SGLT2 Inibitori

Domande e risposte: le prime esperienze in Italia

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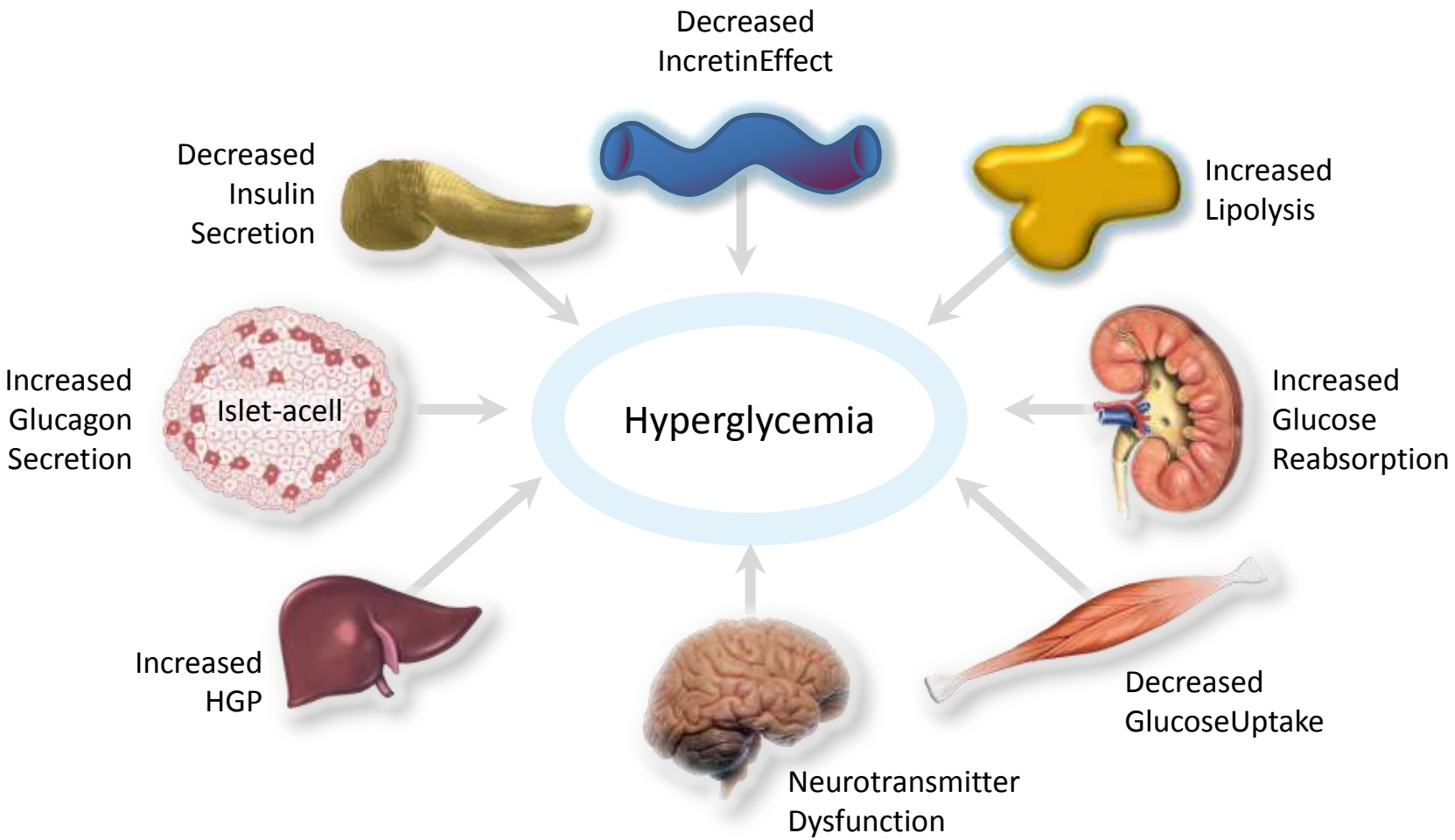
Disclosure Statement

- 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

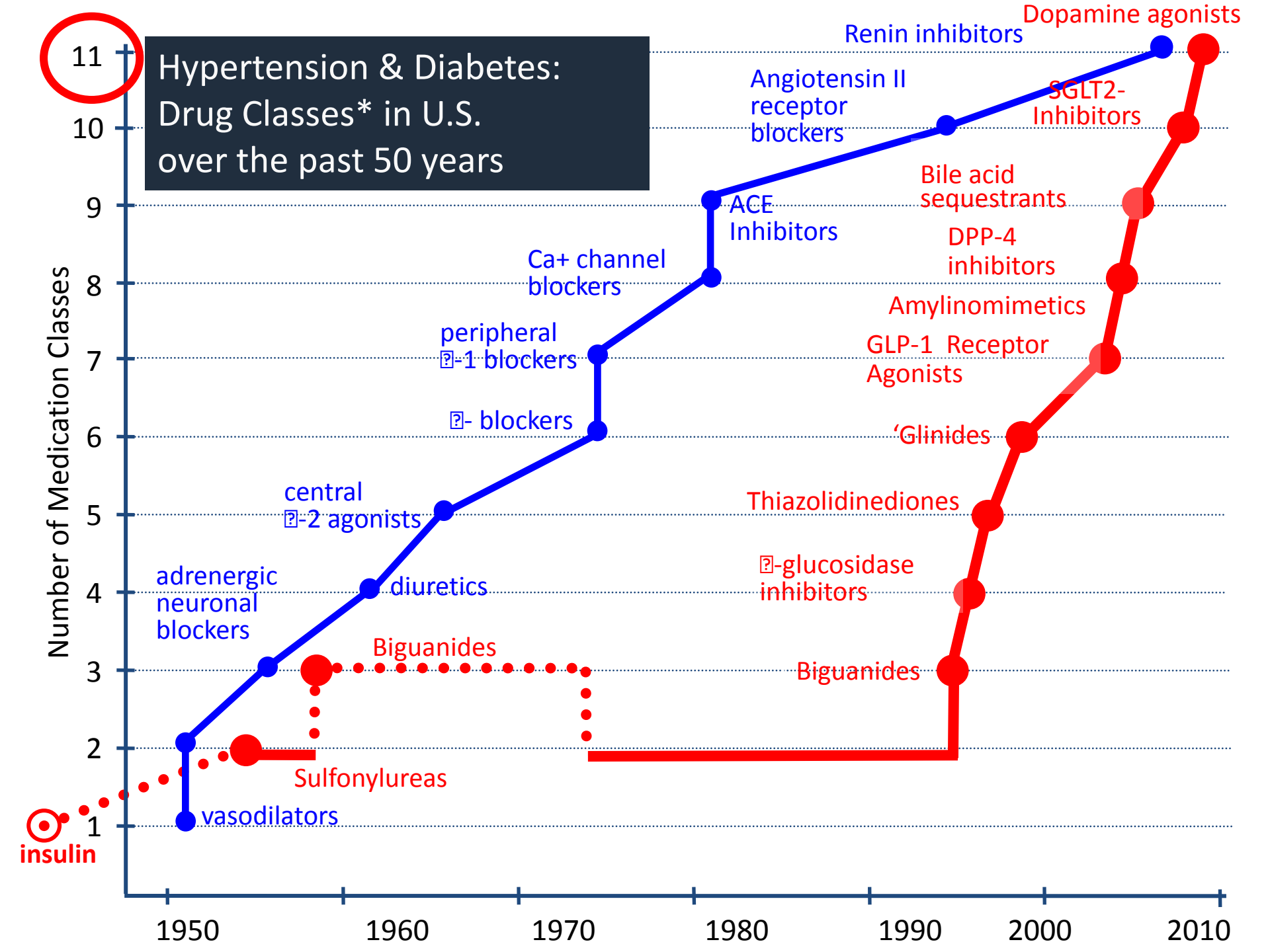
Agenda

- La fisiopatologia del diabete
- Meccanismo d’azione degli inibitori del SGLT2
- Le molecole: efficacia, sicurezza, effetti clinici aggiuntivi
- Gli effetti collaterali
- Esperienza clinica

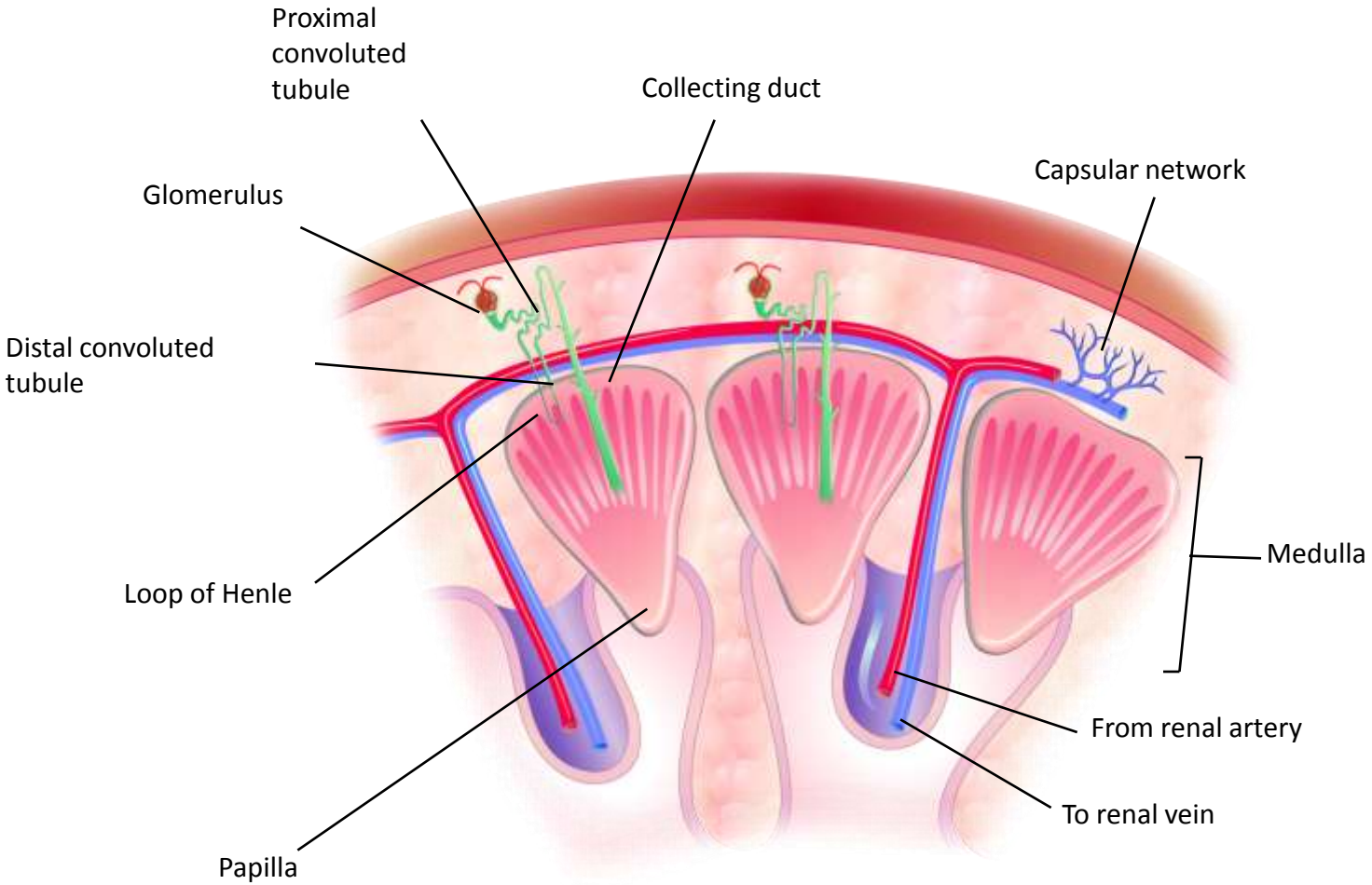
The pathophysiology of diabetes



De Fronzo RA. Diabetes 2009;58:773-795

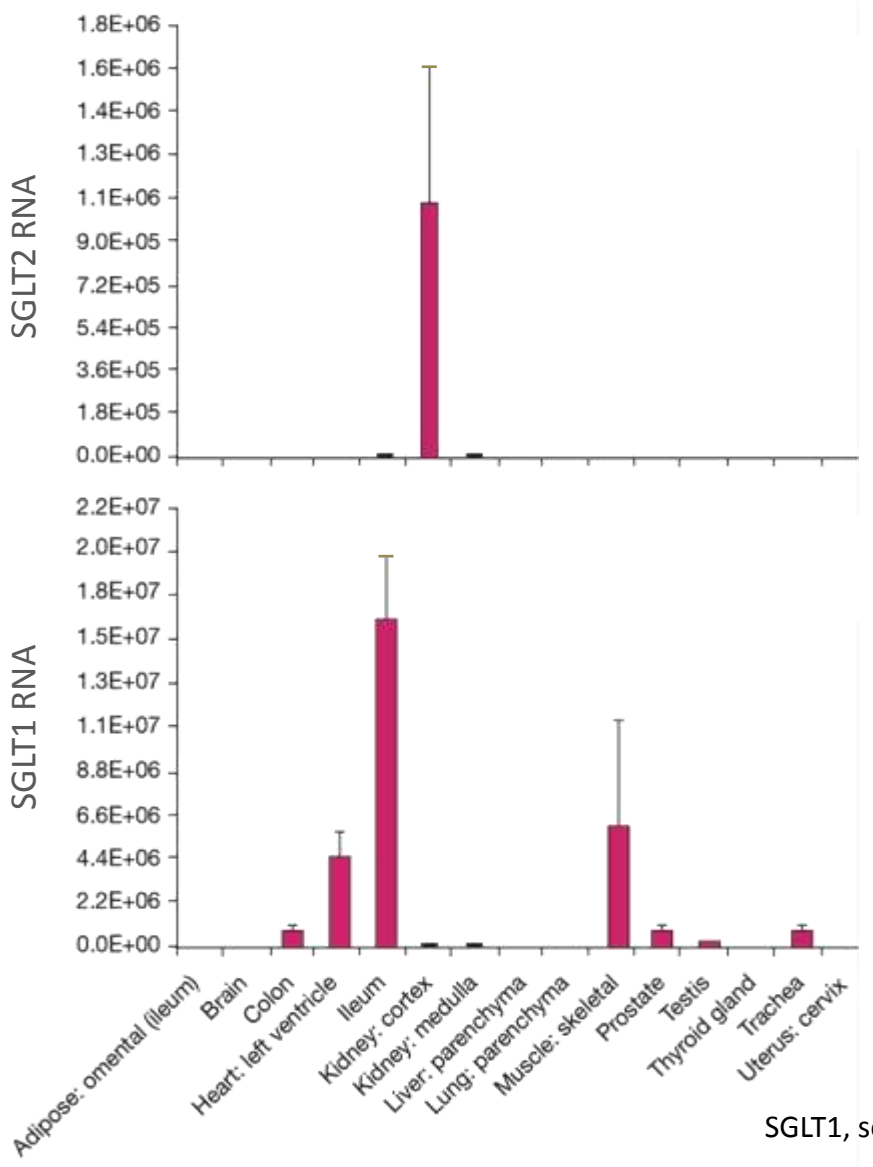

Hypertension & Diabetes:
Drug Classes* in U.S.
over the past 50 years
Number of Medication Classes
11
10
9
8
7
6
5
4
3
2
1
1950
1960
1970
1980
1990
2000
2010
insulin
vasodilators
adrenergic neuronal blockers
central ⍰-2 agonists
peripheral ⍰-1 blockers
⍰- blockers
Ca+ channel blockers
ACE Inhibitors
Angiotensin II receptor blockers
Renin inhibitors
Dopamine agonists
SGLT2-Inhibitors
Bile acid sequestrants
DPP-4 inhibitors
Amylinomimetics
GLP-1 Receptor Agonists
'Glinides
Thiazolidinediones
⍰-glucosidase inhibitors
Biguanides
diuretics
Biguanides
Sulfonylureas

Major functional elements of the kidney



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

SGLT2 expression is mainly in the kidney

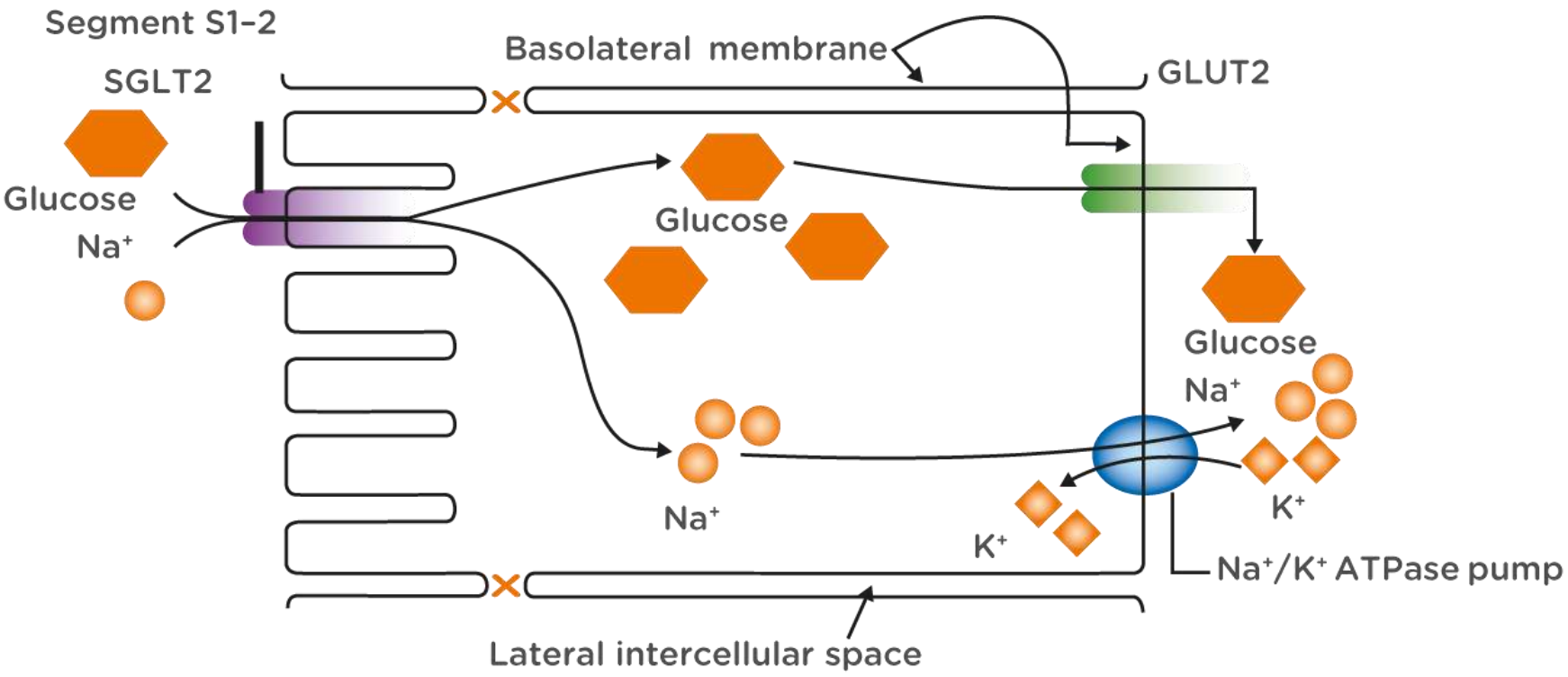


SGLT2 expression
is mainly in the kidney

SGLT1 expression is mainly
in the gastrointestinal tract,
skeletal muscle, heart and, to
a small degree, in the kidney

SGLT1, sodium glucose cotransporter 1; SGLT2, sodium glucose cotransporter 2.
Adapted from: Chen J, et al. *Diabetes Ther*. 2010;1:57–92.

