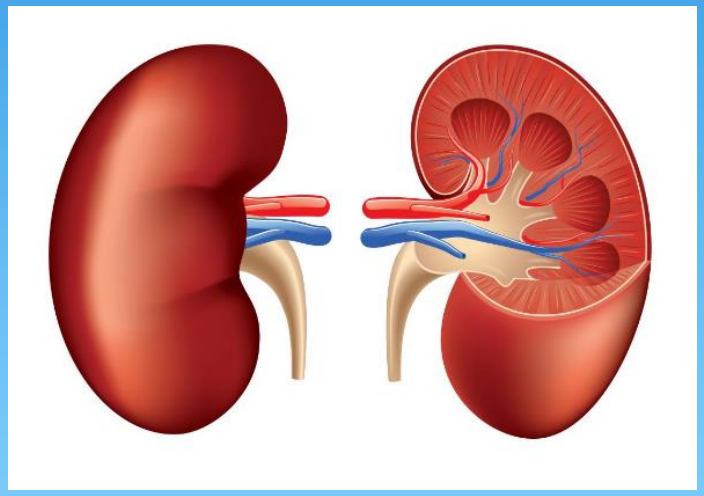
Comprehensive T2D management with SGLT2 inhibitor



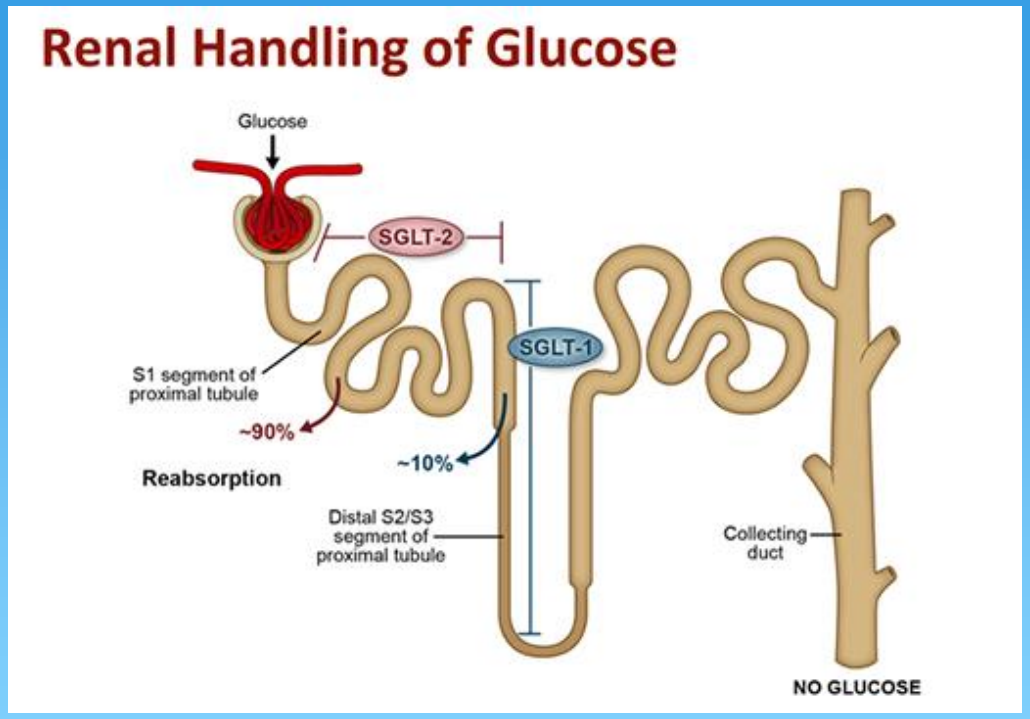
Hyuk-Sang Kwon

The Catholic University of Korea

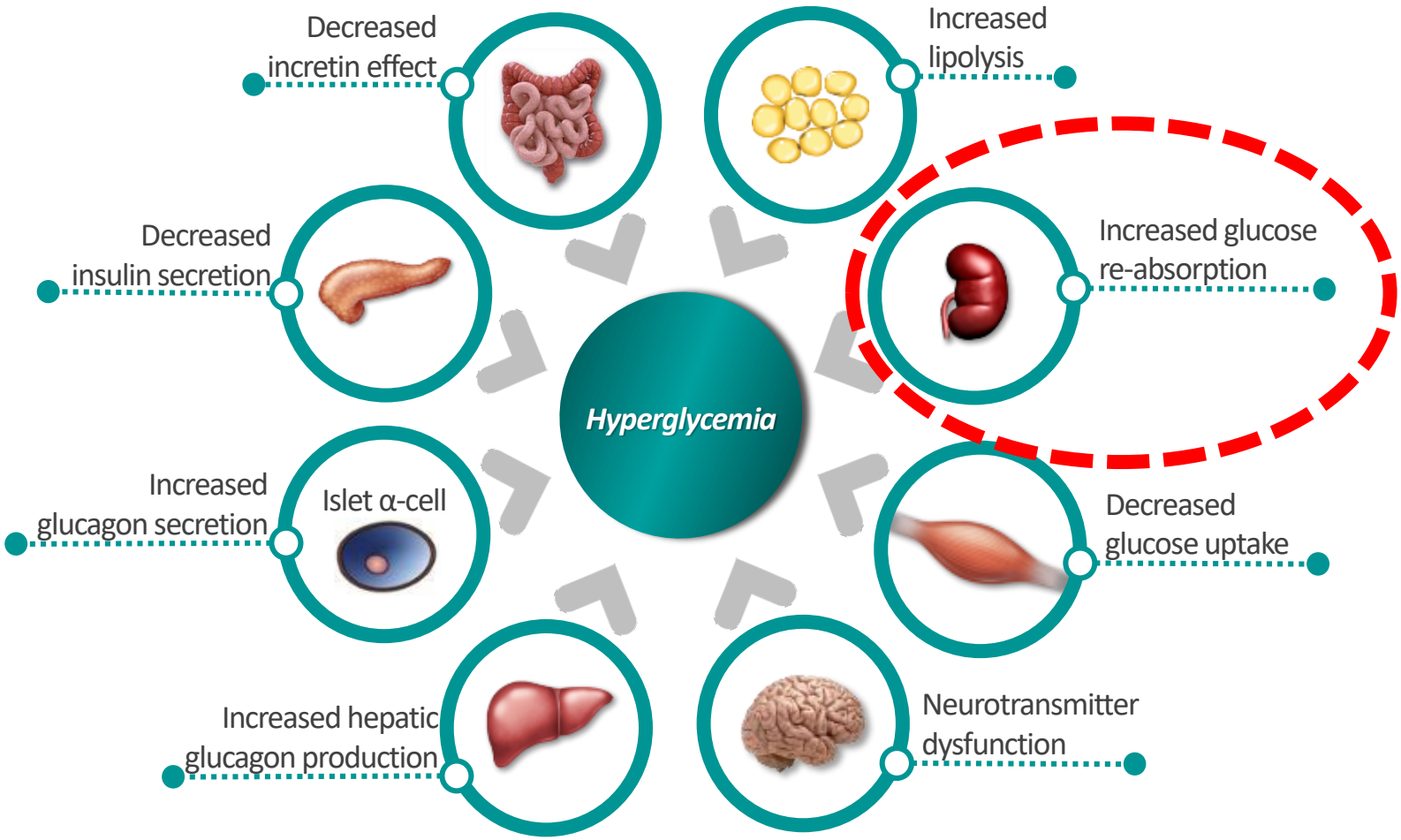
Comprehensive T2D management with SGLT2 inhibitor

