I PERCORSI APPROPRIATI ASSISTENZIALI E TERAPEUTICI IN PREVENZIONE SECONDARIA

Approccio al paziente ad alto rischio cardiovascolare

10 GIUGNO 2022

12.45 ARNI e glifozine: a che punto siamo

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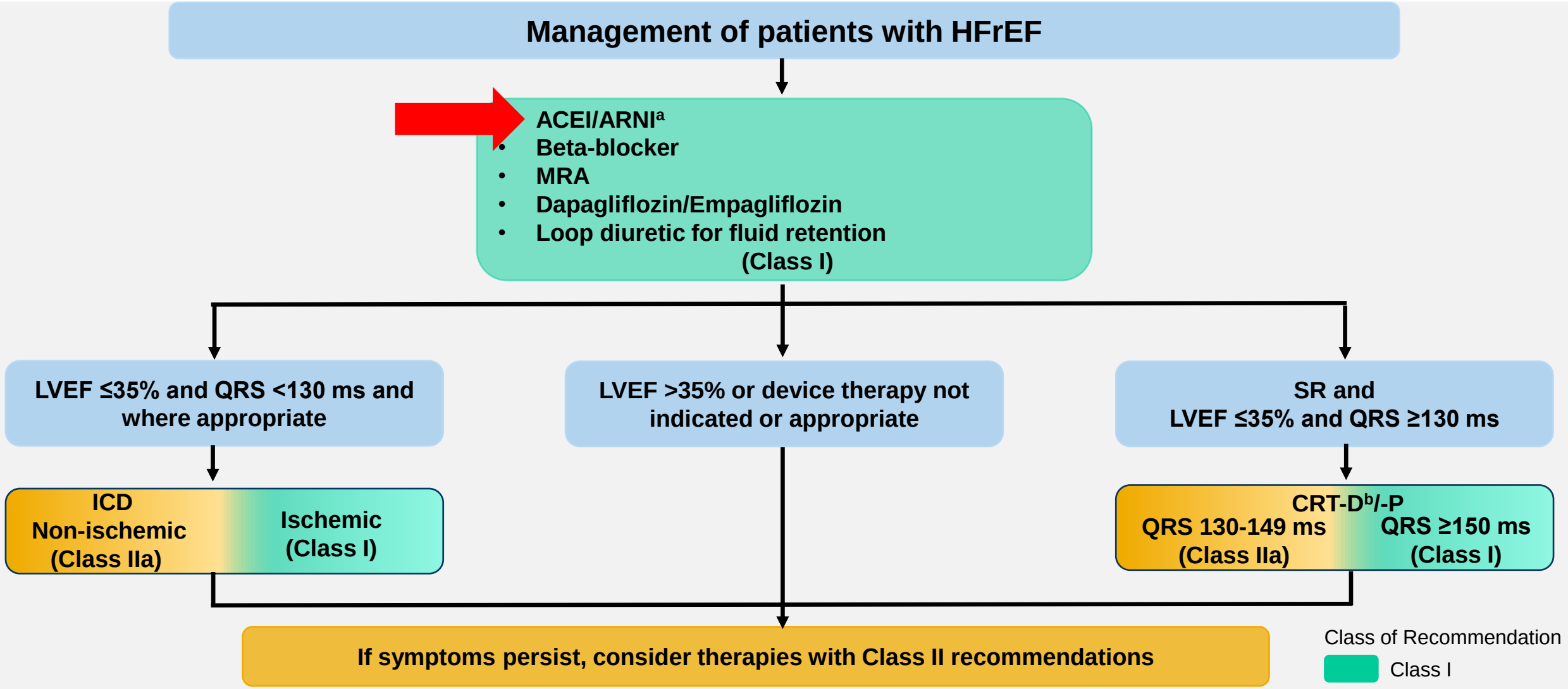
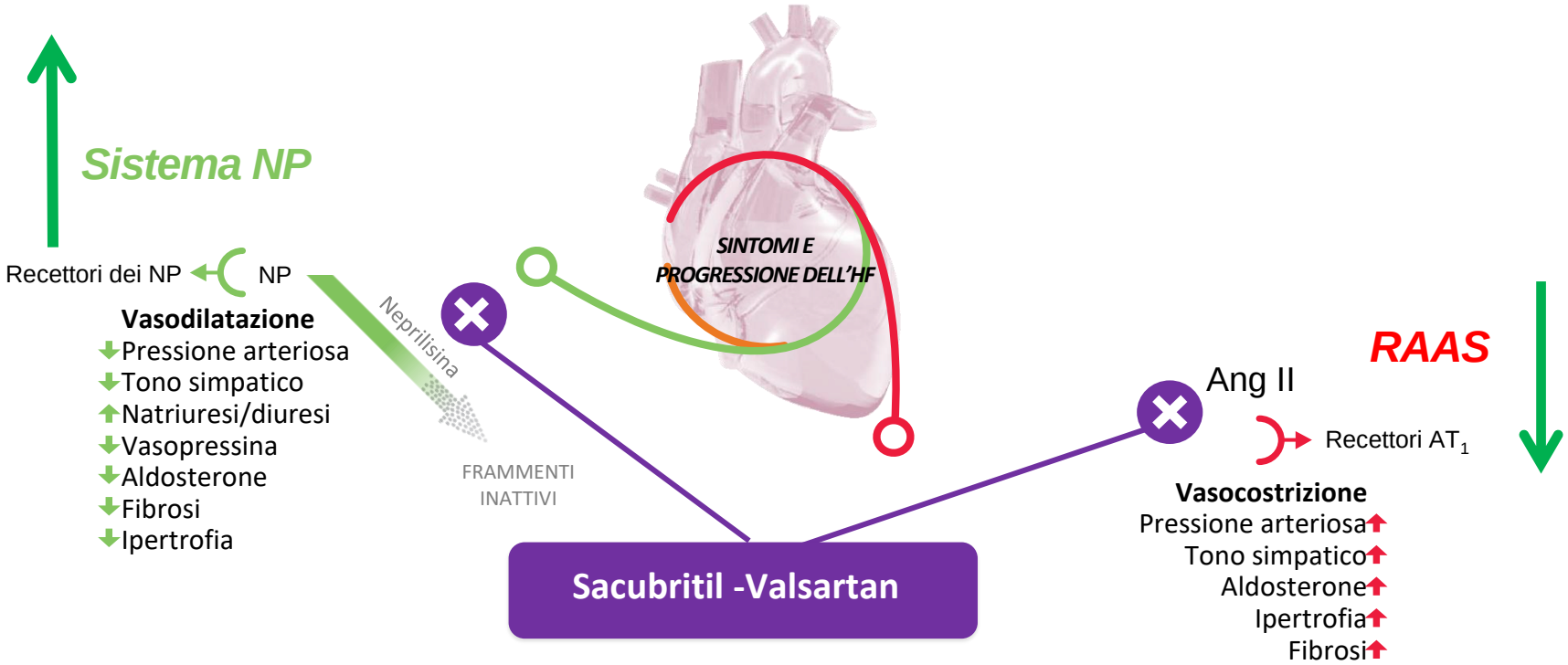
ESC 2021 Heart Failure Guidelines: Dapagliflozin Recommended as one of the Cornerstone Therapies for HFrEF



[a]As a replacement for ACEI; [b]Where appropriate.

McDonagh TA et al. Online ahead of print. *Eur Heart J*. 2021.

Sacubritil/valsartan è il primo farmaco che dimostra un significativo beneficio clinico nel HFrEF con il potenziamento del Sistema NP (bloccando la Neprilisina) ed il simultaneo blocco del RAAS



Sacubritil/valsartan: potenziamento dei peptidi natriuretici e di altri peptidi vasoattivi, con simultanea soppressione del RAAS

1. McMurray et al. Eur J Heart Fail. 2013;15:1062–73;
Rif. Figura: Levin et al. N Engl J Med 1998;339:321–8; Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42;
Kemp & Conte. Cardiovascular Pathology 2012;365–371; Schrier & Abraham N Engl J Med 2009;341:577–85

ESC 2021 Heart Failure Guidelines

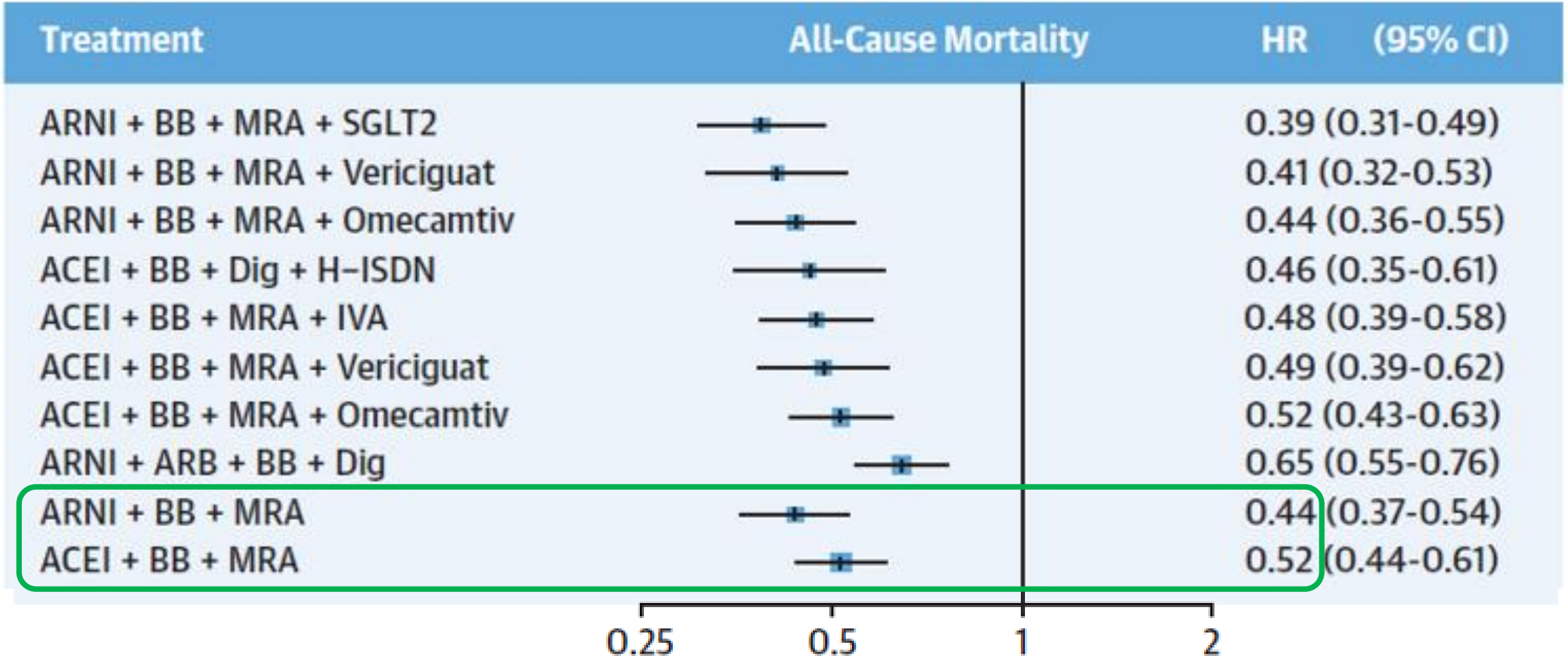
Recommendations	Class[a]	Level[b]
An ACEI is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACEI in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

[a]Class of recommendation; [b]Level of evidence.

ACEI = angiotensin-converting enzyme inhibitor; ESC = European Society of Cardiology; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist.

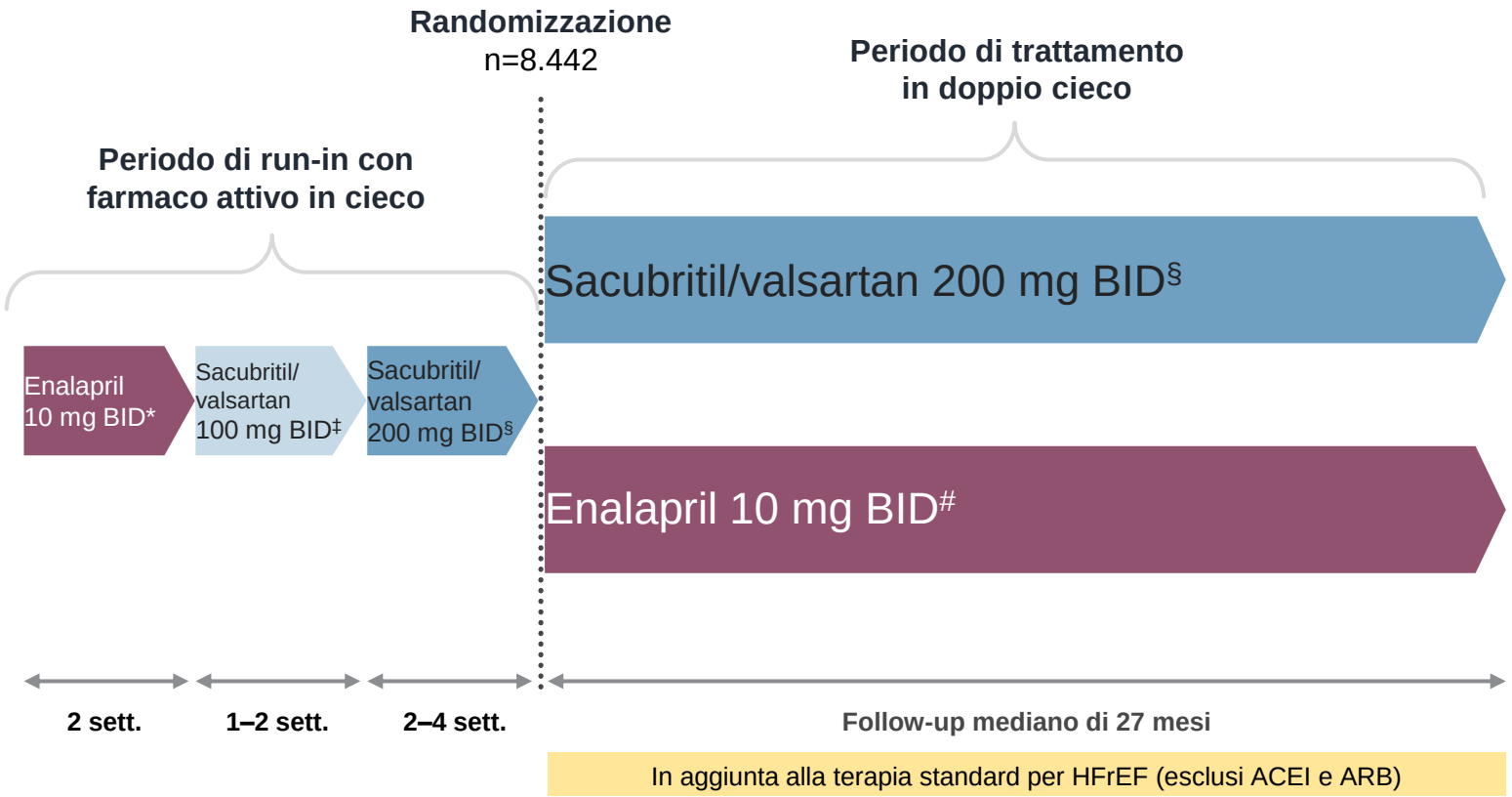
McDonagh TA et al. Online ahead of print. *Eur Heart J*. 2021.

Riduzione del rischio in relazione alle differenti combinazioni di trattamenti farmacologici per lo Scompenso Cardiaco



Tromp, J. et al. J Am Coll Cardiol HF. 2022;10(2):73-84.

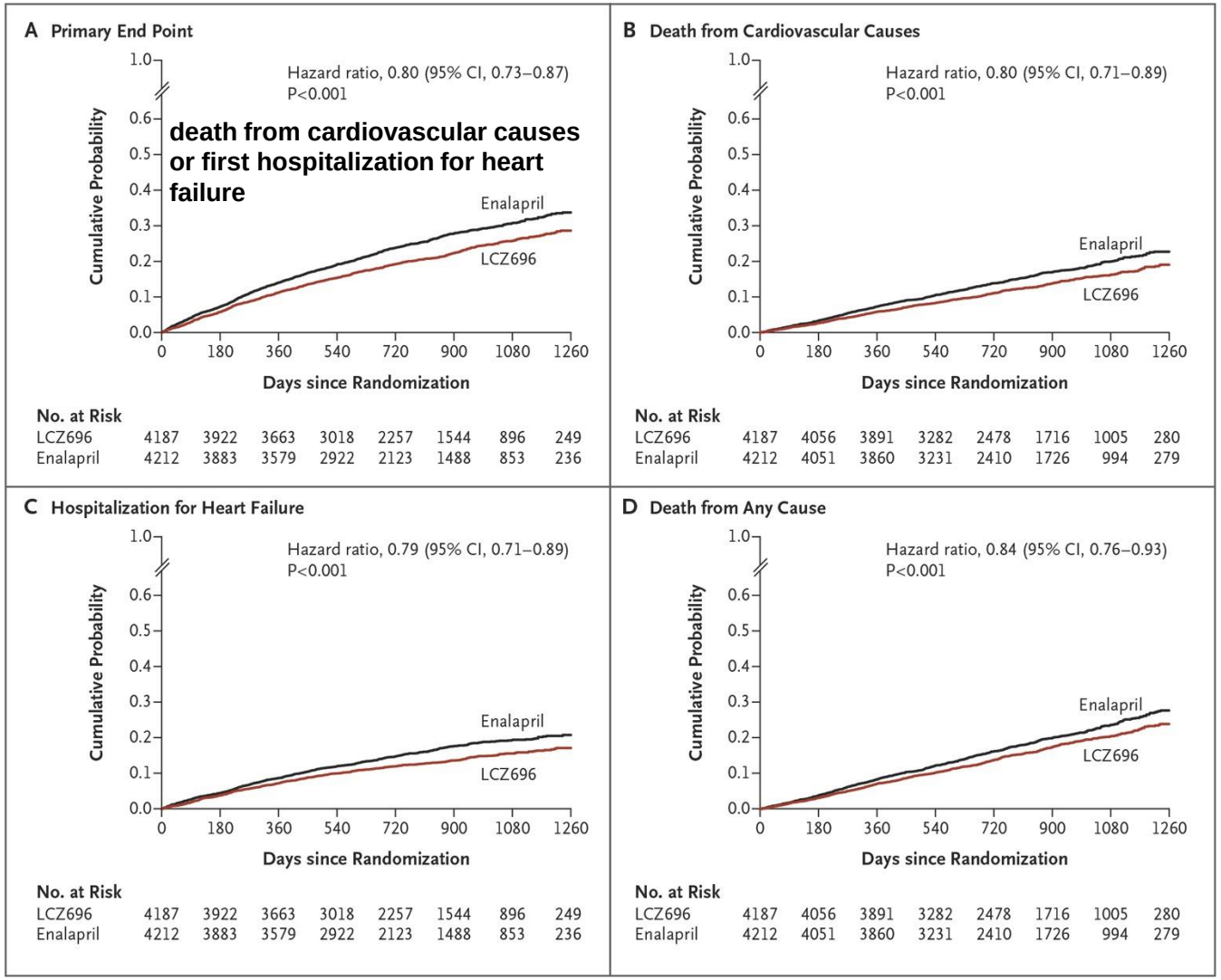
PARADIGM-HF: disegno dello studio



*Enalapril 5 mg BID (10 mg TDD) per 1–2 settimane seguito da enalapril 10 mg BID (20 mg TDD) come dose ottimale di partenza del run-in per quei pazienti trattati con ARB o ACEI a bassa dose; ‡200 mg TDD; §400 mg TDD; #20 mg TDD

McMurray et al. Eur J Heart Fail. 2013;15:1062–73; McMurray et al. Eur J Heart Fail 2014;16:817–25; McMurray et al. N Engl J Med 2014;371:993–1004

Kaplan–Meier Curves for Key Study Outcomes, According to Study Group

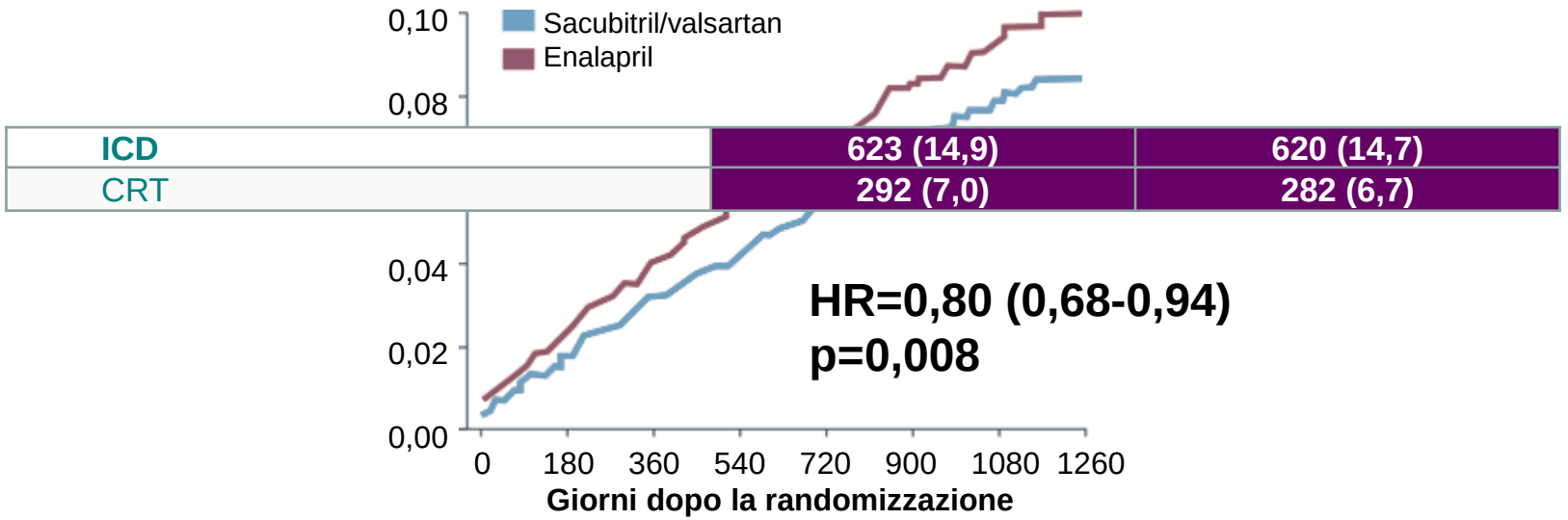


McMurray JJV et al. N Engl J Med 2014;371:993-1004

Sacubritil/Valsartan riduce la morte improvvisa

Il trattamento con Sacubitril/Valsartan ha significativamente ridotto il rischio di morte improvvisa rispetto a Enalapril, HR: 0,80 (IC al 95%; 0,68–0,94, p=0,008).[1]

