

CONGRESSO REGIONALE
AMD-SID LAZIO

II DIABETE OGGI:

UNA MALATTIA SEMPRE PIÙ COMPLESSA



ROMA - 7/8 OTTOBRE 2022 - HOTEL QUIRINALE

GLIFLOZINE E INCRETINE INSIEME: COME, QUANDO E PERCHÉ?

Martina Vitale

UOC Medicina Specialistica Endocrino-Metabolica –
Azienda Ospedaliera Sant'Andrea, Roma

La dr.ssa MARTINA VITALE dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

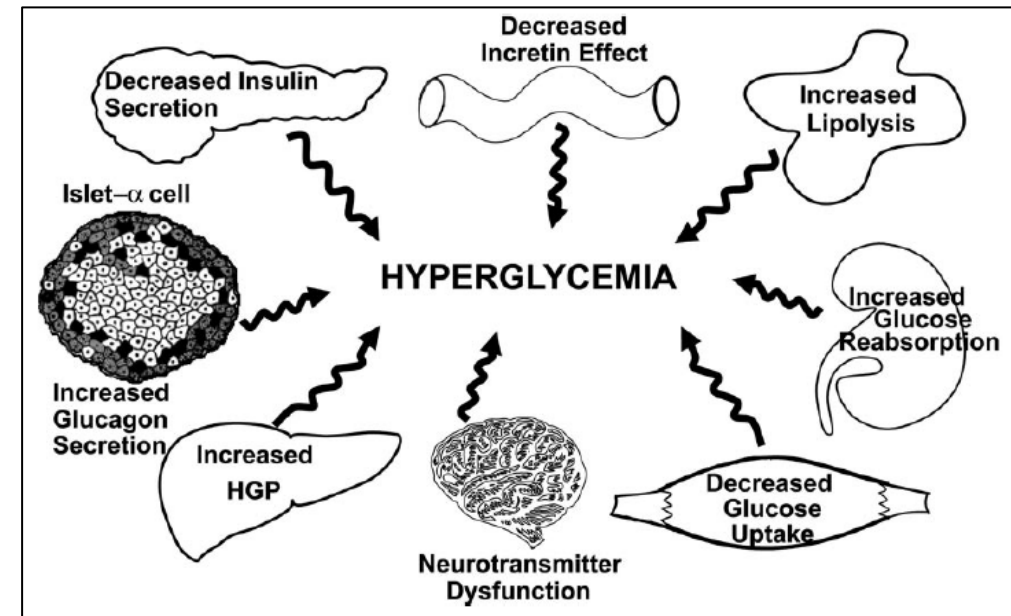
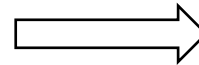
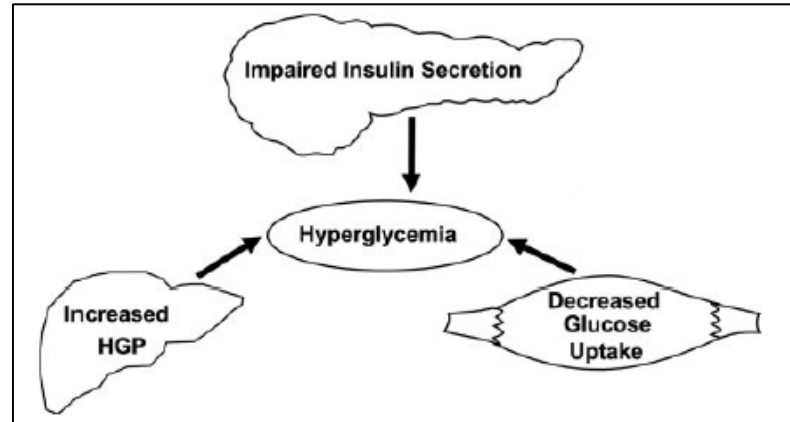
- Novo Nordisk
- Mundipharma

Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

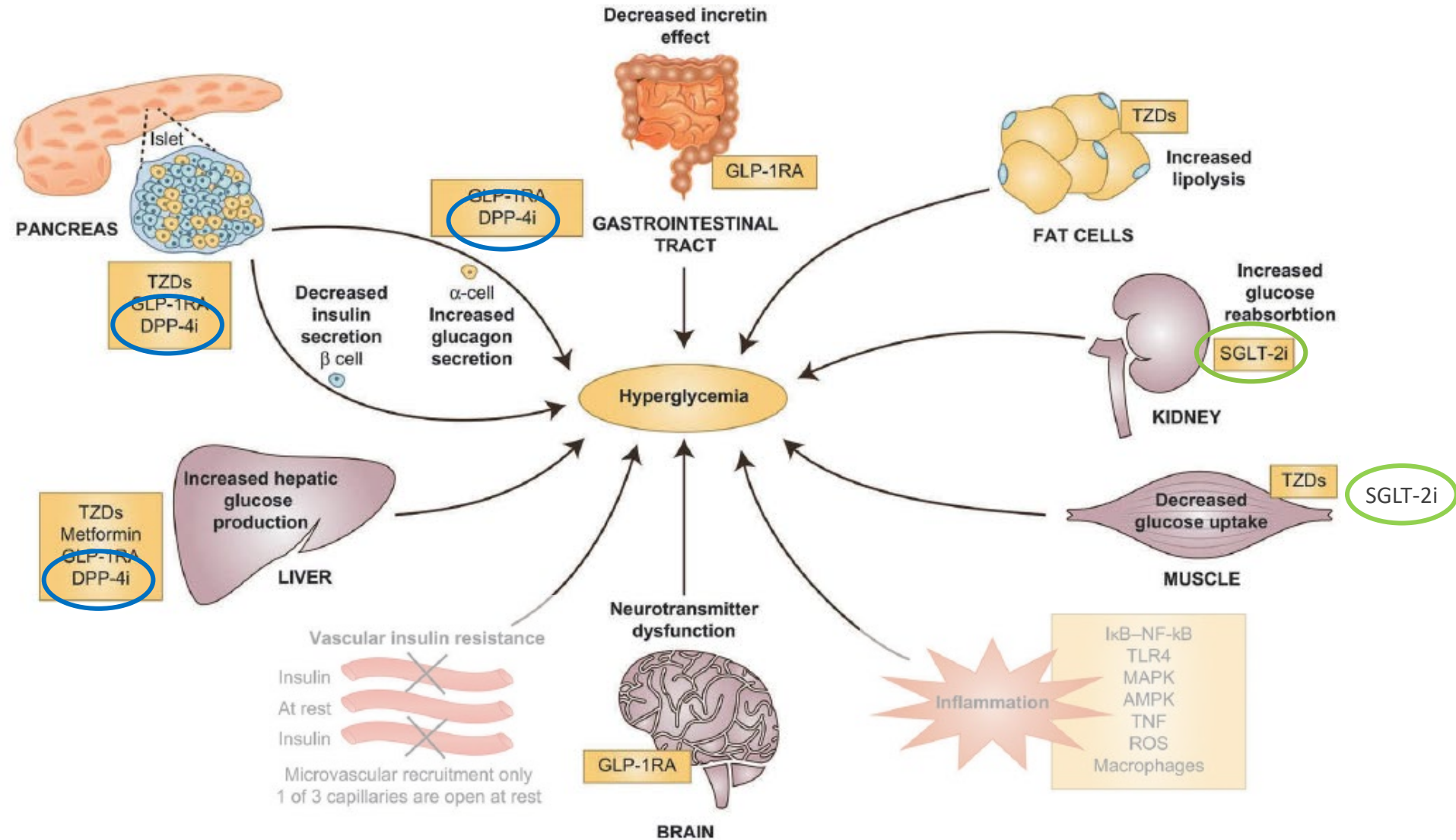
- **INTRODUZIONE - RAZIONALE**
- **LE LINEE GUIDA**
- **STUDI DI EFFICACIA E SICUREZZA**
 - GLP-1 RA + SGLT-2i (simultaneo)
 - GLP-1 RA su SGLT-2i (sequenziale)
 - SGLT-2i su GLP-1 RA (sequenziale)
 - REAL WORLD
 - METANALISI
- **STUDI DI OUTCOME CARDIOVASCOLARE E RENALE**
 - REAL WORLD
 - CVOT
 - METANALISI
 - *ON-GOING*
- **ALTRI OUTCOMES**
 - NAFLD/NASH
 - OBESITÀ
- **TAKE HOME MESSAGES**

From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus

Ralph A. DeFronzo



INTRODUZIONE – RAZIONALE

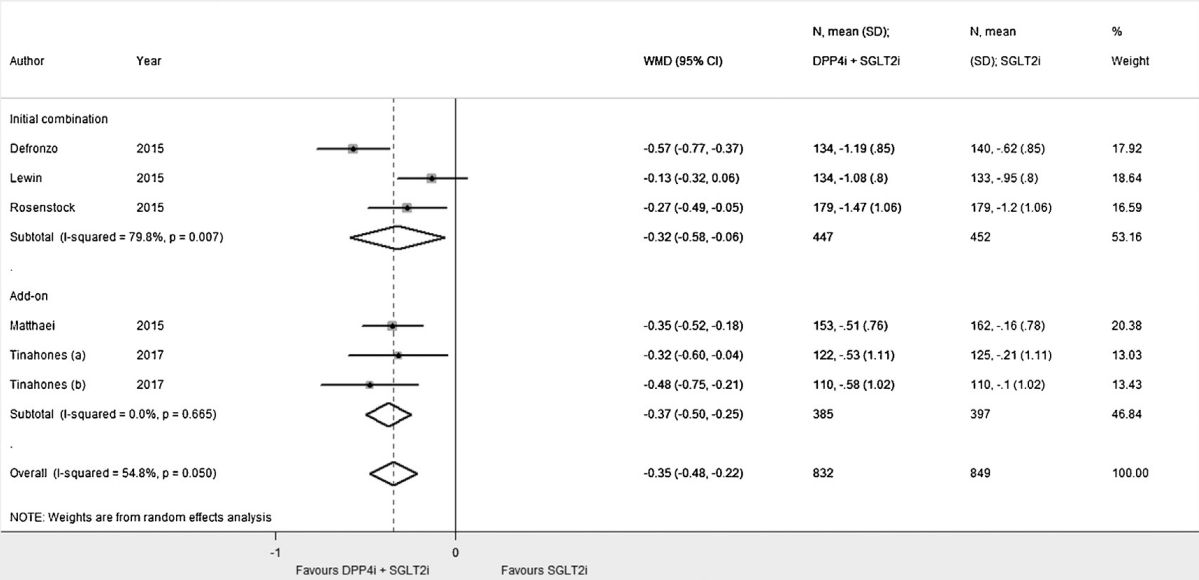
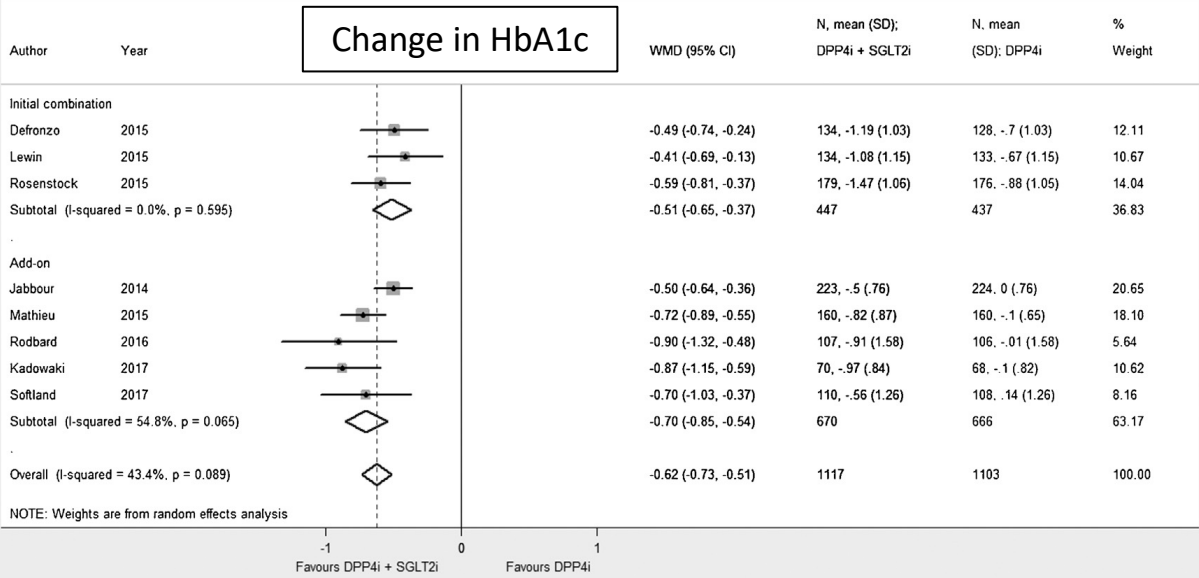


INTRODUZIONE – RAZIONALE

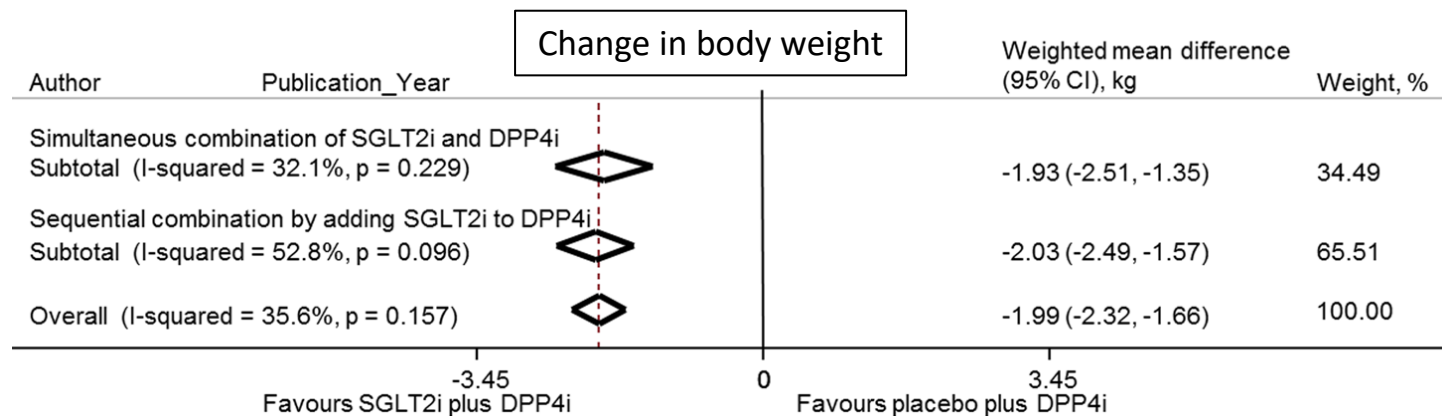
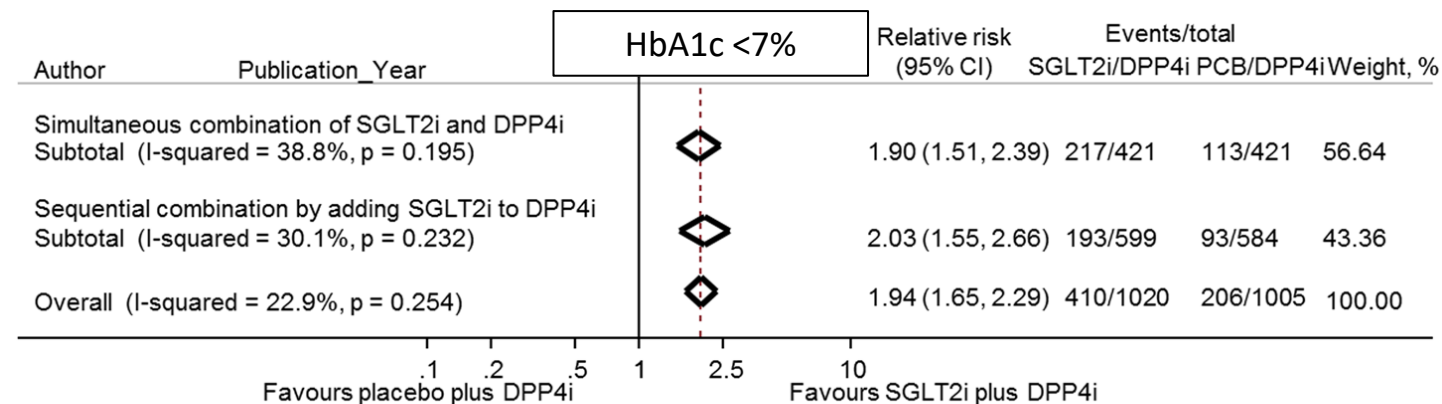
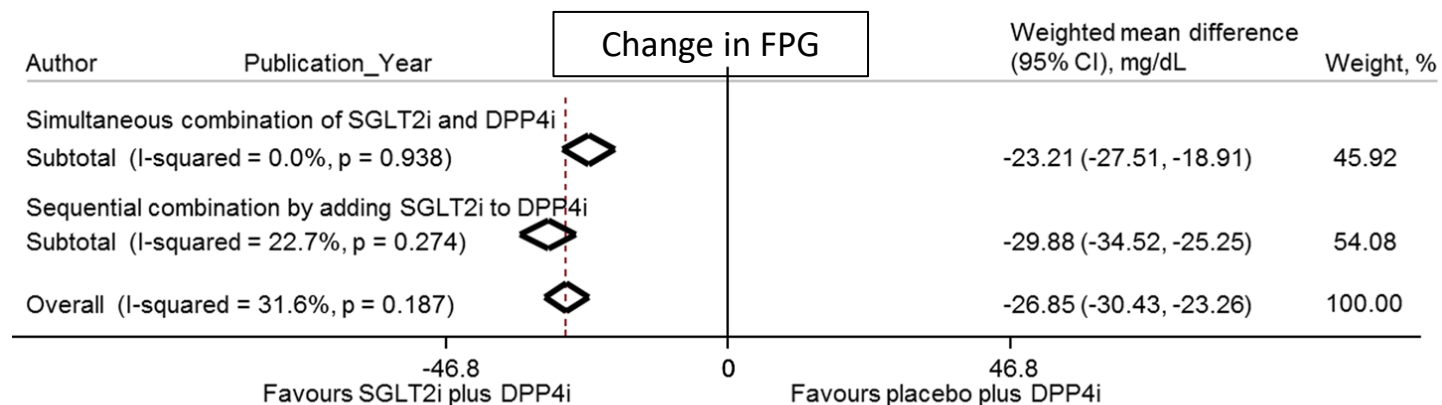
SGLT-2i

+

DPP-4i



INTRODUZIONE – RAZIONALE



INTRODUZIONE – RAZIONALE

Nota AIFA 100_Scheda di prima prescrizione (versione del 28 maggio 2022)

SCHEDA DI VALUTAZIONE E PRESCRIZIONE DI INIBITORI DEL SGLT2, AGONISTI RECETTORIALI DEL GLP1 E INIBITORI DEL DPP4 NEL TRATTAMENTO DEL DIABETE MELLITO TIPO 2

Da compilare a cura del prescrittore che seguirà il paziente nella gestione del trattamento e del follow-up periodico (Specialista SSN, Medico di Medicina Generale).

Scheda di prima prescrizione

Medico prescrittore _____ Tel _____

Specificare se: ☐ Medico di Medicina Generale ☐ Specialista in _____

U.O. _____ Az. Sanitaria _____

Paziente (nome e cognome) _____

Sesso: ☐ M ☐ F Data di Nascita _____ Codice Fiscale _____

Residenza _____

Valutazione

Paziente in trattamento con metformina: ☐ Sì ☐ No, per controindicazione o intolleranza

Mancato raggiungimento/mantenimento degli obiettivi glicemici individuali prefissati o necessità di modificare la terapia in corso anche nel caso di HbA1c a target: ☐ Sì

Indicare le principali motivazioni della strategia terapeutica che si propone di prescrivere:

☐ prevenzione CV secondaria*

☐ rischio CV elevato**

☐ scompenso cardiaco (solo se SGLT2i)

☐ malattia renale cronica*** (solo se SGLT2i)

☐ mancato raggiungimento/mantenimento degli obiettivi glicemici individuali prefissati****

☐ solo per DPP4i: controindicazione o intolleranza a SGLT2i e GLP1-RA (nel paziente a rischio CV elevato o con malattia CV, malattia renale cronica o scompenso cardiaco)

☐ altra motivazione (specificare) _____

*per prevenzione CV secondaria si intende la presenza di malattia cardiovascolare (cardiopatia ischemica, IMA, bypass aortocoronario, angioplastica, procedura di rivascularizzazione coronarica, coronaropatia), malattia cerebrovascolare (pregresso ictus o TIA, rivascularizzazione carotidea) o arteriopatia periferica sintomatica.

**per rischio CV elevato, nel paziente senza malattia CV conclamata, si intende: presenza di danno vascolare aterosclerotico documentato (es. malattia coronarica multivasale o stenosi carotidea >50%); presenza di danno in un organo target; presenza di almeno tre fattori di rischio CV (tra età >50 anni, ipertensione, dislipidemia, obesità, fumo di sigaretta).

***per malattia renale cronica si intende la presenza di GFR <60 mL/min e/o di albuminuria (micro o macro).

****per i DPP4i: solo nel paziente non a rischio CV elevato o senza malattia CV, malattia renale cronica o scompenso cardiaco.

