Simposio AziendaleJanssenCilag

Gli inibitori SGLT2: nuovi obiettivi e nuovi traguardi nel trattamento del diabete di tipo 2

A chi, come e quando somministrare un inibitore SGLT2?

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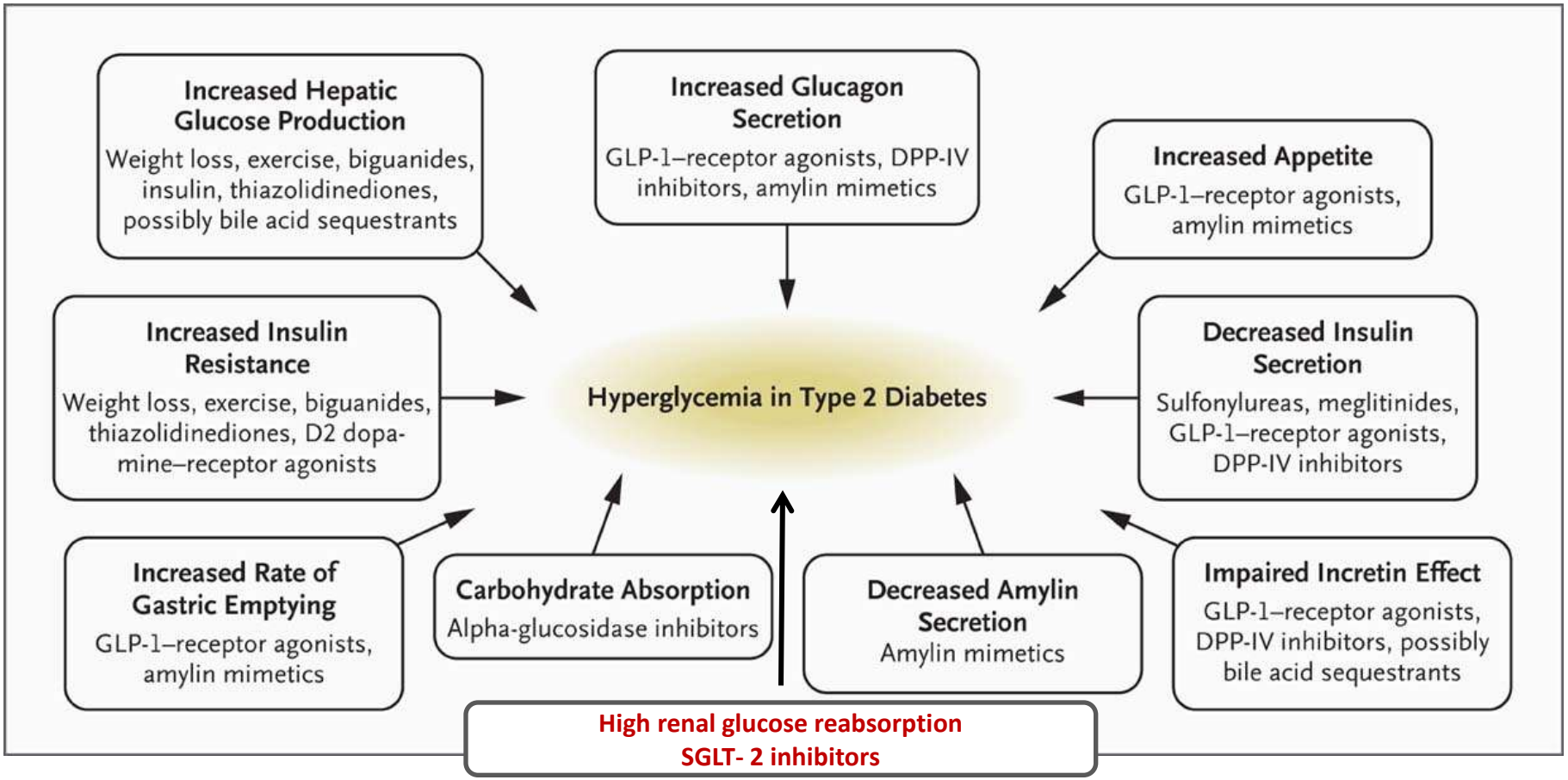
Disclosure Statement

- Stefano Genovese, in the last three years, has received speaking and/or consulting fees from:
  - Abbott Diabetes Care
  - AstraZeneca
  - BoehringerIngelheim
  - Bristol-Myers Squibb
  - Eli Lilly
  - Janssen
  - Lifescan
  - Merck Sharp &Dohme
  - Novartis
  - Novo Nordisk
  - Takeda
- and research grants from
  - Novartis

Characteristics of a “good” drug

- Efficacy
- Safety
- Other Clinical Advantages
- No/Few Adverse Effects
- Reasonable Cost/Value

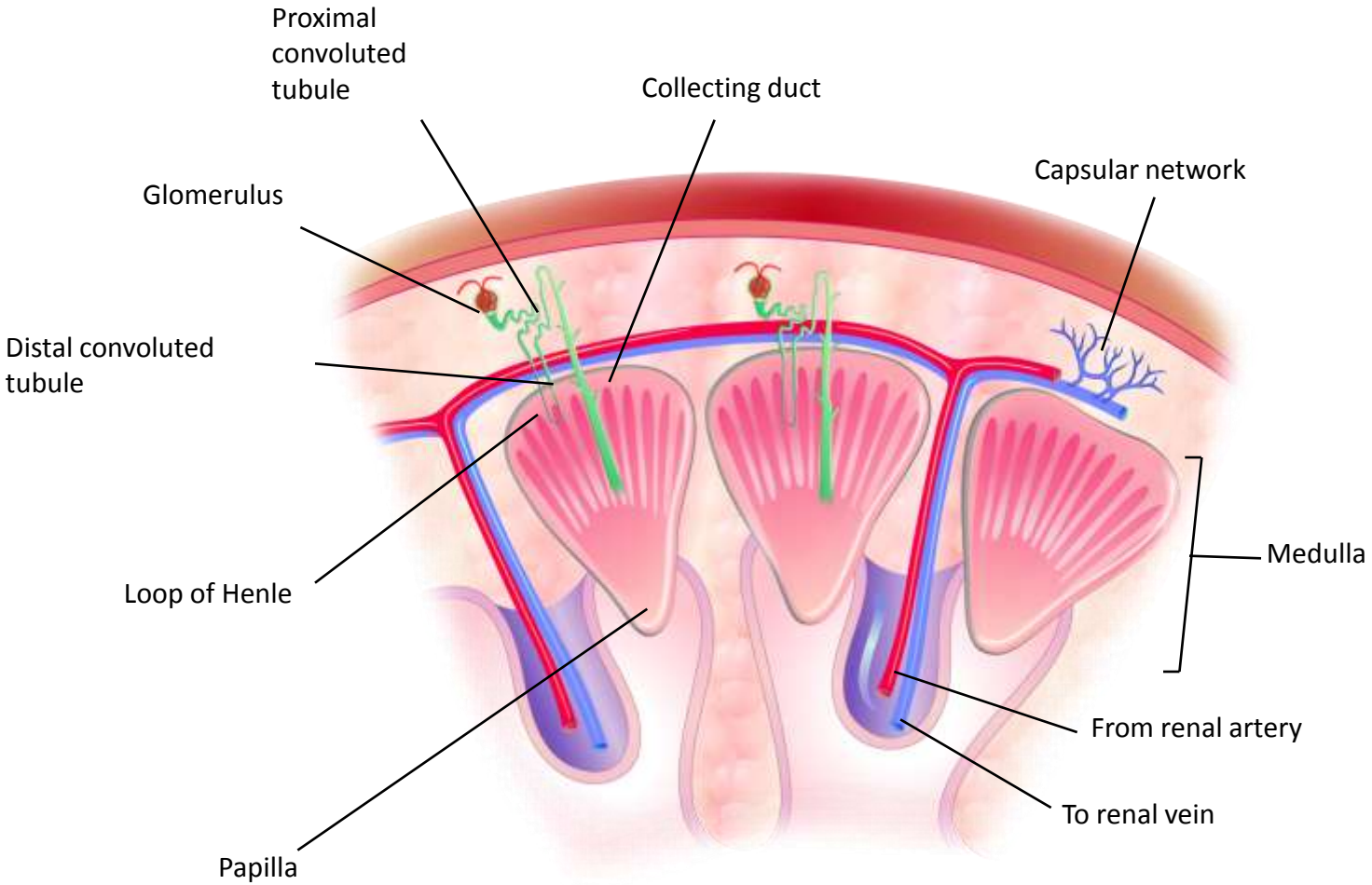
Terapia del diabete tipo 2 basata sulle alterazioni fisiopatologiche



The NEW ENGLAND JOURNAL of MEDICINE

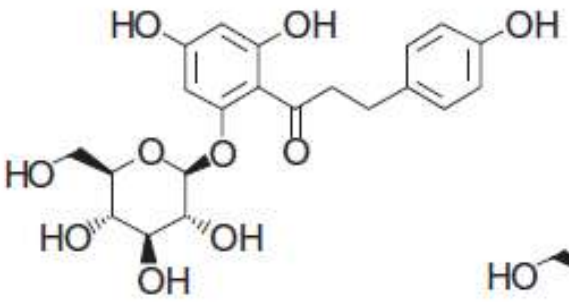
Ismail-Beigi F. N Engl J Med 2012;366:1319-1327

Major functional elements of the kidney

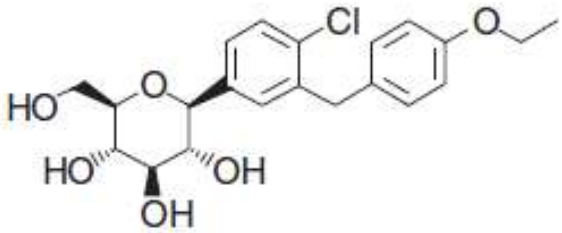


Adapted from Guyton AC, Hall JE. Textbook of Medical Physiology. 11th ed. Philadelphia, PA: Elsevier Saunders; 2006

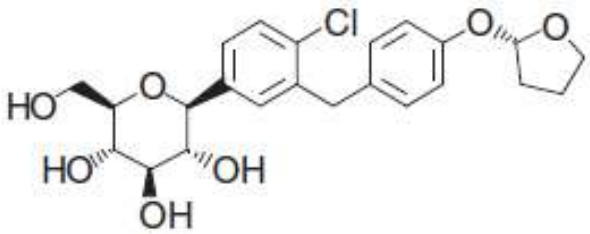
Strutture chimiche degli inibitori di SGLT 2



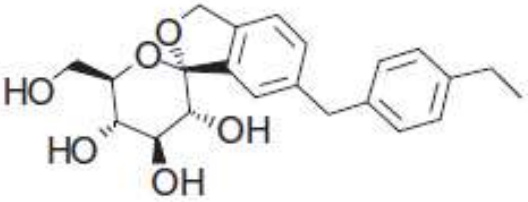
Phlorizin



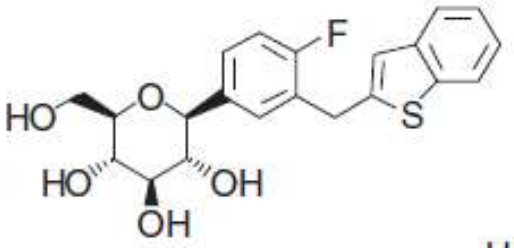
Dapagliflozin



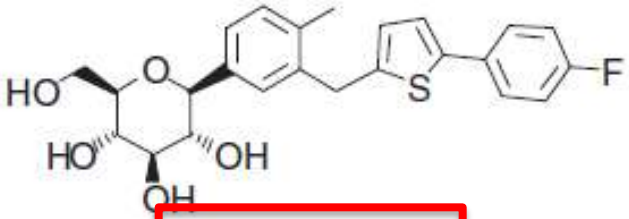
Empagliflozin



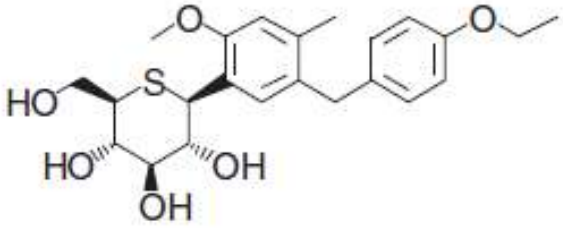
Tofogliflozin



Ipragliflozin



Canagliflozin



Luseogliflozin

Selectivityof SGLT2 inhibitors vs SGLT1

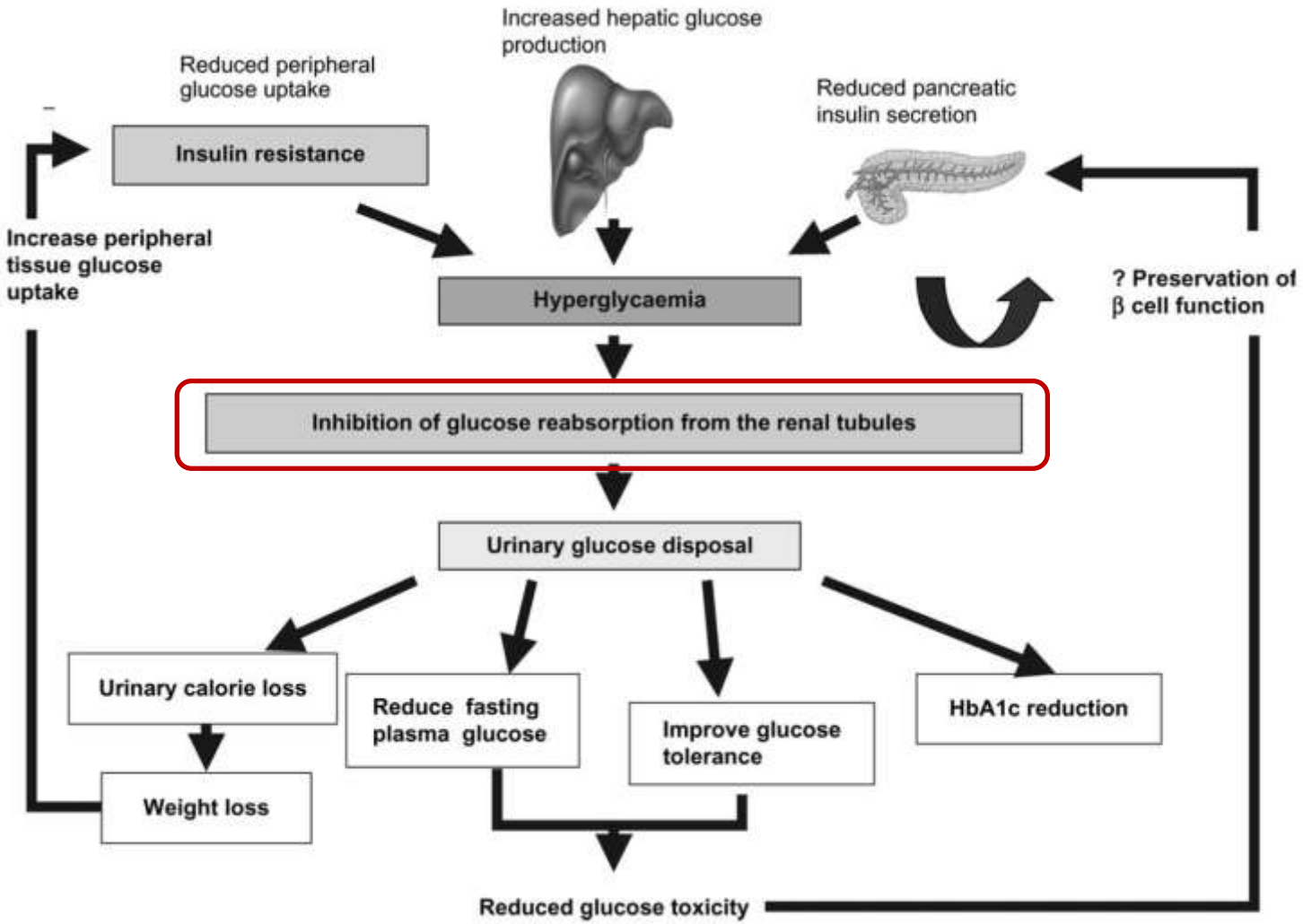
Compound	IC50 (nM)		pIC50 (nM)	
	SGLT2	SGLT1	SGLT2	SGLT1
Empagliflozin	3.1	8,300	8.50±0.02	5.08±0.03
Dapagliflozin	1.2	1,400	8.94±0.06	5.86±0.07
Canagliflozin	2.7	710	8.56±0.02	6.15±0.06
Ipragliflozin	5.3	3,000	8.27±0.04	5.53±0.02
Tofogliflozin	6.4	12,000	8.18±0.12	4.92±0.09

Razionale per l'utilizzo terapeutico degli inibitori del SGLT- 2

- Nei soggetti diabetici tipo 2 e 1 Tm_G è aumentato del 20-40%
- Nelle cellule tubulari renali dei diabetici in cultura sono aumentate rispetto ai non diabetici l'espressione di SGLT- 2, la sua concentrazione e la sua capacità di trasporto di glucosio *(difetto intrinseco o adattamento?)*
- Nel ratto pancreatectomizzato al 90% la resistenza periferica ed epatica all'insulina ed il difetto beta-cellulare acquisito sono totalmente ripristinati dalla florizina
- La glicosuria cronica non è dannosa: la glicosuria renale familiare è una malattia benigna

