AMD
EMILIA ROMAGNA
ASSOCIAZIONE MEDICI DIABETOLOGI

LA PROTEZIONE CARDIOVASCOLARE COMPLETA

18 NOVEMBRE 2022

BOLOGNA

NH HOTEL BOLOGNA DE LA GARE - Piazza XX Settembre, 2

Il valore aggiunto delle terapie antidiabete di nuova generazione: un update sulle evidenze più recenti

Francesca Lugli

GLP1 RAs

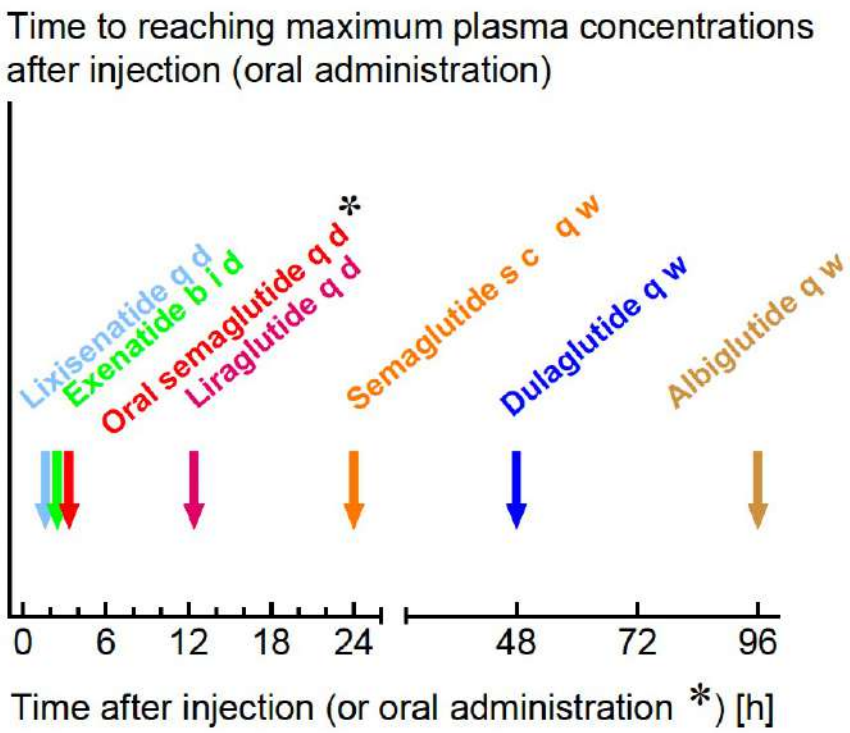
GLP-1 receptor agonists in the treatment of type 2 diabetes – state-of-the-art

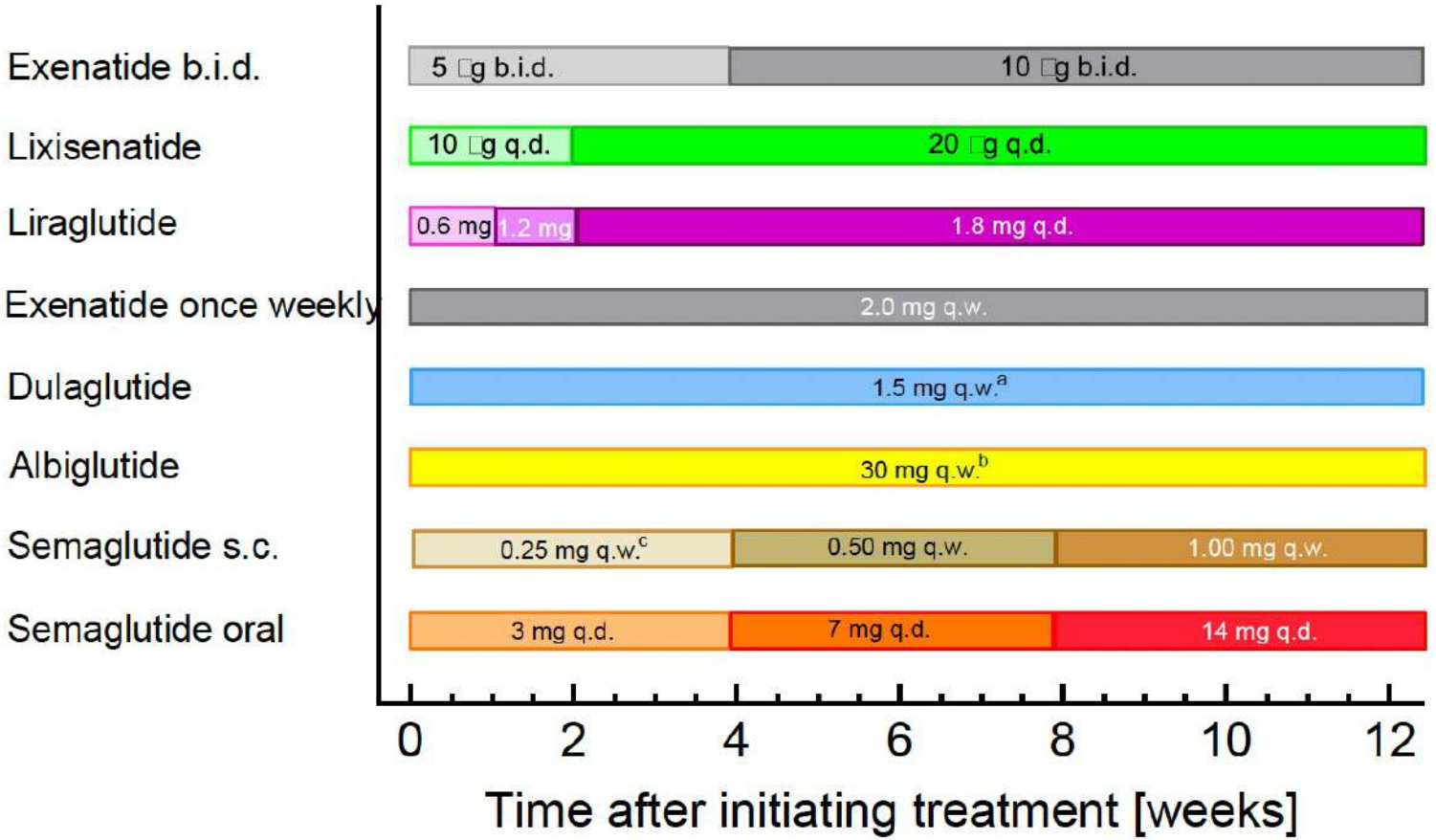
Michael A. Nauck*, Daniel R. Quast, Jakob Wefers, Juris J. Meier

	GLP-1 receptor agonists								Fixed-dose combinations (GLP-1 RA/basal insulin)	
Pen devices for injection										
Drug: Generic/ commercial	Exenatide	Lixisenatide	Liraglutide	Exenatide once weekly,		Dulalgutide	Albiglutide	Semaglutide	iDegLira	iGlarLixi
Single (1) or multiple (x) use?	x	x	x	1	1	1	1	x	x	x
Predefined (p) or variable (v) dosing	p	p	v	p	p	p	p	p	v (for titration)	v (for titration)
Pens available (maximum dose)	a. 5 µg b. 10 µg	a. 10 µg b. 20 µg	a. 0.6 mg b. 1.2 mg c. 1.8 mg	2 mg	2 mg	a. 0.75 mg b. 1.5 mg	a. 30 mg b. 50 mg	a. 0.25 mg b. 0.5 mg c. 1.0 mg	1.8 mg/ iDeg 50 IU per dose	a. 20 µg/iGlar 40 IU per dose or b. 20 µg/iGlar 60 IU per dose
Resuspension necessary?	no	no	no	yes	no*	no	yes	no	no	no
Ease of use	+	+	+	-	(-)	+++	(-)	+	+	+

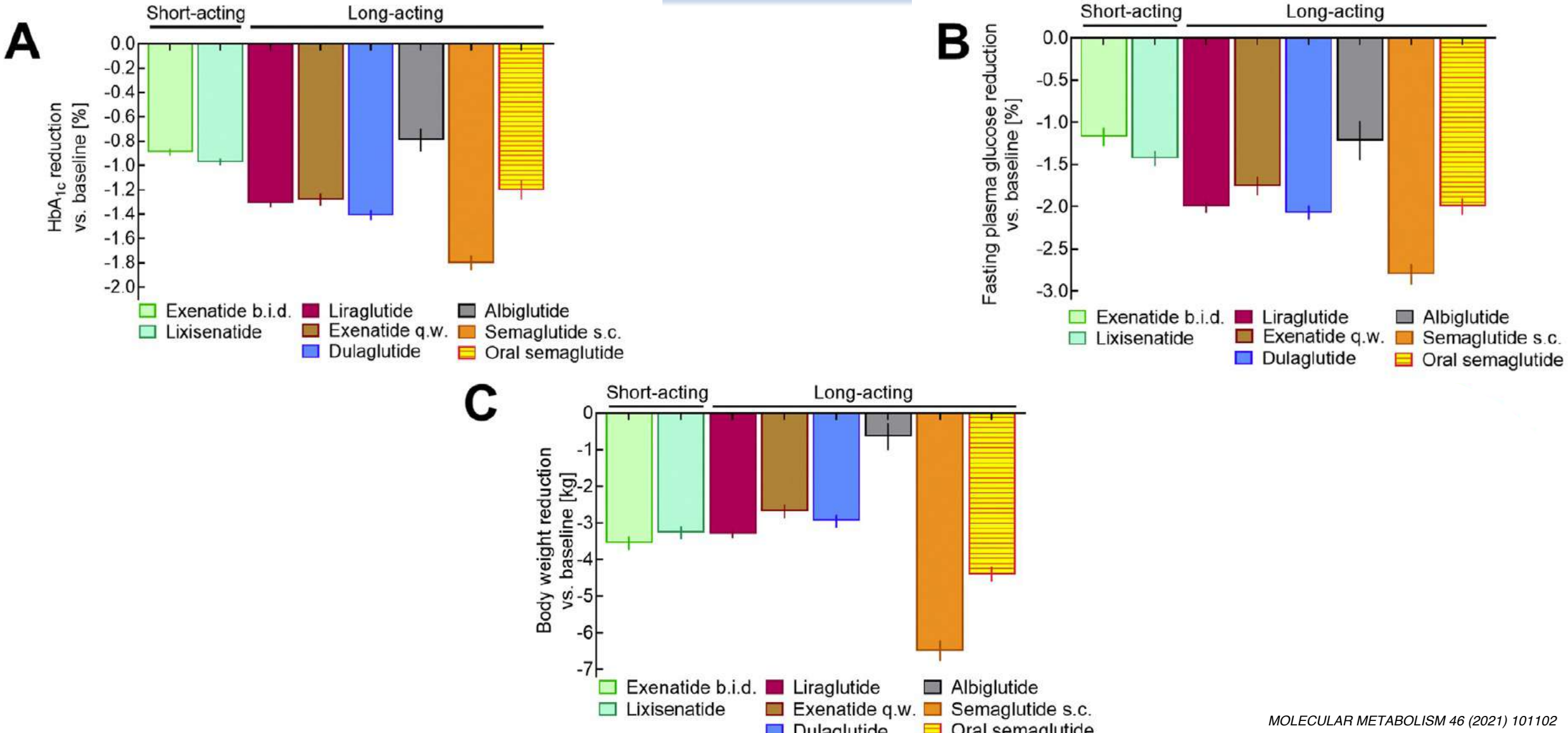
MOLECULAR METABOLISM 46 (2021) 101102

GLP1 RA


Time to reaching maximum plasma concentrations after injection (oral administration)
Lixisenatide q d
Exenatide b i d
Oral semaglutide q d *
Liraglutide q d
Semaglutide s c q w
Dulaglutide q w
Albiglutide q w
0
6
12
18
24
48
72
96
Time after injection (or oral administration *) [h]


Exenatide b.i.d.
5 □g b.i.d.
10 □g b.i.d.
Lixisenatide
10 □g q.d.
20 □g q.d.
Liraglutide
0.6 mg
1.2 mg
1.8 mg q.d.
Exenatide once weekly
2.0 mg q.w.
Dulaglutide
1.5 mg q.w.[a]
Albiglutide
30 mg q.w.[b]
Semaglutide s.c.
0.25 mg q.w.[c]
0.50 mg q.w.
1.00 mg q.w.
Semaglutide oral
3 mg q.d.
7 mg q.d.
14 mg q.d.
0
2
4
6
8
10
12
Time after initiating treatment [weeks]

GLP1 RA



MOLECULAR METABOLISM 46 (2021) 101102

GLP1 RA

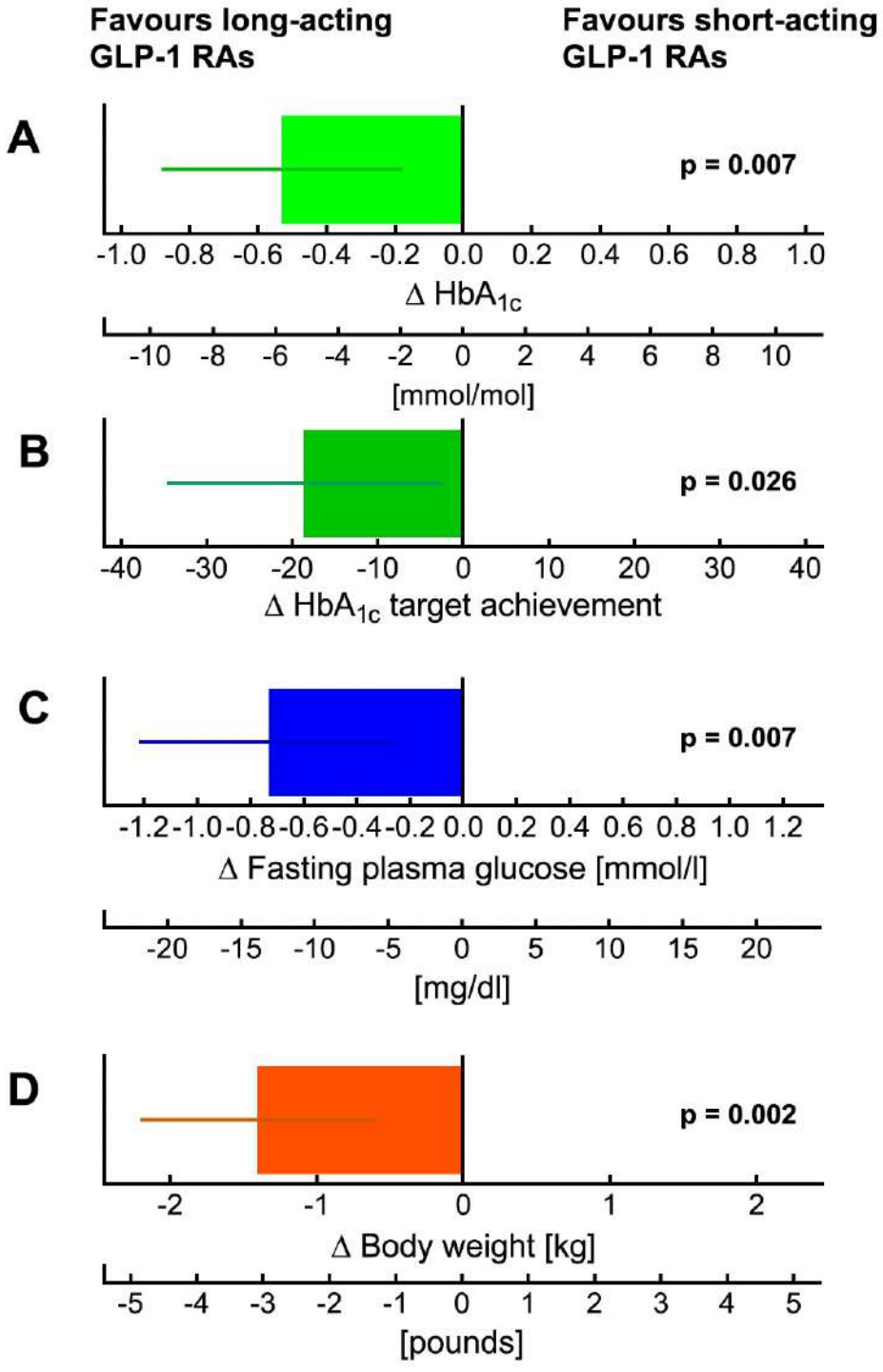
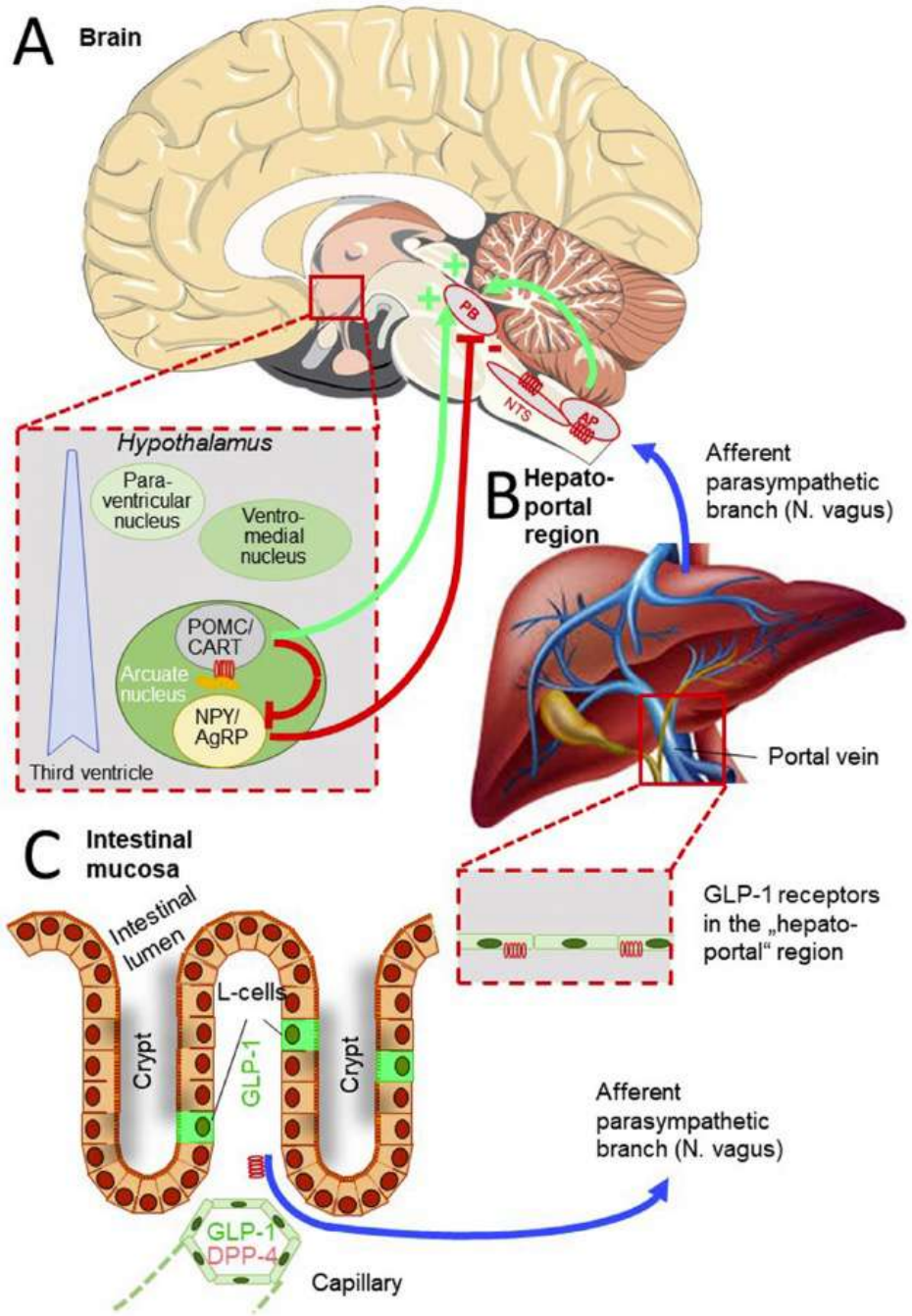
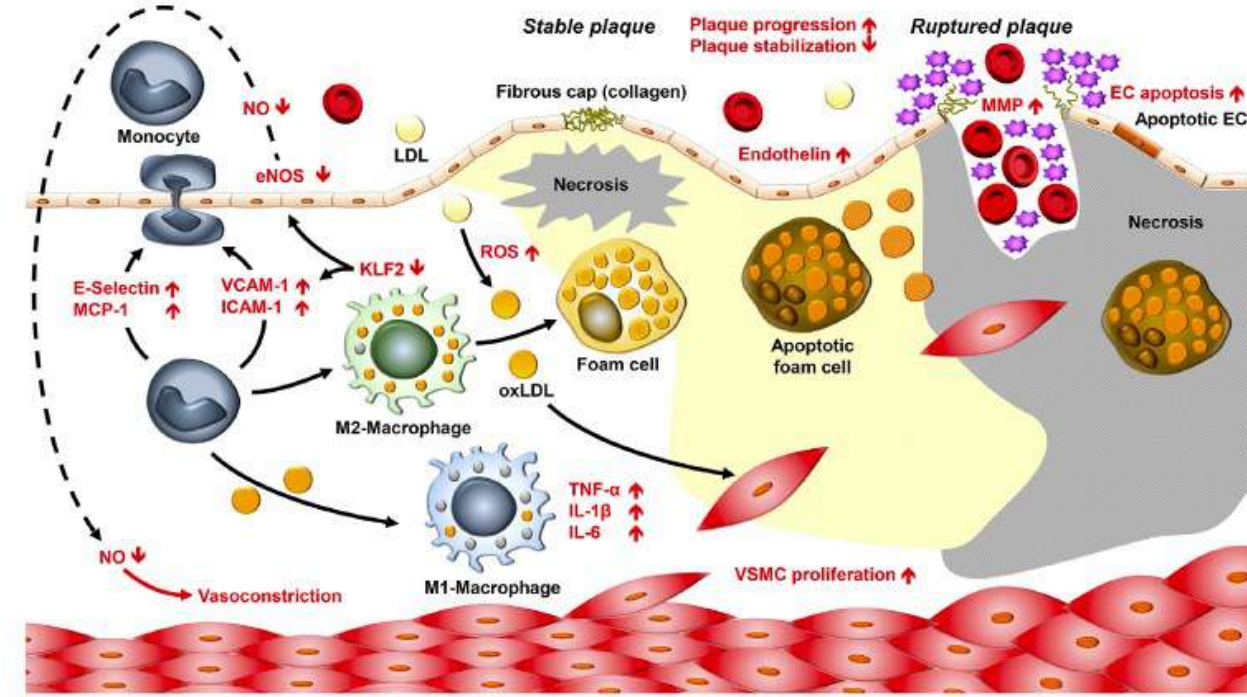
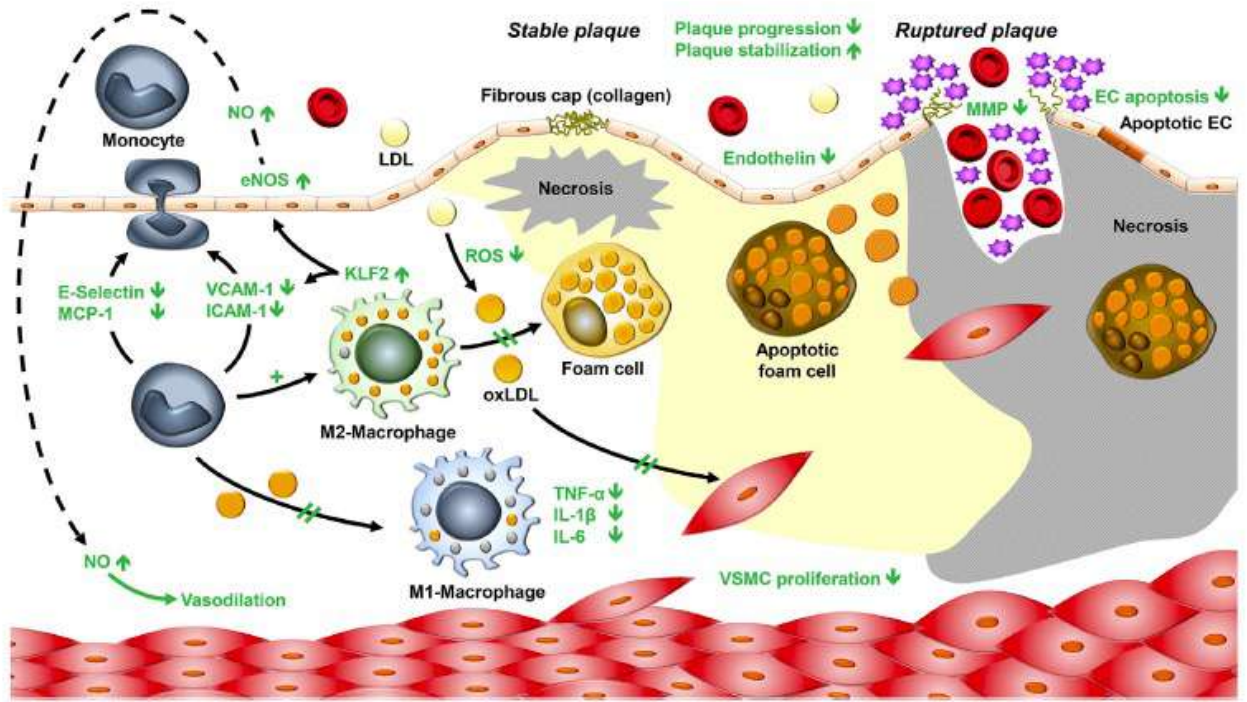


Figure 5: Meta-analysis comparing effects of short- and long-acting GLP-1 receptor agonists added to basal insulin in HbA_{1c} (A), HbA_{1c} target ($\leq$7.0%) achievement (B), fasting plasma glucose (C), and body weight (D). For each variable, the results were significantly better for long-acting compounds (liraglutide, once-weekly exenatide, dulaglutide, and semaglutide based on 6 studies) compared to short-acting compounds (exenatide b.i.d. and lixisenatide based on 8 studies). Both studies with free and fixed-dose combinations were analyzed. Modified from [50].


