VII CORSO NAZIONALE
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DI ENDOCRINOLOGIA CLINICA
17/19 MARZO 2016
BARI

GLIFLOZINE: FRA LUCI E OMBRE

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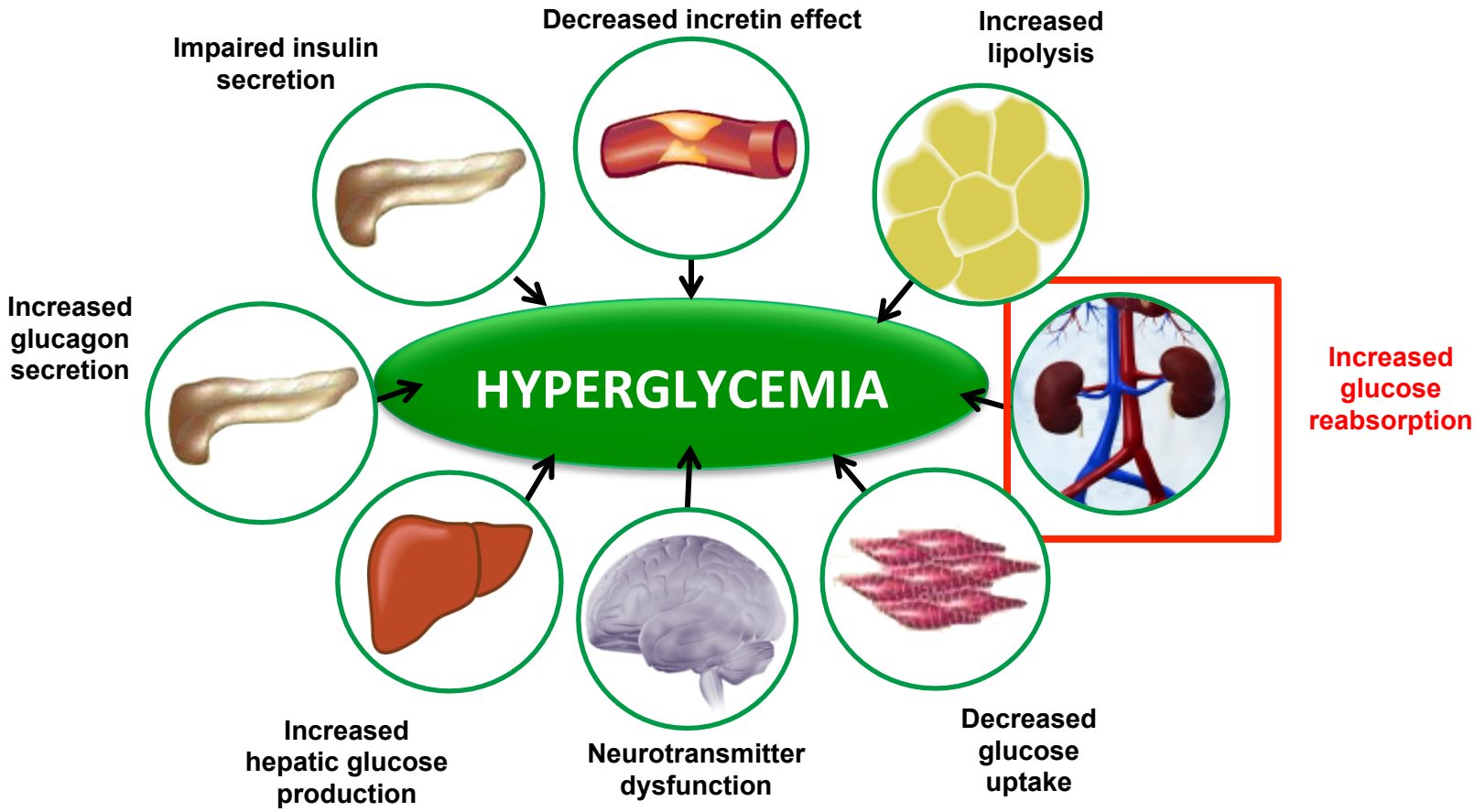
Conflitto di interessi

Boehringer Ingelheim, Eli Lilly, Astrazeneca

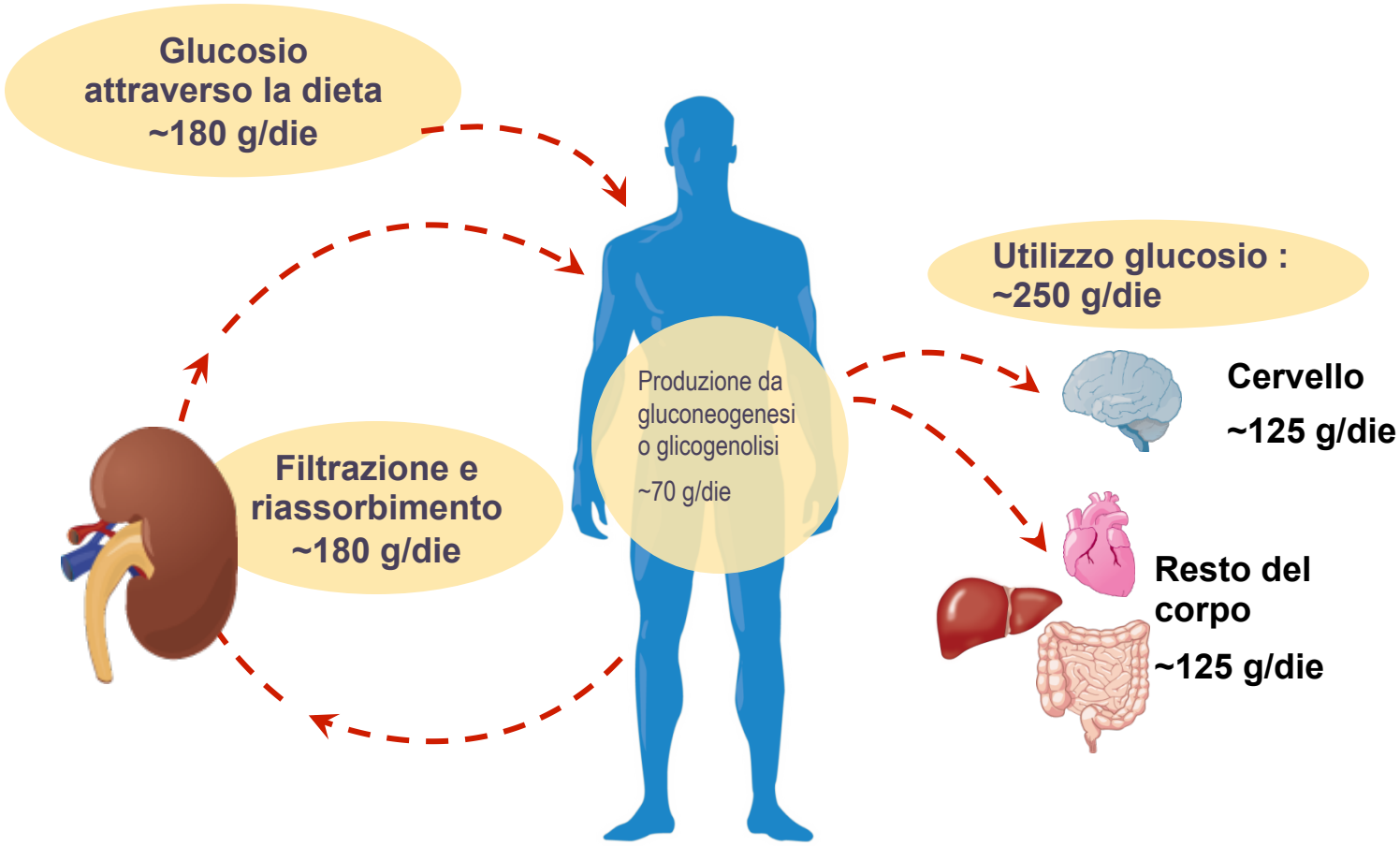
“The Ominous Octet” ed un nuovo bersaglio – il rene



AGI, alpha-glucosidase inhibitor; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; TZD, thiazolidinedione.

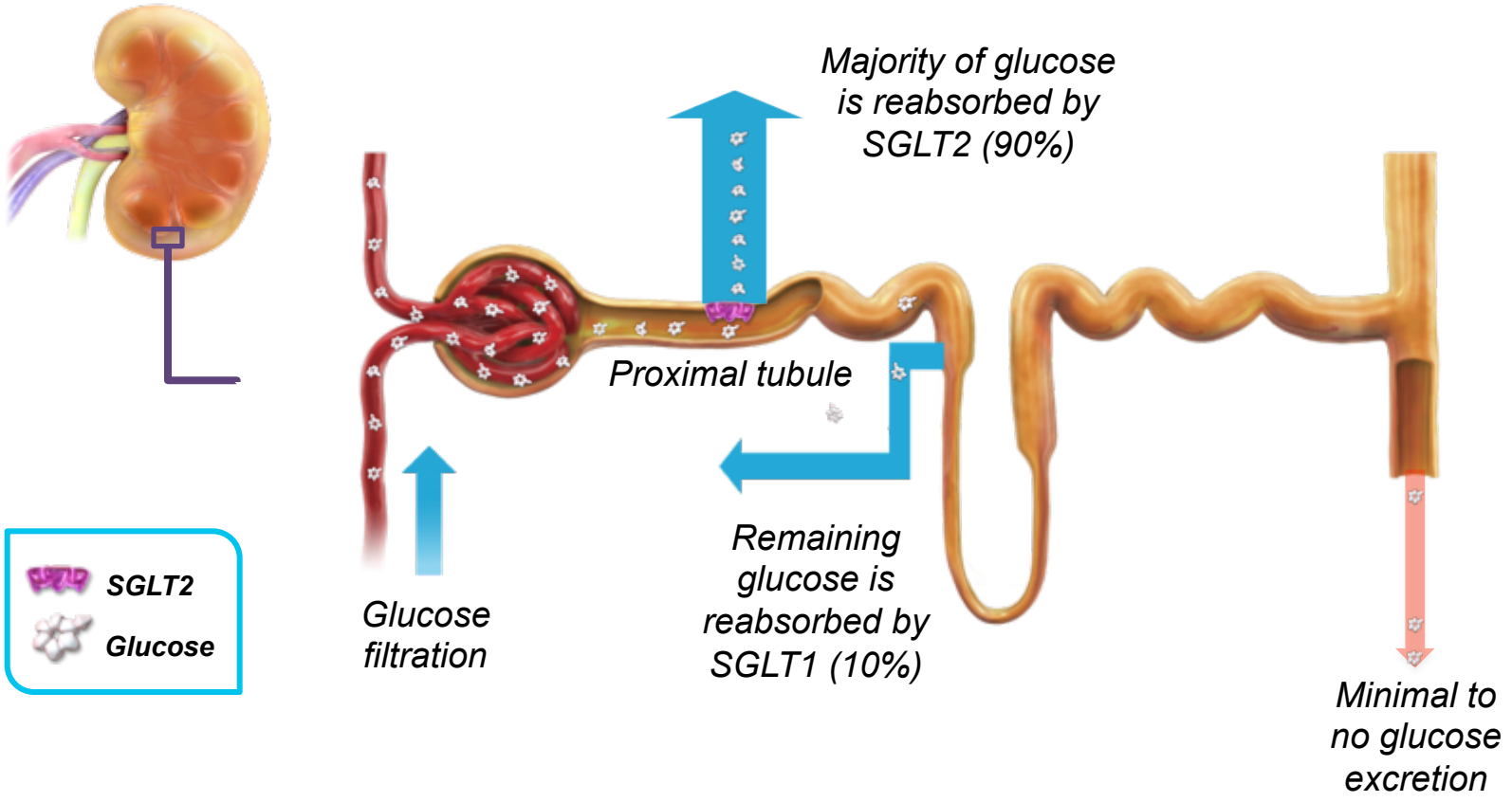
DeFronzo RA. *Diabetes.* 2009;58(4):773–795; Tahrani AA, et al. *Lancet*. 2011;378:182–197.

Il rene gioca un ruolo significativo nel bilancio del glucosio riassorbendo ~180 g di glucosio al giorno



Gerich JE. *Diabetes Med.* Accepted article; doi:10.1111/j.1464-5491. 2009;02894.x; Wright EM, et al. *J Int Med.* 2007;261:32-43.

In normal renal glucose handling, 90% of glucose is reabsorbed by SGLT2[1–4]



Adapted from: 1. Wright EM. *Am J Physiol Renal Physiol* 2001;**280**:F10–18; 2. Lee YJ, *et al. Kidney Int Suppl* 2007;**106**:S27–35; 3. Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21; 4. Marsenic O. *Am J Kidney Dis* 2009;**53**:875–83.

Co-trasportatori Sodio-Glucosio (SGLT)

Quanti e dove si trovano

	LOCALIZZAZIONE	CARATTERISTICHE	Specificità per gli zuccheri	Funzione
SGLT2	**Rene**: tubulo contorto prossimale – segmento S1	Trasporto 1:1* Alta capacità –Bassa affinità	Glucosio	Riassorbimento renale del glucosio
SGLT1	**Intestino tenue** **Rene**: tubulo contorto prossimale – segmento S2 ed S3	Trasporto 2:1* Bassa capacità Alta affinità	Glucosio Galattosio	Assorbimento galattosio Riassorbimento renale del glucosio

- ***Per uno ione Na+ passa una molecola di glucosio**
- ***Per due ioni Na+ passa una molecola di glucosio**

SGLT1/2, sodium-glucose co-transporter-1/2.
Abdul-Ghani MA, *et al. Endocr Pract* 2008;14:782–90.

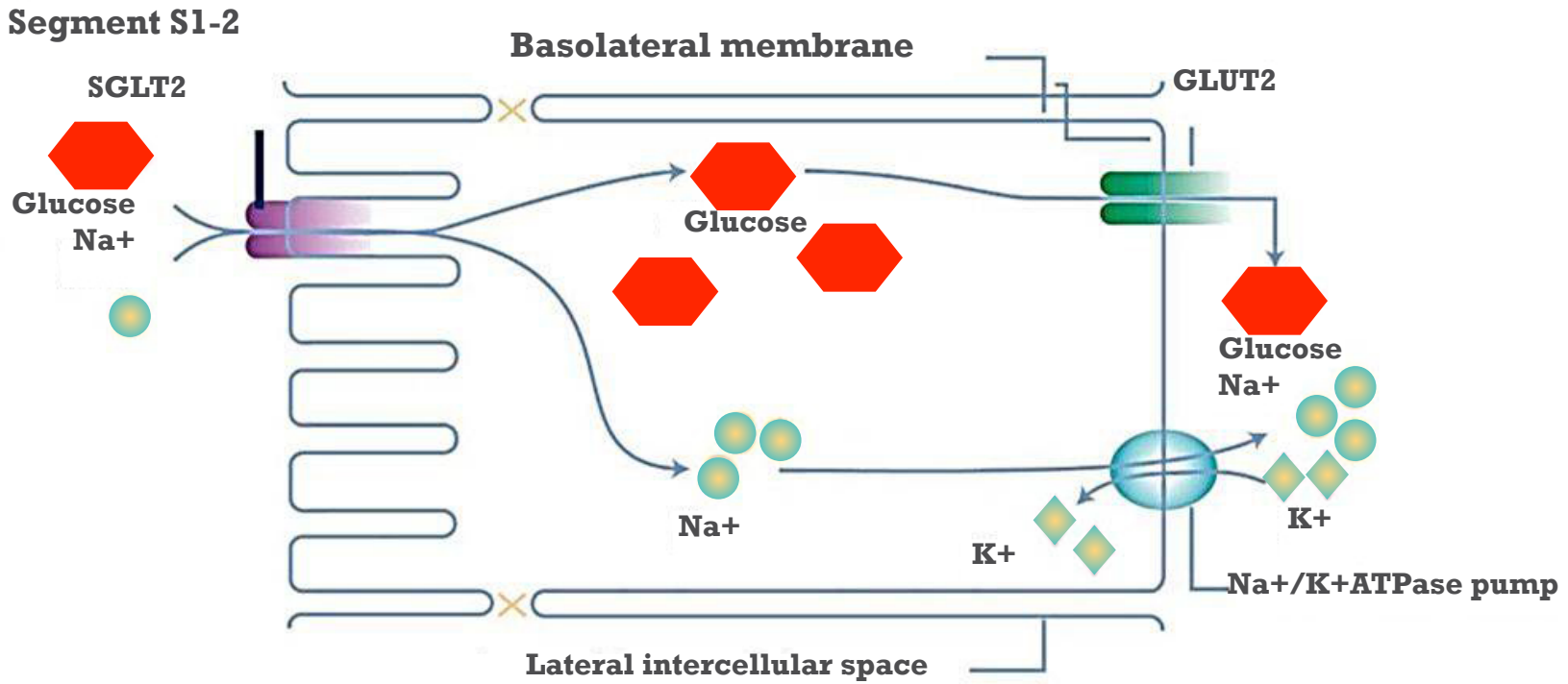
SGLT Family of Transporters

TRANSPORTER	DISTRIBUTION	FUNCTION[1]
SGLT1	Small intestine, heart, trachea, kidney, skeletal muscle[1,2]	Active cotransport of sodium, glucose, and galactose across the brush border of intestine and proximal tubule of kidney
SGLT2	Kidney[1]	Active cotransport of sodium and glucose in the S1 segment of the proximal tubule of kidney
SGLT3	Small intestine, uterus, lungs, thyroid, and testis[1]	Active transport of sodium (not glucose)
SGLT4	Small intestine, kidney, liver, stomach, lung, pancreas, skeletal muscle[1,2]	Transport of glucose and mannose
SGLT5	Kidney, vas deferens, heart, skin, testes[1,2]	Unknown
SGLT6	Spinal cord, kidney, brain, small intestine, skeletal muscle[1,2]	Transport of myo-inositol and glucose

SGLT=sodium-glucose cotransporter.