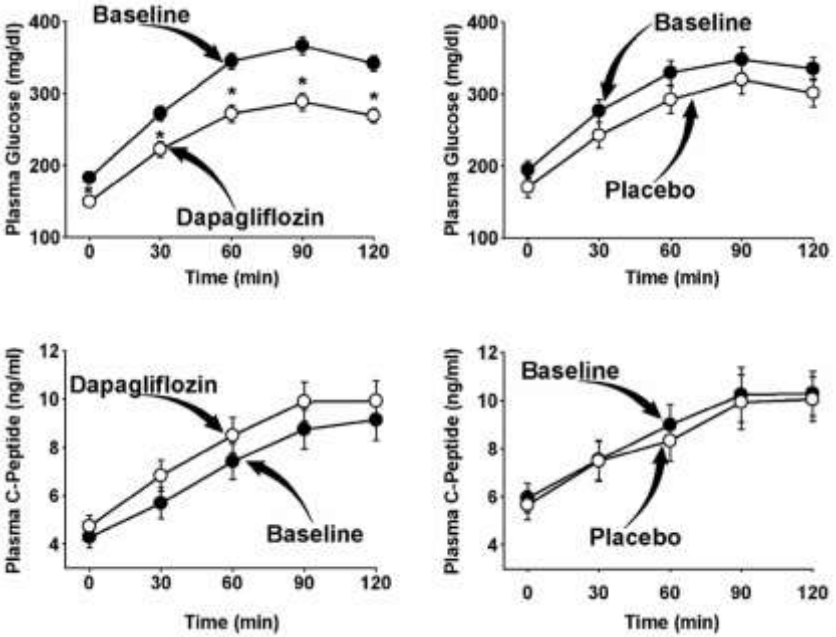
Ferrannini E, Diabetes 2011; 60: 695- 6

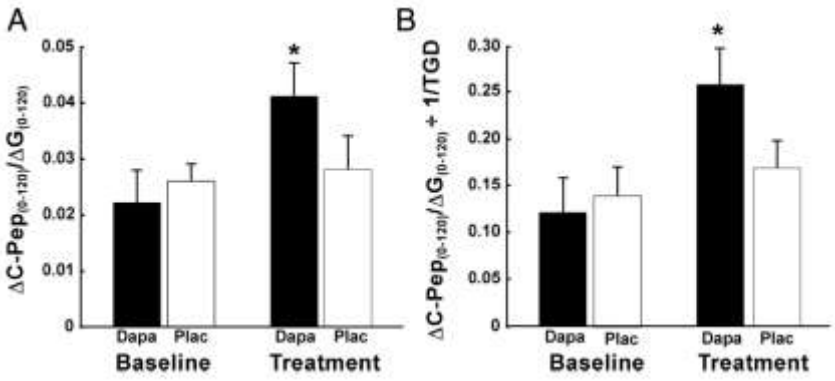
Rappresentazione schematica degli effetti clinici degli inibitori di SGLT- 2

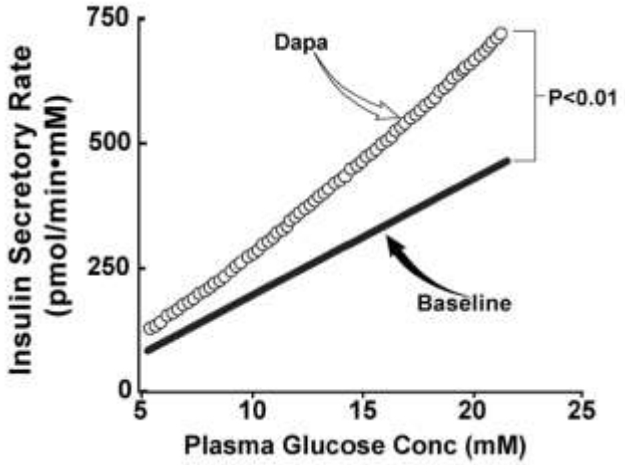


Idris I, Diabetes, Obesity and Metabolism 2009; 11: 79–88

DapagliflozinLowers Plasma GlucoseConcentration and Improves Beta CellFunction





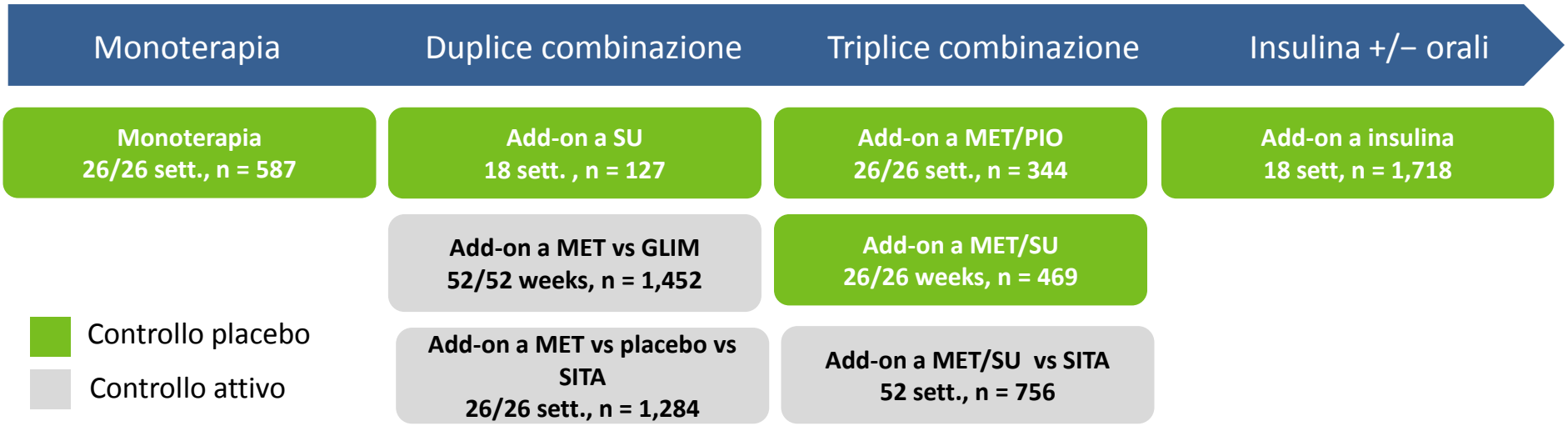


Conclusions: Lowering the plasma glucose concentration with dapagliflozin markedly improves beta cell function, providing strong support in man for the glucotoxic effect of hyperglycemia on beta cell function

Merovci A. et al JClinEndocrinolMetab. 2015 May;100(5):1927-32

Canagliflozin

Canagliflozin clinical trial programme



Studi in popolazioni speciali di diabetici t2
Studi controllati con placebo /add-on a trattamento antidiabetico corrente

Anziani : sicurezza sull'osso e composizione corporea	Insufficienza renale	Sicurezza CV (CANVAS)
26/78 sett., n = 716	26/26 sett., n = 272	eventi , n = 4,330

CV, cardiovasculare; GLIM, glimepiride; MET, metformin; PIO, pioglitazone; SITA, sitagliptin; SU, sulfonylurea.

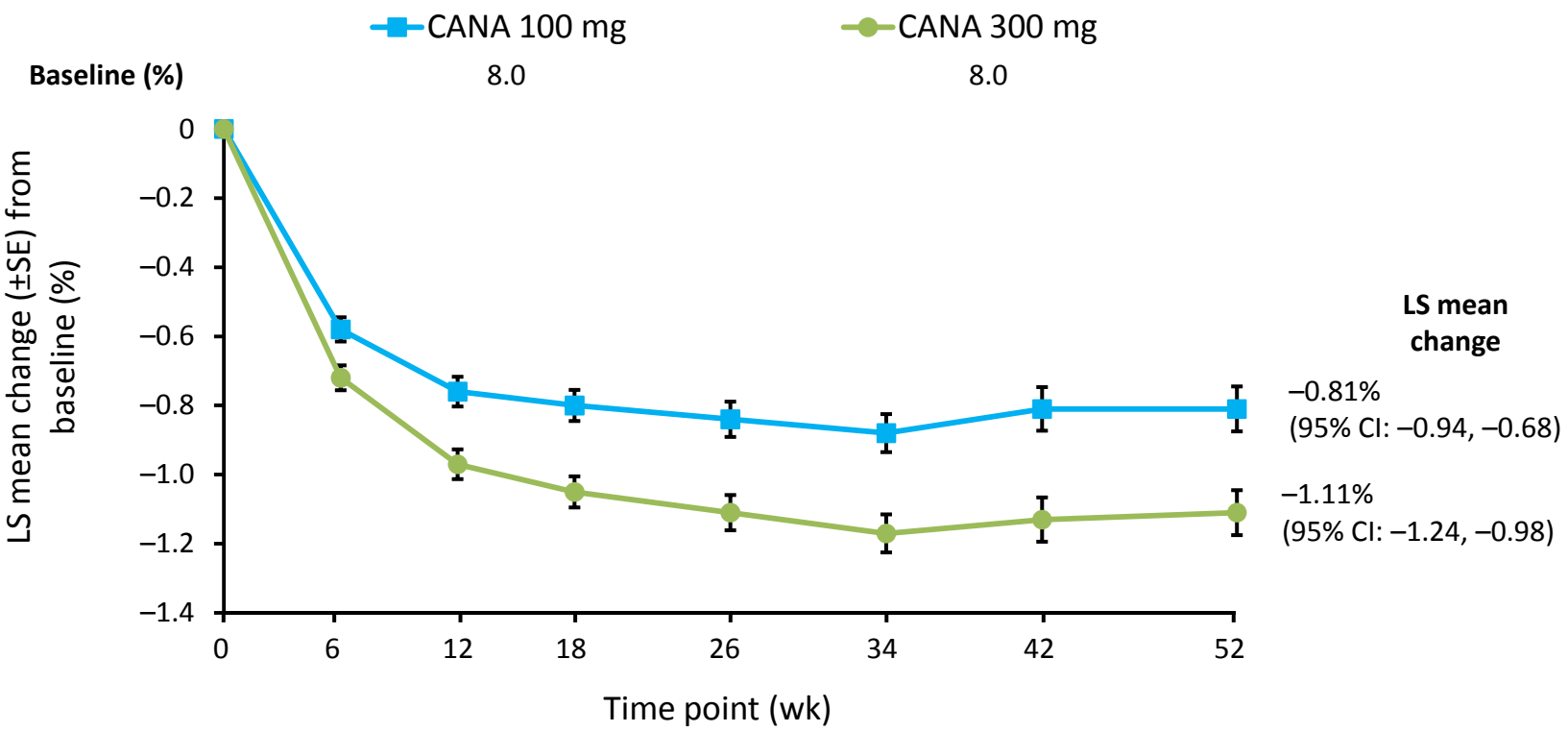
Limitazioni alla rimbosabilità - AIFA

- La prescrizione dei farmaci inibitori di SGLT-2 è soggetta a diagnosi e piano terapeutico rinnovabile ogni 6 mesi da parte di centri specializzati, Universitari o delle Aziende Sanitarie, individuate dalle Regioni e dalle Province autonome di Trento e Bolzano
- La rimborsabilità a carico del S.S.N. in regime di dispensazione RRL-PT/PHT, nel rispetto delle avvertenze della scheda tecnica dei singoli farmaci, è limitata ai pazienti adulti con diabete tipo 2 nelle seguenti condizioni:
  - In monoterapia, nei pazienti intolleranti alla metformina nei quali l'utilizzo di un diverso ipoglicemizzante risulti controindicato o non appropriato.
  - In associazione a metformina (duplice terapia) nei casi in cui l'utilizzo di un diverso ipoglicemizzante risulti controindicato o non appropriato.
  - In associazione a insulina, con o senza metformina

GU Serie generale n. 93 22-4-2015

Monoterapia

Change in A1C (LOCF)

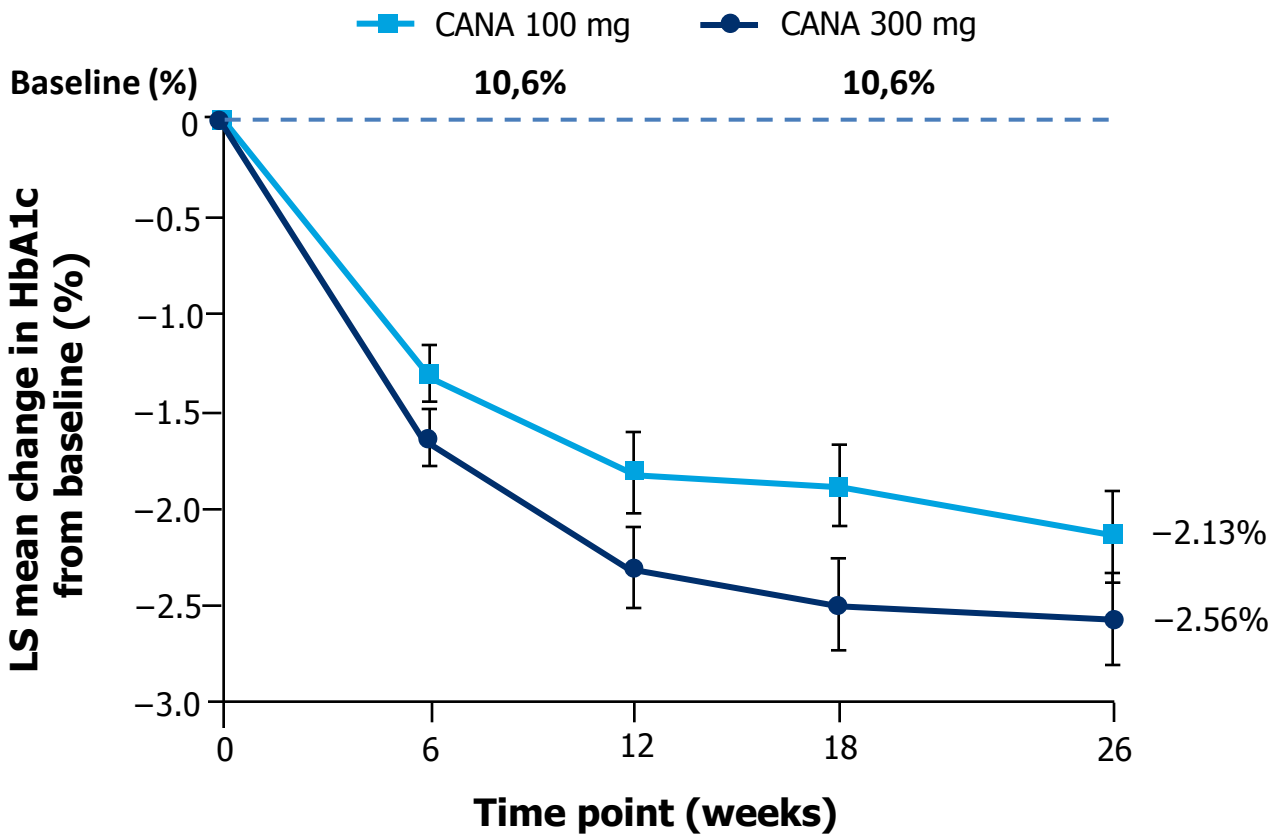


Proportion of subjects who achieved A1C <7.0%: 52.4% (CANA 100 mg) and 64.5% (CANA 300 mg); A1C <6.5%: 22.9% (CANA 100 mg) and 30.1% (CANA 300 mg).

LOCF, last observation carried forward; LS, least squares; SE, standard error; CI, confidence interval.

Stenlöf K et al. Curr Med Res Opin. 2013 Sep 30.

