Type 2 Diabetes Management Update

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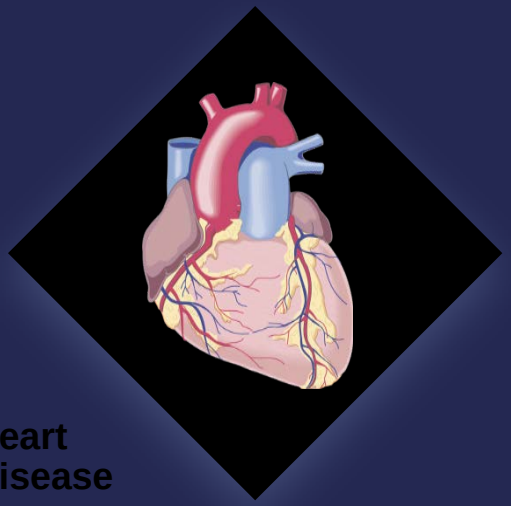
DISCLOSURES

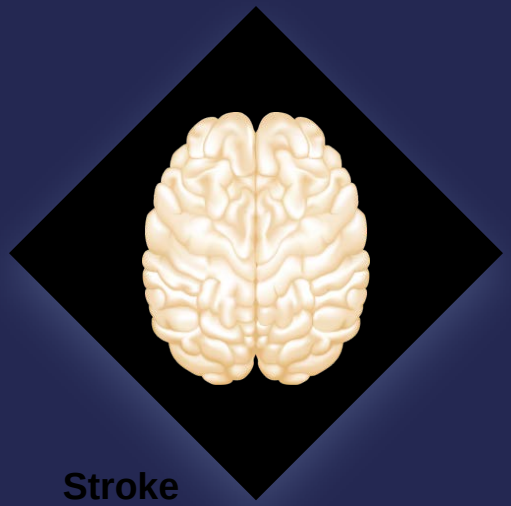
Advisory Boards – Astra – Zeneca , Lilly/Boehringer

Speakers fees - Novo Nordisk , Lilly , MSD , Sanofi

We primarily treat type 2 diabetes mellitus to reduce the risk of long term complications

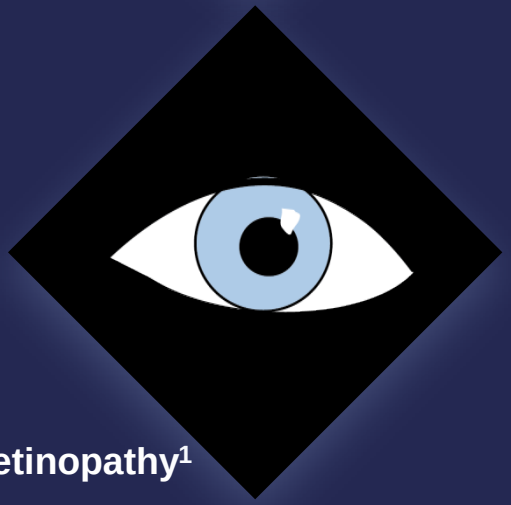


Heart Disease

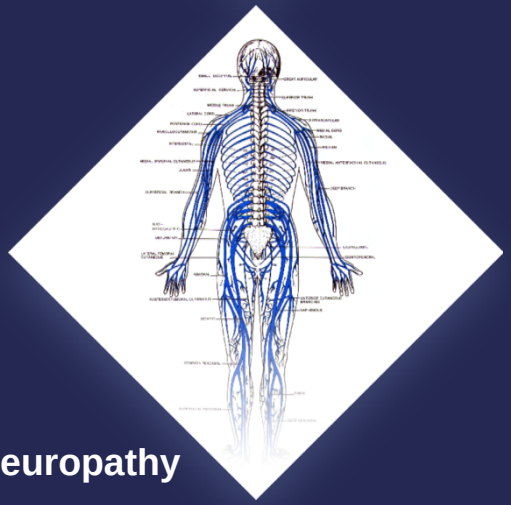


Stroke

Peripheral Vascular Disease[3,4]



Retinopathy[1]



Neuropathy

Chronic Kidney Disease[2]

1.National Health and Medical Research Council. Guidelines for the management of diabetic retinopathy. 2008. Available at www.nhmrc.gov.au/publications/synopses/_files/di15.pdf
2.Kidney Health Australia. Two of a KinD (Kidneys in Diabetes) 2011.
3.Australian Institute of Health and Welfare 2008. Diabetes: Australian facts 2008. Diabetes series no. 8. Cat. no. CVD 40. Canberra: AIHW. and
4.CDC 2011 National Diabetes Fact Sheet, http://www.cdc.gov/diabetes/pubs/estimates11.htm#12

Goals of Type 2 DM Management

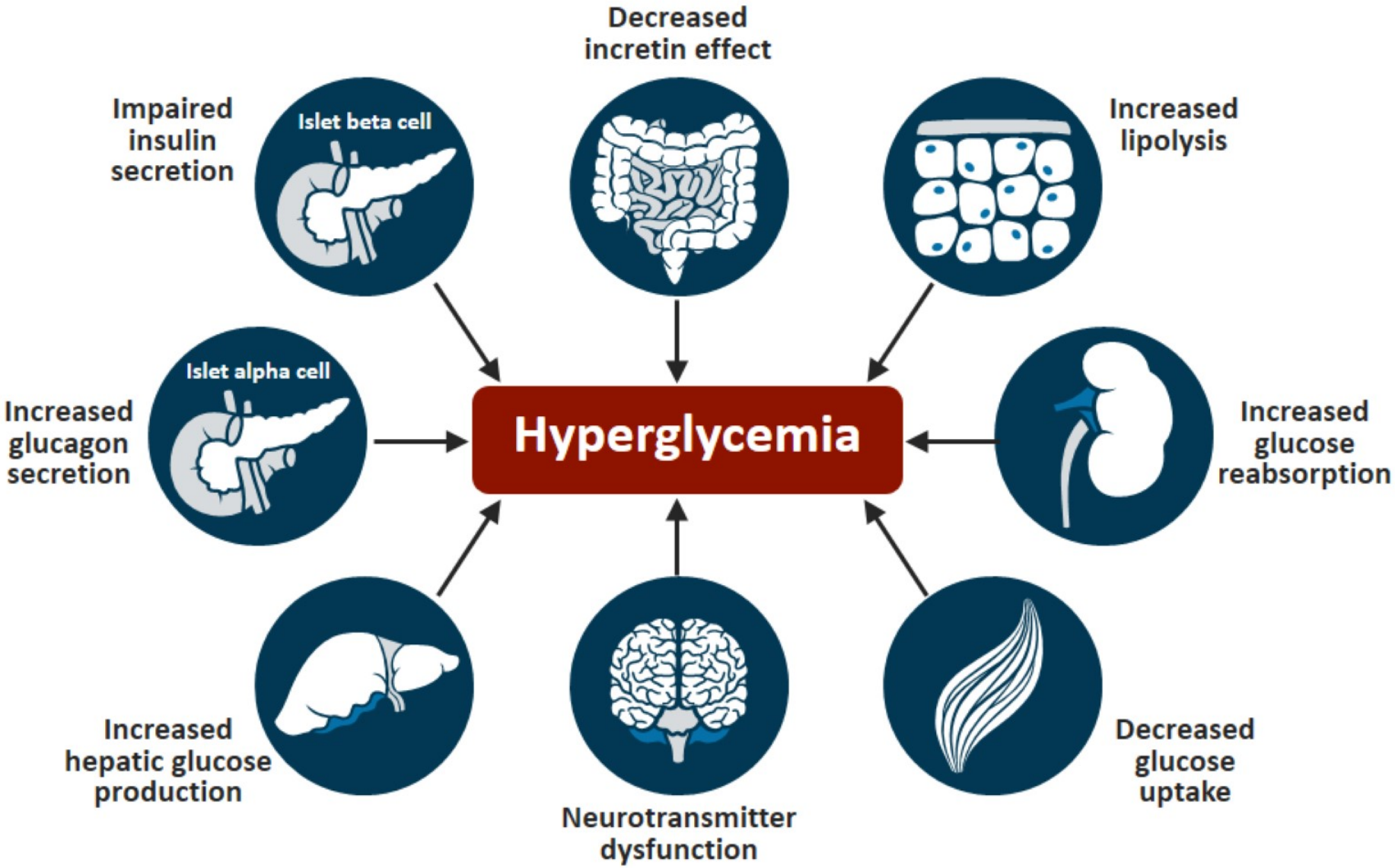
To minimize macrovascular disease

- BP control
- LDL Cholesterol control
- Anti platelet agents
- Smoking cessation
- Glycaemic control – short term no , long term probably

To minimize microvascular disease

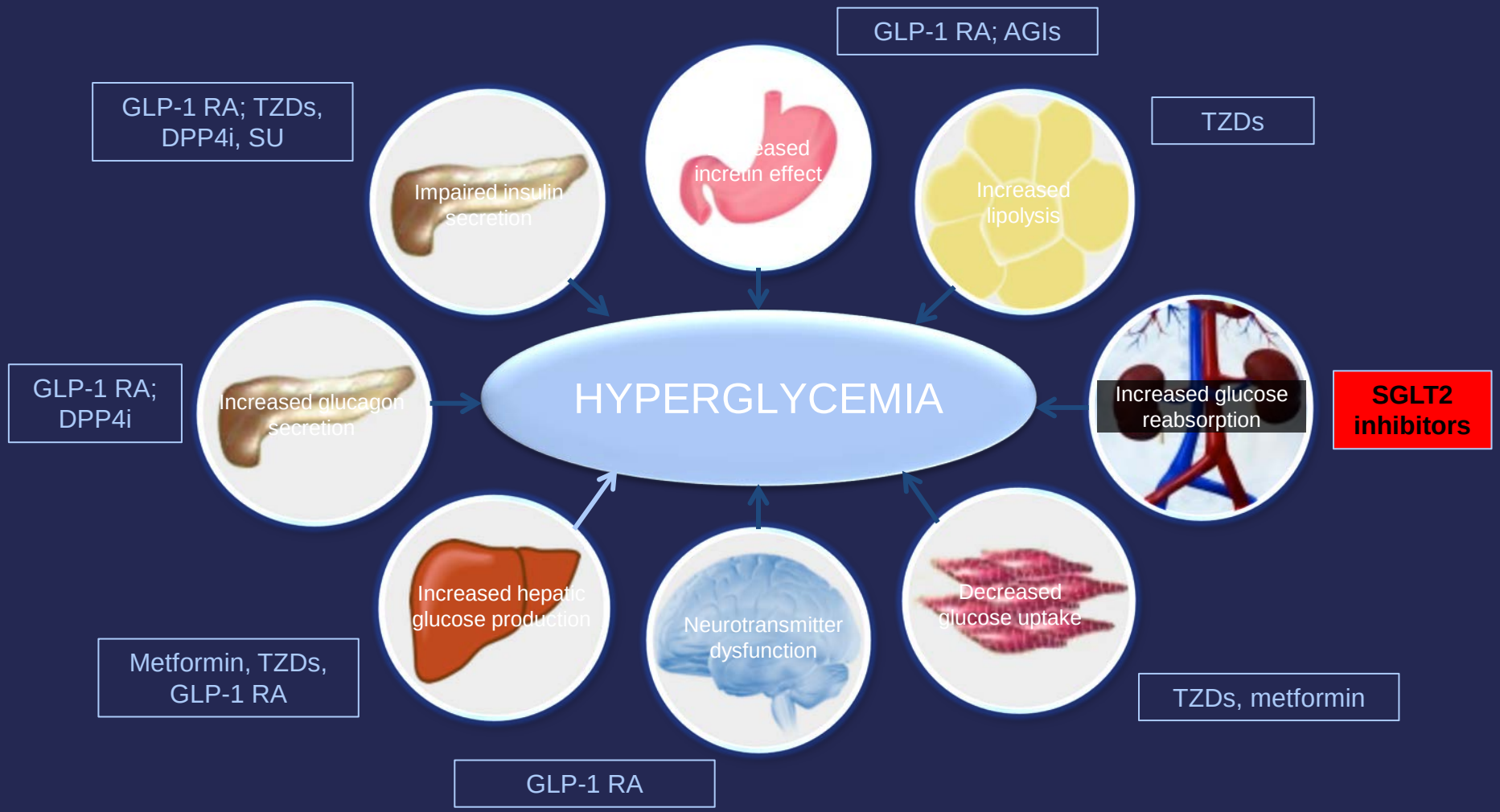
- Glycaemic control
- HbA1c < 7% but individualised
- Laser, anti-VEGF therapy, fenofibrate (retinopathy)
- ACE inhibitors/ARB (nephropathy)

Ominous Octet



DeFronzo RA. *Diabetes*. 2009;58:773-795.[1]

"THE OMINOUS OCTET"



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

1. DeFronzo RA. Diabetes. 2009;58(4):773–795.

Neutral CV Outcome Studies in Type 2 DM

DPP4 Inhibitors –	SAVOR TIMI	saxagliptin
	EXAMINE	alogliptin
	TECOS	sitagliptin
GLP1 Agonists –	ELIXA	lixisenatide

Australian Blood Glucose Treatment Algorithm for Type 2 Diabetes

Lifestyle measures: diet, exercise, weight control.

Determine the individual's HbA1c target, see text and (1). If not at target, mostly commonly 53mmol/mol (7%), move down the algorithm.

1st Line. Metformin is the usual 1st line therapy unless contraindicated or not tolerated.

- **Metformin**
- SU
- DPP-4 inhibitor
- SGLT2 inhibitor
- Insulin #
- Acarbose
- TZD

2nd Line. If metformin was not used 1st line, add it now if not contraindicated.

- SUs are the recommended initial agent to add to metformin.
- If SUs are contra-indicated or not tolerated, another agent is recommended

- **SU**
- **DPP-4 inhibitor**
- **GLP-1 RA**
- **SGLT2 inhibitor**
- **Insulin #**
- **Acarbose**
- **TZD**

3rd Line. Consider triple oral therapy *or* GLP-1R agonist *or* insulin.