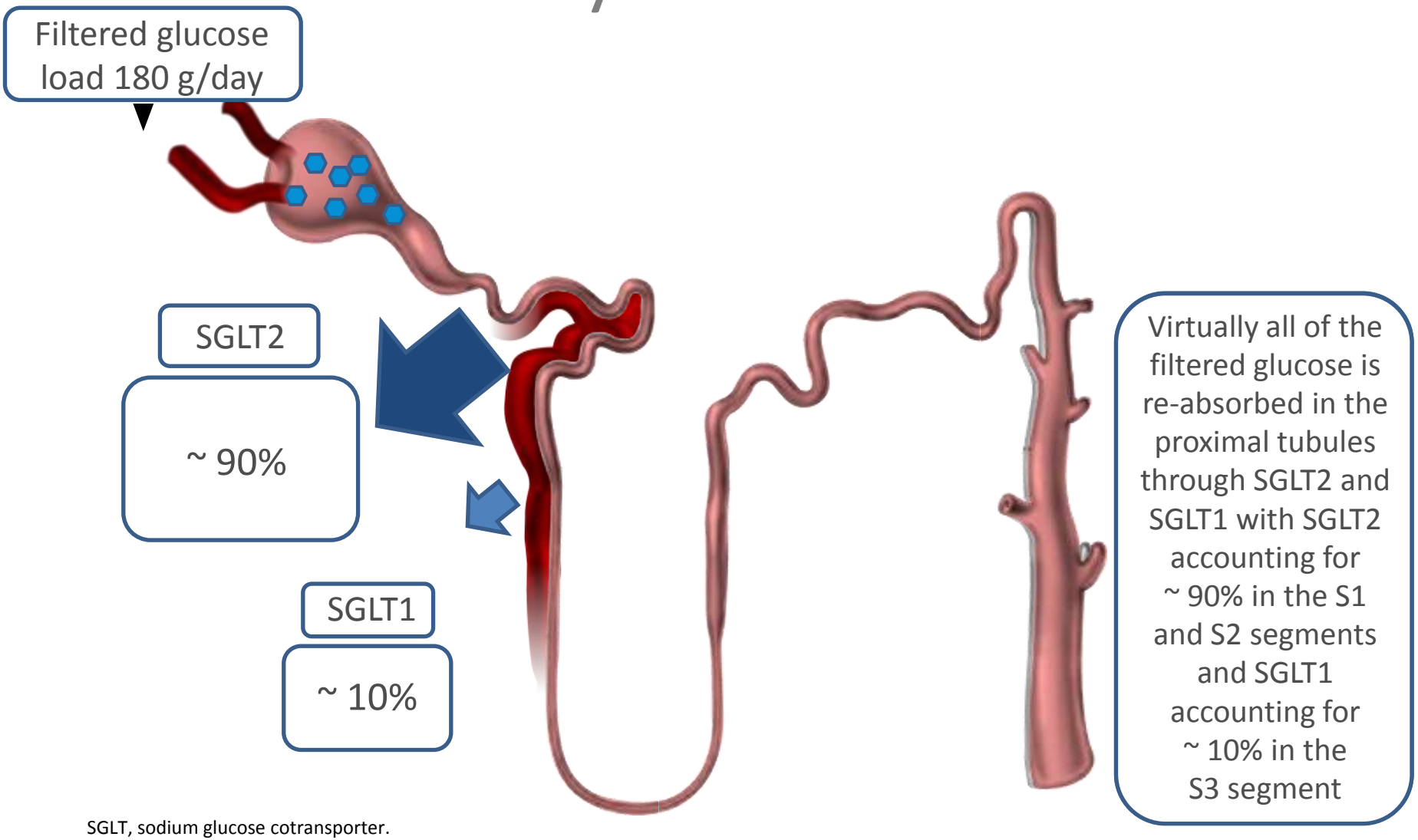
SGLT2



- SGLTs transfer glucose and sodium from the lumen into the cytoplasm of tubular cells through a secondary active transport mechanism
- At the basolateral membrane GLUT2 transfers the intracellular glucose to the interstitium and plasma by a facilitated transport process (via a Na+/K+ ATPase)

Adapted from: Wright EM, et al. *Physiology*2004;19:370–76;
BakrisGL, et al. *Kidney Int*2009;75;1272–1277.

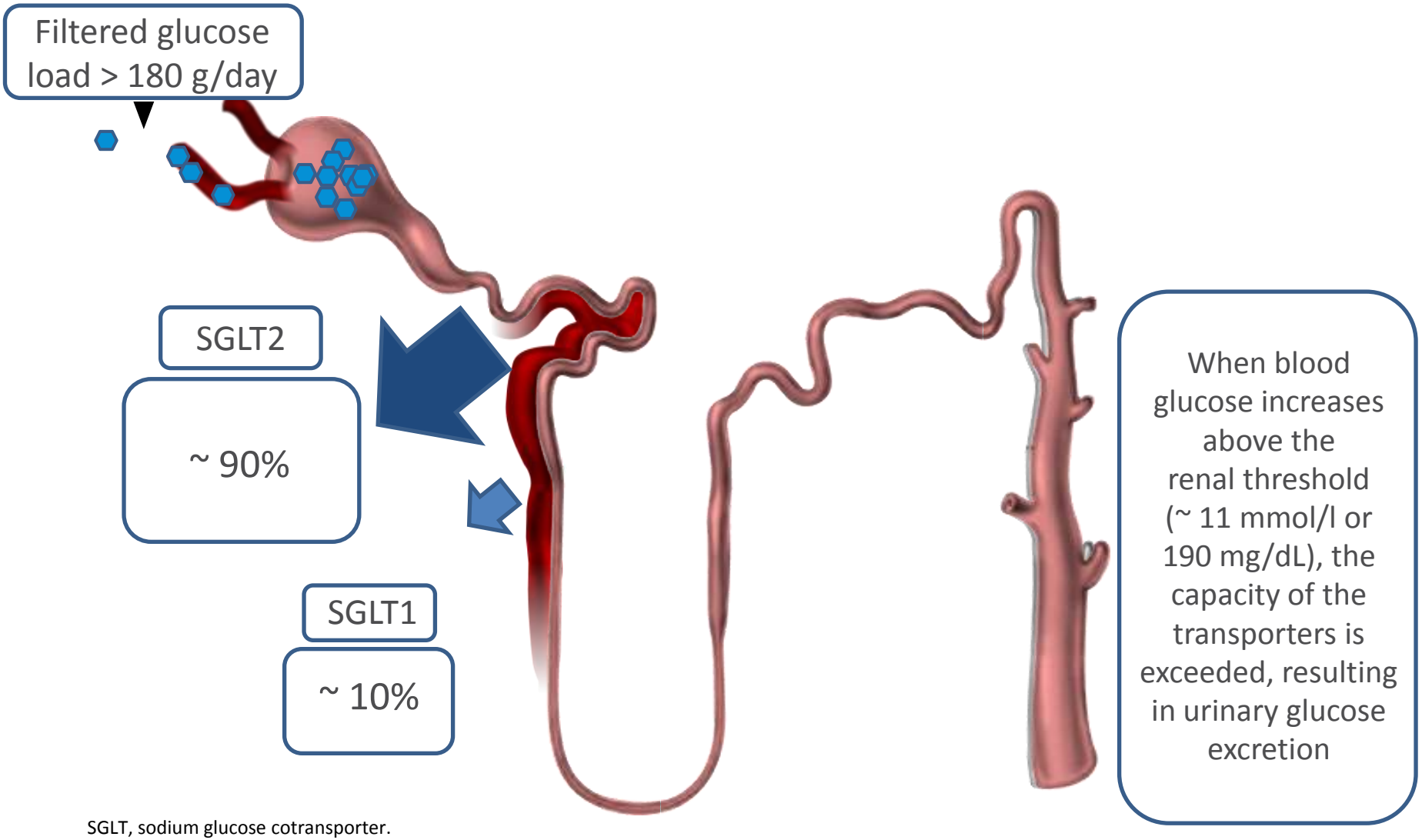
Renal glucose re-absorption under healthy conditions[1,2]



SGLT, sodium glucose cotransporter.

1. Adapted from: Gerich JE. *DiabetMed*. 2010;27:136–142; 2. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

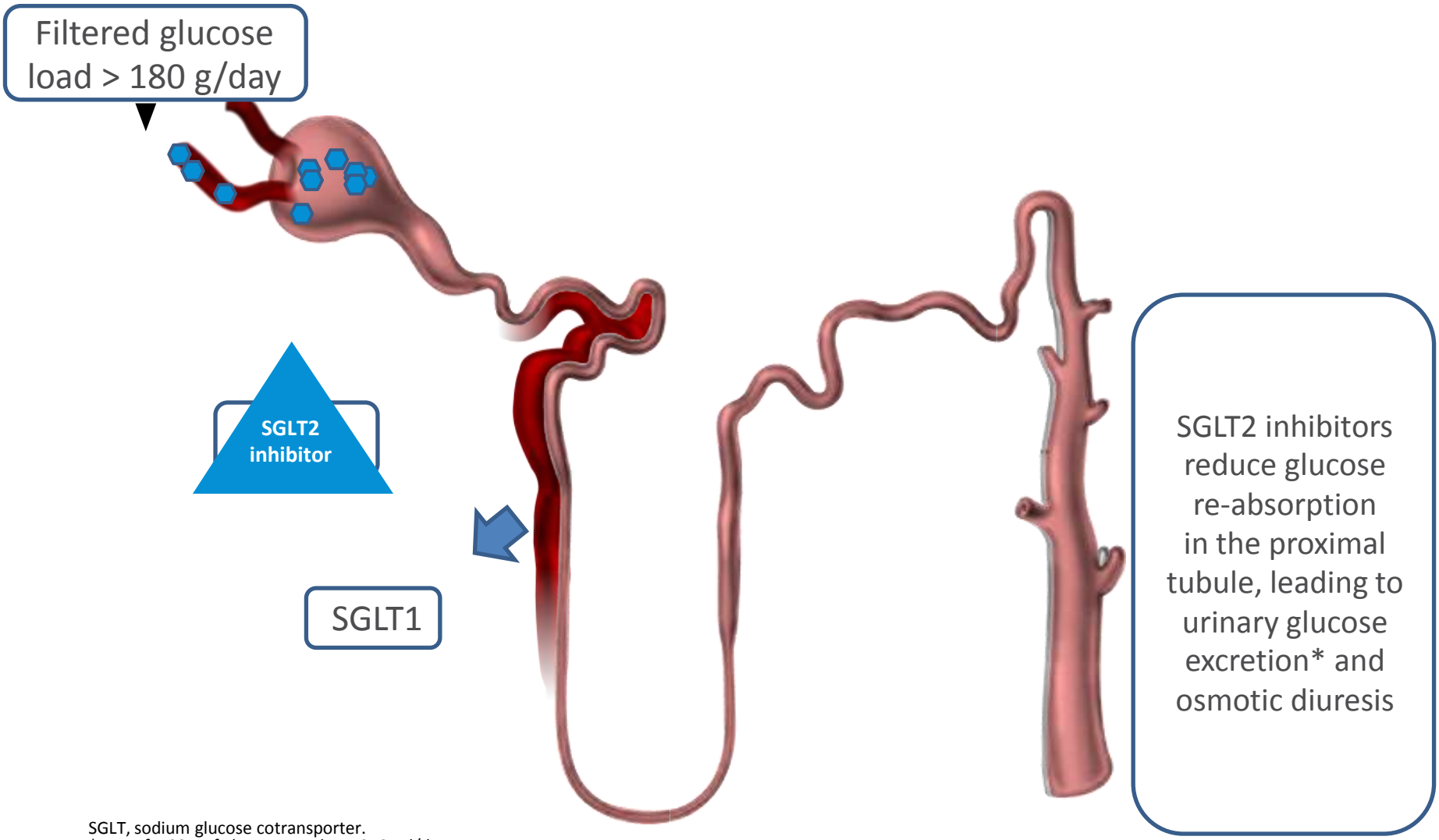
Renal glucose re-absorption in patients with diabetes[1,2]



SGLT, sodium glucose cotransporter.

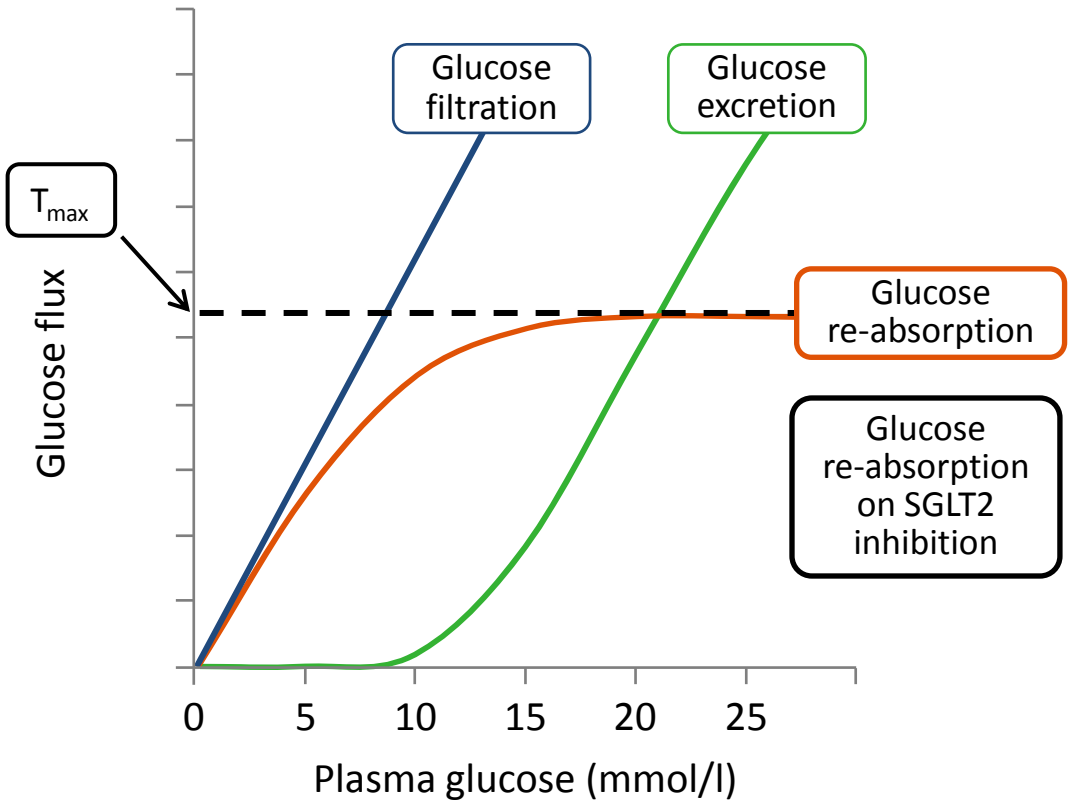
1. Adapted from: Gerich JE. *DiabetMed*. 2010;27:136–142; 2. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

Urinary glucose excretion via SGLT2 inhibition[1]



SGLT, sodium glucose cotransporter.
*Loss of ~ 80 g of glucose per day = 240 cal/day.
1. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

Renal glucose re-absorption and excretion



Glucose re-absorption is increased in T2D...

...reducing the amount of glucose excreted at a given level of blood glucose

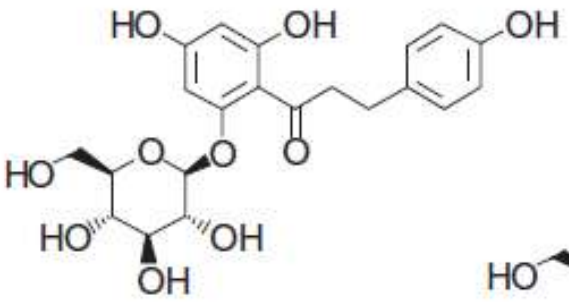
SGLT2 inhibitors lower the amount of glucose that can be re-absorbed, i.e., lower the renal threshold/T_{max}

This increases glucose excretion

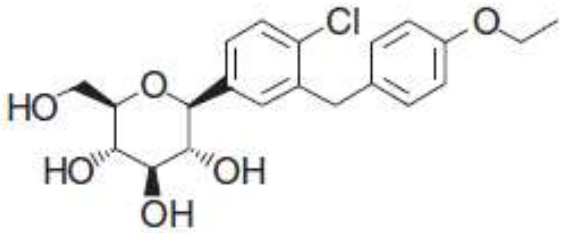
SGLT2, sodium glucose cotransporter2; T2D, Type 2 Diabetes; T_{max}, maximal renal tubule glucose re-absorption capacity.