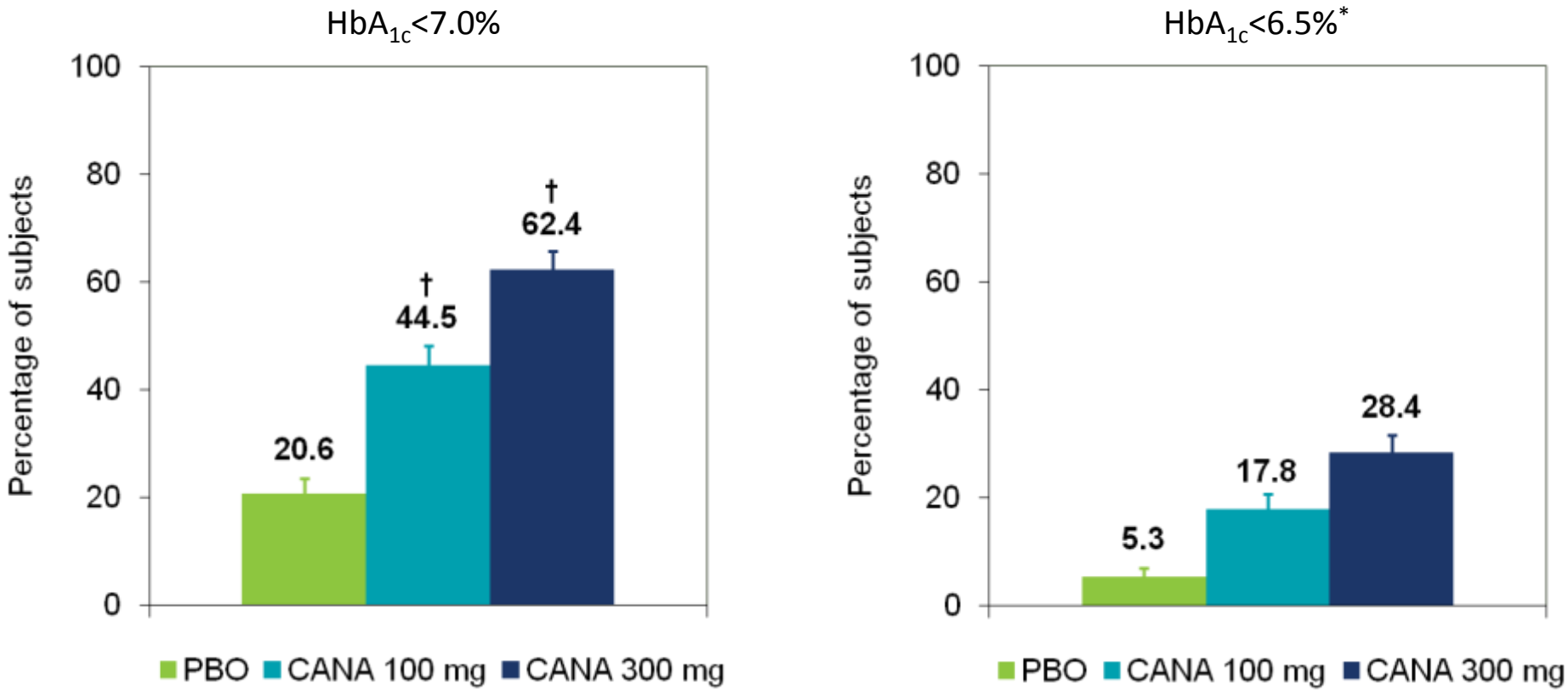
Efficacy – High Glycaemic substudy



Vertical bars represent standard error.
CANA, canagliflozin; LOCF, last observation carried forward; LS, least squares;.

Stenlöf K, et al. Diabetes Obes Metab. 2013;15:372-82

Proportion of Subjects Reaching HbA1c Goals

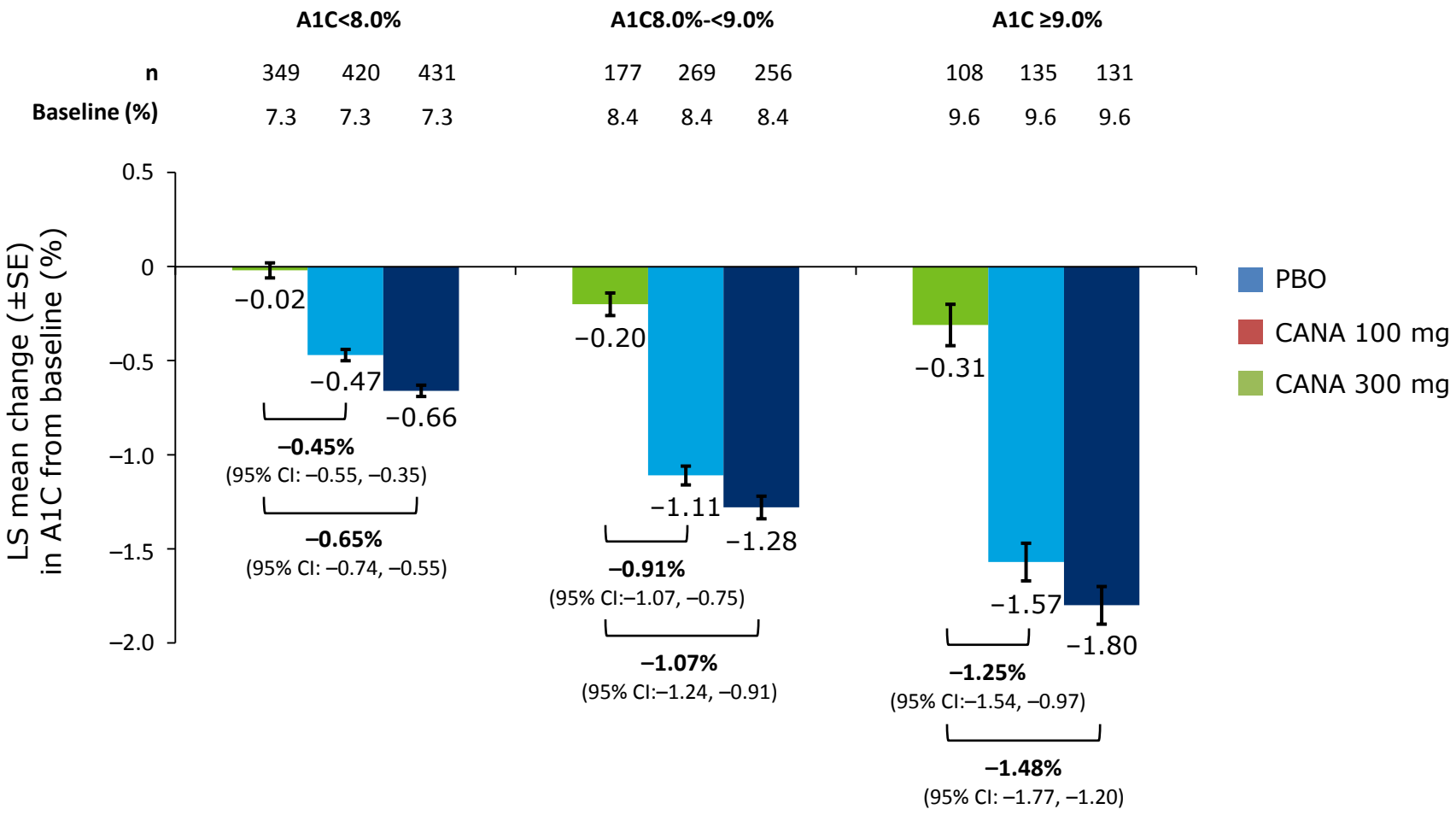


†*P*<0.001 vs placebo; *Statistical comparison for Canagliflozin 100 and 300 mg vs placebo not performed (not pre-specified).

PBO, placebo; CANA, canagliflozin; mITT, modified intent-to-treat; LOCF, last observation carried forward.

Stenlof et al. Diabetes Obes Metab. 2013;15(4):372-82.

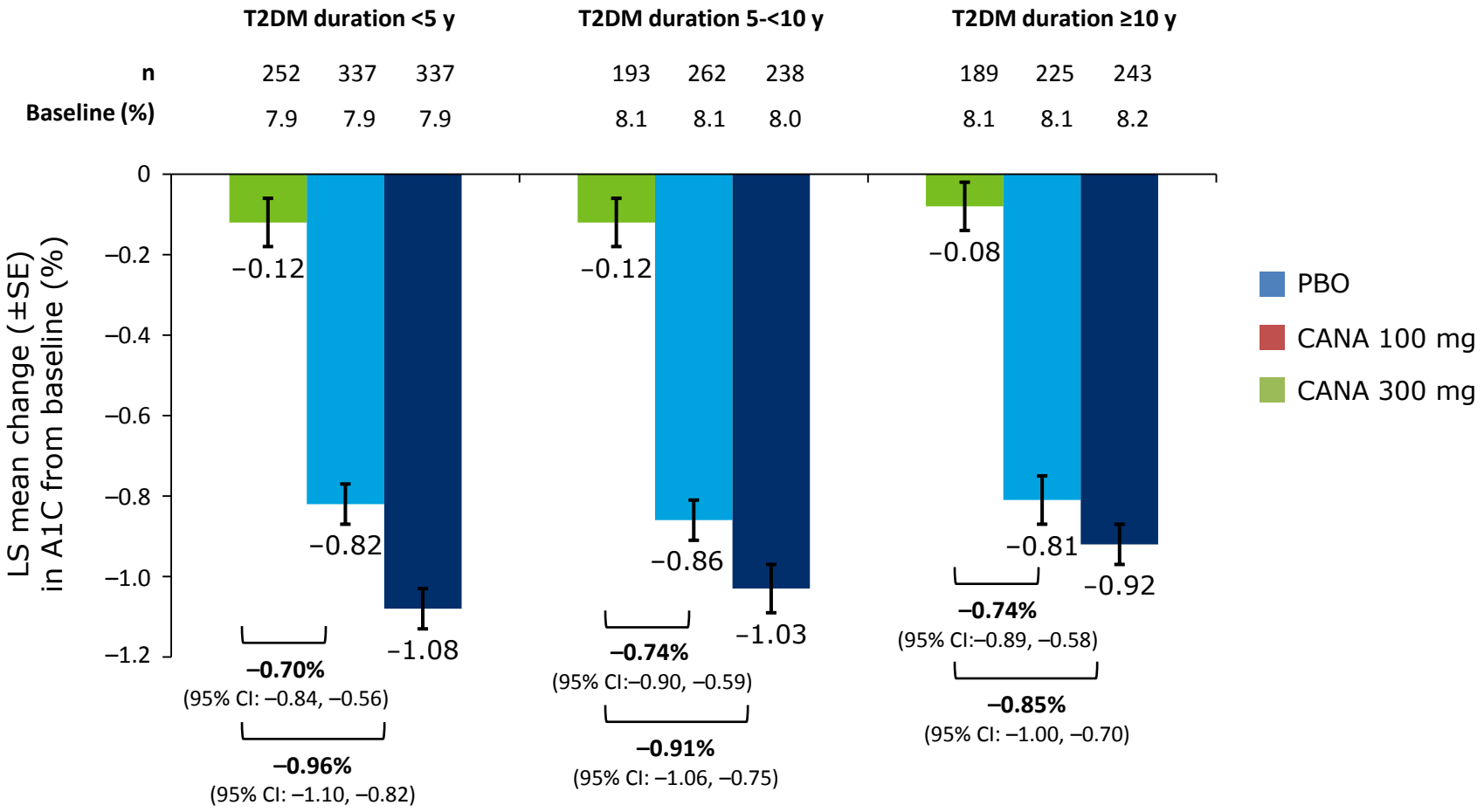
Change in A1C by Baseline A1C (LOCF)



LS, least squares; SE, standard error; CI, confidence interval.

J.P.H. Wildinget al. Journal of Diabetes and Its Complications - DOI:10.1016/j.jdiacomp.2014.12.016

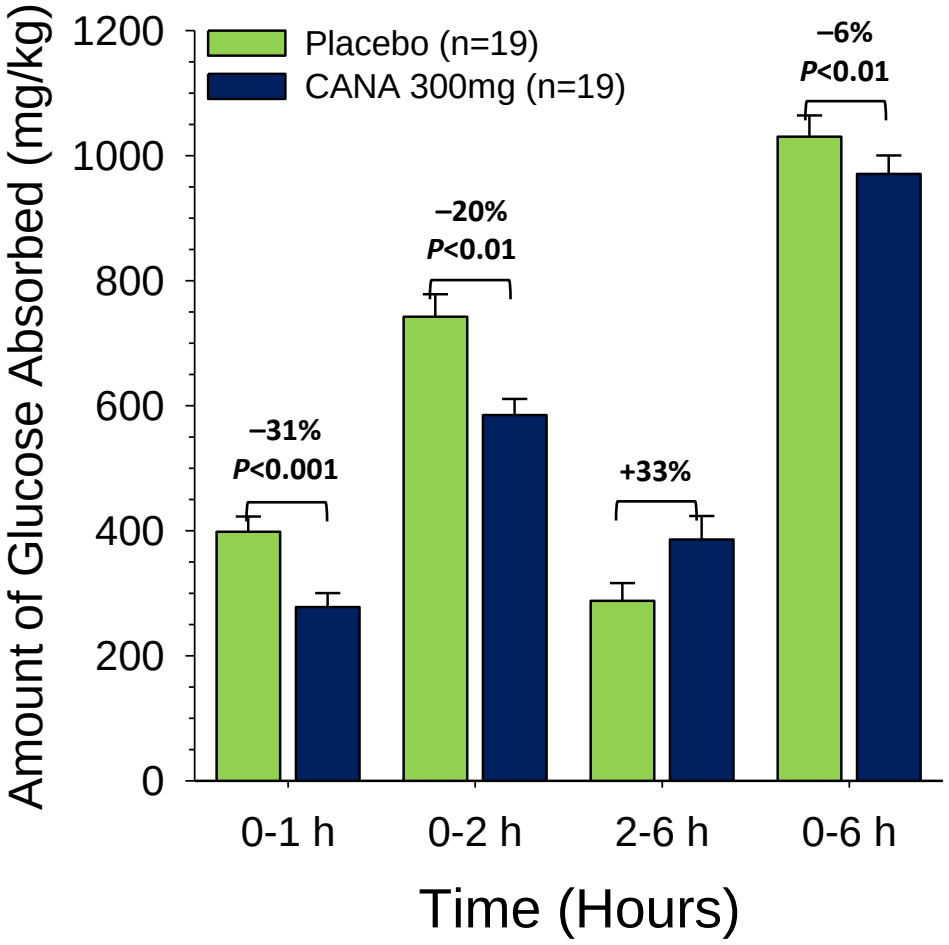
Change in A1C by Known Duration of T2DM (LOCF)



J.P.H. Wildinget al. Journal of Diabetes and Its Complications - DOI:10.1016/j.jdiacomp.2014.12.016

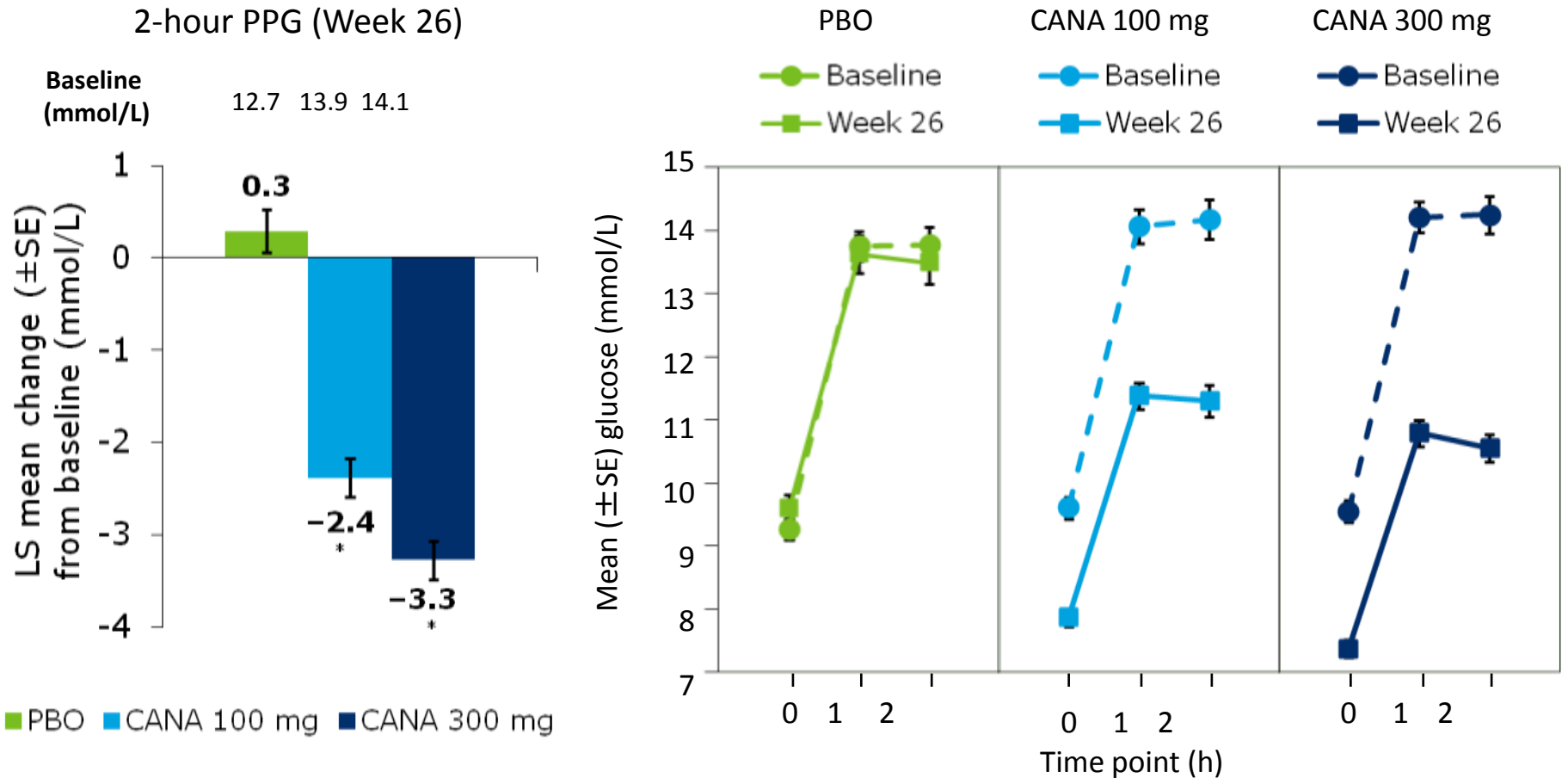
Effect of Canagliflozin 300 mg on Oral Glucose Absorption

As a function of time from ingestion



Polidoriet al.DiabetesCare 36:2154–2161, 2013.

