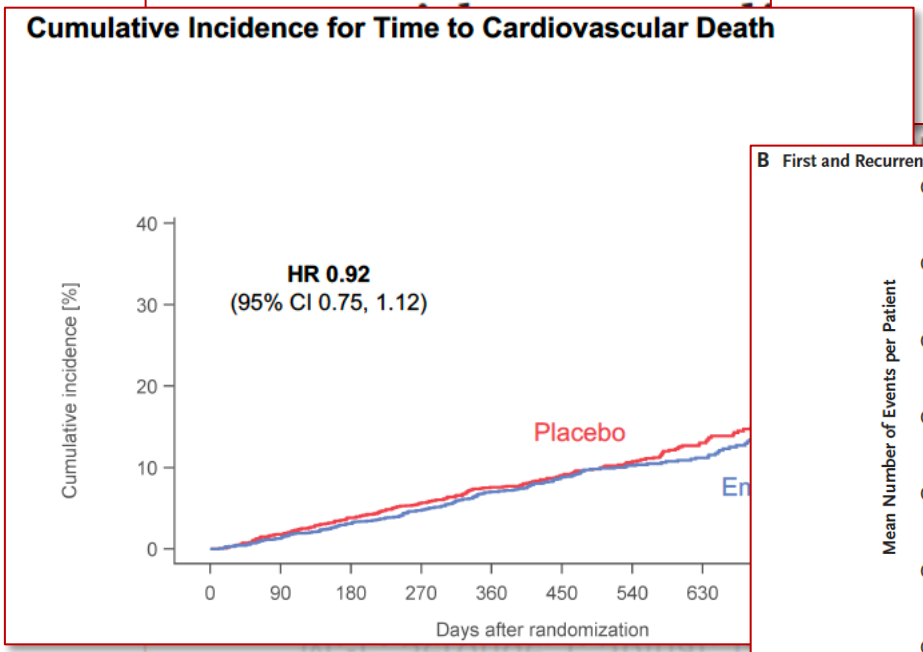

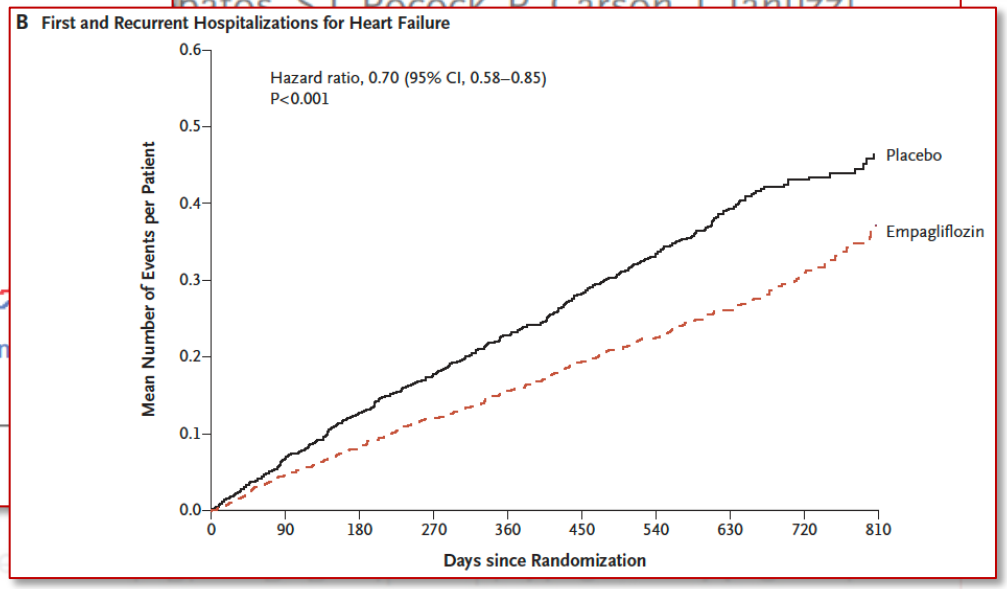