- **DPP-4 inhibitor**
- **SU**
- **GLP-1 RA**
- **Insulin #**
- SGLT2 inhibitor
- **Acarbose**
- **TZD**

THEN:

If on triple oral therapy:
Switch ≥1 oral agent to:
GLP-1RA *or* insulin #
or* another oral agent

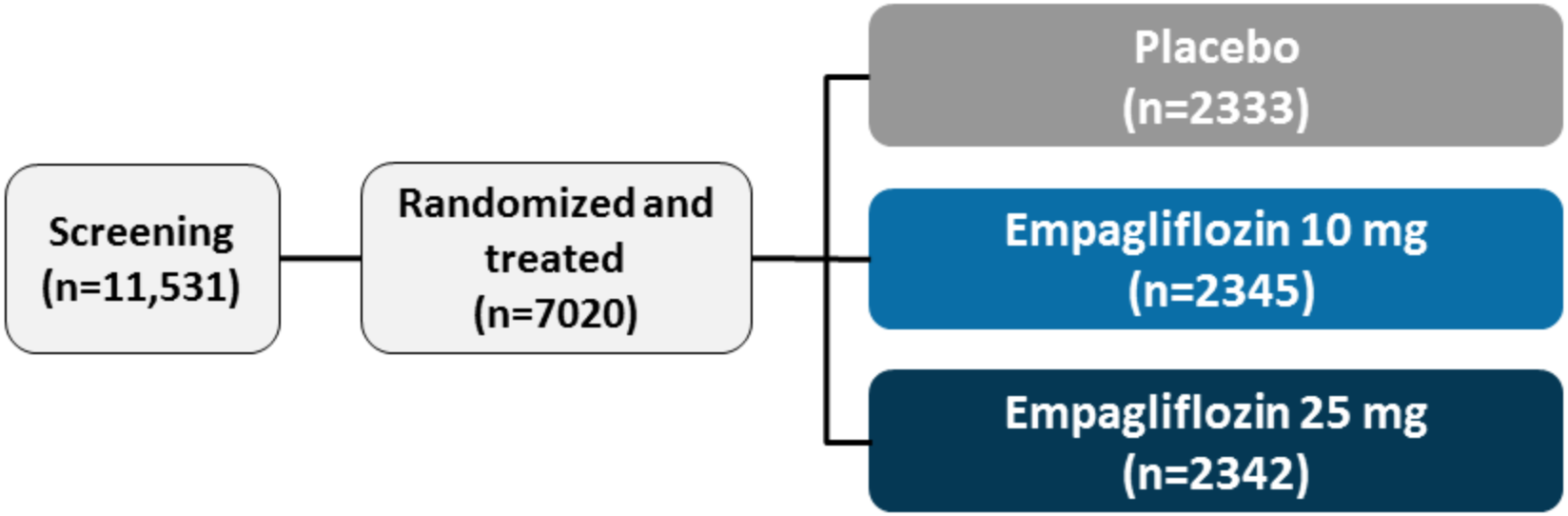
OR

If on a GLP-1RA
Change to: Premixed # *or* Basal insulin #
Add: Basal # *Or* Premixed insulin #

OR

If on insulin #:
Intensify insulin: Basal bolus Insulin *or* Basal plus #

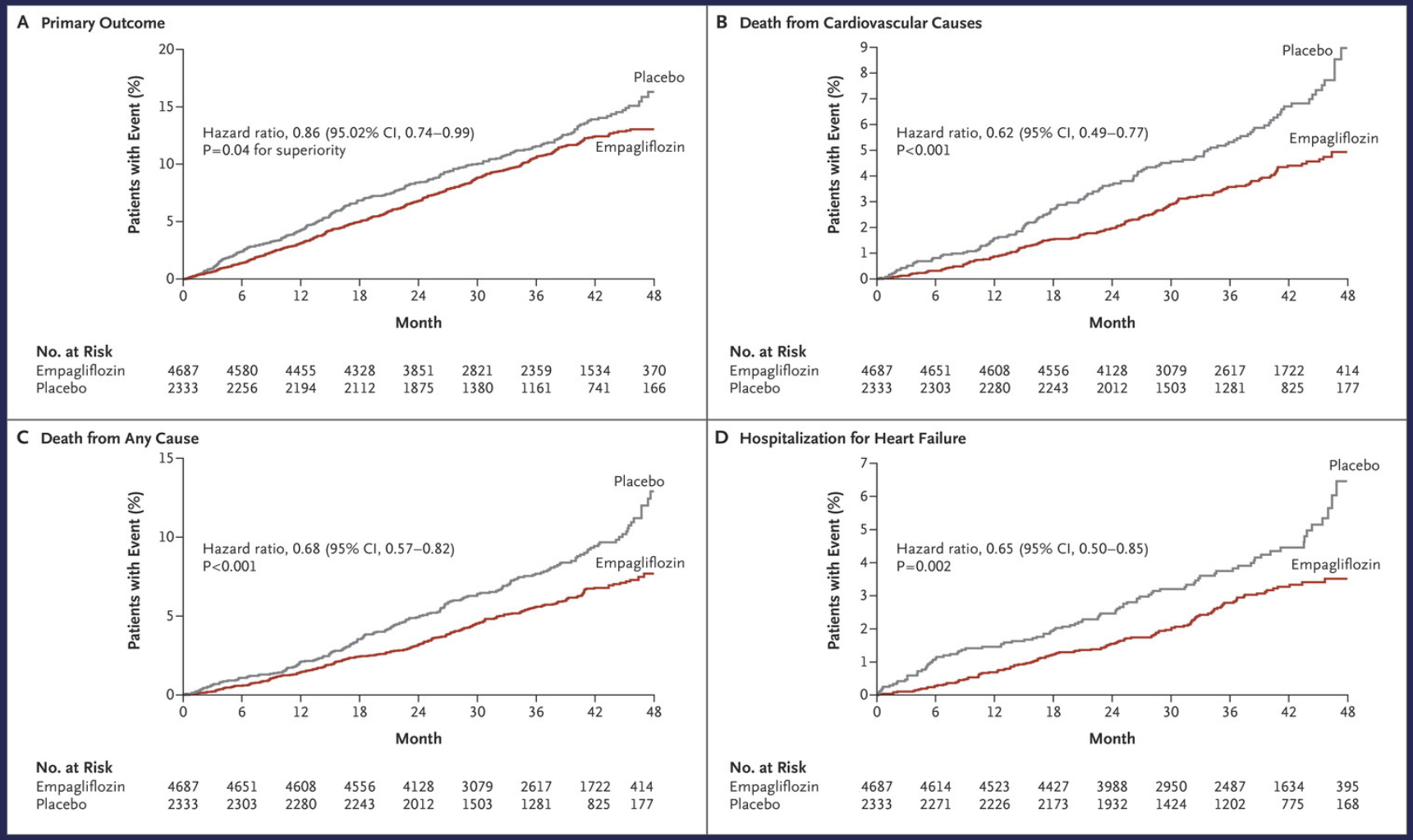
EMPA-REG OUTCOME: Trial Design



- Study medication was given in addition to standard of care
- The trial was to continue until ≥691 patients experienced an adjudicated primary outcome event
- Key inclusion criteria:
  - Adults with T2DM and established CV disease
  - BMI ≤45 kg/m^2; HbA1c 7-9% (drug-naïve subgroup); HbA1c 7–10% (non-drug-naïve subgroup); eGFR ≥30 mL/min/1.73m^2; (MDRD)

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

Cardiovascular Outcomes and Death from Any Cause.



Zinman B et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504720

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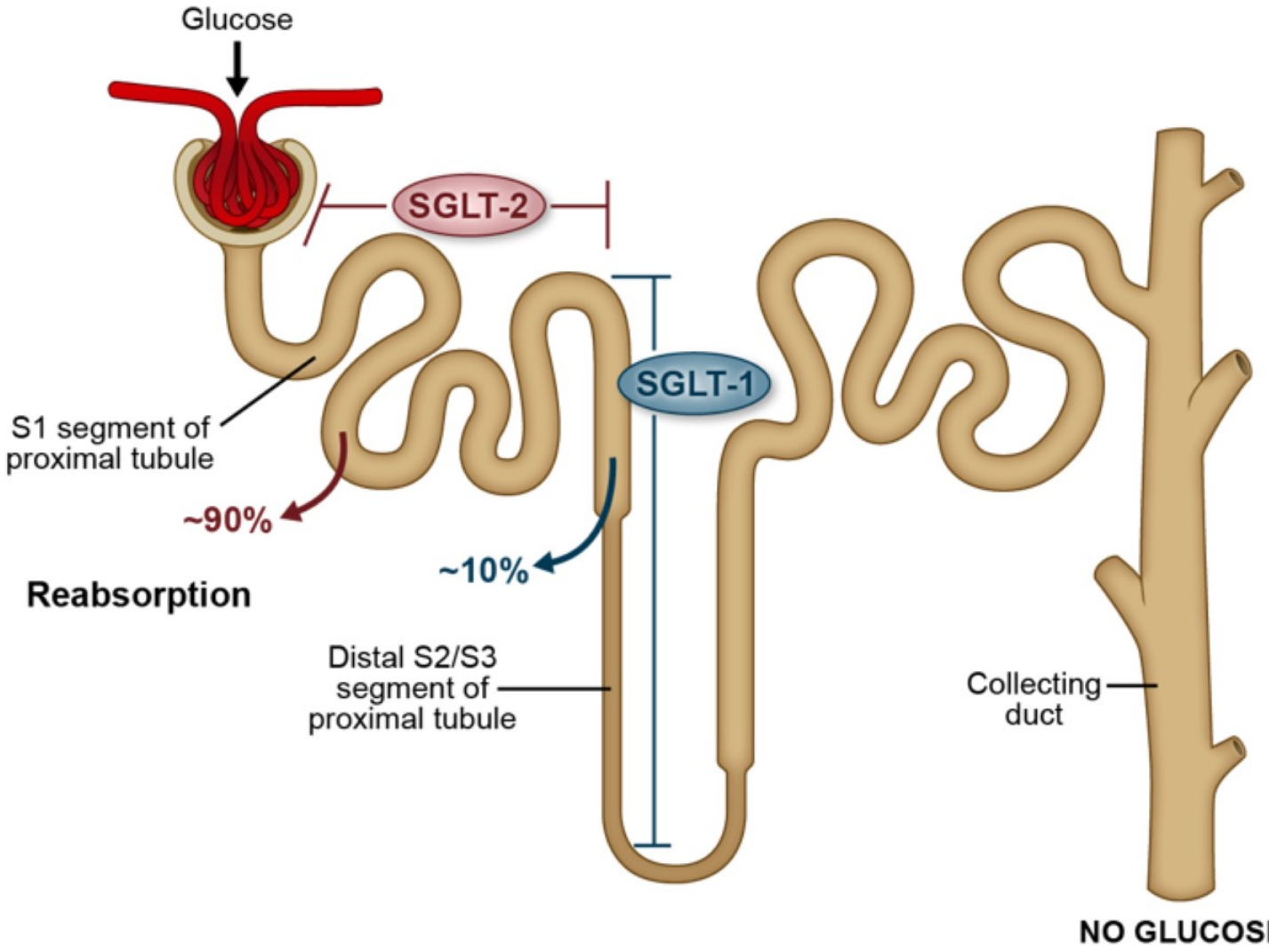
Renal Handling of Glucose



Wright EM, et al. *J Intern Med*. 2007;261:32-43[2]; Kanai Y, et al. *J Clin Invest*. 1994;93:397-404[3]; Wright EM. *Am J Physiol Renal Physiol*. 2001;280:F10-F18.[4]

Altered Renal Glucose Control in T2D

- Renal gluconeogenesis is increased in patients with T2D
  - Renal contribution to hyperglycemia
  - 3-fold increase relative to patients without T2D
- Glucose reabsorption is increased
  - Increased SGLT2 expression and activity in renal epithelial cells from patients with T2D vs normoglycemic individuals

a. Marsenic O. *Am J Kidney Dis*. 2009;53:875-83.[7]; b. Bakris GL, et al. *Kidney Int*. 2009;75:1272-77.[8]; c. Rahmoune H, et al. *Diabetes*. 2005;54:3427-34.[9]

Naturally Occurring Reduction in SGLT2 Function

- Familial renal glucosuria is a rare inherited condition in which SGLT2 lacks activity and is due to mutations in the SGLT2 (*SLC5A2*) gene[a-d]
- The condition is defined by persistent urinary glucose excretion[a,b,d]
- No hyperglycemia or T2D is present[a-d]
- No obvious clinical problems or physiologic compensation despite defect in functional SGLT2[a,b]

a. Santer R, et al. *J Am Soc Neph*. 2003;14:2873-2882[14]; b. Calado J, et al. *Nephrol Dial Transplant*. 2008;23:3874-3879[15]; c. Yu L, et al. *Hum Genet.* 2011;129:335-344[16]; d. Chao EC, Henry RR. *Nat Rev Drug* Discov. 2010;9:551-559.[11]

Rationale for Inhibiting SGLT2 to Manage Hyperglycemia in T2D

- Novel, unique insulin-independent mechanism of action[a]
- Glycemic efficacy anticipated even with worsening β-cell function and insulin resistance[b,c]
- Potential to complement virtually all available antihyperglycemic agents, including insulin[d]
- Low risk of hypoglycemia[d]
- Potential for reduction in supine systolic blood pressure (-2.6 to -6.4 mmHg)[e]
- Negative energy balance due to glucosuria (≈ 200-300 kcal/day) = potential for weight loss[e]

a. Chao EC, et al. *Nat Rev Drug Discov*. 2010;9:551-559[11] ; b. Abdul-Ghani MA, et al. *Endocr Pract.* 2008;14:782-790[10]; c. Marsenic O. *Am J Kidney Dis*. 2009;53:875-883[7] ; d. Basile J. *Postgrad Med*. 2011;123:38-45[12] ; e. List JF, et al. *Diabetes Care*. 2009;32:650-657[13]

FDA-Approved and Investigational SGLT2 Inhibitors

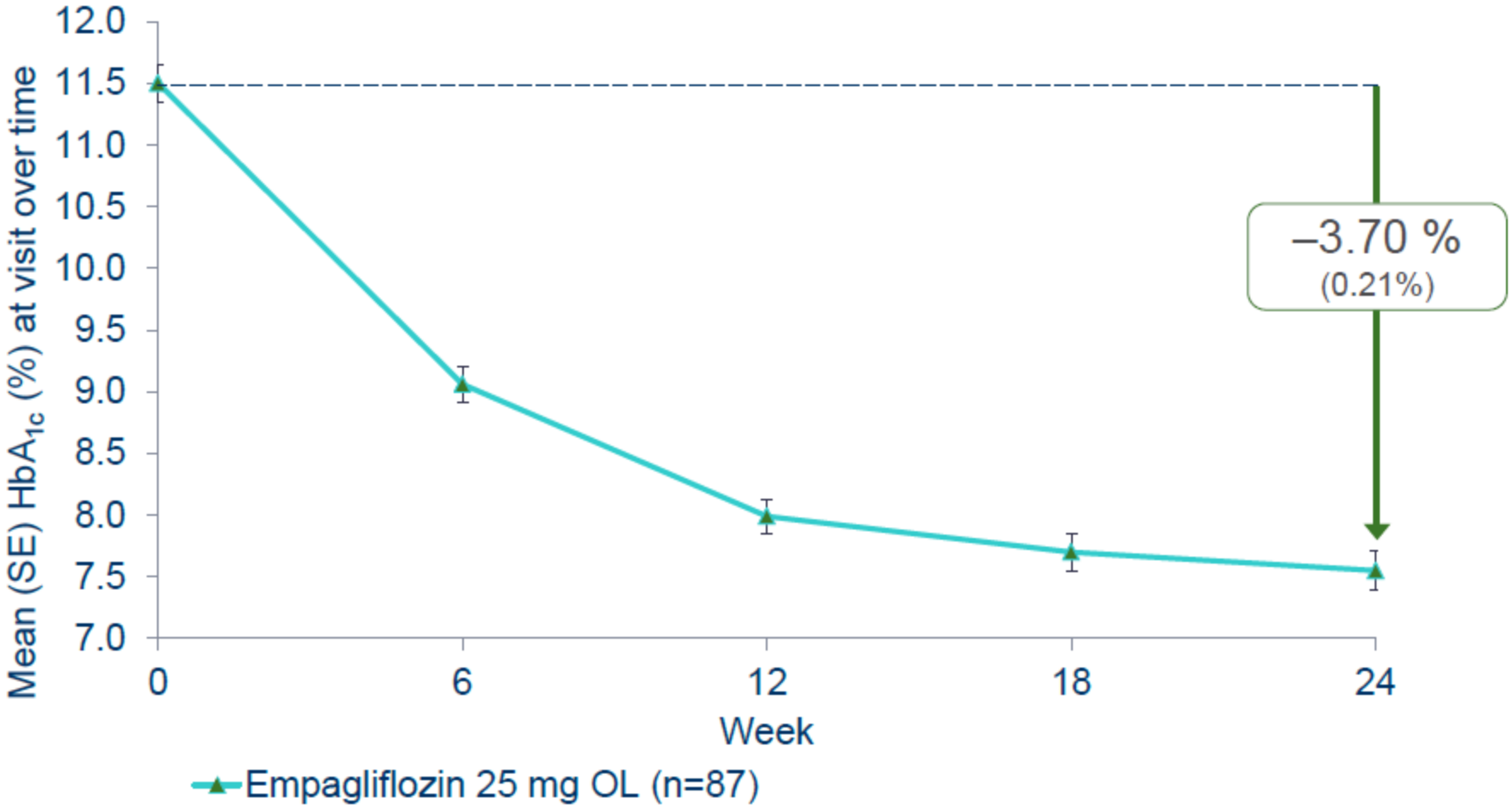
FDA-Approved	Investigational
Canagliflozin	Ertugliflozin*
Dapagliflozin	Ipragliflozin*
Empagliflozin	Luseogliflozin*
	Tofogliflozin*

Limitations include

- **Increased risk for genital mycotic infections**
- **Potential for polyuria**
- **Dose-related increase in LDL-C**
- **Risk for volume depletion/hypotension/dizziness**

*The US FDA has not yet approved this medication for use.