1. Gerich JE. *Diabet Med*. 2010;27:136–142; 2. Adapted from: Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34–42.

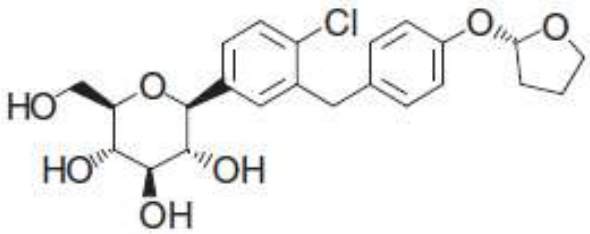
Strutture chimiche degli inibitori di SGLT 2



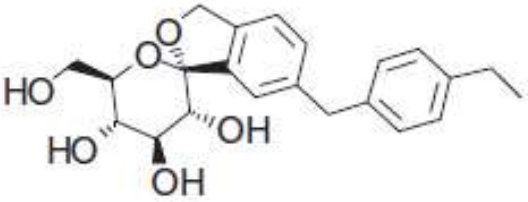
Phlorizin



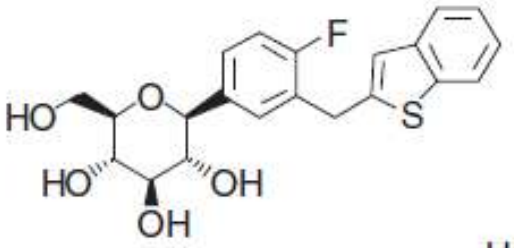
Dapagliflozin



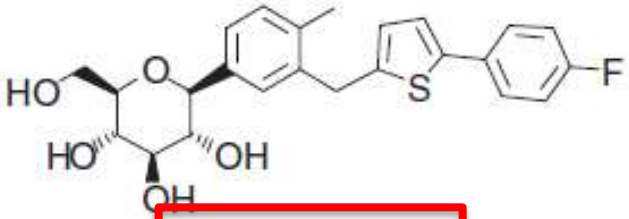
Empagliflozin



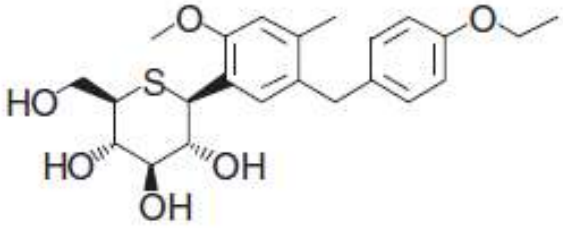
Tofogliflozin



Ipragliflozin



Canagliflozin



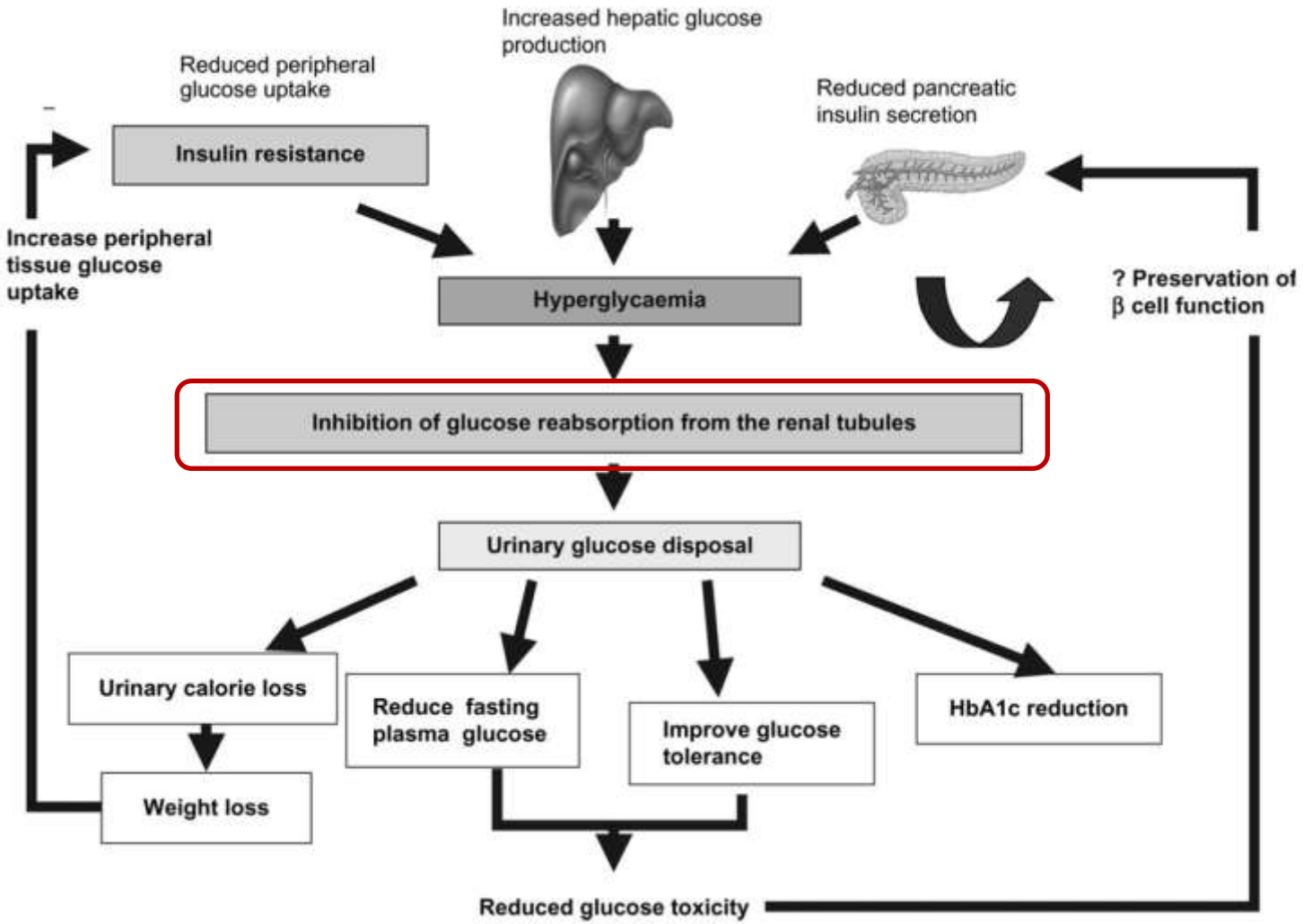
Luseogliflozin

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

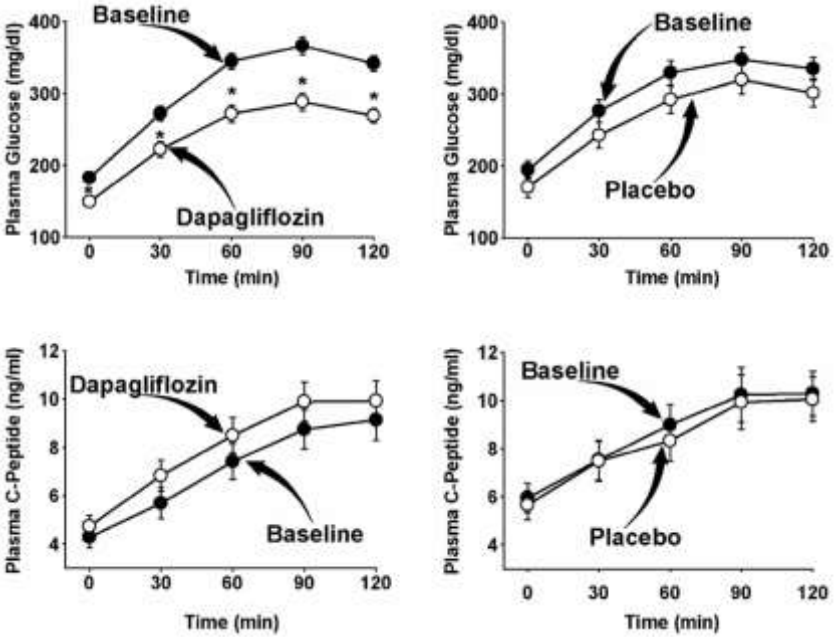
Ferrannini E, Diabetes 2011; 60: 695- 6

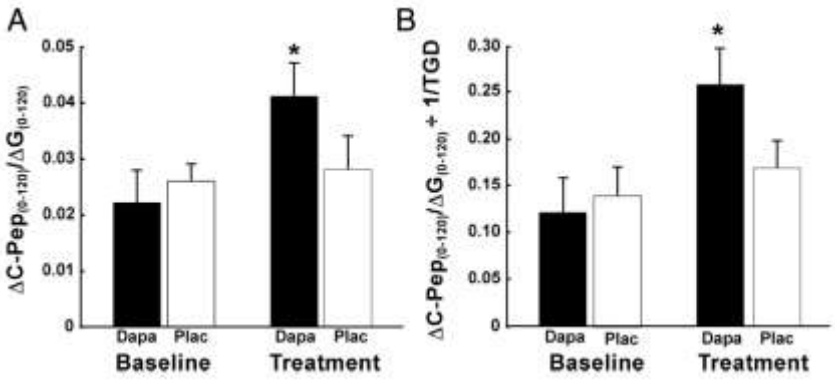
Rappresentazione schematica degli effetti clinici degli inibitori di SGLT- 2

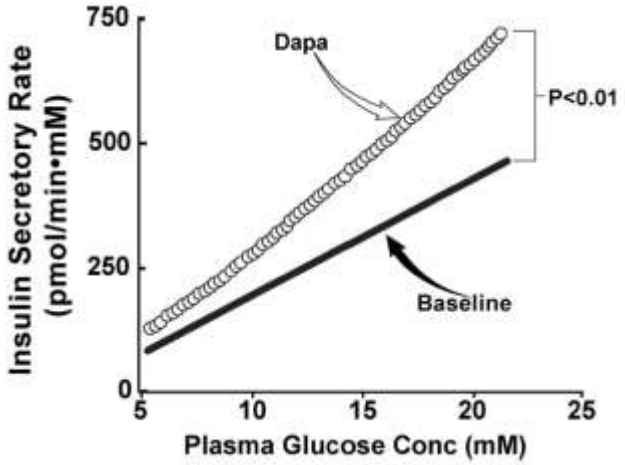


Idris I, Diabetes, Obesity and Metabolism 2009; 11: 79–88

DapagliflozinLowers Plasma GlucoseConcentration and Improves Beta CellFunction

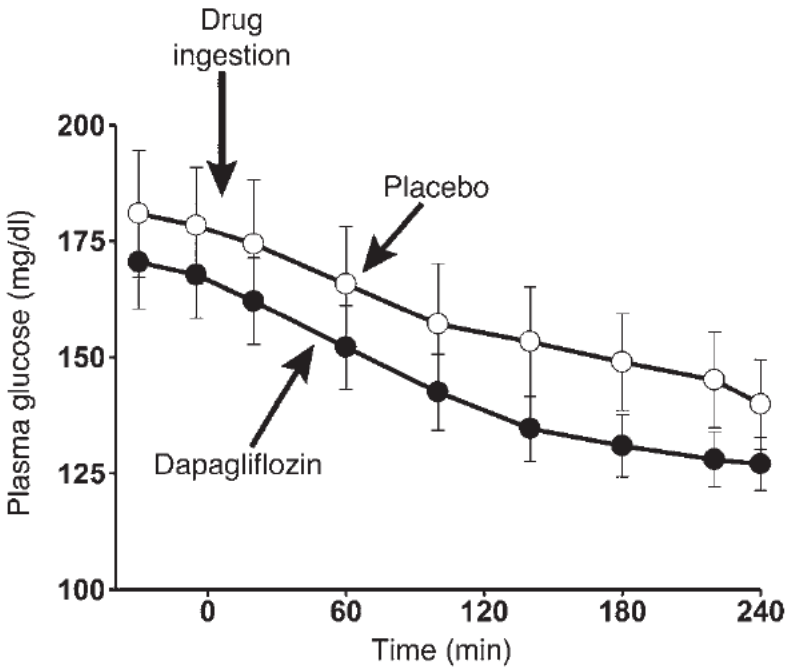


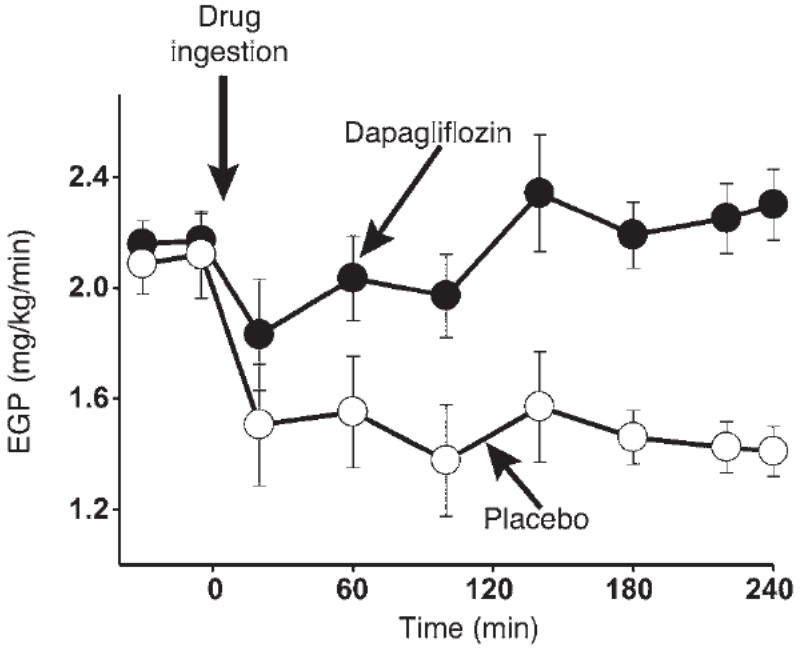


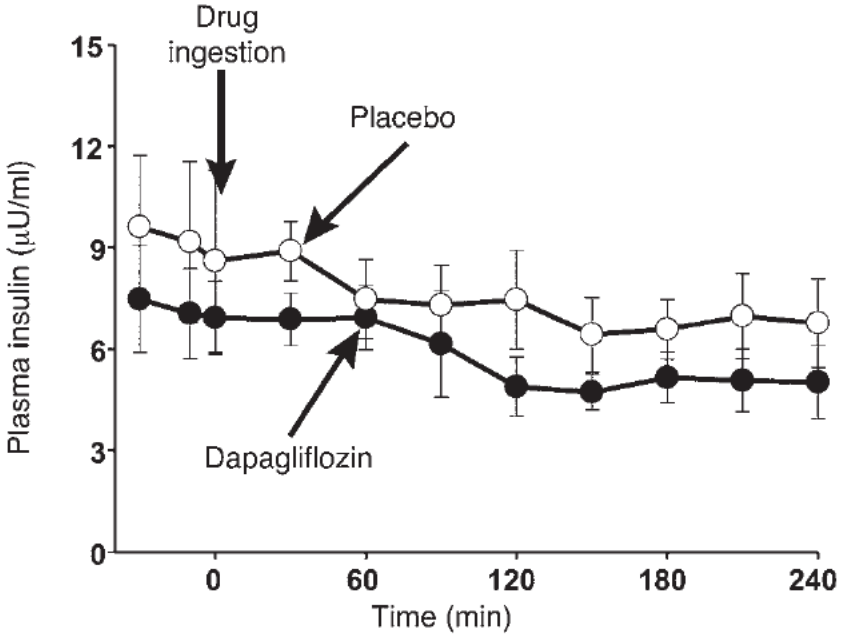


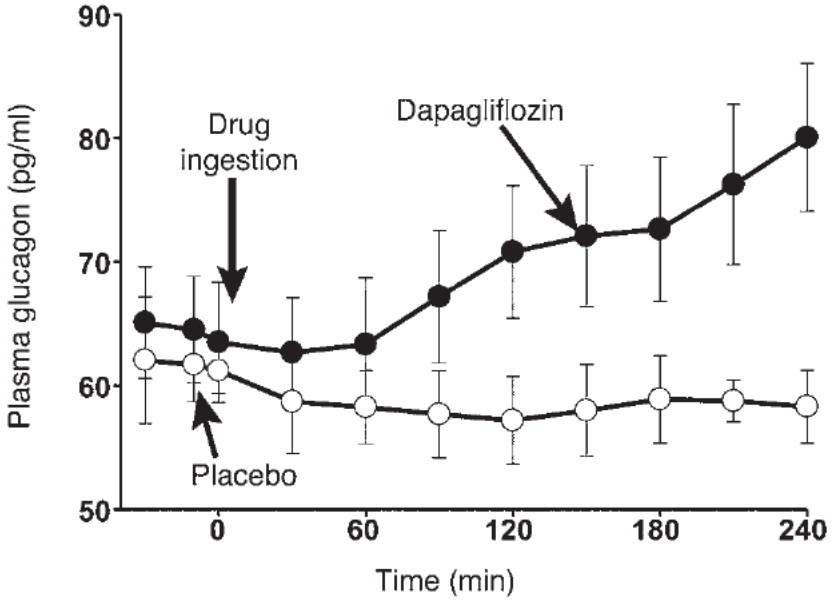
Conclusions: Lowering the plasma glucose concentration with dapagliflozin markedly improves beta cell function, providing strong support in man for the glucotoxic effect of hyperglycemia on beta cell function

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


Drug ingestion
Placebo
Dapagliflozin
Plasma glucose (mg/dl)
200
175
150
125
100
0
60
120
180
240
Time (min)


Drug ingestion
Dapagliflozin
Placebo
EGP (mg/kg/min)
2.4
2.0
1.6
1.2
0
60
120
180
240
Time (min)


Drug ingestion
Placebo
Dapagliflozin
Plasma insulin (μU/ml)
15
12
9
6
3
0
0
60
120
180
240
Time (min)


Drug ingestion
Dapagliflozin
Placebo
Plasma glucagon (pg/ml)
90
80
70
60
50
0
60
120
180
240
Time (min)

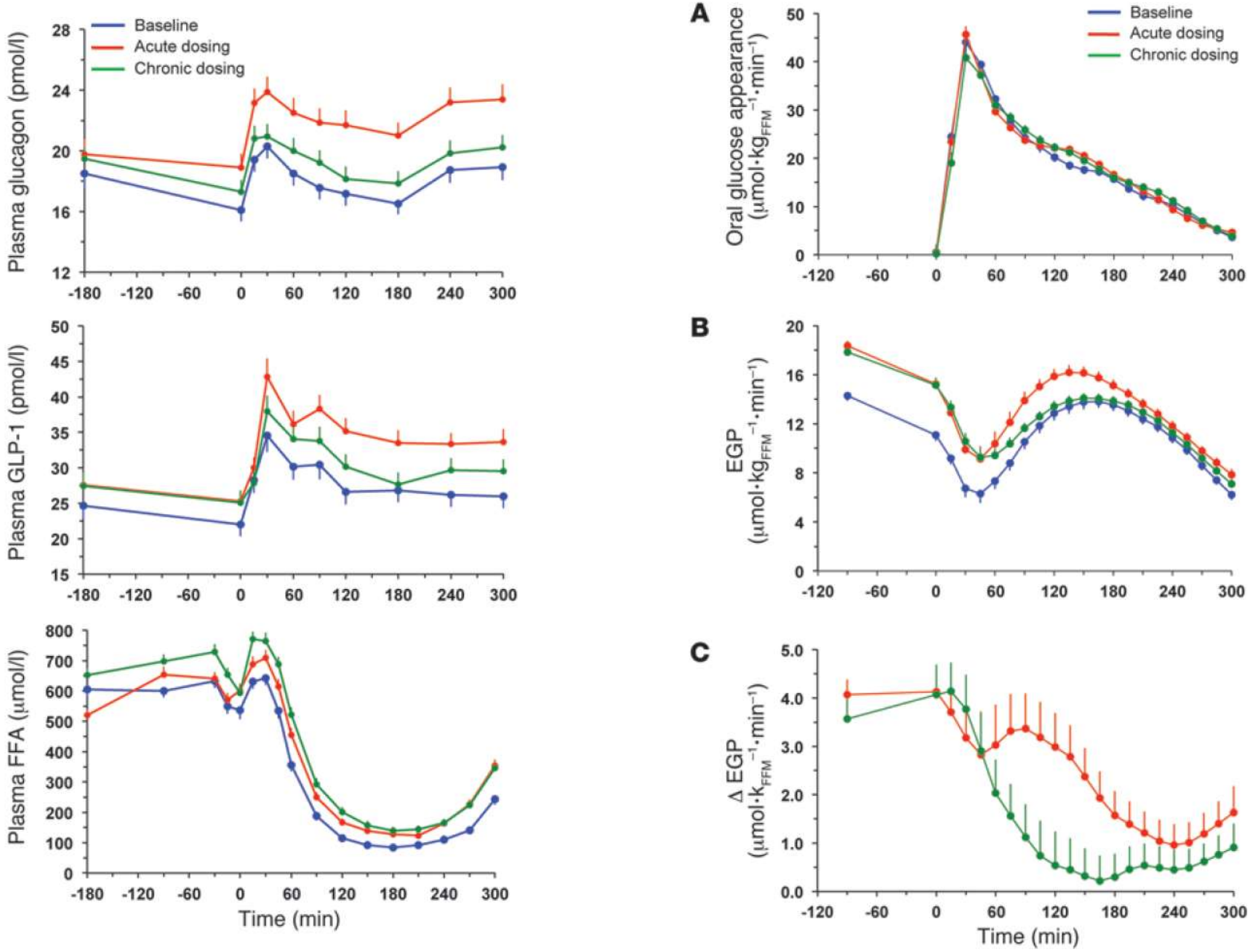
Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients

Ele Ferrannini,[1] Elza Muscelli,[1] Silvia Frascerra,[1] Simona Baldi,[1] Andrea Mari,[2] Tim Heise,[3] Uli C. Broedl,[4] and Hans-Juergen Woerle[4]

[1]Department of Clinical and Experimental Medicine, University of Pisa School of Medicine, Pisa, Italy. [2]CNR Institute of Biomedical Engineering, Padua, Italy. [3]Profil, Neuss, Germany. [4]Boehringer Ingelheim Pharma GmbH and Co. KG, Ingelheim, Germany.