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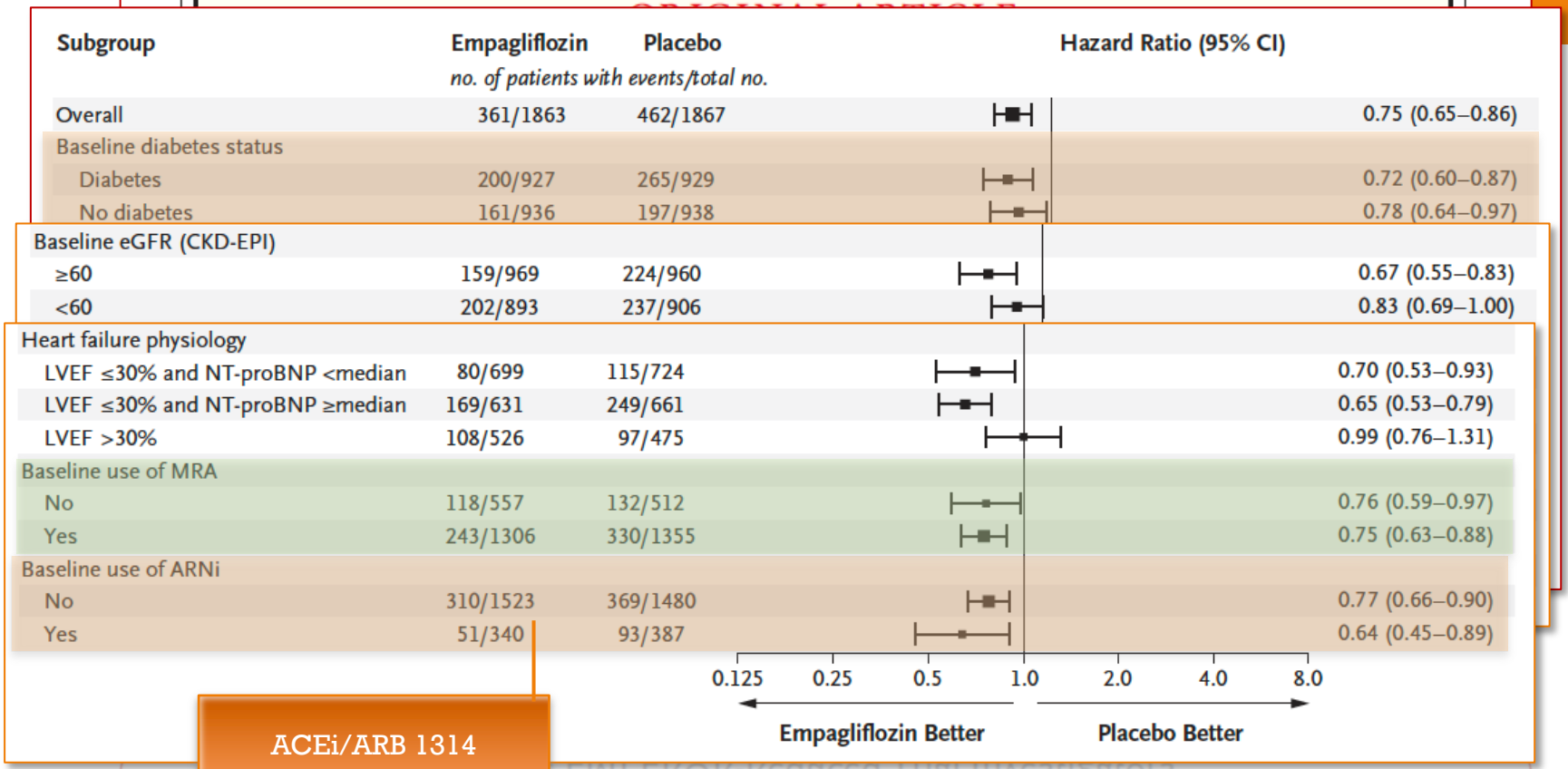


