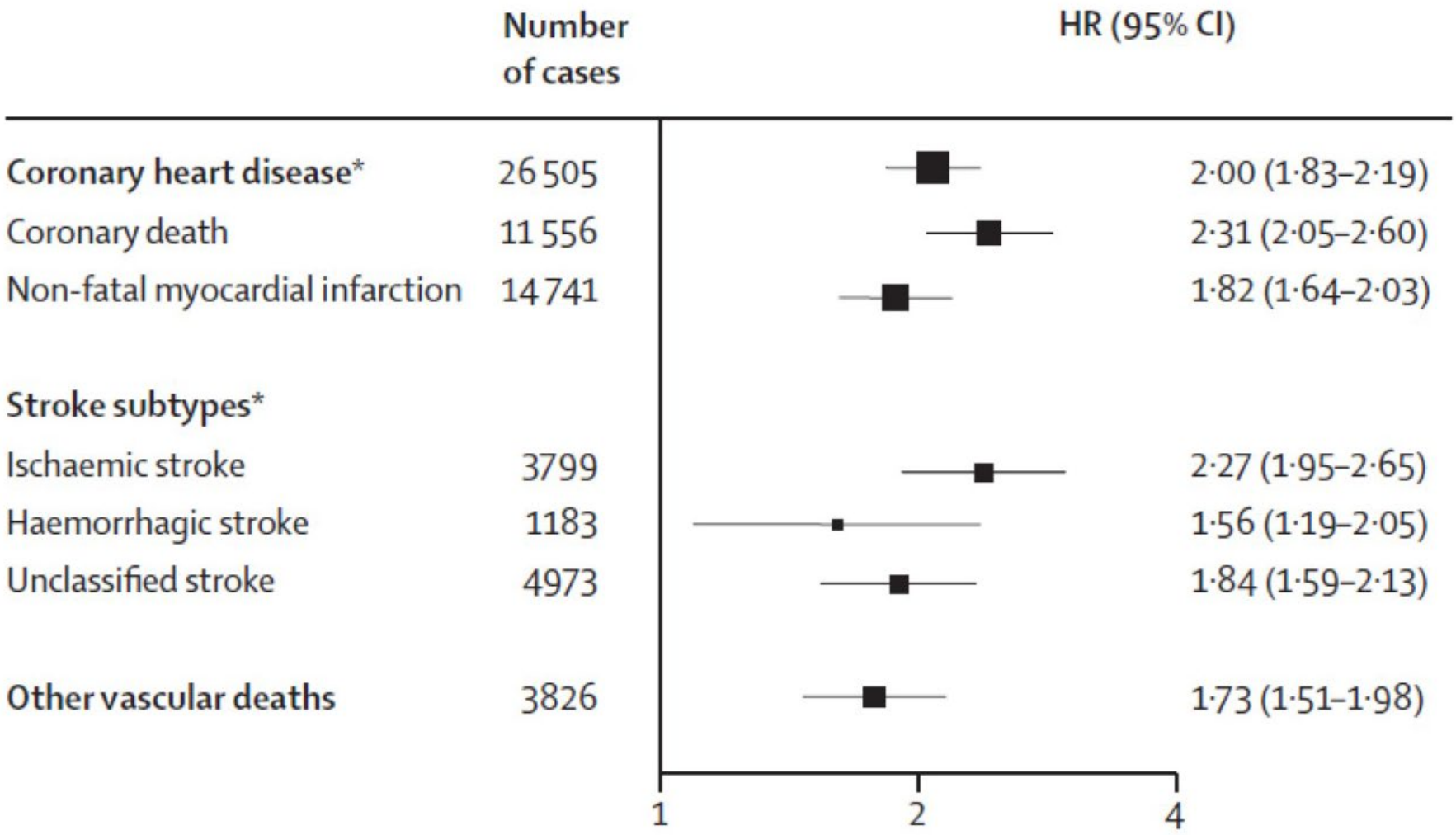
Effetti cardioprotettivi delle glifozine

Giorgio Sesti

FACOLTÀ DI MEDICINA
E PSICOLOGIA

SAPIENZA
UNIVERSITÀ DI ROMA

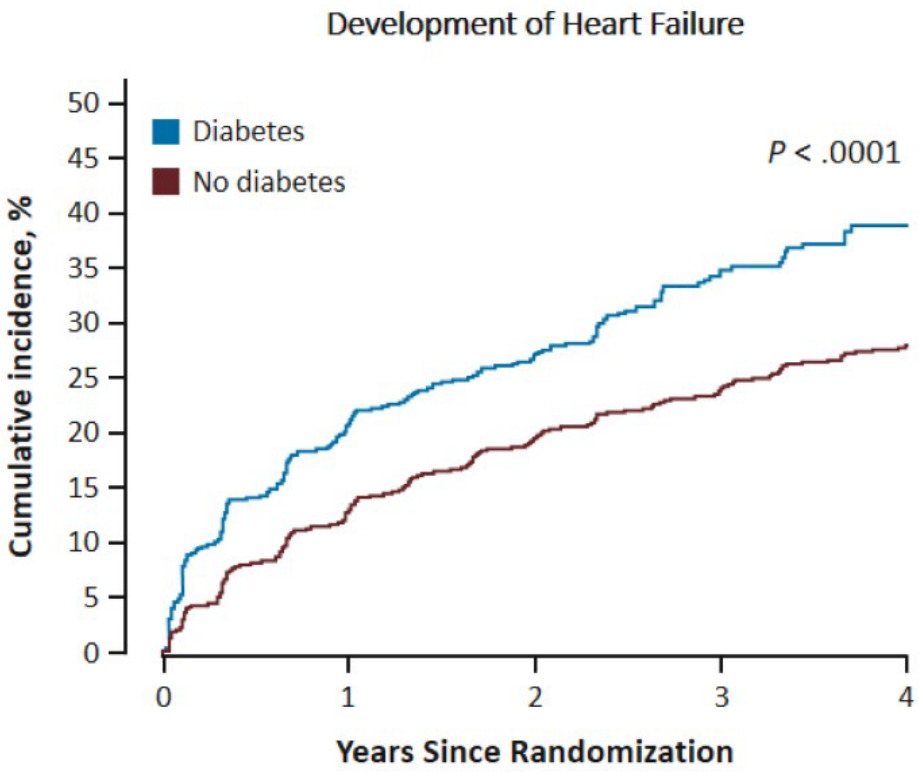
Hazard ratios (HRs) for vascular outcomes in people with versus those without diabetes at baseline

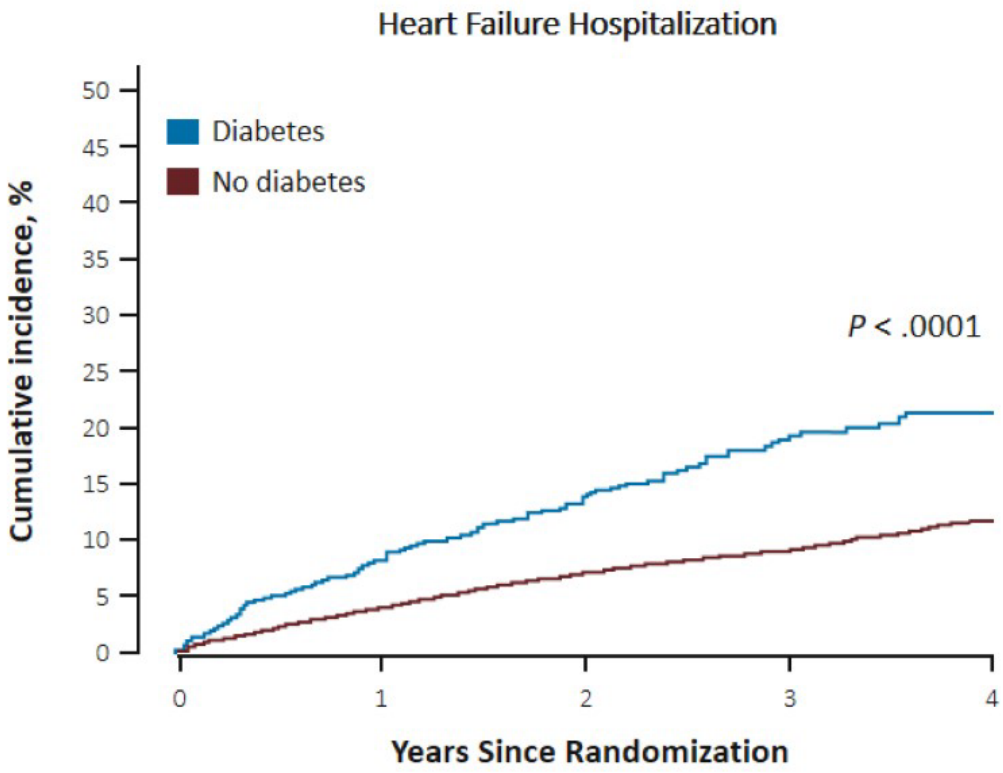


102 prospective studies, 700,000 patients, 8.5 million patient-y follow=up

The Emerging Risk Factors Collaboration Lancet 375: 2215–22, 2010

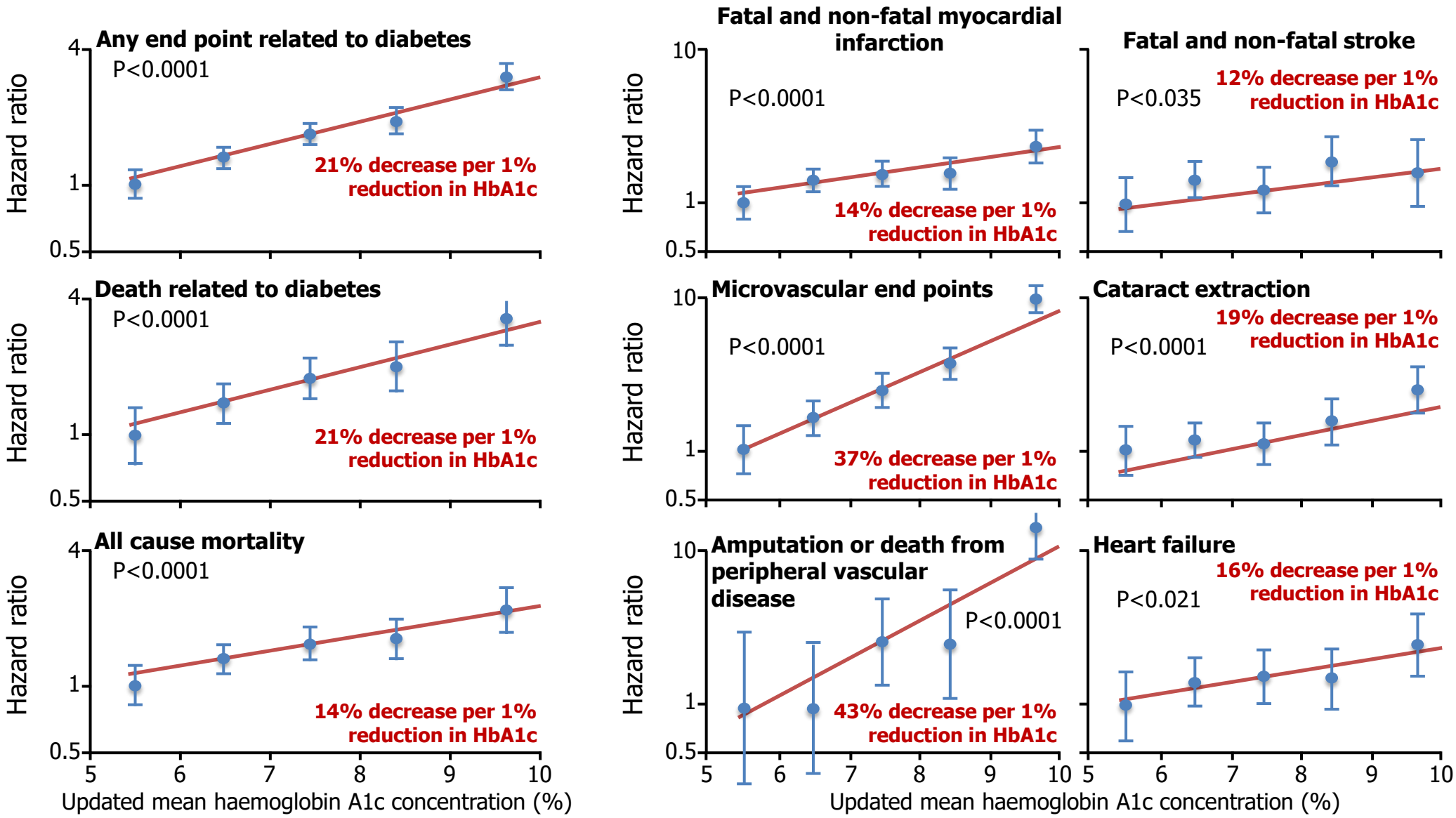
Type 2 diabetes increases risk of developing HF synmptoms and HF hospitalizations





Rørth R, et al. *Diabetes Care*. 2018;41:1285-1291.

Rationale for management of hyperglycaemia



Stratton et al. BMJ 2000;321:405–412

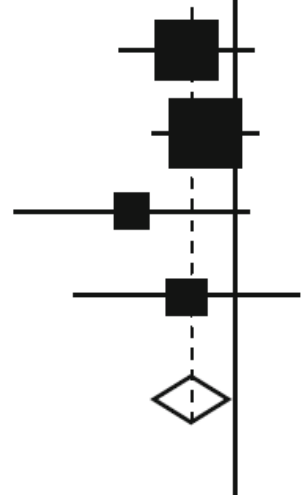
Landmark studies in type 2 diabetes: intensive glucose control on CV outcomes

Study	Duration, y	N	Glycemia	
			Target	Achieved HbA_{1c}, %
UKPDS[a]	10	3867	FPG <6 mmol/L (110 mg/dL)	7.0 vs 7.9
ACCORD[b]	3.5	10,251	HbA_{1c} <6.0%	6.4 vs 7.5
ADVANCE[c]	5	11,140	HbA_{1c} <6.5%	6.5 vs 7.3
VADT[d]	6.3	1791	HbA_{1c} <6.0%	6.9 vs 8.4

a. UKPDS Group *Lancet*. 1998;352:837-853; b. ACCORD Study Group, et al. *N Engl J Med*. 2011;364:818-828; c. ADVANCE Collaborative Group, et al. *N Engl J Med*. 2008;358:2560-2572; d. Duckworth W, et al. *N Engl J Med*. 2009;360:129-139.

UKPDS, ACCORD, ADVANCE, and VADT meta-analysis
MACE

Trials	Number of events (annual event rate, %) More intensive	Less intensive	ΔHbA_{1c} (%)	Hazard ratio (95% CI)
Major cardiovascular events				
ACCORD	352 (2.11)	371 (2.29)	−1.01	0.90 (0.78–1.04)
ADVANCE	557 (2.15)	590 (2.28)	−0.72	0.94 (0.84–1.06)
UKPDS	169 (1.30)	87 (1.60)	−0.66	0.80 (0.62–1.04)
VADT	116 (2.68)	128 (2.98)	−1.16	0.90 (0.70–1.16)
Overall	1,194	1,176	−0.88	0.91 (0.84–0.99) (Q=1.32, p=0.72, I^2=0.0%)