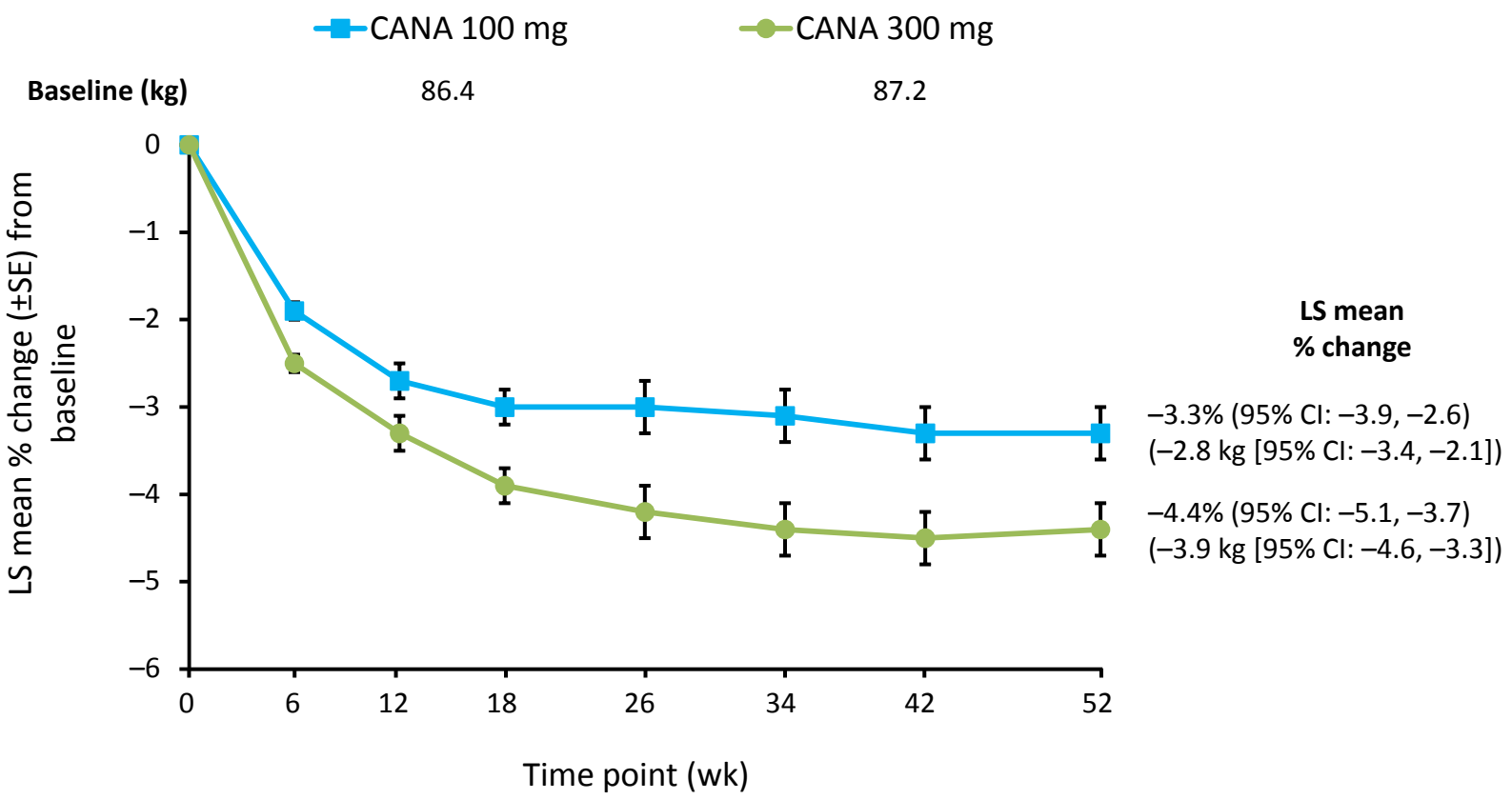
Change in PPG: After a Standardised Meal (LOCF)



PPG, postprandial glucose; LOCF, last observation carried forward; PBO, placebo; CANA, canagliflozin; LS, least squares; SE, standard error.
*$P<0.001$ vs PBO.

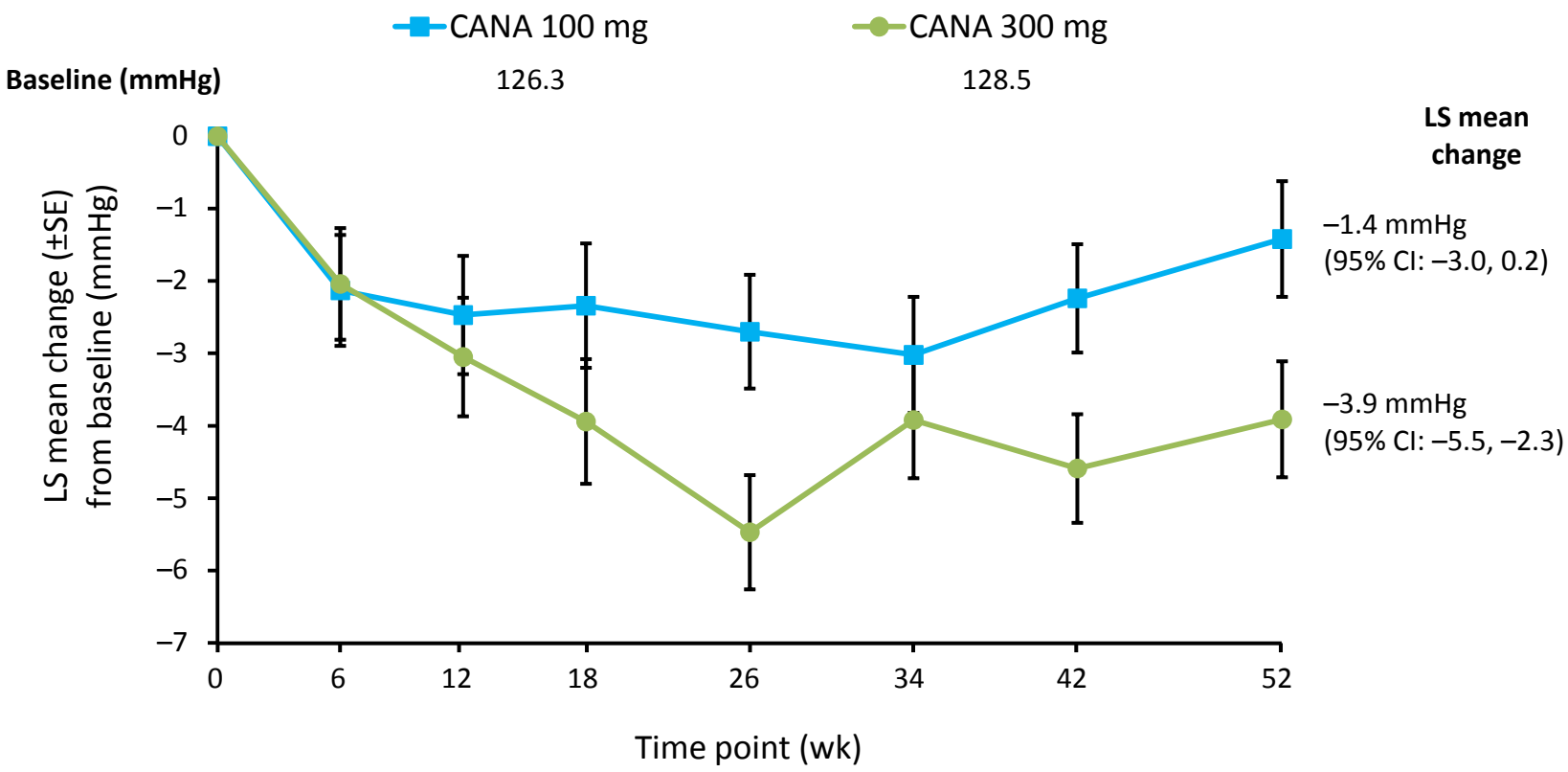
Stenlof et al. Diabetes Obes Metab. 2013;15(4):372-82.

Percent Change in Body Weight (LOCF)



Stenlöf K et al. Curr Med Res Opin. 2013 Sep 30.

Change in Systolic BP (LOCF)

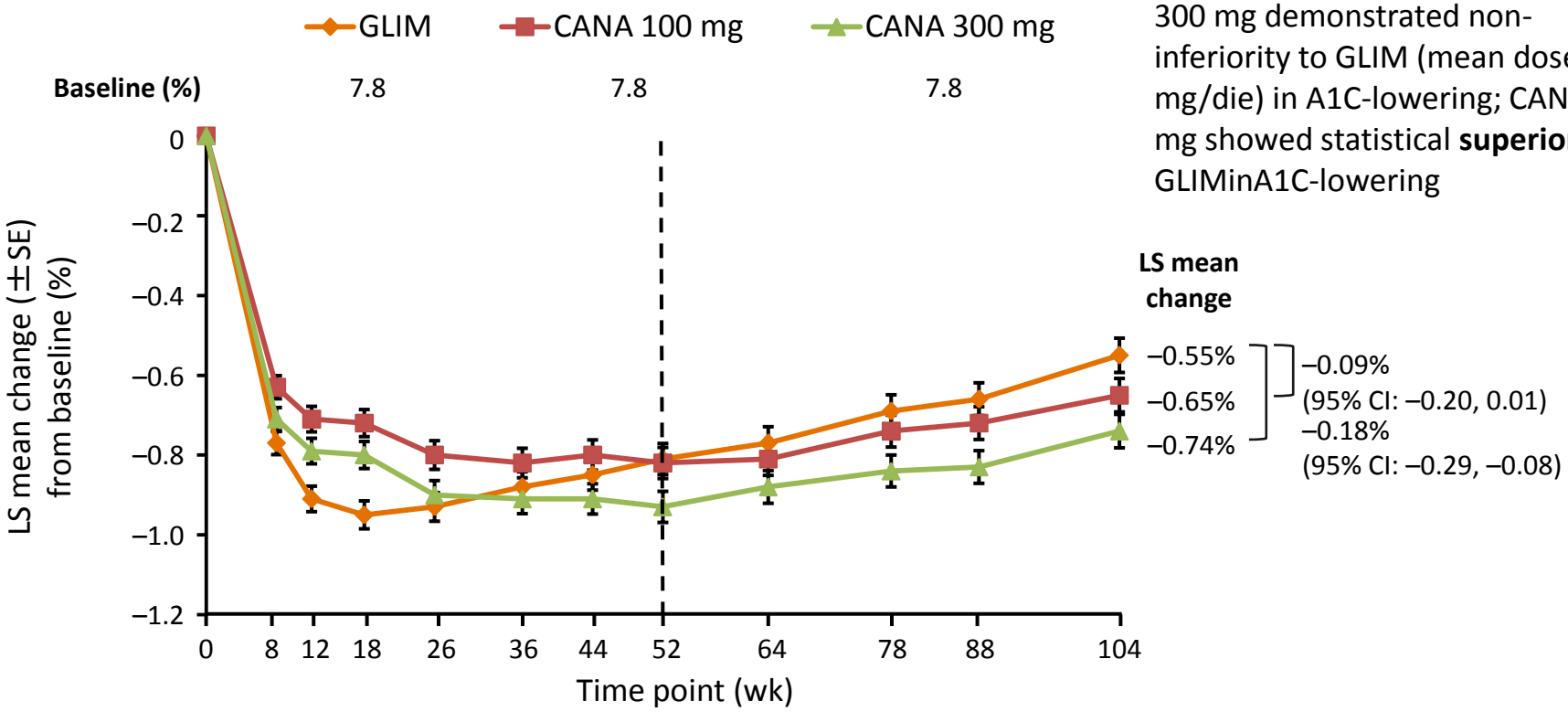


Reductions in diastolic BP with CANA 100 and 300 mg were –0.4 and –0.7 mmHg, respectively, with minimal changes in pulse rate (–2.1 and 0.4 beats per minute).

Stenlöf K et al. Curr Med Res Opin. 2013 Sep 30.

Duplice Terapia

Change in A1C (LOCF)*



At week 52, CANA 100 and CANA 300 mg demonstrated non-inferiority to GLIM (mean dose 5,6 mg/die) in A1C-lowering; CANA 300 mg showed statistical **superiority** to GLIMinA1C-lowering

Proportion of subjects who achieved A1C <7.0%: 42.5% (CANA 100 mg), 50.2% (CANA 300 mg), and 43.9% (GLIM); A1C <6.5%: 20.5% (CANA 100 mg), 26.2% (CANA 300 mg), and 23.8% (GLIM).

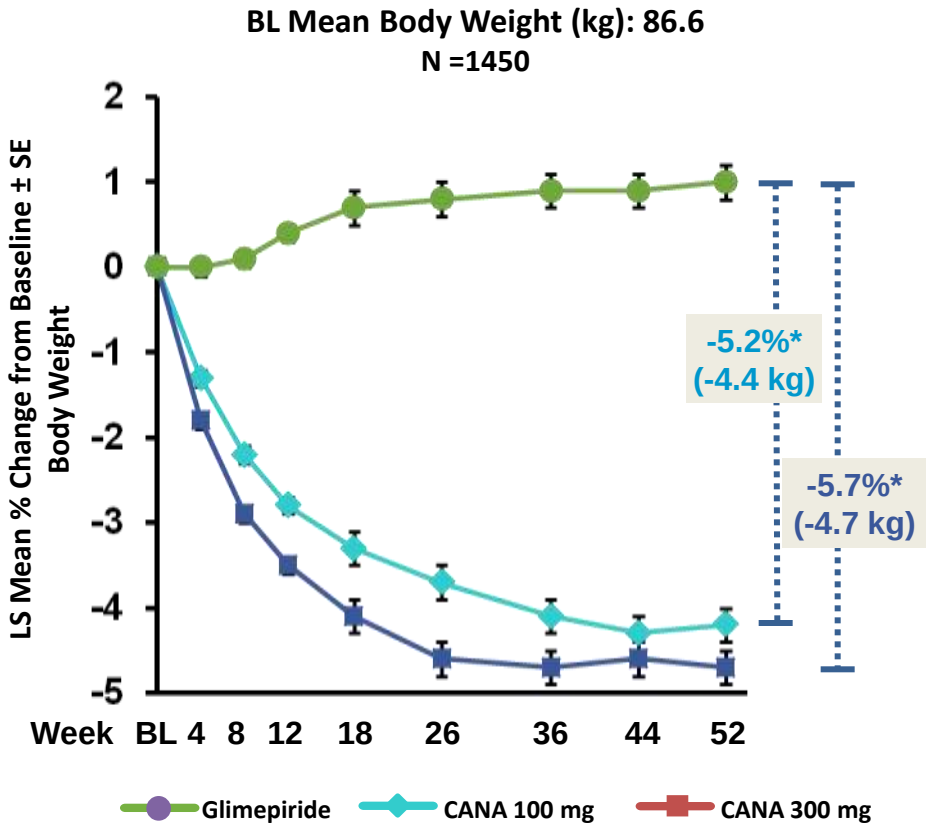
LOCF, last observation carried forward; LS, least squares; SE, standard error; CI, confidence interval.
*N = 1,450 (Baseline); N = 1,405 (Week 8); N = 1,425 (Weeks 12 and 18); N = 1,426 (Weeks 26, 36, 44, 52, 64, 78, 88, and 104).