Empagliflozin, baseline A1c > 10% → large A1c falls



EMPA-REG MONO: study 1245.20

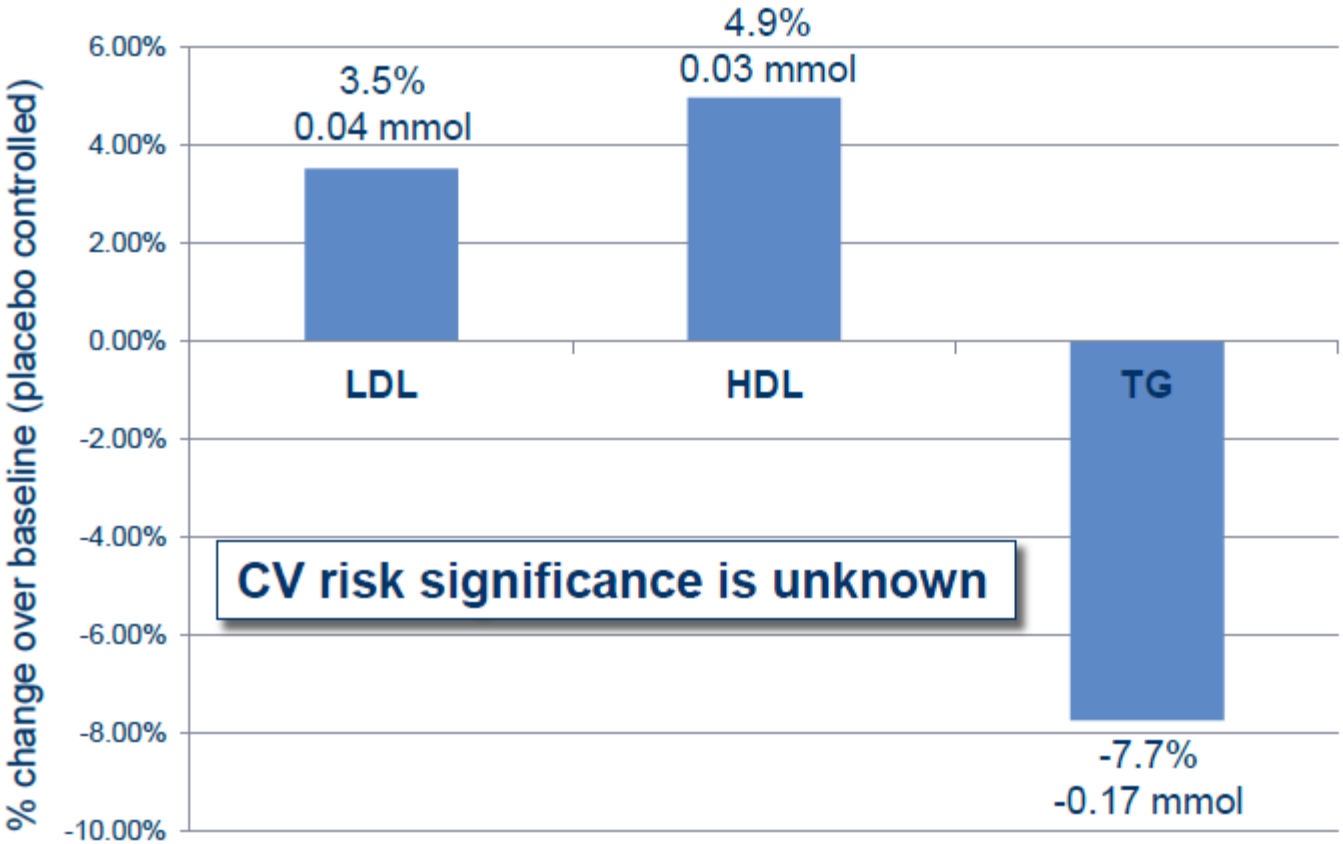
Diabetes Care
hlt797f001

Published online before print June 14, 2014, doi: 10.2337/dc13-3055
Diabetes Care July 2014 vol. 37 no. 7 1815-1823

Improved Glucose Control With Weight Loss, Lower Insulin Doses, and No Increased Hypoglycemia With Empagliflozin Added to Titrated Multiple Daily Injections of Insulin in Obese Inadequately Controlled Type 2 Diabetes

Julio Rosenstock[1,†],
Ante Jelaska[2],
Guillaume Frappin[3],
Afshin Salsali[2],
Gabriel Kim[4],
Hans J. Woerle[4] and
Uli C. Broedl[4]
on behalf of the EMPA-REG MDI Trial Investigators

Small effect on lipids



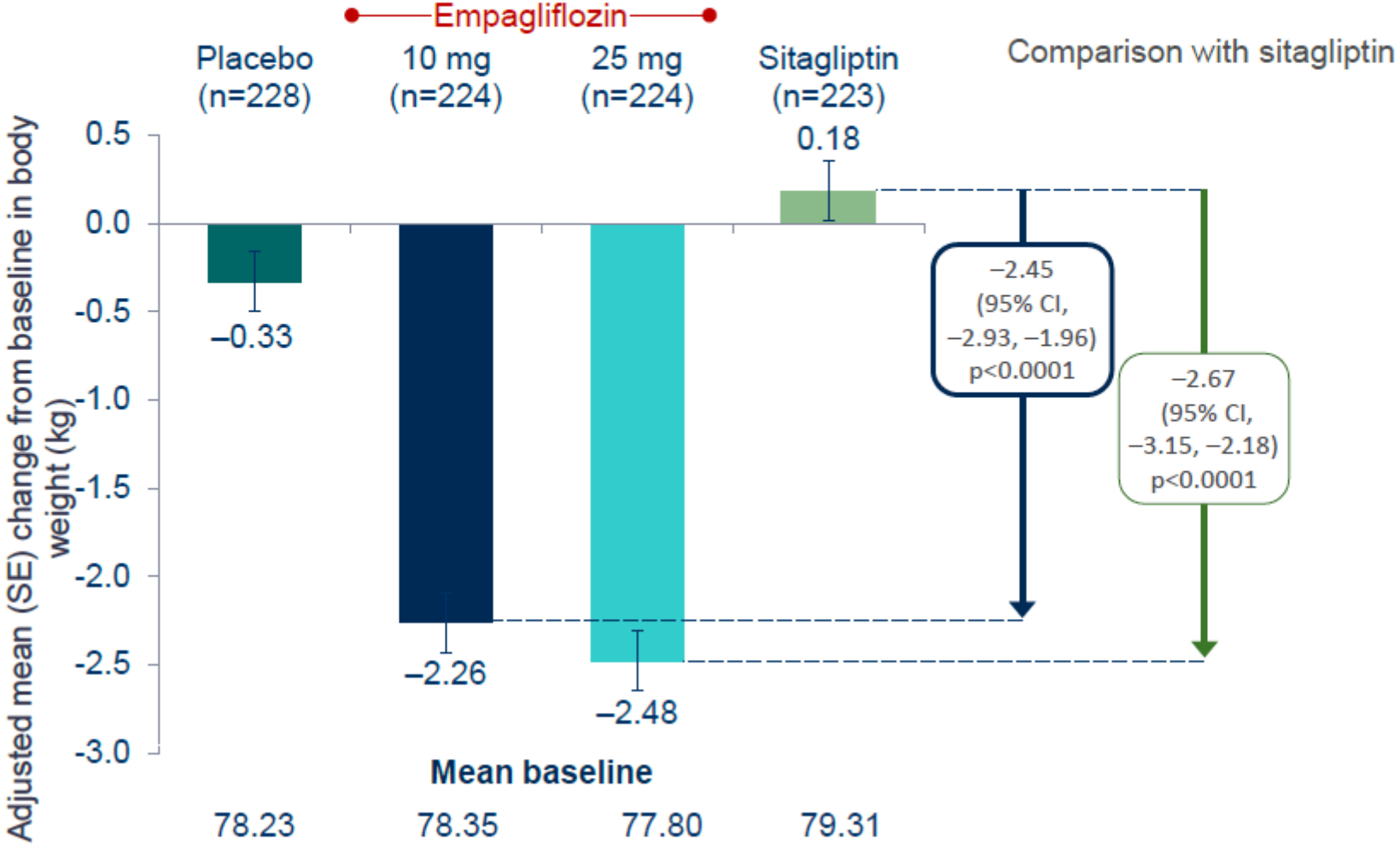
24 week study Empa 10mg vs placebo (young, overweight, baseline A1c >8%)

Blood Pressure lowering

SGLT-2i	Comparator	Systolic BP mmHg	Diastolic BP mmHg	Ref.
Empagliflozin	Placebo	**-4.8***	**-1.9***	1
Dapagliflozin	Placebo	**-2.6***	-0.5	2
Canagliflozin	Placebo	**-5.4***	**-2.0***	3
		*$p < 0.05$		

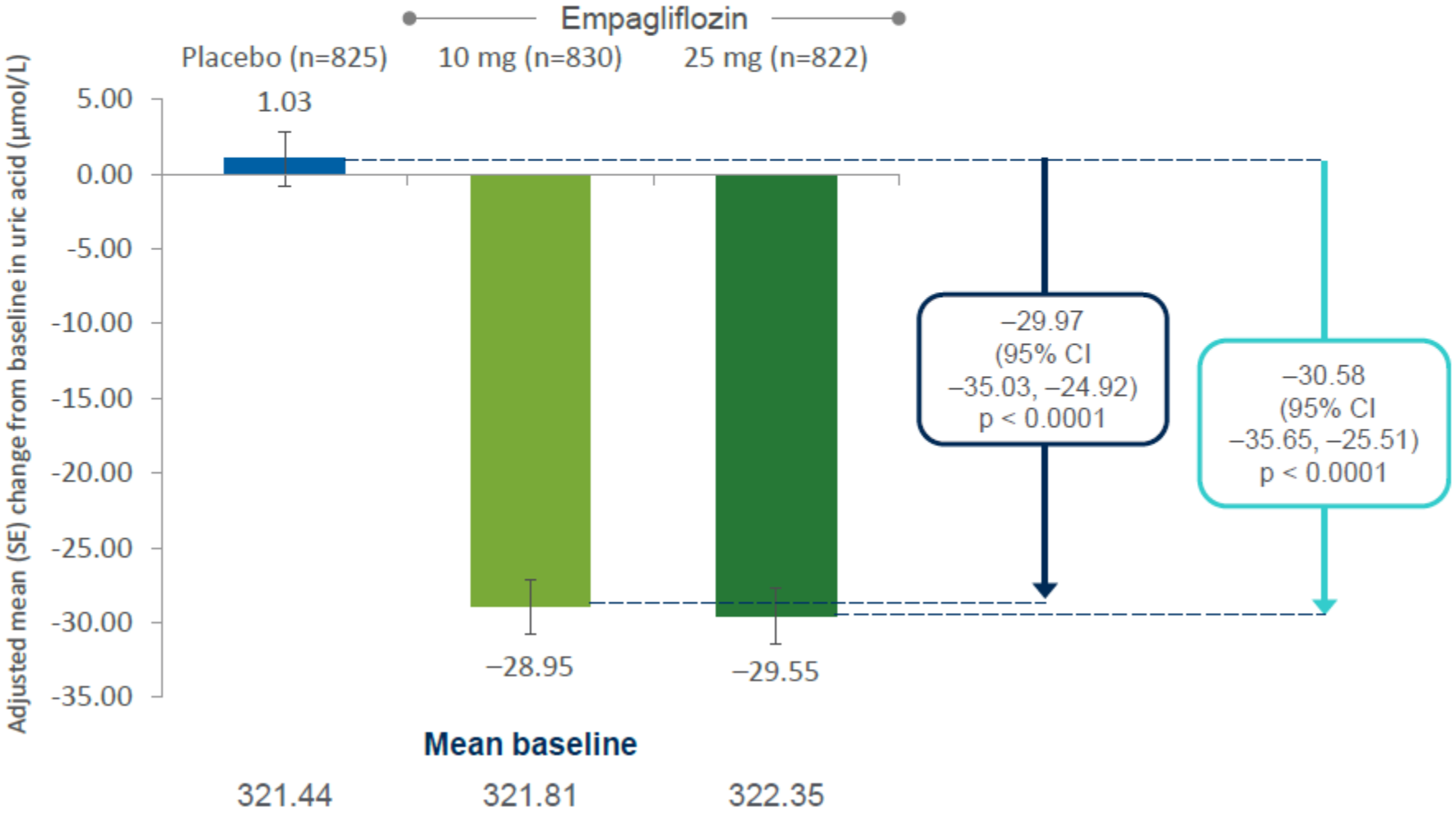
SGLT-2is are not indicated for lowering blood pressure (BP) and BP was not a primary endpoint in clinical trials.

