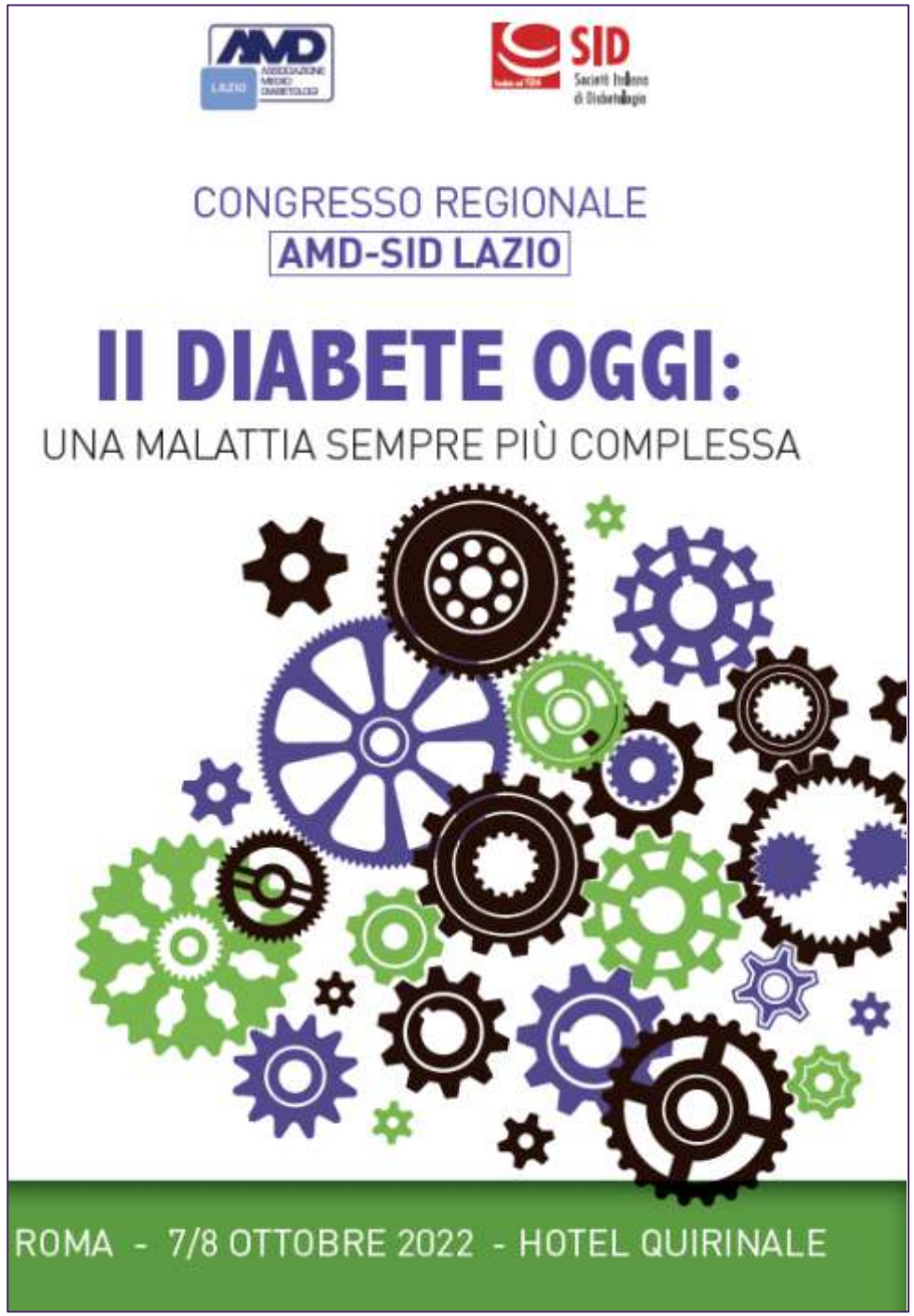


GLIFLOZINE E INCRETINE INSIEME: COME, QUANDO E PERCHÉ?

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

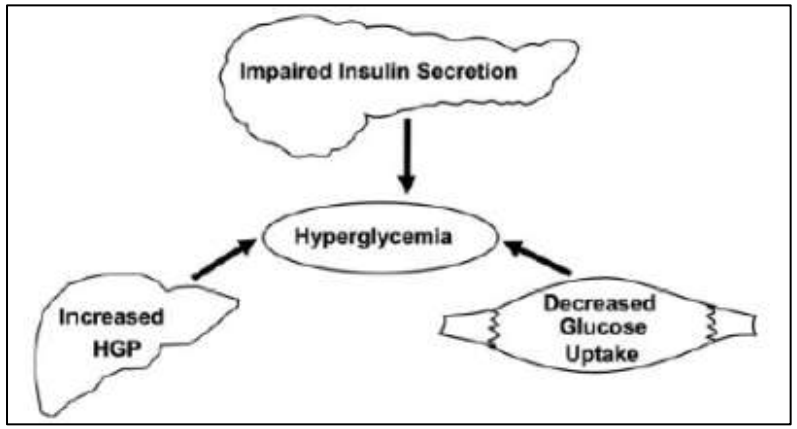
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi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

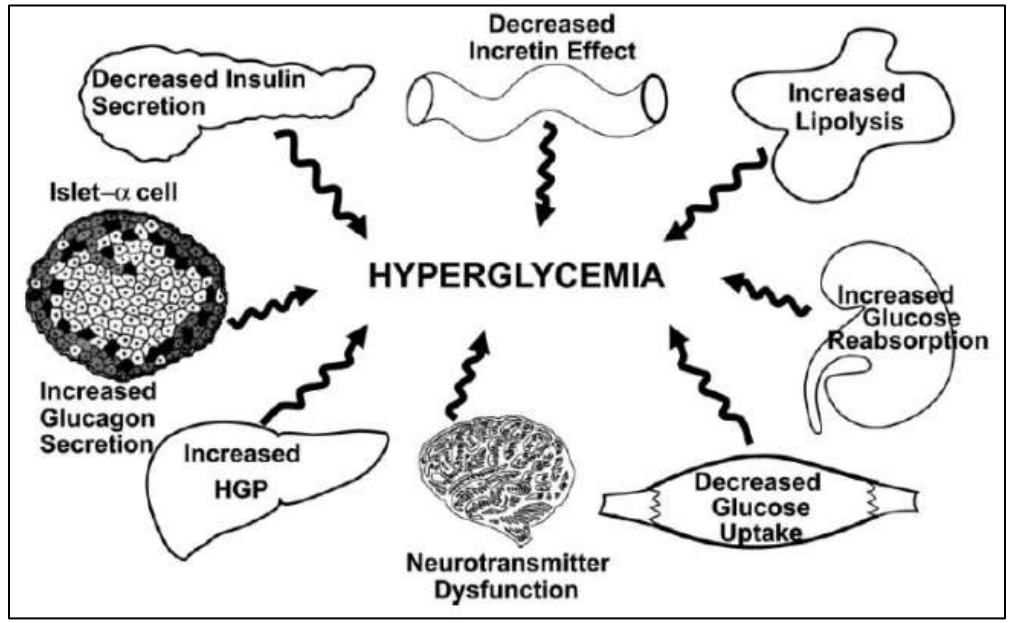
AGENDA

- **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

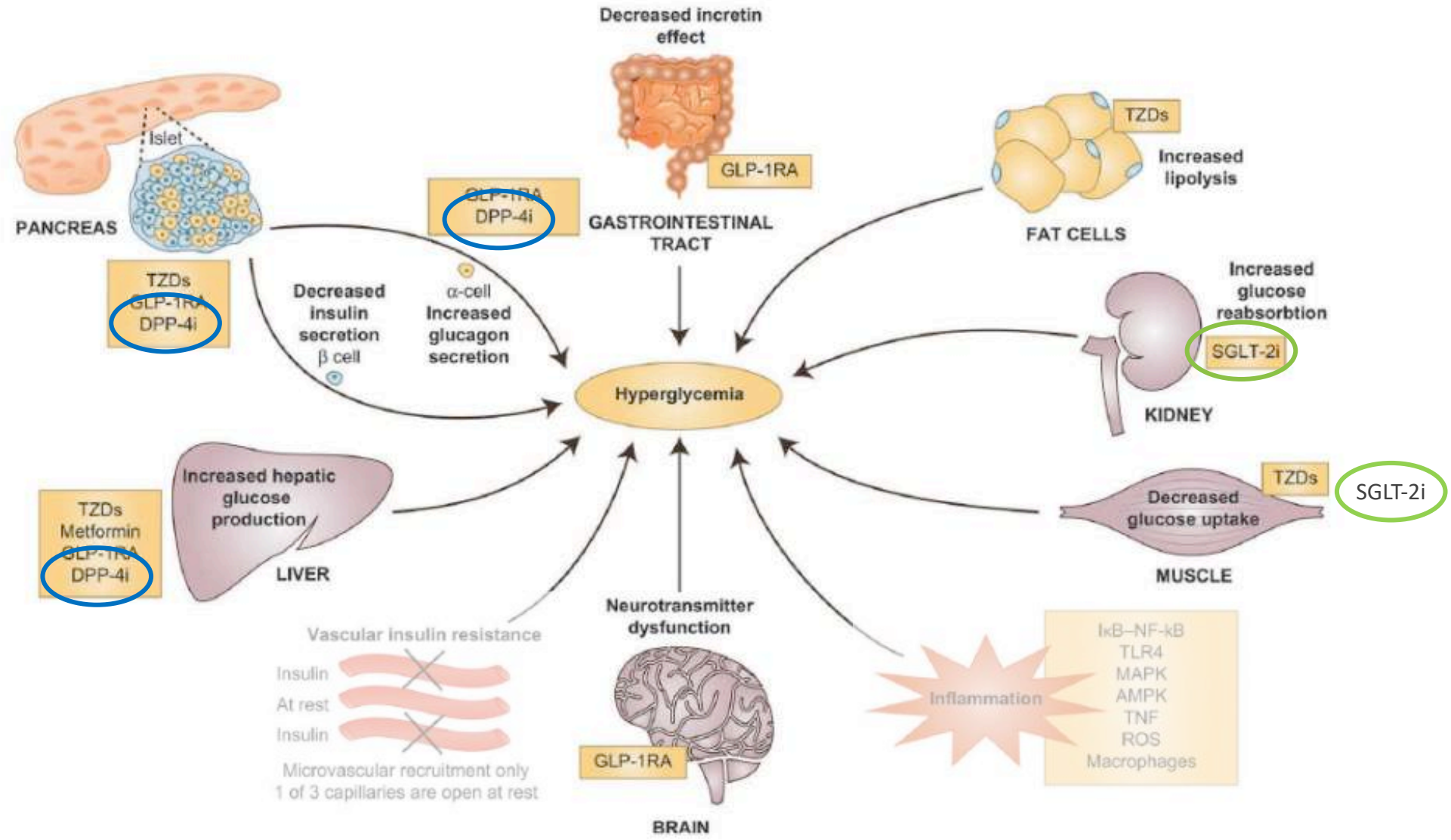
Ralph A. DeFronzo





DeFronzo RA Diabetes. 2009 Apr;58(4):773-95.

INTRODUZIONE – RAZIONALE



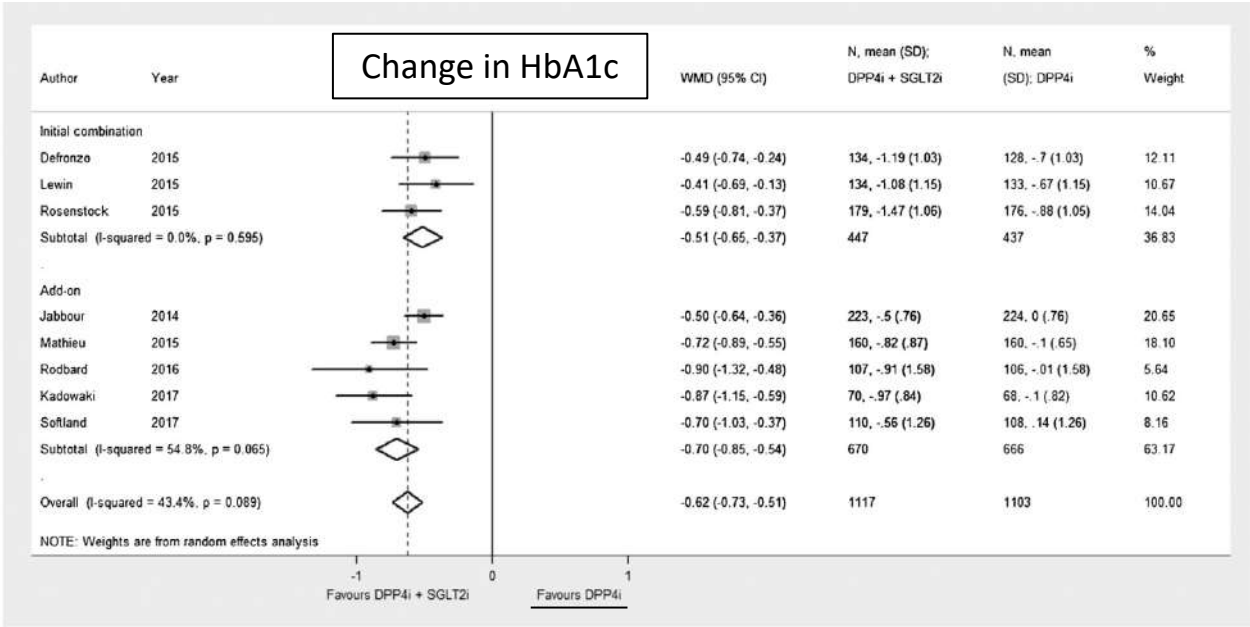
DeFronzo RA et al. Nat Rev Dis Primers. 2015 Jul 23;1:15019.
DeFronzo RA Diabetes Obes Metab. 2017 Oct;19(10):1353-1362.

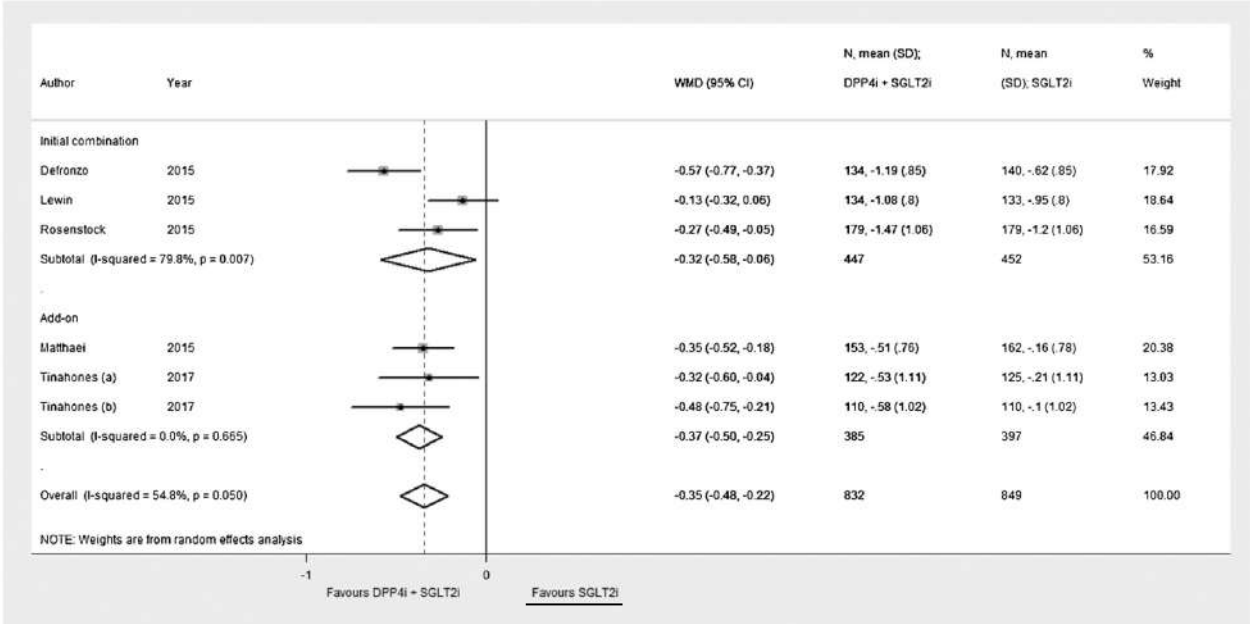
INTRODUZIONE – RAZIONALE

SGLT-2i

+

DPP-4i





Cho JK et al. Diabetes Metab. 2018 Nov;44(5):393-401.

INTRODUZIONE – RAZIONALE

SGLT-2i

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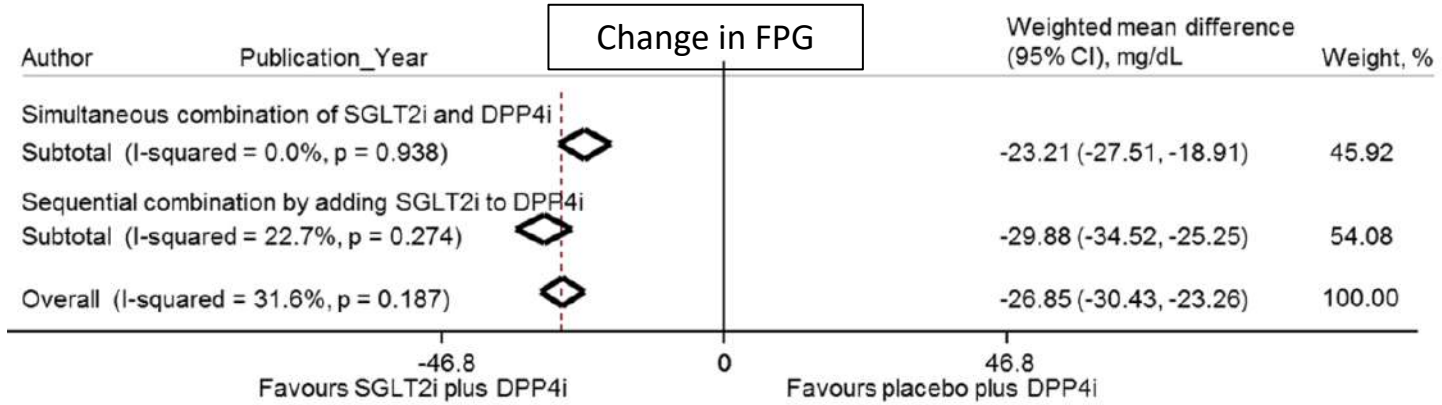
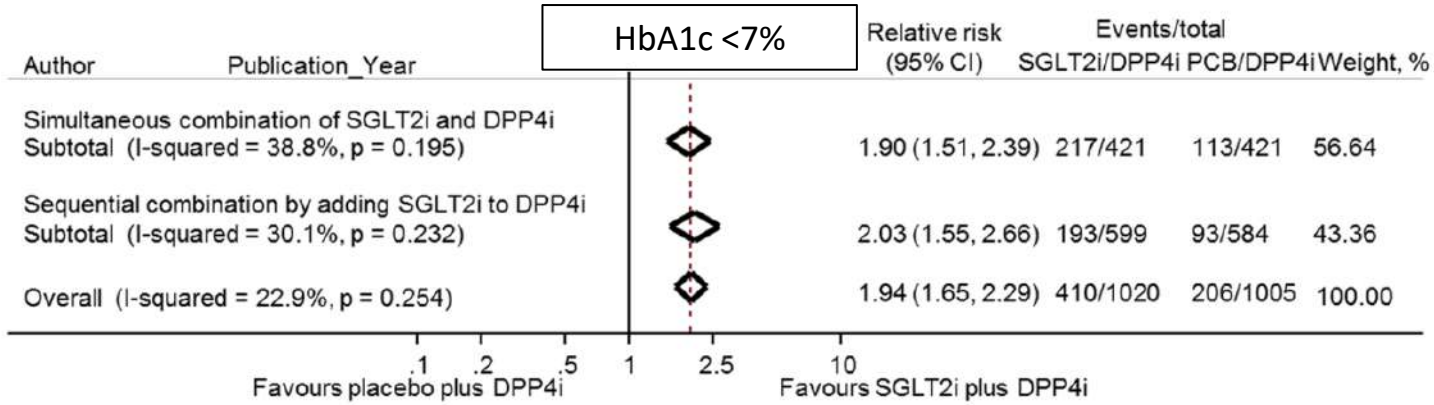
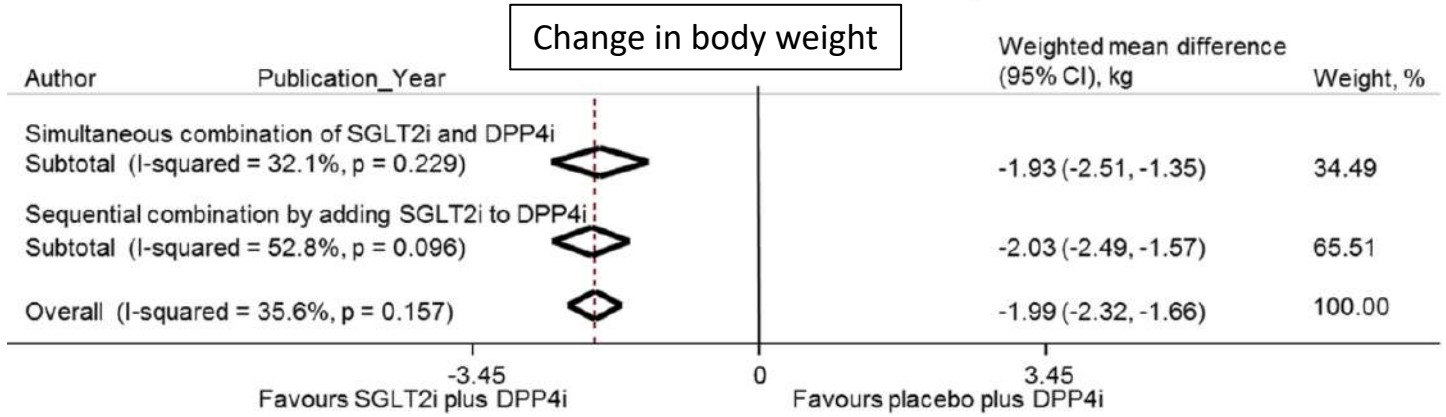






Min SH et al. Sci Rep. 2018 Mar 13;8(1):4466.