Leiter L.A., et al. (2014). Diabetes Care. Sep 9. pii: DC_132762

Changes in Body Composition and Weight

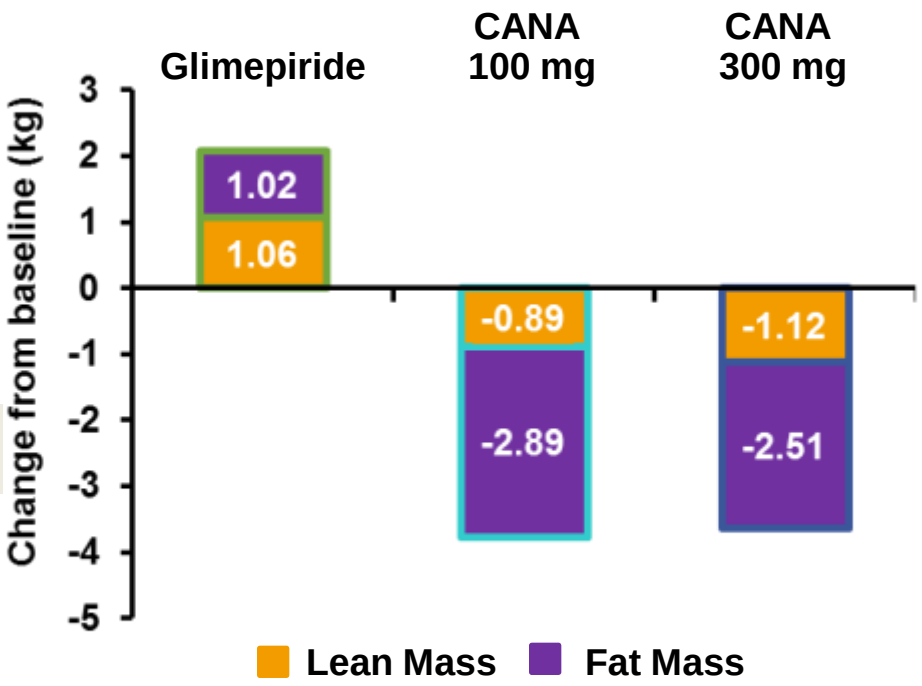
Active (Glimepiride)-controlled Add-on to Metformin Study (DIA3009)

Weight Loss Over Time



* p <0.001
Based on ANCOVA model, data prior to rescue (LOCF)

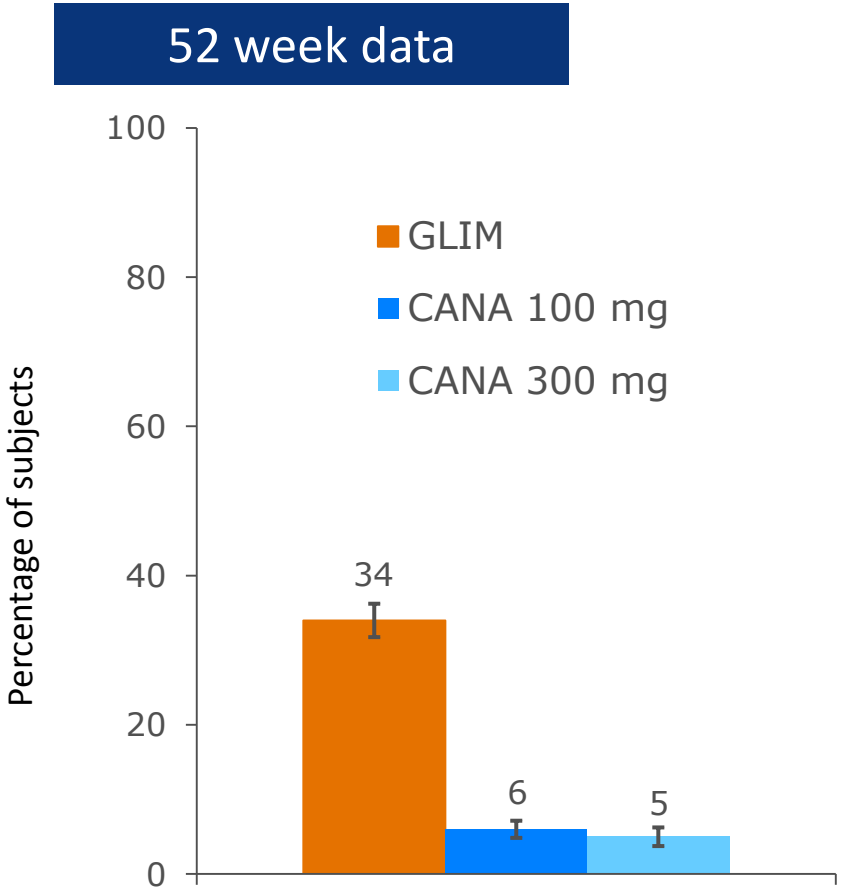
Change in Body Composition (DXA Analysis Subgroup) N=312

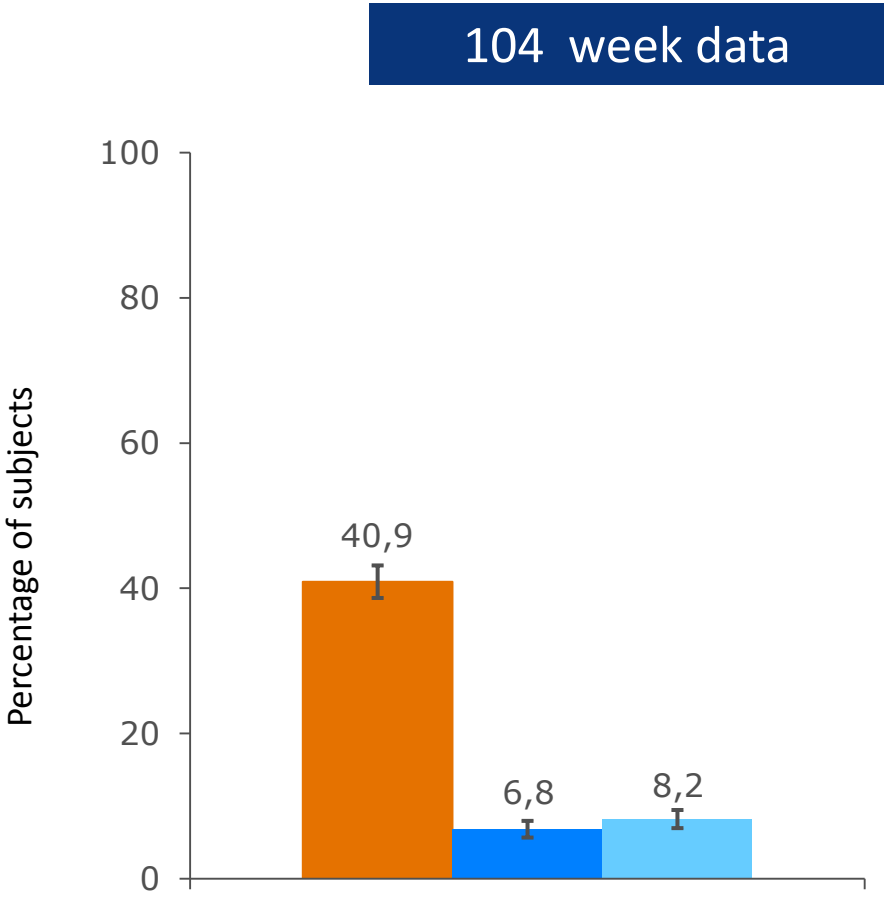


Weight changes relative to glimepiride in DXA analysis subgroup (-5.3 kg and -5.0 kg for CANA 100 mg and 300 mg, respectively) were similar to overall cohort.

Cefalu WT et al. Lancet. 2013; 382(9896):941-50.

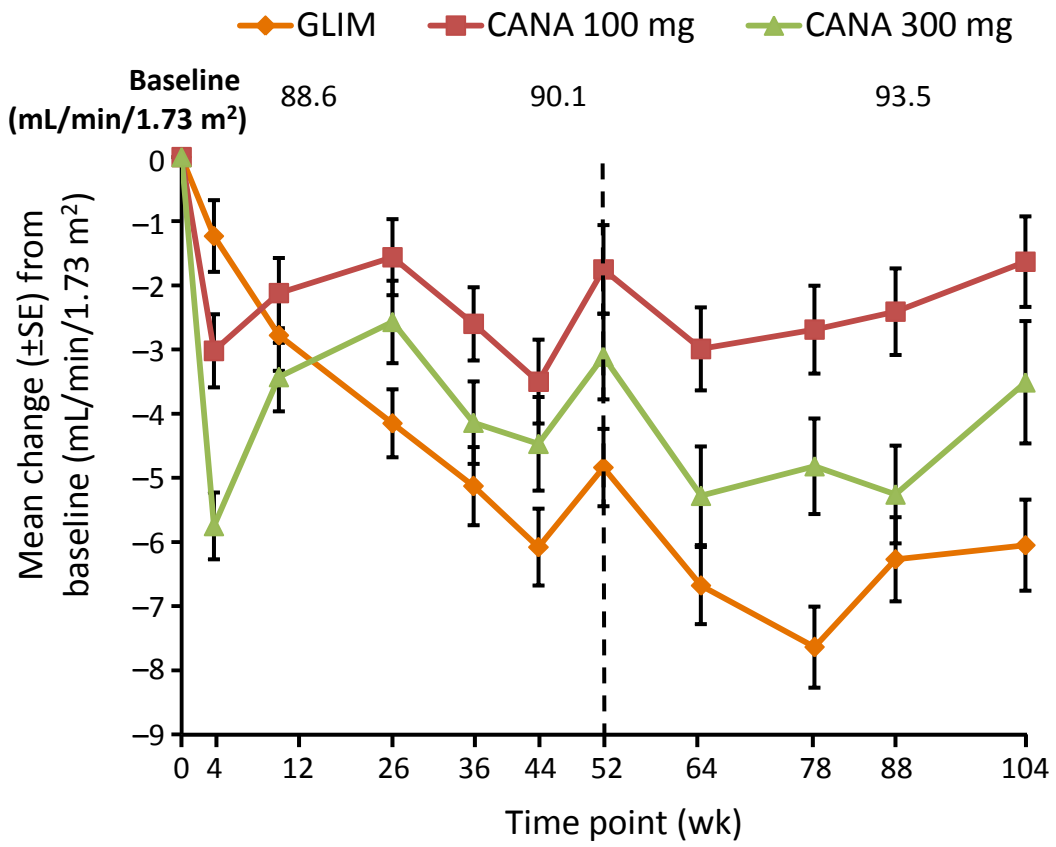
Add on to Metformin vs Glimepiride (DIA3009): Proportion of Subjects With Documented Hypoglycaemia Episodes Through Weeks 52 and 104





Cefalu WT et al. Lancet. 2013; 382(9896):941-50.
LeiterL.A., et al. (2014). Diabetes Care. Sep 9. pii: DC_132762

Change in eGFR Over Time*

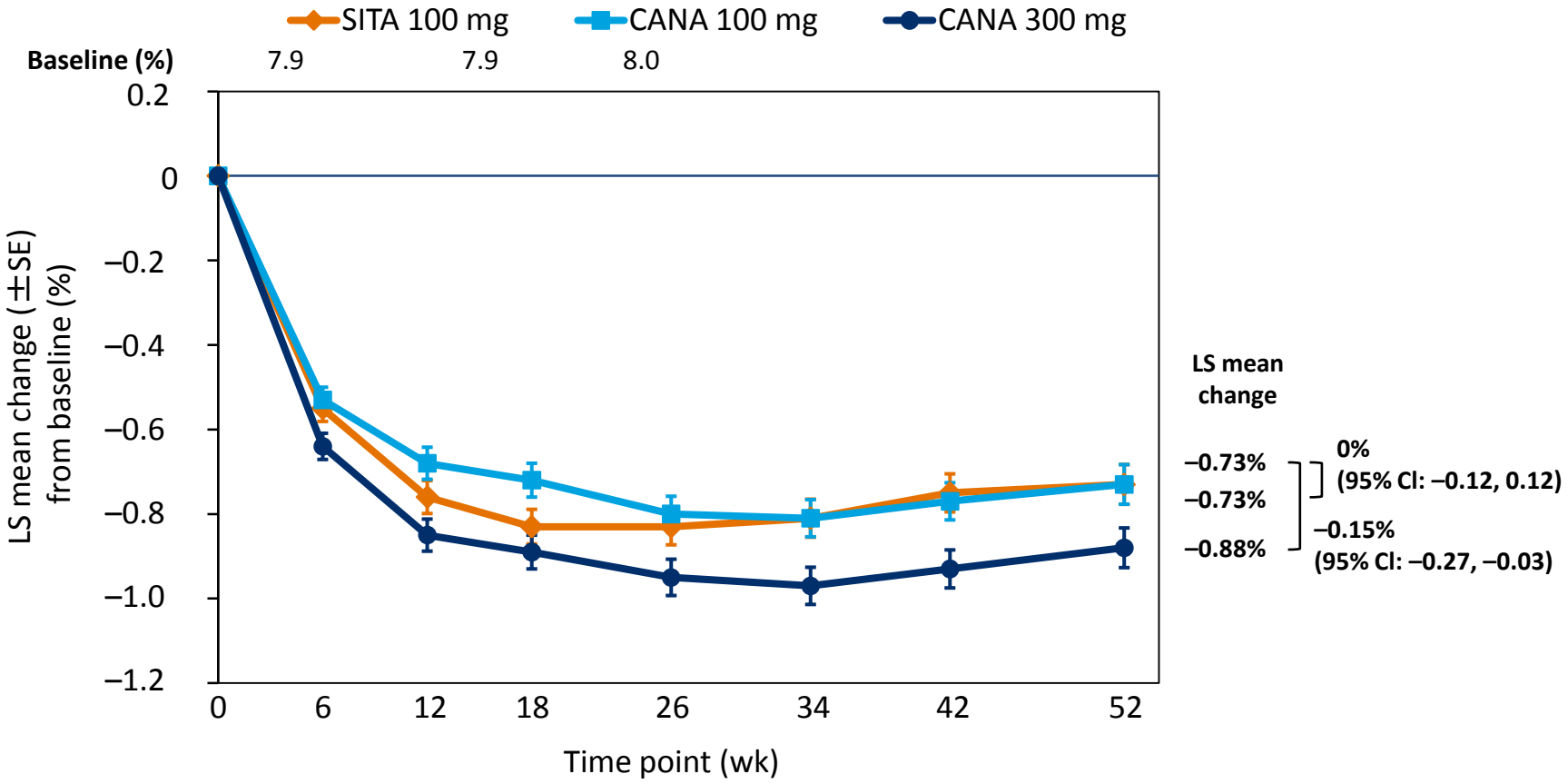


	Mean change (Observed)	Mean change (LOCF)
CANA 100 mg	−1.6 mL/min/1.73 m²	−2.0 mL/min/1.73 m²
CANA 300 mg	−3.5 mL/min/1.73 m²	−3.8 mL/min/1.73 m²
GLIM	−6.1 mL/min/1.73 m²	−6.2 mL/min/1.73 m²

*N = 1,449 (Baseline); N = 1,380 (Week 4); N = 1,332 (Week 12); N = 1,262 (Week 26); N = 1,225 (Week 36); N = 1,175 (Week 44); N = 1,157 (Week 52); N = 1,120 (Week 64); N = 1,059 (Week 78); N = 1,022 (Week 88); N = 970 (Week 104).

Leiter L.A., et al. (2014). Diabetes Care. Sep 9. pii: DC_132762

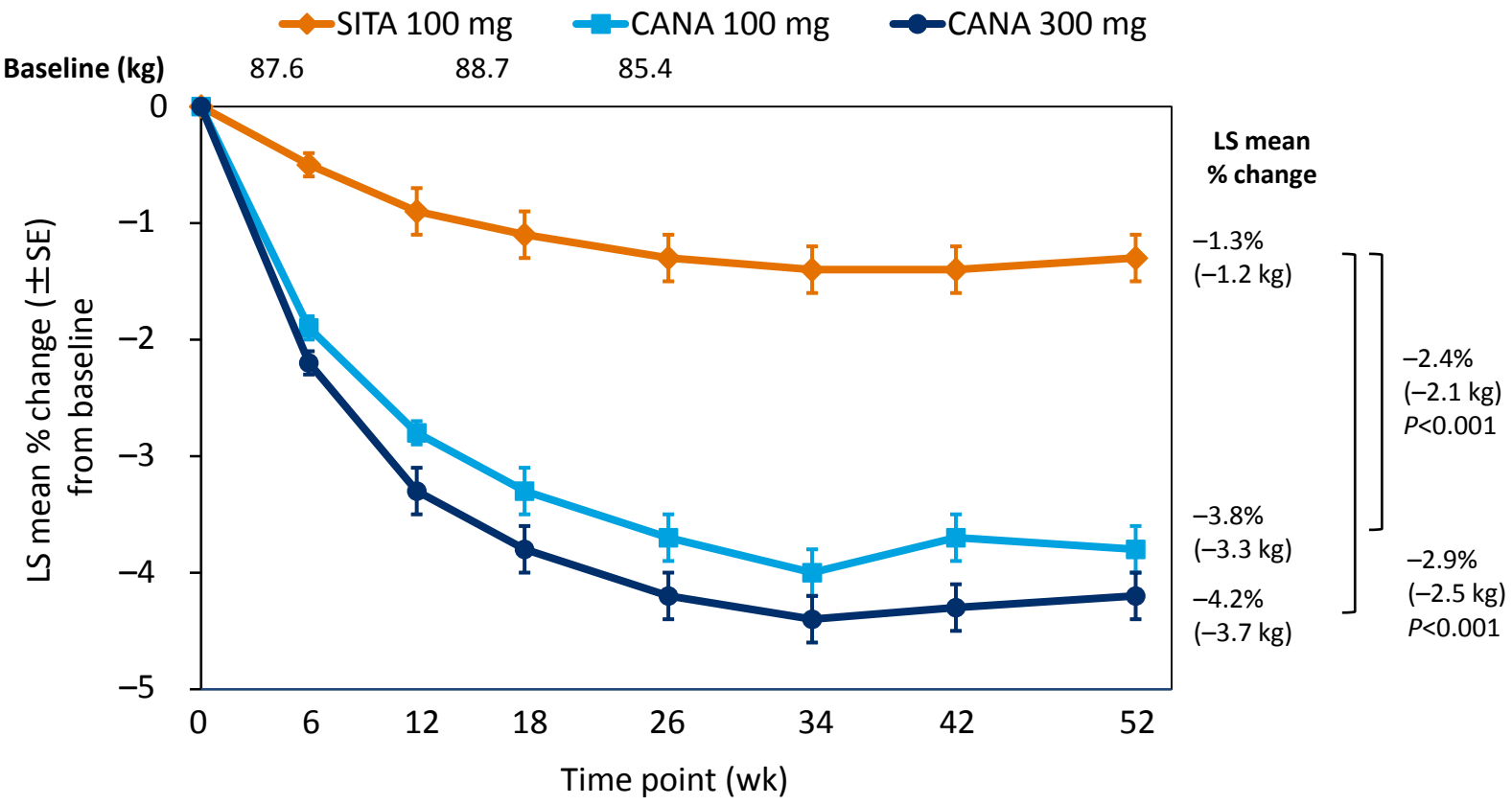
Change in A1C



CANA 100 and CANA 300 mg demonstrated non-inferiority to SITA 100 mg in A1C-lowering; CANA 300 mg showed statistical superiority to SITA 100 mg in A1C-lowering