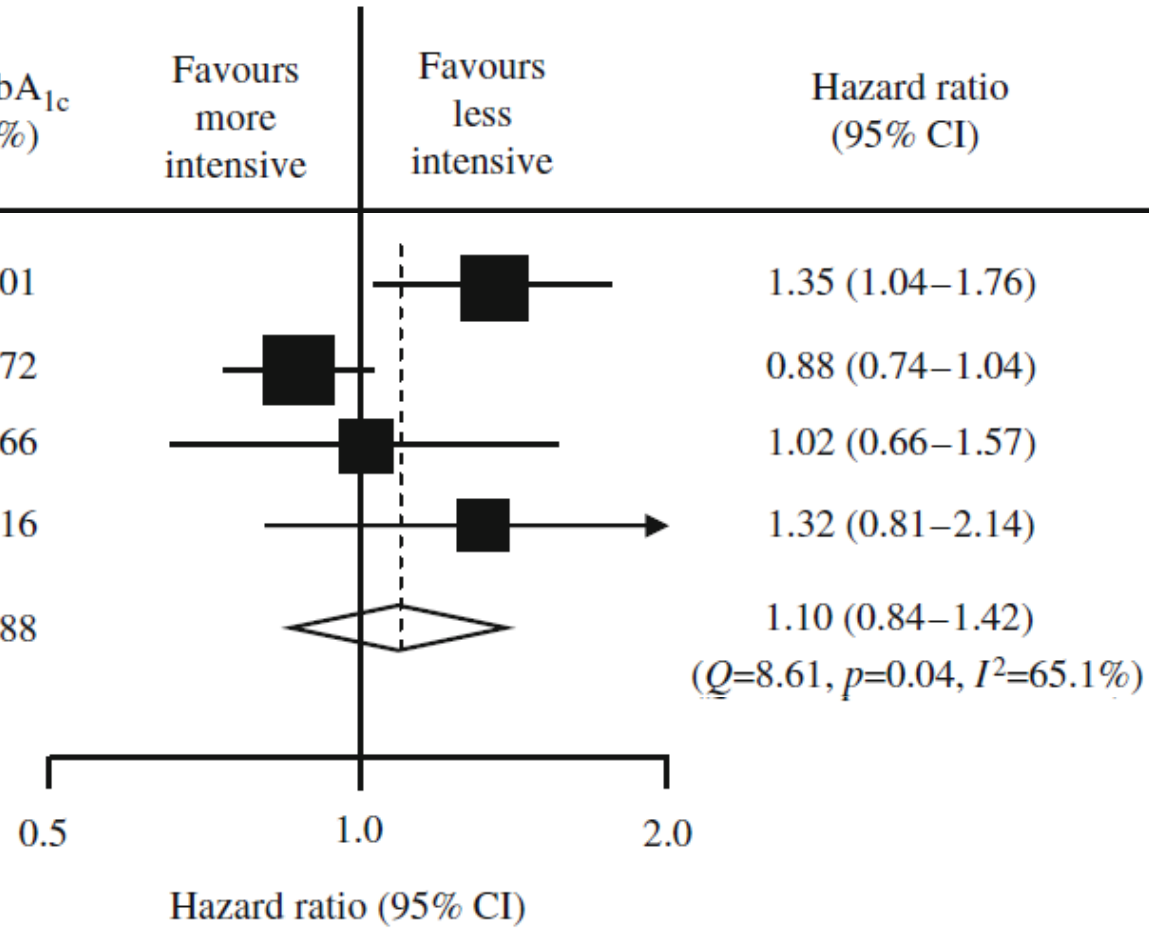


-9% Relative Risk

Turnbull FM et al. Diabetologia 52:2288–2298, 2009

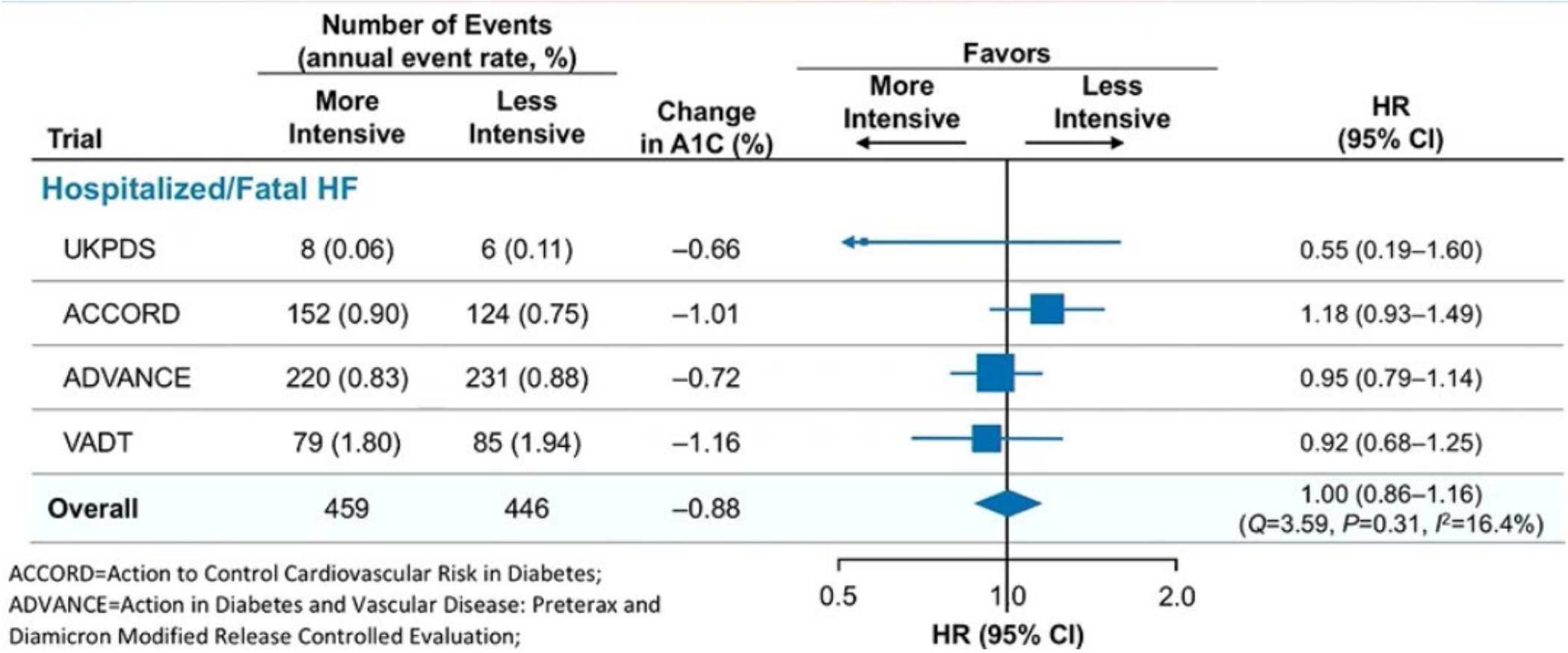
UKPDS, ACCORD, ADVANCE, and VADT meta-analysis
Cardiovascular death

Trials	Number of events (annual event rate, %)		ΔHbA_{1c} (%)	Hazard ratio (95% CI)
	More intensive	Less intensive		
ACCORD	135 (0.79)	94 (0.56)	−1.01	1.35 (1.04–1.76)
ADVANCE	253 (0.95)	289 (1.08)	−0.72	0.88 (0.74–1.04)
UKPDS	71 (0.53)	29 (0.52)	−0.66	1.02 (0.66–1.57)
VADT	38 (0.83)	29 (0.63)	−1.16	1.32 (0.81–2.14)
Overall	497	441	−0.88	1.10 (0.84–1.42) (Q=8.61, p=0.04, I^2=65.1%)



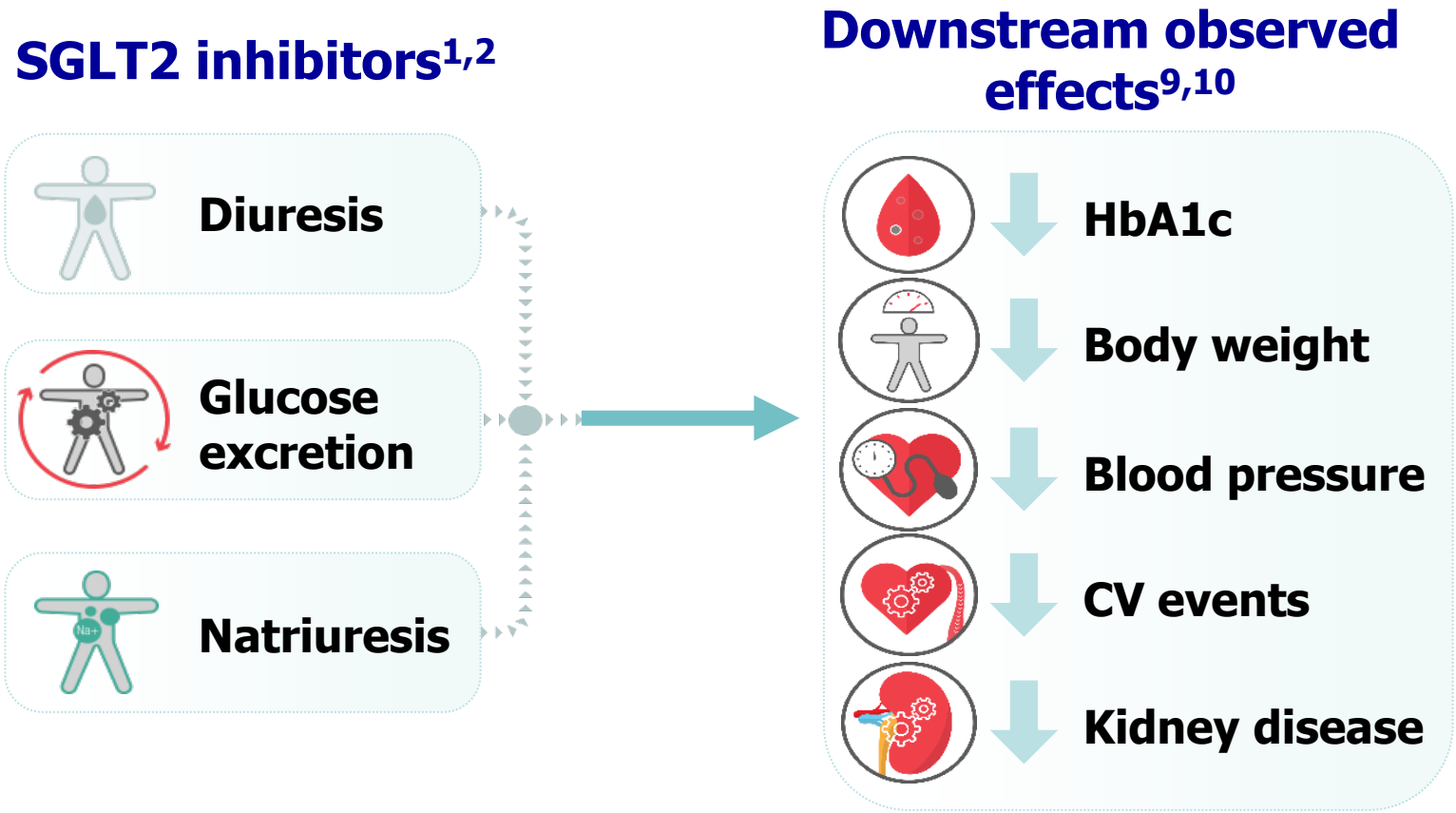
Turnbull FM et al. Diabetologia 52:2288–2298, 2009

Glucose control alone has failed to reduce the risk of adverse HF outcome in T2DM



ACCORD=Action to Control Cardiovascular Risk in Diabetes;
ADVANCE=Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation;

Effects of SGLT2 inhibitors on the cardio-renal-metabolic systems may be mediated via multiple mechanisms



CRM, cardio-renal-metabolic; LV, left ventricular

1. Vallon V & Thomson SC. Diabetologia 2017;60:215; 2. Heise T et al. Clin Ther 2016;38:2265; 4. Zinman B et al. N Engl J Med 2015:373:2117; 5. Wanner C et al. N Engl J Med 2016;375:323

SGLT2 inhibitors cardiovascular outcomes trials

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]	CREDENCE[4]	VERTIS CV
SGLT2 inhibitor	Empagliflozin	Canagliflozin	Dapagliflozin	Canagliflozin	Ertugliflozin
N	7020	10,142	17,160	4401	8246
Duration of follow-up, median, years	3.1	2.4	4.2	2.6	3.0
Age, mean ± SD, years	63.1 ± 8.6	63.3 ± 8.3	63.9 ± 6.8	63.0 ± 9.2	64.4 ± 8.1
Female, %	28.5	35.8	37.4	33.9	30.0
HbA1c, mean ± SD, %	8.1 ± 0.8	8.2 ± 0.9	8.3 ± 1.2	8.3 ± 1.3	8.2 ± 1.0
Diabetes duration, mean ± SD, years	NA	13.5 ± 7.8	11.8 ± 7.8	15.8 ± 8.6	13.0 ± 8.3
Established CV disease, %	100	65.6	40.6	50.4	100
History of HF, %	10.1	14.4	10.0	14.8	23.7
Reduced kidney function (eGFR <60 mL/min/1.73 m^2), %	25.9	20.1	7.4	59.8	21.9

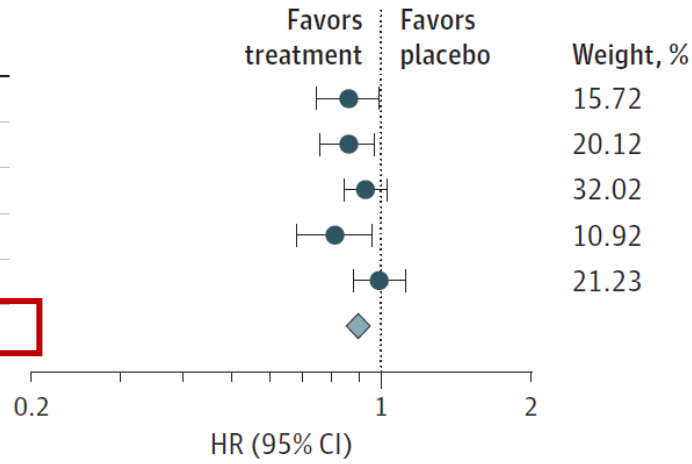
Summary of CVOTs with SGLT2 inhibitors

	EMPA-REG OUTCOME[1] (empagliflozin)	CANVAS Program[2] (canagliflozin)	DECLARE -TIMI 58[3] (dapagliflozin)	CREDENCE[4] (canagliflozin)	VERTIS CV (ertugliflozin)
3-point MACE	**HR 0.86** (95% CI 0.74, 0.99)	**HR 0.86** (95% CI 0.75, 0.97)	**HR 0.93** (95% CI 0.84, 1.03)	**HR 0.80** (95% CI 0.67, 0.95)	**HR 0.97** (95% CI 0.85, 1.11)
CV death	**HR 0.62** (95% CI 0.49, 0.77)	**HR 0.87** (95% CI 0.72, 1.06)	**HR 0.98** (95% CI 0.82, 1.17)	**HR 0.78** (95% CI 0.61, 1.00)	**HR 0.92** (95% CI 0.77, 1.11)
Non-fatal MI	**HR 0.87** (95% CI 0.70, 1.09)	**HR 0.85** (95% CI 0.69, 1.05)	**HR 89** (95% CI 0.77, 1.01)	**HR 0.81[5]** (95% CI 0.59, 1.10)	**HR 1.0** (95% CI 0.86, 1.27)
Non-fatal stroke	**HR 1.24** (95% CI 0.92, 1.67	**HR 0.90** (95% CI 0.71, 1.15)	**HR 1.01** (95% CI 0.84, 1.21)	**HR 0.80[5]** (95% CI 0.56, 1.15)	**HR 1.0** (95% CI 0.76, 1.32)
Hospitalization for HF	**HR 0.65** (95% CI 0.50, 0.85)	**HR 0.67** (95% CI 0.52, 0.87)	**HR 0.73** (95% CI 0.61, 0.88)	**HR 0.61** (95% CI 0.47, 0.80)	**HR 0.70** (95% CI 0.54, 0.90)

1. Zinman B et al. N Engl J Med 2015;373:2117; 2. Neal B et al. N Engl J Med 2017;377:644; 3. Wiviott S et al. N Engl J Med 2019;380:347; 4 Perkovic V et al. N Engl J Med 380(24):2295-2306, 2019; 5 Mahaffey KW et al Circulation 140(9):739-750, 2019

SGLT2 inhibitors cardiovascular outcomes trials: MACE

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	490/4687	37.4	282/2333	43.9	0.86 (0.74-0.99)
CANVAS program	NA/5795	26.9	NA/4347	31.5	0.86 (0.75-0.97)
DECLARE-TIMI 58	756/8582	22.6	803/8578	24.2	0.93 (0.84-1.03)
CREDENCE	217/2202	38.7	269/2199	48.7	0.80 (0.67-0.95)
VERTIS CV	735/5499	40.0	368/2747	40.3	0.99 (0.88-1.12)
Fixed-effects model (Q = 5.22; *df* = 4; *P* = .27; I^2 = 23.4%)					0.90 (0.85-0.95)

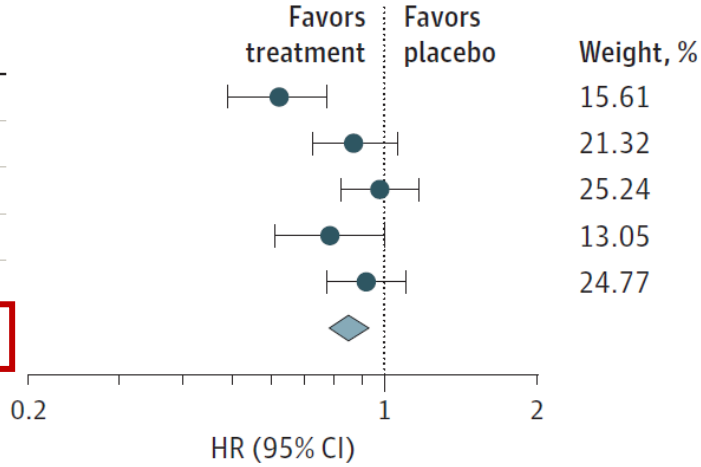


-10% Relative Risk

Mc Guire DK et al. JAMA Cardiol 6(2):148-158, 2021

SGLT2 inhibitors cardiovascular outcomes trials: CV Death

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	172/4687	12.4	137/2333	20.2	0.62 (0.49-0.77)
CANVAS program	NA/5795	11.6	NA/4347	12.8	0.87 (0.72-1.06)
DECLARE-TIMI 58	245/8582	7.0	249/8578	7.1	0.98 (0.82-1.17)
CREDENCE	110/2202	19.0	140/2199	24.4	0.78 (0.61-1.00)
VERTIS CV	341/5499	17.6	184/2747	19.0	0.92 (0.77-1.10)
Fixed-effects model ($Q = 11.22$; $df = 4$; $P = .02$; $I^2 = 64.3\%$)					0.85 (0.78-0.93)



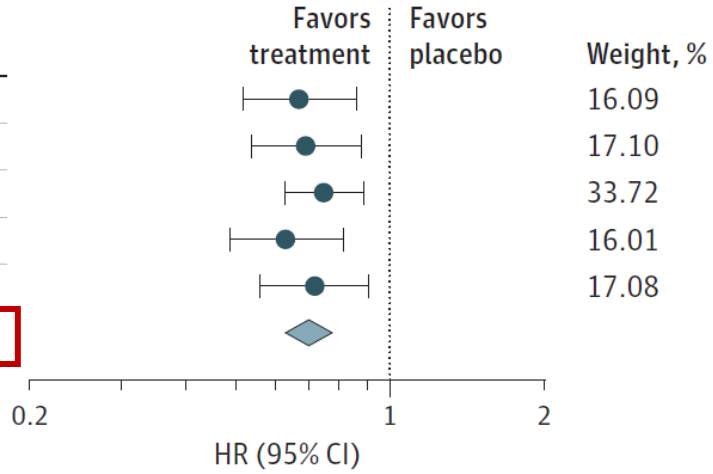
-15% Relative Risk

CI, confidence interval; CV, cardiovascular.