1. • Unmet Needs for SGLT2 inhibitors
2. • CV Protective Effects of SGLT2 inhibitors
3. • Recent Clinical Issues in SGLT2 inhibitors
4. • Take-Home Message

Unmet Needs for SGLT2 inhibitors



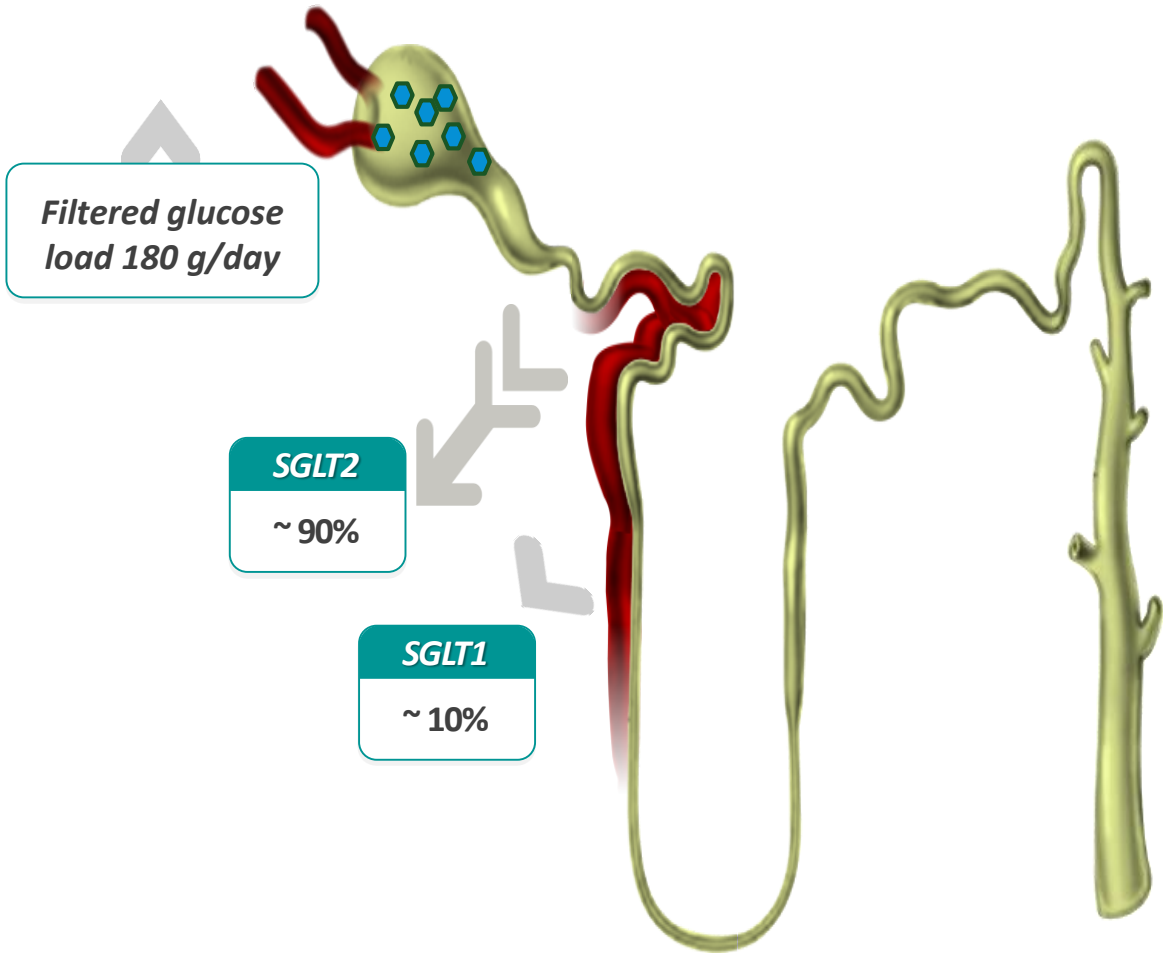
From the triumvirate to the ominous octet: a new paradigm for the treatment of T2D



T2D, Type 2 Diabetes.