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: ☐ Si ☐ 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: ☐ Si

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 aortocoronarico, angioplastica, procedura di rivascolarizzazione coronarica, coronaropatia), malattia cerebrovascolare (pregresso ictus o TIA, rivascolarizzazione 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 DDP4i: 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/m^2) _____
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
GLP1-RA	☐ 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
	☐ exenatide	☐ 5 mcg per 2 vv/die ☐ 10 mcg per 2 vv/die	SGLT2i/DPP4i	☐ empagliflozin/linagliptin	☐ 10/5 mg una volta/die ☐ 25/5 mg una volta/die
	☐ exenatide LAR	☐ 2 mg una volta/settimana		☐ 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 5 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)

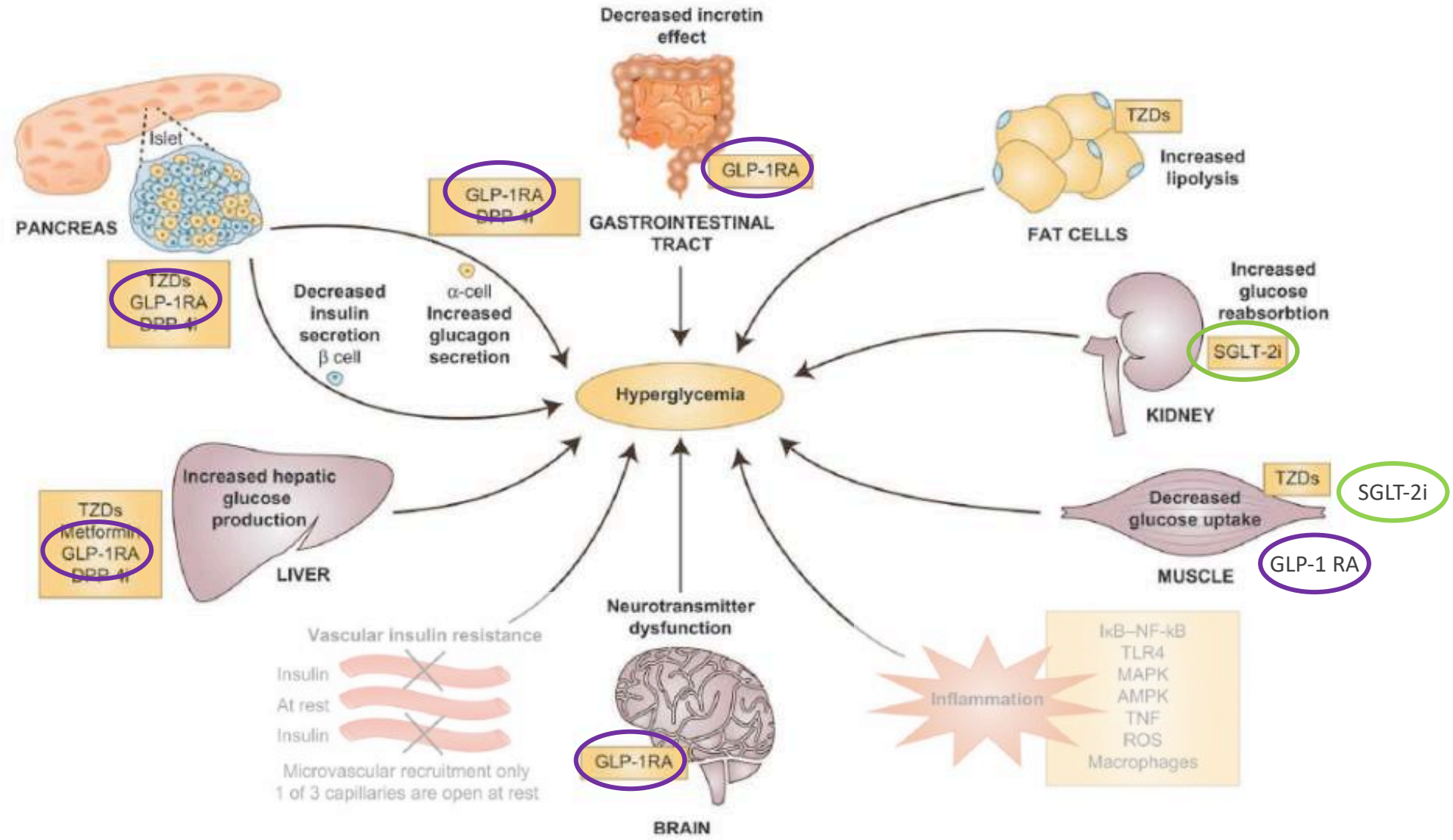
La prescrizione dell'associazione SGLT2i+DPP4i o SGLT2i+GLP1-RA può avvenire esclusivamente da parte di specialisti di strutture diabetologiche individuate dalle Regioni.
La prescrizione delle associazioni estemporanee SGLT2i+DPP4i o SGLT2i+GLP1-RA deve avvenire utilizzando esclusivamente le associazioni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



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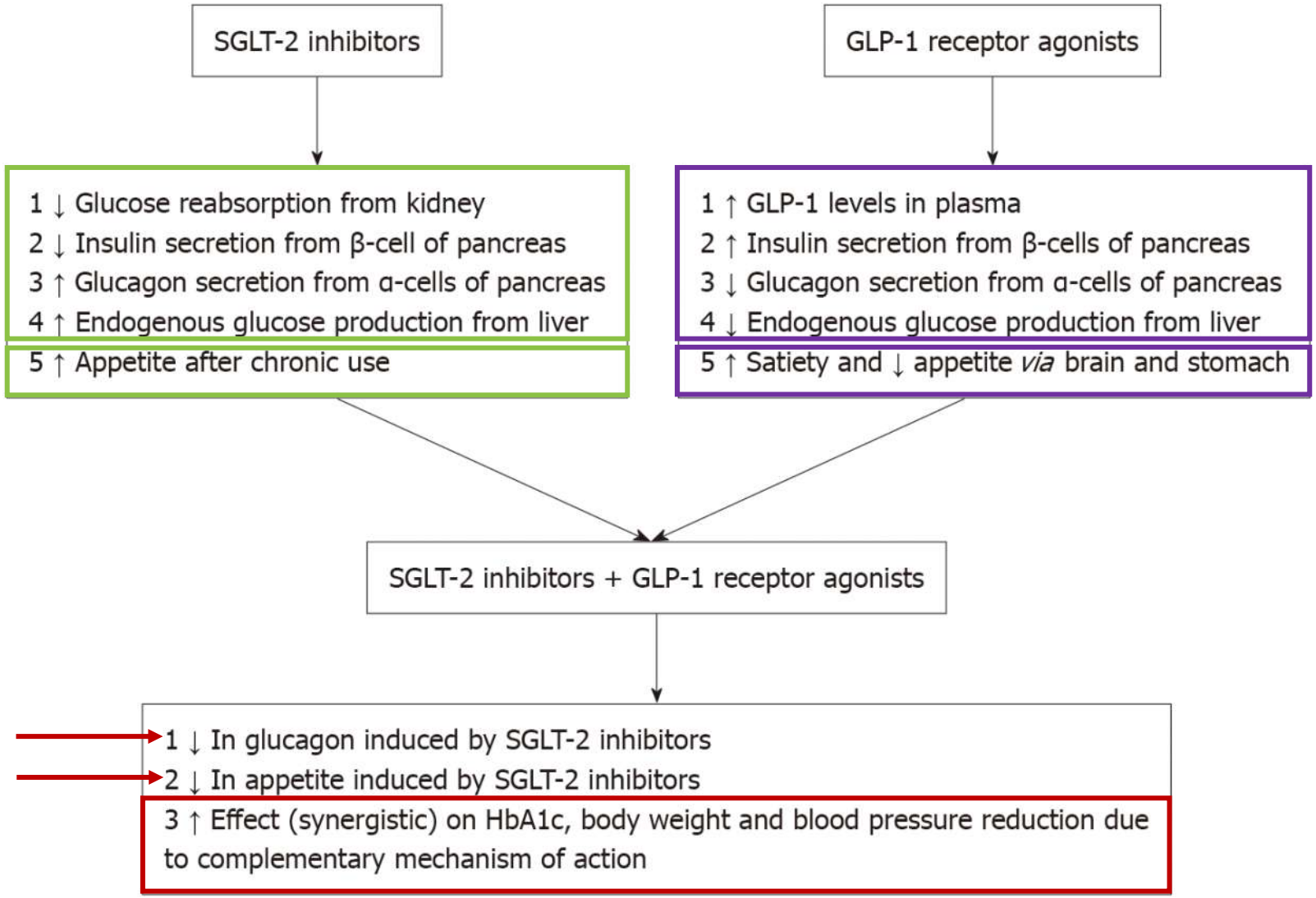
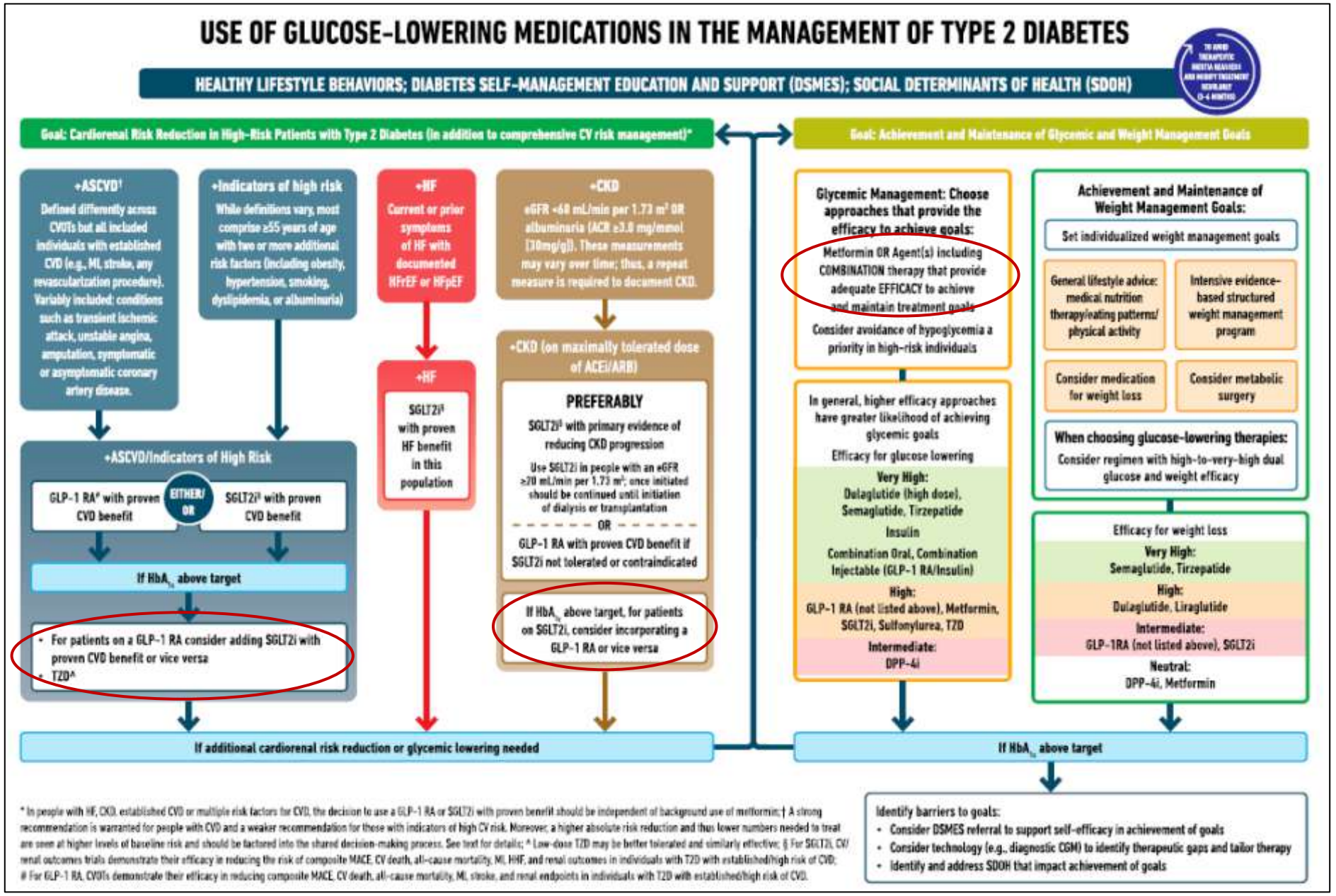


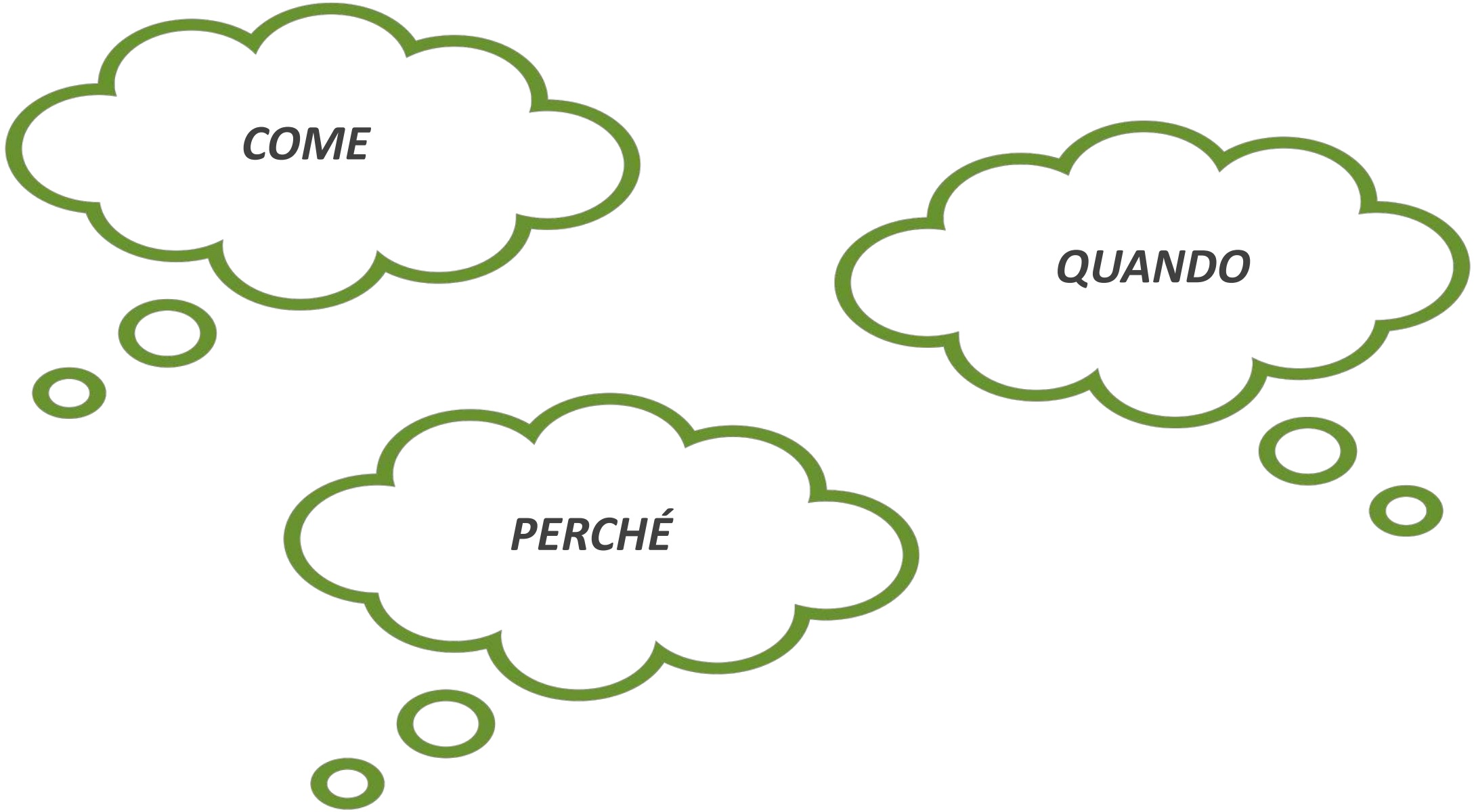
Singh AK et al. World J Cardiol. 2022 Jun 26;14(6):329-342.

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



Davies MJ et al. Diabetes Care. 2022 Sep 23;dci220034.

