DIABETE TIPO 1 E DIABETE TIPO 2: NUOVI FARMACI E NUOVE TECNOLOGIE

SGLT-2 inibitori

Micaela Pellegrino

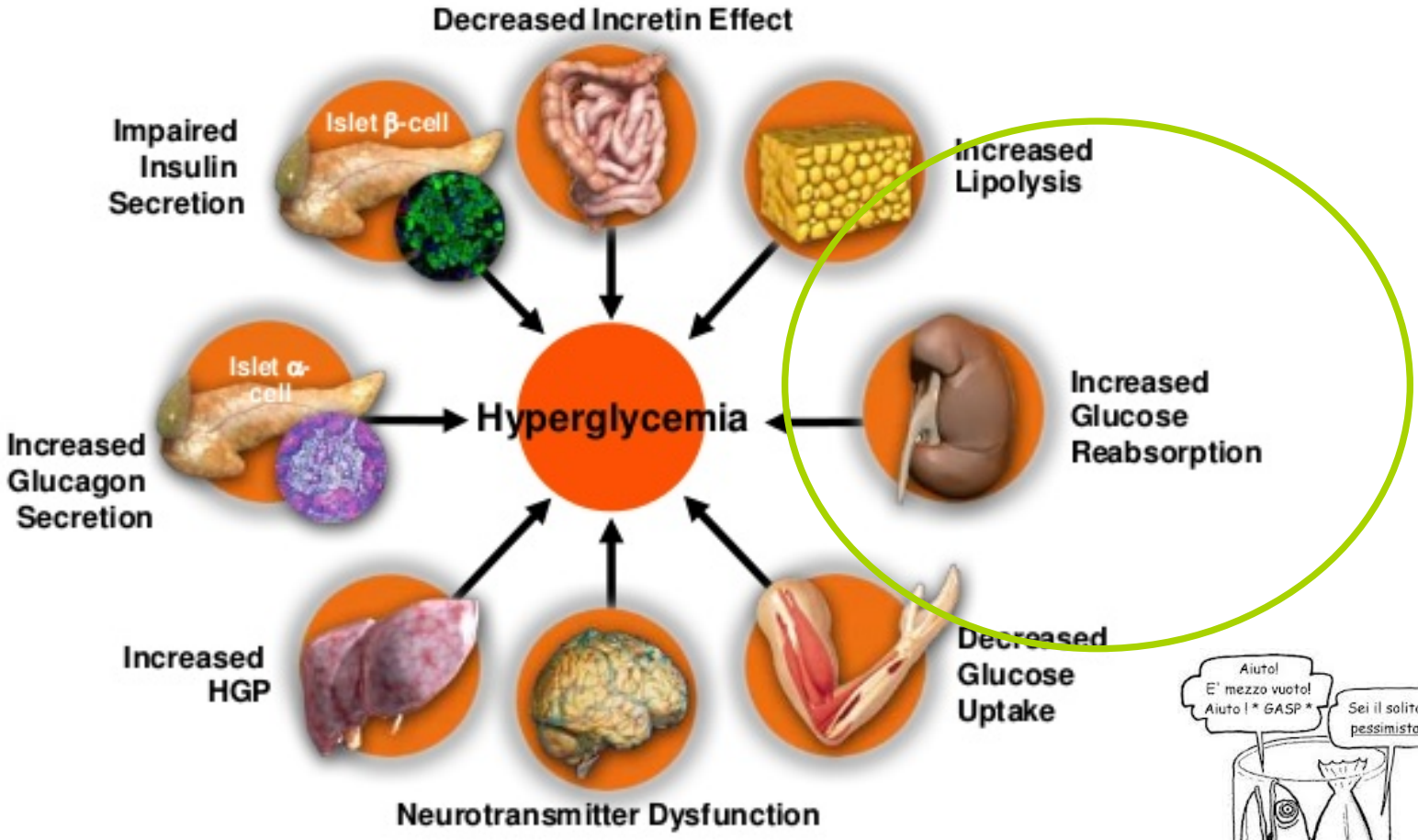
S.C. ENDOCRINOLOGIA E DIABETOLOGIA

A.S.O. S. CROCE E CARLE, CUNEO

SGLT2 inibitori nel DM2

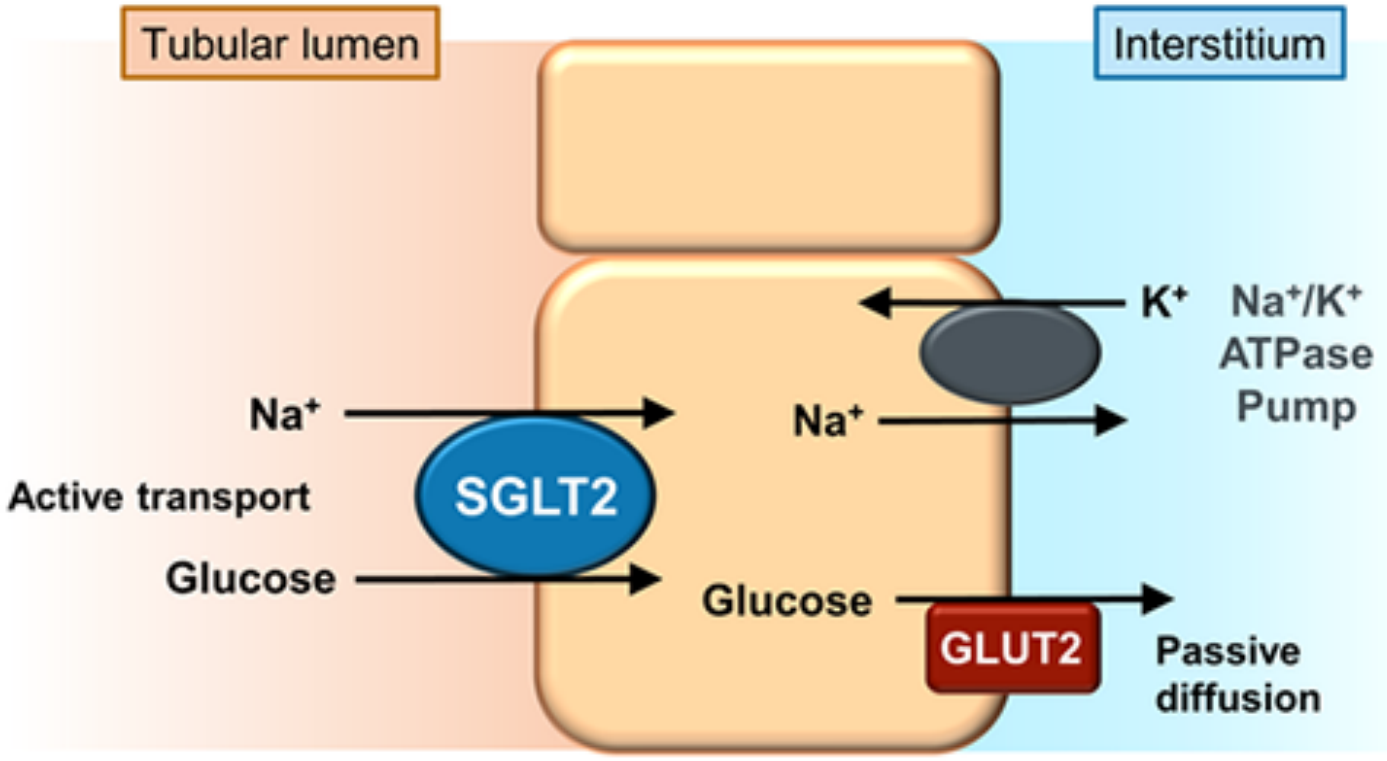
una nuova frontiera terapeutica?

Pathophysiologic Defects in Type 2 Diabetes: The Ominous Octet



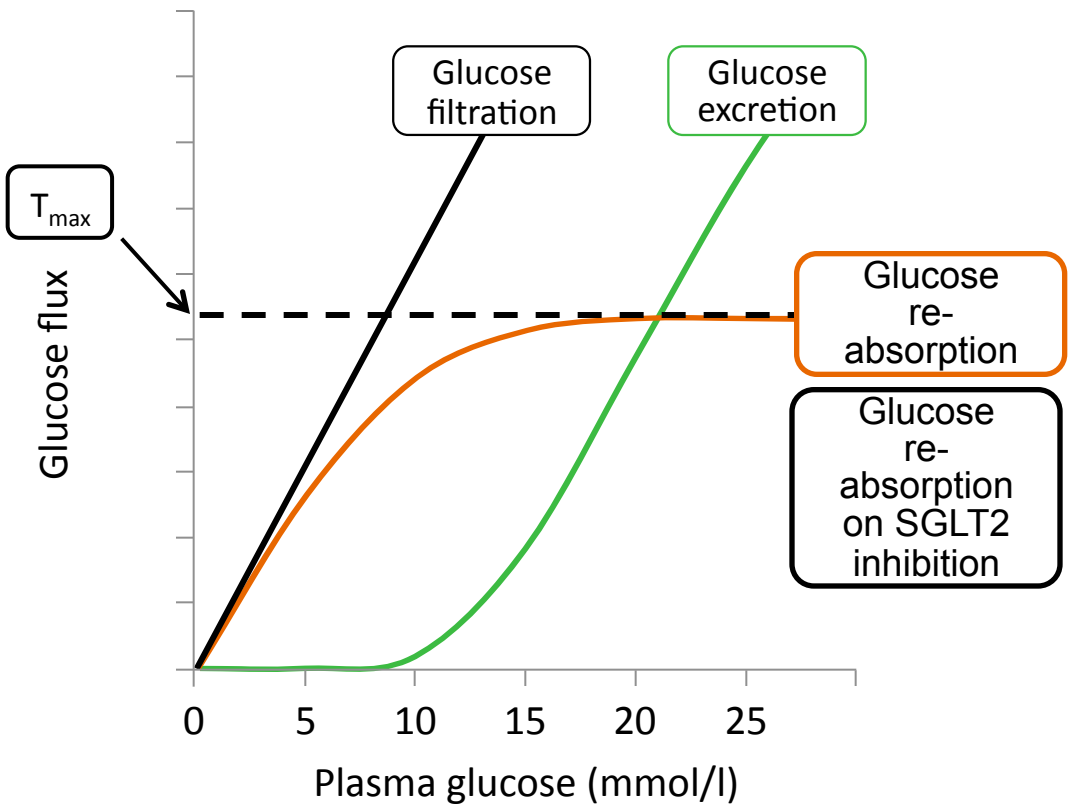
DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

Cellular Glucose Homeostasis



Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42.[3]

Renal glucose re-absorption and excretion



Glucose re-absorption is increased in T2D...

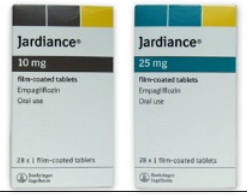
...reducing the amount of glucose excreted at a given level of blood glucose

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

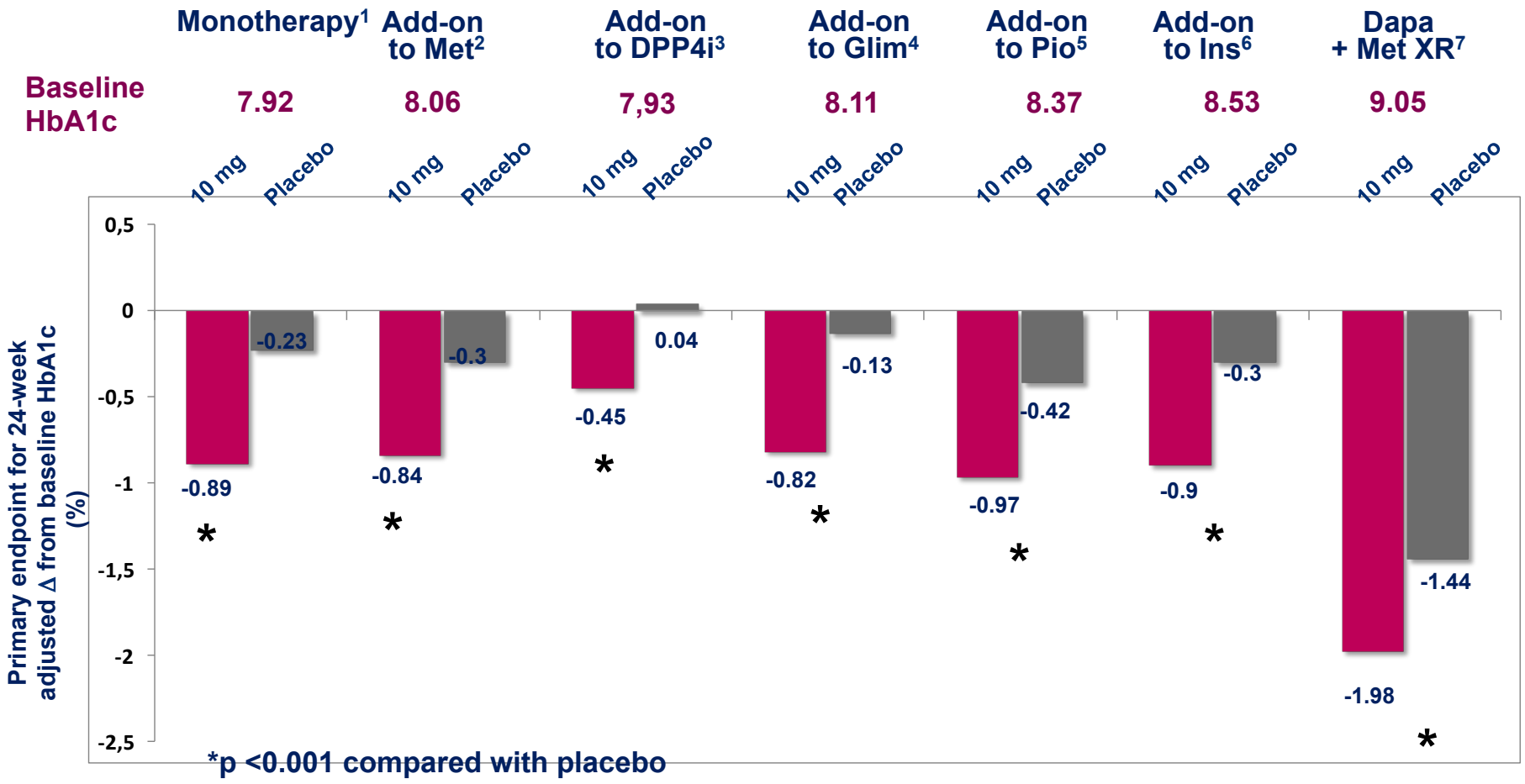
This increases glucose excretion

SGLT2, sodium glucose cotransporter 2; 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.