1. DeFronzo RA. Diabetes. 2009;58:773–795; 2. Tahrani AA, et al. Lancet. 2011;378:182–197.

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

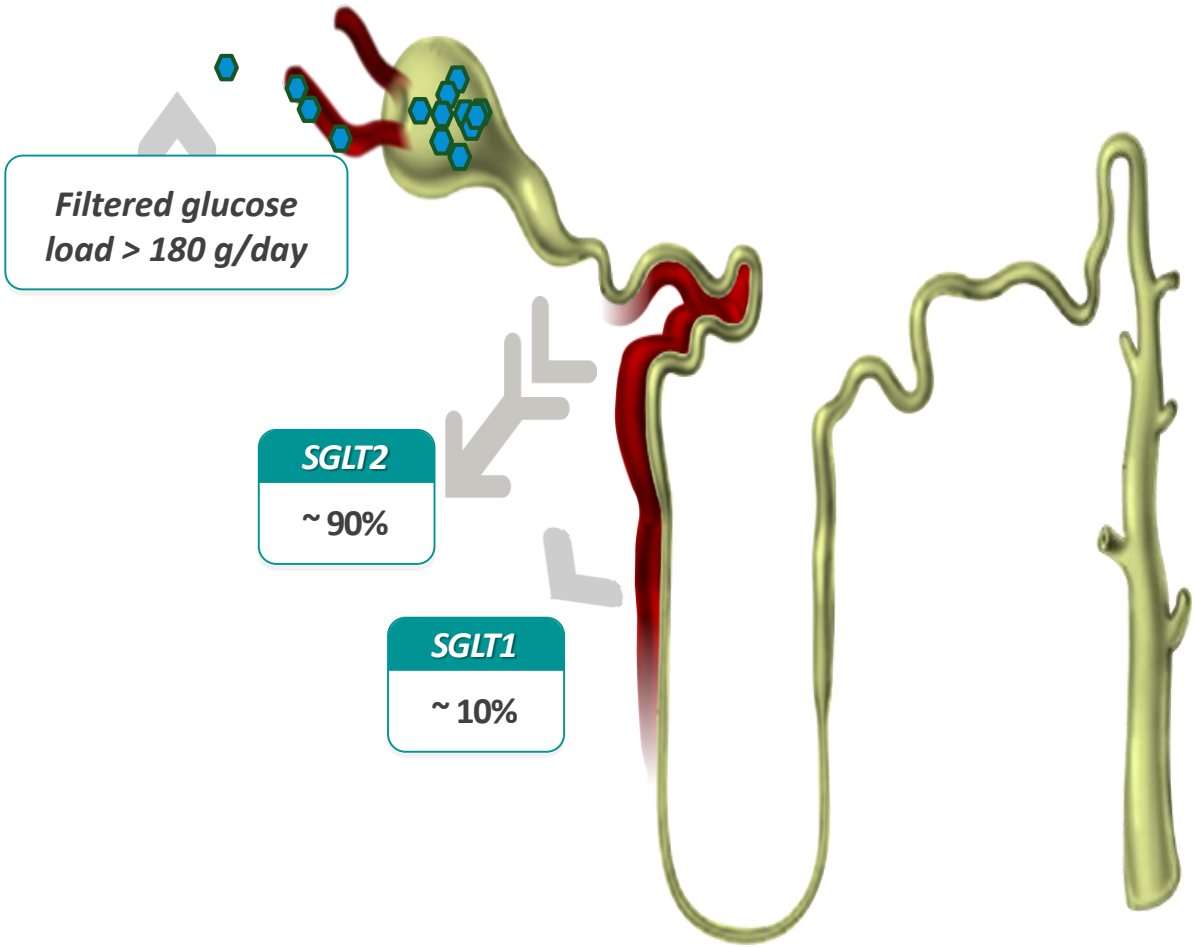


Virtually all of the filtered glucose is re-absorbed in the proximal tubules through SGLT2 and SGLT1 with SGLT2 accounting for ~ 90% in the S1 and S2 segments and SGLT1 accounting for ~ 10% in the S3 segment

SGLT, sodium glucose cotransporter.

1. Gerich JE. Diabet Med. 2010;27:136–142; 2. Bakris GL, et al. Kidney Int. 2009;75;1272–1277.

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



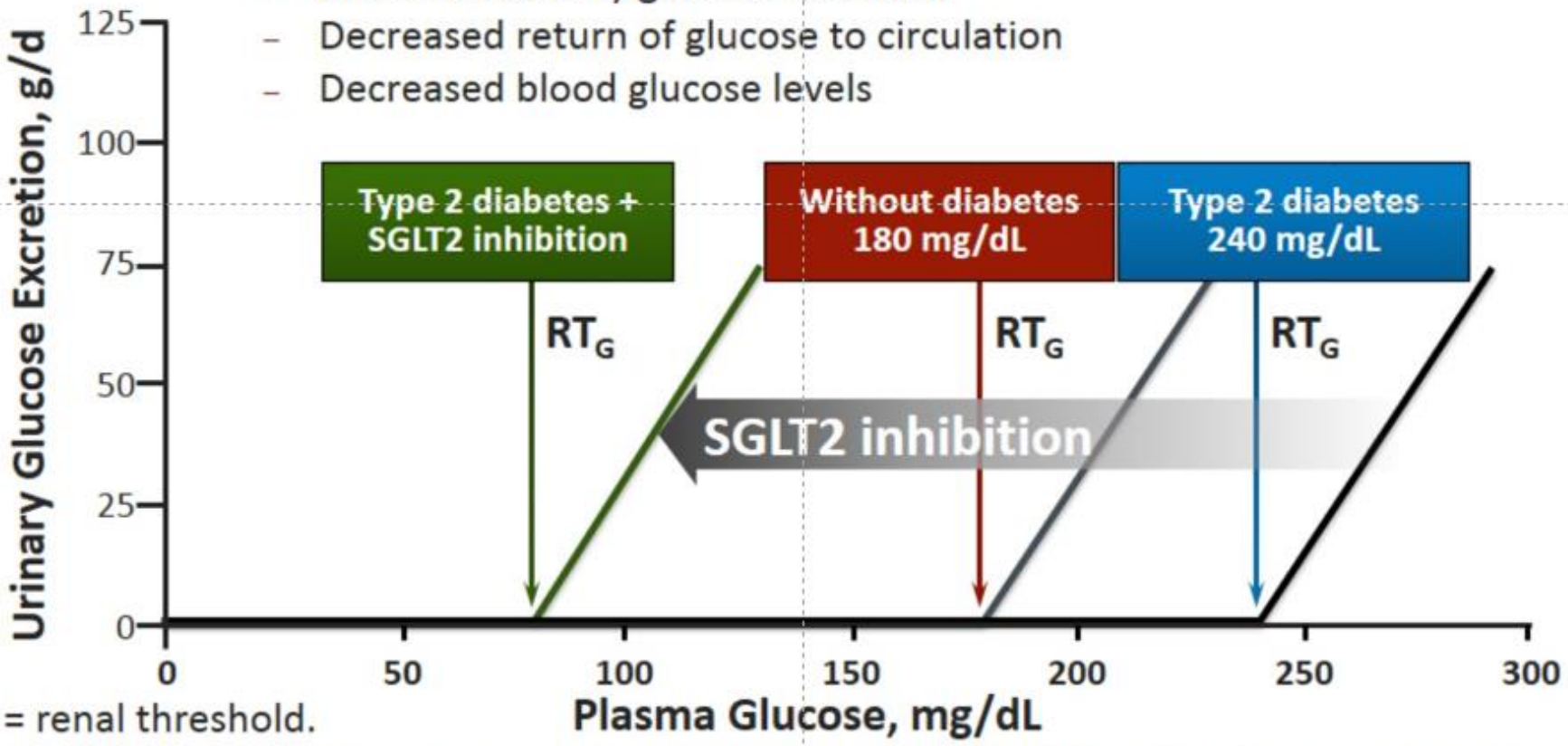
When blood glucose increases above the renal threshold (~ 10 mmol/L or 180 mg/dL), the capacity of the transporters is exceeded, resulting in urinary glucose excretion