Mc Guire DK et al. JAMA Cardiol 6(2):148-158, 2021

SGLT2 inhibitors cardiovascular outcomes trials: HF hospitalization

	Treatment		Placebo		
	No./total No.	Rate/1000 patient-years	No./total No.	Rate/1000 patient-years	Hazard ratio (95% CI)
EMPA-REG OUTCOME	126/4687	9.4	95/2333	14.5	0.65 (0.50-0.85)
CANVAS program	NA/5795	5.5	NA/4347	8.7	0.67 (0.52-0.87)
DECLARE-TIMI 58	212/8582	6.2	286/8578	8.5	0.73 (0.61-0.88)
CREDENCE	89/2202	15.7	141/2199	25.3	0.61 (0.47-0.80)
VERTIS CV	139/5499	7.3	99/2747	10.5	0.70 (0.54-0.90)
Fixed-effects model (Q = 1.39; *df* = 4; *P* = .85; I^2 = 0.0%)					0.68 (0.61-0.76)



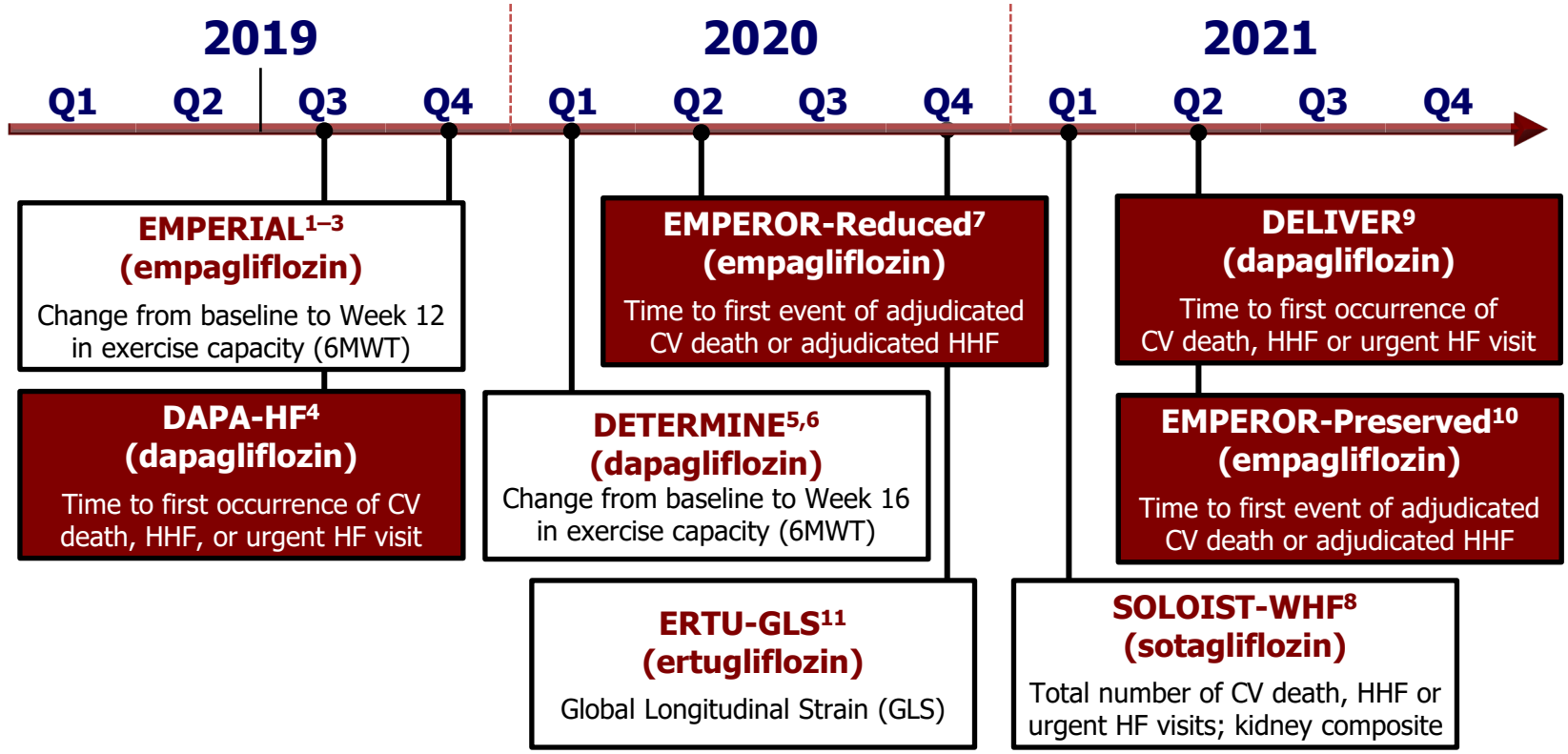
-32% Relative Risk

CI, confidence interval; HHF, hospitalization for heart failure.

Mc Guire DK et al. JAMA Cardiol 6(2):148-158, 2021

Dedicated heart failure trials will SGLT2 inhibitors

Timeline for trial completion



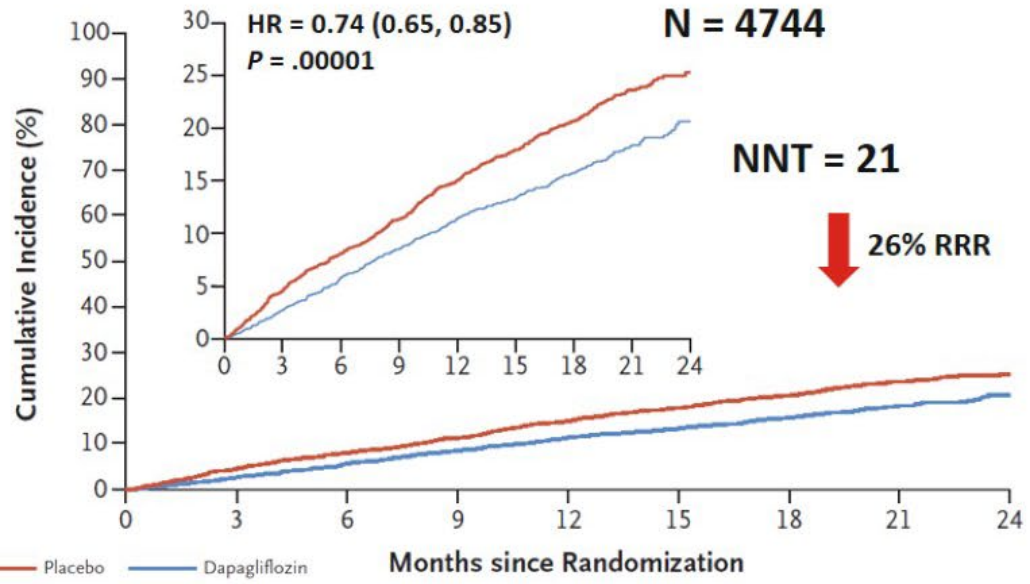
Outcomes listed are key primary endpoints 6MWT, 6-minute walk test; CV, cardiovascular; HF, heart failure; HHF, hospitalisation for heart failure.

1. NCT03448406; 2. NCT03448419; 3. Abraham WT et al. Eur J Heart Fail 2019; doi:10.1002/ejhf.1486; 4. NCT03036124; 5. NCT03877224; 6. NCT03877237; 7. NCT03057977; 8. NCT03521934; 9. NCT03619213; 10. NCT03057951; 11. NCT03717194

DAPA-HF trial: Primary Endpoint

4744 patients with New York Heart Association class II, III, or IV HF and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo

Results: Dapagliflozin significantly reduces the primary endpoint of CV death or worsening of HF (HHF or urgent HF visit)



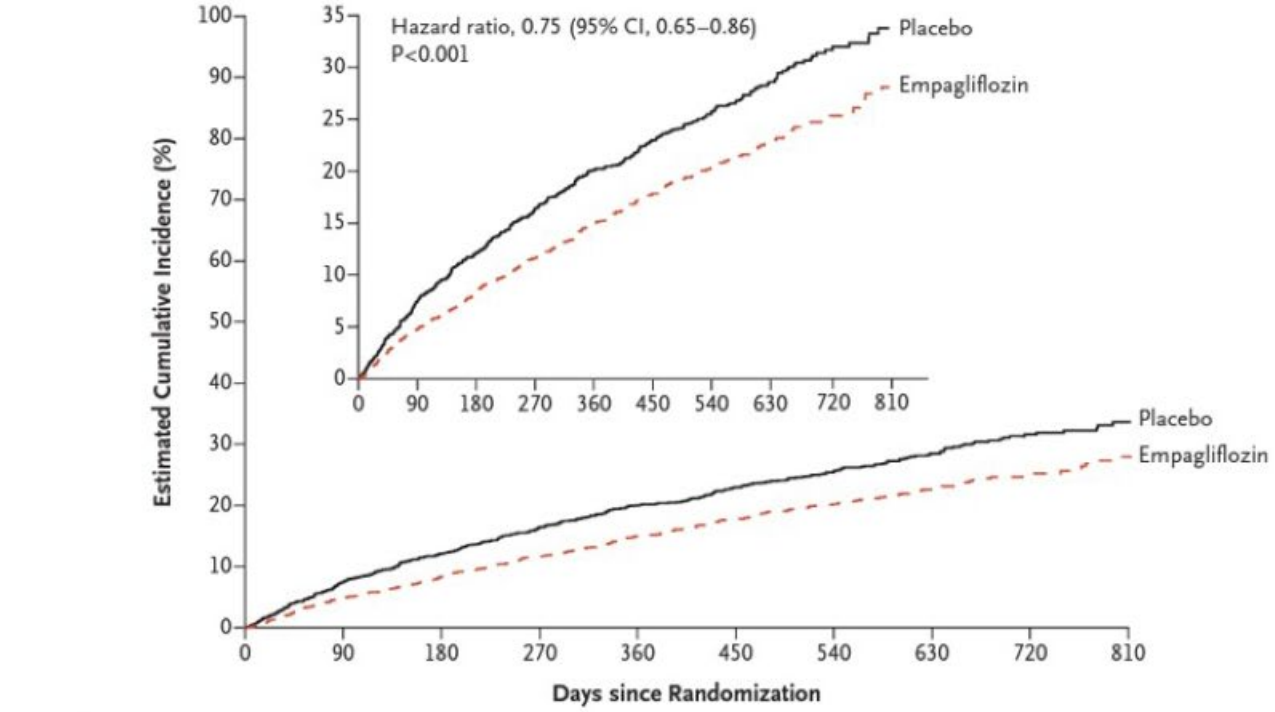
No. at Risk									
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210
Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210

McMurray JJ, et al. *N Engl J Med*. 2019;381:1995-2008; McMurray JJ, et al. *Eur J Heart Fail*. 2019;21:665-675.

EMPEROR-Reduced Primary Endpoint

3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo

Results: Empagliflozin significantly reduced the primary endpoint (CV death or HHF)



RRR 25%

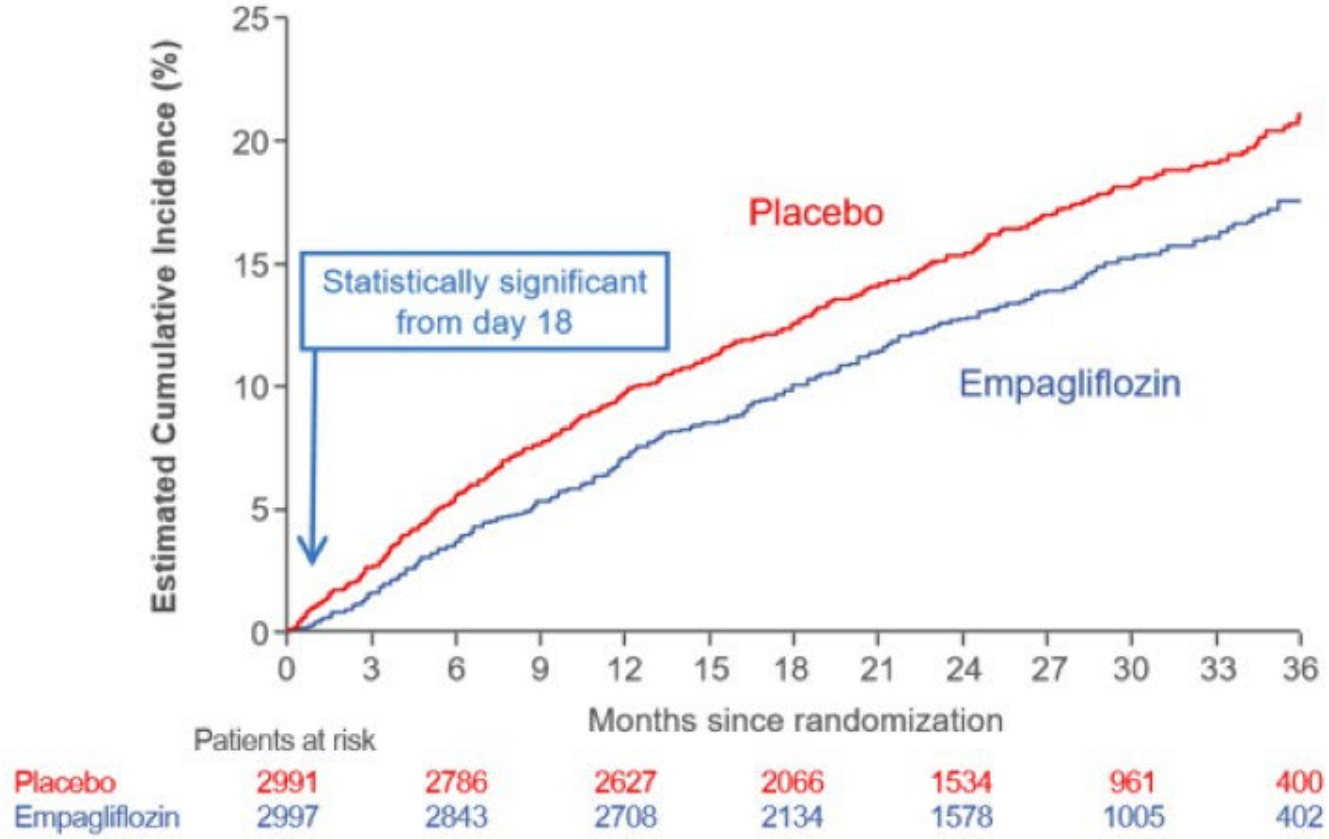
ARR 5.2%

NNT = 19

Packer M et al. N Engl J Med. 383:1413-24, 2020

EMPEROR-Preserved Primary Endpoint
Composite of CV death and HF hospitalization

5988 patients with class II–IV heart failure and LVEF >40% were randomized to receive empagliflozin (10 mg once daily) or placebo



HR 0.79
(95% CI 0.69, 0.90)
P = 0.0003

Placebo:
511 patients with event
Rate: 8.7 per 100 patient-years

Empagliflozin:
415 patients with event
Rate: 6.9 per 100 patient-years

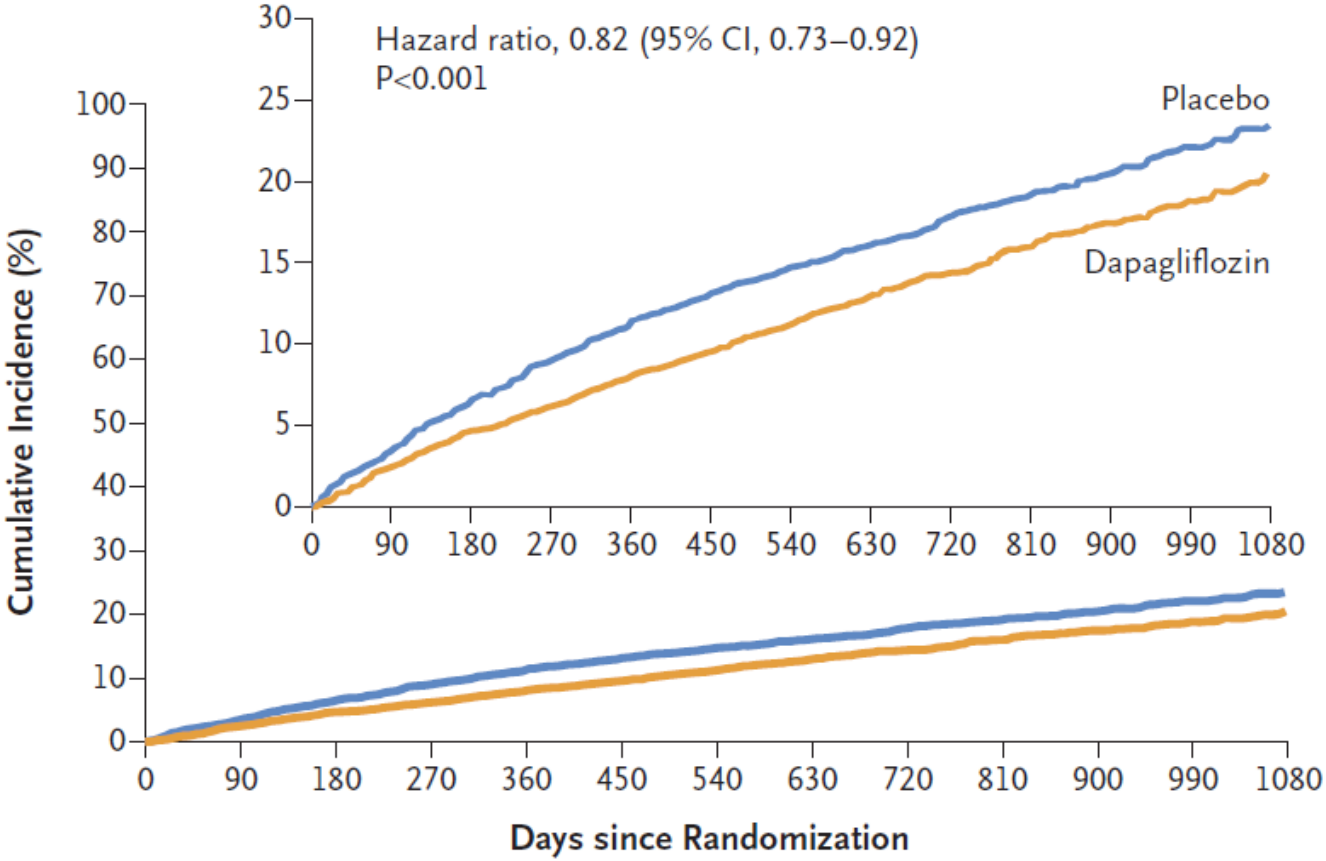
RRR 21%

NNT=31
During a median trial period of 26 months.