			
EMA approval	11/2012	11/2013	2/2014
FDA approval	1/2014	3/2013	8/2014
SGLT2 selectivity over SGLT1	1:1200	1:414	>1:2500
Posology	5-10 mg	100-300 mg	10-25 mg
Half-life	17 h	12-15 h	10-19 h
Absorption (picco)	1.5 h	2.8-4 h	1.5 h

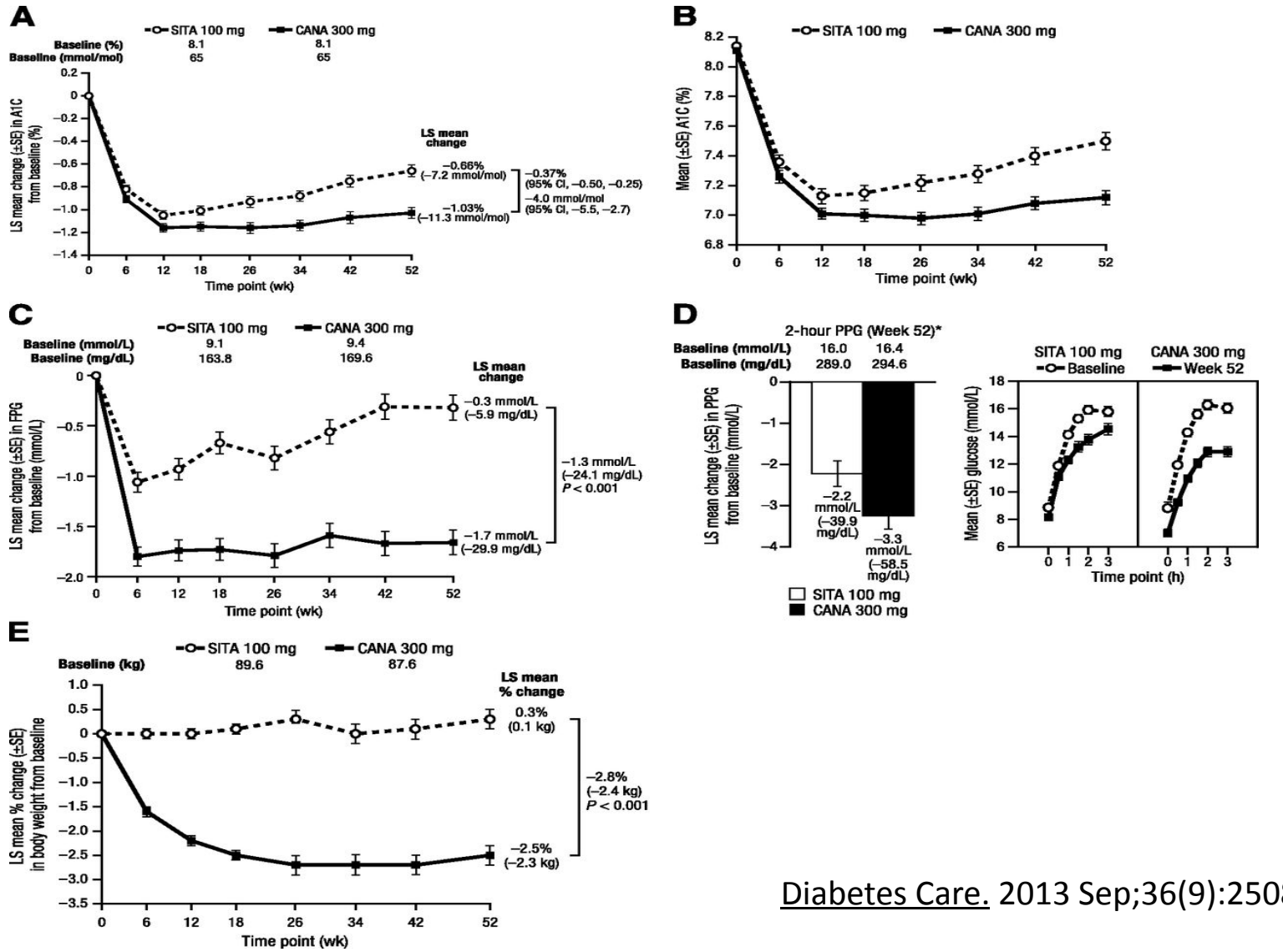
Consistent decreases in HbA1c from baseline at week 24 across all dapagliflozin studies



[1]Ferrannini E, et al. Diabetes Care 2010;33:2217-24. [2]Bailey CJ, et al. Lancet 2010;375:2223-33. [3]Jabbour et al., . Diabetes Care. 2014 Mar;37(3):740-750. ; [4]Strojek K, et al. Diabetes Obes Metab 2011;13:928-38.
[5]Rosenstock J, et al. Diabetes Care. 2012;35(7):1473-1478. [6]Wilding J, et al. Ann Intern Med. 2012;156(6):405-415.
[7]Henry R, et al. Int J Clin Pract. 2012;66(5):446-456.

Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial.

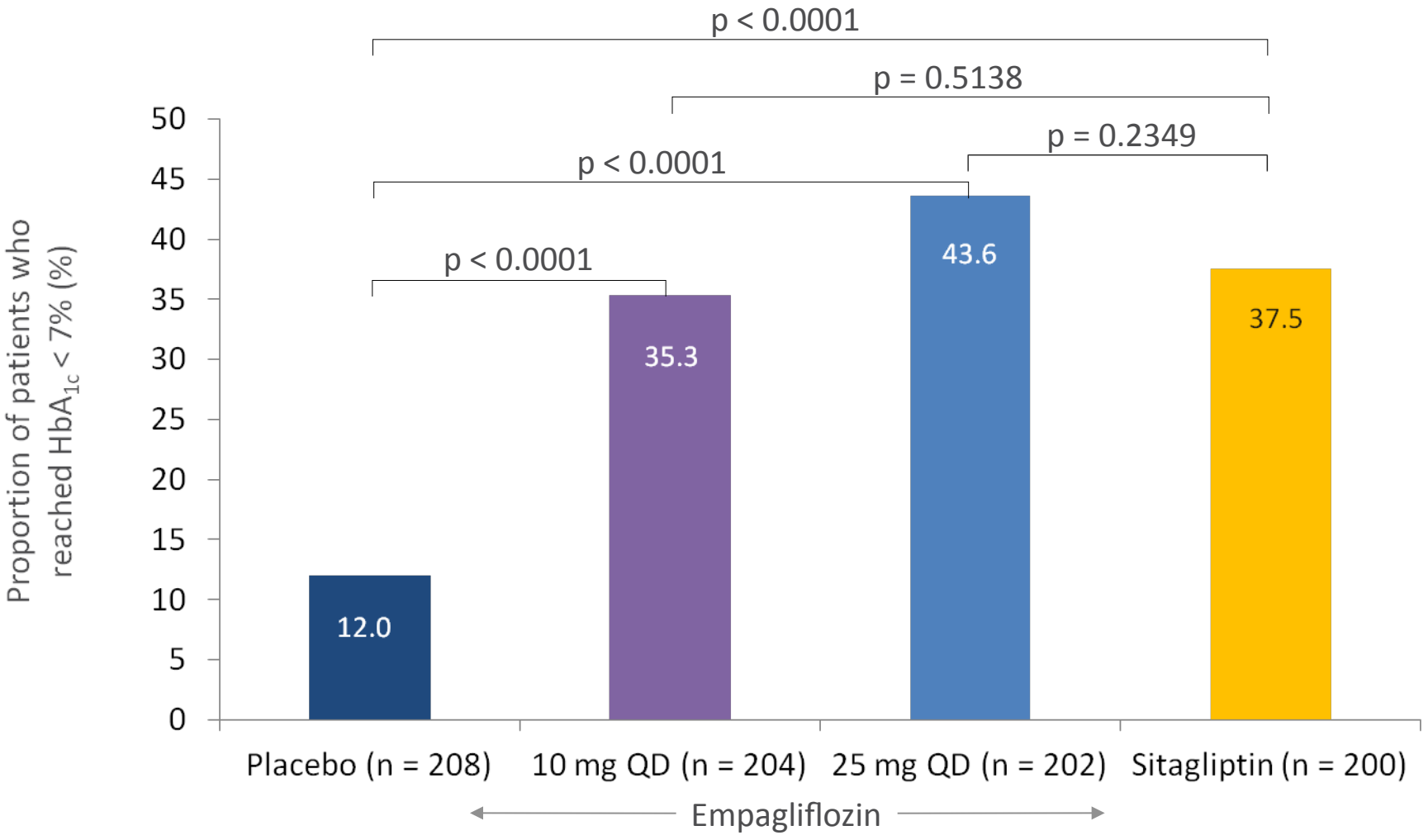
Schernthaner G[1], Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, Kawaguchi M, Canovatchel W, Meininger G.



Diabetes Care. 2013 Sep;36(9):2508-15

24-week empagliflozin monotherapy versus placebo and sitagliptin

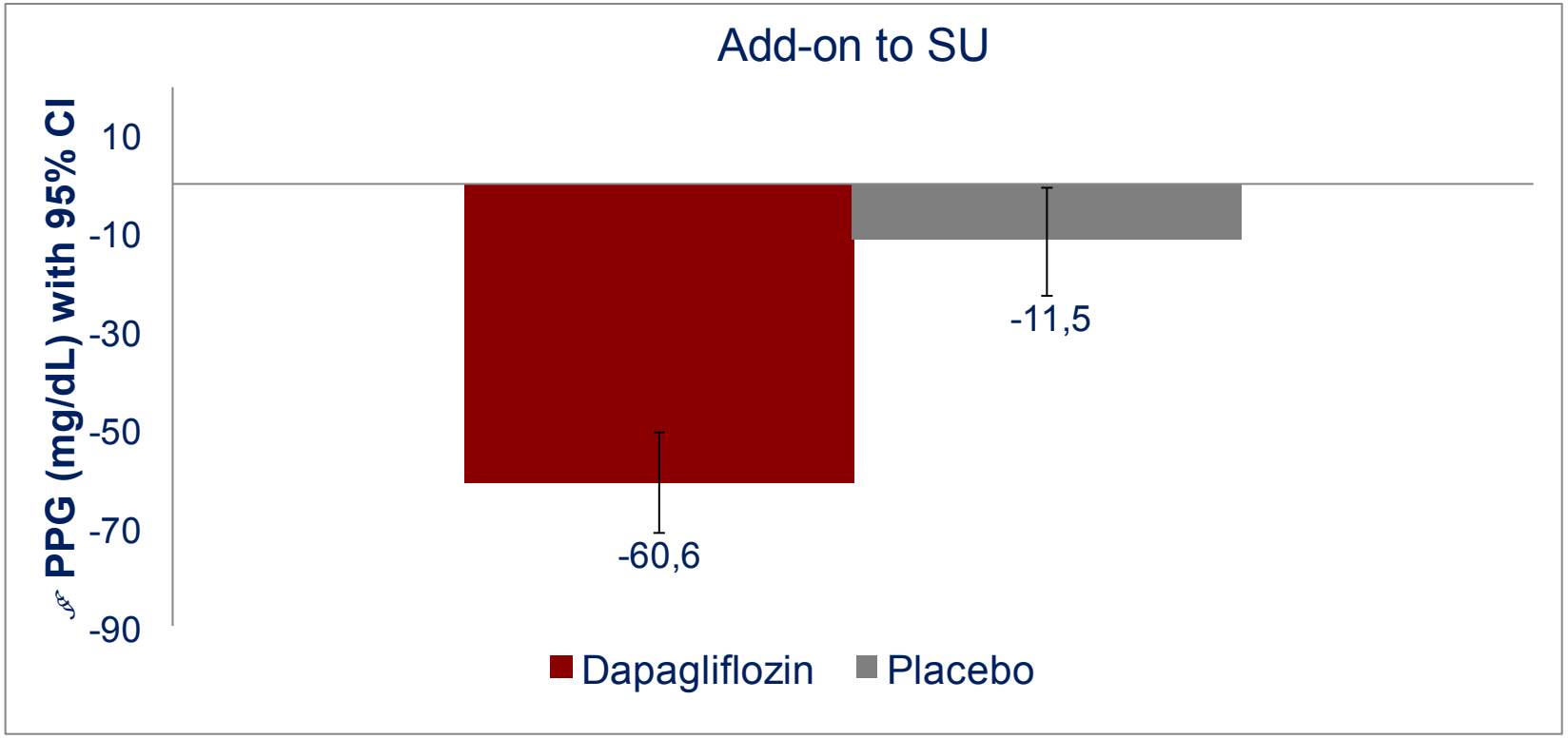
Proportion of patients who reached HbA_{1c} < 7%