Curva di sopravvivenza di Kaplan–Meier per il tempo alla morte improvvisa per trattamento[1]

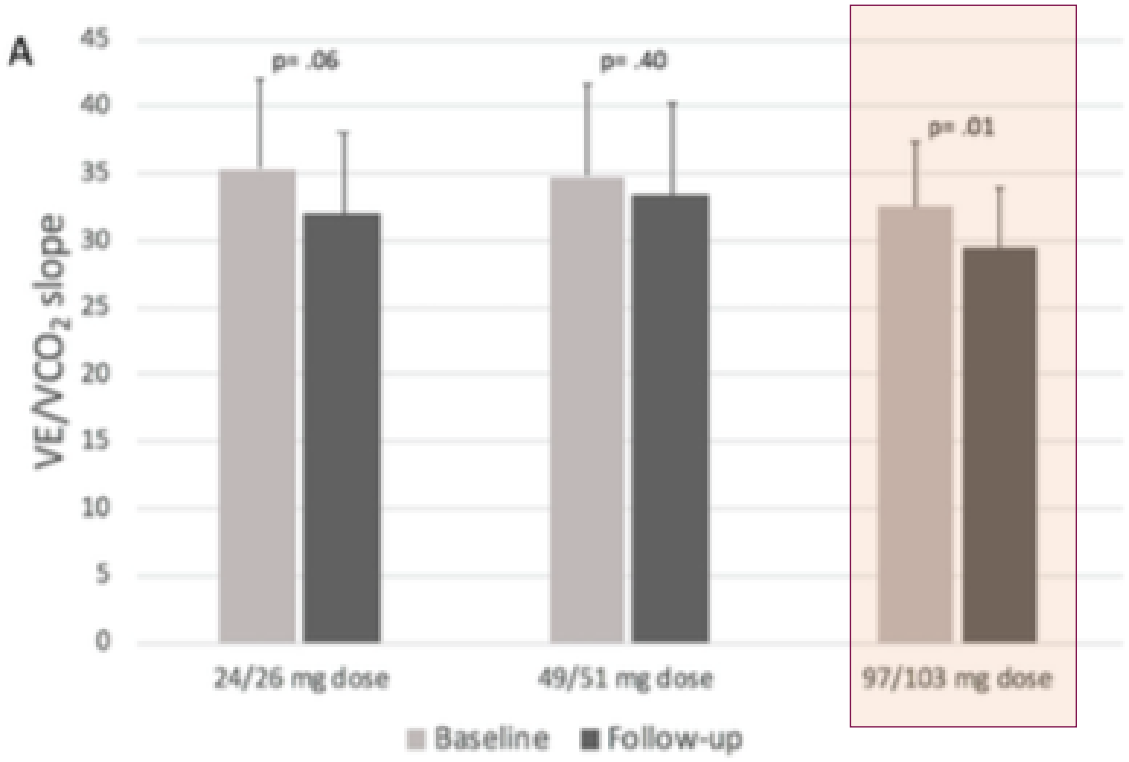


ICD	623 (14,9)	620 (14,7)
CRT	292 (7,0)	282 (6,7)

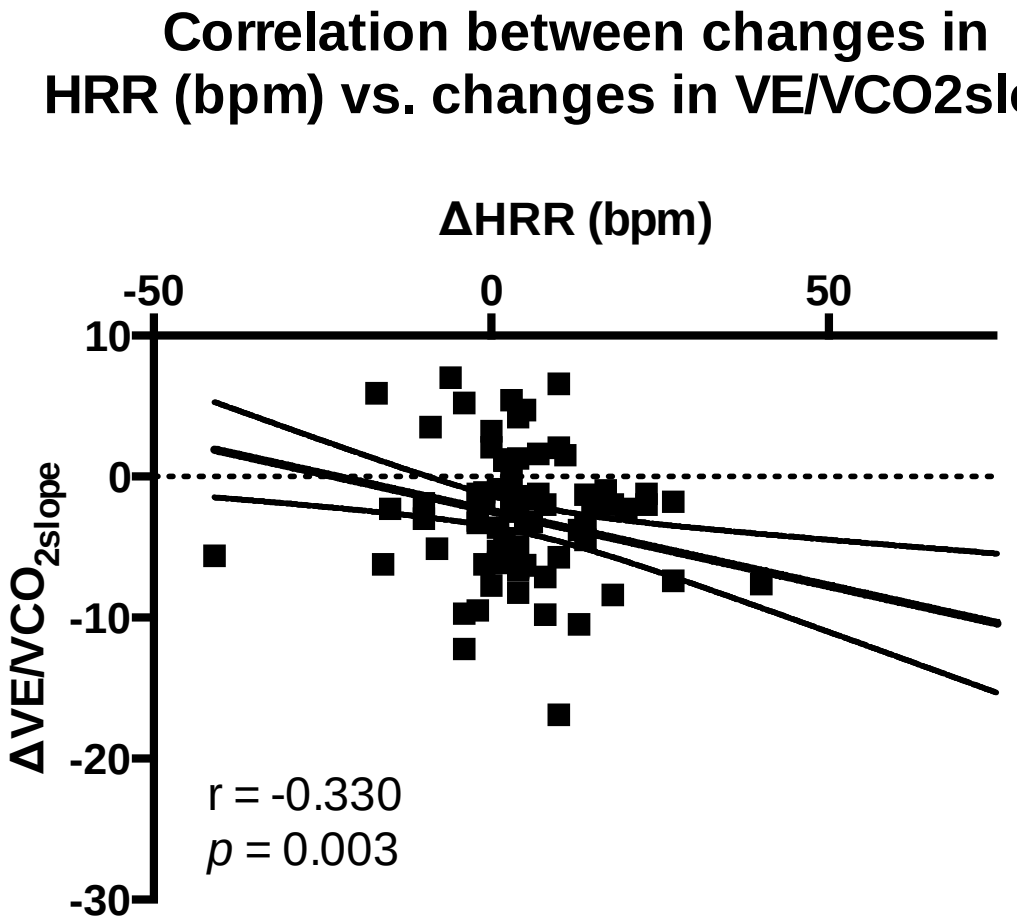
N° pazienti a rischio

Sacubitril/valsartan	4,212	3,860	2,410	994
Enalapril	4,187	3,891	2,478	1,005

Deasy et al. Eur Heart J 2015;36:1990–1997.



Giallauria F et al, J. Clin. Med. 2019, 8, 262



Giallauria F et al, J Clin. Med. 2020, 9, 1897

	PARAGON-HF (N = 4822)	PEP-CHF (N = 850)	I-PRESERVE (N = 4128)	TOPCAT (N = 3445)	CHARM-P (N = 3023)
Treatment arms	Sacubitril/valsartan vs valsartan	Perindopril vs placebo	Irbesartan vs placebo	Spironolactone vs placebo	Candesartan vs placebo
Key inclusion criteria	NYHA functional class II-IV, elevated NT-proBNP. Mildly elevated NT-proBNP if prior HFH, structural heart disease (LAE or LVH)	Clinical diagnosis of DHF with signs/symptoms of HF, ≥2 of the following: LAE/LVH/impaired LV filling/AF	NYHA functional class II-IV + any corroborating evidence (e.g., HF sign), LVH or LAE considered optional corroborating evidence, HFH required unless in NYHA functional class III-IV	≥1 HF symptom + ≥1 HF sign, elevated NP, or HFH	NYHA functional class II to IV, prior CVH
Primary endpoint	CVD and total HFH (first and recurrent)	First of either all-cause death or HFH	First of either all-cause death or CVH	First of either CVD, HFH, or RSD	First of either CVD or HFH

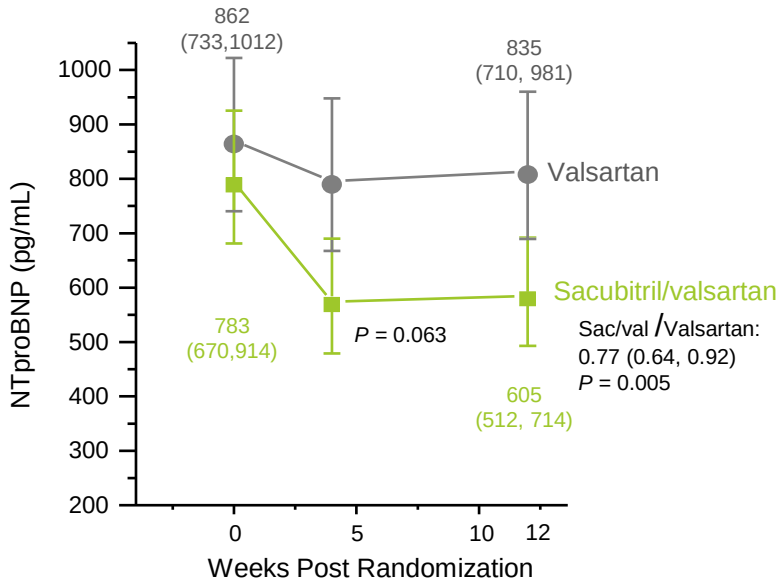
CVD, cardiovascular disease; CVH, cardiovascular hospitalization; DHF, diastolic heart failure; HF, heart failure; HFH, heart failure hospitalization; LAE, left atrial enlargement; LV, left ventricle; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; NP, natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; RSD, resuscitated sudden death

Solomon SD et al. JACC Heart Fail. 2017;5:471-482

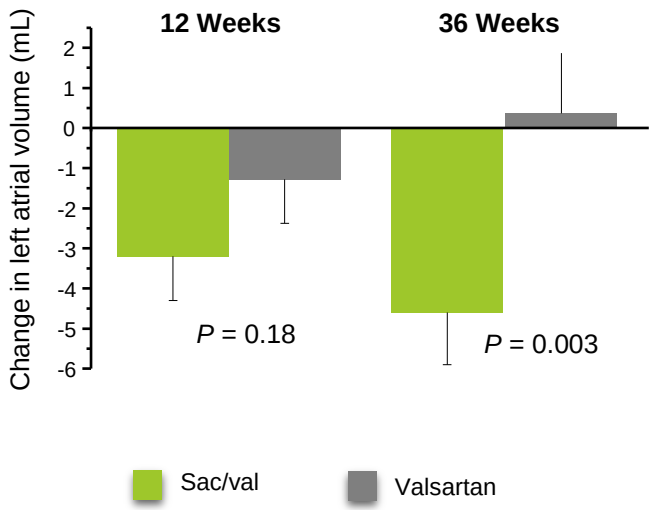
Study design: PARAGON-HF vs previous HFpEF trials

Sacubitril/valsartan is the only medication with positive phase II data in HFpEF (PARAMOUNT)

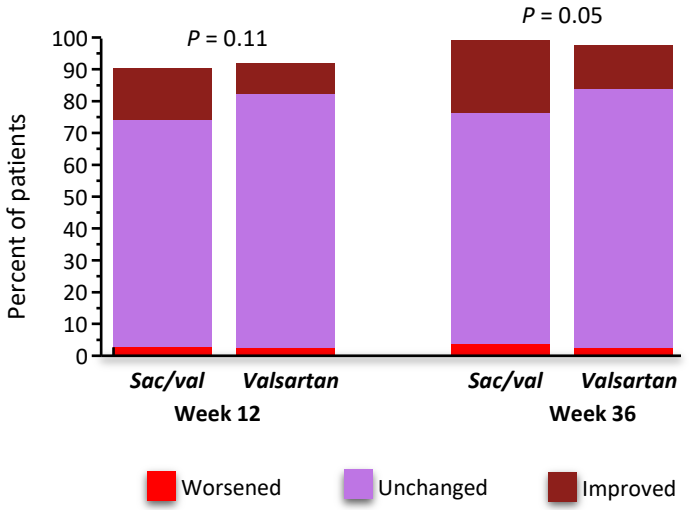
Improvement in NT-proBNP



Improvement in left atrial size



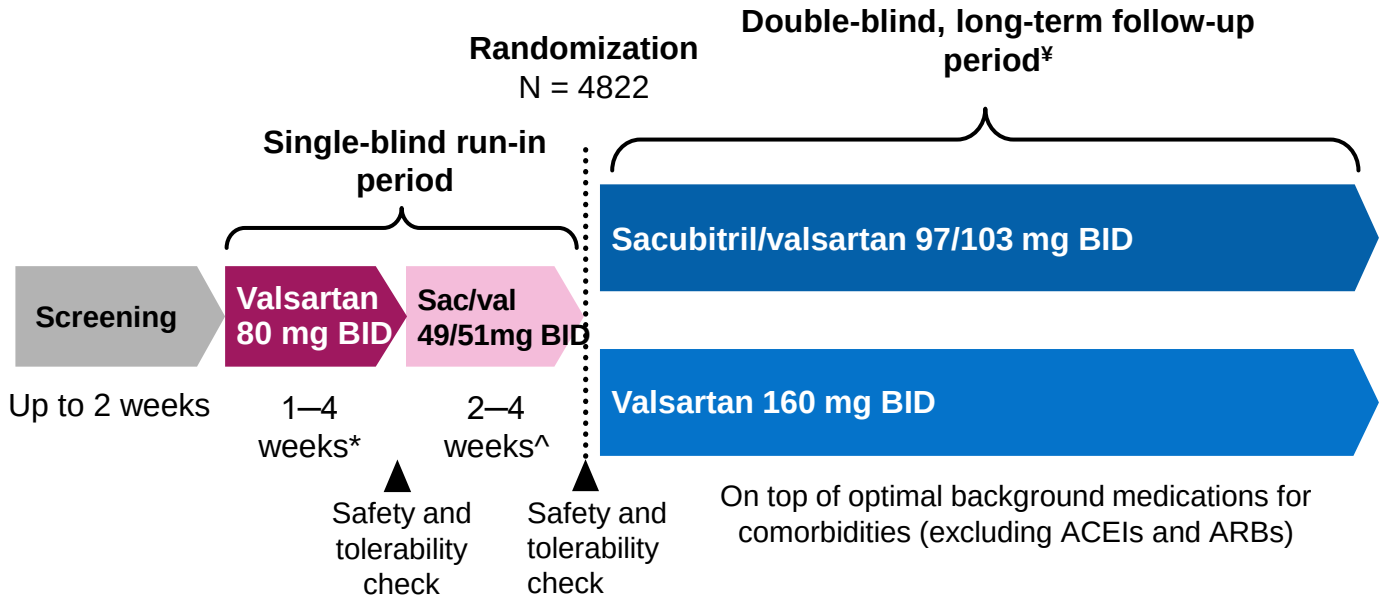
Improvement in NYHA class



HFpEF, heart failure with preserved ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; sac/val, sacubitril/valsartan

Solomon et al. Lancet 2012 380(9851):1387-1395

A randomized, double-blind, parallel group, active-controlled, event driven trial

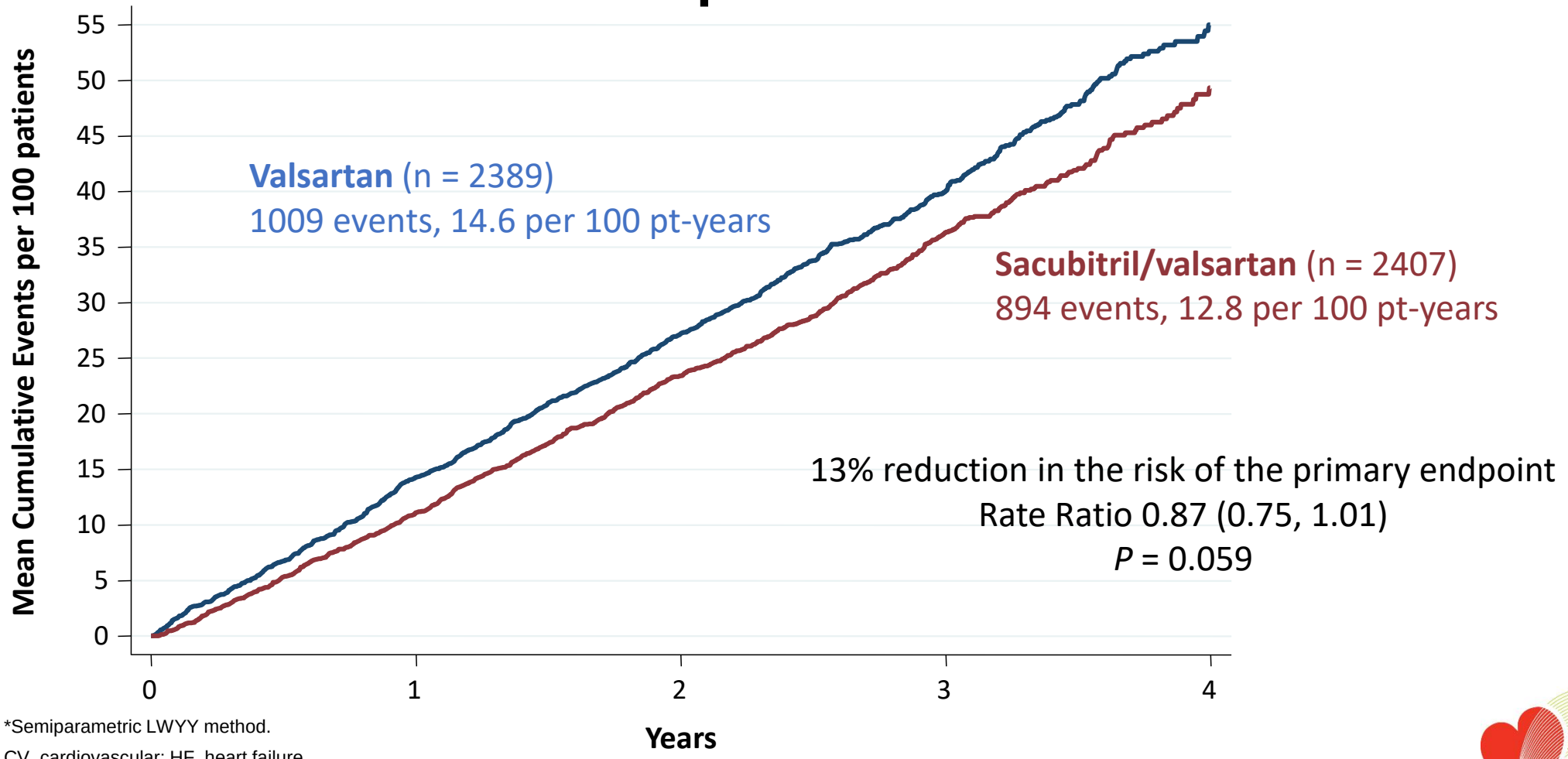


*Eligible patients were exposed to valsartan 80 mg BID for 1–2 weeks. Patients on low pre-study ACEI/ARB doses or those with tolerability concerns were first started on valsartan 40 mg BID 1–2 weeks and then up-titrated to valsartan 80 mg BID for 1–2 weeks
^Patients tolerating valsartan 80 mg BID for 1–2 weeks were switched to sacubitril/valsartan 100 mg BID for 2–4 weeks
¥Follow-up visits occurred at 4, 16, 32, and 48 weeks and every 12 weeks thereafter. All patients were followed until target number of primary composite (CV deaths and total HF hospitalizations) occur or 26 months after randomization of the last patient elapse, whichever occurs last

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BID, twice daily; CV, cardiovascular; HF, heart failure

Solomon SD et al. JACC Heart Fail. 2017;5:471-482

Primary endpoint: Recurrent event analysis of total HF hospitalizations and CV death*



*Semiparametric LWYY method.