SGLT, sodium glucose cotransporter.

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

Inhibiting SGLT2 Promotes Urinary Glucose Excretion

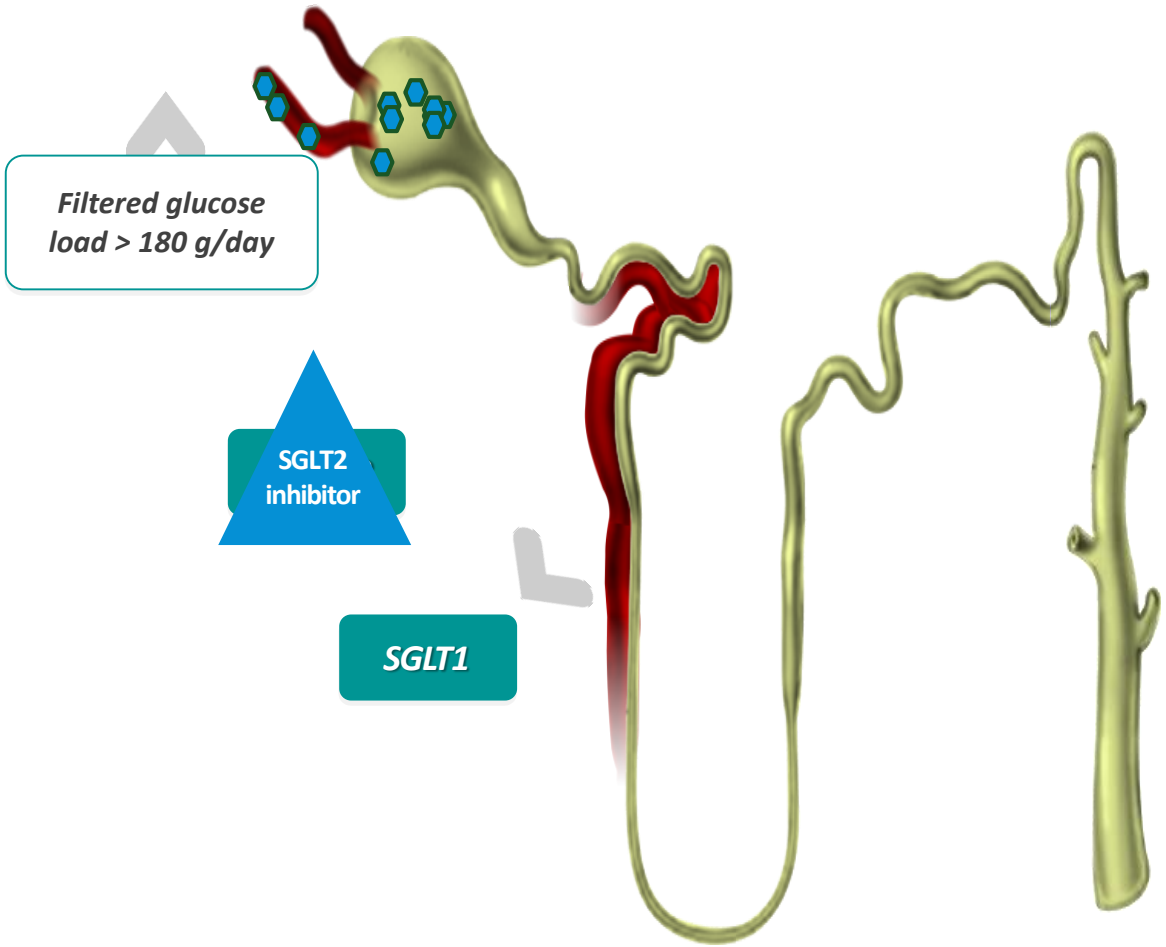
- SGLT2 inhibitors lower the threshold at which glucose is excreted, leading to
  - Increased urinary glucose excretion
  - Decreased return of glucose to circulation
  - Decreased blood glucose levels



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]

Urinary glucose excretion via SGLT2 inhibition[1]



SGLT2 inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion* and osmotic diuresis

SGLT, sodium glucose cotransporter.
*Loss of ~ 80 g of glucose per day = 320 cal/day.

