Riunione annuale congiunta AMD-SID 2022
Il diabete al centro di percorsi innovativi di cura
Napoli (NA), 08 ottobre 2022

GLP-1 agonisti e SGLT-2 inibitori

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WHAT IS THE RATIONALE OF THIS COMBINATION THERAPY IN THE MANAGEMENT OF T2DM?

Since GLP-1RA and SGLT-2I work through different MOA in different organs, combination therapy with these agents is expected to have a **complementary or perhaps synergistic effect on metabolic outcomes**
Combination of GLP-1RA and SGLT-2I can potentially correct seven of the eight pathophysiologic defects (Ominous Octet) of T2DM.

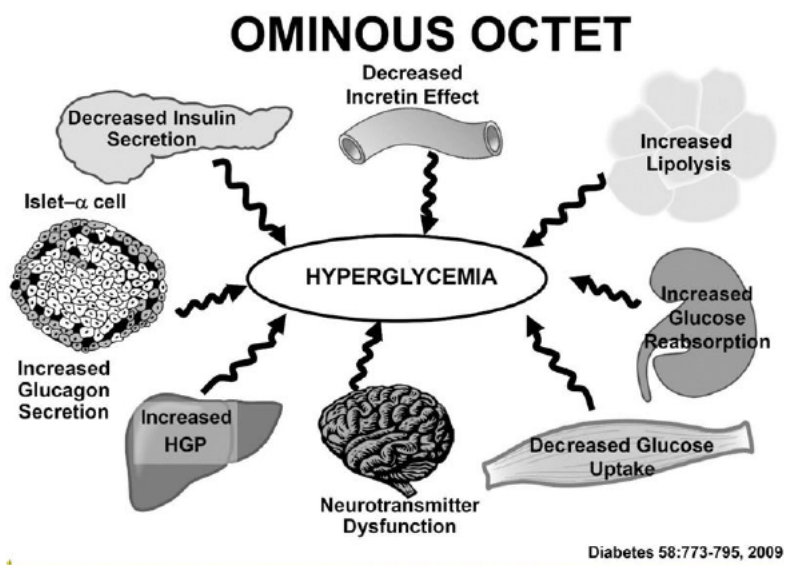


Figure 1.
The Ominous Octet. The pathophysiology of type 2 diabetes mellitus involves at least 8 distinct disturbances that collectively contribute to fasting and postprandial hyperglycemia

COMBINATION THERAPY WITH GLP-1 RECEPTOR AGONIST AND SGLT2 INHIBITOR
Ralph A. DeFronzo, MD

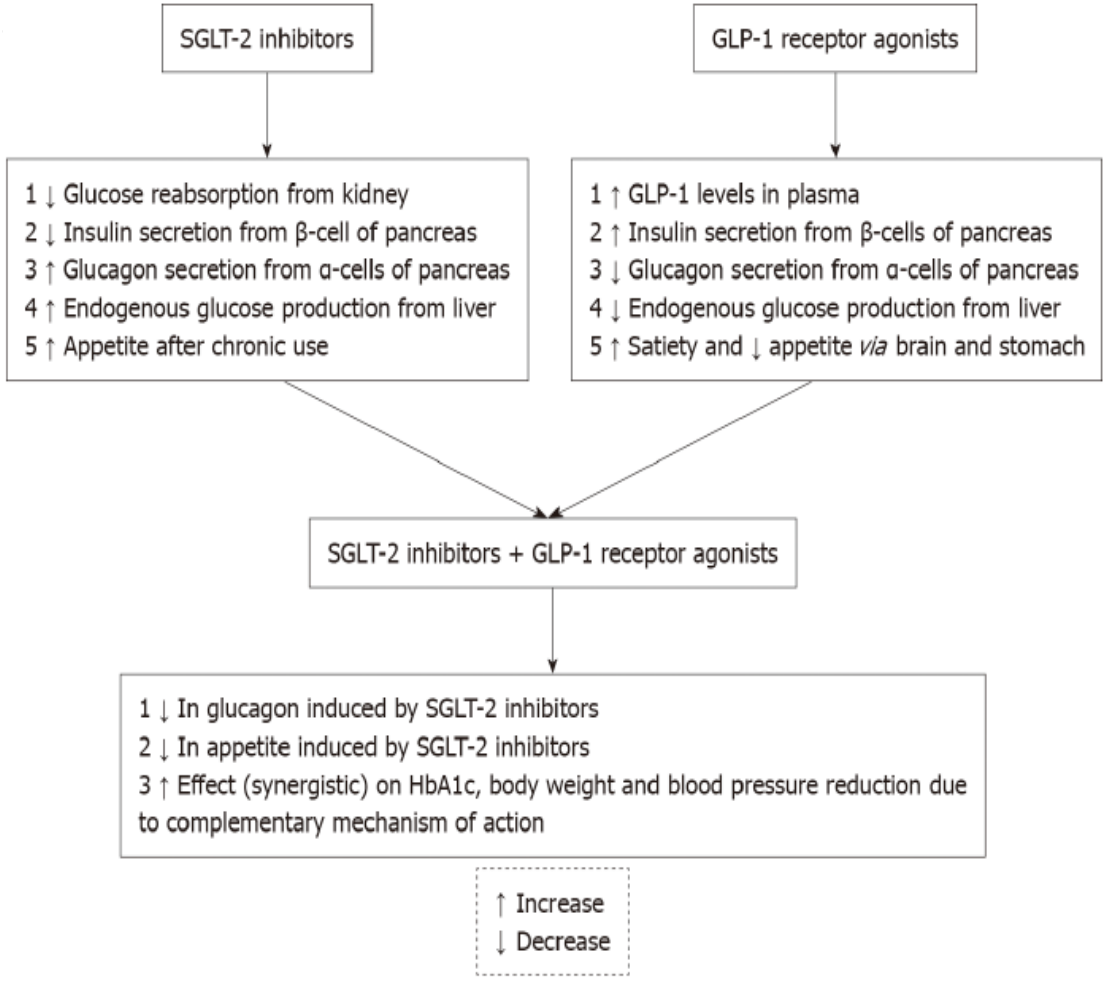
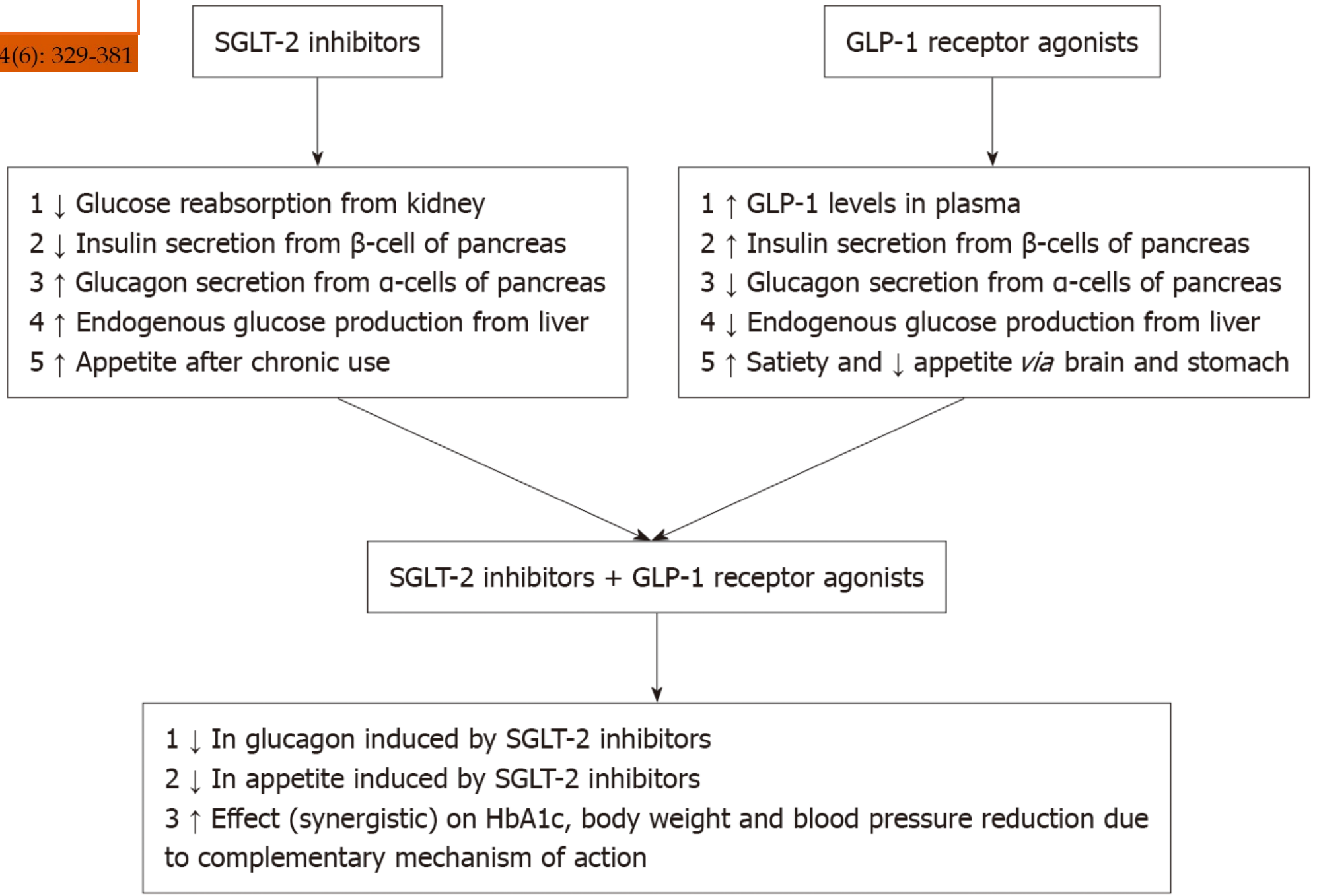


Figure 1 Complementary mechanism of action of SGLT-2 inhibitor and GLP-1 receptor agonist dual therapy.

Singh AK *et al.* GLP-1RA and SGLT-2I dual therapy in T2DM

World Journal of Cardiology
World J Cardiol 2022 June 26; 14(6): 329-381



Combination Therapy

Increasing evidence and rationale:

(1) Increased durability of glycaemic effect, potential to address therapeutic inertia

(2) Simultaneous targeting of multiple pathophysiologic processes characterised by type 2 diabetes

(3) Potential impact on medication burden, adherence, and treatment persistence

(4) Complementary clinical benefits (glycaemia, weight, cardiovascular risk profile)

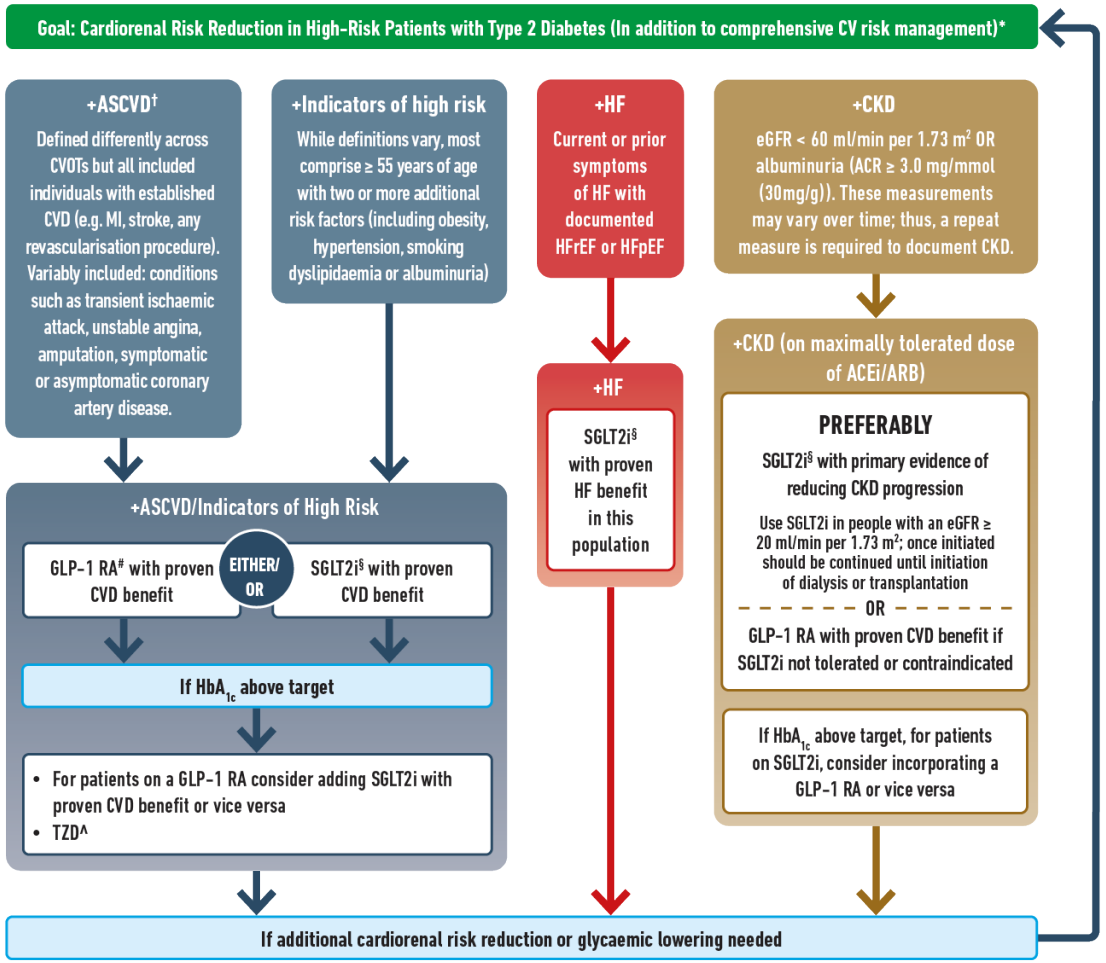
Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)

TO AVOID THERAPEUTIC INERTIA REASSESS AND MODIFY TREATMENT REGULARLY (3–6 MONTHS)



ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CV/renal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

American Diabetes Association®

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB

Diabetes Care 2022; https://doi.org/10.2337/dci22-0034. *Diabetologia* 2022; https://doi.org/10.1007/s00125-022-05787-2.

EASD European Association for the Study of Diabetes

Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

https://doi.org/10.2337/dci22-0034

FIGURE 4: HOLISTIC PERSON-CENTRED APPROACH TO T2DM MANAGEMENT

+CKD (on maximally tolerated dose of ACEi/ARB)

PREFERABLY

SGLT2i with primary evidence of reducing CKD progression

Use SGLT2i in people with an eGFR ≥ 20 ml/min per 1.73 m²; once initiated should be continued until initiation of dialysis or transplantation

OR

GLP-1 RA with proven CVD benefit if SGLT2i not tolerated or contraindicated

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+ASCVD/Indicators of High Risk

GLP-1 RA with proven CVD benefit — EITHER/OR — SGLT2i with proven CVD benefit

If additional cardiorenal risk reduction or glycaemic control needed consider combination SGLT2/GLP-1 RA

+HF

SGLT2i with proven HF benefit in this population

1 = American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1:45(Suppl 1):S144–74.

ACEi, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blockers; ASCVD, Atherosclerotic Cardiovascular Disease; BP, Blood Pressure; CKD, Chronic Kidney Disease; CV, Cardiovascular; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes.

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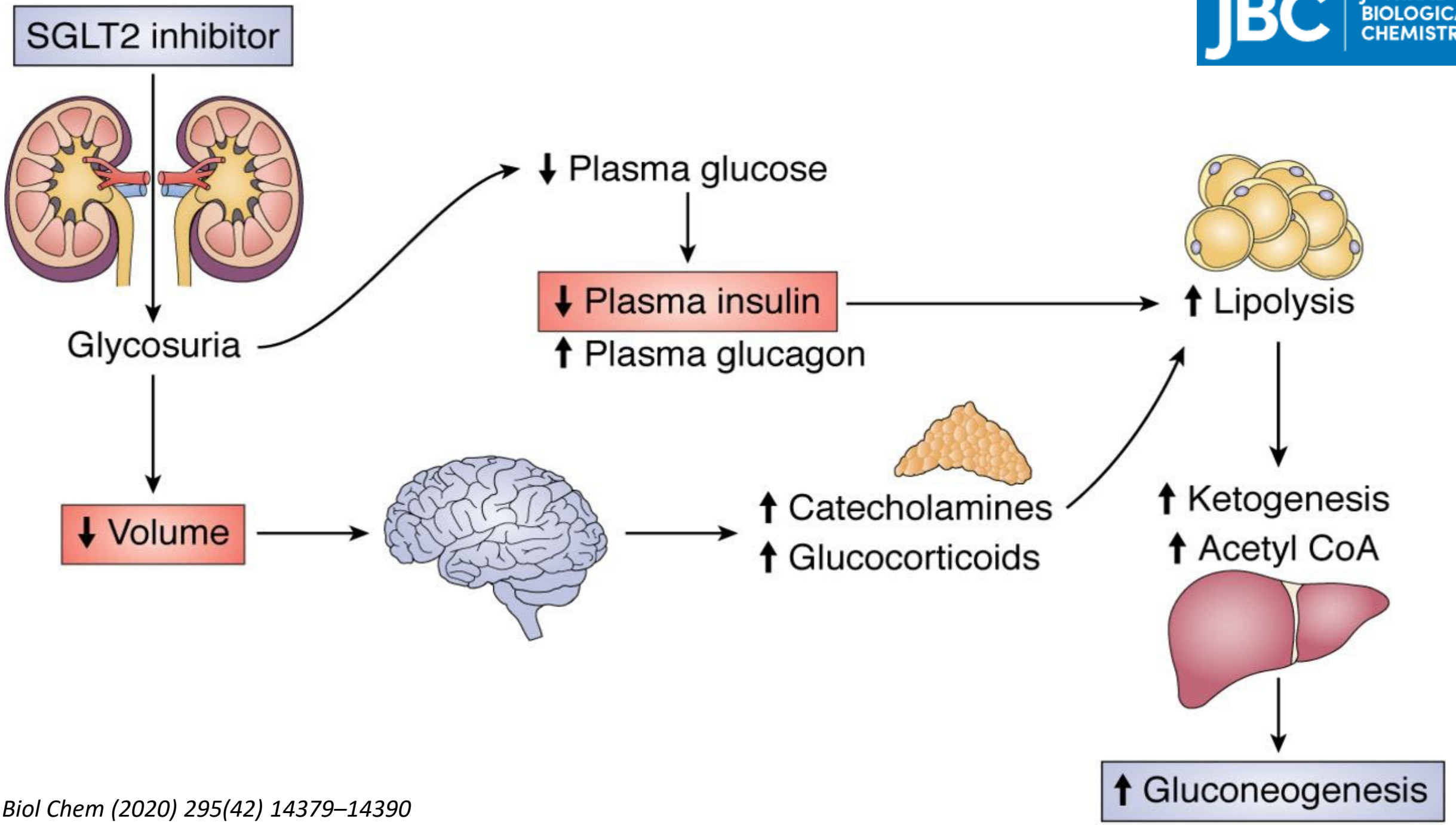
EASD European Association for the Study of Diabetes