Conclusions. **In patients with type 2 diabetes, empagliflozin-induced glycosuria improved β cell function and insulin sensitivity, despite the fall in insulin secretion and tissue glucose disposal and the rise in EGP after one dose, thereby lowering fasting and postprandial glycemia. Chronic dosing shifted substrate utilization from carbohydrate to lipid.**

JClinInvest. 2014 Feb3;124(2):499-508. doi: 10.1172/JCI72227


Baseline
Acute dosing
Chronic dosing
Plasma glucagon (pmol/l)
Plasma GLP-1 (pmol/l)
Plasma FFA (μmol/l)
Time (min)
A
Oral glucose appearance (μmol·kg$_{FFM}^{-1}$·min^{-1})
B
EGP (μmol·kg$_{FFM}^{-1}$·min^{-1})
C
Δ EGP (μmol·k$_{FFM}^{-1}$·min^{-1})
Time (min)

Sodium–glucose linked transporter-2 inhibitors: potential for renoprotection beyond blood glucose lowering?

- SGLT2 inhibitors reduce single-nephron glomerular filtration rate (SNGFR) in the chronically diseased kidney
- Reduction in blood pressure
- Reduction in plasma uric acid
- Cell culture studies indicate that glucose uptake from the tubular lumen, as well as from the basolateral compartment, can contribute to proximal tubular production of extracellular matrix proteins

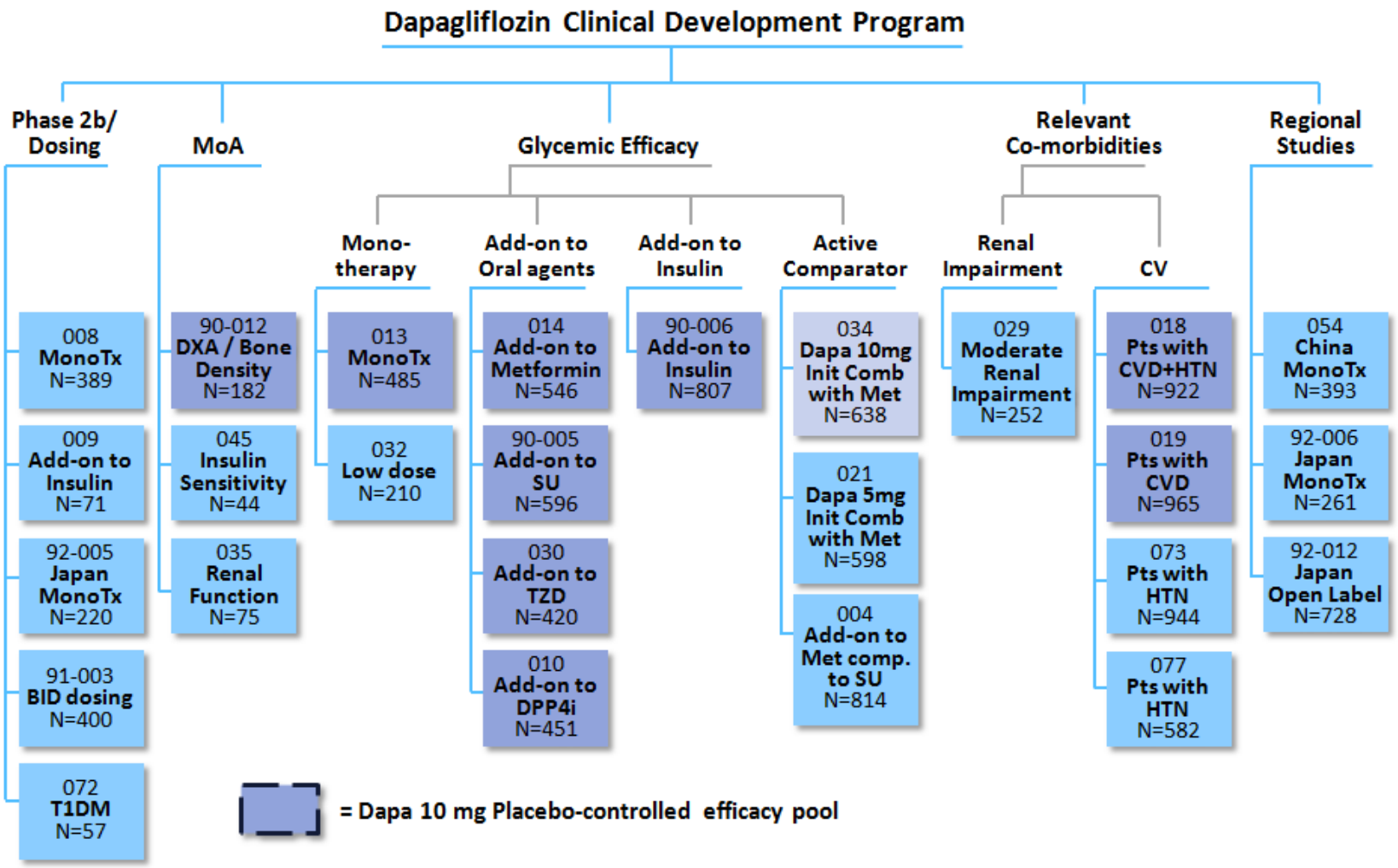
Gilbert RE. Kidney International (2014) 86, 693–700; doi:10.1038/ki.2013.451

I farmaci

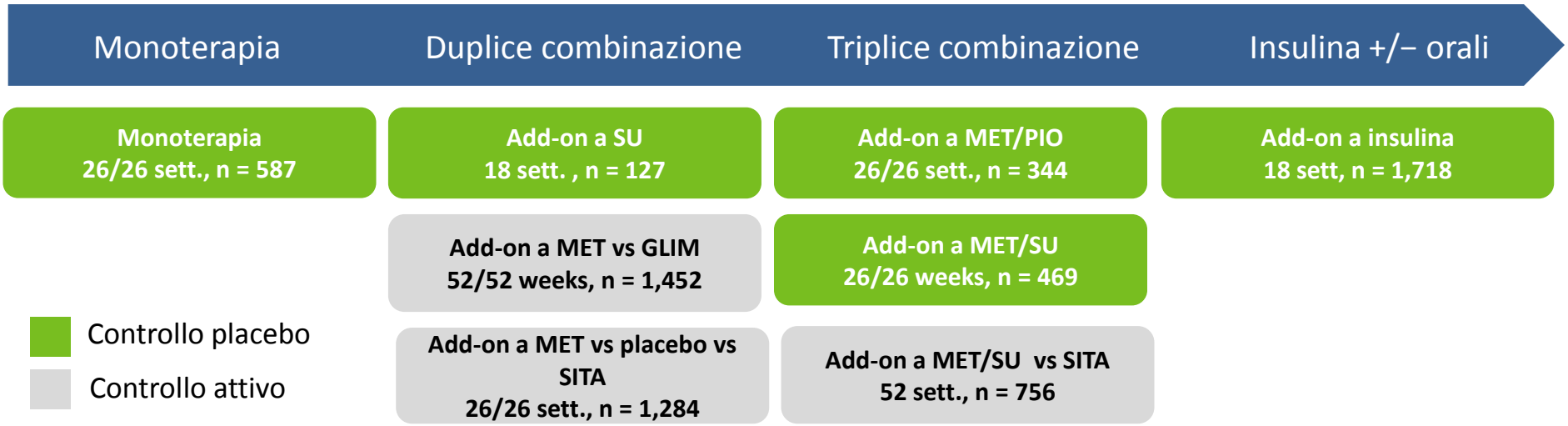
Selectivityof SGLT2 inhibitors vs SGLT1

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

Dapagliflozin Clinical Development Program



Canagliflozin clinical trial programme



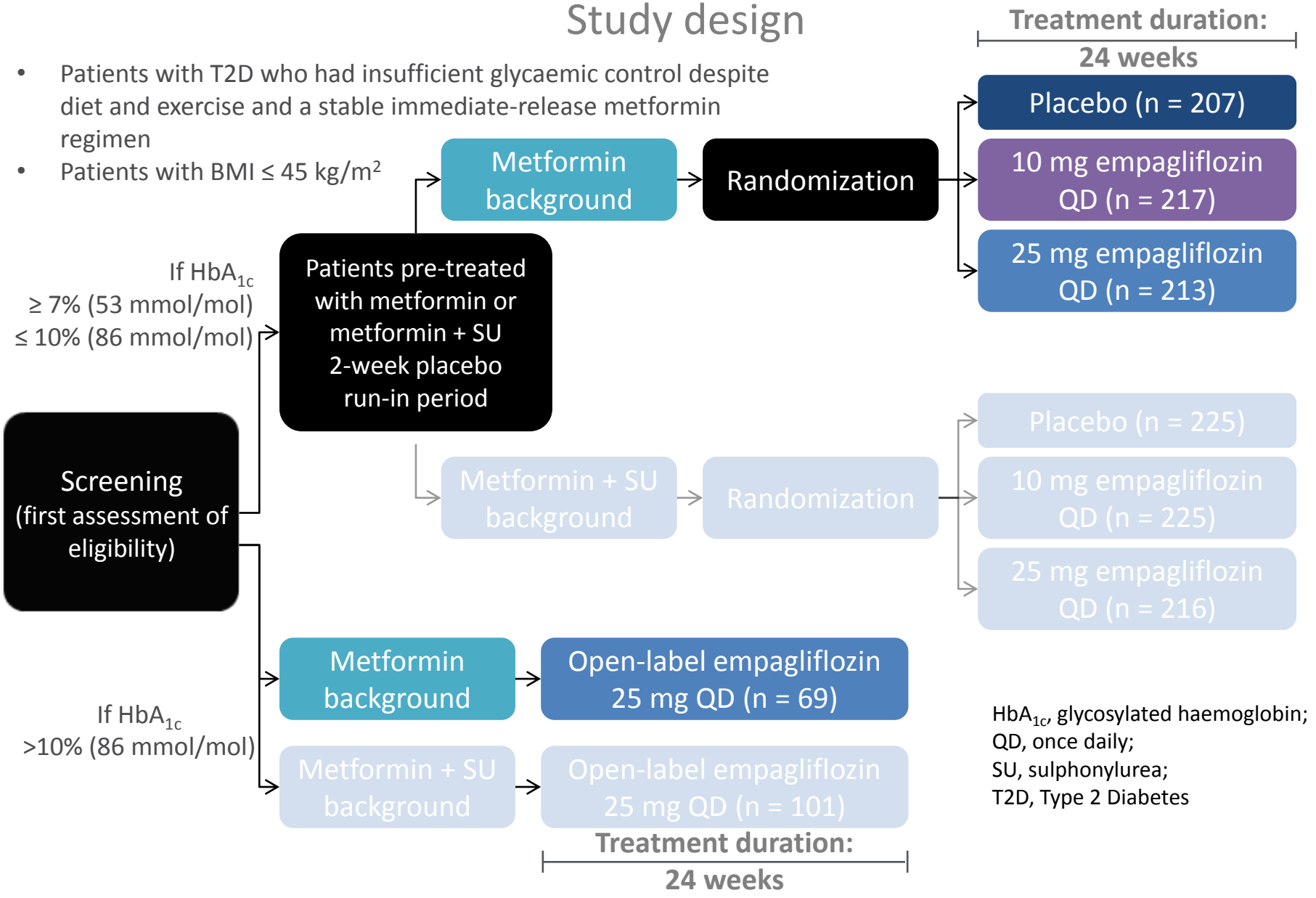
Studi in popolazioni speciali di diabetici t2
Studi controllati con placebo /add-on a trattamento antidiabetico corrente

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.

24-week study with empagliflozin as add-on to metformin
Study design

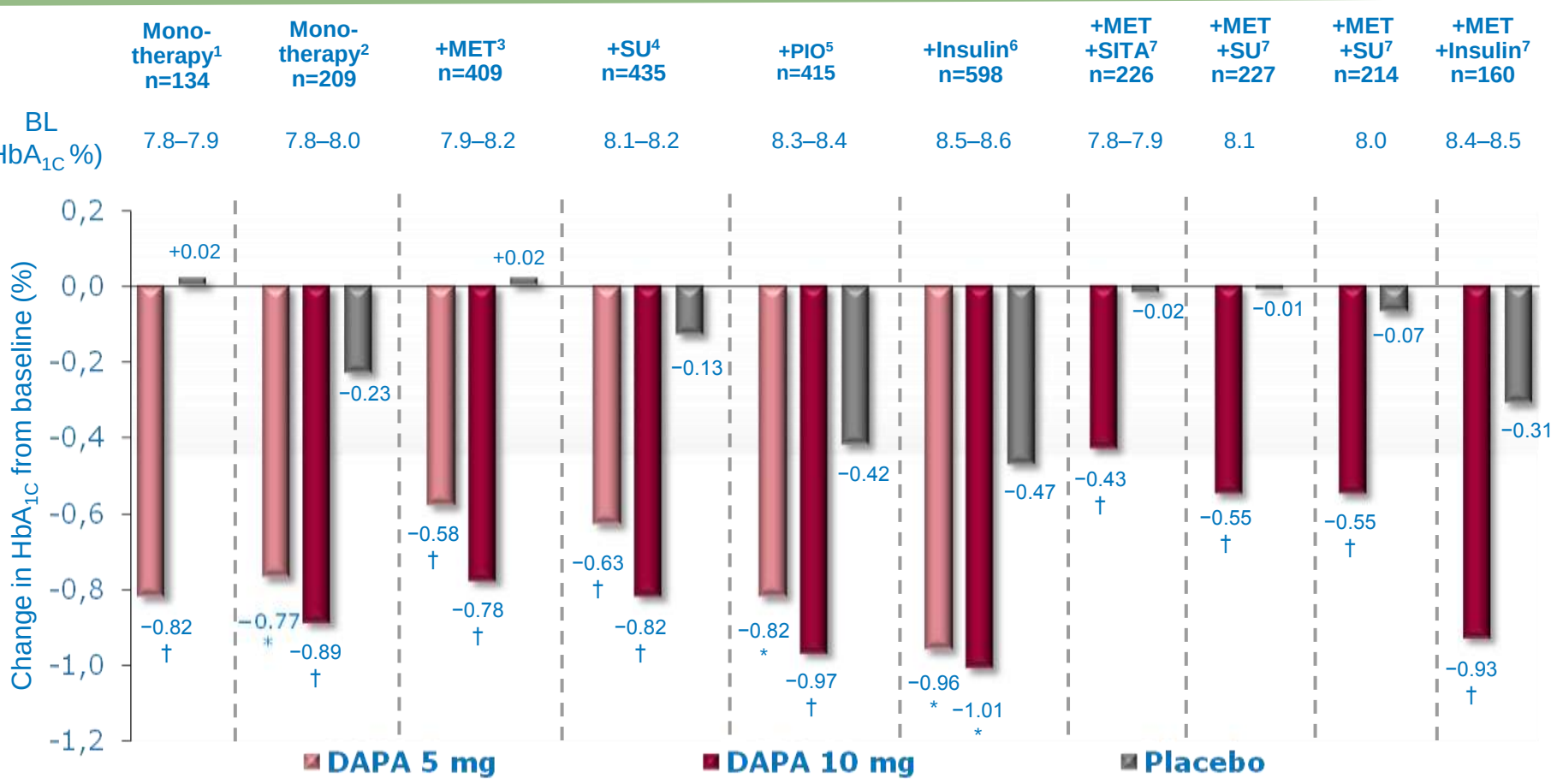
- Patients with T2D who had insufficient glycaemic control despite diet and exercise and a stable immediate-release metformin regimen
- Patients with BMI ≤ 45 kg/m^2



HbA_{1c}, glycosylated haemoglobin;
QD, once daily;
SU, sulphonylurea;
T2D, Type 2 Diabetes

Häring H-U, et al. *Diabetes*. 2014. doi10.2337/dc13-2105

Dapagliflozin Phase III studies: change in HbA_{1C}

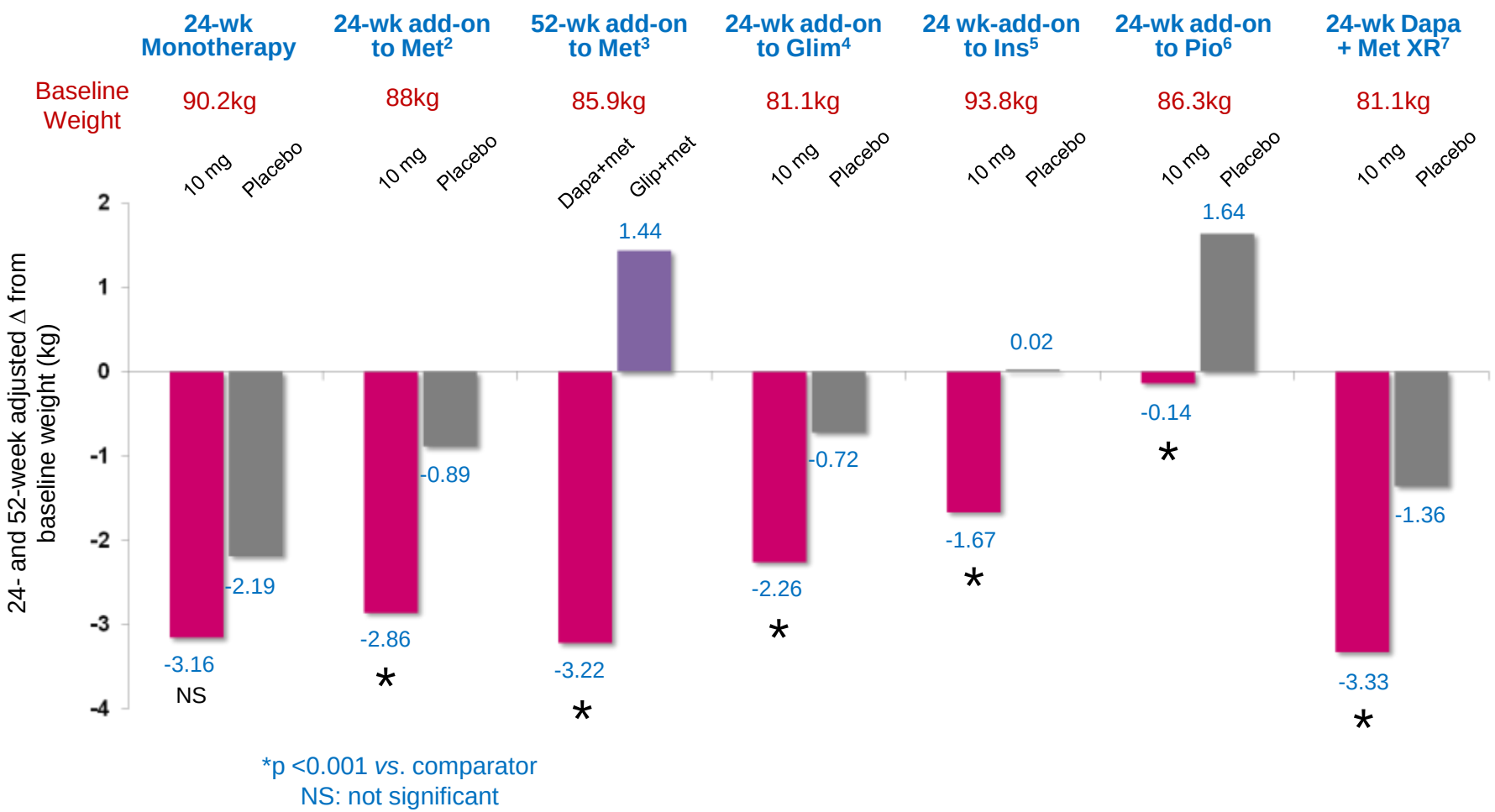


All data are for Week 24, except for reference 3 and 6, which were at week 102 and 48, respectively

Mean change in HbA_{1C} vs placebo: *p<0.001; †p<0.0001.
Baseline HbA_{1C} values represent the range of mean baseline values across the trial arms in each study.
BL, baseline; DAPA, dapagliflozin; MET, metformin; PIO, pioglitazone; SITA, sitagliptin; SU, sulphonylurea.