A
Brain
PB
NTS
AP
Hypothalamus
Para-ventricular nucleus
Ventro-medial nucleus
POMC/ CART
Arcuate nucleus
NPY/ AgRP
Third ventricle
B
Hepato-portal region
Afferent parasympathetic branch (N. vagus)
Portal vein
GLP-1 receptors in the „hepato-portal“ region
C
Intestinal mucosa
Intestinal lumen
L-cells
Crypt
GLP-1
Crypt
GLP-1 DPP-4
Capillary
Afferent parasympathetic branch (N. vagus)


Stable plaque
Plaque progression
Plaque stabilization
Ruptured plaque
Fibrous cap (collagen)
Monocyte
NO
eNOS
LDL
Endothelin
MMP
EC apoptosis
Apoptotic EC
Necrosis
Necrosis
ROS
KLF2
E-Selectin
MCP-1
VCAM-1
ICAM-1
Foam cell
Apoptotic foam cell
oxLDL
M2-Macrophage
TNF-α
IL-1β
IL-6
M1-Macrophage
NO
Vasoconstriction
VSMC proliferation


Stable plaque
Plaque progression
Plaque stabilization
Ruptured plaque
Fibrous cap (collagen)
Monocyte
NO
eNOS
LDL
Endothelin
MMP
EC apoptosis
Apoptotic EC
Necrosis
Necrosis
ROS
KLF2
E-Selectin
MCP-1
VCAM-1
ICAM-1
Foam cell
Apoptotic foam cell
oxLDL
M2-Macrophage
TNF-α
IL-1β
IL-6
M1-Macrophage
NO
Vasodilation
VSMC proliferation

GLP1 RAs

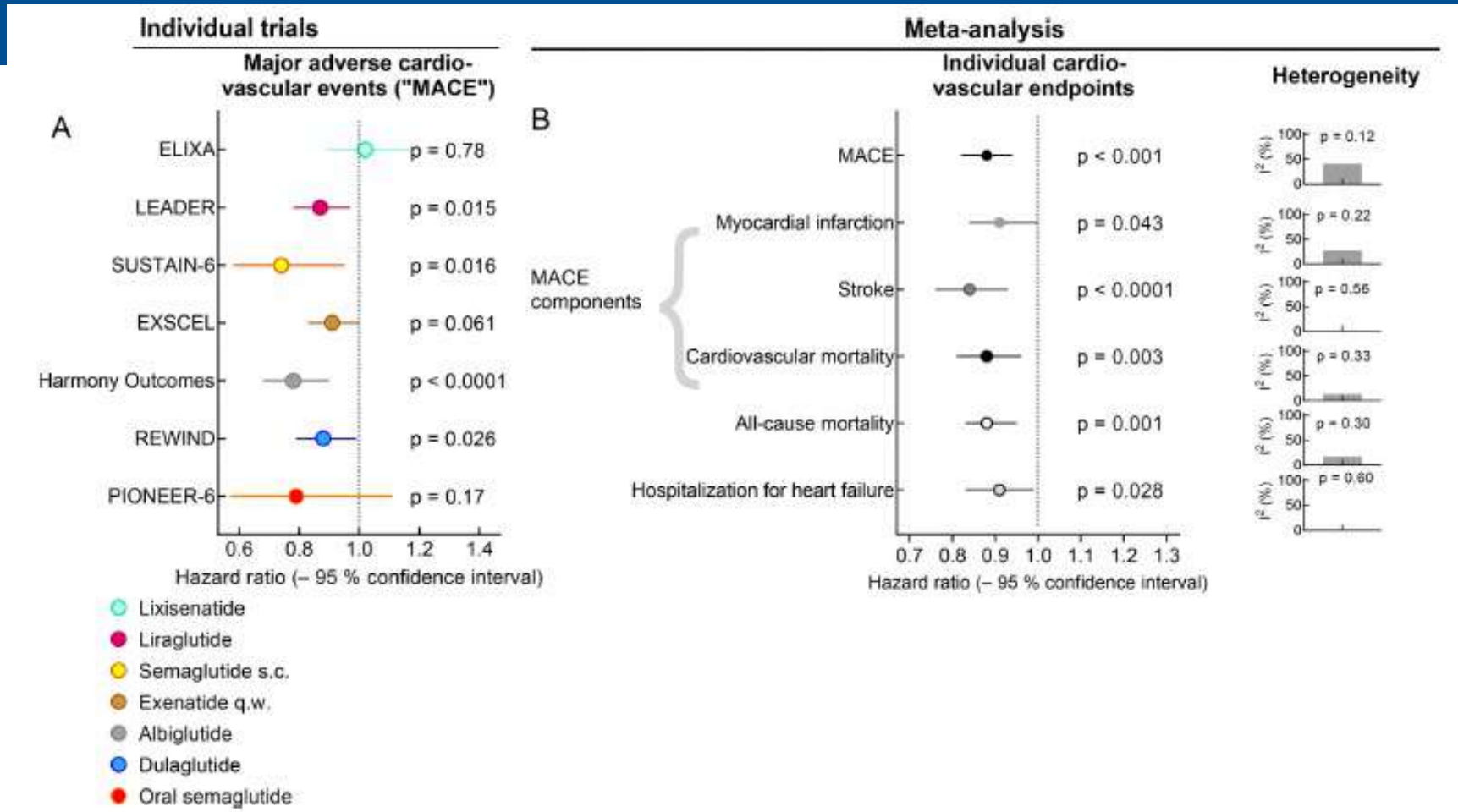
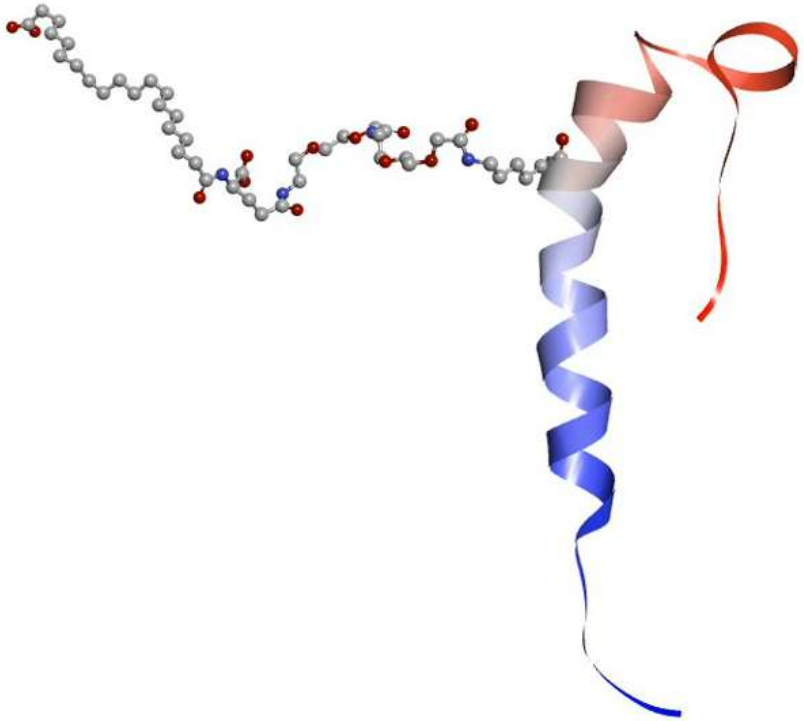


Figure 7: Results of cardiovascular outcome studies comparing GLP-1 RAs with placebo on a background of standard of care. (A) Reduction in major adverse cardiovascular events (MACE: time to first event) in published individual clinical trials. (B) Results of a published meta-analysis [108] analyzing various cardiovascular endpoints across all of the clinical trials shown in panel A. MACE (a combination of either cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) was the primary endpoint in all studies. Meta-analysis results are supplemented with I^2 and related p values indicating the heterogeneity of the analysis of individual endpoints (column of panels to the far right) as reported in [108].

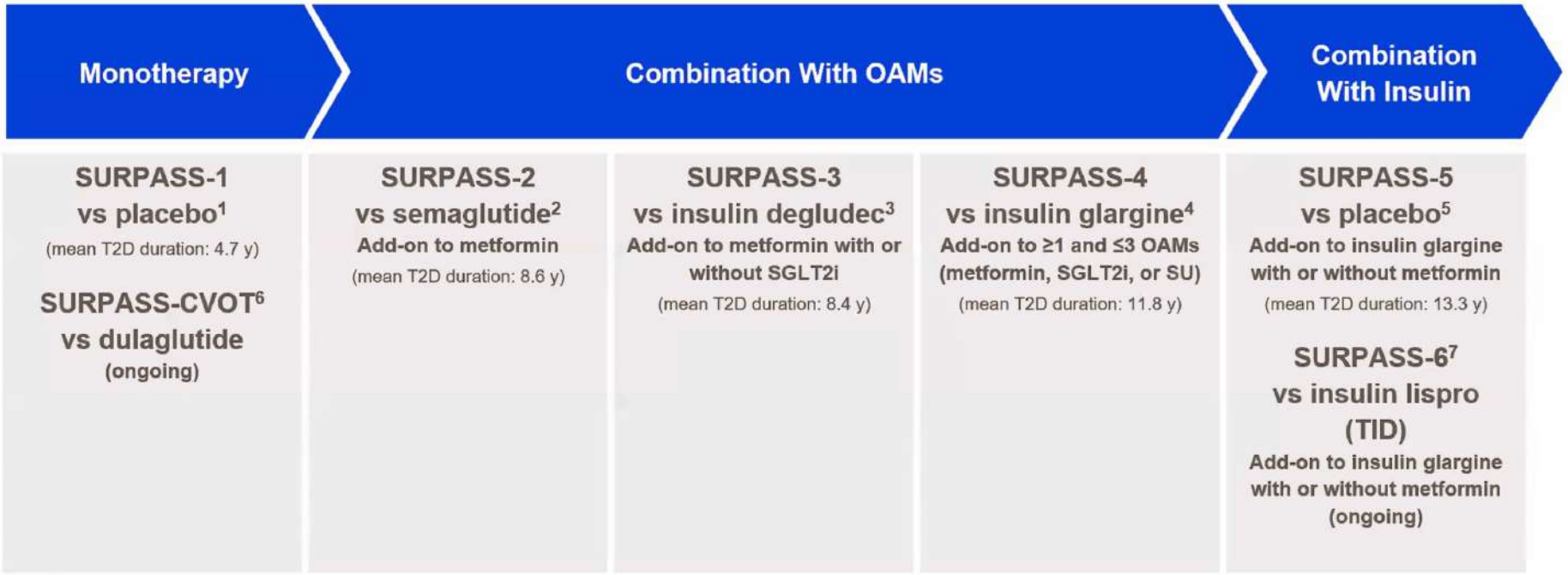
TIRZEPATIDE

- **Tirzepatide (LY3298176) è un peptide lineare di 39 aminoacidi e include un acido grasso C20**
- **È un peptide multifunzionale basato sulla sequenza del GIP nativo che è stato modificato per legarsi sia al recettore del GIP che del GLP-1**
- **L'emivita media è di circa 5 giorni (116,7 ore) e ciò consente un dosaggio una volta alla settimana**
- **Non ci sono stati effetti clinicamente rilevanti dell'insufficienza renale sulla farmacocinetica della tirzepatide; pertanto, i pazienti con insufficienza renale trattati con tirzepatide potrebbero non richiedere aggiustamenti della dose**



1.Coskun T, et al. *Mol Metab*. 2018;18:3-14.
2.Urva S, et al. *Diabetes*. 2020;69(suppl 1):Abstract 971-P.

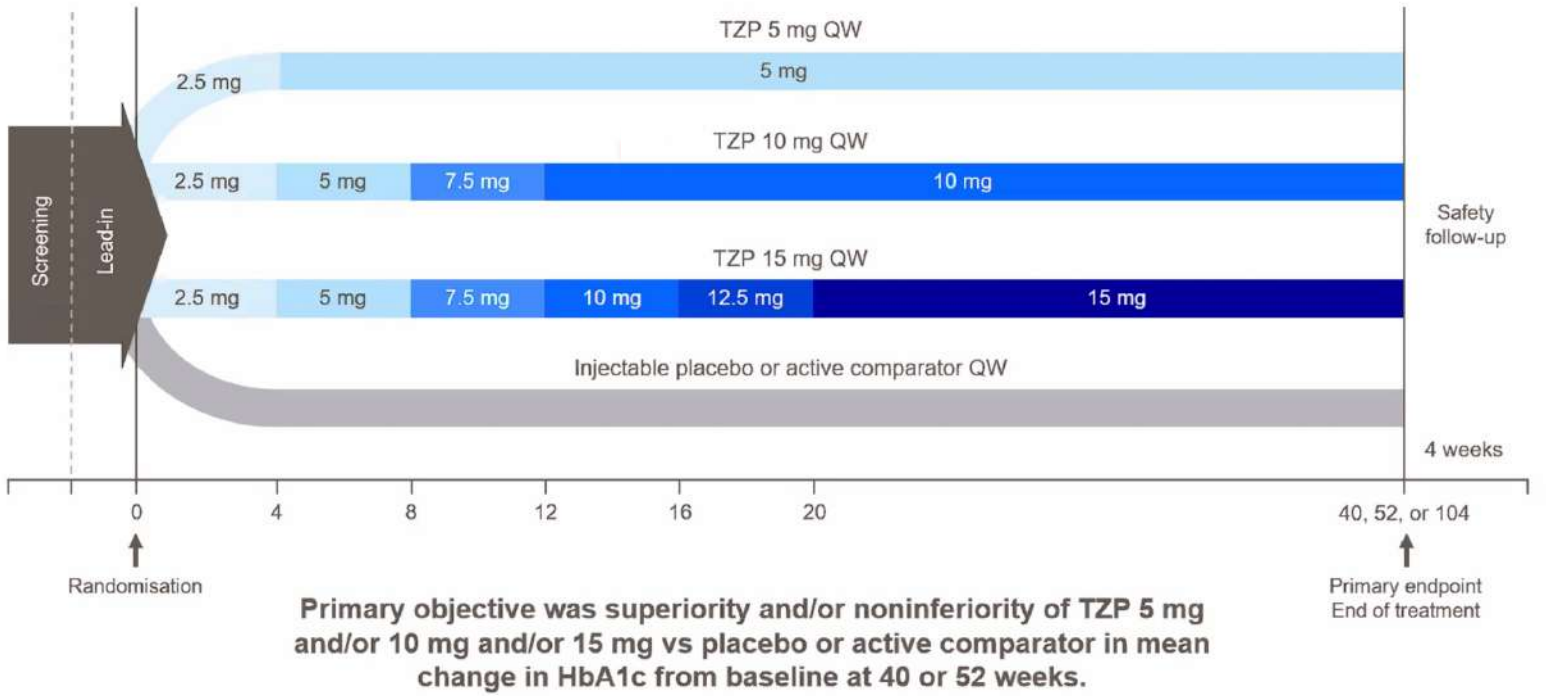
SURPASS GLOBAL REGISTRATION PROGRAM



OAM = Oral AntiHyperglycaemic Medication; SGLT2i = Sodium-Glucose co-transporter-2 inhibitor; SU = Sulphonylurea; TID = Thrice Daily; T2D = Type 2 Diabetes

1. Rosenstock J. et al. *Lancet*, VOLUME 398, ISSUE 10295, P143-155, JULY 10, 2021 - DOI:https://doi.org/10.1016/S0140-6736(21)01324-6
2. Frias JP. et al. *N Engl J Med*, 2021 Aug 5;385(6):503-515 - DOI: 10.1056/NEJMoa2107519
3. Ludvik B. et al. *Lancet*, VOLUME 398, ISSUE 10300, P583-598, AUGUST 14, 2021 - DOI:https://doi.org/10.1016/S0140-6736(21)01443-4
4. Del Prato S. et al. *Lancet*, VOLUME 398, ISSUE 10313, P1811-1824, NOVEMBER 13, 2021- DOI:https://doi.org/10.1016/S0140-6736(21)02188-7
5. Dahl D. et al. *JAMA.* 2022;327(6):534-545 - doi:10.1001/jama.2022.0078
6. SURPASS CVOT Accessed 1 april 2021 – Available at: https://clinicaltrials.gov/ct2/show/NCT04255433
7. SURPASS 6 Accessed 1 april 2021 – Available at: https://clinicaltrials.gov/ct2/show/NCT04537923

SURPASS DISEGNO DEGLI STUDI 1-5



QW = Once Weekly; TZP = Tirzepatide

1. Rosenstock J. et al. *Lancet*, VOLUME 398, ISSUE 10295, P143-155, JULY 10, 2021 - DOI:https://doi.org/10.1016/S0140-6736(21)01324-6
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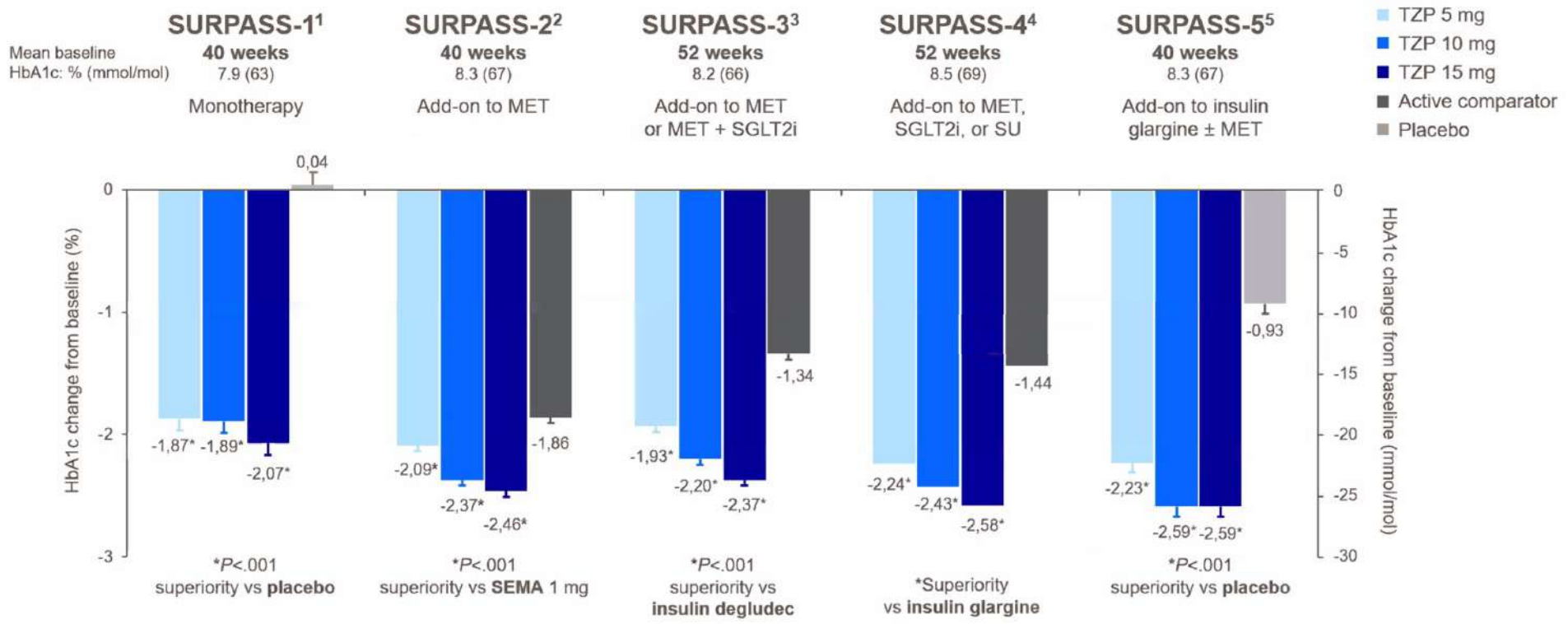
5. Dahl D. et al. *JAMA.* 2022;327(6):534-545 - doi:10.1001/jama.2022.0078

Endpoint Primario: Variazione di HbA1c



Data are LSM (SE); mITT population (efficacy analysis set); MMRM analysis Data labels are % HbA1c
LSM = Least Square Mean; MET = Metformin; mITT = modified Intent-To-Treat; MMRM = mixed model repeated measures;
SGLT2i = Sodium-Glucose co-transporter-2 inhibitor; SEMA = Semaglutide; SU = Sulphonylurea; TZP = Tirzepatide

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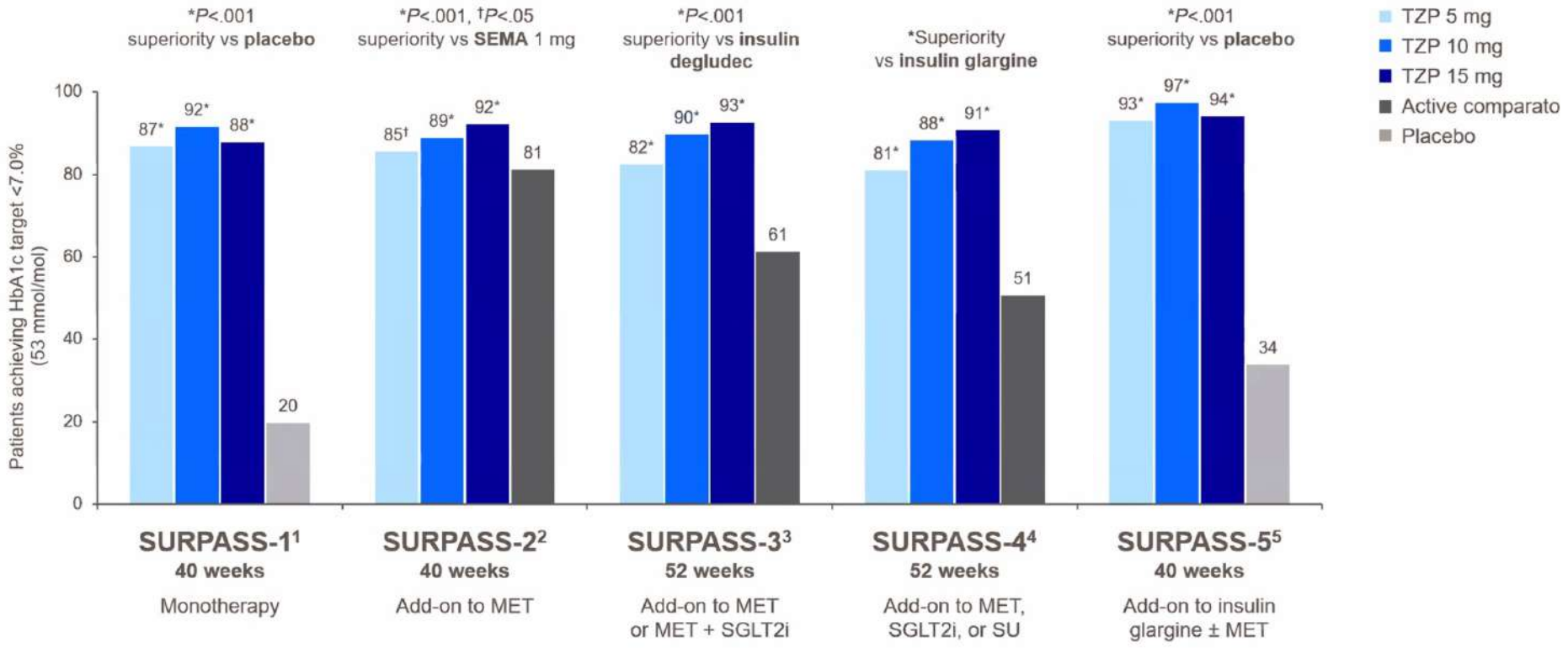
5. Dahl D. et al. *JAMA.* 2022;327(6):534-545 - doi:10.1001/jama.2022.0078

Percentuale di Pazienti che raggiungono HbA1c < 7,0%



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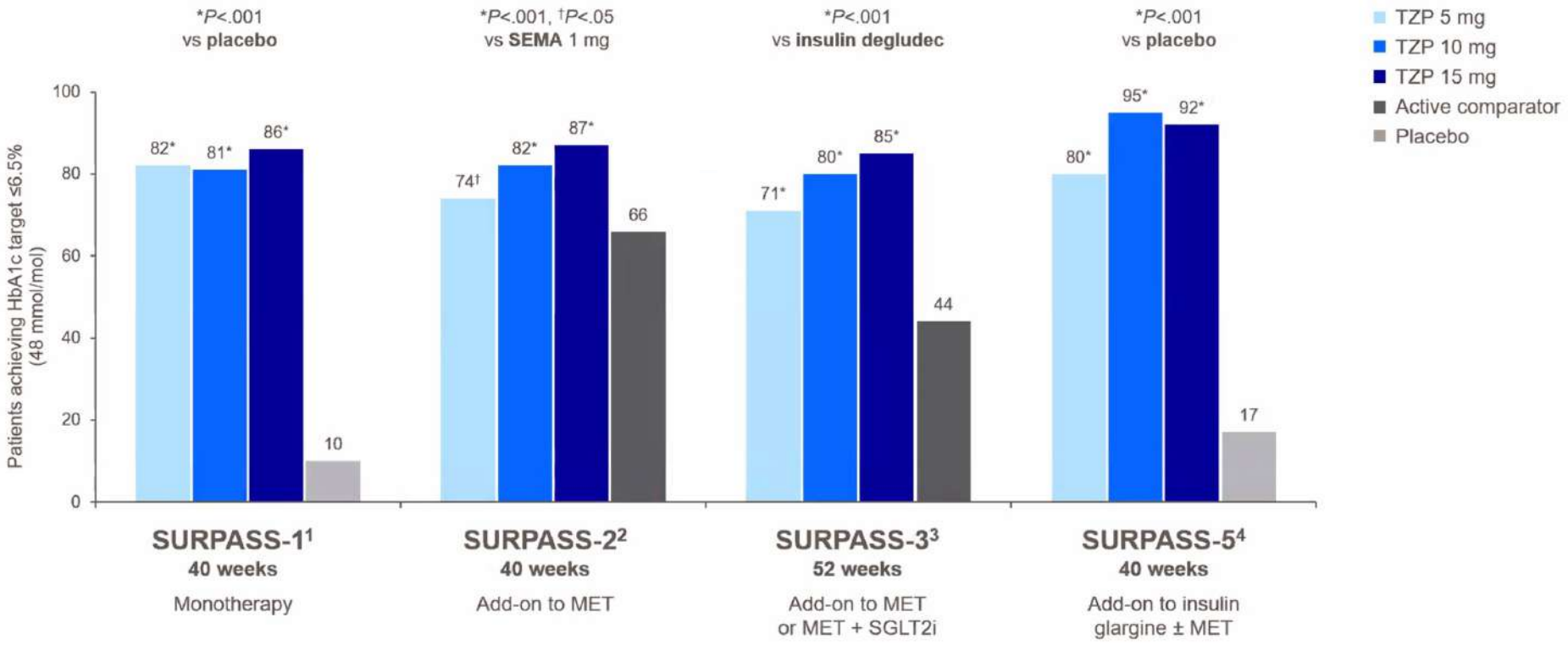
5. Dahl D. et al. *JAMA.* 2022;327(6):534-545 - doi:10.1001/jama.2022.0078