GLIFLOZINE E INCRETINE INSIEME:



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  - GLP-1 RA + SGLT-2i (simultaneo)
  - GLP-1 RA su SGLT-2i (sequenziale)
  - SGLT-2i su GLP-1 RA (sequenziale)
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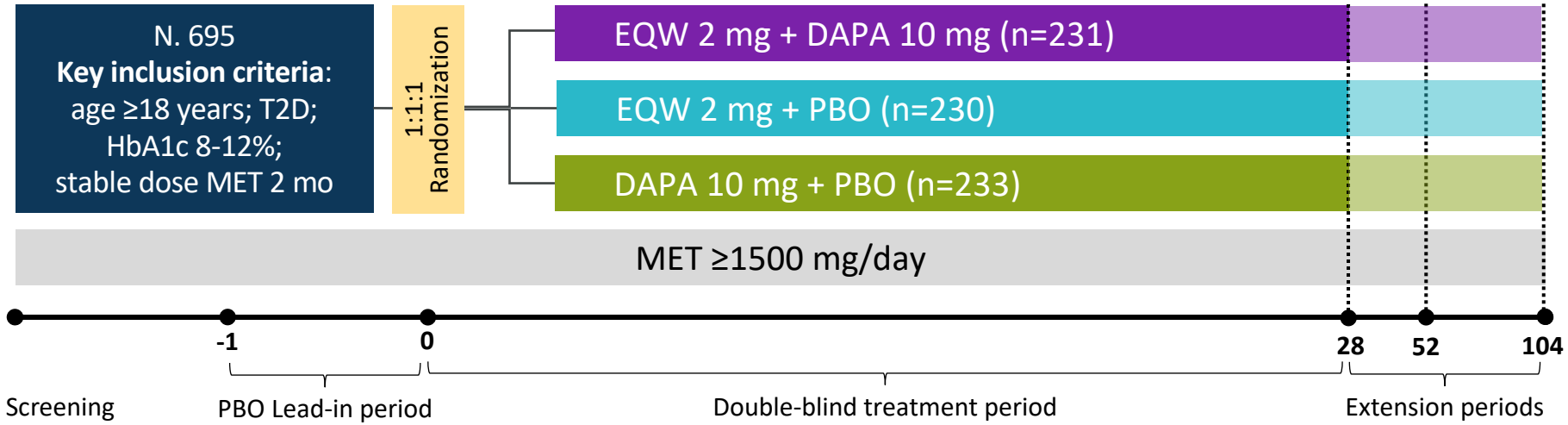
STUDI DI EFFICACIA E SICUREZZA

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

Frías JP et al. Lancet Diabetes Endocrinol. 2016 Dec;4(12):1004-1016.

STUDI DI EFFICACIA E SICUREZZA

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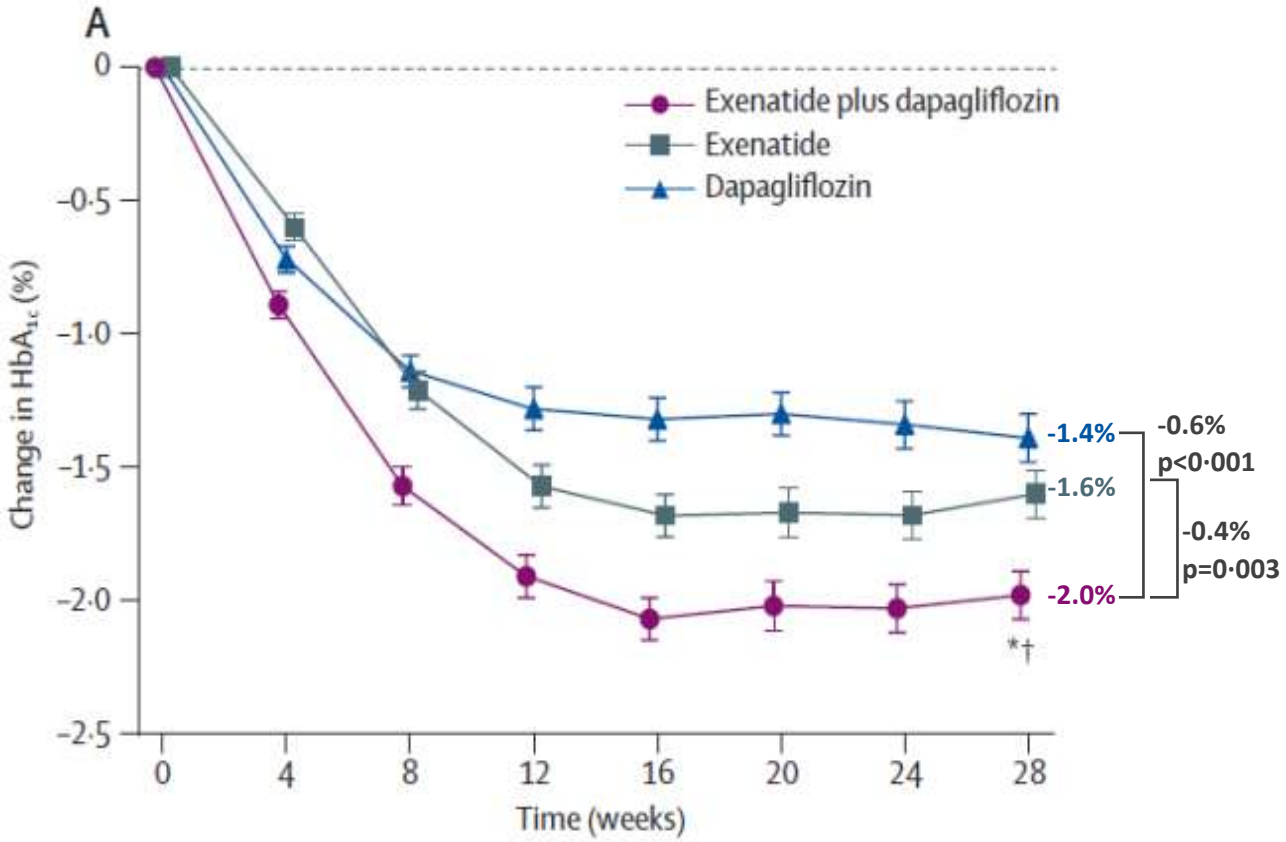
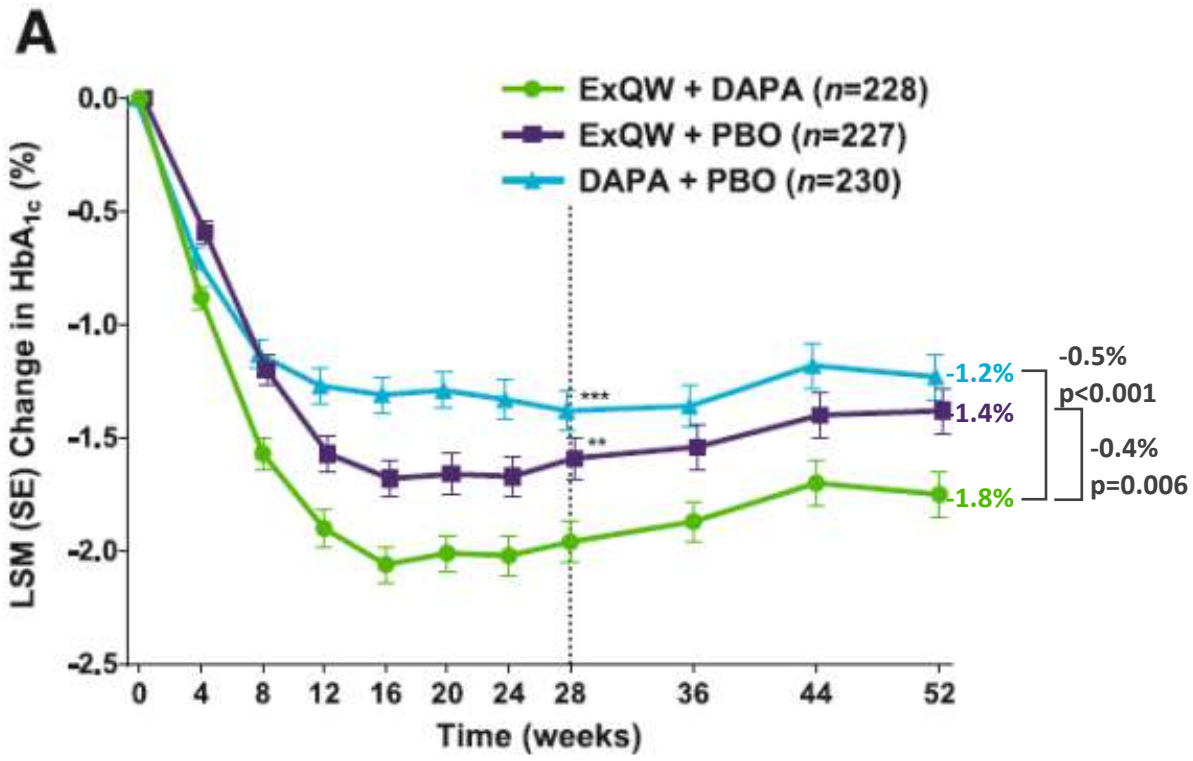
→ *52-Week Results of the DURATION-8 Randomized Controlled Trial*

GLP1RA + SGLT2i





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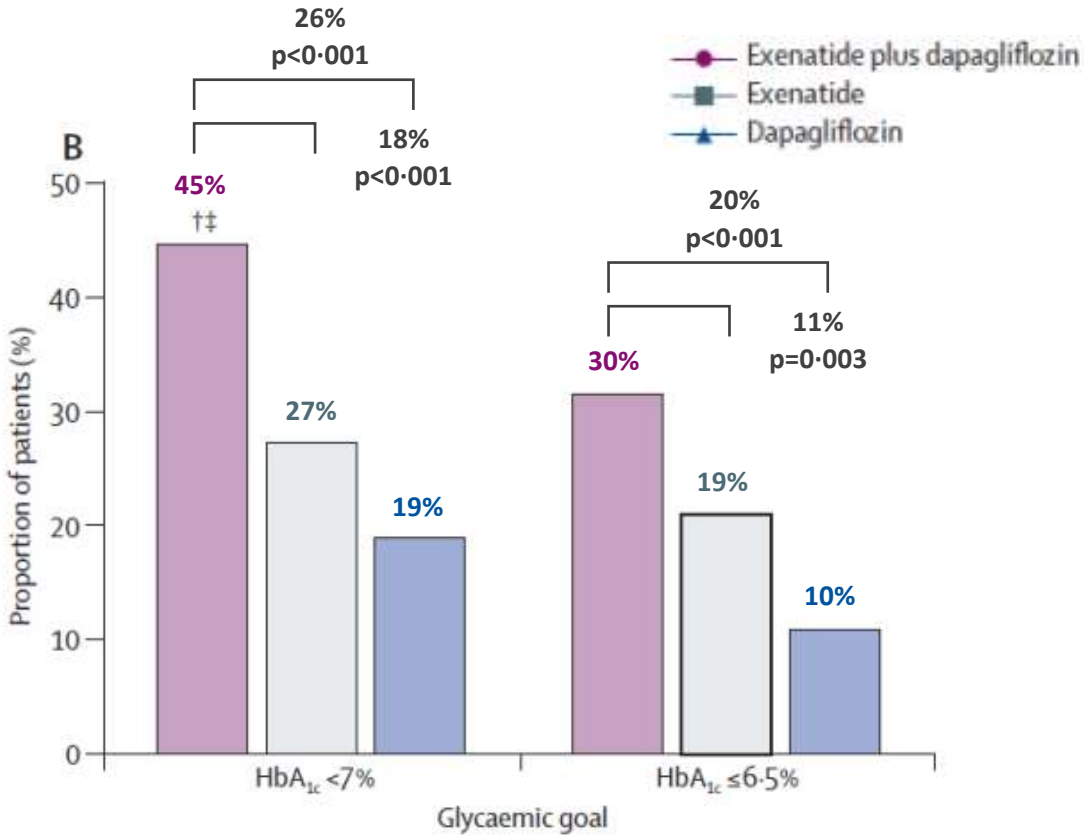

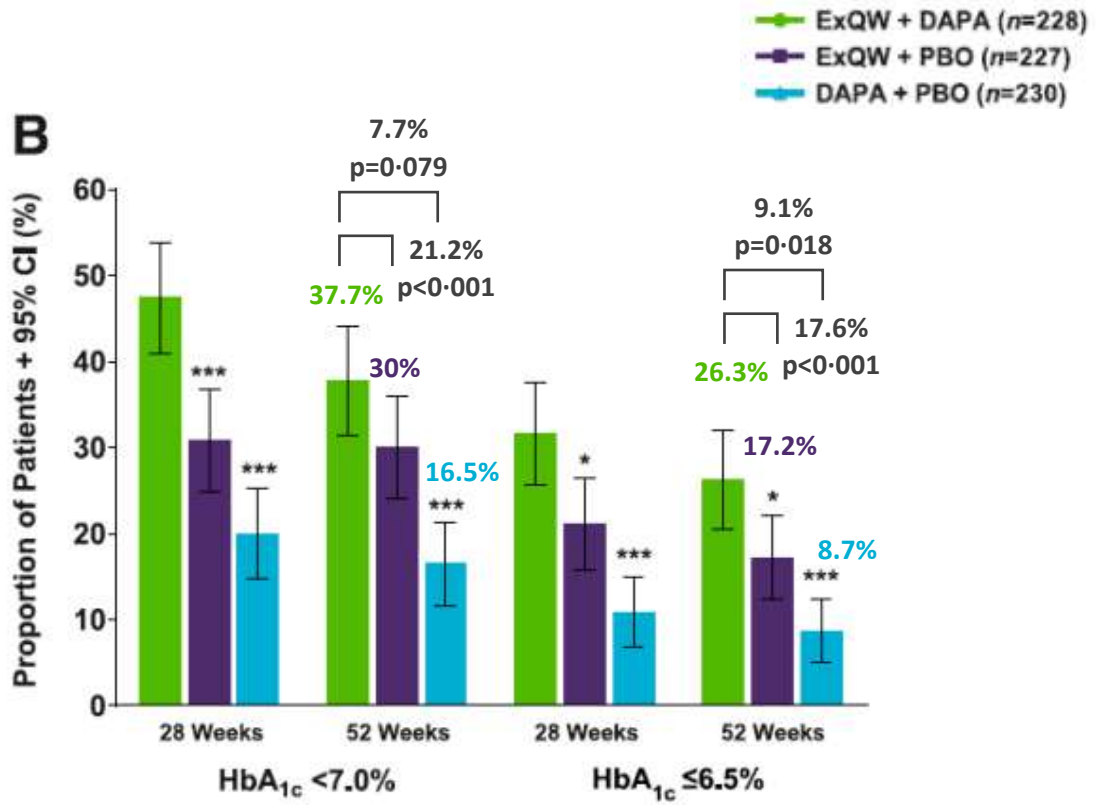

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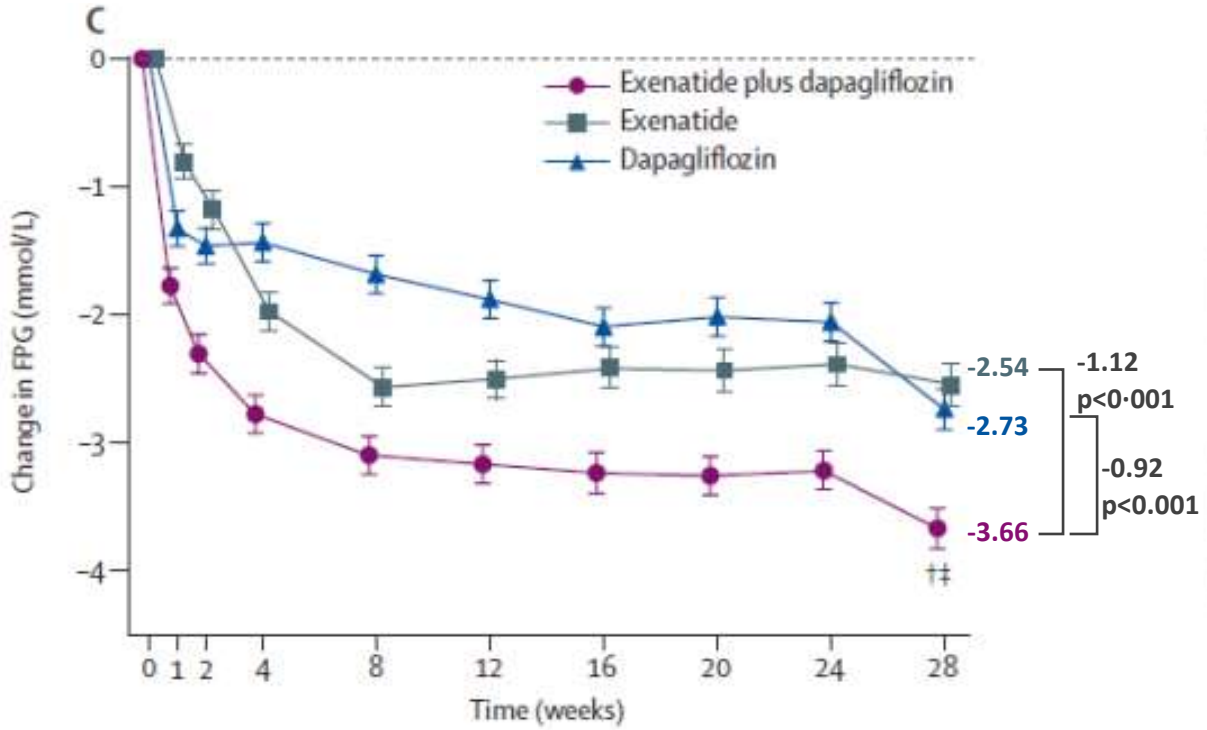