HbA_{1c}, glycosylated haemoglobin; QD, once daily.
Analysis of patients who reached HbA_{1c} < 7.0% at Week 24, used non-completers considered to be failures imputation.
Roden M, et al. *Lancet Diabetes Endocrinol.* 2013; 1: 208–19.

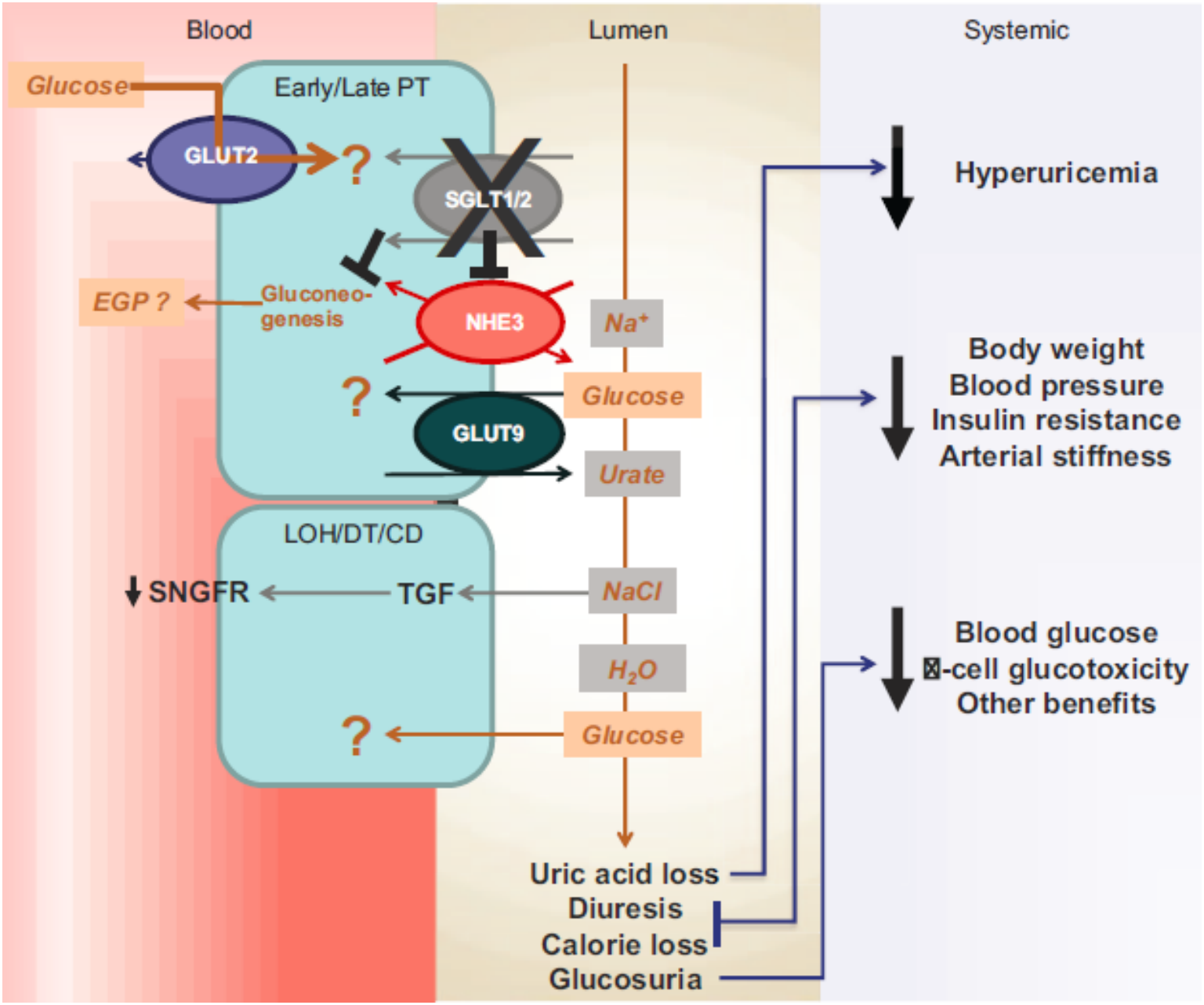
Reduction in post-prandial glucose at Week24

Baseline (mg/dL) **157.3**



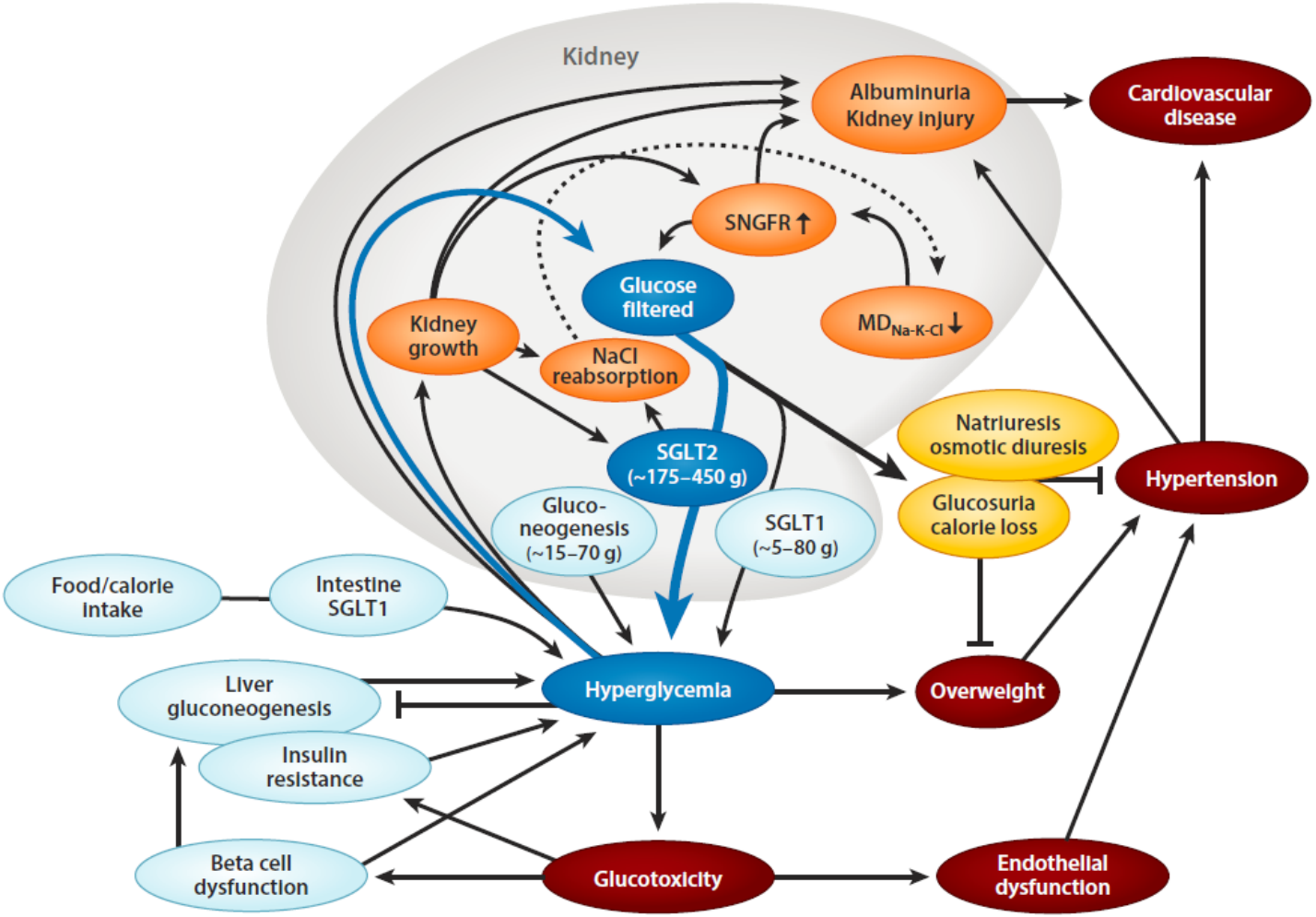
Statistically significant versus placebo by hierarchical testing rule (p<0.001); adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF); SU=sulphonylurea;

Strojek K, Diab Obes Metab 2011;13: 928–938; Food & Drug Administration. Endocrinologic and Metabolic Drugs Advisory Committee: Dapagliflozin BMS-512148. Available from: http://tinyurl.com/7kjf5j7 (Accessed February 2012)

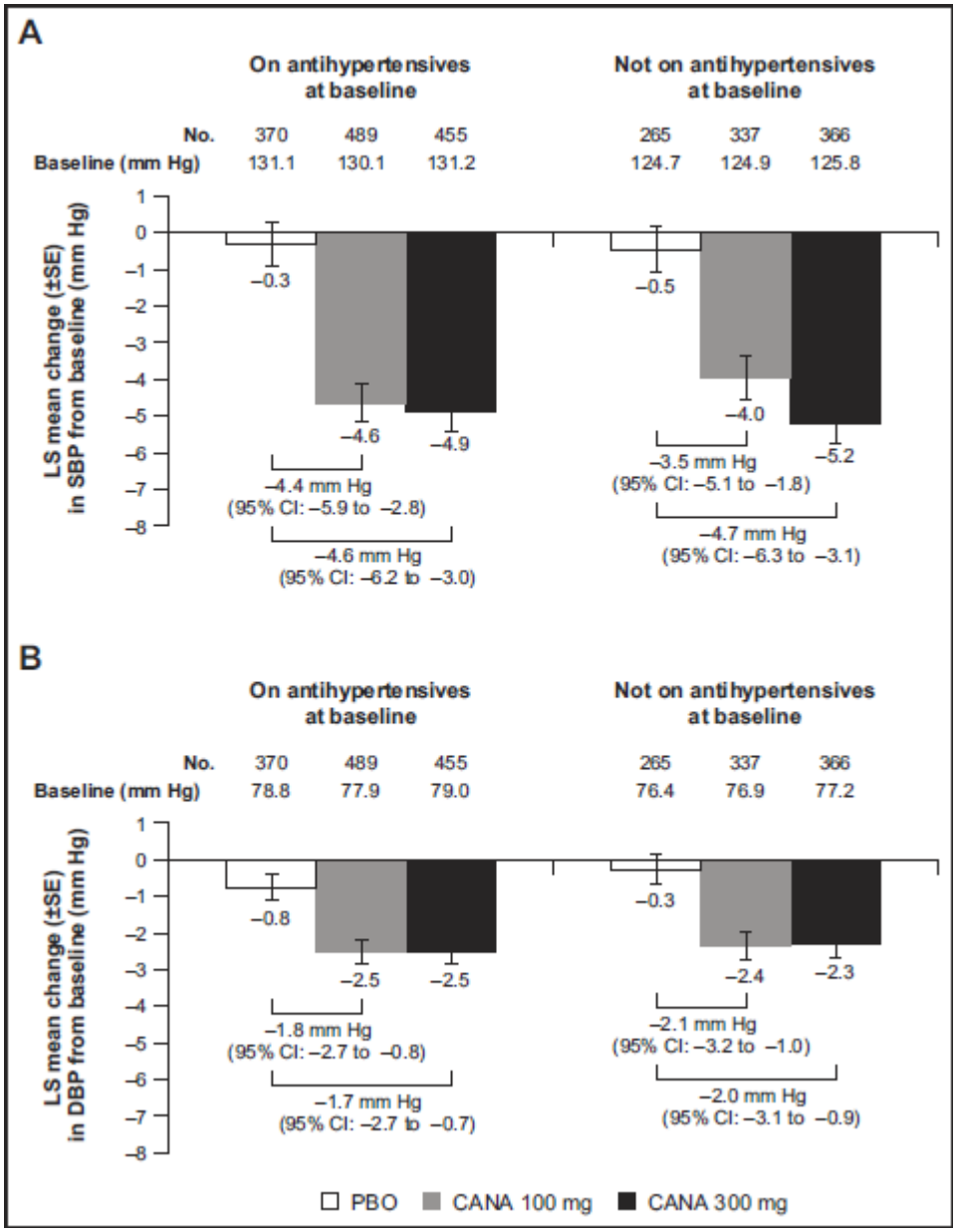


L.A. Gallo et al. Diabetes & Vascular Disease Research 1–12; 2015 DOI: 10.1177/1479164114561992