Percentuale di Pazienti che raggiungono HbA1c < 6.5%



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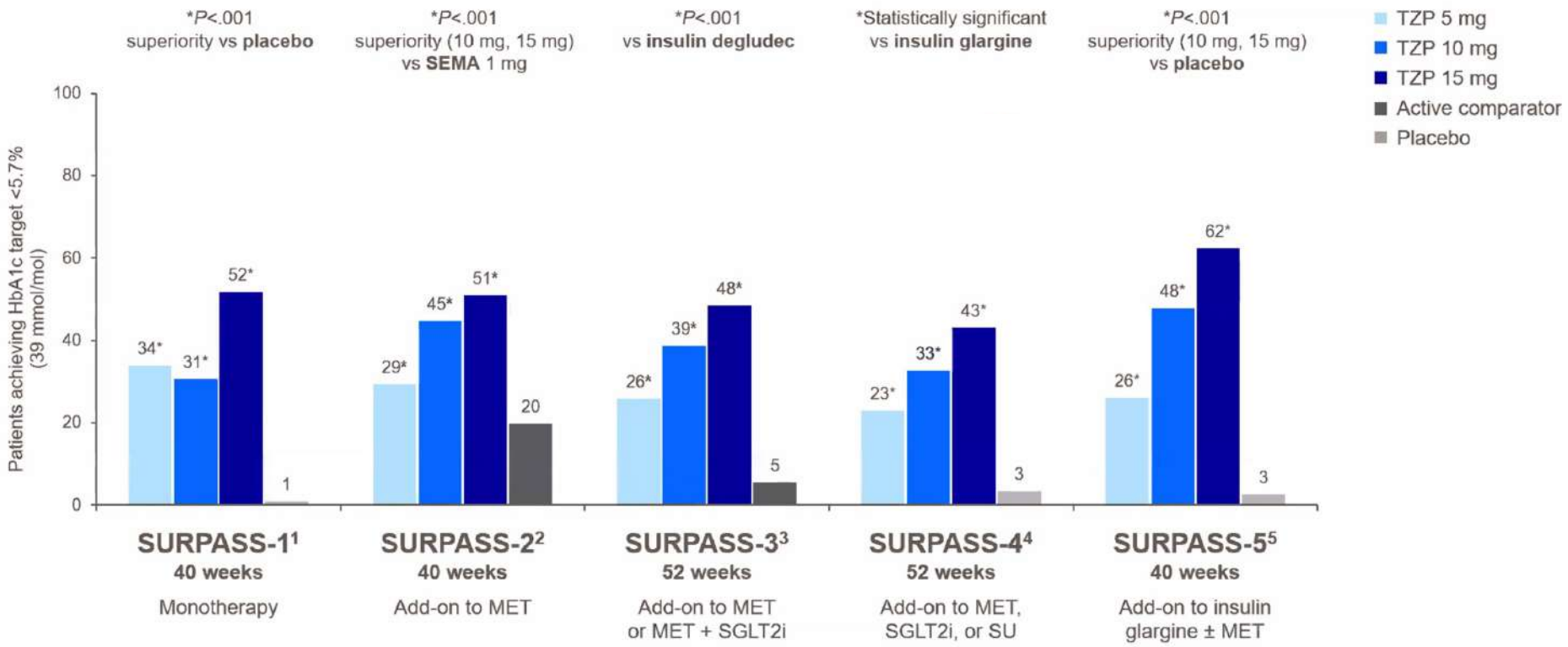
5. Dahl D. et al. *JAMA.* 2022;327(6):534-545 - doi:10.1001/jama.2022.0078

Percentuale di Pazienti che raggiungono HbA1c < 5.7%



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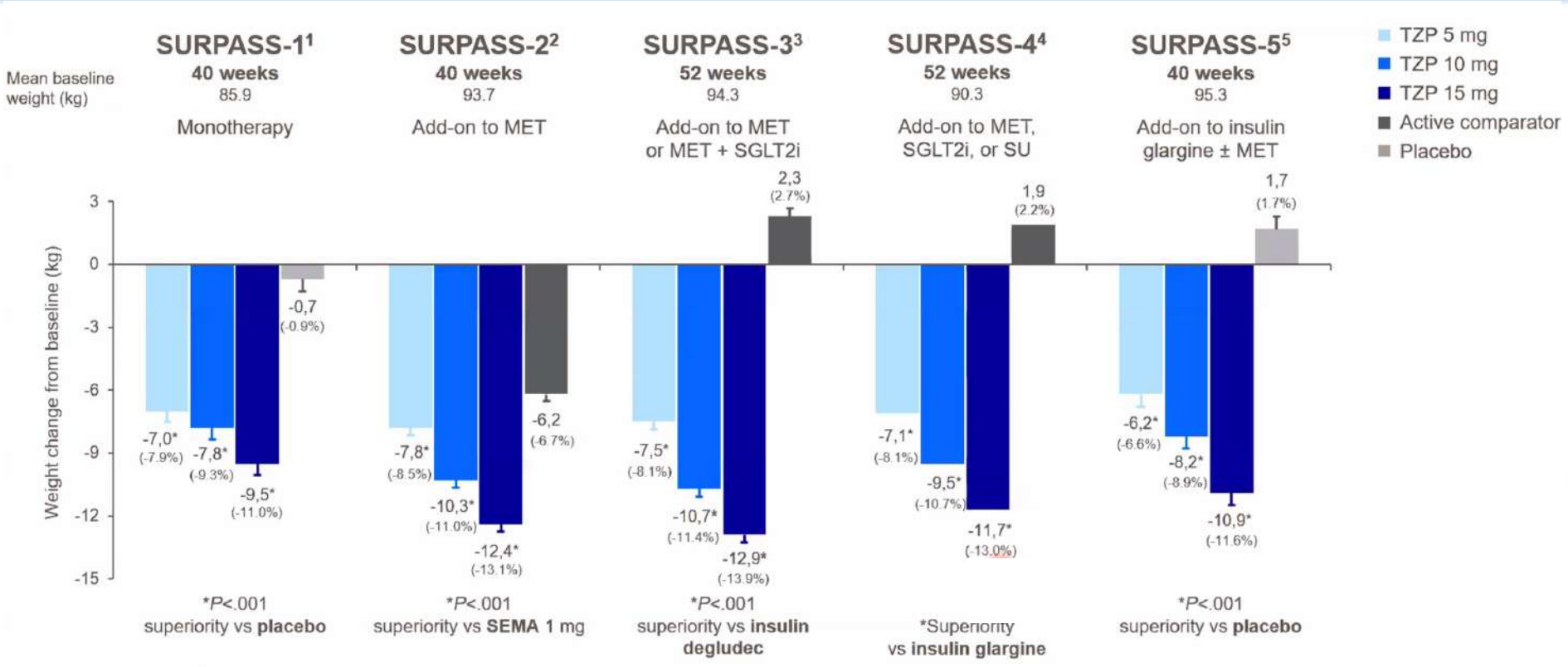
5. Dahl D. et al. *JAMA.* 2022;327(6):534-545 - doi:10.1001/jama.2022.0078

Endpoint Primario: Variazione di Peso Corporeo rispetto al basale



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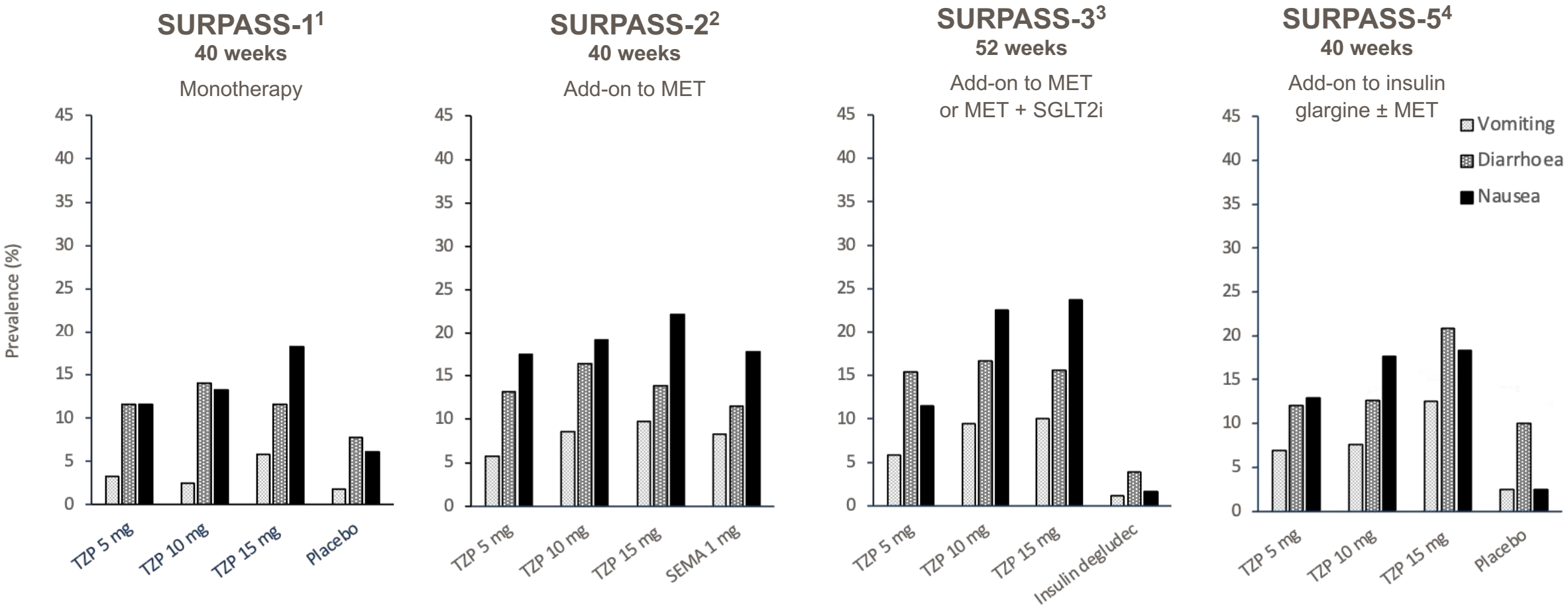
5. Dahl D. et al. *JAMA.* 2022;327(6):534-545 - doi:10.1001/jama.2022.0078

Prevalenza di vomito, diarrea e nausea



- Data are percentage of TEAE with ≥5% frequency in any arm; mITT population (safety analysis set). Note: Patients may be counted in more than 1 category.
- MET = metformin; mITT = modified intent-to-treat; SEMA = semaglutide; SGLT2i = sodium-glucose co-transporter-2 inhibitor; TEAE = treatment-emergent adverse event; TZP = tirzepatide.
- 1. Rosenstock J, et al. Presented at the 81st Scientific Sessions of the ADA. 2021. 2. Frias JP, et al. Presented at the 81st Scientific Sessions of the ADA. 2021. 3. Ludvik B, et al. *Lancet*. 2021; In press. 4. Dahl D, et al. Presented at the 81st Scientific Sessions of the ADA. 2021.

GLP1 RAs e ……..

CLINICAL TRIAL

Effects of Semaglutide on Stroke Subtypes in Type 2 Diabetes: Post Hoc Analysis of the Randomized SUSTAIN 6 and PIONEER 6

W. David Strain, MD; Ofir Frenkel, MD; Martin A. James, FRCP; Lawrence A. Leiter, MD; Søren Rasmussen, PhD; Peter M. Rothwell, FMedSci; Maria Sejersten Ripa, DMSc; Thomas C. Truelsen, TC, DMSc; Mansoor Husain, MD

To examine the pooled effect of s.c. and oral semaglutide on stroke risk, stratified by subtype, in people with T2D at high CV risk, using pooled data from the SUSTAIN 6 and PIONEER 6 trials

Stroke. 2022;53:2749–2757. DOI: 10.1161/STROKEAHA.121.037775

A *post hoc* analysis of stroke data from the SUSTAIN 6 and PIONEER 6 trials

Inclusion criteria

- T2D
- Aged ≥50 years with established CVD*, chronic heart failure, or CKD

or

- ≥60 years with CV risk factors

SUSTAIN 6[1]
N=3,297
Median follow-up: 2.1 years

- OW s.c. semaglutide (0.5 mg or 1 mg)
- Placebo

PIONEER 6[2]
N=3,183
Median follow-up: 15.9 months

- OD oral semaglutide (14 mg)
- Placebo

Pooled analysis

Outcomes

- Effects of semaglutide vs placebo on time to first occurrence of any stroke and stroke subtypes
- Stroke subtypes included:
  - Ischaemic stroke (large artery disease, cardioembolic, small vessel occlusion, other determined aetiology and TOAST aetiology undetermined)
  - Haemorrhagic stroke
  - Stroke subtype unknown

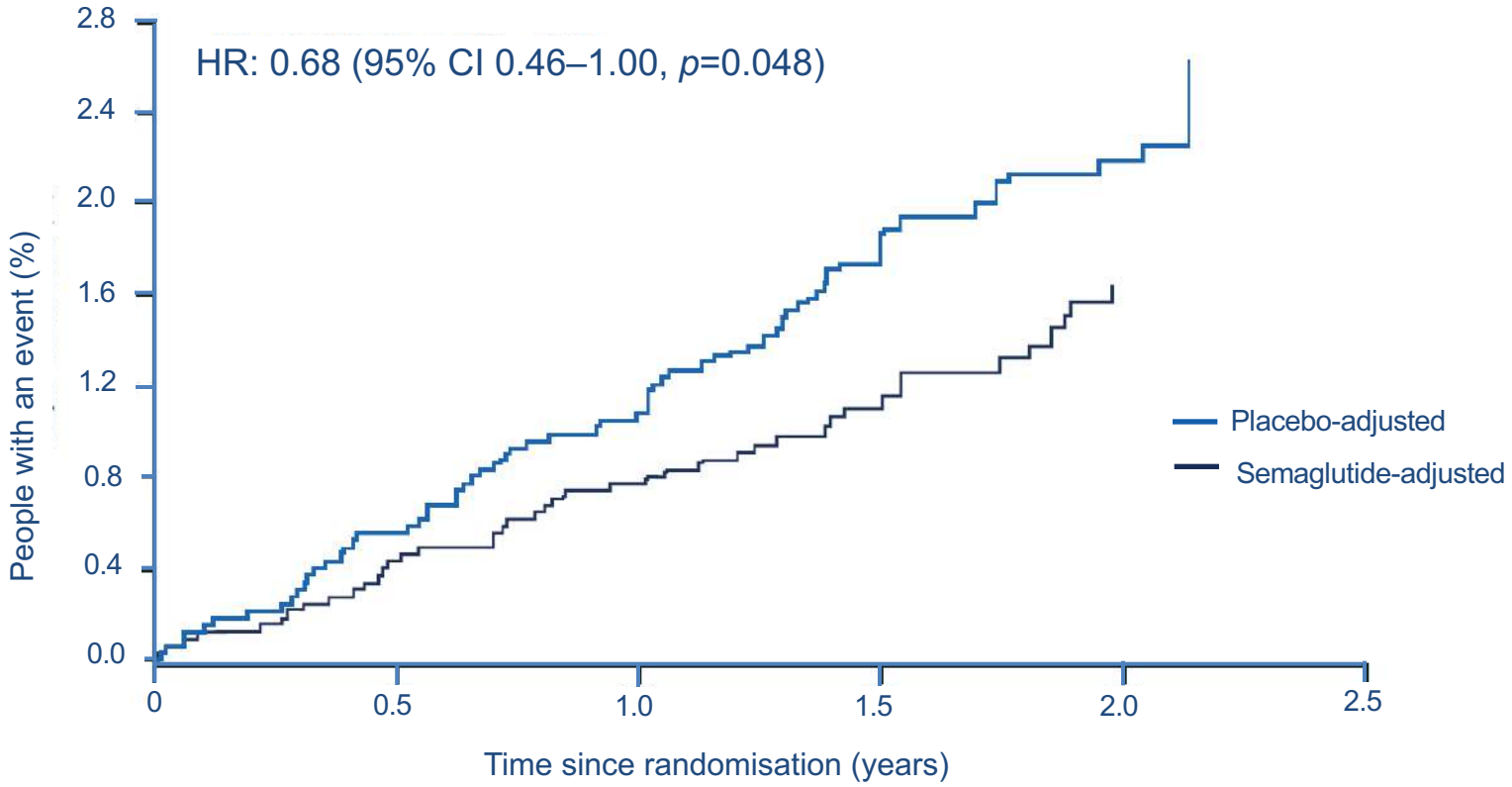
Subgroups

Risk of any stroke was analysed for:

- Overall pooled population
- Prior stroke (yes/no)
- Prior MI (yes/no)
- Prior atrial fibrillation (yes/no)
- Age (< 75 and ≥75 years)
- Sex (female or male)
- SBP (<120, ≥120 and <140, or >140 mmHg)
- eGFR (<60 or ≥60 mL/min/1.73m^2)

- *MI, history of symptomatic coronary heart disease, coronary, carotid or peripheral arterial revascularisation, stroke, transient ischaemic attacks, >50% stenosis of coronary, carotid or lower extremities arteries
- CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; OD, once-daily; OW, once-weekly; SBP, systolic blood pressure; s.c., subcutaneous; TOAST, Trial of Org 10172 in Acute Stroke Treatment; T2D, type 2 diabetes
- 1. Marso et al. N Engl J Med 2016;375:1834–44; 2. Husain et al. N Engl J Med 2019;381:841–51

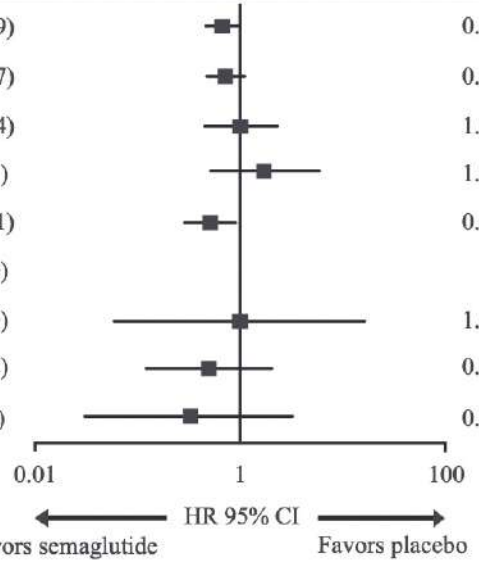
Aalen-Johansen plots for time to first occurrence of any stroke with the pooled semaglutide vs placebo



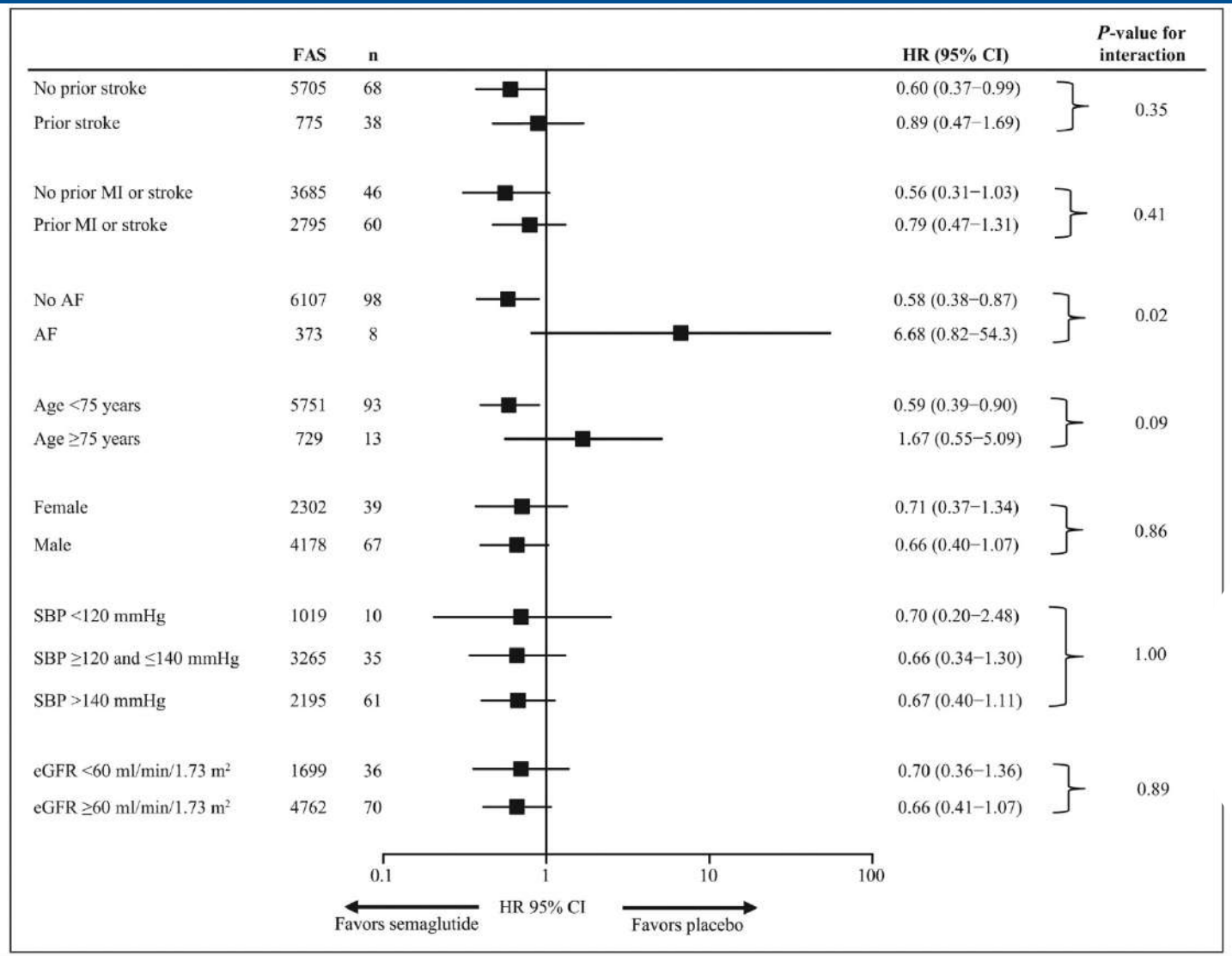
- **Adapted from Figure 1. Semaglutide: N_{events}=43; placebo: N_{events}=63. Aalen-Johansen plots for time to first occurrence of any stroke* with the pooled semaglutide vs placebo in people with T2D at high CV risk, based on pooled data from the SUSTAIN 6 and PIONEER 6 trials. *Included fatal and nonfatal strokes. The cumulative incidence rates for time to first stroke were calculated using Aalen-Johansen method, adjusting for all-cause death as a competing risk. The hazard ratio was estimated from a Cox regression model stratified by trial with treatment (pooled semaglutide vs placebo) as a factor**
- **CI, confidence interval; CV, cardiovascular; HR, hazard ratio; T2D, type 2 diabetes**

Effect of semaglutide vs placebo on risk of any stroke stratified by prior stroke, prior MI or stroke, AF, age, sex, SBP, and eGFR

	n (%)			
	Semaglutide (N=3239)	Placebo (N=3241)	HR (95% CI)	*P*-value
Any stroke	43 (1.3)	63 (1.9)	0.68 (0.46–1.00)	0.048
Ischemic stroke*	39 (1.2)	54 (1.7)	0.72 (0.47–1.08)	0.11
Large artery disease	12 (0.4)	12 (0.4)	1.00 (0.45–2.22)	0.99
Cardioembolic	7 (0.2)	4 (0.1)	1.74 (0.51–5.95)	0.38
Small vessel occlusion	19 (0.6)	37 (1.1)	0.51 (0.29–0.89)	0.017
Other determined aetiology	0 (0.0)	0 (0.0)	N/A	N/A
TOAST etiology undetermined†	1 (0.0)	1 (0.0)	1.00 (0.06–15.9)	1.00
Hemorrhagic stroke	3 (0.1)	6 (0.2)	0.50 (0.12–1.99)	0.32
Stroke subtype unknown	1 (0.0)	3 (0.1)	0.33 (0.03–3.20)	0.34



Effect of semaglutide vs placebo on risk of any stroke stratified by prior stroke, prior MI or stroke, AF, age, sex, SBP, and eGFR



Conclusions

- Semaglutide **reduced** the **risk of any stroke** compared with placebo in people with T2D at high CV risk, an effect that appeared to be mediated mainly through **a significant reduction in risk of small vessel occlusion**

- Compared with placebo, treatment with semaglutide **lowered the risk of stroke irrespective of prior stroke**

GLP1RAs e Rene

Volume 394, Issue 10193, 13–19 July 2019, Pages 131-138

Articles

Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial

Prof Hertzel C Gerstein MD [a], Prof Helen M Colhoun MD [b], Prof Gilles R Dagenais MD [c], Rafael Diaz MD [d], Mark Lakshmanan MD [e], Prof Prem Pais MD [f], Prof Jeffrey Probstfield MD [g], Fady T Botros PhD [e], Prof Matthew C Riddle MD [h], Prof Lars Rydén MD [i], Prof Denis Xavier MD [f], Charles Messan Atisso PhD [e], Leanne Dyal MSc [a], Stephanie Hall BA [a], Purnima Rao-Melacini MSc [a], Gloria Wong BSc [a], Prof Alvaro Avezum MD [j], Prof Jan Basile MD [k], Prof Namsik Chung MD [l], Ignacio Conget MD [m] … William Zigrang

Long-term use of dulaglutide was associated with reduced composite renal outcomes in people with type 2 diabetes.