1. Bakris GL, et al. *Kidney Int*. 2009;75;1272–1277.

The role of the Sodium GLucose co-Transporter

Transporter	Major site of action	Function	Disease Associated with Malfunction
SGLT1	Small intestine, heart, trachea and kidney	Co-transports sodium, glucose and galactose across the brush border of the intestine and proximal tubule of the kidney	Congenital glucose-galactose malabsorption syndrome
SGLT2	Kidney	Co-transports sodium and glucose in the S1 segment of the proximal tubule of the kidney	Familial renal glucosuria
SGLT3	Small intestine, uterus, lungs, thyroid and testis	Transports sodium (not glucose)	Unknown
SGLT4	Small intestine, kidney, liver, stomach and lung	Transports glucose and mannose	Unknown
SGLT5	Kidney	Unknown	Unknown
SGLT6	Spinal cord, kidney, brain, and small intestine	Transports myo-inosotol and glucose	Unknown

1. Grempler R et al. Diabetes, Obesity and Metabolism 2012;14:83–90.

Existing and novel mechanisms to reduce hyperglycemia in Type 2 diabetes

Insulin-independent mechanism

1

Insulin action

- ✓ Thiazolidinediones
- ✓ Metformin

Adipose tissue

muscle and liver

2

Insulin release

- ✓ SUs
- ✓ GLP-1R agonists*
- ✓ DPP4 inhibitors*
- ✓ Meglitinides

Pancreas

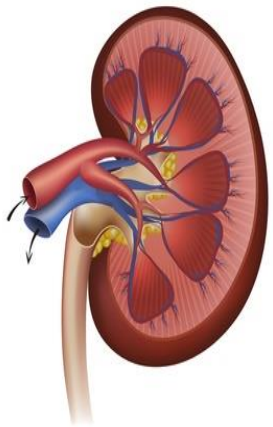
3

Insulin replacement

- ✓ Insulin

Glucose utilisation

SGLT2 inhibition

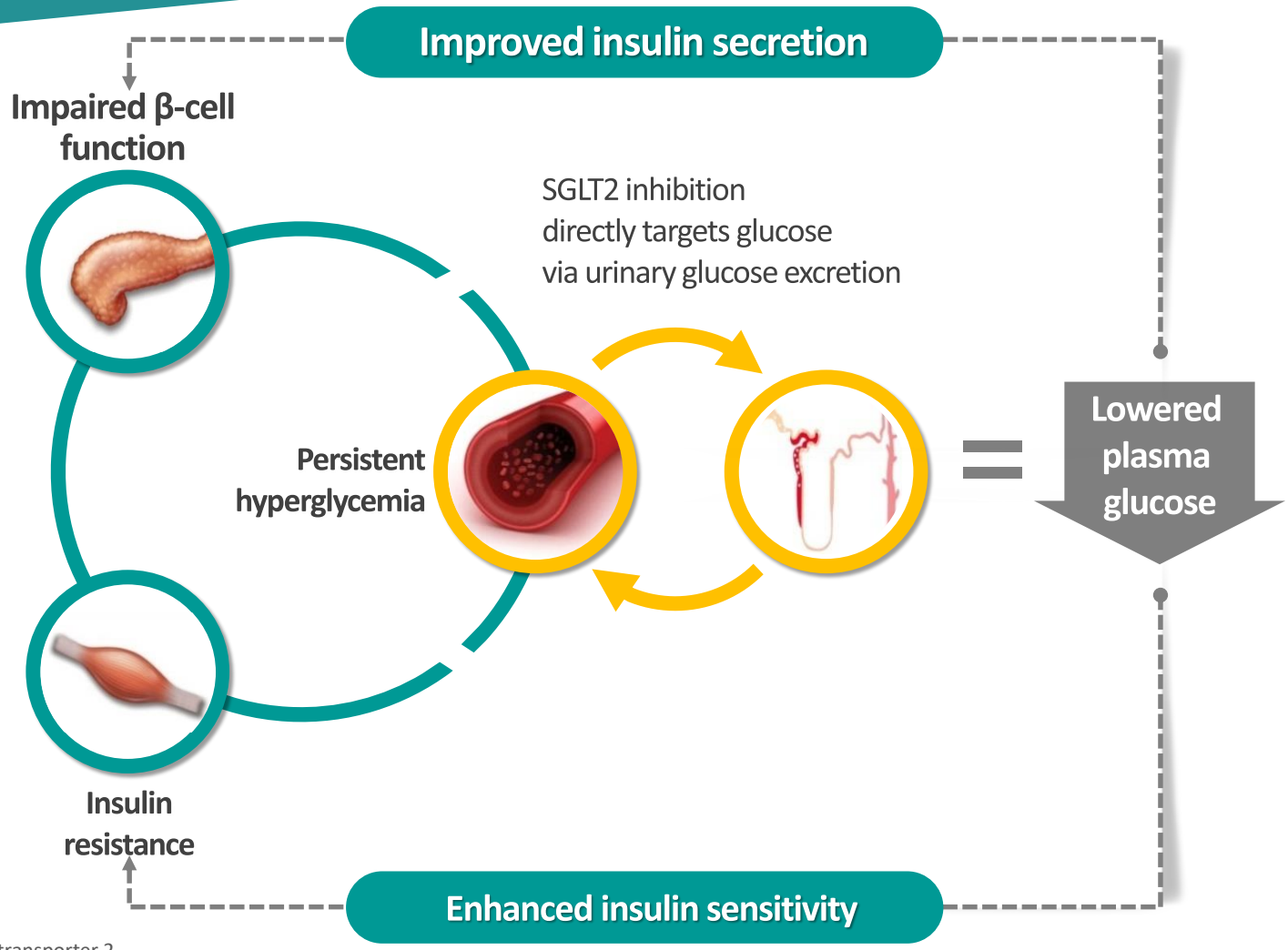


Glucose excretion/caloric loss

*In addition to increasing insulin secretion, which is the major mechanism of action, GLP-1R agonists and DPP4 inhibitors also act to decrease glucagon secretion.
DPP4, dipeptidyl peptidase-4; GLP-1R, glucagon-like peptide-1 receptor; SUs, sulphonylureas.