1. Bailey CJ, *et al. Diabetes Obes Metab* 2012;14:951–9; 2. Ferrannini E, *et al. Diabetes Care* 2010;33:2217–24; 3. Bailey CJ, *et al. BMC Medicine* 2013;11:43; 4. Strojek K, *et al. Diabetes Obes Metab* 2011;13:928–38; 5. Rosenstock J, *et al. Diabetes Care* 2012;35:1473–8; 6. Wilding JPH, *et al. Ann Intern Med* 2012;156:405–15;
7. Jabbour S, *et al.* Presented at the 73rd American Diabetes Association Scientific Sessions, Chicago, USA; 21–25 June 2013: Abstract 1176-P.

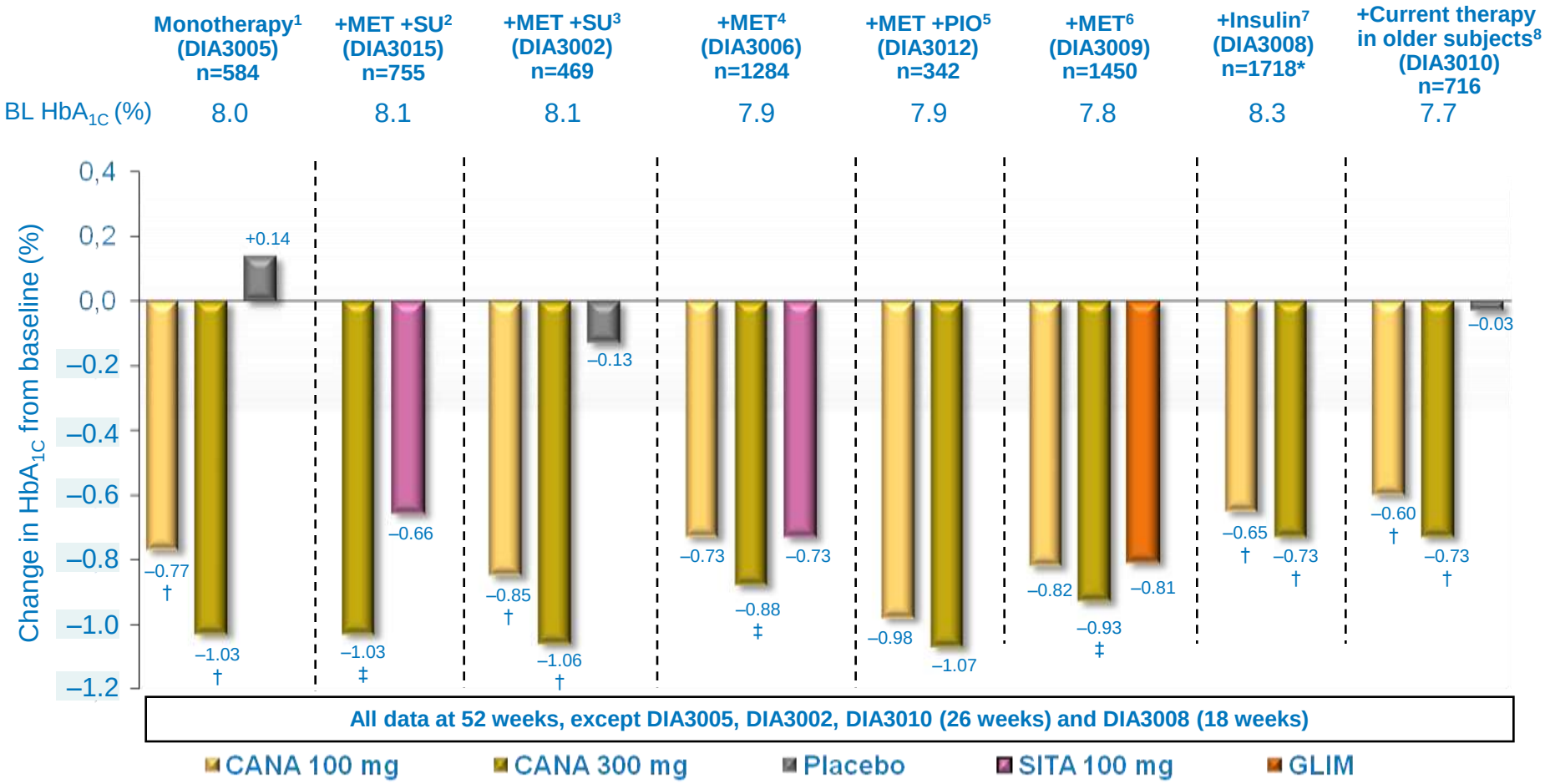
Body weight reduction with dapagliflozin



*p <0.001 *vs.* comparator
NS: not significant

[1]Ferrannini E, et al. *Diabetes Care* 2010;33:2217–2224; [2]Bailey CJ, et al. *Lancet* 2010;375:2223–2233; [3]Nauck MA, et al.*Diabetes Care* 2011;34:2015-2022; [4]Strojek K, et al. *Diabetes Obes Metab* 2011;13:928-938 [5]Wilding J, et al. *Diabetes* 2010;59 (Suppl 1):A21–A22 [Abstract 0078-OR]; [6]Rosenstock J, et al. *71st ADA Scientific Sessions*, San Diego, 24–28 June, 2011 [Abstract 0986-P]; [7]Henry R, et al. *71st ADA Scientific Sessions*, San Diego, 24-28 June, 2011 Abstract 307-OR.

Canagliflozin Phase III studies: change in HbA_{1C}

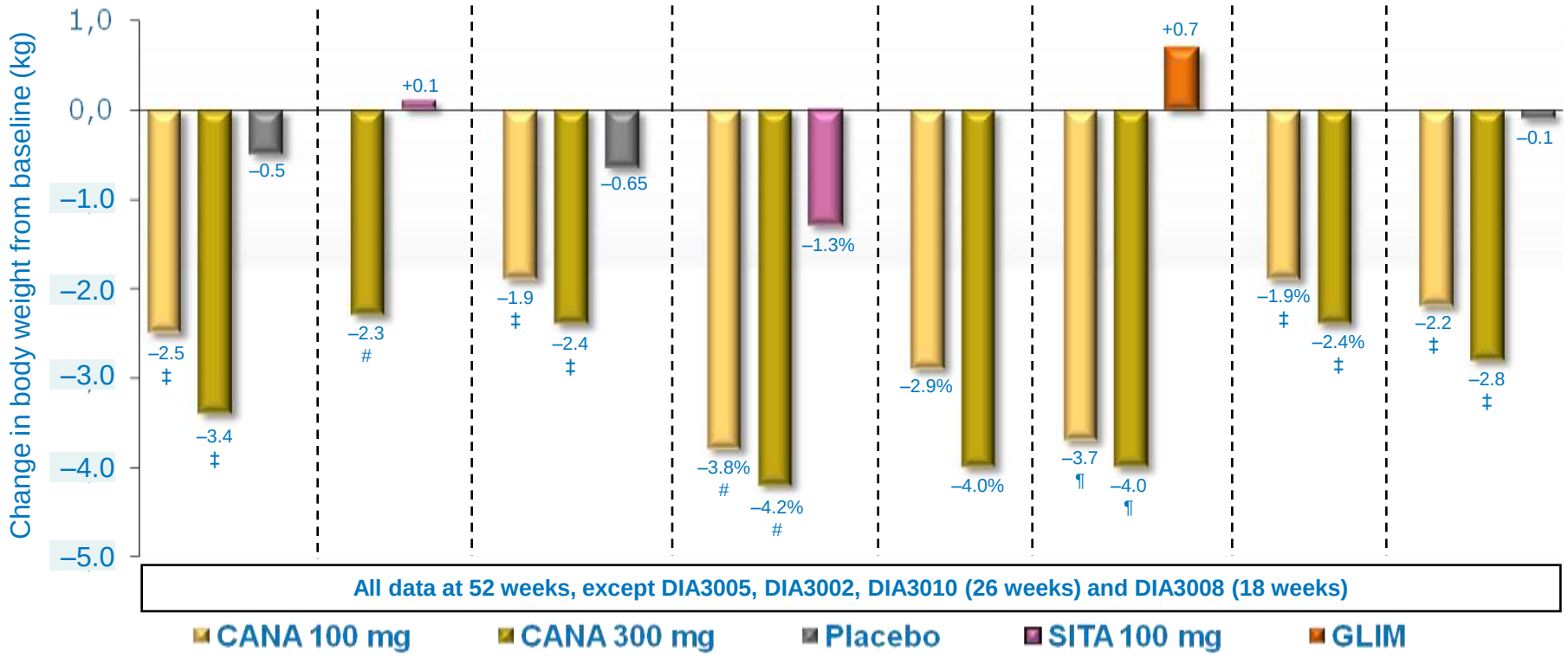


BL, baseline; CANA, canagliflozin; GLIM, glimepiride; MET, metformin; PIO, pioglitazone; SITA, sitagliptin; SU, sulphonylurea.
*Data are presented as placebo-subtracted LS mean change. †P<0.001 vs placebo. ‡Superior to comparator. Data-adjusted mean change from baseline using ANCOVA.

1. Stenlof K, *et al. Diabetes Obes Metab* 2013;15:372–82; 2. Schernthaner G, *et al. Diabetes Care* 2013;36:1–9; 3. Wilding J, *et al. Diabetologia* 2012;55(Suppl 1):Abstract 766; 4. Gonzalez F, *et al*. Presented at the 73rd American Diabetes Association Scientific Sessions, Chicago, USA; 21–25 June 2013. Abstract 238-OR; 5. Forst T, *et al*. Presented at the 73rd American Diabetes Association Scientific Sessions, Chicago, USA; 21–25 June 2013. Abstract 1098; 6. Cefalu W, *et al. Lancet* 2013. Epub ahead of print; doi:10.1016/S0140-6736(13)60683-2; 7. Matthews D, *et al. Diabetologia* 2012;55(Suppl 1):Abstract 764; 8. Bode B, *et al. Hosp Pract (1995)* 2013;41:72–81.

Canagliflozin Phase III studies: change in body weight

	+Monotherapy[1] (DIA3005) n=584	+MET +SU[2] (DIA3015) n=755	+MET +SU[3] (DIA3002) n=469	+MET[4] (DIA3006)* n=1284	+MET +PIO[5] (DIA3012)* n=342	+MET[6] (DIA3009) n=1450	+Insulin[7] (DIA3008)*† n=1718	+Current therapy in older subjects[8] (DIA3010) n=716
BL weight (kg)	86.8	88.3	92.8	–	–	86.6	97.0	89.5



CANA, canagliflozin; GLIM, glimepiride; MET, metformin; PIO, pioglitazone; SITA, sitagliptin; SU, sulphonylurea.
*Data are presented as percentage change from baseline; †Data are presented as placebo-subtracted LS mean change.
‡p<0.001 vs placebo; #p<0.001 vs sitagliptin; ¶p<0.0001 vs glimepiride.
Data-adjusted mean change from baseline using ANCOVA.

1. Stenlof K, *et al. Diabetes Obes Metab* 2013;15:372–82; 2. Schernthaner G, *et al*. *Diabetes Care* 2013; 36:1–9; 3. Wilding J, *et al*. *Diabetologia* 2012;55(Suppl 1):Abstract 766; 4. Gonzalez F, *et al*. Presented at the 73rd American Diabetes Association Scientific Sessions, Chicago, USA; 21–25 June 2013: Abstract 238-OR; 5. Forst T, *et al*. Presented at the 73rd American Diabetes Association Scientific Sessions, Chicago, USA; 21–25 June 2013: Abstract 1098; 6. Cefalu W, *et al*. *Lancet* 2013. Epub ahead of print; 7. Matthews D, *et al*. *Diabetologia* 2012;55(Suppl 1):Abstract 764; 8. Bode B, *et al*. *Hosp Pract (1995)* 2013;41:72–81.

Phase III pooled efficacy and cardiovascular risk factor analysis

Placebo-corrected change* from baseline in HbA_{1c}

Pooled data from 4 pivotal Phase III trials

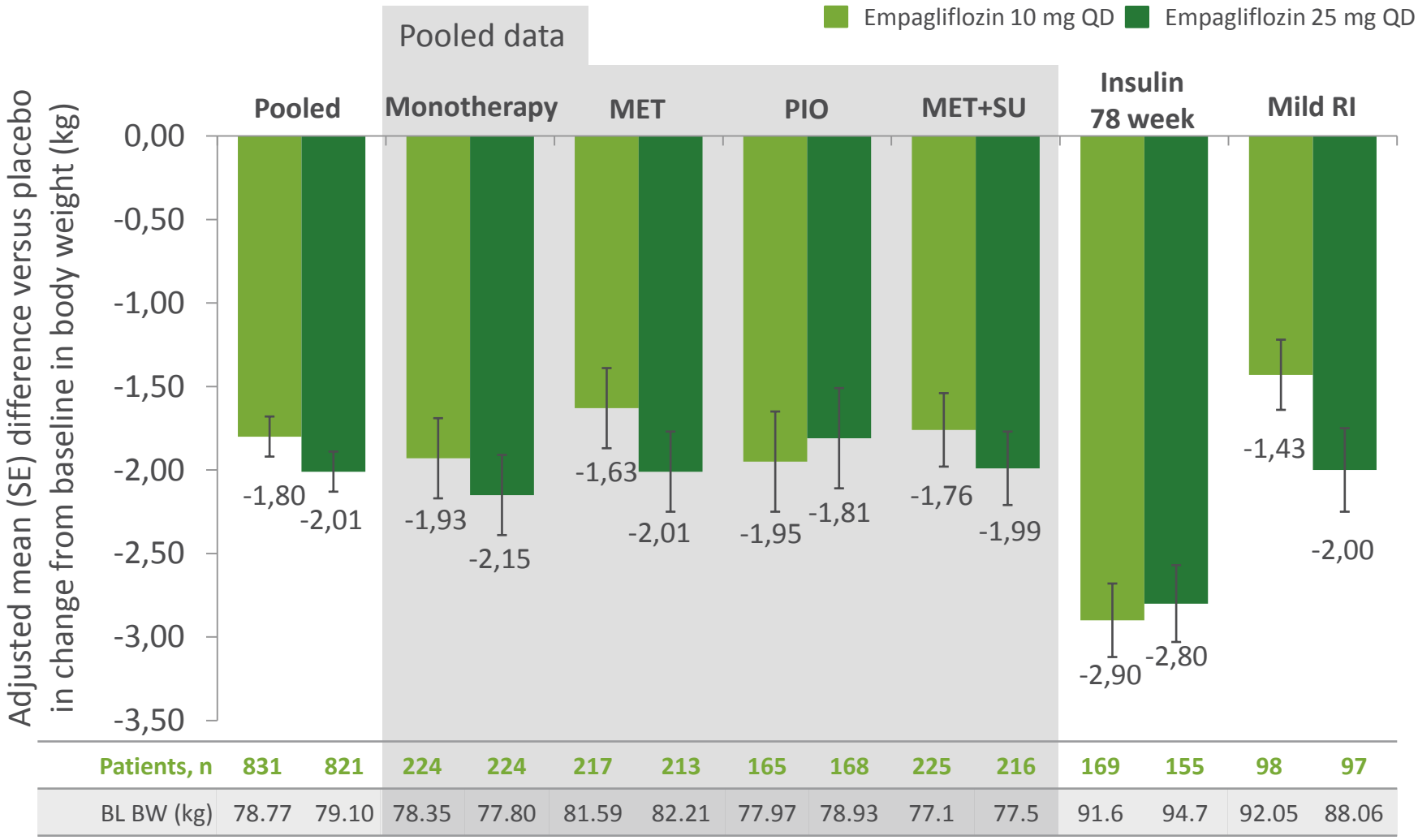
	Pooled		Monotherapy		MET		PIO		MET+SU		Insulin 78 week		Mild RI	
Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL HbA_{1c}, %	7.98	7.96	7.87	7.86	7.94	7.86	8.07	8.06	8.07	8.10	8.27	8.27	8.02	8.01

BL, baseline; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SE, standard error; SU, sulphonylurea.

*All statistically significant unless otherwise marked.

Hach T, et al., Häring H-U, et al., Rosenstock J, et al., Barnett A, et al. *Diabetes*. 2013;(Suppl 1) (P69-LB, P1092, P1102, P1104, respectively);
Kovacs C, et al. *Diabetes ObesMetab*. 2013 Aug 1. doi: 10.1111/dom.12188; Häring H-U, et al. *Diabetes Care*. 2014. doi:10.2337/dc12-2673.
Barnett A, et al. Lancet Diabetes Endocrinol. 2014 May;2(5):369-84. doi: 10.1016/S2213-8587(13)70208-0
Rosenstock J, et al Poster:931, 49th Annual Meeting of the European Association for the Study of Diabetes, 23–27 September 2013

Phase III pooled efficacy and cardiovascular risk factor analysis
Placebo-corrected change* from baseline in body weight



	Pooled		Monotherapy		MET		PIO		MET+SU		Insulin 78 week		Mild RI	
Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL BW (kg)	78.77	79.10	78.35	77.80	81.59	82.21	77.97	78.93	77.1	77.5	91.6	94.7	92.05	88.06

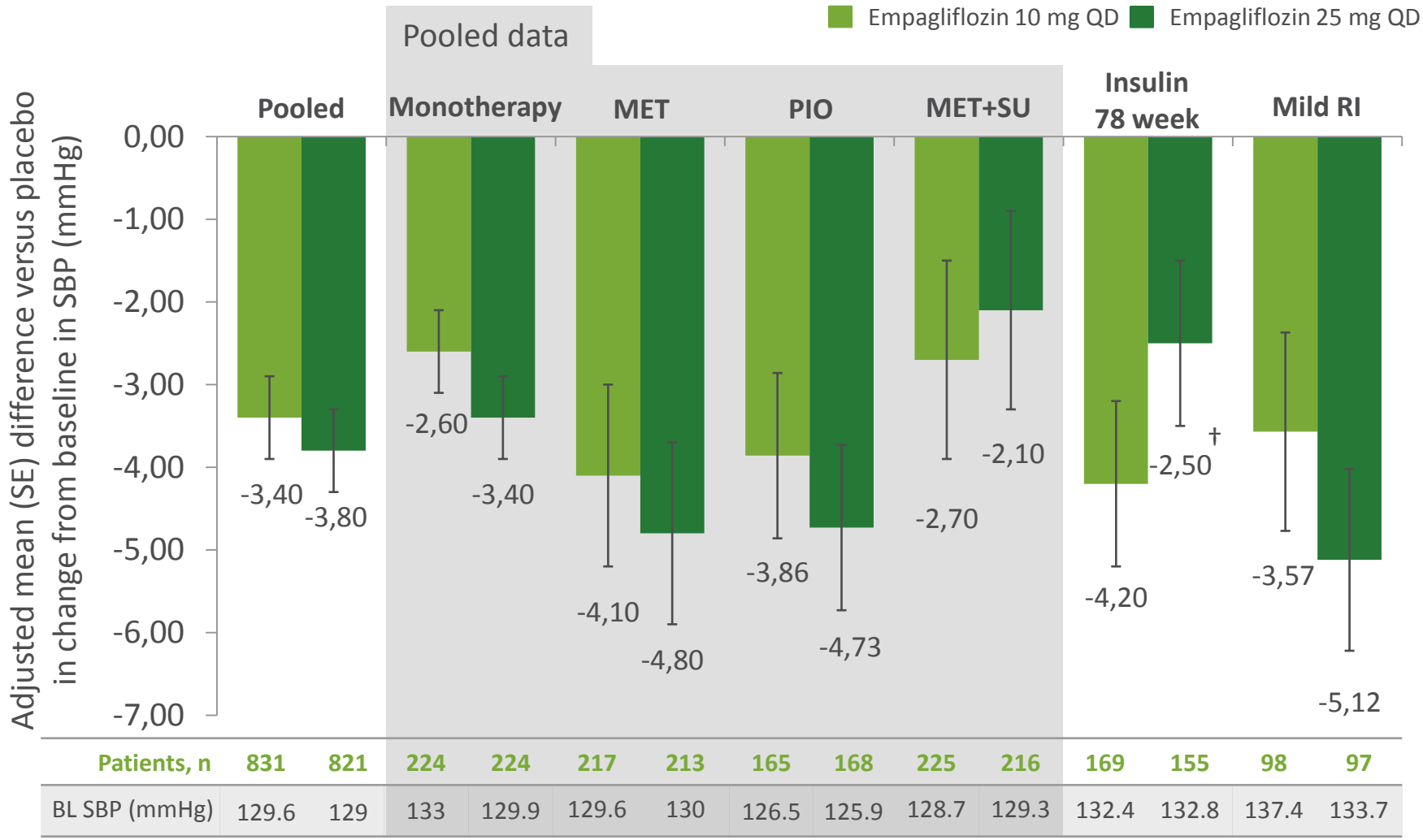
BL, baseline; BW, body weight; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SE, standard error; SU, sulphonylurea.
*All statistically significant unless otherwise marked.