Anker SD et al. N Engl J Med 385:1451-61, 2021

Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction: the DELIVER Trial - Composite of occurrence of worsening HF or cardiovascular death

6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo

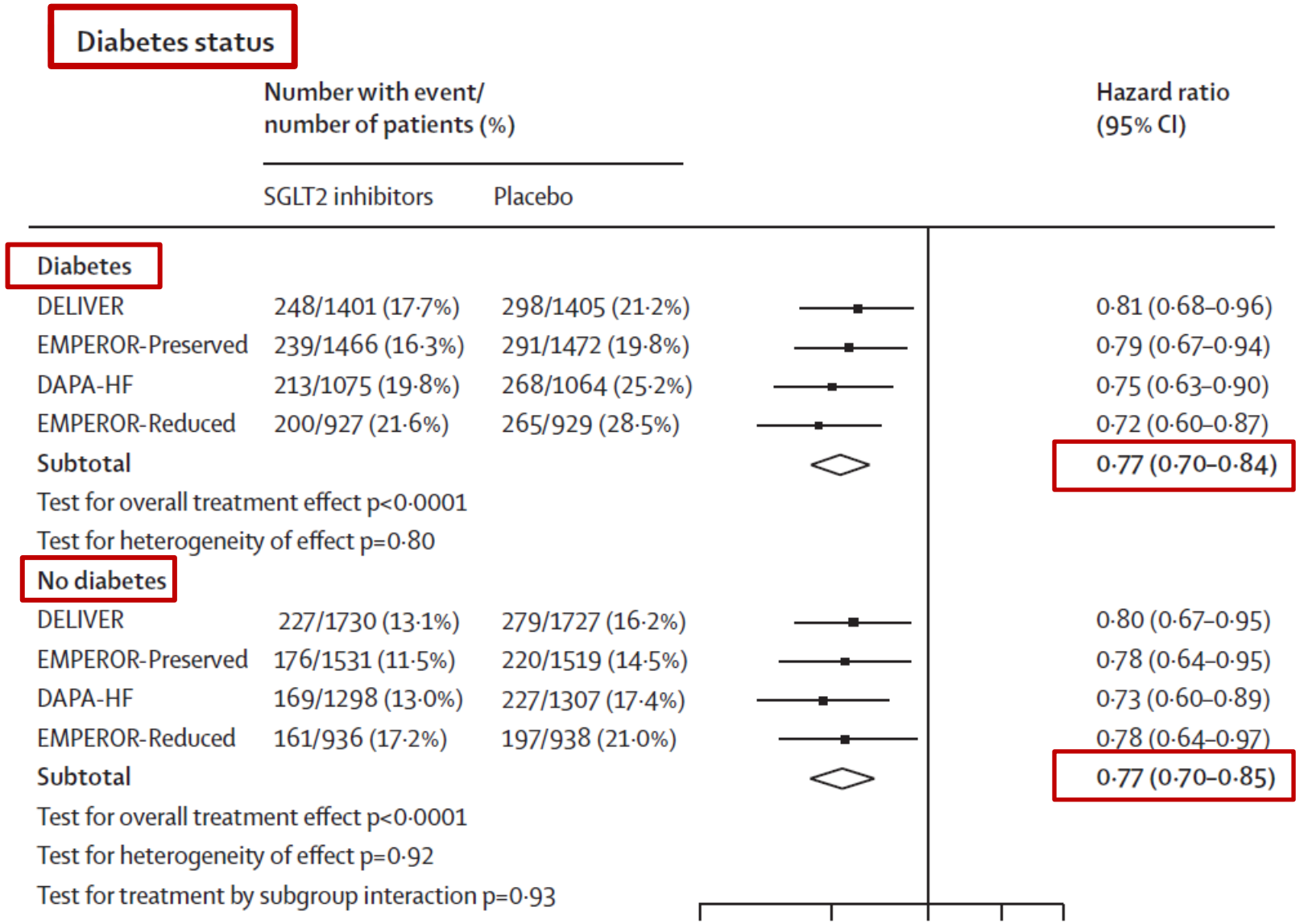


No. at Risk

Placebo	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383
Dapagliflozin	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389

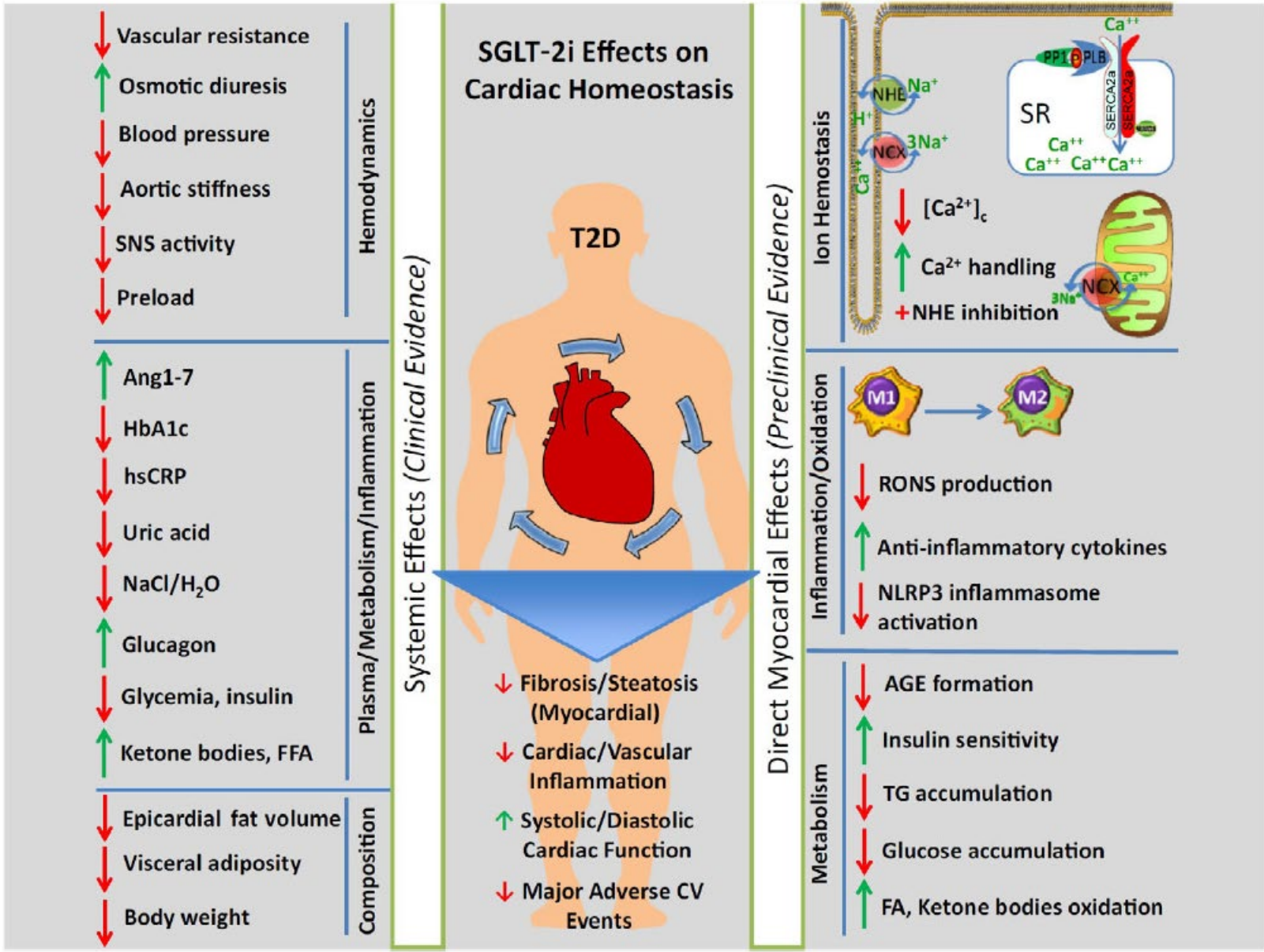
Solomon SD et al. N Engl J Med 387:1089-98, 2022

Treatment effects of SGLT2 inhibitors on the composite of cardiovascular death or first hospitalisation for heart failure



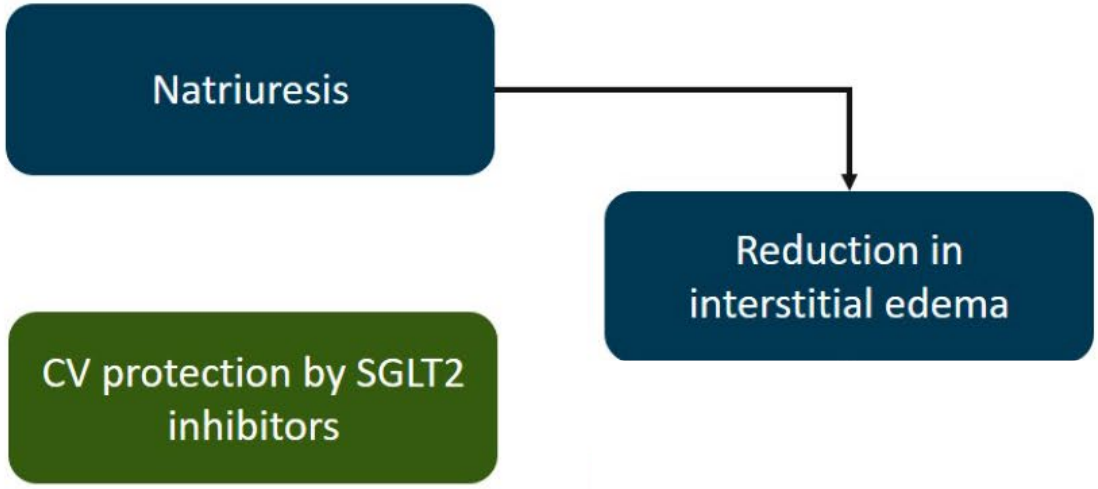
Vaduganathan M et al. Lancet 2022 Aug 26;S0140-6736(22)01429-5. doi: 10.1016/S0140-6736(22)01429-5. Online ahead of print

Impact of SGLT-2i–mediated systemic and direct myocardial effects on cardiac homeostasis



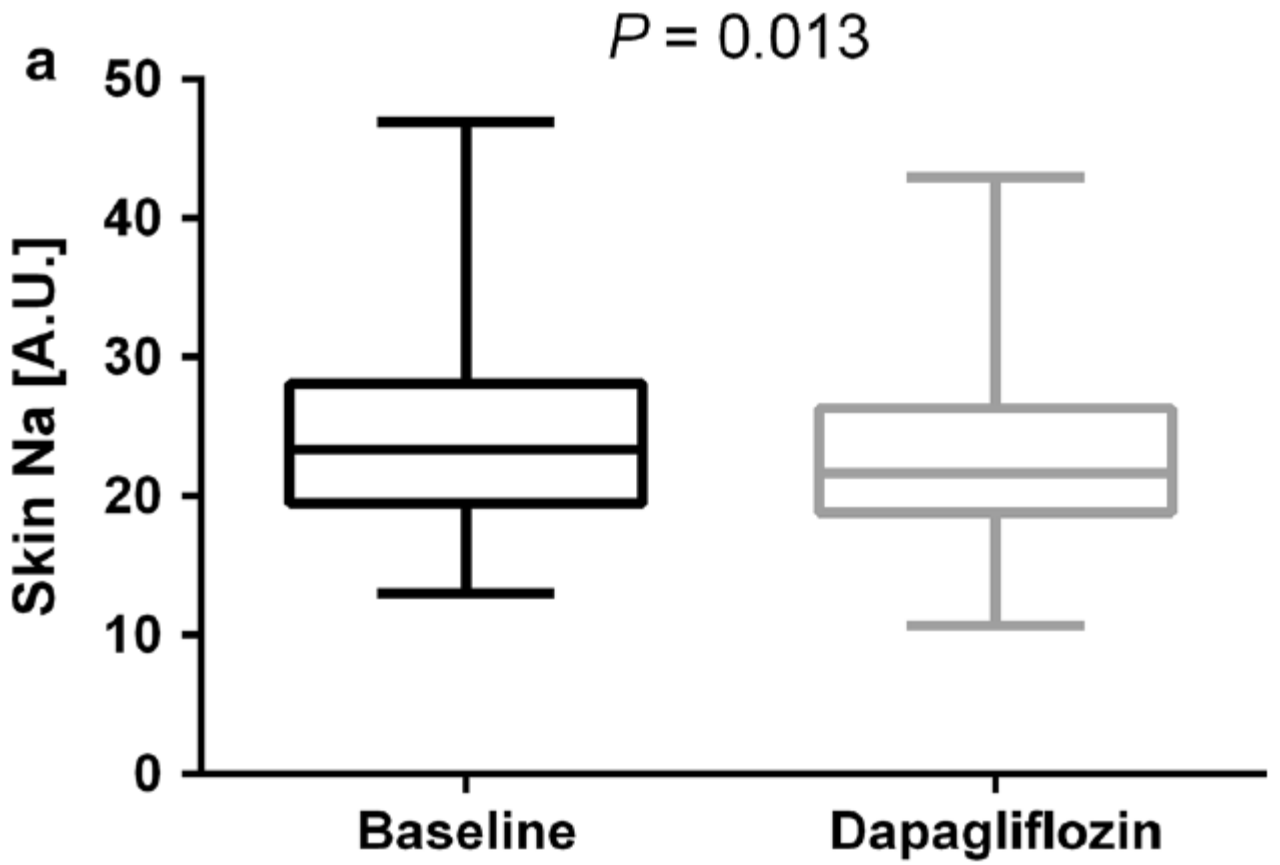
Chilton RJ Diabetes Obes Metab. 1–14, 2019

CV protection of SGLT2 inhibitors



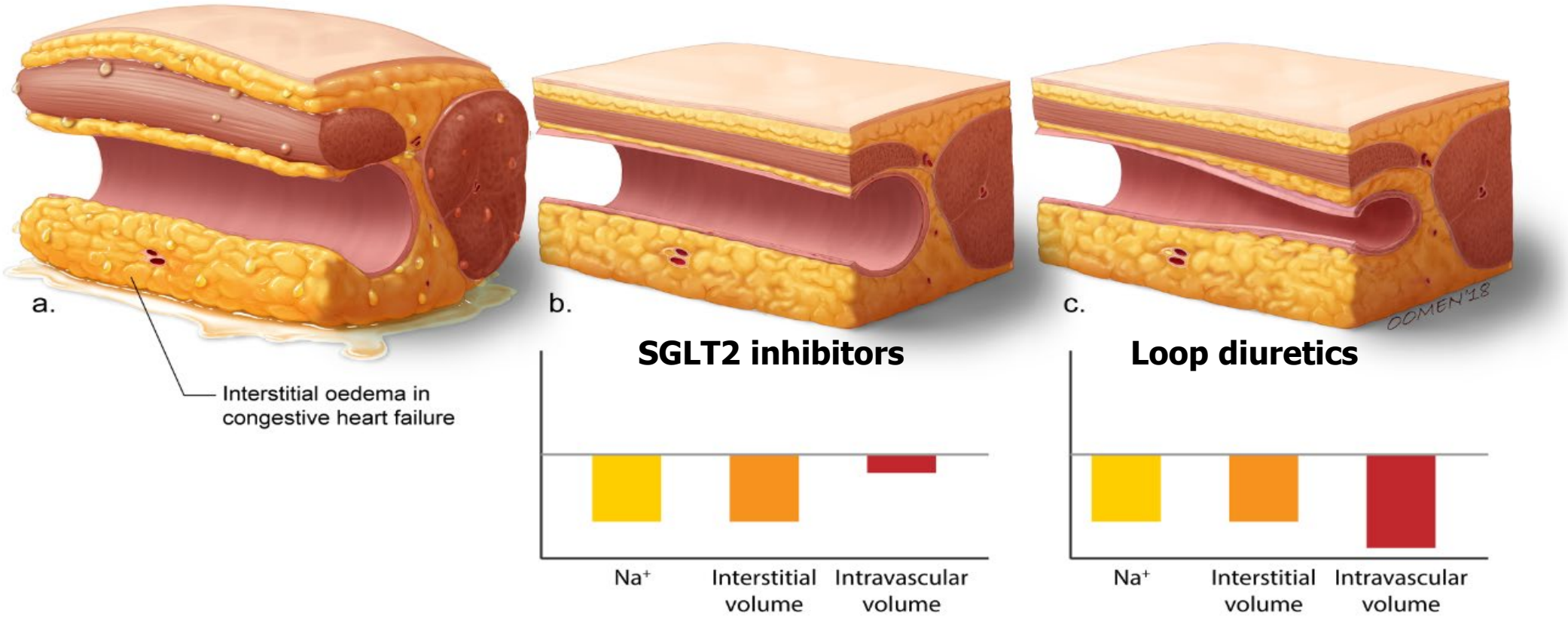
Farkouh ME, et al. *J Am Coll Cardiol.* 2018;71:2507-2510.