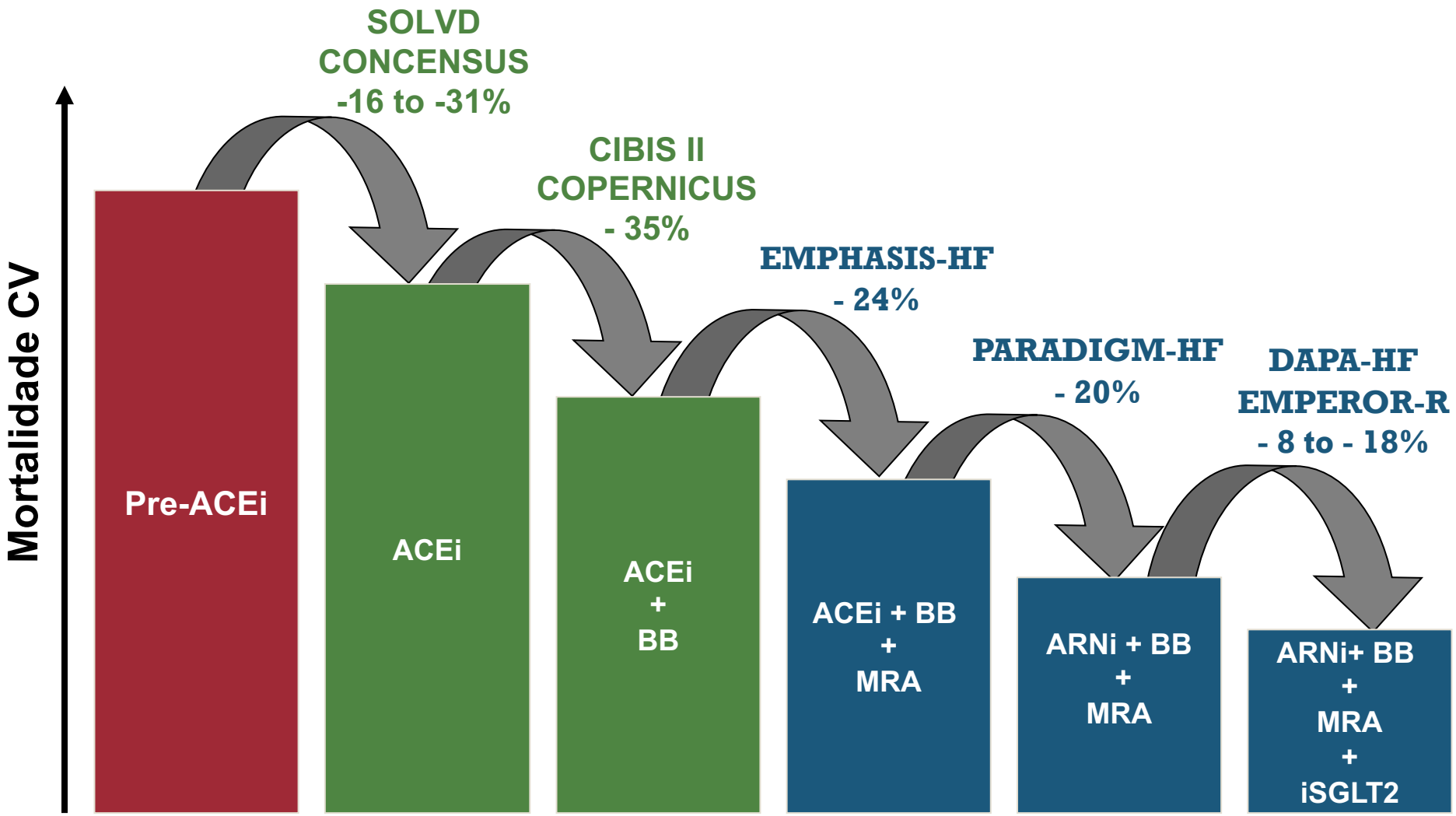
Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	361/1863	462/1867	0.75 (0.65–0.86)
Baseline diabetes status			
Diabetes	200/927	265/929	0.72 (0.60–0.87)
No diabetes	161/936	197/938	0.78 (0.64–0.97)
Baseline eGFR (CKD-EPI)			
≥60	159/969	224/960	0.67 (0.55–0.83)
<60	202/893	237/906	0.83 (0.69–1.00)
Heart failure physiology			
LVEF ≤30% and NT-proBNP <median	80/699	115/724	0.70 (0.53–0.93)
LVEF ≤30% and NT-proBNP ≥median	169/631	249/661	0.65 (0.53–0.79)
LVEF >30%	108/526	97/475	0.99 (0.76–1.31)
Baseline use of MRA			
No	118/557	132/512	0.76 (0.59–0.97)
Yes	243/1306	330/1355	0.75 (0.63–0.88)
Baseline use of ARNi			
No	310/1523	369/1480	0.77 (0.66–0.90)
Yes	51/340	93/387	0.64 (0.45–0.89)

ACEi/ARB 1314

no RAASi 209 (11,2%)

DOI: 10.1056/NEJMoa2022190

Evolução do tratamento farmacológico da IC com FE reduzida



Estimating lifetime be
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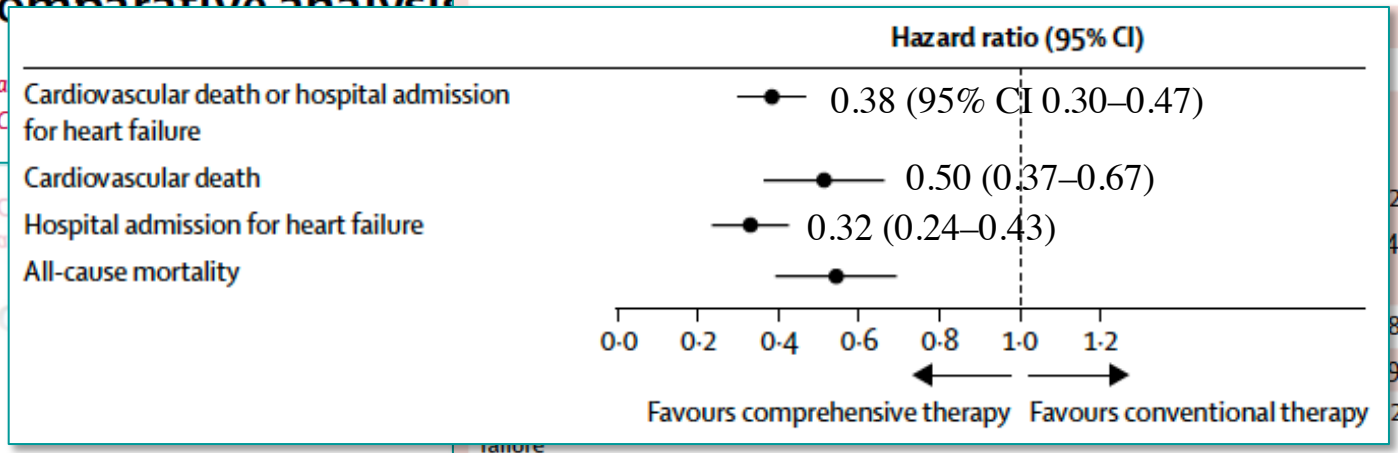
Muthia
Gregg C