Peso corporeo (kg) _____ Altezza (m) _____ BMI (kg/m²) _____

HbA1c recente (mmol/mol) _____ Obiettivo individuale di HbA1c (mmol/mol) _____

eGFR secondo formula CKD-EPI (mL/min) _____

Albuminuria: ☐ non valutata ☐ assente ☐ microalbuminuria ☐ macroalbuminuria/proteinuria

Nota AIFA 100_Scheda di prima prescrizione (versione del 28 maggio 2022)

Strategia terapeutica (selezionare farmaco e posologia)

Categoria	Farmaco	Posologia	Categoria	Farmaco	Posologia
SGLT2i	☐ canagliflozin	☐ 100 mg una volta/die ☐ 300 mg una volta/die	SGLT2i/MF	☐ canagliflozin/metformina	☐ 50/850 mg per 2 vv/die ☐ 50/1000 mg per 2 vv/die ☐ 150/850 mg per 2 vv/die ☐ 150/1000 mg per 2 vv/die
	☐ dapagliflozin	☐ 10 mg una volta/die		☐ dapagliflozin/metformina	☐ 5/850 mg per 2 vv/die ☐ 5/1000 mg per 2 vv/die
	☐ empagliflozin	☐ 10 mg una volta/die ☐ 25 mg una volta/die		☐ empagliflozin/metformina	☐ 5/850 mg per 2 vv/die ☐ 5/1000 mg per 2 vv/die ☐ 12,5/850 mg per 2 vv/die ☐ 12,5/1000 mg per 2 vv/die
	☐ ertugliflozin	☐ 5 mg una volta/die ☐ 15 mg una volta/die		☐ ertugliflozin/metformina	☐ 2,5/1000 mg per 2 vv/die ☐ 7,5/1000 mg per 2 vv/die
DPP4i	☐ alogliptin	☐ 6,25 mg una volta/die ☐ 12,5 mg una volta/die ☐ 25 mg una volta/die	DPP4i/MF	☐ alogliptin/metformina	☐ 12,5/850 mg per 2 vv/die ☐ 12,5/1000 mg per 2 vv/die
	☐ linagliptin	☐ 5 mg una volta/die		☐ linagliptin/metformina	☐ 2,5/850 mg per 2 vv/die ☐ 2,5/1000 mg per 2 vv/die
	☐ saxagliptin	☐ 2,5 mg una volta/die ☐ 5 mg una volta/die		☐ saxagliptin/metformina	☐ 2,5/850 mg per 2 vv/die ☐ 2,5/1000 mg per 2 vv/die
	☐ sitagliptin	☐ 25 mg una volta/die ☐ 50 mg una volta/die ☐ 100 mg una volta/die		☐ sitagliptin/metformina	☐ 50/850 mg per 2 vv/die ☐ 50/1000 mg per 2 vv/die
	☐ vildagliptin	☐ 50 mg per 2 vv/die ☐ 50 mg una volta/die		☐ vildagliptin/metformina	☐ 50/850 mg per 2 vv/die ☐ 50/1000 mg per 2 vv/die
	☐ dulaglutide	☐ 0,75 mg una volta/sett ☐ 1,5 mg una volta/sett ☐ 3,0 mg una volta/sett ☐ 4,5 mg una volta/sett	DPP4i/TZD	☐ alogliptin/pioglitazone	☐ 12,5/30 mg una volta/die ☐ 12,5/45 mg una volta/die ☐ 25/30 mg una volta/die ☐ 25/45 mg una volta/die
GLP1-RA	☐ exenatide	☐ 5 mcg per 2 vv/die ☐ 10 mcg per 2 vv/die		☐ empagliflozin/linagliptin	☐ 10/5 mg una volta/die ☐ 25/5 mg una volta/die
	☐ exenatide LAR	☐ 2 mg una volta/settimana	SGLT2i/ DPP4i	☐ saxagliptin/dapagliflozin	☐ 5/10 mg una volta/die
	☐ liraglutide	☐ 0,6 mg una volta/die ☐ 1,2 mg una volta/die ☐ 1,8 mg una volta/die		☐ ertugliflozin/sitagliptin	☐ 5/100 mg una volta/die ☐ 15/100 mg una volta/die
	☐ lixisenatide	☐ 10 mcg una volta/die ☐ 20 mcg una volta/die	GLP1-RA/ insulina	☐ insulina degludec/liraglutide penna	dosi unitarie una volta/die (da 10 a 50U di degludec e da 0,36 a 1,8 mg di liraglutide)
	☐ semaglutide orale	☐ 3 mg una volta/die ☐ 7 mg una volta/die ☐ 14 mg una volta/die		☐ insulina glargine/lixisenatide penna 10-40	dosi unitarie una volta/die (da 10 a 40U di glargine e da 2 a 20 mcg di lixisenatide)
	☐ semaglutide s.c.	☐ 0,25 mg una volta/sett ☐ 0,50 mg una volta/sett ☐ 1,0 mg una volta/sett		☐ insulina glargine/lixisenatide penna 30-60	dosi unitarie una volta/die (da 30 a 60U di glargine e da 10 a 20 mcg di lixisenatide)

La prescrizione dell'associazione SGLT2i+DPP4i o SGLT2i+GLP1-RA può avvenire esclusivamente da parte di specialisti di strutture diabetologiche individuate dalle Regioni.

La prescrizione delle associazioni estemporanee SGLT2i+DPP4i o SGLT2i+GLP1-RA deve avvenire utilizzando esclusivamente le associazioni tra molecole autorizzate in RCP.

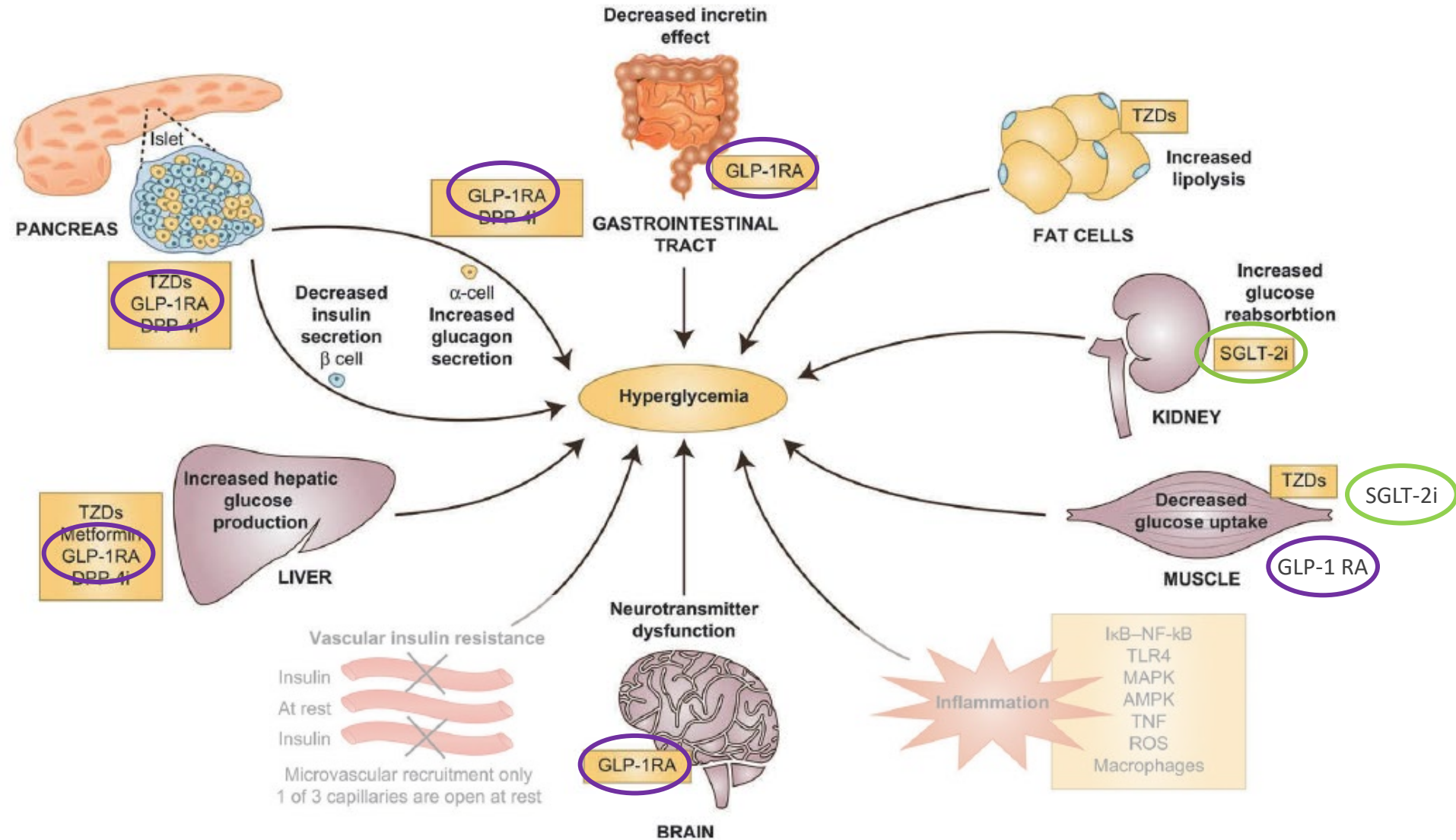
Indicare l'eventuale altra terapia antidiabetica associata: _____

Data prevista per il Follow up: _____
la validità della prima prescrizione è al massimo di 6 mesi

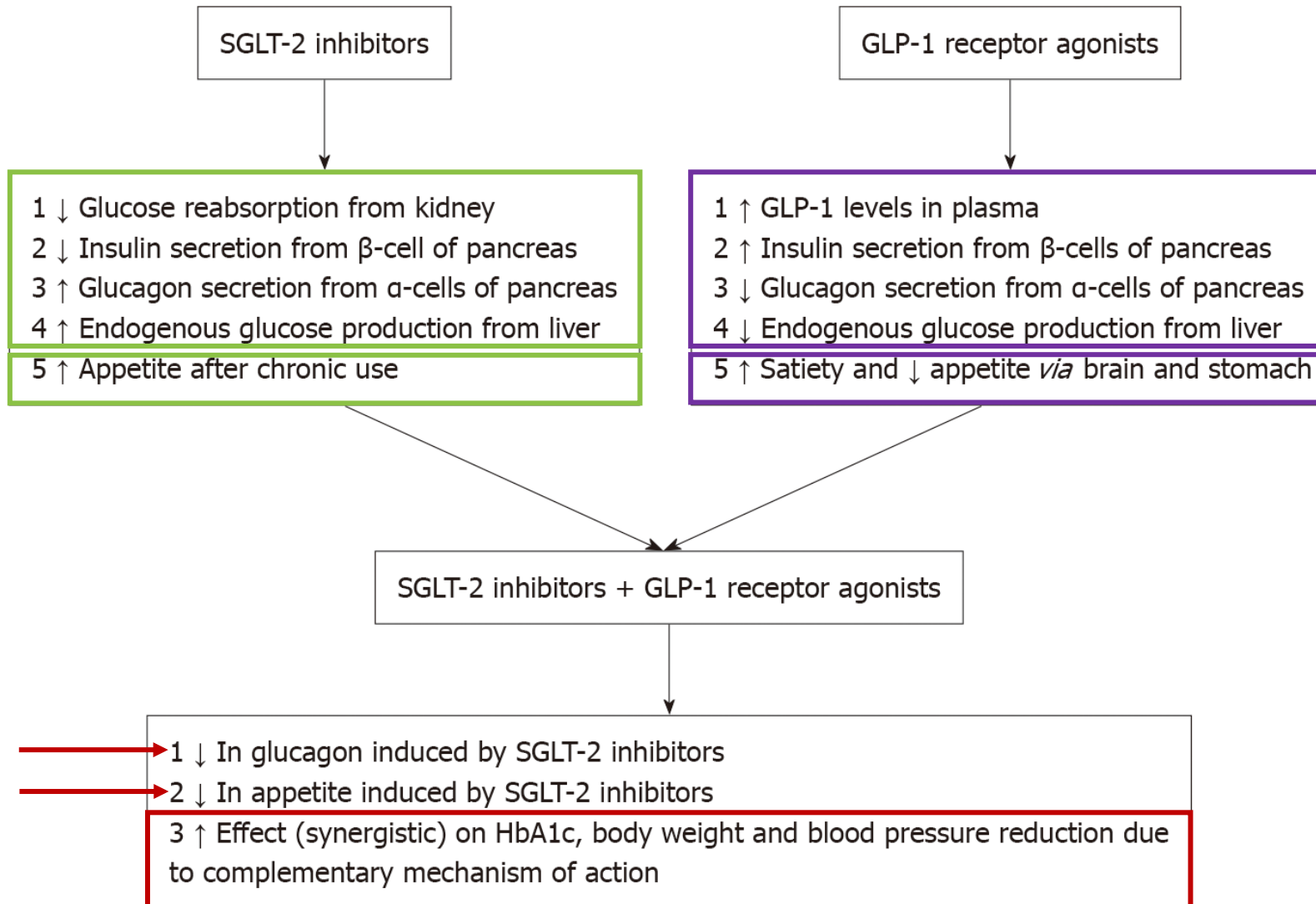
Data di valutazione _____

Timbro e Firma del Medico

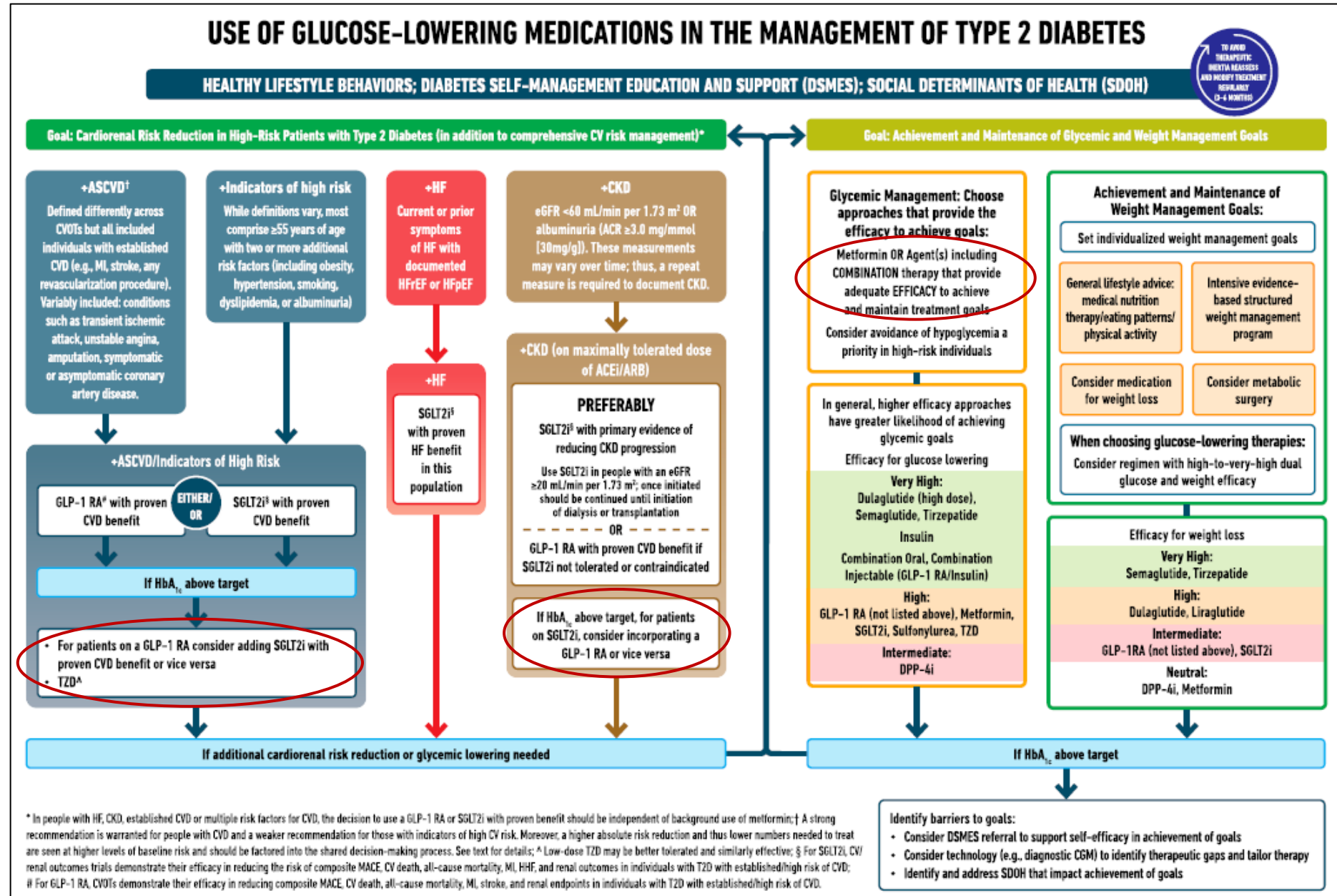
INTRODUZIONE – RAZIONALE



INTRODUZIONE – RAZIONALE



Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by ADA/EASD



GLIFLOZINE E INCRETINE INSIEME:



COME



QUANDO



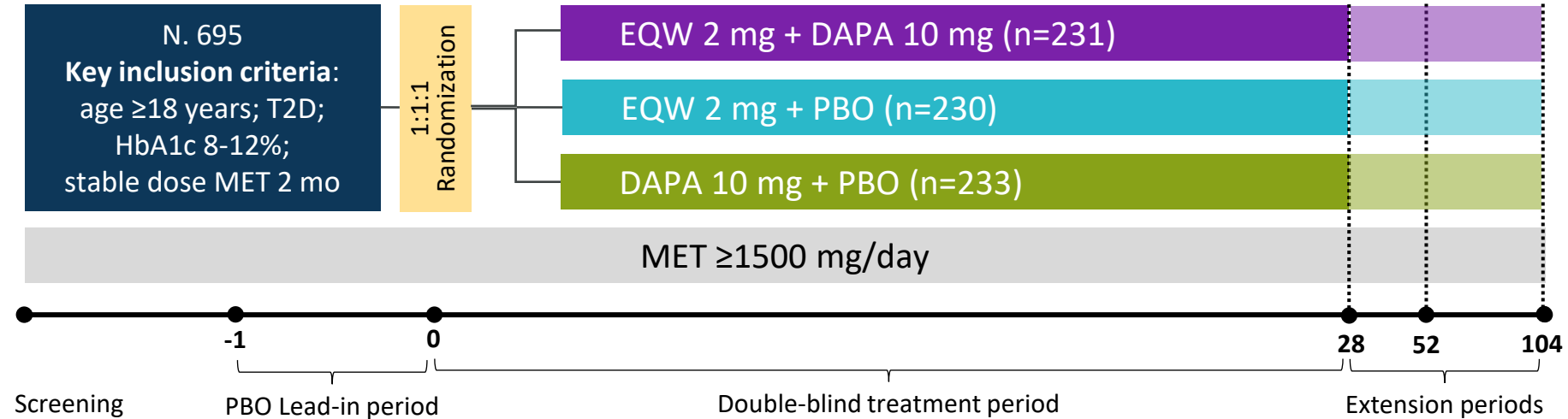
PERCHÉ

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STUDI DI EFFICACIA E SICUREZZA

Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (**DURATION-8**):
a 28 week, multicenter, double-blind, phase 3, randomised controlled trial

GLP1RA +
SGLT2i



Primary Endpoint

- Change in HbA1c from baseline to week 28

Secondary Endpoints

- Proportion of patients achieving HbA1c <7%
- Change in FPG
- Change in 2-hour PPG
- Change in body weight
- Change in SBP
- Proportion of patients achieving weight loss ≥5%