JBC JOURNAL OF BIOLOGICAL CHEMISTRY

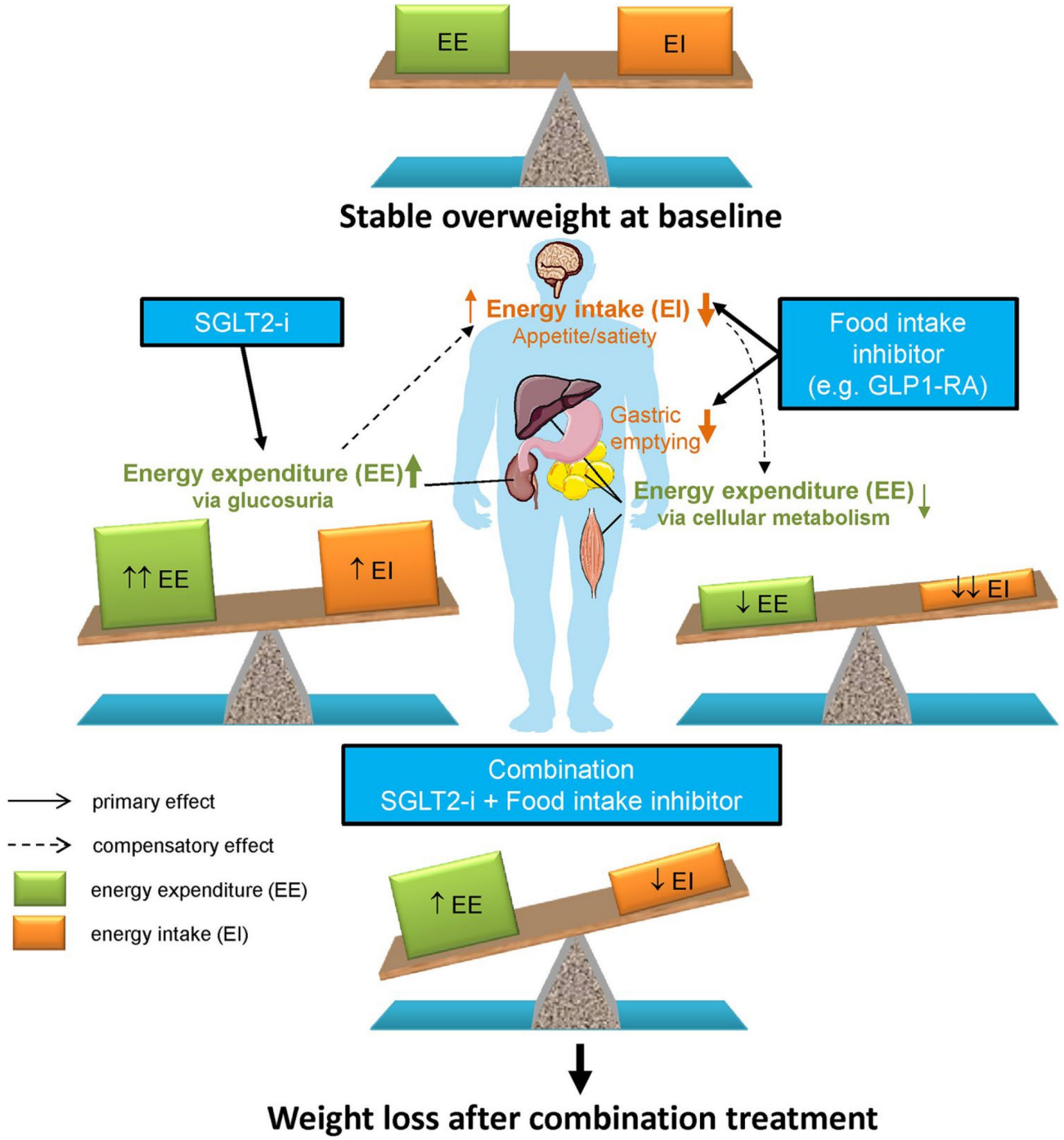


J Biol Chem (2020) 295(42) 14379–14390

Drugs (2019) 79:219–230
https://doi.org/10.1007/s40265-019-1057-0

LEADING ARTICLE

Emerging Role of SGLT-2 Inhibitors for the Treatment of Obesity



An SGLT2 inhibitor in combination with a drug that reduces food intake is appealing as a means to mitigate the physiologic mechanisms that counteract weight loss.

1. The increased food intake evoked by energy loss during SGLT2 inhibition could partly be prevented by an appetite-reducing therapy.

2. The reduced cellular energy expenditure occurring after weight loss achieved by an appetite-reducing drug may be balanced by the urinary caloric loss secondary to glucosuria

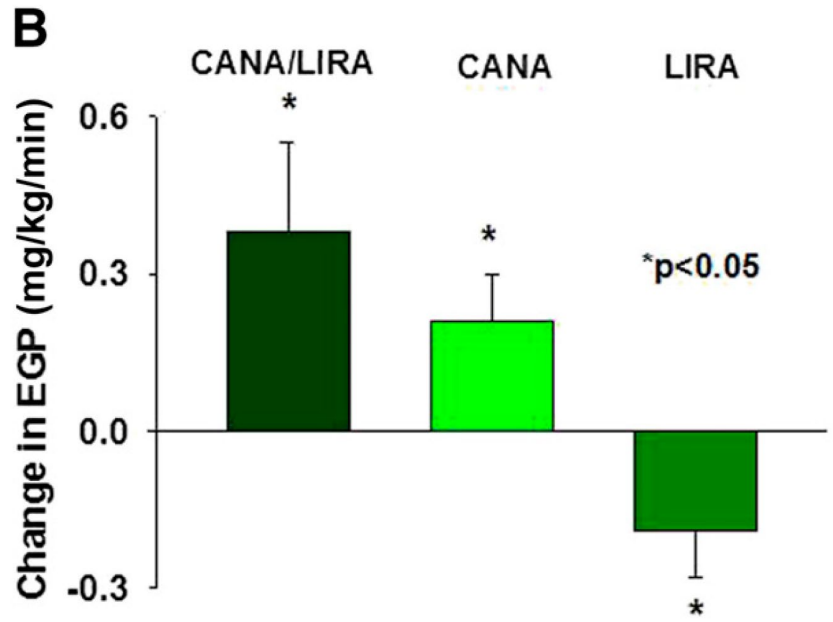
Combination Therapy With Canagliflozin Plus Liraglutide Exerts Additive Effect on Weight Loss, but Not on HbA_{1c}, in Patients With Type 2 Diabetes

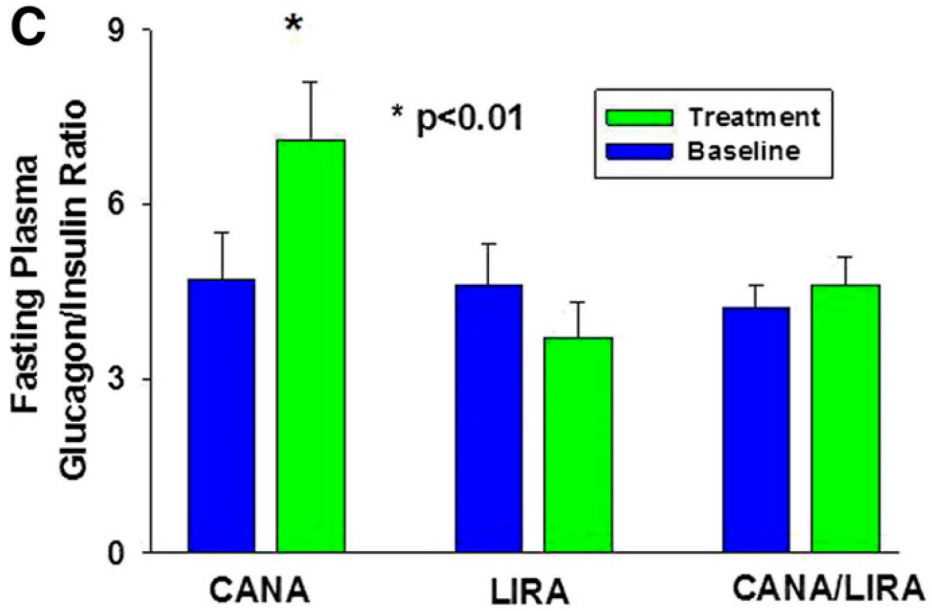
Diabetes Care 2020;43:1234–1241 | https://doi.org/10.2337/dc18-2460

Forty-five patients with poorly controlled type 2 diabetes mellitus on metformin with or without sulfonylurea received a 9-h measurement of EGP, after which they were randomized to receive

1) liraglutide 1.2 mg/day (LIRA),
2) canagliflozin 100 mg/day (CANA)
3) Liraglutide 1.2 mg plus canagliflozin 100 mg (CANA/LIRA) for 16 weeks.

At 16 weeks, the EGP measurement was repeated.

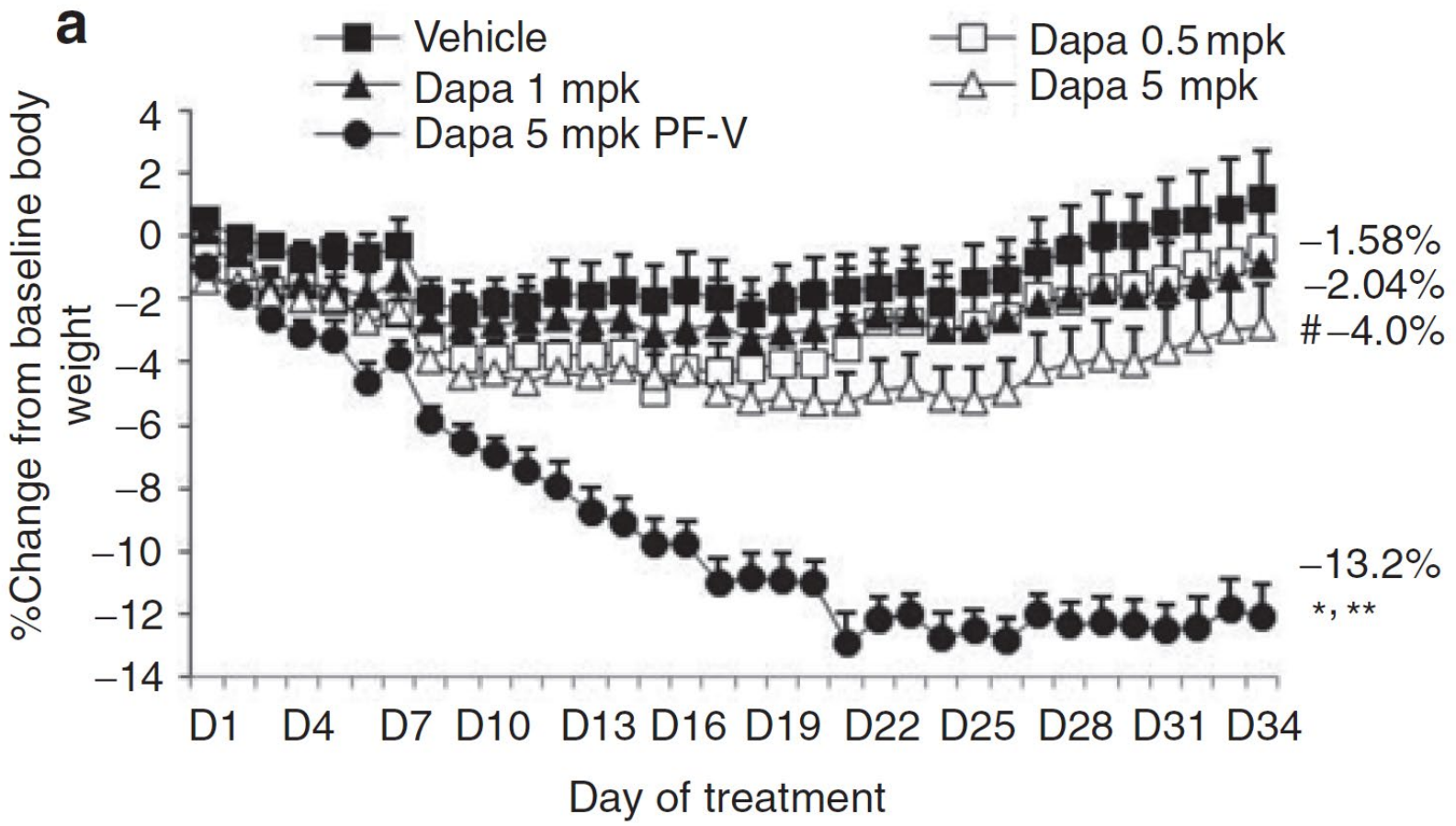




La somministrazione in cronico di un SGLT-2i può condurre a un effetto plateau sulla riduzione del peso dovuto a aumento compensatorio dell'appetito che può parzialmente compensare il calo ponderale

Nei roditori, l'escrezione urinaria persistente di glucosio indotta da dapagliflozin si associa a iperfagia compensatoria, che ha attenuato il calo ponderale indotto dalla inibizione di SGLT2.

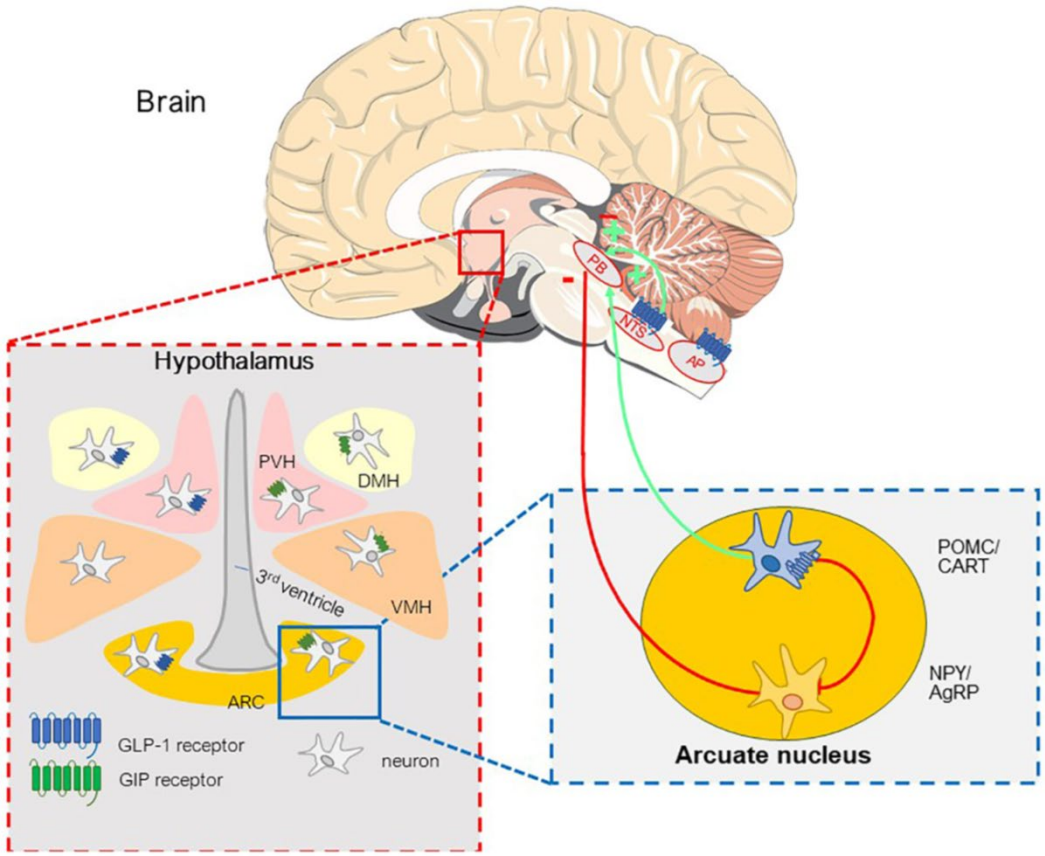
Pertanto, è possibile che la perdita di peso indotta da dapagliflozin possa essere migliorata con la dieta ristretta in calorie.