Comparison	EMPHASIS-HF[6] (n=2737) Eplerenone vs placebo	PARADIGM-HF[9] (n=8399) Sacubitril–valsartan vs enalapril	DAPA-HF[8] (n=4744) Dapagliflozin vs placebo
Enrolment period	2006–10	2009–12	2017–18
Median follow-up, months	21 (10–33)	27 (19–36)	18 (13–21)
Age, years	69 (8)	64 (11)	66 (11)
Sex			
Men	2127 (78%)	6567 (78%)	3635 (77%)
Women	610 (22%)	1832 (22%)	1109 (23%)
Systolic blood pressure, mm Hg	124 (17)	121 (15)	122 (16)
			72 (12)
			31 (7)
			0
			203 (68%)
			498 (32%)
			43 (1%)
			818 (38%)
			983 (42%)
			251 (47%)
Diuretics	2326 (85%)	6738 (80%)	4008 (84%)
ACE inhibitor, ARB, or ARNI*	2557 (93%)	8379 (100%)	4442 (94%)
β blocker	2374 (87%)	7811 (93%)	4558 (96%)
Mineralocorticoid receptor antagonist	..	4671 (56%)	3370 (71%)



Lancet 2020; 396: 121–28

Estimating lifetime
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Muthiah Vaduganathan, Brian L Claggett, Pard
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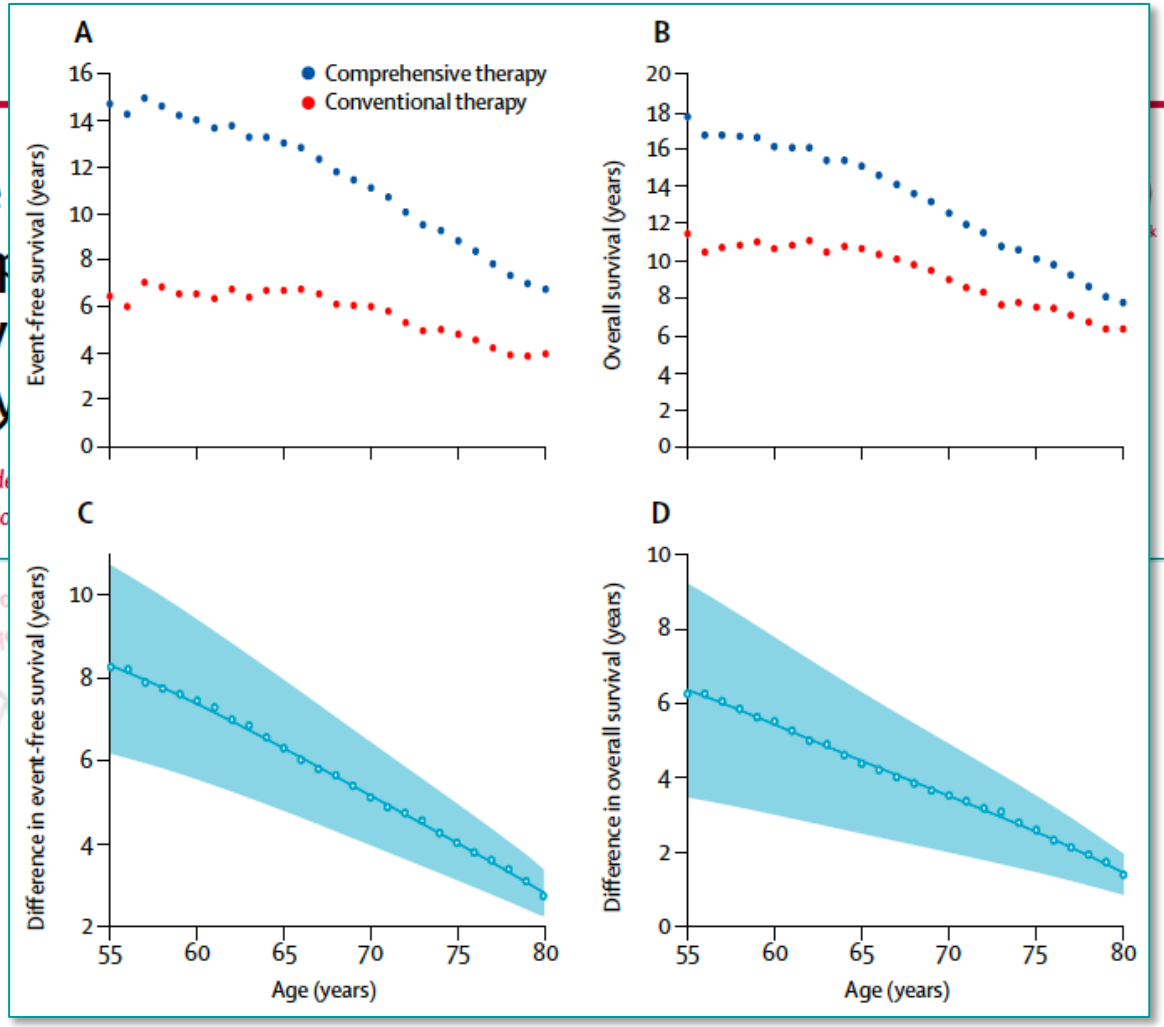


Lancet 2020; 396: 121–28

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiote

John J.V. McMurra
Martin P. Lefkov
Scott D.