Empagliflozin - Weight loss



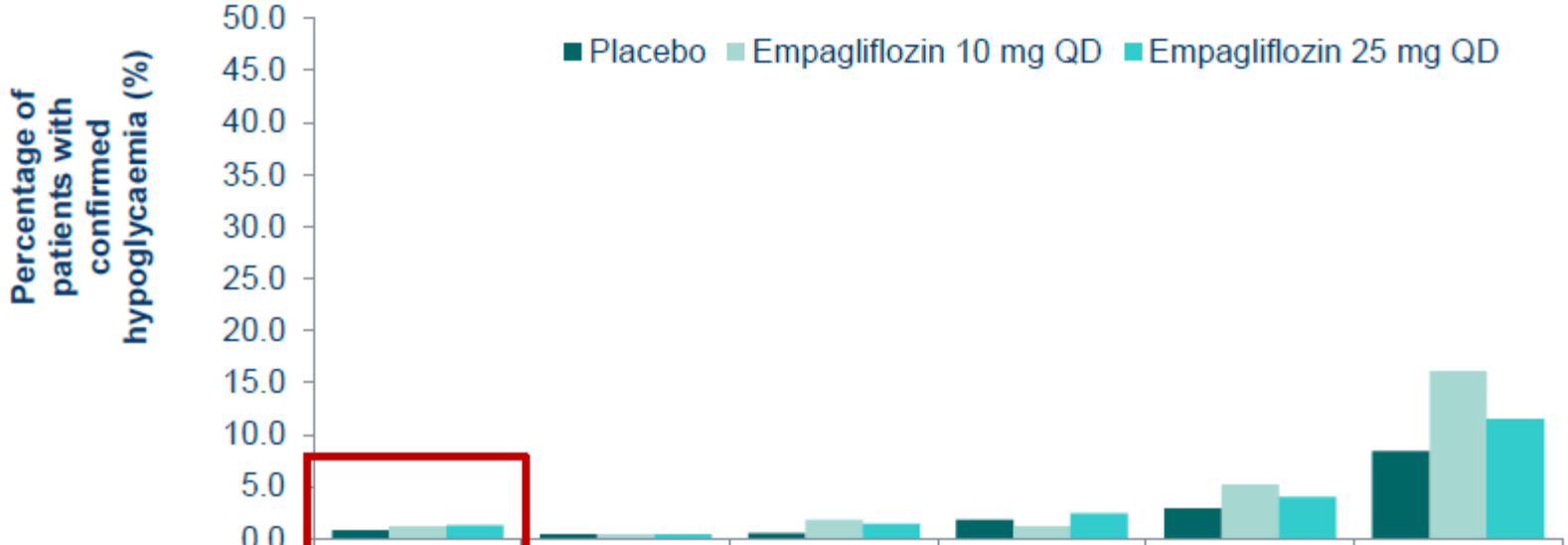
EMPA-REG MONO: study 1245.20

Phase III Empa pooled data – Change from baseline in uric acid



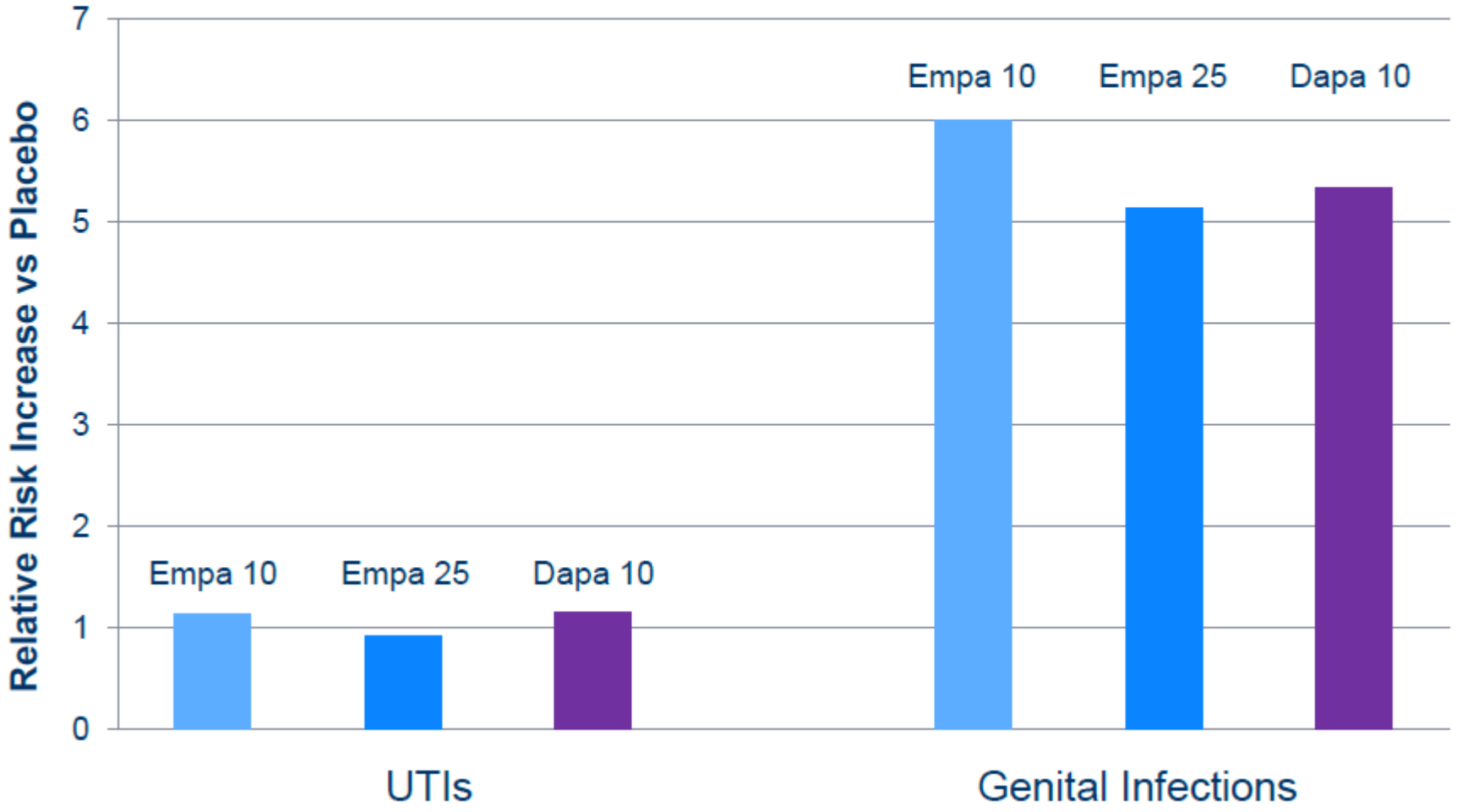
Pooled data from four pivotal Phase III trials

Phase III Empa pooled data: low incidence of hypos if no SU[1,2,3,4]



	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

UTIs and Genital Infections



eGFR restrictions

- Dependent on renal function for action
  - Urinary Glucose Excretion α GFR
  - **Lower GFR = lower SGLT-2i potency**
- Current restriction:
  - **eGFR >45** for **Empa / Cana**
  - **eGFR >60** for **Dapa**

- No known long term-effect on eGFR[1]
  - No increase in microalbuminuria

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

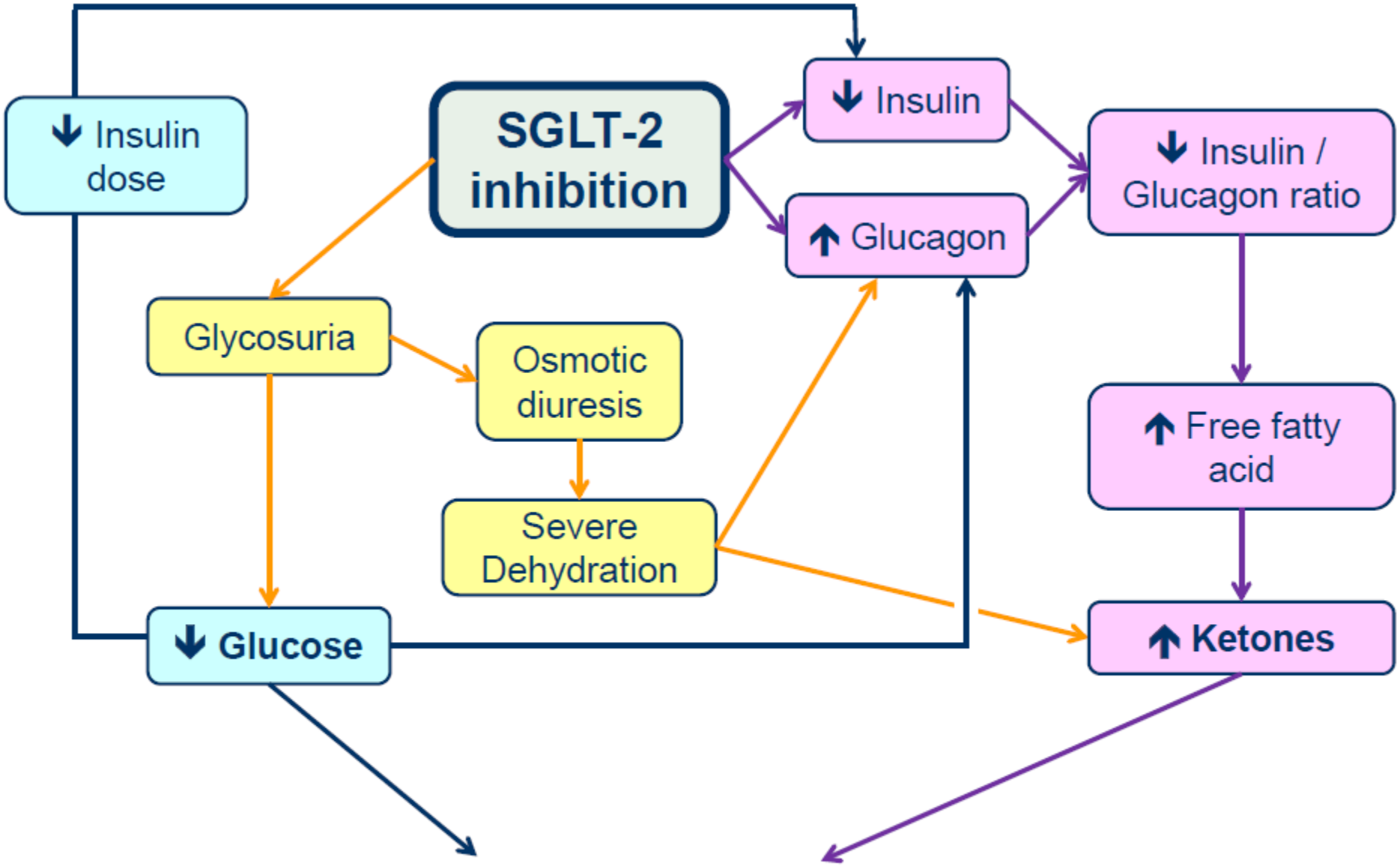
Drug Safety Communications

FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood

15 May 2015

Safety Announcement

- **20 cases DKA**, 2013 – 2014
  - Most T2DM, just a few T1DM, most hospitalised
- **Mean 2 weeks from initiation**
  - Range 1-175 days from initiation
- Almost all cases BGL <11mmol ("*euglycaemic*")
- 50% trigger identified (illness, infection, ↓insulin dose, alcohol)
  - This means 50% no cause identified


↓ Insulin dose
SGLT-2 inhibition
↓ Insulin
↑ Glucagon
↓ Insulin / Glucagon ratio
Glycosuria
Osmotic diuresis
Severe Dehydration
↑ Free fatty acid
↓ Glucose
↑ Ketones
Euglycaemic Ketoacidosis

EMPA –REG - Lessons and Cautions

- 1. Empagliflozin 10 or 25mg daily provided major rapid reduction in CV and all cause mortality and heart failure hospitalisation compared to standard therapy not including empagliflozin in type 2 diabetic patients with established CV disease.
- 2. NNT over 3 years to prevent 1 death = 39
- 3. May or may not be class effect . CV outcome study results for canagliflozin (CANVAS) expected 2017 and dapagliflozin (DECLARE) 2019
- 4. Longer term effects are as yet unknown
- 5. Empagliflozin was well tolerated other than genital infections. No increase in serious UTI , DKA , fractures ,dehydration or acute kidney injury
- 6. This is a secondary prevention study – may or may not apply to patients without established CV disease

EMPA-REG – Putative Mechanisms

- 1. Glycaemia , insulin
- 2. BP , lipids
- 3. Weight ,visceral adiposity
- 4. Urate
- 5. Vascular stiffness
- 6. Intrarenal effects
- 7. Sympathetic outflow
- 8. Oxidative stress

Diabetes Care
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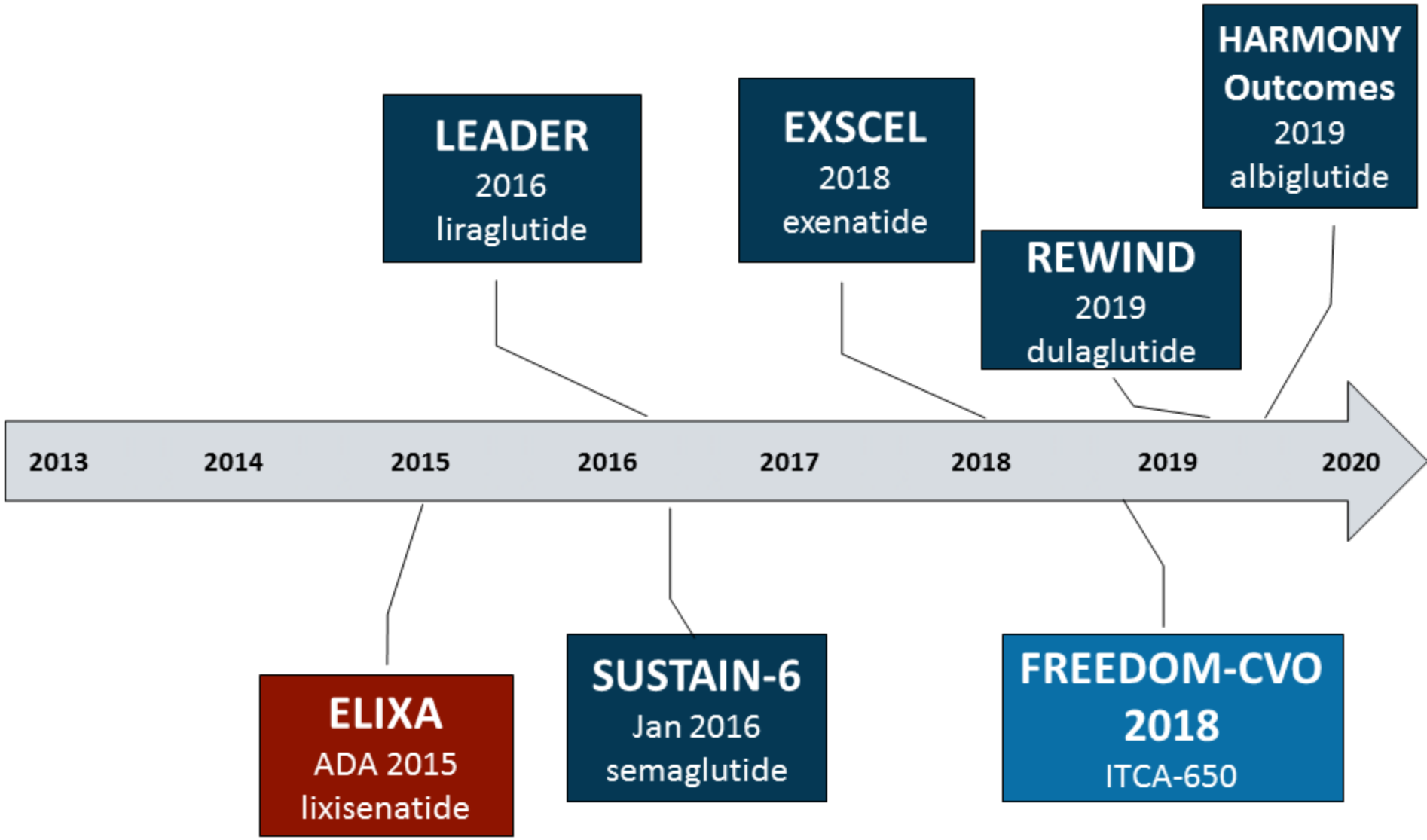
10.2337/dc13-2955
Diabetes Care September 30, 2014

Exploring the Potential of the SGLT2 Inhibitor Dapagliflozin in Type 1 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

Robert R. Henry[1,2],
Julio Rosenstock[3],
Steven Edelman[1,2],
Sunder Mudaliar[1,2],
Alexandros-Georgios Chalamandaris[4],
Sreeneeranj Kasichayanula[5],
Allyson Bogle[5],
Nayyar Iqbal[5],
James List[5] and
Steven C. Griffen[5]