Hach T, et al., Häring H-U, et al., Rosenstock J, et al., Barnett A, et al. *Diabetes*. 2013;(Suppl 1) (P69-LB, P1092, P1102, P1104, respectively);
Kovacs C, et al. *Diabetes ObesMetab*. 2013 Aug 1. doi: 10.1111/dom.12188; Häring H-U, et al. *Diabetes Care*. 2014. doi:10.2337/dc12-2673.
Barnett A, et al. Lancet Diabetes Endocrinol. 2014 May;2(5):369-84. doi: 10.1016/S2213-8587(13)70208-0
Rosenstock J, et al Poster:931, 49th Annual Meeting of the European Association for the Study of Diabetes, 23–27 September 2013

Pooled data from 4 pivotal Phase III trials

Phase III pooled efficacy and cardiovascular risk factor analysis

Placebo-corrected change* from baseline in SBP



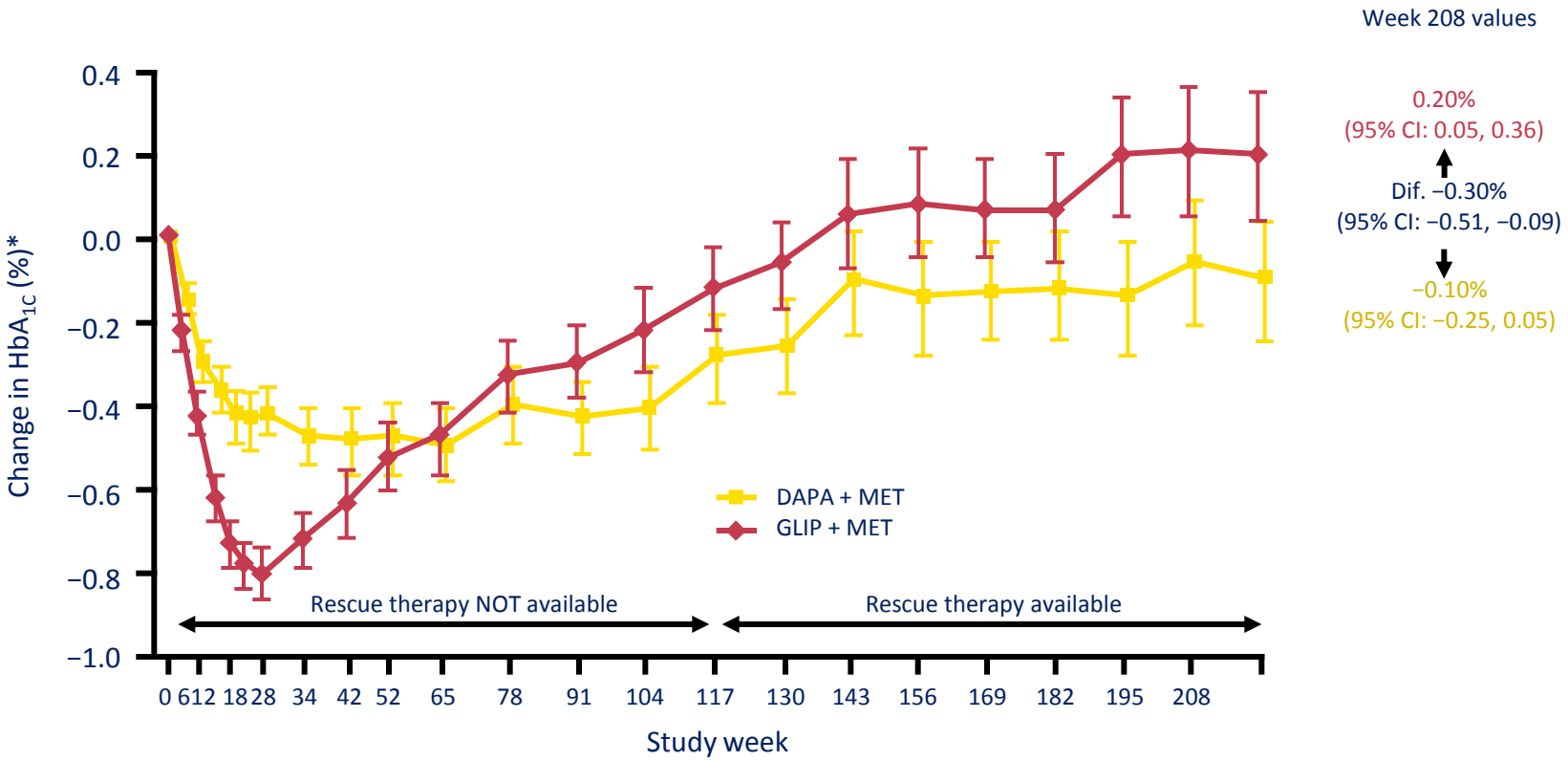
	Pooled		Monotherapy		MET		PIO		MET+SU		Insulin 78 week		Mild RI	
Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL SBP (mmHg)	129.6	129	133	129.9	129.6	130	126.5	125.9	128.7	129.3	132.4	132.8	137.4	133.7

BL, baseline ; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SBP, systolic blood pressure; SE, standard error; SU, sulphonylurea.
*All statistically significant unless otherwise marked. †Not statistically significant.

Hach T, et al., Häring H-U, et al., Rosenstock J, et al., Barnett A, et al. *Diabetes*. 2013;(Suppl 1) (P69-LB, P1092, P1102, P1104, respectively);
Kovacs C, et al. *Diabetes ObesMetab*. 2013 Aug 1. doi: 10.1111/dom.12188; Häring H-U, et al. *Diabetes Care*. 2014. doi:10.2337/dc12-2673.
Barnett A, et al. Lancet Diabetes Endocrinol. 2014 May;2(5):369-84. doi: 10.1016/S2213-8587(13)70208-0
Rosenstock J, et al Poster:931, 49th Annual Meeting of the European Association for the Study of Diabetes, 23–27 September 2013

Pooled data from 4 pivotal Phase III trials

Dapagliflozin: glycaemic control over 4 years vsglipizide



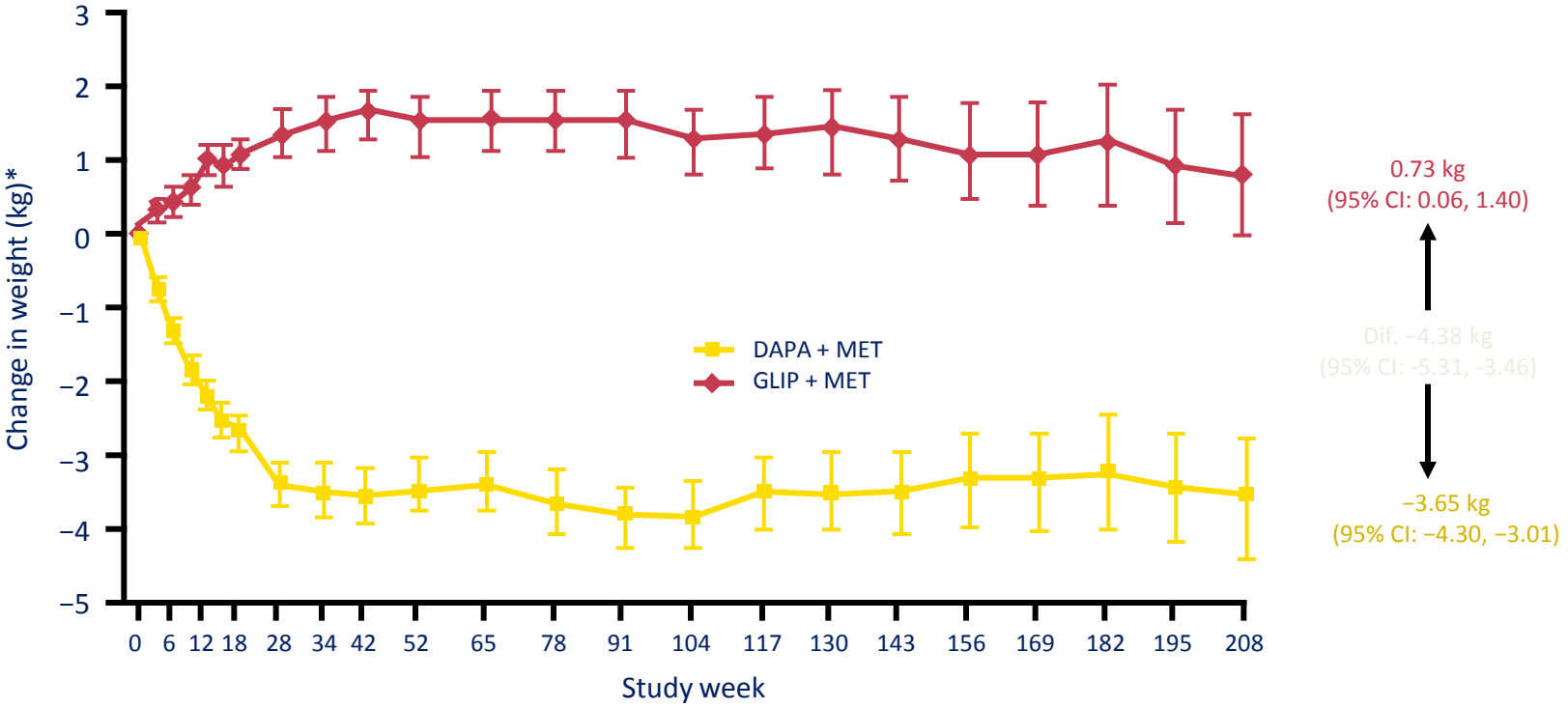
Sample size (includingdataafterrescue), n

DAPA + MET	400	321	233	79
GLIP + MET	401	315	208	71

DAPA, dapagliflozin; GLIP, glipizide; MET, metformin.
*Data are adjusted mean change from baseline ± 95% CI derived from a longitudinal repeated-measures mixed model.

Del Prato S, et al. Presented at the 73rd American Diabetes Association Scientific Sessions, Chicago, USA; 21–25 June 2013: Abstract 62-LB.

Dapagliflozin: weight loss over 4 years vsglipizide



Sample size (includingdataafterrescue), n

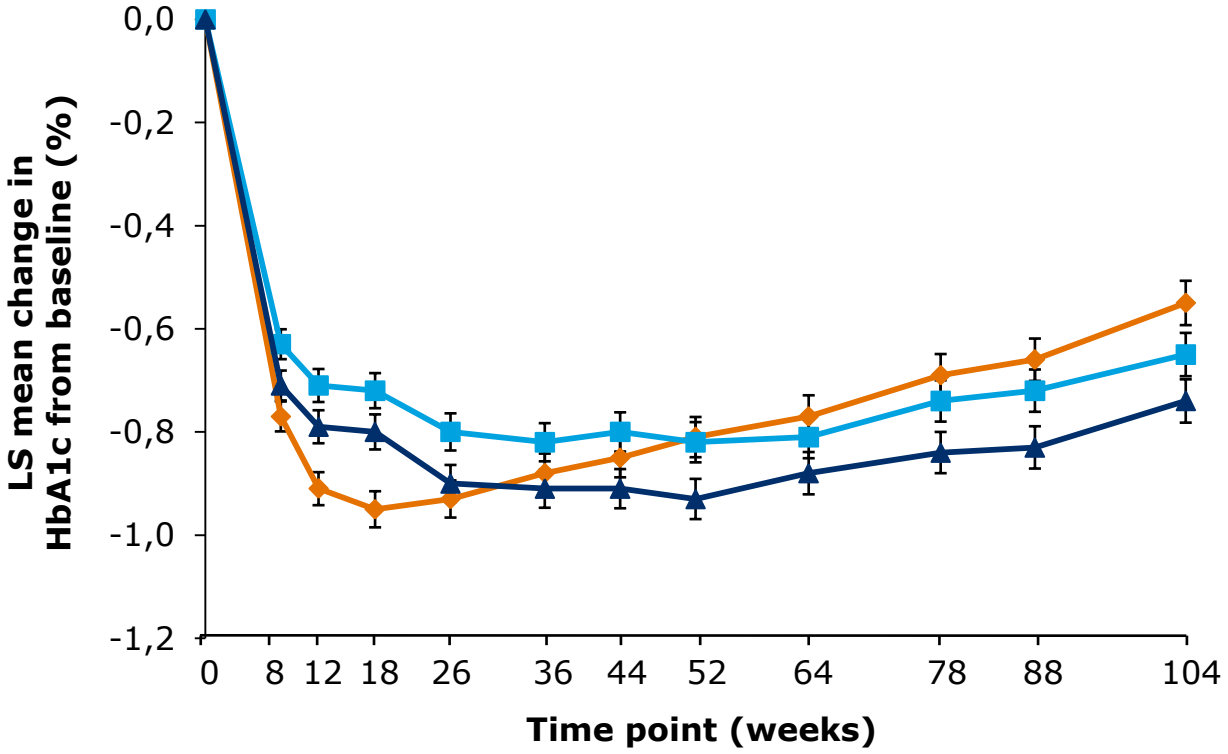
DAPA + MET	400	323	234	159
GLIP + MET	401	315	211	140

DAPA, dapagliflozin; MET, metformin; PIO, pioglitazone; SITA, sitagliptin; SU, sulphonylurea.
***Data are adjusted mean change from baseline ± 95% CI derived from a longitudinal repeated-measures mixed model.**

Del Prato S, et al. Presented at the 73rd American Diabetes Association Scientific Sessions, Chicago, USA; 21–25 June 2013: Abstract 62-LB.

Canagliflozin: sustained reduction in HbA1c (LOCF) vs glimepiride

as add-on to metformin over 104 weeks



Mean difference from baseline HbA1c at 104 weeks

GLIM	−0.55%
CANA 100 mg	−0.65%
CANA 300 mg	−0.74%

Difference vs GLIM

CANA 100mg −0.09%
95% CI −0.20, 0.01

CANA 300mg −0.18%
95% CI −0.29, −0.08

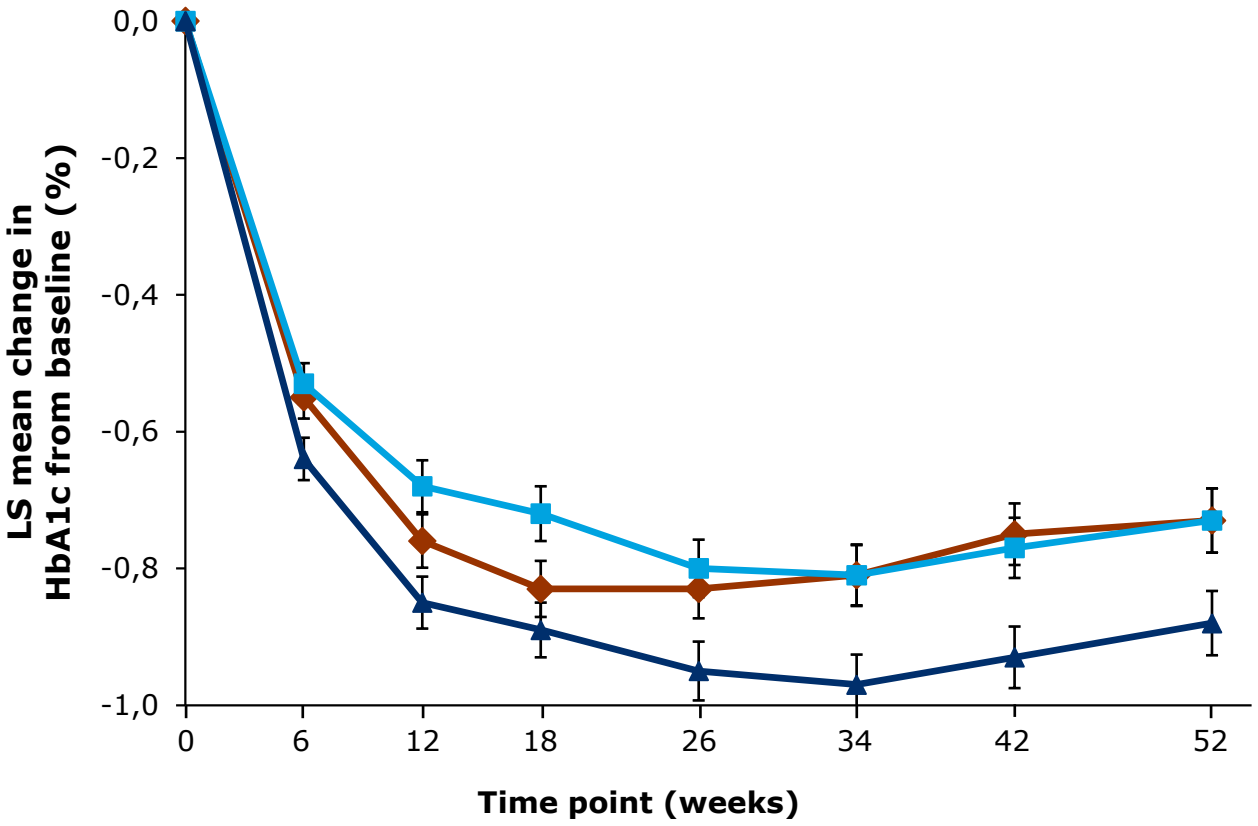
- Reduction in HbA1c at 104 weeks was numerically greater for canagliflozin 100 mg vs glimepiride and reached statistical significance for canagliflozin 300 mg[a,b]

Vertical bars represent standard error.
CANA, canagliflozin; CI, confidence interval; GLIM, glimepiride;LOCF, last observation carried forward; LS, least squares.

Cefalu WT, et al. Poster presented at the 73rd scientific sessions of the American Diabetes Association (ADA), 2013; abstract 65-LB.