The role of SGLT2 in the diabetic kidney: potential for blood glucose-dependent effects of SGLT2 inhibition on the cardiovascular system



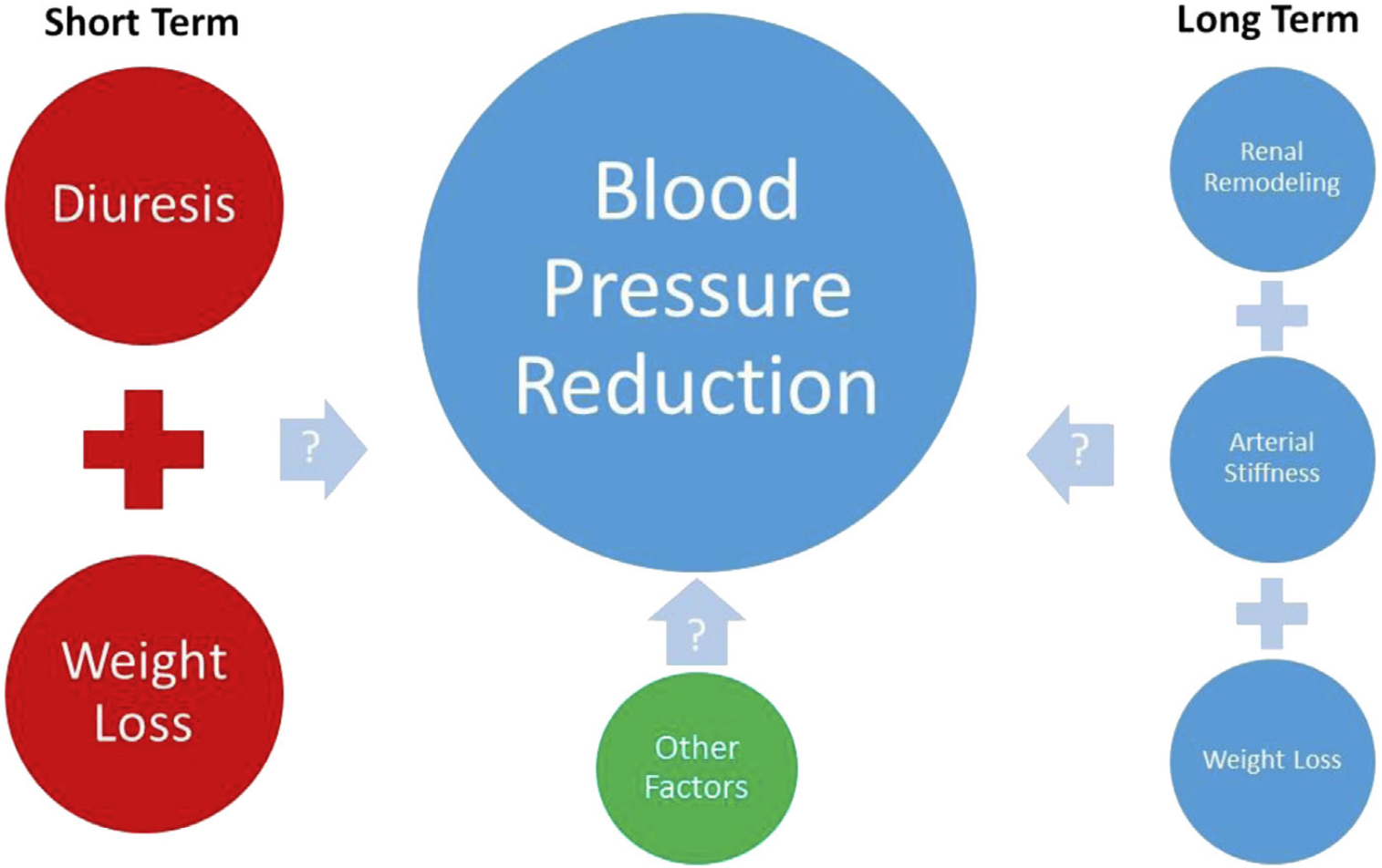
Vallon V. *Annu. Rev. Med*. 2015. 66:255-70



Changes on SBP and DBP for patients taking or not taking antihypertensive medications

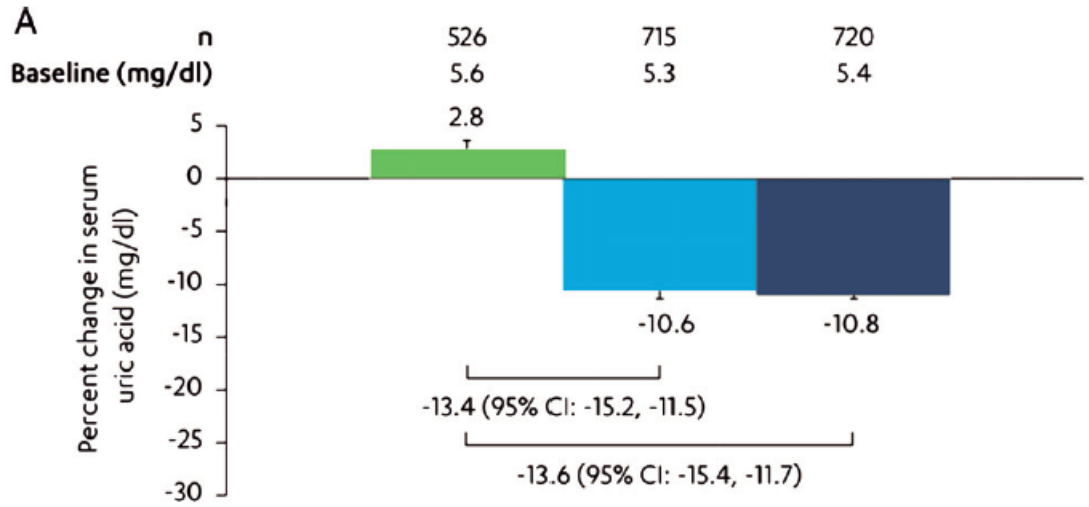
Weir R. et al.
J. Clin Hyper.
2014 16 (12):875-82

FIGURE 3. Change in (A) systolic blood pressure (SBP) and (B) diastolic blood pressure (DBP) for patients taking antihypertensive medications (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and/or diuretics) and not taking antihypertensive medications at baseline (last observation carried forward [LOCF]). LS indicates least-squares; SE, standard error; CI, confidence interval; PBO, placebo; CANA, canagliflozin.



G. Maliha et al. Journal of the American Society of Hypertension 9(1) (2015

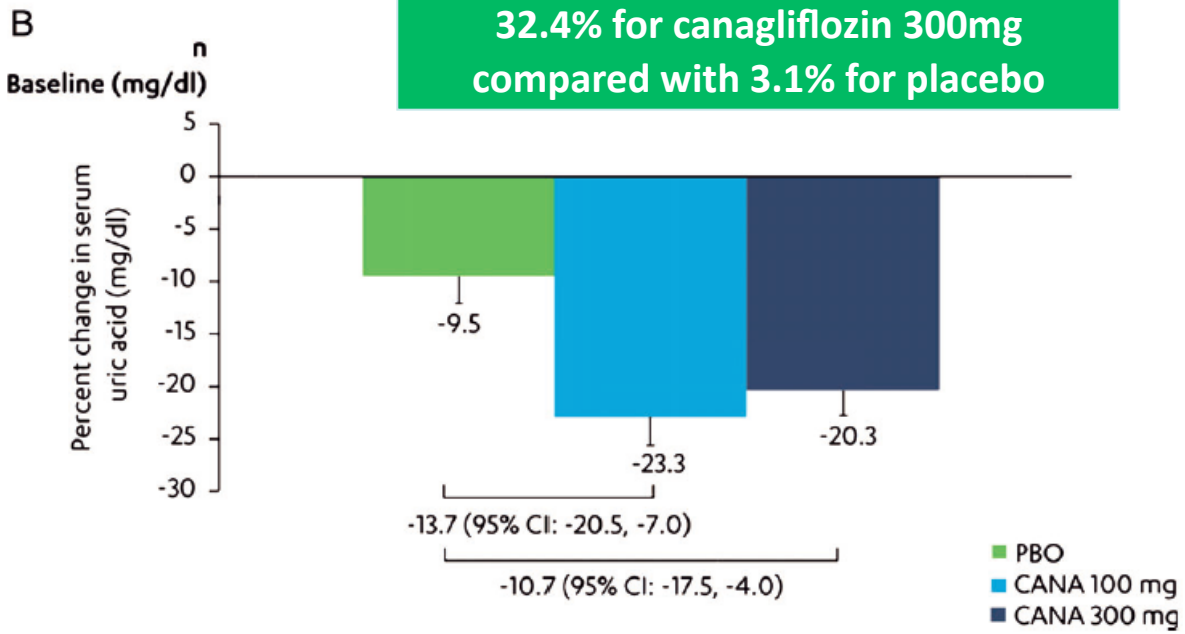
Effect of canagliflozin on serum uric acid in patients with type 2 diabetes mellitus



A) Percent change in serum uric acid levels in the overall pooled cohort

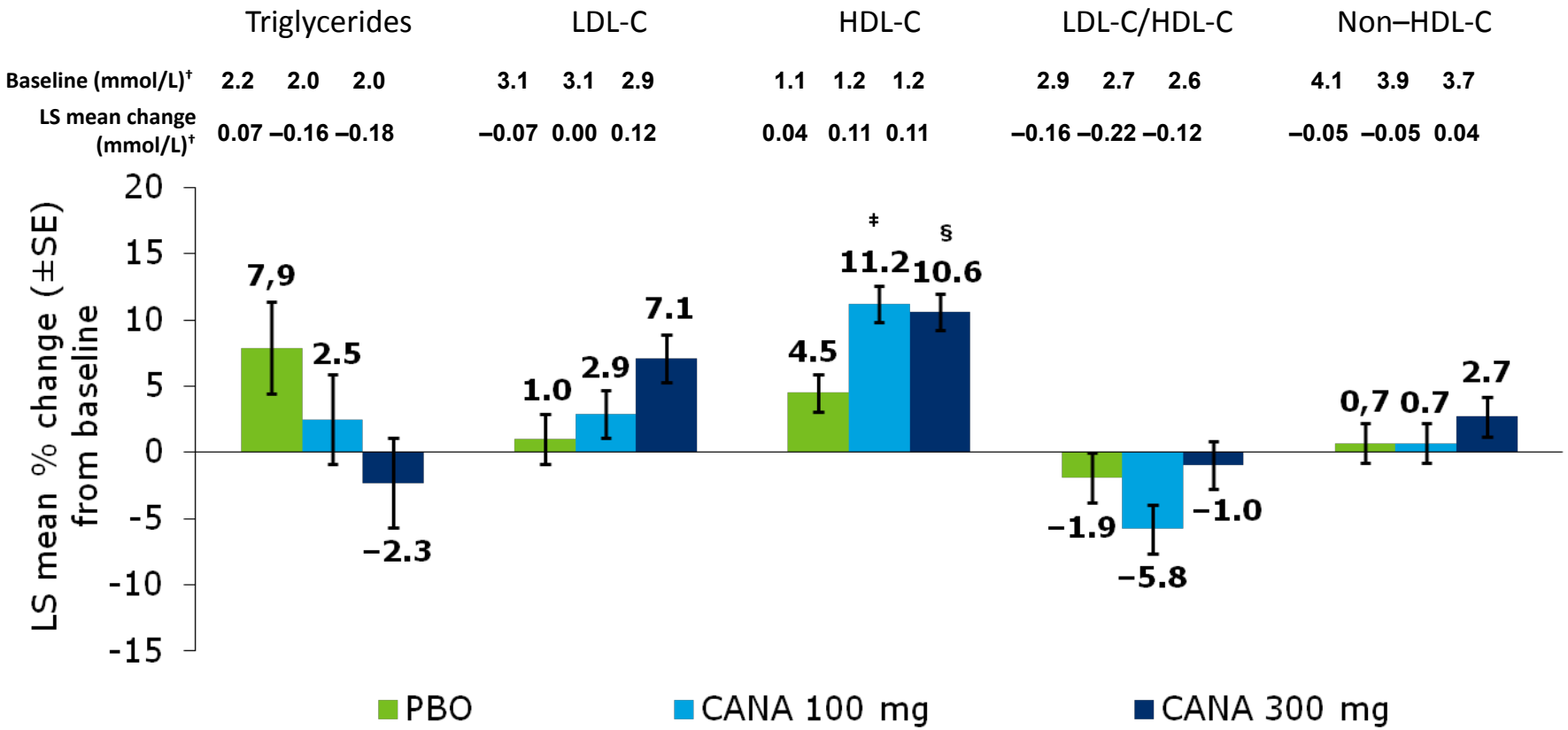
In the cohort with hyperuricaemia, the proportion of patients achieving serm uric acid levels<6mg/dl at week 26 was 23.5% for canagliflozin 100mg and 32.4% for canagliflozin 300mg compared with 3.1% for placebo

B) Percent change in serum uric acid levels in the subset of patients with hyperuricaemia (baseline serum uric acid ≥8mg/dl).