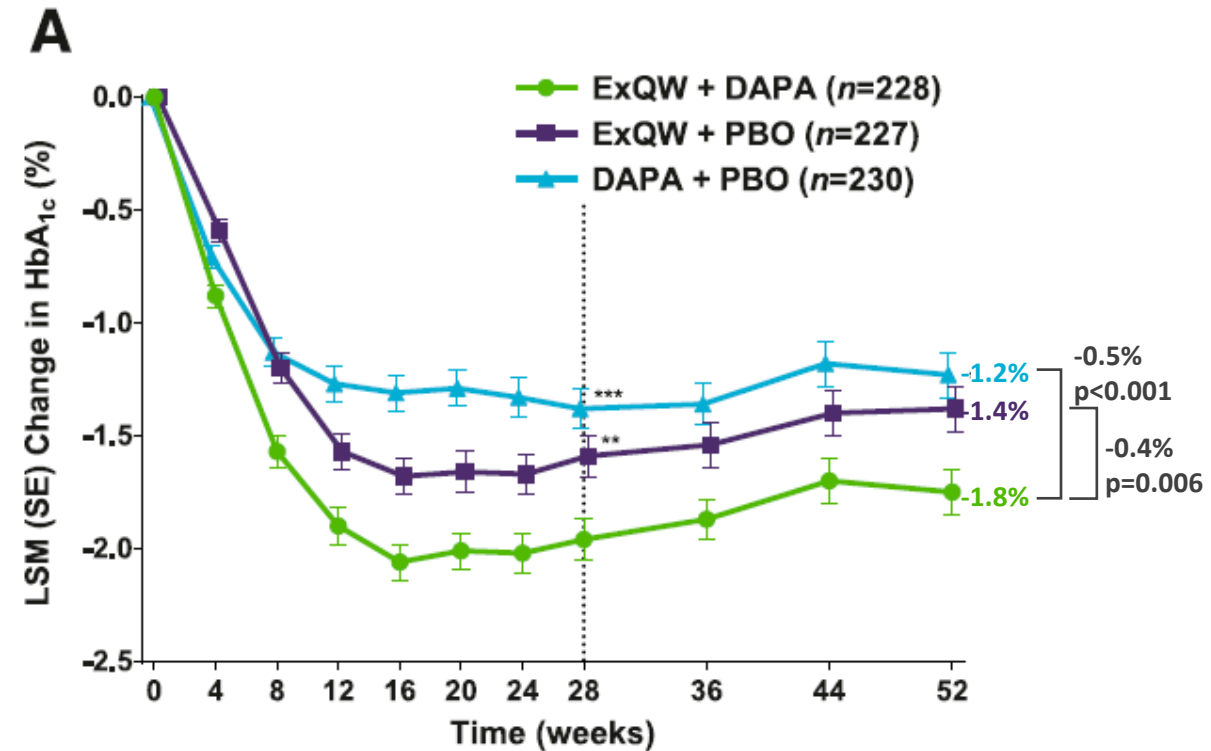
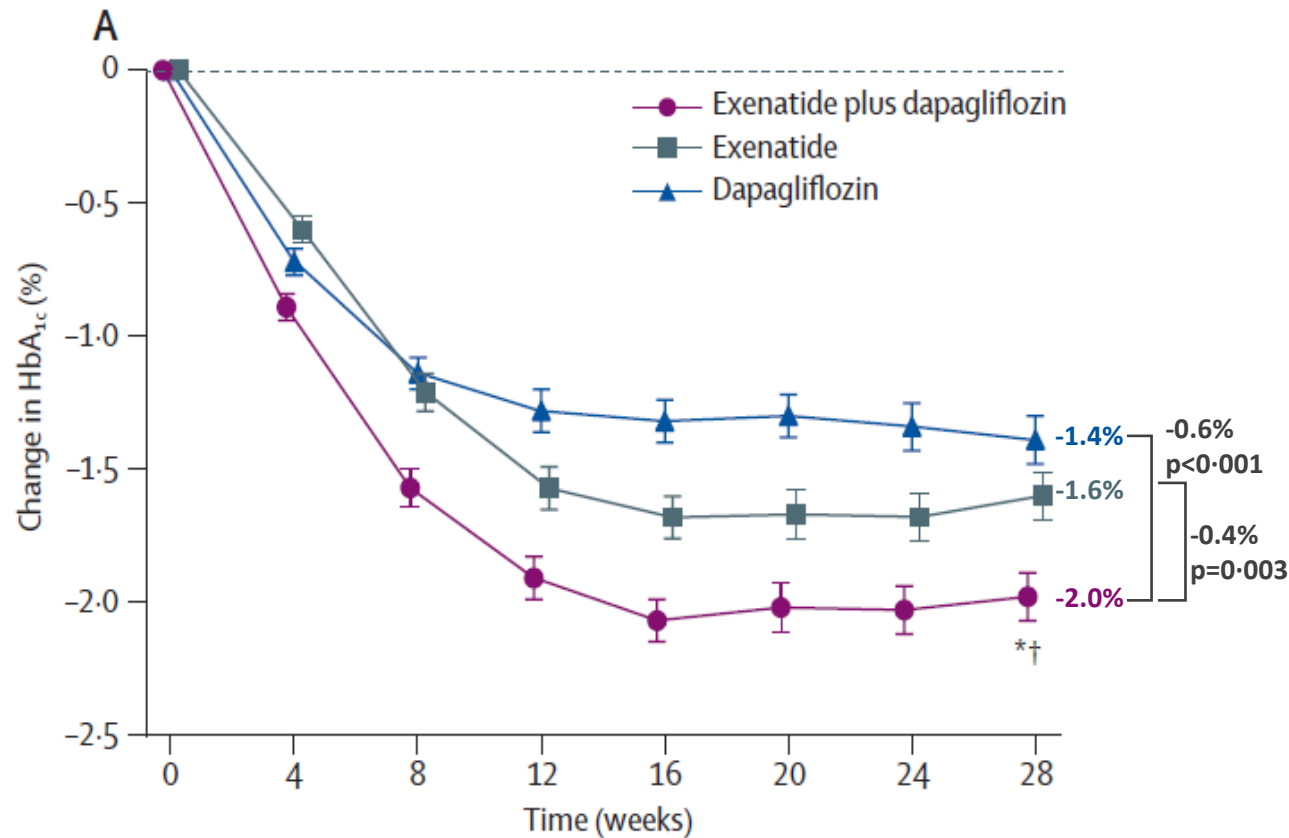
Exploratory Endpoints

- Proportion of patients achieving HbA1c ≤6.5%
- Change in six-point SMBG profile
- Change from baseline in fasting lipids
- Change in HbA1c by baseline HbA1c
- Change in weight by baseline HbA1c

STUDI DI EFFICACIA E SICUREZZA

Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (**DURATION-8**):
a 28 week, multicenter, double-blind, phase 3, randomized controlled trial
→ 52-Week Results of the DURATION-8 Randomized Controlled Trial

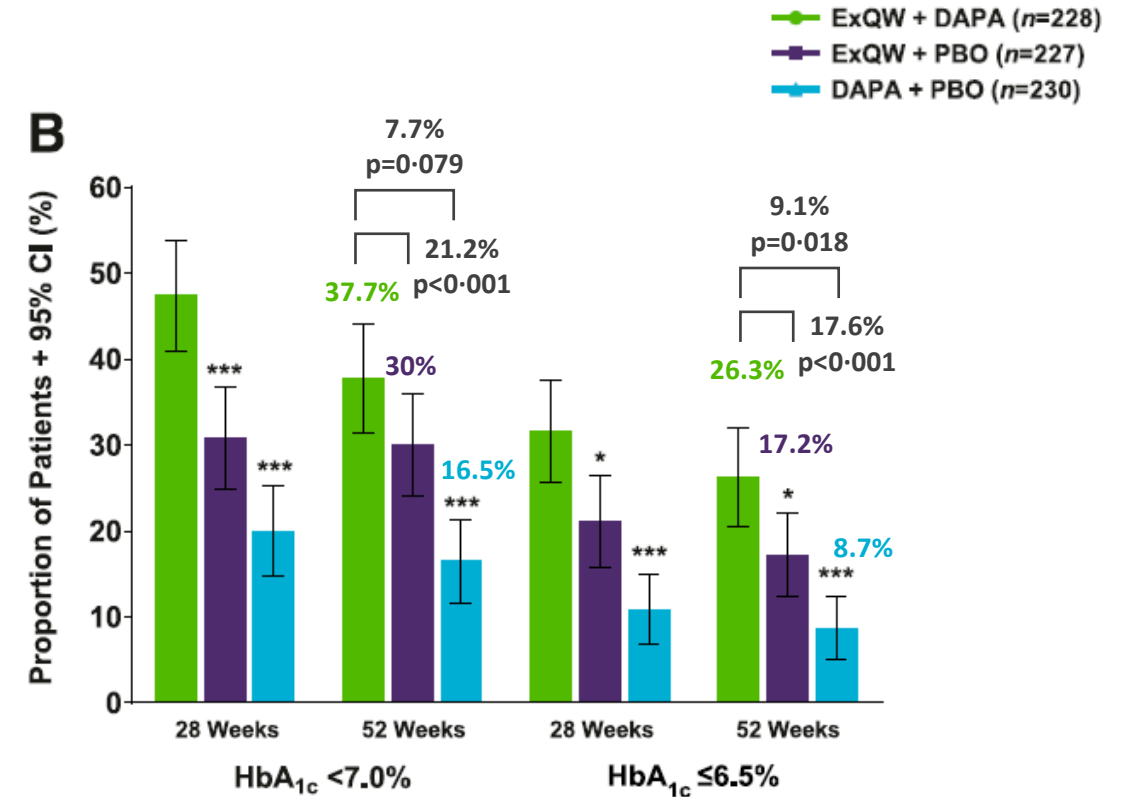
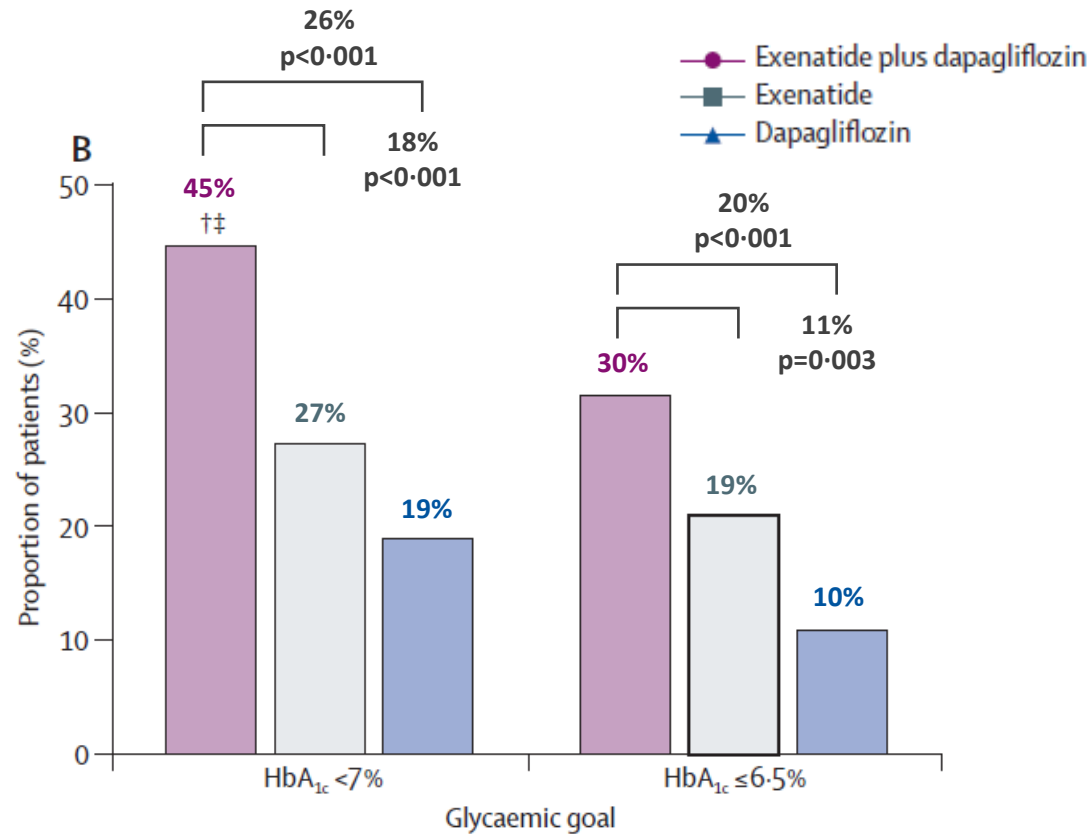
GLP1RA +
SGLT2i



STUDI DI EFFICACIA E SICUREZZA

Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (**DURATION-8**):
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→ *52-Week Results of the DURATION-8 Randomized Controlled Trial*

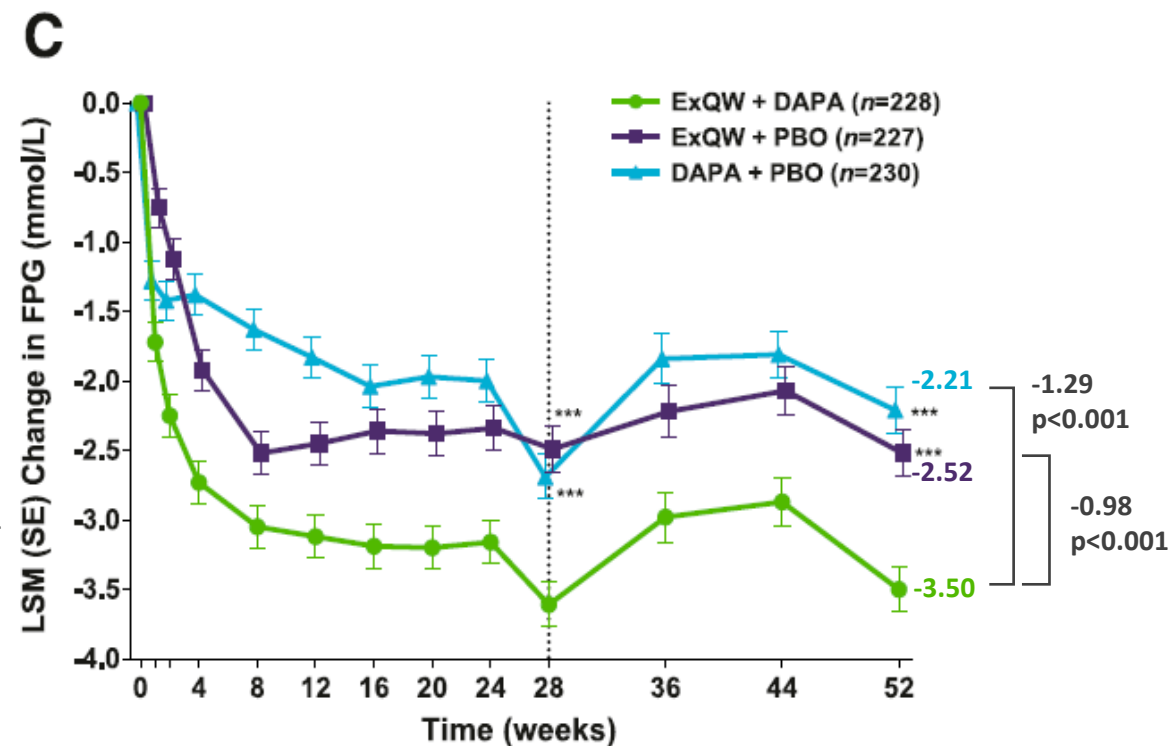
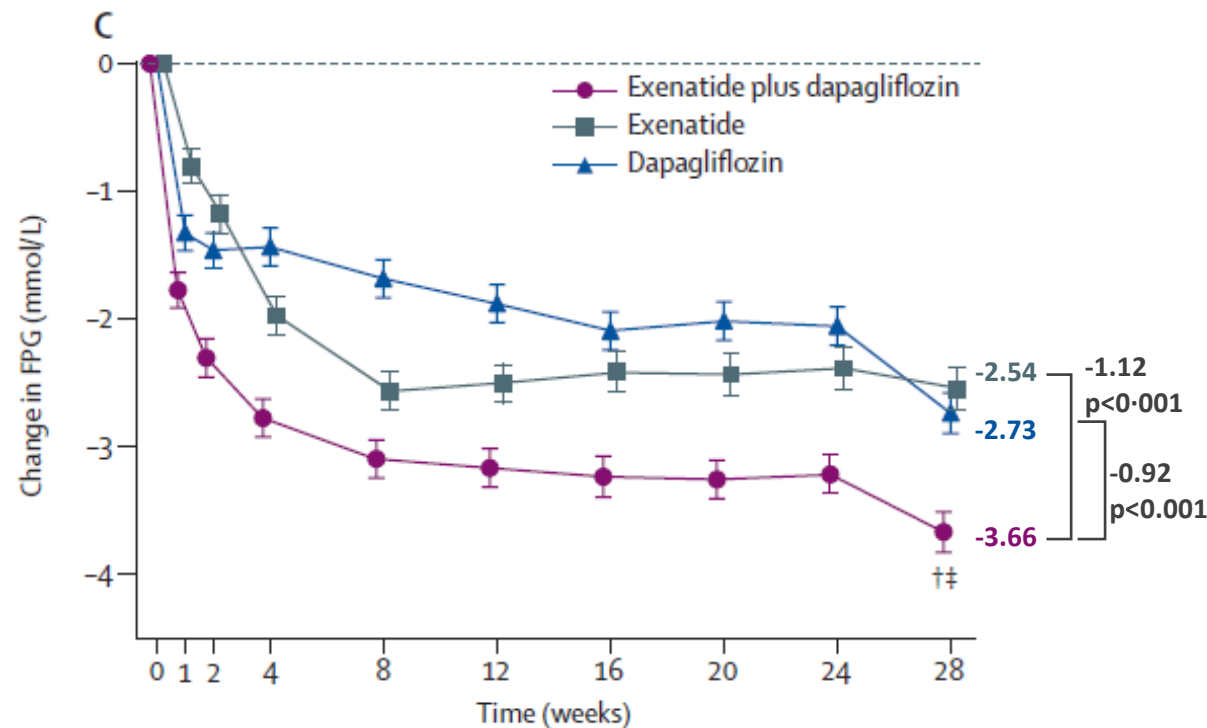
GLP1RA +
SGLT2i



STUDI DI EFFICACIA E SICUREZZA

Exenatide once weekly plus dapagliflozin once daily versus exenatide or dapagliflozin alone in patients with type 2 diabetes inadequately controlled with metformin monotherapy (**DURATION-8**):
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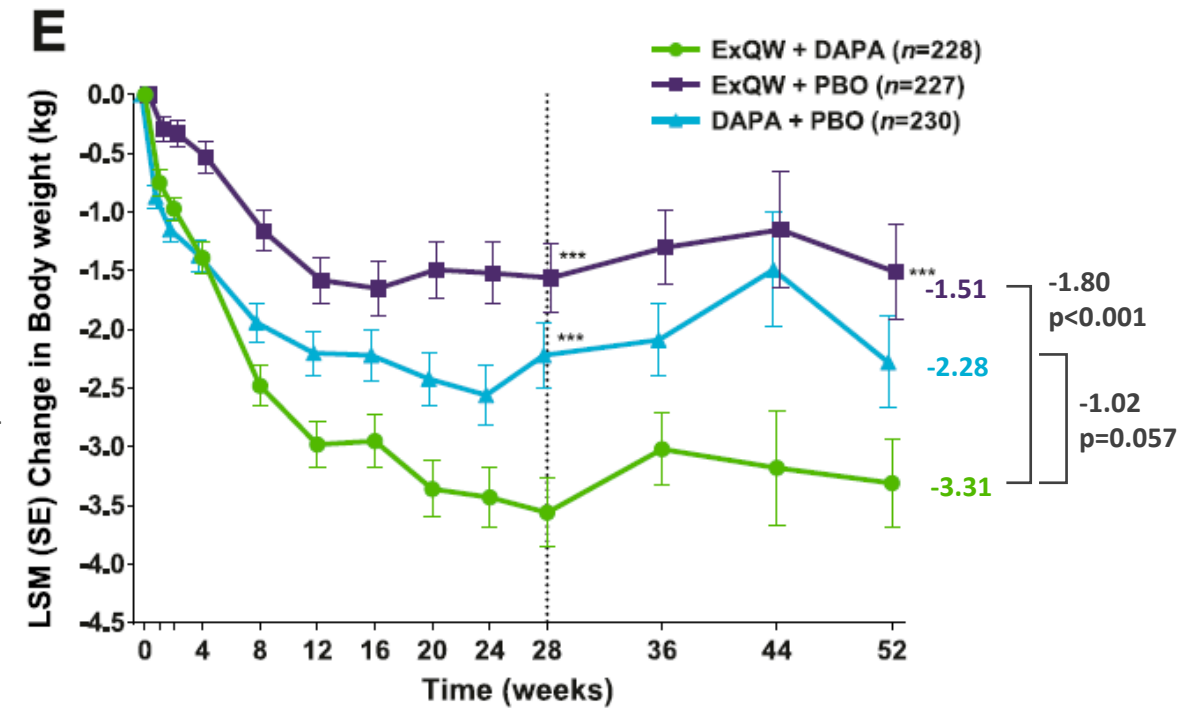
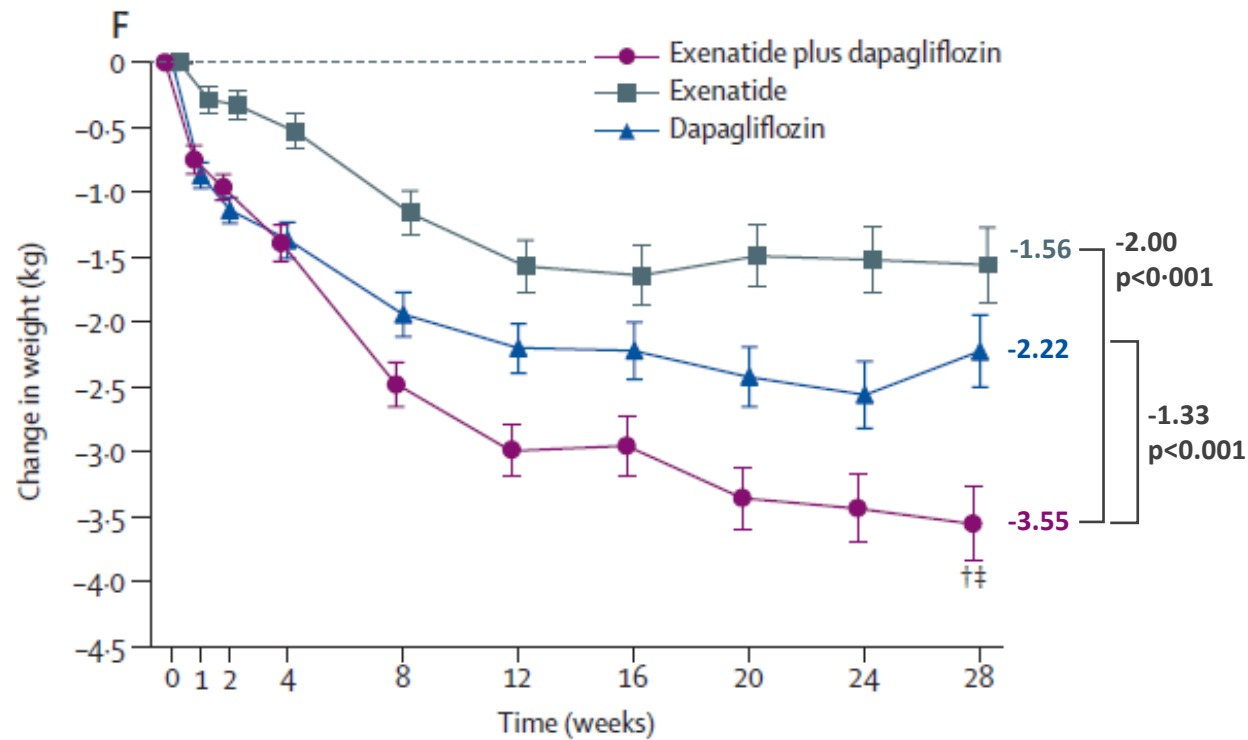
GLP1RA +
SGLT2i