GLP1RAs e Rene

Volume 6, Issue 8, August 2018, Pages 605-617

Articles

Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial

Prof Katherine R Tuttle MD [a], Mark C Lakshmanan MD [b], Prof Brian Rayner PhD [c], Robert S Busch MD [d], Alan G Zimmermann PhD [b, †], D Bradley Woodward MD [b], Fady T Botros PhD [b]

In patients with type 2 diabetes and moderate-to-severe chronic kidney disease, once-weekly dulaglutide produced glycaemic control similar to that achieved with insulin glargine, with reduced decline in eGFR. Dulaglutide seems to be safe to use to achieve glycaemic control in patients with moderate-to-severe chronic kidney disease.

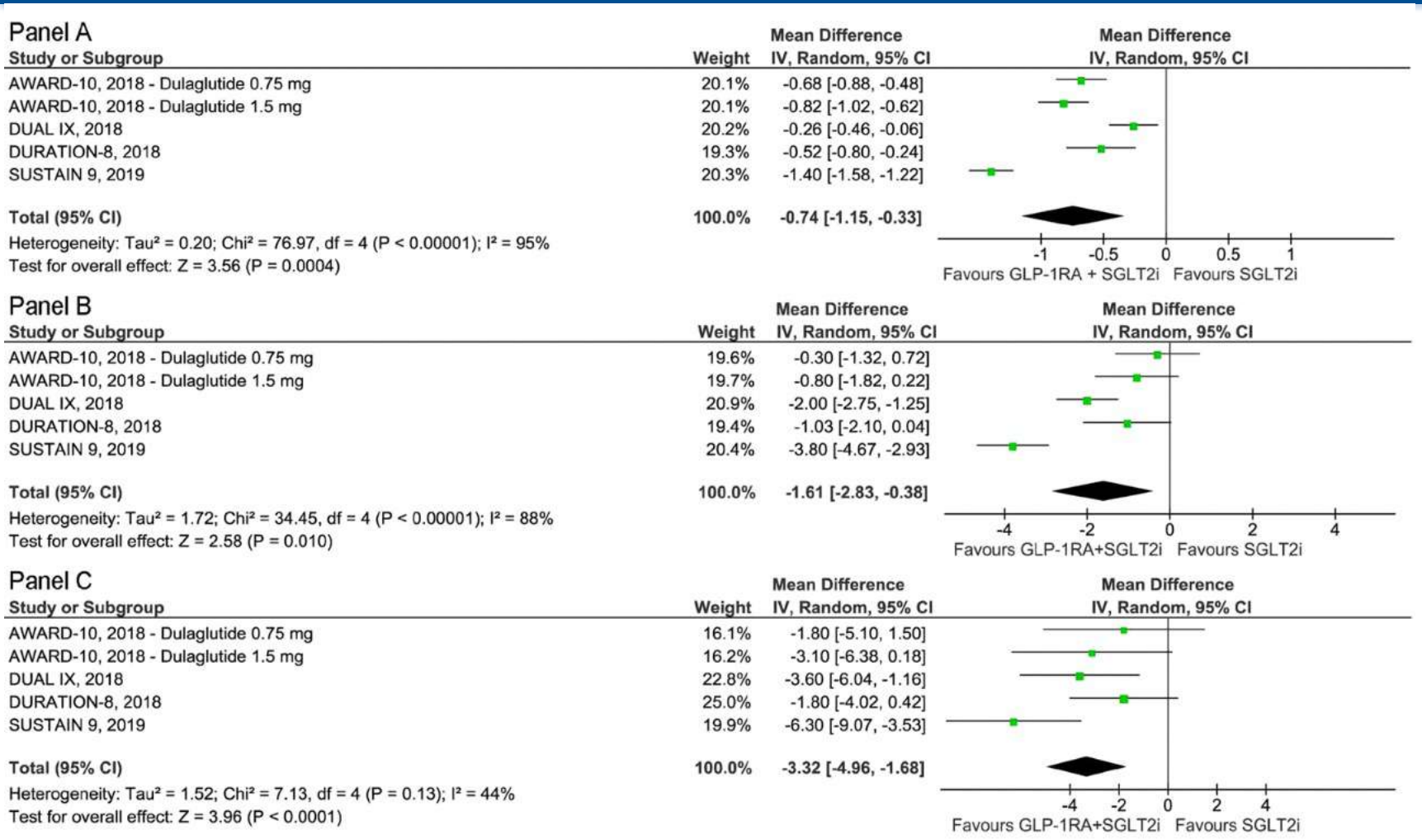
GLP1 RAs + SGLT2i

Efficacy and safety of GLP-1 receptor agonists as add-on to SGLT2 inhibitors in type 2 diabetes mellitus: A meta-analysis

Marco Castellana, Angelo Cignarelli, Francesco Brescia, Sebastio Perrini, Annalisa Natalicchio, Luigi Laviola & Francesco Giorgino*

Scientific RepoRtS | (2019) 9:19351 | https://doi.org/10.1038/s41598-019-55524-w

GLP1 RAs + SGLT2i



Forest plots of meta-analysis for change in HbA1c (panel A), body weight (panel B), and systolic blood pressure (panel C) from baseline to the last available follow-up

In patients with inadequately controlled type 2 diabetes mellitus, the addition of GLP-1RA to SGLT2i proved to be effective on HbA1c, body weight, SBP, and lipid profile. The chance of achieving HbA1c < 7% is increased, with no further risk of hypoglycemia.

Scientific RepoRtS | (2019) 9:19351 | https://doi.org/10.1038/s41598-019-55524-w

GLP1 RAs e Neuroprotezione

Glucagon-Like Peptide-1: A Focus on Neurodegenerative Diseases

*Maddalena Grieco[1], Alessandra Giorgi[1], Maria Cristina Gentile[2], Maria d'Erme[1], Susanna Morano[2], Bruno Maras[1] and Tiziana Filardi[2]**

[1] Department of Biochemical Sciences, Faculty of Pharmacy and Medicine, Sapienza University of Rome, Rome, Italy,
[2] Department of Experimental Medicine, Faculty of Medicine and Dentistry, Sapienza University of Rome, Rome, Italy

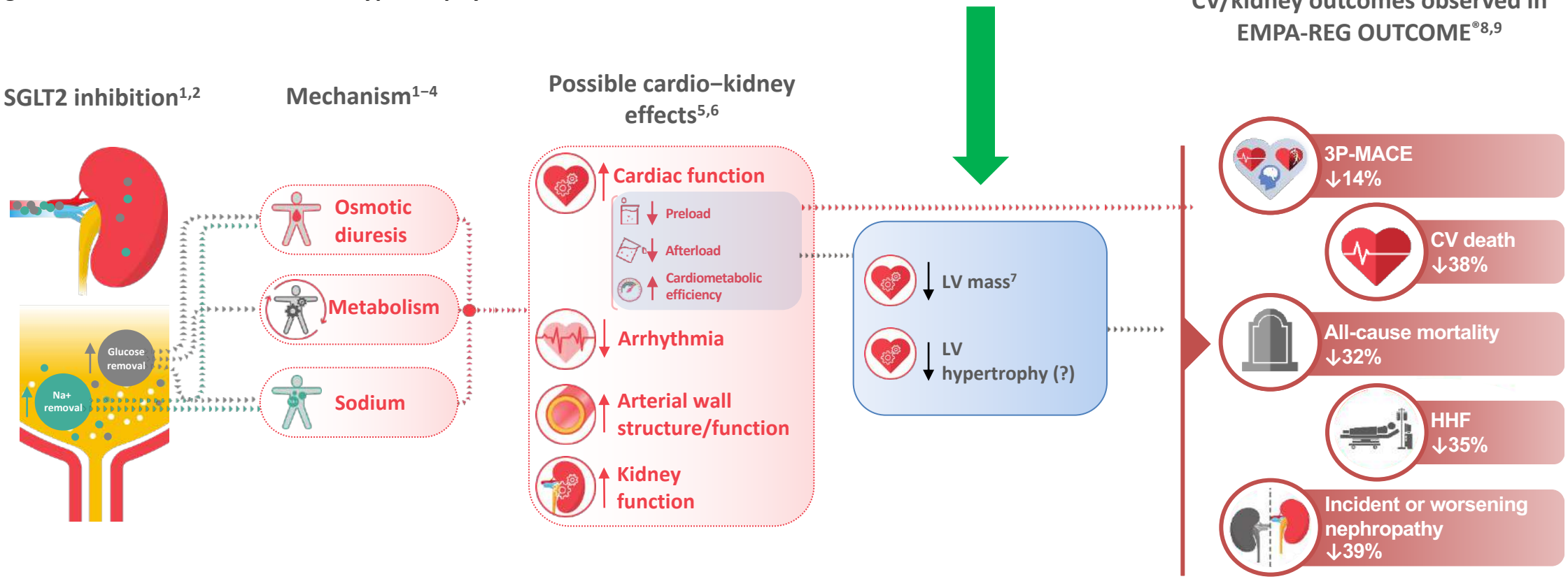
Modulation of GLP-1 activity can influence amyloid β peptide aggregation in Alzheimer's disease and dopamine levels in Parkinson's disease.

GLP-1 receptor agonists (GLP-1RAs) showed beneficial actions on brain ischemia in animal models, such as the reduction of cerebral infarct area and the improvement of neurological deficit, acting mainly through inhibition of oxidative stress, inflammation, and apoptosis.

MINI REVIEW published: 18 October 2019 doi: 10.3389/fnins.2019.01112

SGLT2 i e Protezione Cardio Renale

Empagliflozin decreased LV mass and hypertrophy, and increased cardiac function



CV, cardiovascular; LV, left ventricular; SGLT2, sodium-glucose co-transporter-2

1. Heise T *et al.* Diabetes *Obes Metab* 2013;15:613; 2. Heise T *et al. Clin Ther* 2016;38:2265; 3. Ferrannini G *et al. Diabetes Care* 2015;38:1730; 4. Briand F *et al. Diabetes* 2016;65:2032; 5. Heerspink HJ *et al. Circulation* 2016;134:752; 6. Inzucchi S *et al. Diab Vasc Dis Res* 2015;12:90; 7. Verma S *et al. AHA* 2018; oral presentation; 8. Zinman B *et al. N Engl J Med* 2015;373:2117; 9. Wanner C *et al. N Engl J Med* 2016;375:323

SGLT2 i e Protezione Cardio Renale

	EMPA-REG OUTCOME (Empagliflozin)	**CANVAS program** (Canagliflozin)	**DECLARE-TIMI58** (Dapagliflozin)	**VERTIS-CV** (Ertugliflozin)
3P-MACE non-inferiority	✓	✓	✓	✓
3P-MACE Superiority	**HR 0.86 [CI: 0.74 - 0.99] RRR: 14 %**	**HR 0.86 [CI: 0.75 - 0.97] RRR: 14 %**	HR 0.93 [CI: 0.84 - 1.03]	Not tested for superiority
CV death or hHF	**HR: 0.66* [CI: 0.55 – 0.79] RRR: 34 %**	**HR 0.72 [CI: 0.55 - 0.94] RRR: 28 %**	**HR 0.83 [CI: 0.73 - 0.95] RRR: 17 %**	HR 0.88 [CI: 0.75 – 1.03]
CV death	**HR: 0.62* [CI: 0.49 - 0.77] RRR: 38 %**	HR 0.87 [CI: 0.72 -1.06]	HR 0.98 [CI: 0.82 - 1.17]	HR 0.92 [CI: 0.77 - 1.11]
hHF	**HR: 0.65* [CI: 0.50 - 0.85] RRR: 35 %**	**HR 0.67 [CI: 0.52 - 0.87] RRR: 33 %**	**HR 0.73 [CI: 0.61 – 0.88] RRR: 27 %**	**HR 0.70 [CI: 0.54 – 0.90] RRR: 30 %**
Renal Composite (most comparable)	**HR: 0.54 [CI: 0.40 – 0.75] RRR: 36 %**	**HR 0.59* [CI: 0.44 - 0.79] RRR: 41 %**	**HR 0.53 [CI: 0.43 – 0.66] RRR: 47 %**	HR 0.81 [CI: 0.63 – 01.04] Did not include Albuminuria
All-Cause mortality	**HR: 0.68* [CI: 0.57 – 0.82] RRR: 32 %**	HR 0.87 [CI: 0.74 - 1.01]	HR 0.93 [CI: 0.82 – 1.04]	N/A

Primary and Co-primary endpoints are in cursive. Statistically significant endpoints are in bold. Due to differences in study design, inclusion criteria and study population direct comparison can and should not be drawn between trials but are purely illustrative.

Zinman et al. 2015; Neal B et al. 2017; Wiviott SD *et al.* 2018; Cannon N Engl J Med 2020;383:1425-35

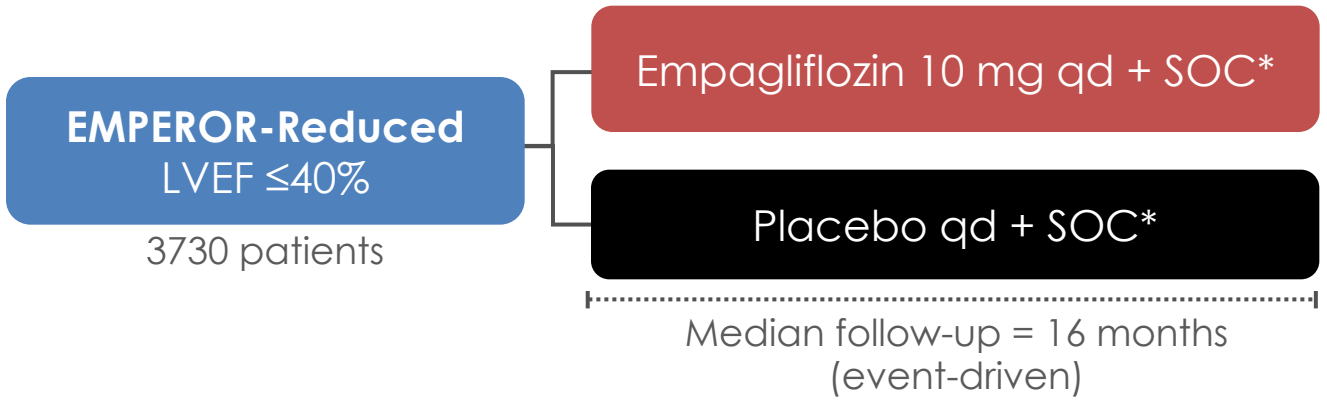
EMPEROR- Reduced

Phase III randomised double-blind placebo-controlled trial

Aim: To investigate the safety and efficacy of empagliflozin versus placebo on top of guideline-directed medical therapy in patients with HF with **reduced ejection fraction**

Population: T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV)

Study design[1–3]



Confirmatory endpoints[1,2]

COMPOSITE PRIMARY ENDPOINT

Time to first event of adjudicated CV death or adjudicated HHF

SECONDARY ENDPOINTS

- **First and recurrent adjudicated HHF events**
- **eGFR slope: change from baseline**

*Guideline-directed medical therapy

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; qd, once daily; SOC, standard of care; T2D, type 2 diabetes; eGFR Slope = rate of decline, a measure for long-term renal function;

1. ClinicalTrials.gov. NCT03057977 (accessed Aug 2020); 2. Packer M *et al. Eur J Heart Fail* 2019;21:1270; 3. Packer M et al. New England Journal of Medicine 2020 DOI: 10.1056/NEJMoa2022190

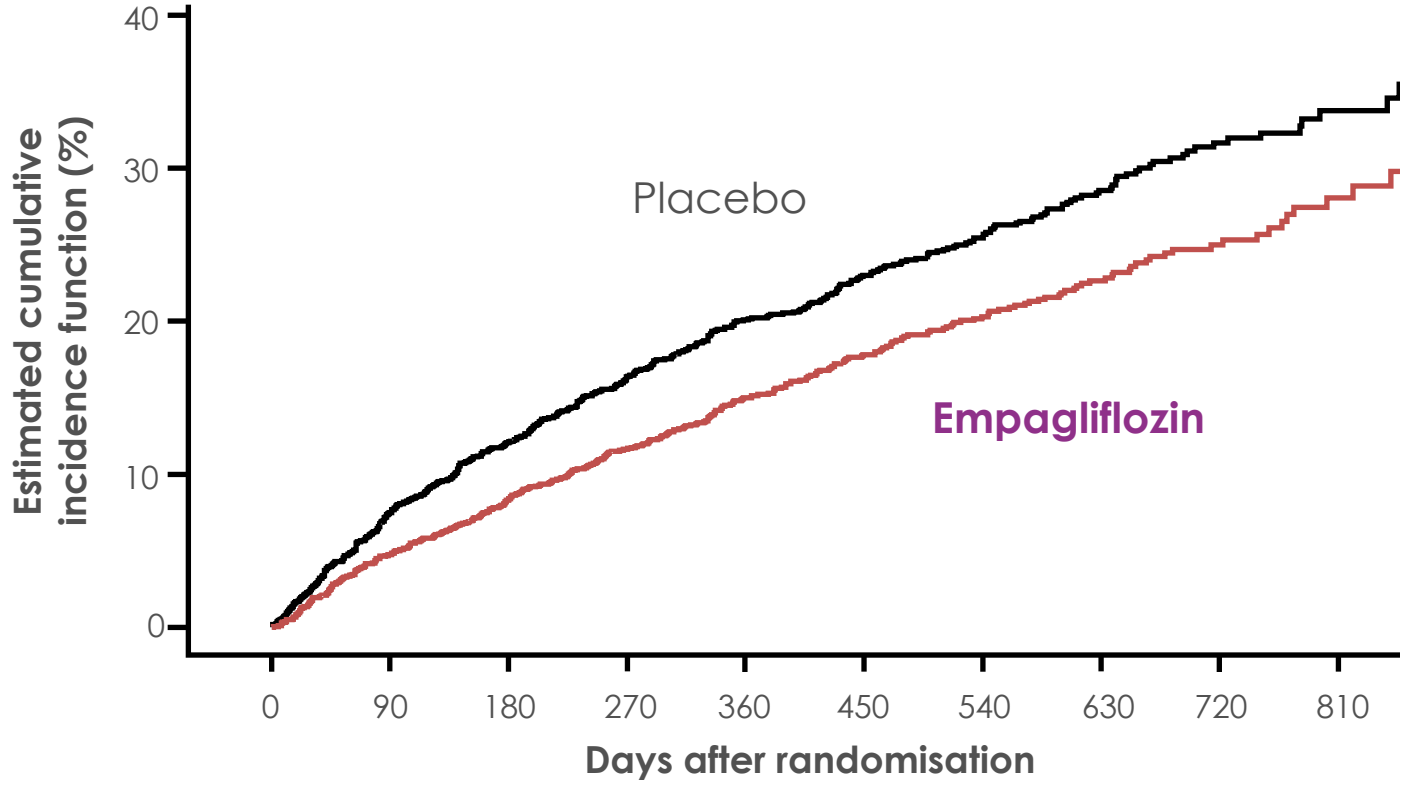
Specific endpoints for hierarchical testing

	EMPEROR-Reduced
	Primary endpoint*: Adjudicated CV death or heart failure hospitalisation
	Key secondary endpoint**: Adjudicated first and recurrent heart failure hospitalisations
	Key secondary endpoint***: eGFR slope

The primary outcome and the first two secondary outcomes were included in a hierarchical testing procedure, as described in the Statistical Analysis section. *The primary outcome was a composite of adjudicated cardiovascular death or hospitalization for heart failure, analyzed as the time to the first event. **The first secondary outcome was the occurrence of all adjudicated hospitalizations for heart failure, including first and recurrent events. ***The second secondary outcome was the rate of the decline in the estimated GFR during double-blind treatment.

Packer M et al. New England Journal of Medicine 2020 DOI: 10.1056/NEJMoa2022190

Primary endpoint: First adjudicated CV death or hospitalisation for heart failure



Patients at risk										
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

RRR 25%

NNT = 19

HR 0.75
(95% CI 0.65, 0.86)
p<0.001

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

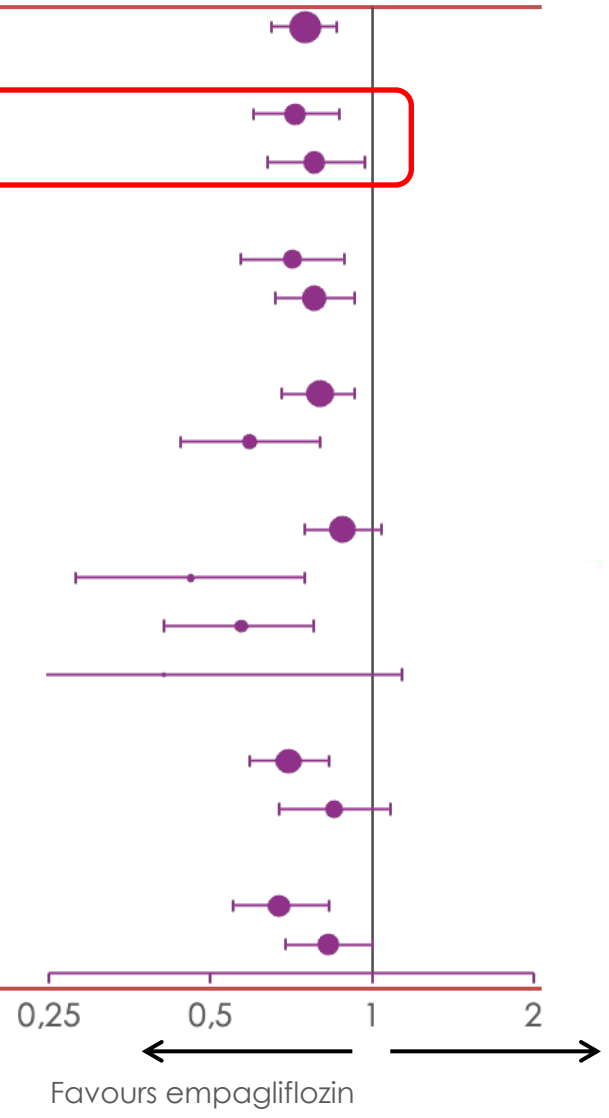
Placebo:
462 patients with event
Rate: 21.0/100 patient-years

Cox regression model including covariates age, baseline eGFR, geographic region, baseline diabetes status, sex, LVEF and treatment.
LVEF, left ventricular ejection fraction; RRR, relative risk reduction; NNT: Number needed to treat