Davies et al. *Diabetes, Obesity and Metabolism* 2015.doi:10.1111/dom.12439

Change in Fasting Plasma Lipids at Week 26 (LOCF)*- Canagliflozin monotherapy



LOCF, last observation carried forward; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; LS, least squares; SE, standard error; PBO, placebo; CANA, canagliflozin; NS, not significant.

*P = NS for CANA 100 and 300 mg vs PBO for triglycerides; Statistical comparison for CANA 100 and 300 mg vs PBO not performed (not pre-specified) for LDL-C, LDL-C/HDL-C, and non–HDL-C.

‡Unit of mol/mol for LDL-C/HDL-C.

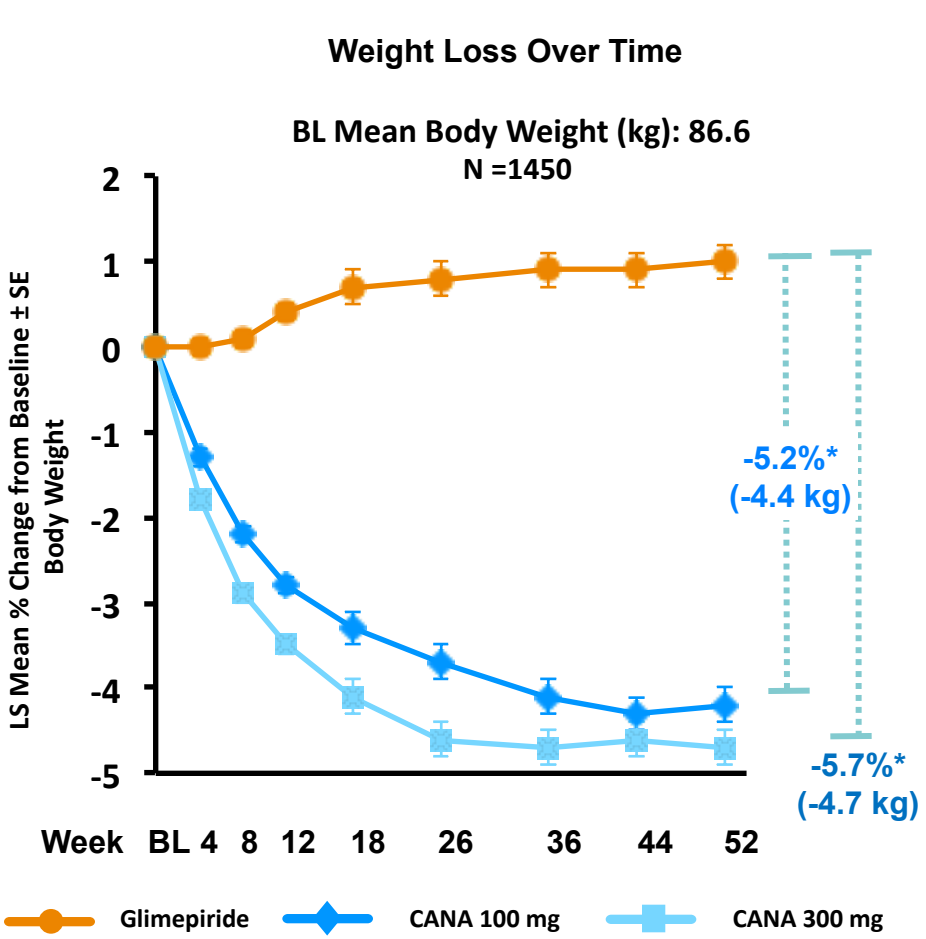
‡P <0.001 vs PBO.

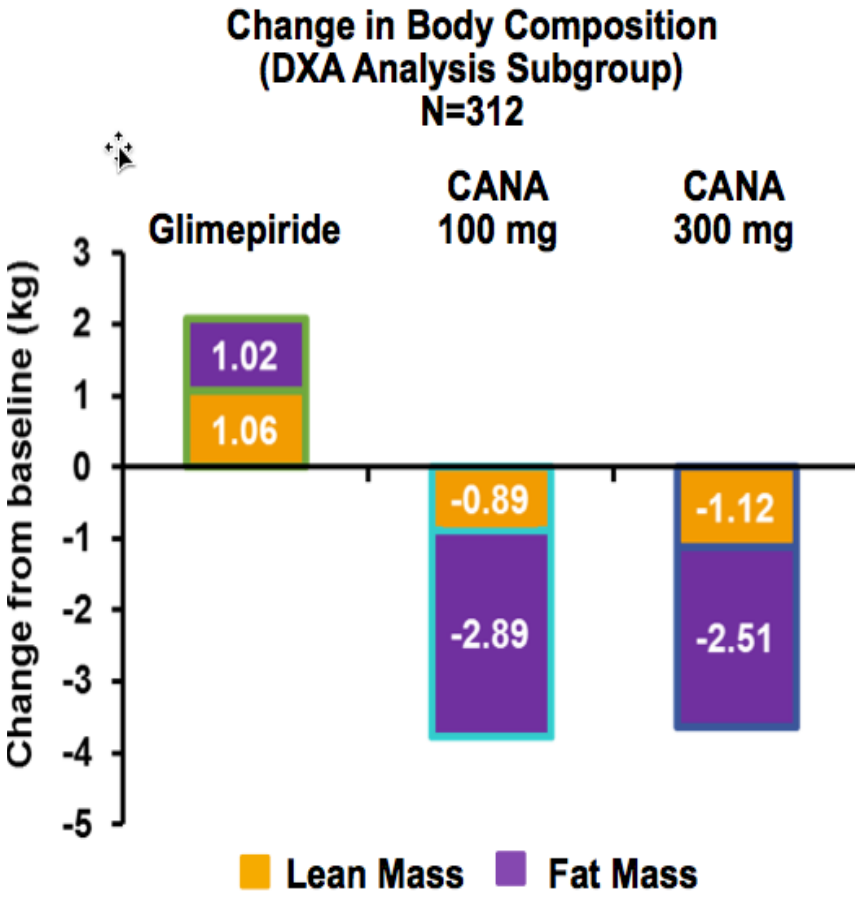
§P <0.01 vs PBO.

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

Add on to Metformin vs Glimepiride: Changes in Body Composition and Weight

52 week data

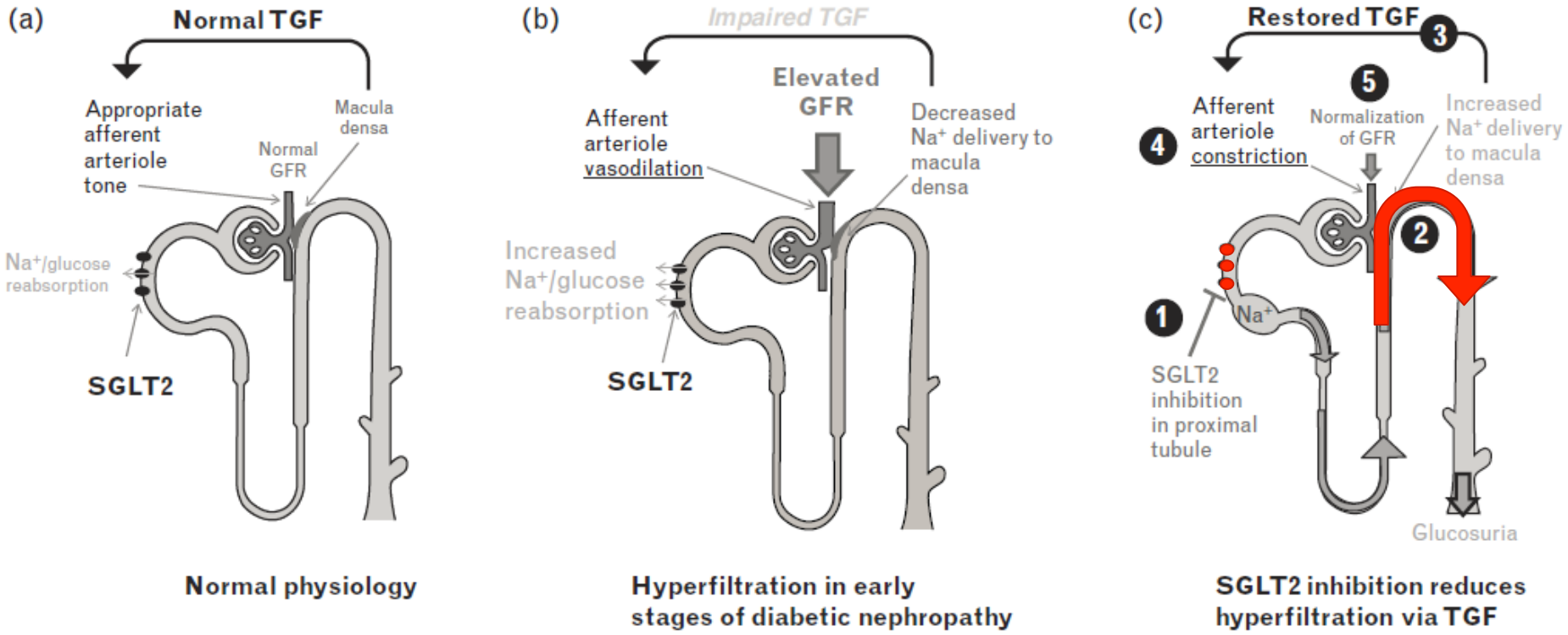




Weight changes relative to glimepiride in DXA analysis subgroup (-5.3 kg and -5.0 kg for CANA 100 mg and 300 mg, respectively) were similar to overall cohort.

Toubro S. et al. Poster presented CODHy, 2012; Barcelona, Spain.
Cefalu WT et al. Lancet. 2013; 382(9896):941-50.

Tubuloglomerular feedback and sodium–glucose cotransporter-2 inhibition



GFR, glomerular filtration rate;
SGLT2, sodium–glucose cotransporter-2; TGF, tubuloglomerular feedback.

Curr Opin Nephrol Hypertens 2015, 24:96–103; DOI:10.1097/MNH.0000000000000084

STANDARD ITALIANI PER LA CURA DEL DIABETE MELLITO

VERSIONE AGGIORNATA 2016

2. DIABETE TIPO 2

RACCOMANDAZIONI

Numerosi trial clinici randomizzati dimostrano che, in aggiunta a metformina, sulfoniluree, repaglinide, acarbose, pioglitazone, inibitori di DPP-4 (gliptine), agonisti del recettore del GLP-1, **inibitori di SGLT-2 (gliflozine)** e insulina sono capaci di ridurre significativamente la HbA1c, con effetto tanto maggiore quanto più alto è il valore di partenza (Livello della prova I, Forza della raccomandazione A)

Nei pazienti con pregressi eventi cardiovascolari maggiori non sufficientemente controllati con la metformina, o con intolleranza o controindicazioni alla metformina, **gli inibitori SGLT-2 dovrebbero essere considerati farmaci di prima scelta** (Livello della prova II Forza della raccomandazione B).