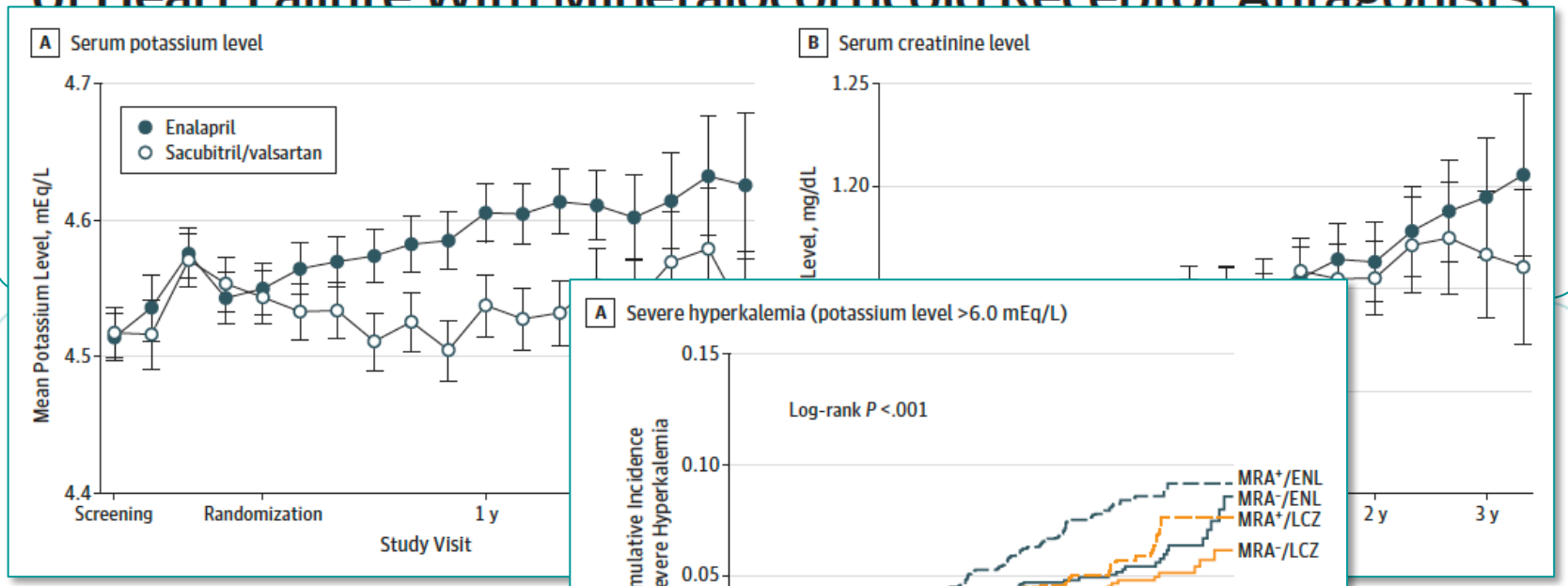
Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

Research

JAMA Cardiology | Original Investigation

Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists



JAMA Cardiol. 2017;2(1):79-85

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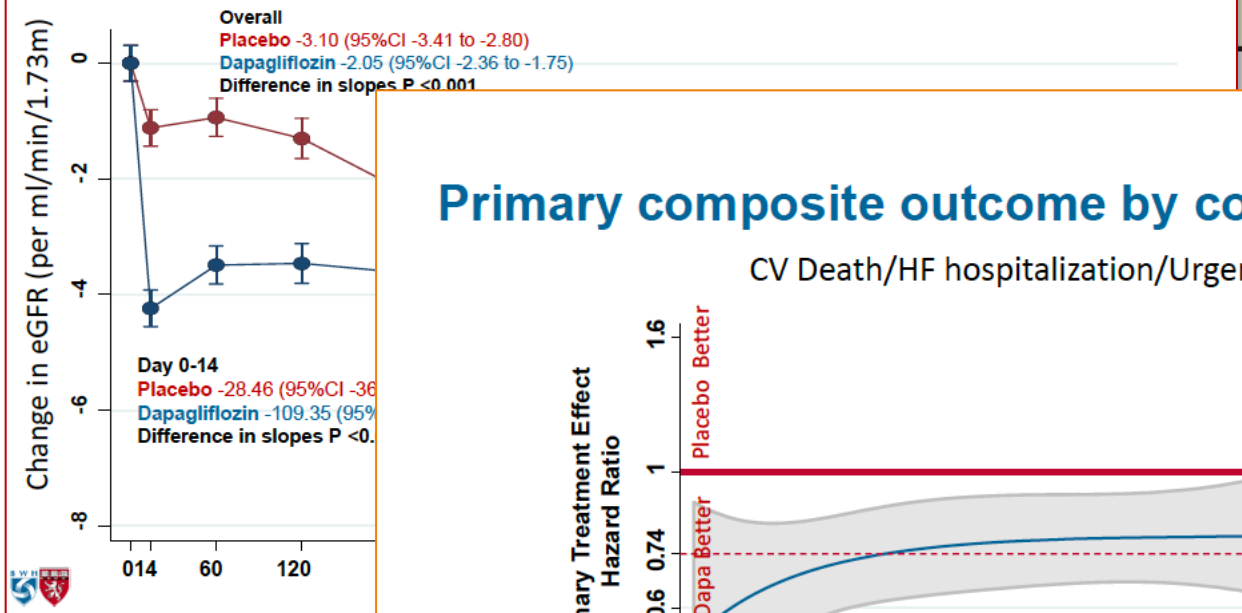
Change in eGFR per ml/min/1.73m^2 per year