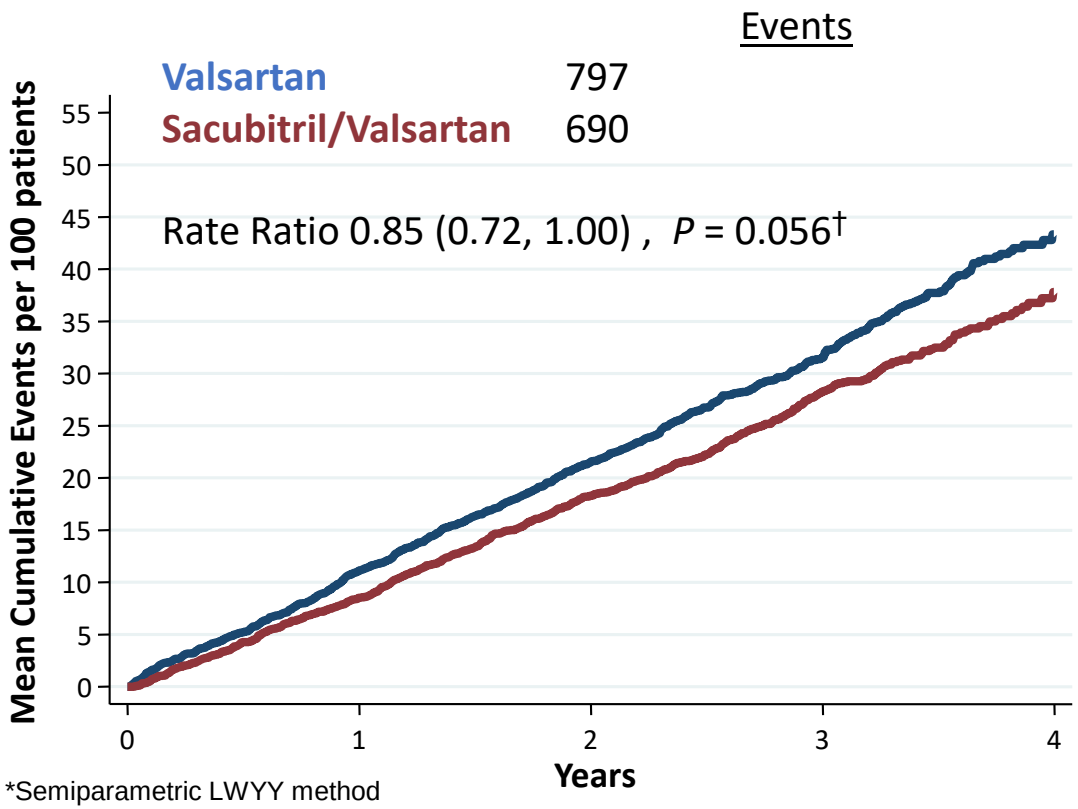
CV, cardiovascular; HF, heart failure

Solomon S, et al. N Engl J Med. 2019

PARAGONHF

HF hospitalizations and CV Death

Heart Failure Hospitalizations*

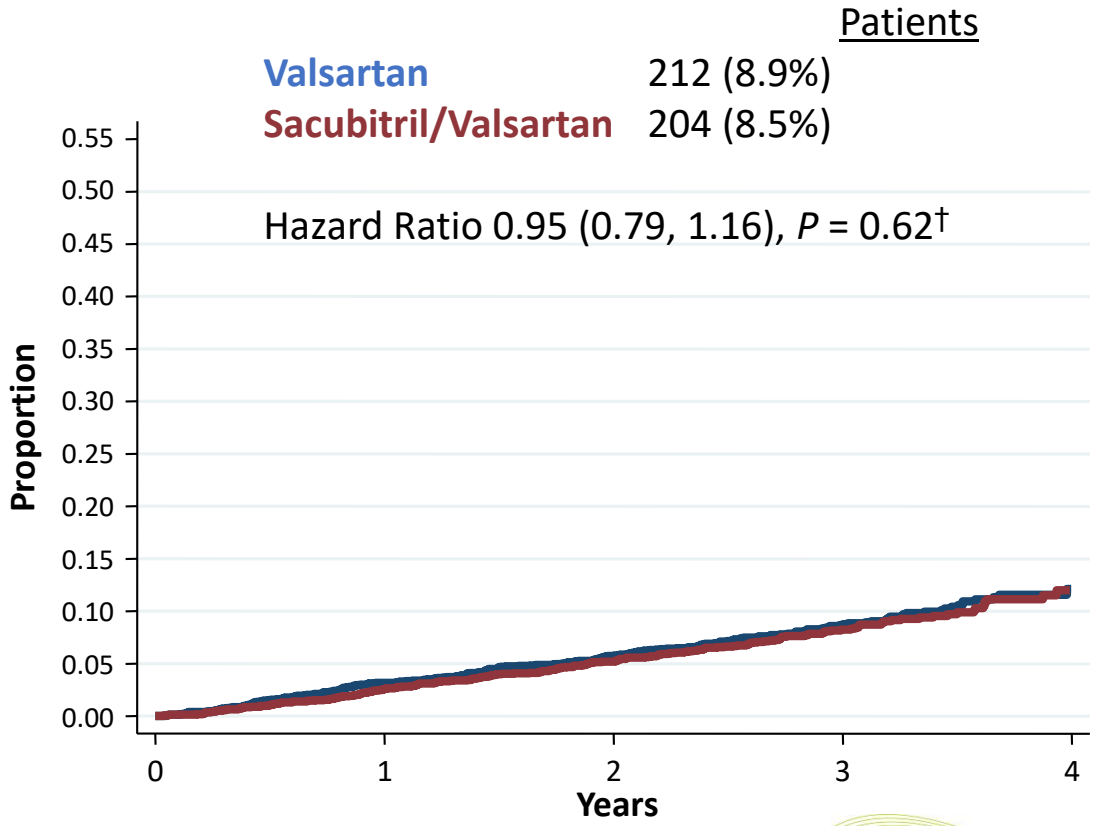


*Semiparametric LWYY method

†p-values not included in manuscript, but were included in the ESC Hotline presentation

Solomon S, et al. N Engl J Med. 2019

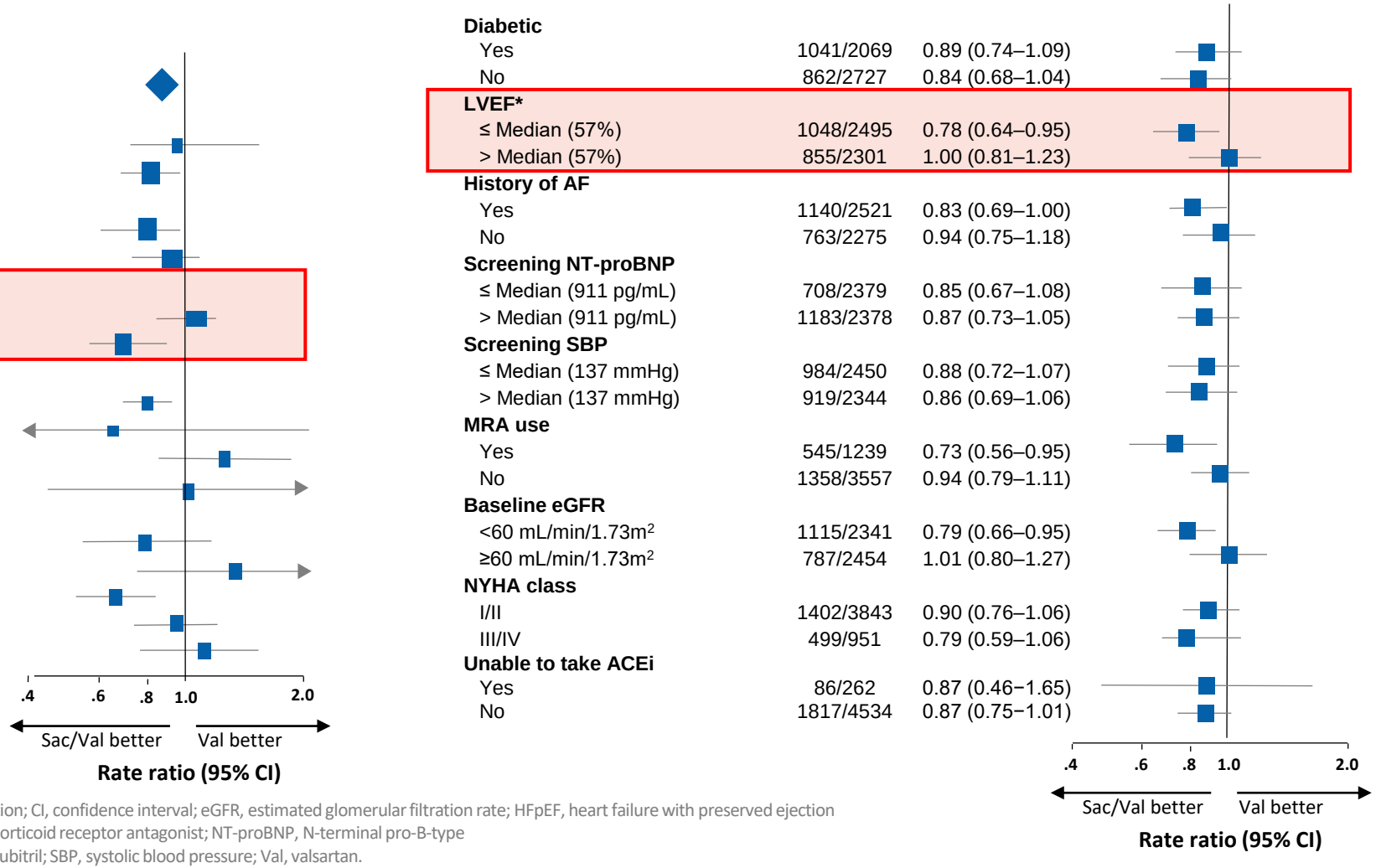
Cardiovascular Death*



PARAGONHF

Outcomes data support a greater clinical benefit with sacubitril/valsartan for some HFpEF populations, particularly in patients with a lower-than-normal ejection fraction, and in women

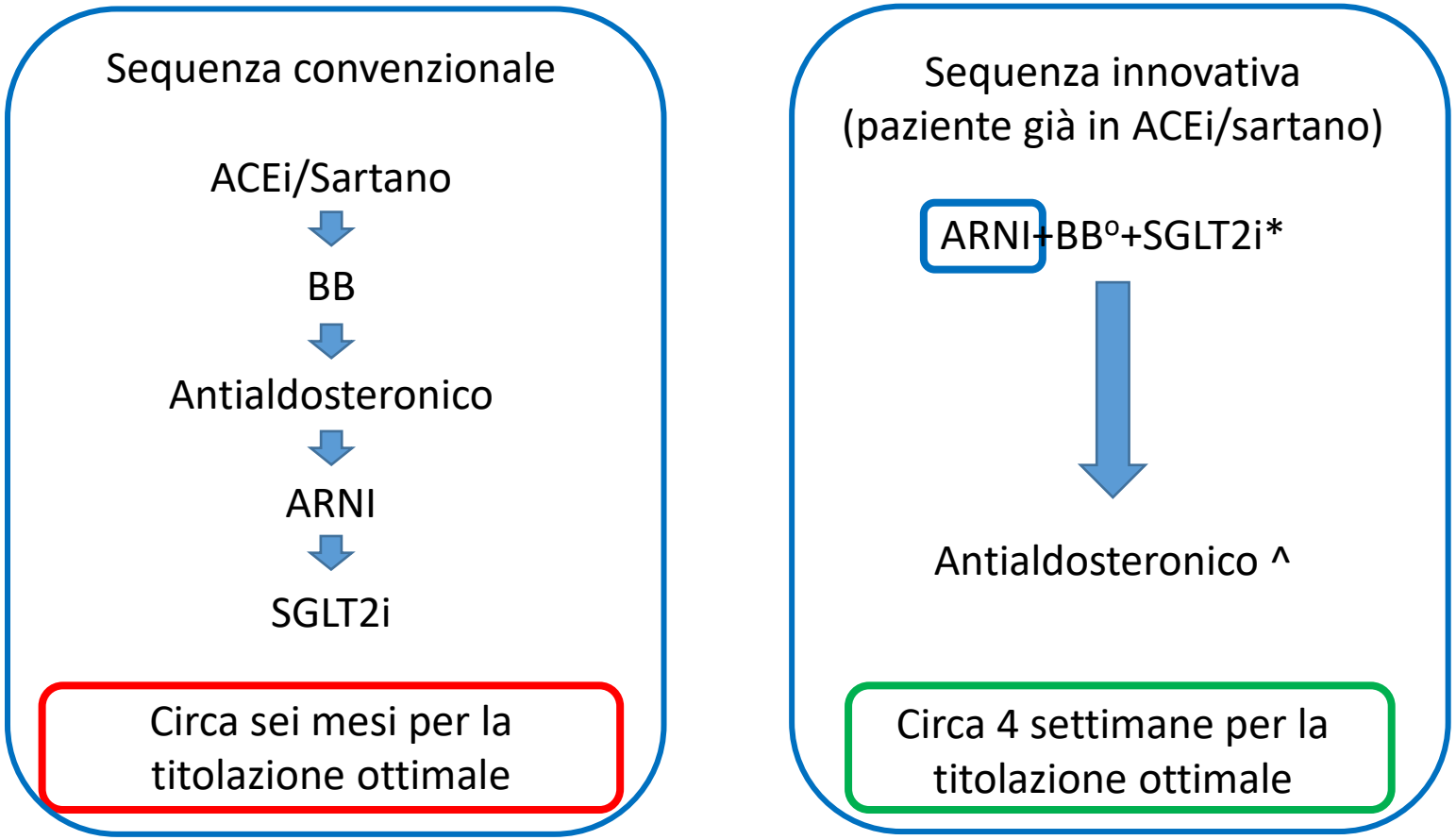
Subgroup overall	No. of events/ patients	Hazard ratio (95% CI)
Overall	**1903/4796**	**0.87 (0.75–1.01)**
Age (years)		
<65	276/825	0.99 (0.64–1.53)
≥65	1627/3971	0.85 (0.73–0.99)
Age (years)		
<75	938/2597	0.82 (0.66–1.02)
≥75	965/2199	0.92 (0.76–1.11)
Sex		
Male	980/2317	1.03 (0.85–1.25)
Female	923/2479	0.73 (0.59–0.90)
Race		
White	1542/3907	0.83 (0.71–0.97)
Black	89/102	0.69 (0.24–1.99)
Asian	237/607	1.25 (0.87–1.79)
Other	35/180	1.03 (0.47–2.28)
Region		
North America	478/559	0.80 (0.57–1.14)
Latin America	83/370	1.33 (0.75–2.36)
Western Europe	544/1390	0.69 (0.53–0.89)
Central Europe	466/1715	0.97 (0.76–1.24)
Asia-Pacific/Other	332/762	1.10 (0.79–1.52)
Diabetic		
Yes	1041/2069	0.89 (0.74–1.09)
No	862/2727	0.84 (0.68–1.04)
LVEF*		
≤ Median (57%)	1048/2495	0.78 (0.64–0.95)
> Median (57%)	855/2301	1.00 (0.81–1.23)
History of AF		
Yes	1140/2521	0.83 (0.69–1.00)
No	763/2275	0.94 (0.75–1.18)
Screening NT-proBNP		
≤ Median (911 pg/mL)	708/2379	0.85 (0.67–1.08)
> Median (911 pg/mL)	1183/2378	0.87 (0.73–1.05)
Screening SBP		
≤ Median (137 mmHg)	984/2450	0.88 (0.72–1.07)
> Median (137 mmHg)	919/2344	0.86 (0.69–1.06)
MRA use		
Yes	545/1239	0.73 (0.56–0.95)
No	1358/3557	0.94 (0.79–1.11)
Baseline eGFR		
<60 mL/min/1.73m^2	1115/2341	0.79 (0.66–0.95)
≥60 mL/min/1.73m^2	787/2454	1.01 (0.80–1.27)
NYHA class		
I/II	1402/3843	0.90 (0.76–1.06)
III/IV	499/951	0.79 (0.59–1.06)
Unable to take ACEi		
Yes	86/262	0.87 (0.46–1.65)
No	1817/4534	0.87 (0.75–1.01)



ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; CI, confidence interval; eGFR, estimated glomerular filtration rate; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; Sac, sacubitril; SBP, systolic blood pressure; Val, valsartan.

Solomon SD, et al. *N Engl J Med* 2019;381:1609–20.

Position paper ANMCO: Duplice, triplice o quadruplice terapia nello scompenso sistolico? Evidenze e nuove strategie



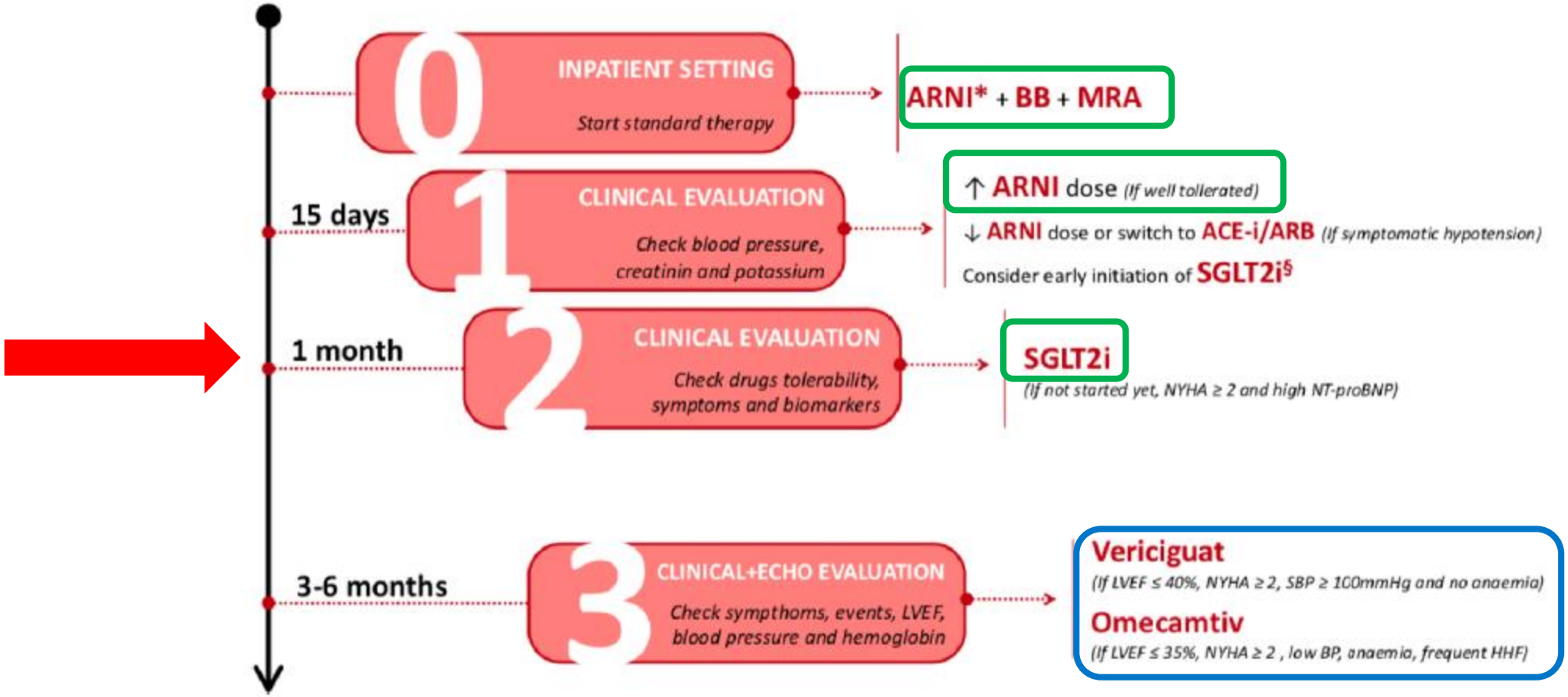
°In pazienti con scompenso cardiaco avanzato l'inizio del BB può seguire la stabilizzazione con inibitori del sistema renina-angiotensina e diuretici.

*In pazienti ospedalizzati l'inizio degli SGLT2i dovrebbe essere posticipato alla fase post-dimissione.

^In pazienti significativamente ipotesi l'inizio dell'antialdosteronico può essere anticipato rispetto ad ARNI

MODIFICATA DA: Di Lenarda et al. G ITAL CARDIOL 30 Jul 2021; VOL 22 PAG 6

Come abbinare i nuovi farmaci per la gestione dell'HFrEF nel paziente ricoverato e subito dopo la dimissione



*ARNI should be withheld in favour of ACEi/ARBs in case of persisting low blood pressure with hypotension events during the hospitalization.

§ SGLT2i may be considered preferentially in patients not tolerating ARNi

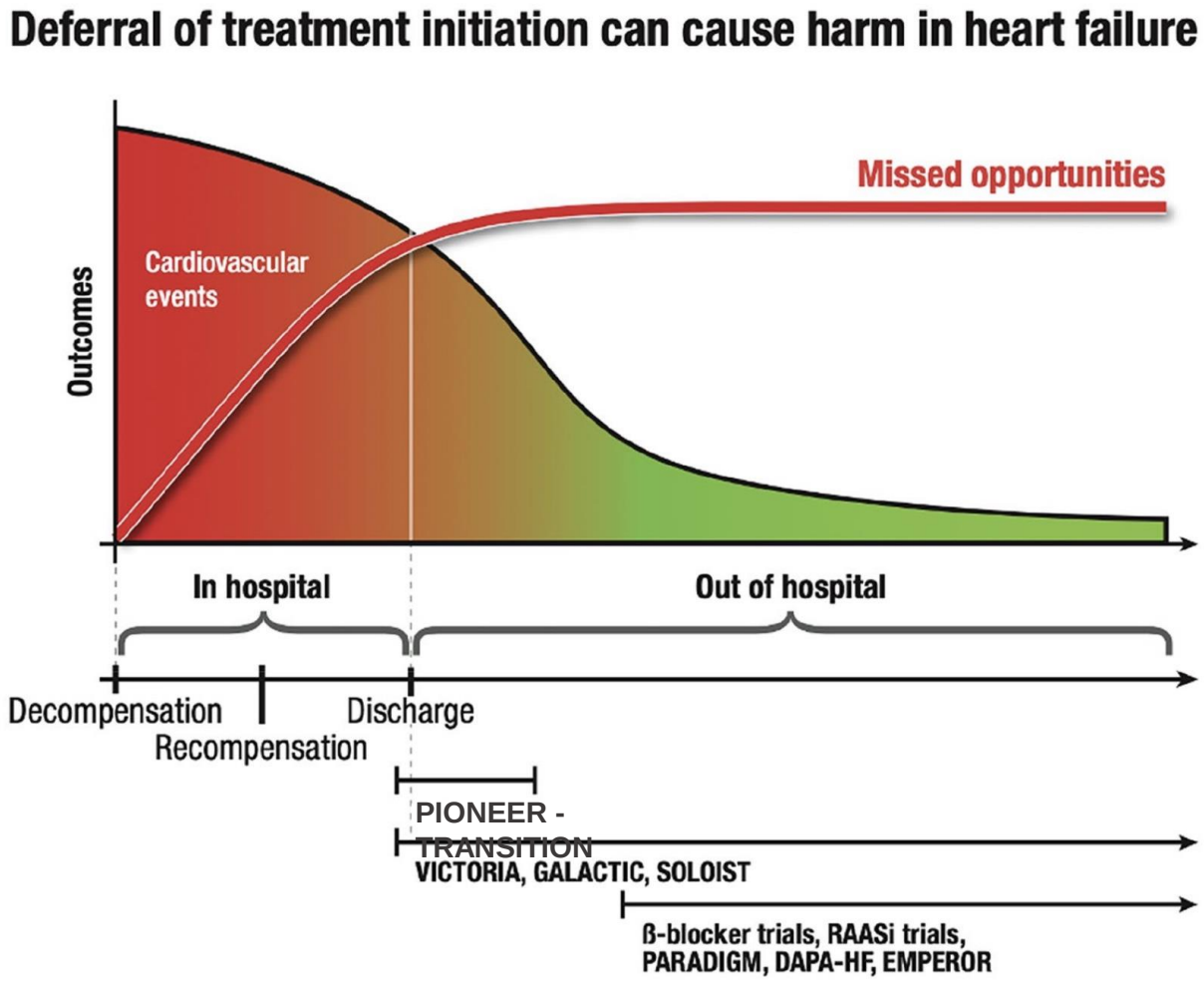
Sinagra et al., Eur J Intern Med. 2021 Aug;90:10-15.

INIZIO DEL TRATTAMENTO FARMACOLOGICO IN-HOSPITAL

Recommendations for management of patients after HF hospitalization	
It is recommended that patients hospitalized for HF be carefully evaluated to exclude persistent signs of congestion before discharge and to optimize oral treatment.	I
It is recommended that evidence-based oral medical treatment be administered before discharge.	I
An early follow-up visit is recommended at 1—2 weeks after discharge to assess signs of congestion, drug tolerance, and start and/or uptitrate evidence-based therapy.	I

McDonagh TA et al_LG ESC HF 2021 Eur Heart J. 2021 Sep 21;42(36):3599-3726

Perchè ritardare l'inizio del trattamento nel paziente ospedalizzato?