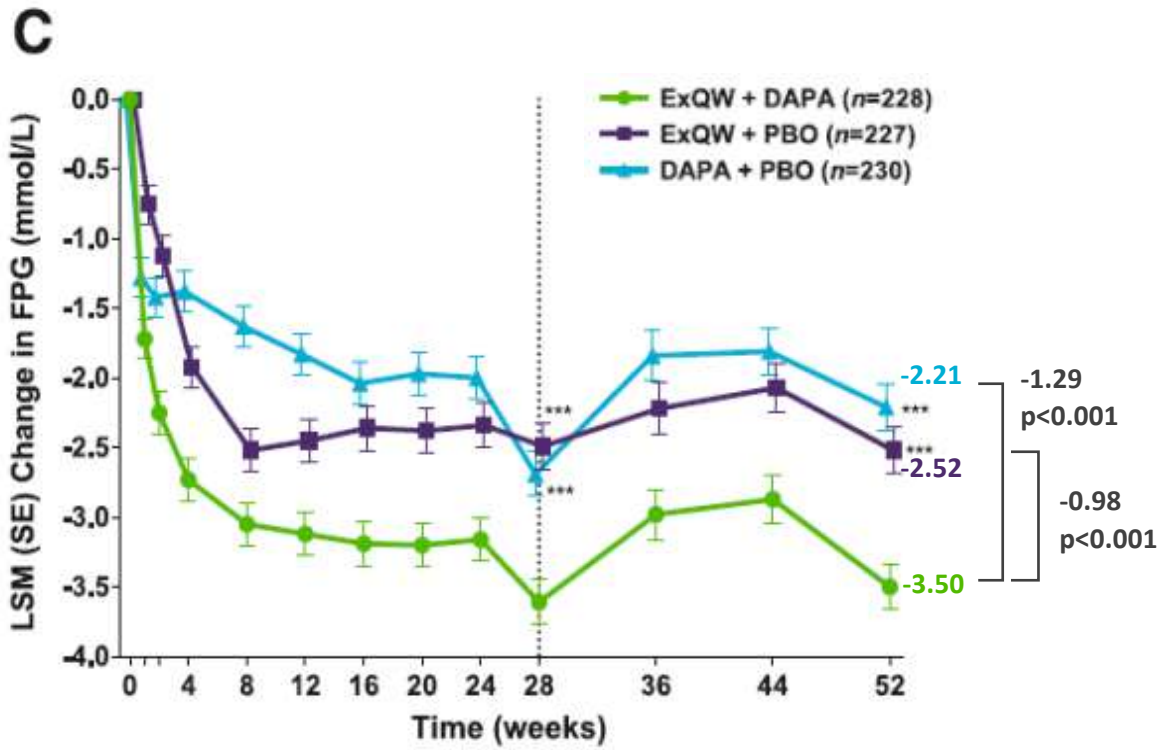

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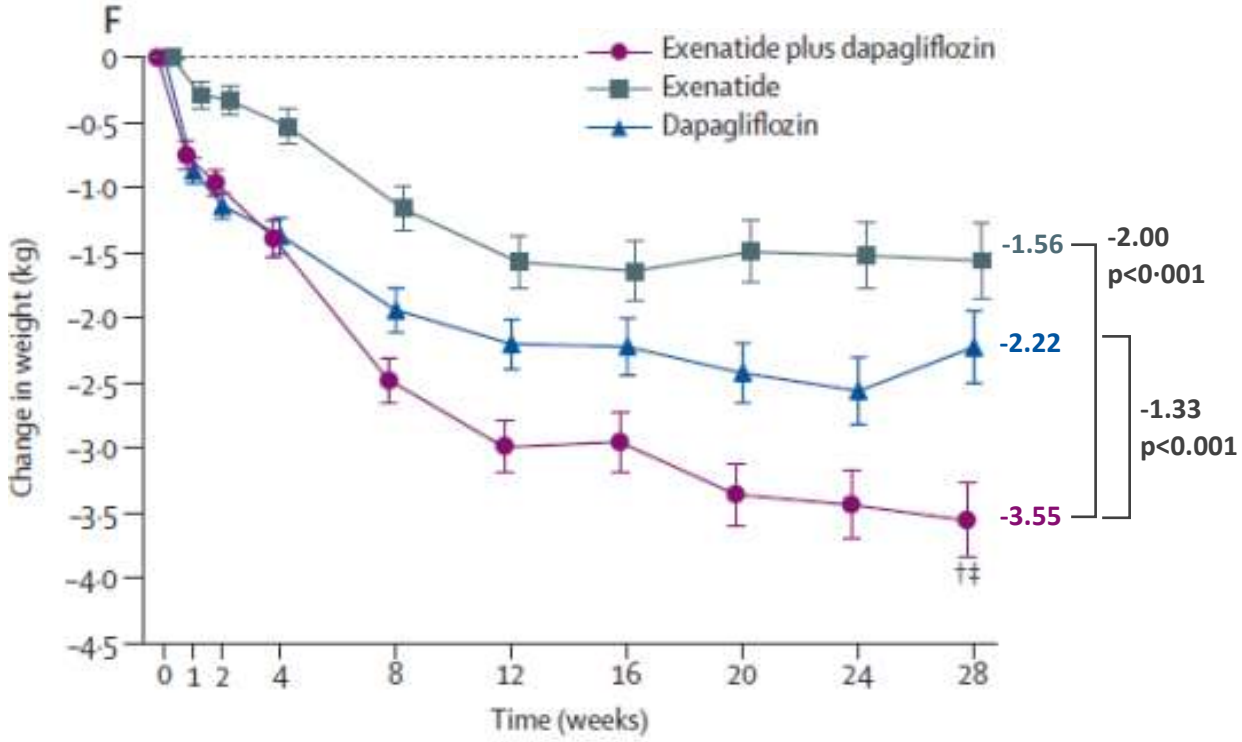

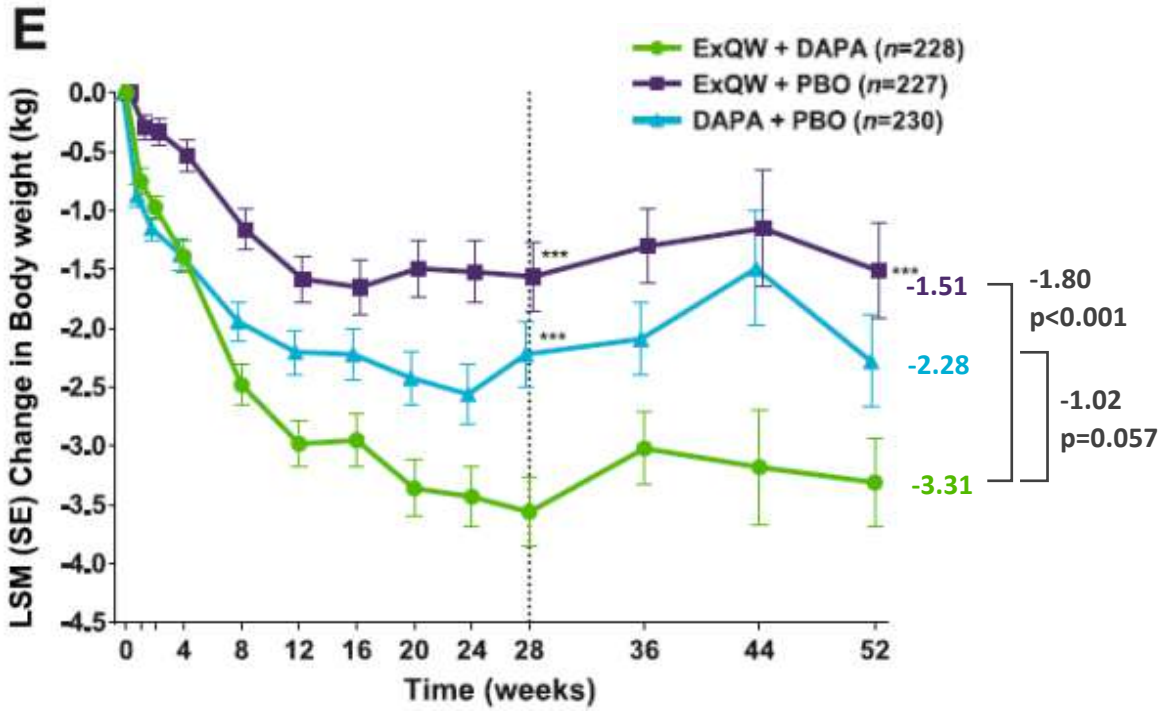

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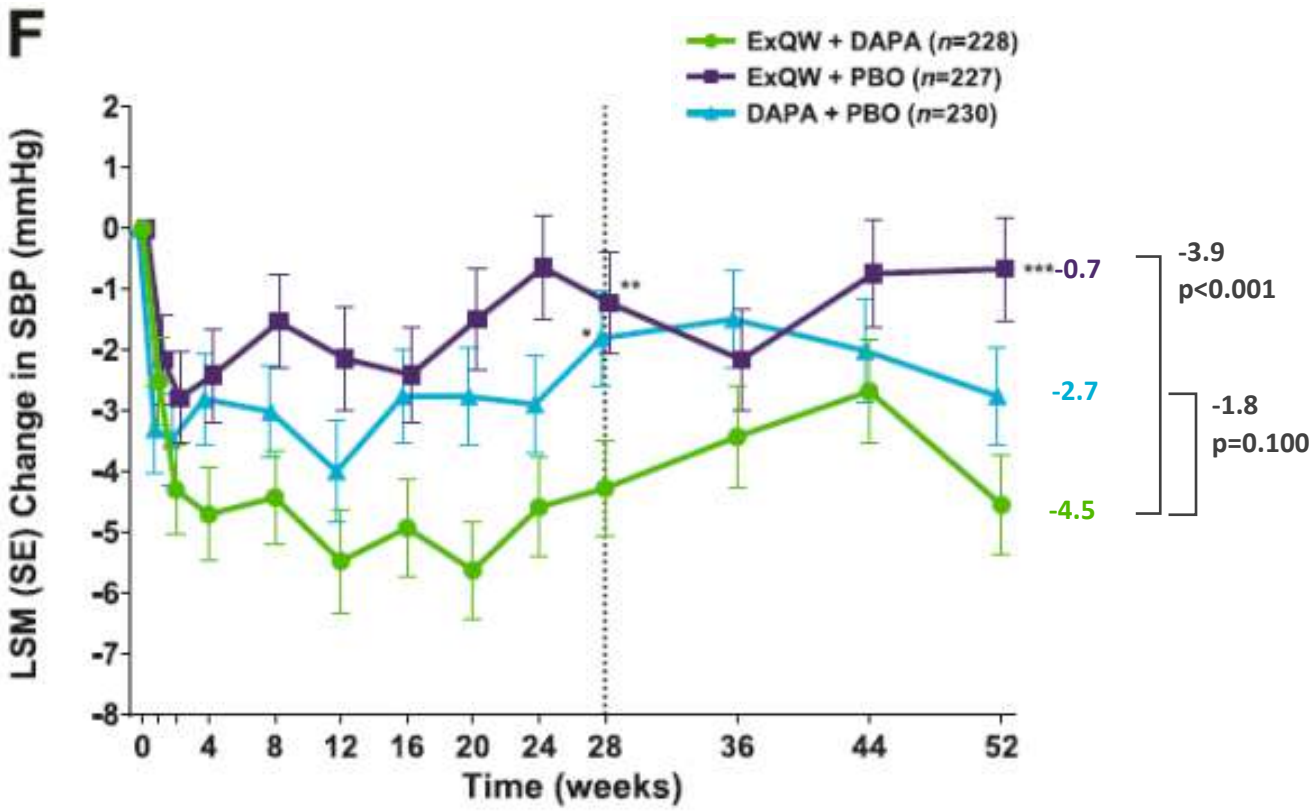

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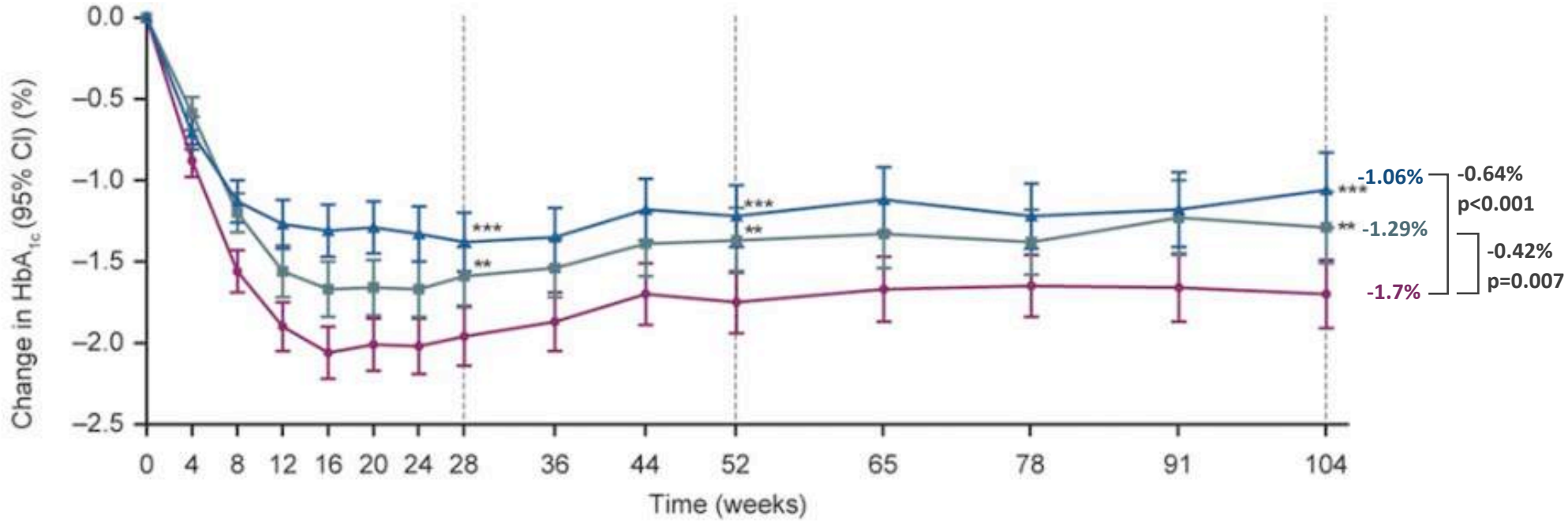
STUDI DI EFFICACIA E SICUREZZA

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



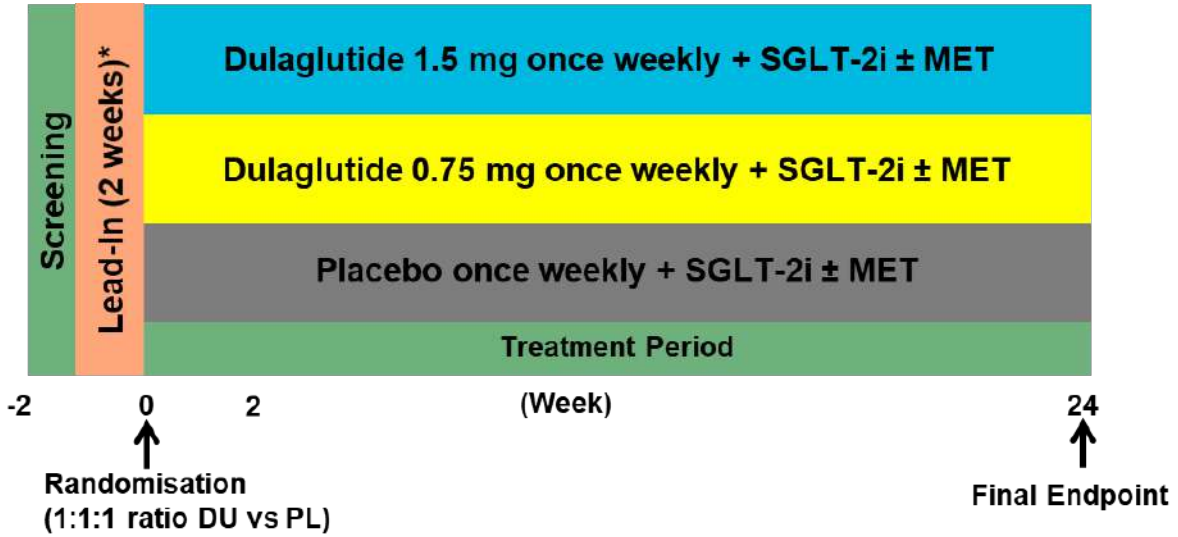
Jabbour SA et al. Diabetes Care. 2020 Oct;43(10):2528-2536.

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 ≥7.0% and ≤9.5%
  - BMI ≤45 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 ≤6.5%
- change in six-point SMBG profile
- change in fasting glucagon concentration

Exploratory Endpoints

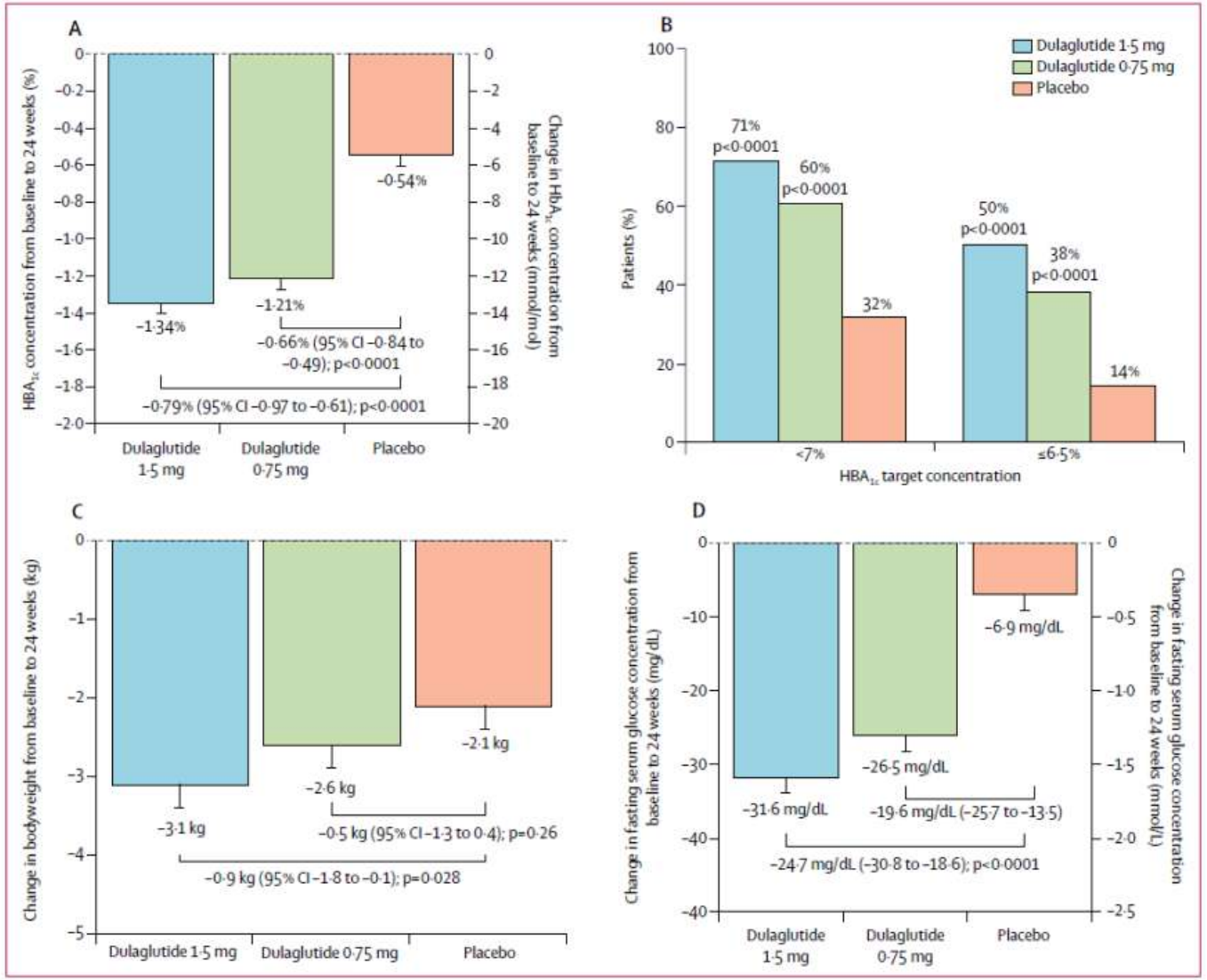
- proportion of patients with HbA1c <7.0% with no bodyweight gain and no documented symptomatic hypoglycaemia
- proportion of patients with HbA1c <7.0% with bodyweight loss >5% and no documented symptomatic hypoglycaemia

Ludvik B et al. Lancet Diabetes Endocrinol. 2018 May;6(5):370-381.

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

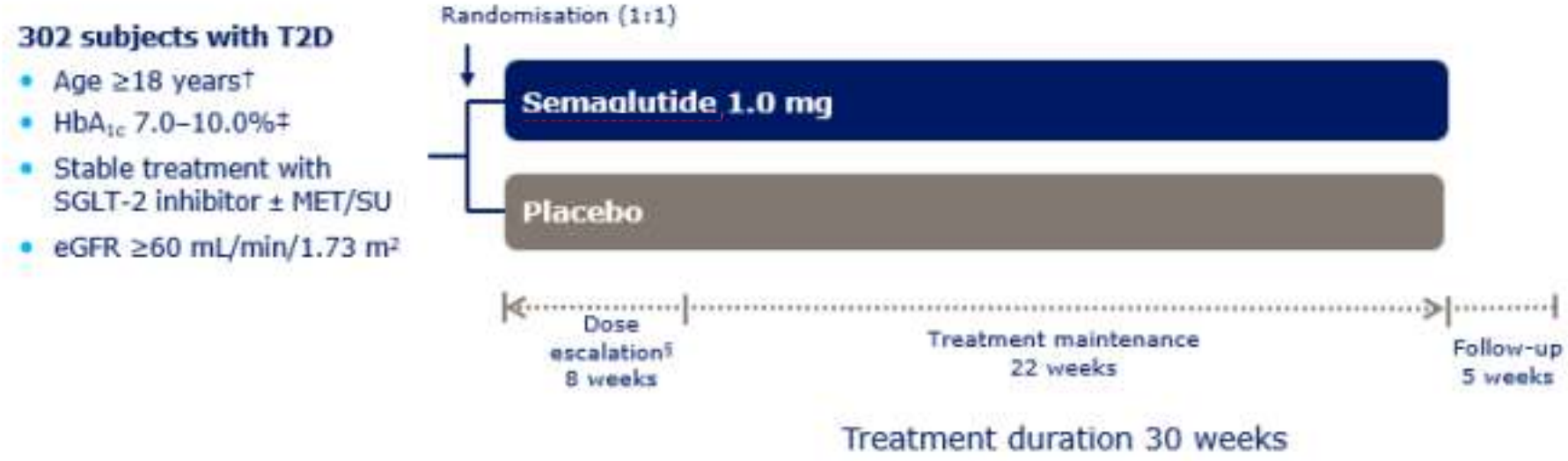


Ludvik B et al. Lancet Diabetes Endocrinol. 2018 May;6(5):370-381.