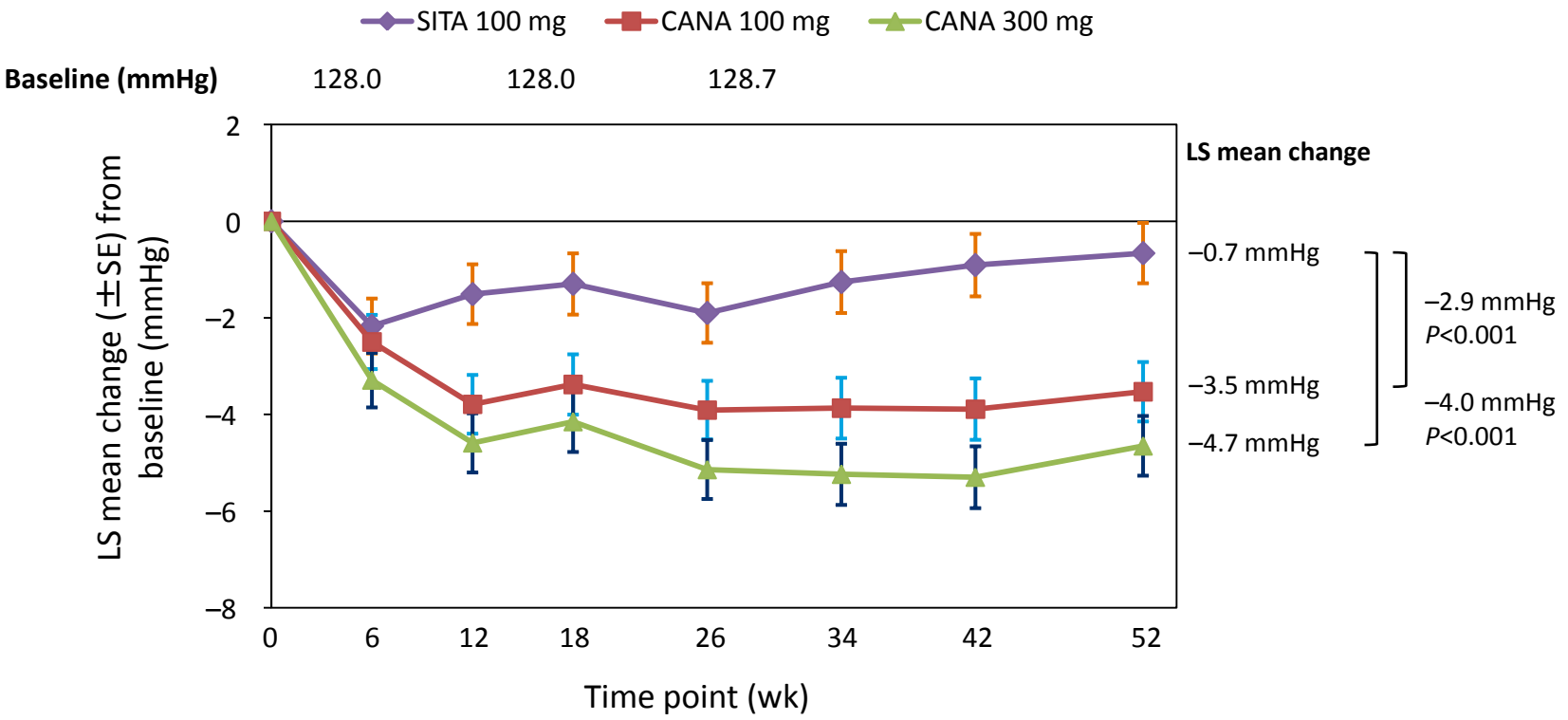
Lavalle-González FJ et al. Diabetologia. 2013 - 56:2582-2592

Percent Change in Body Weight



Lavalle-González FJ et al. Diabetologia. 2013 - 56:2582-2592

Change in Systolic BP

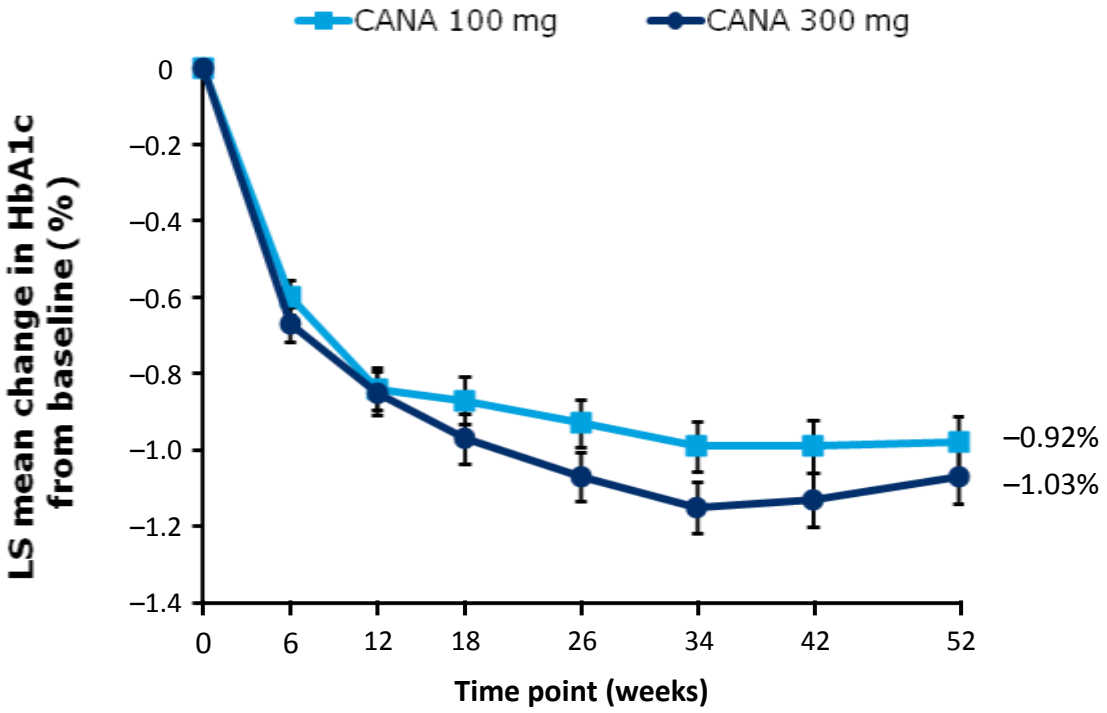


- With CANA 100 and 300 mg and SITA 100 mg, LS mean changes from baseline in diastolic BP were −1.8, –1.8, and –0.3 mmHg, respectively; no notable changes in pulse rate were observed across groups

Lavalle-González FJ et al. Diabetologia. 2013 - 56:2582-2592

Triplice terapia

Canagliflozin: riduzione di HbA1c aggiunta metformina + pioglitazone a 52 settimane

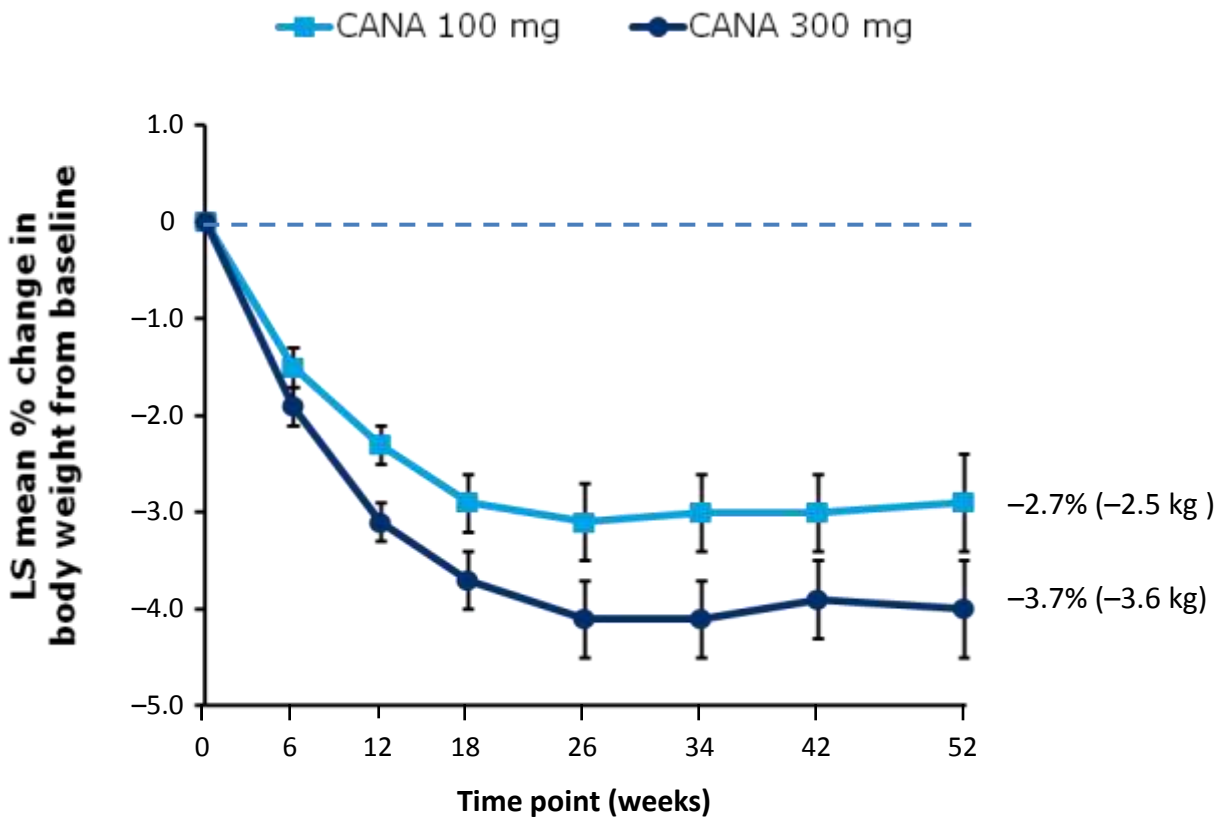


Proportion of subjects who achieved HbA1c <7.0%: 52.2% (canagliflozin 100 mg), 66.1% (canagliflozin 300 mg)

Vertical bars represent standard error.
CANA, canagliflozin; CI, confidence interval; LS, least squares; SE, standard error.

Forst T, et al. Diabetes ObesMetab. 2014 Feb 15. [Epubahead of print]

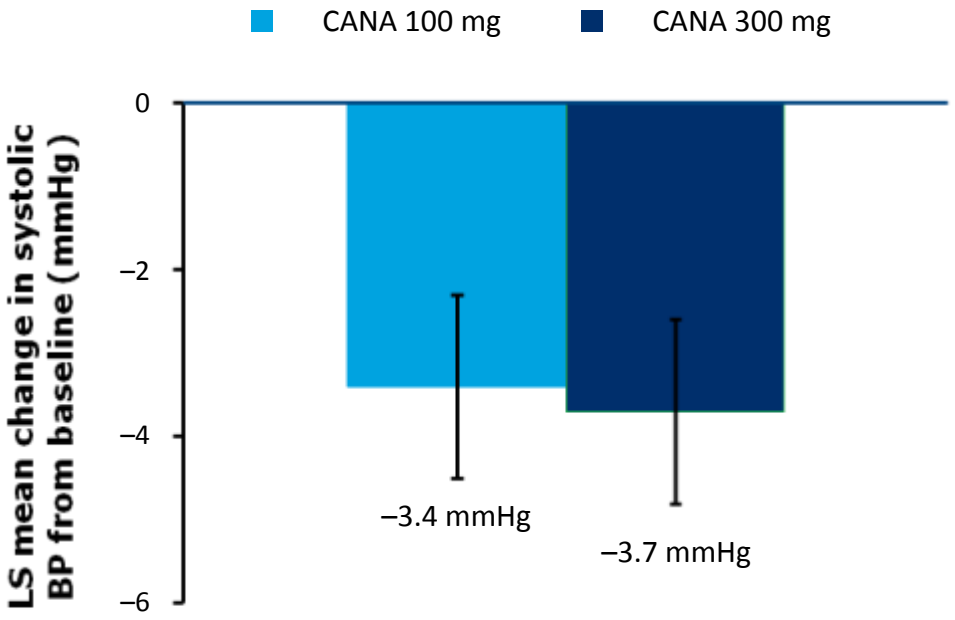
Canagliflozin: riduzione del peso corporeo aggiunta metformina + pioglitazone a 52 settimane



Vertical bars represent standard error.
CANA, canagliflozin; LS, least squares.

Forst T, et al. Diabetes ObesMetab. 2014 Feb 15. [Epubahead of print]

Canagliflozin: riduzione della PAS aggiunta metformina + pioglitazone a 52 settimane



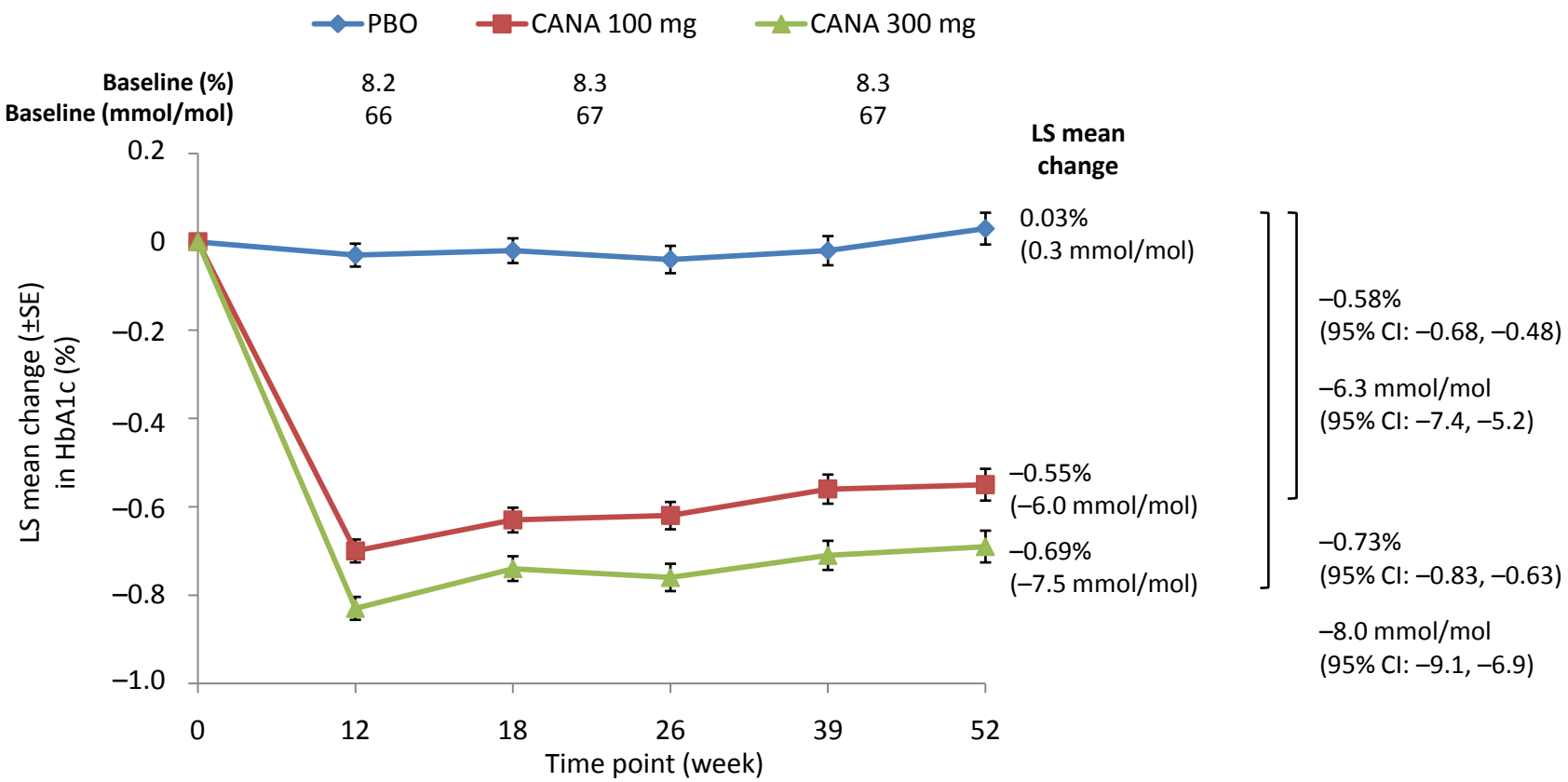
Reductions in diastolic BP with canagliflozin 100 mg and 300 mg were –2.5 mmHg and –2.7 mmHg, respectively, with minimal changes in pulse rate (0.5 bpm and –1.0 bpm)

Vertical bars represent standard error.
BP, blood pressure; bpm, beats per minute; CANA, canagliflozin; LS, least squares.