1. Bays H. *Curr Med Res Opin.* 2009;25:671-681.
2. Chen J et al. *Diabetes Ther.* 2010;1:57-92.

SGLT2 is a sodium glucose cotransporter

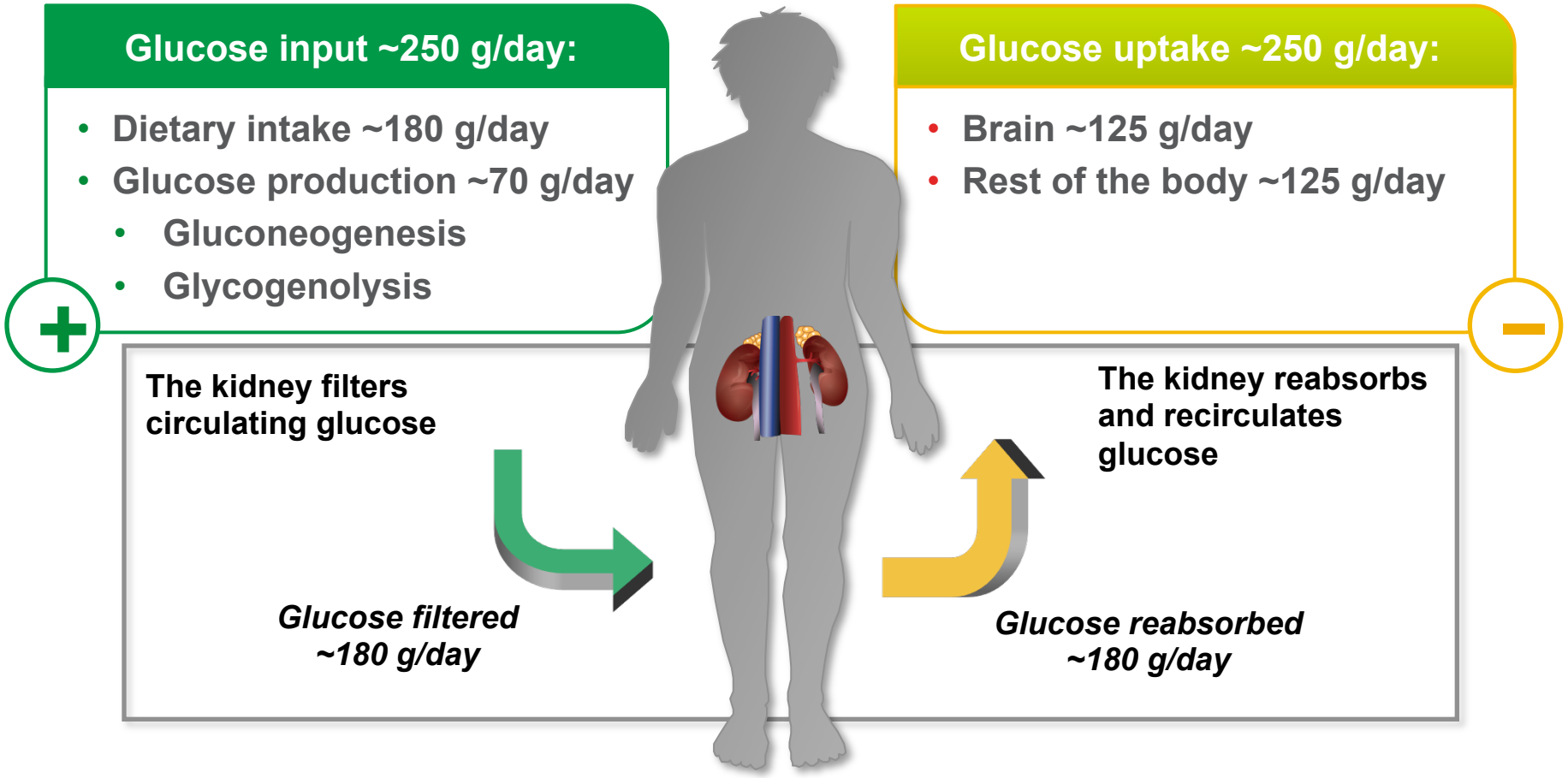


- SGLTs transfer glucose and sodium (Na^+:glucose coupling ratio for SGLT1=2:1 and for SGLT2=1:1) from the lumen into the cytoplasm of tubular cells through a secondary active transport mechanism

1. Wright EM, et al. *Physiology*. 2004;19:370–376; 2. Bakris GI, et al. *Kidney Int*. 2009;75:1272–1277.

Normal glucose homeostasis[1,2]

Net balance ~0 g/day



1. Wright EM. *Am J Physiol Renal Physiol* 2001;280:F10–18; 2. Gerich, JE. *Diabetes Obes Metab* 2000;2:345–50.

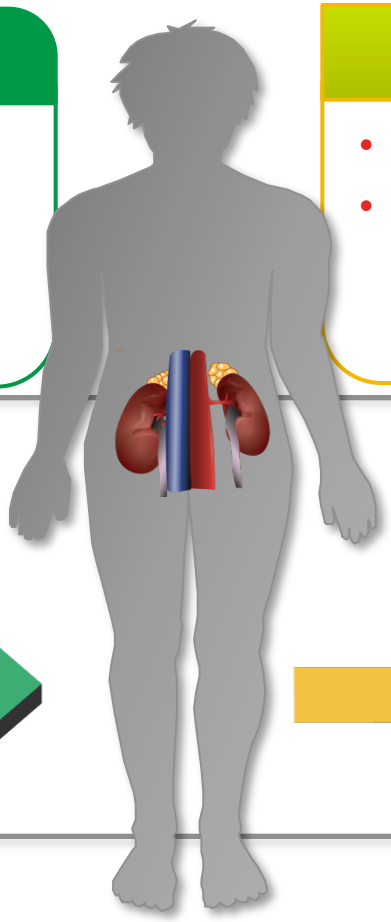
Glucose handling in Type 2 diabetes[1,2]

Glucose input >280 g/day:

- Dietary intake >180 g/day
- Glucose production ~100 g/day
  - Gluconeogenesis*
  - Glycogenolysis

Glucose uptake >250 g/day:

- Brain ~125 g/day
- Rest of the body >125 g/day



Average blood glucose concentration 150 mg/dL
Kidney filters all circulating glucose

Glucose filtered ~270 g/day

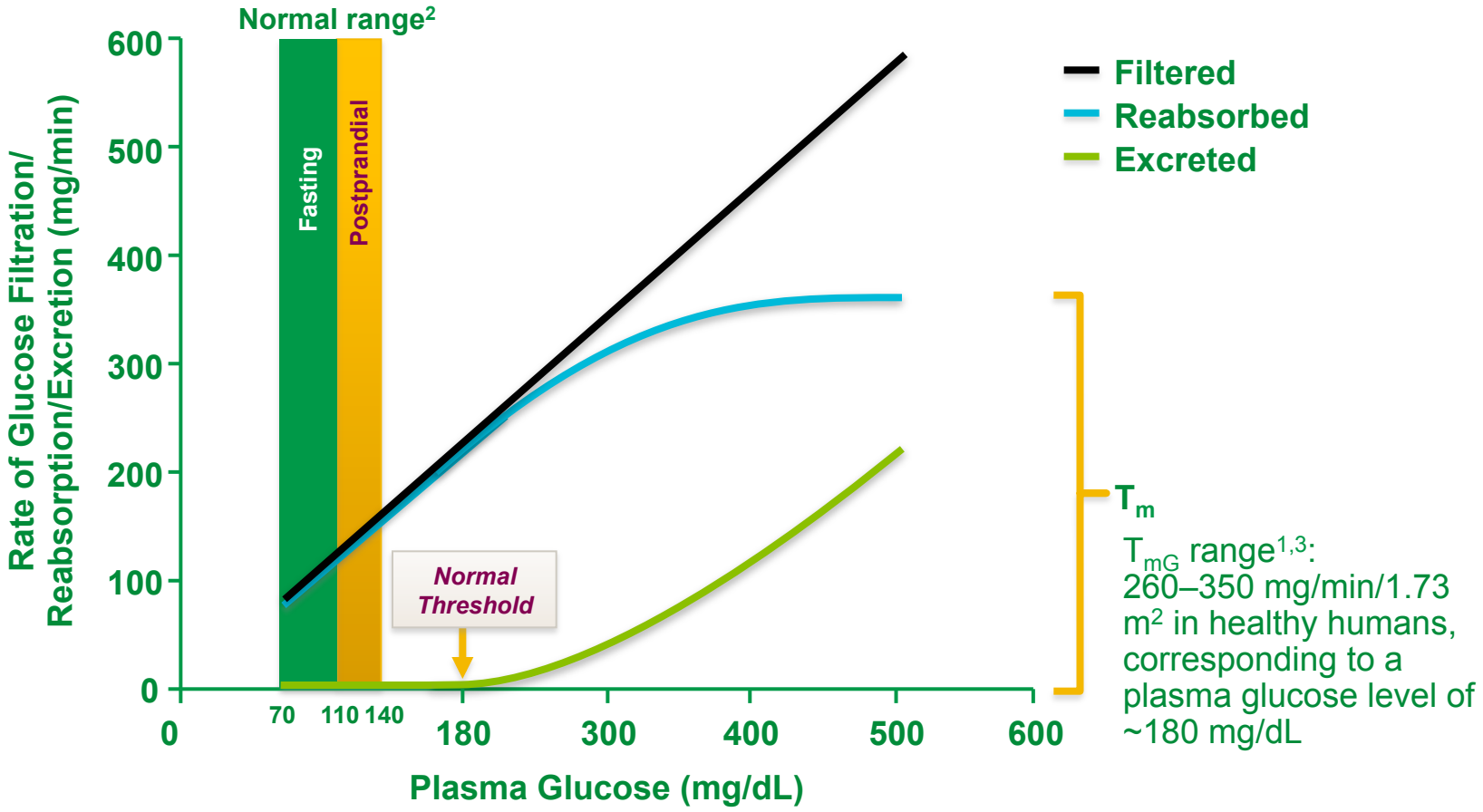
Increased reabsorption and recirculation of glucose

Above the renal threshold for glucose (~200 mg/dL), glucose is excreted in the urine (glucosuria)

*Elevated glucose production in patients with Type 2 diabetes attributed to hepatic and renal gluconeogenesis.[2]

1. Gerich JE. *Diabet Med* 2010;27:136–42; 2. Abdul-Ghani MA, DeFronzo RA. *Endocr Pract* 2008;14:782–90.

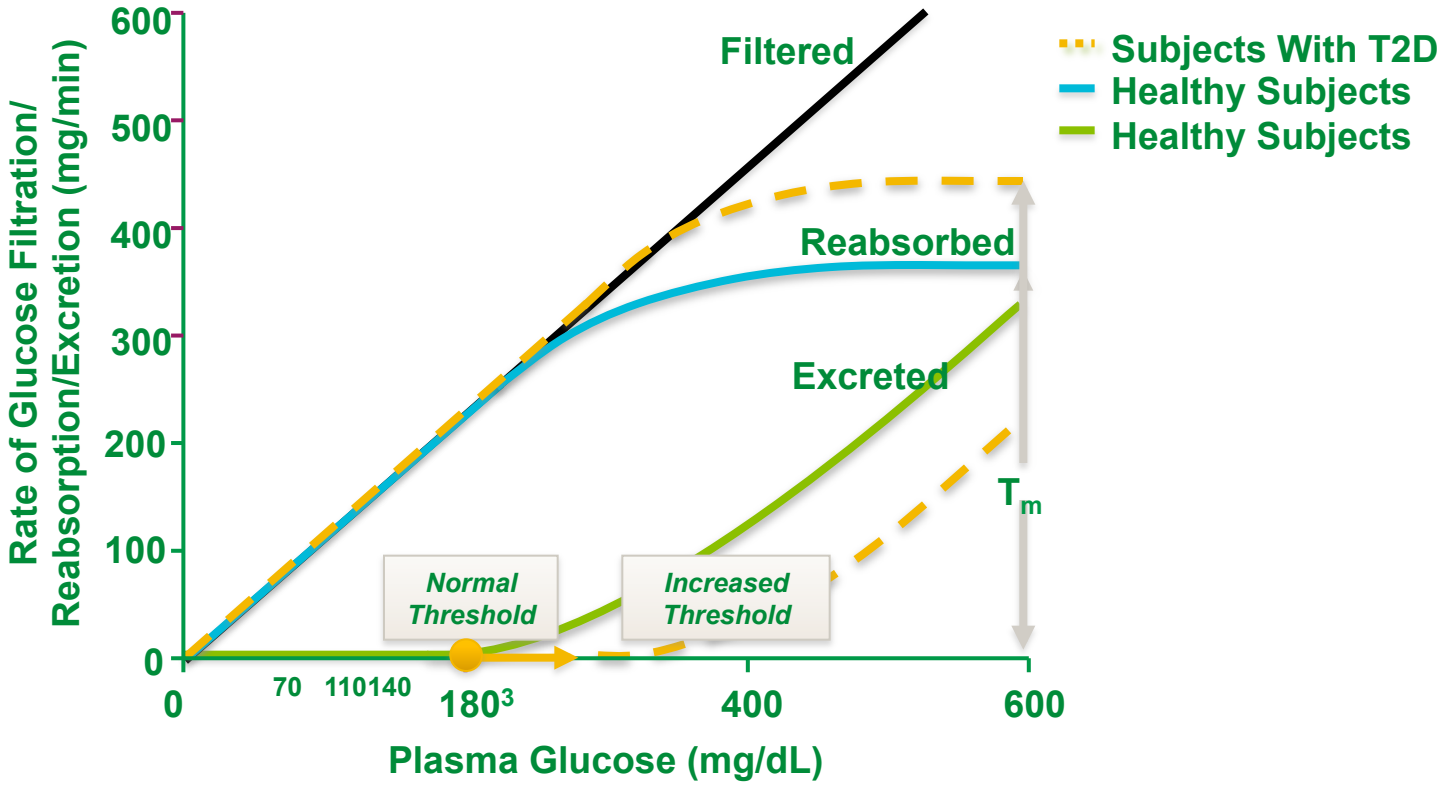
Renal Glucose Transporters Have a Finite Capacity, Beyond Which Glucose Appears in the Urine[1–3]



T_m=tubular maximum; T_{mG}=tubular maximum for glucose.

1. Abdul-Ghani MA et al. *Expert Opin Pharmacother*. 2013;14:1695-1703. Diagram adapted with permission.
2. Cryer PE. In: Fauci AS et al, eds. New York, NY: RR Donnelly and Sons, Inc;2008:2305-2310.
3. Marsenic O. *Am J Kidney Dis*. 2009;53:875-883.

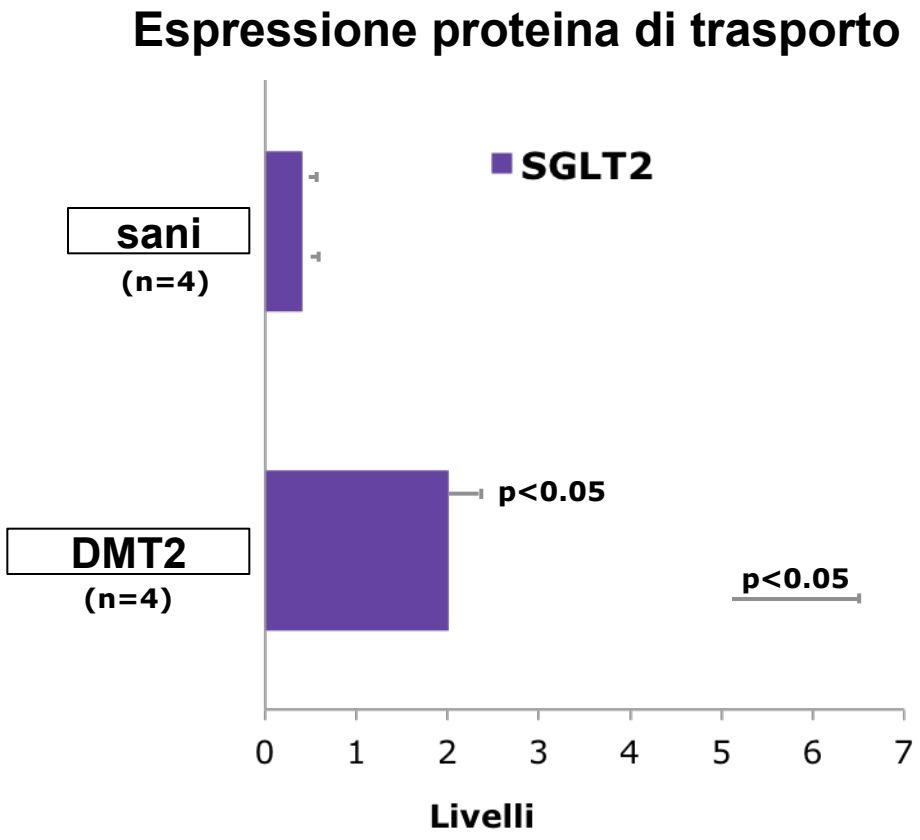
Increased Excretion Threshold and Increased Glucose Reabsorption Exacerbates Hyperglycemia in Type 2 Diabetes[1–3]

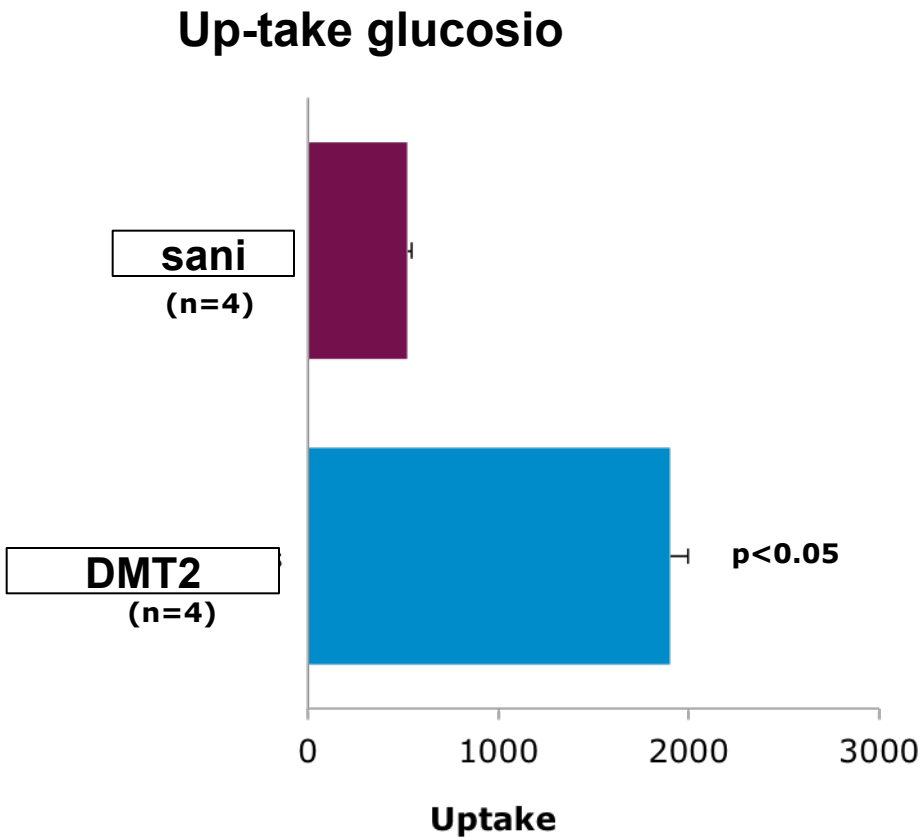


T2D=type 2 diabetes; T_m=tubular maximum.

1. Bays H. *Curr Med Res Opin*. 2009;25:671-681. Diagram adapted with permission.
2. DeFronzo RA et al. *Diabetes Care*. 2013;36:3169-3176.
3. Abdul-Ghani M et al. *Curr Diab Rep*. 2012;12:230-238. Diagram adapted with permission.

Maggiore espressione di SGLT2 e maggiore uptake di glucosio nel DMT2





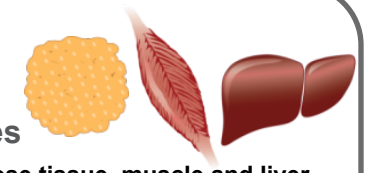
Rahmoune H, *et al*. *Diabetes* 2005;54:3427–34.

Insulin-dependent and -independent mechanisms to reduce hyperglycaemia in Type 2 diabetes[1–4]

Insulin-dependent mechanisms

1 Insulin action

- Metformin
- Thiazolidinediones



Adipose tissue, muscle and liver

2 Insulin release

- Sulphonylureas
- GLP-1R agonists*
- DPP4 inhibitors*
- Meglitinides

Pancreas

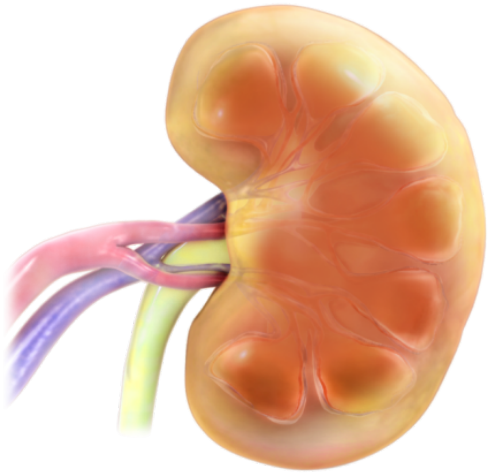
3 Insulin replacement

- Insulin

Glucose utilisation

Insulin-independent mechanism

SGLT2 inhibition

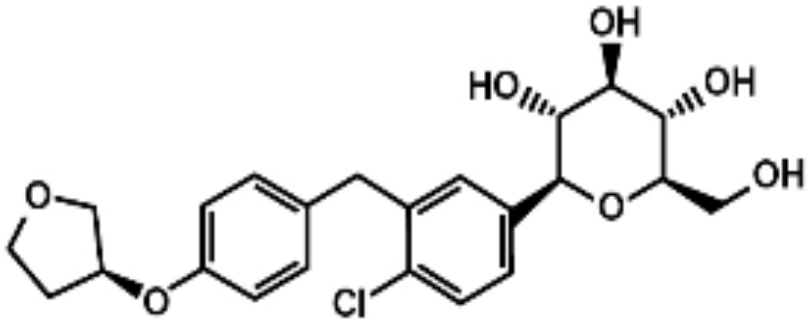


Glucose excretion/caloric loss

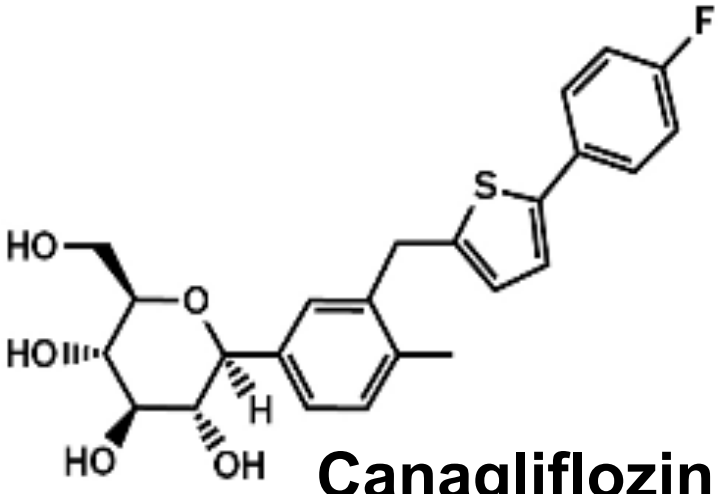
Dapagliflozin is not indicated for the management of obesity or high blood pressure.[5] Weight change was a secondary endpoint in clinical trials.[5,6]
*In addition to increasing insulin secretion, which is the major MoA, GLP-1 agonists and DPP4 inhibitors also act to decrease glucagon secretion.
DPP4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor.