Packer M et al. New England Journal of Medicine 2020 DOI: 10.1056/NEJMoa2022190

Subgroups: Primary endpoint

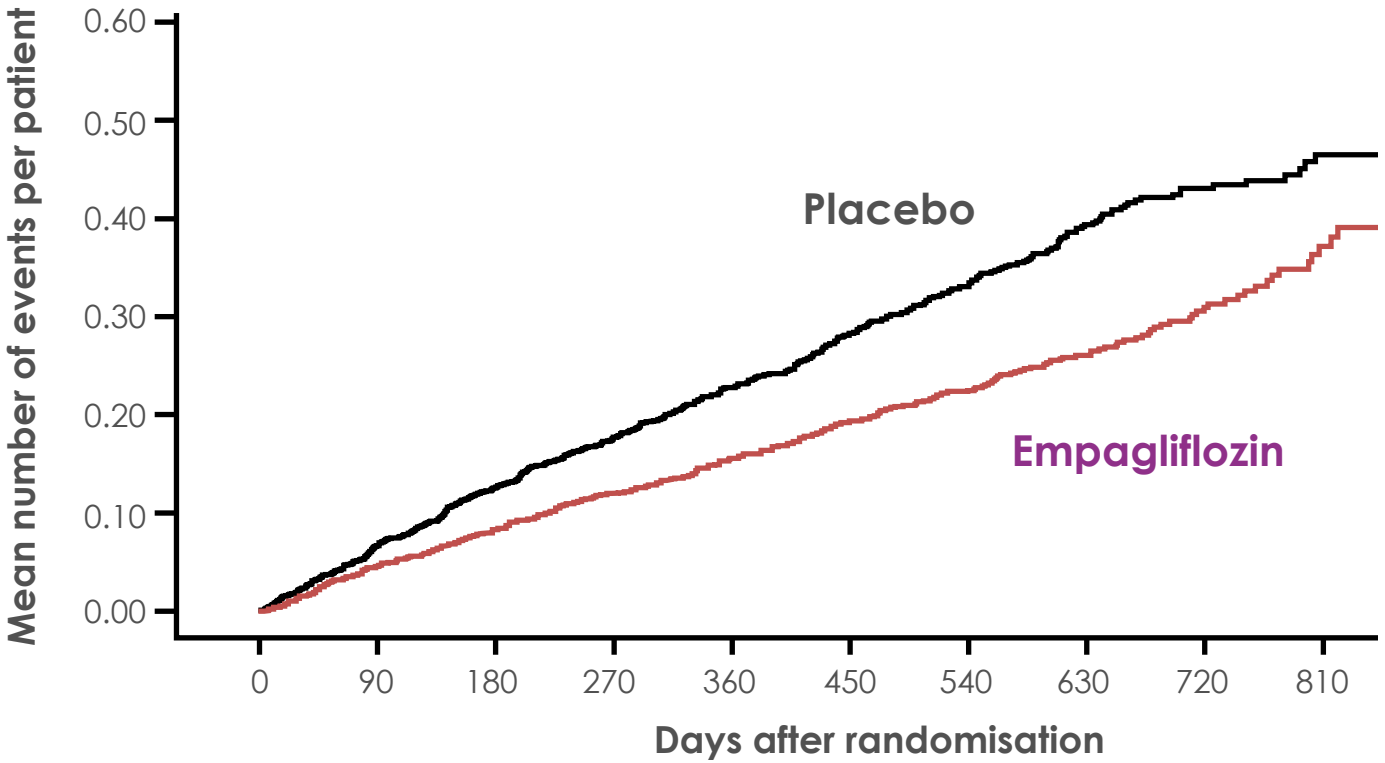
	Empagliflozin 10 mg	Placebo		
	n with event/N analysed		HR (95% CI)	HR (95% CI)
Overall	361/1863	462/1867	0.75 (0.65, 0.86)	
Baseline diabetes status				
Diabetic	200/927	265/929	**0.72 (0.60, 0.87)**	
Non-diabetic	161/936	197/938	**0.78 (0.64, 0.97)**	
Age, years				
<65	128/675	193/740	0.71 (0.57, 0.89)	
≥65	233/1188	269/1127	0.78 (0.66, 0.93)	
Sex				
Male	294/1426	353/1411	0.80 (0.68, 0.93)	
Female	67/437	109/456	0.59 (0.44, 0.80)	
Race				
White	264/1325	289/1304	0.88 (0.75, 1.04)	
Black/African-American	24/123	48/134	0.46 (0.28, 0.75)	
Asian	62/337	99/335	0.57 (0.41, 0.78)	
Other	5/51	14/63	0.41 (0.15, 1.14)	
Baseline BMI				
<30	226/1263	322/1300	0.70 (0.59, 0.83)	
≥30	135/600	140/567	0.85 (0.67, 1.08	
Baseline eGFR (CKD-EPI), ml/min/1.73 m²				
≥60	159/969	224/960	0.67 (0.55, 0.83)	
<60	202/893	237/906	0.83 (0.69, 1.00)	



CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Packer M et al. New England Journal of Medicine 2020 DOI: 10.1056/NEJMoa2022190

Key secondary: Adjudicated total hospitalisations for heart failure (first and recurrent)



Patients at risk										
Placebo	1867	1820	1762	1526	1285	1017	732	497	275	135
Empagliflozin	1863	1826	1768	1532	1283	1008	732	495	272	118

RRR 30%

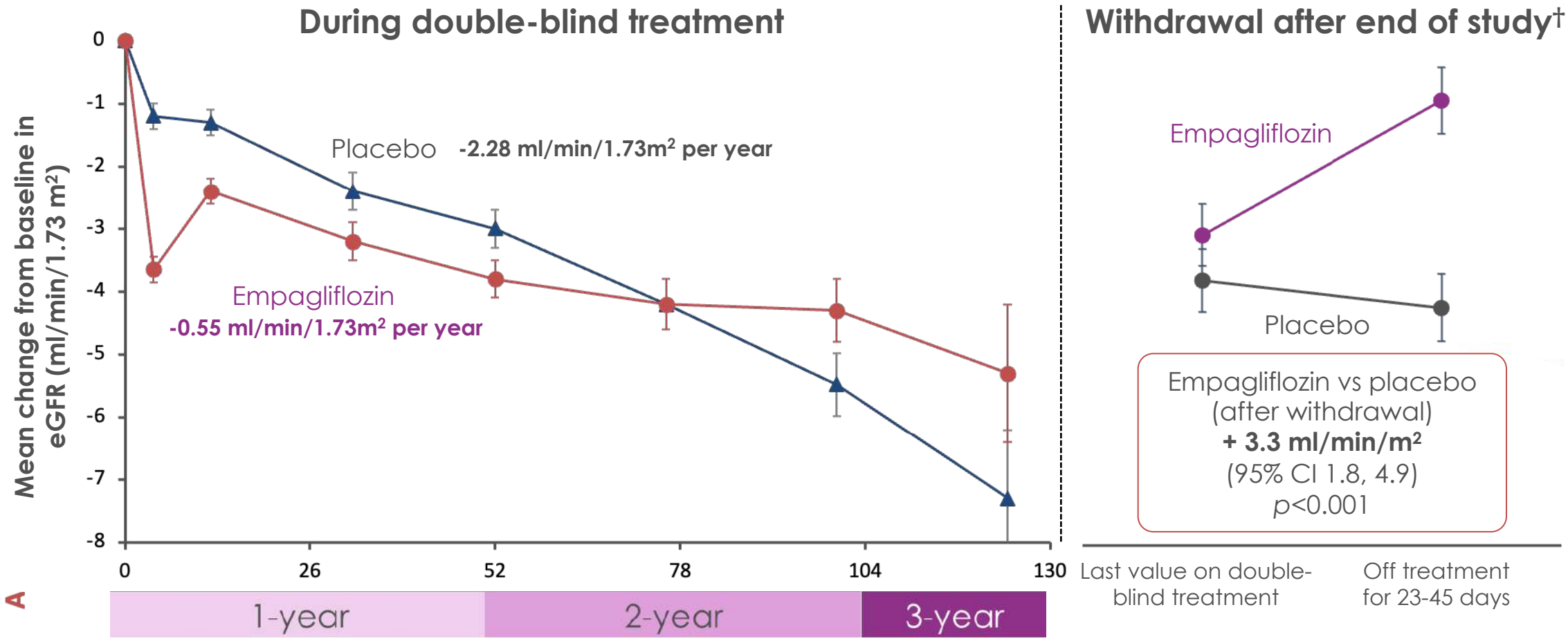
HR 0.70
(95% CI 0.58, 0.85)
p<0.001

Emagliflozin: 388 events
Placebo: 553 events

Analysis of first and recurrent HHF accounting for CV death as terminal event using a joint frailty model. Model includes covariates age, baseline eGFR, treatment, region, baseline diabetes status, sex, and baseline LVEF, estimated dependence between adjudicated HHF and adjudicated CV death, and variance of frailty; LVEF, left ventricular ejection fraction

Packer M et al. New England Journal of Medicine 2020 DOI: 10.1056/NEJMoa2022190

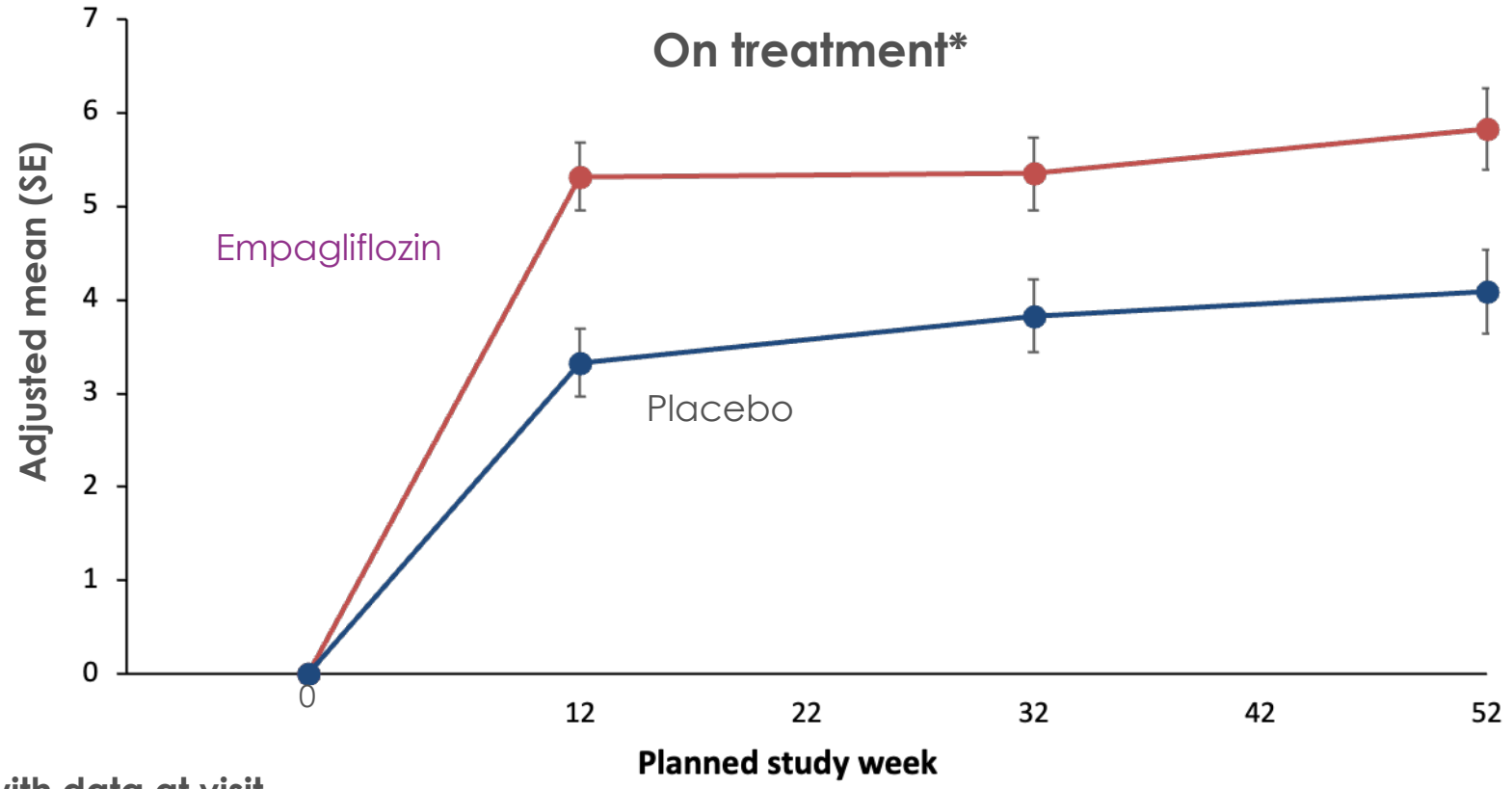
Change in eGFR* from baseline



MMRM includes age and baseline eGFR(CKD-EPI)cr as linear covariates and baseline score by visit, visit by treatment, sex, region, baseline LVEF, week reachable and baseline diabetes as fixed effects. *(CKD-EPI); †Analysis was performed in 966 patients with paired data. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; LVEF, left ventricular ejection fraction; MMRM, mixed model repeated measures.

Packer M et al. New England Journal of Medicine 2020 DOI: 10.1056/NEJMoa2022190

Quality of life: KCCQ-CSS at 52 weeks



Change from baseline (95% CI) at Week 52

Empagliflozin: **5.8 ± 0.4**
Placebo: **4.1 ± 0.4**

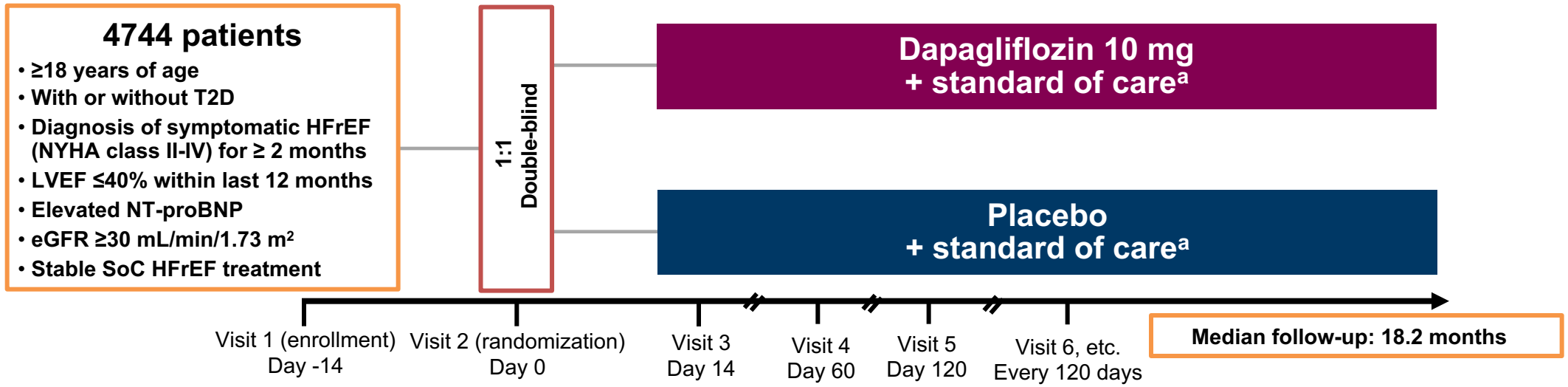
Absolute difference
1.7
(95% CI 0.5, 3)
p=0.0058

N with data at visit

Placebo	1701	1688	1505	1151
Empagliflozin	1734	1720	1561	1176

All models include covariates age, baseline eGFR, region, baseline diabetes status, sex and baseline LVEF
*No imputation for death; KCCQ-CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LVEF, left ventricular ejection fraction
1. Packer M et al. New England Journal of Medicine 2020 DOI: 10.1056/NEJMoa2022190

Assessing Dapagliflozin in Patients with Chronic HFrEF With or Without T2D[1,2]



Primary Endpoint

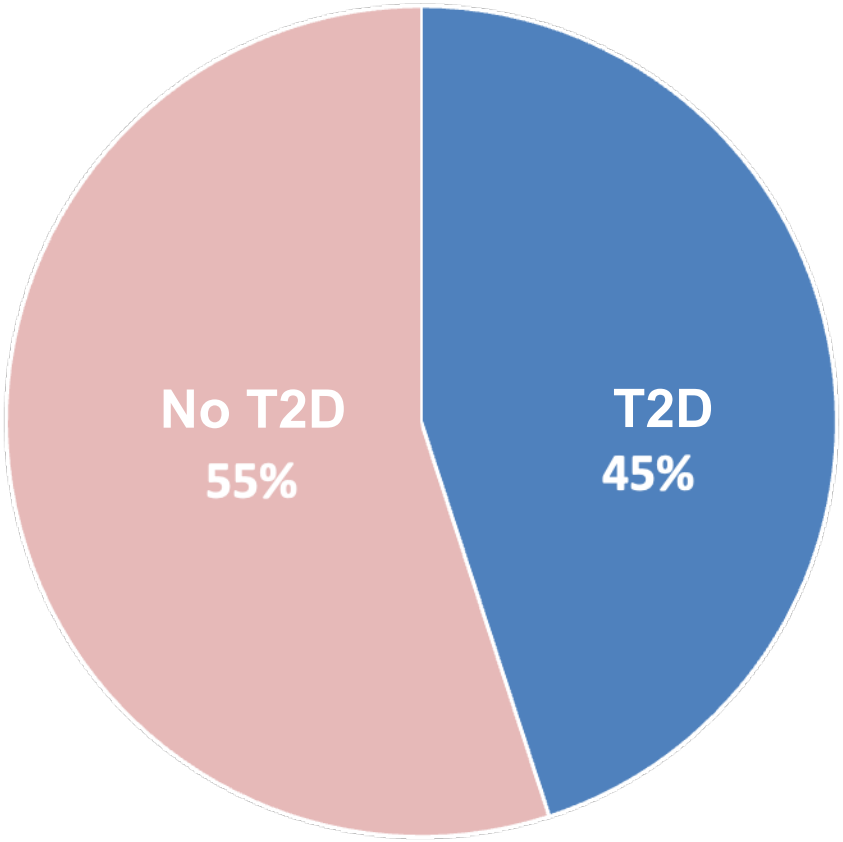
- Time to first occurrence of any of the components of the composite: CV death or hHF or an urgent HF visit

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/1.73m², 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. Article and study protocol. *N Engl J Med*. 2019;381:1995-2008.

Majority of Patients in DAPA-HF Did Not Have Type 2 Diabetes



N=4744

No T2D (n=2605)

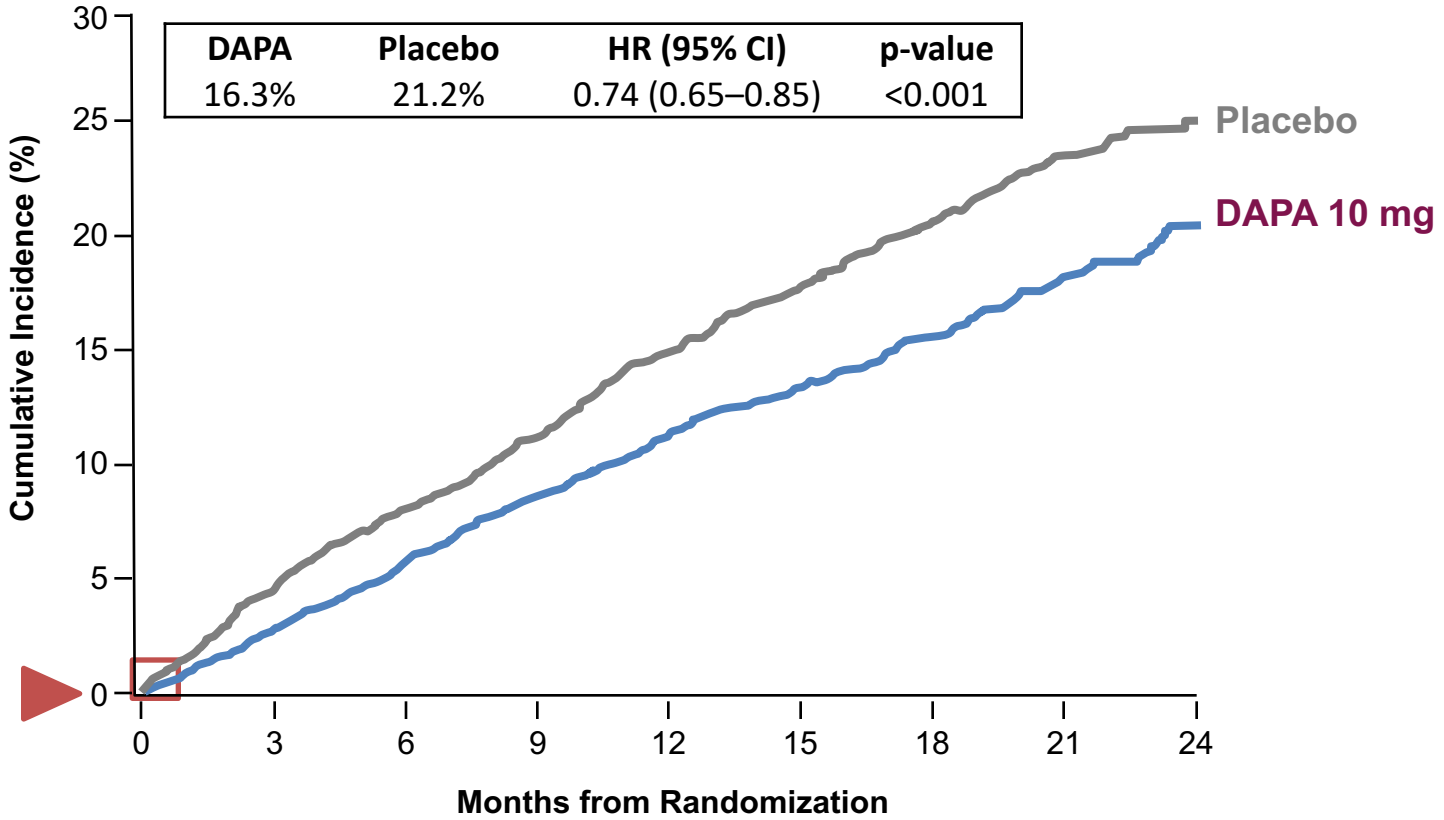
- Normal HbA1c (HbA1c <5.7% at Visits 1 and 2): n=839; 17.7%
- Prediabetes (HbA1c ≥5.7-<6.5% at Visit 1 or 2): n=1748; 36.8%
- HbA1c single measurement <5.7% or not available: n=18; 0.4%

T2D (n=2139)

- Pre-existing diagnosis of T2D: n=1983; 41.8%
- Previously undiagnosed T2D (HbA1c ≥6.5% at Visits 1 and 2): n=156; 3.3%

- HbA1c = glycated hemoglobin; T2D = type 2 diabetes.
- Petrie MC et al. *JAMA*. 2020;323:1353-1368.

Primary Endpoint: CV Death or hHF or an Urgent HF Visit[1,2]



26% RRR

4.9% ARR

NNT=21

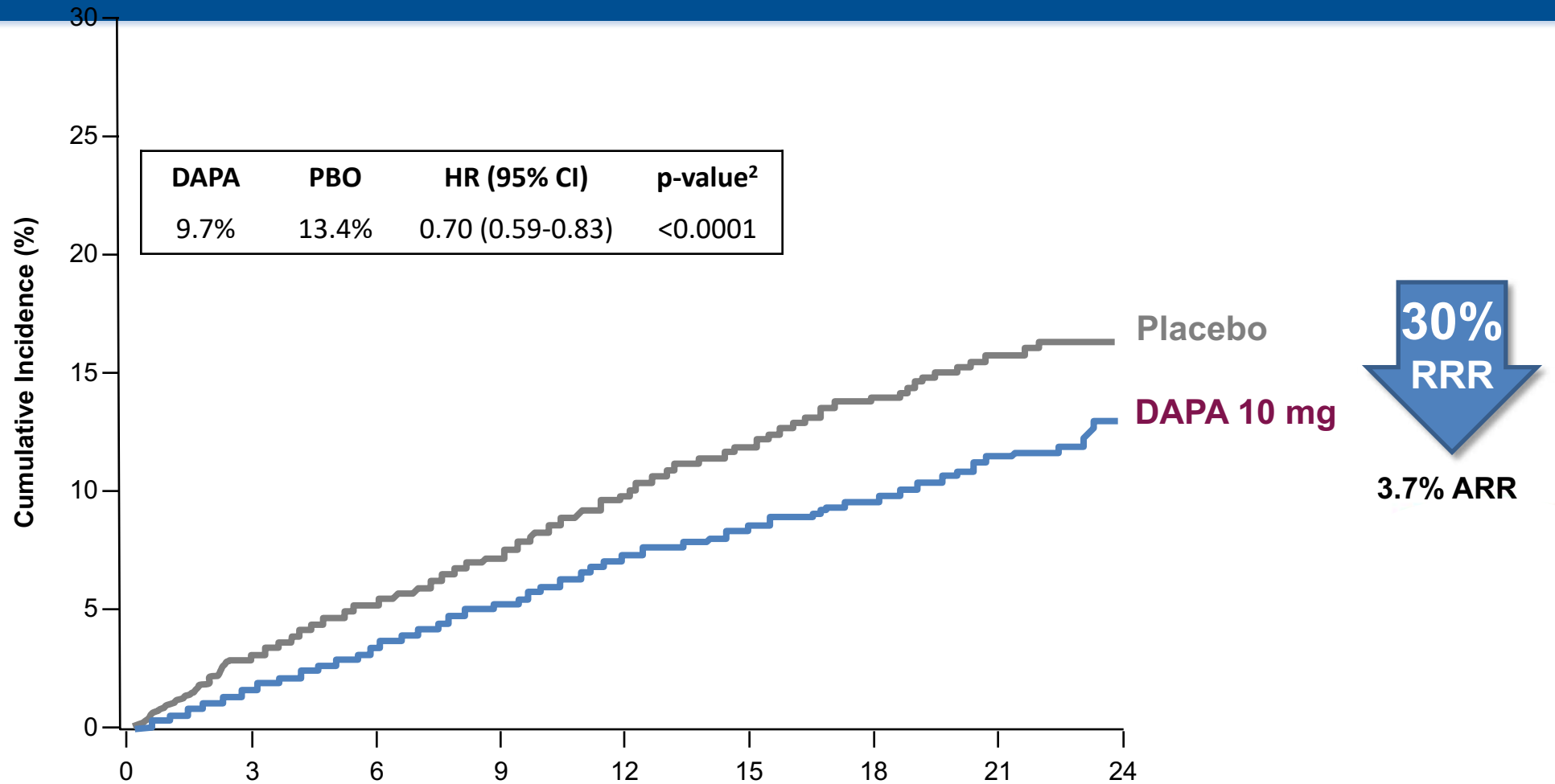
Number at Risk

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

- 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. Berg DD et al. *JAMA Cardiol*. 2021;6:499-507.

Hospitalization for Heart Failure (hHF)[1]

DAPA	PBO	HR (95% CI)	p-value[2]
9.7%	13.4%	0.70 (0.59-0.83)	<0.0001



Number at Risk									
DAPA 10 mg	2373	2306	2223	2153	2007	1563	1147	613	210
Placebo	2371	2264	2168	2082	1924	1483	1101	596	212

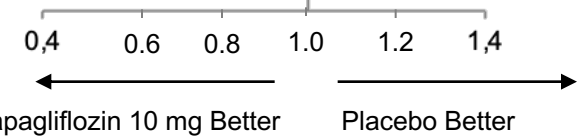
- ARR = absolute risk reduction; DAPA = dapagliflozin; HR = hazard ratio; PBO = placebo; RRR = relative risk reduction.
- 1. McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008; 2. Docherty KF et al. *Circulation*. 2020;142:1623-1632.