Dapagliflozin reduces sodium tissue content of the skin as measured by ^{23}Na-MRI imaging in T2DM subjects



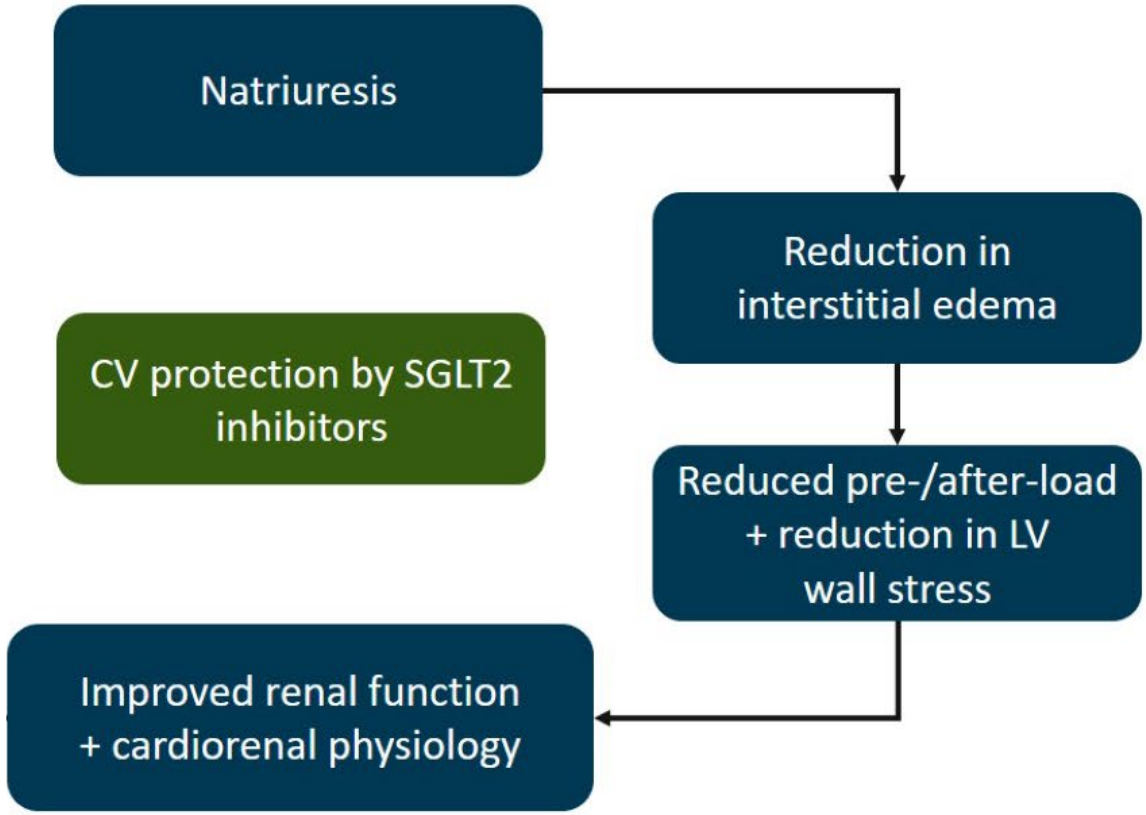
Karg MV et al. Cardiovasc Diabetol 17:5, 2018

SGLT2 inhibitors may differentially regulate the interstitial vs intravascular compartment when compared with loop diuretics thus limiting the reflex neuro-humoral stimulation that occurs in response to intravascular volume contraction with traditional diuretics



Verma and McMurray Diabetologia 61:2108–2117, 2018

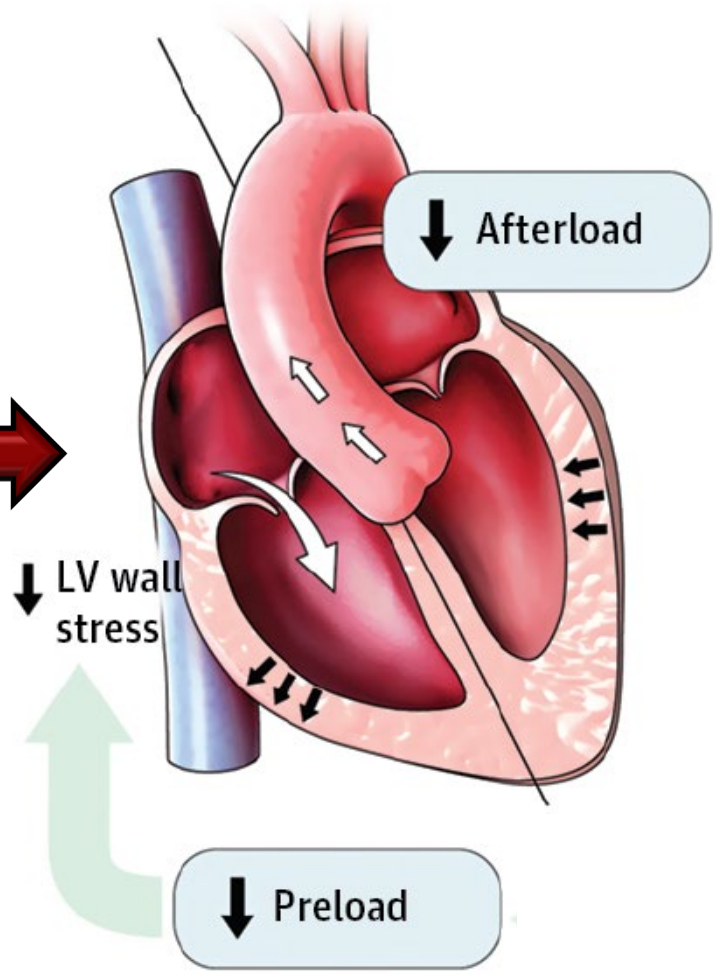
CV protection of SGLT2 inhibitors



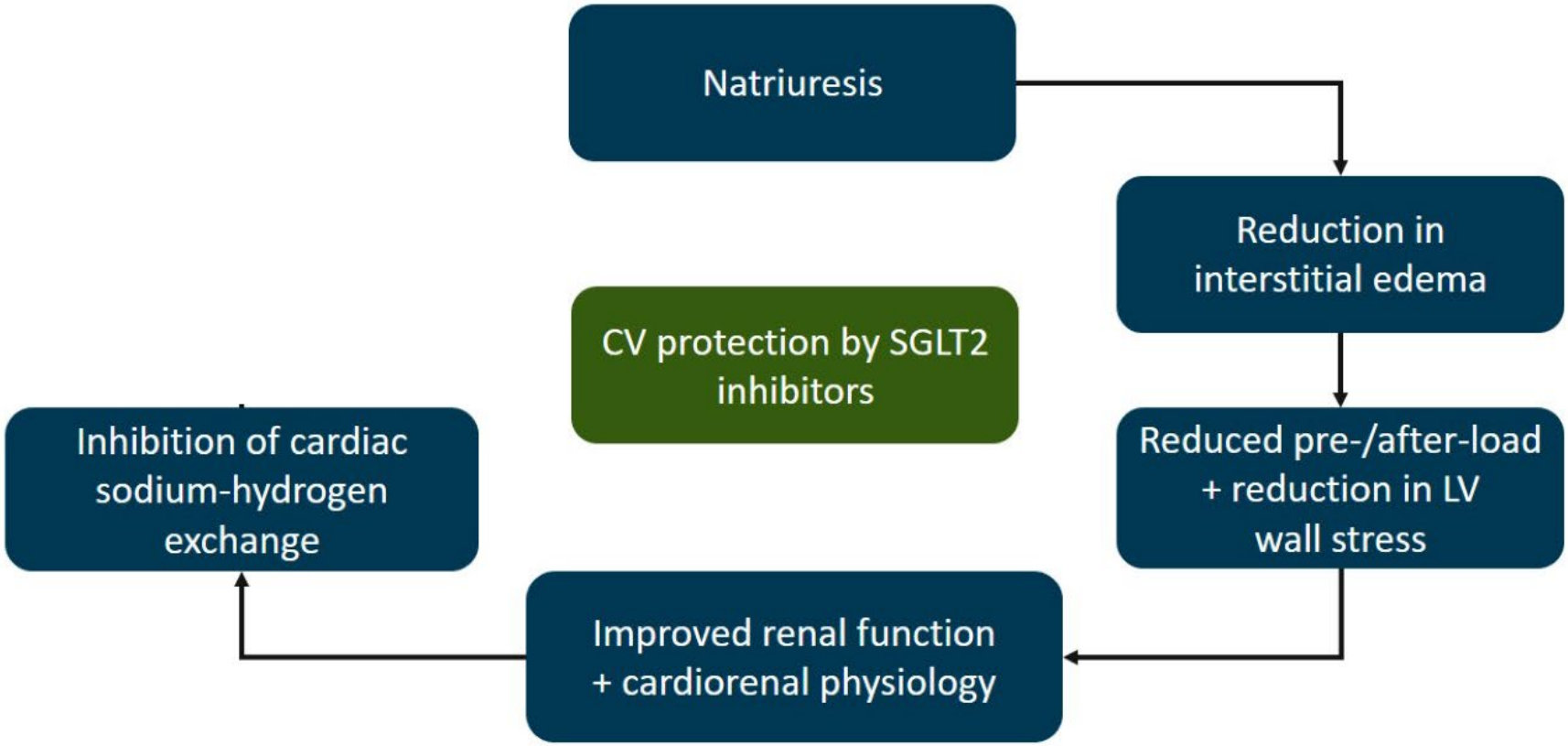
Farkouh ME, et al. *J Am Coll Cardiol.* 2018;71:2507-2510.

SGLT2 inhibitors may exert their beneficial actions via improvement of ventricular loading conditions, secondary to a reduction in preload due to the diuretic and natriuretic effects and afterload

- ↓ Sodium tissue content
- ↓ Blood pressure
- ↓ Arterial stiffness
- ↑ Vasodilation

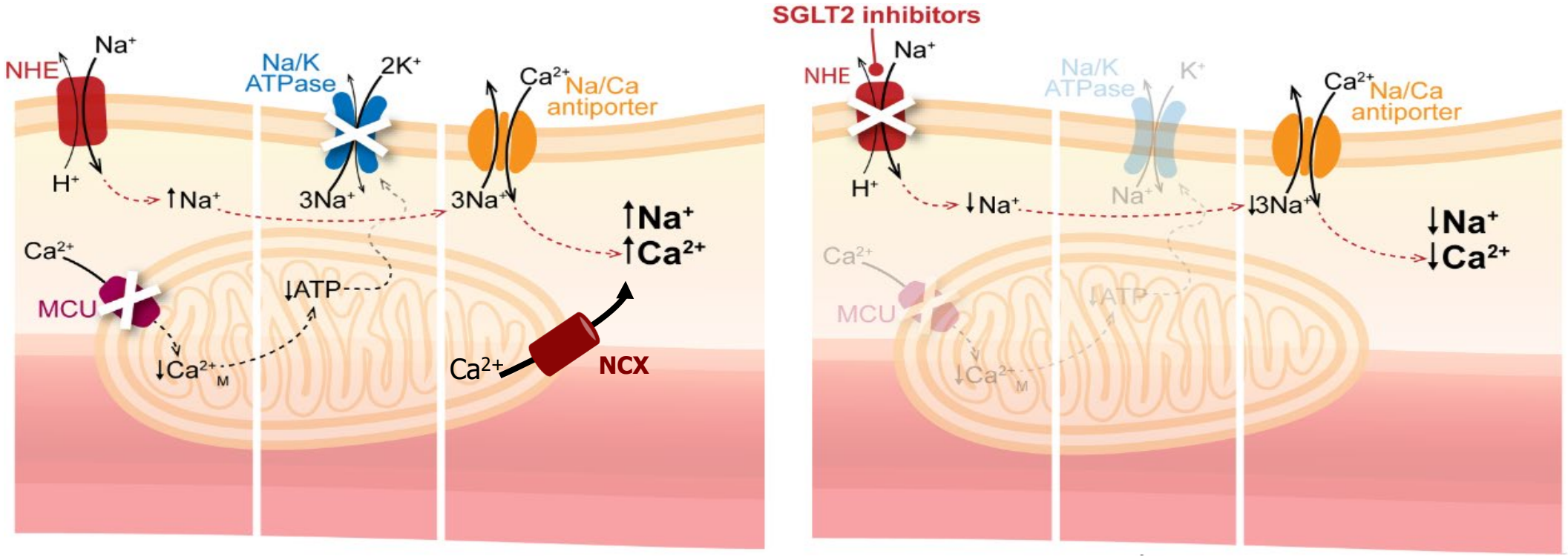


CV protection of SGLT2 inhibitors



Farkouh ME, et al. *J Am Coll Cardiol.* 2018;71:2507-2510.

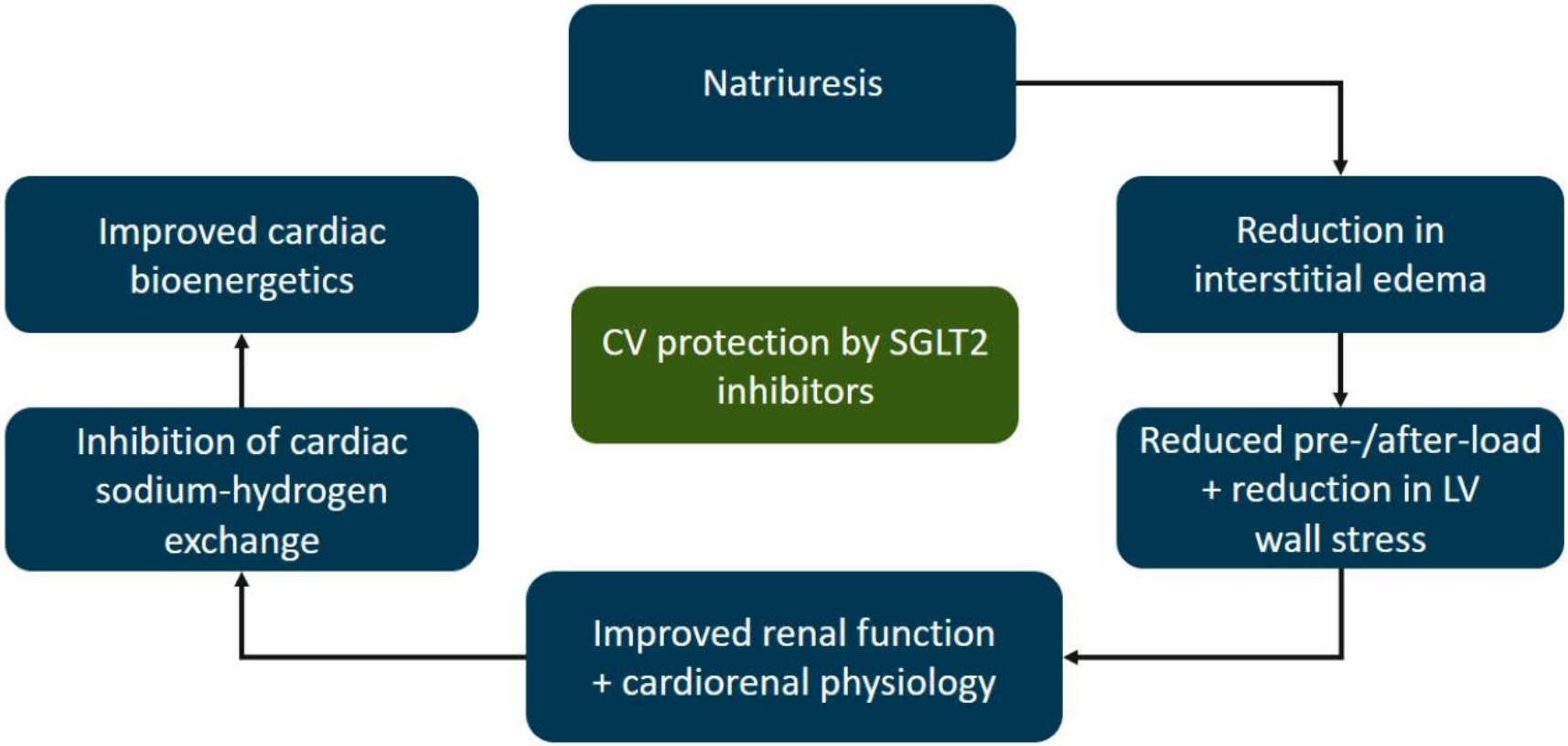
SGLT2 inhibition and direct effects on Na^+/H^+ exchanger 1 in the myocardium



MCU: mitochondrial Ca2+ uniporter
NCX: Na+/Ca2+ exchanger

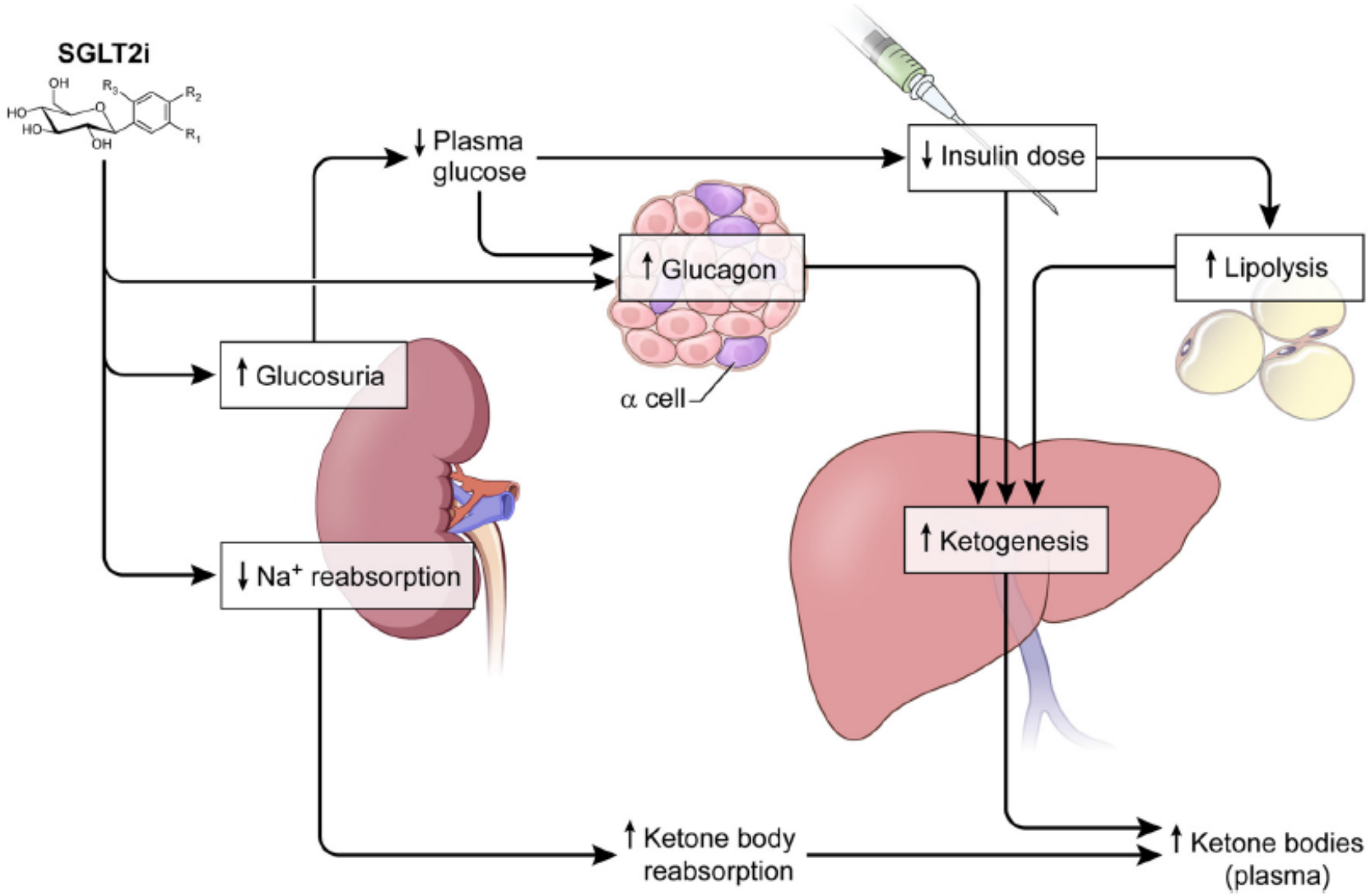
Verma and McMurray Diabetologia 61:2108–2117, 2018

CV protection of SGLT2 inhibitors



Farkouh ME, et al. *J Am Coll Cardiol.* 2018;71:2507-2510.