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



Primary Endpoint:

Change in HbA1c from baseline to week 30

Secondary Endpoints:

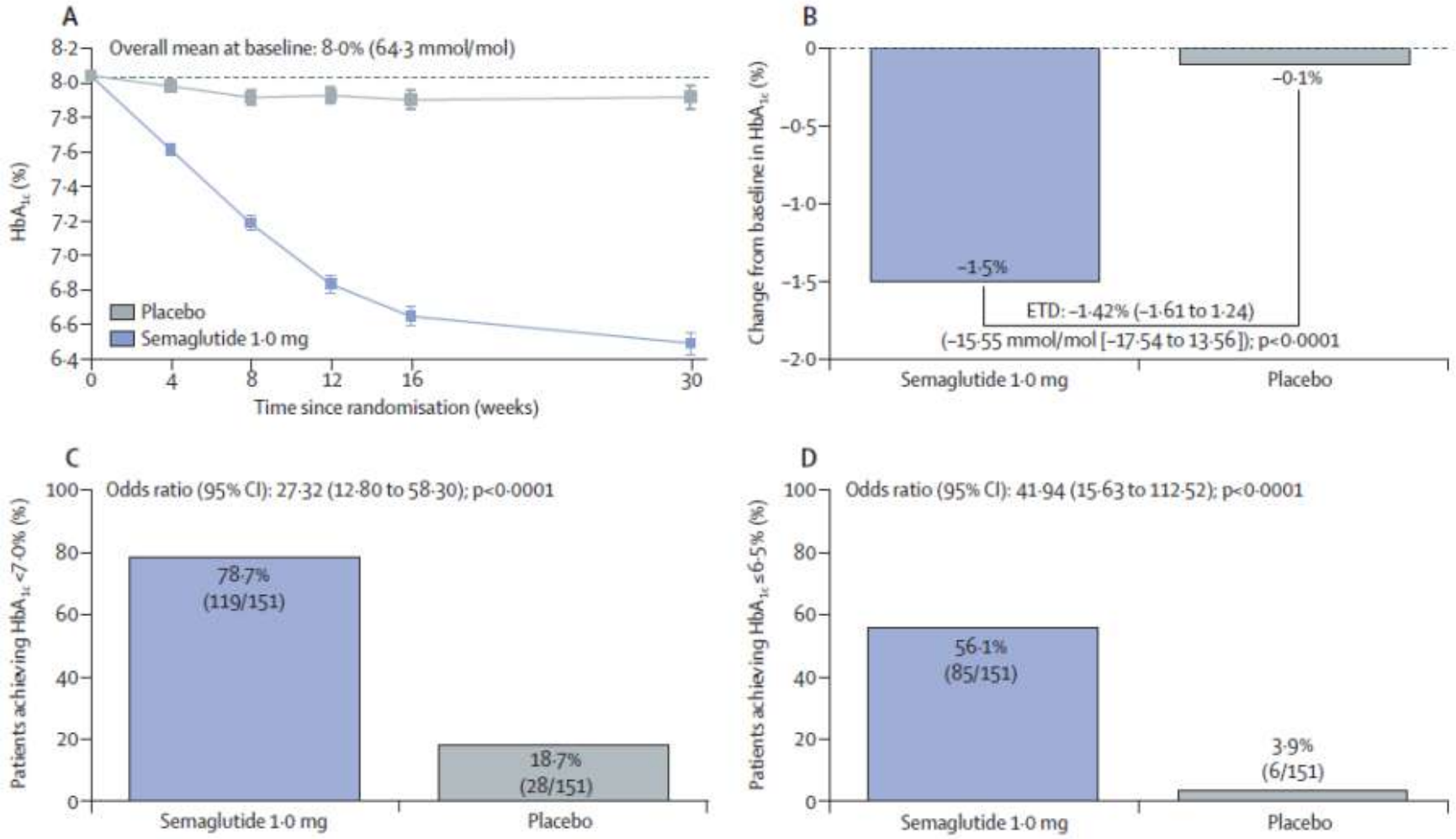
- percentage of patients achieving HbA1c <7.0%
- change in bodyweight
- change in FPG
- percentage of patients achieving HbA1c ≤6.5%
- change in seven-point SMBG profile

Zinman B et al. Lancet Diabetes Endocrinol. 2019 May;7(5):356-367.

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

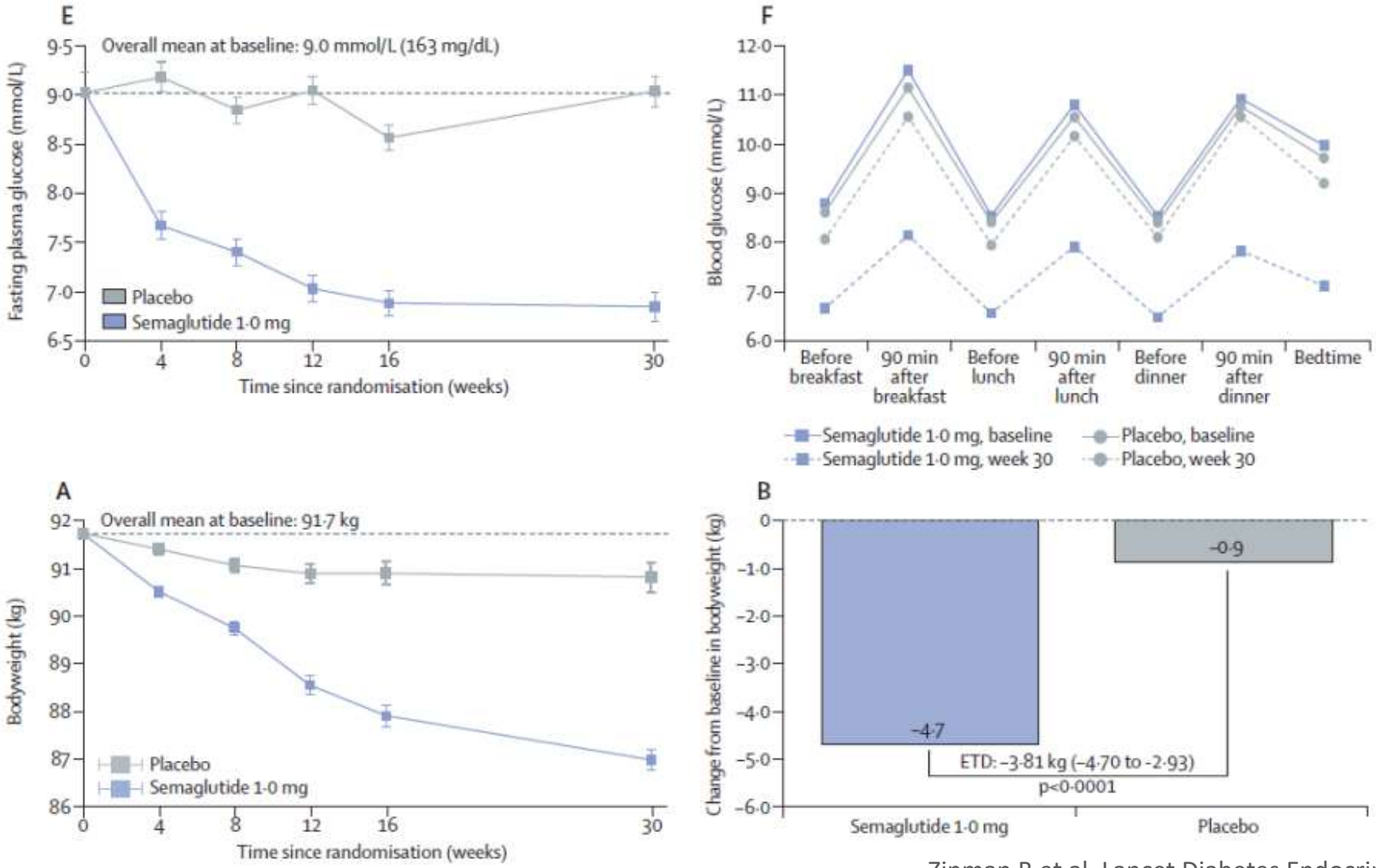


Zinman B et al. Lancet Diabetes Endocrinol. 2019 May;7(5):356-367.

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



Zinman B et al. Lancet Diabetes Endocrinol. 2019 May;7(5):356-367.

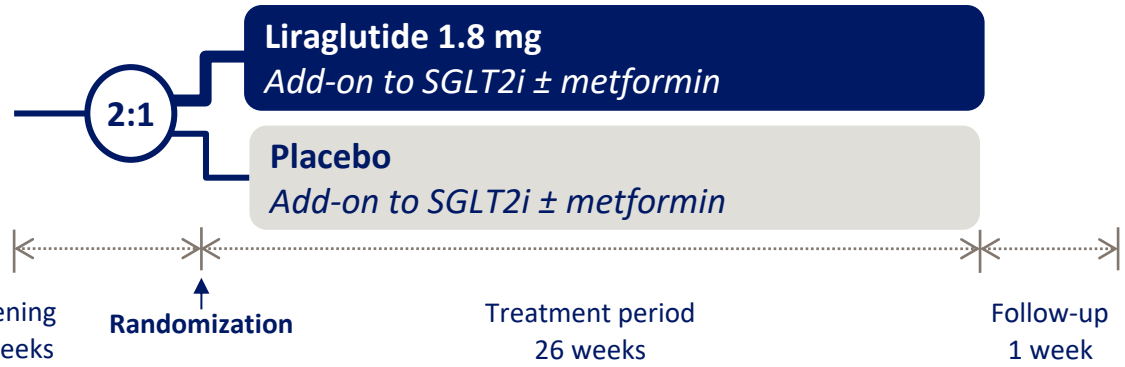
STUDI DI EFFICACIA E SICUREZZA

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 m^2



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

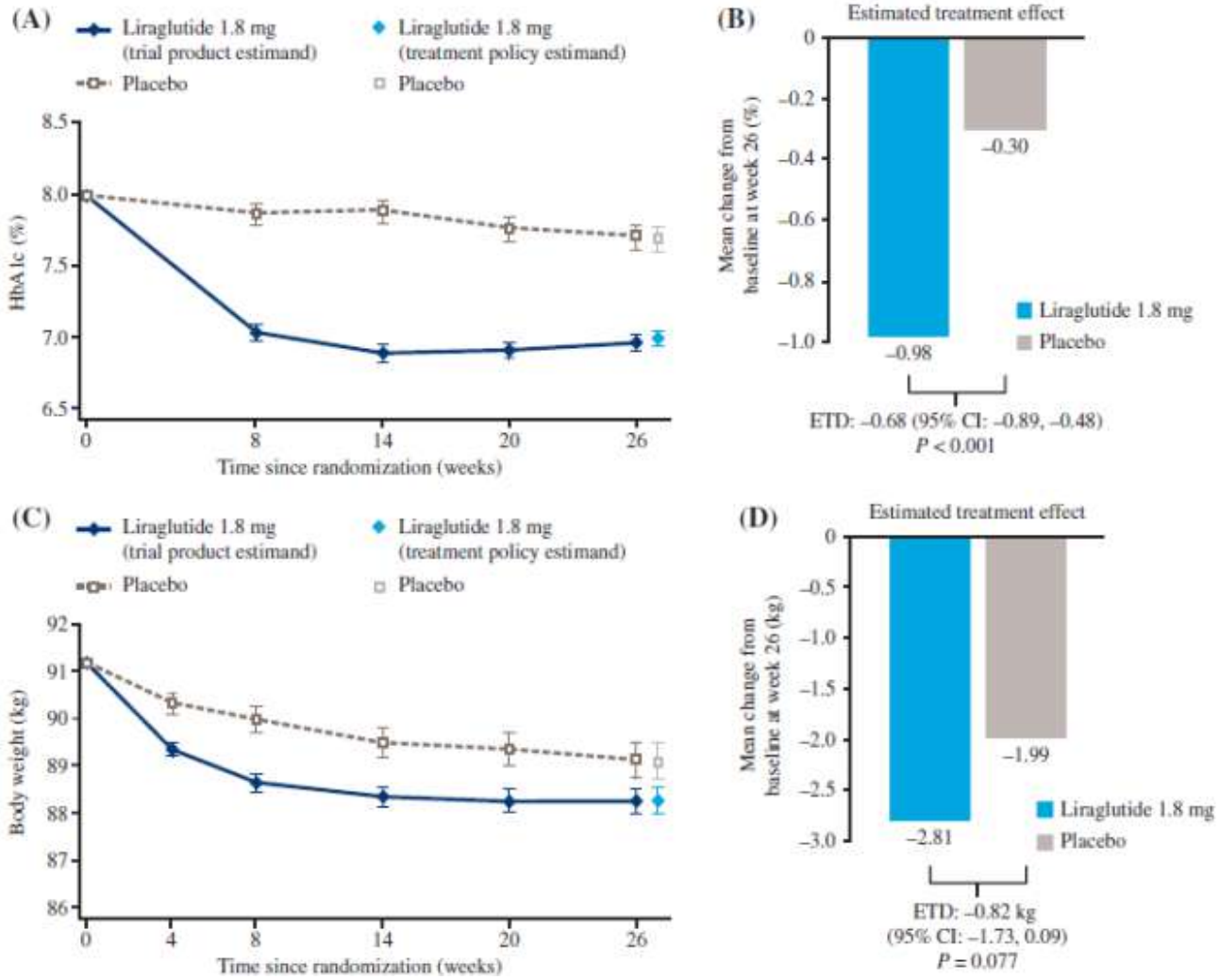
- % of patients achieving HbA1c treatment targets
- % of patients achieving body weight treatment targets
- % of patients achieving HbA1c targets without hypoglycaemia or with weight loss/no gain

Blonde L et al. Diabetes Obes Metab. 2020 Jun;22(6):929-937.

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



Blonde L et al. Diabetes Obes Metab. 2020 Jun;22(6):929-937.

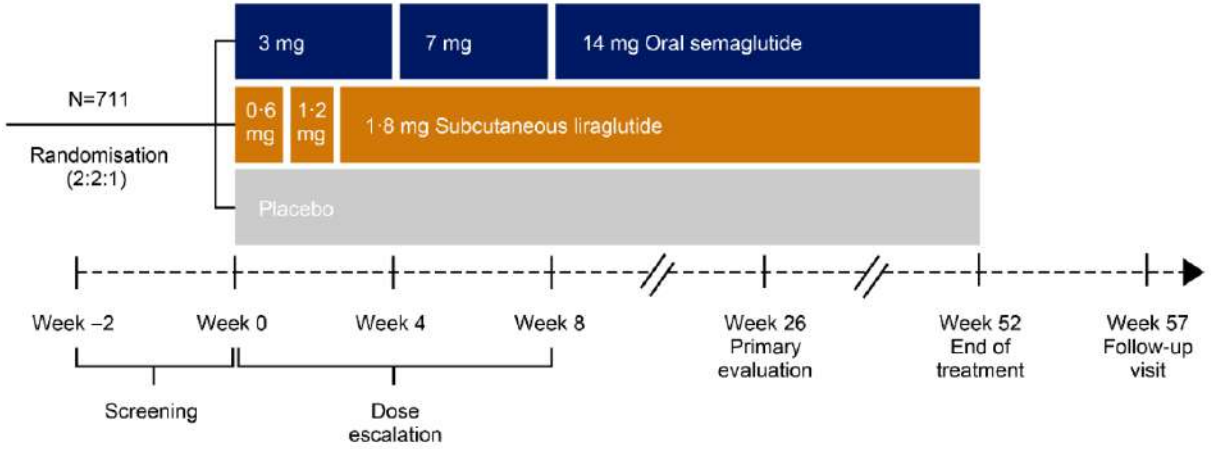
STUDI DI EFFICACIA E SICUREZZA

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 ≤7.0% or ≤6·5%
- % of patients achieving weight loss of 5% or more or 10% or mor

Pratley R et al. Diabetes 2020;69(Supplement_1):927-P

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

Key results

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

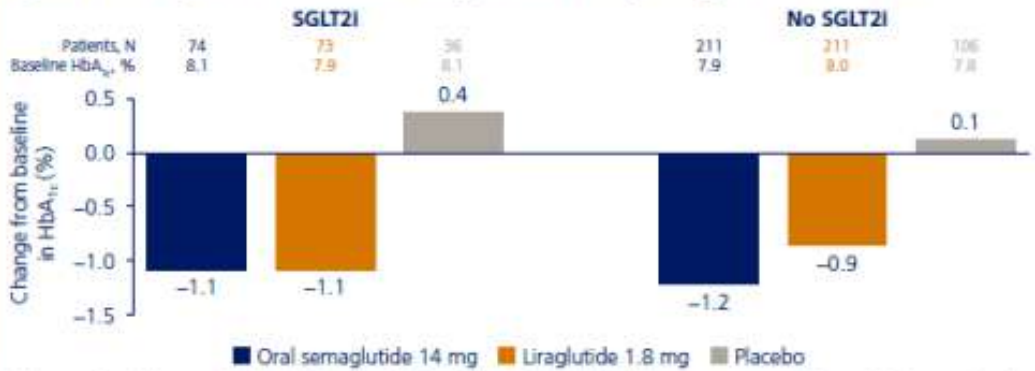
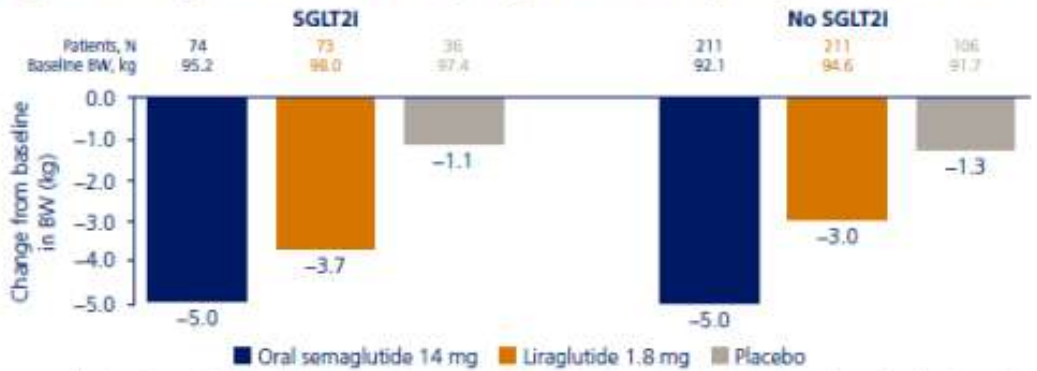


Figure 2: Change from baseline in body weight at week 52 by background SGLT2i use



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.

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.