1. Washburn WN. *J Med Chem* 2009;**52**:1785–94; 2. Bailey CJ. *Curr Diab Rep* 2009;**9**:360–7; 3. Srinivasan BT, *et al. Postgrad Med J* 2008;**84**:524–31;
4. Rajesh R, *et al. Int J Pharma Sci Res* 2010;**1**:139–47; 5. Dapagliflozin. Summary of product characteristics, 2014; 6. Bailey CJ, *et al. Lancet* 2010;**375**:2223–33.

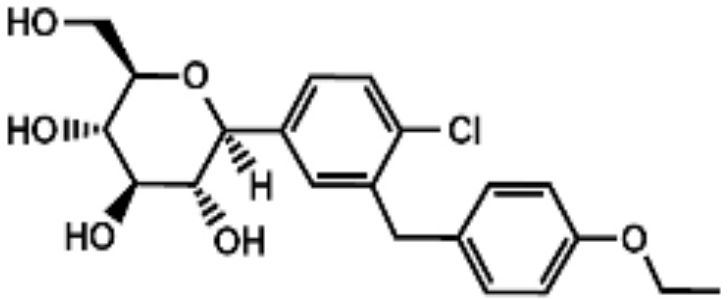
Phlorizin



Empagliflozin

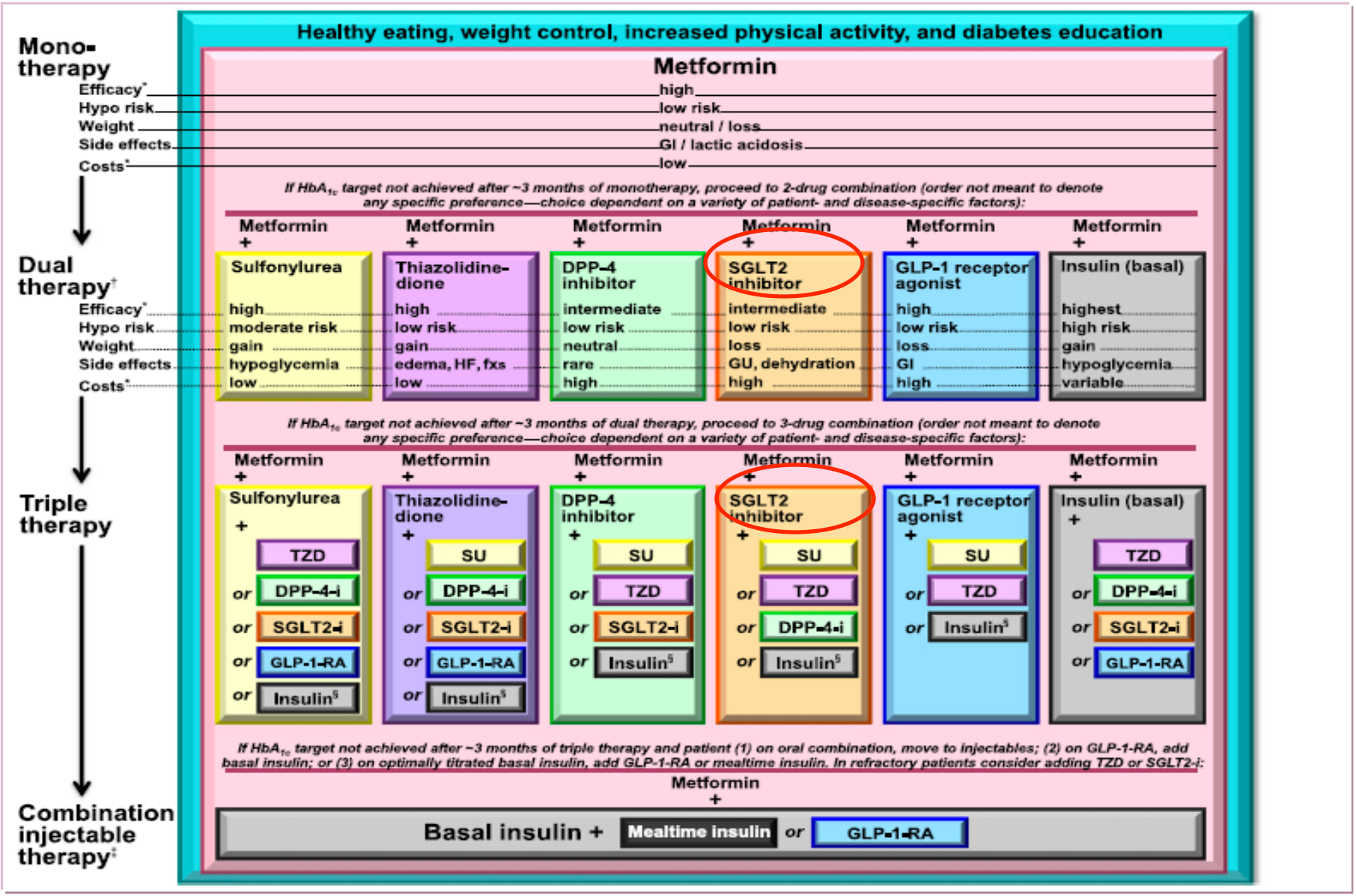


Canagliflozin



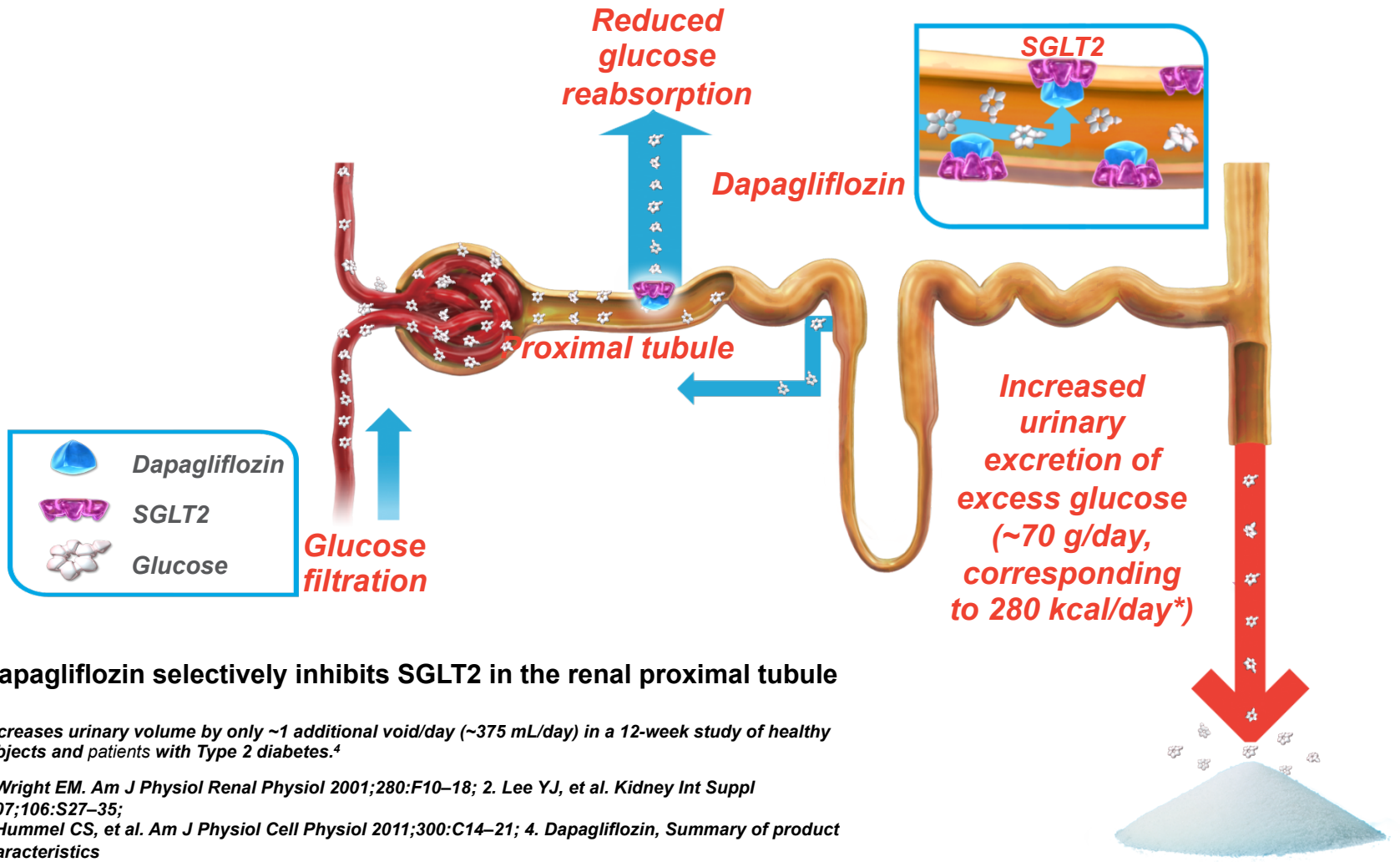
Dapagliflozin

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes



Inzucchi et al *Diabetes Care* 2015;38:140–149

Dapagliflozin: A novel insulin-independent approach to remove excess glucose[1–3]

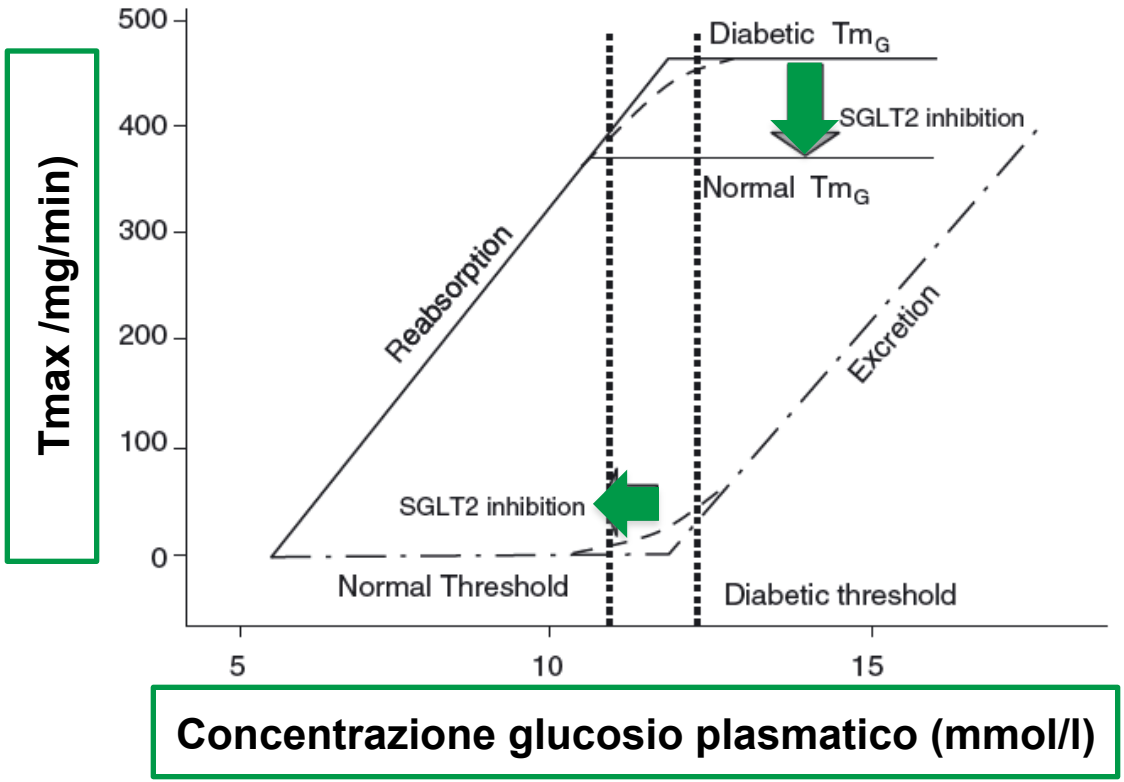


Dapagliflozin selectively inhibits SGLT2 in the renal proximal tubule

**Increases urinary volume by only ~1 additional void/day (~375 mL/day) in a 12-week study of healthy subjects and patients with Type 2 diabetes.[4]*

1. Wright EM. Am J Physiol Renal Physiol 2001;280:F10–18; 2. Lee YJ, et al. Kidney Int Suppl 2007;106:S27–35;
3. Hummel CS, et al. Am J Physiol Cell Physiol 2011;300:C14–21; 4. Dapagliflozin, Summary of product characteristics

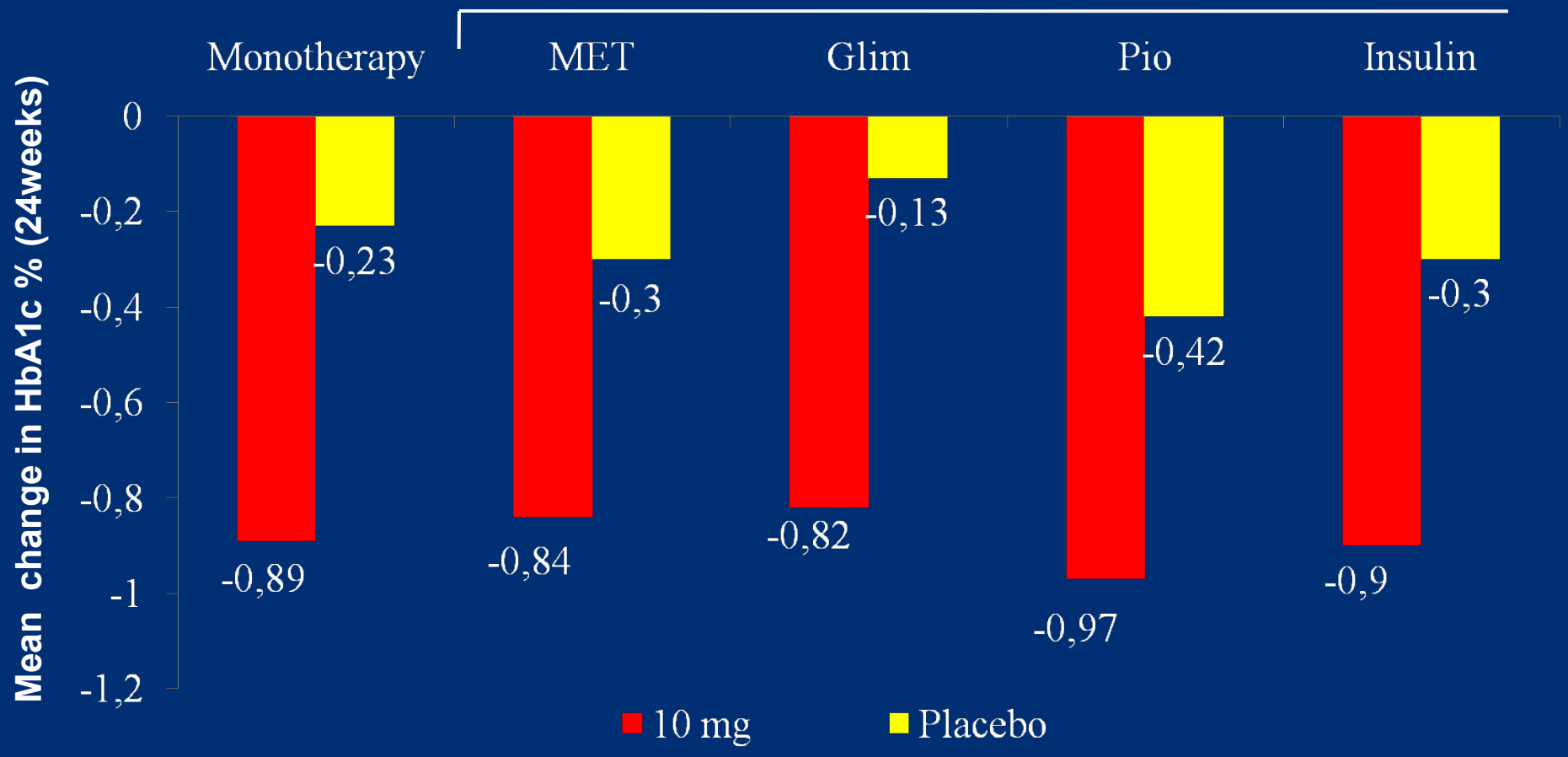
Dapagliflozin abbassa la soglia renale



Arrows represent reduction in renal glucose threshold after dapagliflozin treatment.
DeFronzo RA, *et al. Diabetes Care* 2013;**36**:3169–76.

Decreases in HbA1c from baseline in Dapagliflozin studies

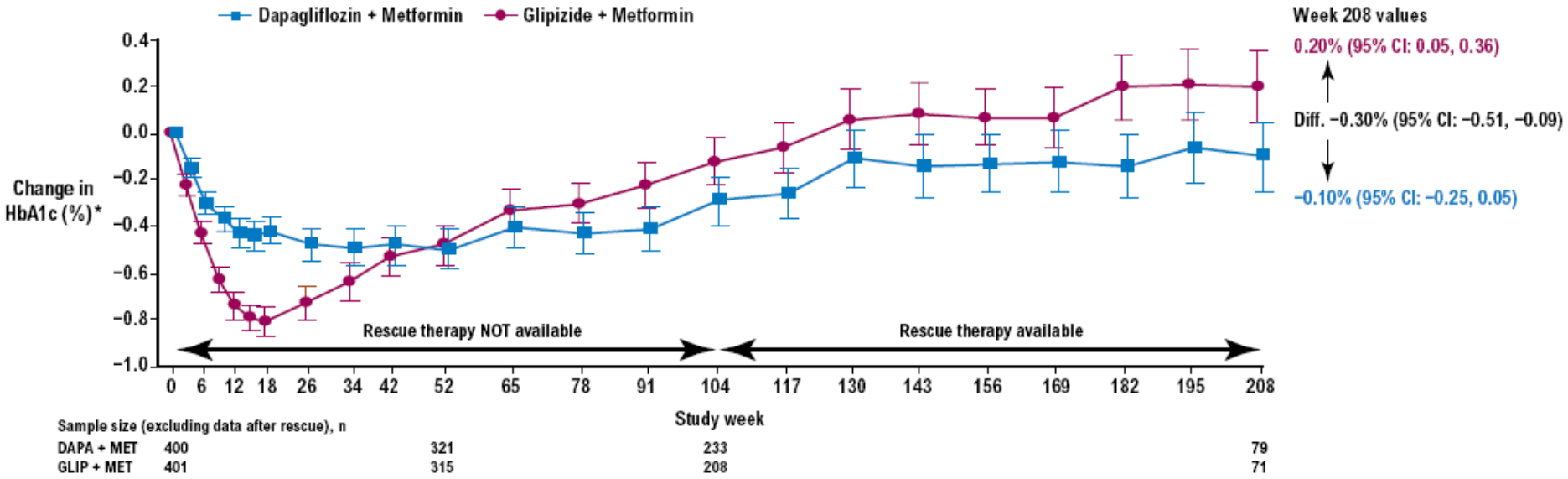
Add on Combinations with



Baseline HbA1c 7.93-8.53
P<0.001 vs Placebo

Dapagliflozin Versus Sulfonylurea as Add-on to Metformin: Change in HbA1c Over 208 Weeks

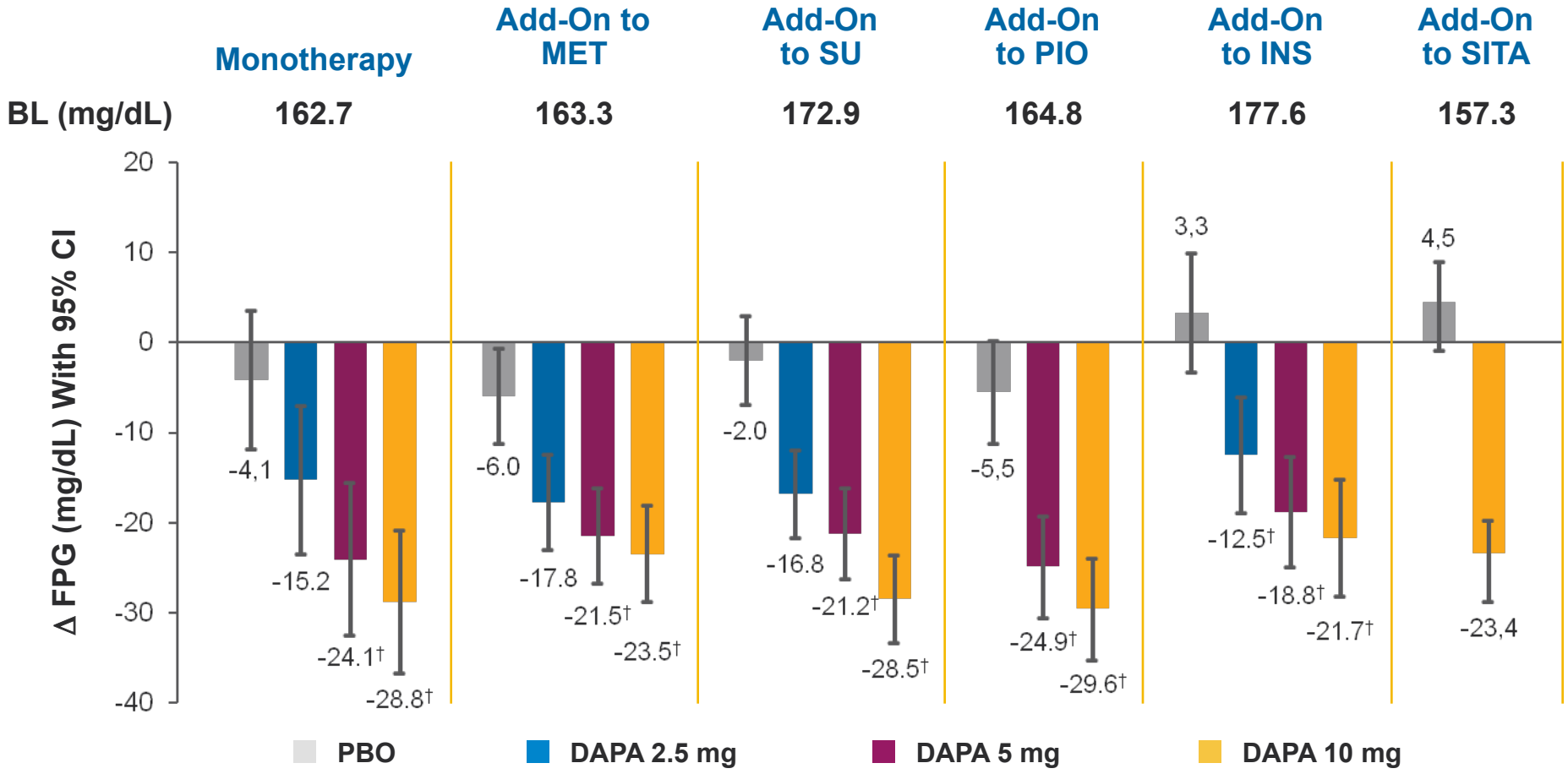
- HbA1c durability was better with dapagliflozin than glipizide
  - The rise from 52–208 weeks was less compared with glipizide, giving a significant difference between treatments at 208 weeks



*Data are adjusted mean change from baseline ±95% CI derived from a longitudinal repeated-measures mixed model.