STUDI DI EFFICACIA E SICUREZZA

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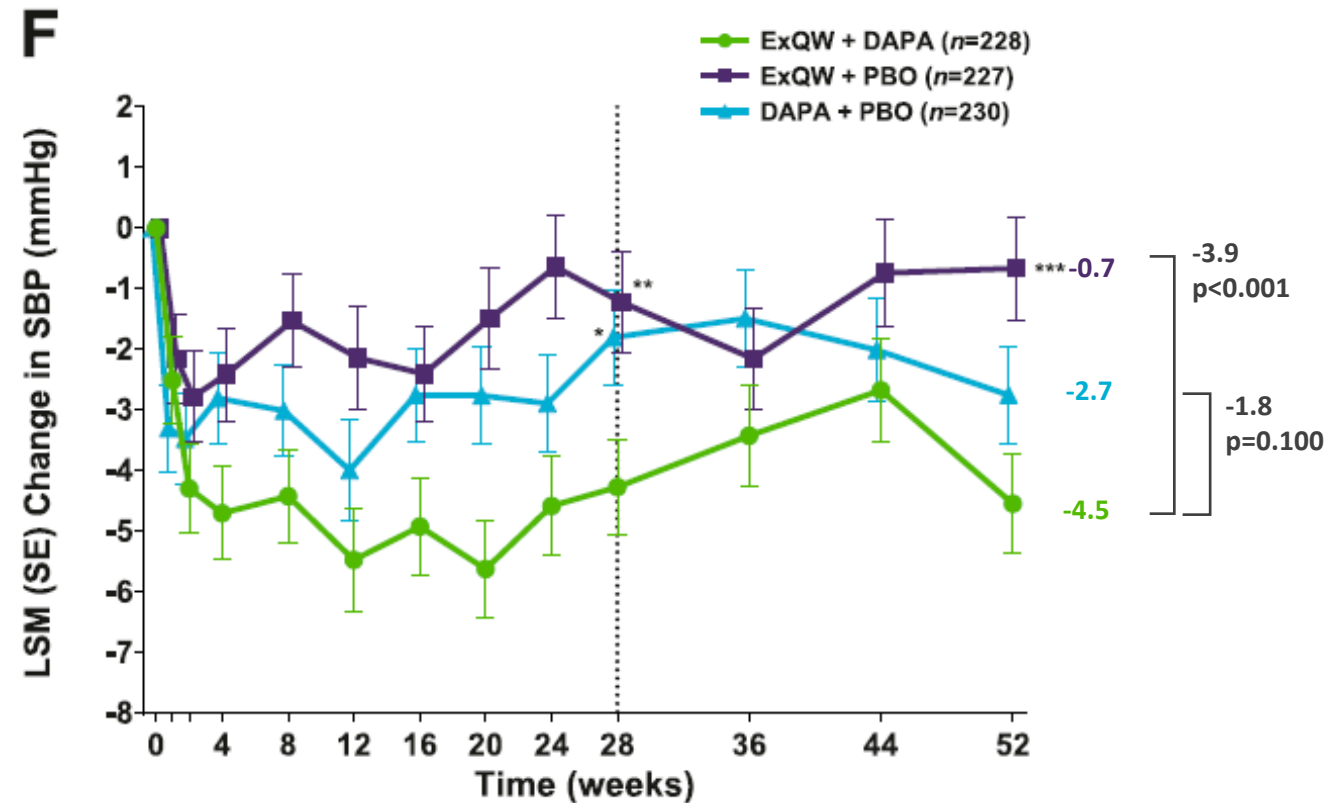
GLP1RA +
SGLT2i



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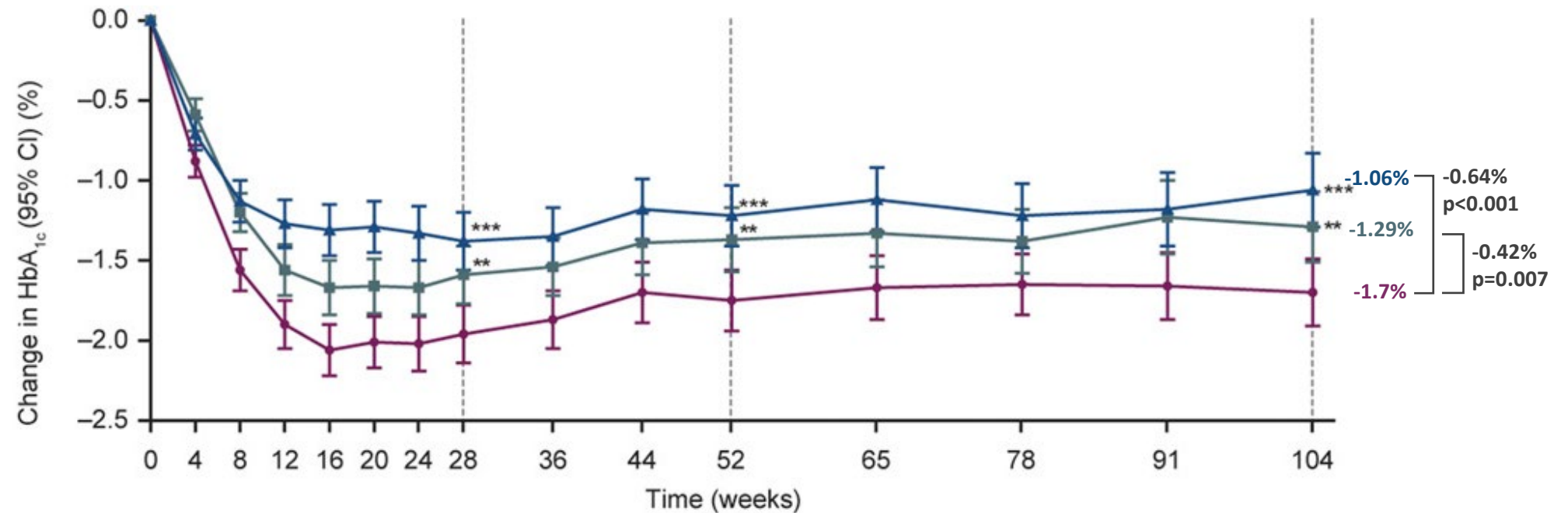
GLP1RA +
SGLT2i



STUDI DI EFFICACIA E SICUREZZA

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

GLP1RA +
SGLT2i

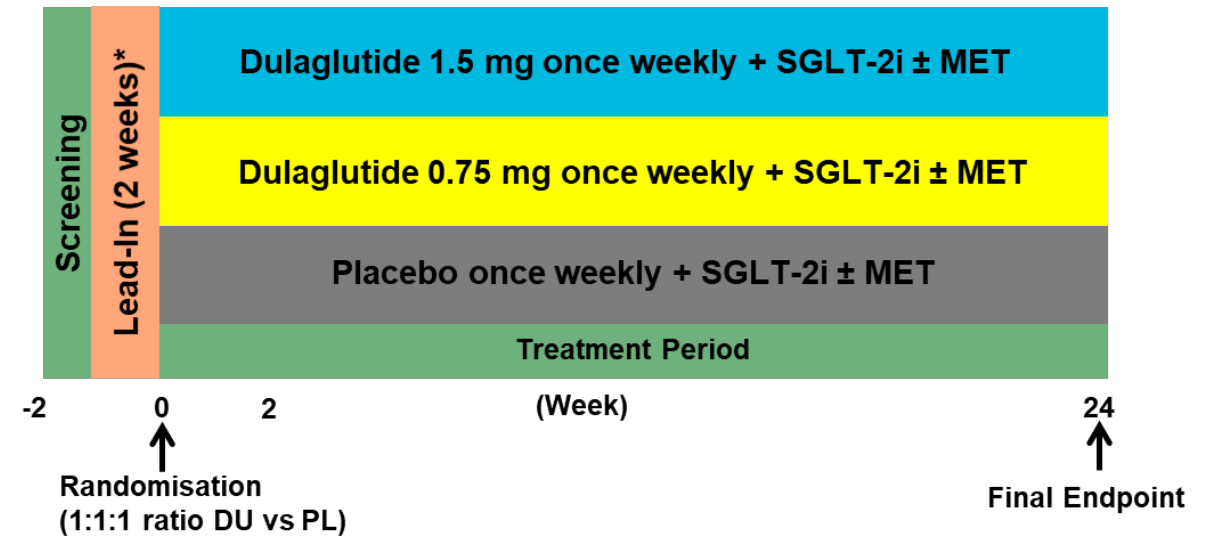


STUDI DI EFFICACIA E SICUREZZA

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

GLP1RA su
SGLT2i

- **Key inclusion criteria** (N 424)
 - T2D
 - HbA1c $\geq 7.0\%$ and $\leq 9.5\%$
 - BMI $\leq 45 \text{ kg/m}^2$
 - Stable doses (>3 months) of an SGLT2 inhibitor (with or without metformin)



Primary Endpoint:

Change in HbA1c from baseline to week 24

Secondary Endpoints:

- percentage of patients achieving HbA1c $< 7.0\%$
- change in bodyweight
- change in FPG
- percentage of patients achieving HbA1c $\leq 6.5\%$
- change in six-point SMBG profile
- change in fasting glucagon concentration

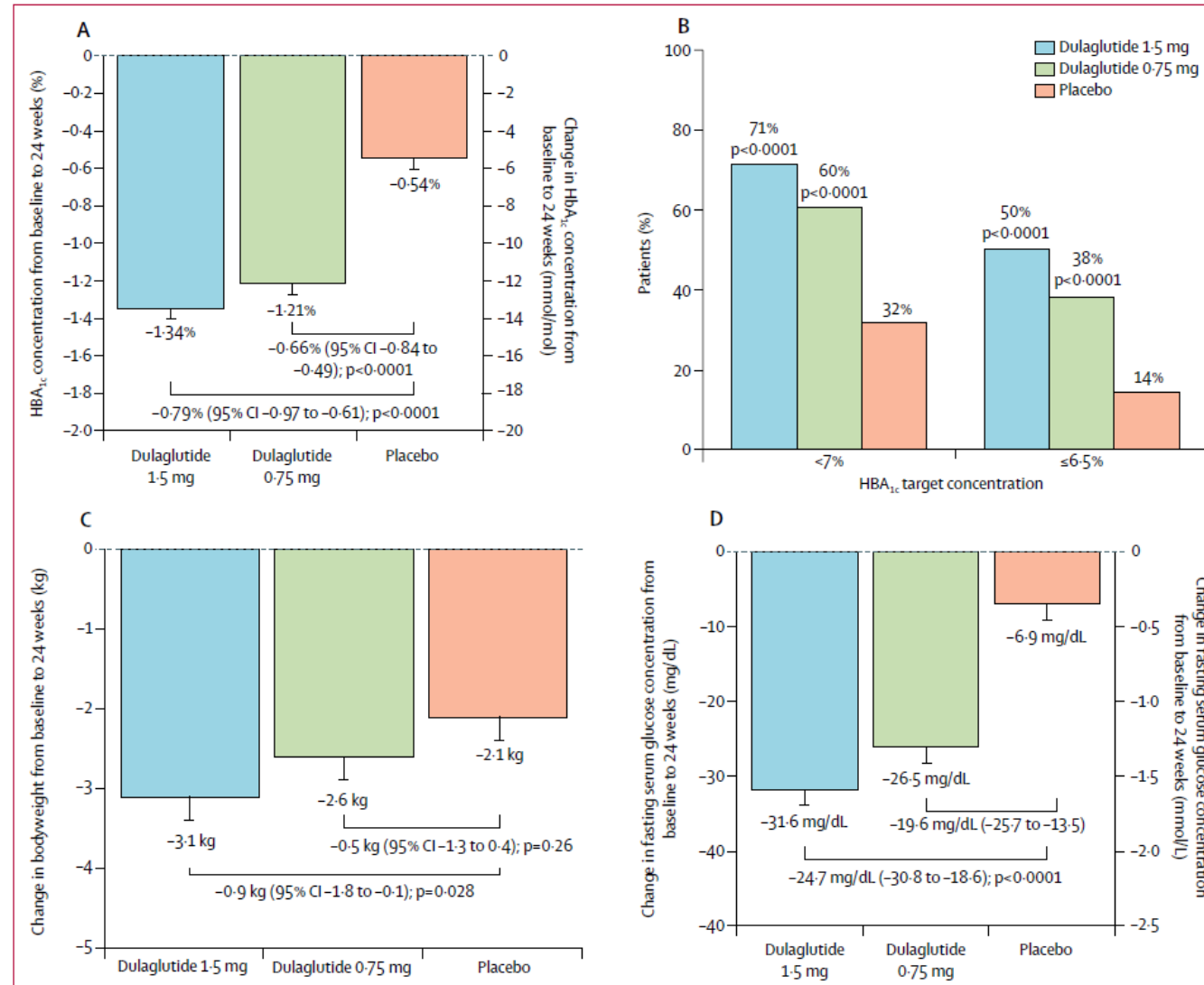
Exploratory Endpoints

- proportion of patients with HbA1c $< 7.0\%$ with no bodyweight gain and no documented symptomatic hypoglycaemia
- proportion of patients with HbA1c $< 7.0\%$ with bodyweight loss $> 5\%$ and no documented symptomatic hypoglycaemia

STUDI DI EFFICACIA E SICUREZZA

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

GLP1RA su
SGLT2i



STUDI DI EFFICACIA E SICUREZZA

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

GLP1RA su
SGLT2i

302 subjects with T2D

- Age ≥ 18 years[†]
- HbA_{1c} 7.0–10.0%[‡]
- Stable treatment with SGLT-2 inhibitor $\pm$ MET/SU
- eGFR ≥ 60 mL/min/1.73 m²

Randomisation (1:1)

Semaglutide 1.0 mg

Placebo

Dose
escalation[§]
8 weeks

Treatment maintenance
22 weeks

Follow-up
5 weeks

Treatment duration 30 weeks

Primary Endpoint:

Change in HbA_{1c} from baseline to week 30

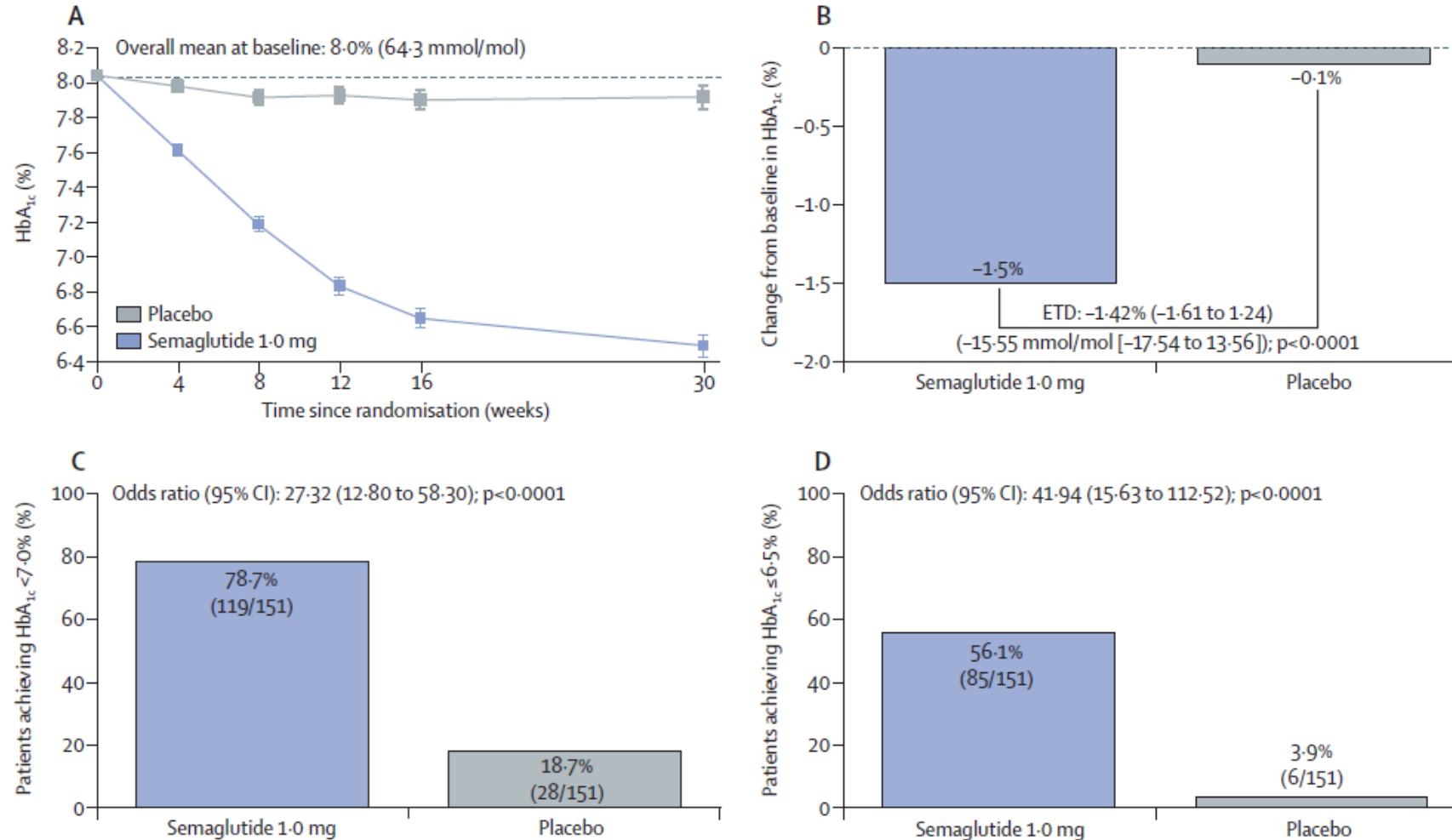
Secondary Endpoints:

- percentage of patients achieving HbA_{1c} $< 7.0\%$
- change in bodyweight
- change in FPG
- percentage of patients achieving HbA_{1c} $\leq 6.5\%$
- change in seven-point SMBG profile

STUDI DI EFFICACIA E SICUREZZA

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

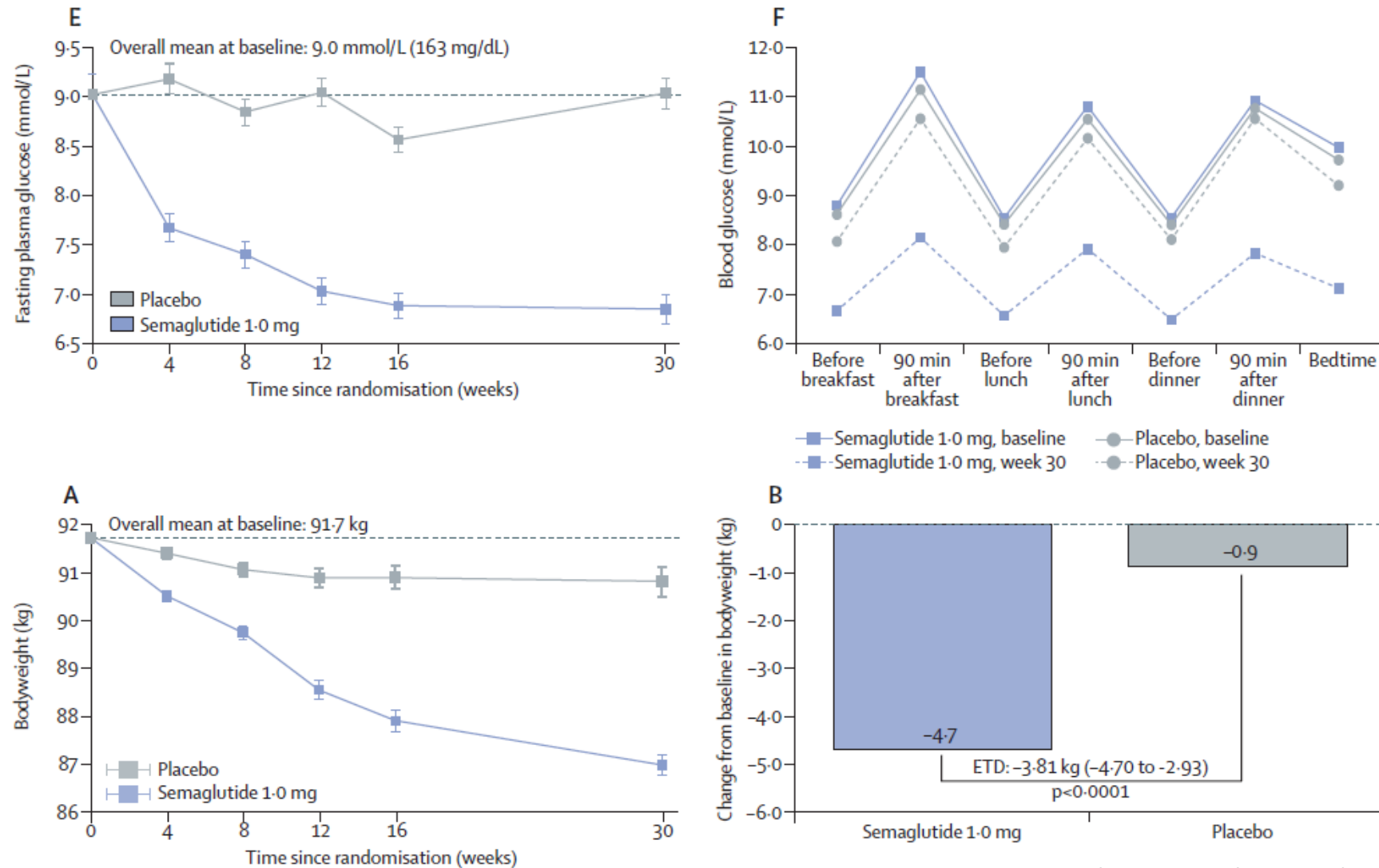
GLP1RA su
SGLT2i



STUDI DI EFFICACIA E SICUREZZA

Semaglutide once weekly as add-on to SGLT-2 inhibitor therapy in type 2 diabetes (**SUSTAIN 9**):
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GLP1RA su
SGLT2i