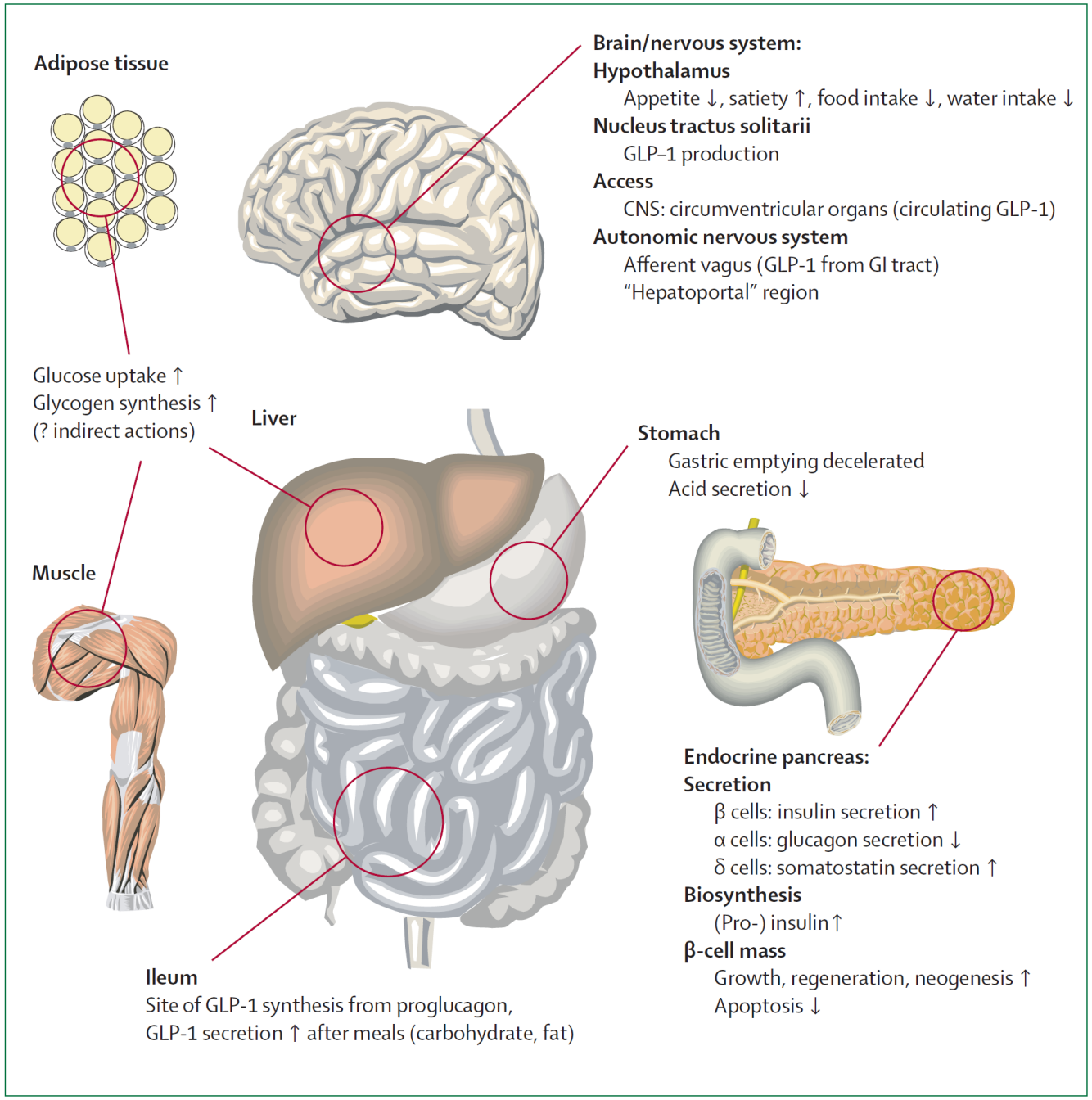


Obesity (2012) 20, 1645–1652.

GLP-1RA
delays gastric emptying and is associated with appetite suppression

Lancet 2006; 368: 1696–705;
Diabetes Obes Metab. 2021;23(Suppl. 3):5–29.





Inclusive data from Review and Metanalysis

- **HbA1c lowering** with simultaneous combination therapy of GLP-1RA and SGLT-2I was found **to be less than additive** compared to the sum of HbA1c lowering with either agent.
- **Body weight** lowering appeared to be **nearly additive.**
- **SBP lowering** was **more than additive** with simultaneous GLP-1RA and SGLT-2I combination therapy when compared to the sum effect with either agent alone across the RCTs.

OPINION REVIEW

Metabolic and cardiovascular benefits with combination therapy of SGLT-2 inhibitors and GLP-1 receptor agonists in type 2 diabetes

Awadhesh Kumar Singh, Ritu Singh

World J Cardiol 2022

Table 3 Effect of simultaneous application of GLP-1 receptor agonists + SGLT-2I therapy on HbA1c (%), body weight (kg), and systolic blood pressure (mmHg) in randomized controlled trialx

Ref.	Parameters studied	Duration (wk)	(A) ΔGLP-1 RA	(B) ΔSGLT-2I	(C) ΔGLP-1 RA + SGLT-2I	(A + B) ΔSum of GLP-1 RA and SGLT2i	Effect of (C) compared to (A + B)
Frias *et al*[16], 2016; Jabbour *et al*[17], 2018; Birnbaum *et al*[18], 2018	HbA1c	28	-1.60	-1.40	-2.00	-3.00	Less than additive
		52	-1.38	-1.23	-1.75	-2.61	Less than additive
		104	-1.29	-1.06	-1.70	-2.35	Less than additive
Ikonomidis *et al*[19], 2018	HbA1c	12	-1.30	-0.80	-1.50	-2.10	Less than additive
Ali *et al*[12], 2020	HbA1c	16	-1.44	-0.89	-1.67	-2.33	Less than additive
Frias *et al*[16], 2016; Jabbour *et al*[17], 2018; Birnbaum *et al*[18], 2018	Body weight	28	-1.56	-2.22	-3.55	-3.78	Nearly additive
		52	-1.51	-2.28	-3.31	-3.79	Nearly additive
		104	-0.80	-3.00	-2.50	-3.80	Less than additive
Ikonomidis *et al*[19], 2018	Body weight	12	NR	NR	NR	NR	NR
Ali *et al*[12], 2020	Body weight	16	-1.90	-3.50	-6.00	-5.40	More than additive
Frias *et al*[16], 2016; Jabbour *et al*[17], 2018; Birnbaum *et al*[18], 2018	SBP	28	-1.20	-1.80	-4.30	-3.00	More than additive
		52	-0.70	-2.70	-4.50	-3.40	More than additive
		104	-0.10	-1.10	-3.10	-1.20	More than additive
Ikonomidis *et al*[19], 2018	SBP	12	-3.00	-4.00	-4.00	-7.00	Less than additive
Ali *et al*[12], 2020	SBP	16	-5.10	-5.20	-14.10	-10.30	More than additive

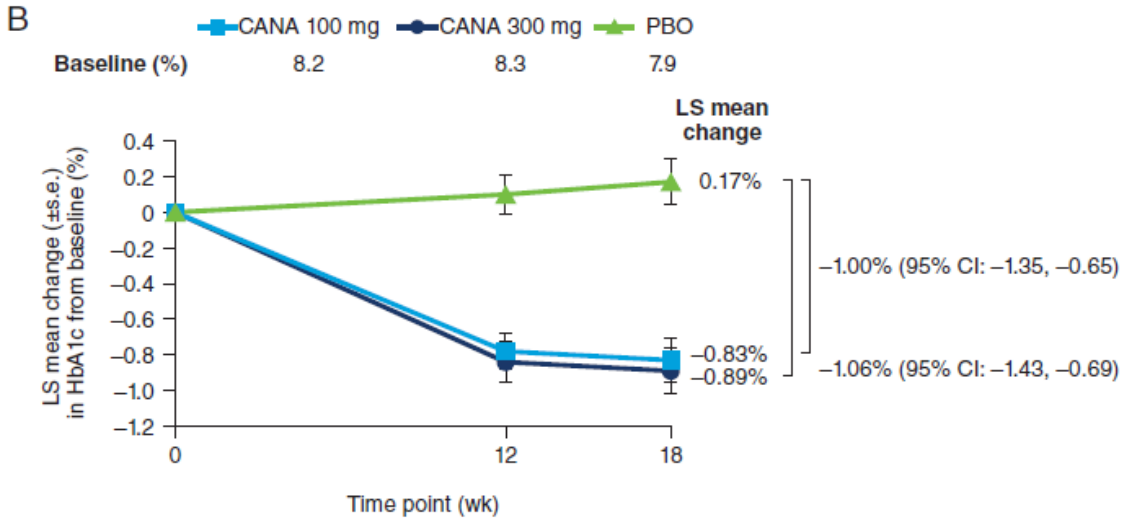
Efficacy and safety of canagliflozin when used in conjunction with incretin-mimetic therapy in patients with type 2 diabetes

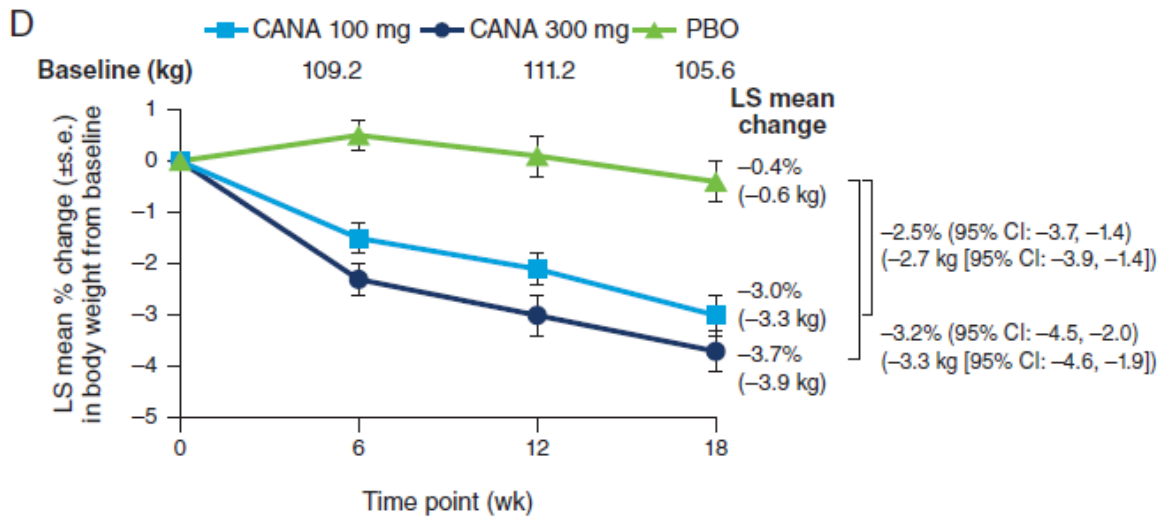
G. Fulcher[1], D. R. Matthews[2], V. Perkovic[3], D. de Zeeuw[4], K. W. Mahaffey[5], C. Mathieu[6], V. Woo[7], C. Wysham[8], G. Capuano[9], M. Desai[9], W. Shaw[9], F. Vercruysse[10], G. Meininger[9] & B. Neal[3] on behalf of the CANVAS trial collaborative group

Diabetes, Obesity and Metabolism 18: 82–91, 2016.

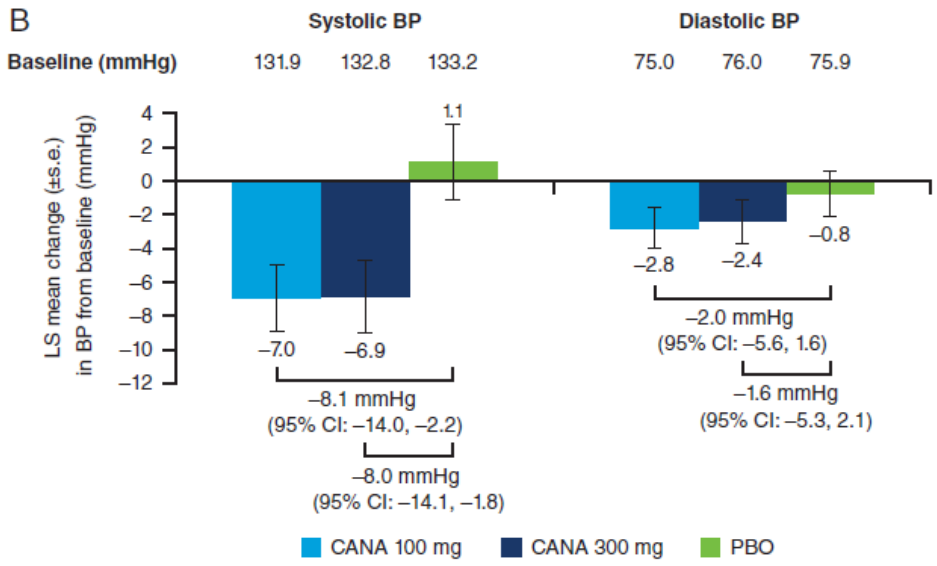
Methods: CANVAS is a double-blind, placebo-controlled study that randomized participants to canagliflozin 100 or 300 mg or placebo added to routine therapy. The present *post hoc* analysis assessed the efficacy and safety of canagliflozin 100 and 300 mg compared with placebo in subsets of patients from CANVAS who were taking background DPP-4 inhibitors or GLP-1 receptor agonists with or without other antihyperglycaemic agents at week 18.

Of the 4330 patients in CANVAS, 316 were taking DPP-4 inhibitors and 95 were taking GLP-1 receptor agonists.





Change in glycated haemoglobin (HbA1c) and body weight in the glucagon-like peptide-1(GLP-1) receptor agonist (B, D) subsets over 18weeks .



Patients, n (%)	GLP-1 receptor agonist subset		
	CANA 100 mg (n = 35)	CANA 300 mg (n = 30)	PBO (n = 30)
Any AE	22 (62.9)	22 (73.3)	23 (76.7)
AEs leading to discontinuation	2 (5.7)	3 (10.0)	0
AEs related to study drug†	10 (28.6)	11 (36.7)	7 (23.3)
Serious AEs	2 (5.7)	5 (16.7)	1 (3.3)
Deaths	0	0	0
AEs of special interest			
Genital mycotic infections			
Male‡,§	1 (3.6)	2 (10.5)	1 (5.3)
Female¶,**	0	5 (45.5)	0
UTIs	2 (5.7)	4 (13.3)	2 (6.7)
Osmotic diuresis–related AEs††	5 (14.3)	4 (13.3)	1 (3.3)
Volume depletion–related AEs‡‡	0	3 (10.0)	1 (3.3)
Hypoglycaemia episodes			
Patients on insulin, SU or meglitinide, n	29	22	26
Documented hypoglycaemia§§	11 (37.9)	11 (50.0)	4 (15.4)
Severe hypoglycaemia	0	1 (4.5)	0
Patients not on insulin, SU or meglitinide, n	6	8	4
Documented hypoglycaemia§§	0	1 (12.5)	0
Severe hypoglycaemia	0	0	0

Reductions in systolic BP were observed with both doses of canagliflozin in combination with either DPP-4 inhibitors or GLP-1 receptor agonists; modest changes in diastolic BP were also observed (B)

Higher incidences of genital mycotic infections and osmotic diuresis–related adverse events (AEs) were seen with canagliflozin compared with placebo.

The incidence of hypoglycaemia was numerically higher with canagliflozin versus placebo;
nearly all events occurred in patients on background insulin or insulin secretagogues.

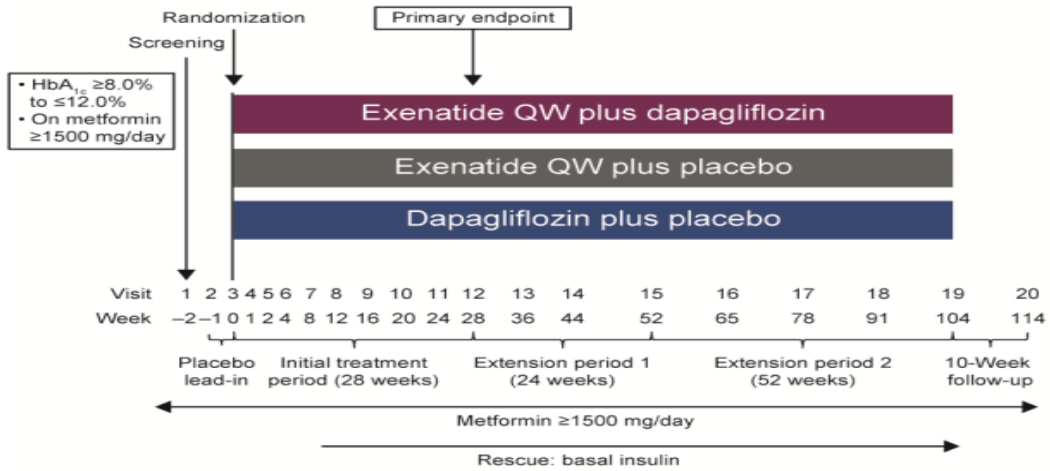
Conclusions: In patients on background incretin mimetics, canagliflozin improved HbA1c, body weight and BP, with an increased incidence of AE related to SGLT2 inhibition.

Efficacy and Safety Over 2 Years of Exenatide Plus Dapagliflozin in the DURATION-8 Study: A Multicenter, Double-Blind, Phase 3, Randomized Controlled Trial

Diabetes Care 2020;43:2528–2536 | https://doi.org/10.2337/dc19-1350

Serge A. Jabbour,[1] Juan P. Frías,[2] Azazuddin Ahmed,[3] Elise Hardy,[4] Jasmine Choi,[5] C. David Sjöström,[6] and Cristian Guja[7]

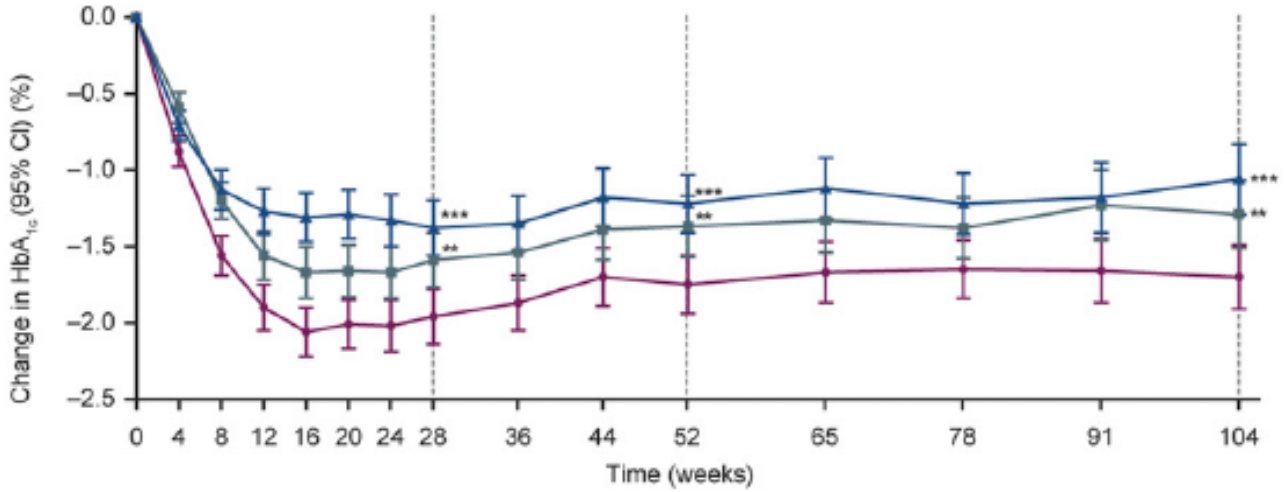
Supplementary Figure S1: Trial design



Change in HBA1c

At **week 28**, the combination of exenatide QW plus dapagliflozin was superior to exenatide QW plus placebo or dapagliflozin plus placebo in reducing HbA1c .