Canagliflozin: HbA1c reduction vssitagliptin

as add-on to metformin at 52 weeks



Mean difference from baseline HbA1c at 52 weeks

SITA 100 mg –0.73%

CANA 100 mg –0.73%

CANA 300 mg –0.88%

Difference vs SITA

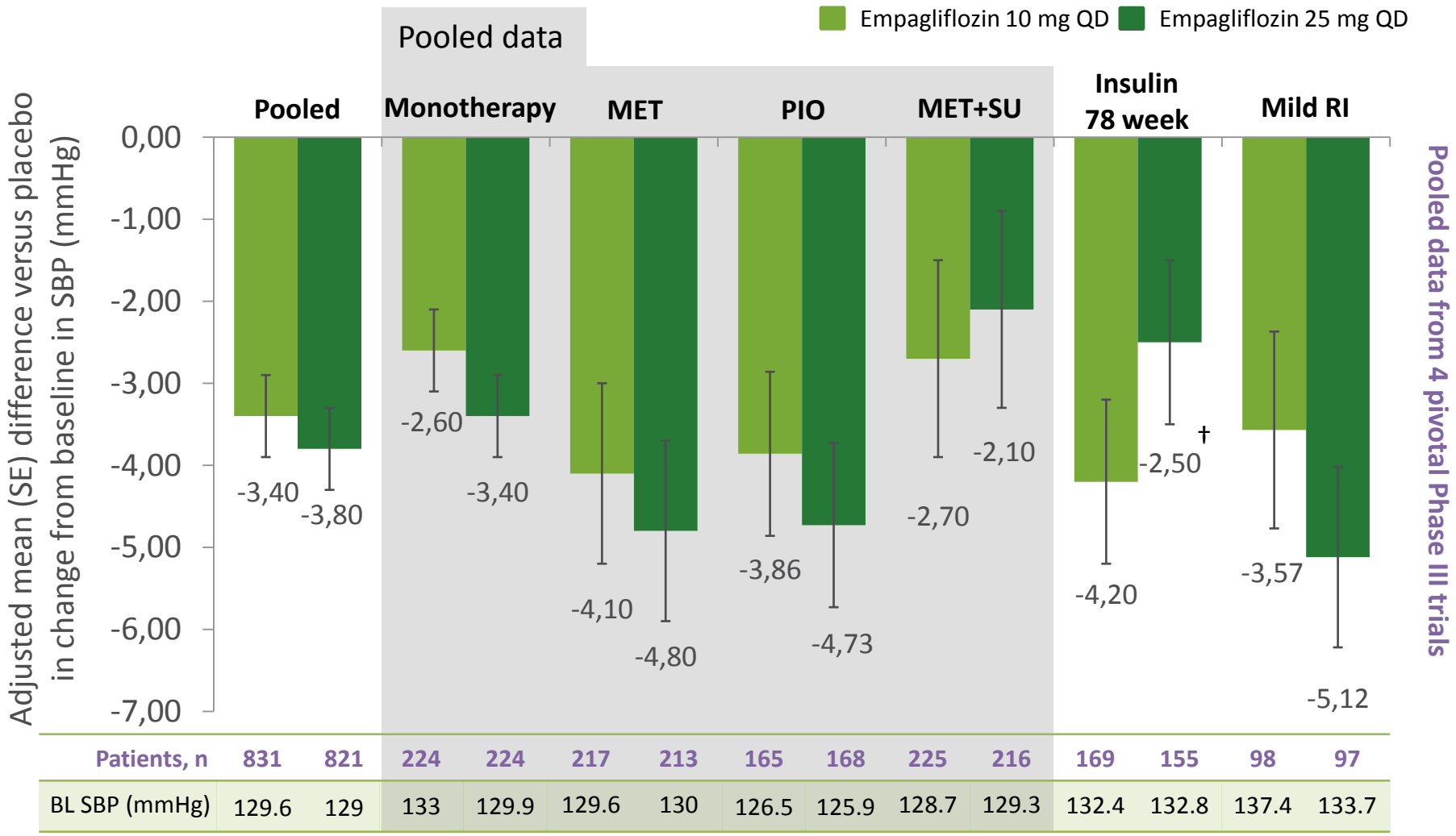
CANA 100mg 0.00%
95% CI -0.12, 0.12

CANA 300mg –0.15%
95% CI -0.27, -0.03

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

Lavalle-González FJ, et al. Diabetologia. 2013;56:2582-92.

Phase III pooled efficacy and cardiovascular risk factor analysis
Placebo-corrected change* from baseline in SBP

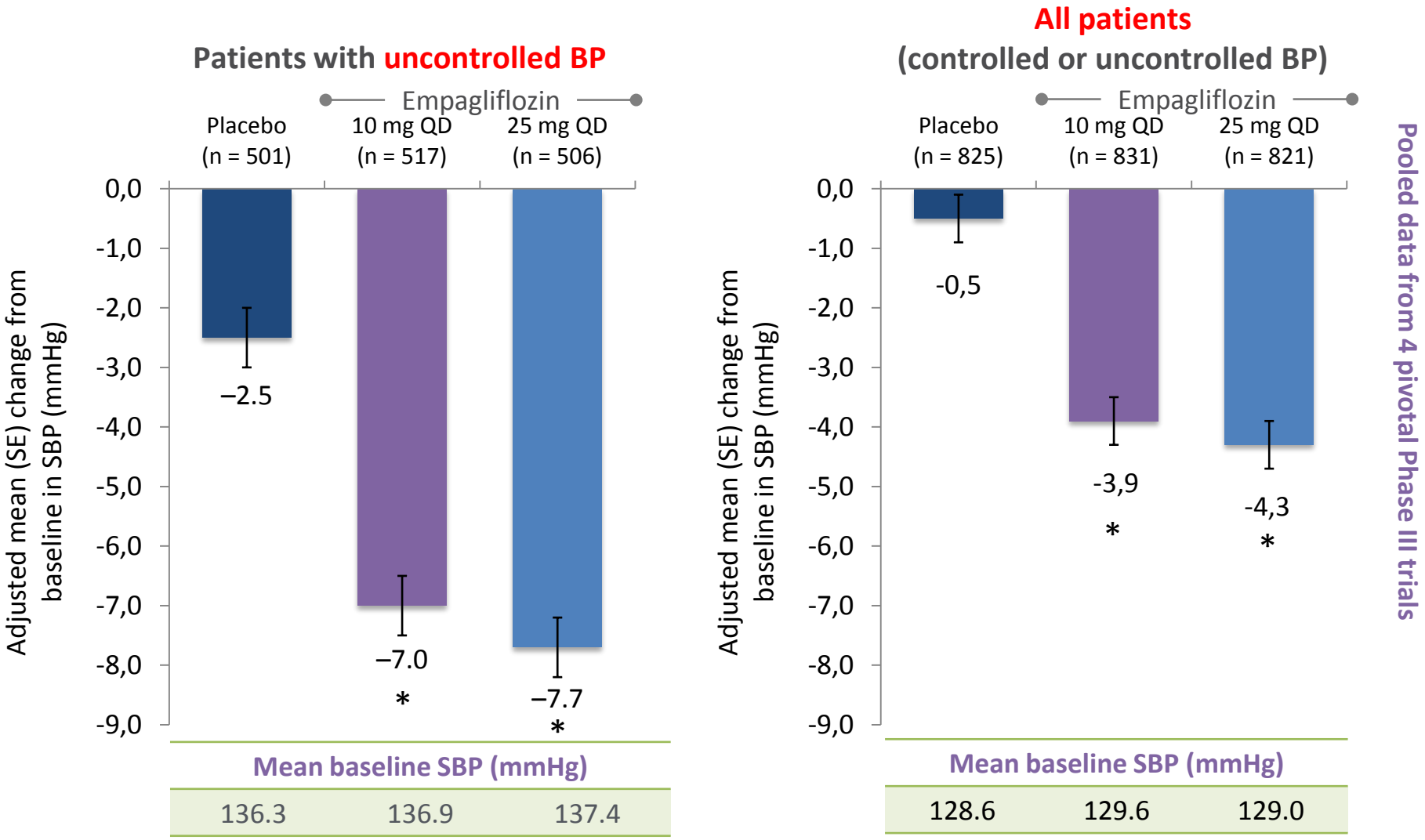


	Pooled		Monotherapy		MET		PIO		MET+SU		Insulin 78 week		Mild RI	
Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
BL SBP (mmHg)	129.6	129	133	129.9	129.6	130	126.5	125.9	128.7	129.3	132.4	132.8	137.4	133.7

BL, baseline ; MET, metformin; PIO, pioglitazone; QD, once daily; RI, renal impairment; SBP, systolic blood pressure; SE, standard error; SU, sulphonylurea.
*All statistically significant unless otherwise marked. †Not statistically significan

Hach T, et al., Häring H-U, et al., Rosenstock J, et al., Barnett A, et al. *Diabetes*. 2013;(Suppl 1) (P69-LB, P1092, P11
Kovacs C, et al. *Diabetes ObesMetab*. 2013 Aug 1. doi: 10.1111/dom.12188; Häring H-U, et al. *Diabetes Care*. 2014
Barnett A, et al. Lancet Diabetes Endocrinol. 2014 May;2(5):369-84. doi: 10.1016
Rosenstock J, et al Poster:931, 49th Annual Meeting of the European Association for the Study of Diabete

Phase III pooled efficacy and cardiovascular risk factor analysis
Change from baseline in SBP by BP control at baseline
(SBP < 130 mmHg and DBP < 80 mmHg)

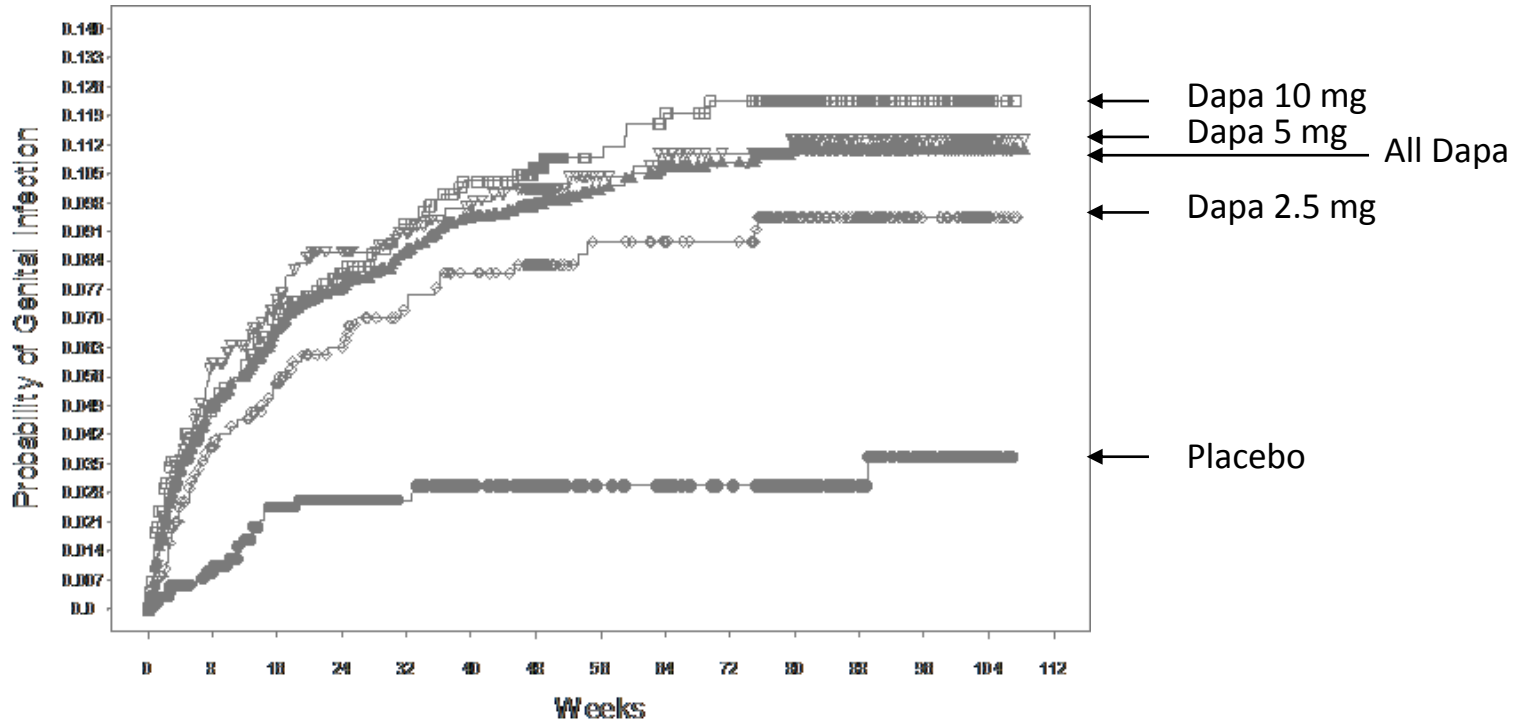


BP, blood pressure; DBP, diastolicblood pressure; QD, once daily; SBP, systolic blood pressure; SE, standard error.
Comparisons versus placebo: *p < 0.001. FAS (LOCF).

Hach T, et al. *Diabetes*. 2013;(Suppl 1) (P69-LB).

Effetti collaterali

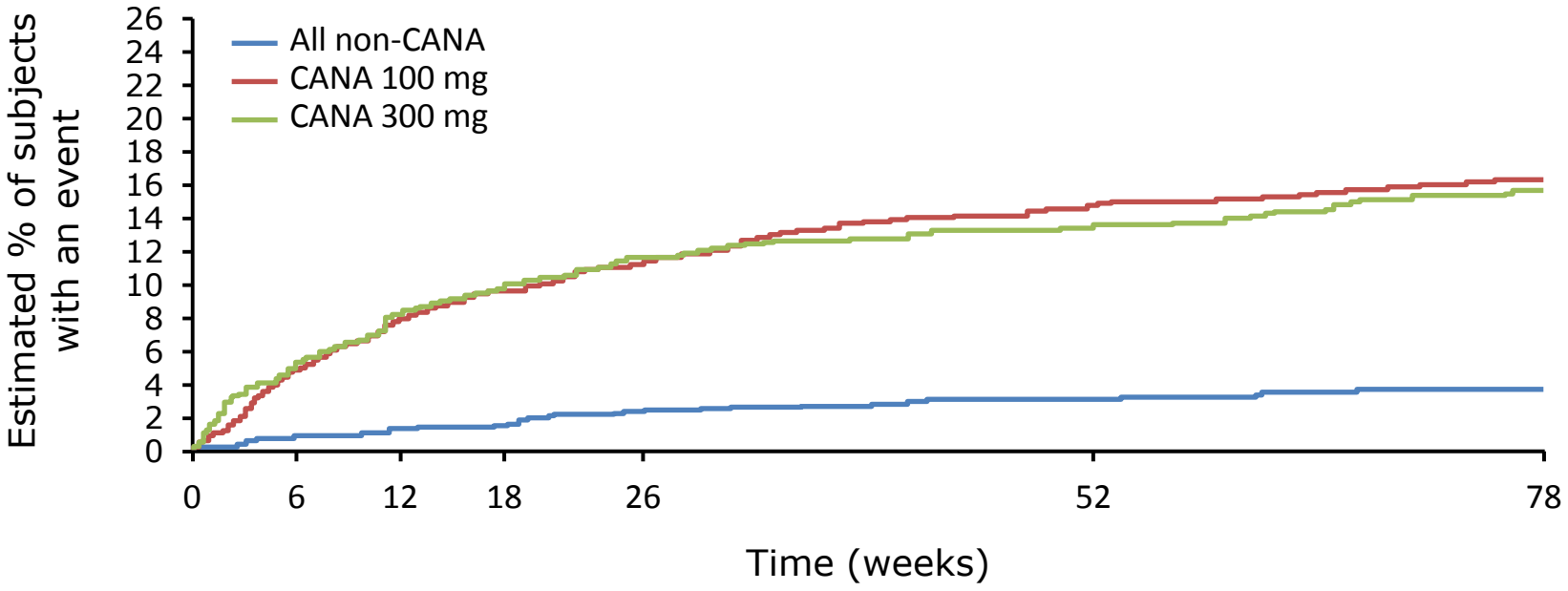
Time to first event suggestive of vulvovaginitis, balanitis and other infections



	Number of patients at risk														
Dapa 10 mg	768	702	667	637	614	596	519	326	320	314	250	198	172	9	0
Placebo	694	650	608	583	564	545	470	262	257	248	190	145	123	12	0

Placebo-controlled, pooled population, short- and long-term treatment periods; DAPA=dapagliflozin

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).

Pooled data on Urinary Tract Infections and Genital Infections

	Placebo (n=825)	Empagliflozin 10 mg (n=830)	Empagliflozin 25 mg (n=822)
Events consistent with UTIs			
Patients with events consistent with UTI, n (%)	68 (8.2)	77 (9.3)	62 (7.5)
Male, n/N (%)	16/424 (3.8)	9/463 (1.9)	5/464 (1.1)
Female, n/N (%)	52/401 (13.0)	68/367 (18.5)	57/358 (15.9)
Patients with events consistent with UTI leading to treatment discontinuation, n (%)	1 (0.1)	2 (0.2)	1 (0.1)
Events consistent with GIs			
Patients with events consistent with genital infection, n (%)	6 (0.7)	35 (4.2)	30 (3.6)
Male, n/N (%)	2/424 (0.5)	12/463 (2.6)	5/464 (1.1)
Female, n/N (%)	4/401 (1.0)	23/367 (6.3)	25/358 (7.0)
Patients with events leading to treatment discontinuation, n (%)	0	1 (0.1)	2 (0.2)

Poster 74-LB American Diabetes Association (ADA) 73rd Session, 21-25 June 2013, Chicago, IL, USA

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Prevalence and recurrence of urinary tract and genital infections among adults with and without type 2 diabetes mellitus in the general population: a longitudinal cohort study

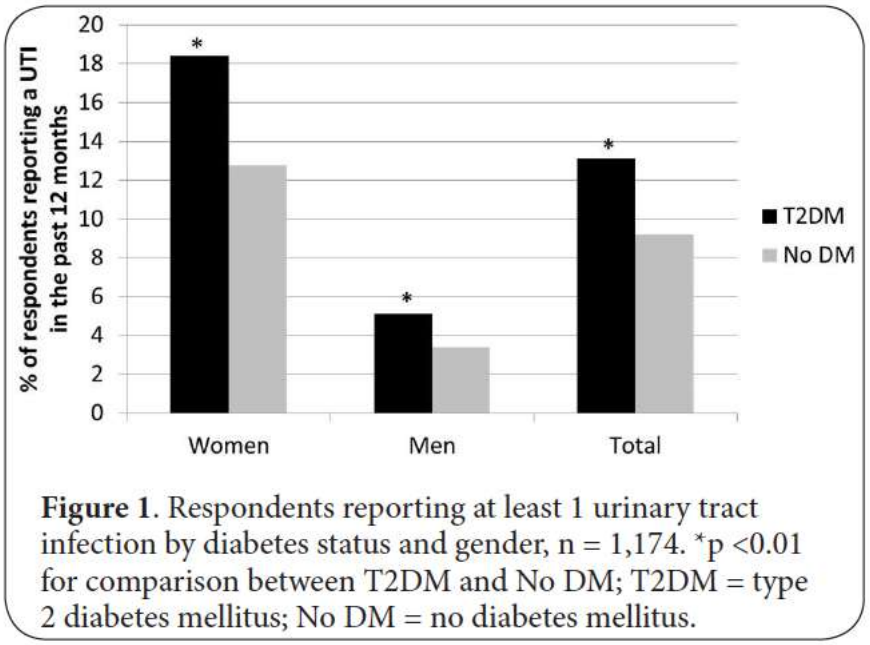


Figure 1. Respondents reporting at least 1 urinary tract infection by diabetes status and gender, n = 1,174. *p <0.01 for comparison between T2DM and No DM; T2DM = type 2 diabetes mellitus; No DM = no diabetes mellitus.