Primary Outcome by Diabetes Status[1]

Dapagliflozin significantly reduced the primary endpoint, regardless of diabetes status and HbA1c in the no T2D group

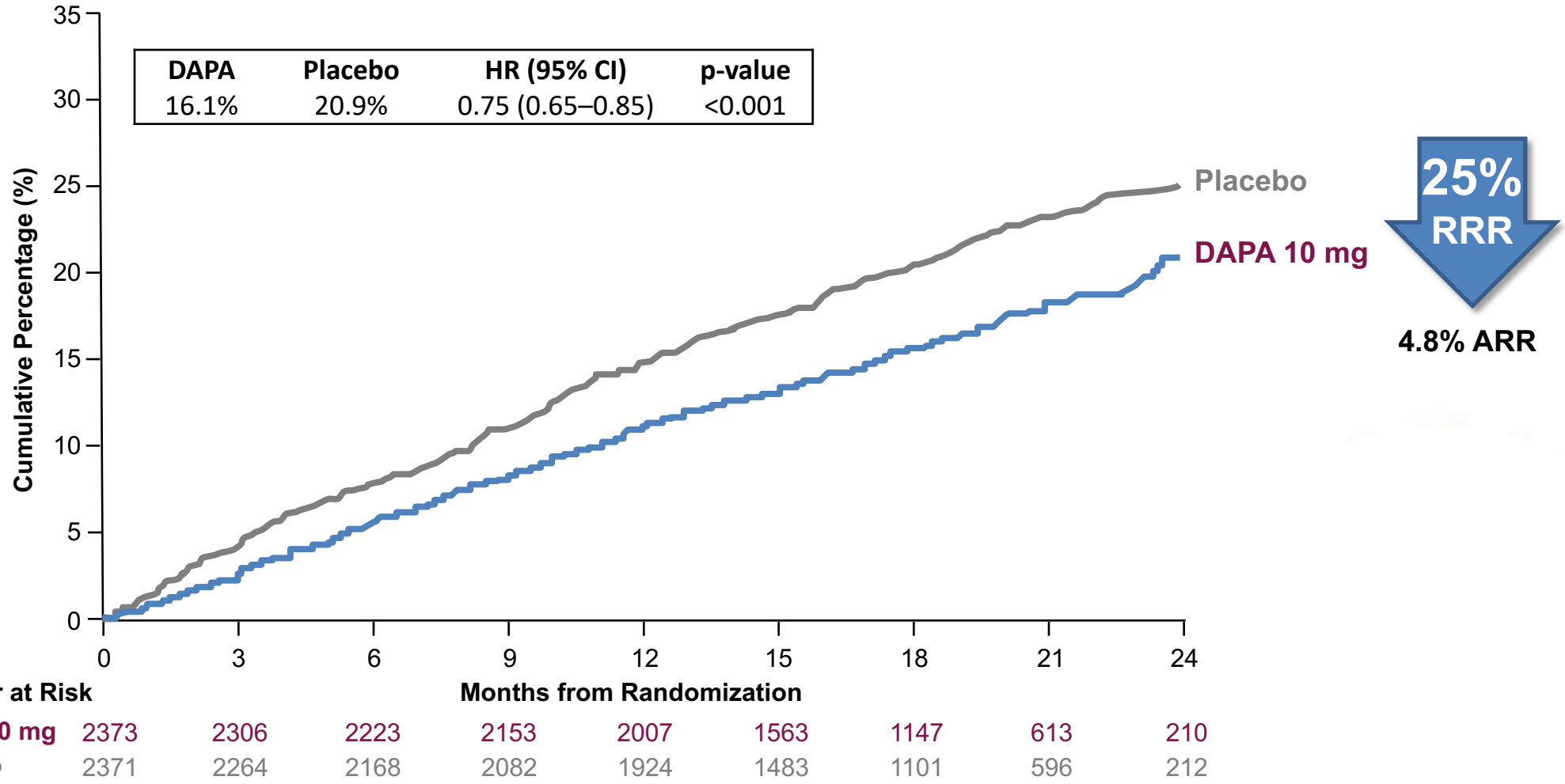
CV death or hHF or urgent HF visit

Outcome	Dapagliflozin 10 mg, n/N (%)	Placebo, n/N (%)	HR (95% CI)	Interaction p-value[b]
Total population	386/2373 (16.3)	502/2371 (21.2)	0.74 (0.65-0.85)	
T2D[a]	215/1075 (20.0)	271/1064 (25.5)	0.75 (0.63-0.90)	0.80
No T2D	171/1298 (13.2)	231/1307 (17.7)	0.73 (0.60-0.88)	
Normo-glycemic (HbA1c <5.7%)	53/438 (12.1)	71/419 (16.9)	0.67 (0.47-0.96)	0.72
Pre-diabetes (HbA1c ≥5.7-<6.5%)	118/860 (13.7)	160/888 (18.0)	0.74 (0.59-0.94)	



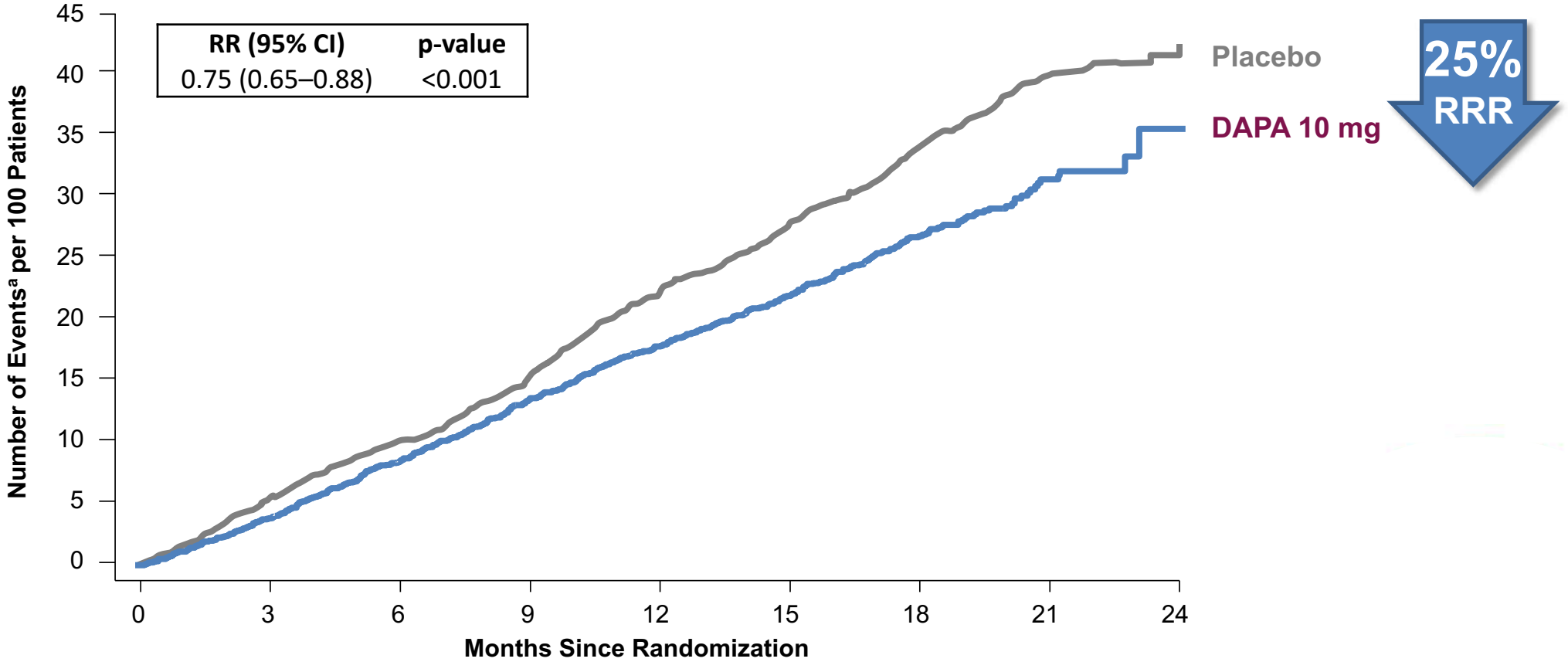
- [a]Includes 1983 patients with a pre-existing diagnosis of diabetes and 156 patients with previously undiagnosed diabetes (HbA1c ≥6.5% at Visits 1 and 2); [b]A non-significant result for an interaction test can be interpreted as consistency of effect across the subgroup.[2]
- CV = cardiovascular; HbA1c = glycated hemoglobin; HF = heart failure; hHF = hospitalization for heart failure; HR = hazard ratio; T2D = type 2 diabetes.
- 1. Petrie MC et al. *JAMA*. 2020;323:1353-1368; 2. Alosh M et al. *J Biopharm Stat*. 2015;25:1161-1178.

Secondary Endpoint: CV Death or hHF[1,2]



- ARR = absolute risk reduction; CV = cardiovascular; DAPA = dapagliflozin; hHF = hospitalization for heart failure; HR = hazard ratio; 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.

Secondary Endpoint: Number of hHF[a] and CV Death Events[1,2]



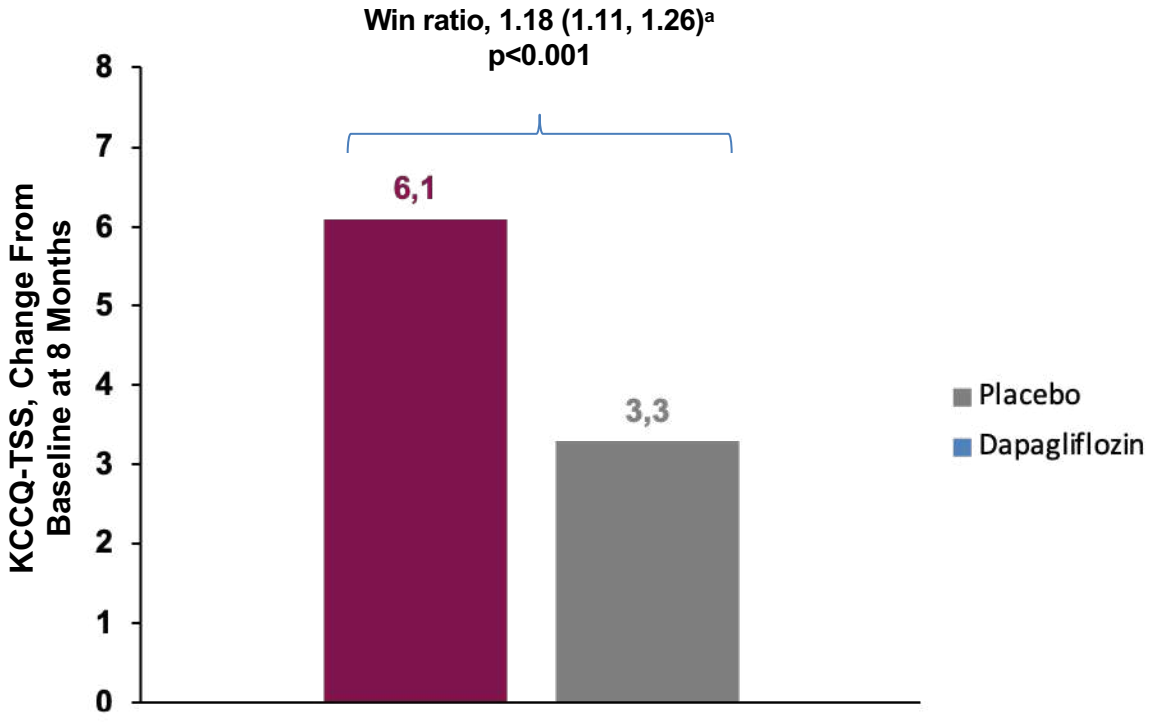
Number at Risk

DAPA 10 mg	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo	2371	2330	2279	2230	2091	1636	1219	664	234

- [a]Including first and repeat hospitalizations.
- CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; hHF = hospitalization for heart failure; RR = rate ratio; 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.

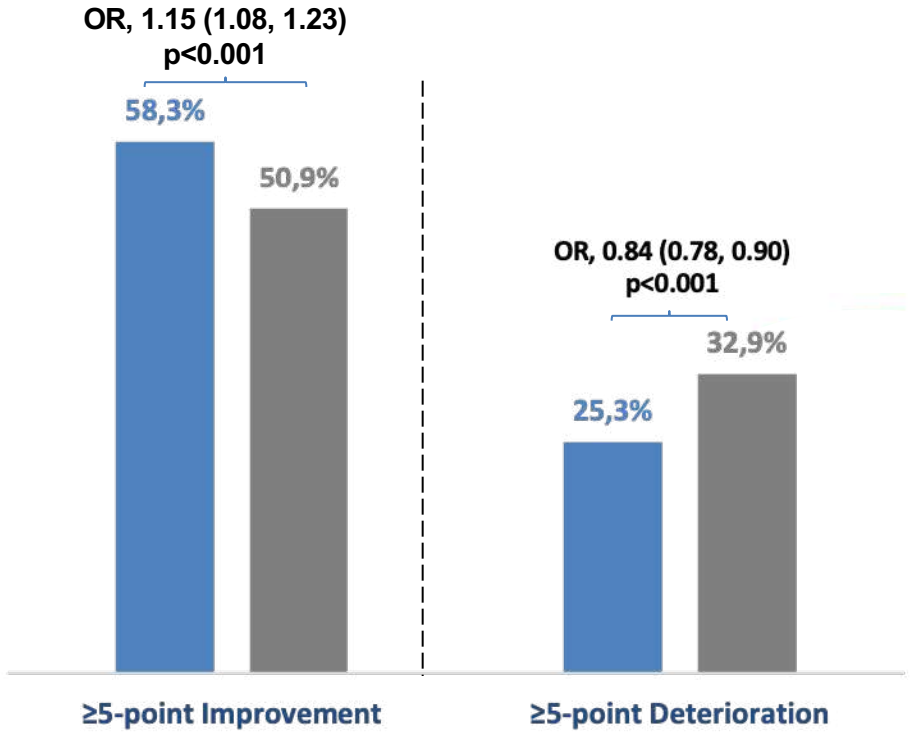
Secondary Endpoint: Health Status Assessed By Change from Baseline in KCCQ-TSS at 8 Months

Patients on dapagliflozin were 18% more likely to have symptom benefit (improvement in KCCQ-TSS) compared to placebo



Symptom improvement was more common and deterioration was less common with dapagliflozin

Proportion of patients with clinically meaningful change (≥5 points)[b] in KCCQ-TSS



- [a]Win ratio >1 indicates superiority of dapagliflozin over placebo; [b]Taking account of death.
- KCCQ-TSS = Kansas City Cardiomyopathy Questionnaire Total Symptom Score; OR = odds ratio.
- McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008.

Trial inclusion and exclusion criteria

Inclusion criteria

EMPEROR-Reduced[1,2]		DAPA-HF[3]
Age ≥18 years (Japan, age ≥20 years) at screening		Age ≥18 years
Chronic HF NYHA class II–IV		Chronic HF NYHA class II–IV
HFrEF (LVEF ≤40%)		HFrEF (LVEF ≤40%)
Elevated NT-proBNP		
EF (%)	**NT-proBNP (pg/ml)** Patients without AF*	**NT-proBNP ≥600 pg/ml or NT-proBNP ≥400 pg/ml in patients with HHF within 12 months** Patients without AF†
≥36 to ≤40	≥2500	
≥31 to ≤35	≥1000	
≤30	≥600	
≤40% + HHF within 12 months	≥600	
Further inclusion criteria apply		Further inclusion criteria apply

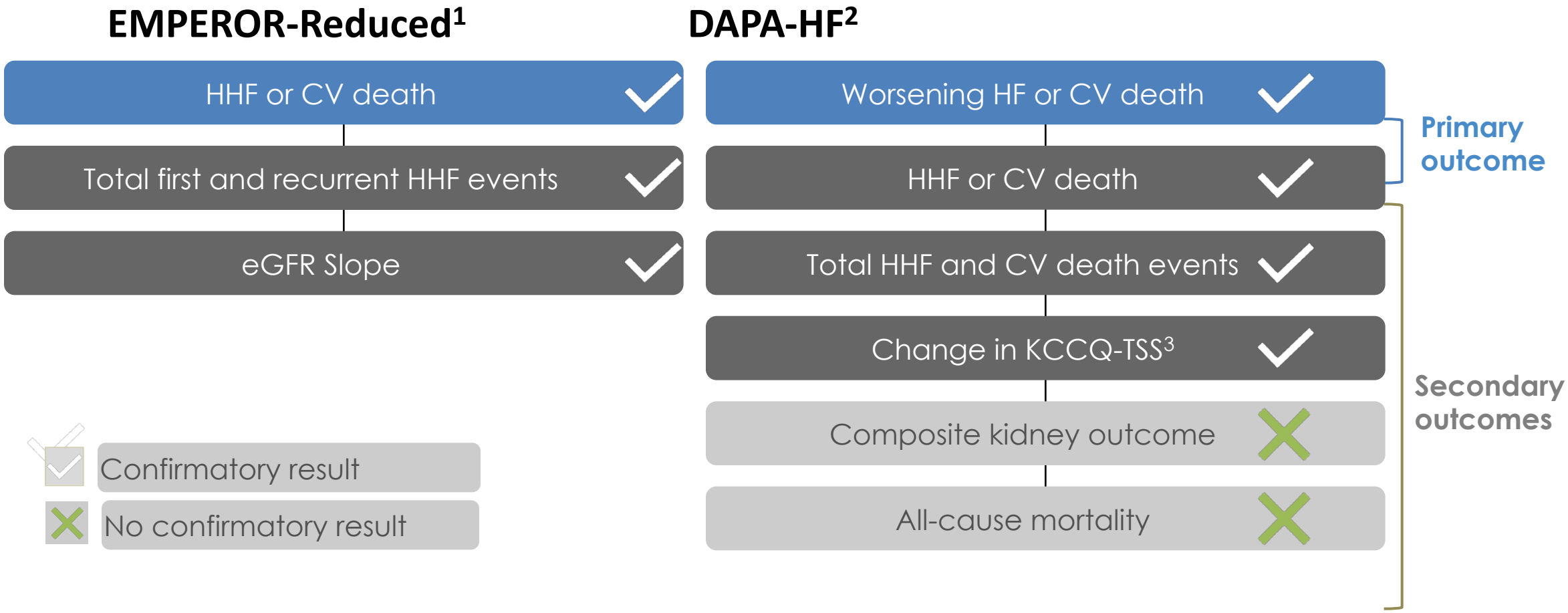
EMPEROR-Reduced
eGFR <20 ml/min/1.73 m²
or requiring dialysis

eGFR exclusion criteria
Further exclusion criteria apply

DAPA-HF
eGFR <30 ml/min/1.73 m²
or rapidly declining renal function

***The cut off for patients with AF is doubled in EMPEROR-Reduced;** †In DAPA-HF patients with AF or atrial flutter were required to have NT-proBNP ≥900 pg/ml regardless of history of HHF
AF, atrial fibrillation; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association
1. Parker et al DOI: 10.1056/NEJMoa2022190 2. Zannad F *et al. ESC-HF* 2018; poster P1755; 3. McMurray JJV *et al. N Engl J Med.* 2019;381:1995 1 Parker et al DOI: 10.1056/NEJMoa2022190

Outcome of endpoint hierarchical statistical testing: Comparison of EMPEROR-Reduced and DAPA-HF



Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology

*Change from baseline at 8 months

HF, heart failure; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NR, not reported

1.Packer M et al. New England Journal of Medicine 2020 DOI: 10.1056/NEJMoa2022190; 2. McMurray JJV et al. N Engl J Med 2014;371:993; 3. McMurray JJV et al. N Engl J Med 2019;381:1995

Baseline characteristics

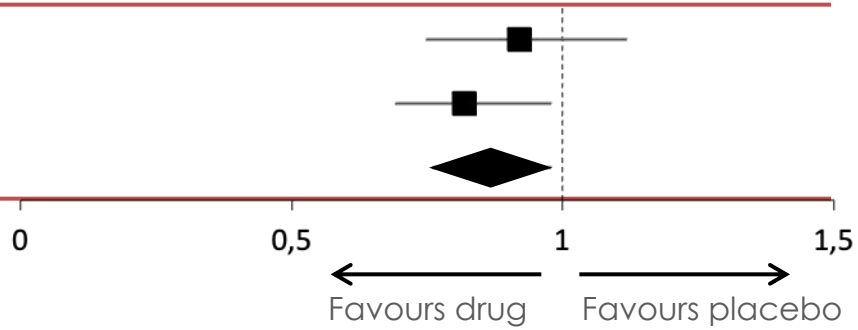
	EMPEROR-Reduced		DAPA-HF	
	Empagliflozin	Placebo	Dapagliflozin	Placebo
Number of participants	1863	1867	2373	2371
Mean±SD age, years	67.2±10.8	66.5±11.2	66.2 ± 11.0	66.5 ± 10.8
Females	437 (23.5%)	456 (24.4%)	564 (23.8%)	545 (23.0%)
NYHA II	1399 (75.1%)	1401 (75.0%)	1606 (67.7%)	1597 (67.4%)
NYHA III	455 (24.4%)	455 (24.4%)	747 (31.5%)	751 (31.7%)
NYHA IV	9 (0.5%)	11 (0.6%)	20 (0.8%)	23 (1.0%)
LVEF (%), mean ± SD	**27.7 ± 6.0**	**27.2 ± 6.1**	**31.2±6.7**	**30.9±6.9**
NT-proBNP, pg/ml, median (IQR)	**1887.0 (1077.0–3429.0)**	**1926.0 (1153.0–3525.0)**	**1428 (857-2655)**	**1446 (857-2641)**
Hospitalisation for HF	577 (31.0%)	574 (30.7%)	1124 (47.4%)	1127 (47.5%)
Diabetes	927 (49.8%)	929 (49.8%)	1075 (45.3%)	1064 (44.9%)
eGFR, ml/min/1.73 m^2 (CKD-EPI)	**61.8±21.7**	**62.2 ±21.5**	**66.0 ± 19.6**	**65.5 ± 19.3**
HF medications /devices				
ACE inhibitor	867 (46.5%)	836 (44.8%)	1332 (56.1%)	1329 (56.1%)
ARB	451 (24.2%)	457 (24.5%)	675 (28.4%)	632 (26.7%)
MRA	1306 (70.1%)	1355 (72.6%)	1696 (71.5%)	1674 (70.6%)
ARNI	**340 (18.3%)**	**387 (20.7%)**	**250 (10.5%)**	**258 (10.9%)**
ICD or CRT-D	578 (31%)	593 (31.8%)	622 (26.2%)	620 (26.1%)
CRT-D or CRT-P	220 (11.8%)	222 (11.9%)	190 (8.0%)	164 (6.9%)

Zannad F. Et al. Lancet https://doi.org/10.1016/S0140-6736(20)31824-9 1

Mortality

CV death

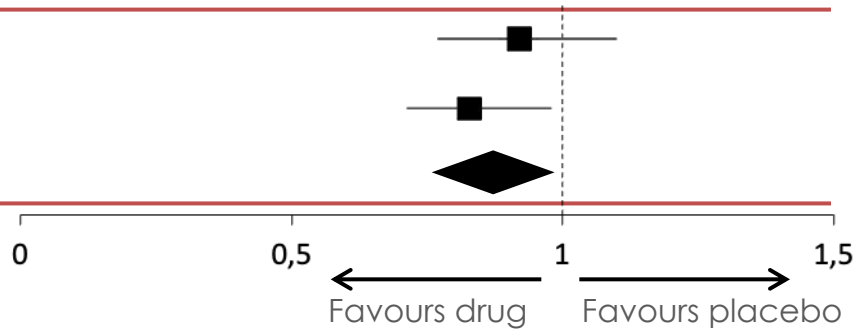
Trial	SGLT2i, n/N (%)	Placebo, n/N (%)	HR (95% CI)	HR (95% CI)
EMPEROR-Reduced	187/1863 (10.0)	202/1867 (10.8)	0.92 (0.75, 1.12)	
DAPA-HF	227/2373 (9.6)	273/2371 (11.5)	0.82 (0.69, 0.98)	
Total			0.86 (0.76, 0.98)	



Test for overall treatment effect, p=0.027
Test for heterogeneity of effect, p=0.40 I^2=0%

All-cause death

Trial	SGLT2i, n/N (%)	Placebo, n/N (%)	HR (95% CI)	HR (95% CI)
EMPEROR-Reduced	249/1863 (13.4)	266/1867 (14.2)	0.92 (0.77, 1.10)	
DAPA-HF	276/2373 (11.6)	329/2371 (13.9)	0.83 (0.71, 0.97)	
Total			0.87 (0.77, 0.98)	



Test for overall treatment effect, p=0.018
Test for heterogeneity of effect, p=0.39 I^2=0%

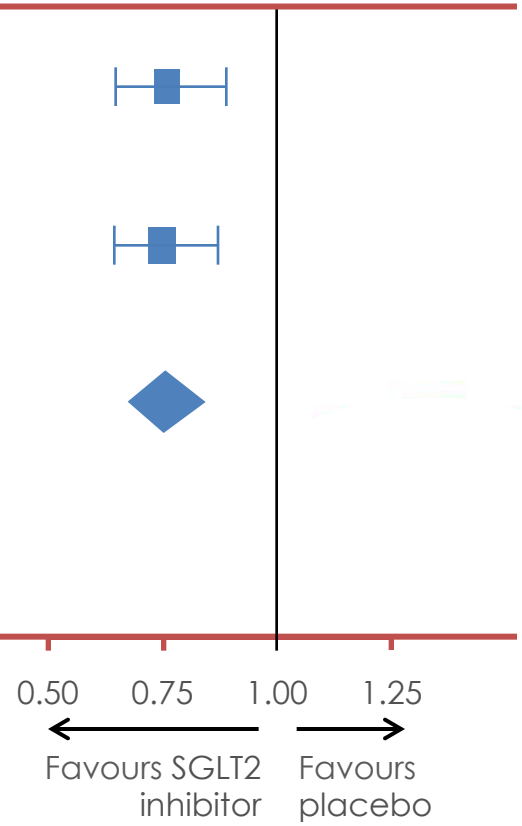
HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitor

Zannad F. Et al. https://doi.org/10.1016/S0140-6736(20)31824-9 1

All (first and recurrent) hospitalisation for heart failure or cardiovascular death

	SGLT2 inhibitor	Placebo	
	n with event/N analysed (%)		RR (95% CI)
EMPEROR-Reduced[1]	575/1863 (30.9)	753/1867 (40.3)	0.76 (0.65, 0.89)
DAPA-HF	567/2373 (23.9)	742/2371 (31.3)	0.75 (0.65, 0.88)
Total			0.75 (0.68, 0.84)

Test for overall treatment effect, $p<0.0001$
Test for heterogeneity of effect, $p=0.91$ $I^2=0\%$

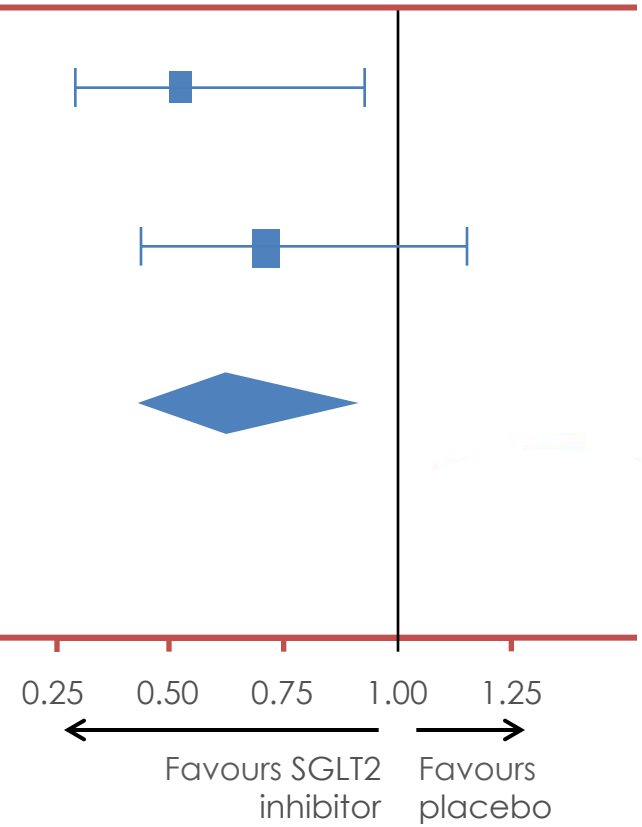


[1] DAPA-HF analysis approach (LWYY)
Zannad F. Et al. https://doi.org/10.1016/S0140-6736(20)31824-9 1

First kidney composite[1]

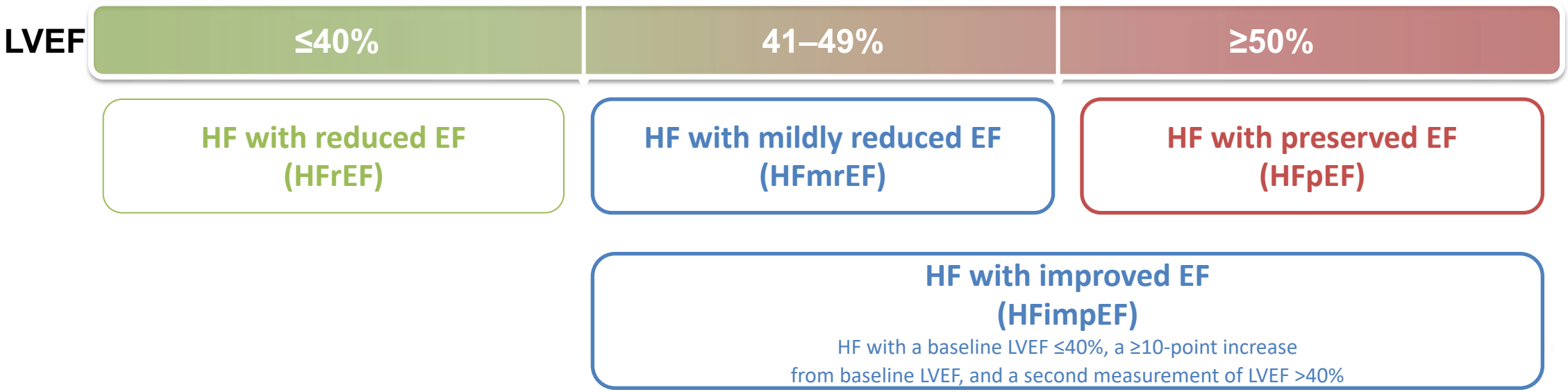
	SGLT2 inhibitor	Placebo	
	n with event/N analysed (%)		HR (95% CI)
EMPEROR-Reduced	18/1863 (1.0)	33/1867 (1.8)	0.52 (0.29, 0.92)
DAPA-HF	28/2373 (1.2)	39/2371 (1.6)	0.71 (0.44, 1.16)
Total			0.62 (0.43, 0.90)

Test for overall treatment effect, p=0.0128
Test for heterogeneity of effect, p=0.42 I^2=0%



[1]Aligned with DAPA-HF definition. Chronic dialysis or renal transplant or sustained reduction of ≥ 50% eGFR(CKD-EPI)cr or a sustained eGFR <15 mL/min/1.73m2 (for patients with baseline eGFR ≥30) or sustained eGFR <10 mL/min/1.73m2 (for patients with baseline eGFR <30 mL/min/1.73m2).
Zannad F. Et al. https://doi.org/10.1016/S0140-6736(20)31824-9 18

The new universal definition of heart failure classifies the different phenotypes according to LVEF



EF, ejection fraction; HF, heart failure; LVEF, left ventricular ejection fraction.

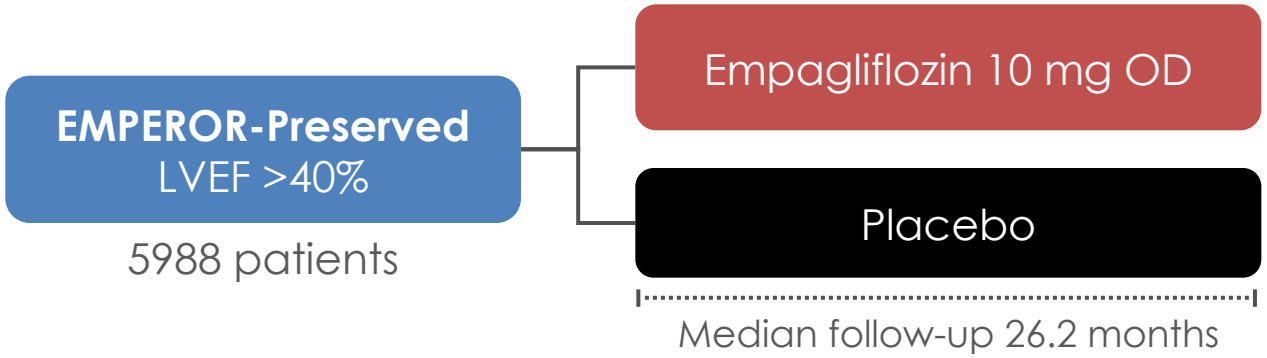
Bozkurt B *et al*. *Eur J Heart Fail.* 2021;23:352.

EMPEROR-Preserved study design

Phase III trial* in patients with HFpEF

Aim: To investigate the safety and efficacy of empagliflozin versus placebo in patients with HF with **preserved ejection fraction**

Population: T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV)



COMPOSITE PRIMARY ENDPOINT

- **Time to first event of adjudicated CV death or adjudicated HHF**

CONFIRMATORY KEY SECONDARY ENDPOINTS

- **First and recurrent adjudicated HHF**
- **Slope of change in eGFR (CKD-EPI) from baseline**

*Randomized, double-blind, placebo-controlled trial.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OD, once daily; T2D, type 2 diabetes.

EMPEROR-Preserved: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

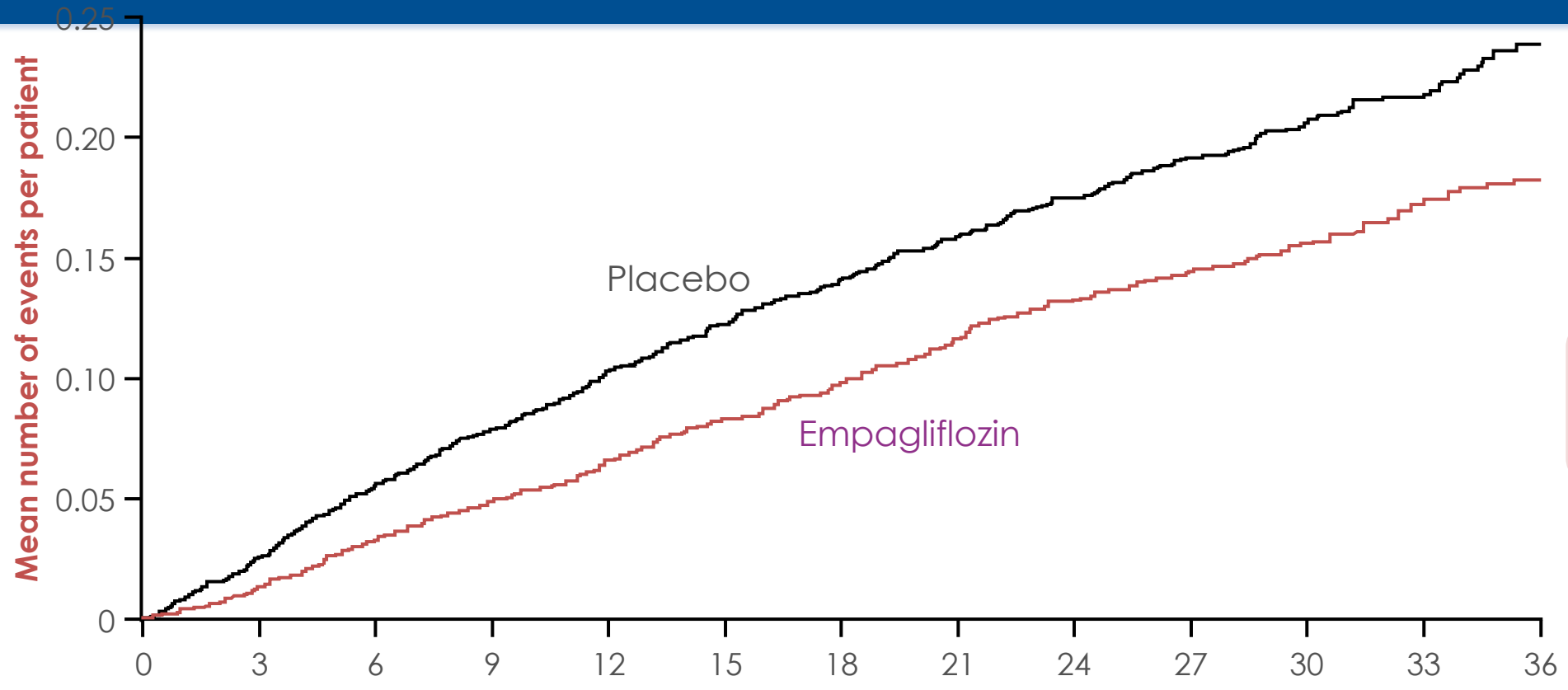
• Age ≥18 years
• Chronic HF NYHA class II–IV
• **LVEF >40%**
• **NT-proBNP:**
  • **>300 pg/mL** in patients without AF
  • **>900 pg/mL** in patients with AF
• **Structural changes in the heart** (increases in left atrial size or left ventricular mass) **or HHF within 12 months of screening**
	• MI, coronary artery bypass graft surgery or other major CV surgery, stroke or TIA ≤90 days before visit
	• Heart transplant recipient, or listed for heart transplant
	• Acute decompensated HF
	• SBP ≥180 mmHg at randomization
	• Symptomatic hypotension and/or SBP <100 mmHg
	• eGFR <20 mL/min/1.73 m^2 or requiring dialysis

Further criteria apply

AF, atrial fibrillation; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TIA, transient ischaemic attack.

Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038

EMPEROR-Preserved: Key secondary endpoint – adjudicated total HHF (first and recurrent)



RRR 27%

HR: 0.73
(95% CI: 0.61, 0.88)
p<0.001

Patients at risk

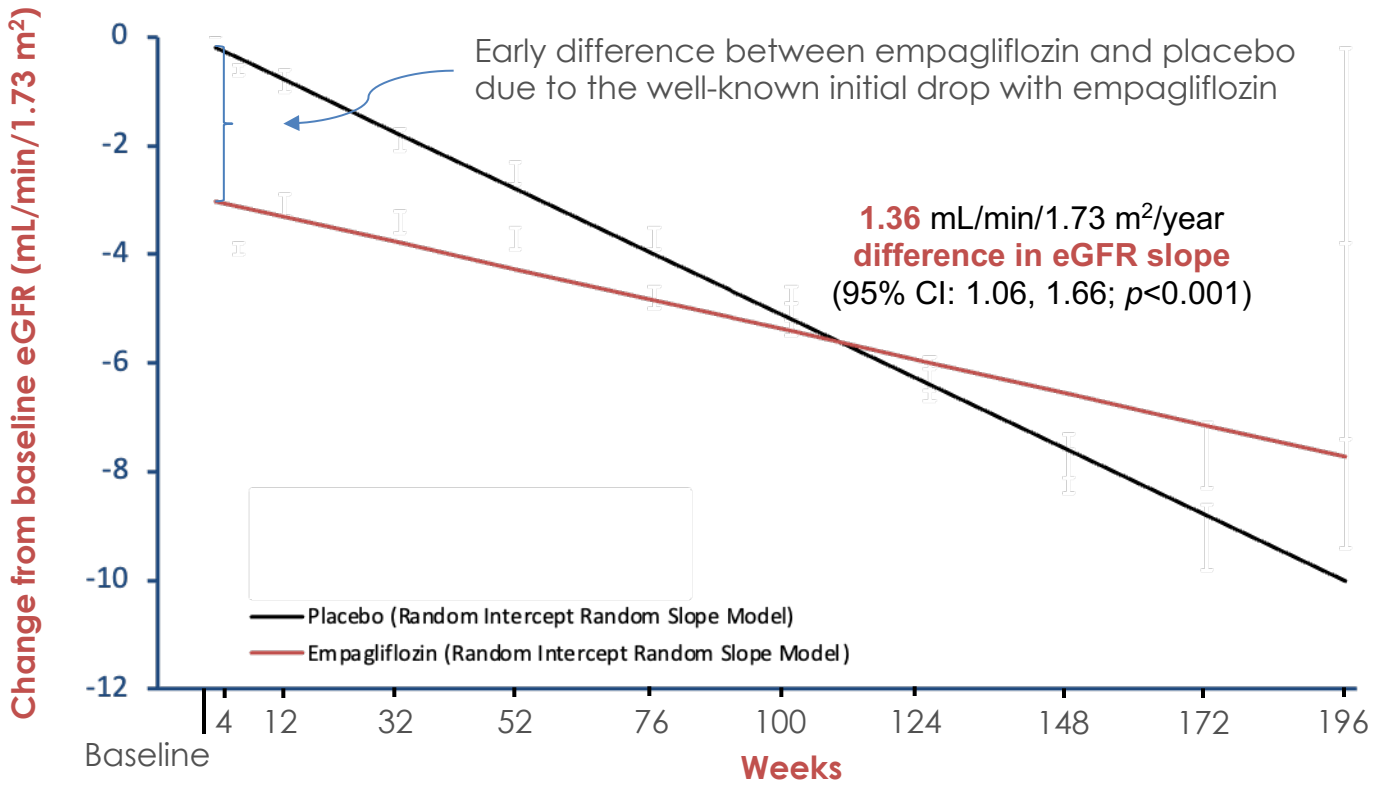
Placebo	2991	2945	2901	2855	2816	2618	2258	1998	1695	1414	1061	747	448
Empagliflozin	2997	2962	2913	2869	2817	2604	2247	1977	1684	1429	1081	765	446

Empagliflozin: 407 patients with event
Placebo: 541 patients with event

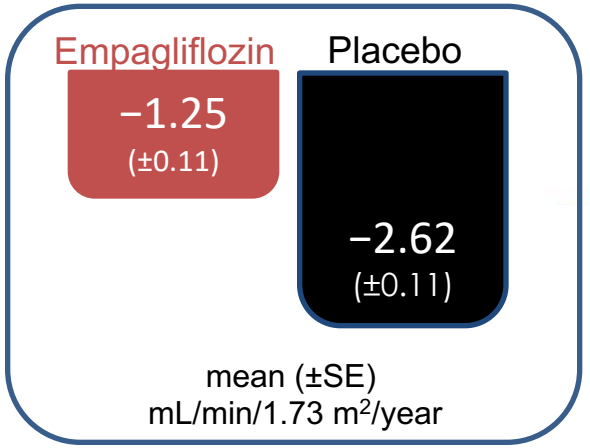
CI, confidence interval; HHF, hospitalization for heart failure; HR, hazard ratio; RRR, relative risk reduction.

Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038.

Empagliflozin protected the kidney by significantly slowing the decline in kidney function



The rate of eGFR decline in patients treated with empagliflozin was half that of patients treated with placebo



eGFR slope = rate of decline (and is a measure for long-term renal function). eGFR slope is analysed based on on-treatment data using a random coefficient model including age, baseline eGFR and baseline LVEF as linear covariates and sex, region, baseline diabetes status, and baseline by time and treatment by time interactions as fixed effects; the model allows for randomly varying slope and intercept between patients.

eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; SE, standard error.

Developed from data reported in Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038.

EMPEROR-Preserved: Specific endpoints for hierarchical testing

		EMPEROR-Preserved	
	Primary endpoint: Adjudicated CV death or HHF	Confirmatory*	**HR: 0.79 (95% CI: 0.69, 0.90) *p*<0.001**
	Key secondary endpoint: Adjudicated first and recurrent HHF	Confirmatory†	**HR: 0.73 (95% CI: 0.61, 0.88) *p*<0.001**
	Key secondary endpoint: eGFR slope	Confirmatory‡	**+1.36 mL/min/1.73 m^2 per year *p*<0.001**

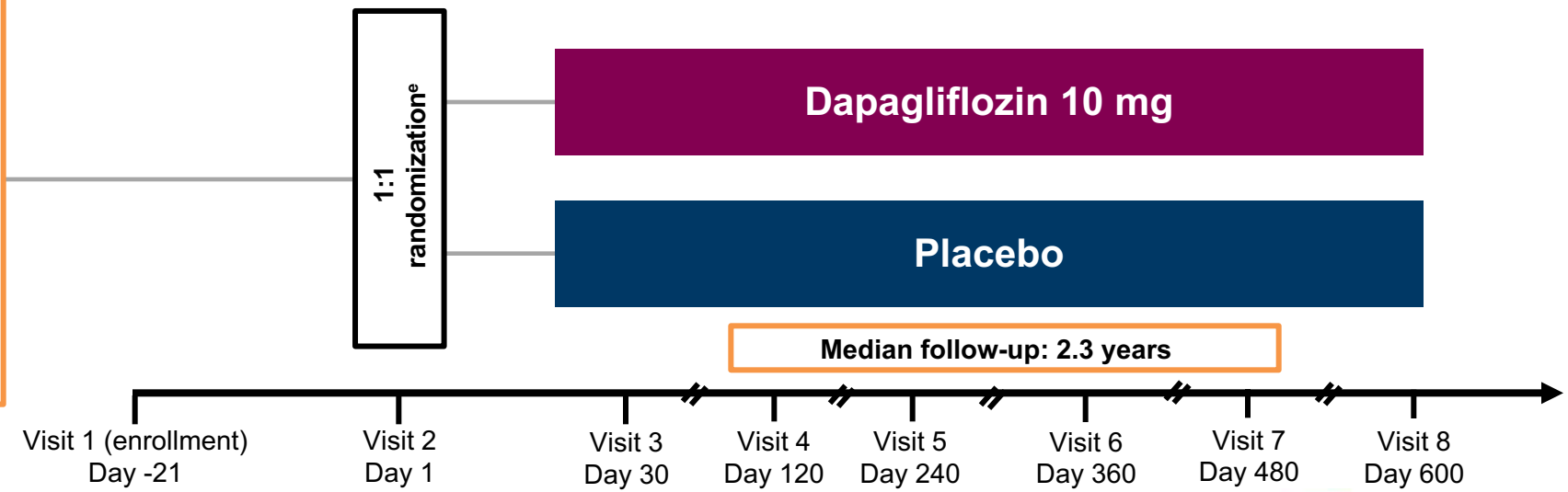
*Cox regression with a=0.0497. †Joint frailty model that included CV death as source of information censoring. ‡Random coefficient model. See slide notes for more information.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; HR, hazard ratio.
Anker S *et al. N Engl J Med*. 2021; 10.1056/NEJMoa2107038.

DELIVER

Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure[1,2,3]

6263 Patients

- ≥40 years of age with or without T2D
- LVEF >40%[a] and evidence of structural heart disease[b] within 12 months
- Symptomatic NYHA Class II-IV HF at enrollment and typical signs/symptoms of HF ≥6 weeks before enrollment with at least intermittent need for diuretic treatment
- Elevated NT-proBNP levels
- eGFR[c] ≥25 mL/min/1.73 m^2
- Ambulatory or hospitalized off IV HF therapy[d] for ≥24 hours



Primary Endpoint

- Time to first occurrence of any component of the composite of CV death or worsening HF events (hHF or urgent HF visit)
  - Full patient population
  - Patients with LVEF <60%

Secondary Endpoints

- Total number of HF events (first and recurrent) and CV deaths in the full patient population and in patients with LVEF <60%
- Change from baseline in KCCQ-TSS at 8 months
- Time to occurrence of CV death
- Time to occurrence of death from any cause

- [a]Patients with an LVEF ≤40% were also included; [b]LV hypertrophy or LA enlargement; [c]Based on Chronic Kidney Disease-Epidemiology Collaboration Equation; [d]Including diuretics; [e]Stratified by T2D status (established diagnosis/HbA1c ≥6.5% at enrollment).
- 1. Solomon SD et al. *Eur J Heart Fail.* 2021;23(7):1217-1225; 2. Solomon SD et al. *JACC Heart Fail*. 2022;10(3):184-197; 3. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022.

Largest and broadest trial to date in patients with heart failure and mildly reduced or preserved ejection fraction[1]

DELIVER

6263 Patients[2]

- Age ≥40 with/without T2D
- NYHA class II-IV
- LVEF >40%[a] with structural heart disease[b]
- Ambulatory or hospitalized[c]
- Elevated NT-proBNP levels
- eGFR ≥25 mL/min/1.73 m²

DAPA 10 mg n=3131

Placebo n=3132

Median follow-up: 2.3 years

Baseline characteristics[1,2]

1011 pg/mL
Median NT-proBNP

54%
Average LVEF

55%
Without T2D

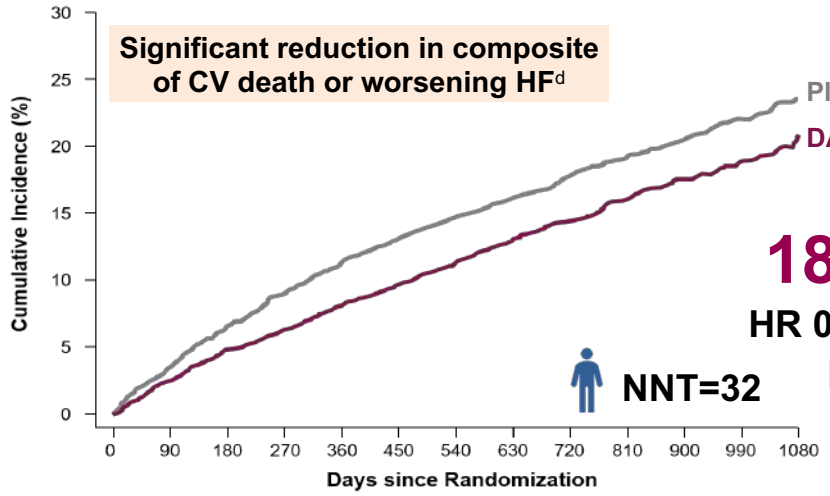
50%
With an eGFR <60 mL/min/1.73 m²

10%
Hospitalized or recently discharged

~18%
With prior LVEF ≤40%

Primary Endpoint[2,3]

Significant reduction in composite of CV death or worsening HF[d]



18% RRR
HR 0.82 (0.73-0.92)
p=0.0008

- All individual components occurred less frequently in the DAPA group
- Treatment benefit was consistent across all prespecified subgroups

Secondary Endpoints[2]

- **Significant reduction** in **total[e] worsening HF events[d]** and **CV deaths**
- **Significant improvement** in **HF symptoms**
- **Mortality** rates **numerically lower**

Safety

Results **consistent with the well-established safety profile**[2-4]

SGLT2 inhibitors, including **dapagliflozin,** are **recommended in patients with HF regardless of LVEF** in Treatment Guidelines[5]

100 years of commitment to CVD with more to come in HF

- [a]Prior LVEF ≤40% also included; [b]LV hypertrophy or LA enlargement; [c]Off IV HF therapy (including diuretics) for ≥24 hours; [d]hHF or urgent HF visit; [e]First and recurrent.

DELIVER Extends the Benefit of Dapagliflozin Across the Range of LVEF

>11,000 patients with HF[1,2]

HFrEF | HFmrEF | HFpEF

DAPA-HF[1]

EF ≤40%

- Significant reduction in the composite of CV death or worsening HF[a] as well as each individual component
- Reduction in all-cause mortality
- HF symptom benefit
- Consistent benefit across a broad population

DELIVER[2,3]

EF >40%

- Largest and broadest trial to date in patients with EF >40%
- Significant reduction in the composite of CV death or worsening HF[a], with all components contributing
- HF symptom benefit
- Consistent benefit across all subgroups

- [a]hHF or an urgent HF visit.
- CV = cardiovascular; EF = ejection fraction; HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure.
- 1. McMurray JJV et al. *N Engl J Med*. 2019;381(21):1995-2008; 2. Solomon SD et al. *JACC Heart Fail*. 2022;10(3):184-197; 3. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022.