The differences between treatment groups were maintained **at week 52 and week 104**.



*p <0.05 , **p < 0.01, ***p < 0.001 vs. exenatide QW plus dapagliflozin

Change in Body weight

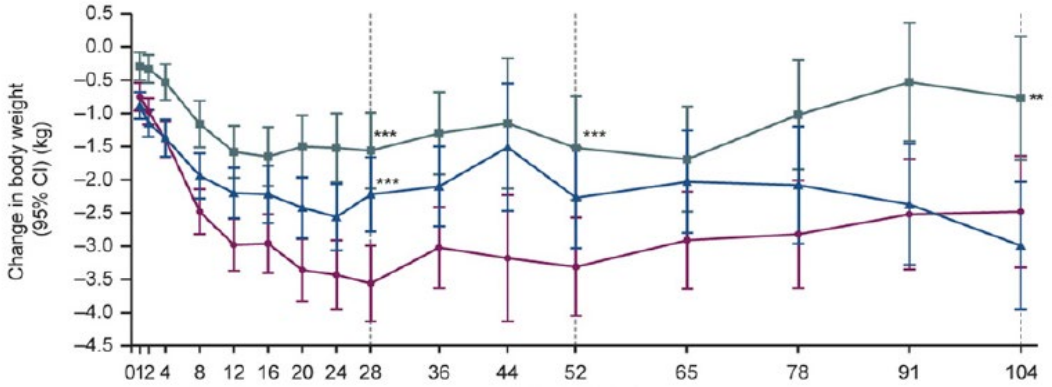
At week 28, exenatide QW plus dapagliflozin was superior to exenatide QW plus placebo and dapagliflozin plus placebo in reducing body weight, and the differences between treatment groups were maintained **at week 52**.

Between weeks 91 and 104, there was an additional decrease in body weight in the dapagliflozin plus placebogroup, resulting in a numerically greater weight loss at week 104 with dapagliflozin plus placebo versus exenatide QW plus dapagliflozin.

Rescue therapy

Between baseline and week 28, low numbers of patients received rescue therapy, with similar rescue rates across the treatment groups through week 24.

After week 24, a greater proportion of patients in the dapagliflozin plus placebo group received rescue therapy versus the exenatide QW plus dapagliflozin and exenatideQWplus placebo groups (Supplementary Fig. 4).



Supplementary Figure S4: Kaplan-Meier plot showing the proportion of patients rescued or discontinued due to lack of glycemic control during the 104-week treatment period (ITT population)

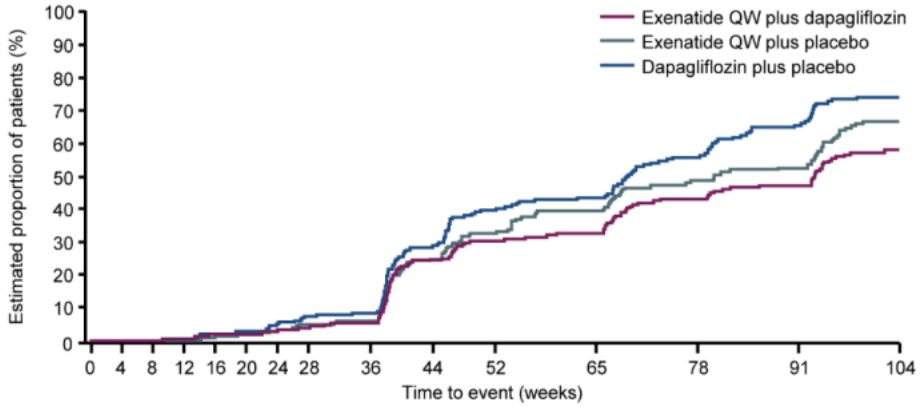


Table 3—Number of patients with AEs in the safety analysis set

	Exenatide QW plus dapagliflozin (n = 231)	Exenatide QW plus placebo (n = 230)	Dapagliflozin plus placebo (n = 233)
Any AE	165 (71.4)	161 (70.0)	156 (67.0)
Any SAE	17 (7.4)	18 (7.8)	18 (7.7)
Any AE with outcome of death	3 (1.3)	1 (0.4)	2 (0.9)
AEs leading to discontinuation of study treatment	16 (6.9)	14 (6.1)	12 (5.2)
AEs leading to study withdrawal	15 (6.5)	10 (4.3)	8 (3.4)
AEs occurring in ≥5% of patients			
Upper respiratory tract infection	15 (6.5)	17 (7.4)	22 (9.4)
Urinary tract infection	19 (8.2)	15 (6.5)	16 (6.9)
Nausea	13 (5.6)	26 (11.3)	10 (4.3)
Injection-site nodule	20 (8.7)	14 (6.1)	13 (5.6)
Diarrhea	13 (5.6)	17 (7.4)	11 (4.7)
Headache	16 (6.9)	12 (5.2)	12 (5.2)
Nasopharyngitis	15 (6.5)	8 (3.5)	12 (5.2)
Vomiting	8 (3.5)	12 (5.2)	7 (3.0)
Genital infection AEs			
Any genital infection	12 (5.2)	5 (2.2)	18 (7.7)
AEs of special interest			
Gastrointestinal AEs	48 (20.8)	55 (23.9)	38 (16.3)
Volume depletion–related AEs	3 (1.3)	1 (0.4)	5 (2.1)
Hematocrit >55%	5 (2.2)	2 (0.9)	5 (2.1)
Pancreatitis-related AEs	3 (1.3)	1 (0.4)	0
Pancreatic carcinoma–related AEs	1 (0.4)	0	0
Acute renal failure–related AEs	0	2 (0.9)	3 (1.3)
Adjudicated CV AEs	4 (1.7)	4 (1.7)	4 (1.7)
Adjudicated hepatic AEs	0	1 (0.4)	1 (0.4)
Injection-site–related AEs	32 (13.9)	27 (11.7)	18 (7.7)
Thyroid neoplasm–related AEs	0	0	0
Hypoglycemia	16 (6.9)	8 (3.5)	9 (3.9)
Major	0	0	0
Minor	4 (1.7)	0	1 (0.4)
Other	16 (6.9)	8 (3.5)	8 (3.4)
Anti-exenatide antibodies			
Week 104	43 (29.5)	34 (26.0)	—
Injection-site–related AEs by anti-exenatide antibody levels			
Negative	3 (1.3)	3 (1.3)	—
High positive (≥625)	18 (7.8)	10 (4.3)	—
Low positive (<625)	11 (4.8)	14 (6.1)	—
Any positive	29 (12.6)	24 (10.4)	—

Data are n (%). AEs occurring in ≥5% of patients are listed by Medical Dictionary for Regulatory Activities–preferred (MedDRA version 20.1) term; preferred terms for remaining AE categories are not listed. SAE, serious AE.

SAFETY ANALYSIS

Exenatide QW plus dapagliflozin was well tolerated over 104 weeks, with similar proportions of AEs and serious AEs across all treatment groups

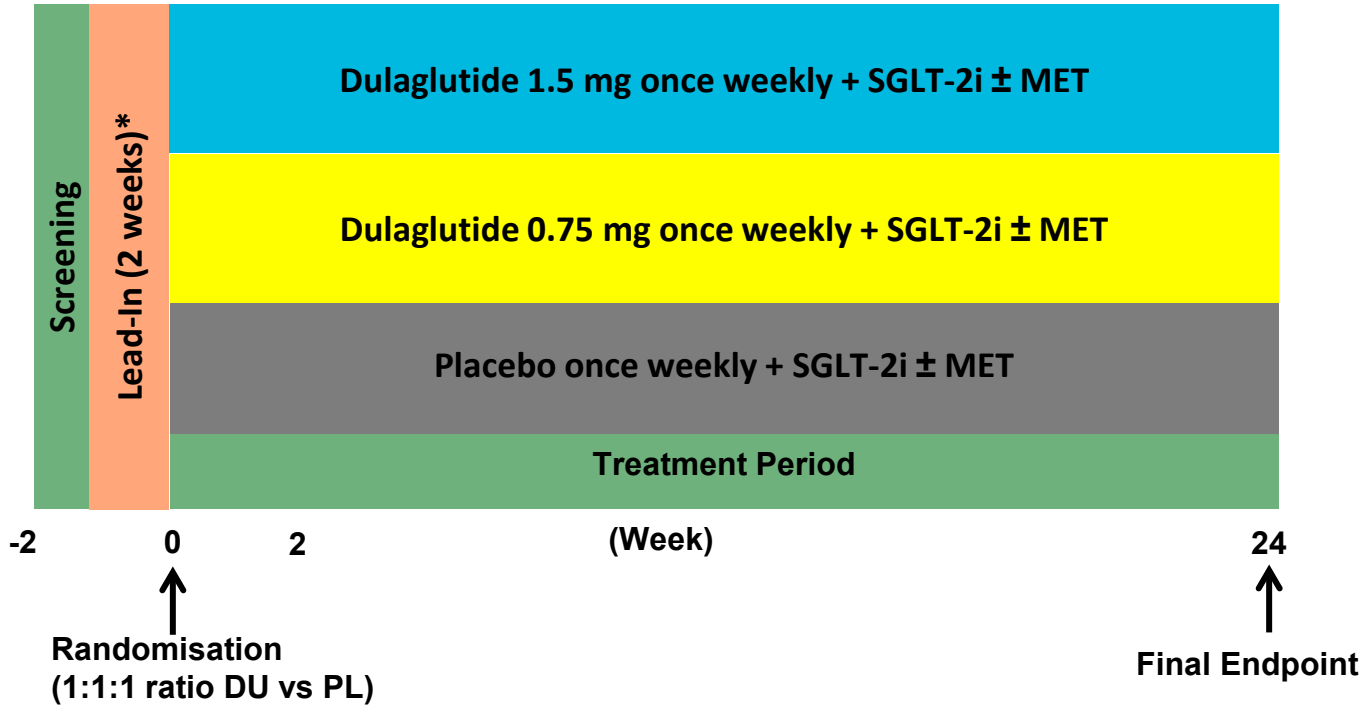
The most commonly reported AEs during the 104-week treatment period were upper respiratory tract infections, urinary tract infections, nausea, injection-site nodules, diarrhea, headaches, nasopharyngitis, and vomiting

At week 104, four (1.7%) patients in each treatment group had experienced an adjudicated CV event

Dulaglutide as add-on therapy to SGLT2 inhibitors in patients with inadequately controlled type 2 diabetes (AWARD-10): a 24-week, randomised, double-blind, placebo-controlled trial

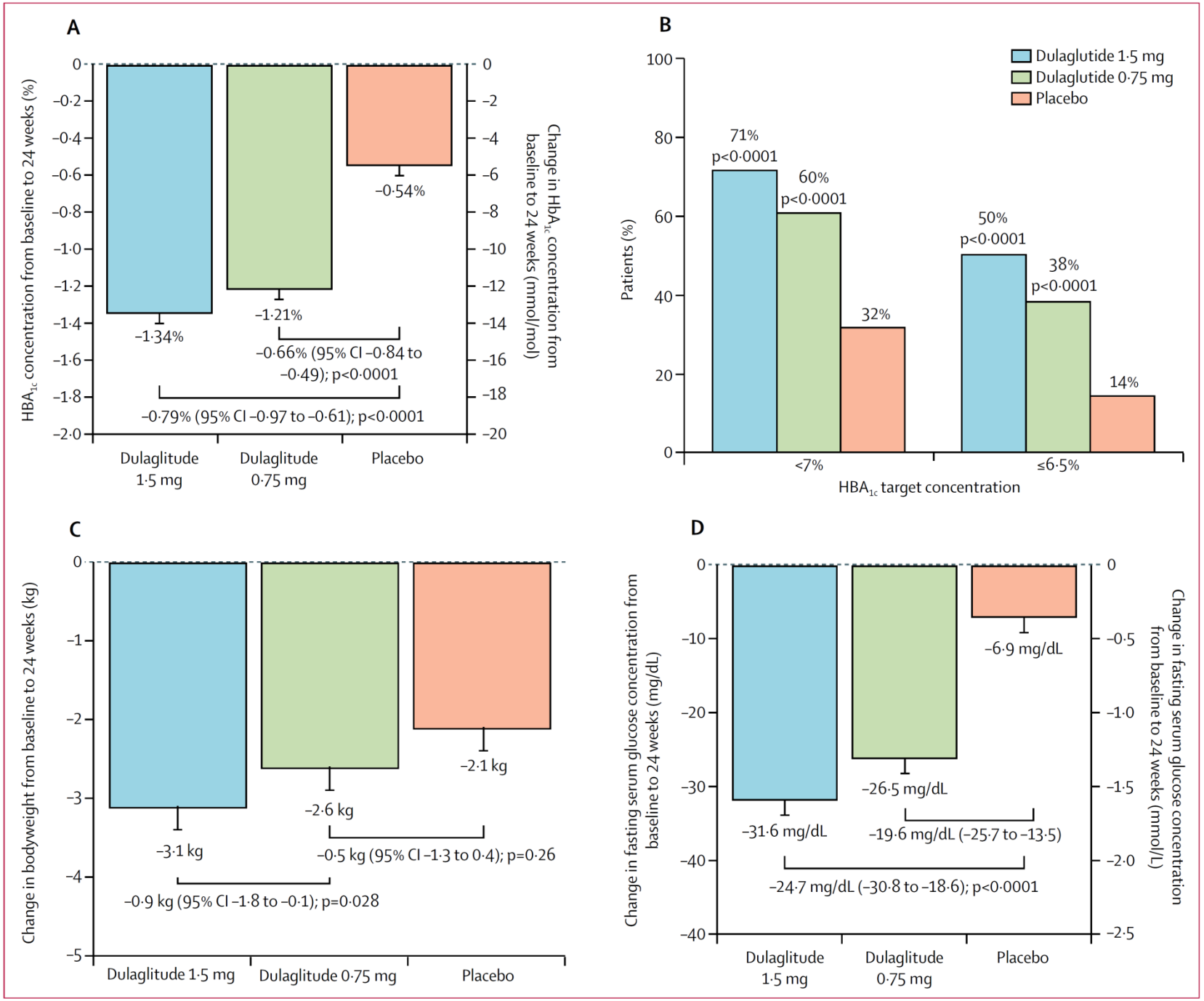
- Key inclusion criteria
  - T2D
  - HbA1c ≥7·0% and ≤9·5%
  - BMI ≤45 kg/m^2
  - SGLT-2i at locally approved doses ± metformin ≥1500 mg/day

- Key exclusion criteria
  - T1D
  - History of pancreatitis
  - Ketoacidosis or hyperosmolar state/coma
  - Recent CV event or active cancer



BMI=body mass index; CV=cardiovascular; HbA1c=glycated haemoglobin; MET=metformin; SGLT-2is=sodium-glucose co-transporter-2 inhibitors; *Patients requiring adjustment (metformin <1500 mg/day; eGFR 45-59 ml/min/1.73 m^2) completed 12-week lead-in

Ludvik et al. *Lancet Diabetes Endocrinol* 2018.



Ludvik et al. *Lancet Diabetes Endocrinol* 2018.

SAFETY ANALYSIS:

Treatment-emergent adverse events were more common in patients treated with dulaglutide than in patients who received placebo, mainly because of an increased incidence of gastrointestinal adverse events.

Nausea , diarrhoea and vomiting were more common with dulaglutide than with placebo.

One episode of severe hypoglycaemia was reported in the dulaglutide 0·75 mg group. Two patients receiving dulaglutide 1·5 mg died, but these deaths were not considered to be related to study drug.

CONCLUSIONS:

Dulaglutide as add-on treatment to SGLT2 inhibitors (with or without metformin) resulted in significant and clinically relevant improvements in glycaemic control, with acceptable tolerability that is consistent with the established safety profile of dulaglutide

	Dulaglutide 1·5 mg (n=142)	Dulaglutide 0·75 mg (n=141)	Placebo (n=140)
Deaths	2 (1%)	0	0
Serious adverse events	5 (4%)	3 (2%)	5 (4%)
Adjudication confirmed			
Pancreatic events	0	0	0
Cardiovascular events	0	0	3 (2%)
Cardiovascular death	0	0	0
Non-fatal myocardial infarction	0	0	2 (1%)
Unstable angina	0	0	1 (1%)
Renal and urinary disorders	1 (1%)	3 (2%)	4 (3%)
Treatment-emergent adverse events (patients with ≥1 adverse event)	95 (67%)	83 (59%)	81 (58%)
Treatment-emergent adverse events (≥5% of patients in either group)			
Gastrointestinal disorders	46 (32%)	29 (21%)	24 (17%)
Nausea	21 (15%)	7 (5%)	5 (4%)
Diarrhoea	8 (6%)	14 (10%)	4 (3%)
Other			
Back pain	13 (9%)	12 (9%)	10 (7%)
Headache	8 (6%)	5 (4%)	13 (9%)
Study or study-drug discontinuation, or both, due to adverse events	4 (3%)	0	0
Pancreatic enzymes, LOCF, units per L			
Pancreatic amylase	4·0 (1·0 to 10·0)	4·0 (−1·0 to 8·0)	0·0 (−3·0 to 3·0)
Lipase	7·0 (−3·0 to 16·0)	5·0 (−4·0 to 12·0)	−1·0 (−8·0 to 5·0)
Patients with enzyme concentrations ≥1 x ULN			
Pancreatic amylase	12 (9%)	10 (7%)	6 (4%)
Lipase	29 (20%)	22 (16%)	18 (13%)
Patients with enzyme concentrations ≥3 x ULN			
Pancreatic amylase	1 (1%)	0	0
Lipase	3 (2%)	1 (1%)	1 (1%)
Adverse events of interest associated with SGLT2 inhibitors			
Amputation	0	0	0
Diabetic ketoacidosis	0	0	0
Hypotensive episodes or syncope	0	1 (1%)	1 (1%)
Genital Infections	0	0	1 (1%)
Fractures	1 (1%)	1 (1%)	1 (1%)

Data are n (%) or median (IQR). LOCF=last observation carried forward. SGLT2=sodium-glucose co-transporter-2. ULN=upper limit of normal.