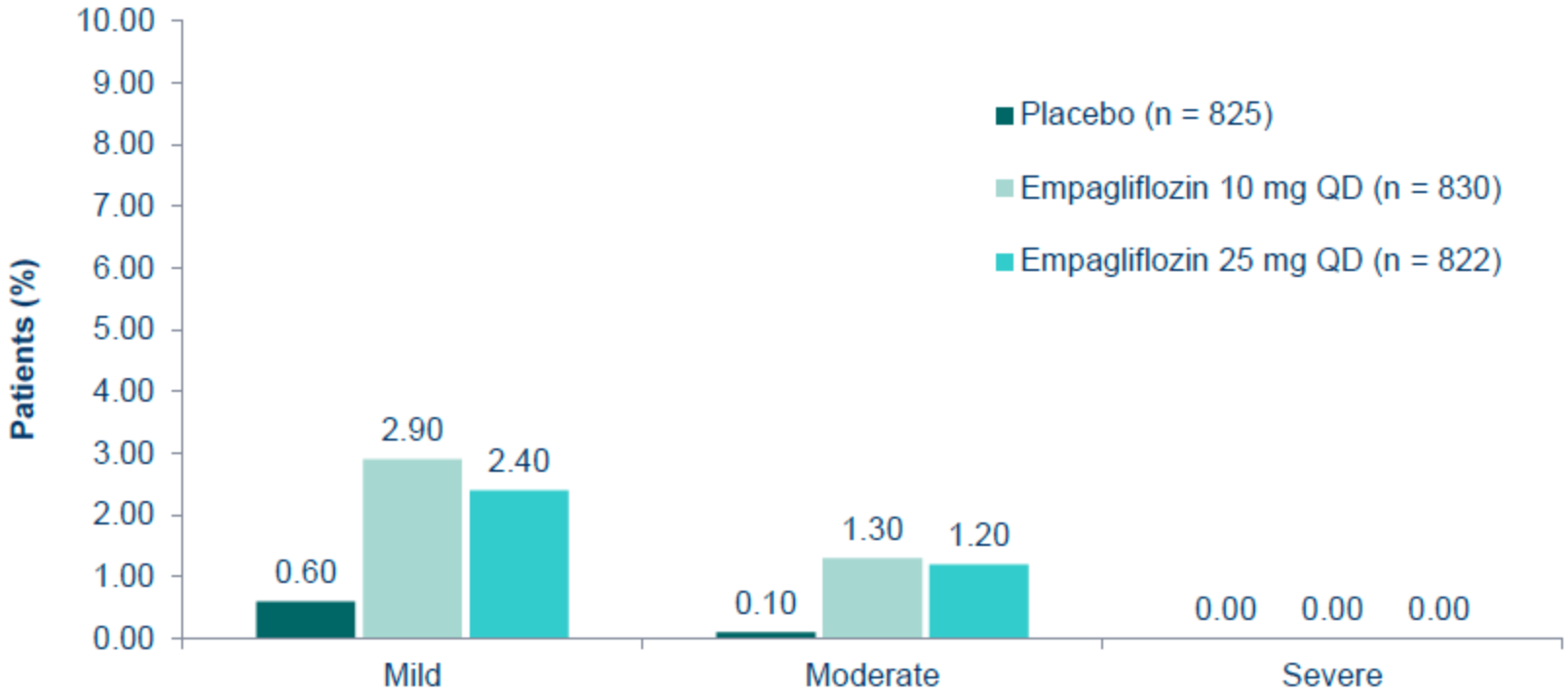
Timeline of Future GLP-1 RA CV Outcome Trials



ClinicalTrials.gov

QUESTIONS?

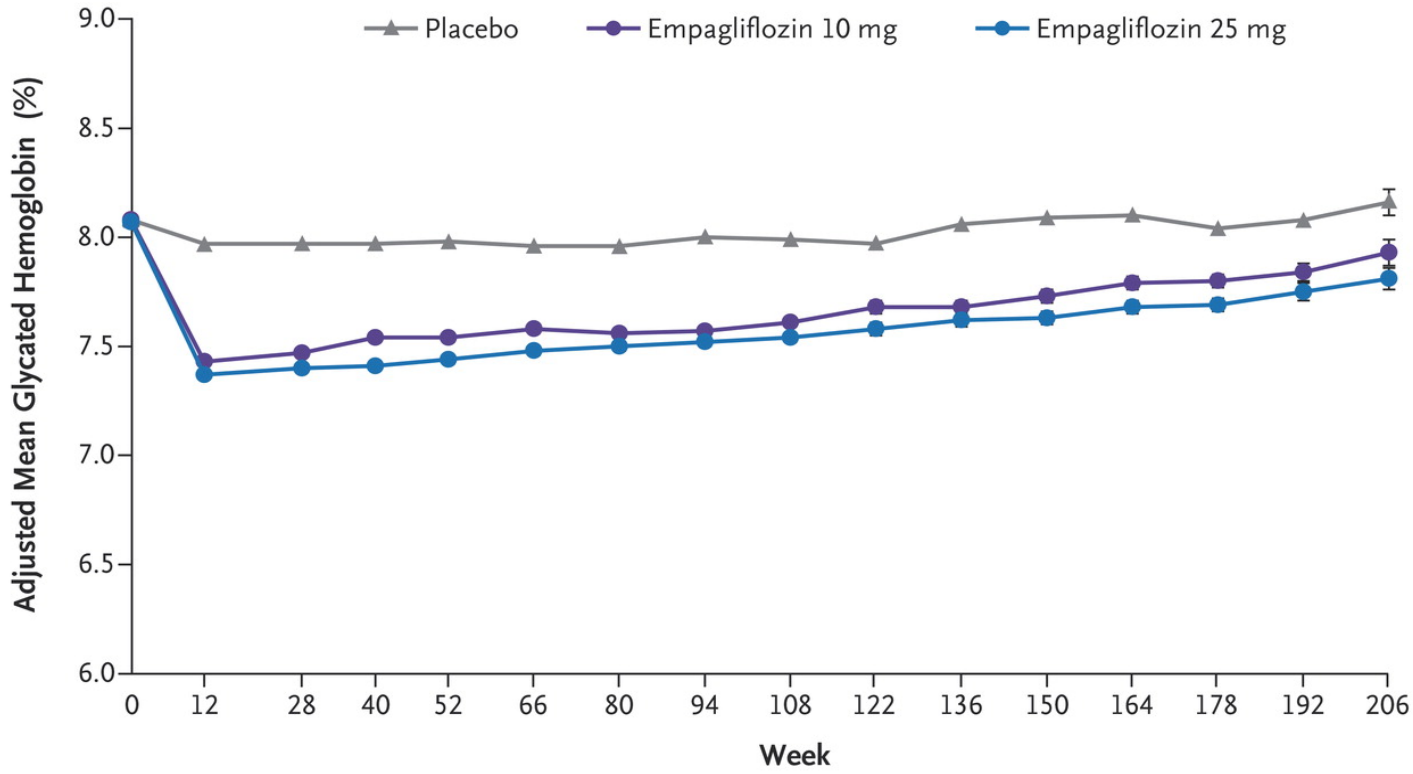
Phase III pooled analysis
Genital infection events



- 98% **mild-moderate** in severity
- Easily treated with **standard therapy**
- Almost all **single episodes**

Pooled data from 4 pivotal Phase III trials

Glycated Hemoglobin Levels.



No. at Risk

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

Zinman B et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504720

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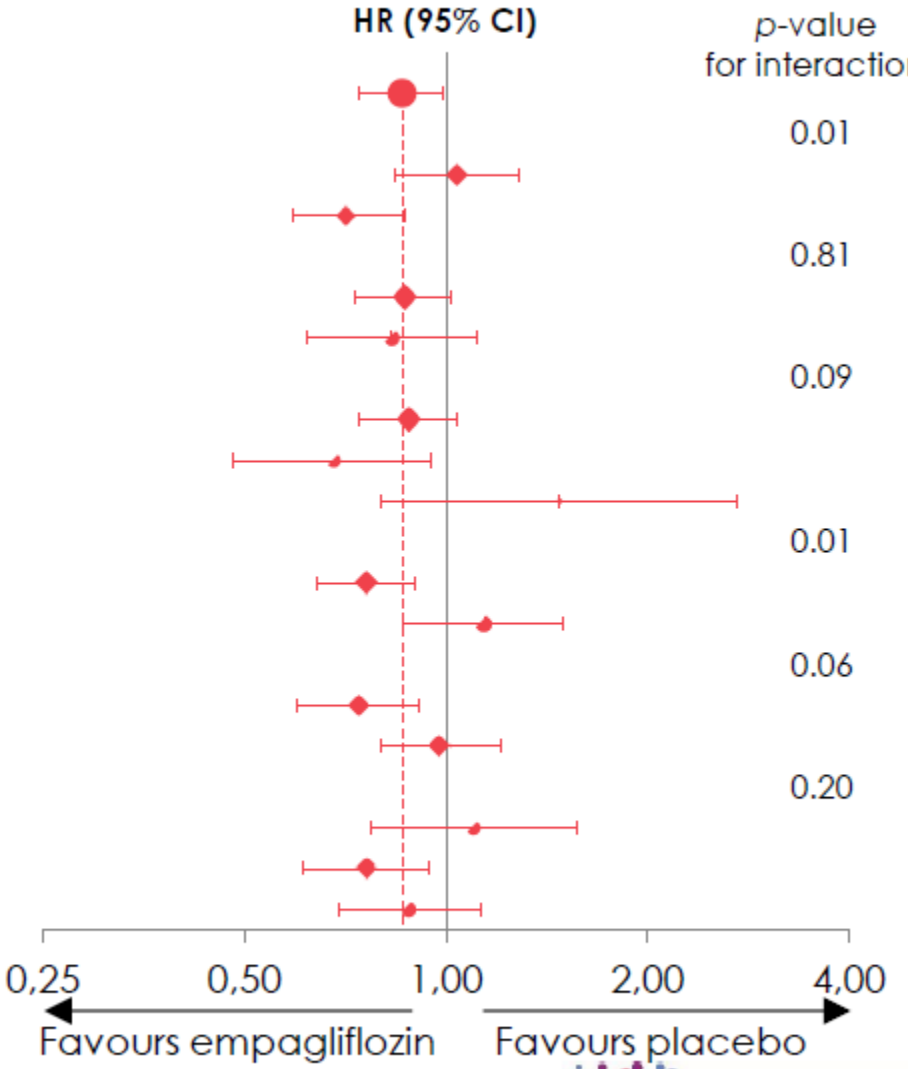
3-point MACE: subgroup analysis

	Empagliflozin	Placebo
All patients	4687	2333
Age, years		
<65	2596	1297
≥65	2091	1036
Sex		
Male	3336	1680
Female	1351	653
Race		
White	3403	1678
Asian	1006	511
Black/African-American	237	120
HbA1c, %		
<8.5	3212	1607
≥8.5	1475	726
Body mass index, kg/m^2		
<30	2279	1120
≥30	2408	1213
eGFR, mL/min/1.73m^2		
≥90	1050	488
60 to <90	2425	1238
<60	1212	607



For the test of homogeneity of the treatment group difference among subgroups with no adjustment for multiple tests. eGFR, estimated glomerular filtration rate (according to Modification of Diet in Renal Disease equation)

EMPA-REG OUTCOME®

EMPA-REG - EASD Stockholm Sept 2015

- 7020 adult type 2DM patients with established CV disease
- BMI<45, HbA1C 7-10% , eGFR >30
- Empagliflozin 10 or 25 mg v placebo in combination with optimal standard care
- Outcome CV morbidity and mortality
- Excellent retention , follow-up and reasonable baseline care

Historical Selective Targeting (Phlorizin)

- 1835, French chemists isolated phlorizin, from bark of apple trees
- Early 1970s, research with phlorizin revealed location (proximal tubule brush border) of active-transport system responsible for glucose reabsorption and also that phlorizin had a much higher affinity for these transporters than did glucose
- Phlorizin pursued as an antihyperglycemic medication
  - Poorly absorbed from the GI tract and inhibits SGLT1 (primarily found in the GI tract) and SGLT2
- Thus, not well studied in humans

Ehrenkranz JR, et al. *Diabetes Metab Res Rev*. 2005;21:313-318.[17]

SGLT2 Inhibitors – How Sweet it is!

Steve Stranks

RGH Grand Round

Oct 2 2015

Adverse Events.

Table 2. Adverse Events.*

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)

* Data are for patients who had one or more event and who had received at least one dose of a study drug. All events occurred within 7 days after the last receipt of the study drug.
† P<0.001 for the comparison with placebo.
‡ P<0.05 for the comparison with placebo.
§ P<0.01 for the comparison with placebo.
¶ A confirmed hypoglycemic adverse event was a plasma glucose level of less than 70 mg per deciliter (3.9 mmol per liter) or an event requiring assistance.
‖ The definition of urinary tract infection was based on 79 preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA). Percentages were calculated as the proportions of all men and all women with the event.
** Complicated urinary tract infection was defined as pyelonephritis, urosepsis, or a serious adverse event consistent with urinary tract infection. A breakdown of such events according to MedDRA preferred terms is provided in Table S13 in Section R in the Supplementary Appendix.
†† The definition of genital infection was based on 88 MedDRA preferred terms. Percentages were calculated as the proportions of all men and all women with the event.
‡‡ The definition of volume depletion was based on 8 MedDRA preferred terms.
§§ The definitions of acute renal failure and thromboembolic event were based on 1 standardized MedDRA query for each.
¶¶ The definition of ketoacidosis was based on 4 MedDRA preferred terms.
‖‖ The definition of bone fracture was based on 62 MedDRA preferred terms.