STUDI DI EFFICACIA E SICUREZZA

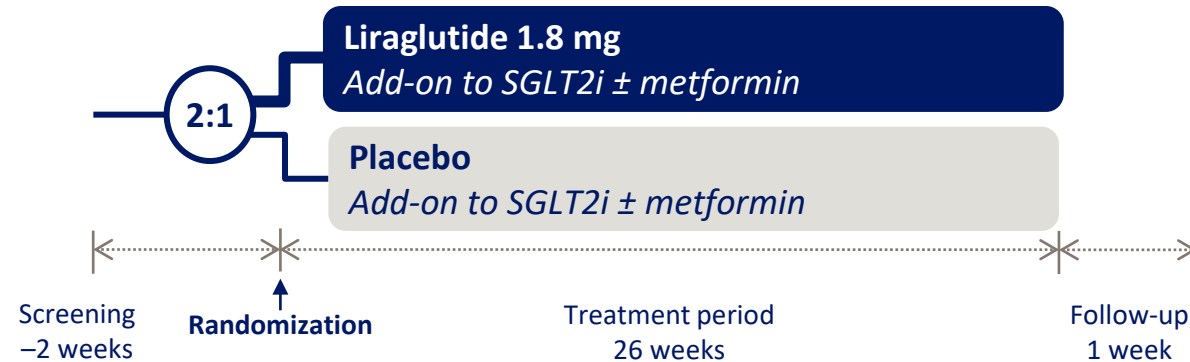
Liraglutide as add-on to sodium-glucose co-transporter-2 inhibitors in patients with inadequately controlled type2 diabetes:

LIRA-ADD2SGLT2i, a 26-week, randomized, double-blind, placebo-controlled trial

GLP1RA su
SGLT2i

n=303 patients

- T2D
- HbA1c 7.0–9.5%
- Stable dose of SGLT2i as monotherapy or in combination with stable dose of metformin
- No history of DKA while on SGLT2i
- eGFR ≥ 60 mL/min/1.73 m²



Trial information

- Double-blinded
- Randomized (2:1)
- Stratification by use of metformin (Yes/No)

Primary endpoint

Change in HbA1c from baseline at Week 26

Confirmatory secondary endpoint

Change in BW from baseline at Week 26

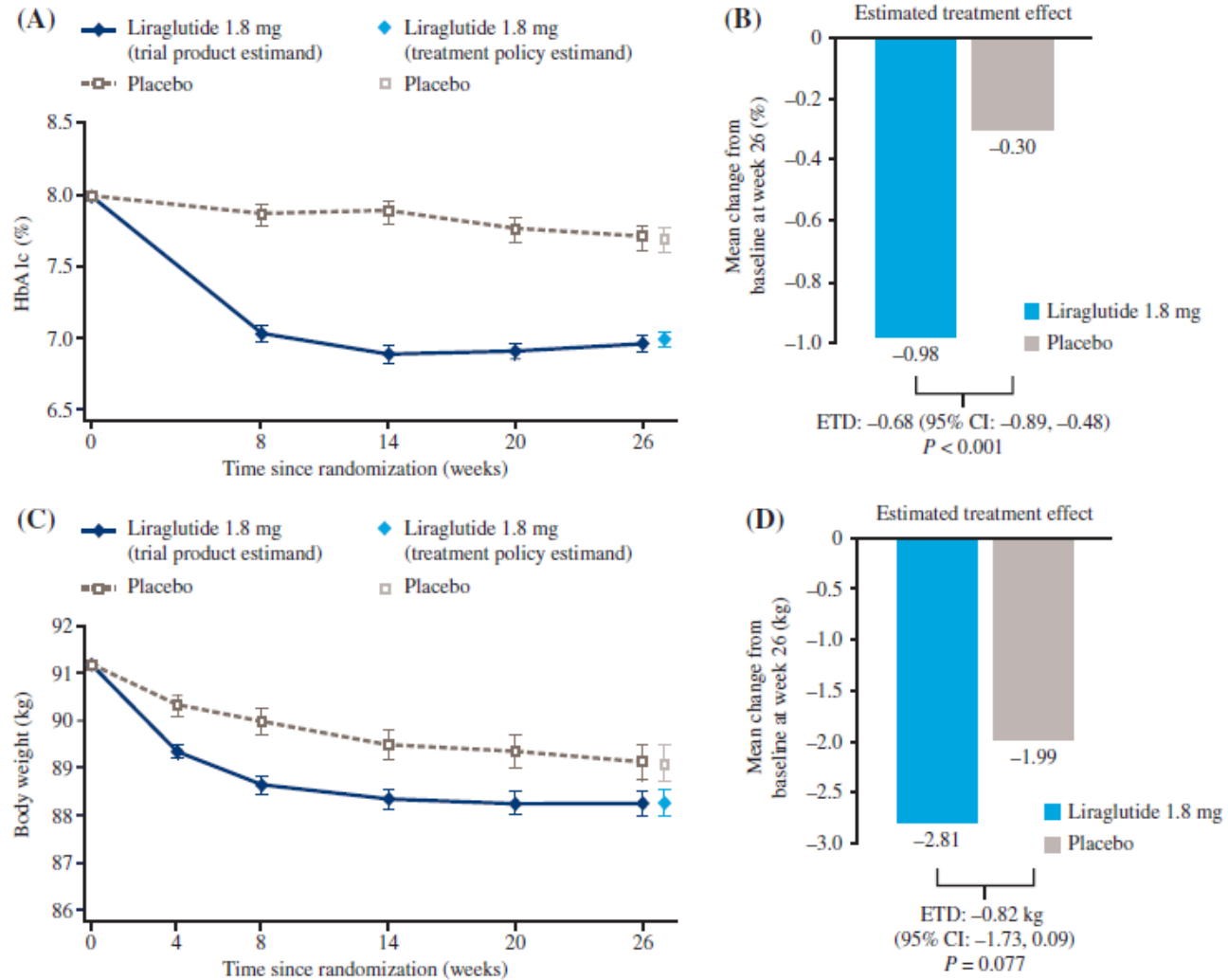
Supportive secondary endpoints

- % of patients achieving HbA1c treatment targets
- % of patients achieving body weight treatment targets
- % of patients achieving HbA1c targets without hypoglycaemia or with weight loss/no gain

STUDI DI EFFICACIA E SICUREZZA

Liraglutide as add-on to sodium-glucose co-transporter-2 inhibitors in patients with inadequately controlled type2 diabetes:
LIRA-ADD2SGLT2i, a 26-week, randomized, double-blind, placebo-controlled trial

GLP1RA su
SGLT2i



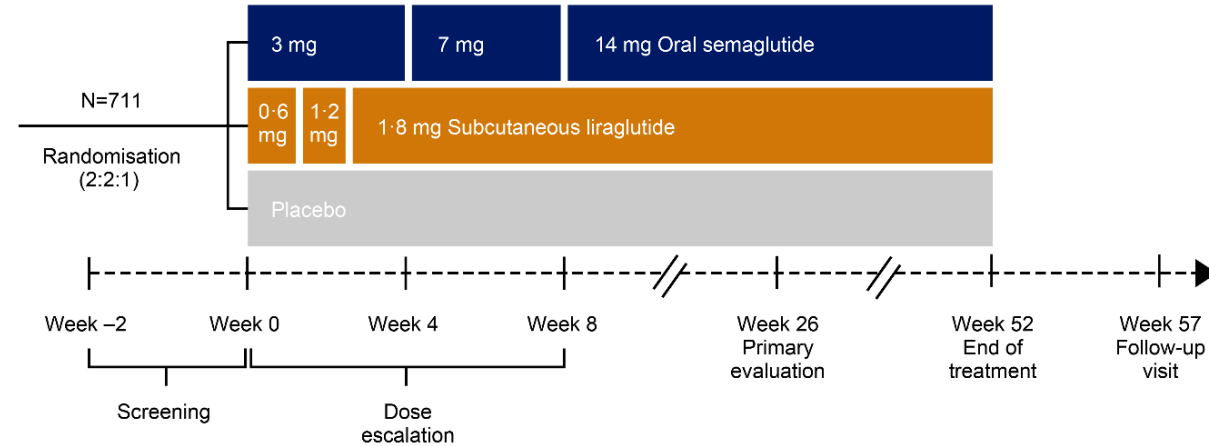
STUDI DI EFFICACIA E SICUREZZA

Effect of Oral Semaglutide with or without background SGLT2i in Patients with T2D: Subgroup Analysis of **PIONEER 4**

GLP1RA su
SGLT2i

n=711 patients

- T2D
- HbA1c 7.0–9.5%
- Stable dose of metformin with or without a sodium-glucose co-transporter-2 inhibitor.



Trial information

- Double-blind, double-dummy
- Randomized (2:2:1)
- Stratified by background glucose-lowering medication and country of origin

Primary endpoint

Change in HbA1c from baseline at Week 26

Confirmatory secondary endpoint

Change in BW from baseline at Week 26

Supportive secondary endpoints

- change from baseline to week 52 in HbA1c and bodyweight
- change from baseline to weeks 26 and 52 in FPG, seven-point SMBG and fasting lipids
- % of patients achieving HbA1c $\leq 7.0\%$ or $\leq 6.5\%$
- % of patients achieving weight loss of 5% or more or 10% or more

Effect of Oral Semaglutide with or without background SGLT2i in Patients with T2D:
Subgroup Analysis of **PIONEER 4**

GLP1RA su
SGLT2i

Key results

Figure 1: Change from baseline in HbA_{1c} at week 52 by background SGLT2i use

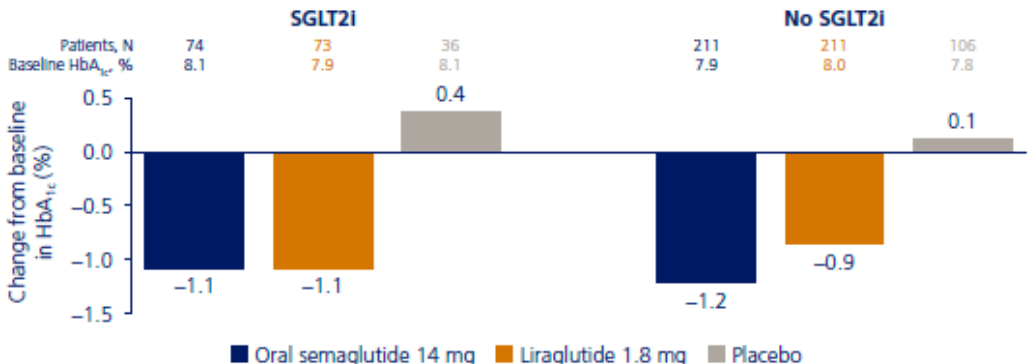
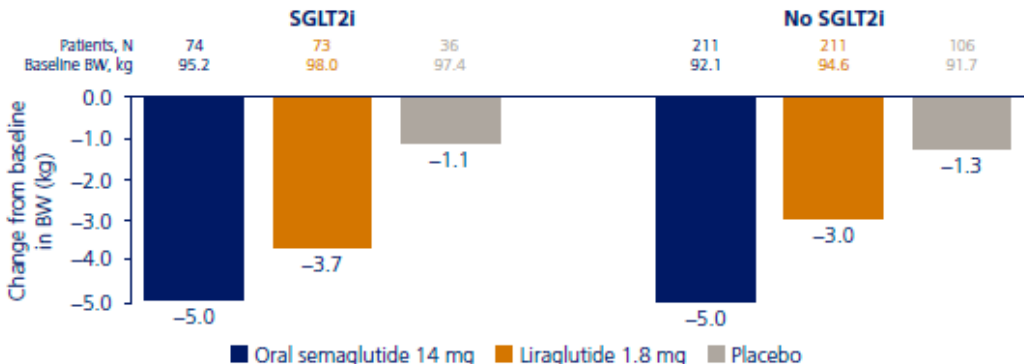


Figure 2: Change from baseline in body weight at week 52 by background SGLT2i use



Data are estimated means for the trial product estimand (on trial product without rescue medication use). Changes from baseline were analyzed using a mixed model for repeated measures with treatment, region, baseline glucose-lowering background medication and interaction between treatment and baseline glucose-lowering background medication as categorical fixed effects and baseline value as covariate, all nested within visit, and an unstructured residual covariance matrix. BW, body weight; N, total number of patients in each subgroup (full analysis set); SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Oral semaglutide at week 52

HbA_{1c}
(%)

Body weight
(kg)



Conclusion

- Improvements in HbA_{1c} and body weight, and safety profile, were similar after 1 year in patients with T2D treated with GLP-1RA, with or without background SGLT2i.

STUDI DI EFFICACIA E SICUREZZA

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

CANVAS

SGLT2i su
GLP1RA

- 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

Efficacy Endpoints: change from baseline in

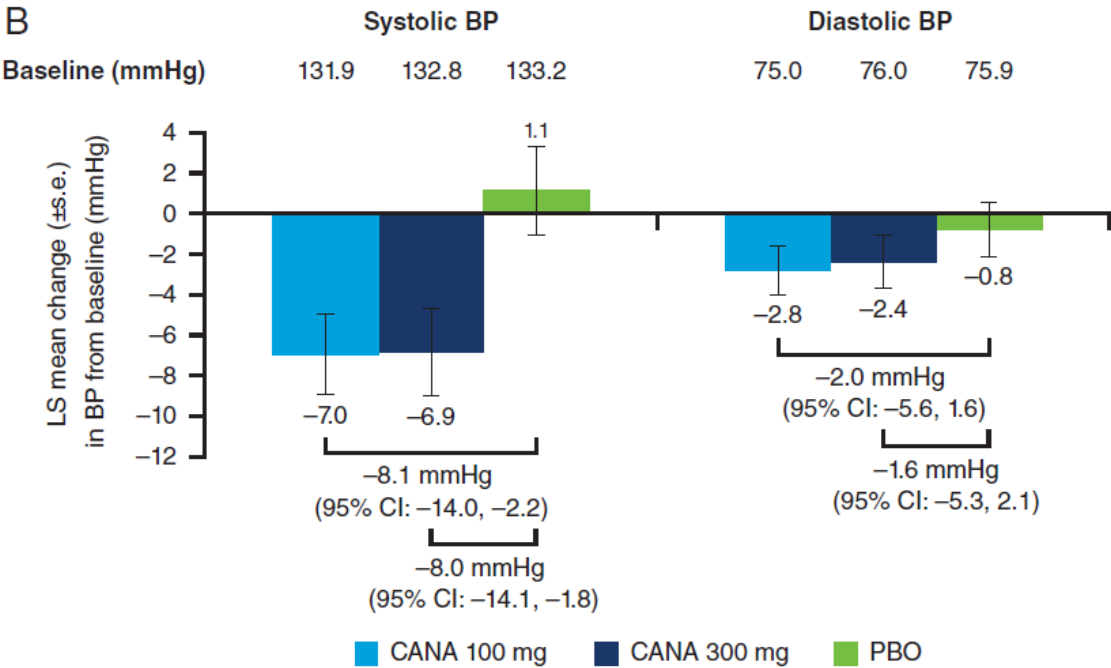
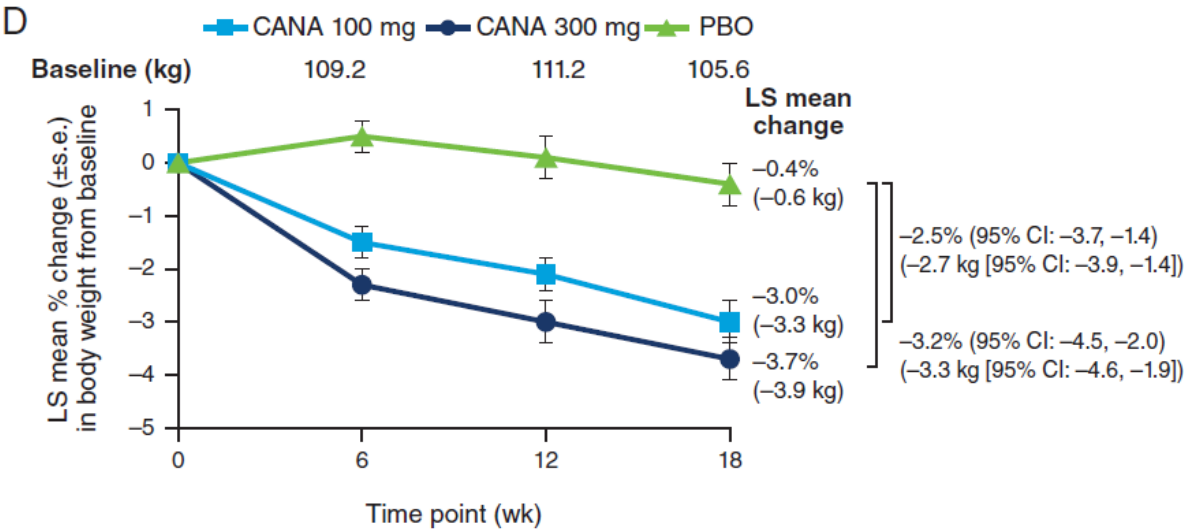
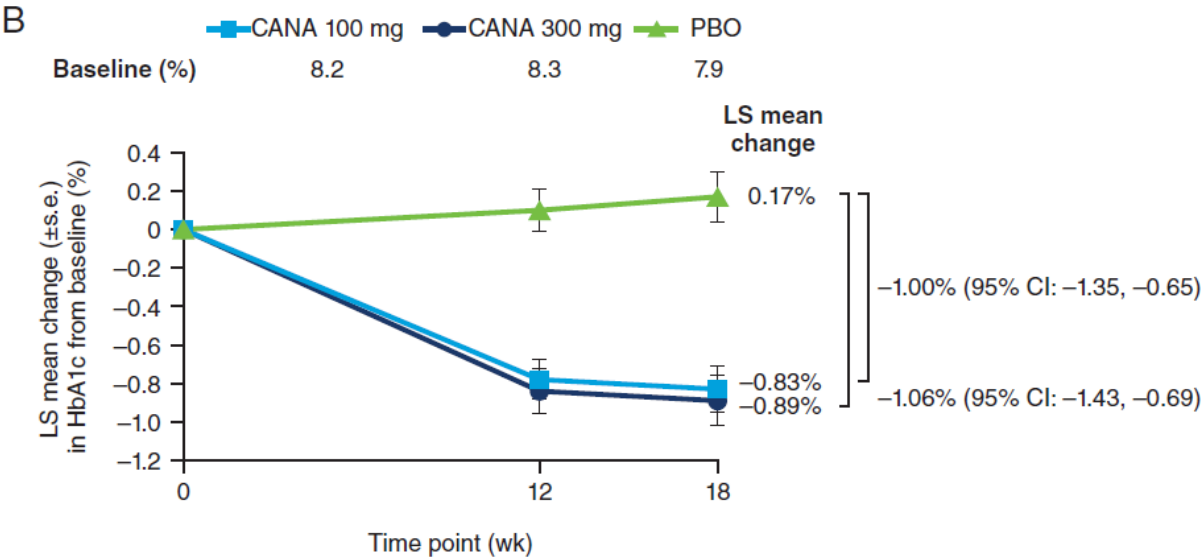
- | | |
|--------------------------------|---|
| - glycated haemoglobin (HbA1c) | - bodyweight |
| - fasting plasma glucose (FPG) | - fasting plasma lipids |
| - systolic BP | - proportion of patients reaching HbA1c <7.0% |

DPP-4 inhibitor subset			GLP-1 receptor agonist subset		
CANA 100 mg (n = 103)	CANA 300 mg (n = 111)	PBO (n = 102)	CANA 100 mg (n = 35)	CANA 300 mg (n = 30)	PBO (n = 30)

STUDI DI EFFICACIA E SICUREZZA

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

SGLT2i su
GLP1RA

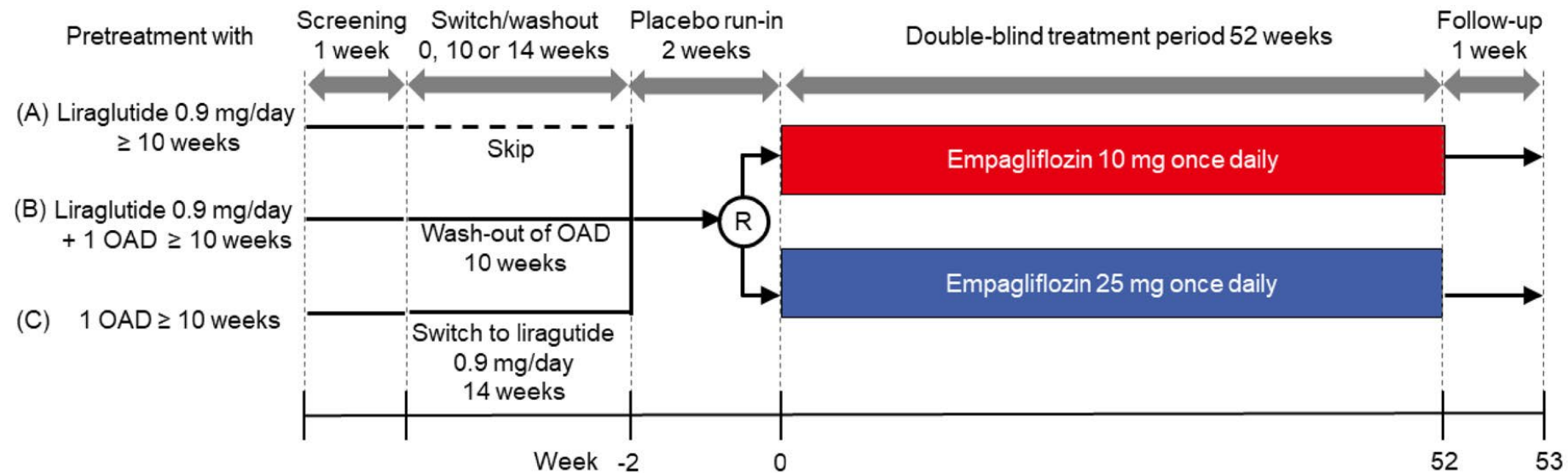


STUDI DI EFFICACIA E SICUREZZA

Safety and Efficacy of Empagliflozin as Add-On Therapy to GLP-1 Receptor Agonist (Liraglutide) in Japanese Patients with Type 2 Diabetes Mellitus: A Randomised, Double-Blind, Parallel-Group Phase 4 Study