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.

SGLT2 inhibition lowers glycemia independently of β-cell function and insulin resistance



SGLT2, sodium glucose cotransporter 2.

1. DeFronzo RA. *Diabetes*. 2009;58:773–795. 2. Poitout V, Robertson RP. *Endocrinology*. 2002;143:339–342. 3. Robertson RP, et al. *Diabetes*. 2003;52:581–587. 4. DeFronzo RA. *Diabetes Obes Metab*. 2012;14:5–14.
5. Del Prato S. Diabet Med. 2009;26:1185–1192.

Advantage of SGLT2 inhibitors due to Insulin-independent mechanism

No Hypoglycemia

HbA_{1C} ↓by 0.5-1.0% vs placebo
(5.5-11 mmol/mol)

glucose resorption ↓
urinary glucose excretion ↑
~ 80 g/day

Weight

modest weight loss
~2kg over 6-12 mo.

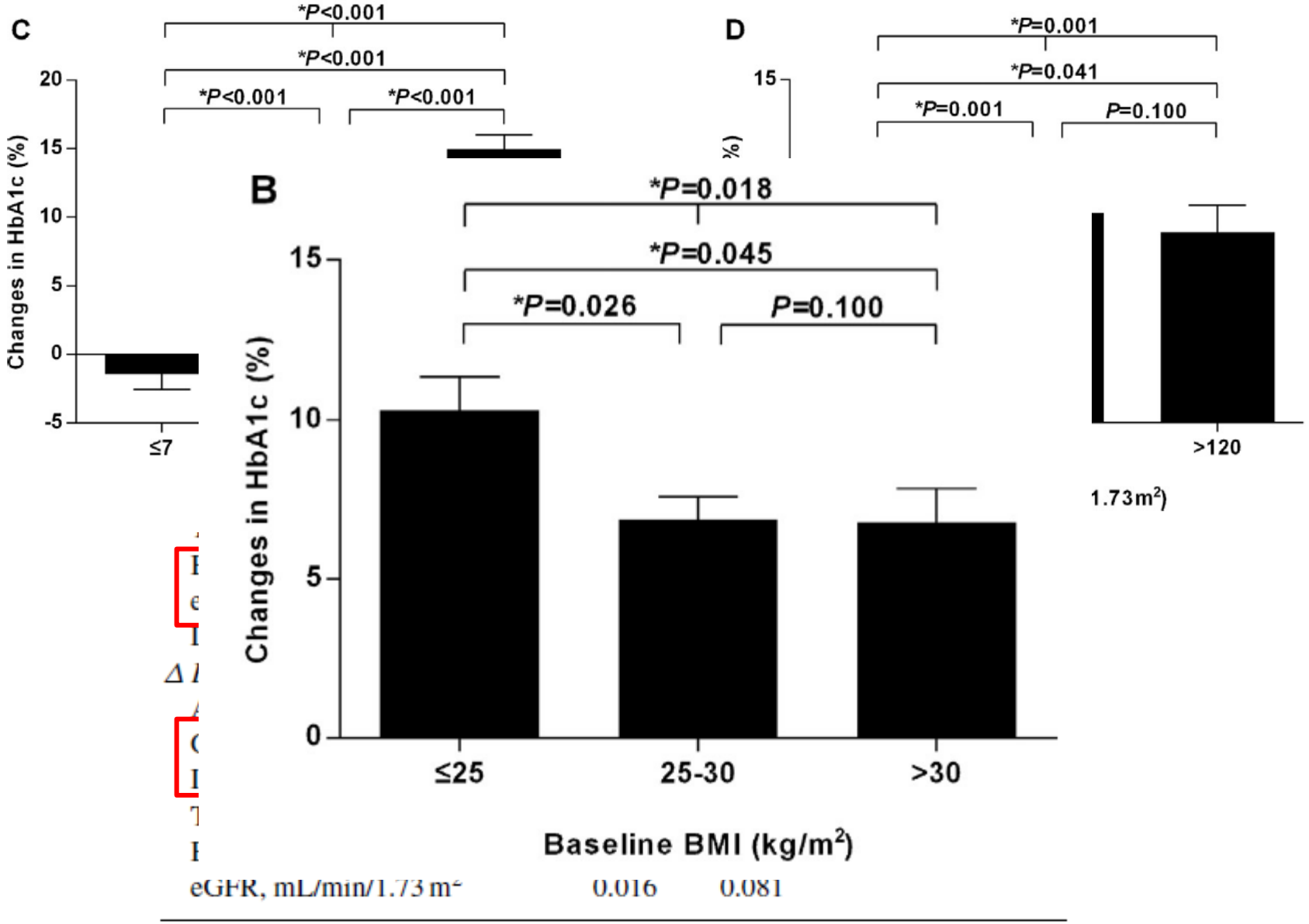
Blood pressure

SBP ↓ & DBP ↓
~2-4/~1-2mmHg

Effective at all stage of T2DM

1. SE Inzucchi et al. Diabetologia. 2015 Mar;58(3):429-42.

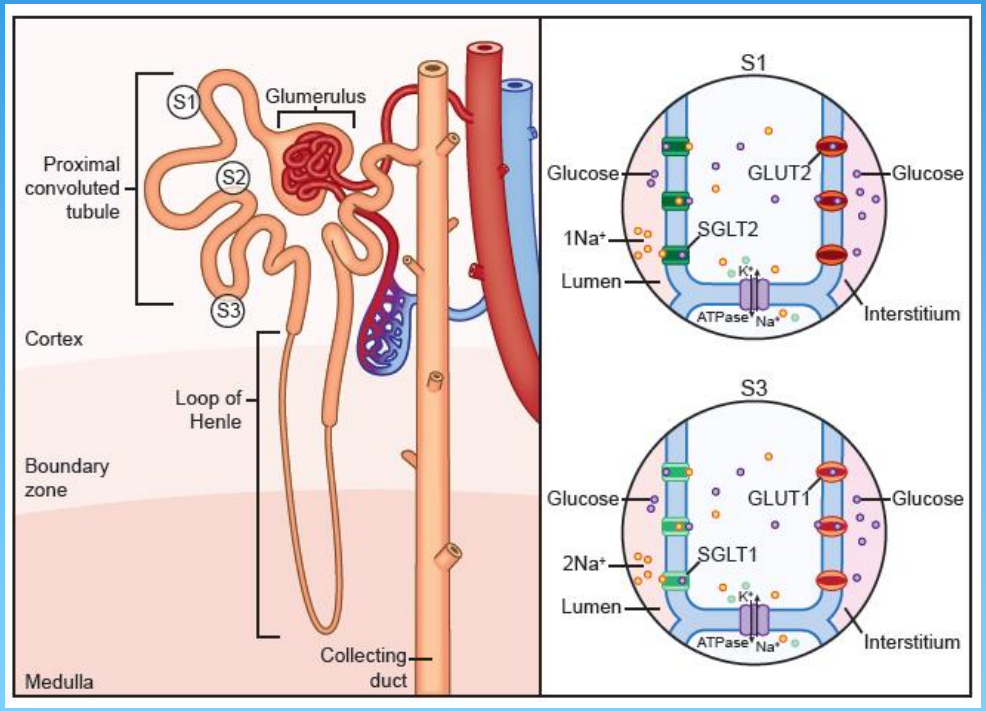