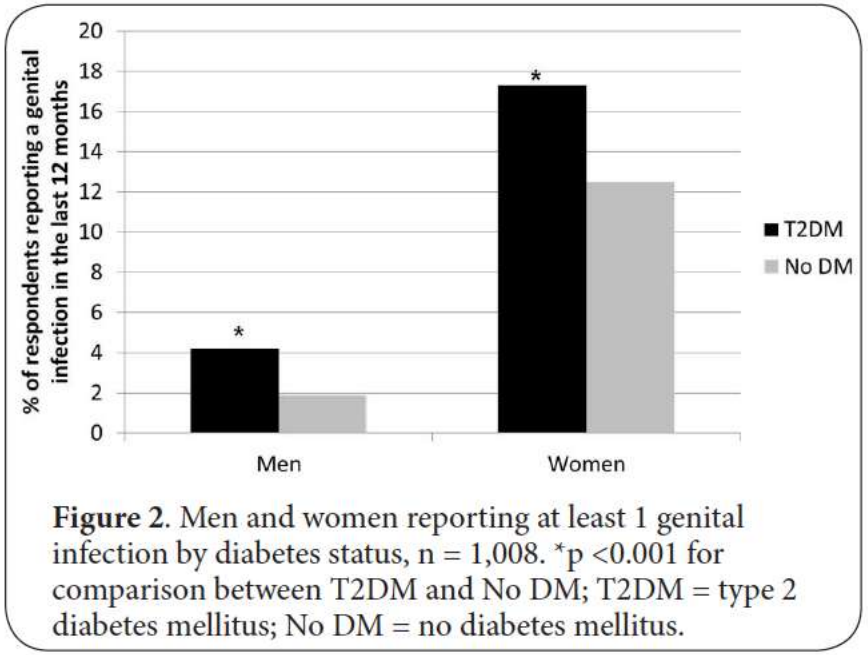


Figure 2. Men and women reporting at least 1 genital infection by diabetes status, n = 1,008. *p <0.001 for comparison between T2DM and No DM; T2DM = type 2 diabetes mellitus; No DM = no diabetes mellitus.

Grandyet al. Journal ofDiabetesResearch&ClinicalMetabolism 2013, http://www.hoajonline.com/journals/pdf/2050-0866-2-5.pdf

Esperienza Clinica

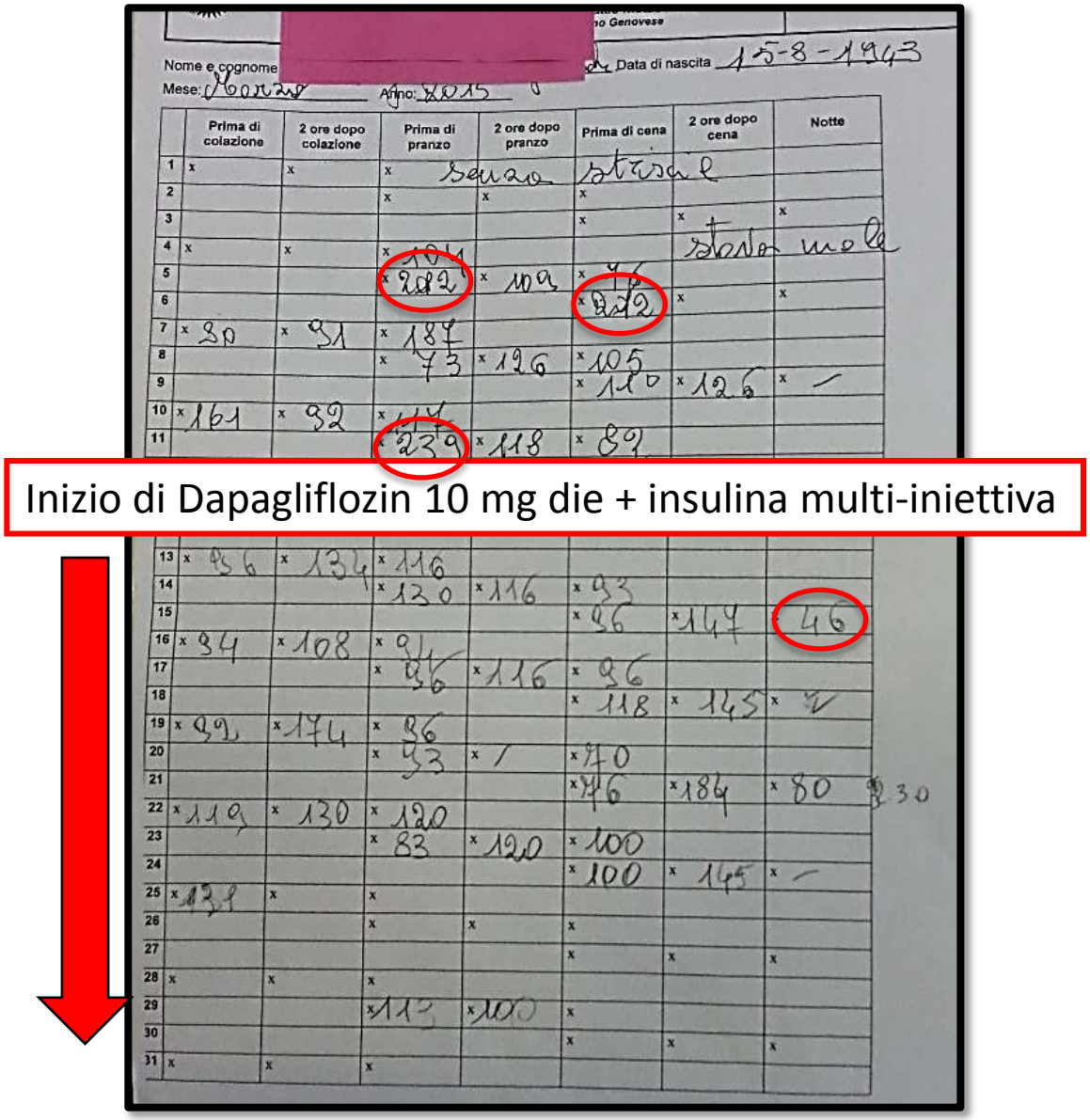
Esperienza clinica con Dapagliflozin IRCCS MultiMedica - Baseline

Caratteristiche Basali (50 pazienti)	Media ± DS
Età (anni)	68 ± 10
Peso (kg)	86 ± 24
BMI (kg/m^2)	30 ±6
Circonferenza vita (cm)	105 ± 12
Glicemia a digiuno (mg/dl)	162 ± 55
HbA1c (%)	8,1 ± 1,4
PAS (mm Hg)	130 ± 14
PAD (mm Hg)	78 ±7
Ipoglicemie (% pazienti)	10
Iperglicemie (% pazienti)	76

Esperienza clinica con Dapagliflozin IRCCS MultiMedica – Follow-up a 45 gg

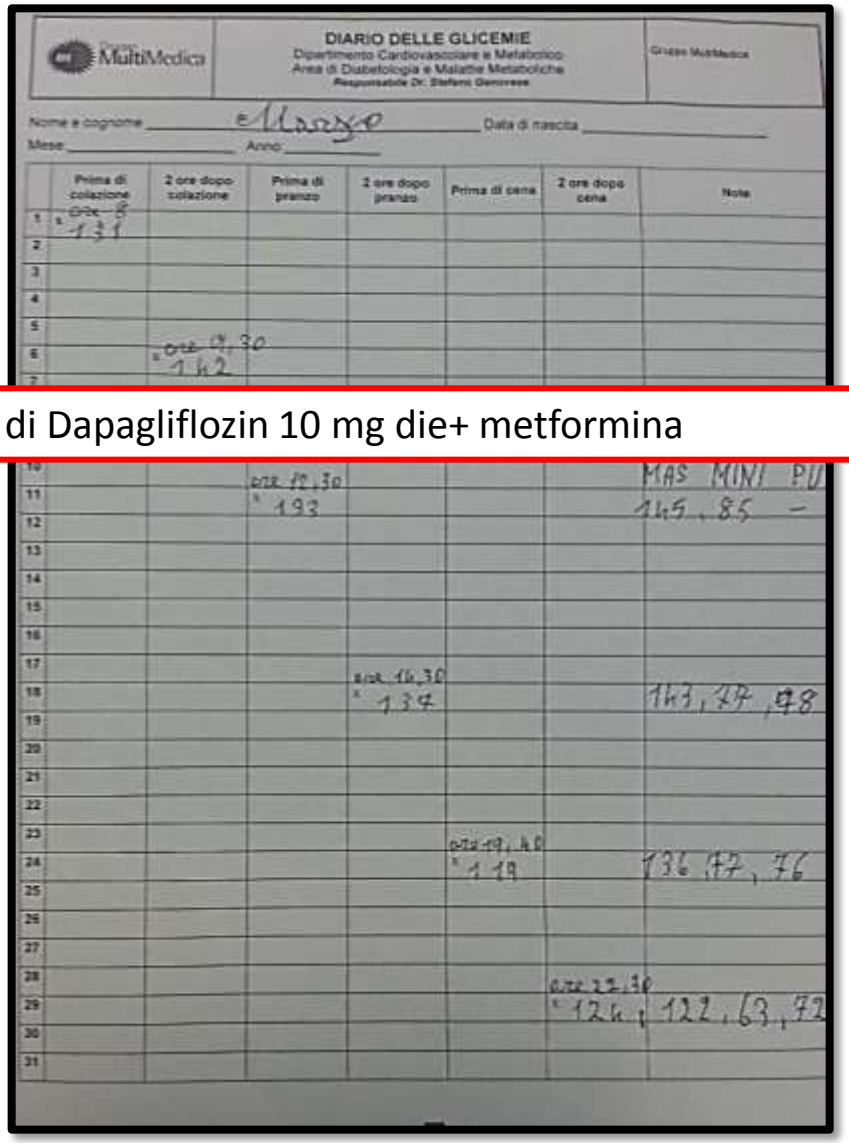
Caratteristiche (9 pazienti)	BaselineMedia ± DS	Follow-up Media ± DS
Età (anni)	68± 6,5	
Peso (kg)	82 ± 21	80 ± 21
BMI (kg/m^2)	28 ±4	28 ±4
Circonferenza vita (cm)	104 ± 15	102 ± 14
Glicemia a digiuno (mg/dl)	145 ± 35	128 ± 36
HbA1c (%)	8,2 ± 1,4	8,0 ± 0,6
PAS (mm Hg)	130 ± 14	131 ± 17
PAD (mm Hg)	79 ± 13	76 ±8
Ipoglicemie (% pazienti)	11	0
Iperglicemie (% pazienti)	66	22

Femmina, 72 anni, T2DM da 28 anni, in terapia insulinica multi-iniettiva
Motivo del cambio di terapia: HbA1c non a target



Femmina, 64 anni, T2DM da 13 anni, in terapia con metformina 2500 mg

Motivo del cambio di terapia: HbA1c non a target



Riduzione della PA

Caso Clinico 1 - Anamnesi

- Paziente maschio di 67 anni
- Diabete mellito di tipo 2, noto dal 1998
- Terapia in corso (che assume in modo discontinuo):
  - Glibenclamide 2,5 mg + metformina 400 mg 1cpx2/die (a colazione e cena)

Prima visita (novembre 2013)

- Dati antropometrici:
  - Statura 178 cm
  - Peso 82 kg
  - BMI 25,88 kg/m^2
  - Circonferenza vita 94 cm
- Parametri:
  - Pressione sistolica 176 mm Hg
  - Pressione diastolica 100 mm Hg
  - Frequenza cardiaca 80 bpm
- Prescrizione:
  - Ramipril5 mg 1cp/die (al mattino)

Due settimane dopo

- Esami di laboratorio:
  - Glicemia a digiuno 263 mg/dl
  - Emoglobina glicata 88 mmol/mol (10,2%)
  - Colesterolo totale 128 mg/dl
  - Colesterolo HDL 58 mg/dl
  - Trigliceridi 91 mg/dl
  - Colesterolo LDL (calc.) 51,8 mg/dl
  - eGFR 74 ml/min/1,7
  - Microalbuminuria 94,78 mg/l

Terapia

- Metformina 1000 mg
  - 1cpx2/die (dopo colazione e dopo cena)
- Gliclazide 30 mg
  - 3cp/die (a pranzo)
- Insulina Detemir
  - 14 UI (alla sera prima di coricarsi)
- Ramipril5 mg
  - 1cp/die (al mattino)

Aprile 2014

- Dati antropometrici:
  - Statura 178 cm
  - Peso 78 kg
  - BMI 24,66 kg/m^2
- Parametri:
  - Pressione sistolica 154 mm Hg
  - Pressione diastolica 90 mm Hg
  - Frequenza cardiaca 78 bpm
- Esami di laboratorio:
  - Glicemia a digiuno 90 mg/dl
  - Emoglobina glicata 73 mmol/mol (8,8%)
  - Colesterolo totale 147 mg/dl
  - Colesterolo HDL 77mg/dl
  - Trigliceridi 90 mg/dl
  - Colesterolo LDL (calc.) 52 mg/dl
  - Microalbuminuria 86,67 mg/l
- “Dal diario delle glicemie si rileva discreto controllo della glicemia a digiuno con valori mediamente <150 mg/dl, ma presenza di valori quasi sempre >200 mg/dl negli altri orari della giornata”

Terapia

- Metformina 1000 mg
  - 1cpx2/die (dopo colazione e dopo cena)
- Gliclazide 30 mg
  - 3cp/die (a pranzo)
- Insulina Detemir
  - 14 UI (alla sera prima di coricarsi)
- Dapagliflozin 10 mg
  - 1cp/die (al mattino)
- Ramipril 10 mg
  - 1cp/die (al mattino)

Giugno 2014

- Dati antropometrici:
  - Statura 178 cm
  - Peso 77 kg
  - BMI 24,3 kg/m^2
  - Circonferenza vita 94 cm
- Parametri:
  - Pressione sistolica 148 mm Hg
  - Pressione diastolica 78 mm Hg
  - Frequenza cardiaca 74 bpm
- Esami di laboratorio:
  - Glicemia a digiuno 87 mg/dl
  - Emoglobina glicata 53,01 mmol/mol (7,0%)
- “Dal diario delle glicemie dell’ultimo mese si rilevano valori mediamente <100 mg/dl al mattino a digiuno, <120 mg/dl prima dei pasti e <140 mg/dl dopo i pasti”

Terapia

- Metformina 1000 mg
  - 1cpx2/die (dopo colazione e dopo cena)
- Gliclazide 30 mg
  - 2cp/die (a pranzo)
- Insulina Detemir
  - 18 UI (alla sera prima di coricarsi)
- Dapagliflozin 10 mg
  - 1cp/die (al mattino)
- Ramipril 10 mg
  - 1cp/die (al mattino)

Settembre 2014

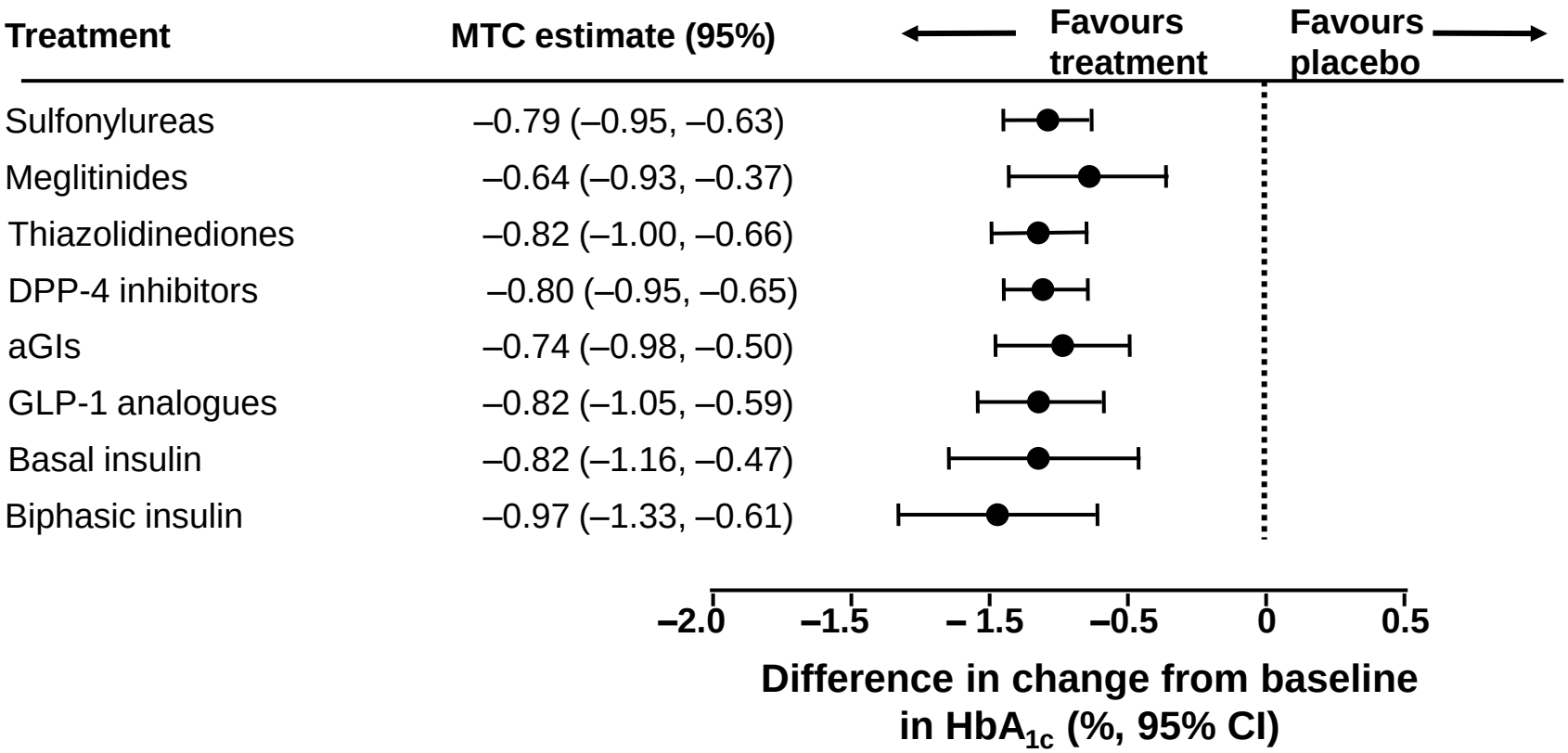
- Esami di laboratorio:
  - Glicemia a digiuno 88 mg/dl
  - Emoglobina glicata 48 mmol/mol (6,5%)
  - Colesterolo totale 143 mg/dl
  - Colesterolo HDL 62 mg/dl
  - Trigliceridi 232 mg/dl
  - Colesterolo LDL (calc.) 34,6 mg/dl
  - Microalbuminuria 68,03 mg/l

What next after metformin?

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

Effects of antidiabetic drugs added to metformin therapy on glycaemic control in T2DM

HbA_{1c} reduction *vs* placebo



DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; T2D, type 2 diabetes.

McIntosh B *et al*. *Open Med* 2011;**5**:e35–48.

What next after metformin?

	Metformin	SU	TZD	Acarbose	DPPIV-I	GLP1-RA	SGLT2
Route	Oral	Oral	Oral	Oral	Oral	SC	Oral
Dose/wk	7-21	7-21	7-14	7-21	7-14	1-14	7
HbA1c	↓↓↓	↓↓↓	↓↓↓	↓↓	↓↓(↓)	↓↓↓	↓↓↓
Weight	-/↓	↑↑	↑↑↑	-	-	↓↓↓ *	↓↓↓
BP	-	↑	-/↓	-	-	↓	↓↓↓
Hypos	-	↑↑↑	-	-	-	-	-
SMBG	-	↑↑↑	-	-	-	-	-
Durability	↑(↑)	No	↑↑↑	NA	↑↑	↑↑	↑↑↑
AE	+	++(+)	+++	+	-	+	+(+)

* Majority of patients

Author's personal opinion

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).