SGLT2i su
GLP1RA

TRIAL DESIGN

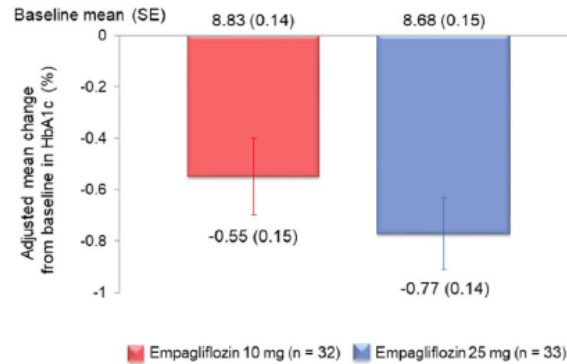


STUDI DI EFFICACIA E SICUREZZA

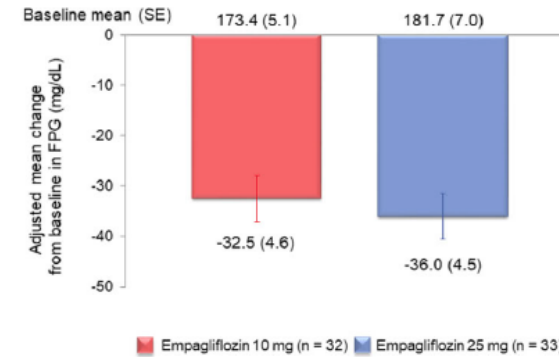
Safety and Efficacy of Empagliflozin as Add-On Therapy to GLP-1 Receptor Agonist (Liraglutide) in Japanese Patients with Type 2 Diabetes Mellitus: A Randomised, Double-Blind, Parallel-Group Phase 4 Study

SGLT2i su
GLP1RA

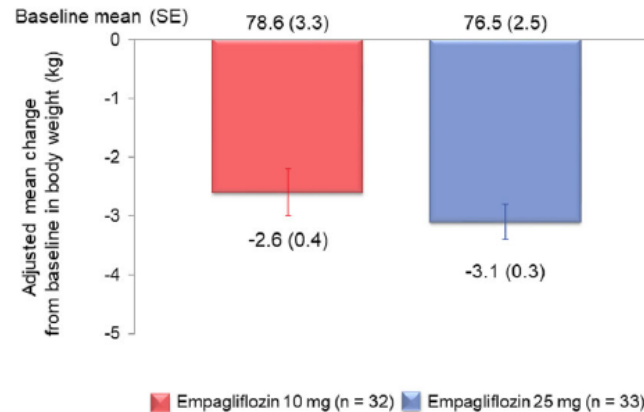
(a) HbA1c



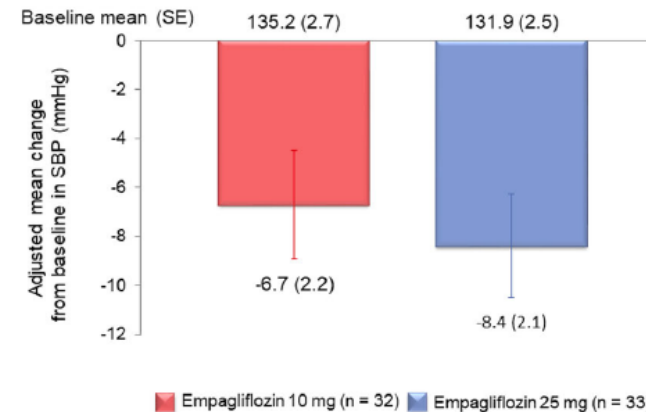
(b) FPG



(c) Body weight



(d) SBP



- Empagliflozin as an add-on to liraglutide for 52 weeks was well tolerated and led to clinically meaningful and sustained improvements in glycaemic control, body weight and blood pressure in Japanese patients with T2DM.

STUDI DI EFFICACIA E SICUREZZA

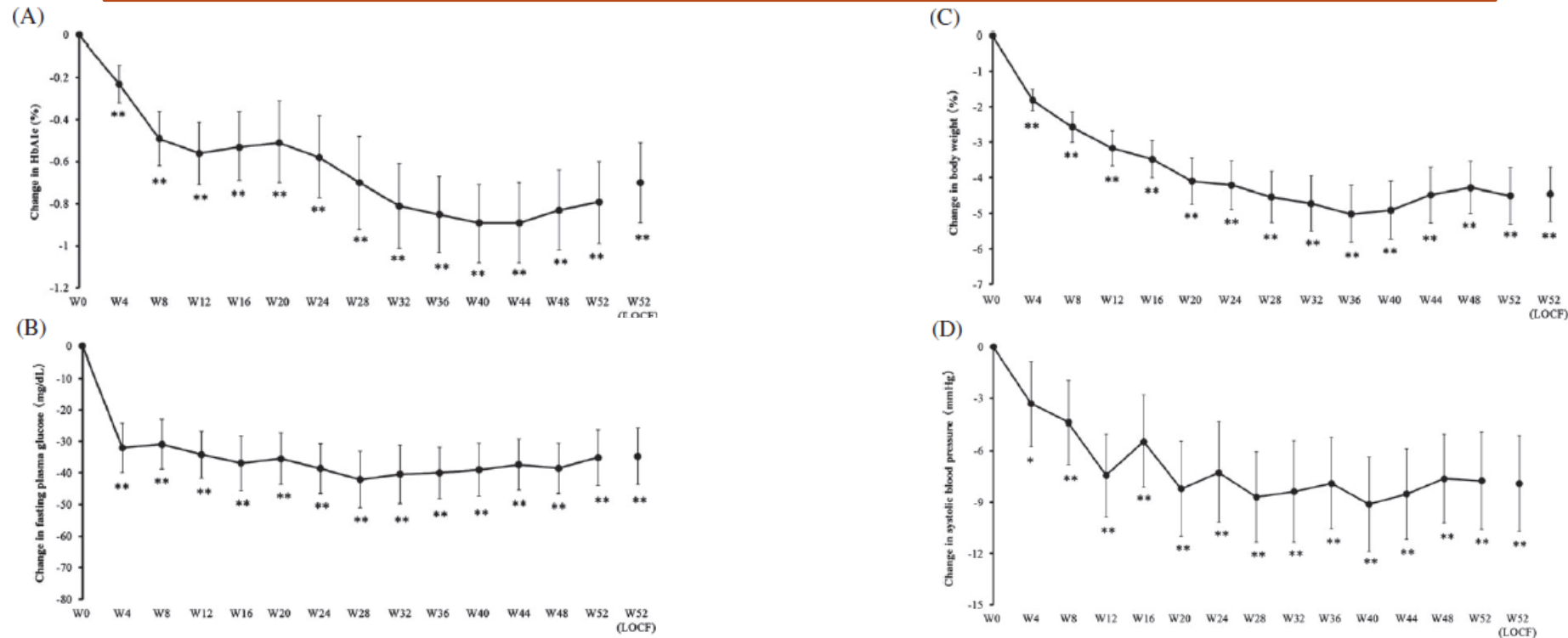
Efficacy and safety of canagliflozin as add-on therapy to a glucagon-like peptide-1 receptor agonist in Japanese patients with type 2 diabetes mellitus: A 52-week, open-label, phase IV study

SGLT2i su
GLP1RA

TRIAL DESIGN

Non-randomized, uncontrolled, open-label post-marketing (phase IV) study conducted in Japan

→ liraglutide (0.6 or 0.9 mg OD) for ≥ 12 weeks + canagliflozin 100 mg OD for 52 weeks



➤ These findings suggest that the long-term combination of canagliflozin with a GLP-1RA is effective and well tolerated in Japanese patients with T2DM.

STUDI DI EFFICACIA E SICUREZZA

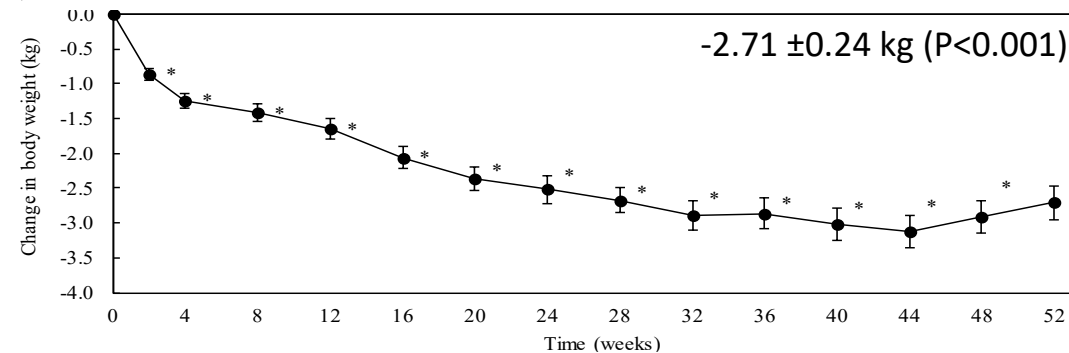
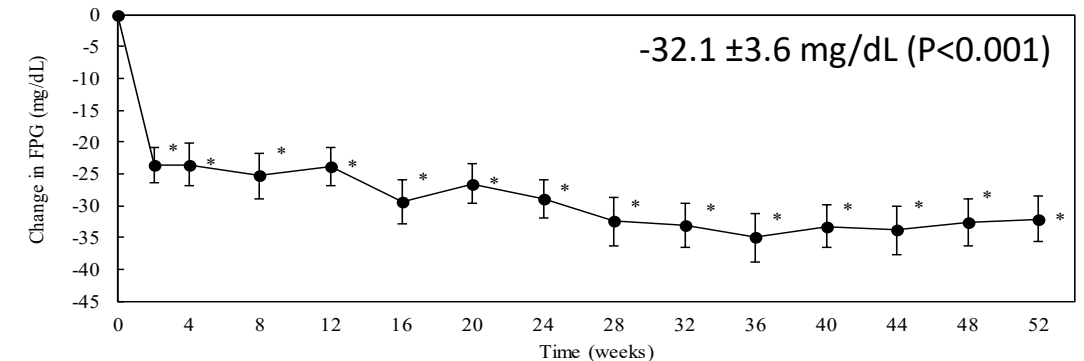
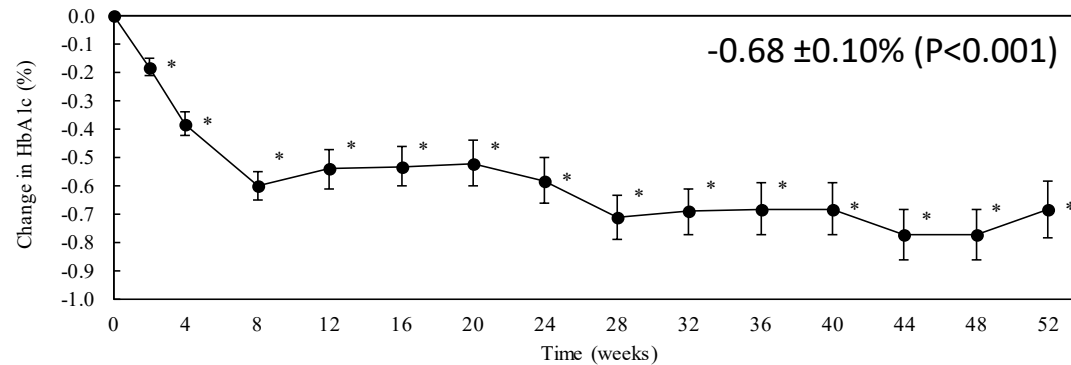
Sodium-glucose cotransporter-2 inhibitor luseogliflozin added to glucagon-like peptide1 receptor agonist liraglutide improves glycemic control with bodyweight and fat mass reductions in Japanese patients with type 2 diabetes: A 52-week, open-label, single-arm study

SGLT2i su
GLP1RA

TRIAL DESIGN

Multicenter, open-label, single-arm clinical study conducted in Japan

→ liraglutide (fixed dose OD) for ≥12 weeks + luseogliflozin 2.5-5 mg OD for 52 weeks



➤ Luseogliflozin added to liraglutide was well tolerated and improved glycemic control with bodyweight and fat mass reductions in Japanese type 2 diabetes patients.

Short Communication

Drug/Regimen

Diabetes Metab J 2022;46:658-662
<https://doi.org/10.4093/dmj.2021.0232>
pISSN 2233-6079 · eISSN 2233-6087

DIABETES & METABOLISM JOURNAL

dmj



Clinical Efficacy of Sodium-Glucose Cotransporter 2 Inhibitor and Glucagon-Like Peptide-1 Receptor Agonist Combination Therapy in Type 2 Diabetes Mellitus: Real-World Study

Hwi Seung Kim^{1,2,*}, Taekwan Yoon^{3,4}, Chang Hee Jung^{1,2}, Joong-Yeol Park^{1,2}, Woo Je Lee^{1,2}

- Higher baseline HbA1c level was associated with a significantly greater reduction of HbA1c

The combined treatment was well tolerated, and few adverse events were detected.
The dropout and hypoglycemia rates were minimal.

Clinical Therapeutics/Volume 42, Number 2, 2020

GLP1 Receptor Agonist and SGLT2 Inhibitor Combination: An Effective Approach in Real-world Clinical Practice

Olaia Díaz-Trastoy, MD¹; Rocío Villar-Taibo, MD, PhD²; Mildred Sifontes-Dubón, MD³; Hector Mozo-Peñalver, PharmD⁴; Ignacio Bernabeu-Morón, MD, PhD²; José M. Cabezas-Agrícola, MD²; Virginia Muñoz-Leira, MD²; Roberto Peinó-García, MD, PhD²; Aurelio Martís-Sueiro, MD²; José M. García-López, MD, PhD²; and Miguel A. Martínez-Olmos, MD, PhD²

- Simultaneous combination SGLT2i/GLP1 RA led to a greater decrease in HbA1c than when they were started sequentially
- The combination therapy were observed in patients with a short (<10 years) and along (>10 years) evolution of their diabetes



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DIABETES
CANADA



Original Research

Combination Therapy With Glucagon-Like Peptide-1 Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors in Older Patients With Type 2 Diabetes: A Real-World Evidence Study

Juana Carretero Gómez MD^{a,*}; José Carlos Arévalo Lirio MD^a; Ricardo Gómez Huelgas PhD^{b,c}; Dolores García de Lucas PhD^d; Lourdes Mateos Polo PhD^e; José Manuel Varela Aguilar PhD^f; Jose Miguel Seguí Ripoll PhD^g; Javier Ena PhD^h on behalf of the Diabetes, Obesity, and Nutrition Spanish Working Group



>65 years of age

- Patients who had the highest baseline A1C levels saw greater decreases in A1C levels and weight
- Simultaneous combination can lead to faster weight loss and A1C decreases than when they are started sequentially

STUDI DI EFFICACIA E SICUREZZA – META ANALISI

Ref.	Types of studies included, <i>n</i>	Comparator arm	<i>N</i>	Δ HbA1c (%), (95%CI)	Δ Weight (kg), (95%CI)	Δ SBP (mmHg), (95%CI)	Adverse events (GI, GTI, Hypo's) with SGLT-2I + GLP-1RA vs SGLT-2I
Zhou <i>et al</i> [31], 2019	RCT, 3	GLP-1RA + SGLT-2I vs SGLT-2I	1421	-0.80 (-1.14; -0.45)	-1.46 (-2.38; -0.54)	-2.88 (-4.52; -1.25)	Increased risk of GI S/E (RR: 1.68; 95%CI: 1.14-2.47) but similar GTI (RR: 0.82; 95%CI: 0.39-1.75) and hypo's (RR: 2.10; 95%CI: 0.75-5.90) in combo arm
Castellana <i>et al</i> [32], 2019	RCT, 4	GLP-1RA + SGLT-2I vs SGLT-2I	1610	-0.74 (-1.15; -0.33)	-1.61 (-2.83; -0.38)	-3.32 (-4.96; -1.68)	Similar hypo's (RR: 1.43; 95%CI: 0.46-4.52). GTI and GI S/E not reported
Patoulas <i>et al</i> [33], 2019	RCT, 3	GLP-1RA + SGLT-2I vs SGLT-2I	1042	-0.91 (-1.41; -0.42)	-1.95 (-3.83; -0.07)	-3.64 (-6.24; -1.03)	Increased risk of nausea (RR: 3.21; 95%CI: 1.36-7.54) and hypo's (RR: 2.62; 95%CI: 1.15-5.96) in combo arm. GTI not reported
Mantsiou <i>et al</i> [34], 2020	RCT, 7	GLP-1RA + SGLT-2I vs SGLT-2I	1913	-0.85 (-1.19; -0.52)	-1.46 (-2.94; +0.03)	-2.66 (-5.26; -0.06)	No difference in severe hypo's (OR: 2.39; 95%CI: 0.47-12.27). GTI and GI S/E not reported
		GLP-1RA + SGLT-2I vs GLP-1RA		-0.61 (-1.09; -0.14)	-2.59 (-3.68; -1.51)	-4.13 (-7.28; -0.99)	No difference in severe hypo's (OR: 1.38; 95%CI: 0.14-13.14). GTI and GI S/E not reported

STUDI DI EFFICACIA E SICUREZZA – META ANALISI

Ref.	Parameters studied	Duration (wk)	(A) Δ GLP-1 RA	(B) Δ SGLT-2i	(C) Δ GLP-1 RA + SGLT-2i	(A + B) Δ Sum of GLP-1 RA and SGLT2i	Effect of (C) compared to (A + B)
Frias <i>et al</i> [16], 2016; Jabbour <i>et al</i> [17], 2018; Birnbaum <i>et al</i> [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
	HbA1c	12	-1.30	-0.80	-1.50	-2.10	Less than additive
	HbA1c	16	-1.44	-0.89	-1.67	-2.33	Less than additive
Frias <i>et al</i> [16], 2016; Jabbour <i>et al</i> [17], 2018; Birnbaum <i>et al</i> [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
	Body weight	12	NR	NR	NR	NR	NR
	Body weight	16	-1.90	-3.50	-6.00	-5.40	More than additive
Frias <i>et al</i> [16], 2016; Jabbour <i>et al</i> [17], 2018; Birnbaum <i>et al</i> [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
	SBP	12	-3.00	-4.00	-4.00	-7.00	Less than additive
	SBP	16	-5.10	-5.20	-14.10	-10.30	More than additive

HbA1c

Less than additive

Body weight

Almost additive

SBP

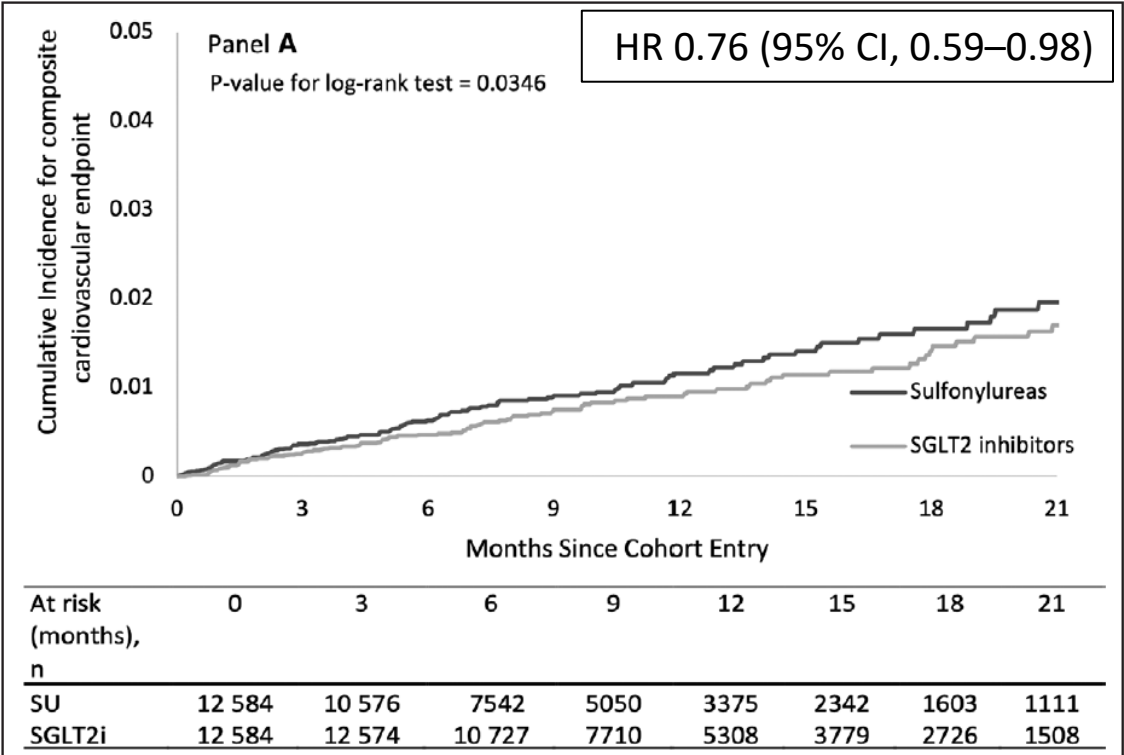
More than additive

- INTRODUZIONE - RAZIONALE
- LE LINEE GUIDA
- STUDI DI EFFICACIA E SICUREZZA
 - GLP-1 RA + SGLT-2i (simultaneo)
 - GLP-1 RA su SGLT-2i (sequenziale)
 - SGLT-2i su GLP-1 RA (sequenziale)
 - REAL WORLD
 - METANALISI
- **STUDI DI OUTCOME CARDIOVASCOLARE E RENALE**
 - REAL WORLD
 - CVOT
 - METANALISI
 - *ON-GOING*
- **ALTRI OUTCOMES**
 - NAFLD/NASH
 - OBESITÀ
- TAKE HOME MESSAGES