Del Prato S, et al. ADA 2013; poster 62-LB.

Fasting Plasma Glucose at Week 24 Across Studies

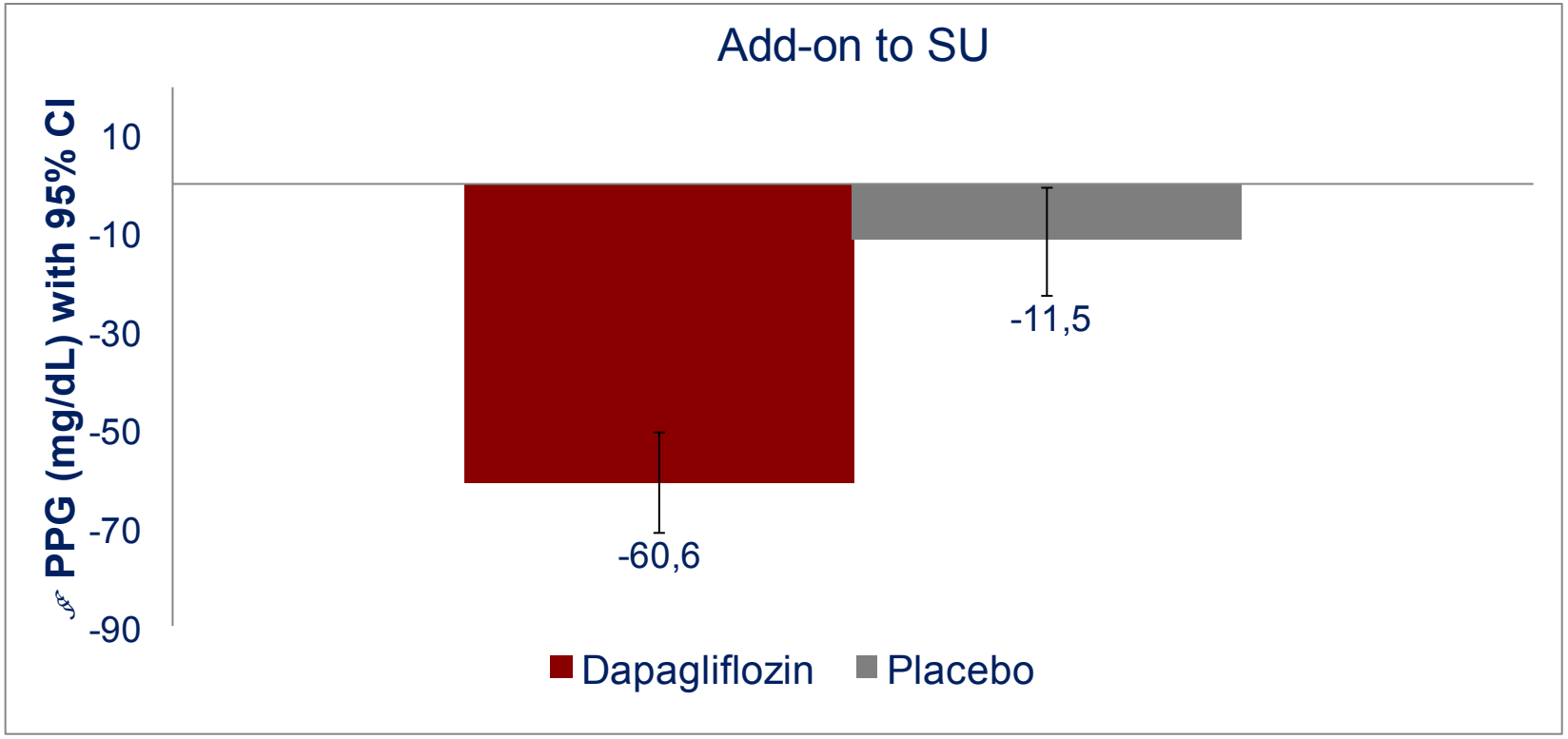


Statistically significant vs placebo by hierarchical testing rule: **P*<0.05; †*P*<0.001.
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF).
FDA Advisory Committee Meeting slides (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM264314.pdf)

Jabbour SA et al. Presented at ADA 2012; Poster #1071-P.

Reduction in post-prandial glucose at Week 24

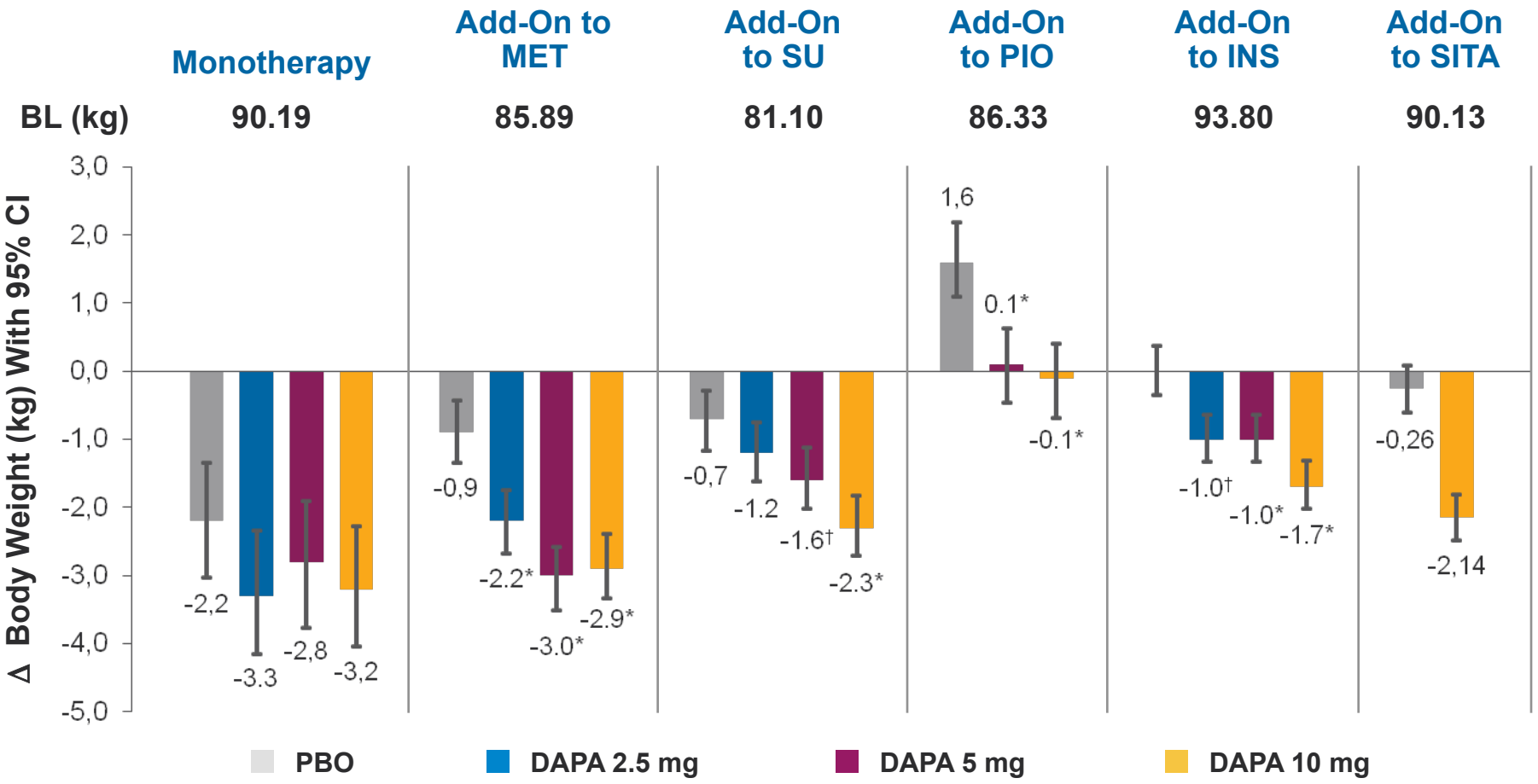
Baseline (mg/dL) **157.3**



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)

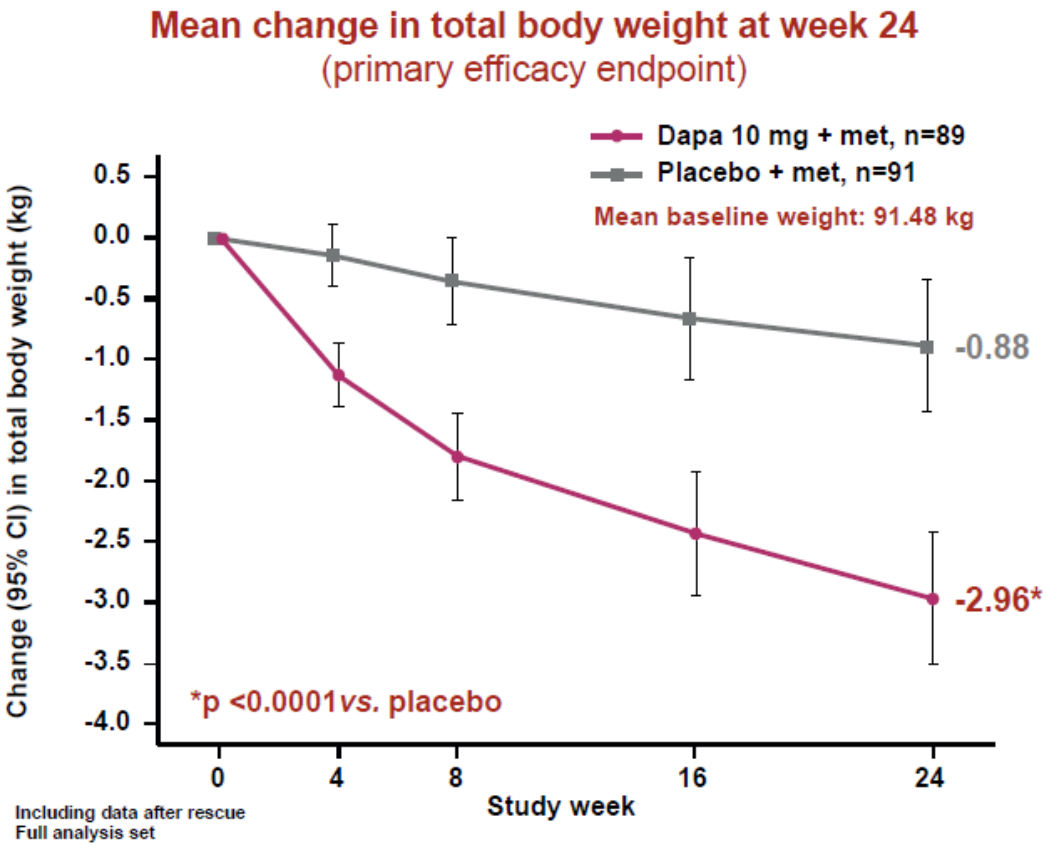
Body Weight at Week 24 Across Studies

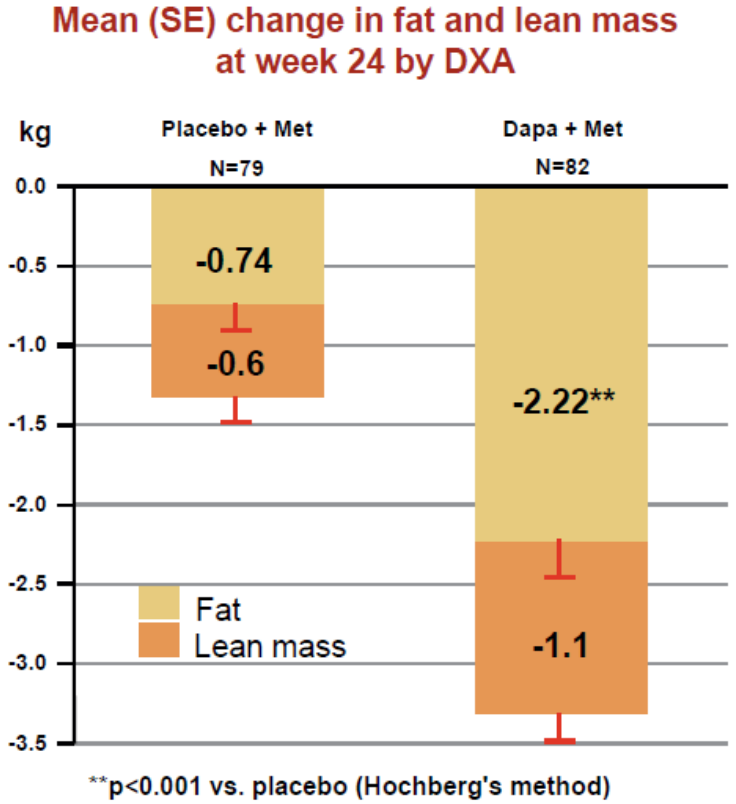


Statistically significant vs placebo by hierarchical testing rule: †$P<0.05$; *$P<0.001$.
Adjusted mean change from baseline using ANCOVA, excluding data after rescue (LOCF).
FDA Advisory Committee Meeting slides (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM264314.pdf)

Dapagliflozin reduces total body weight and fat mass at week 24

DXA: dual X-ray absorptiometry

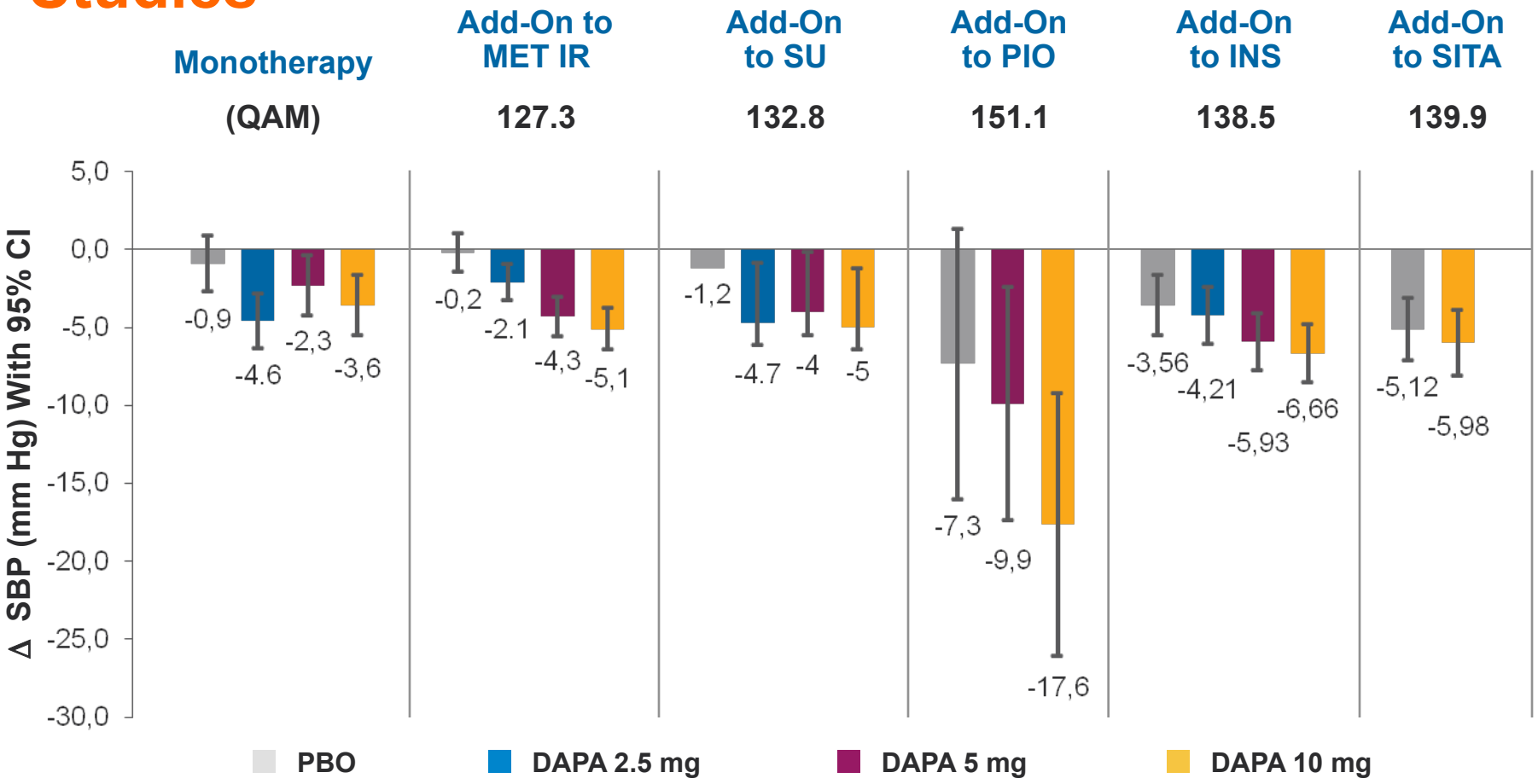




Dapagliflozin is not indicated for the management of obesity.2 Weight change was a secondary endpoint in clinical trials.2,3
*Data are adjusted mean change from baseline derived from a mixed model and include data after rescue therapy.