Zinman B et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504720

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Patient Education Pointers

SGLT2 Inhibitors

Consideration	Patient Education Pointers
Use with other medications	Take once daily All medicines that reduce blood glucose levels can cause hypoglycemia, but SGLT2 inhibitors are unlikely to cause hypoglycemia unless they are used with sulfonylureas or insulin
Dehydration and hypotension	Dehydration may increase the risk for hypotension Maintain adequate fluid intake
Adverse effects	Most common adverse effects (5% or greater incidence) for all agents in this class were female genital mycotic infections, UTIs, increased urination, and nasopharyngitis

Encourage patients to read the Medication Guide with every prescription refill

INVOKANA® PI 2015[22]; FARXIGA® PI 2015[23]; JARDIANCE® PI 2015.[24]

Greater Dose-Ranging Effects on A1C Levels Than on Glucosuria With LX4211, a Dual Inhibitor of Sodium Glucose Transporters SGLT1 and SGLT2, in Type 2 Diabetes on Metformin Monotherapy

Julio Rosenstock,[1] William T. Cefalu,[2] Pablo Lapuerta,[3] Brian Zambrowicz,[3] Ike Ogbaa,[3] Phillip Banks,[3] and Arthur Sands[3]

Diabetes Care 2014;37:1–8 | DOI: 10.2337/dc14-0890

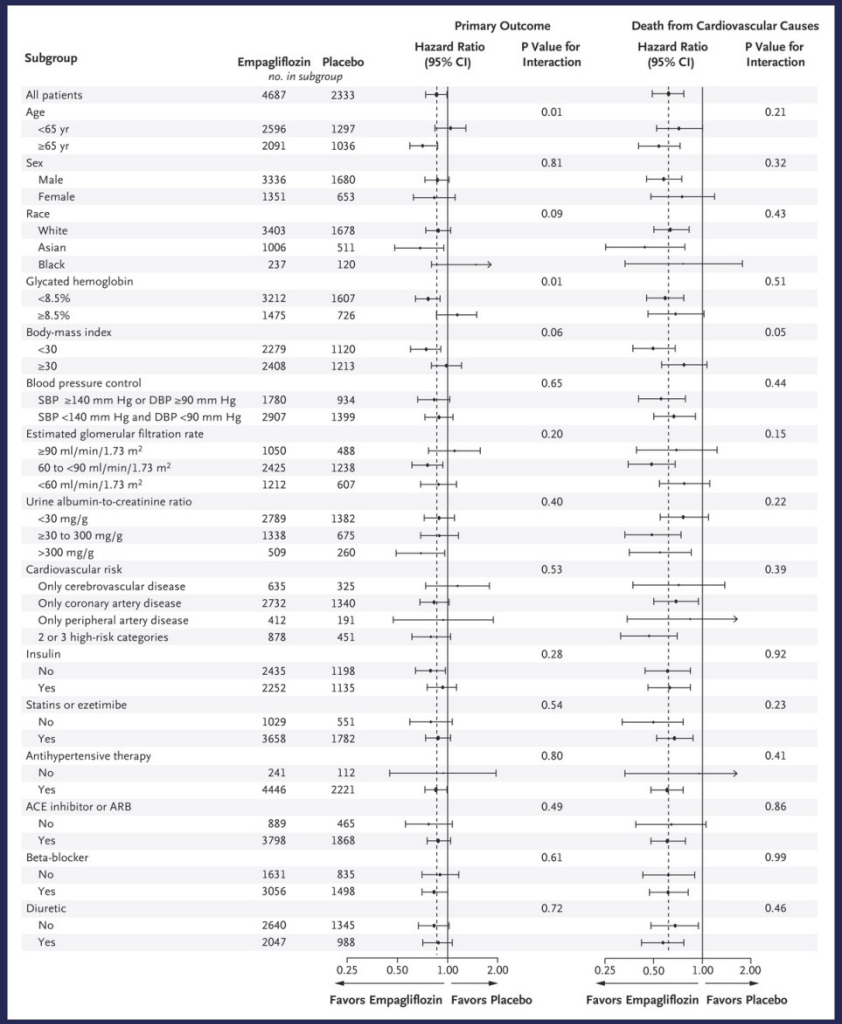
Prescribing Information for SGLT2 Inhibitors

SGLT2 Inhibitor	eGFR
Canagliflozin[a]	Limit to 100 mg if eGFR 45 to 60 mL/min/1.73 m^2; do not use if eGFR < 45 mL/min/1.73 m^2
Dapagliflozin[b]	Do not use if eGFR < 60 mL/min/1.73 m^2
Empagliflozin[c]	Do not use if eGFR < 45 mL/min/1.73 m^2

- Assess kidney function and volume status
- Dapagliflozin: imbalance of bladder cancer
- Canagliflozin: hyperkalemia; increases in digoxin levels
- Empagliflozin: diuretics may enhance volume depletion

a. INVOKANA® PI 2015[22]; b. FARXIGA® PI 2015[23]; c. JARDIANCE® PI 2015.[24]

Subgroup Analyses for the Primary Outcome and Death from Cardiovascular Causes.



Subgroup	Empagliflozin	Placebo	Primary Outcome: Hazard Ratio (95% CI)	Primary Outcome: P Value for Interaction	Death from Cardiovascular Causes: Hazard Ratio (95% CI)	Death from Cardiovascular Causes: P Value for Interaction
	no. in subgroup					
All patients	4687	2333				
Age				0.01		0.21
<65 yr	2596	1297				
≥65 yr	2091	1036				
Sex				0.81		0.32
Male	3336	1680				
Female	1351	653				
Race				0.09		0.43
White	3403	1678				
Asian	1006	511				
Black	237	120				
Glycated hemoglobin				0.01		0.51
<8.5%	3212	1607				
≥8.5%	1475	726				
Body-mass index				0.06		0.05
<30	2279	1120				
≥30	2408	1213				
Blood pressure control				0.65		0.44
SBP ≥140 mm Hg or DBP ≥90 mm Hg	1780	934				
SBP <140 mm Hg and DBP <90 mm Hg	2907	1399				
Estimated glomerular filtration rate				0.20		0.15
≥90 ml/min/1.73 m²	1050	488				
60 to <90 ml/min/1.73 m²	2425	1238				
<60 ml/min/1.73 m²	1212	607				
Urine albumin-to-creatinine ratio				0.40		0.22
<30 mg/g	2789	1382				
≥30 to 300 mg/g	1338	675				
>300 mg/g	509	260				
Cardiovascular risk				0.53		0.39
Only cerebrovascular disease	635	325				
Only coronary artery disease	2732	1340				
Only peripheral artery disease	412	191				
2 or 3 high-risk categories	878	451				
Insulin				0.28		0.92
No	2435	1198				
Yes	2252	1135				
Statins or ezetimibe				0.54		0.23
No	1029	551				
Yes	3658	1782				
Antihypertensive therapy				0.80		0.41
No	241	112				
Yes	4446	2221				
ACE inhibitor or ARB				0.49		0.86
No	889	465				
Yes	3798	1868				
Beta-blocker				0.61		0.99
No	1631	835				
Yes	3056	1498				
Diuretic				0.72		0.46
No	2640	1345				
Yes	2047	988				

Zinman B et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504720

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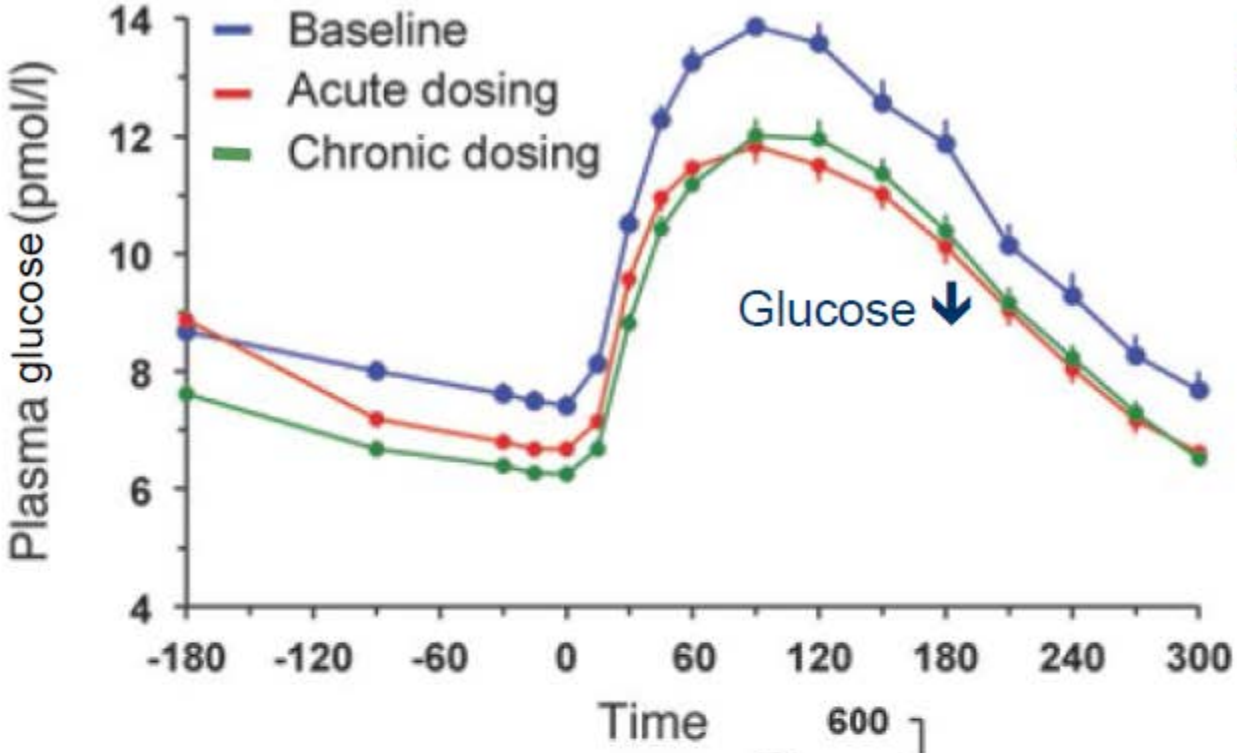
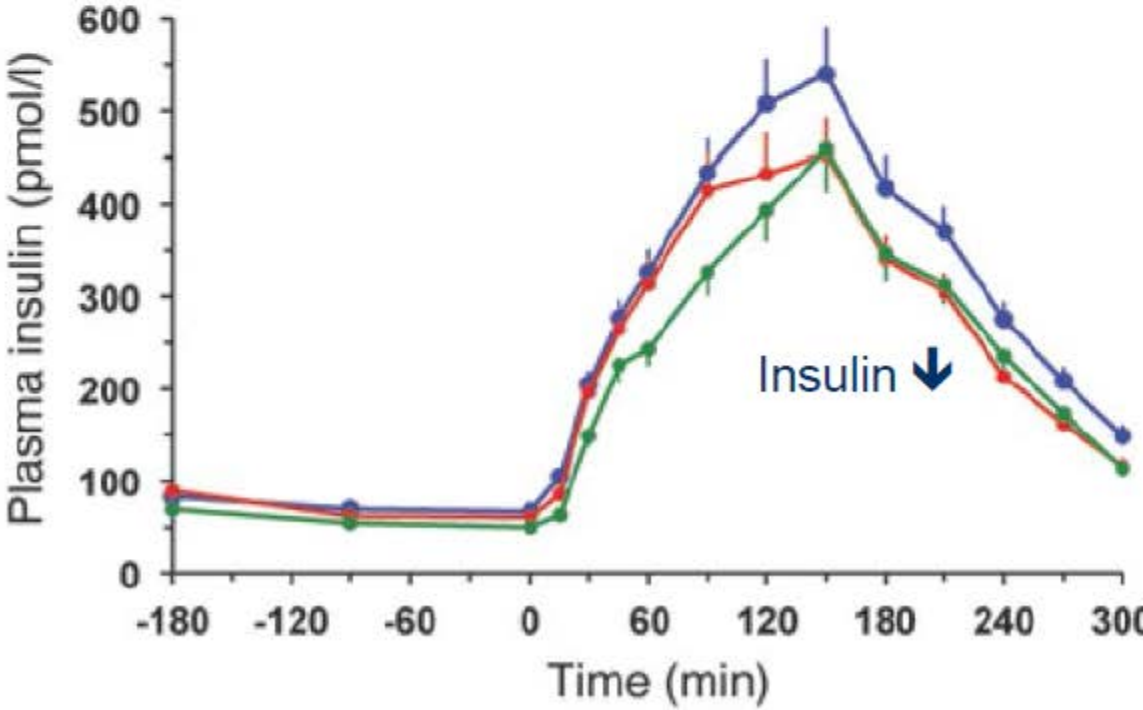
But how would SGLT-2i cause euglycaemic DKA?

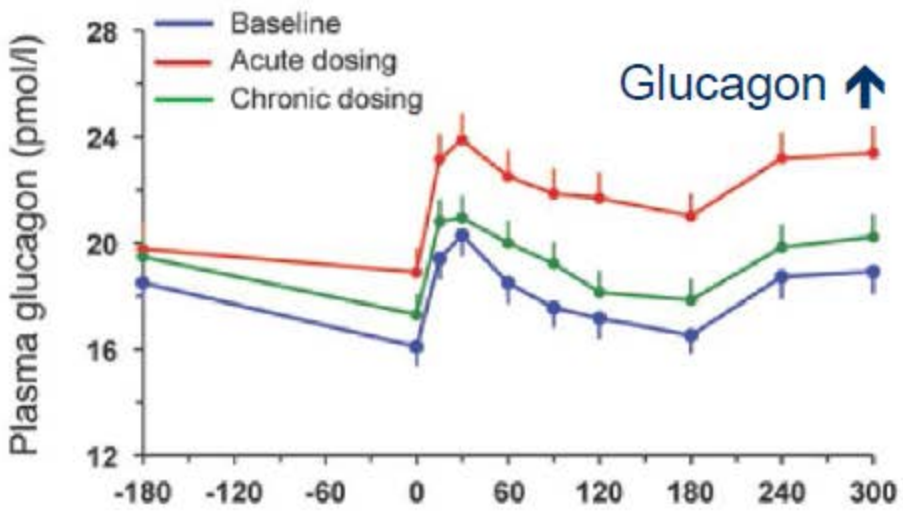
- 2 articles from **Feb 2014** hold the key
- **Journal of Clinical Investigation**
  - Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. **Ele Ferrannini** et al 2014;124(2):499–508
  - Dapagliflozin improves muscle insulin sensitivity but enhances endogenous glucose production. Aurora Merovci, **Ralph DeFronzo** et al 2014;124(2):509–514

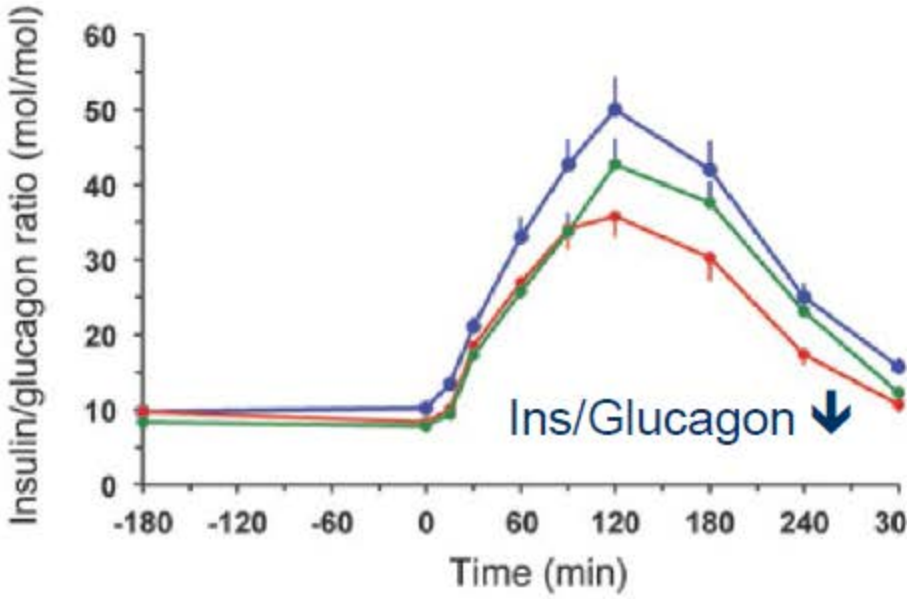


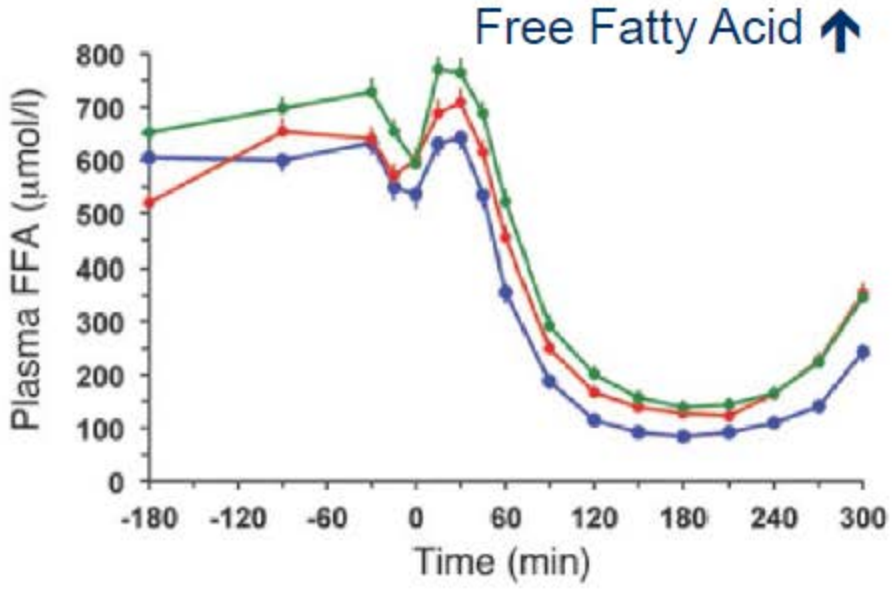
Acute = 1 single dose
Chronic = 4 weeks of empagliflozin