Abdin et al. Clinical Research in Cardiology (2021) 110:1150–1158, modificata

SACUBITRIL/VALSARTAN nel trattamento del paziente
IN-HOSPITAL

11.3.11 Pre-discharge assessment and post-discharge management planning

In those admitted with ADHF, oral OMT should be continued, except for possible dose reduction or withdrawal if there is haemodynamic instability (symptomatic hypotension), severely impaired renal function or hyperkalaemia. Once haemodynamic stabilization is achieved with i.v. therapy, treatment should be optimized before discharge.[467] Treatment optimization has three major aims. First, to relieve congestion. Second, to treat comorbidities, such as iron deficiency, that have an impact on post-discharge outcome.[512] Third, to initiate, or restart oral, OMT with beneficial effects on outcome. Doses may be uptitrated before discharge and/or in the early post-discharge phase.

Studies have shown that such optimization of medical treatment is associated with a lower risk of 30-day readmission, although prospective randomized trials have not been performed, to date.[103,467,513] Retrospective analyses show that discontinuation or dose reduction of beta-blocker therapy during an AHF hospitalization is associated with worse outcomes.[514] Initiation of ARNI in recently hospitalized stable patients with HFrEF, including those who are ACE-I/ARB naïve, is safe and may be considered in this setting.[106,107] Safety and

Nel paziente in **acuto** la **OMT** dovrebbe essere **mantenuta**. In caso di ipotensione, peggioramento della funzionalità renale o iperkalemia considerare la riduzione della dose

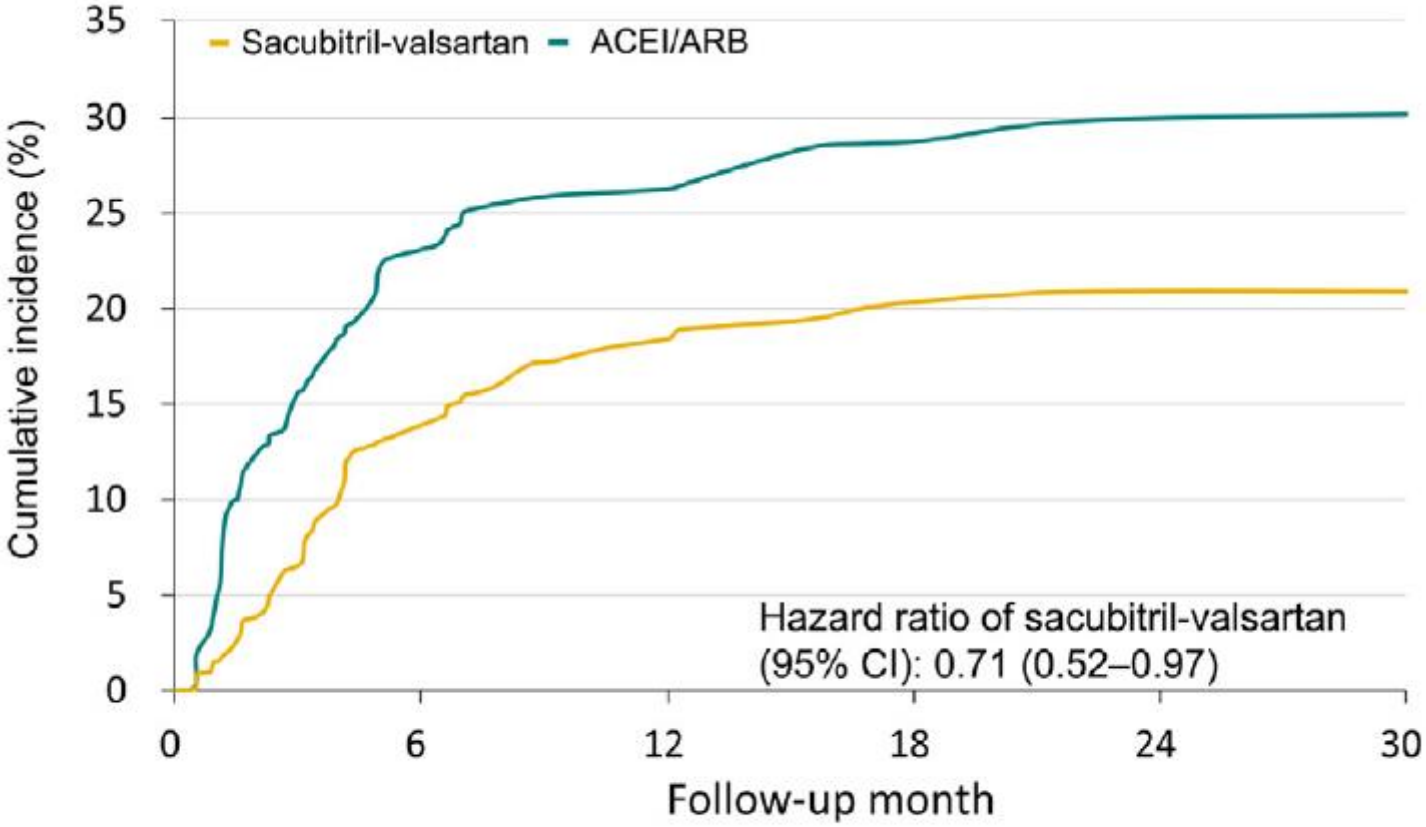
L'ottimizzazione terapeutica ha **3 obiettivi**: ridurre la **congestione**, trattare le **comorbidità**, iniziare la **OMT**

5.3.4 Angiotensin receptor-neprilysin inhibitor

Therefore, it is recommended that an ACE-I or ARB is replaced by sacubitril/valsartan in ambulatory patients with HFrEF, who remain symptomatic despite optimal treatment outlined above. Two studies have examined the use of ARNI in hospitalized patients, some of whom had not been previously treated with ACE-I. Initiation in this setting appears safe and reduces subsequent CV death or HF hospitalizations by 42% compared to enalapril.[106,107,131] As such, initiation

McDonagh TA et al_LG ESC HF 2021 Eur Heart J. 2021 Sep 21;42(36):3599-3726

Analisi composita di morte per tutte le cause ed ospedalizzazione per arresto cardiaco



No. of weighted patients at risk [censored]:

Sacubitril-valsartan	3276 [0]	1238 [1455]	580 [1926]	239 [2226]	118 [2334]	10 [2442]
ACEI/ARB	3645 [0]	1717 [1163]	1046 [1351]	674 [1609]	456 [1769]	270 [1920]

D.-Y. Chen et al. / EClinicalMedicine 41 (2021) 101149

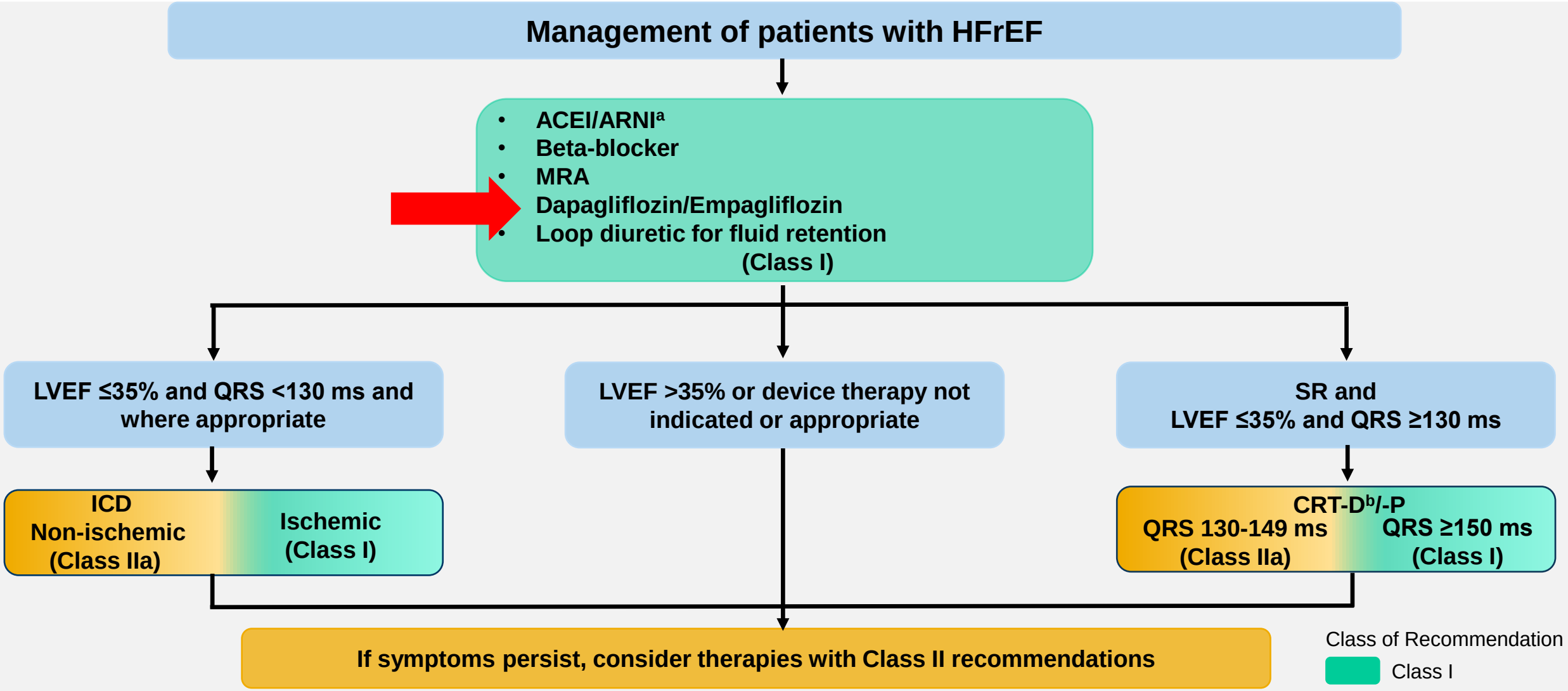
Outcome Clinici Renali di Efficacia e Tollerabilità

Outcome	Data after IPTW[a]			
	Sacubitril/valsartan	ACEI/ARB	HR or SHR for Sacubitril/valsartan (95% CI)[b]	*P* value
Safety outcomes [c]				
Worsening renal function [d]	744 (22.7)	878 (24.1)	1.08 (0.97–1.20)	0.16
Composite of decline of eGFR >50% or progression to ESRD	498 (15.2)	718 (19.7)	0.97 (0.84–1.13)	0.73
Decline in eGFR >50% from baseline	288 (8.8)	477 (13.1)	0.93 (0.79–1.09)	0.35
Progression to ESRD	278 (8.5)	328 (9.0)	1.15 (0.86–1.53)	0.33
Creatinine ≥2.5 mg/dL	793 (24.2)	755 (20.7)	0.94 (0.81–1.08)	0.35
Creatinine ≥3 mg/dL	678 (20.7)	612 (16.8)	1.12 (0.95–1.31)	0.18
Potassium ≥6 mg/dL	174 (5.3)	230 (6.3)	1.07 (0.84–1.36)	0.59

Il rischio di peggioramento della funzionalità renale, 50% di declino dell'eGFR dal basale, progressione ad ESRD, aumento della creatinina a 2.5 mg/dL o 3 mg/dL, ed iperkaliemia severa non cambiano significativamente tra il gruppo con sacubitril/valsartan e ACEi/ARB.

Il rischio di peggioramento della funzionalità renale e progressione ad ESRD erano simili tra il sottogruppo con malattia renale cronica (CKD) (eGFR <60 mL/min/1.73 m_2) e senza CKD (eGFR 60 mL/min/1.73 m_2)

ESC 2021 Heart Failure Guidelines: Dapagliflozin Recommended as one of the Cornerstone Therapies for HFrEF



[a]As a replacement for ACEI; [b]Where appropriate.

McDonagh TA et al. Online ahead of print. *Eur Heart J*. 2021.

ESC 2021 Heart Failure Guidelines: Dapagliflozin is Recommended in Patients with HFrEF to Reduce the Risk of HF Hospitalization and Mortality

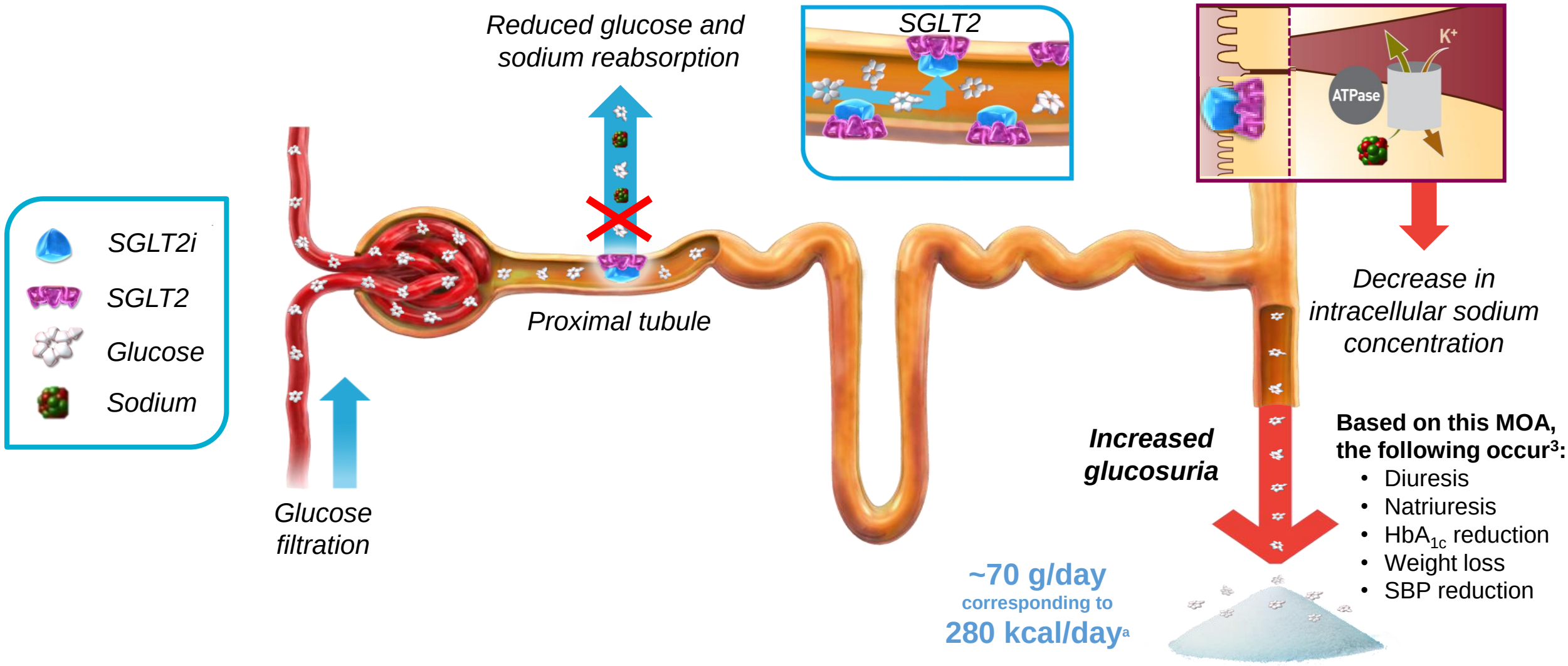
Recommendations	Class[a]	Level[b]
An ACEI is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A
Sacubitril/valsartan is recommended as a replacement for an ACEI in patients with HFrEF to reduce the risk of HF hospitalization and death.	I	B

[a]Class of recommendation; [b]Level of evidence.

ACEI = angiotensin-converting enzyme inhibitor; ESC = European Society of Cardiology; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist.

McDonagh TA et al. Online ahead of print. *Eur Heart J*. 2021.

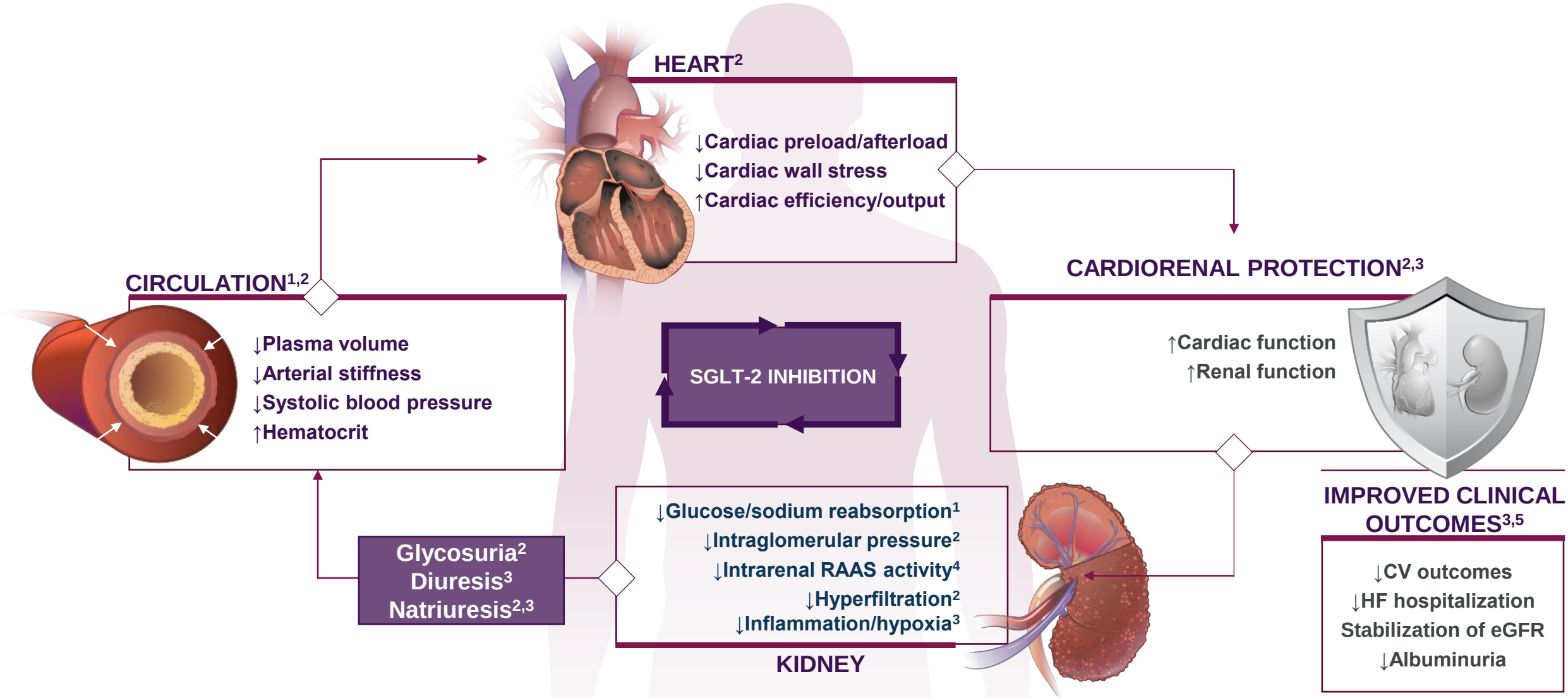
SGLT2 inhibition: An insulin-independent approach to remove excess glucose by reducing the renal threshold[1–3]



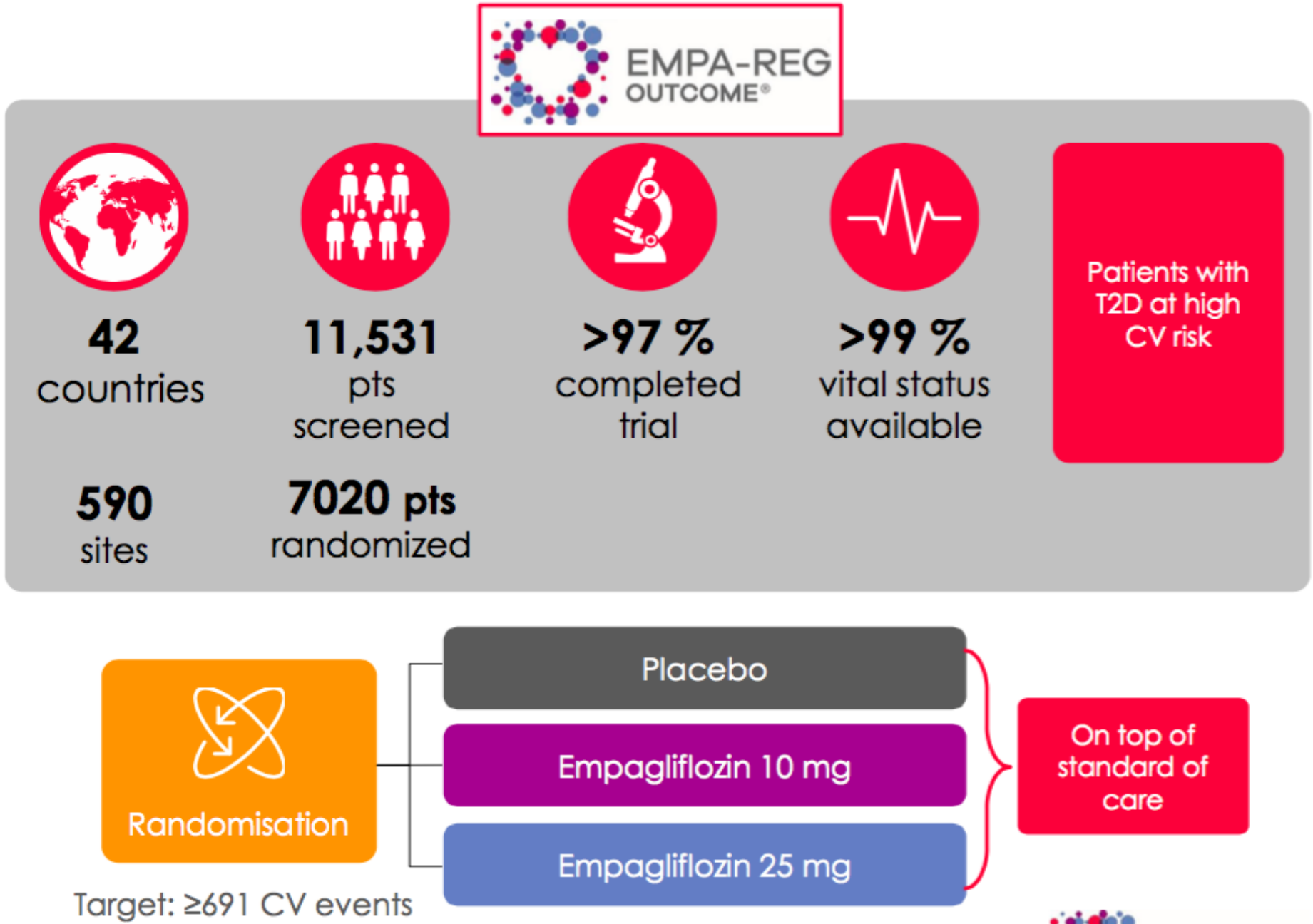
SGLT2i, sodium–glucose co-transporter 2 inhibitor