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

N ENGL J MED 373;22 NEJM.ORG NOVEMBER 26, 2015

Multicentre (590 sites in 42 countries), randomized, double blind, placebo controlled trial

PATIENTS

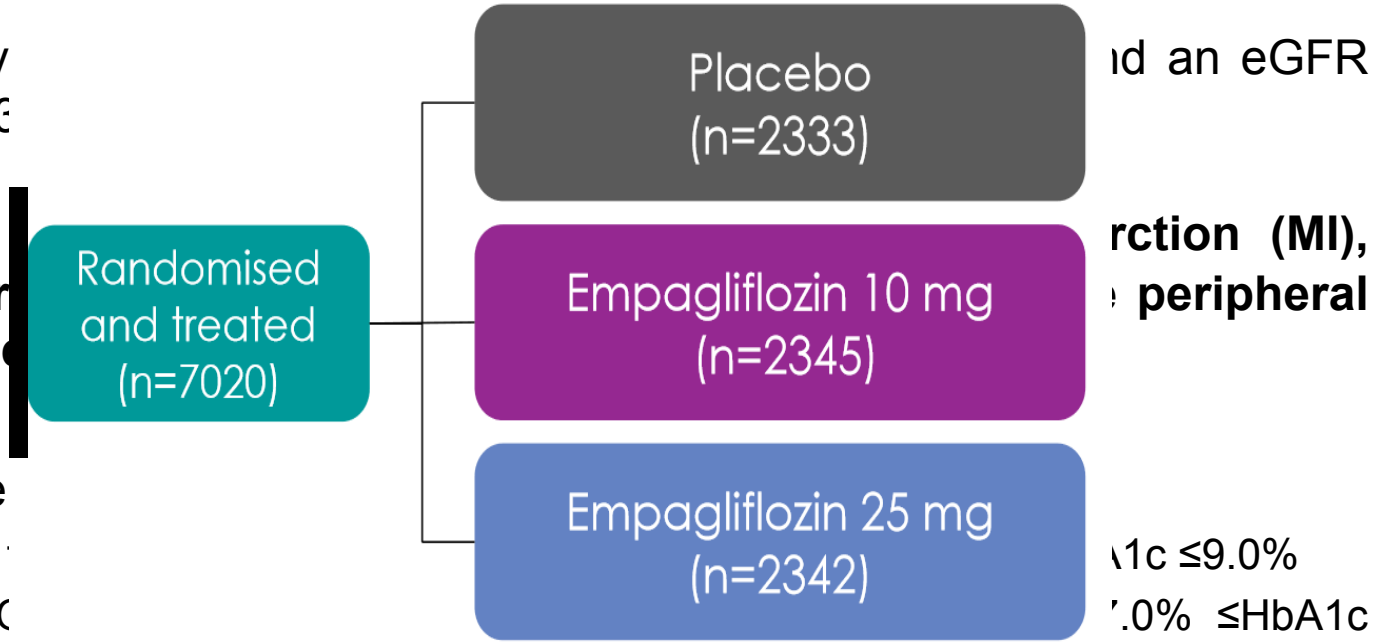
✓Adults (≥18 y … ≥30 ml/min/1.73 … d an eGFR

✓**Established … coronary arter… arterial disease** … **rction (MI), … peripheral**

✓Glucose-lowe…

A. no GLT…

B. stable … ≤10.0% … A1c ≤9.0% … .0% ≤HbA1c



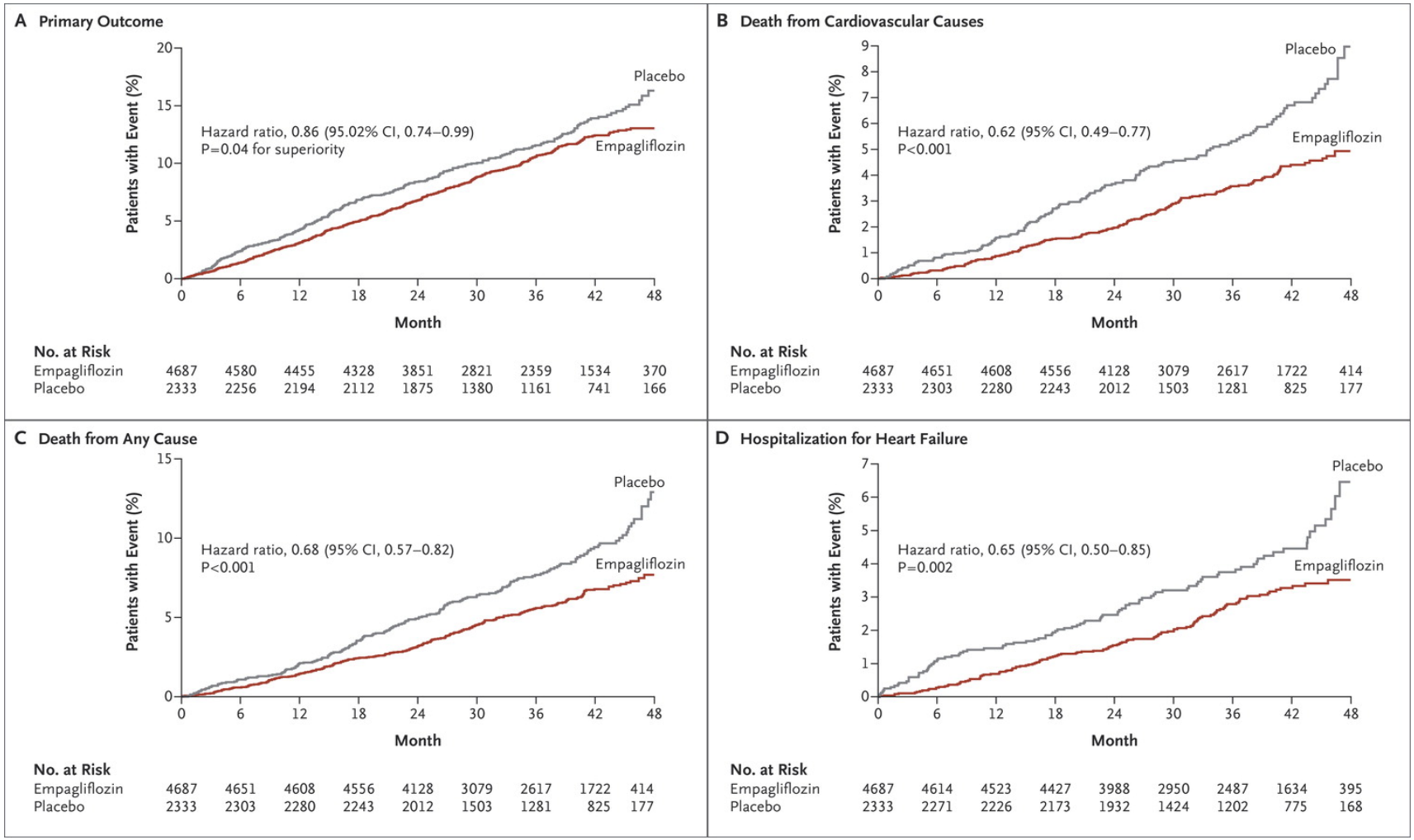
I. Primary outcome (3-point MACE): a composite of death from CV causes, nonfatal MI (excluding silent MI) or nonfatal stroke

II. Key secondary outcome: a composite of the primary outcome + hospitalization for unstable angina

ADVERSE EVENTS OF SPECIAL INTEREST

- Hypoglycemic adverse events (≤70 mg/dl)
- Urinary tract infection (UTI), genital infection
- Volume depletion, acute renal failure, diabetic ketoacidosis
- Bone fracture, thromboembolic events

Cardiovascular Outcomes and Death from Any Cause.



Zinman B et al. N Engl J Med 2015;373:2117-2128.

American Heart Journal Volume 166, Number 2

Rationale, design, and baseline characteristics of the **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy (CANVAS)

A randomized placebo-controlled trial

Bruce Neal, PhD, a,g Vlado Perkovic, PhD, a,g Dick de Zeeuw, PhD, b,g Kenneth W. Mahaffey, MD, c,g Greg Fulcher, MD, d,g

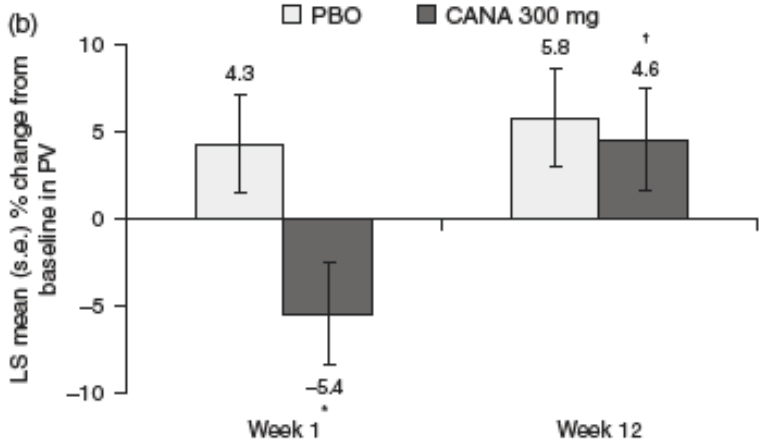
Peter Stein, MD, e,g Mehul Desai, MD, e,g Wayne Shaw, DSL, e,g Joel Jiang, PhD, e,g Frank Vercruysse, MD, e,g

Gary Meininger, MD, e,g and David Matthews, DPhil f,g New South Wales, Australia; Groningen, The Netherlands;

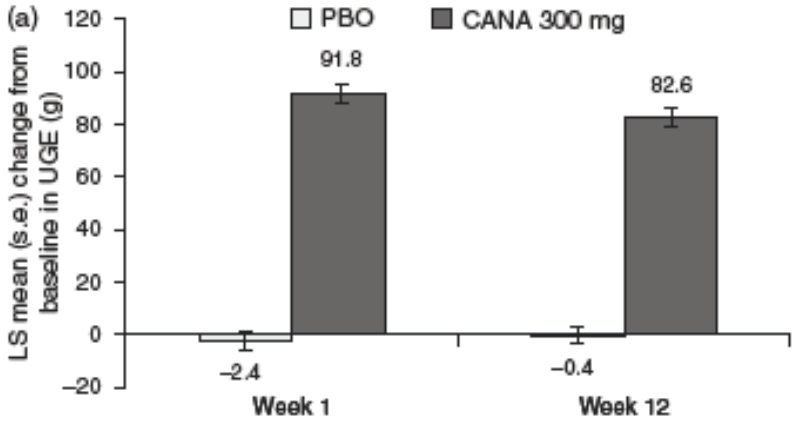
Durham, NC; Raritan, NJ; and Oxford, United Kingdom

Event	Placebo (N=2333)	Empagliflozin, 10 mg (N=2345)	Empagliflozin, 25 mg (N=2342)	Pooled Empagliflozin (N=4687)
	number of patients (percent)			
Any adverse event	2139 (91.7)	2112 (90.1)	2118 (90.4)	4230 (90.2)†
Severe adverse event	592 (25.4)	536 (22.9)	564 (24.1)	1100 (23.5)‡
Serious adverse event				
Any	988 (42.3)	876 (37.4)	913 (39.0)	1789 (38.2)†
Death	119 (5.1)	97 (4.1)	79 (3.4)	176 (3.8)§
Adverse event leading to discontinuation of a study drug	453 (19.4)	416 (17.7)	397 (17.0)	813 (17.3)§
Confirmed hypoglycemic adverse event¶				
Any	650 (27.9)	656 (28.0)	647 (27.6)	1303 (27.8)
Requiring assistance	36 (1.5)	33 (1.4)	30 (1.3)	63 (1.3)
Event consistent with urinary tract infection‖	423 (18.1)	426 (18.2)	416 (17.8)	842 (18.0)
Male patients	158 (9.4)	180 (10.9)	170 (10.1)	350 (10.5)
Female patients	265 (40.6)	246 (35.5)	246 (37.3)	492 (36.4)‡
Complicated urinary tract infection**	41 (1.8)	34 (1.4)	48 (2.0)	82 (1.7)
Event consistent with genital infection††	42 (1.8)	153 (6.5)	148 (6.3)	301 (6.4)†
Male patients	25 (1.5)	89 (5.4)	77 (4.6)	166 (5.0)†
Female patients	17 (2.6)	64 (9.2)	71 (10.8)	135 (10.0)†
Event consistent with volume depletion‡‡	115 (4.9)	115 (4.9)	124 (5.3)	239 (5.1)
Acute renal failure§§	155 (6.6)	121 (5.2)	125 (5.3)	246 (5.2)§
Acute kidney injury	37 (1.6)	26 (1.1)	19 (0.8)	45 (1.0)†
Diabetic ketoacidosis¶¶	1 (<0.1)	3 (0.1)	1 (<0.1)	4 (0.1)
Thromboembolic event§§	20 (0.9)	9 (0.4)	21 (0.9)	30 (0.6)
Bone fracture‖‖	91 (3.9)	92 (3.9)	87 (3.7)	179 (3.8)

Change from baseline in Plasma Volume (PV), Urinary Glucose Excretion (UGE) and 24-h urine volume



Least squares mean (s.e.) percent change in plasma volume at weeks 1 and 12.
CANA, canagliflozin; LS, least squares; PBO, placebo; PV, plasma volume; s.d., standard deviation; s.e., standard error. *p=0.02 vs. PBO; †p=0.076 vs. PBO



Least squares mean (s.e.) change in urinary glucose excretion at weeks 1 and 12.
CANA, canagliflozin; PBO,placebo; LS, least squares; s.e., standard error; UGE, urinary glucose excretion

24-h urine volume, ml	Placebo	CANA 300mg	Difference vs placebo (IC95%)
Mean (s.d.) baseline value	3272.2 (1231.8)	3100.2 (844.9)	
ΔLSM (s.e.) at week 1	108.3 (194.4)	269.3 (200.1)	161.0 (−397.6, 719.6)
ΔLSM (s.e.) at week 12	100.4 (194.4)	149.1 (200.1)	48.7 (−509.9, 607.3)

Sha S. et al. Diabetes, Obesity and Metabolism 16: 1087–1095, 2014.