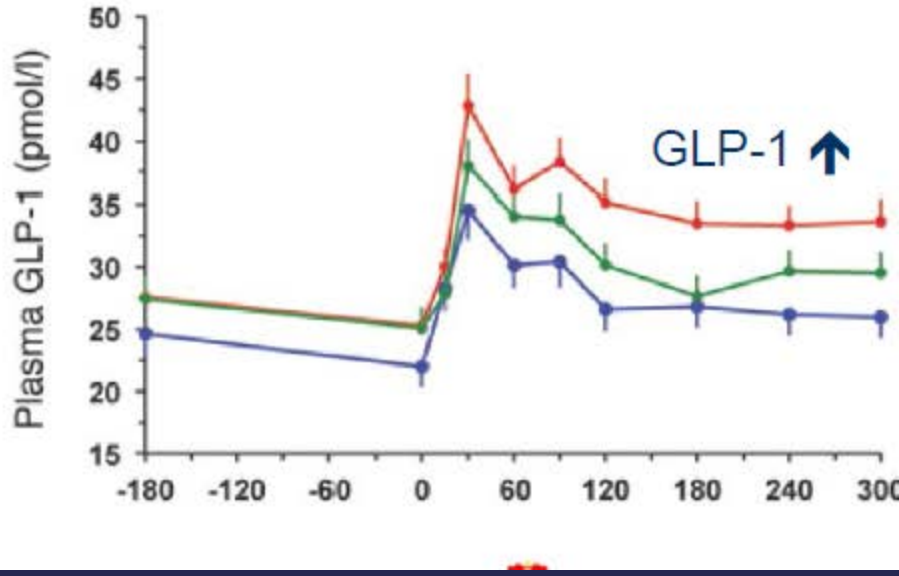


Ele Ferrannini et al, JCI, 2014;124(2):499–508

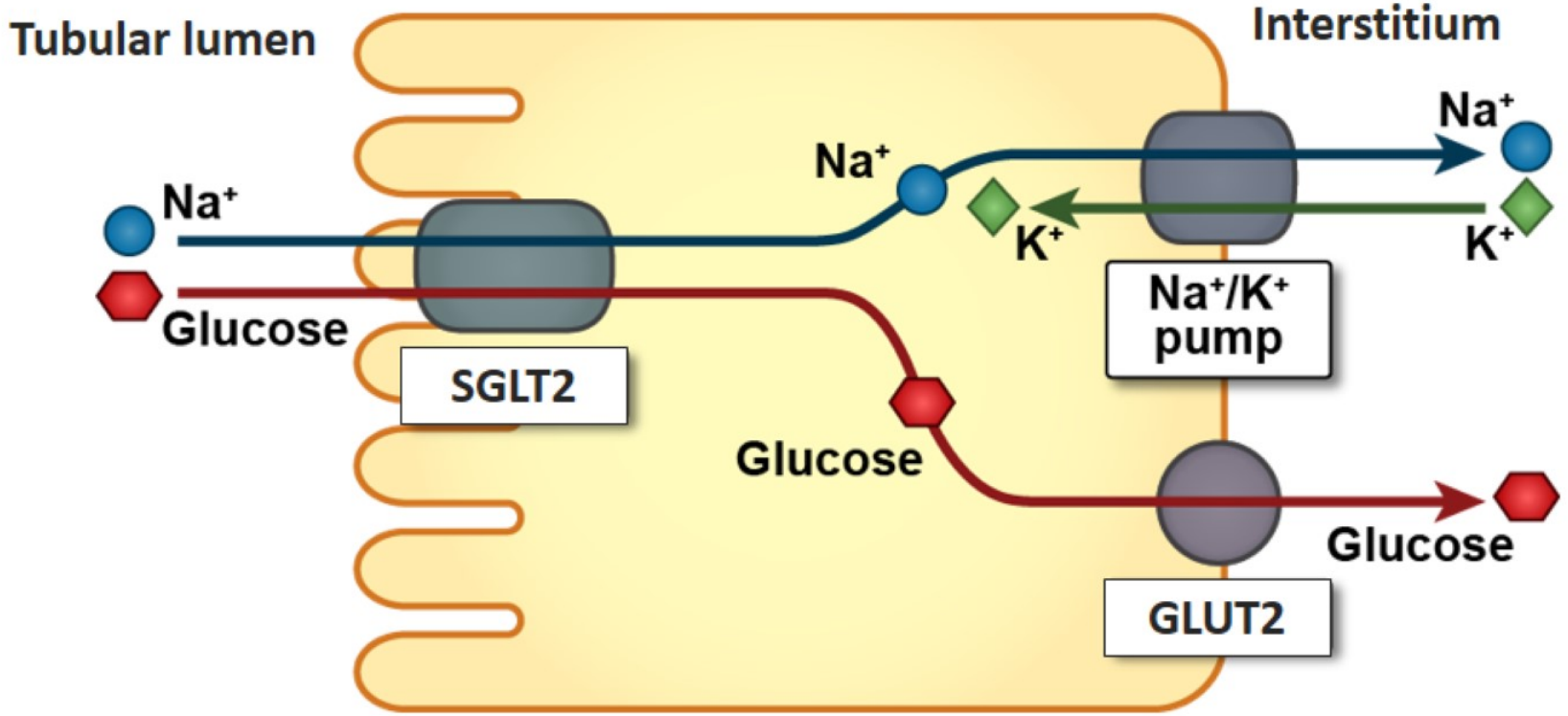

Baseline
Acute dosing
Chronic dosing
Glucagon ↑
Plasma glucagon (pmol/l)
28
24
20
16
12
-180 -120 -60 0 60 120 180 240 300


Ins/Glucagon ↓
Insulin/glucagon ratio (mol/mol)
60
50
40
30
20
10
0
-180 -120 -60 0 60 120 180 240 30
Time (min)


Free Fatty Acid ↑
Plasma FFA (µmol/l)
800
700
600
500
400
300
200
100
0
-180 -120 -60 0 60 120 180 240 300
Time (min)


GLP-1 ↑
Plasma GLP-1 (pmol/l)
50
45
40
35
30
25
20
15
-180 -120 -60 0 60 120 180 240 300

Active (SGLT2) and Passive (GLUT2) Glucose Transport in a Renal Proximal Tubule Cell



Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42.[6]

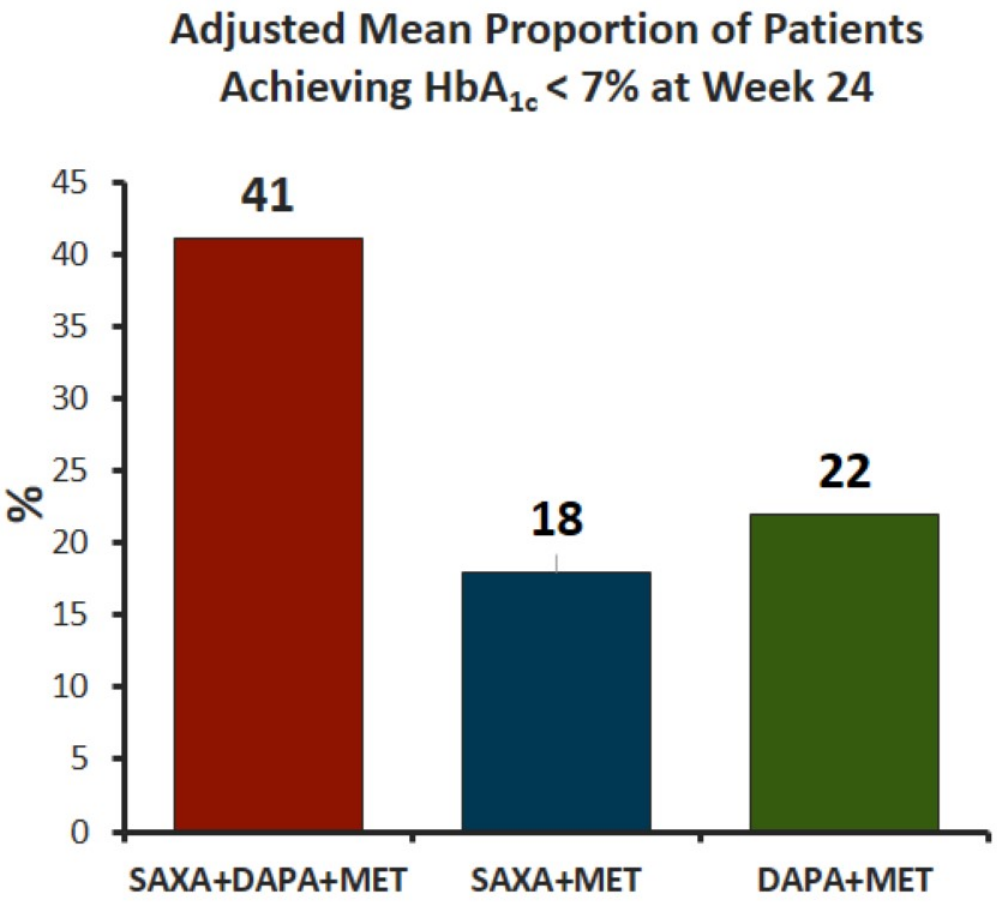
SGLT2 inhibitors increase glucagon levels

- Plasma Glucose
- Plasma Insulin
- Glycosuria –neural reflex directly to alpha cells
  - neural reflex via central sympathetic outflow
- Direct effect of dapagliflozin on alpha cells

Efficacy of Dapagliflozin/Saxagliptin Added to Metformin

- Baseline HbA_{1c} = 8.9%

Adjusted mean (95% CI) change from baseline in HbA_{1c} at week 24
SAXA+DAPA+MET = –1.5%
SAXA+MET = –0.9%
DAPA+MET = –1.2%



SAXA = saxagliptin. DAPA = dapagliflozin. MET = metformin.

Rosenstock J, et al. *Diabetes Care*. 2015;38:376-383.[26]

Efficacy of Empagliflozin/Linagliptin Added to Metformin

- Empagliflozin vs linagliptin vs empagliflozin and linagliptin as add-on to metformin over 24 weeks
- Combination therapy with empagliflozin/linagliptin was superior to either component ($P < .001$) at all doses
- Efficacy was maintained at week 52
- Baseline HbA_{1c} = 8% (7.9% for Combo 25/5 mg)

DeFronzo RA, et al. *Diabetes Care*. 2015;38:384-393.[25]

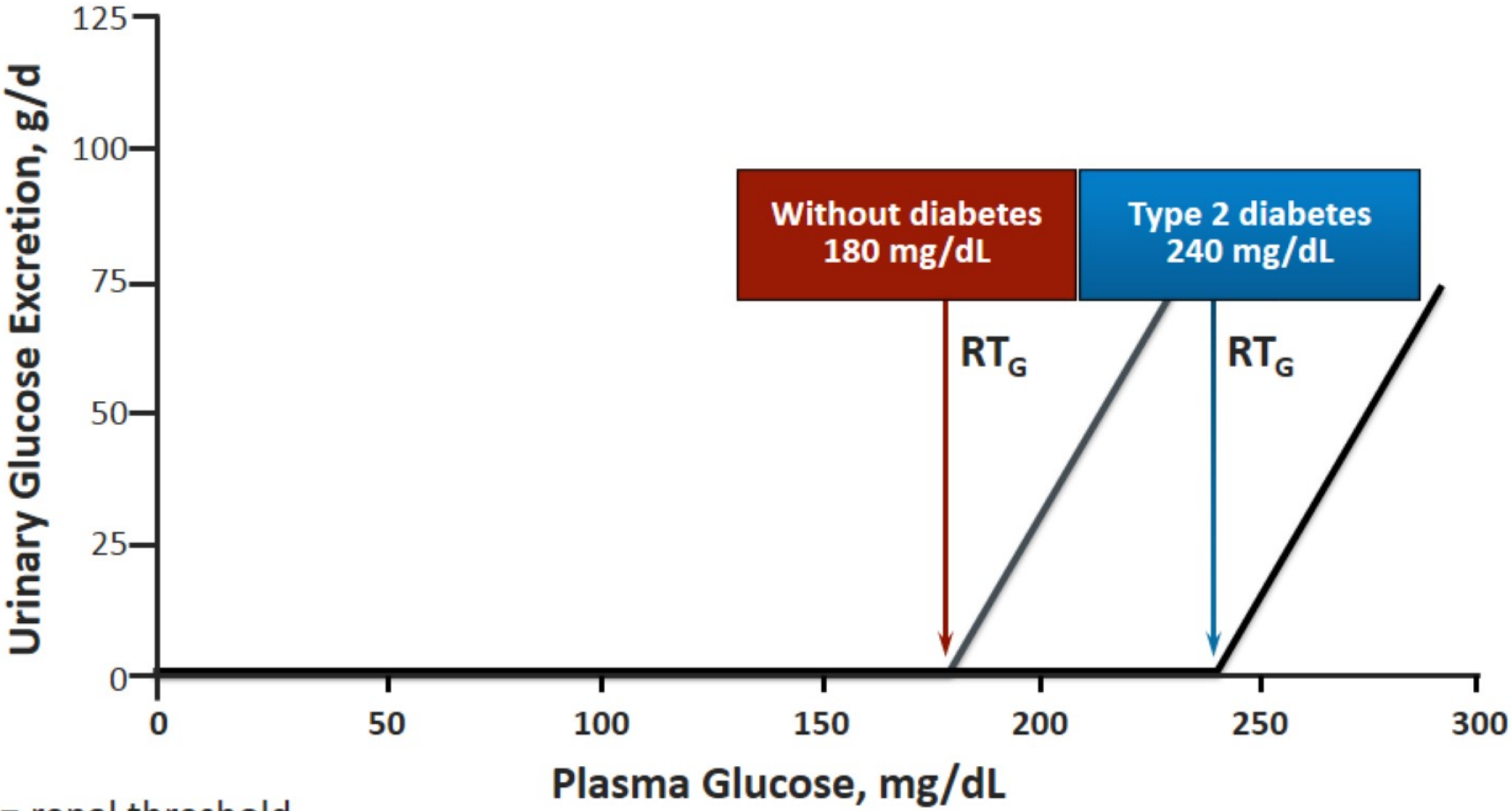
Efficacy and Safety Data

SGLT2 Inhibitors as Monotherapy

- Reduction in HbA_{1c} of approximately 0.6%-1.2%[a-c]
  - Canagliflozin 100 and 300 mg significantly reduced HbA_{1c} from baseline vs placebo (-0.77, -1.03, and 0.14%, respectively; $P < .001$ for both)[a]
- Hypoglycemia was not significantly increased in any of these 3 studies; no severe hypoglycemic events reported[a-c]
- Average weight loss: 2.3-3.4 kg[a-c]
- Proposed mechanism for blood pressure decrease include osmotic diuresis, weight loss after a week or so, and mild natriuresis[a-c]

a. Stenlöf K, et al. *Diabetes Obes Metab.* 2013;15:372-82[18]; b. Ferrannini E, et al. *Diabetes Care.* 2010;33:2217-2224[19]; c. Roden M, et al. *Lancet Diabetes Endocrinol.* 2013;1:208-219.[20]