Primary composite outcome by continuous eGFR

DOI: 10.1056/NEJMoa1911303

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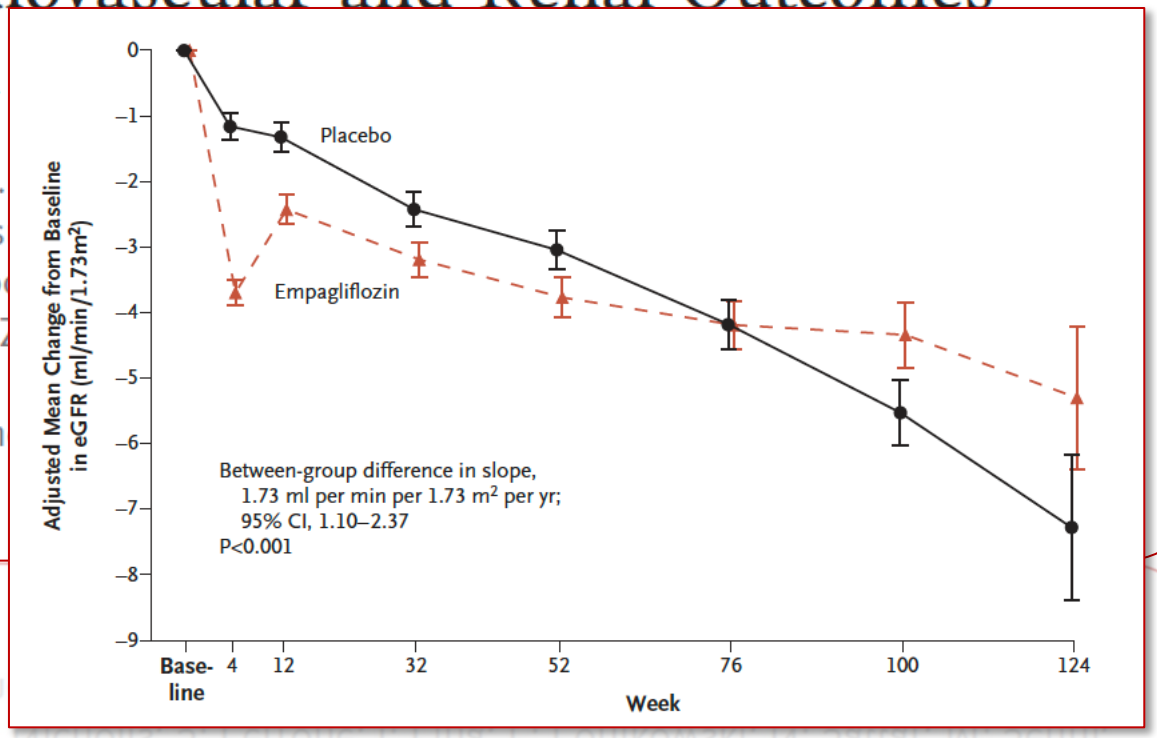
ORIGINAL ARTICLE

Cardiovascular and Renal Outcomes with

M. Packer, S.D.
S. Verma, H. Ts
D. Cotton, E. Bo
S. Janssens, J.
B. Merkely, S.J.
M.-F. Seron



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ESC European Society of Cardiology