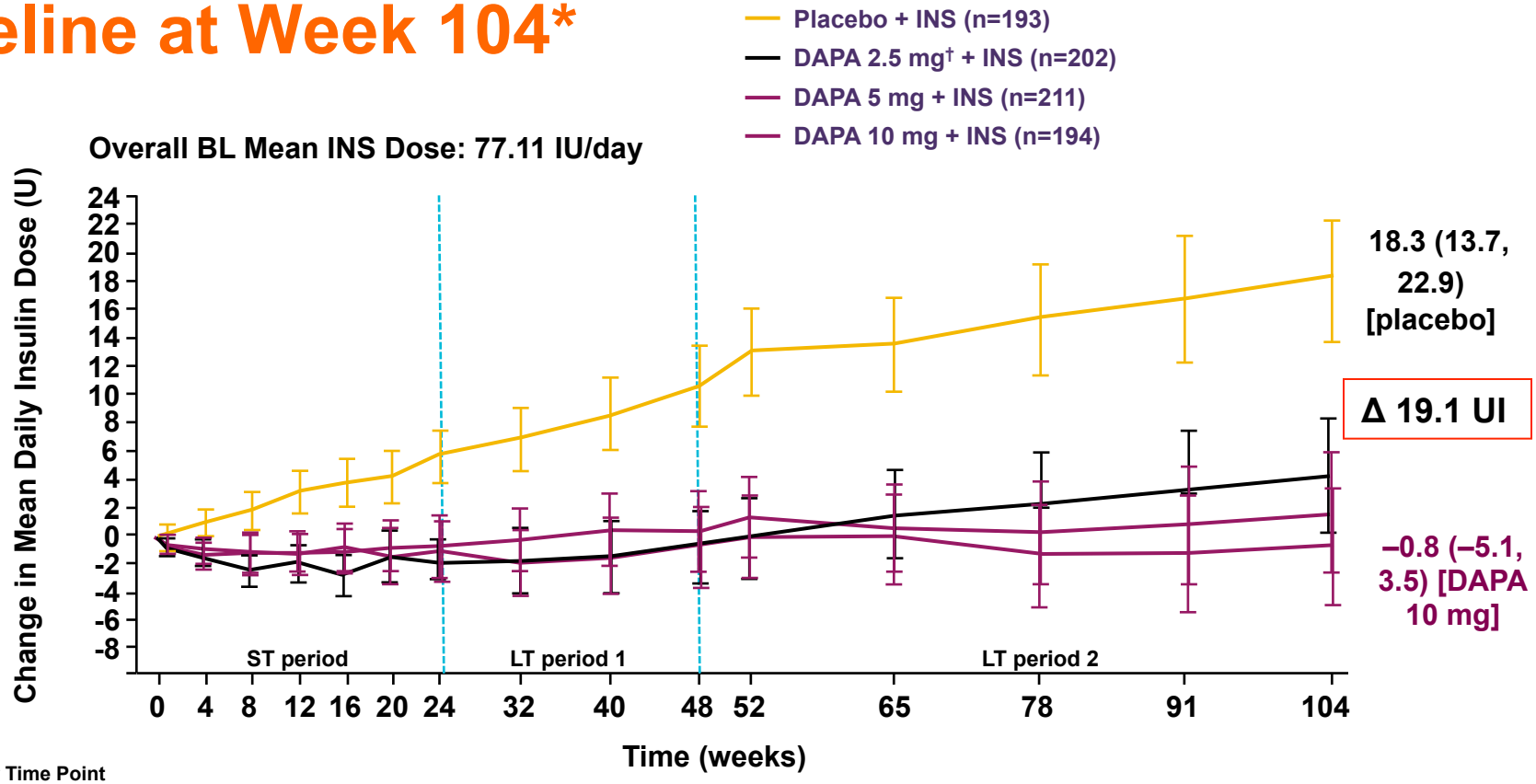
1. Bolinder J, et al. Diabetes Obes Metab 2014;16:159–69; 2. Dapagliflozin. Summary of product characteristics, 2014;
3. Bailey CJ, et al. Lancet 2010;375:2223–33.

Systolic Blood Pressure at Week 24 Across Studies



FDA Advisory Committee Meeting slides (www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM264314.pdf)

Mean Change in Mean Daily INS Dose From Baseline at Week 104*



Sample Size per Time Point															
Placebo + INS	191	185	176	171	170	165	168	164	158	157	121	118	114	110	104
DAPA 2.5 mg + INS	200	197	189	187	186	181	180	174	176	173	144	142	140	136	130
DAPA 5/10 mg + INS	209	202	194	194	190	188	187	183	181	172	147	142	134	132	128
DAPA 10 mg + INS	194	189	185	183	180	178	177	175	173	166	145	146	144	142	140

* Data are adjusted mean change and 95% CI derived from repeated measures ANCOVA using the full analysis set and include data after INS up-titration.

† DAPA 2.5 mg is not an approved dose.

DAPA=dapagliflozin; INS=insulin; ST=short term; LT=long term; BL=baseline; IU=insulin unit; CI=confidence interval; ANCOVA=analysis of covariance.

Wilding JPH et al. *Diabetes Obes Metab*. 2013. doi:10.1111/dom.12187.

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

ABSTRACT

BACKGROUND

The effects of empagliflozin, an inhibitor of sodium–glucose cotransporter 2, in addition to standard care, on cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk are not known.

This article was published on September 17, 2015, at NEJM.org.

EMPA-REG OUTCOME®

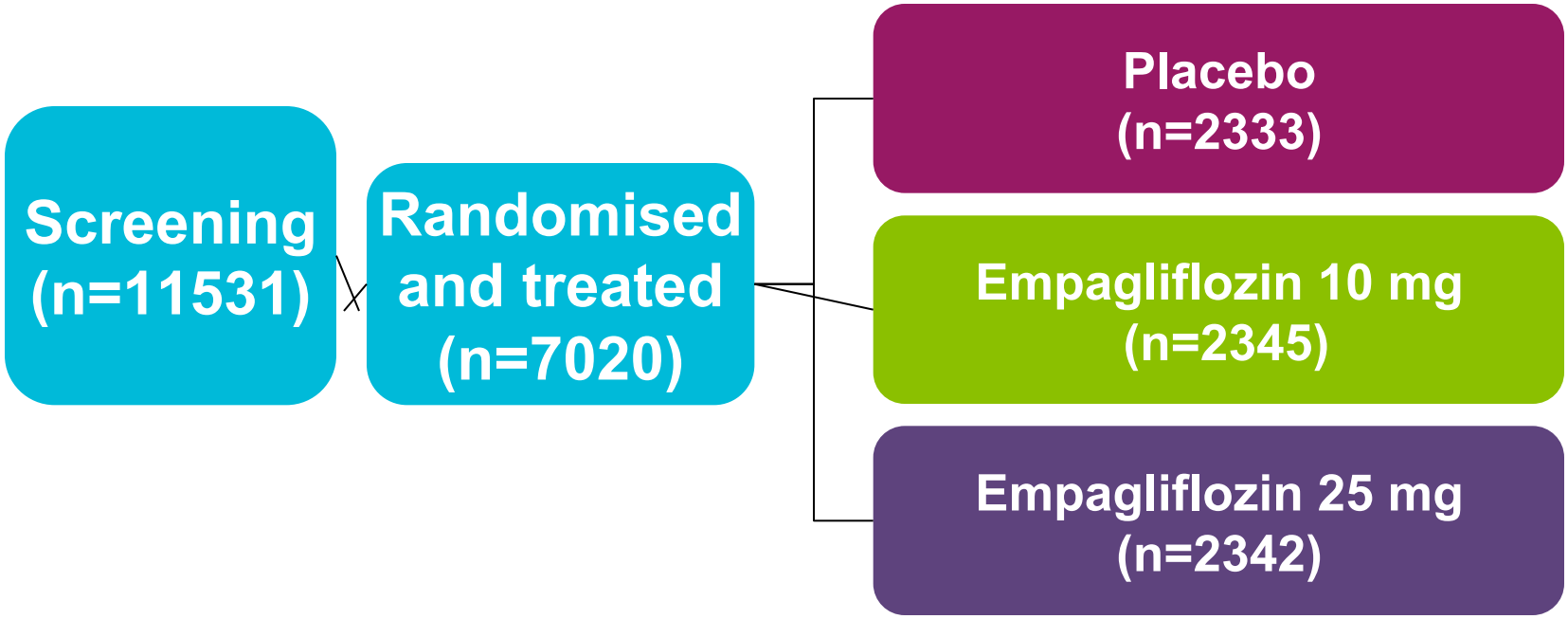
- Randomised, double-blind, placebo-controlled CV outcomes trial

- **Objective**
  To examine the long-term effects of empagliflozin versus placebo, in addition to standard of care, on CV morbidity and mortality in patients with type 2 diabetes and high risk of CV events

CV, cardiovascular

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

Trial design



- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

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Pre-specified primary and key secondary outcomes

- Primary outcome
  - **3-point MACE:** Time to first occurrence of CV death, non-fatal MI or non-fatal stroke

- Key secondary outcome
  - **4-point MACE:** Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina

CV, cardiovascular; MI, myocardial infarction; MACE, Major Adverse Cardiovascular Event

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

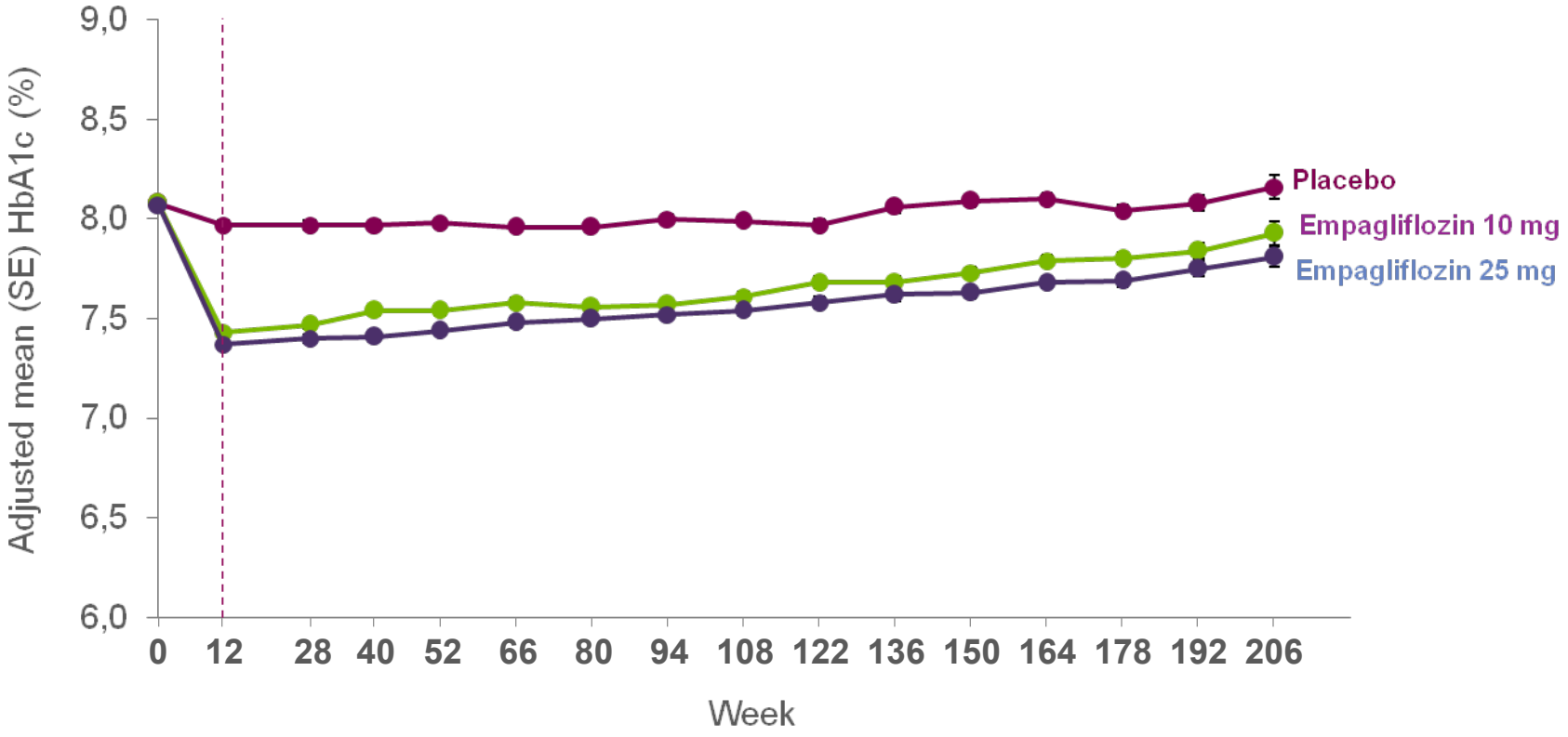
Additional analyses

- Changes from baseline in:
  - HbA1c
  - Weight
  - Waist circumference
  - Systolic and diastolic blood pressure
  - Heart rate
  - LDL cholesterol
  - HDL cholesterol

- Safety and tolerability
  - Adverse events

HDL, high density lipoprotein; LDL, low density lipoprotein

HbA1c

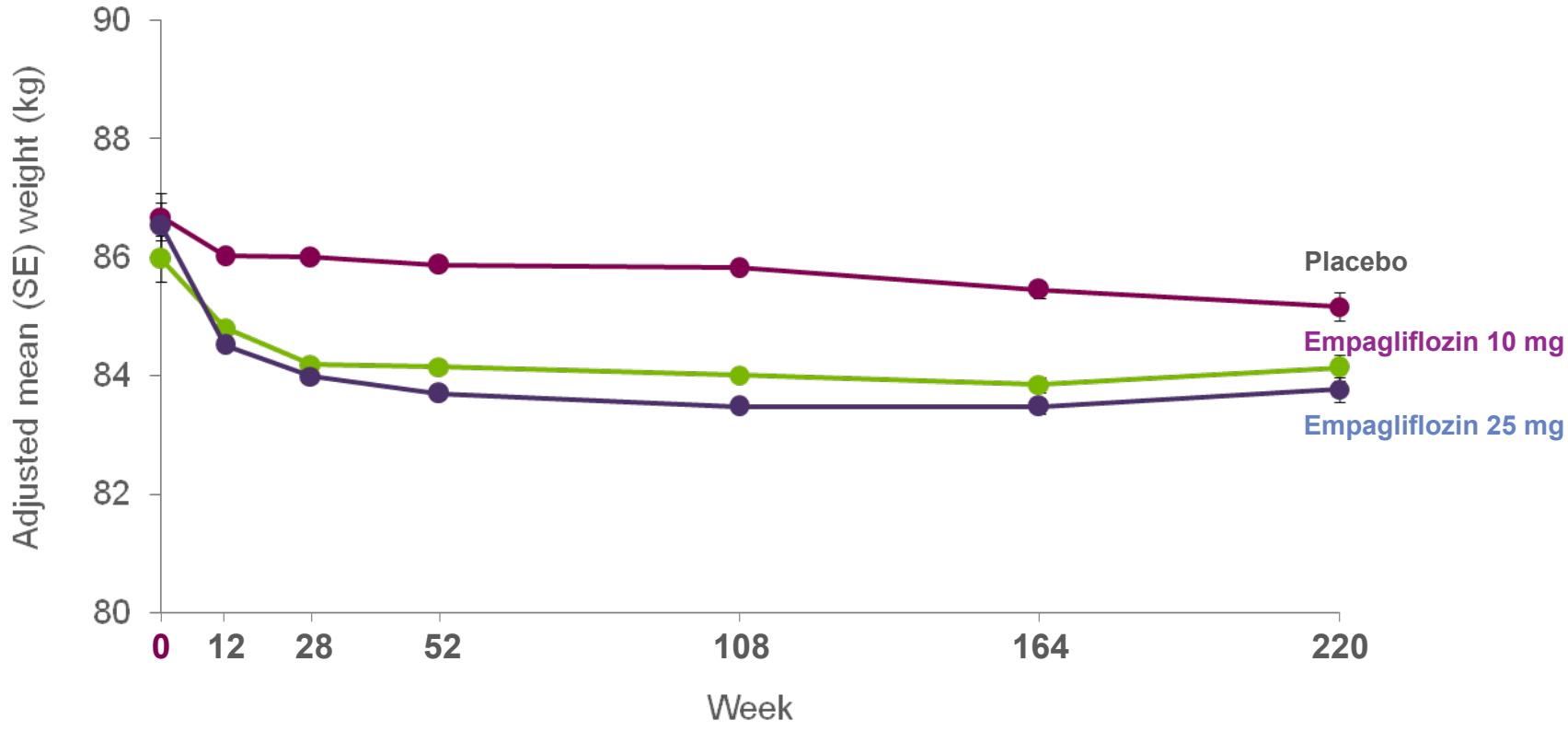


Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)
X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

Weight

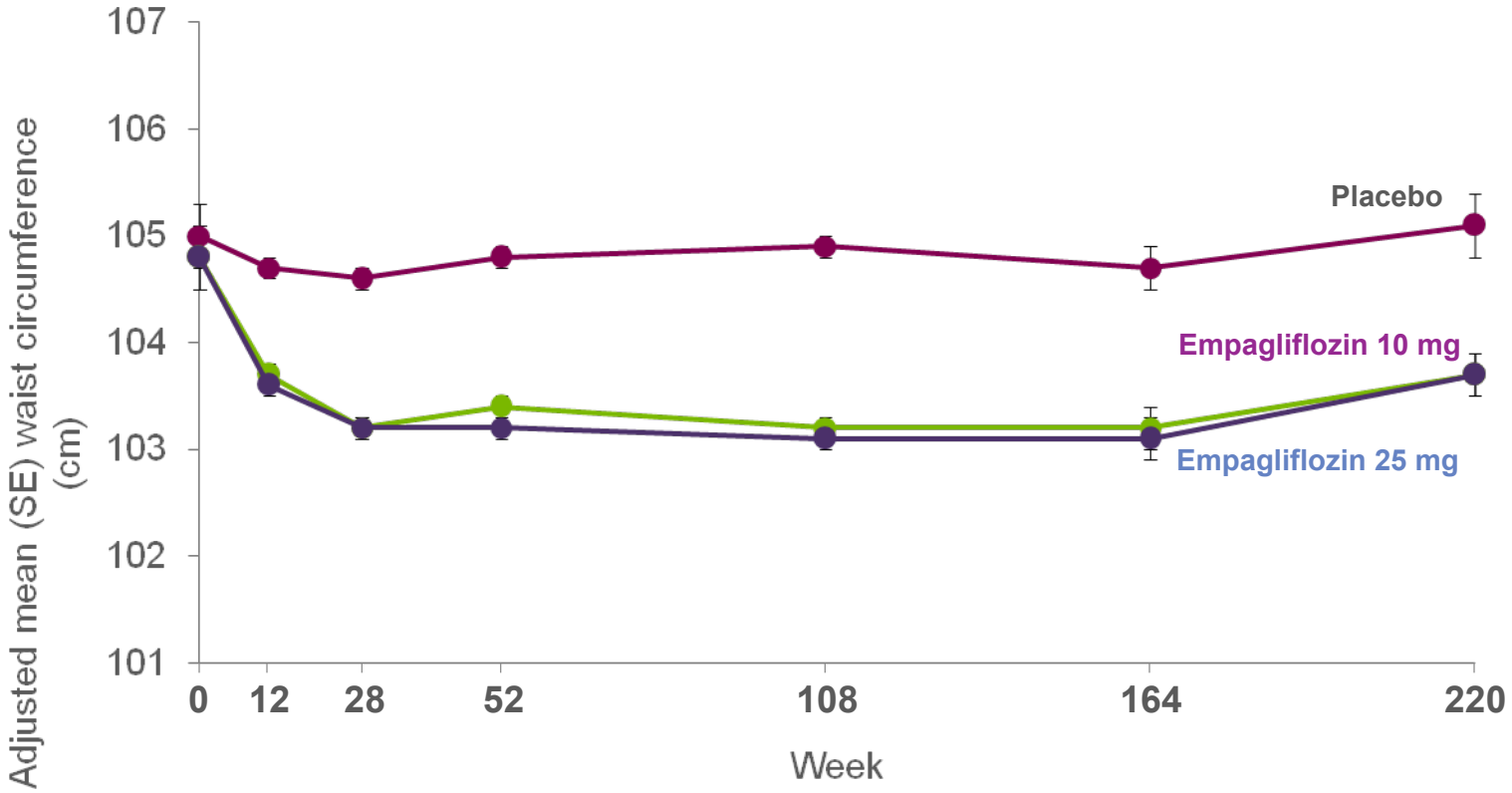


Placebo	2285	1915	2215	2138	1598	1239	425
Empagliflozin 10 mg	2290	1893	2238	2174	1673	1298	483
Empagliflozin 25 mg	2283	1891	2226	2178	1678	1335	489

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)
X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