Adverse events in patients receiving dapagliflozin 10 mg

- AEs observed in ≥2% of patients receiving dapagliflozin 10 mg (monotherapy or combination therapy) and ≥1% more frequently than controls (24 week)

System organ class	Very common (≥1/10)	Common* (≥1/100 to <1/10)	Uncommon† (≥1/1000 to <1/100)
Infections and infestations		Vulovaginitis, balanitis and related genital infections Urinary tract infections‡	Vulvovaginal pruritus
Metabolism and nutrition disorders	Hypoglcaemia (when used with SU or insulin)		Volume depletion Thirst
Gastrointestinal disorders			Constipation
Skin and subcutaneous tissue disorders			Hyperhidrosis
Musculoskeletal and connective tissue disorders		Back pain	
Renal and urinary disorders		Dysuria Polyuria	Nocturia
Investigations		Dyslipidaemia Haematocrit increased	Blood creatinine increased Blood urea increased

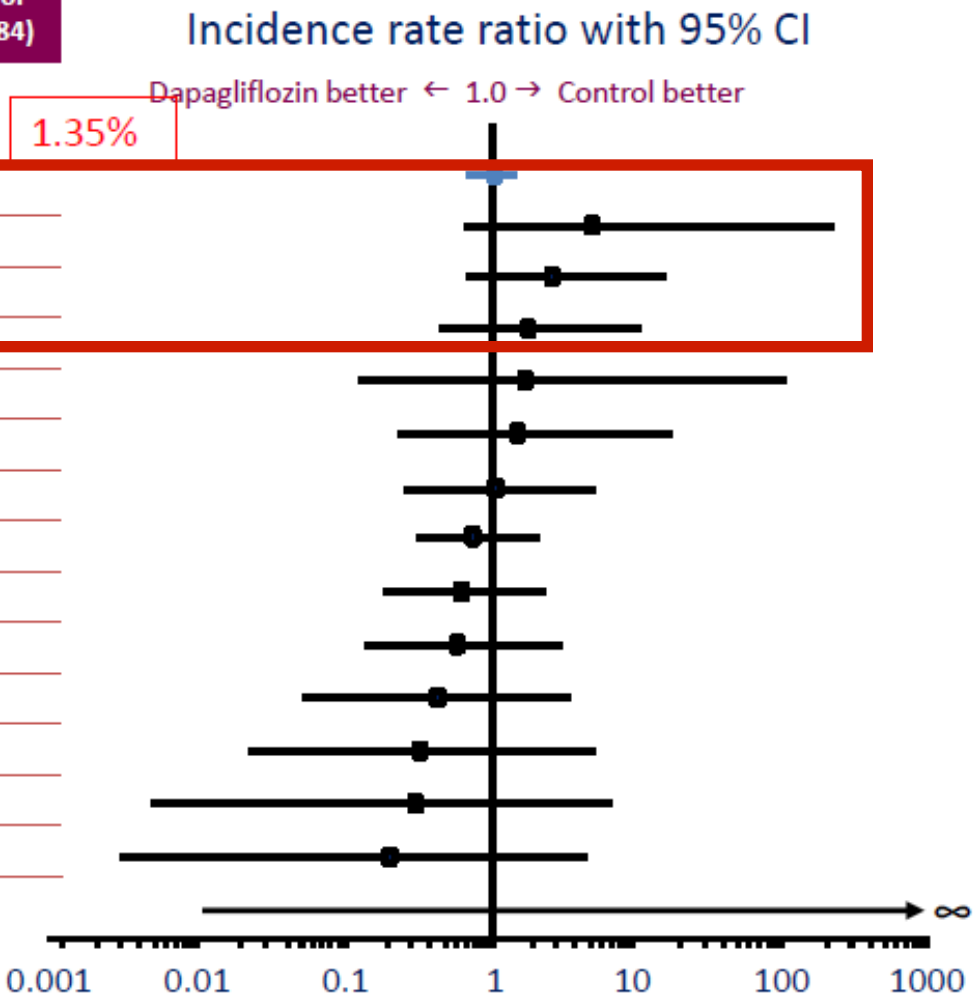
**In ≥2% of patients on dapagliflozin 10 mg and ≥1% more frequently than placebo; †in ≥0.2% of patients on dapagliflozin 10 mg and ≥0.1% more frequently than placebo; ‡urinary tract infections were reported in 4.3% of patients treated with dapagliflozin 10 mg compared with 3.7% for placebo; SU=sulphonylurea;*

Dapagliflozin draft Summary of Product Characterisitcs April 2012

Tumour incidence balanced across organ systems

Dapagliflozin:control exposure ratio ~1.8

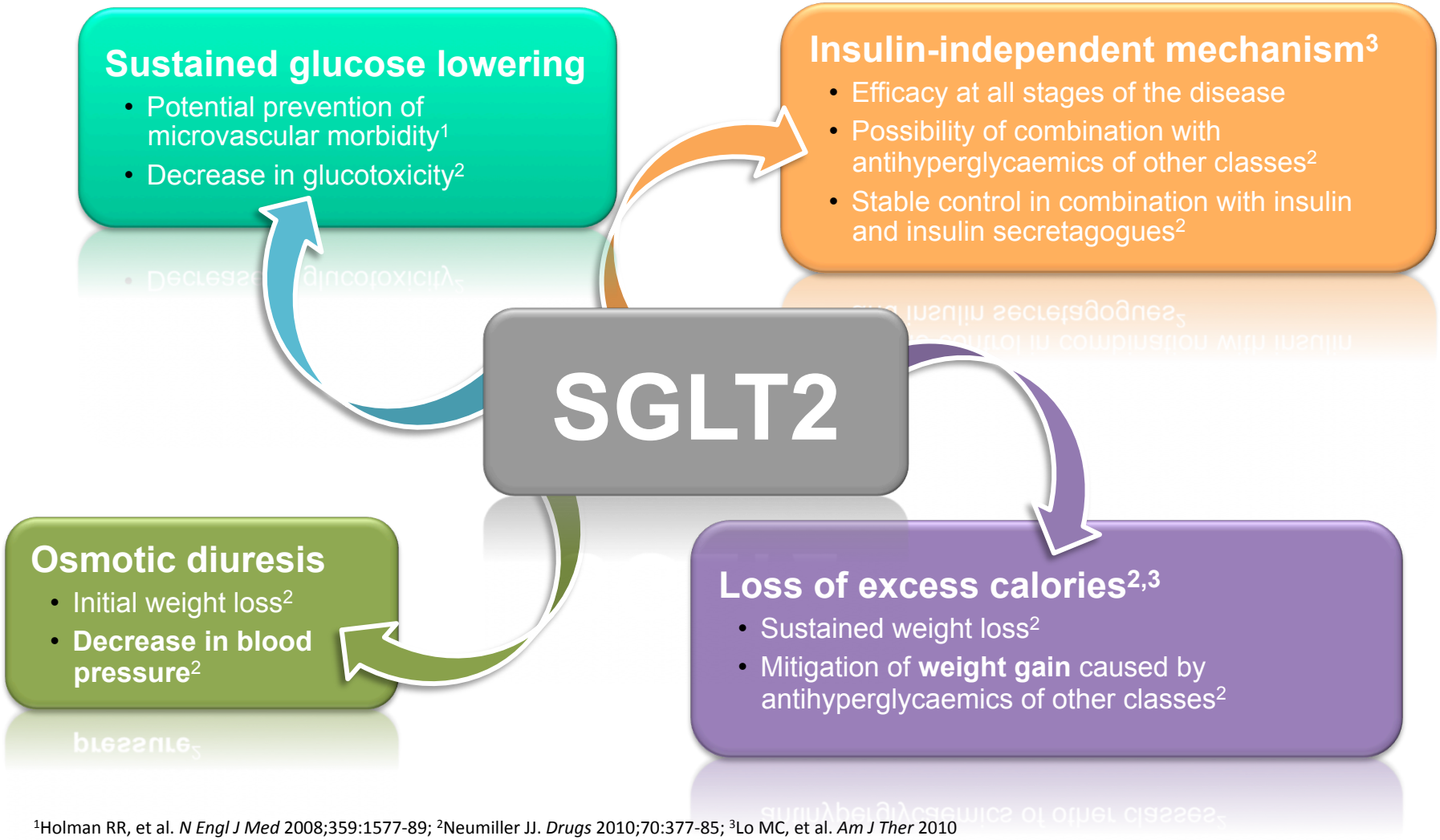
Tumour origin	Events (n)			
	All dapagliflozin (N=5501)		Control (N=3184)	
Subjects with tumour events*	81	1.47%	43	1.35%
Bladder	9		1	
Prostate (male only)	10		3	
Breast (female only)	10		3	
Hepatobiliary	3		1	
Pancreatic	5		2	
Thyroid and endocrine	7		4	
Skin	15		10	
Respiratory and mediastinal	8		6	
GI	6		4	
Blood and lymphatic	3		3	
Metastases and site unspecified	2		2	
Female reproductive	1		2	
Renal tract	1		2	
Musculoskeletal and soft tissue	1		0	



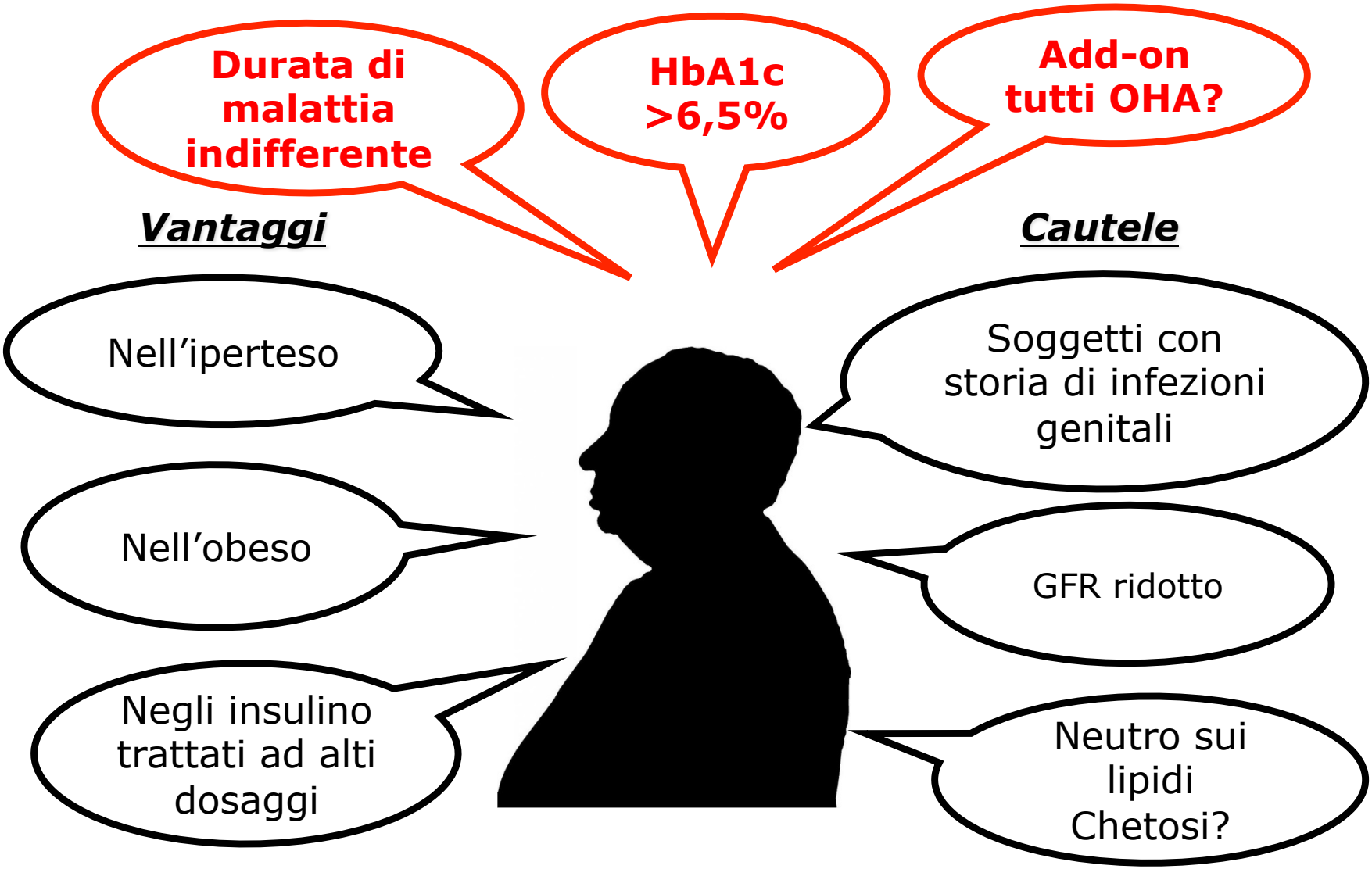
*Incidence rate ratio = 1.047 (95% CI, 0.702 to 1.579)

Johnsson K, et al. EASD 2012. Poster 743; Wilding J. Presented at the Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy)-Latin America, 2nd Congress. 2012, Rio de Janeiro, Brazil.