Dapagliflozin Significantly Reduced the Risk of Each Endpoint Across the Range of LVEF

DAPA-HF ◀ Pre-specified patient-level pooled analysis ▶ DELIVER

Death

CV death

14% RRR

1.5% ARR
p=0.01

HR: 0.86
95% CI: 0.76-0.97

All-cause death

10% RRR

1.5% ARR
p=0.03

HR: 0.90
95% CI: 0.82-0.99

hHF

Total[a] hHF

29% reduction

6.0% ARR
p<0.001

RR: 0.71
95% CI: 0.65-0.78

First hHF

26% RRR

3.2% ARR
p<0.001

HR: 0.74
95% CI: 0.66-0.82

MACE

CV death, MI, or stroke

10% RRR

1.3% ARR
p=0.045

HR: 0.90
95% CI: 0.81-1.00

Effect was consistent across the full range of LVEF

- [a]First and repeat.
- Jhund PS et al. Online ahead of print. *Nat Med*. 2022.

DAPA-HF + DELIVER Pooled Analysis

Pre-specified, patient-level pooled analysis

Study Design[1,2,3]

DAPA-HF
LVEF ≤40%; N=4744
+
DELIVER
LVEF >40%; N=6263

N=11,007

DAPA 10 mg n=5504

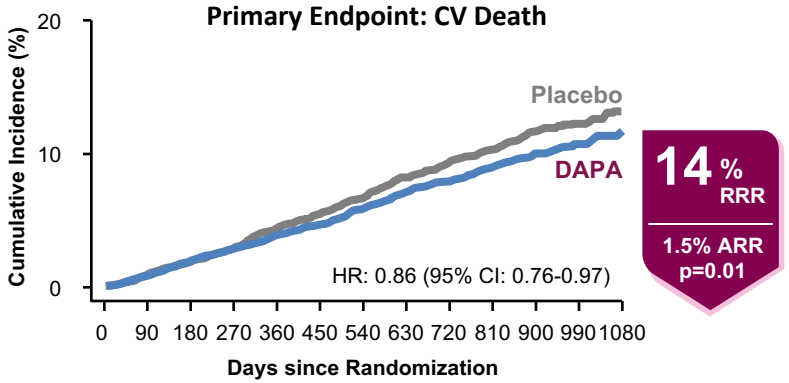
Placebo n=5503

Median Follow-up: 22 months

Purpose[1]

- Examine the effect of DAPA across the LVEF range given the attenuation seen in patients with higher LVEFs in other HF medication trials
- Outcomes:
  - ❖ CV death
  - ❖ Total[a] hHF
  - ❖ CV death or hHF
  - ❖ All-cause death
  - ❖ MACE[b]

DAPA significantly reduced the risk of death and hHF across the LVEF range[1]

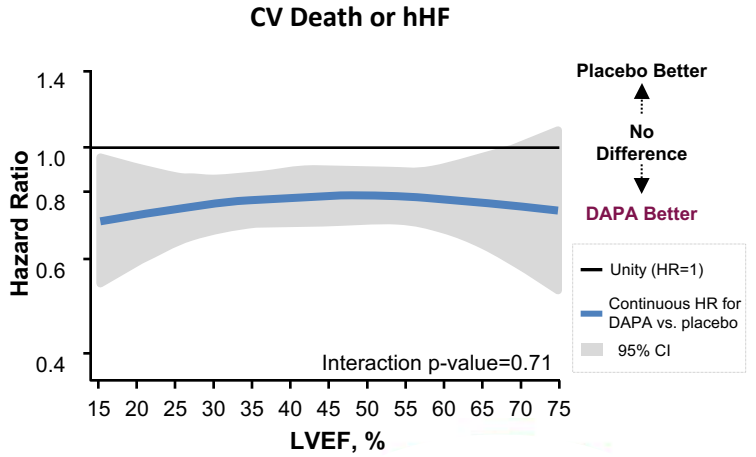


All-cause death
10 % RRR
1.5% ARR p=0.03
HR: 0.90
95% CI: 0.82-0.99

Total[a] hHF
29 % reduction
6.0% ARR p<0.001
RR: 0.71
95% CI: 0.65-0.78

First hHF
26 % RRR
3.2% ARR p<0.001
HR: 0.74
95% CI: 0.66-0.82

DAPA significantly reduced the risk of CV death or hHF across the LVEF range[1]



DAPA reduced the risk of CV death or hHF by 22%
HR: 0.78 (95% CI: 0.72-0.86); p<0.001

SGLT2 inhibitors, including **dapagliflozin,** are **recommended in patients with HF regardless of LVEF** in Treatment Guidelines[4]

- [a]First and recurrent; [b]Composite of CV death, MI, or stroke.
- 1. Jhund PS et al. Online ahead of print. *Nat Med.* 2022; *2.* McMurray JJV et al. *N Engl J Med.* 2019;381(21):1995-2008; 3. Solomon SD et al. Online ahead of print. *N Engl J Med*. 2022; 4. Heidenreich PA et al. *J Am Coll Cardiol*. 2022;79(17):e263-e421.

DAPA-CKD:
Dapagliflozin in Patients With Chronic Kidney Disease[1,2]

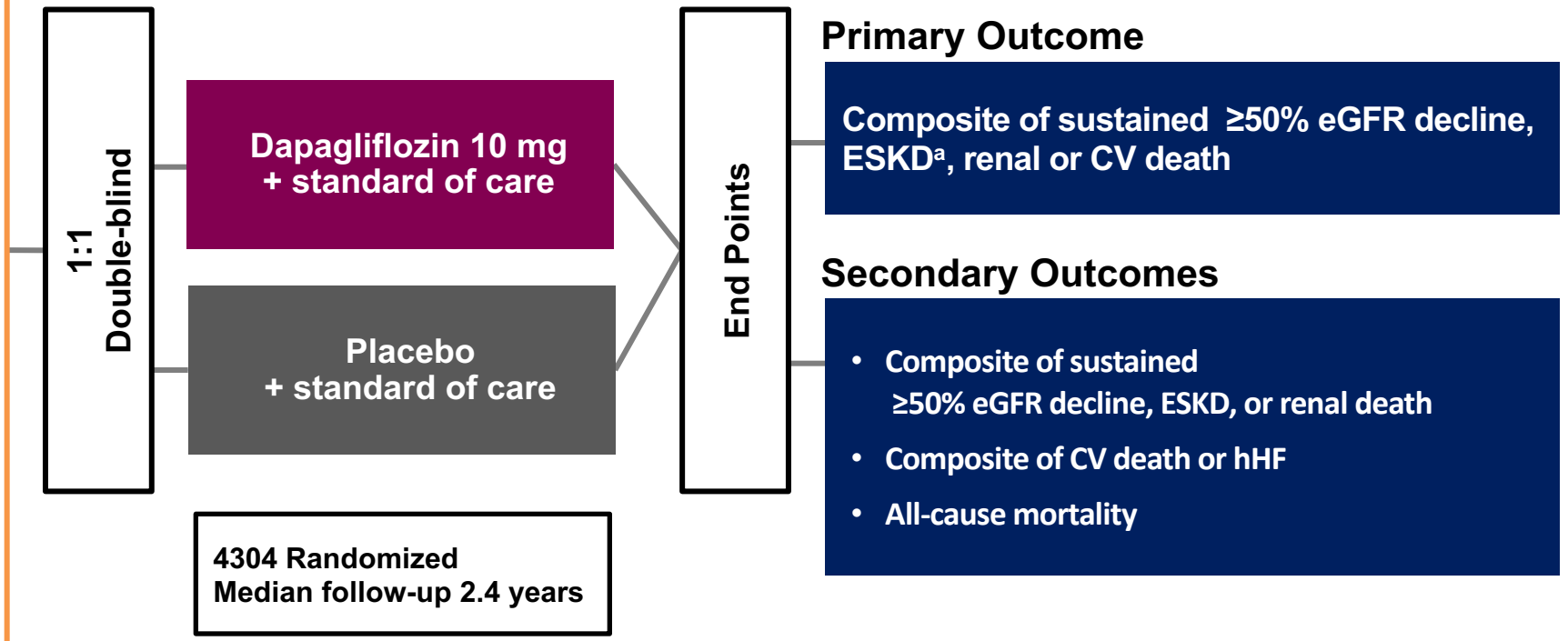
Objective

Key Inclusion Criteria

- ≥18 years of age
- eGFR ≥25 to ≤75 mL/min/1.73m^2
- UACR ≥200 to ≤5000 mg/g
- Stable dose of ACEi/ARB for ≥4 weeks
- With and without T2D

Key Exclusion Criteria

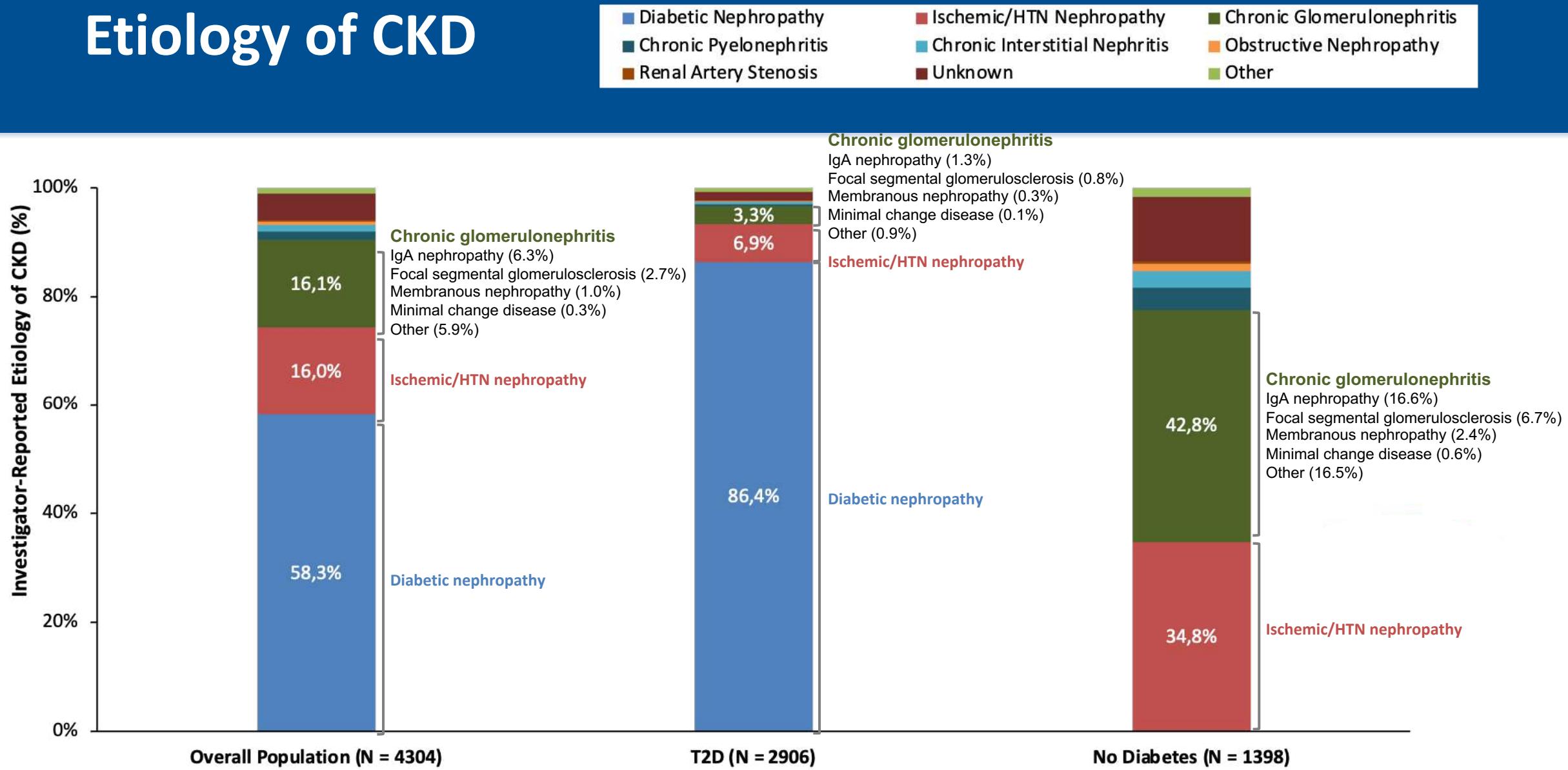
- T1D
- Polycystic kidney disease, lupus nephritis, ANCA-associated vasculitis
- Immunosuppressive therapy ≤6 months prior to enrollment



eal or hemodialysis) for more than 28 days, renal transplantation or sustained eGFR <15mL/min/1.73m^2 for at least 28 days.

- ACEi = angiotensin-converting enzyme inhibitor; ANCA = anti-neutrophil cytoplasmic antibody; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; hHF = hospitalization for heart failure; T1D = type 1 diabetes; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.
- 1. Heerspink HJL et al. *Nephrol Dial Transplant*. 2020;35:274–282; 2. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446.

Etiology of CKD



- HTN = hypertensive; IgA = immunoglobulin A; T2D = type 2 diabetes.
- Wheeler DC et al. *Nephrol Dial Transplant*. 2020;35:1700–1711.

End Points

- **DAPA-CKD[1], the first dedicated renal outcomes trial to assess the efficacy and safety of an SGLT-2 inhibitor in patients with CKD with and without T2D, demonstrated:**

39% RRR for the primary composite endpoint (≥50% sustained decline in eGFR, ESKD, renal or CV death)	**44%** RRR for the renal composite (≥50% sustained decline in eGFR, ESKD, or renal death)	**29%** RRR for the composite of CV death or hospitalization for heart failure	**31%** RRR all-cause mortality

- Consistent clinical benefits in patients with CKD across major subgroups including in patients **with and without T2D,** and by baseline eGFR and UACR categories
- Dapagliflozin was well-tolerated for the treatment of CKD (in patients with and without T2D) and data **confirm the known safety profile**
- **DAPA-CKD** builds upon the evidence for dapagliflozin in the prevention of hHF and worsening of renal disease in **DECLARE[2]** and reduction in the risk of worsening HF and CV death in **DAPA-HF[3]**

- **CKD = chronic kidney disease; CV = cardiovascular; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HF = heart failure; hHF = hospitalization for heart failure; RRR = relative risk reduction; SGLT-2 = sodium glucose co-transporter 2; T2D = type 2 diabetes; UACR = urinary albumin-to-creatinine ratio.**
- **1. Heerspink HJL et al. *N Engl J Med*. 2020; 383:1436-1446. 2. Wiviott SD. et al. *N Engl J Med.* 2019;380:347-357. 3. McMurray JJV et al. *N Engl J Med.* 2019;381:1995-2008.**

DAPA-CKD Expands the Cardiorenal and Mortality Benefit of Dapagliflozin to Patients With CKD

	DECLARE-TIMI 58	DAPA-HF	DAPA-CKD
	N = 17,160[1,2]	N = 4744[3,4]	N = 4304[5,6]
Patient Population	T2D	HFrEF with or without T2D	CKD with or without T2D
Mean eGFR	85 mL/min/1.73 m^2	66 mL/min/1.73 m^2	43 mL/min/1.73 m^2
Primary Endpoint	• **hHF or CV death** 0.83 (0.73, 0.95) p=0.005	• **CV death or worsening HF (hHF or urgent hHF visit)** 0.74 (0.65, 0.85) p<0.001	• **≥50% eGFR decline, ESKD, or renal or CV death** 0.61 (0.51-0.72) p=0.000000028
Key Secondary Endpoints	• **eGFR decrease ≥40% to <60, ESKD or renal death** 0.53 (0.43, 0.66) p<0.0001[a]	• **All-cause mortality** 0.83 (0.71-0.97) p=0.022[b]	• **All-cause mortality** 0.69 (0.53-0.88) p=0.0035 • **CV death or hHF** 0.71 (0.55, 0.92) p=0.0089

- [a] Because the trial met only one of its dual primary composite outcomes for superiority (CV death or hospital admission for heart failure), all other analyses of additional outcomes should be considered hypothesis generating only; [b]Nominal p-value.
- CKD = chronic kidney disease; CV = cardiovascular; 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; T2D = type 2 diabetes.
- 1. Wiviott SD. et al. *N Engl J Med.* 2019;380:347-357; 2. Mosenzon O et al. *Lancet Diabetes Endocrinol.* 2019;7:606-617; 3. McMurray JJV et al. *N Engl J Med.* 2019;381:1995-2008; 4. McMurray J. Presented at: ESC Congress; August 31-September 4, 2019; Paris, France; 5. Heerspink HJL. Presented at: ESC Congress – The Digital Experience; August 29 - September 1, 2020; 6. Heerspink HJL et al. *N Engl J Med.* 2020; 383:1436-1446.

Renal

CV

Mortality

Empa-Kidney

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

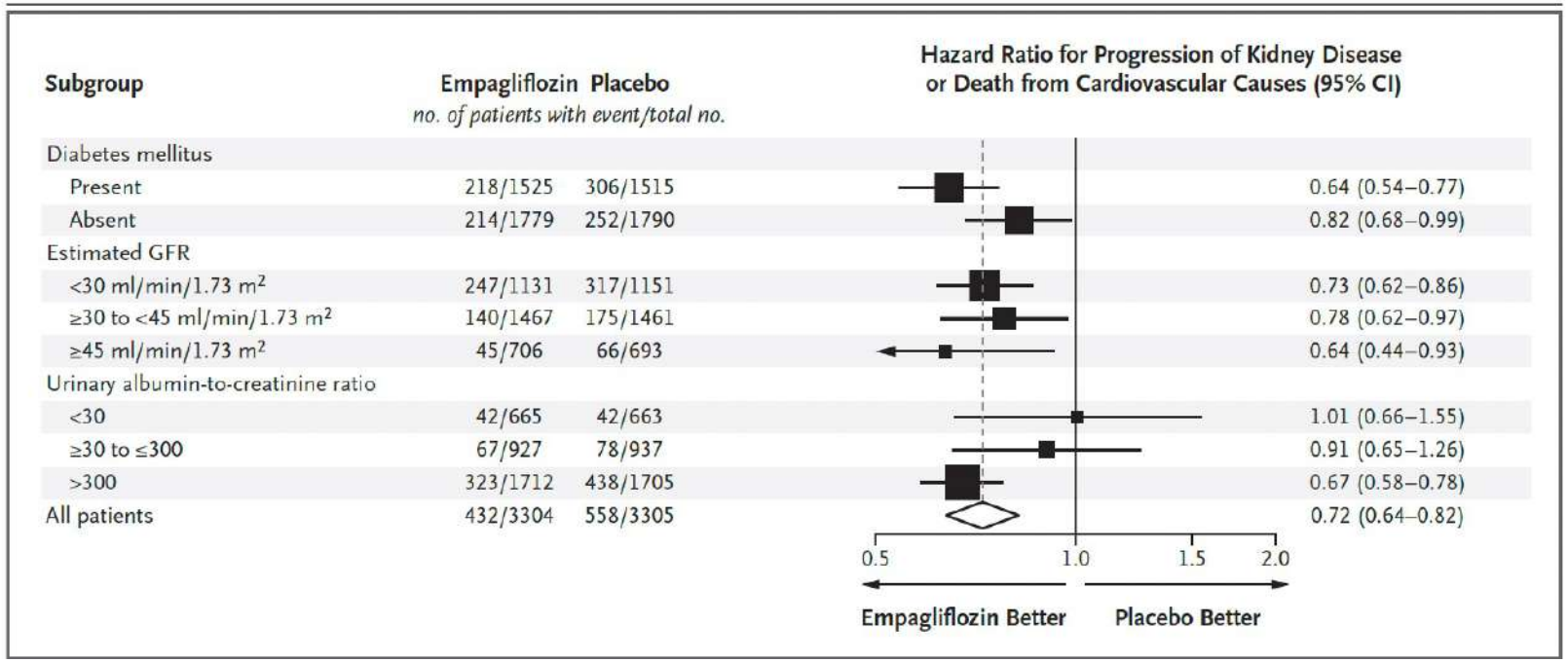
The EMPA-KIDNEY Collaborative Group*

Characteristic	Empagliflozin (N=3304)	Placebo (N=3305)
Cause of kidney disease — no. (%)		
Diabetic kidney disease	1032 (31.2)	1025 (31.0)
Hypertensive or renovascular disease	706 (21.4)	739 (22.4)
Glomerular disease	853 (25.8)	816 (24.7)
Other	387 (11.7)	421 (12.7)
Unknown	326 (9.9)	304 (9.2)

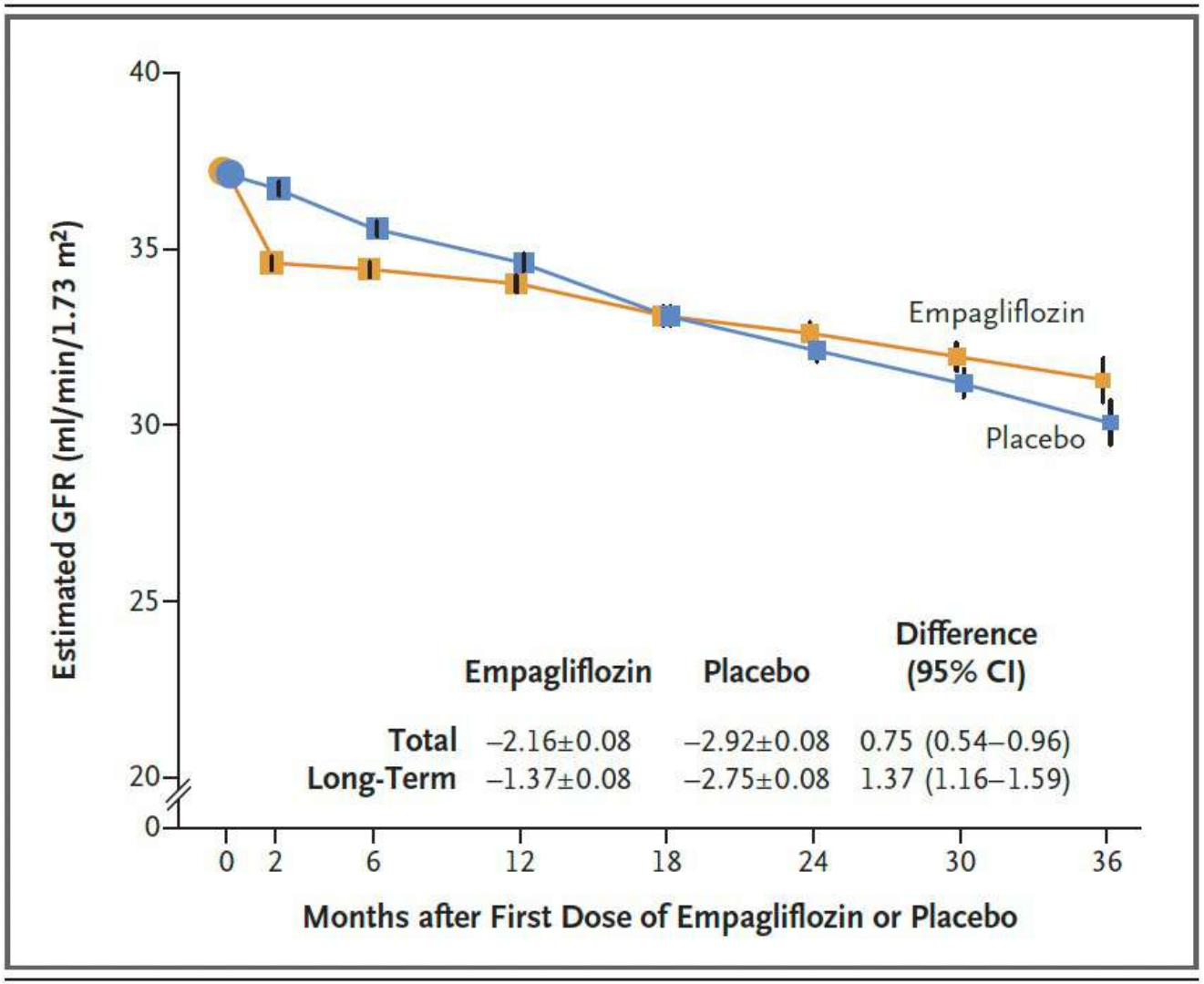
DOI: 10.1056/NEJMoa22

Empa-Kidney

Outcome	Empagliflozin (N=3304)		Placebo (N=3305)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no. of events/100 patient-yr*	*no. (%)*	*no. of events/100 patient-yr*		
Primary outcome: progression of kidney disease or death from cardiovascular causes	432 (13.1)	6.85	558 (16.9)	8.96	0.72 (0.64–0.82)	<0.001
Key secondary outcomes†						
Hospitalization for heart failure or death from cardiovascular causes	131 (4.0)					
Hospitalization for any cause‡	—					
Death from any cause	148 (4.5)					
Other secondary outcomes						
Progression of kidney disease	384 (11.6)					
Death from cardiovascular causes	59 (1.8)					
End-stage kidney disease or death from cardiovascular causes§	163 (4.9)					
Safety outcomes						



Empa-Kidney



Among a broad range of patients with CKD who were at risk for disease progression, including a large number of patients without diabetes, with an eGFR of less than 30 ml per minute per 1.73 m2, and with a low urinary albumin-tocreatinine ratio, empagliflozin treatment led to a lower risk of progression of kidney disease or death from cardiovascular causes than placebo.

Grazie per l’attenzione!!!