Table 2: **Adverse events**

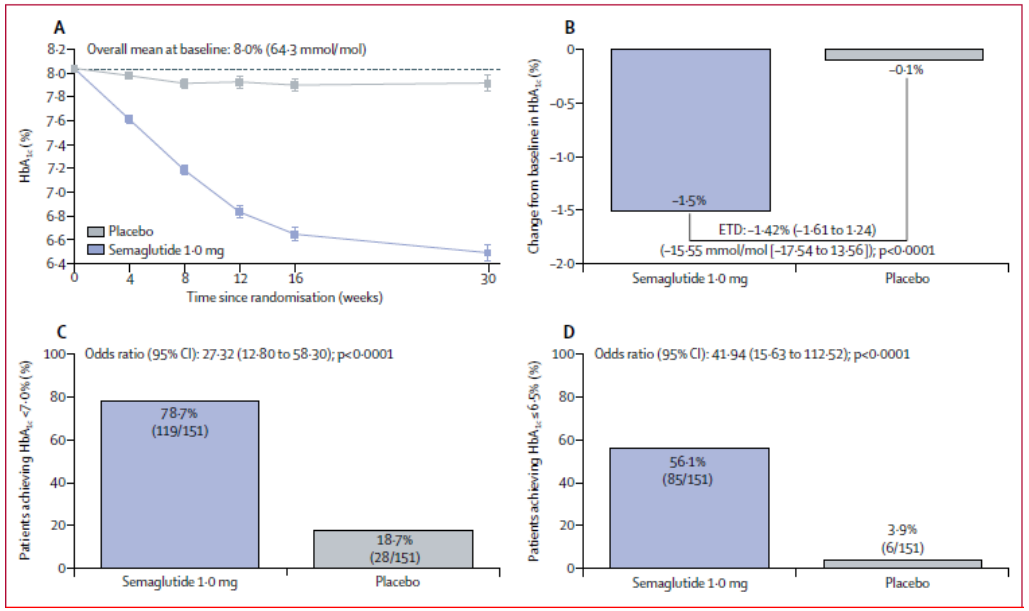
Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (SUSTAIN 9): a randomised, placebo-controlled trial

Lancet Diabetes Endocrinol 2019

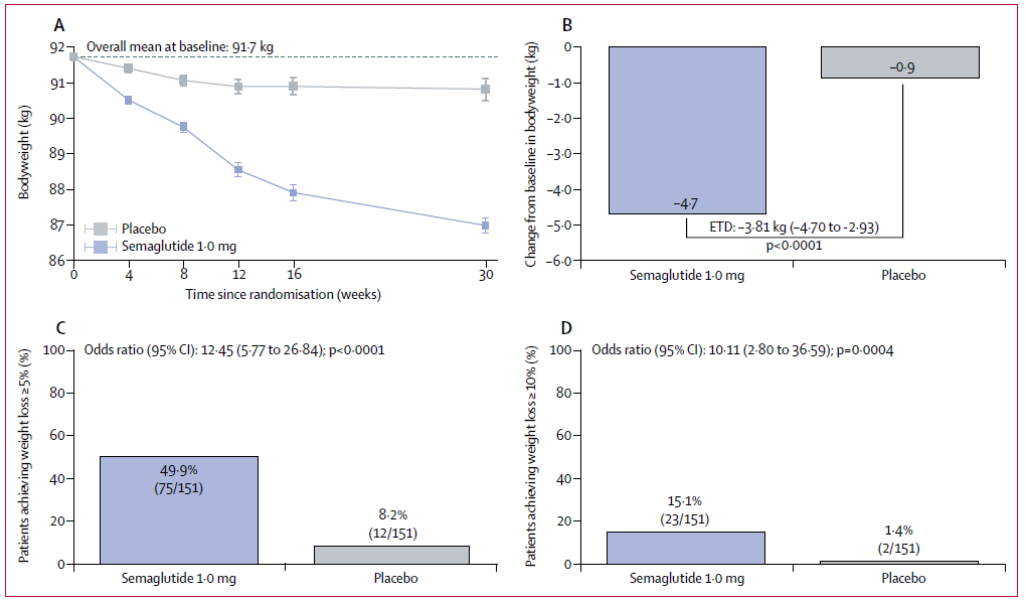
Bernard Zinman, Vaishali Bhosekar, Robert Busch, Ingrid Holst, Bernhard Ludvik, Desirée Thielke, James Thrasher, Vincent Woo, Athena Philis-Tsimikas

Methods: Adults with type 2 diabetes and HbA1c 7·0–10·0% despite at least 90 days of treatment with an SGLT-2 inhibitor, were randomly assigned (1:1) to receive subcutaneous semaglutide 1·0 mg or volume-matched placebo once weekly for 30 weeks, after a dose-escalation schedule of 4 weeks of 0·25 mg semaglutide or placebo and 4 weeks of 0·5 mg semaglutide or placebo. Existing antidiabetic medications, including SGLT-2 inhibitor treatment, were continued for the duration of the trial.

Primary outcome:
change in HbA1c from baseline to week 30



Confirmatory secondary outcome :
change in bodyweight over the same period



Other prespecified secondary outcomes endpoints:

-change from baseline to week 30 in fasting plasma glucose concentration
- mean (across all meals) sevenpoint self-measured blood glucose concentration
- mean postprandial glucose increment
- fasting blood lipid (total cholesterol, LDL cholesterol, HDL cholesterol,and triglycerides) concentrations;
-BMI and waist circumference
-systolic and diastolic blood pressure

	Overall baseline, mean (SD)	Semaglutide 1·0 mg (n=151)	Placebo (n=151)	Estimated treatment difference (95% CI)	Estimated treatment ratio (95% CI)	p value
Change from baseline to week 30						
Fasting plasma glucose, mmol/L	9·0 (2·1)	−2·2 (0·1)	0·0 (0·2)	−2·20 (−2·62 to −1·78)	..	<0·0001
Seven-point SMBG, mmol/L	9·8 (1·8)	−2·4 (0·2)	−0·4 (0·2)	−2·06 (−2·49 to −1·62)	..	<0·0001
Seven-point SMBG, increment across meals, mmol/L	NA	−1·0 (0·1)	0·0 (0·1)	−1·05 (−1·44 to −0·65)	..	<0·0001
BMI, kg/m²	31·9 (6·6)	−1·7 (0·1)	−0·3 (0·1)	−1·35 (−1·66 to −1·04)	..	<0·0001
Waist circumference, cm	107·2 (15·5)	−4·5 (0·5)	−1·7 (0·4)	−2·83 (−4·08 to −1·59)	..	<0·0001
Systolic blood pressure, mm Hg	127·9 (14·5)	−4·7 (1·0)	1·6 (1·0)	−6·32 (−9·12 to −3·52)	..	<0·0001
Diastolic blood pressure, mm Hg	78·8 (8·8)	−0·9 (0·6)	0·5 (0·6)	−1·43 (−3·04 to 0·19)	..	0·0831
Pulse rate, beats per min	74·1 (10·4)	3·4 (0·7)	0·3 (0·7)	3·06 (1·06 to 5·07)	..	0·0027
Ratio, week 30 to baseline*						
eGFR†, mL/min per 1·73 m²	95·2 (15·2)	0·99 (7·7)	1·00 (7·6)	..	NA	NA
Total cholesterol, mmol/L	4·5 (25·5)‡	0·91 (0·01)	1·03 (0·02)	..	0·88 (0·85 to 0·92)	<0·0001
HDL cholesterol, mmol/L	1·1 (26·0)‡	0·99 (0·01)	1·01 (0·01)	..	0·98 (0·95 to 1·02)	0·2846
LDL cholesterol, mmol/L	2·3 (43·1)‡	0·90 (0·02)	1·04 (0·02)	..	0·87 (0·81 to 0·93)	<0·0001
Triglycerides, mmol/L	1·8 (56·2)‡	0·80 (0·03)	0·98 (0·03)	..	0·82 (0·75 to 0·90)	<0·0001

SAFETY ANALYSIS

Gastrointestinal adverse events were most common and were reported in 56 (37·3%) patients in the semaglutide group and 20 (13·2%) in the placebo group.

Severe or blood glucose-confirmed symptomatic hypoglycaemia was rare, with four events occurring in four (2·7%) patients in the semaglutide group, one of whom was receiving a sulphonylurea

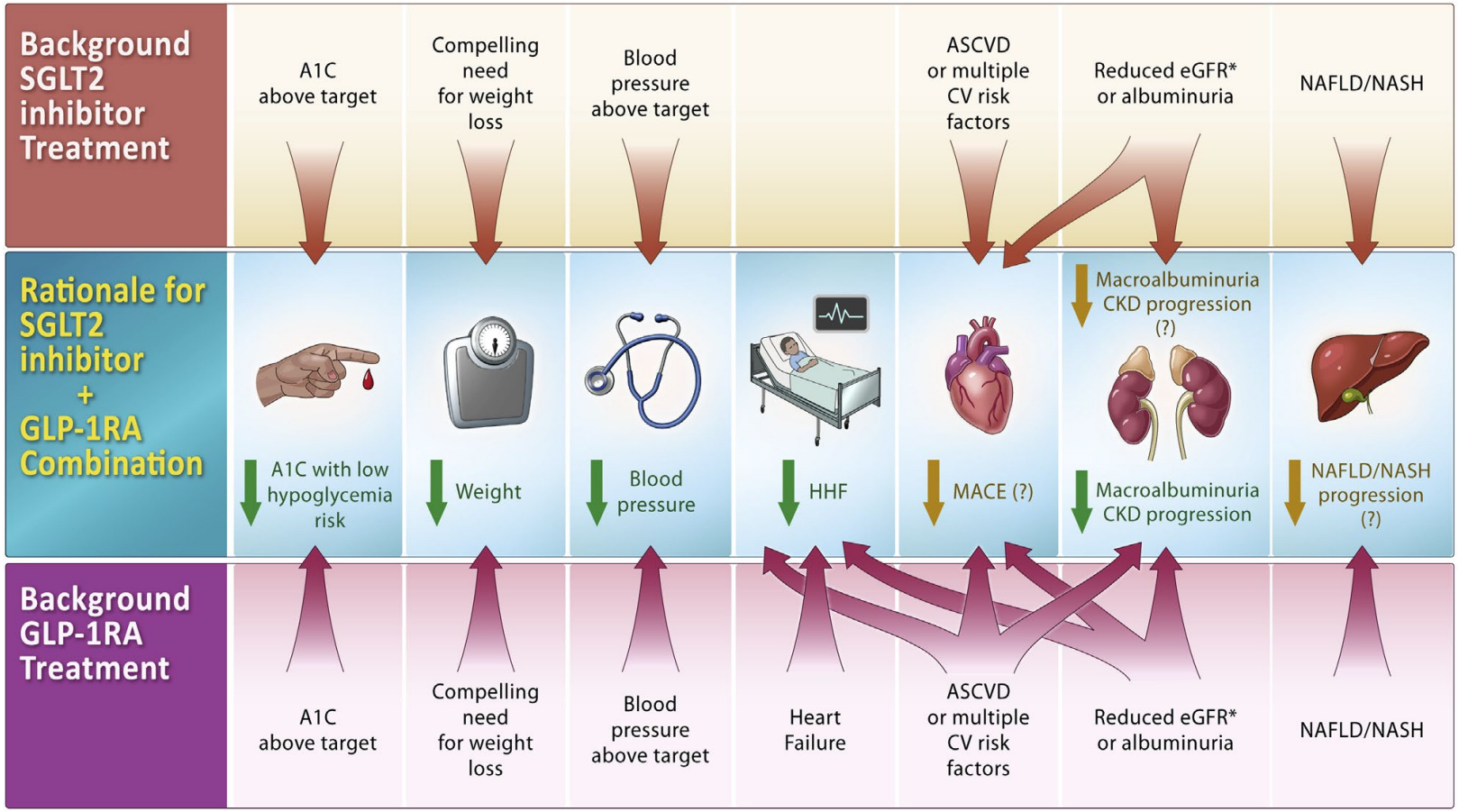
Gastrointestinal adverse events	56 (37·3%)	133	144·0	20 (13·2%)	42	43·6
Severe	2 (1·3%)	3	3·2	0	..	..
Moderate	21 (14·0%)	42	45·5	5 (3·3%)	5	5·2
Mild	46 (30·7%)	88	95·2	16 (10·6%)	37	38·4
Gastrointestinal adverse events in ≥5% of patients by preferred term						
Nausea	29 (19·3%)	37	40·0	5 (3·3%)	7	7·3
Diarrhoea	17 (11·3%)	21	22·7	9 (6·0%)	11	11·4
Vomiting	14 (9·3%)	21	22·7	3 (2·0%)	3	3·1
Constipation	10 (6·7%)	10	10·8	0	..	..
Hypoglycaemia*	17 (11·3%)	28	30·3	3 (2·0%)	4	4·2
Severe or blood glucose-confirmed hypoglycaemia	4 (2·7%)	4	4·3	0	..	..

DO WE GET AN ADDITIONAL CV AND RENAL BENEFIT BY COMBINING BOTH CLASSES OF DRUGS?

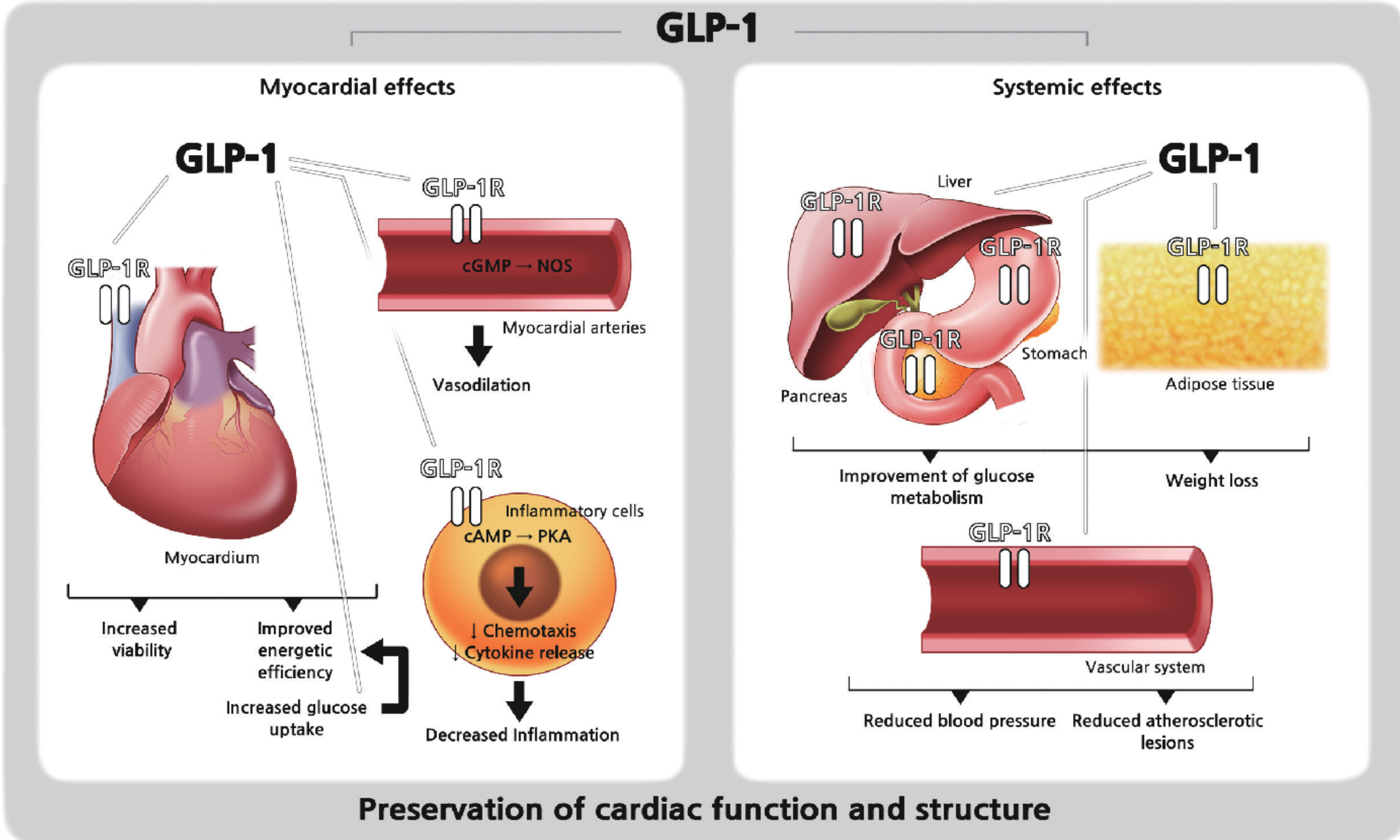
GLP-1RA primarily reduce the risk of atherosclerotic cardiovascular diseases with a modest effect on kidney function and minimal effect on heart failure.

SGLT-2I significantly reduced the risk of heart failure hospitalizations (HHF) and improved kidney
function with a modest effect on ASCVD.