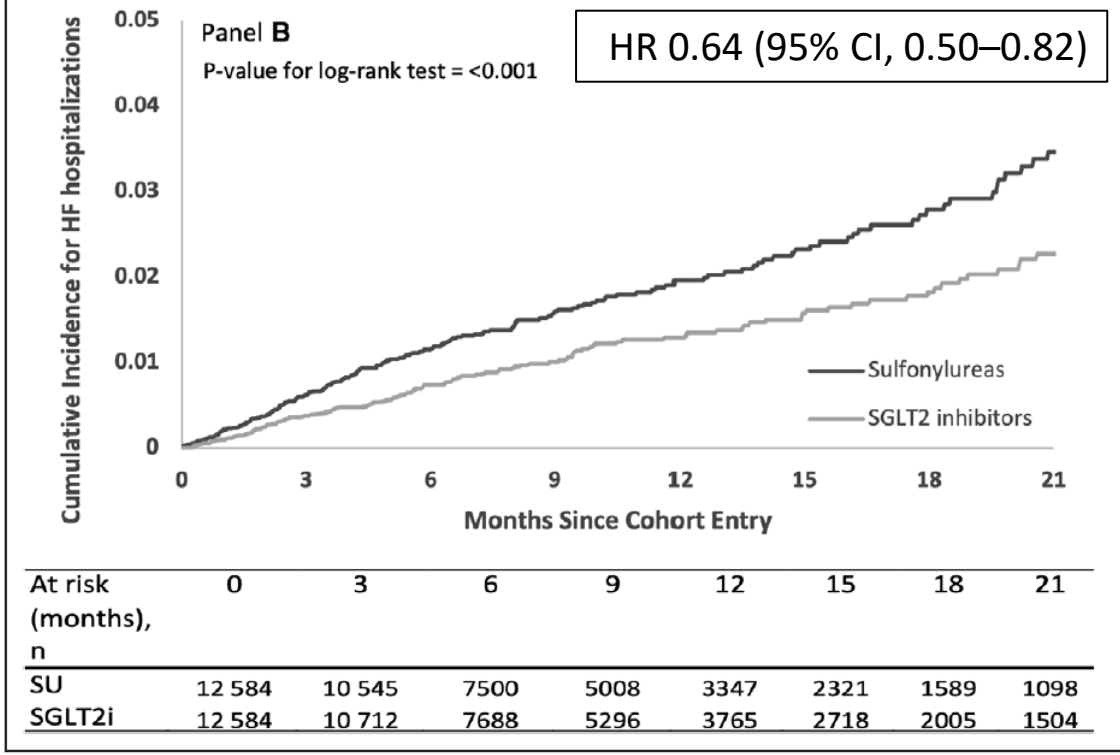
STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – REAL WORLD

Risk of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Addition of SGLT2 Inhibitors Versus Sulfonylureas to Baseline GLP-1RA Therapy

SGLT2i su
GLP1RA



Composite of myocardial infarction hospitalizations, stroke hospitalizations, and all-cause mortality



HF hospitalizations

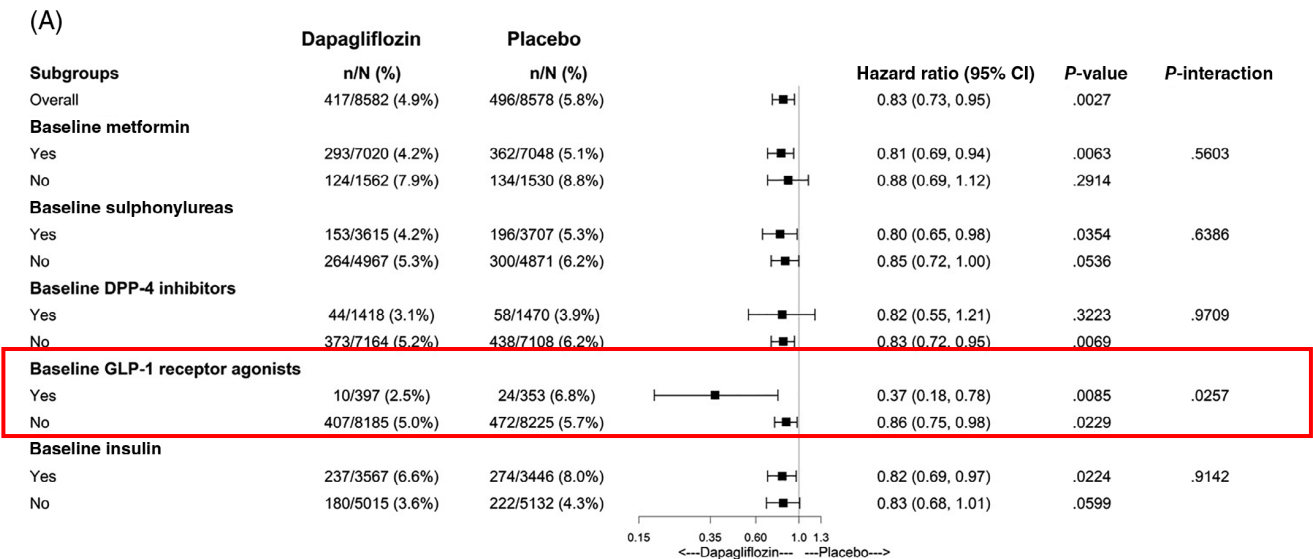
STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – CVOT

Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents: Post hoc analyses from **DECLARE-TIMI 58**

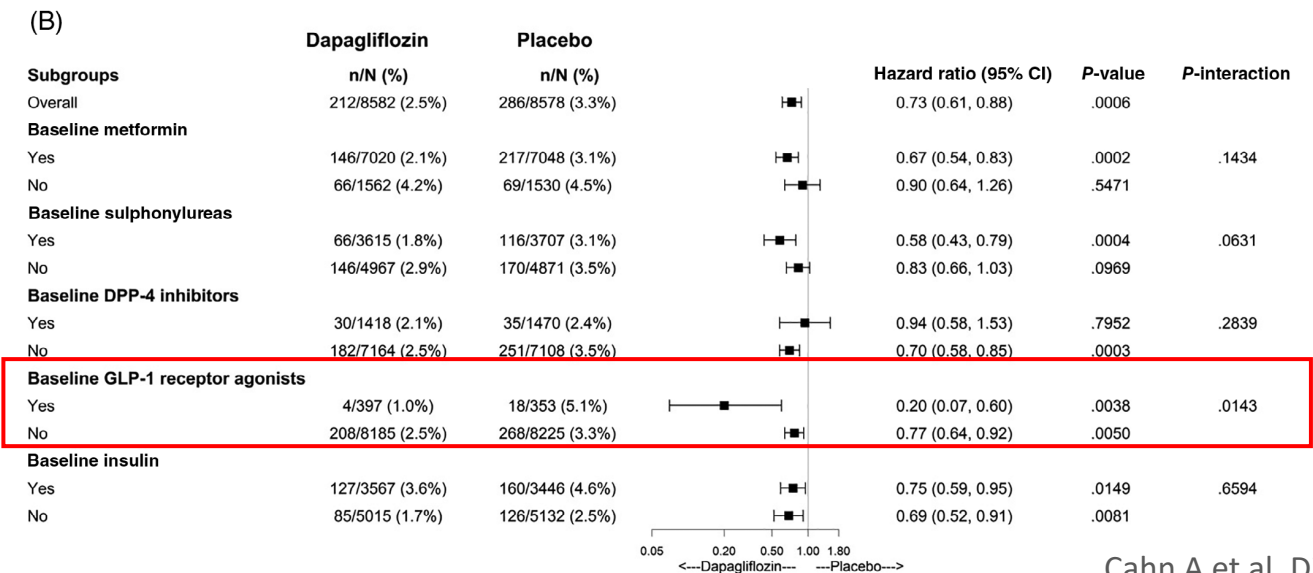


N=750

CV Death/hHF

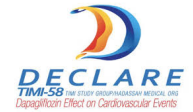


hHF



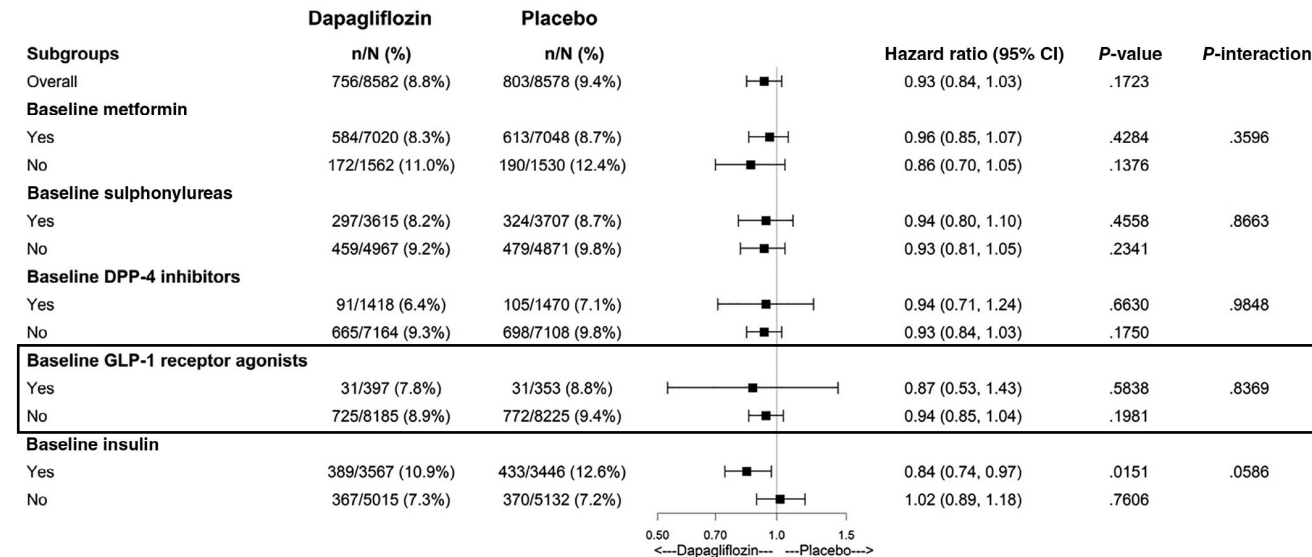
STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – CVOT

Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents:
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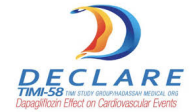
N=750

MACE



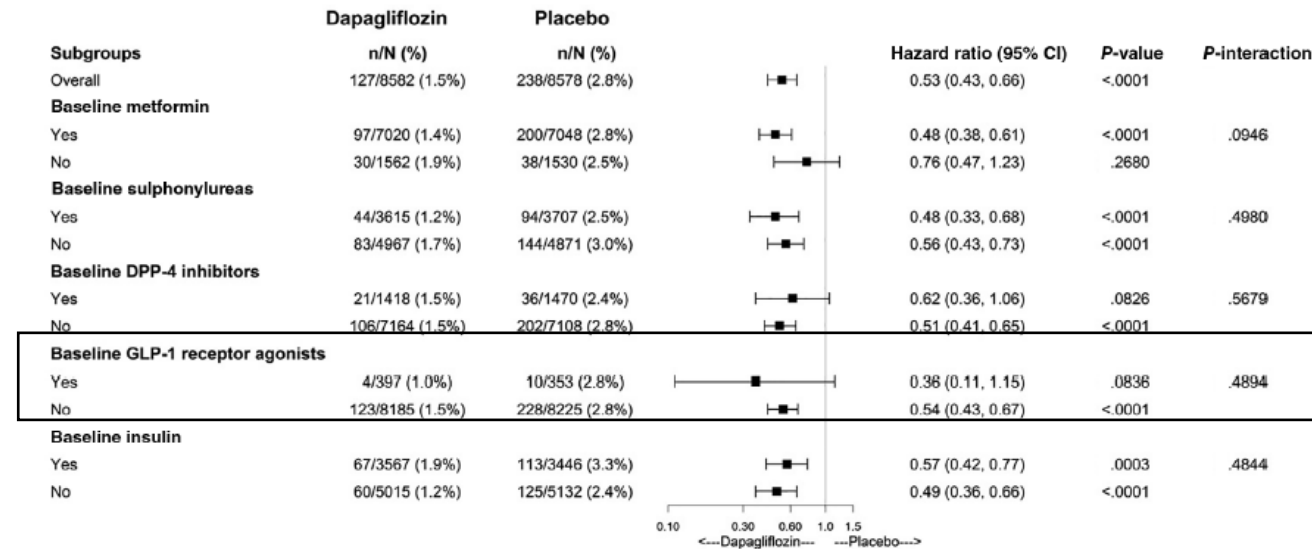
STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – CVOT

Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents:
Post hoc analyses from **DECLARE-TIMI 58**

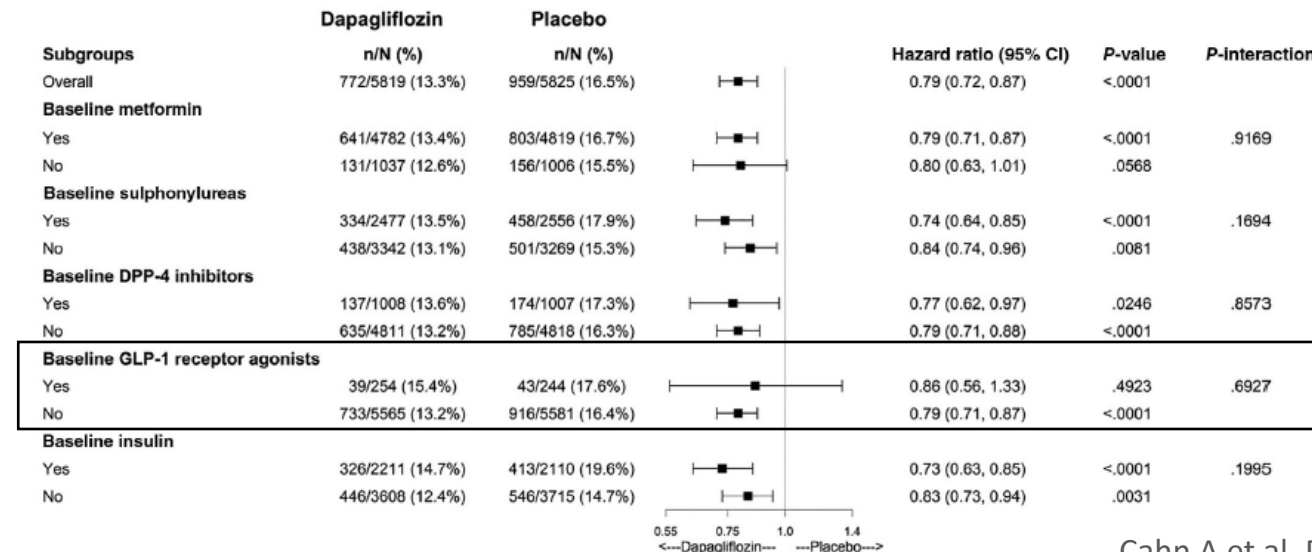


N=750

Composite
renal outcome



New onset
albuminuria



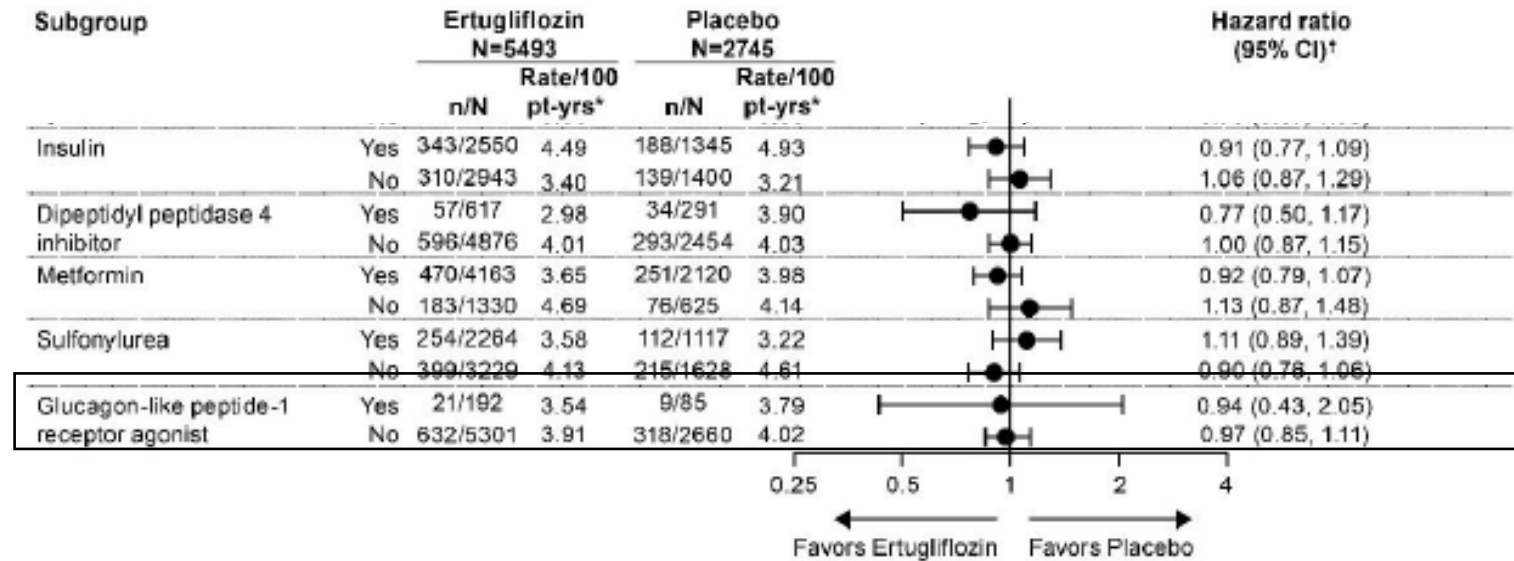
STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – CVOT

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

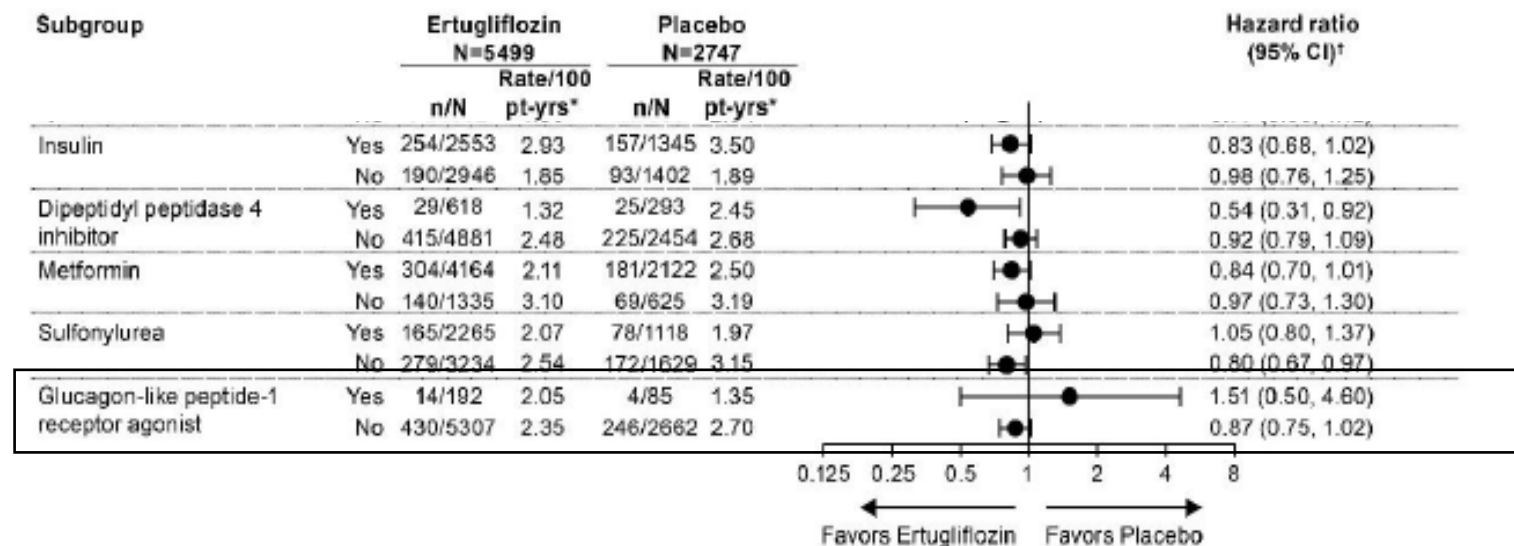
VERTIS CV

N=277

MACE



CV Death/hHF

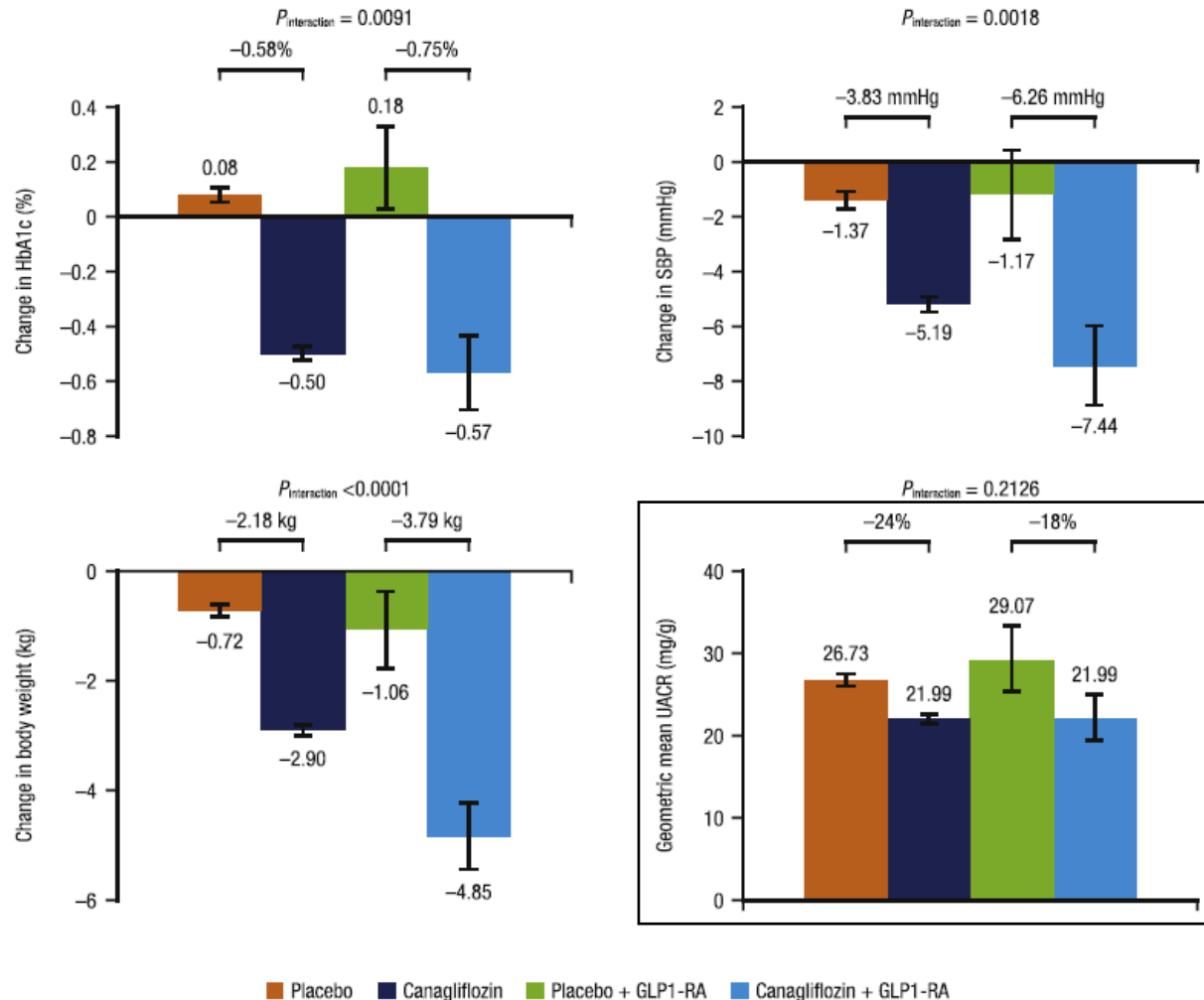


STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – CVOT

The effects of combination canagliflozin and glucagon-like peptide-1receptor agonist therapy on intermediate markers of cardiovascular risk in the **CANVAS program**