Potential mechanisms whereby adjunctive therapy with SGLT2 inhibitors may promote ketosis and increase the risk of ketoacidosis in type 1 diabetics



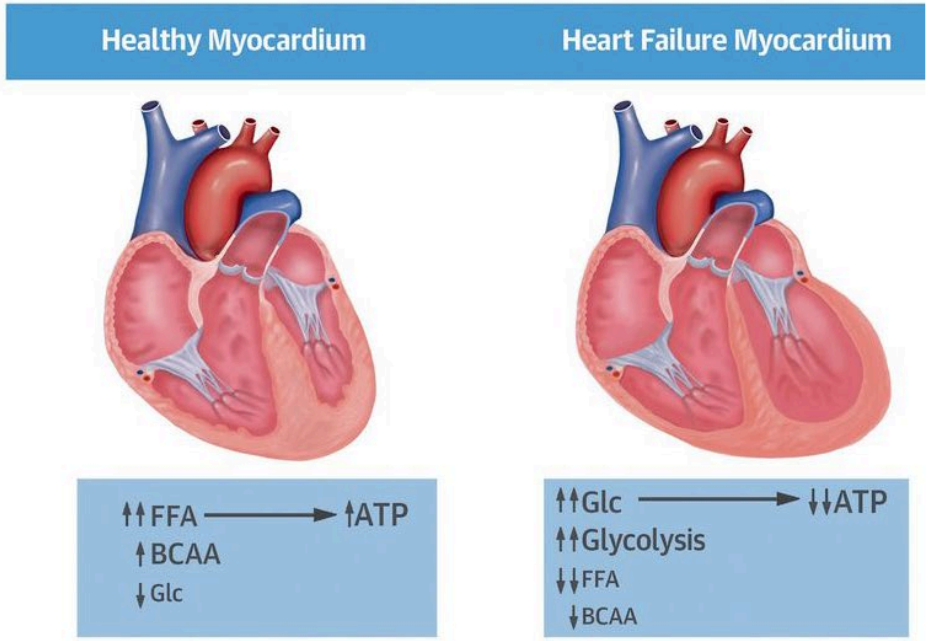
Fuel energetics of various substrates

Substrate	P/O ratio***	Energy liberated, kcal/mol of 2-carbon units
Glucose	2.58	223.6
Pyruvate	2.50*	185.7*
Palmitate	2.33**	298**
BHOB	2.50*	243.6*

*Although the difference in energy produced by BHOB (per oxygen atom consumed) is comparable to pyruvate, more energy is derived from BHOB vs. pyruvate due to BHOB being more reduced. If pyruvate were burned in a bomb calorimeter, it would liberate 185.7 kcal/mol of 2-carbon units, whereas the combustion of BHOB would liberate 31% more calories (243.6 calories/2-carbon unit). **Combustion of palmitate generates 298 kcal/mol of 2-carbon units, but there is loss of ATP due to uncoupling proteins generating heat instead of ATP. ***P/O ratio reflects the number of molecules of ATP produced per atom of oxygen reduced by the mitochondrial electron transport chain.

Mudaliar S et al. Diabetes Care 39:1115–1122, 2016

Postulated effects of SGLT2 inhibitors on heart failure



Santos-Gallego, C.G. et al. J Am Coll Cardiol. 2019;73(15):1931-44.

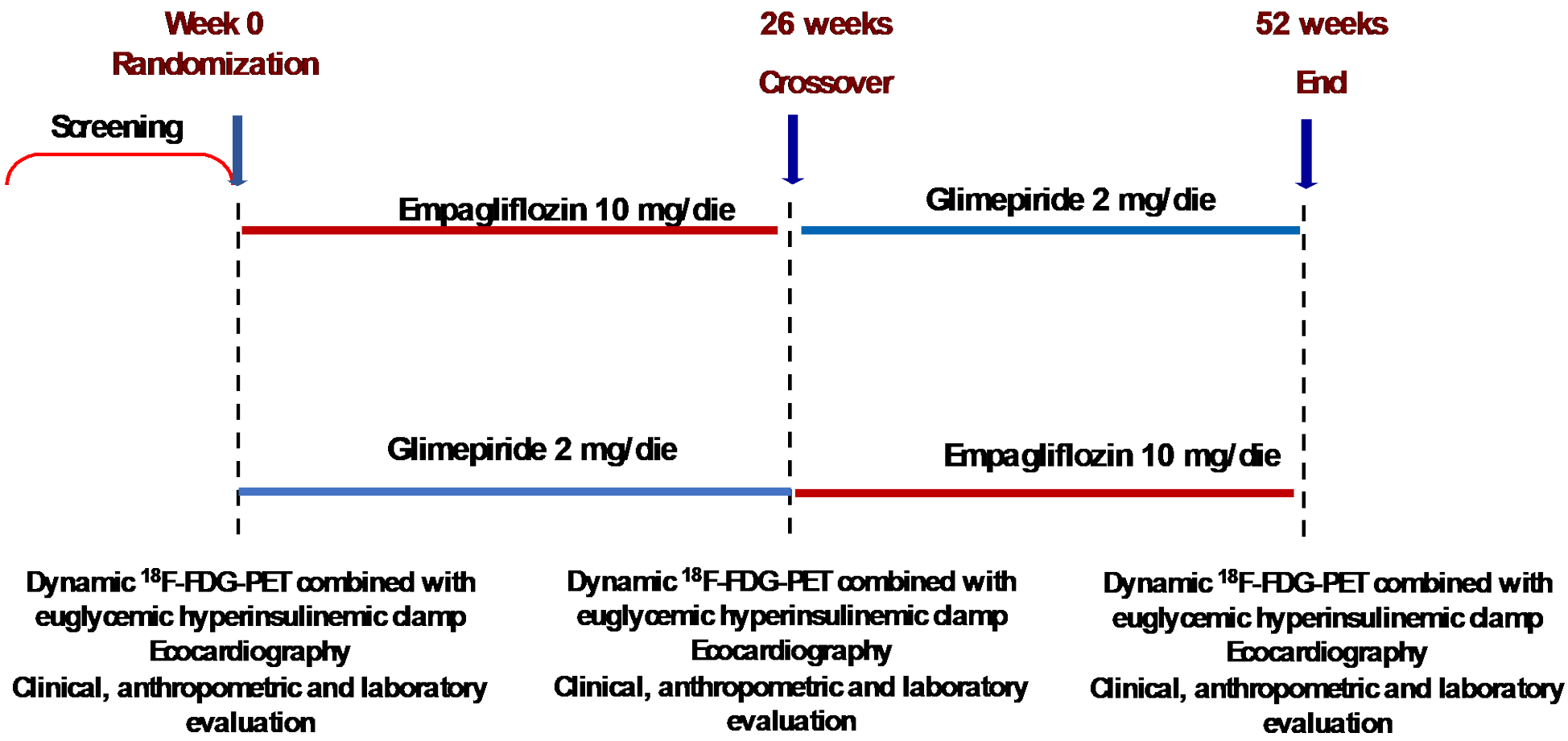
BCAA: Branched chain amino acids
FFA: Free fatty acids

To investigate the cardioprotective mechanism of SGLT2i we performed a 26-week, randomized, open-label, cross-over, active-comparator study to determine the effects of empagliflozin 10 mg versus glimepiride 2 mg daily on myocardial glucose metabolic rate assessed by cardiac dynamic 18F-FDG PET combined with a euglycemic-hyperinsulinemic clamp in 23 patients with type 2 diabetes (FIORE trial).

We also measured cardiac geometry, myocardial mechano-energetic efficiency, and systolic and diastolic function by echocardiography.

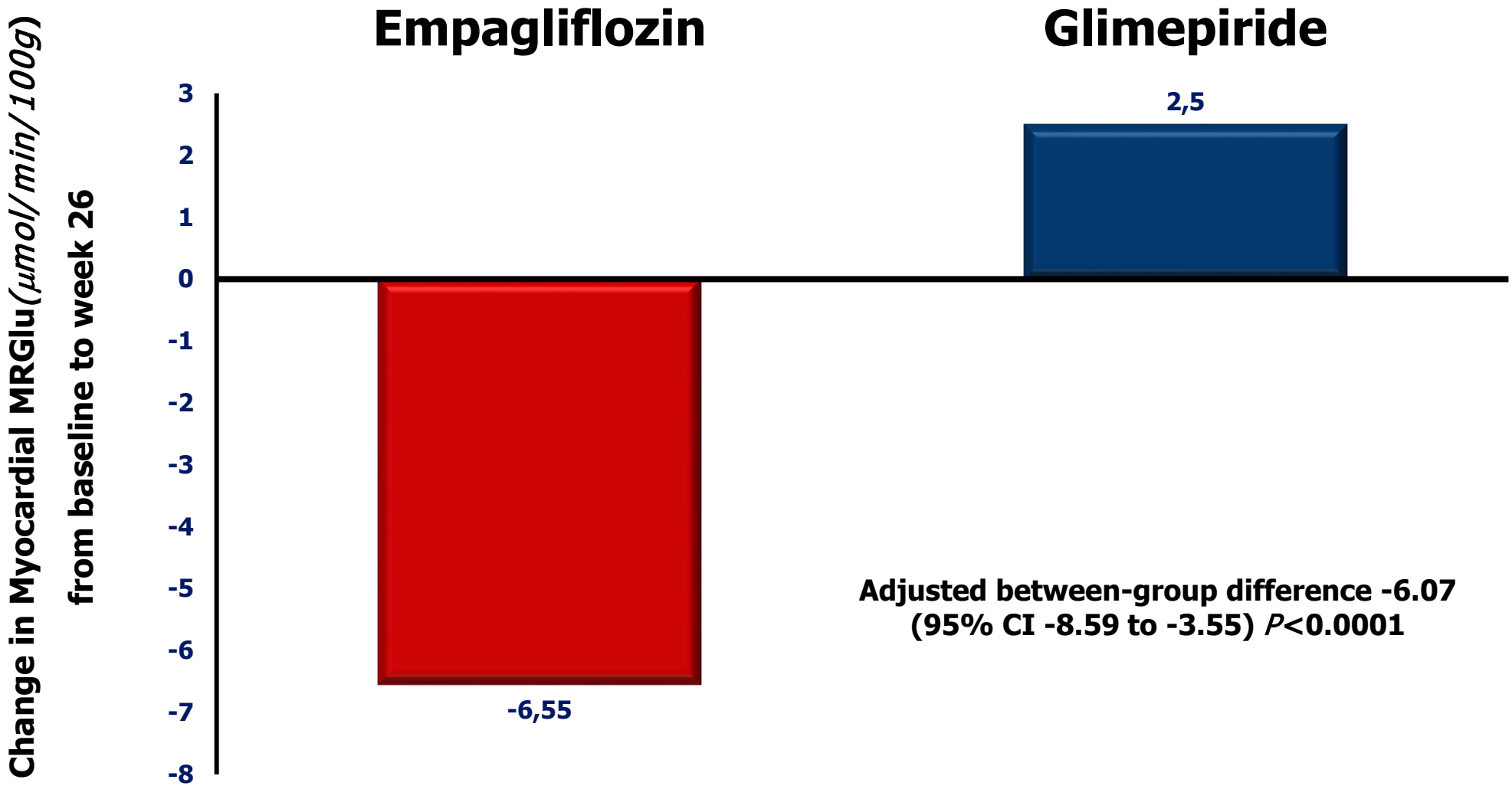
Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022

Study design



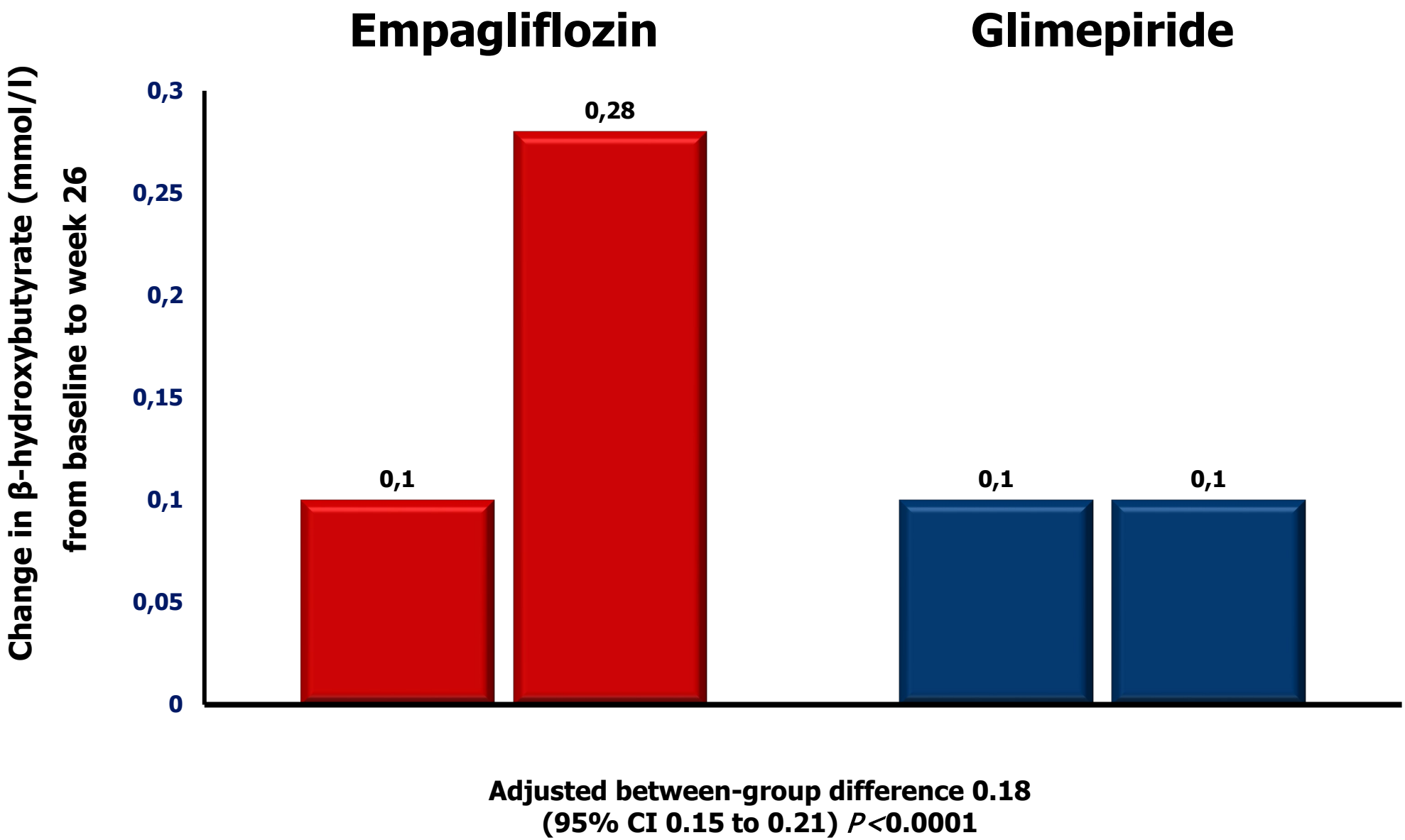
Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022

Change in myocardial glucose metabolic rate from baseline to week 26



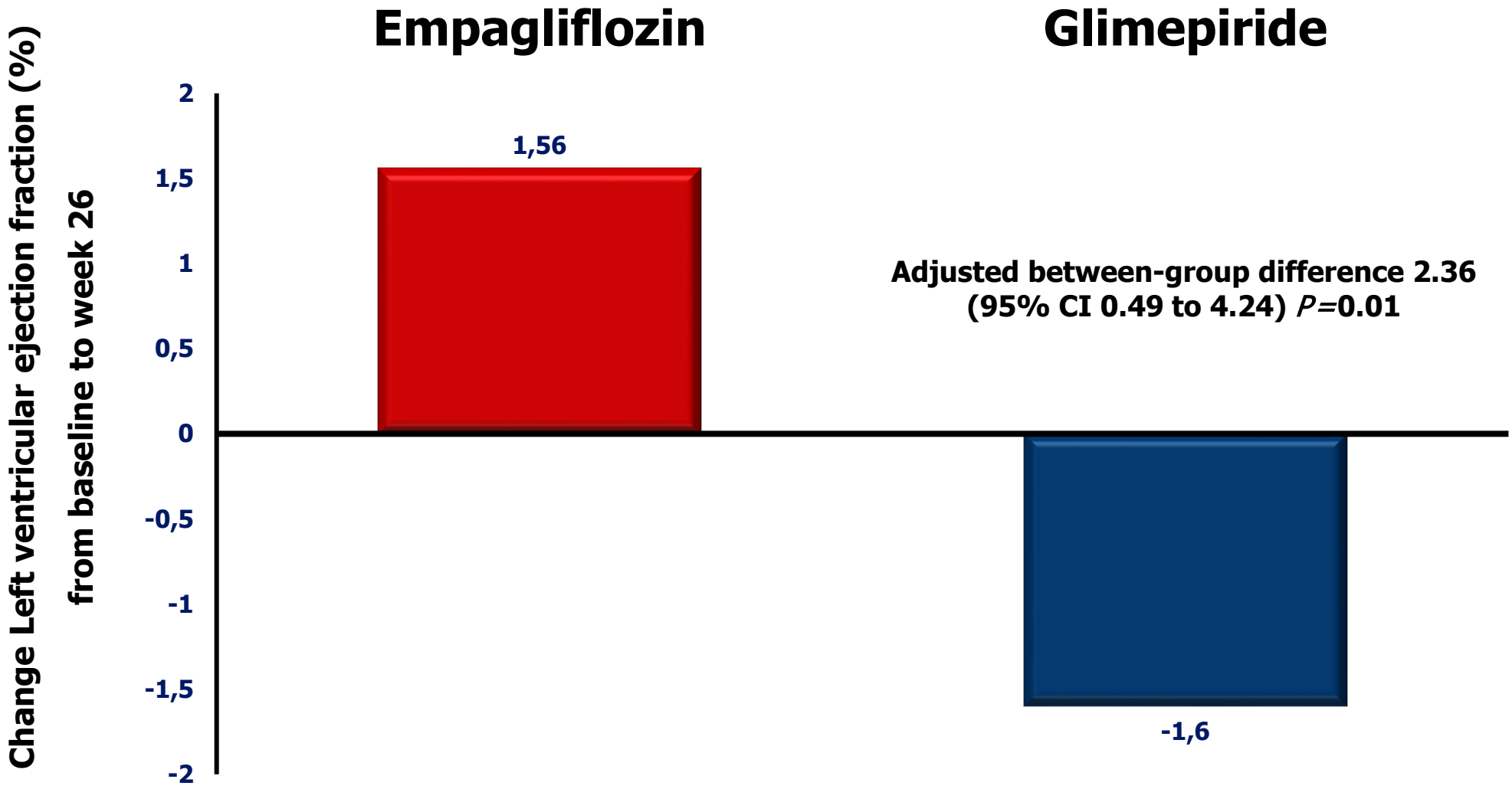
Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022