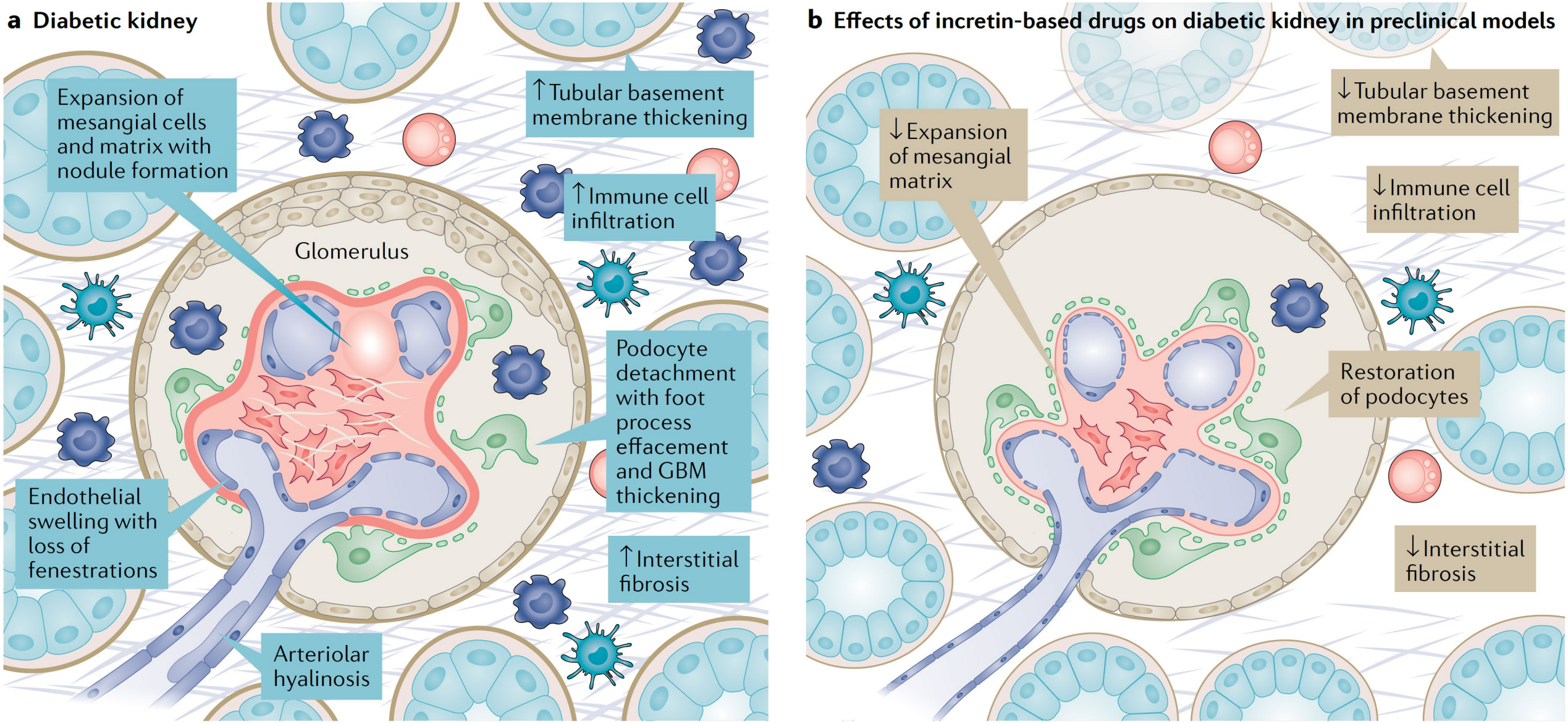
Consequently, it is alluring to consider that combination therapy of SGLT-2I and GLP-1RA would achieve greater metabolic and cardio-renal benefits in patients with T2DM, compared with either class of drugs alone.



Practical Considerations and Rationale for Glucagon-like Peptide-1 Receptor Agonist Plus Sodium-Dependent Glucose Cotransporter-2 Inhibitor Combination Therapy in Type 2 Diabetes Ronald M. Goldenberg MD. et Al. Can J Diabetes(2020)



Endocrinol Metab (Seoul). 2016;31(2):258-74



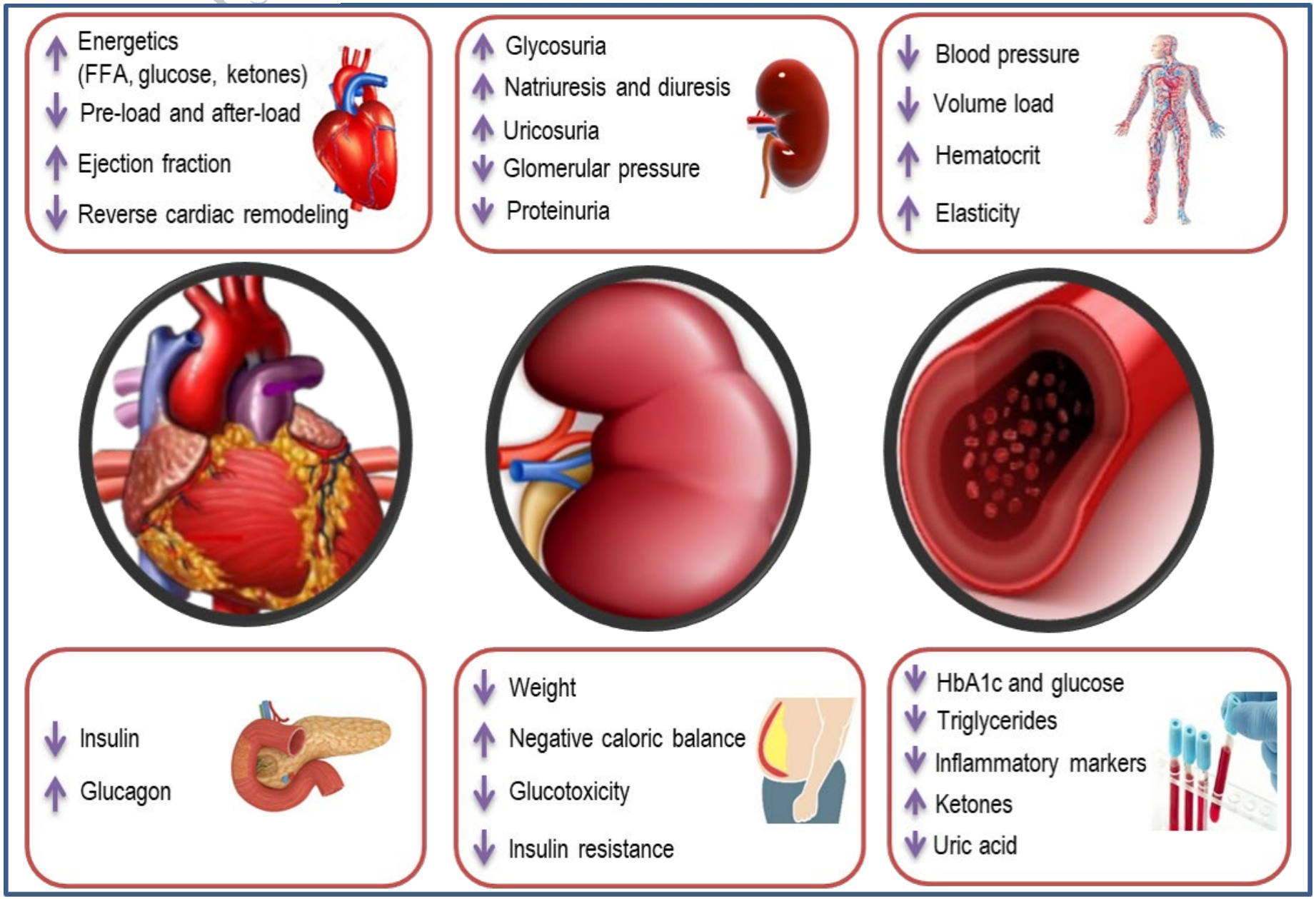
Nat Rev Nephrol. 2021;17(4):227-244

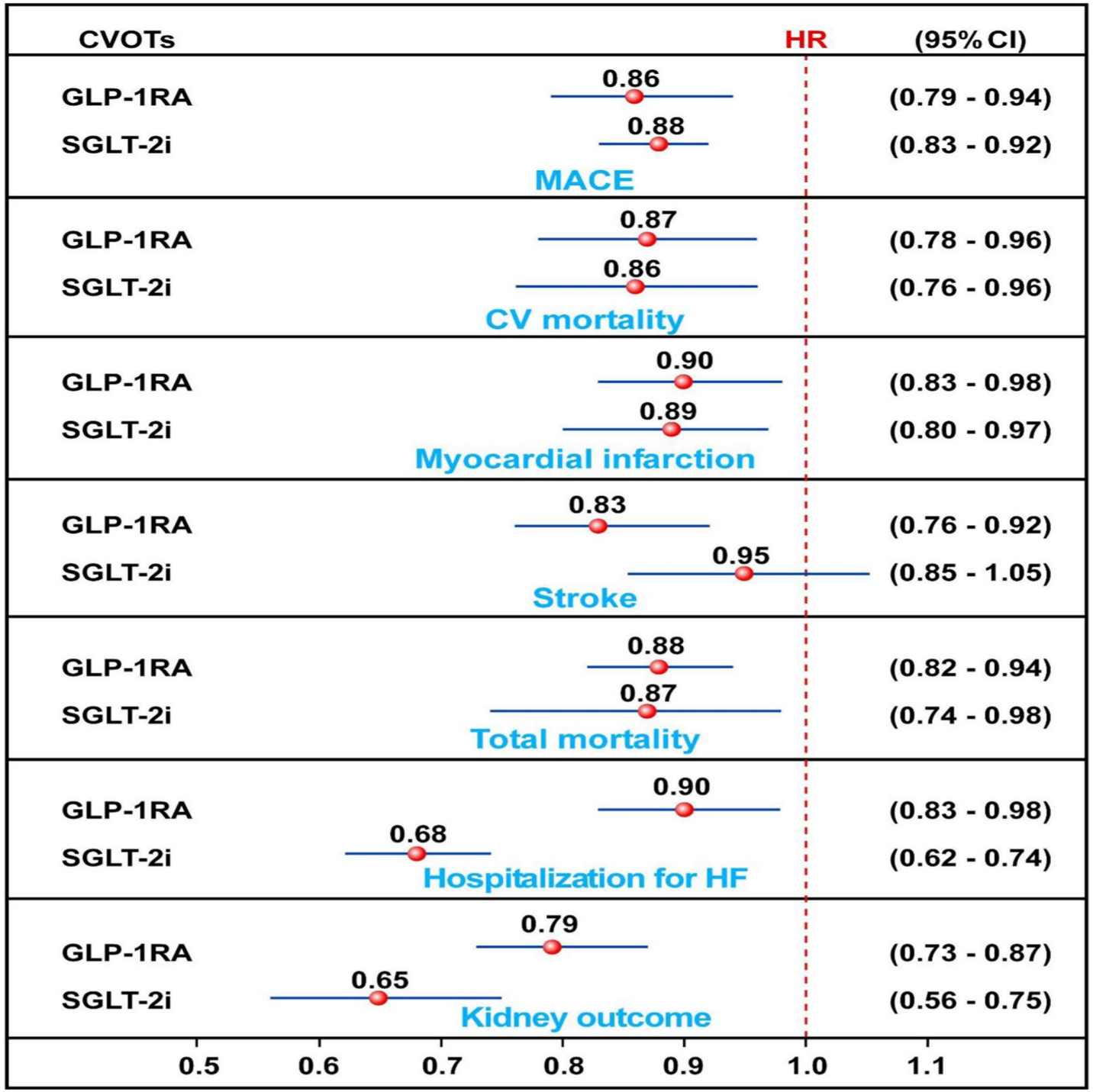
Type 2 diabetes and the kidney: Insights from cardiovascular outcome trials

Dario Giugliano MD[1] | Luca De Nicola MD[2] | Maria I. Maiorino MD[3] | Giuseppe Bellastella MD[1] | Katherine Esposito MD[3]

DIABETES, OBESITY AND METABOLISM
A JOURNAL OF PHARMACOLOGY AND THERAPEUTICS

Diabetes Obes Metab. 2019;21(8):1790–1800





COMMENTARY Open Access

GLP-1 receptor agonists vs. SGLT-2 inhibitors: the gap seems to be leveling off

Dario Giugliano[1,2*], Lorenzo Scappaticcio[1,2], Miriam Longo[1], Giuseppe Bellastella[1,2] and Katherine Esposito[2,3]

Cardiovasc Diabetol (2021) 20:205
https://doi.org/10.1186/s12933-021-01400-9

CARDIO VASCULAR DIABETOLOGY

Clegg et al. Cardiovasc Diabetol (2019) 18:138
https://doi.org/10.1186/s12933-019-0942-x

Cardiovascular Diabetology

ORIGINAL INVESTIGATION Open Access

Effects of exenatide and open-label SGLT2 inhibitor treatment, given in parallel or sequentially, on mortality and cardiovascular and renal outcomes in type 2 diabetes: insights from the EXSCEL trial

Lindsay E. Clegg[1*], Robert C. Penland[2], Srinivas Bachina[2], David W. Boulton[1], Marcus Thuresson[3], Hiddo J. L. Heerspink[4], Stephanie Gustavson[5], C. David Sjöström[6], James A. Ruggles[7], Adrian F. Hernandez[8], John B. Buse[9], Robert J. Mentz[8] and Rury R. Holman[10]

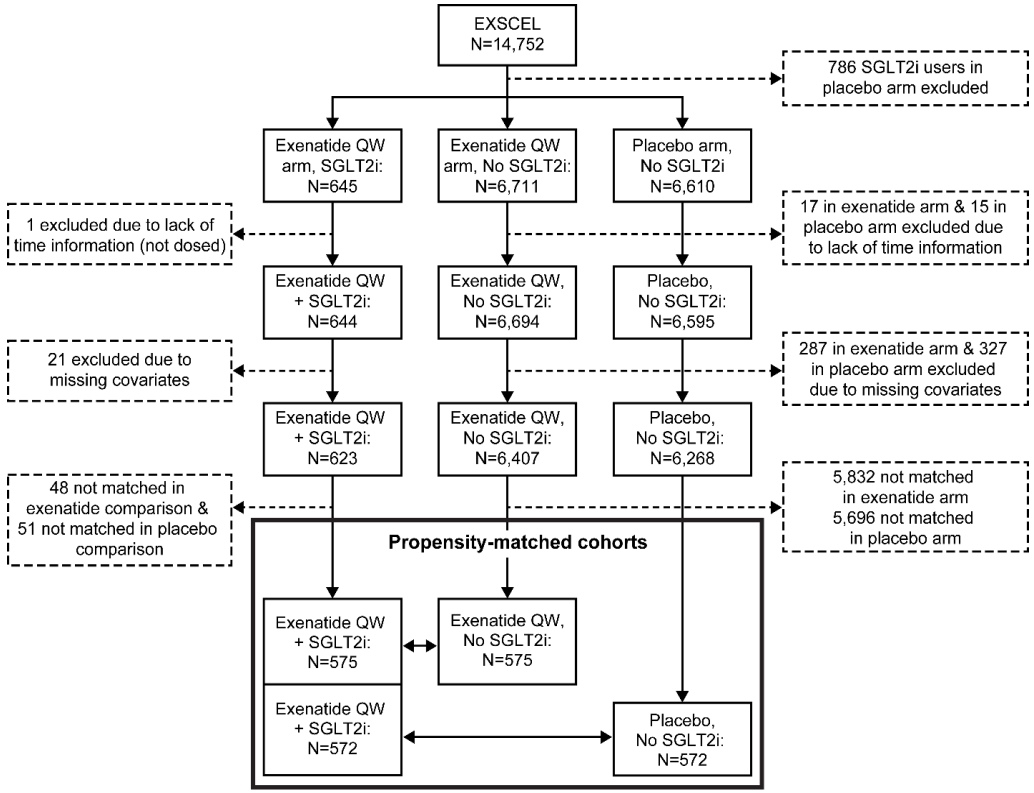
METHODS:

In the EXSCEL cardiovascular outcomes trial EQW arm, SGLT2i drop-in occurred in 8.7% of participants.

These EQW+SGLT2i users were propensity-matched to:
(1) placebo-arm participants not taking SGLT2i;
(2) EQW-arm participants not taking SGLT2i

Time-to-first major adverse cardiovascular event (MACE) and all-cause mortality (ACM) were compared using Cox regression analyses.

eGFR slopes were quantified using mixed model repeated measurement analyses.



Outcome		Number of events	Combination: Events per 100 pt-yrs	Comparator: Events per 100 pt-yrs	Adjusted hazard ratio (95% CI)
MACE	vs. placebo	57	3.29	4.81	0.68 (0.39-1.17)
	vs. exenatide	54	3.27	4.38	0.85 (0.48-1.49)
All-cause mortality	vs. placebo	30	1.00	2.71	0.38 (0.16-0.90)
	vs. exenatide	32	0.99	2.96	0.41 (0.17-0.95)
CV death	vs. placebo	16	0.28	1.65	0.17 (0.04-0.77)
	vs. exenatide	17	0.28	1.77	0.21 (0.05-0.93)
Serious hypoglycemia	vs. placebo	18	0.94	1.25	0.67 (0.26-1.76)
	vs. exenatide	18	0.93	1.25	0.77 (0.30-1.99)

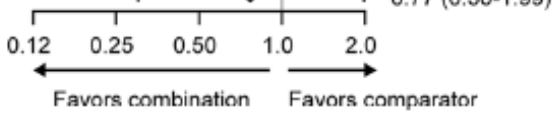


Fig. 2 Cardiovascular, mortality, and safety outcomes with combination exenatide QW+SGLT2i in the propensity-matched cohorts. Additional details are found in Additional file 1: Tables S3, S4, and Kaplan–Meier curves in Additional file 1: Figures S5–S9. Hazard ratio adjusted for age, duration of diabetes, prior cardiovascular disease, heart failure, sex, microalbuminuria, macroalbuminuria, eGFR, and HbA1c, all evaluated at first known SGLT2i usage or equivalent visit in comparator groups. MACE: major adverse cardiovascular events; CV: cardiovascular; pt-yrs: participant-years

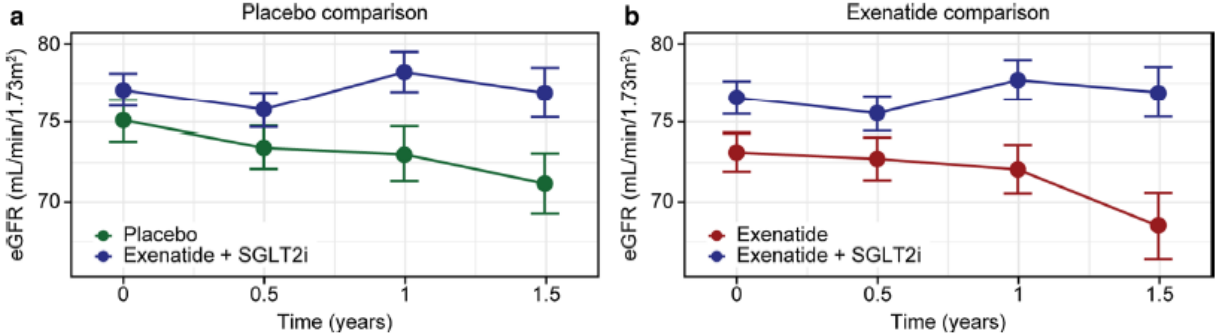


Fig. 3 Geometric mean (+/− standard error) eGFR in the propensity-matched cohorts. **a** Placebo comparison. **b** Exenatide comparison. Time zero is the time of first visit with known SGLT2i use/matching. The small differences in eGFR at matching (t=0) also reflect restrictions on SGLT2i use in moderate renal impairment. eGFR slopes prior to matching are shown in Additional file 1: Figure S11. Blue: combination exenatide + SGLT2i cohorts; green: placebo cohort; red: exenatide cohort. eGFR, estimated glomerular filtration rate; SGLT2i, sodium-glucose co-transporter-2 inhibitor

Conclusions:

This *post hoc* analysis supports the hypothesis that combinatorial EQW and SGLT2i therapy may provide benefit on cardiovascular outcomes and mortality.