Waist circumference

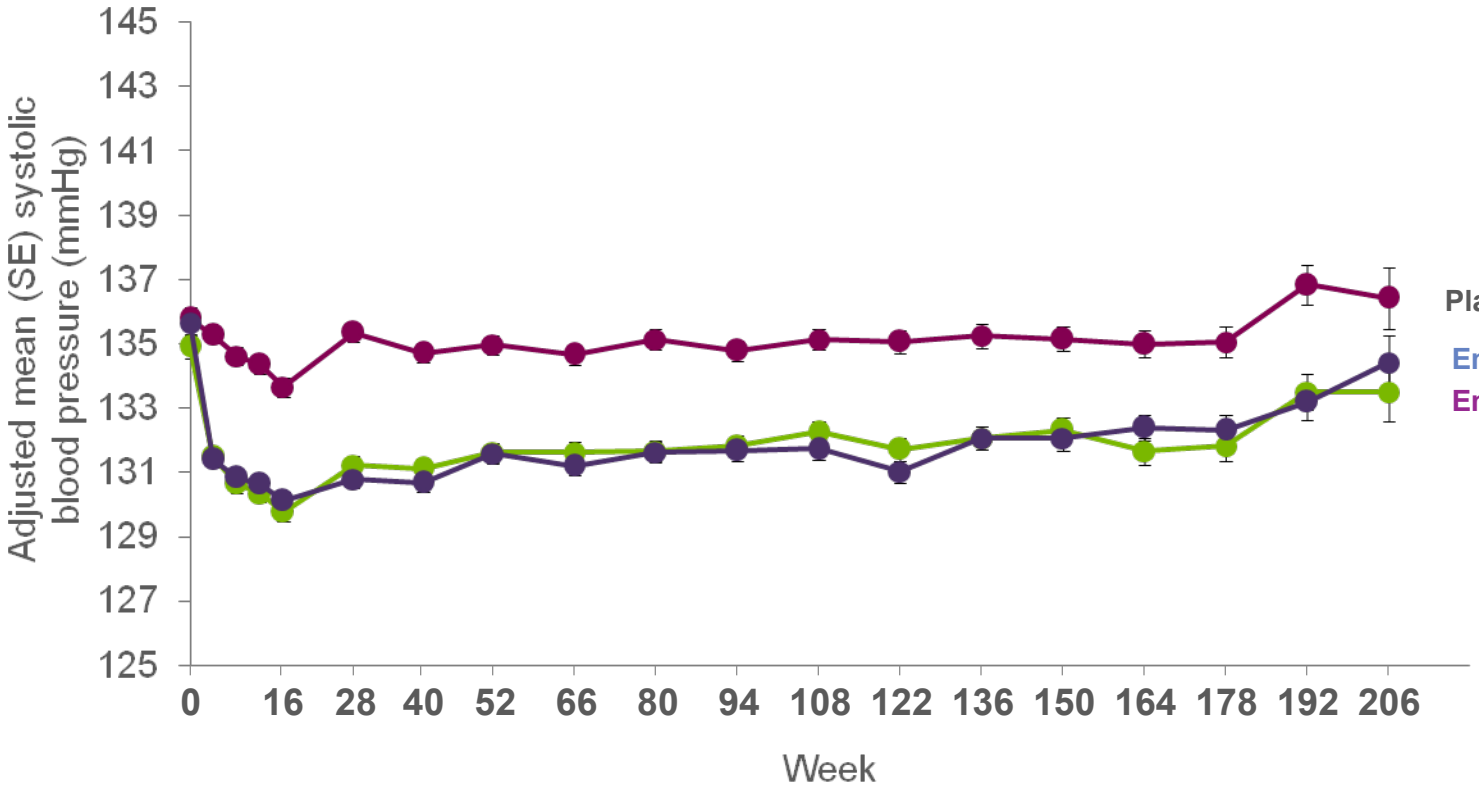


Placebo	2259 1869	2183	2110	1562	1220	418
Empagliflozin 10 mg	2272 1836	2219	2155	1644	1285	475
Empagliflozin 25 mg	2273 1857	2209	2157	1648	1329	486

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)
X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

Systolic blood pressure

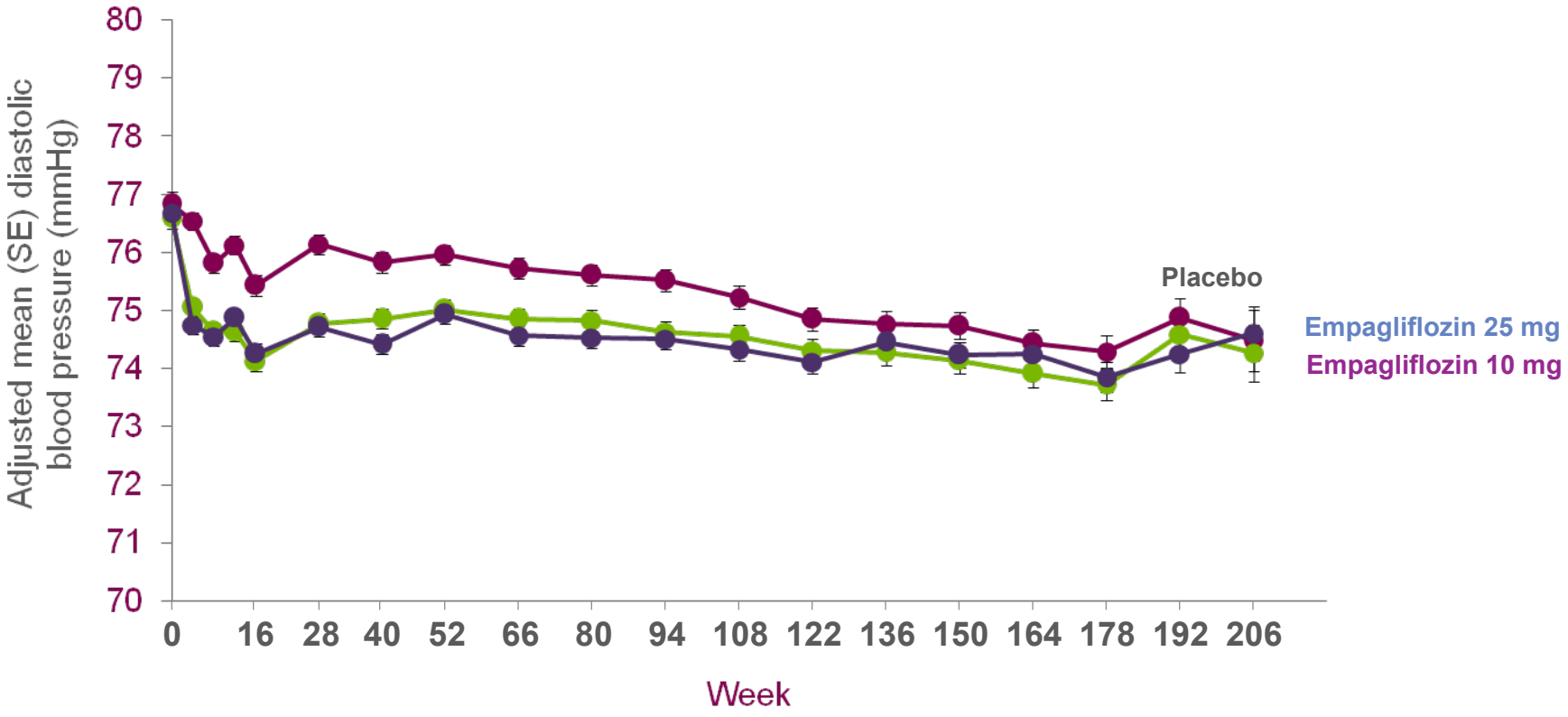


Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)
X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

Diastolic blood pressure

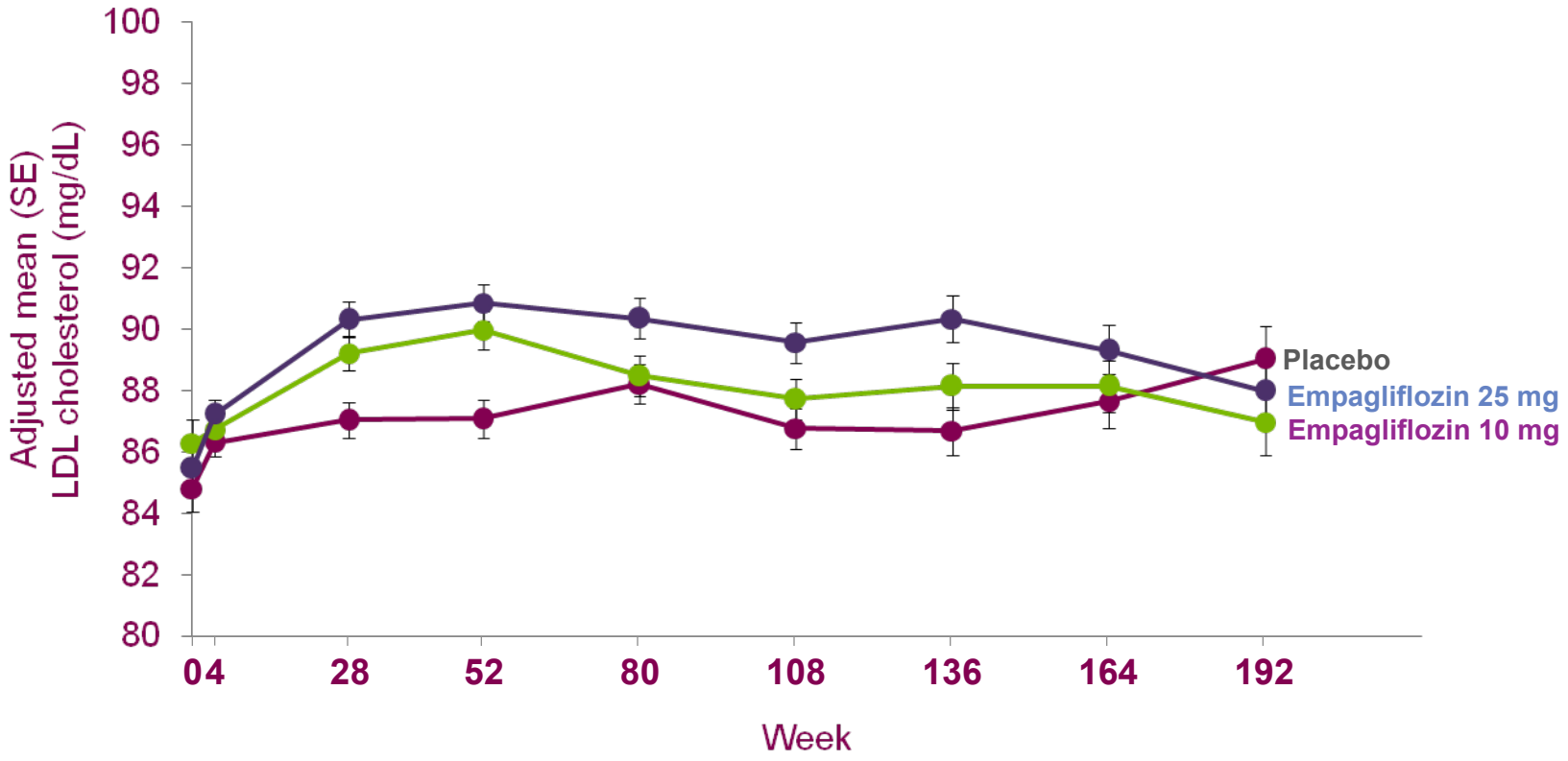


Placebo	2322	2235	2203	2161	2133	2073	2024	1974	1771	1492	1274	1126	981	735	450	171
Empagliflozin 10 mg	2322	2250	2235	2193	2174	2125	2095	2072	1853	1556	1327	1189	1034	790	518	199
Empagliflozin 25 mg	2323	2247	2221	2197	2169	2129	2102	2066	1878	1571	1351	1212	1070	842	528	216

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)
X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

Low-density lipoprotein cholesterol

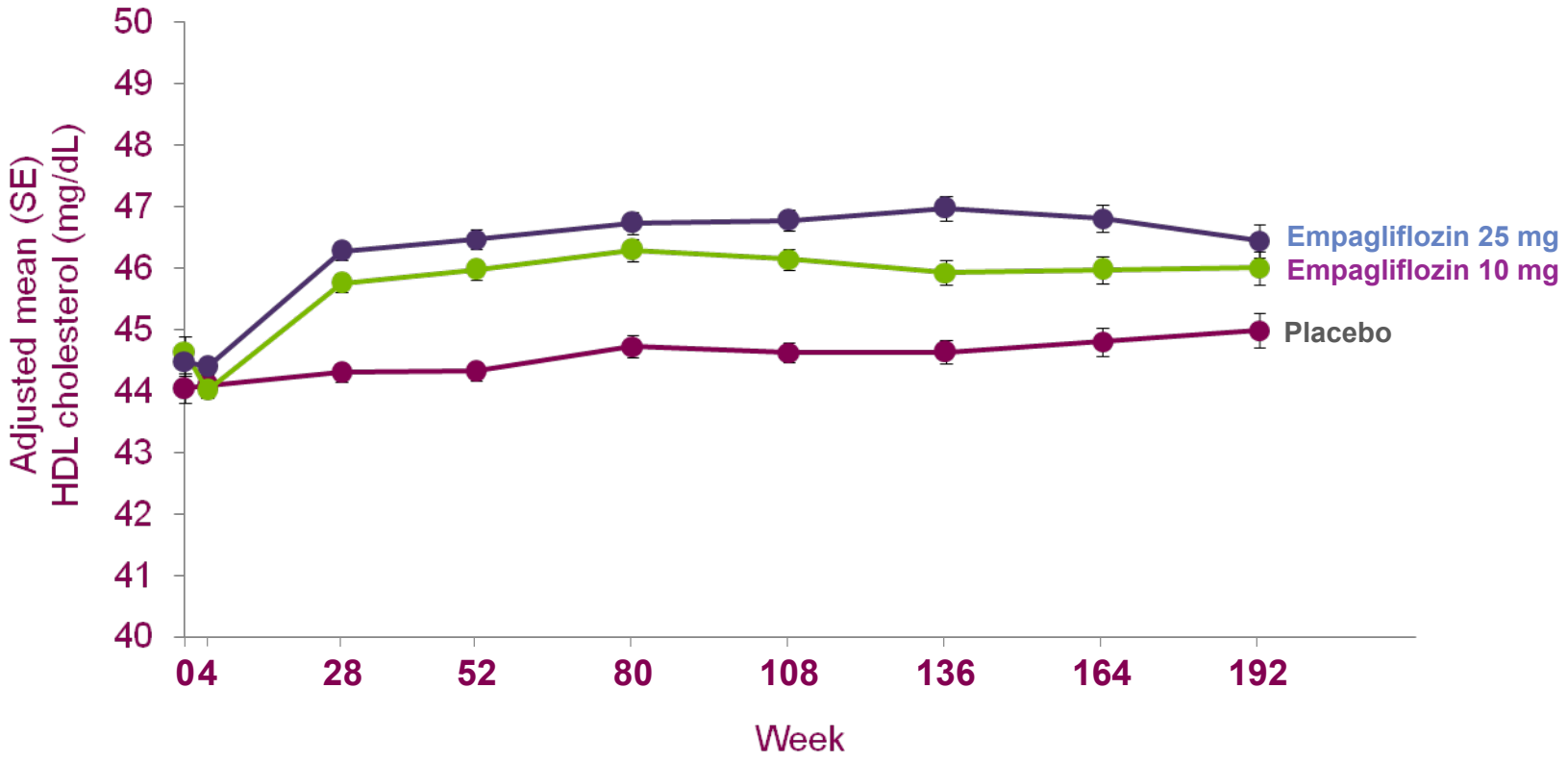


Placebo	2297 2273	2179	2104	2006	1932	1419	1086	694
Empagliflozin 10 mg	2294 2269	2205	2143	2072	1998	1474	1133	740
Empagliflozin 25 mg	2287 2256	2188	2132	2060	2020	1503	1169	779

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)
X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

High-density lipoprotein cholesterol

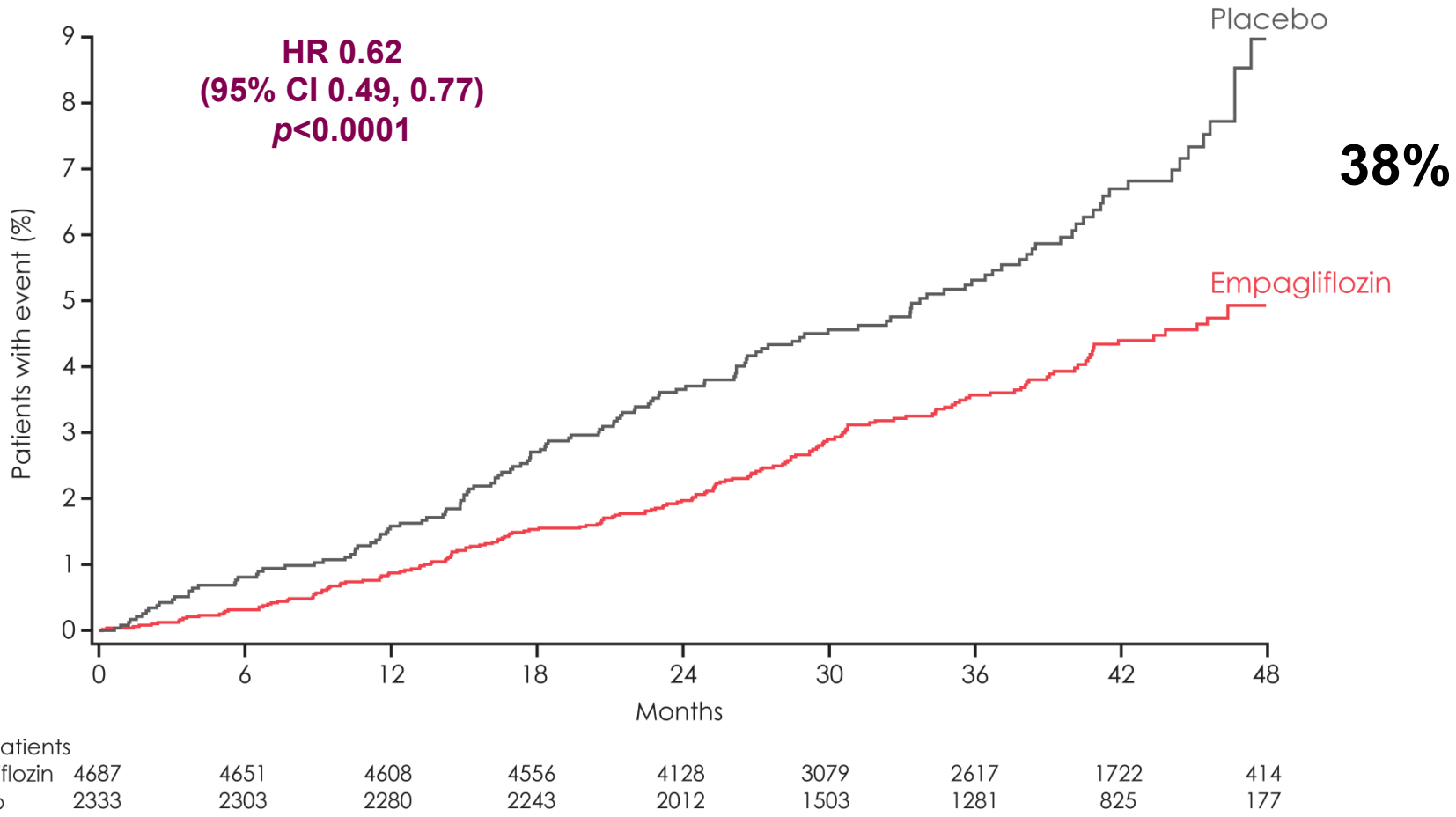


Placebo	2297 2273	2181	2104	2007	1932	1419	1087	694
Empagliflozin 10 mg	2295 2270	2209	2144	2074	2001	1475	1134	741
Empagliflozin 25 mg	2289 2259	2191	2135	2064	2022	1507	1170	779

All patients (including those who discontinued study drug or initiated new therapies) were included in this mixed model repeated measures analysis (intent-to-treat)
X-axis: timepoints with reasonable amount of data available for pre-scheduled measurements