1. Marsenic O. *Am J Kidney Dis* 2009;53:875–885; 2. AstraZeneca. Dapagliflozin Summary of Product Characteristics; 3. Mudaliar S, et al. *Diabetes Care* 2016;39:1115–1122

SGLT-2 Inhibition Improves Hemodynamic Parameters in Patients With Type 2 Diabetes Leading to Cardiorenal Protection



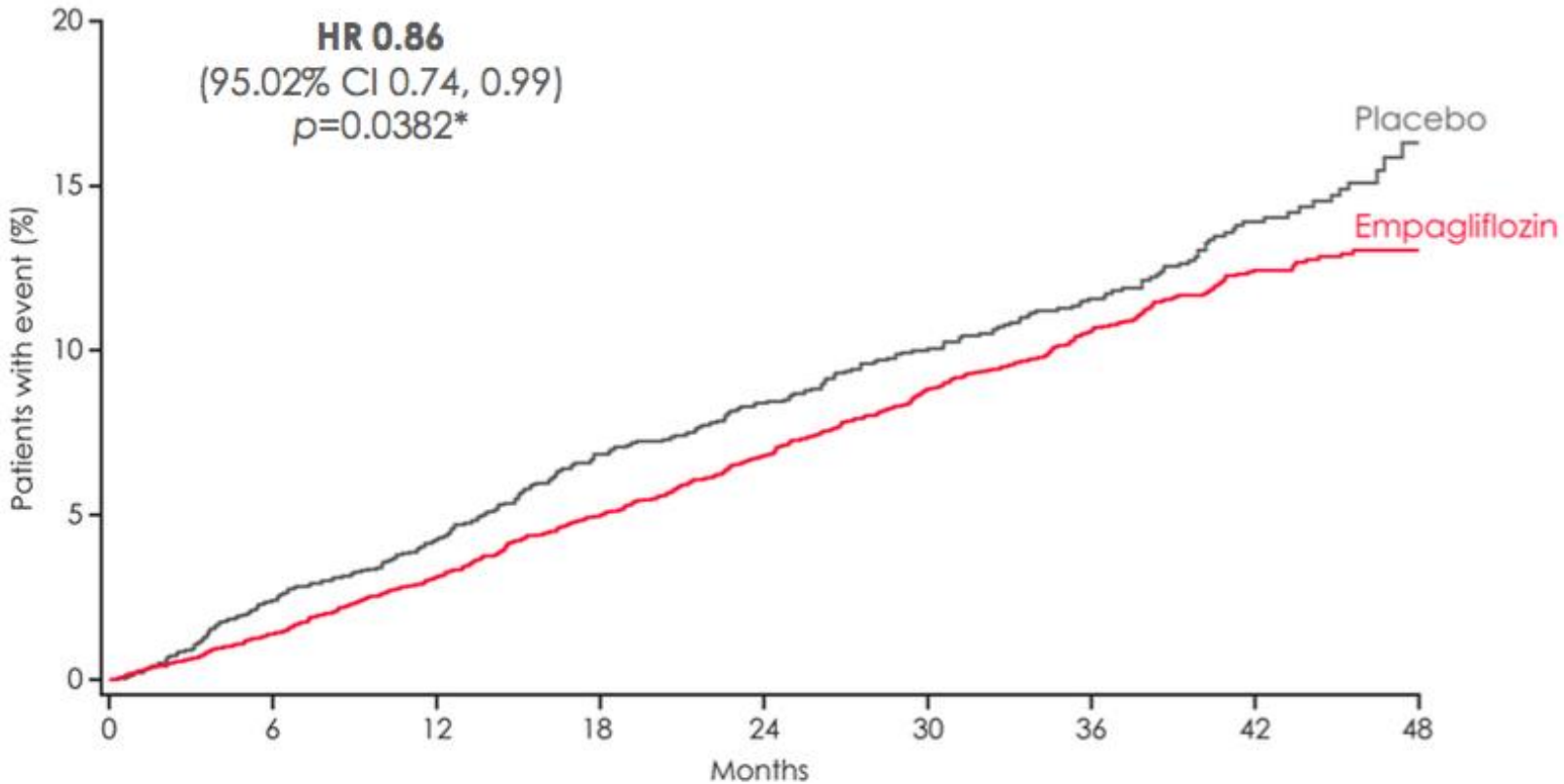
1. Sattar N et al. *Diabetologia*. 2016;59(7):1333-1339. 2. Verma S et al. *JAMA Cardiol*. 2017;2(9):939-940. 3. Scheen RJ. *Circ Res*. 2018;122:1439-1459. 4. Shin SJ, et al. *PLoS One*. 2016;11:e0165703. 5. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32.



CV, cardiovascular.

EMPA-REG OUTCOME® N Engl J Med 2015;373:2117-28

Primary outcome: 3-point MACE



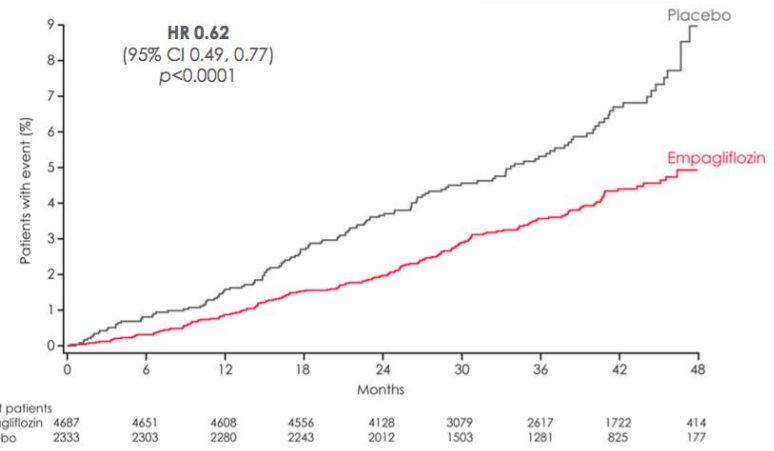
No. of patients									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

EMPA-REG OUTCOME®

EMPA-REG OUTCOME® N Engl J Med 2015;373:2117-28.

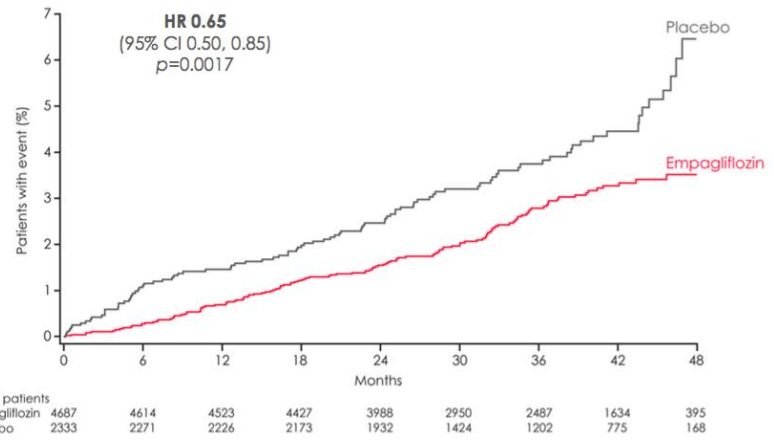
CV death



Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME® N Engl J Med 2015;373:2117-28.

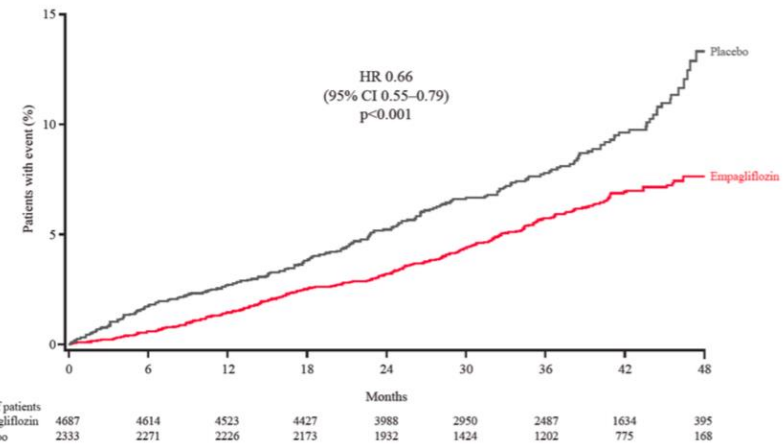
Hospitalisation for heart failure



Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME® N Engl J Med 2015;373:2117-28.

Heart failure hospitalisation or CV death

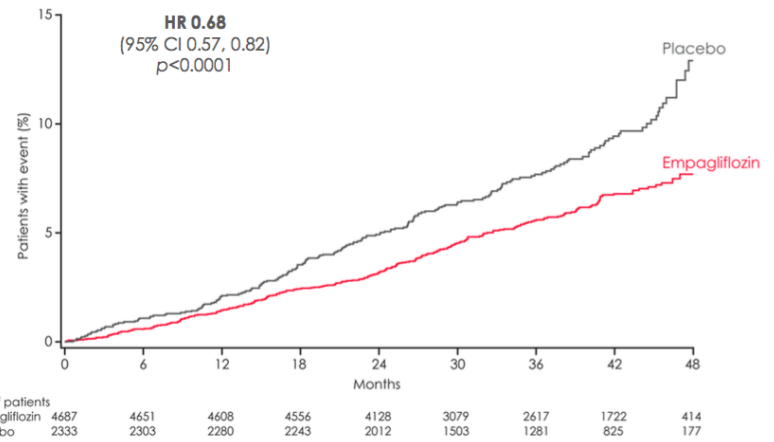


Cumulative incidence function. Patients treated with at least one dose of study drug.
HR, hazard ratio; CI, confidence interval.

Heart Failure Outcomes with Empagliflozin in Patients with Type 2 Diabetes at High Cardiovascular Risk: Results of the EMPA-REG OUTCOME® Trial -David Fitchett et al. Eur Heart J 2016; DOI: http://dx.doi.org/10.1093/eurheartj/ehv728

EMPA-REG OUTCOME® N Engl J Med 2015;373:2117-28.

All-cause mortality



Kaplan-Meier estimate. HR, hazard ratio

EMPA-REG OUTCOME® N Engl J Med 2015;373:2117-28.

EMPEROR-Reduced Trial

Effect of Empagliflozin on Cardiovascular and Renal Events in Heart Failure With a Reduced Ejection Fraction

Milton Packer MD and Faiez Zannad MD, on behalf of the EMPEROR-Reduced Executive Committee, Trial Committees, Investigators and Coordinators

Baylor University Medical Center, Dallas TX, Imperial College, London UK
Université de Lorraine, Inserm INI-CRCT, CHRU, Nancy, France

Disclosures for presenter: Abbvie, Actavis, Akcea, Amgen, Amarin, AstraZeneca, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Eli LillyJohnson & Johnson, NovoNordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics and Theravance

EMPEROR-Reduced Trial Specified Only Three Endpoints to be Tested in Hierarchical Manner

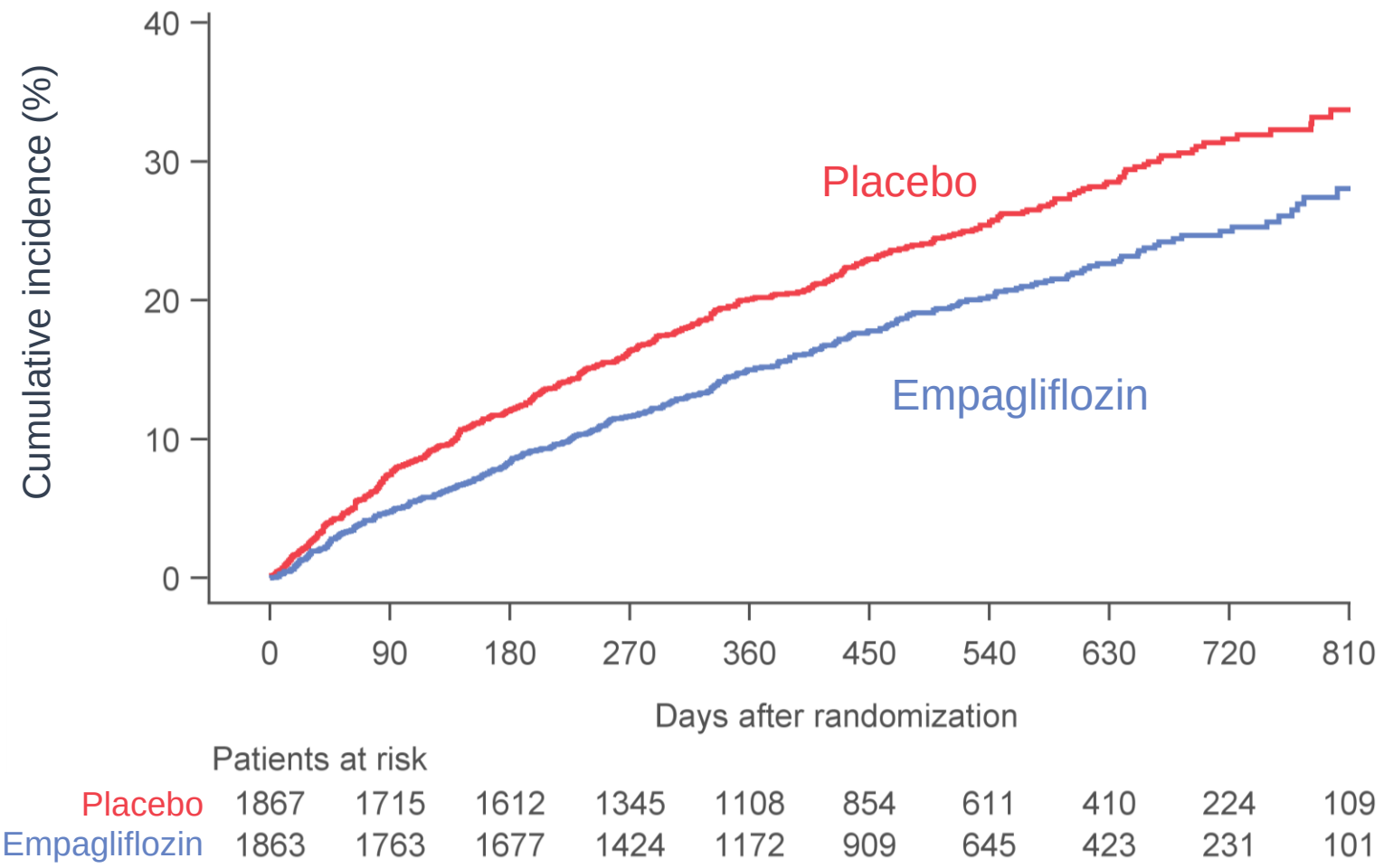
Primary Endpoint
Composite of cardiovascular death or heart failure hospitalization

First Secondary Endpoint
Total (first and recurrent heart failure hospitalizations)

Second Secondary Endpoint
Slope of decline in glomerular filtration rate over time

Other prespecified endpoints: Composite renal endpoint, KCCQ clinical summary score, total number of hospitalizations for any reason, all-cause mortality, new onset diabetes

EMPEROR-Reduced: Time to Cardiovascular Death or Hospitalization for Heart Failure (Primary Endpoint)



462 patients with event
Rate: 21.0/100 patient-years

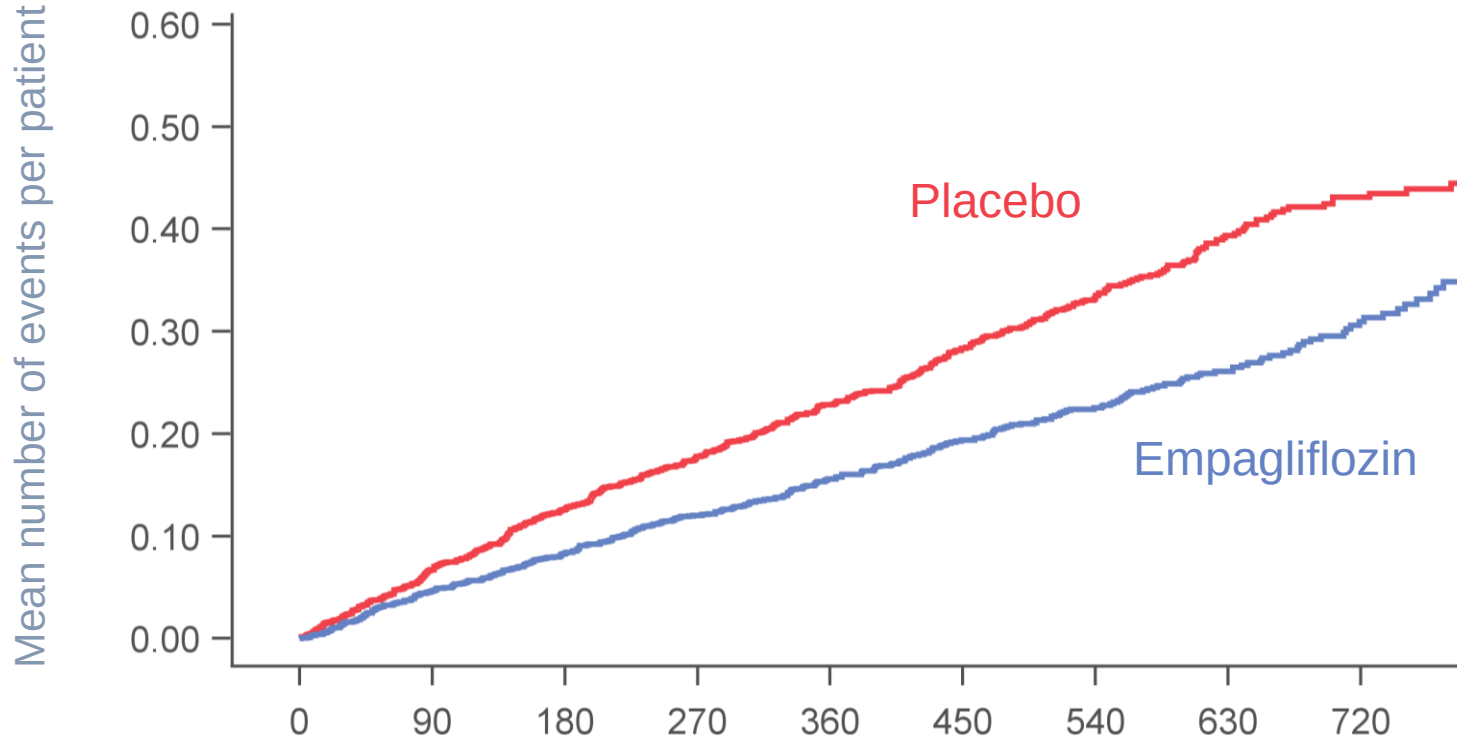
361 patients with event
Rate: 15.8/100 patient-years

HR 0.75
(95% CI 0.65, 0.86)
P < 0.0001

EMPEROR-Reduced: Effect on Individual Components of the Primary Endpoint

	Empagliflozin (n=1863)		Placebo (n=1867)		Hazard ratio (95% CI)	P value
	Number of events (%)	Events/100 patient-yr	Number of events (%)	Events/100 patient-yr		
Primary composite outcome	361 (19.4%)	15.8	462 (24.7%)	21.0	0.75 (0.65 – 0.86)	<0.0001
First hospitalization for heart failure	246 (13.2%)	10.7	342 (18.3%)	15.5	0.69 (0.59 – 0.81)	
Cardiovascular death	187 (10.0%)	7.6	202 (10.8%)	8.1	0.92 (0.75 – 1.12)	

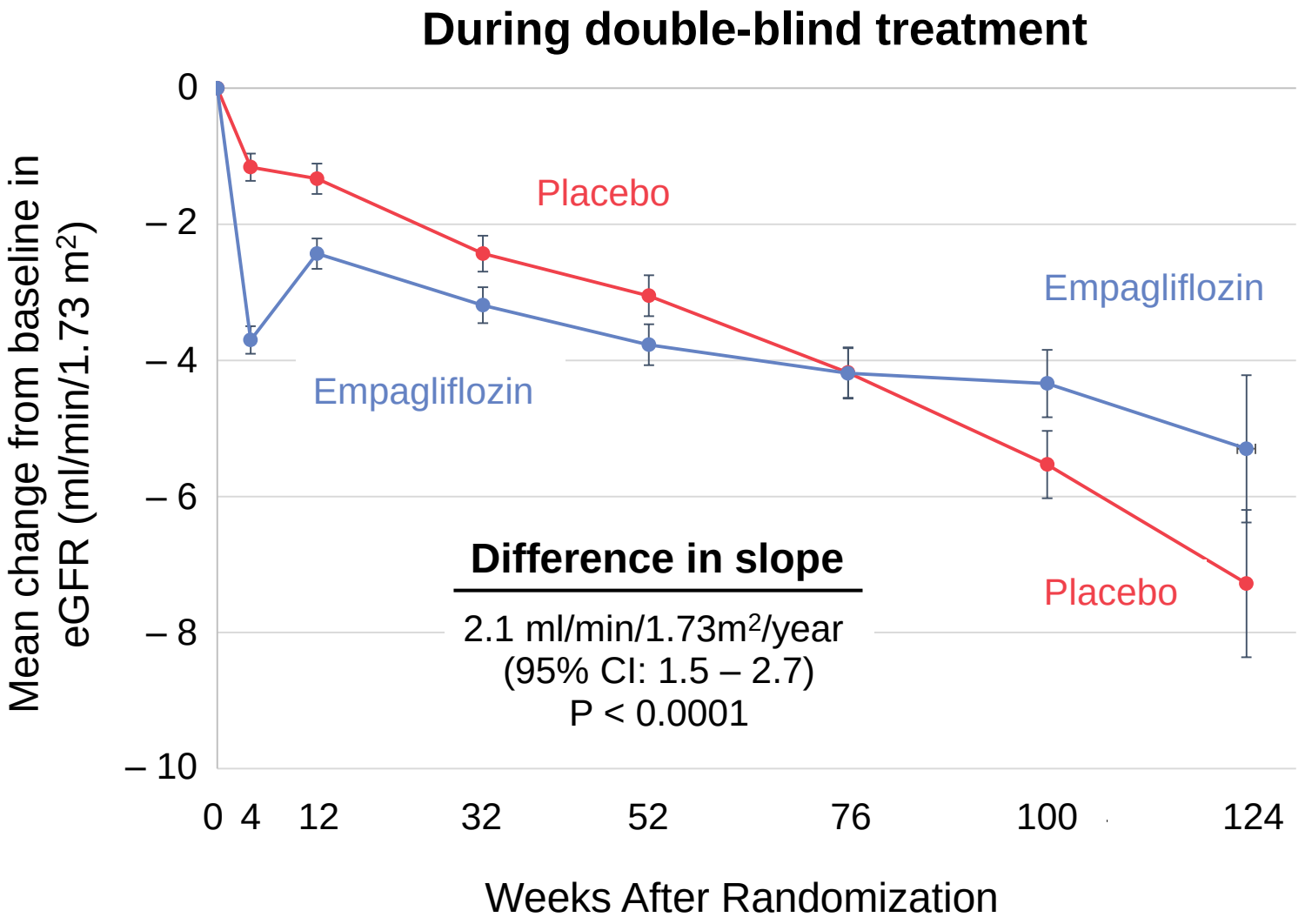
EMPEROR-Reduced: Total Hospitalizations for Heart Failure (First and Recurrent) — Hierarchical Endpoint #2