Change in β-hydroxybutyrate from baseline to week 26



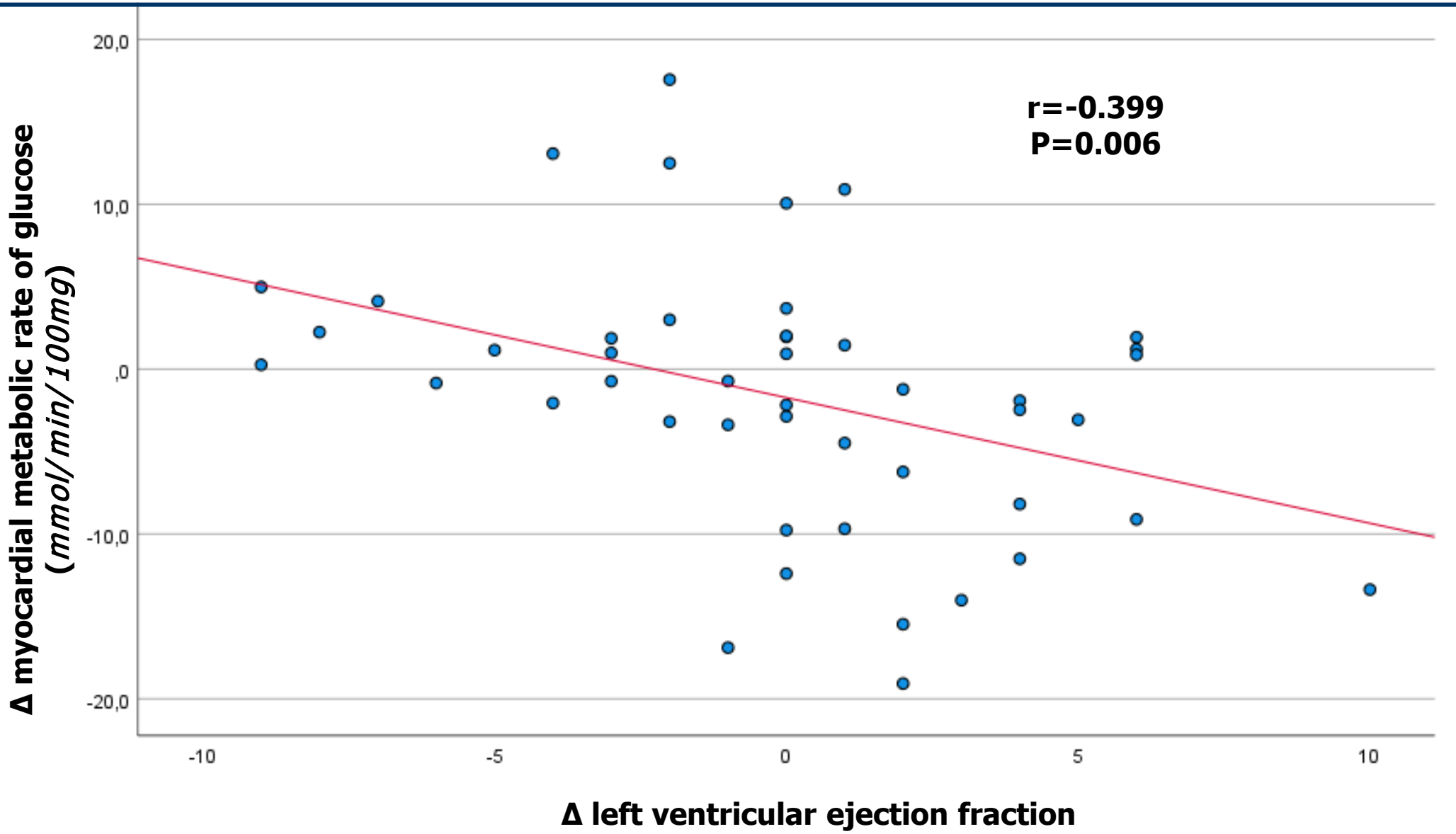
Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022

Change in left ventricular ejection fraction from baseline to week 26



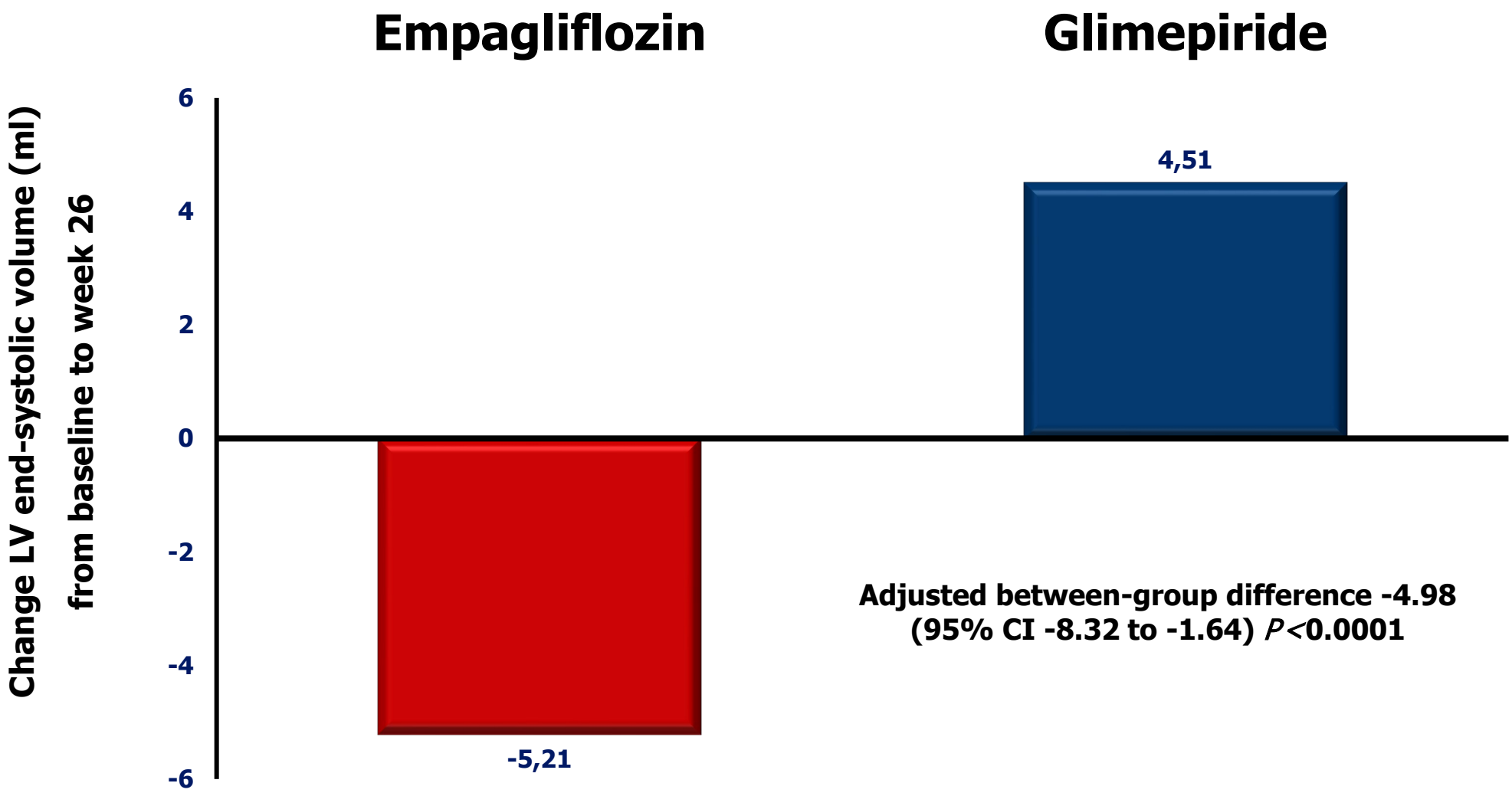
Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022

Changes in myocardial MrGlu were inversely correlated with changes in LV ejection fraction from baseline to week 26



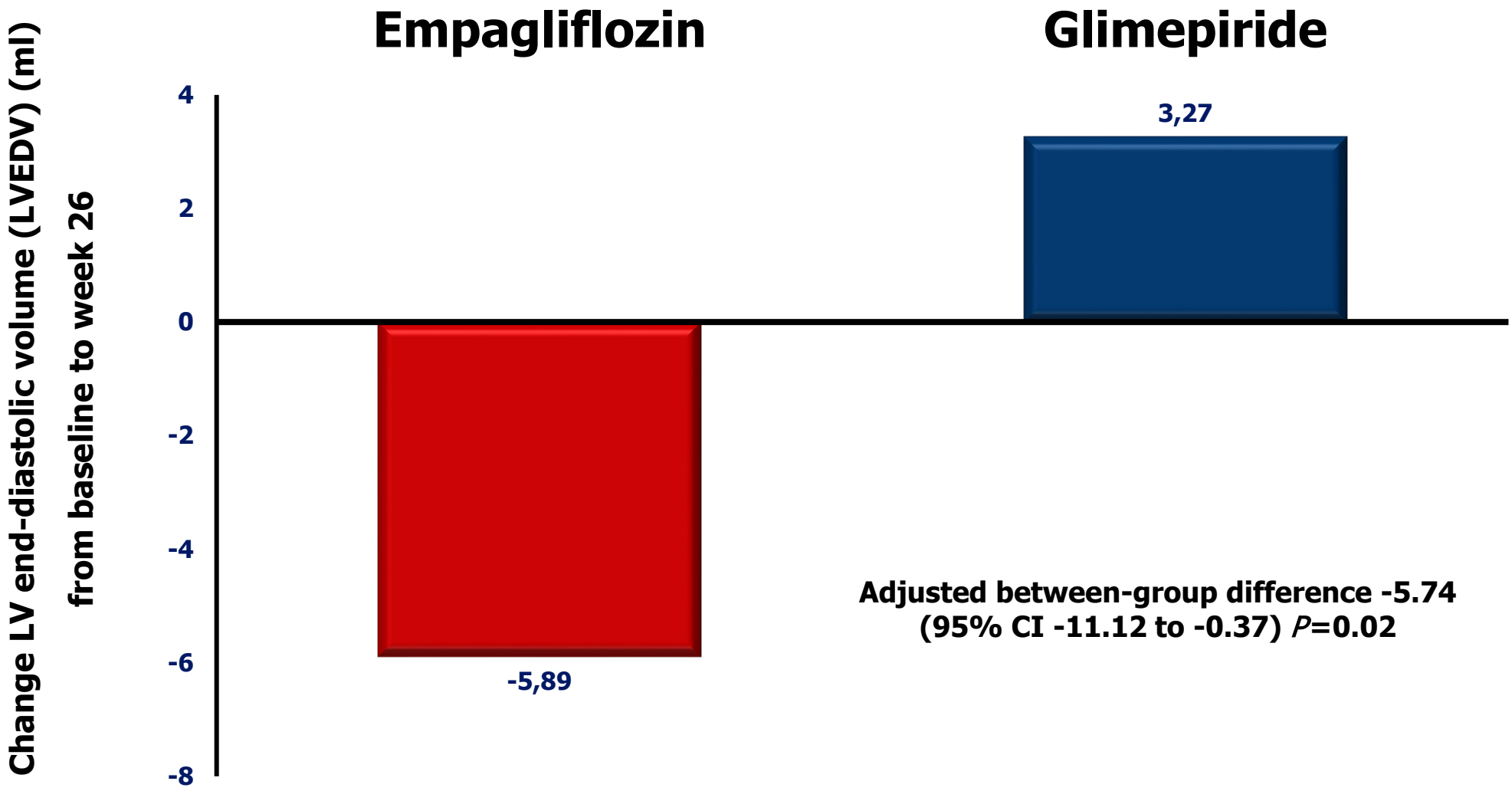
Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022

Change in LV end-systolic volume from baseline to week 26



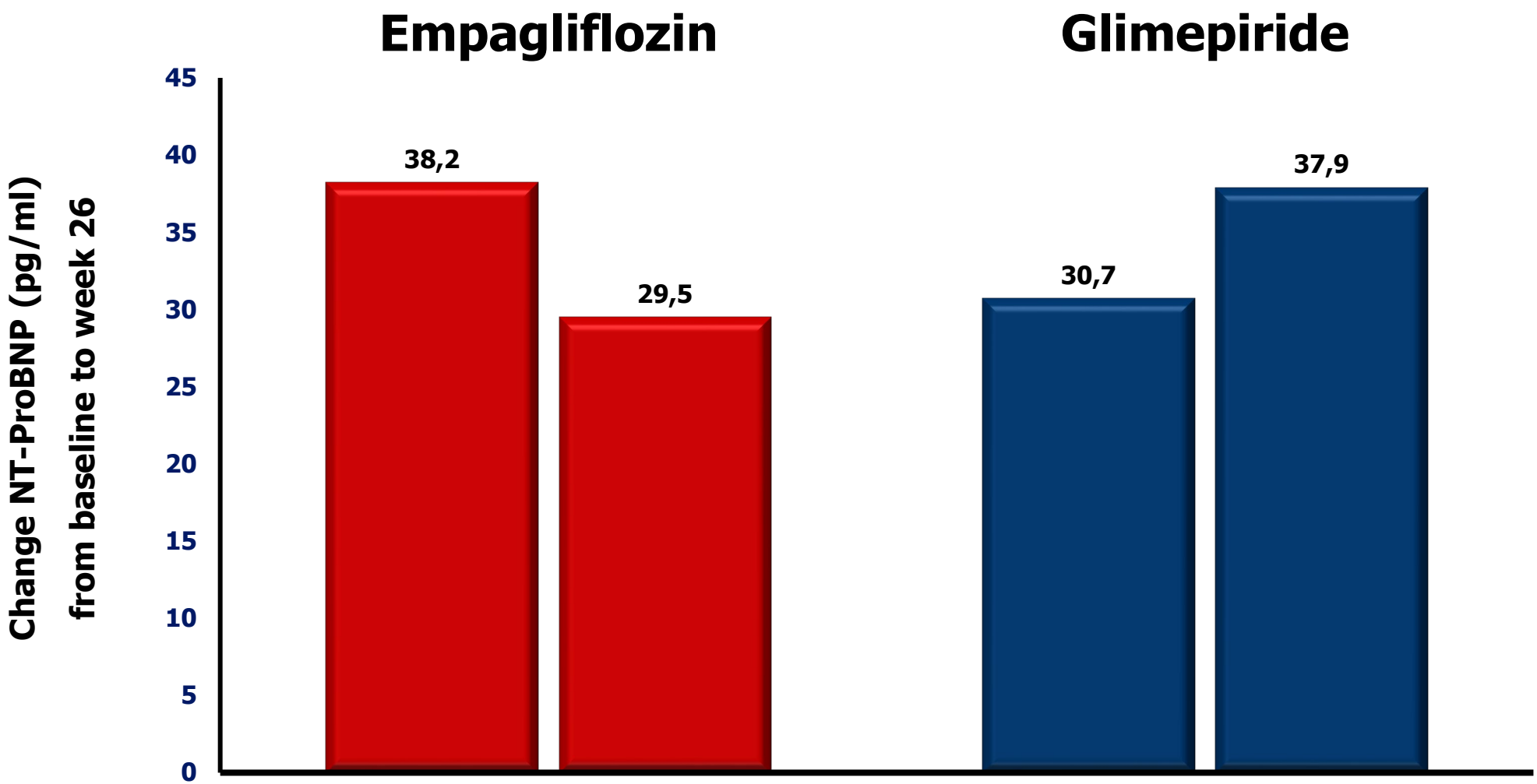
Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022

Change in LV end-diastolic volume from baseline to week 26



Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022

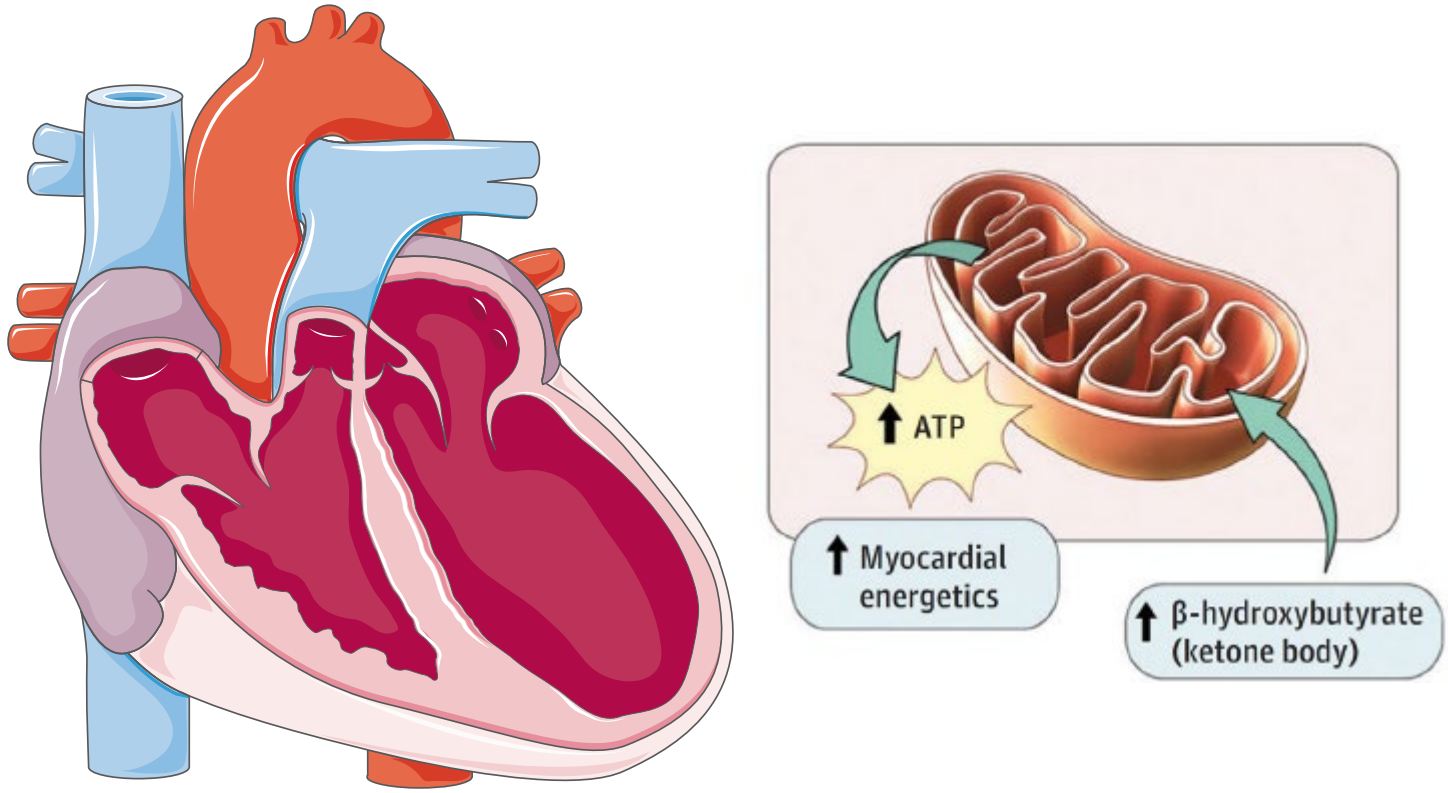
Change in NT-ProBNP from baseline to week 26