Pratley R et al. Diabetes 2020;69(Supplement_1):927-P

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

CANVAS

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

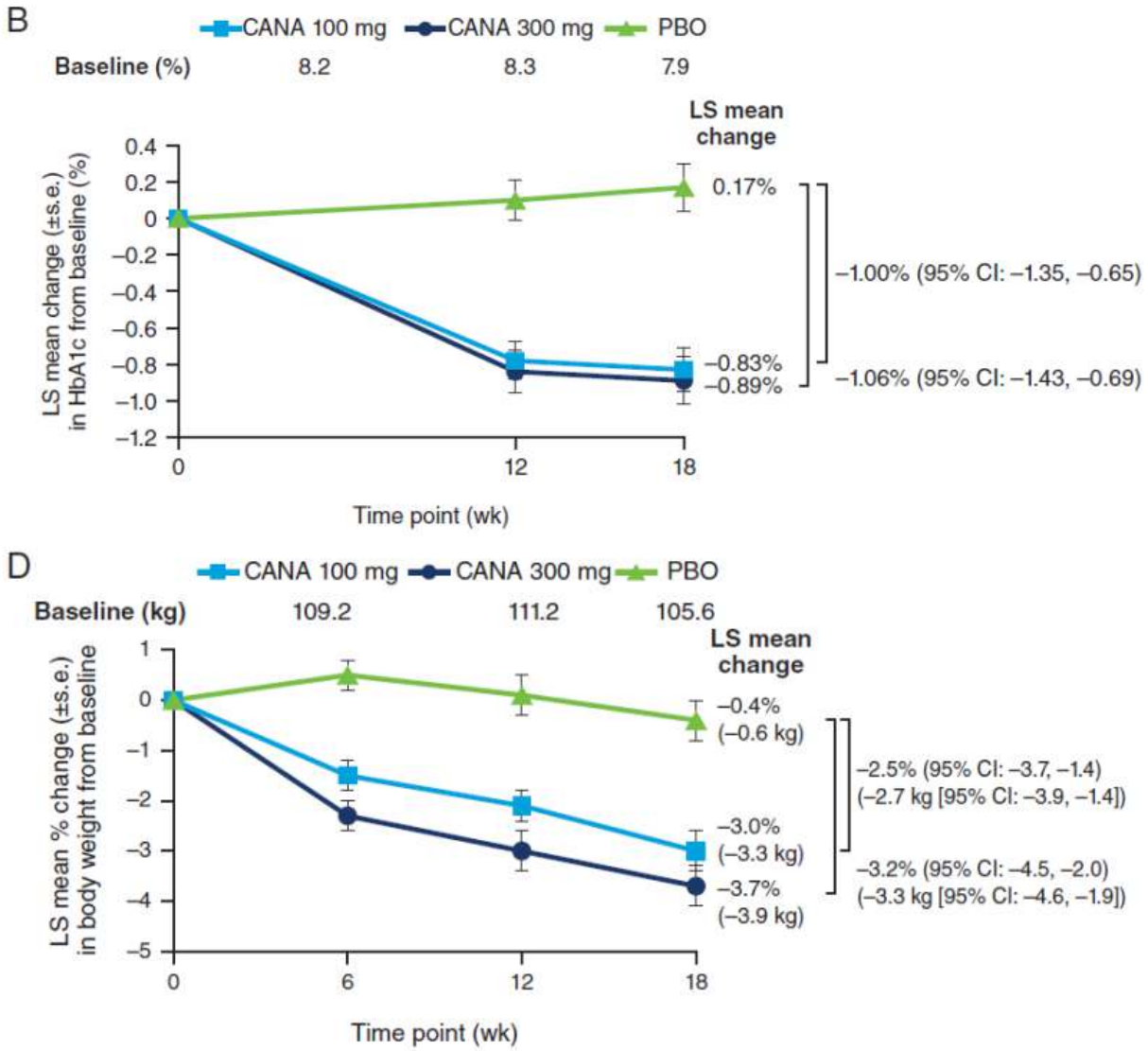
DPP-4 inhibitor subset			GLP-1 receptor agonist subset		
CANA 100 mg (n = 103)	CANA 300 mg (n = 111)	PBO (n = 102)	CANA 100 mg (n = 35)	CANA 300 mg (n = 30)	PBO (n = 30)

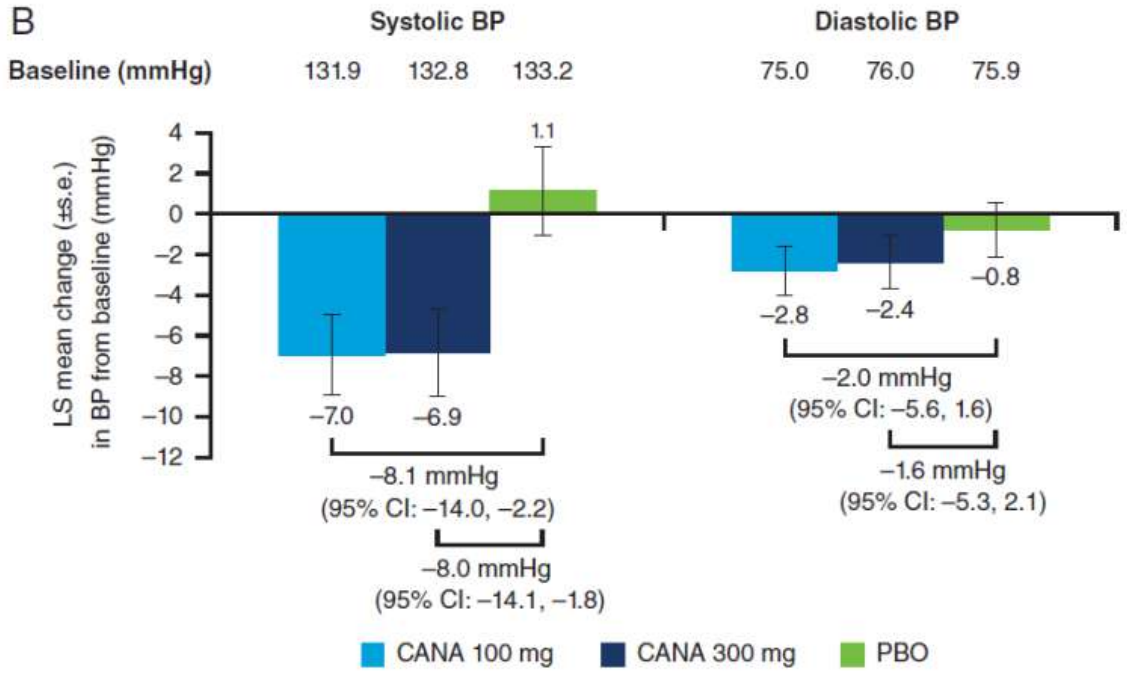
Fulcher G al. Diabetes Obes Metab. 2016 Jan;18(1):82-91.

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





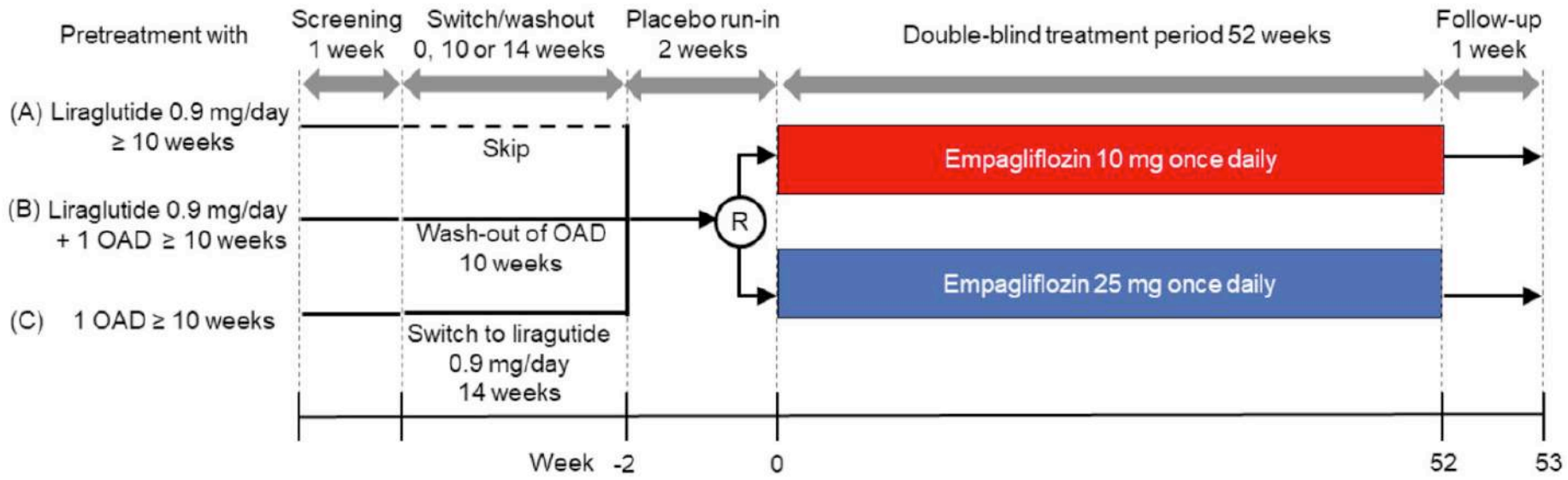
Fulcher G al. Diabetes Obes Metab. 2016 Jan;18(1):82-91.

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

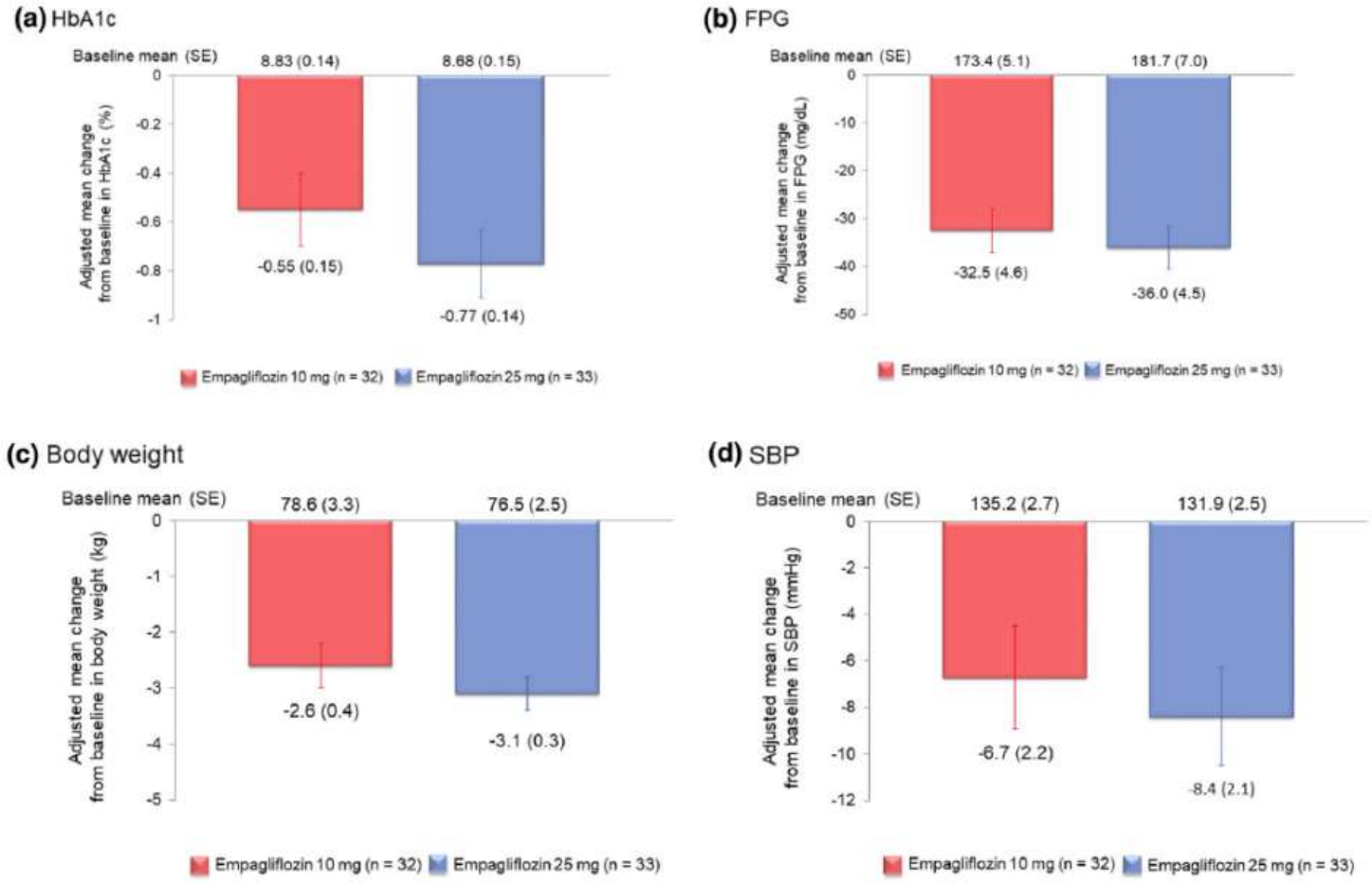


Terauchi Y et al. Diabetes Ther. 2019 Jun;10(3):951-963.

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



- 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.

Terauchi Y et al. Diabetes Ther. 2019 Jun;10(3):951-963.

STUDI DI EFFICACIA E SICUREZZA

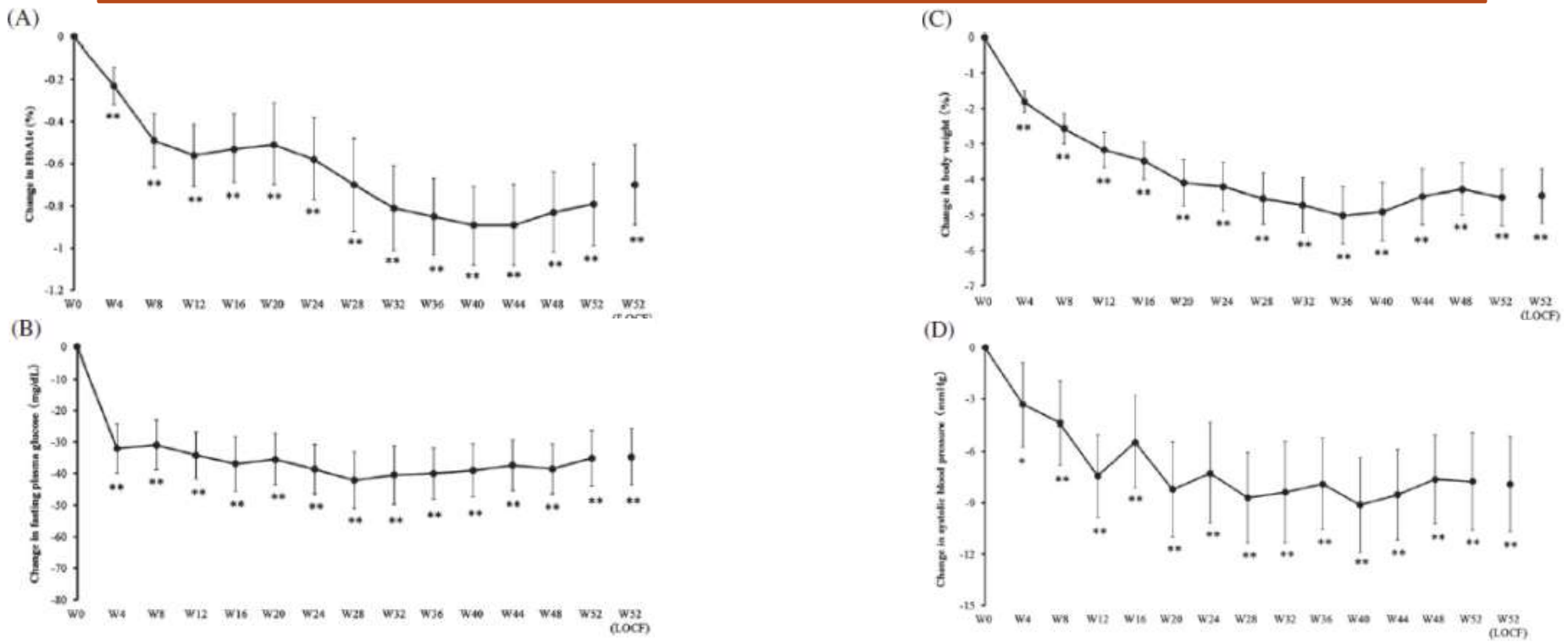
Efficacy and safety of canagliflozin as add-on therapy to a glucagon-like peptide-1 receptor agonist in Japanese patients with type 2 diabetes mellitus: A 52-week, open-label, phase IV study

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.

Harashima SI al. Diabetes Obes Metab. 2018 Jul;20(7):1770-1775.

STUDI DI EFFICACIA E SICUREZZA

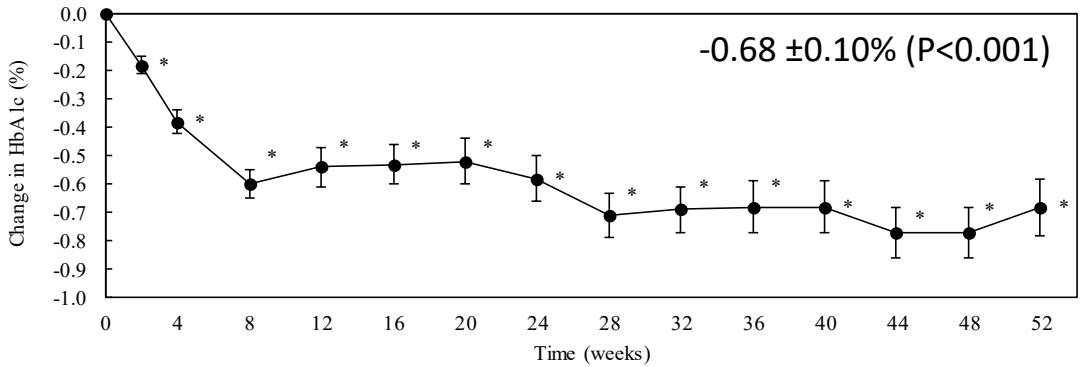
Sodium-glucose cotransporter-2 inhibitor luseogliflozin added to glucagon-like peptide1 receptor agonist liraglutide improves glycemic control with bodyweight and fat mass reductions in Japanese patients with type 2 diabetes: A 52-week, open-label, single-arm study

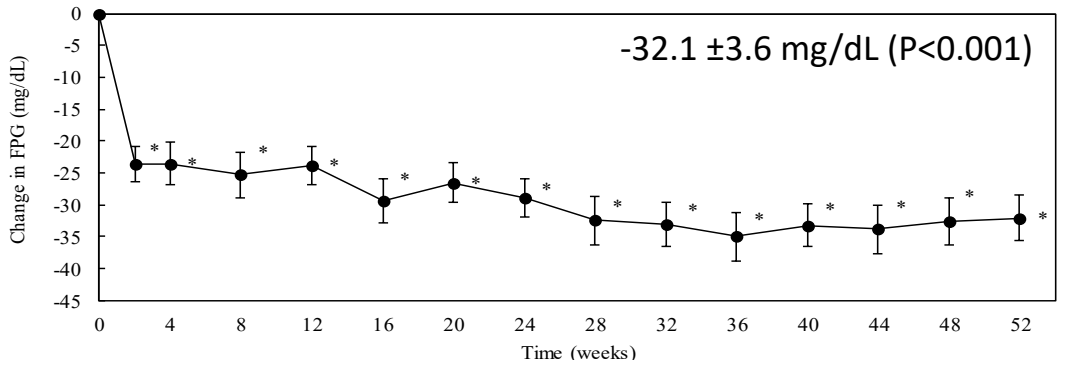
SGLT2i su GLP1RA

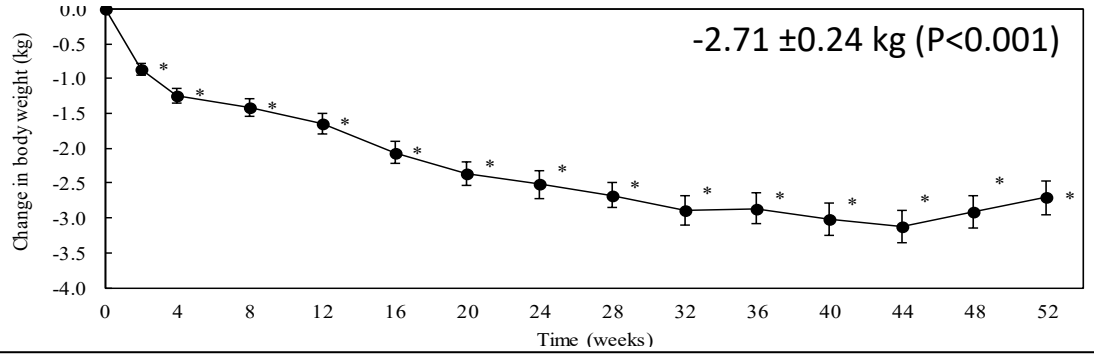
TRIAL DESIGN

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.