Forst T, et al. Diabetes ObesMetab. 2014 Feb 15. [Epubahead of print]

Add on a insulina

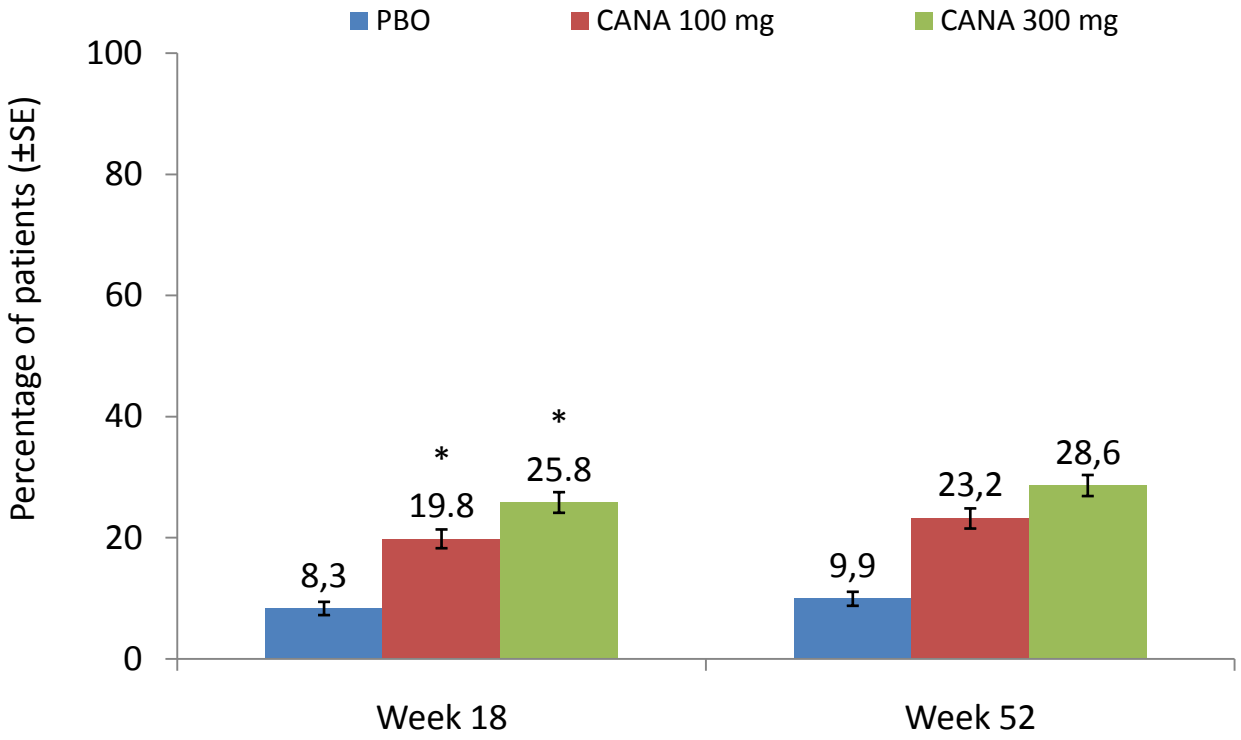
CANVAS Insulin Substudy (DIA3008): Change in HbA1c (LOCF)



CANA, canagliflozin; CI, confidence interval; LOCF, last observation carried forward; LS, least squares; PBO, placebo; SE, standard error.

Neal B. et al. Diabetes Care DOI: 10.2337/dc14-1237

CANVAS Insulin Substudy (DIA3008): Proportion of Patients Reaching HbA1c <7.0% at Weeks 18 and 52

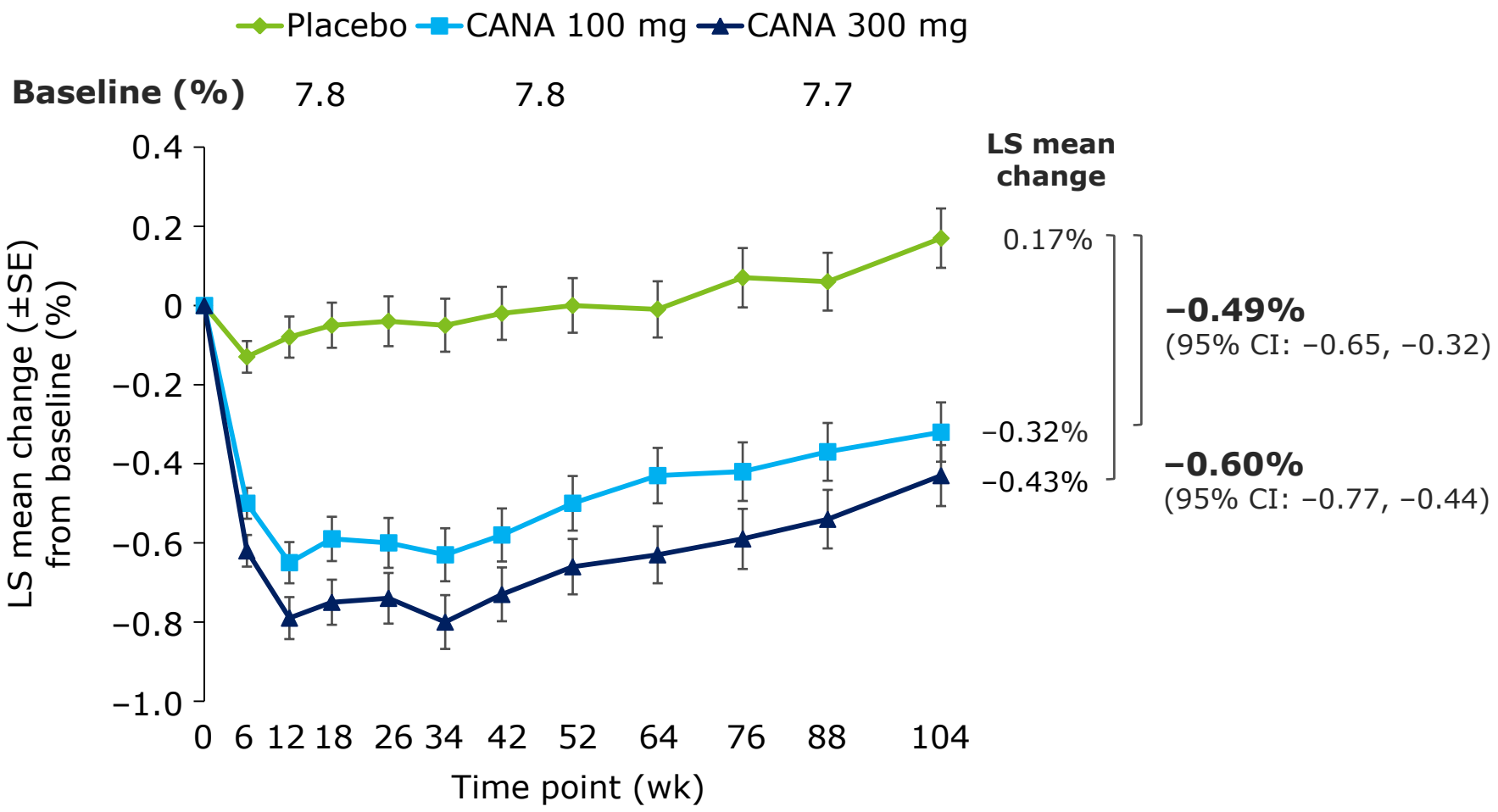


CANA, canagliflozin; PBO, placebo; SE, standard error.
*P<0.001 vs PBO.

Neal B. et al. Diabetes Care DOI: 10.2337/dc14-1237

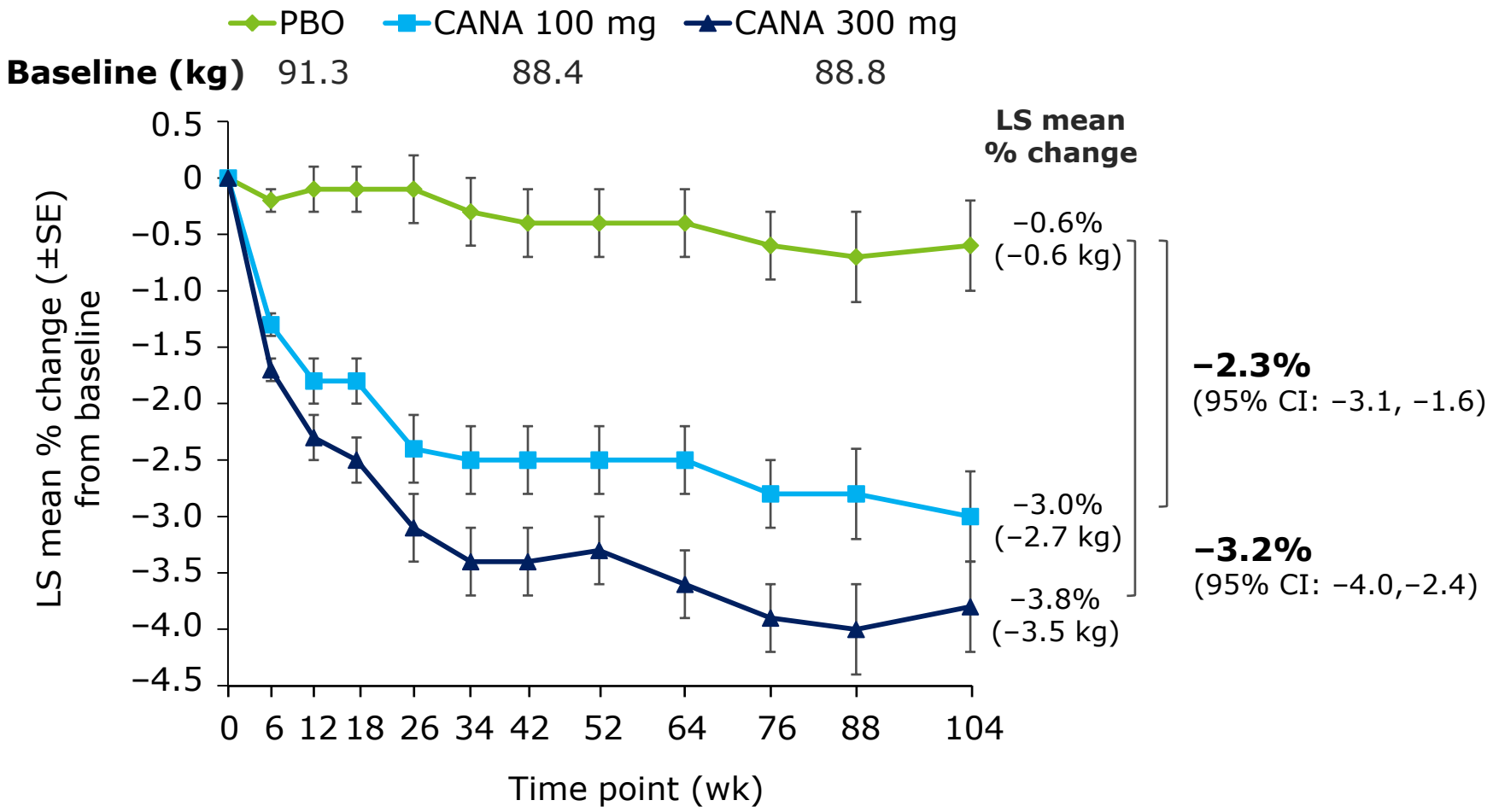
Anziani e IRC

Canagliflozin in Older Patients (104 Weeks): Change in HbA1c (LOCF) from Baseline



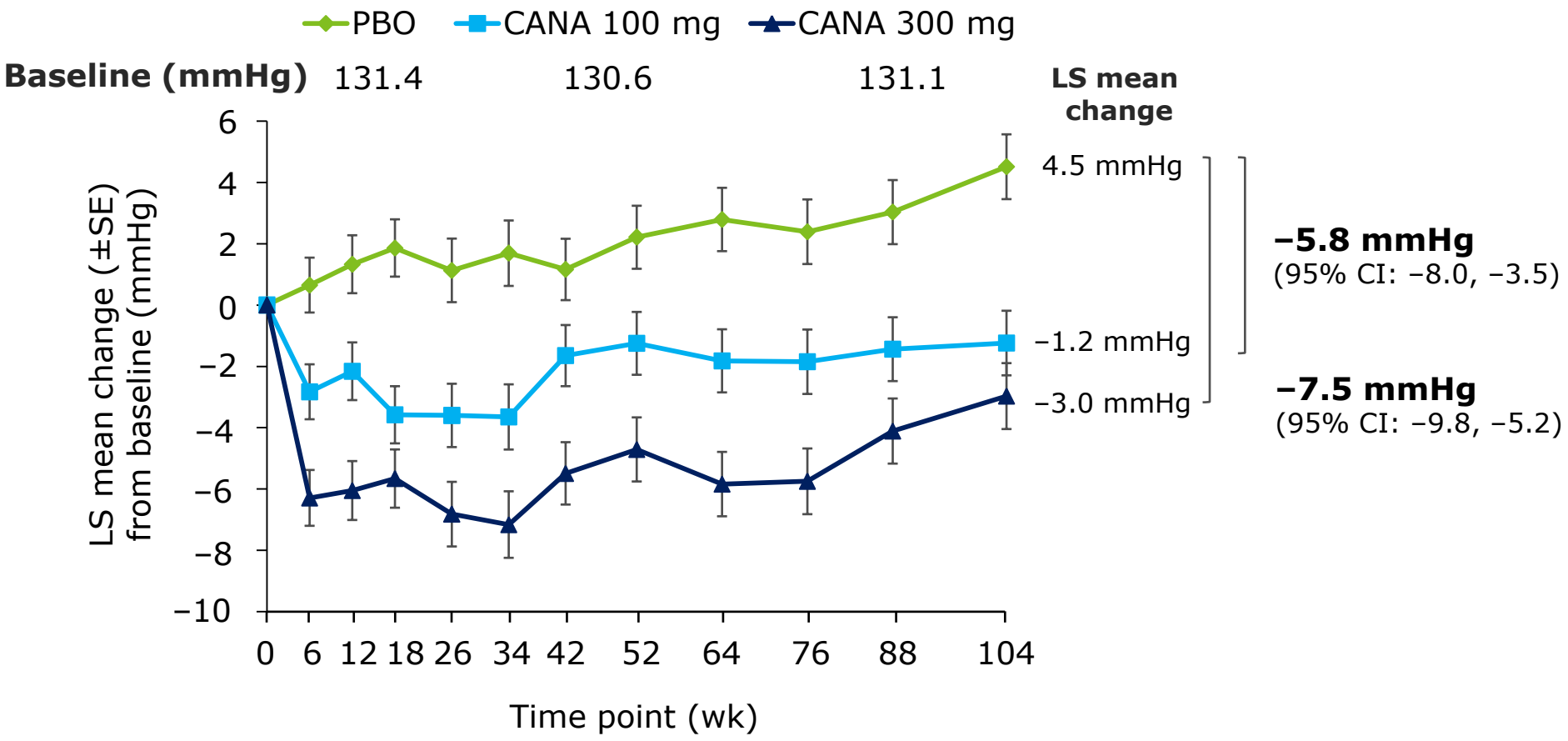
Diabetes Obes Metab. 2015 Mar;17(3):294-303. doi: 10.1111/dom.12428

Canagliflozin in Older Patients (104 Weeks): Percent Change in Body Weight (LOCF) from Baseline



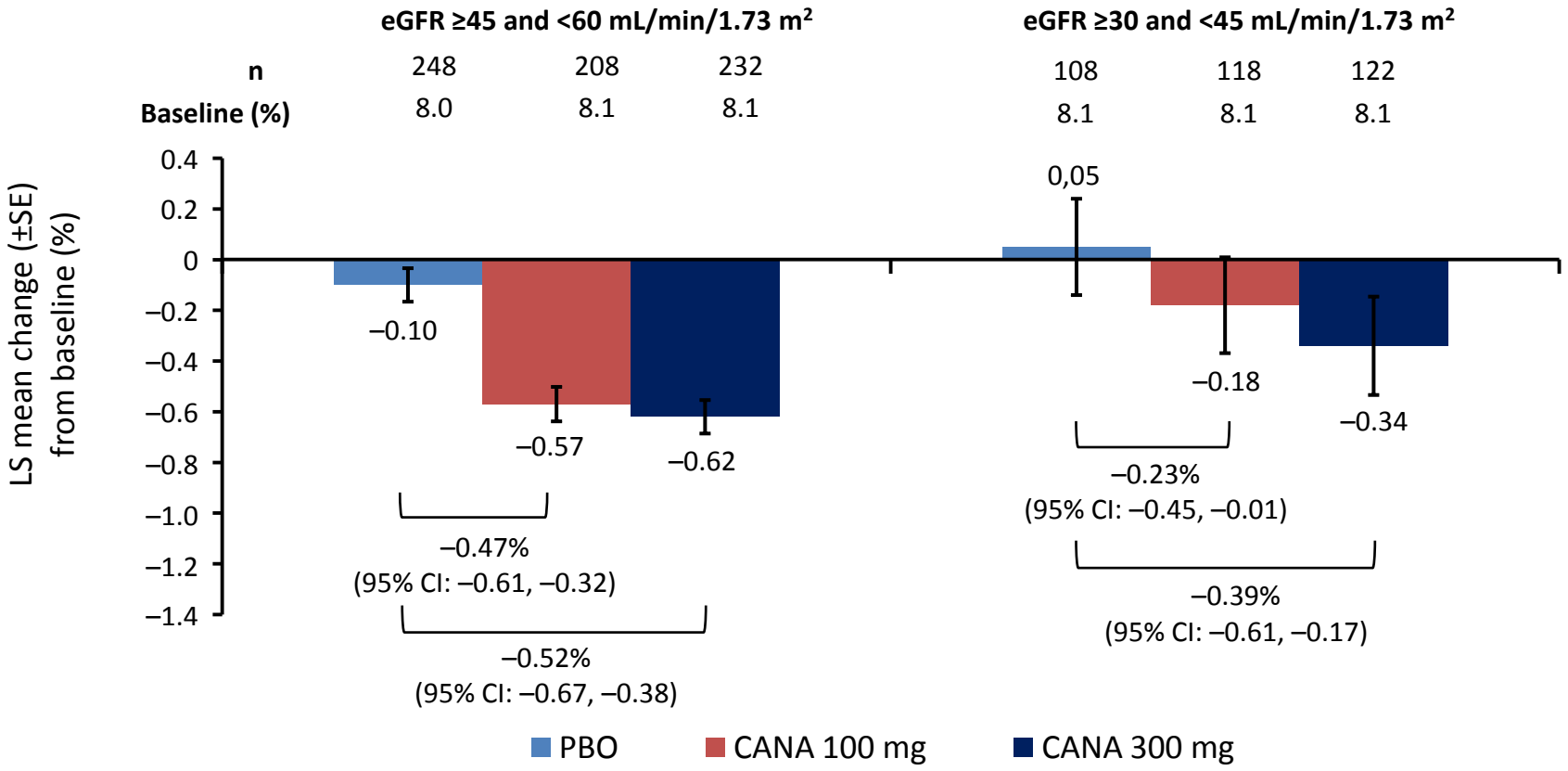
Diabetes Obes Metab. 2015 Mar;17(3):294-303. doi: 10.1111/dom.12428