European Journal of Heart Failure (2020) 22, 713–722
doi:10.1002/ejhf.1713

RESEARCH ARTICL

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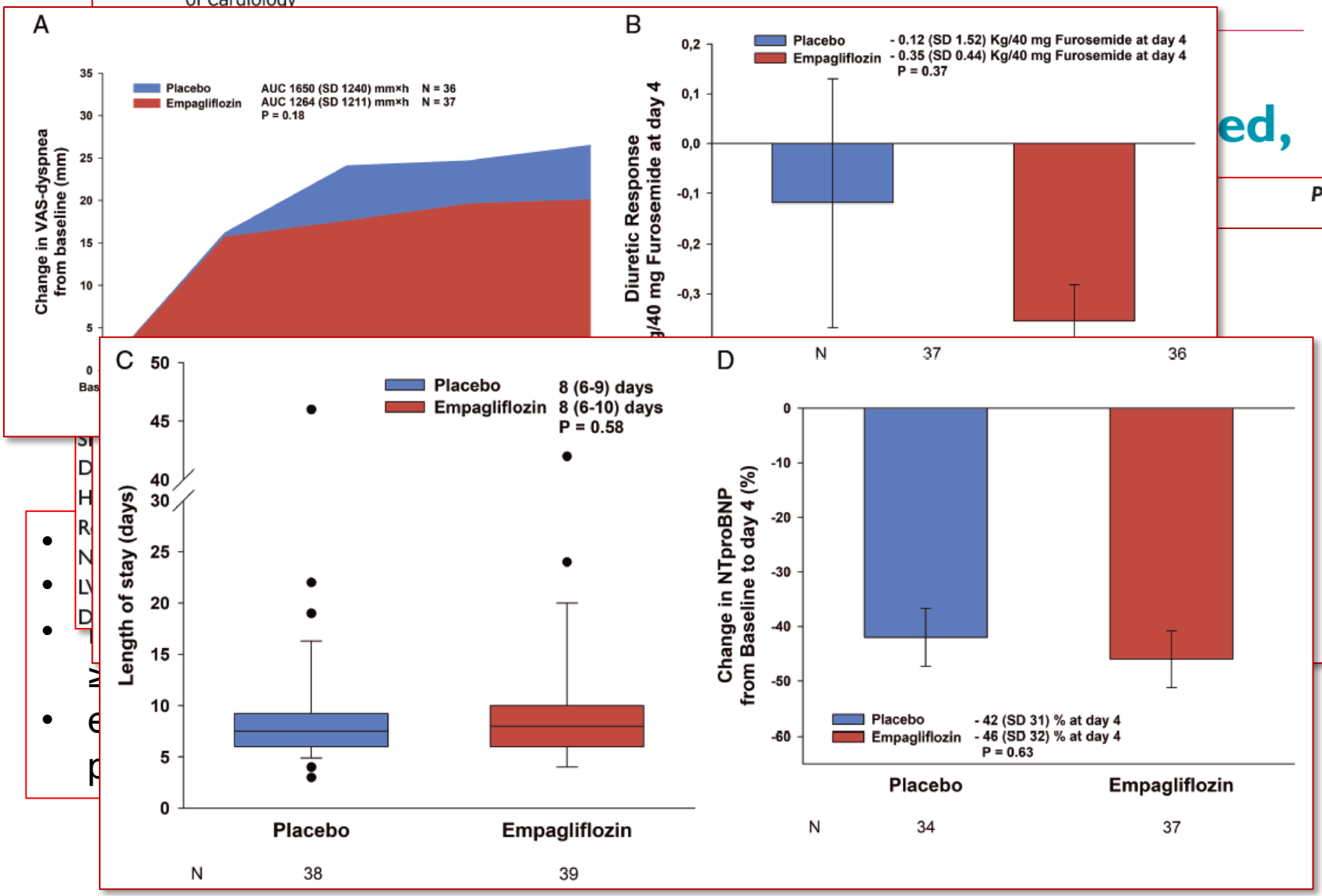
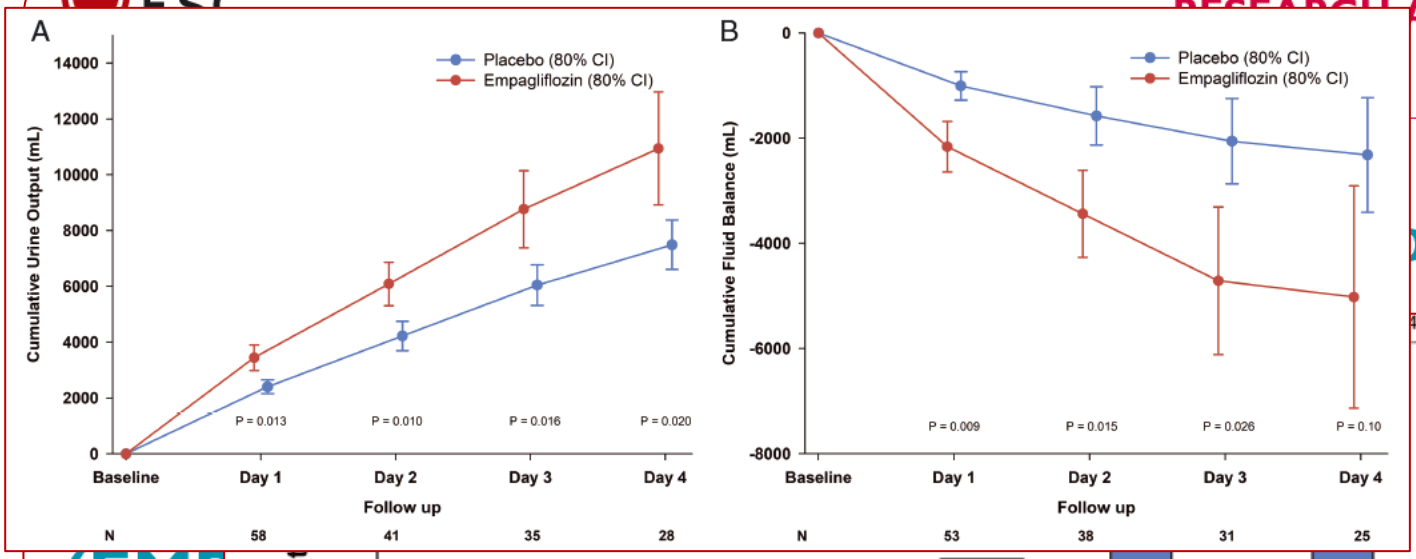
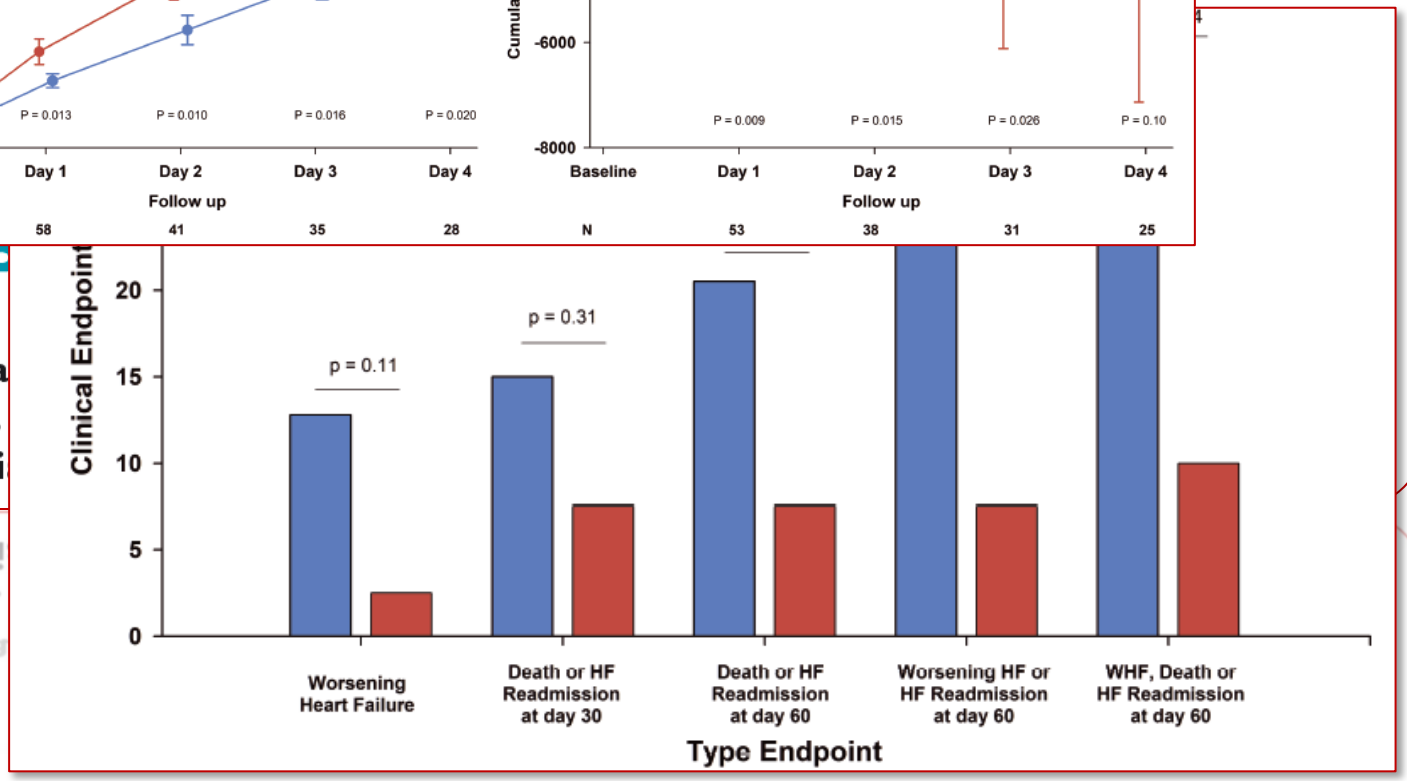
ed,

	P-value
	0.51
	0.45
	0.52
	0.69
	0.81
	NA
	0.36
	0.054
	0.78
	0.14
	0.72
	0.97
	0.99




A
Placebo (80% CI)
Empagliflozin (80% CI)
Cumulative Urine Output (mL)
14000
12000
10000
8000
6000
4000
2000
0
P = 0.013
P = 0.010
P = 0.016
P = 0.020
Baseline
Day 1
Day 2
Day 3
Day 4
Follow up
N
58
41
35
28
B
Placebo (80% CI)
Empagliflozin (80% CI)
Cumulative Fluid Balance (mL)
0
-2000
-4000
-6000
-8000
P = 0.009
P = 0.015
P = 0.026
P = 0.10
Baseline
Day 1
Day 2
Day 3
Day 4
Follow up
N
53
38
31
25


Clinical Endpoint
20
15
10
5
0
p = 0.11
p = 0.31
Worsening Heart Failure
Death or HF Readmission at day 30
Death or HF Readmission at day 60
Worsening HF or HF Readmission at day 60
WHF, Death or HF Readmission at day 60
Type Endpoint

European Hear
doi:10.1093/eur

2021 ESC treatment

The Task For
heart failure c

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