Seino Y et al. J Diabetes Investig. 2018 Mar;9(2):332-340.

STUDI DI EFFICACIA E SICUREZZA – REAL WORLD

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

dmj DIABETES & METABOLISM JOURNAL

Check for updates

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,*], 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

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, MD[1]; Rocío Villar-Taibo, MD, PhD[2]; Mildred Sifontes-Dubón, MD[3]; Hector Mozo-Peñalver, PharmD[4]; Ignacio Bernabeu-Morón, MD, PhD[2]; José M. Cabezas-Agrícola, MD[2]; Virginia Muñoz-Leira, MD[2]; Roberto Peinó-García, MD, PhD[2]; Aurelio Martís-Sueiro, MD[2]; José M. García-Ló MD, PhD[2]; and Miguel A. Martínez-Olmos, MD, PhD[2]

- Simultan combination SGLT2i/GLP1 RA led to r decrease in HbA1c than when they

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

he combination therapy were observed in patients short (<10 years) and along (>10 years) evolution of their diabetes

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

ELSEVIER

DIABETES CANADA

CJD

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 Lorido 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, *n*	Comparator arm	*N*	ΔHbA1c (%), (95%CI)	ΔWeight (kg), (95%CI)	ΔSBP (mmHg), (95%CI)	Adverse events (GI, GTI, Hypo's) with SGLT-2I + GLP-1RA *vs* SGLT-2I
Zhou *et al* [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 *et al*[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
Patoulias *et al* [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 *et al* [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

Singh AK et al. World J Cardiol. 2022 Jun 26;14(6):329-342.

STUDI DI EFFICACIA E SICUREZZA – META ANALISI

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)
Frías *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
Frías *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
Frías *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

HbA1c — *Less than additive*

Body weight — *Almost additive*

SBP — *More than additive*

Singh AK et al. World J Cardiol. 2022 Jun 26;14(6):329-342.

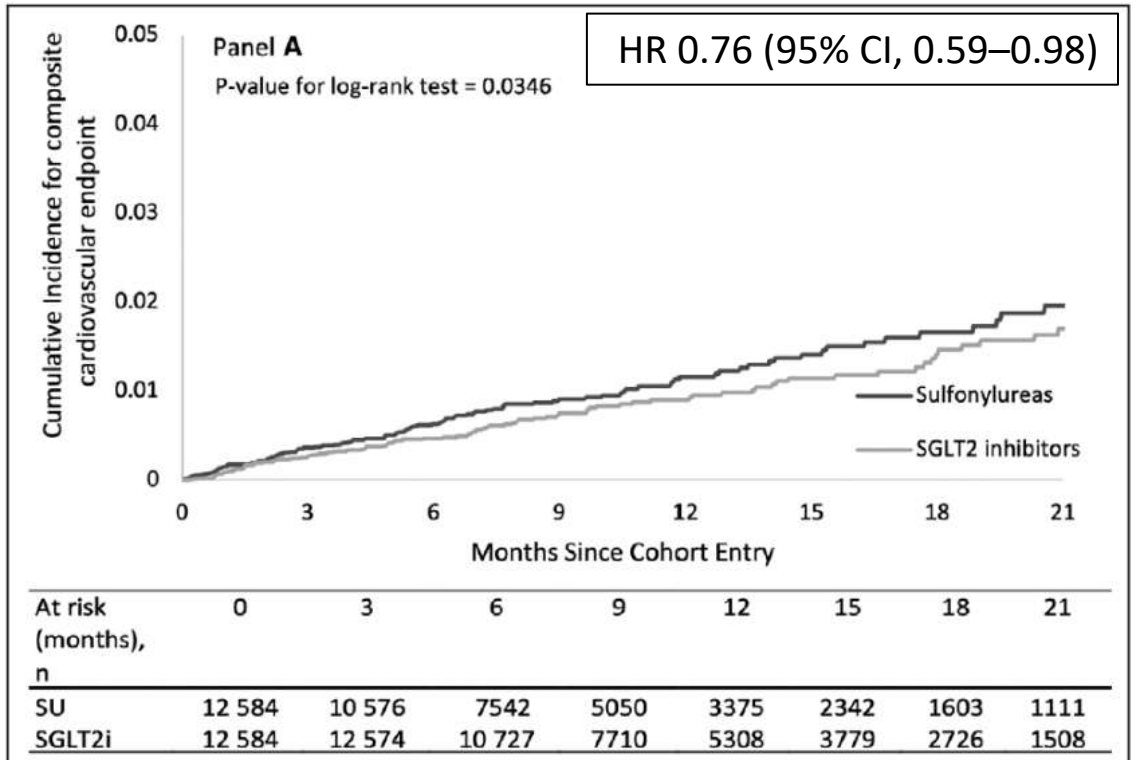
AGENDA

- **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

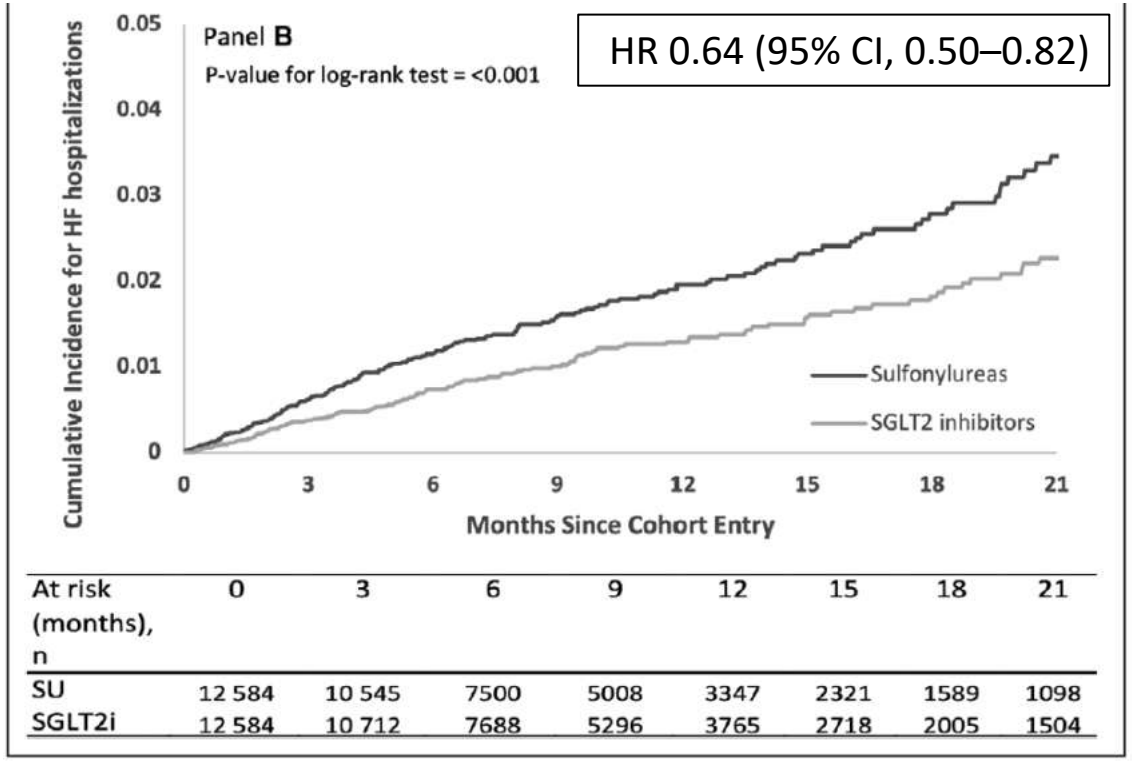
Risk of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Addition of SGLT2 Inhibitors Versus Sulfonylureas to Baseline GLP-1RA Therapy

SGLT2i su GLP1RA



At risk (months), n	0	3	6	9	12	15	18	21
SU	12 584	10 576	7542	5050	3375	2342	1603	1111
SGLT2i	12 584	12 574	10 727	7710	5308	3779	2726	1508

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



At risk (months), n	0	3	6	9	12	15	18	21
SU	12 584	10 545	7500	5008	3347	2321	1589	1098
SGLT2i	12 584	10 712	7688	5296	3765	2718	2005	1504

HF hospitalizations

Dave VC et al. Circulation. 2021 Feb 23;143(8):770-779.

STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – CVOT

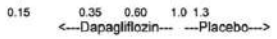
Cardiorenal outcomes with dapagliflozin by baseline glucose-lowering agents: Post hoc analyses from **DECLARE-TIMI 58**

N=750

CV Death/hHF

(A)

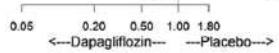
Subgroups	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	*P*-value	*P*-interaction
Overall	417/8582 (4.9%)	496/8578 (5.8%)	0.83 (0.73, 0.95)	.0027	
Baseline metformin					
Yes	293/7020 (4.2%)	362/7048 (5.1%)	0.81 (0.69, 0.94)	.0063	.5603
No	124/1562 (7.9%)	134/1530 (8.8%)	0.88 (0.69, 1.12)	.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	



hHF

(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	



Cahn A et al. Diabetes Obes Metab. 2021 Jan;23(1):29-38.

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

MACE

Subgroups	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	*P*-value	*P*-interaction
Overall	756/8582 (8.8%)	803/8578 (9.4%)	0.93 (0.84, 1.03)	.1723	
Baseline metformin					
Yes	584/7020 (8.3%)	613/7048 (8.7%)	0.96 (0.85, 1.07)	.4284	.3596
No	172/1562 (11.0%)	190/1530 (12.4%)	0.86 (0.70, 1.05)	.1376	
Baseline sulphonylureas					
Yes	297/3615 (8.2%)	324/3707 (8.7%)	0.94 (0.80, 1.10)	.4558	.8663
No	459/4967 (9.2%)	479/4871 (9.8%)	0.93 (0.81, 1.05)	.2341	
Baseline DPP-4 inhibitors					
Yes	91/1418 (6.4%)	105/1470 (7.1%)	0.94 (0.71, 1.24)	.6630	.9848
No	665/7164 (9.3%)	698/7108 (9.8%)	0.93 (0.84, 1.03)	.1750	
Baseline GLP-1 receptor agonists					
Yes	31/397 (7.8%)	31/353 (8.8%)	0.87 (0.53, 1.43)	.5838	.8369
No	725/8185 (8.9%)	772/8225 (9.4%)	0.94 (0.85, 1.04)	.1981	
Baseline insulin					
Yes	389/3567 (10.9%)	433/3446 (12.6%)	0.84 (0.74, 0.97)	.0151	.0586
No	367/5015 (7.3%)	370/5132 (7.2%)	1.02 (0.89, 1.18)	.7606	

Cahn A et al. Diabetes Obes Metab. 2021 Jan;23(1):29-38.

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

Subgroups	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	*P*-value	*P*-interaction
Overall	127/8582 (1.5%)	238/8578 (2.8%)	0.53 (0.43, 0.66)	<.0001	
Baseline metformin					
Yes	97/7020 (1.4%)	200/7048 (2.8%)	0.48 (0.38, 0.61)	<.0001	.0946
No	30/1562 (1.9%)	38/1530 (2.5%)	0.76 (0.47, 1.23)	.2680	
Baseline sulphonylureas					
Yes	44/3615 (1.2%)	94/3707 (2.5%)	0.48 (0.33, 0.68)	<.0001	.4980
No	83/4967 (1.7%)	144/4871 (3.0%)	0.56 (0.43, 0.73)	<.0001	
Baseline DPP-4 inhibitors					
Yes	21/1418 (1.5%)	36/1470 (2.4%)	0.62 (0.36, 1.06)	.0826	.5679
No	106/7164 (1.5%)	202/7108 (2.8%)	0.51 (0.41, 0.65)	<.0001	
Baseline GLP-1 receptor agonists					
Yes	4/397 (1.0%)	10/353 (2.8%)	0.38 (0.11, 1.15)	.0838	.4894
No	123/8185 (1.5%)	228/8225 (2.8%)	0.54 (0.43, 0.67)	<.0001	
Baseline insulin					
Yes	67/3567 (1.9%)	113/3446 (3.3%)	0.57 (0.42, 0.77)	.0003	.4844
No	60/5015 (1.2%)	125/5132 (2.4%)	0.49 (0.36, 0.66)	<.0001	

New onset albuminuria

Subgroups	Dapagliflozin n/N (%)	Placebo n/N (%)	Hazard ratio (95% CI)	*P*-value	*P*-interaction
Overall	772/5819 (13.3%)	959/5825 (16.5%)	0.79 (0.72, 0.87)	<.0001	
Baseline metformin					
Yes	641/4782 (13.4%)	803/4819 (16.7%)	0.79 (0.71, 0.87)	<.0001	.9169
No	131/1037 (12.6%)	156/1006 (15.5%)	0.80 (0.63, 1.01)	.0568	
Baseline sulphonylureas					
Yes	334/2477 (13.5%)	458/2556 (17.9%)	0.74 (0.64, 0.85)	<.0001	.1694
No	438/3342 (13.1%)	501/3269 (15.3%)	0.84 (0.74, 0.96)	.0081	
Baseline DPP-4 inhibitors					
Yes	137/1008 (13.6%)	174/1007 (17.3%)	0.77 (0.62, 0.97)	.0246	.8573
No	635/4811 (13.2%)	785/4818 (16.3%)	0.79 (0.71, 0.88)	<.0001	
Baseline GLP-1 receptor agonists					
Yes	39/254 (15.4%)	43/244 (17.6%)	0.86 (0.56, 1.33)	.4923	.6927
No	733/5565 (13.2%)	916/5581 (16.4%)	0.79 (0.71, 0.87)	<.0001	
Baseline insulin					
Yes	326/2211 (14.7%)	413/2110 (19.6%)	0.73 (0.63, 0.85)	<.0001	.1995
No	446/3608 (12.4%)	546/3715 (14.7%)	0.83 (0.73, 0.94)	.0031	

Cahn A et al. Diabetes Obes Metab. 2021 Jan;23(1):29-38.