Adjusted between-group difference -15.87 (95% CI -24.67 to -7.07) *P*=0.001

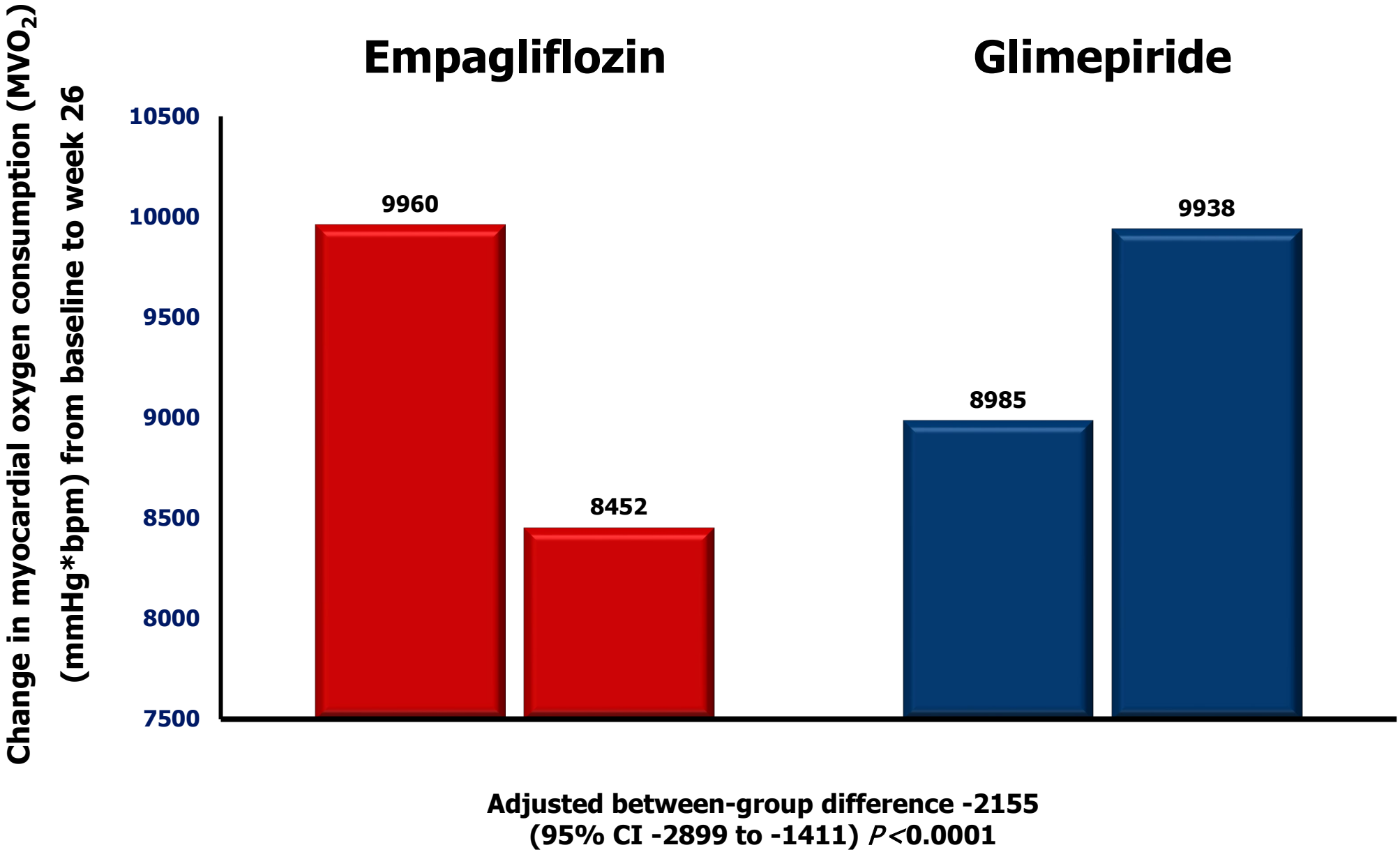
Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022

Potential mechanism of changes in energy production, cardiac load, aortic compliance and ventricular filling pressure with SGLT-2 inhibitors



Modified from Chilton RJ Diabetes Obes Metab. 1–14, 2019

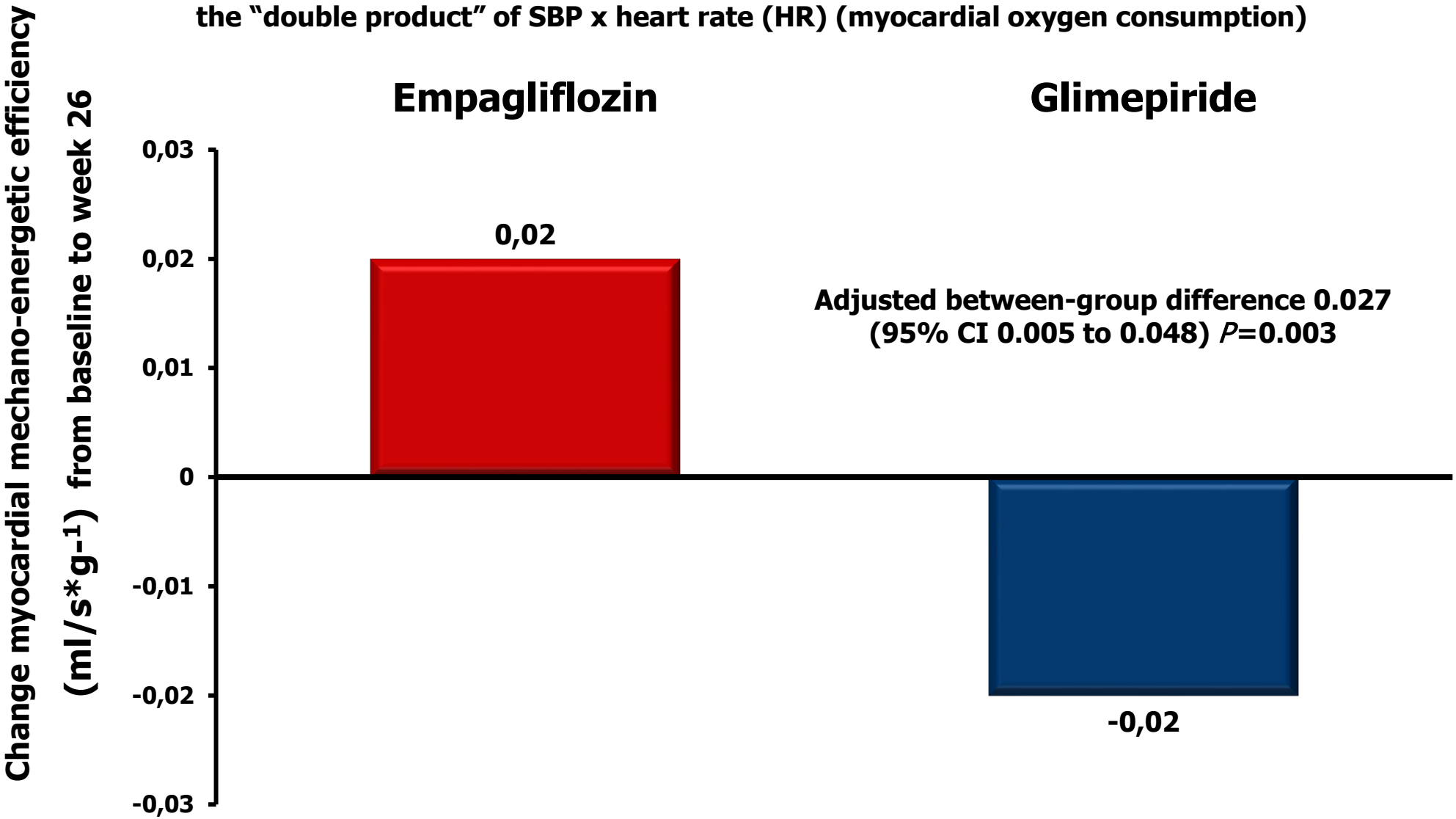
Change in myocardial oxygen consumption (mmHg x bpm) from baseline to week 26



Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022

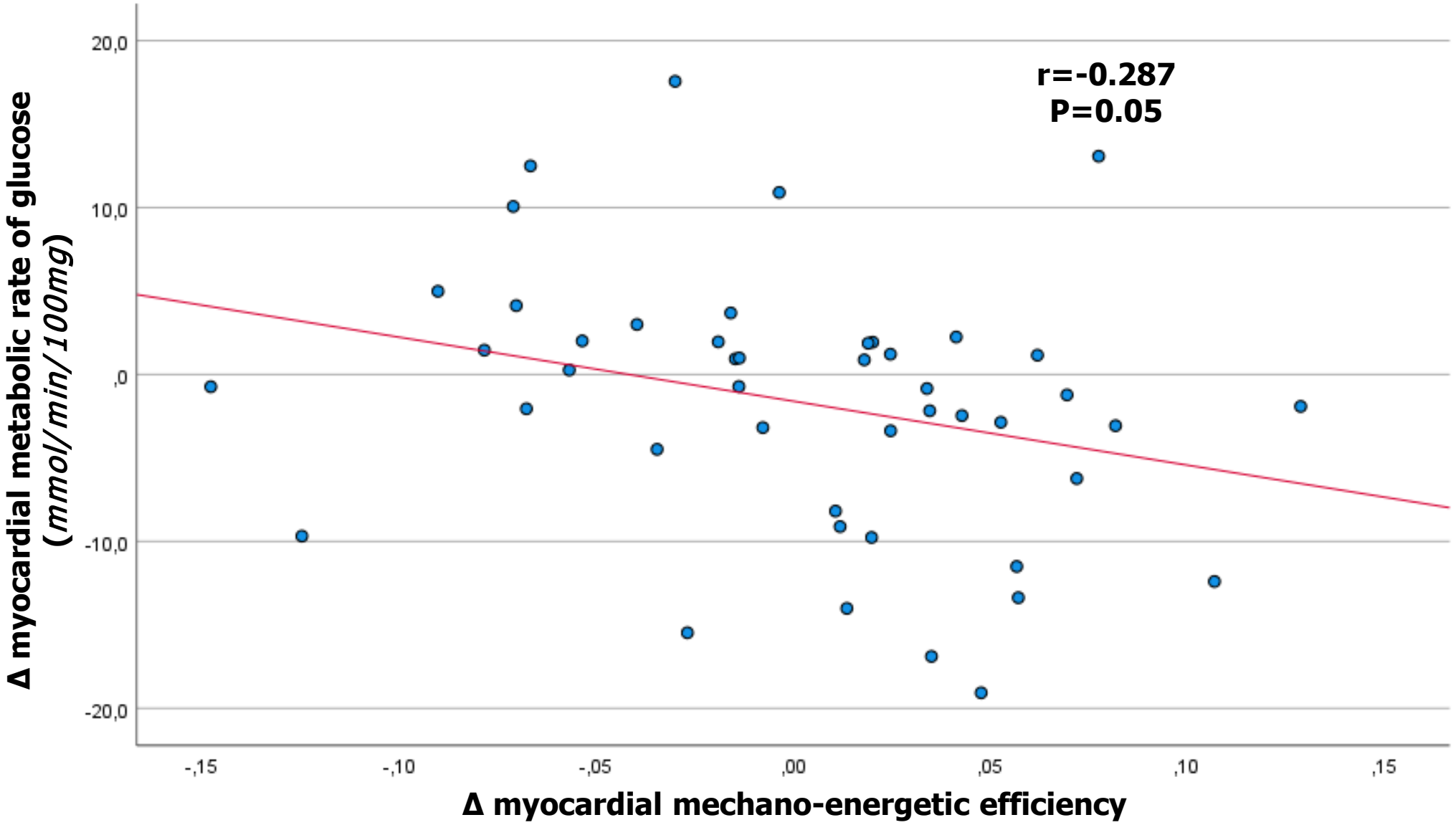
Change in myocardial mechano-energetic efficiency from baseline to week 26

Myocardial mechano-energetic efficiency can be estimated as:
systolic blood pressure (SBP) x stroke volume (SV) (stroke work)
the "double product" of SBP x heart rate (HR) (myocardial oxygen consumption)

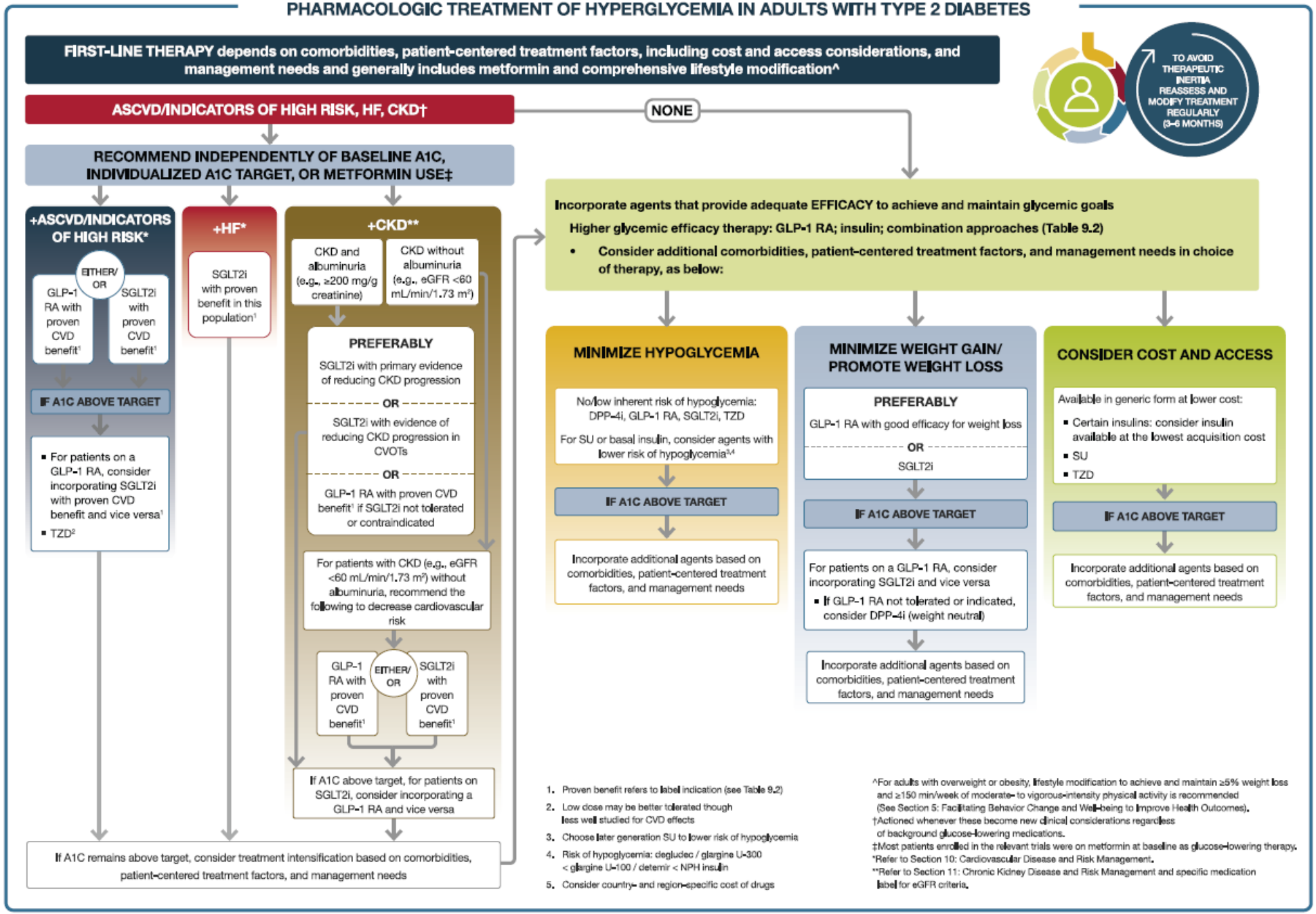


Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022

Changes in myocardial MrGlu were inversely correlated with changes in myocardial mechano-energetic efficiency from baseline to week 26



Succurro E et al. Diabetes Obes Metab. 24 (12):2319-2330, 2022



American Diabetes Association.

Diabetes Care 45 (Suppl. 1):S125-S143, 2022

Linea Guida della SID e dell'AMD
La terapia del diabete mellito tipo 2

- **Si raccomanda l'uso di metformina, SGLT-2i e GLP-1 RA come farmaci di prima scelta per il trattamento a lungo termine in pazienti con diabete di tipo 2 con pregressi eventi cardiovascolari e senza scompenso cardiaco.**
- **Pioglitazone, DPP-4i, acarbosio ed insulina dovrebbero essere considerati farmaci di seconda scelta.**
  - *Forza della raccomandazione: forte. Qualità delle prove: moderata.*

Le associazioni tra più farmaci devono essere prescritte secondo le indicazioni delle rispettive schede tecniche.

Linea Guida della SID e dell'AMD
La terapia del diabete mellito tipo 2

- **Si raccomanda l'uso di SGLT-2i come farmaci di prima scelta per il trattamento a lungo termine di pazienti con diabete di tipo 2 con scompenso cardiaco.**
- **I GLP-1 RA e metformina dovrebbero essere considerati come farmaci di seconda scelta, mentre DPP-4i, acarbosio ed insulina come farmaci di terza scelta.**

Forza della raccomandazione: forte. Qualità delle prove: moderata.

Inibitori SGLT2

Agonisti recettore GLP-1 | **Metformina**

Inibitori DPP4** | Acarbose | Insulina

Le associazioni tra più farmaci devono essere prescritte secondo le indicazioni delle rispettive schede tecniche.

THANK YOU !

Now it’s time for discussion.