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

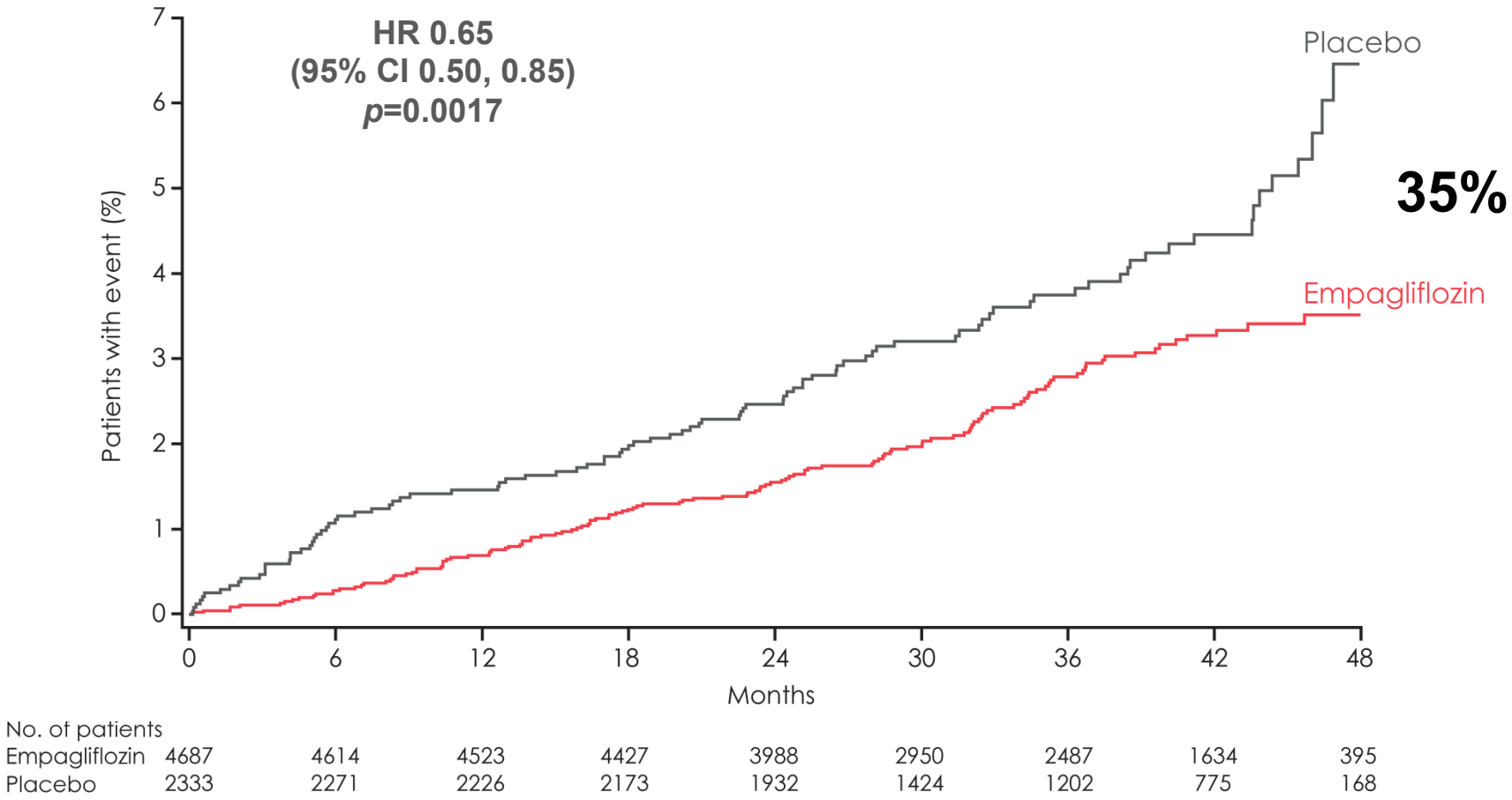
CV death



Cumulative incidence function. HR, hazard ratio

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

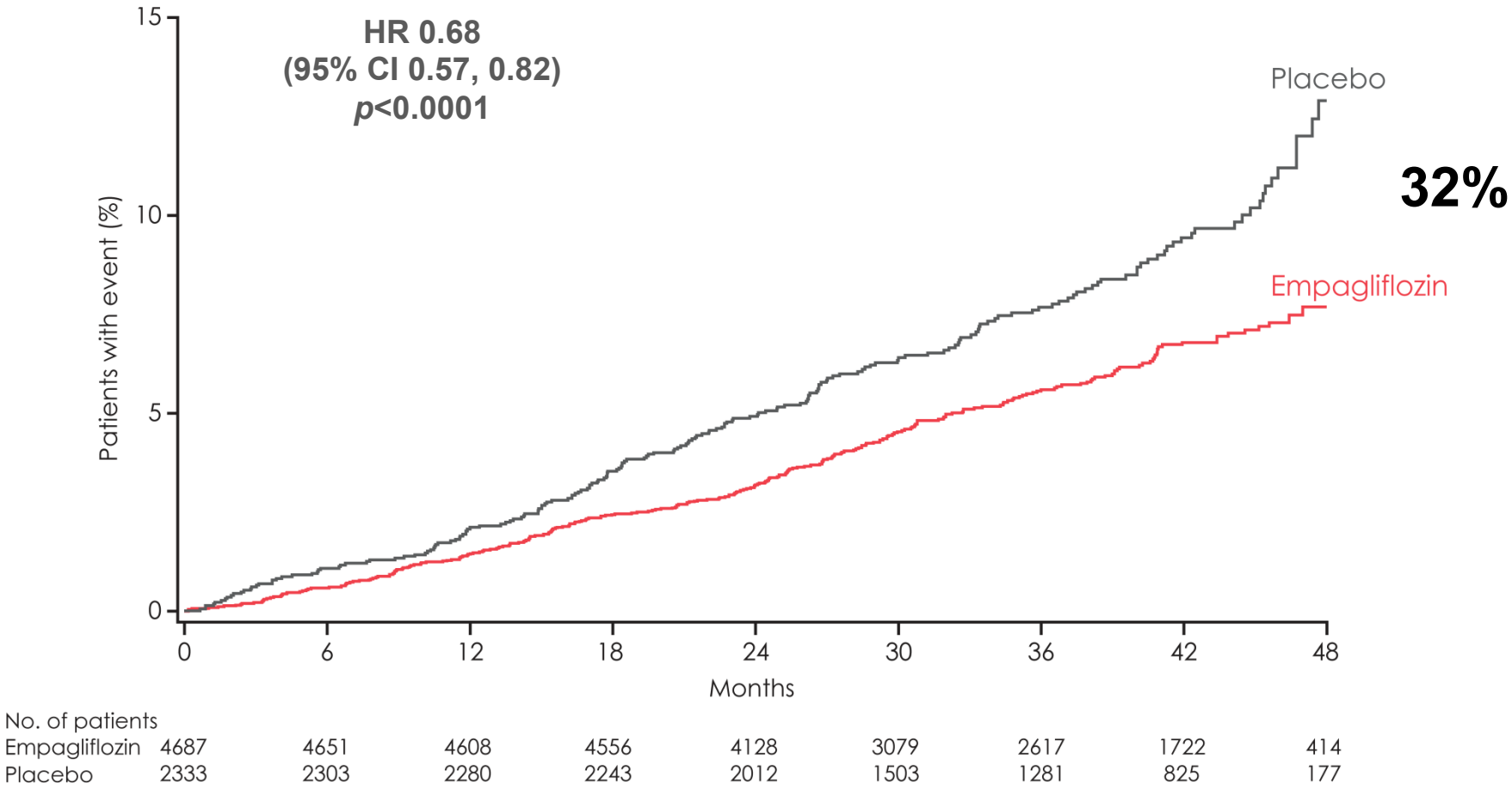
Hospitalisation for heart failure



Cumulative incidence function. HR, hazard ratio

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

All-cause mortality



Kaplan-Meier estimate. HR, hazard ratio

From: https://s3-eu-west-1.amazonaws.com/mevents/easd/empa-reg-slide-kit.pptx

Low incidence of hypoglycemia with DAPA relative to PBO: pooled analysis

	PBO-controlled pool (short-term)		PBO-controlled pool (short- plus long-term)	
	DAPA 10 mg (N=2360)	PBO (N=2295)	DAPA 10 mg (N=2026)	PBO (N=1956)
All events of hypoglycemia	309 (13.1)	242 (10.5)	378 (18.7)	290 (14.8)
Major events	2 (0.1)	1 (< 0.1)	4 (0.2)	2 (0.1)
Minor events	276 (11.7)	211 (9.2)	352 (17.4)	266 (13.6)

Major episodes of hypoglycemia were uncommon and balanced across PBO and DAPA groups

DAPA, dapagliflozin; PBO, placebo.

Increased risk of hypoglycemia when added to SU and insulin

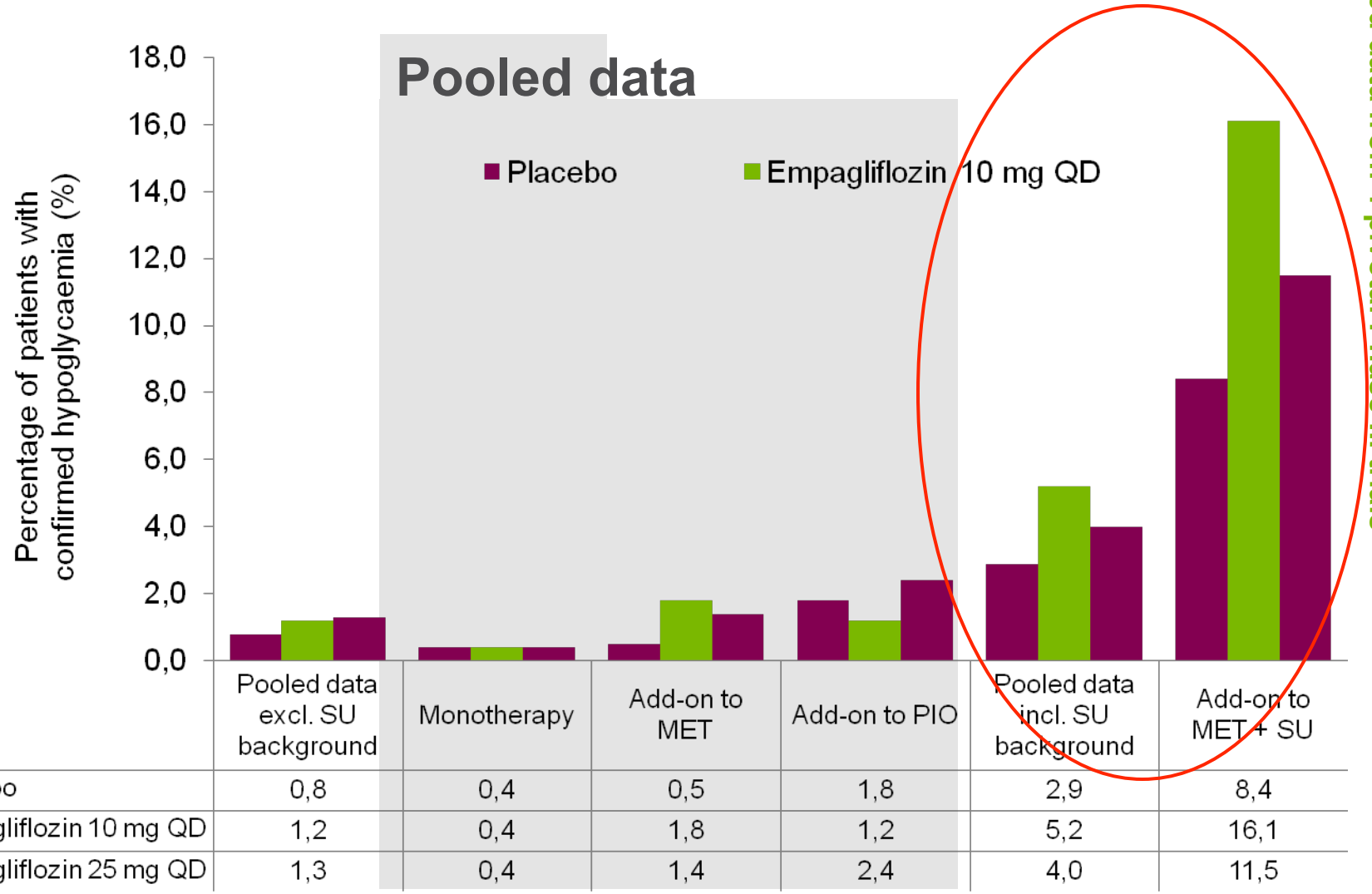
	Number of patients, n/N (%)	
	DAPA 10 mg	PBO
Active Comparator Studies		
Dapa vs SU (add-on to MET)	14/406 (3.5)	162/408 (40.8)
Dapa vs MET	2/219 (0.9)	6/208 (2.9)
PBO-controlled Studies		
Monotherapy	2/70 (2.9)	2/75 (2.7)
Add-on to MET	5/135 (3.7)	4/137 (2.9)
Add-on to TZD	0/140 (0.0)	1/139 (0.7)
Add-on to DPP-4i	5/225 (2.2)	3/226 (1.3)
Add-on to SU	11/151 (7.3)	7/146 (4.8)
Add-on to INS	83/196 (42.3)	69/197 (35.0)

- In monotherapy and add-on to MET, pioglitazone, and DPP-4i studies, the rate of hypoglycemia was similar on DAPA vs PBO
- An increased risk of hypoglycemic events is observed when used as an add-on to SU and INS (agents with known side effects of hypoglycemia)

DAPA, dapagliflozin; DPP-4i, dipeptidyl peptidase-4 inhibitor; INS, insulin; MET, meformin; PBO, placebo; SU, sulfonylurea; TZD, thiazolidinedione.

Phase III pooled safety and tolerability analysis
Low incidence of hypoglycaemia with empagliflozin if used without SU

Pooled data from 4 pivotal Phase III trials



	Pooled data excl. SU background	Monotherapy	Add-on to MET	Add-on to PIO	Pooled data incl. SU background	Add-on to MET + SU
Placebo	0,8	0,4	0,5	1,8	2,9	8,4
Empagliflozin 10 mg QD	1,2	0,4	1,8	1,2	5,2	16,1
Empagliflozin 25 mg QD	1,3	0,4	1,4	2,4	4,0	11,5

MET, metformin; PIO, pioglitazone; QD, once daily; SU, sulphonylurea.

1. Pooled data adapted from Hach T, et al. Abstract no 69-LB; 2. Individual studies adapted from abstracts 1085, 1092. Presented at the 73rd Scientific Sessions of the American Diabetes Association. June 21–25, 2013. Chicago, Illinois; 3 Kovacs C, et al. *Diabetes Obes Metab*. 2013 Aug 1. doi: 10.1111/dom.12188; 4. Häring H-U, et al. *Diabetes Care*. 2014. doi:10.2337/dc12-2673.

Genital infections and UTIs

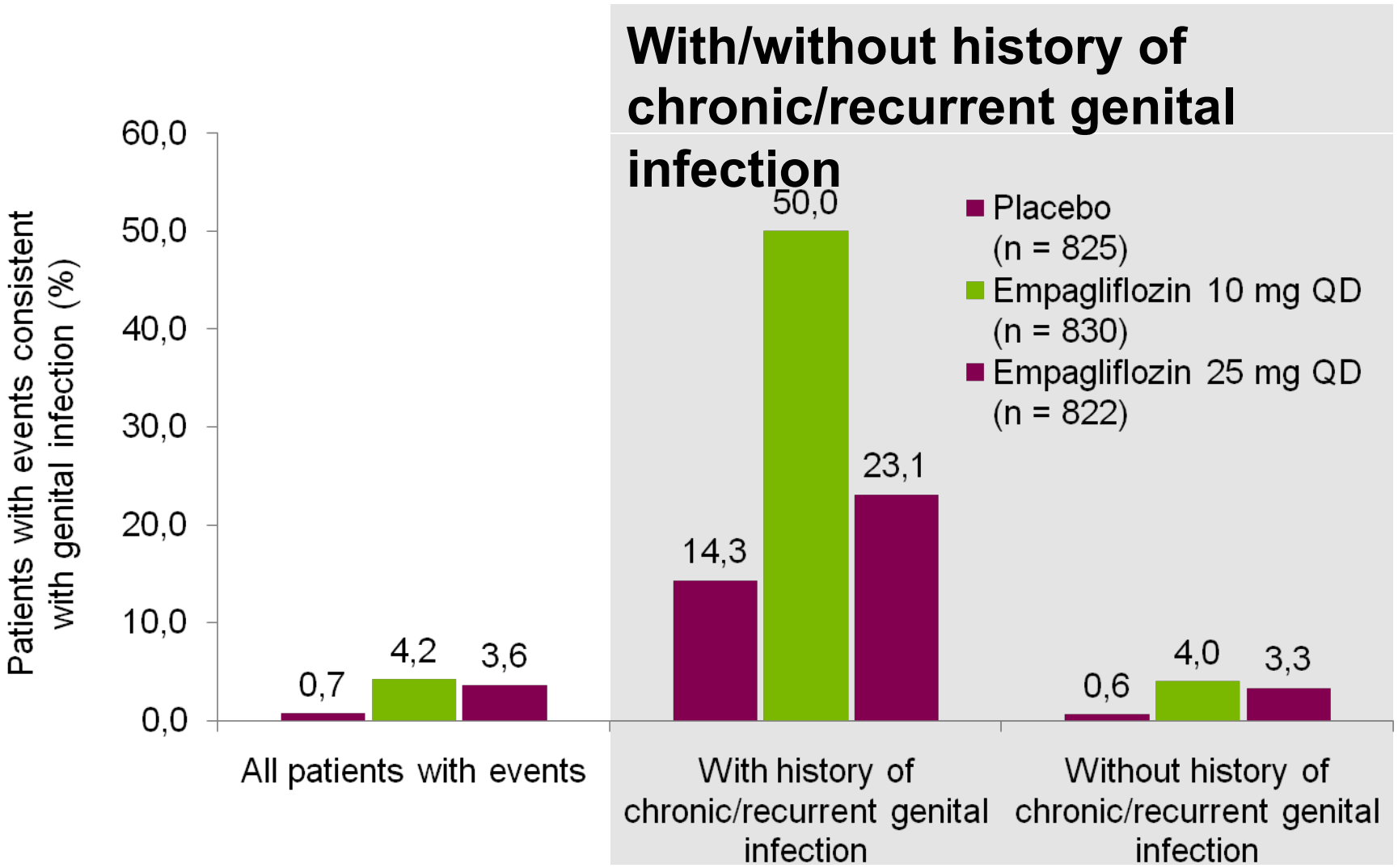
	PBO-controlled pool (short-term)		PBO-controlled pool (short- plus long-term)	
	DAPA 10 mg	PBO	DAPA 10 mg	PBO
Genital infection, n (%)	N=2360 130 (5.5)	N=2295 14 (0.6)	N=2026 156 (7.7)	N=1956 19 (1.0)
UTI in females, n (%)	N=1003 84 (8.4)	N=952 11 (1.2)	N=852 98 (11.5)	N=799 15 (1.9)
UTI in males, n (%)	N=1357 46 (3.4)	N=1343 3 (0.2)	N=1174 58 (4.9)	N=1157 4 (0.3)

- Events of genital infections were more common in females than males
- Most frequently reported genital infections: vulvovaginal mycotic infection, balanitis, and vaginal infections
- No events in the PBO-controlled pool were serious; most were managed with antimicrobial therapy

DAPA, dapagliflozin; PBO, placebo; UTI, urinary tract infection.