Canagliflozin in Older Patients (104 Weeks): Change in Systolic BP (LOCF) from Baseline



Diabetes Obes Metab. 2015 Mar;17(3):294-303. doi: 10.1111/dom.12428

Change in A1C by Baseline eGFR Subgroup (LOCF)*

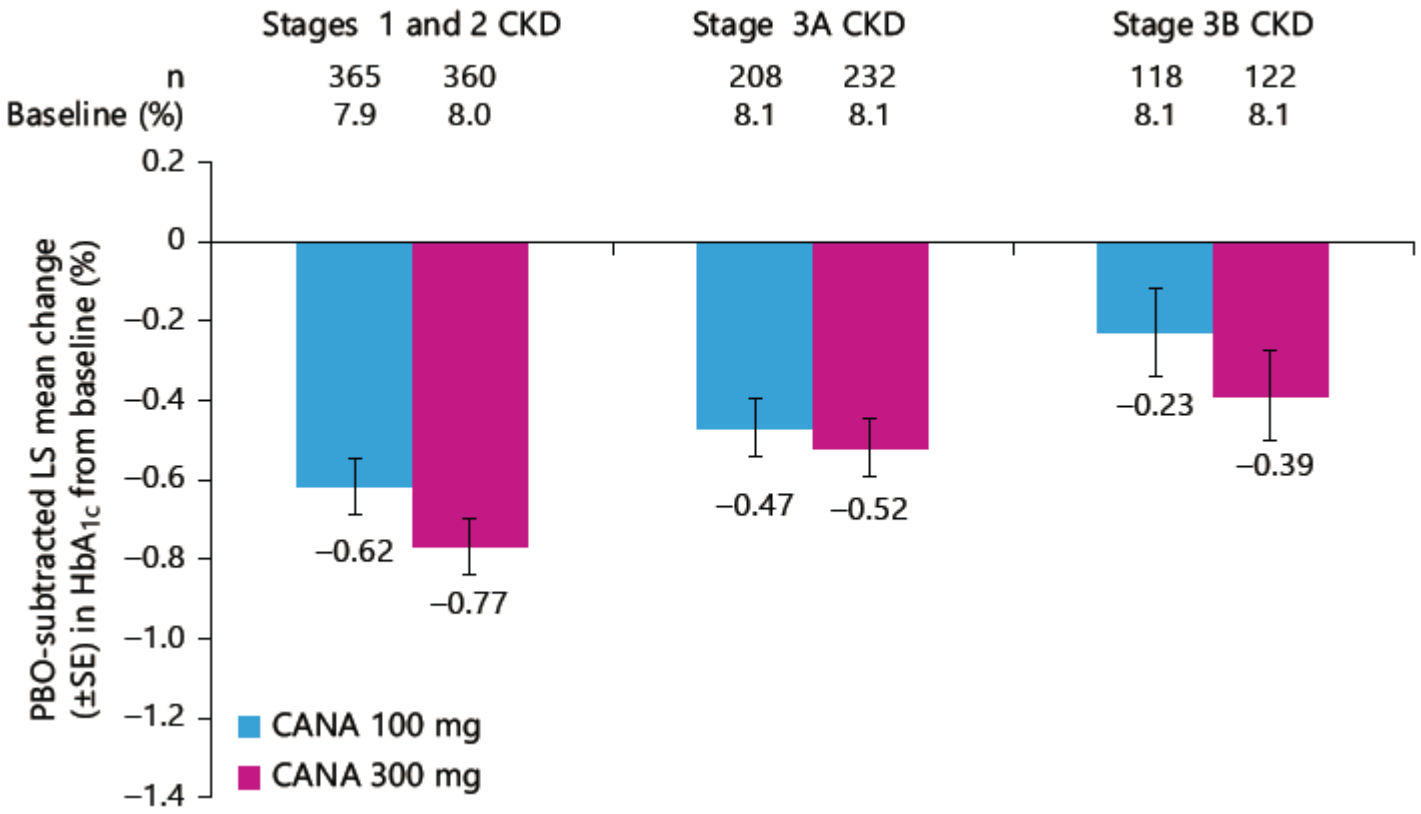


*Statistical comparison for CANA 100 and 300 mg vs PBO not performed (not pre-specified).

This pooled analysis includes some data from patients treated with canagliflozin 300mg and with eGFR 30- 45 that is not expected to be included in the EU label

Woo V et al. Poster presented at the 73rd Scientific sessions of the American Diabetes Association (ADA), 2013; Jun. 21-25; Chicago, Illinois, (73-LB).

Comparisonofplacebo-subtractedeffect of canagliflozin in people with stages 1 and 2 CKD versus stage 3 CKD



Stage 3A CKD (Cronic Kidney Disease) eGFR≥45 and <60 mL/min/m^2
Stage 3B CKD (Cronic Kidney Disease) eGFR ≥30 and <45 mL/min/m^2

Yamout H., et al. (2014). Am J Nephrol; 40:64-74.

Effetti collaterali

Canagliflozin in Older Patients (104 Weeks): Summary of Overall Safety and Selected AEs

Subjects, n (%)	PBO (n = 237)	CANA 100 mg (n = 241)	CANA 300 mg (n = 236)
Any AE	204 (86.1)	212 (88.0)	212 (89.8)
AEs leading to discontinuation	16 (6.8)	11 (4.6)	24 (10.2)
AEs related to study drug[†]	94 (39.7)	103 (42.7)	119 (50.4)
Serious AEs	41 (17.3)	40 (16.6)	43 (18.2)
Deaths	0	2 (0.8)	0
UTI	24 (10.1)	35 (14.5)	39 (16.5)
Genital mycotic infection Male Female	2 (1.4) 4 (4.3)	7 (5.6) 28 (23.9)	14 (10.9) 20 (18.7)
Osmotic diuresis-related AEs[‡]	13 (5.5)	22 (9.1)	29 (12.3)
Volume-related AEs	4 (1.7)	13 (5.4)	14 (5.9)

All AEs are reported for regardless of rescue medication.
[†]Possibly, probably, or very likely related to study drug, as assessed by investigators.
[‡]Includes dry mouth, dry throat, micturition disorder, micturition urgency, nocturia, pollakiuria, polydipsia, polyuria, thirst, and urine output increased.

Diabetes Obes Metab. 2015 Mar;17(3):294-303. doi: 10.1111/dom.12428

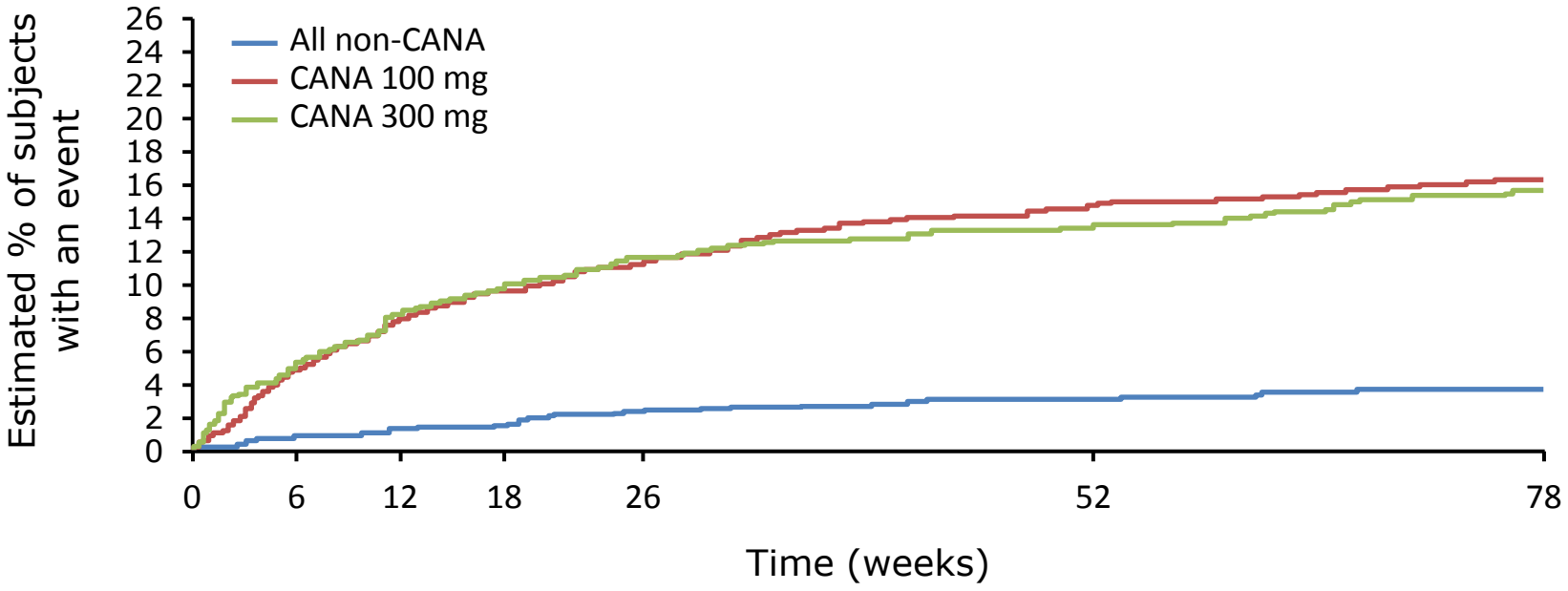
Add on to MetforminvsGlimepiride: Summary of Overall Safety and Selected AEs Over 104 Weeks*

	GLIM (n = 482)	CANA 100 mg (n = 483)	CANA 300 mg (n = 485)
Any AE	378 (78.4)	354 (73.3)	378 (77.9)
AEs leading to discontinuation	35 (7.3)	30 (6.2)	46 (9.5)
AEs related to study drug[†]	134 (27.8)	138 (28.6)	159 (32.8)
Serious AEs	69 (14.3)	47 (9.7)	47 (9.7)
Deaths	2 (0.4)	3 (0.6)	3 (0.6)
Genital mycotic infection Male[‡,§] Female[‖,¶]	 5 (1.9) 6 (2.7)	 24 (9.5) 32 (13.9)	 22 (9.1) 38 (15.6)
Urinary Tract Infection (UTI)	33 (6.8)	51 (10.6)	42 (8.7)
Osmotic diuresis-related AEs[#]	10 (2.1)	28 (5.8)	32 (6.6)
Volume-related AEs**	11 (2.3)	8 (1.7)	12 (2.5)

*All AEs are reported for regardless of rescue medication.
[†]Possibly, probably, or very likely related to study drug, as assessed by investigators.
[‡]GLIM, n = 263; CANA 100 mg, n = 252; CANA 300 mg, n = 241.
[§]Including balanitis, balanitis candida, balanoposthitis, genital candidiasis, genital infection fungal, and posthitis.
[‖]GLIM, n = 219; CANA 100 mg, n = 231; CANA 300 mg, n = 244.
[¶]Including genital infection fungal, vaginal infection, vulvitis, vulvovaginal candidiasis, vulvovaginal mycotic infection, and vulvovaginitis.
[#]Including dry mouth, micturition urgency, nocturia, pollakiuria, polydipsia, polyuria, thirst, and urine output increased.
**Including BP decreased, dehydration, dizziness postural, hypotension, orthostatic hypotension, presyncope, and syncope.

Leiter L.A., et al. (2014). Diabetes Care. Sep 9. pii: DC_132762.

Kaplan-Meier Plot of Time to First Female Genital Mycotic Infection



All non-CANA	1,338	1,312	1,250	1,209	1,135	993	443
CANA 100 mg	1,289	1,217	1,143	1,087	1,034	908	421
CANA 300 mg	1,319	1,243	1,153	1,101	1,036	945	440

Nyirjesy P et al. Poster at the 73rd Scientific sessions of the American Diabetes Association (ADA), 2013; Jun. 21-25; Chicago (P1069).

Characteristics of a “good” drug

- Efficacy
- Safety
- Other Clinical Advantages
- No/Few Adverse Effects
- Reasonable Cost/Value

Figura 2. Flow-chart per la terapia del diabete mellito di tipo 2.

Iniziare con solo intervento su stile di vita (se non grave scompenso metabolico [ref. 1])

↓

Aggiungere gradualmente metformina, fino alla dose di almeno 2g/die

↓

Add on a metformina	Ipoglic.	Peso	Effetti indesid.	CVD	Fattori rischio CV	Scomp. cardiaco	Effetti GI	Costo
Gliptina	1A	1B	Rari	1A	1B	2B (2)	1A	Elevato
A.R. GLP-1	1A	1A	Non indicato in IRC	3B	1A	2B	1C	Elevato
Sulfonilurea o repaglinide	1D	1D	Non indicato in IRC (3)	3C (2)	1B	1B	1A	Basso
Pioglitazione	1A	1D	Fratture	1A	1A	1E	1A	Medio
Acarbosio	1A	1D	Rari	2B	2B	3C	1C	Basso
Gliflozina	1A	1A	Infezioni GU	3C	2B	2B	1A	???
Insulina basale	1D	1A	Rari	1B	1A	1B	1A	Medio

In presenza di un fallimento della terapia iniziale volta a modificare lo stile di vita, prescrivere metformina, che dovrà accompagnare sempre, se tollerata e non controindicata, ogni altro farmaco, alla dose di almeno 2 g/die. Se fallisce la metformina, aggiungere un secondo o anche un terzo farmaco secondo lo schema indicato, valutando comunque la possibilità di inserire una terapia insulinica, anche temporaneamente. Sebbene un approccio fisiopatologico nella scelta del farmaco da associare alla metformina appaia il più razionale, non esiste alcuna evidenza che lo stesso sia maggiormente efficace o indicato. Al contrario, i possibili effetti collaterali o pleiotropici dei farmaci sono noti e dimostrati e devono essere considerati nella scelta terapeutica.

Nota: in presenza di HbA_{1c}>2% all'obiettivo, iniziare direttamente terapia combinata, eventualmente anche con insulina solo saxagliptin: minimo rischio per scompenso cardiaco; non dati per altre molecole alcuni farmaci di questa classe non hanno metabolismo renale, ma non hanno comunque indicazione in scheda tecnica solo per glibenclamide, possibili rischi cardiaci.

Colori:
- effetto o parametro negativo o sconsigliato
- effetto o parametro parzialmente negativo o sconsigliato
- effetto o parametro positivo o probabilmente positivo
- il farmaco non ha effetti significativi sul parametro o viene dato un giudizio neutro

Sigle: rappresentano il grado di evidenza (1-6) e di forza (A-E).

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Sulfonilurea o repaglinide	1D	1D	Non indicato in IRC (3)	3C (2)	1B	1B	1A	Basso
Pioglitazione	1A	1D	Fratture	1A	1A	1E	1A	Medio
Acarbosio	1A	1D	Rari	2B	2B	3C	1C	Basso
Gliflozina	1A	1A	Infezioni GU	3C	2B	2B	1A	
Insulina basale	1D	1A	Rari	1B	1A	1B	1A	Medio

In presenza di un fallimento della terapia iniziale volta a modificare lo stile di vita, prescrivere metformina, che dovrà accompagnare sempre, se tollerata e non controindicata, ogni altro farmaco, alla dose di almeno 2 g/die. Se fallisce la metformina, aggiungere un secondo o anche un terzo farmaco secondo lo schema indicato, valutando comunque la possibilità di inserire una terapia insulinica, anche temporaneamente. Sebbene un approccio fisiopatologico nella scelta del farmaco da associare alla metformina appaia il più razionale, non esiste alcuna evidenza che lo stesso sia maggiormente efficace o indicato. Al contrario, i possibili effetti collaterali o pleiotropici dei farmaci sono noti e dimostrati e devono essere considerati nella scelta terapeutica.

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