Lindsay E. Clegg1* , Robert C. Penland2, Srinivas Bachina2, David W. Boulton1, Marcus Thuresson3, Hiddo J. L. Heerspink4, Stephanie Gustavson5, C. David S

Cardiovascular and Renal Outcomes with Efpeglenatide in Type 2 Diabetes

Hertzel C. Gerstein, M.D., Naveed Sattar, M.D., Ph.D., Julio Rosenstock, M.D., Chinthanie Ramasundarahettige, M.Sc., Richard Pratley, M.D., Renato D. Lopes, M.D., Ph.D., Carolyn S.P. Lam, M.B., B.S., Ph.D., Nardev S. Khurmi, M.D., Laura Heenan, M.Sc., Stefano Del Prato, M.D., Leanne Dyal, M.Sc., and Kelley Branch, M.D. for the AMPLITUDE-O Trial Investigators*

15% of patients in both arms was taking a SGLT-2 inhibitor!

Table 2. Adjudicated First Events.*

Event	Efpeglenatide, 4 or 6 mg (N=2717)		Placebo (N=1359)		Hazard Ratio (95% CI)	P Value for Noninferiority	P Value for Superiority
	no. of participants (%)	*no. of events/100 person-years*	*no. of participants (%)*	*no. of events/100 person-years*			
Primary outcome: incident MACE†	189 (7.0)	3.9	125 (9.2)	5.3	0.73 (0.58–0.92)	<0.001‡	0.007
Expanded MACE composite outcome event§	257 (9.5)	5.4	158 (11.6)	6.8	0.79 (0.65–0.96)		0.02
Composite renal outcome event¶	353 (13.0)	7.7	250 (18.4)	11.6	0.68 (0.57–0.79)		<0.001
MACE or death from noncardiovascular causes	216 (7.9)	4.5	143 (10.5)	6.0	0.73 (0.59–0.91)		0.004
Kidney-function outcome event‖	121 (4.5)	2.5	76 (5.6)	3.1	0.77 (0.57–1.02)		0.07
MACE, death from noncardiovascular causes, hospitalization for heart failure, or kidney-function outcome event	243 (8.9)	5.1	164 (12.1)	7.0	0.71 (0.59–0.87)		
Myocardial infarction	91 (3.3)	1.9	58 (4.3)	2.4	0.75 (0.54–1.05)		
Nonfatal myocardial infarction	85 (3.1)	1.7	53 (3.9)	2.2	0.78 (0.55–1.10)		
Stroke	47 (1.7)	1.0	31 (2.3)	1.3	0.74 (0.47–1.17)		
Nonfatal stroke	41 (1.5)	0.8	25 (1.8)	1.0	0.80 (0.48–1.31)		
Cardiovascular mortality	75 (2.8)	1.5	50 (3.7)	2.1	0.72 (0.50–1.03)		
Total mortality	111 (4.1)	2.2	69 (5.1)	2.8	0.78 (0.58–1.06)		
Coronary revascularization	126 (4.6)	2.6	66 (4.9)	2.8	0.93 (0.69–1.26)		
Unstable angina	6 (0.2)	0.1	4 (0.3)	0.2	0.55 (0.13–2.35)		
Incident macroalbuminuria	348 (12.8)	7.6	244 (18.0)	11.3	0.68 (0.58–0.80)		
Heart failure	40 (1.5)	0.8	31 (2.3)	1.3	0.61 (0.38–0.98)		

N Engl J Med 2021; 385:896-907

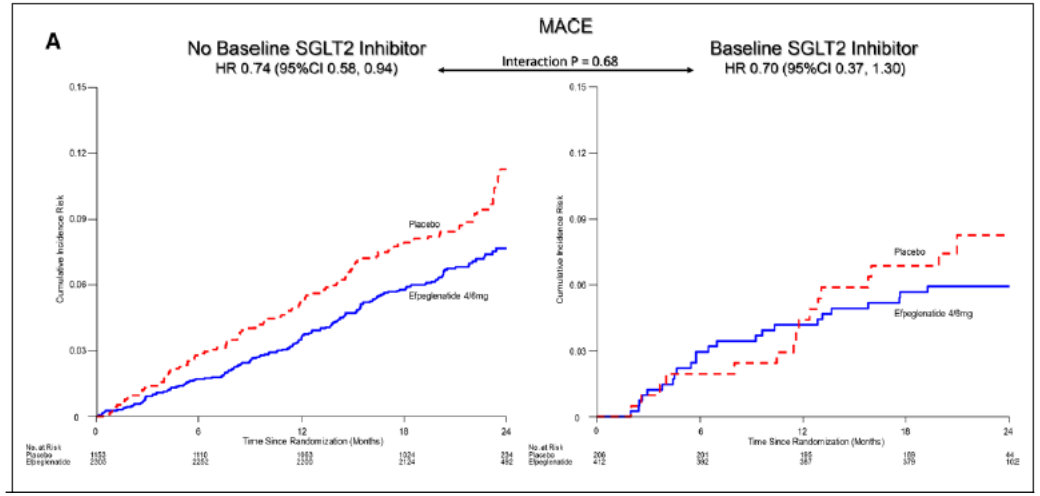
ORIGINAL RESEARCH ARTICLE Circulation

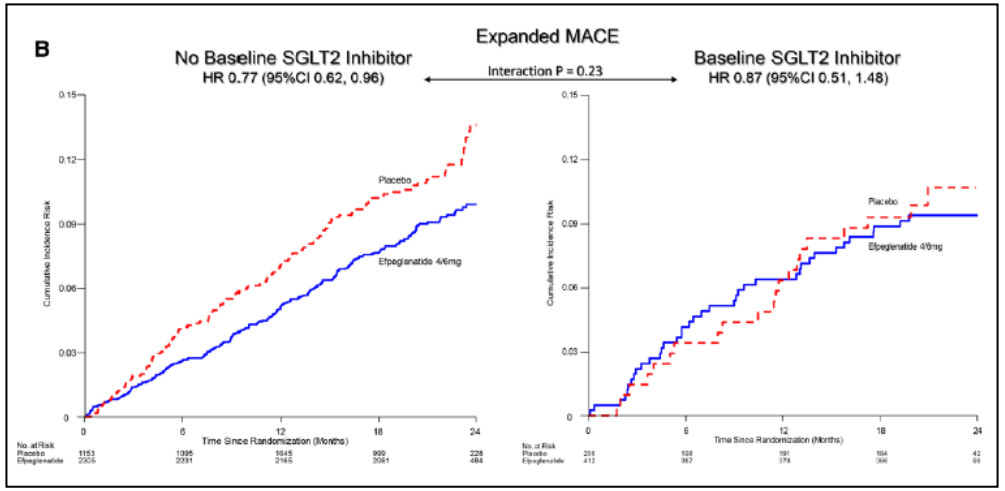
Efpeglenatide and Clinical Outcomes With and Without Concomitant Sodium-Glucose Cotransporter-2 Inhibition Use in Type 2 Diabetes: Exploratory Analysis of the AMPLITUDE-O Trial

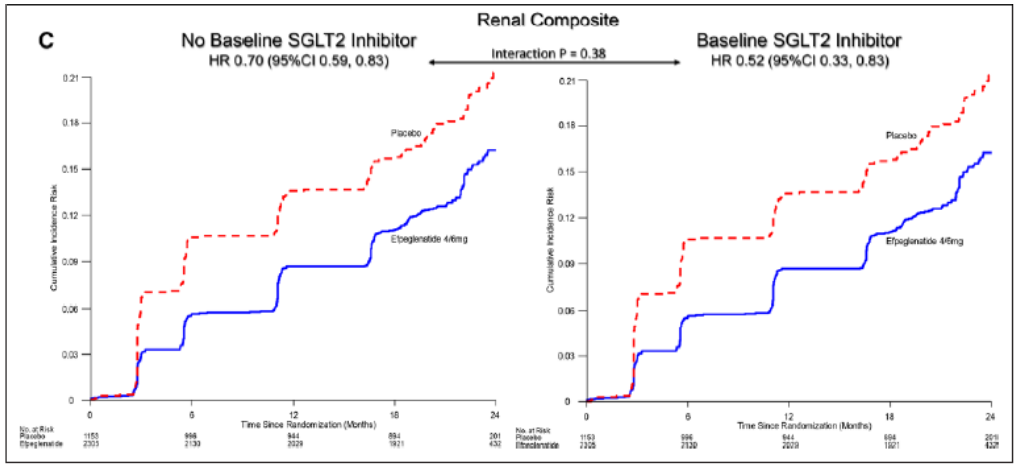
BACKGROUND: The AMPLITUDE-O trial reported that once-weekly injections of the GLP1-RA efpeglenatide (versus placebo) reduced MACEs, coronary revascularization, or unstable angina hospitalization (expanded MACEs); a renal composite outcome; and MACEs or death in people with type 2 diabetes and cardiovascular or renal disease.

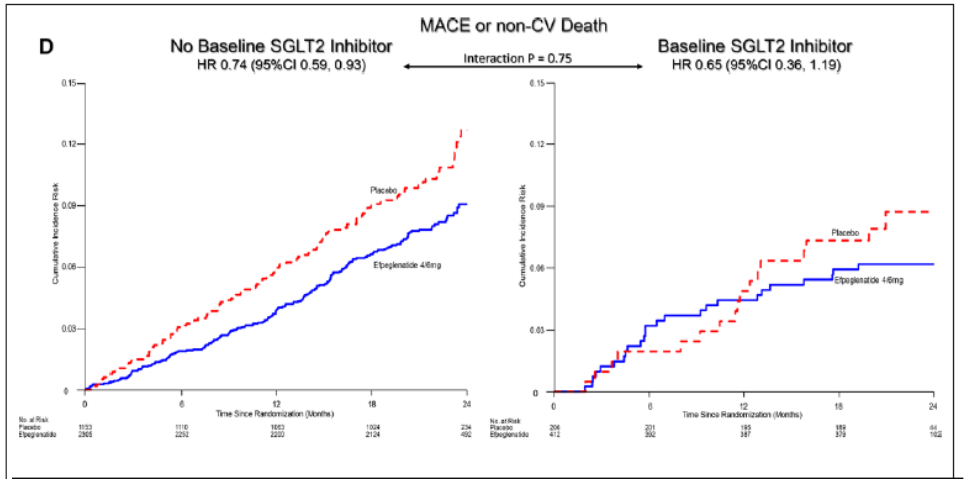
The trial uniquely stratified randomization by baseline or anticipated use of SGLT2 inhibitors and included the highest prevalence at baseline (N=618, 15.2%) of SGLT2 inhibitor use among glucagon-like peptide-1 receptor agonistcardiovascular outcome trials to date.

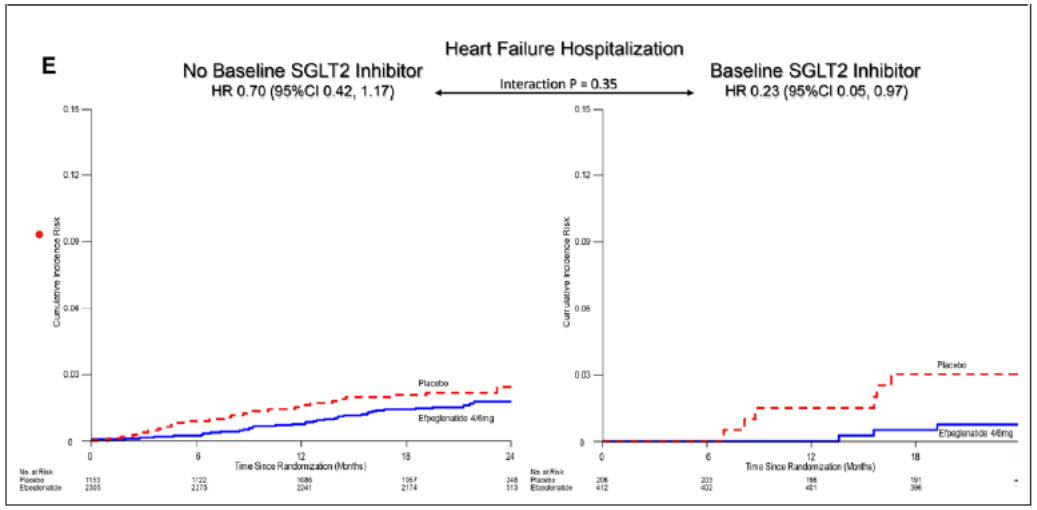
Its results were analyzed to estimate the combined effect of SGLT2 inhibitors and efpeglenatide on clinical outcomes.











CONCLUSIONS: The efficacy and safety of efpeglenatide appear to be independent of concurrent SGLT2 inhibitor use. These data support combined SGLT2 inhibitor and glucagon-like peptide-1 receptor agonist therapy in type 2 diabetes.

Carolyn S.P. Lam , MBBS, PhD; Chinthanie Ramasundarahettige, MSc; Kelley R.H. Branch , MD, MSc; Naveed Sattar , MD, PhD; Julio Rosenstock, MD; Richard Pratley , MD; Stefano Del Prato , MD; Renato D. Lopes , MD, PhD; Elisabeth Niemoeller, MD; Nardev S. Khurmi , MD; Seungjae Baek , MD, PhD; Hertzel C. Gerstein, MD, MSc

DECLARE TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG

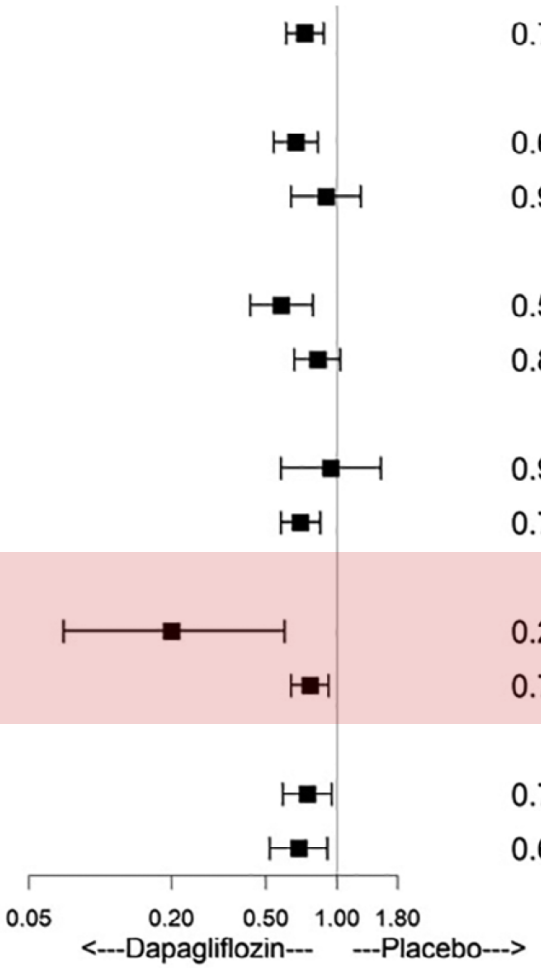
DIABETES OBESITY AND METABOLISM

HHF

Diabetes Obes Metab. 2021;23:29–38.

(B)

Subgroups	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	*P*-value	*P*-interaction
Overall	212/8582 (2.5%)	286/8578 (3.3%)	0.73 (0.61, 0.88)	.0006	
Baseline metformin					
Yes	146/7020 (2.1%)	217/7048 (3.1%)	0.67 (0.54, 0.83)	.0002	.1434
No	66/1562 (4.2%)	69/1530 (4.5%)	0.90 (0.64, 1.26)	.5471	
Baseline sulphonylureas					
Yes	66/3615 (1.8%)	116/3707 (3.1%)	0.58 (0.43, 0.79)	.0004	.0631
No	146/4967 (2.9%)	170/4871 (3.5%)	0.83 (0.66, 1.03)	.0969	
Baseline DPP-4 inhibitors					
Yes	30/1418 (2.1%)	35/1470 (2.4%)	0.94 (0.58, 1.53)	.7952	.2839
No	182/7164 (2.5%)	251/7108 (3.5%)	0.70 (0.58, 0.85)	.0003	
Baseline GLP-1 receptor agonists					
Yes	4/397 (1.0%)	18/353 (5.1%)	0.20 (0.07, 0.60)	.0038	.0143
No	208/8185 (2.5%)	268/8225 (3.3%)	0.77 (0.64, 0.92)	.0050	
Baseline insulin					
Yes	127/3567 (3.6%)	160/3446 (4.6%)	0.75 (0.59, 0.95)	.0149	.6594
No	85/5015 (1.7%)	126/5132 (2.5%)	0.69 (0.52, 0.91)	.0081	



DECLARE TIMI-58 TIMI STUDY GROUP/HADASSAH MEDICAL ORG

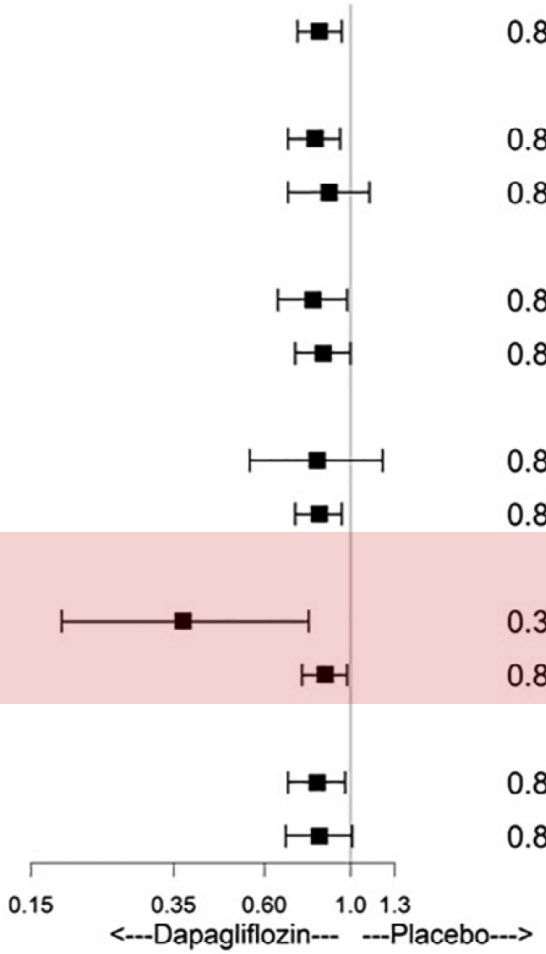
DIABETES OBESITY AND METABOLISM

Diabetes Obes Metab. 2021;23:29–38.