Phase III pooled safety and tolerability analysis
Events consistent with genital infection

Pooled data from 4 pivotal Phase III trials

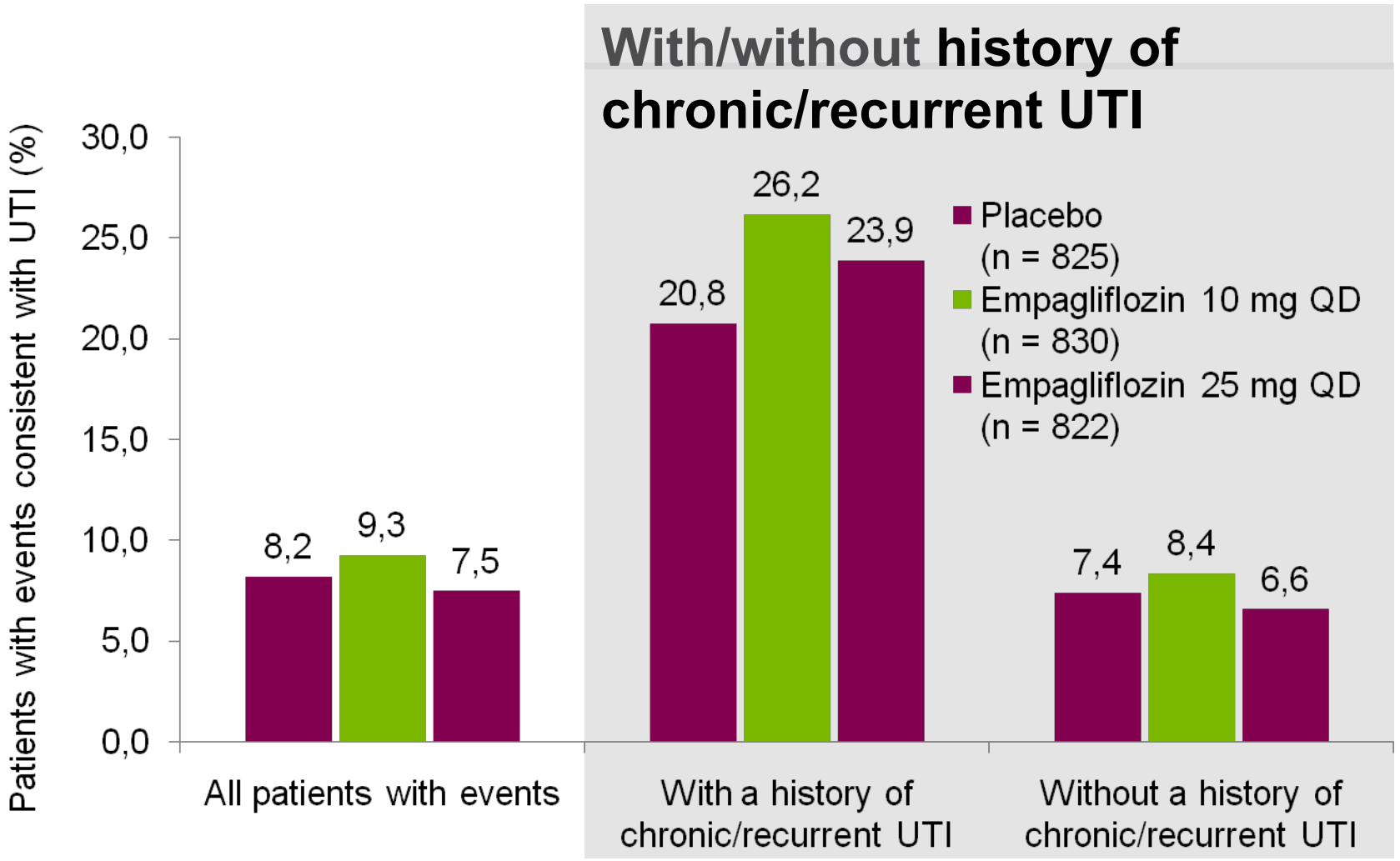


QD, once daily.

Kim G, et al. *Diabetes*. 2013;(Suppl 1) (P74-LB).

Phase III pooled safety and tolerability analysis
Events consistent with UTI

Pooled data from 4 pivotal Phase III trials



QD, once daily; UTI, urinary tract infection.

Kim G, et al. *Diabetes.* 2013;(Suppl 1) (P74-LB).

Advanced age, antihypertensive therapy and renal impairment were risk factors for volume depletion events

Volume depletion by patient subgroup n/N (%)	DAPA 10 mg (N=2360)	PBO (N=2295)
Any antihypertensive medication		
Yes	26/1785 (1.5)	16/1797 (0.9)
No	1/575 (0.2)	1/498 (0.2)
Diuretic		
Yes	15/897 (1.7)	9/918 (1.0)
No	12/1463 (0.8)	8/1377 (0.6)
Loop diuretic		
Yes	6/236 (2.5)	4/267 (1.5)
No	21/2124 (1.0)	13/2028 (0.6)

DAPA, dapagliflozin; PBO, placebo.

Johnsson K, et al. Presented at the 74th Scientific Sessions of the American Diabetes Association (ADA), San Francisco, CA, USA, June 13–17, 2014. 1031-P.

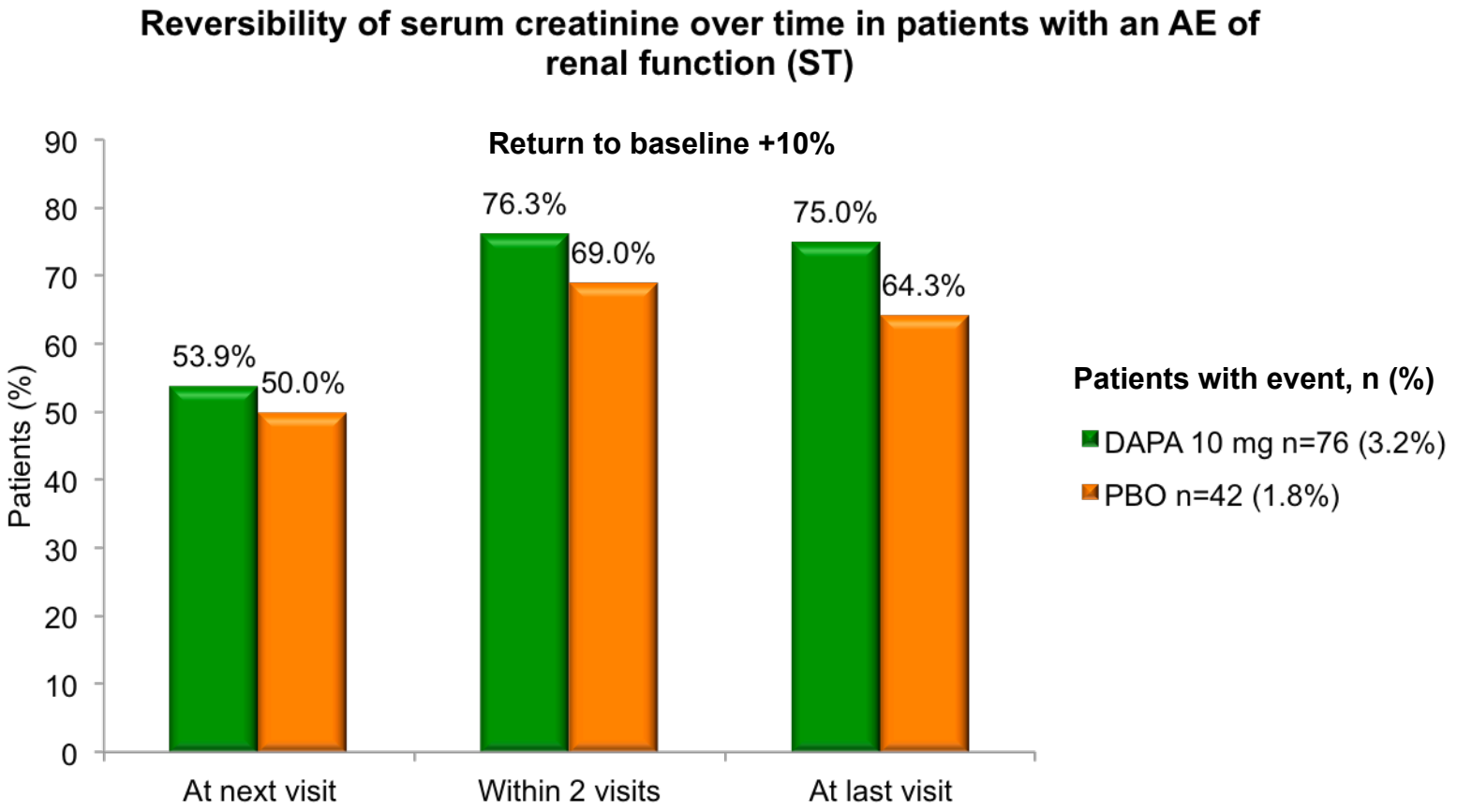
Advanced age, antihypertensive therapy and renal impairment were risk factors for volume depletion events (continued)

Volume depletion by patient subgroup n/N (%)	DAPA 10 mg (N=2360)	PBO (N=2295)
ACEi/ARB		
Yes	22/1574 (1.4)	16/1577 (1.0)
No	5/786 (0.6)	1/718 (0.1)
Age, y		
< 65	16/1695 (0.9)	11/1584 (0.7)
≥ 65	11/665 (1.7)	6/711 (0.8)
≥ 75	3/98 (3.1)	1/81 (1.2)
eGFR, mL/min/1.73m^2		
≥ 30–< 60	5/265 (1.9)	4/268 (1.5)
≥ 60	22/2094 (1.1)	13/2025 (0.6)

DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; PBO, placebo.

Johnsson K, et al. Presented at the 74th Scientific Sessions of the American Diabetes Association (ADA), San Francisco, CA, USA, June 13–17, 2014. 1031-P.

Serum creatinine increases were transient and reversible in patients with renal function AEs



AEs, adverse events; DAPA, dapagliflozin; PBO, placebo; ST, short term.

Ptaszynska A, et al. Presented at the 74th Scientific Sessions of the American Diabetes Association (ADA), San Francisco, CA, USA, June 13–17, 2014. P-1036.

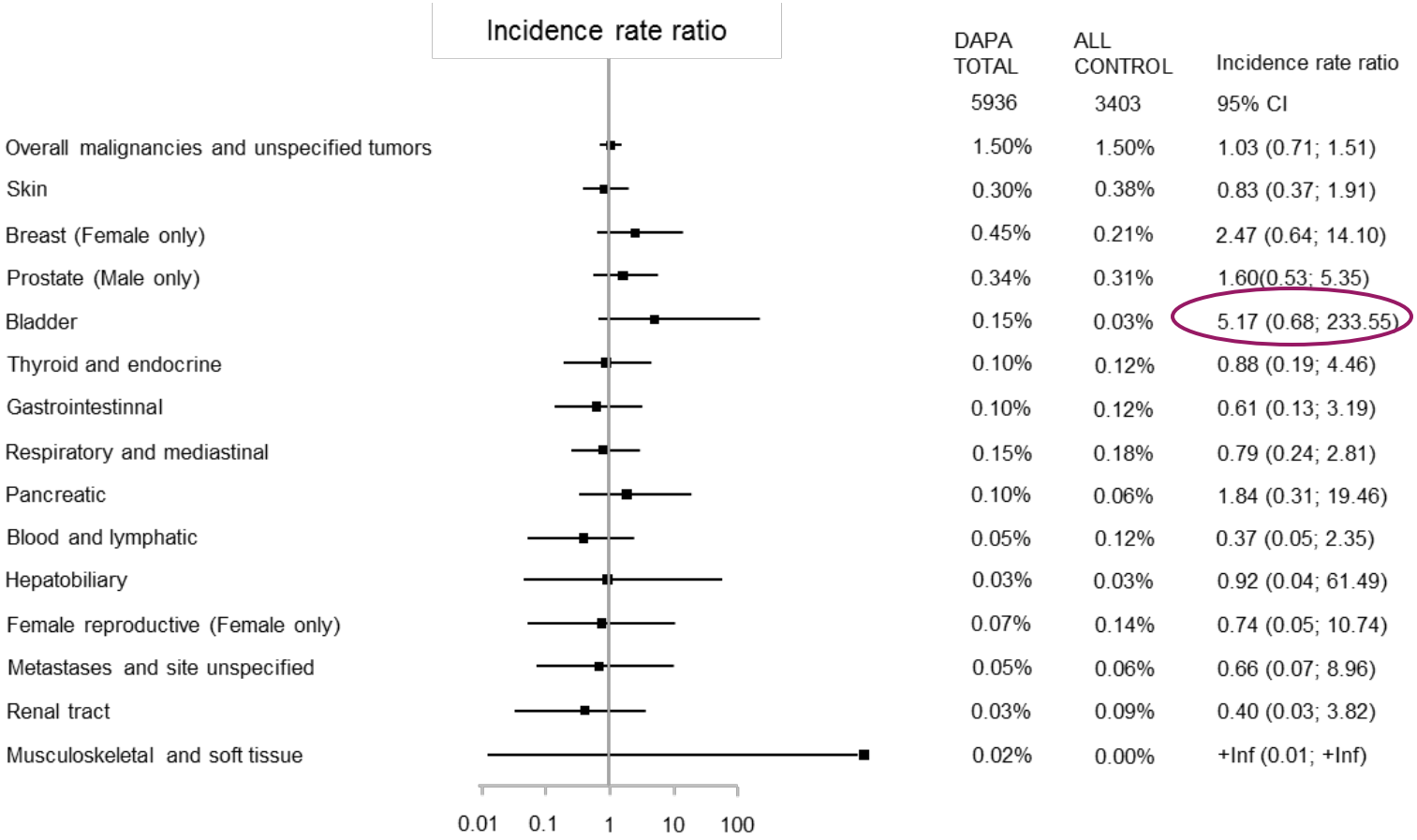
Laboratory data: Haematocrit

- In the placebo-controlled (short-term) pool, small dose-dependent changes from baseline were observed in the haematocrit (up to 2.3% mean increase for dapagliflozin 10 mg)
- Marked abnormalities of increased haemoglobin or haematocrit occurred in few patients

	Placebo-controlled pool (short term)		Placebo-controlled pool (short + long term)	
Events	**Dapagliflozin 10 mg (n=2360)**	**Placebo (n=2295)**	**Dapagliflozin 10 mg (n=2026)**	**Placebo (n=1956)**
Haematocrit (>55%), n	31 **(1.3%)**	8 **(0.4%)**	42 **(2.1%)**	11 **(0.6%)**
Haematocrit (>60%), n	3 **(0.1%)**	2 **(0.1%)**	4 **(0.2%)**	2 **(0.1%)**
Haemoglobin (>18 g/dL), n	36 **(1.5%)**	11 **(0.5%)**	45 **(2.2%)**	14 **(0.7%)**
Haemoglobin (>20 g/dL), n	0	2 **(0.1%)**	0	2 **(0.1%)**

EMDAC Background document. Available at: http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/endocrinologicandmetabolicdrugsadvisorycommittee/ucm378079.pdf.
Last accessed September 2014.

There was no overall imbalance in malignancies



	DAPA TOTAL	ALL CONTROL	Incidence rate ratio
	5936	3403	95% CI
Overall malignancies and unspecified tumors	1.50%	1.50%	1.03 (0.71; 1.51)
Skin	0.30%	0.38%	0.83 (0.37; 1.91)
Breast (Female only)	0.45%	0.21%	2.47 (0.64; 14.10)
Prostate (Male only)	0.34%	0.31%	1.60(0.53; 5.35)
Bladder	0.15%	0.03%	5.17 (0.68; 233.55)
Thyroid and endocrine	0.10%	0.12%	0.88 (0.19; 4.46)
Gastrointestinnal	0.10%	0.12%	0.61 (0.13; 3.19)
Respiratory and mediastinal	0.15%	0.18%	0.79 (0.24; 2.81)
Pancreatic	0.10%	0.06%	1.84 (0.31; 19.46)
Blood and lymphatic	0.05%	0.12%	0.37 (0.05; 2.35)
Hepatobiliary	0.03%	0.03%	0.92 (0.04; 61.49)
Female reproductive (Female only)	0.07%	0.14%	0.74 (0.05; 10.74)
Metastases and site unspecified	0.05%	0.06%	0.66 (0.07; 8.96)
Renal tract	0.03%	0.09%	0.40 (0.03; 3.82)
Musculoskeletal and soft tissue	0.02%	0.00%	+Inf (0.01; +Inf)

Non-significant imbalances in the diagnosis of different tumor types were observed

CI, confidence interval; DAPA, dapagliflozin; Inf, inferred.

The proportions of patients with fractures were small and balanced for DAPA vs PBO

	PBO-controlled pool (short-term)		PBO-controlled pool (short- plus long-term)	
	DAPA 10 mg	PBO	DAPA 10 mg	PBO
Events, n (%)	N=2360 8 (0.3)	N=2295 17 (0.7)	N=2026 23 (1.1)	N=1956 32 (1.6)

DAPA, dapagliflozin; PBO, placebo.

DAPA does not affect bone mineral density and markers of bone formation and resorption

Mean (SD)	DAPA 10 mg (N=91)		PBO (N=91)		Difference vs PBO (95% CI)	*P*-value
	Baseline	Mean change	Baseline	Mean change		
Lumbar spine BMD (L1-4), g/cm^2*	1.18	0.69	1.19	0.47	0.22 (–0.89, 1.34)	0.7013
Femoral neck BMD g/cm^2*	0.97	–0.85	0.94	0.09	–0.94 (–2.21, 0.35)	0.1521
Total hip BMD, g/cm^2*	1.10	–0.82	1.05	–0.37	–0.45 (–1.32, 0.43)	0.3105
CTX, ng/mL	0.22	0.02	0.23	0.02	0.01 –0.02, 0.04)	0.6918
NTX, nM BCE	8.87	0.50	8.94	0.61	-0.10 (–1.04, 0.83)	0.8275
Osteocalcin, ng/mL	14.09	0.11	15.06	–0.14	0.25 (–1.35, 1.86)	0.7557
Bone-specific ALP (Week 50), U/L	17.17	–1.58	16.54	–2.29	0.71 (–0.55, 1.97)	0.2664
P1NP, µg/L	26.98	1.66	27.36	0.50	1.16 (–2.16, 4.48)	0.4906

*DAPA 10 mg N=68, PBO N=71. BMD, bone mineral density; CTX, C-terminal cross-linking telopeptides of type 1 collagen; DAPA, dapagliflozin; NTX=N-terminal cross-linking telopeptides of type 1 collagen; PBO, placebo; P1NP=procollagen type 1 N- terminal propeptide (µg/L).

Ptaszynska A, et al. Presented at the 74th Scientific Sessions of the American Diabetes Association (ADA), San Francisco, CA, USA, June 13–17, 2014. 1085-P.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 February 2016
EMA/100751/2016

SGLT2 inhibitors: PRAC makes recommendations to minimise risk of diabetic ketoacidosis

Healthcare professionals should be aware of possible atypical cases

If diabetic ketoacidosis is suspected or confirmed, treatment should be stopped immediately and should not be re-started unless another cause for the ketoacidosis is identified and resolved.

Healthcare professionals should exercise caution in patients with risk factors for ketoacidosis and inform patients of the risk factors. These include low reserve of insulin-secreting cells, conditions that restrict food intake or can lead to severe dehydration, a sudden reduction in insulin or an increased requirement for insulin due to illness, surgery or alcohol abuse.

The benefits of SGLT2 inhibitors continue to outweigh their risks in the treatment of type 2 diabetes. The PRAC reminds healthcare professionals that these medicines are not authorised for treating type 1 diabetes, noting that some cases of ketoacidosis had occurred with off-label use.

The PRAC's recommendations will now be forwarded to the Committee for Medicinal Products for Human Use (CHMP) for the adoption of EMA's final opinion. Further details will be published at the time of the CHMP opinion.

NOTA INFORMATIVA IMPORTANTE CONCORDATA CON LE AUTORITA' REGOLATORIE EUROPEE E CON L'AGENZIA ITALIANA DEL FARMACO (AIFA)

14 marzo 2016

Sono stati riportati rari casi, ma gravi e a volte con pericolo di vita e fatali, di chetoacidosi diabetica in pazienti in trattamento con inibitori SGLT2 per il diabete di tipo2. In un certo numero di queste segnalazioni, la condizione clinica si è presentata in maniera atipica, con solo un moderato aumento dei livelli ematici di glucosio. Il manifestarsi della chetoacidosi diabetica in maniera così atipica in pazienti con diabete potrebbe ritardarne la diagnosi ed il trattamento.

Riassunto delle raccomandazioni aggiornate

- Il rischio di chetoacidosi diabetica deve essere considerato in caso di sintomi non specifici come nausea, vomito, anoressia, dolori addominali, sete eccessiva, difficoltà di respirazione, stato confusionale, inusuale stanchezza o sonnolenza. I medici devono informare i pazienti dei segni e sintomi di acidosi metabolica e consigliare loro di consultare immediatamente un medico se si sviluppano tali segni e sintomi.
- Nei pazienti in cui si sospetta o viene diagnosticata la chetoacidosi diabetica, il trattamento con gli inibitori SGLT2 deve essere interrotto immediatamente.
- Non è raccomandato l'inizio di un nuovo trattamento con gli inibitori SGLT2 in pazienti con precedente diagnosi di chetoacidosi diabetica manifestatasi in corso di trattamento con inibitori SGLT2, a meno che un altro chiaro fattore scatenante siastato identificato e risolto.
- Il trattamento deve essere interrotto nei pazienti che sono ospedalizzati per interventi di chirurgia maggiore o per gravi patologie acute. In entrambi i casi, il trattamento con inibitori SGLT2 può essere ripreso una volta che le condizioni del paziente si sono stabilizzate.

Le informazioni per gli operatori sanitari nel Riassunto delle Caratteristiche del Prodotto (RCP) e le informazioni per i pazienti contenute nel foglio illustrativo verranno aggiornate di conseguenza.

SGLT2 INHIBITORS: SUMMARY

Potential benefits

- Insulin – indipendent
- HbA1c lowering
- Reduction in:
  - FPG
  - PPG
  - Weigth
- Reduction in blood pressure
- Reduction in uric acid
- Reduction in CV risk

Potential risks

- Renal function
- Diuretic effect
  - Hypovolaemia
  - Hypotension
  - Dehydration
- Bone mineral metabolism
- Urinary tract infections, vulvovaginitis, balanitis
- Rare or unexpected events