Clinical parameters affecting SGLT2 inhibitors



eGFR, mL/min/1.73 m² 0.016 0.081

Diabetes &Metabolism43(2017)191–194

CV Protective Effects of SGLT2 inhibitors



EMPA-REG Outcome® patients had high CV risk

More than 99% had already CVD history

Approximately 50% had previous MI

More than 50% had long-standing diabetes for more than 10 years

Results were achieved on top of standard of care

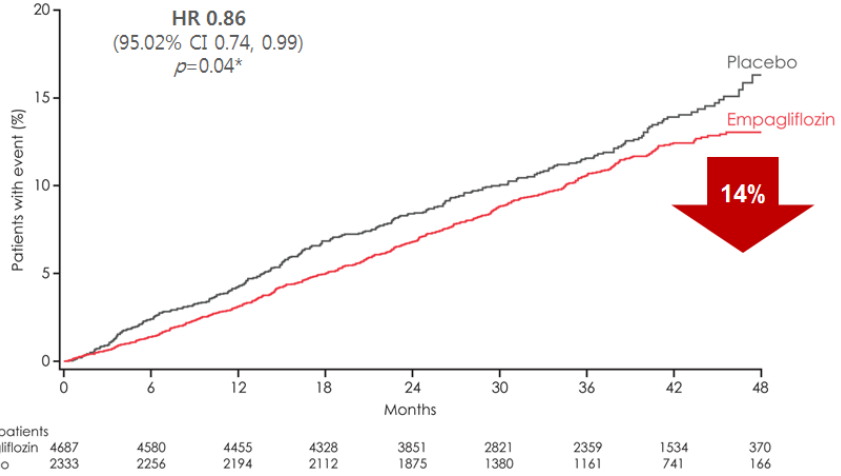
95%	77%	89%	98%
Antihypertensive	Statins	Anticoagulants	Glucose-lowering medication

Patients' **CV risk factors, including glucose, were actively managed** in placebo and empagliflozin treatment arms

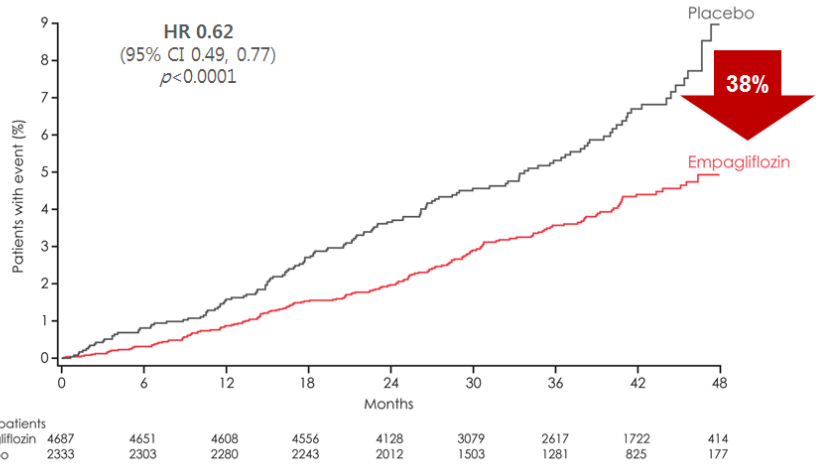
Zinman B, et al; New England Journal of Medicine 2015;(DOI: 10.1056/NEJMoal1504720)

CV outcome

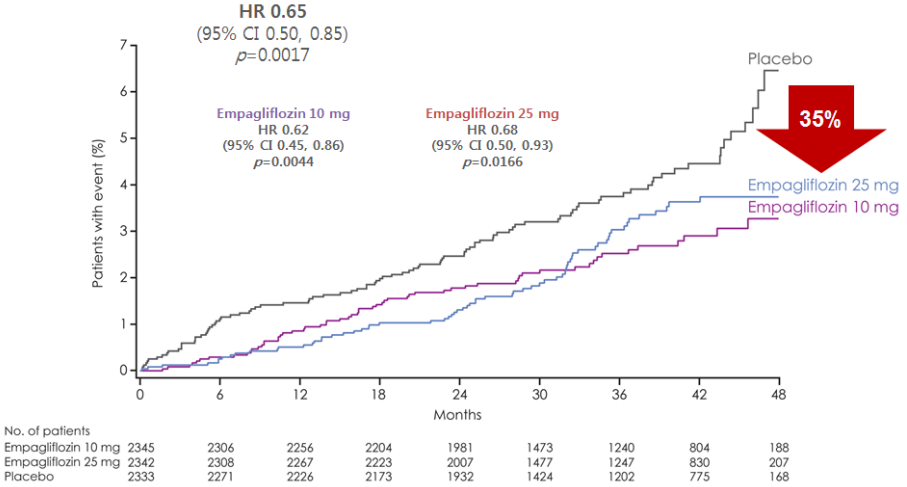
Primary outcome
3-point MACE (CV death, non-fatal MI, non-fatal stroke)