CV death/HHF

(A)

Subgroups	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	*P*-value	*P*-interaction
Overall	417/8582 (4.9%)	496/8578 (5.8%)	0.83 (0.73, 0.95)	.0027	
Baseline metformin					
Yes	293/7020 (4.2%)	362/7048 (5.1%)	0.81 (0.69, 0.94)	.0063	.5603
No	124/1562 (7.9%)	134/1530 (8.8%)	0.88 (0.69, 1.12)	.2914	
Baseline sulphonylureas					
Yes	153/3615 (4.2%)	196/3707 (5.3%)	0.80 (0.65, 0.98)	.0354	.6386
No	264/4967 (5.3%)	300/4871 (6.2%)	0.85 (0.72, 1.00)	.0536	
Baseline DPP-4 inhibitors					
Yes	44/1418 (3.1%)	58/1470 (3.9%)	0.82 (0.55, 1.21)	.3223	.9709
No	373/7164 (5.2%)	438/7108 (6.2%)	0.83 (0.72, 0.95)	.0069	
Baseline GLP-1 receptor agonists					
Yes	10/397 (2.5%)	24/353 (6.8%)	0.37 (0.18, 0.78)	.0085	.0257
No	407/8185 (5.0%)	472/8225 (5.7%)	0.86 (0.75, 0.98)	.0229	
Baseline insulin					
Yes	237/3567 (6.6%)	274/3446 (8.0%)	0.82 (0.69, 0.97)	.0224	.9142
No	180/5015 (3.6%)	222/5132 (4.3%)	0.83 (0.68, 1.01)	.0599	



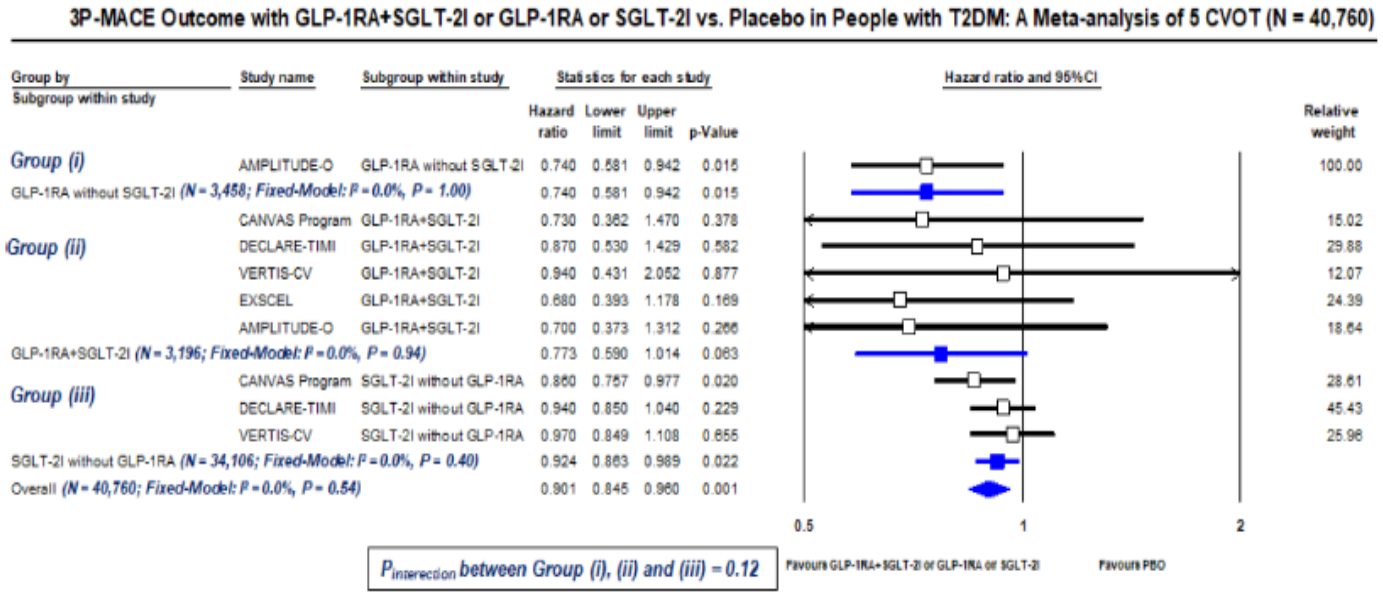
Inclusive data from Review and Metanalysis

OPINION REVIEW

Metabolic and cardiovascular benefits with combination therapy of SGLT-2 inhibitors and GLP-1 receptor agonists in type 2 diabetes

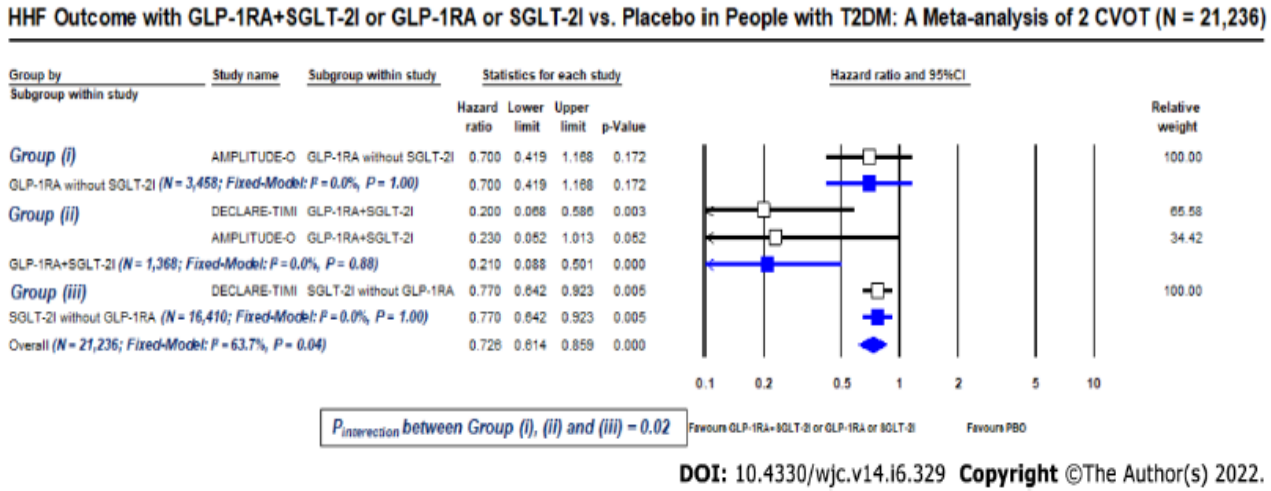
Awadhesh Kumar Singh, Ritu Singh

World J Cardiol 2022



DOI: 10.4330/wjc.v14.i6.329

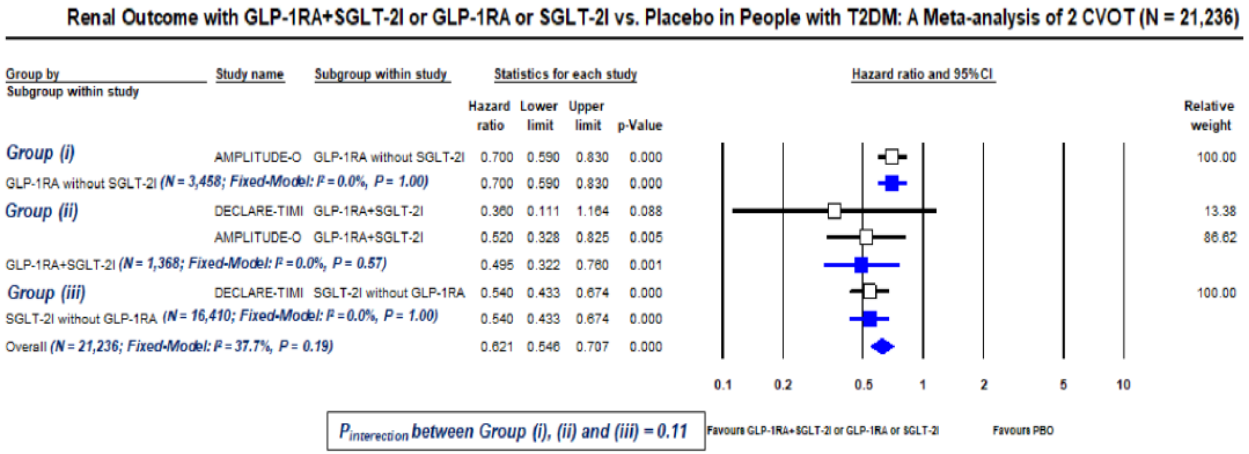
The pooled data of five CVOT suggested: No significant difference (*P* interection = 0.12) was noted on 3P-MACE outcome between the combination therapy, GLP-1RA without SGLT-2I or SGLT-2I without GLP-1RA against placebo



DOI: 10.4330/wjc.v14.i6.329 **Copyright** ©The Author(s) 2022.

The pooled data of two RCTs that reported **the outcomes of HHF and renal composite** suggested

a greater benefit (*P*interaction = 0.02) on HHF outcomes with GLP-1RA plus SGLT-2I dual therapy compared with GLP-1RA without SGLT-2I and SGLT-2I without GLP-1RA against placebo



DOI: 10.4330/wjc.v14.i6.329 **Copyright** ©The Author(s) 2022.

No significant difference (*P* interection = 0.11) was noted on the composite of renal outcome between the combination therapy, GLP-1RA without SGLT-2I or SGLT-2I without GLP-1RA against placebo

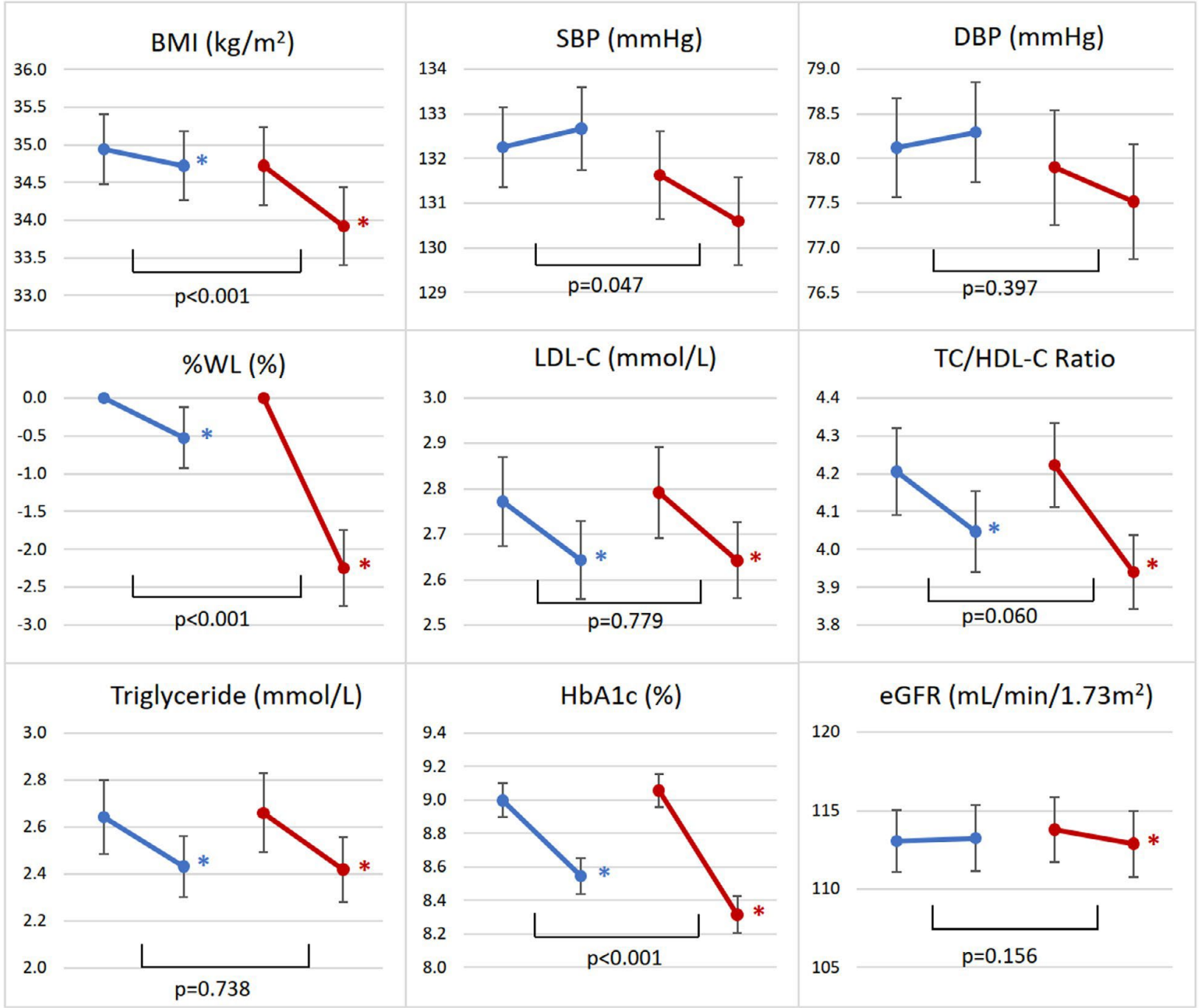
Journal of the American Heart Association

ORIGINAL RESEARCH

Switching to Versus Addition of Incretin-Based Drugs Among Patients With Type 2 Diabetes Taking Sodium-Glucose Cotransporter-2 Inhibitors

What Are the Clinical Implications?

- While no significant differences in the risks of various clinical end points were identified between switching and add-on approaches in the current study, they should be interpreted with caution given the relatively short follow-up period and hence the small number of events that occurred.
- Meanwhile, several metabolic benefits of the combination ("Add-on") approach were significantly greater than that of switching, including better glycemic control, reduction in weight and blood pressure over 12-month follow-up.
- Further studies with longer observation periods and randomized controlled trials are needed to clarify the risks and benefits of the 2 treatment modalities.



J Am Heart Assoc. 2022;11:e023489

PREvention of Cardiovascular and DiabEtic kidNey Disease in Type 2 Diabetes (PRECIDENTD)

ClinicalTrials.gov Identifier: NCT05390892

Recruitment Status : Recruiting
First Posted : May 25, 2022
Last Update Posted : September 27, 2022

See Contacts and Locations

Sponsor:
Brigham and Women's Hospital

Collaborator:
Patient-Centered Outcomes Research Institute

Information provided by (Responsible Party):
Brendan M. Everett, Brigham and Women's Hospital

Study Description

Go to

Brief Summary:

PRECIDENTD is a randomized, open label, pragmatic clinical trial designed to compare rates of the total number of cardiovascular, kidney, and death events among three alternative treatments for patients with type 2 diabetes (T2D) and either established atherosclerotic cardiovascular disease (ASCVD) or at high risk for ASCVD. To accomplish this objective, we will randomly assign 9,000 patients with established T2D and ASCVD or high-risk for ASCVD in a 1:1:1 allocation to SGLT2i, GLP-1RA, or the combination. Participants will be followed for the occurrence of the trial primary endpoint of the total (first and recurrent) number of episodes of myocardial infarction (MI), stroke, arterial revascularization, hospitalization for heart failure, development of end-stage kidney disease, kidney transplantation, and mortality, counting all events from randomization until end of study.

https://www.clinicaltrials.gov/ct2/show/NCT05390892

ONGOING TRAILS

DECREASE;NCT03361098 : Dapagliflozin plus exenatide on central regulation of appetite in diabetes type 2. It is a double-blind, 16-wk RCT (*n* = 65) investigating the separate and combined actions of GLP-1RA plus SGLT-2I on food intake, body weight, activity within the central satiety and reward circuits in response to food-related stimuli, and whether the combination can prevent the increased intake observed with SGLT2-I in obese T2DM.

EXENDA, NCT003007329 : Effects of combined dapagliflozin and exenatide *vs* dapagliflozin and placebo on ectopic lipids in patients with uncontrolled type 2 diabetes mellitus . It is a triple-blind, 24-wk RCT (*n* = 34) investigating the effect of combination therapy *vs* SGLT-2I alone on hepatic lipid content (primary outcome) and myocardial and pancreatic lipid content (secondary outcome) as measured by magnetic resonance spectroscopy

RESILIENT; EudraCT 2015-005242-60 : Randomized, controlled, double blind study ongoing to assess mechanistic effects of combination therapy of dapagliflozin with exenatide QW vs dapagliflozin alone in obese (BMI > 30 kg/m2) patients with type 2 diabetes mellitus. This study is evaluating the effect of exenatide QW plus dapagliflozin *vs* dapagliflozin alone compared with placebo on adjusted mean reduction in total body fat mass (as determined by dual-energy X-ray absorptiometry, DEXA) after 32 wk of treatment (*n* = 110).

DECADE, EudraCT 2017-004709-42: A 6-wk (*n* = 17), open-label, randomized, cross-over study to evaluate the albuminuria lowering effect of dapagliflozin, exenatide, and their combination in patients with type 2 diabetes) is currently underway.

Thank you for attention!!

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Università degli Studi della Campania "Luigi Vanvitelli"

Dipartimento di Scienze Mediche e Chirurgiche Avanzate

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