Patients at risk									
Placebo	1867	1820	1762	1526	1285	1017	732	497	275
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272

HR 0.70
(95% CI 0.58, 0.85)
P = 0.0003

EMPEROR-Reduced: Slope of Decline in Glomerular Filtration Rate — Hierarchical Endpoint #3



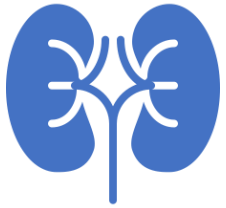
In 966 patients, eGFR was reassessed at the end of the trial 23-42 days after the withdrawal of double-blind therapy, thus allowing unconfounded assessment of the effects of treatment. Over 16 months, eGFR deteriorated by

– 4.2 ml/min/1.73 m² on placebo

– 0.9 m/min/1.73 m² on empagliflozin

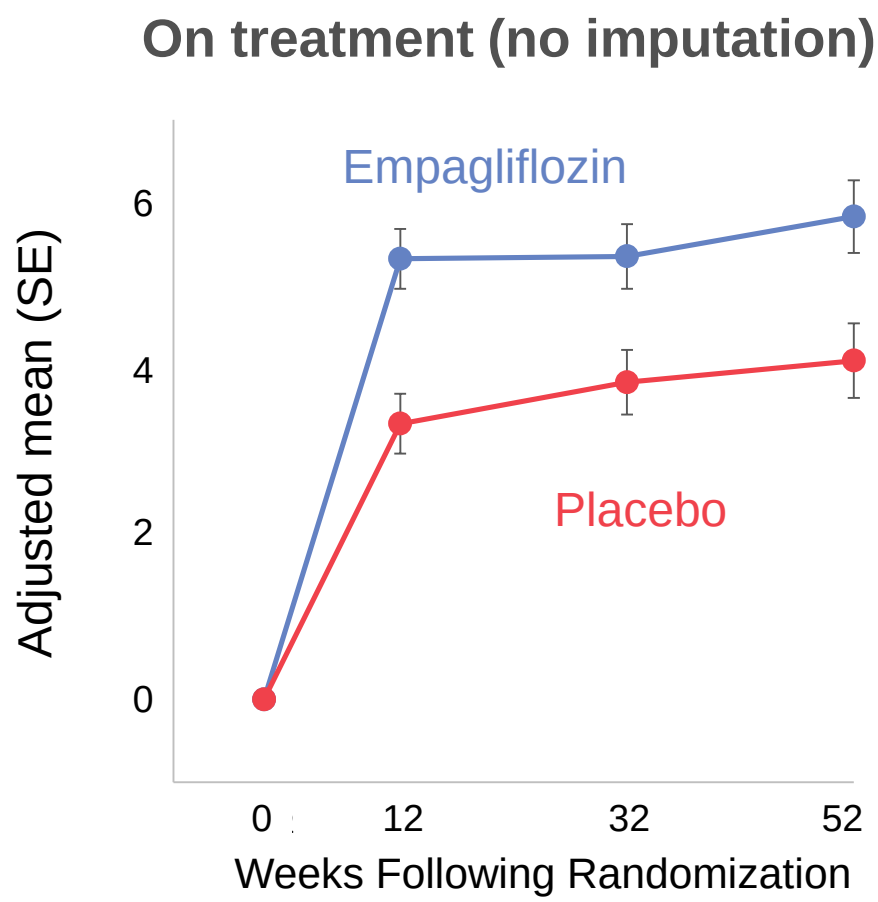
P < 0.0001

EMPEROR-Reduced Achieved All Three Hierarchically Specified Endpoints at P < 0.001

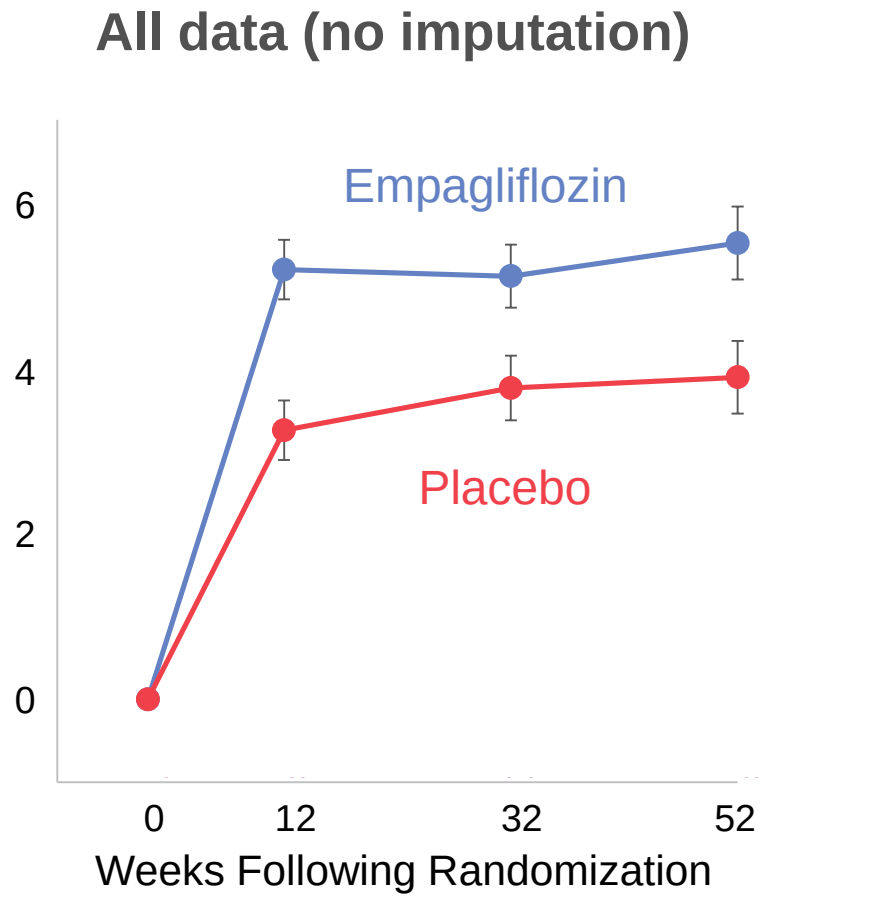
	**Primary Endpoint** Composite of cardiovascular death or heart failure hospitalization	**Achieved** **P < 0.001**
	**First Secondary Endpoint** Total (first and recurrent heart failure hospitalizations)	**Achieved** **P < 0.001**
	**Second Secondary Endpoint** Slope of decline in glomerular filtration rate over time	**Achieved** **P < 0.001**

Also achieved success on composite renal endpoint, KCCQ clinical summary score, and total number of hospitalizations for any reason (all nominal P < 0.01)

EMPEROR-Reduced: KCCQ Clinical Summary Score At 52 Weeks (No Imputation for Death)

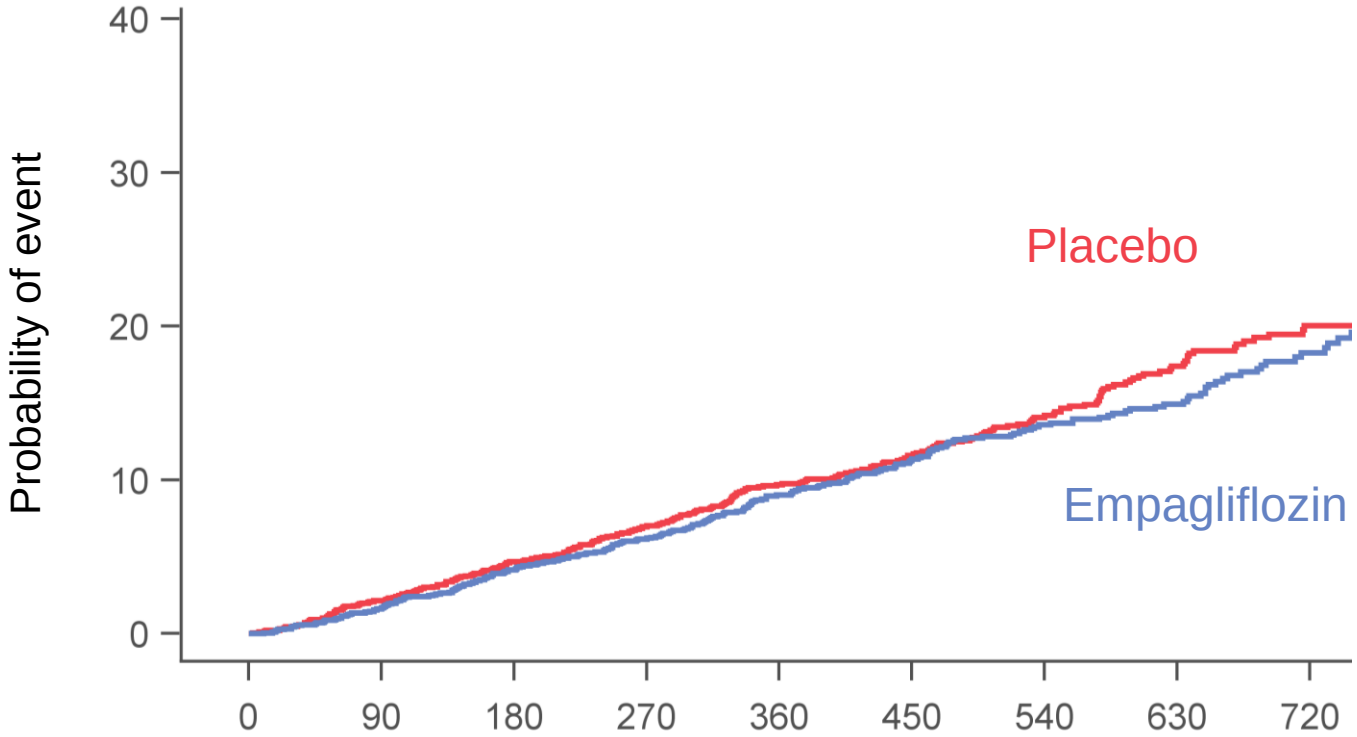


Adjusted mean difference 1.75
(95% CI: 0.51, 2.99)



Adjusted mean difference 1.61
(95% CI: 0.39, 2.84)

EMPEROR-Reduced: All-Cause Mortality



Patients at risk

Placebo	1867	1825	1770	1534	1294	1027	743	507	282
Empagliflozin	1863	1829	1772	1537	1289	1015	742	506	281

266 patients with event
Rate: 10.7/100 patient-years

249 patients with event
Rate: 10.1/100 patient-years

HR 0.92
(95% CI 0.77, 1.10)

Dapagliflozin [DAPACARE program] Addresses the Cardiorenal Burden Across the Spectrum of Patients With and Without T2D[1-4]

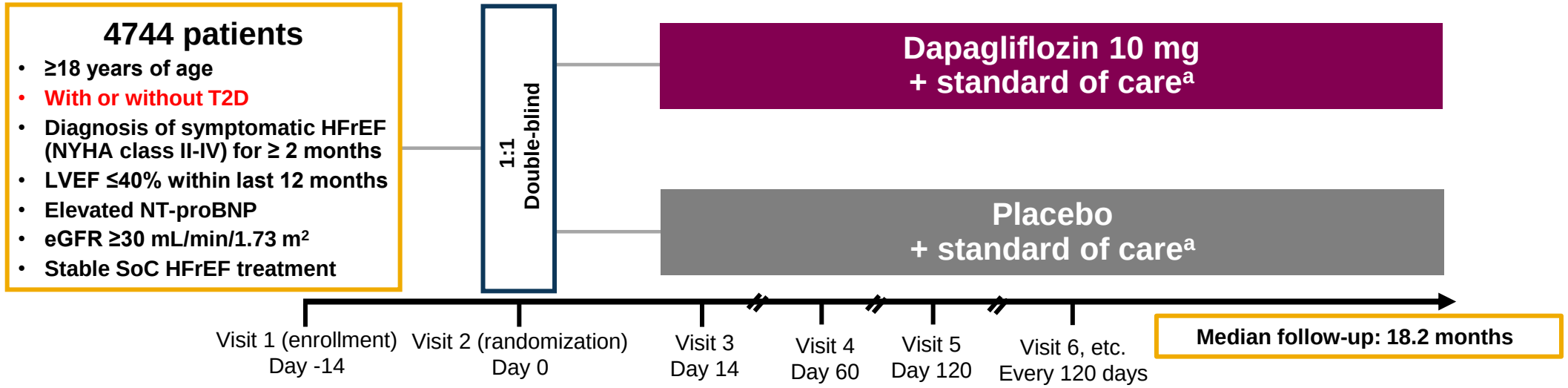
	DAPAHF	DECLARE TIMI-58	DAPACKD
Patient Population	**N = 4744** **HFrEF** **eGFR ≥30 mL/min/1.73 m²**	**N = 17,160** **ASCVD or Multiple CV Risk Factors** **eGFR ≥60 mL/min/1.73 m²**	**N = 4304** **CKD** **eGFR ≥25 to ≤75 mL/min/1.73 m²**
Glycemic Status	**With (45%) or Without (55%) T2D**	**With T2D**	**With (68%) or Without (32%) T2D**
Mean eGFR	**66 mL/min/1.73 m²**	**85.2 mL/min/1.73 m²**	**43 mL/min/1.73 m²**
Primary Endpoint	**CV death or worsening HF[a]** 0.74 (0.65, 0.85) p<0.001	**hHF or CV death** 0.83 (0.73, 0.95) p=0.005	**≥50% eGFR Decline, ESKD, or Renal or CV Death** 0.61 (0.51-0.72) p=0.000000028
Summary	**Confirming dapagliflozin as the new standard of care for patients with HFrEF with and without T2D[5]**	**Largest, broadest SGLT2 inhibitor CVOT in patients with T2D**	**FIRST and ONLY SGLT2 inhibitor renal outcomes trial in patients with CKD with and without T2D**

[a]Worsening HF includes hHF or urgent HF visit.

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; CVOT = cardiovascular outcomes trial; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; SGLT2 = sodium-glucose cotransporter 2; T2D = type 2 diabetes.

1. McMurray JJV et al. *N Engl J Med.* 2019;381:1995-2008; 2. Wiviott SD et al. *N Engl J Med.* 2019;380:347-357; 3. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020; 4. Heerspink HJL et al. Online ahead of print. *N Engl J Med*. 2020; 5. Vaduganathan M et al. *Lancet*. 2020;396:121-128.

The DAPA-HF Study Assessed the Safety and Efficacy of Dapagliflozin in Patients With Established HFrEF With or Without T2D[1,2]



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[b] or renal death
- Time to death from any cause

[a]Patients were treated according to regional standard of care for HF. Dose reduction or discontinuation of standard of care therapy was discouraged unless all other measures failed. Changes in standard of care medications was at the discretion of the investigator; [b]Defined as sustained eGFR <15 mL/min/1.73m^2, chronic dialysis treatment, or receiving a renal transplant.

1. McMurray JJV et al. Article and supplementary appendix. *Eur J Heart Fail.* 2019;21:665-675; 2. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008.

Baseline Characteristics and Medical History did not Differ Between Treatment Groups, With More Than Half of the Population Without T2D

Characteristic	DAPA 10 mg (n=2373)	Placebo (n=2371)
Mean age, yr	66.2 ± 11.0	66.5 ± 10.8
Female, n (%)	564 (23.8)	545 (23.0)
Race[a], n (%)		
White	1662 (70.0)	1671 (70.5)
Black	122 (5.1)	104 (4.4)
Asian	552 (23.3)	564 (23.8)
Other	37 (1.6)	32 (1.3)
Region, n (%)		
North America	335 (14.1)	342 (14.4)
South America	401 (16.9)	416 (17.5)
Europe	1094 (46.1)	1060 (44.7)
Asia-Pacific	543 (22.9)	553 (23.3)
Heart rate, beats/min	71.5 ± 11.6	71.5 ± 11.8
Systolic blood pressure, mmHg	122.0 ± 16.3	121.6 ± 16.3
Body-mass index (kg/m^2)	28.2 ± 6.0	28.1 ± 5.9

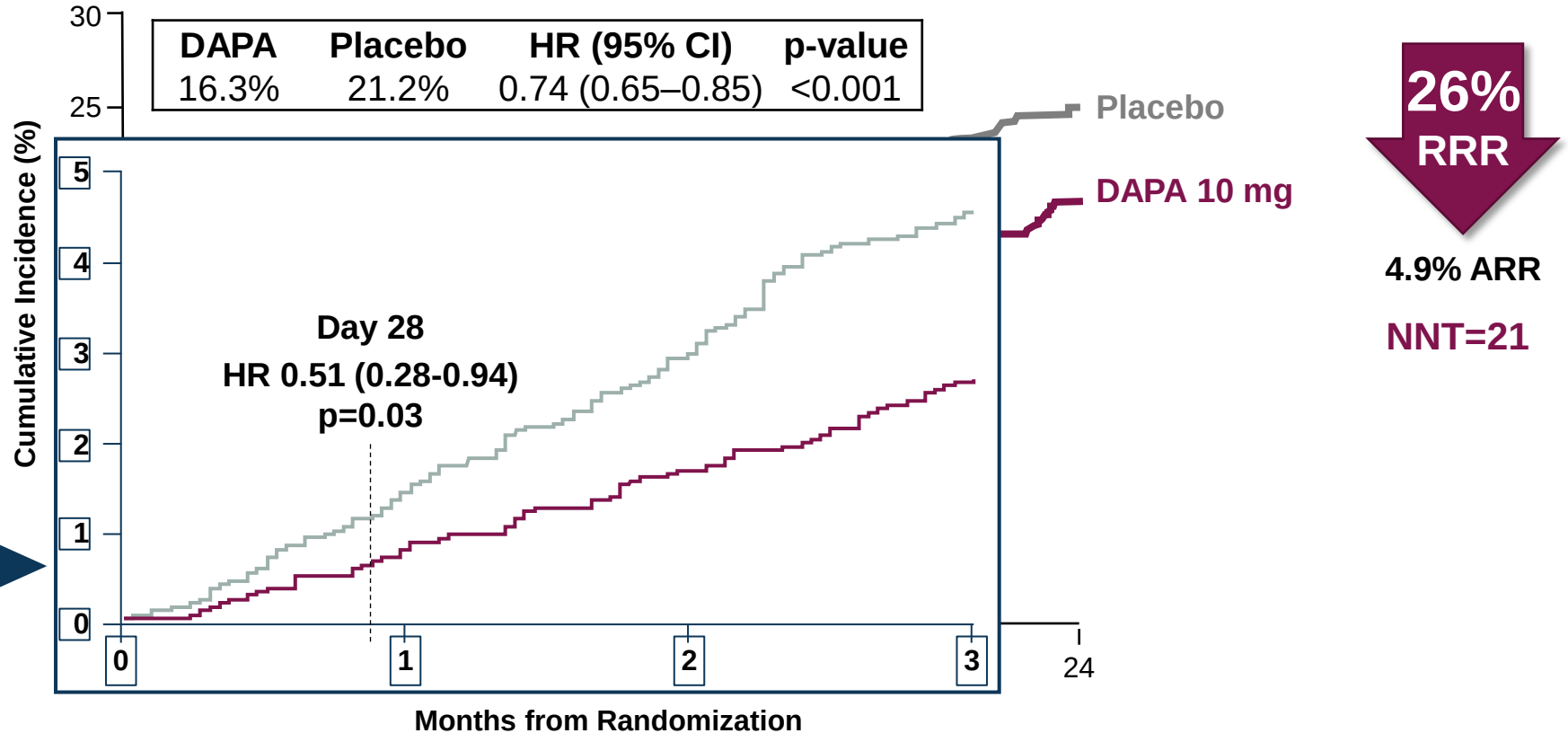
Medical History	DAPA 10 mg (n=2373)	Placebo (n=2371)
Hospitalization for HF, n (%)	1124 (47.4)	1127 (47.5)
Atrial fibrillation, n (%)	916 (38.6)	902 (38.0)
Diabetes mellitus[b], n (%)	993 (41.8)	990 (41.8)
Estimated GFR, mL/min/1.73m^2	66.0 ± 19.6	65.5 ± 19.3
Estimated GFR <60 mL/min/1.73m^2, n/total N (%)	962/2372 (40.6)	964/2371 (40.7)
Device therapy, n (%)		
ICD[c]	622 (26.2)	620 (26.1)
CRT[d]	190 (8.0)	164 (6.9)

Plus-minus values are means ± SD.

[a]Reported by investigators; [b]Includes 156 patients with previously undiagnosed diabetes (HbA1c ≥6.5% at screening and randomization); [c]Either implantable cardioverter-defibrillator or cardiac resynchronization therapy with a defibrillator; [d]Cardiac-resynchronization therapy with or without a defibrillator.

McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008.