N=407



Primary cardiovascular outcome (MACE):

Cana+GLP1RA vs Placebo+GLP1RA: HR 0.73 (0.36-1.46)

Cana vs Placebo: HR 0.86 (0.76-0.98)

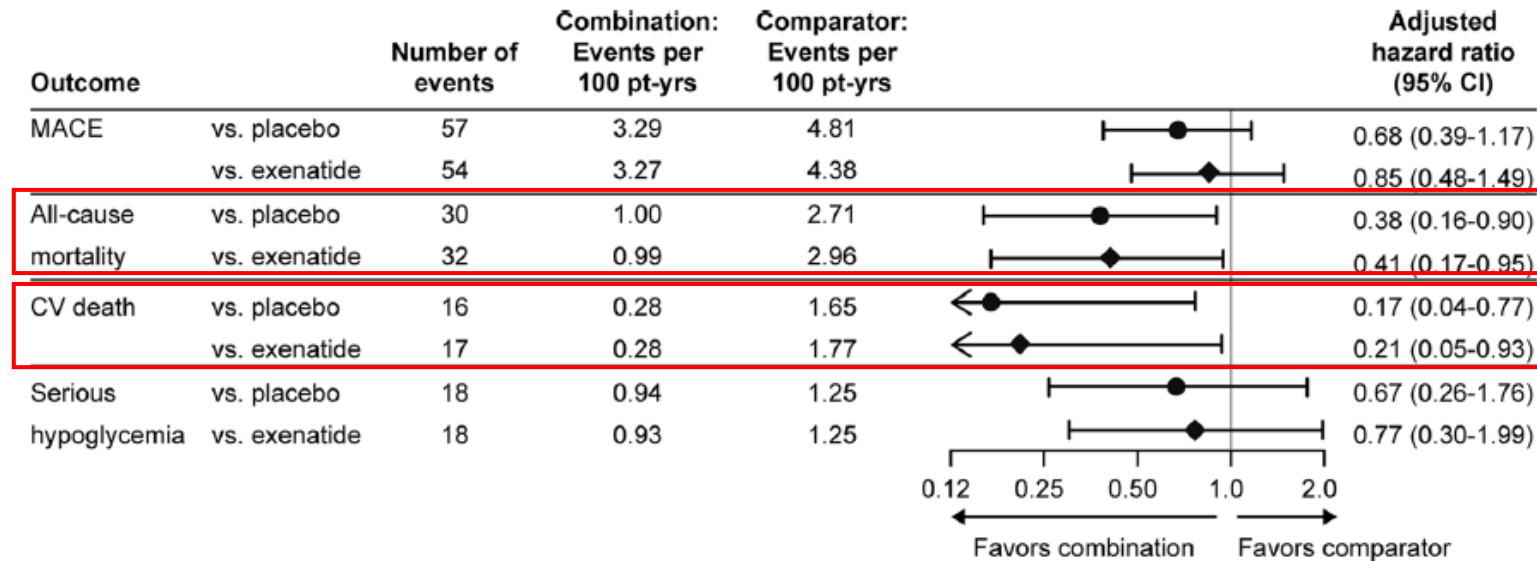
P interaction= 0.94

Composite adverse renal outcome (40% decline in eGFR, end-stage kidney disease or renal death):

P interaction= 0.43

STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – CVOT

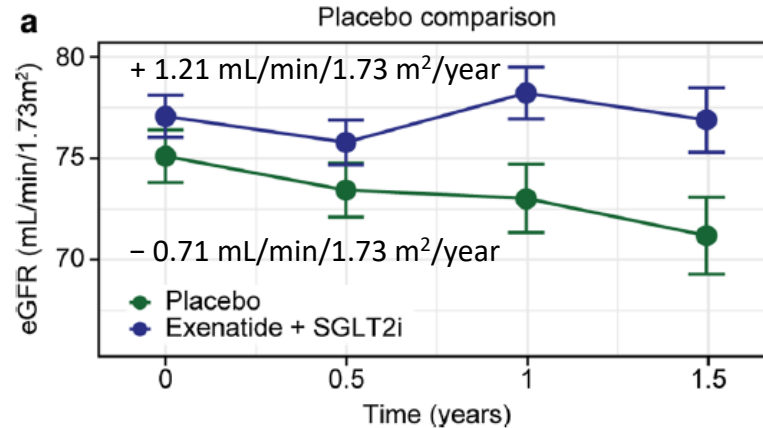
Effects of exenatide and open-label SGLT2 inhibitor treatment, given in parallel or sequentially, on mortality and cardiovascular and renal outcomes in type 2 diabetes: insights from the **EXSCEL** trial



hHF:	vs placebo	HR 0.98 (0.28-3.45)
	vs exenatide	HR 0.51 (0.18-1.48)
hHF+CV Death:	vs placebo	HR 0.41 (0.17-0.98)
	vs exenatide	HR 0.41 (0.17-0.95)

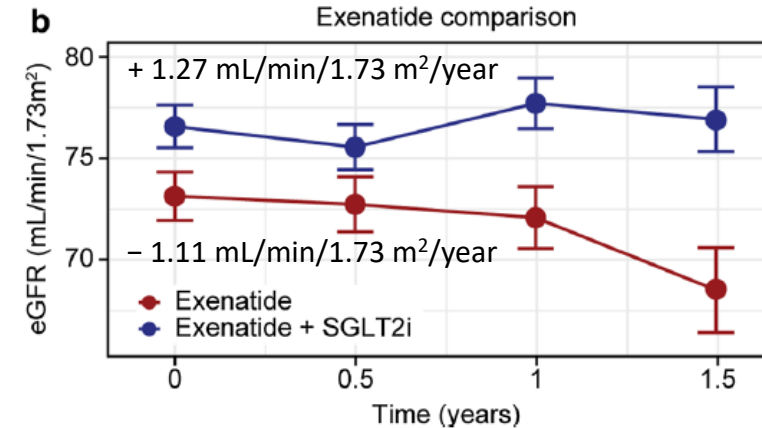
STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – CVOT

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



estimated treatment effect:

+ 1.94 mL/min/1.73 m²/year (p < 0.001)



estimated treatment effect:

+ 2.38 mL/min/1.73 m²/year (p < 0.001)

Renal_1 (composite of a persistent 40% reduction in eGFR, renal dialysis, or renal transplant):

vs placebo HR 0.30 (0.06-1.52)

vs exenatide HR 0.22 (0.05-1.00)

Renal_2 (composite of Renal_1 plus new macroalbuminuria):

vs placebo HR 0.42 (0.15-1.22)

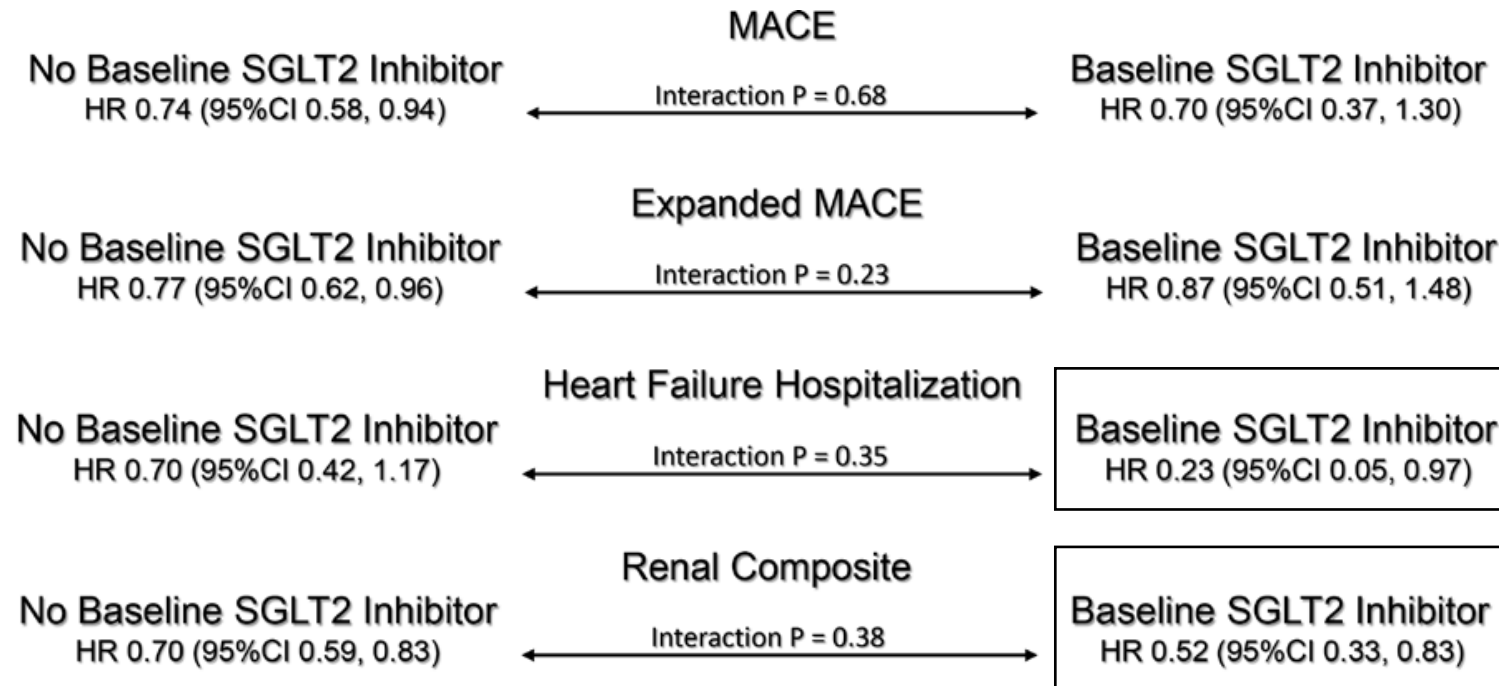
vs exenatide HR 0.39 (0.14-1.09)

STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – CVOT

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



N=618
(15%)



STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – *ON GOING*

PREvention of Cardiovascular and Diabetic kidney Disease in Type 2 Diabetes (**PRECIDENTD**)

TRIAL DESIGN:

Randomized, open label, pragmatic clinical trial

Start: September 2022 » End: April 2028

- SGLT2 inhibitor (empagliflozin, dapagliflozin, canagliflozin)
- GLP-1 RA (dulaglutide, liraglutide, semaglutide)
- Combination drug (SGLT2 inhibitor and GLP-1 RA)

Key inclusion criteria: (n 9000)

- Type 2 diabetes
- HbA1c $\geq 6.5\%$ if on no-medication or $>6\%$ if on glucose-lowering medication
- Secondary prevention cohort (at least 70% of cohort): Age 40 to 80 years, Evidence of established atherosclerotic cardiovascular disease (ASCVD)
- Primary prevention cohort (capped at 30% of cohort): Age 60-80 years and at least 1 additional high-risk feature

Primary Endpoint:

- **Total (first and recurrent) cardiovascular, kidney, and death events**

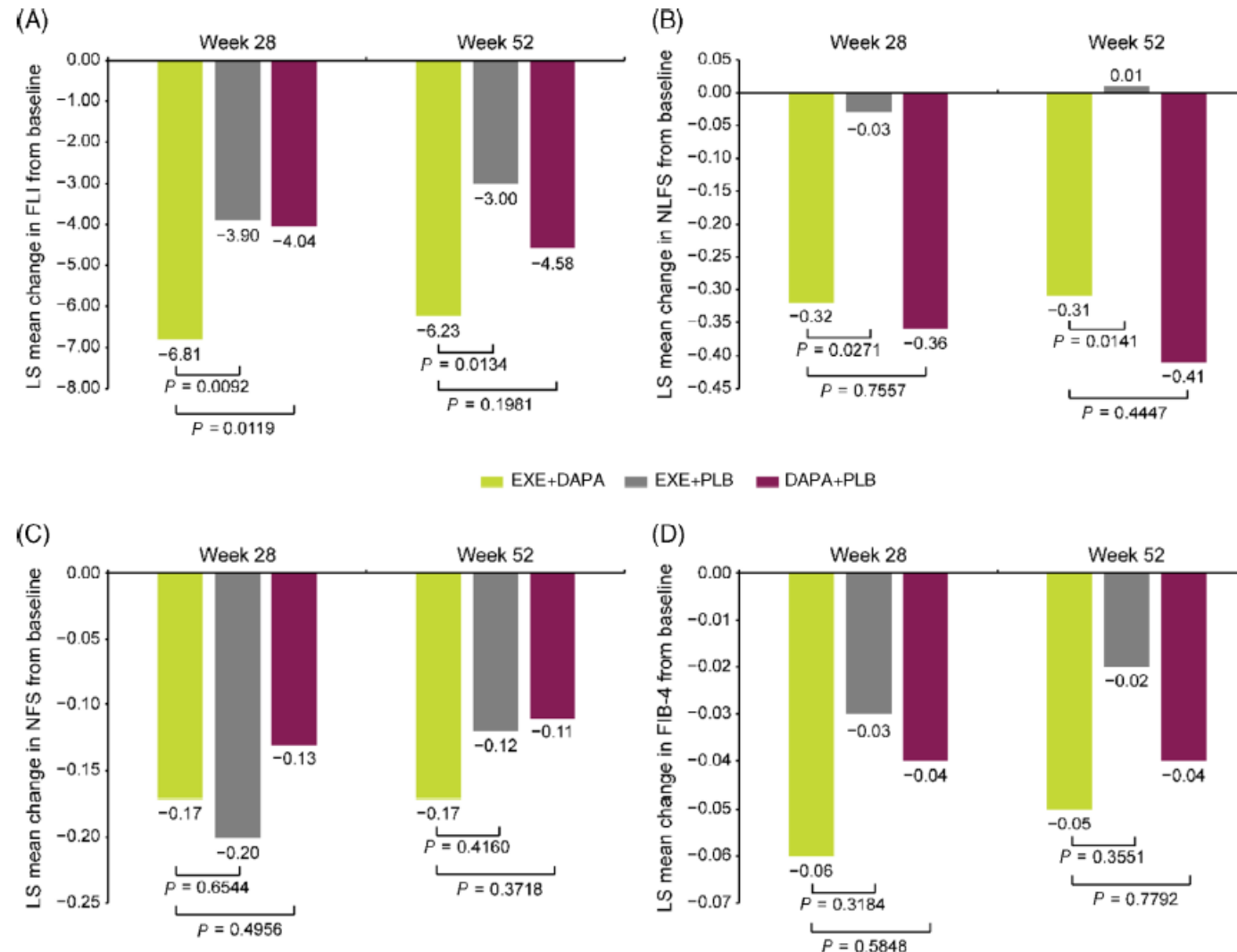
(myocardial infarction, stroke, arterial revascularization, hHF, ESKD, kidney transplantation, and mortality) [Time Frame: Through study completion, an average of 3 years of follow up for each participant]

ALTRI OUTCOMES – NAFLD/NASH

Exenatide and dapagliflozin combination improves markers of liver steatosis and fibrosis in patients with type 2 diabetes

A post hoc analysis of DURATION-8

GLP1RA +
SGLT2i

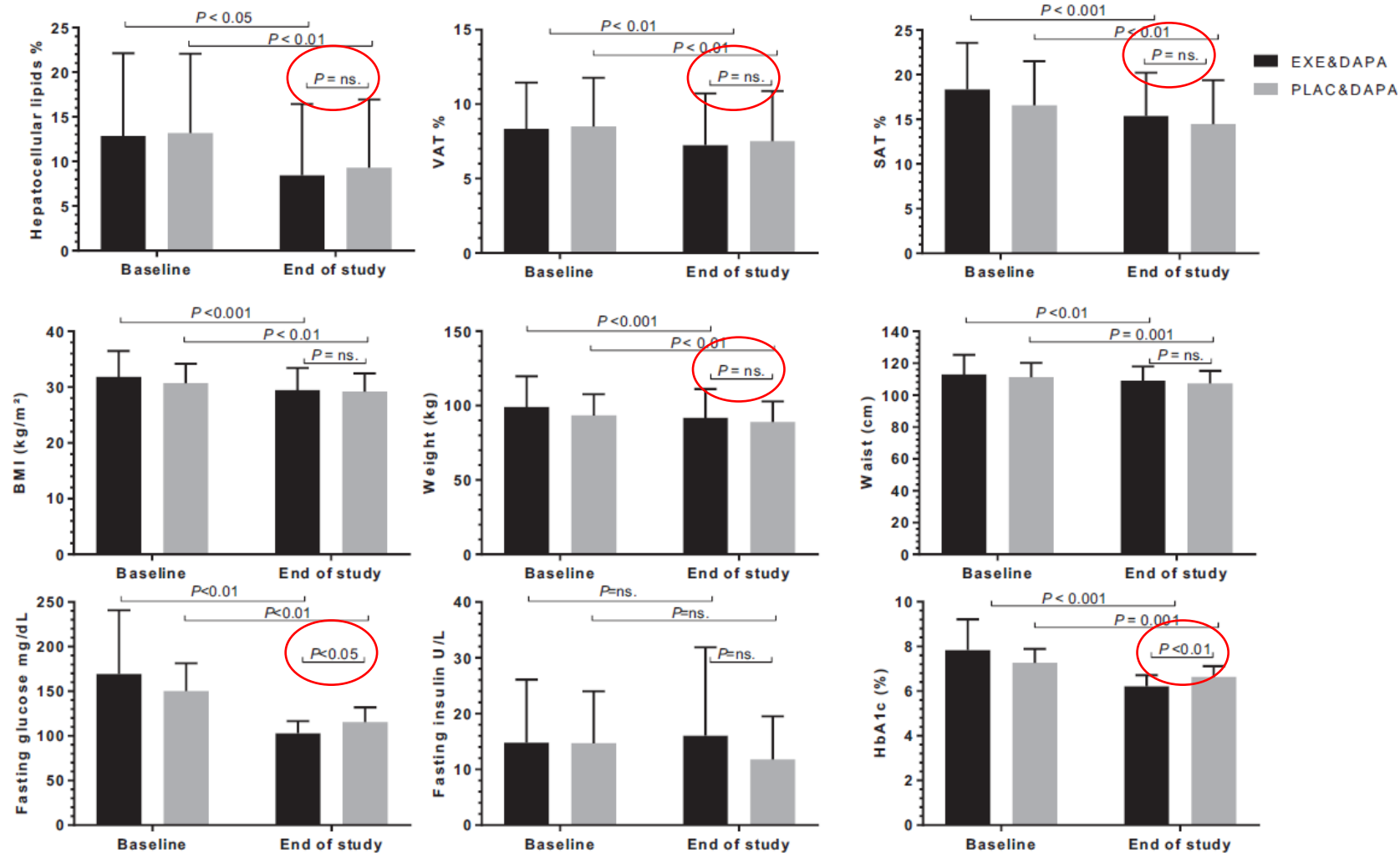


ALTRI OUTCOMES – NAFLD/NASH

Combined exenatide and dapagliflozin has no additive effects on reduction of hepatocellular lipids despite better glycaemic control in patients with T2DM treated with metformin:

EXENDA, a 24-week, prospective, randomized, placebo-controlled pilot trial

GLP1RA +
SGLT2i



TAKE HOME MESSAGES

GLIFLOZINE E INCRETINE INSIEME:

COME

- Simultaneo (GLP-1 RA + SGLT-2i)
- Sequenziale (GLP-1 RA su SGLT-2i)
- Sequenziale (SGLT-2i su GLP-1 RA)
 - Nota 100

QUANDO

- Efficacia su HbA1c
- Efficacia su peso corporeo
- *Protezione cardiorenale?*
 - *NASH/NAFLD?*
- Storia di malattia breve/lunga
 - Anziani

PERCHÉ

PERCHÉ NO?