Renal Threshold for Glucose Excretion

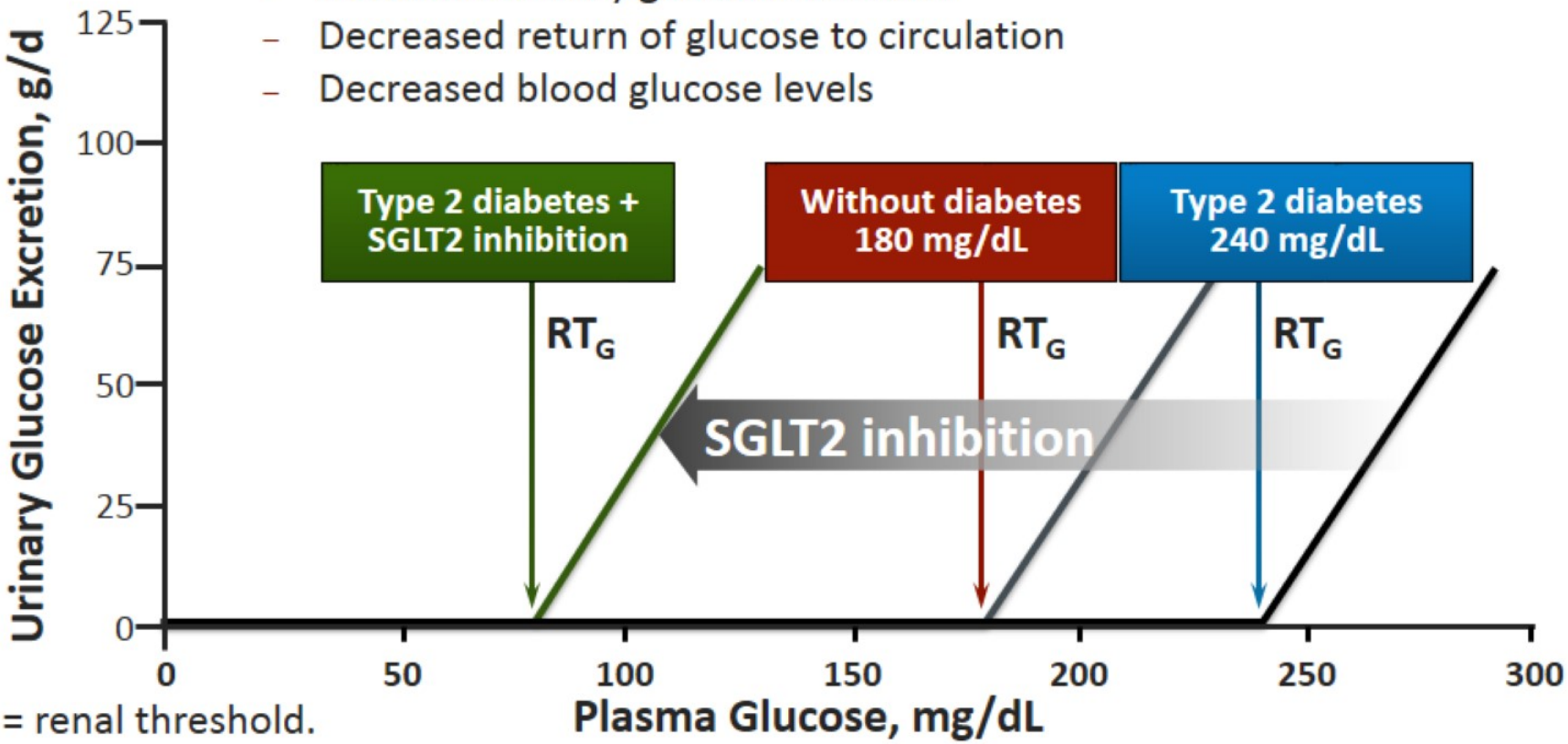


RT = renal threshold.

Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42[6]; Abdul-Ghani MA, DeFronzo RA. *Endocr Pract*. 2008;14:782-790.[10]

Inhibiting SGLT2 Promotes Urinary Glucose Excretion

- SGLT2 inhibitors lower the threshold at which glucose is excreted, leading to
  - Increased urinary glucose excretion
  - Decreased return of glucose to circulation
  - Decreased blood glucose levels



RT = renal threshold.

Nair S, Wilding JP. *J Clin Endocrinol Metab*. 2010;95:34-42[6]; Abdul-Ghani MA, et al. *Endocr Pract*. 2008;14:782-790[10]; Chao EC, et al. *Nat Rev Drug Discov*. 2010;9:551-559.[11]

Primary and Secondary Cardiovascular Outcomes.

Table 1. Primary and Secondary Cardiovascular Outcomes.

Outcome	Placebo (N=2333)		Empagliflozin (N=4687)		Hazard Ratio (95% CI)	P Value
	no. (%)	*rate/1000 patient-yr*	*no. (%)*	*rate/1000 patient-yr*		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74–0.99)	
Noninferiority						<0.001†
Superiority						0.04†
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*	333 (14.3)	52.5	599 (12.8)	46.4	0.89 (0.78–1.01)	
Noninferiority						<0.001†
Superiority						0.08†
Death						
From any cause	194 (8.3)	28.6	269 (5.7)	19.4	0.68 (0.57–0.82)	<0.001
From cardiovascular causes	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49–0.77)	<0.001
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70–1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70–1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70–2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74–1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72–1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89–1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92–1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51–1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50–0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55–0.79)	<0.001

* Data were analyzed with the use of a four-step hierarchical-testing strategy for the pooled empagliflozin group versus the placebo group in the following order: noninferiority for the primary outcome, noninferiority for the key secondary outcome, superiority for the primary outcome, and superiority for the key secondary outcome. Each successive hypothesis could be tested, provided that those preceding it met the designated level of significance. Data are based on Cox regression analyses in patients who received at least one dose of a study drug.
† One-sided P values are shown for tests of noninferiority, and two-sided P values are shown for tests of superiority.
‡ Silent myocardial infarction was analyzed in 2378 patients in the empagliflozin group and 1211 patients in the placebo group.

Zinman B et al. N Engl J Med 2015. DOI: 10.1056/NEJMoa1504720

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Sodium-Glucose Cotransporters

	SGLT1	SGLT2
Site	Mostly intestine with some kidney	Almost exclusively kidney
Sugar specificity	Glucose or galactose	Glucose
Affinity for glucose	High Km = 0.4 mM	Low Km = 2 mM
Capacity for glucose transport	Low	High
Role	Dietary glucose absorption Renal glucose reabsorption	Renal glucose reabsorption

Lee YJ, et al. *Kidney Int Suppl*. 2007;S27-S35.[5]

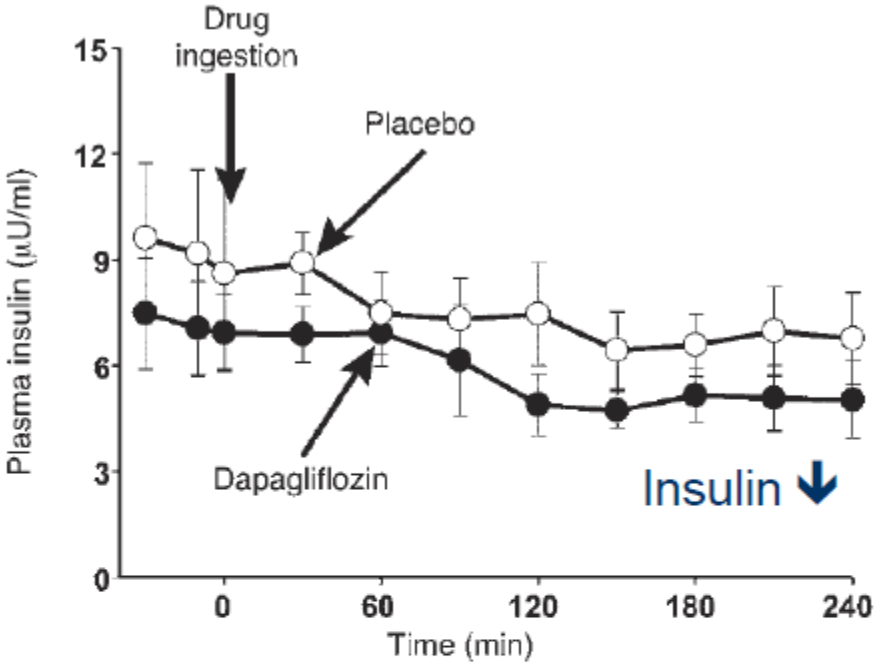
Kidneys Play an Important Role in Handling Glucose

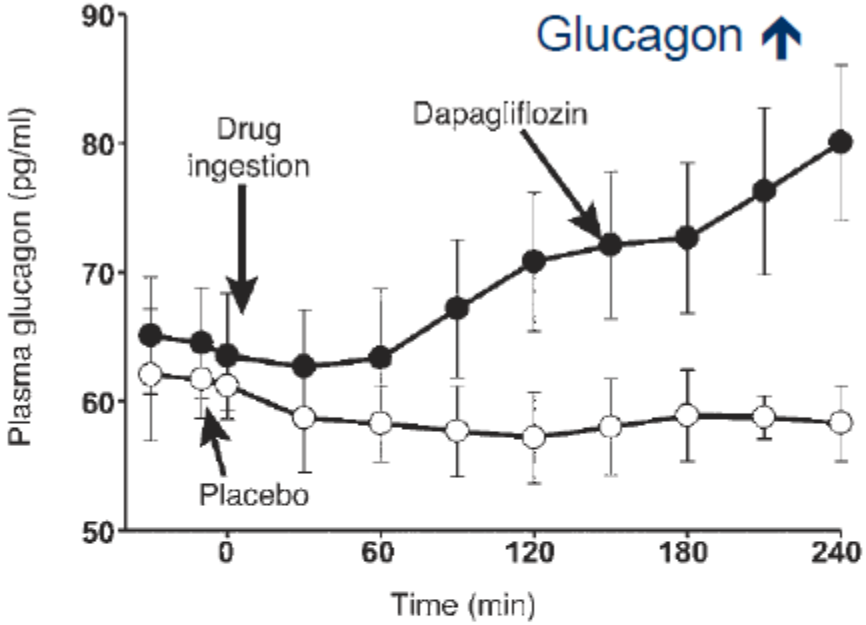
Total glucose stored in body	~450 g
Glucose in Western diet	~180 g/d
Renal glucose filtration and reabsorption	~180 g/d
Urinary glucose	0 g

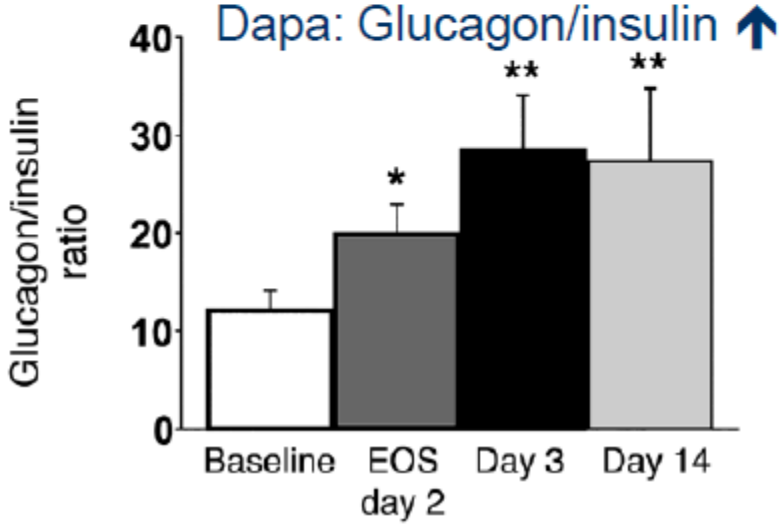
Virtually all glucose is reabsorbed in the proximal tubules and reenters the circulation in a healthy person; Virtually no glucose is excreted in urine

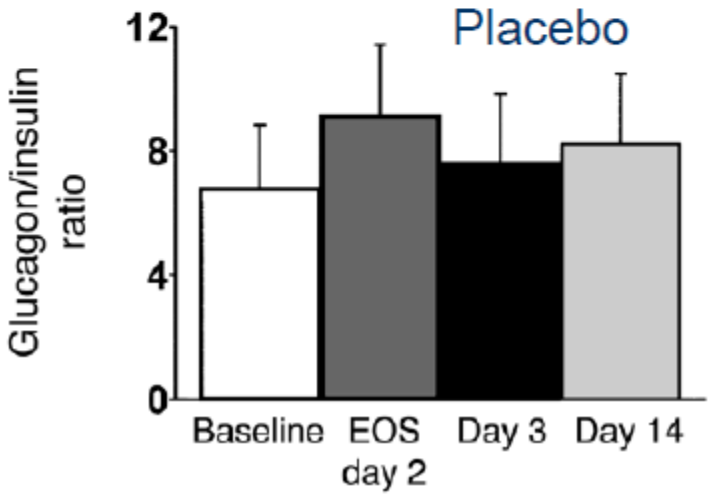
Wright EM, et al. *J Intern Med*. 2007;261:32-43.[2]

- 2 weeks of dapagliflozin





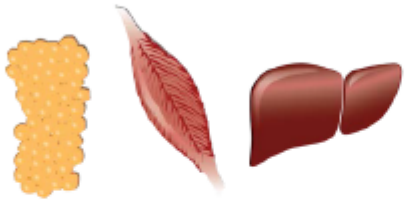




SGLT2 inhibition: an insulin-independent target in T2D

Insulin-dependent mechanisms

1 Insulin action
- Thiazolidinediones
- Metformin



Adipose tissue, muscle, and liver

2 Insulin release
- Sulphonylureas
- GLP-1 agonists*
- DPP-4 inhibitors*
- Meglitinides

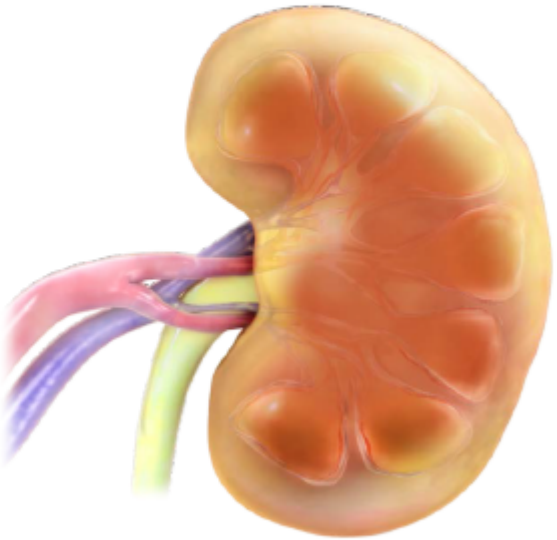
Pancreas

3 Insulin replacement
- Insulin

Enhance glucose utilisation

Insulin-independent mechanism

SGLT2 Inhibition



Glucose excretion