Dapagliflozin Significantly Reduced the Relative Risk of CV Death or Worsening HF[a] on Top of Standard of Care by 26%[1]



Number at Risk

DAPA 10 mg	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

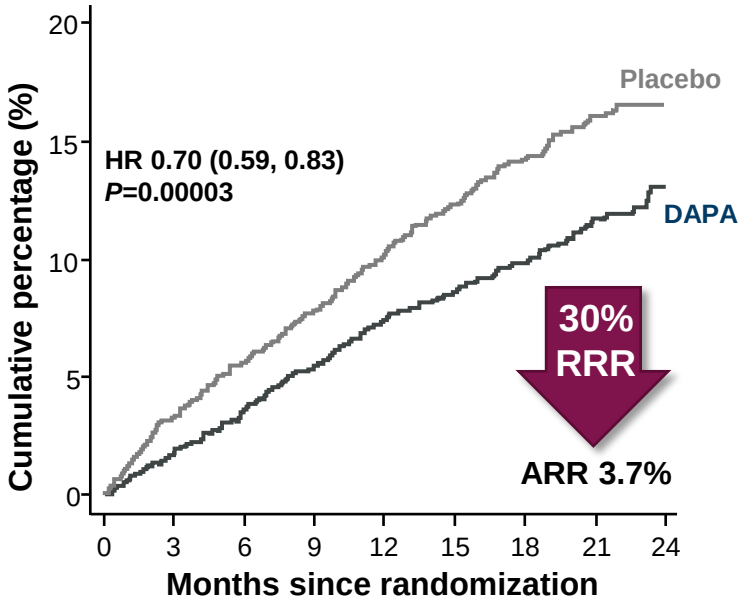
[a]Worsening HF includes hHF or urgent HF visit.

ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; NNT = number needed to treat; RRR = relative risk reduction.

1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 2. Sabatine MS et al. Presented at: AHA Scientific Sessions; November 16-18, 2019; Philadelphia, PA.

These significant effects were consistent across all components of the primary endpoint and all-cause mortality[1,2]

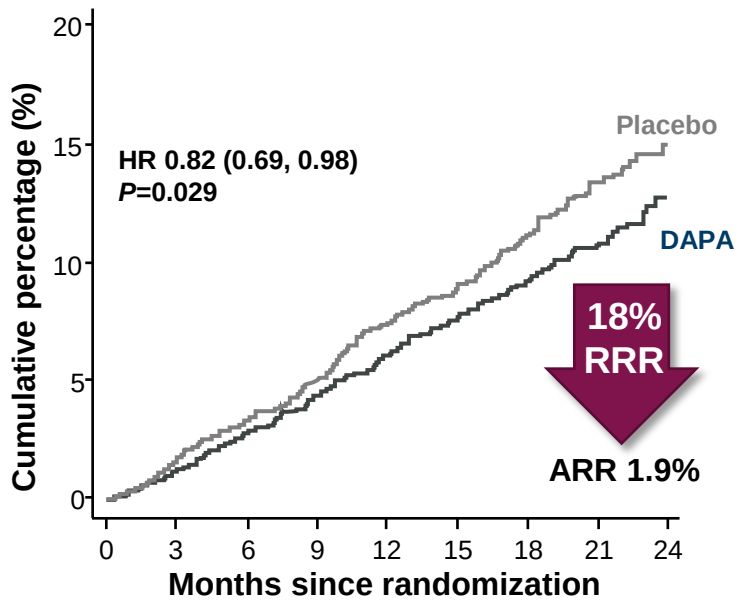
Worsening HF event



Number at risk

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

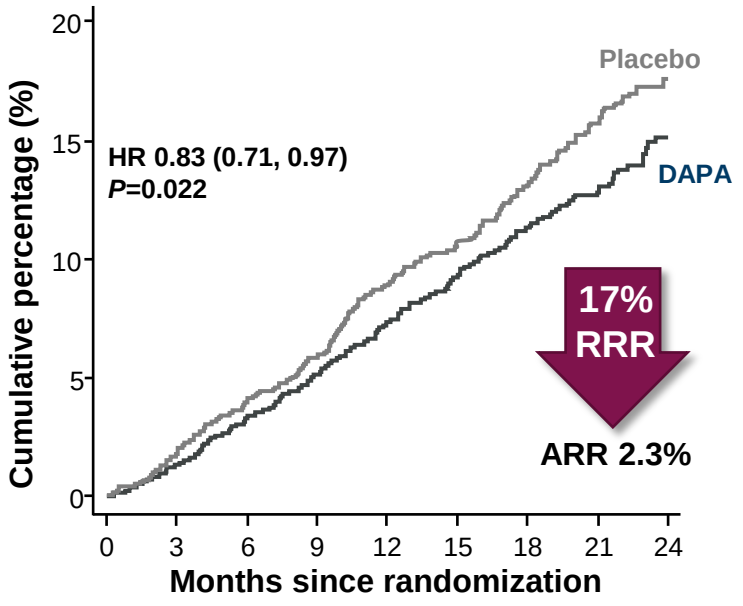
CV death



Number at risk

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

All-cause death



Number at risk

DAPA	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

[a]Defined as unplanned hospitalization for HF or urgent HF visit requiring intravenous therapy.

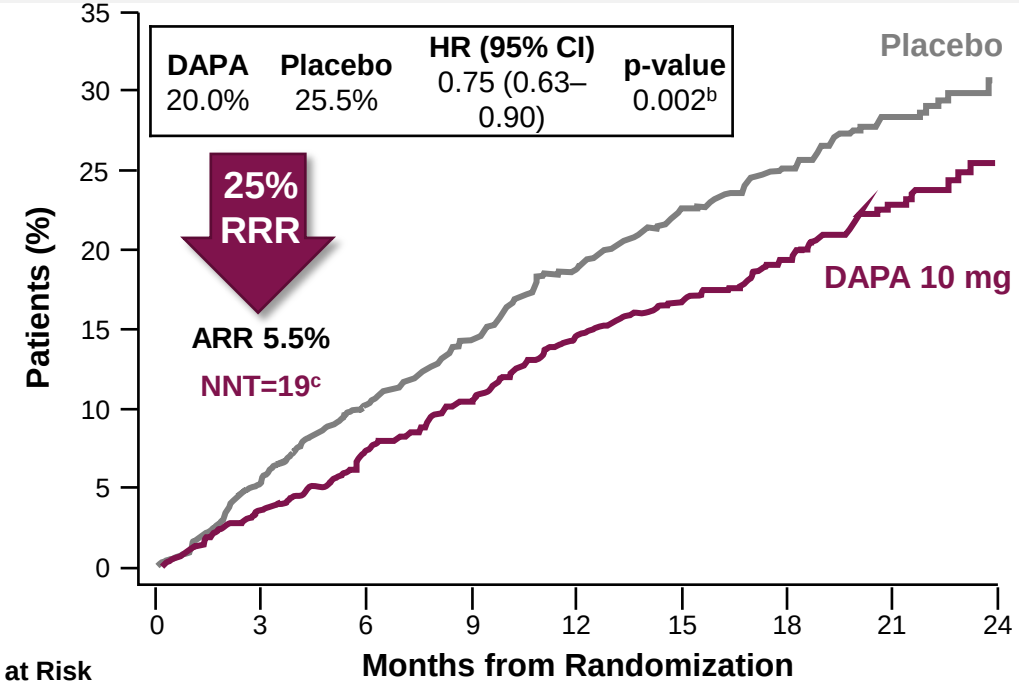
ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; HR = hazard ratio; PBO = placebo; RRR = relative risk reduction.

1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 2. McMurray J. Presented at: ESC Congress; August 31-September 4, 2019; Paris, France.

Primary Outcome: CV Death, hHF, or Urgent HF Visit by Diabetes Status[1]

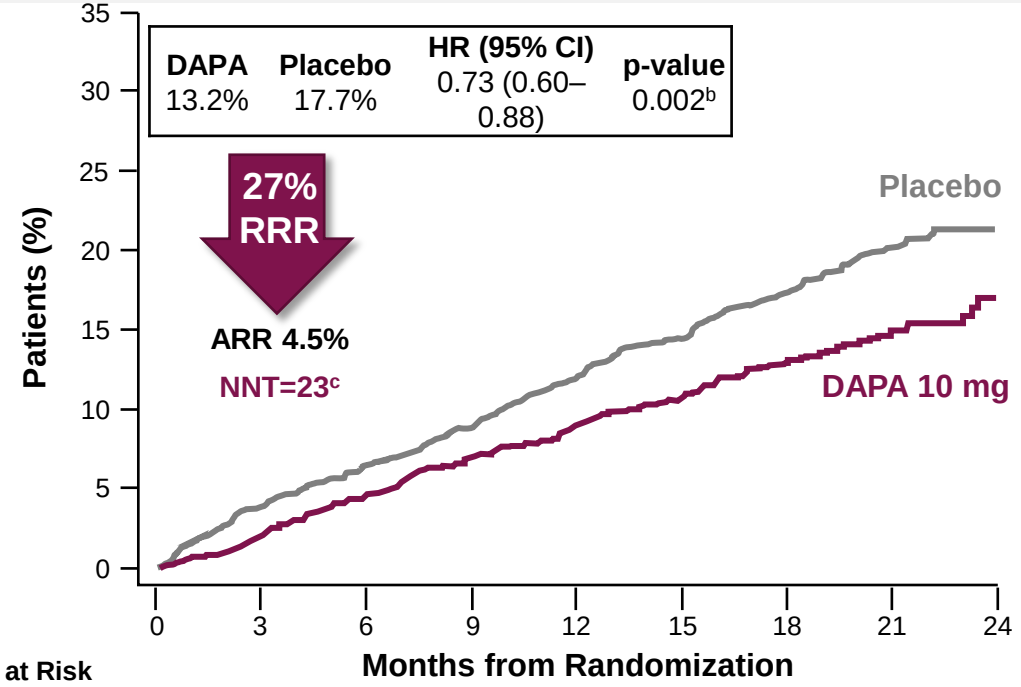
Dapagliflozin significantly reduced the primary endpoint, regardless of diabetes status

T2D[a]



Number at Risk									
DAPA 10 mg	1075	1037	994	955	876	678	500	259	88
Placebo	1064	1005	949	899	816	630	469	253	89

No T2D



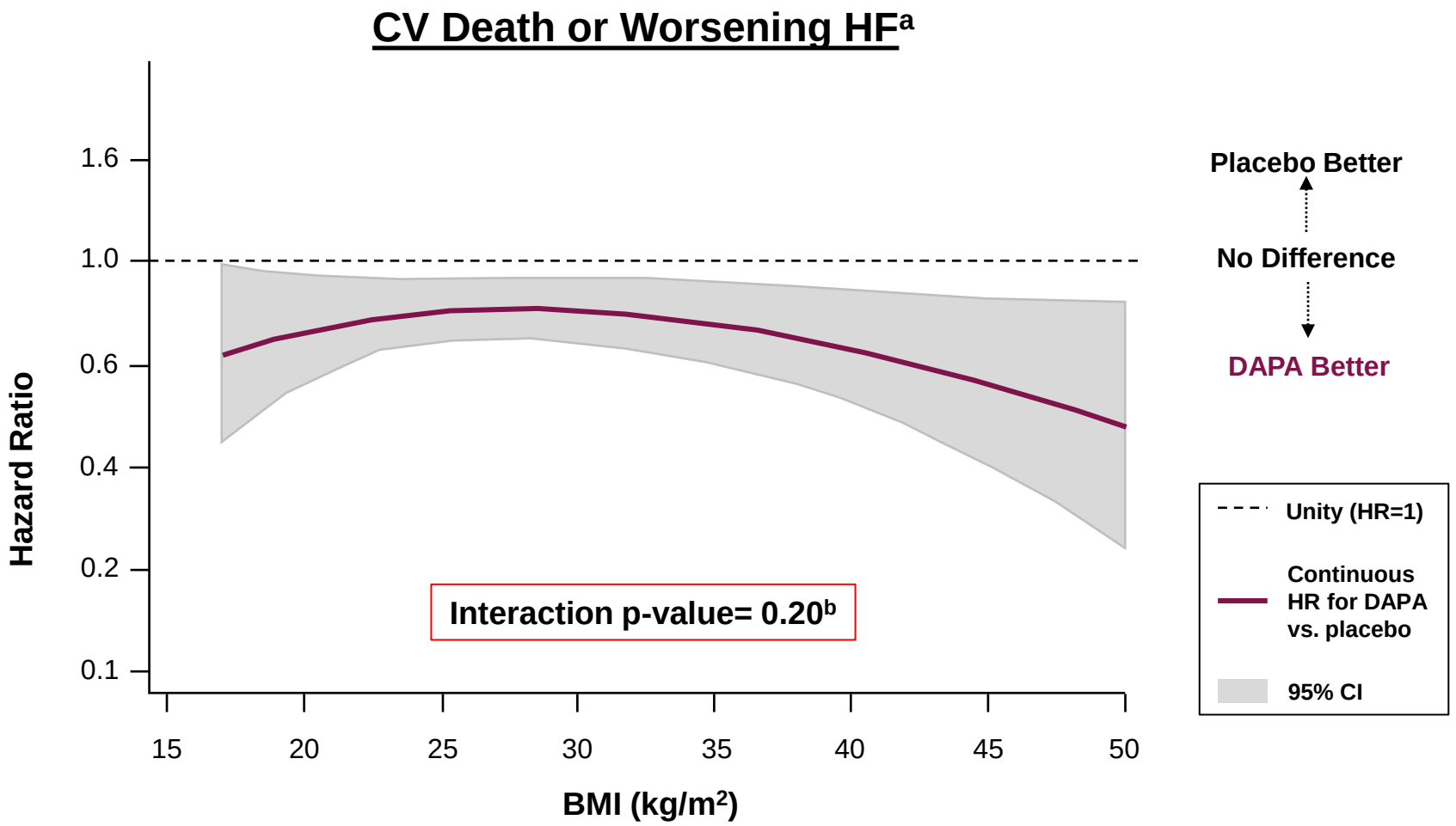
Number at Risk									
DAPA 10 mg	1298	1268	1227	1192	1126	882	646	353	122
Placebo	1307	1253	1214	1176	1101	848	627	340	121

Interaction p-value=0.80[d]

[a]Includes 1983 patients with a pre-existing diagnosis of diabetes and 156 patients with previously undiagnosed diabetes (HbA1c ≥6.5% at Visits 1 and 2); [b]Nominal p-value; [c]NNT = 1/ARR; [d]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]

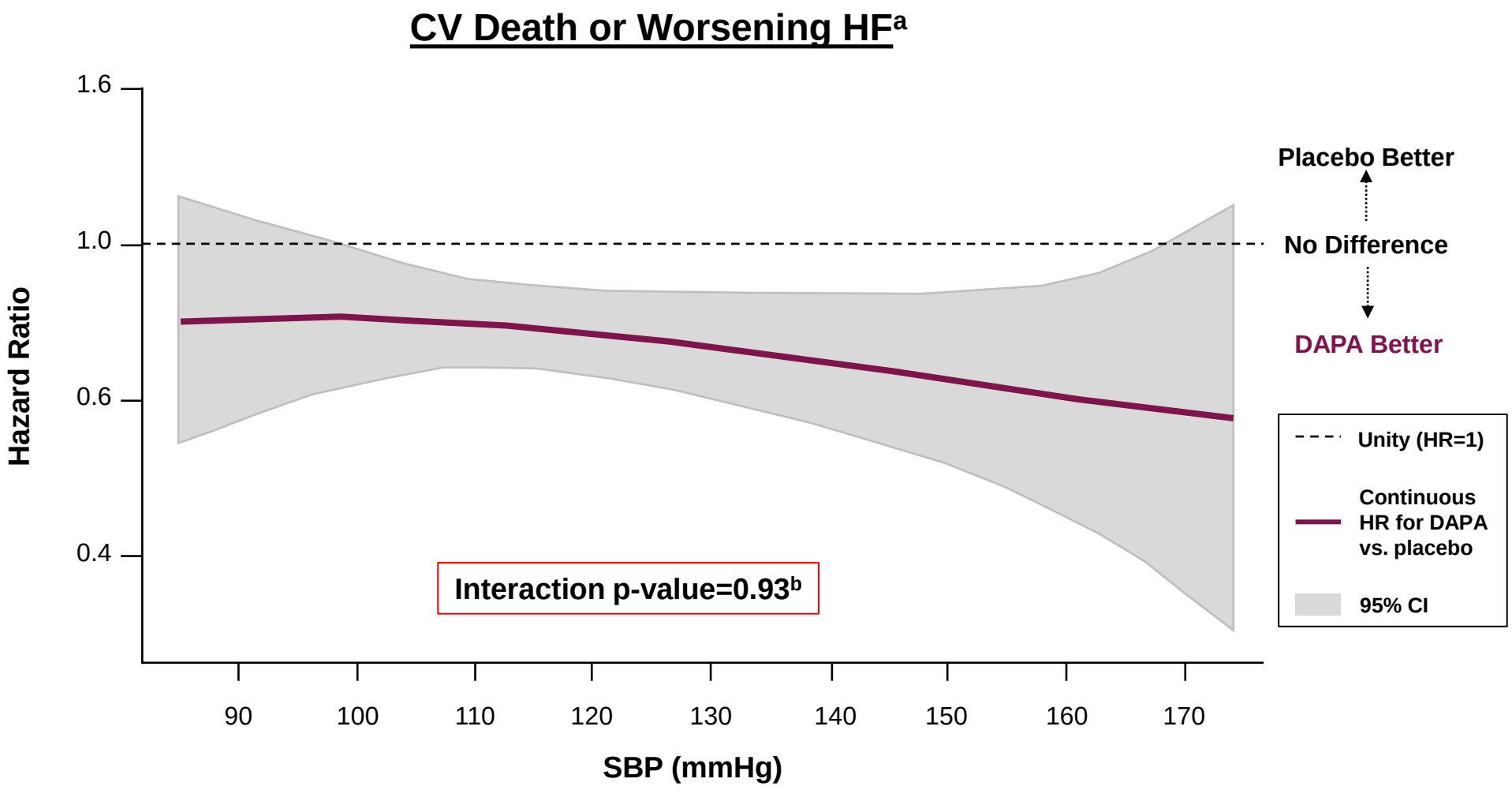
1. Petrie MC et al. *JAMA*. 2020;323:1353-1368; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

Dapagliflozin Consistently Reduced the Primary Endpoint, Regardless of Baseline BMI[1]



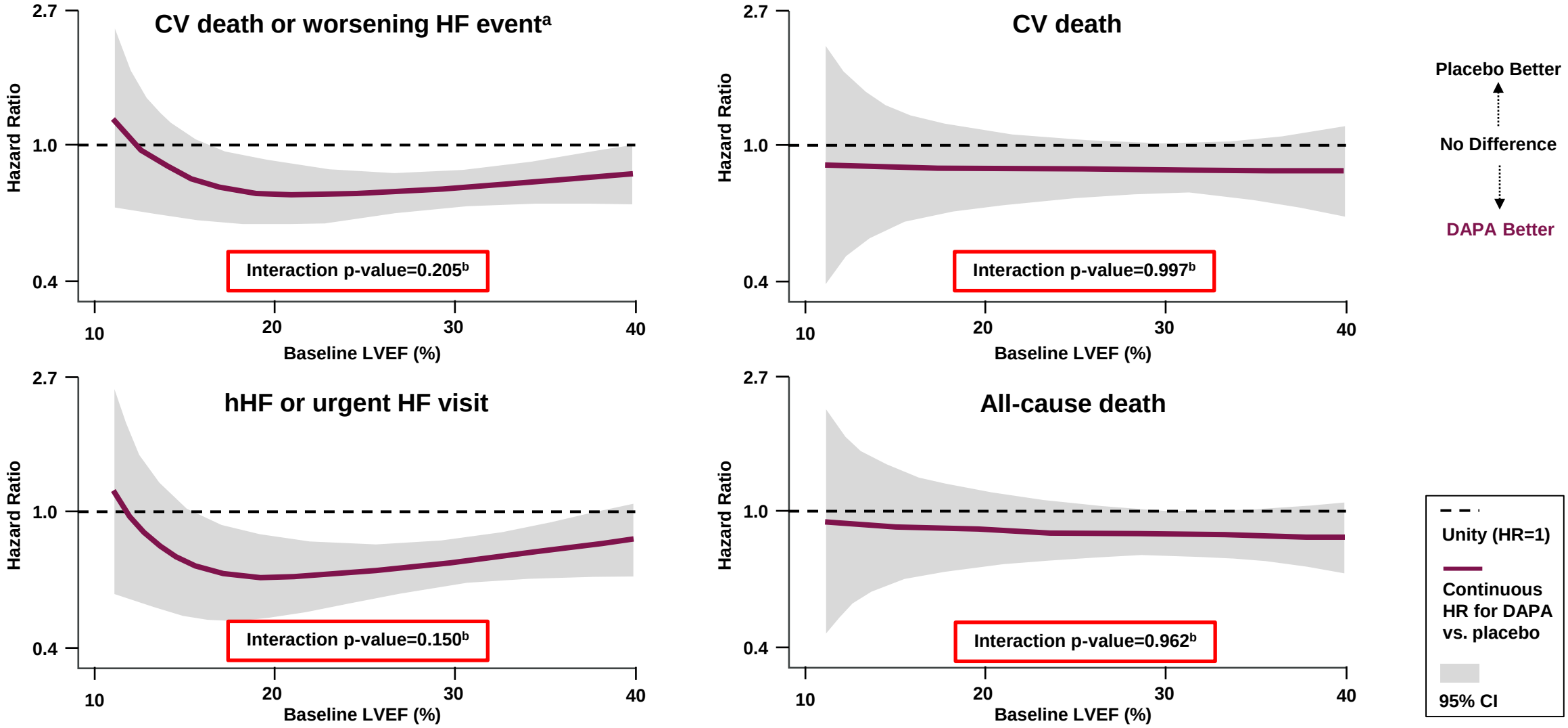
[a]Worsening HF includes hHF or urgent HF visit; [b]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]
BMI = body mass index; CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio.
1. Adamson C et al. Article and supplementary appendix online ahead of print. *Eur J Heart Fail*. 2021; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

Dapagliflozin Consistently Reduced the Primary Endpoint, Regardless of Baseline SBP[1]