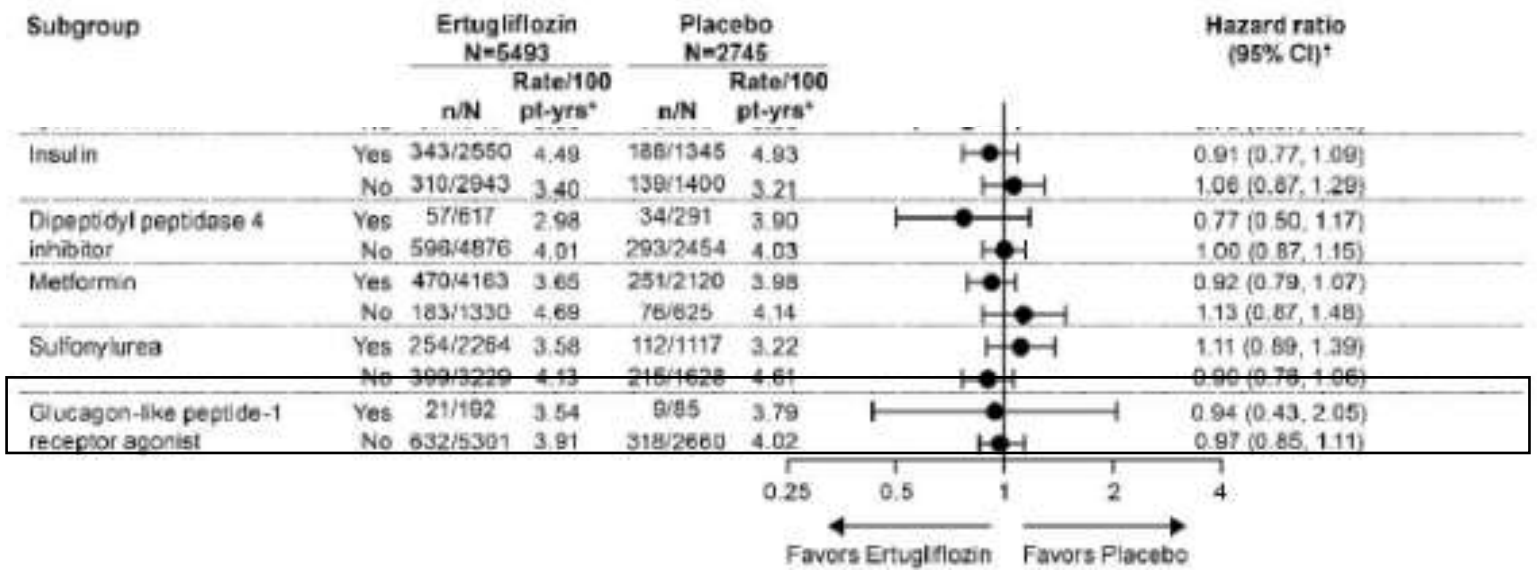
STUDI DI OUTCOME CARDIOVASCOLARE E RENALE – CVOT

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

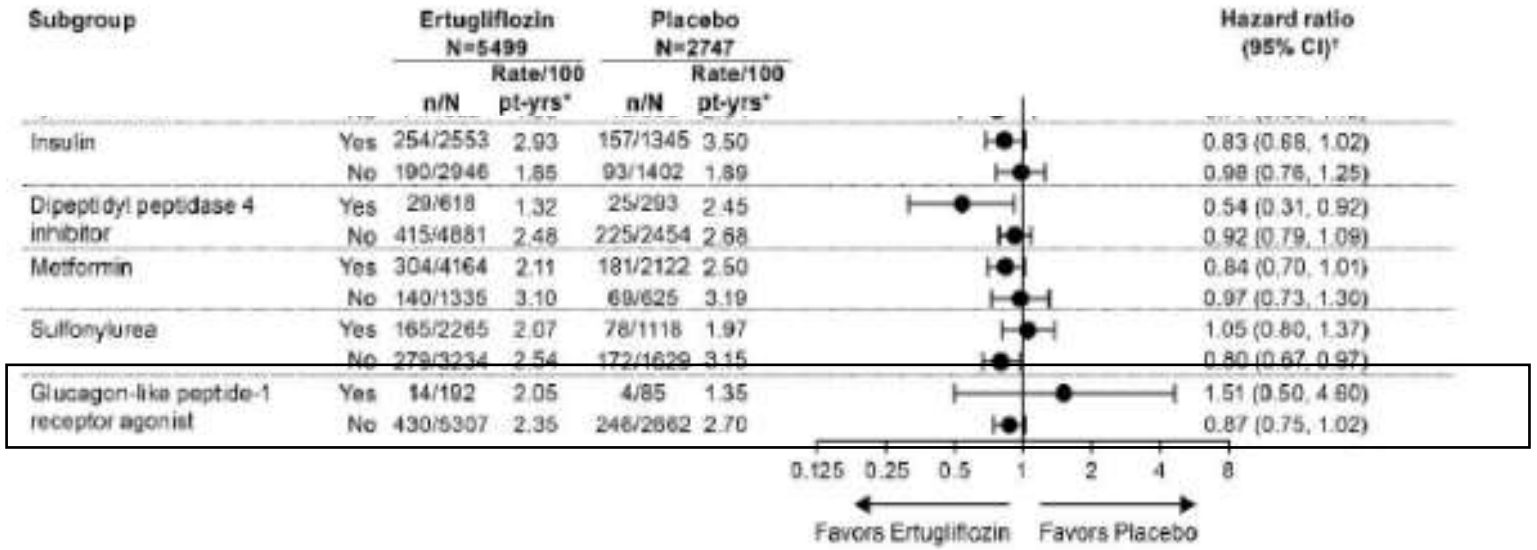
VERTIS CV

N=277

MACE



CV Death/hHF



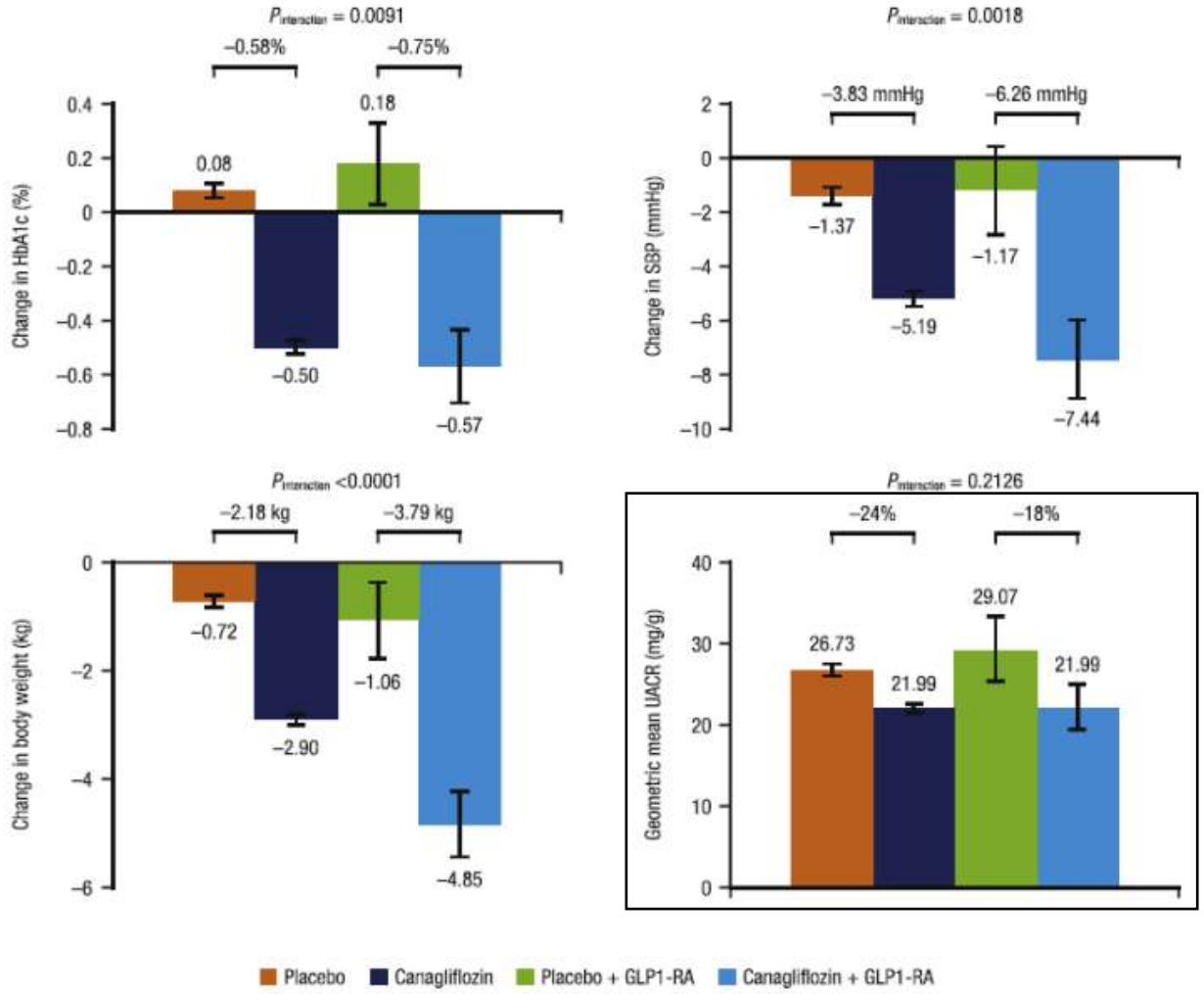
Cannon PC et al. N Engl J Med. 2020 Oct 8;383(15):1425-1435.

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**

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

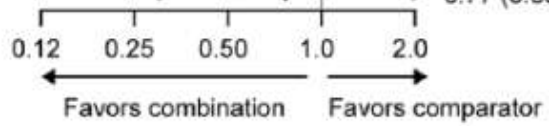
Arnott C et al. Int J Cardiol. 2020 Nov 1;318:126-129.

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

EXSCEL

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)



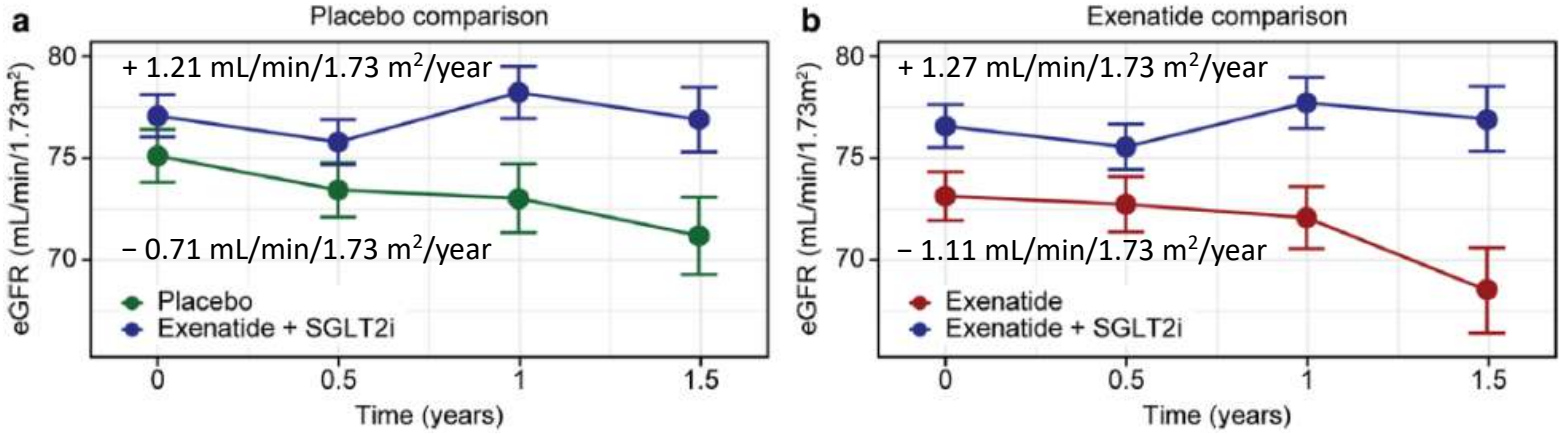
hHF:	vs placebo	HR 0.98 (0.28-3.45)
	vs exenatide	HR 0.51 (0.18-1.48)
hHF+CV Death:	vs placebo	HR 0.41 (0.17-0.98)
	vs exenatide	HR 0.41 (0.17-0.95)

Clegg LE et al. Cardiovasc Diabetol. 2019 Oct 22;18(1):138.

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

EXSCEL



estimated treatment effect:
+ 1.94 mL/min/1.73 m^2/year ($p < 0.001$)

estimated treatment effect:
+ 2.38 mL/min/1.73 m^2/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):

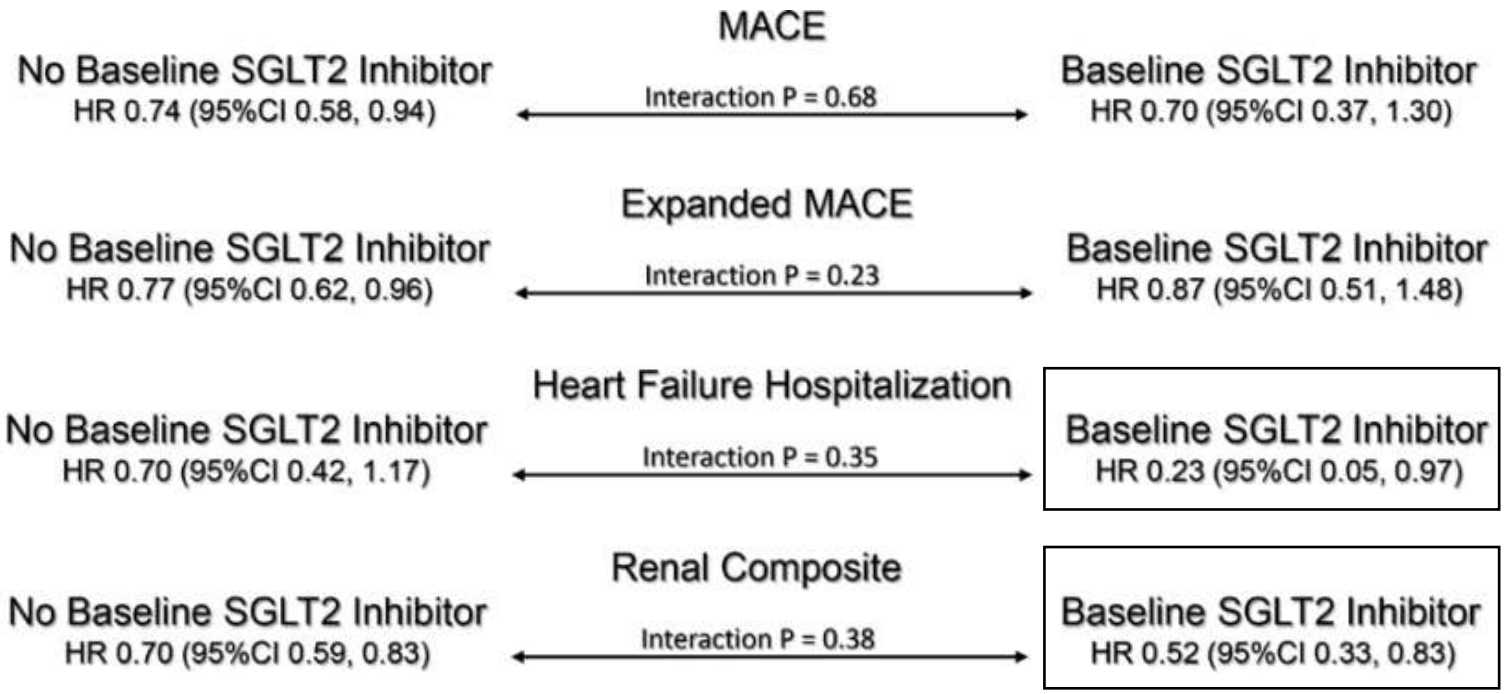
vs placebo	HR 0.42 (0.15-1.22)
vs exenatide	HR 0.39 (0.14-1.09)

Clegg LE et al. Cardiovasc Diabetol. 2019 Oct 22;18(1):138.

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%)



Lam CSP et al. Circulation. 2022 Feb 22;145(8):565-574.

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 ≥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]

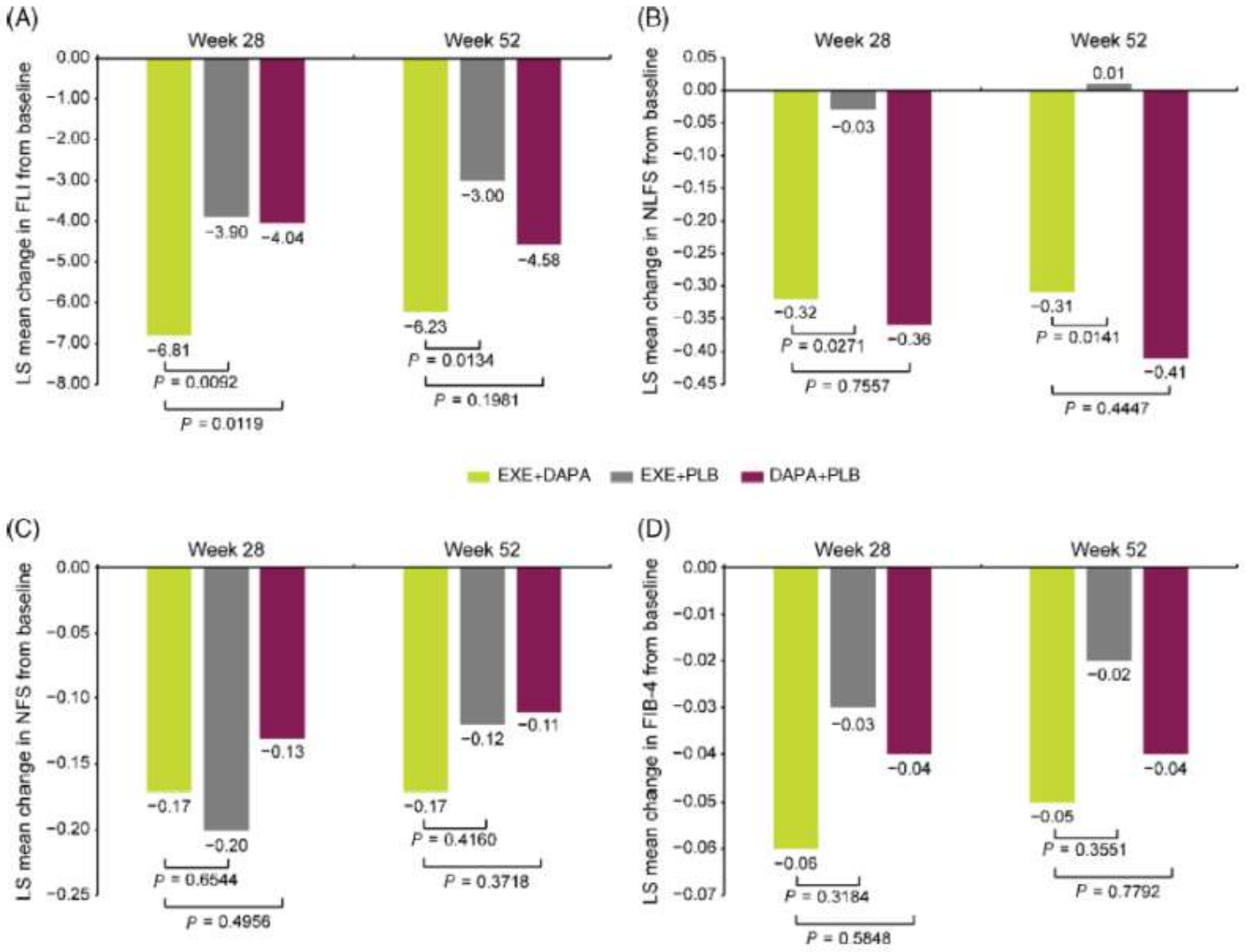
https://www.clinicaltrials.gov/ct2/show/record/NCT05390892

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

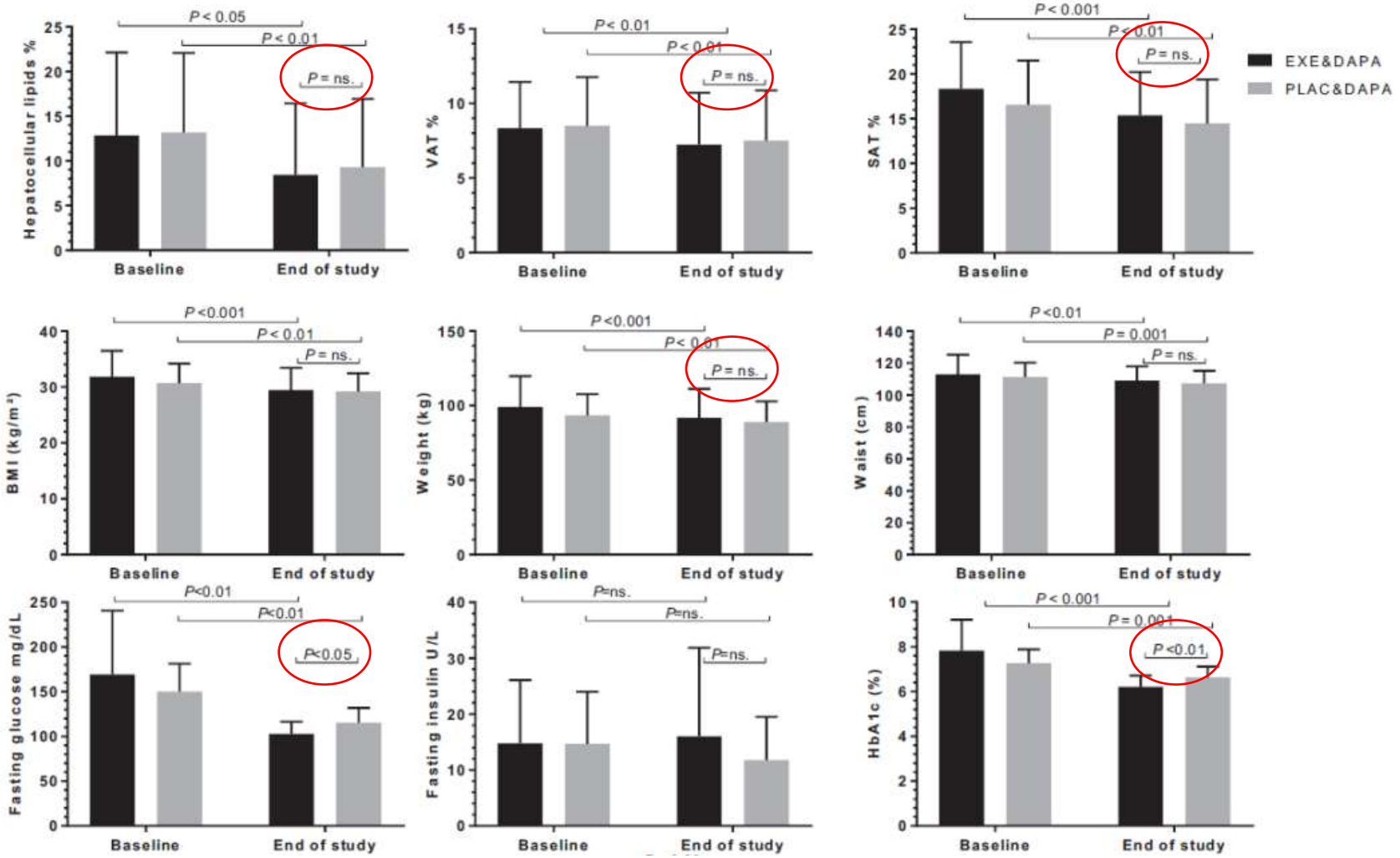


Gastaldelli A et al. Diabetes Obes Metab. 2020 Mar;22(3):393-403.

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



Harreiter J et al. Diabetes Obes Metab. 2021 May;23(5):1129-1139.

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)
- <u>Nota 100</u>

QUANDO

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

PERCHÉ

PERCHÉ NO?