Treatment with an SGLT2 inhibitor: clinical benefits in type 2 diabetes mellitus



[1]Holman RR, et al. *N Engl J Med* 2008;359:1577-89; [2]Neumiller JJ. *Drugs* 2010;70:377-85; [3]Lo MC, et al. *Am J Ther* 2010



Profilo del paziente tipo SGLT2 inibitore

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IN BRIEF

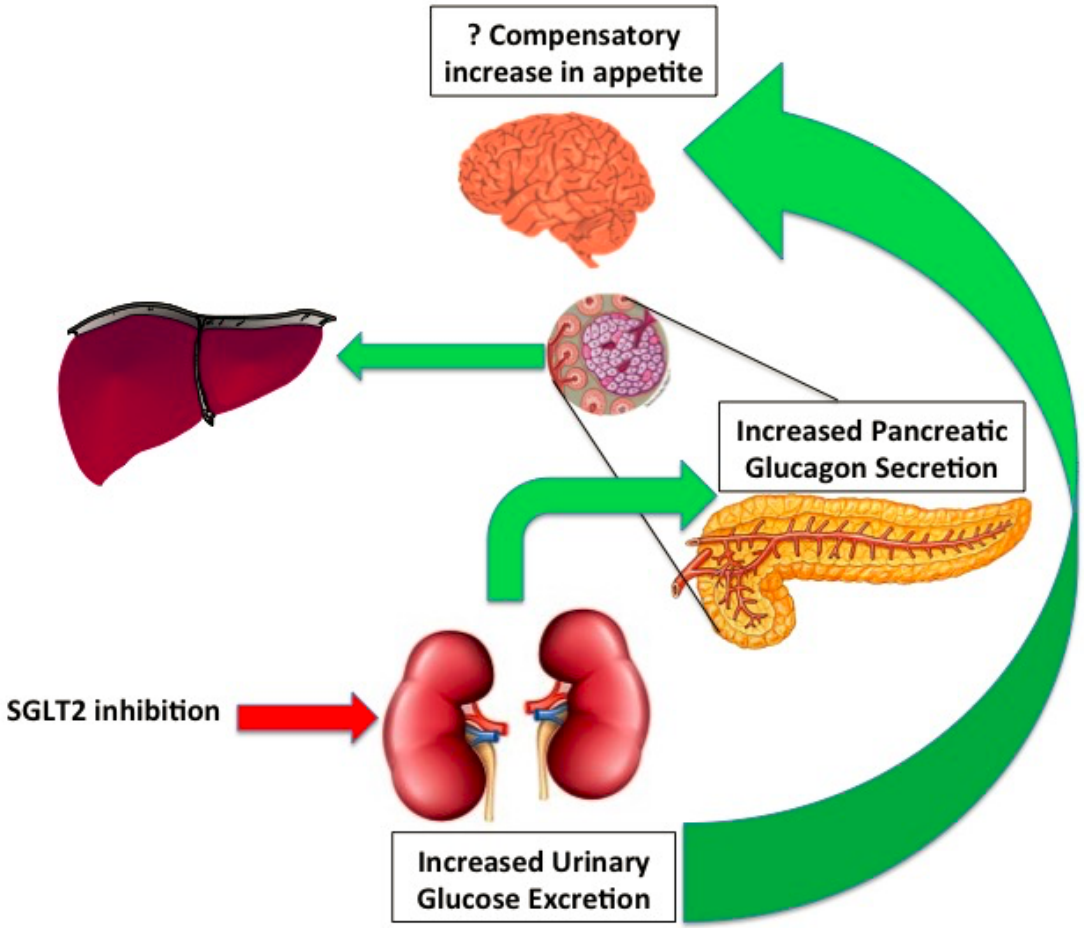
Ketoacidosis with SGLT2 Inhibitors

The FDA has warned that use of an SGLT2 (sodium-glucose co-transporter 2) inhibitor for treatment of type 2 diabetes may lead to ketoacidosis.[1] Three SGLT2 inhibitors, canagliflozin *(Invokana, Invokamet)*, dapagliflozin *(Farxiga, Xigduo XR)*, and empagliflozin *(Jardiance, Glyxambi)*, are approved for treatment of type 2 diabetes in the US. Between March 2013 and June 2014, 20 cases of ketoacidosis requiring emergency room visits or hospitalization were reported in patients who had recently started taking an SGLT2 inhibitor; the median time to onset of symptoms after initiation of therapy was 2 weeks (range 1-175 days). SGLT2 inhibitors decrease renal glucose reabsorption and increase urinary glucose excretion, resulting in a reduction in blood glucose levels. The mechanism by which these drugs could cause ketoacidosis has not been established.

Diabetic ketoacidosis (DKA) occurs primarily in patients with type 1 diabetes; it is characterized by elevated blood glucose levels (usually ≥250 mg/dL), a high anion gap, glucosuria, and ketonuria.[2] Unlike typical cases of DKA, most ketoacidosis cases associated with SGLT2 inhibitors have occurred in patients with type 2 diabetes, and in some patients glucose levels were <200 mg/dL. Only half of the 20 cases were associated with a recognizable DKA-precipitating factor, such as infection, reduced caloric intake, or reduced insulin dose. Other factors that may contribute to the development of high anion gap metabolic acidosis, such as hypovolemia, hypoxemia, reduced oral intake, acute renal impairment, and a history of alcohol use, were identified in some patients.[1] ■

1. FDA drug safety communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Available at: www.fda.gov/Drugs/DrugSafety/ucm446845.htm. Accessed June 11, 2015.
2. AE Kitabchi et al. Hyperglycemic crises in adult patients with diabetes. Diabetes Care 2009; 32:1335.

Compensatory metabolic adaptations to SGLT2 inhibition



Rajeev SP. Diabetes Obes Metab. 2015. [Epub ahead of print]

Energy balance following sodium-glucose co-transporter-2 (SGLT2) inhibition

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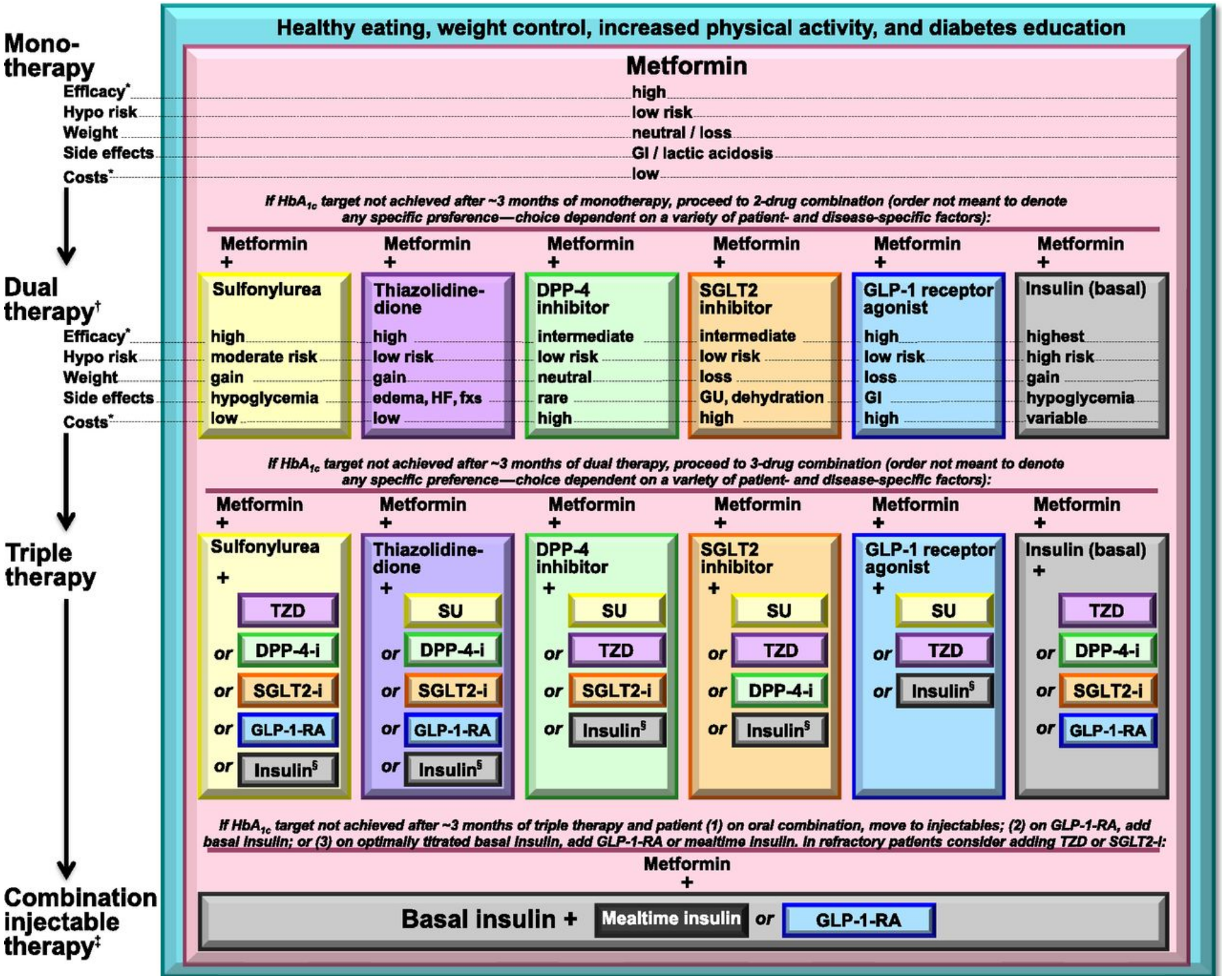
SGLT2 inhibitors lower glycaemia by inducing urinary glucose excretion (UGE), with the attendant calorie loss. Evidence suggests that the resulting weight loss (WL) is less than expected from UGE.

Conclusion: Chronic glycosuria elicits an adaptive increase in energy intake, particularly in leaner patients with preserved renal function. Combining SGLT2 inhibition with strategies to maintain energy intake or curb appetite is expected to be associated with major WL.


Healthy eating, weight control, increased physical activity, and diabetes education
Mono-therapy
Metformin
Efficacy*
high
Hypo risk
low risk
Weight
neutral / loss
Side effects
GI / lactic acidosis
Costs*
low
If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Dual therapy†
Metformin + Sulfonylurea
Efficacy* high
Hypo risk moderate risk
Weight gain
Side effects hypoglycemia
Costs* low
Metformin + Thiazolidine-dione
high
low risk
gain
edema, HF, fxs
low
Metformin + DPP-4 inhibitor
intermediate
low risk
neutral
rare
high
Metformin + SGLT2 inhibitor
intermediate
low risk
loss
GU, dehydration
high
Metformin + GLP-1 receptor agonist
high
low risk
loss
GI
high
Metformin + Insulin (basal)
highest
high risk
gain
hypoglycemia
variable
If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):
Triple therapy
Metformin + Sulfonylurea + TZD or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + Thiazolidine-dione + SU or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin§
Metformin + DPP-4 inhibitor + SU or TZD or SGLT2-i or Insulin§
Metformin + SGLT2 inhibitor + SU or TZD or DPP-4-i or Insulin§
Metformin + GLP-1 receptor agonist + SU or TZD or Insulin§
Metformin + Insulin (basal) + TZD or DPP-4-i or SGLT2-i or GLP-1-RA
If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGLT2-i:
Combination injectable therapy‡
Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA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