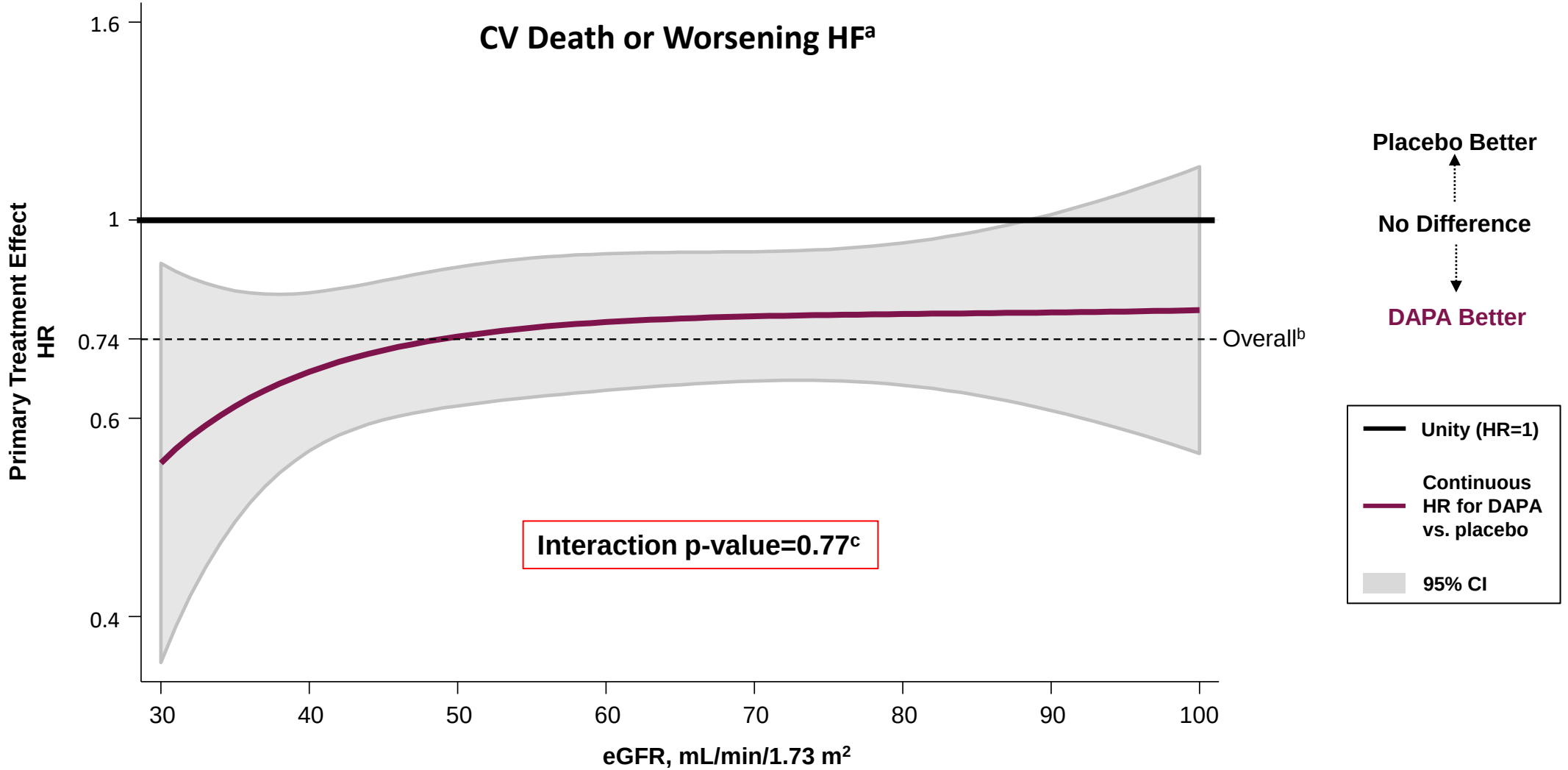
[a]Worsening HF includes hHF or urgent HF visit; [b]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]
CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; SBP = systolic blood pressure.
1. Serenelli M et al. *Eur Heart J*. 2020; 41:3402-3418; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

Dapagliflozin Effect Consistent Across the Range of LVEF for the Primary Composite Outcome, Individual Components, and All-Cause Death[1]



[a]Worsening HF includes hHF or urgent HF visit; [b]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]
CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction.
1. Dewan P et al. *Eur J Heart Fail*. 2020;22:1247-1258; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

Dapagliflozin Benefit Consistent Across the Spectrum of Baseline eGFR



[a]Worsening HF includes hHF or urgent HF visit; [b]Indicates HR for the overall DAPA-HF trial population; [c]A nonsignificant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]

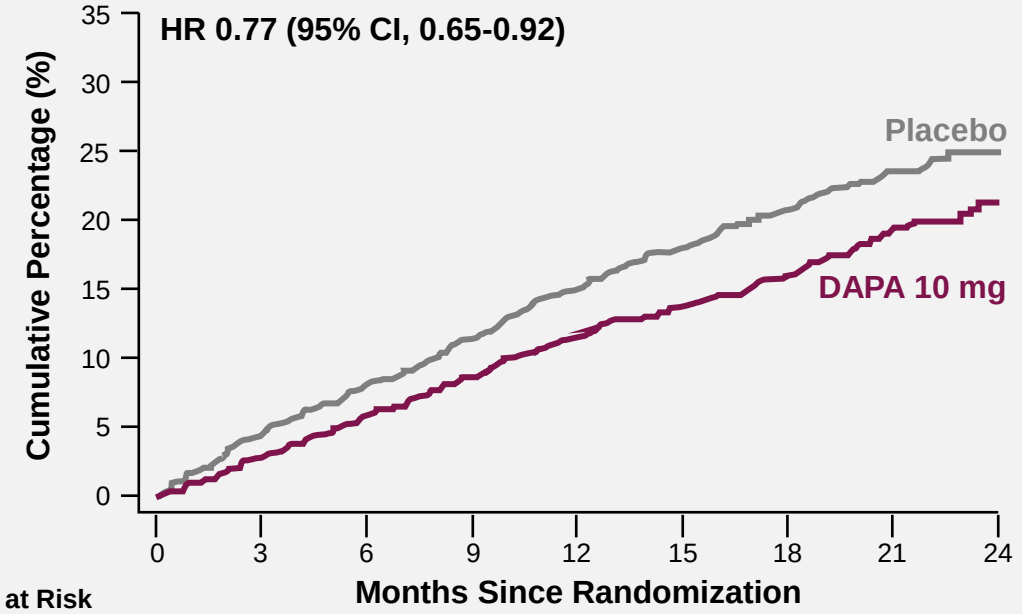
CV = cardiovascular; DAPA = dapagliflozin; eGFR = estimated glomerular filtration rate; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio.

1. Jhund PS et al. *Circulation*. 2021;143:298-309; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

Dapagliflozin Consistently Reduced the Primary Endpoint in Patients with HF of Ischemic and Non-ischemic Etiology[1]

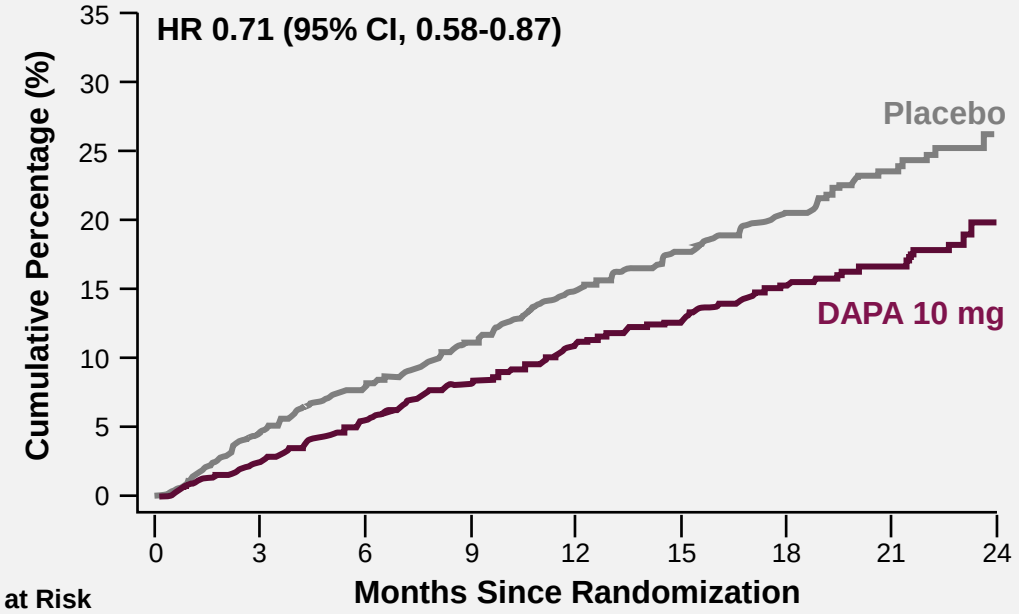
CV Death or Worsening HF[a]

Ischemic (n=2674)



Number at Risk									
DAPA 10 mg	1316	1277	1232	1189	1115	888	658	354	137
Placebo	1358	1294	1237	1185	1098	862	645	342	135

Non-ischemic (n=2070)



Number at Risk									
DAPA 10 mg	1057	1028	989	958	887	672	488	258	73
Placebo	1013	964	926	890	819	616	451	251	75

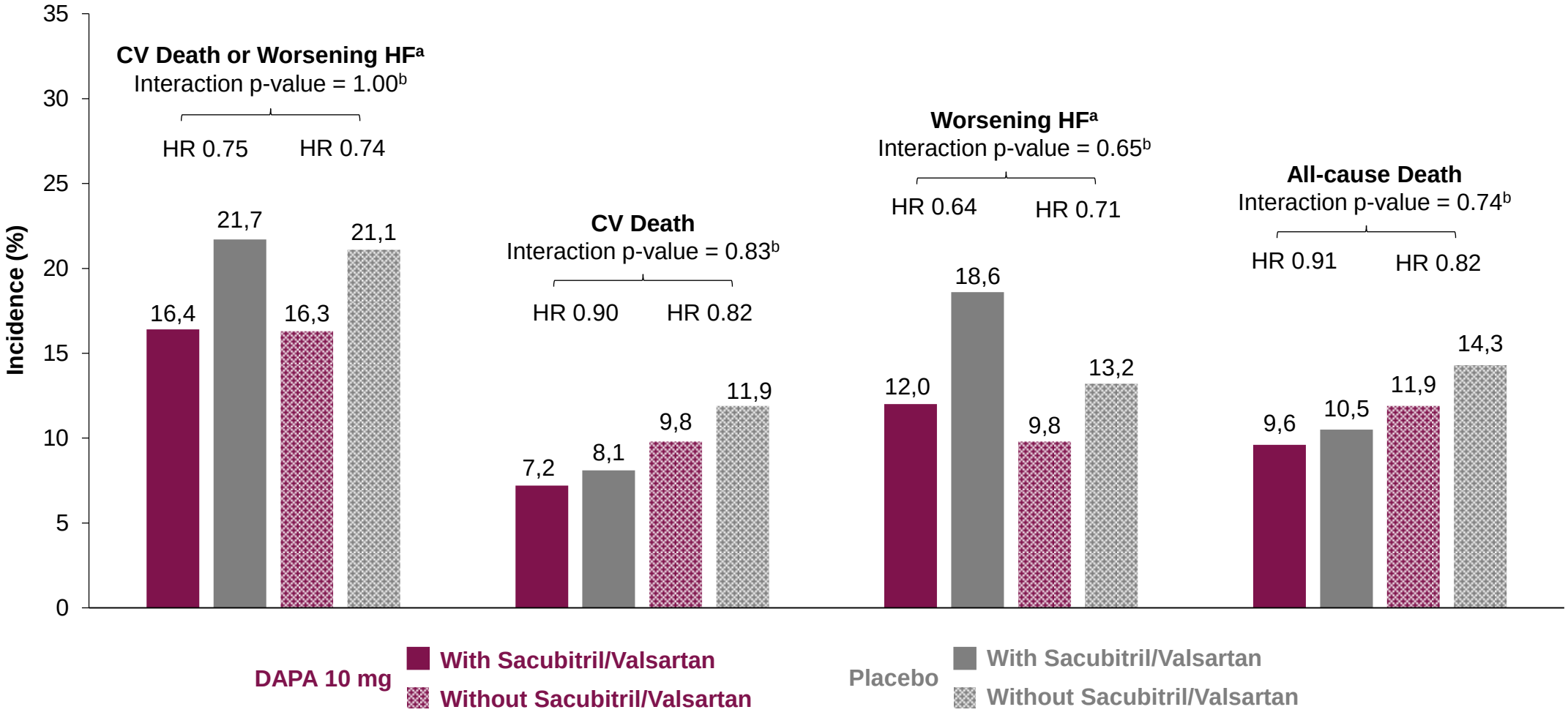
Interaction p-value=0.55[b]

[a]Worsening HF includes hHF or urgent HF visit; [b]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]

CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; T2D = type 2 diabetes.

1. Butt JH. Presented at: ESC HFA Discoveries Virtual Meeting; June 5-19, 2020; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

Benefit of Dapagliflozin on Efficacy Endpoints was Consistent Regardless of Sacubitril/Valsartan Use[1]



[a]Worsening HF includes hHF or urgent HF visit; [b]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]
CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio.

1. Solomon SD et al. *JACC Heart Fail*. 2020;8:811-818; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

Benefit of Dapagliflozin on Efficacy Endpoints was Consistent Regardless of Use of Sacubitril/Valsartan

	Patients Taking Sacubitril/Valsartan		Patients not Taking Sacubitril/ Valsartan		
	Placebo (n = 258)	Dapagliflozin (n = 250)	Placebo (n = 2,113)	Dapagliflozin (n = 2,123)	p Value for Interaction
Primary outcome					
Events	56 (21.7)	41 (16.4)	446 (21.1)	345 (16.3)	
Event rate per 100 patient-yrs	17.8 (13.7–23.1)	13.1 (9.6–17.7)	15.6 (14.2–17.1)	11.6 (10.4– 12.9)	
Unadjusted hazard ratio (95% CI)	0.75 (0.50–1.13)		0.74 (0.65–0.86)		1.00
CV death					
Events	21 (8.1)	18 (7.2)	252 (11.9)	209 (9.8)	
Event rate per 100 patient-yrs	6.1 (4.0–9.3)	5.4 (3.4–8.5)	8.2 (7.3–9.3)	6.7 (5.9–7.7)	
Unadjusted hazard ratio (95% CI)	0.90 (0.48–1.69)		0.82 (0.68–0.98)		0.83
HF hospitilization/urgent visit					
Events	48 (18.6)	30 (12.0)	278 (13.2)	207 (9.8)	
Event rate per 100 patient-yrs	15.2 (11.5–20.2)	9.6 (6.7–13.7)	9.7 (8.6-10.9)	7.0 (6.1-8.0)	
Unadjusted hazard ratio (95% CI)	0.64 (0.41–1.02)		0.71 (0.60–0.85)		0. 65

- **Event rate** for the primary composite (and specifically for worsening HF) was higher in patients who received sacubitril/valsartan, while event rate for CV death was slightly lower
- The **benefit of dapagliflozin was similar** in those who were and were not receiving sacubitril/valsartan with respect to the composite primary endpoint (HR 0.75 Vs 0.74 respectively), and single components

Solomon SD et al. JACC Heart Fail. 2020

Safety Outcomes by Sacubitril/Valsartan Use

All safety outcomes were similar between dapagliflozin and placebo, regardless of background ARNI use

Event, n (%)	With Sacubitril/Valsartan Use			Without Sacubitril/Valsartan Use		
	DAPA 10 mg (n=250)	Placebo (n=258)	p-value	DAPA 10 mg (n=2118)	Placebo (n=2110)	p-value
AE leading to treatment discontinuation	15 (6.0)	19 (7.4)	0.60	96 (4.5)	97 (4.6)	0.94
Volume depletion	27 (10.8)	31 (12.0)	0.60	151 (7.1)	131 (6.2)	0.24
Renal AE	25 (10.0)	25 (9.7)	1.00	128 (6.0)	145 (6.9)	0.29
Fracture	6 (2.4)	7 (2.7)	1.00	43 (2.0)	43 (2.0)	1.00
Amputation	2 (0.8)	1 (0.4)	1.00	11 (0.5)	11 (0.5)	1.00
Major hypoglycemia	0 (0.0)	0 (0.0)	---	4 (0.2)	4 (0.2)	1.00

AE = adverse event; ARNI = angiotensin-receptor neprilysin inhibitor; DAPA = dapagliflozin.

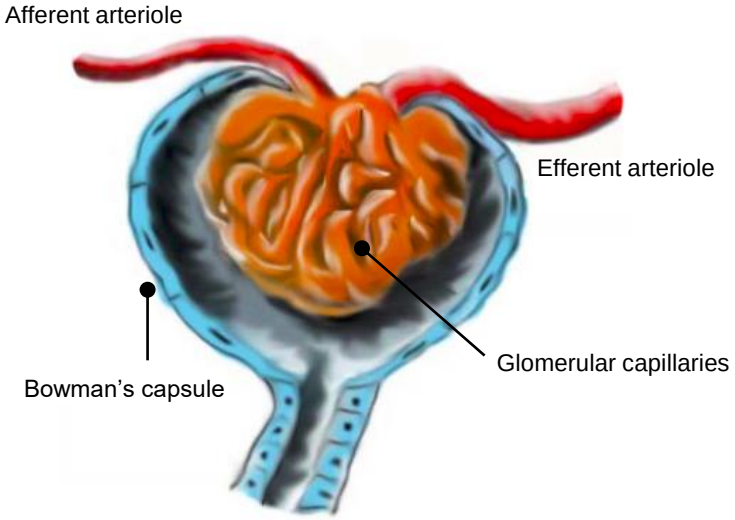
Solomon SD et al. *JACC Heart Fail*. 2020;8:811-818.

SGLT2 inhibition and RAAS blockade both reduce glomerular hyperfiltration by complimentary mechanisms[1-3]

SGLT2 inhibitors

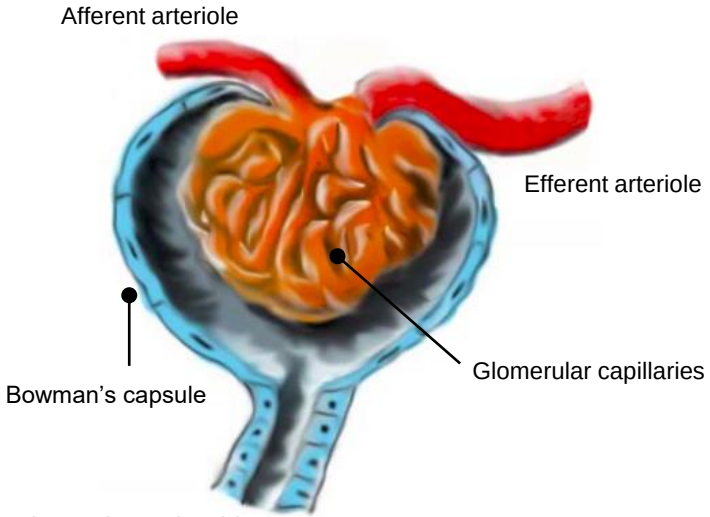
Afferent constriction[1-3]

Due to increased Na+ delivery to the macula densa[1-3]



RAAS blockade

Efferent vasodilation[1]



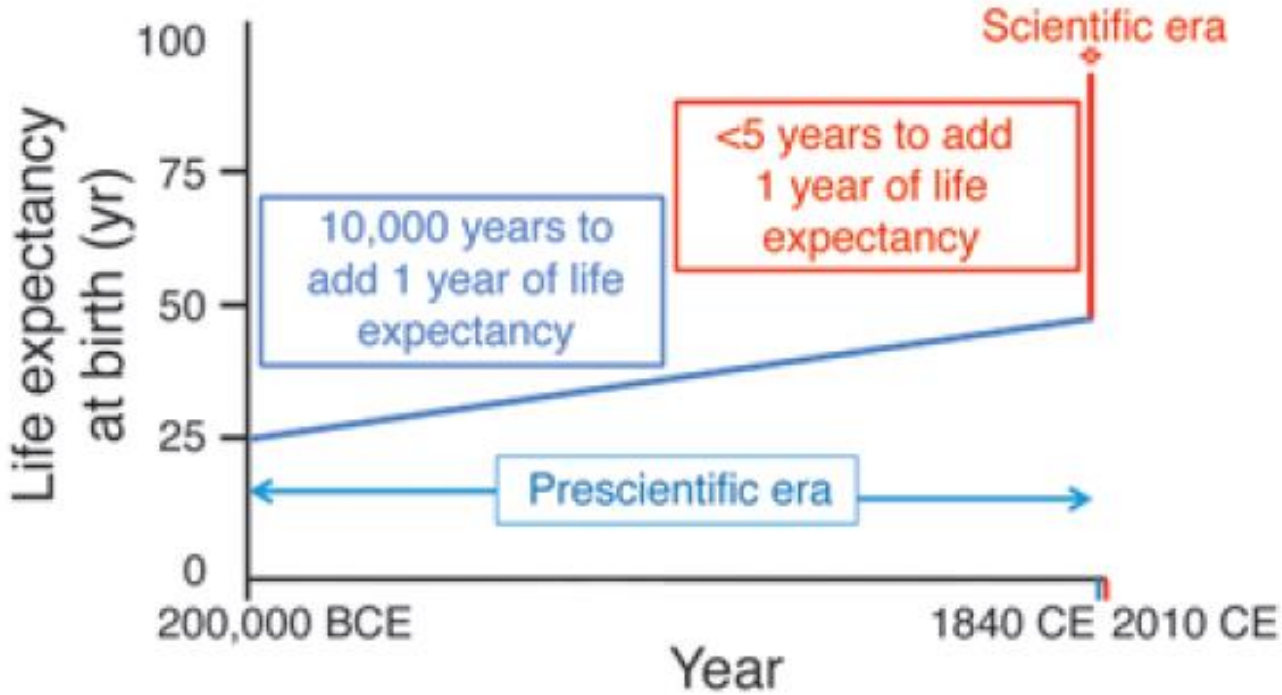
CLINICAL IMPLICATIONS

- **Decreased glomerular pressure[1,3]**
- **Reduction in albuminuria[1,2]**

- **Decreased glomerular pressure[1,3]**
- **Reduction in albuminuria[4]**

SGLT2, sodium-glucose cotransporter 2; Na, sodium; RAAS, renin-angiotensin-aldosterone system.

1. Van Bommel EJ, et al. *Clin J Am Soc Nephrol*. 2017;12(4):700-710. 2. Seidu S, et al. *Prim Care Diabetes*. 2018;12(3):265-283. 3. Cherney DZ, et. al. *Circulation*. 2014 Feb 4;129(5):587-97. 4. Heerspink HJ, et al. *Diabetes Care*. 2011;34 Suppl 2:S325-9. 5. Adapted from: Shiraishi M, et al. *FASEB J*. 2003;17(15):2284-6.



J Clin Invest. 2012; 122(11): 4293–4299.

GRAZIE!

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