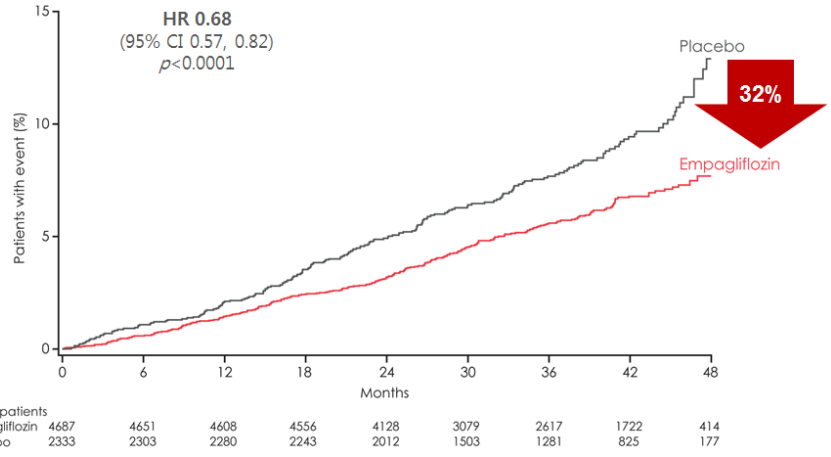
CV death



Hospitalization for heart failure



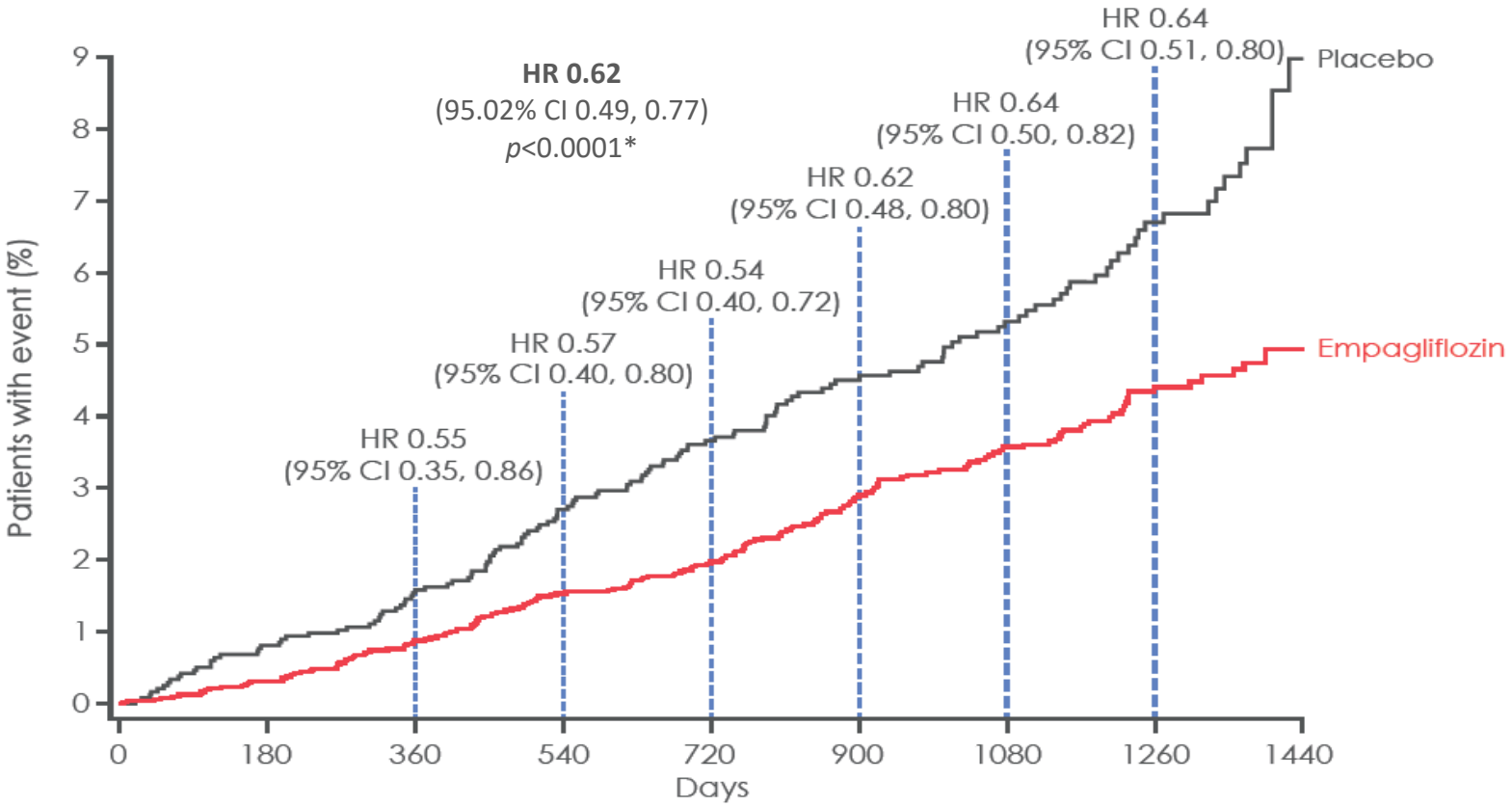
All-cause mortality



* Two-sided tests for superiority were conducted (statistical significance was indicated if p<0.0498)

Zinman B, et al., NEJM, 2015

Cardiovascular death
Hazard ratios and 95% CIs over time

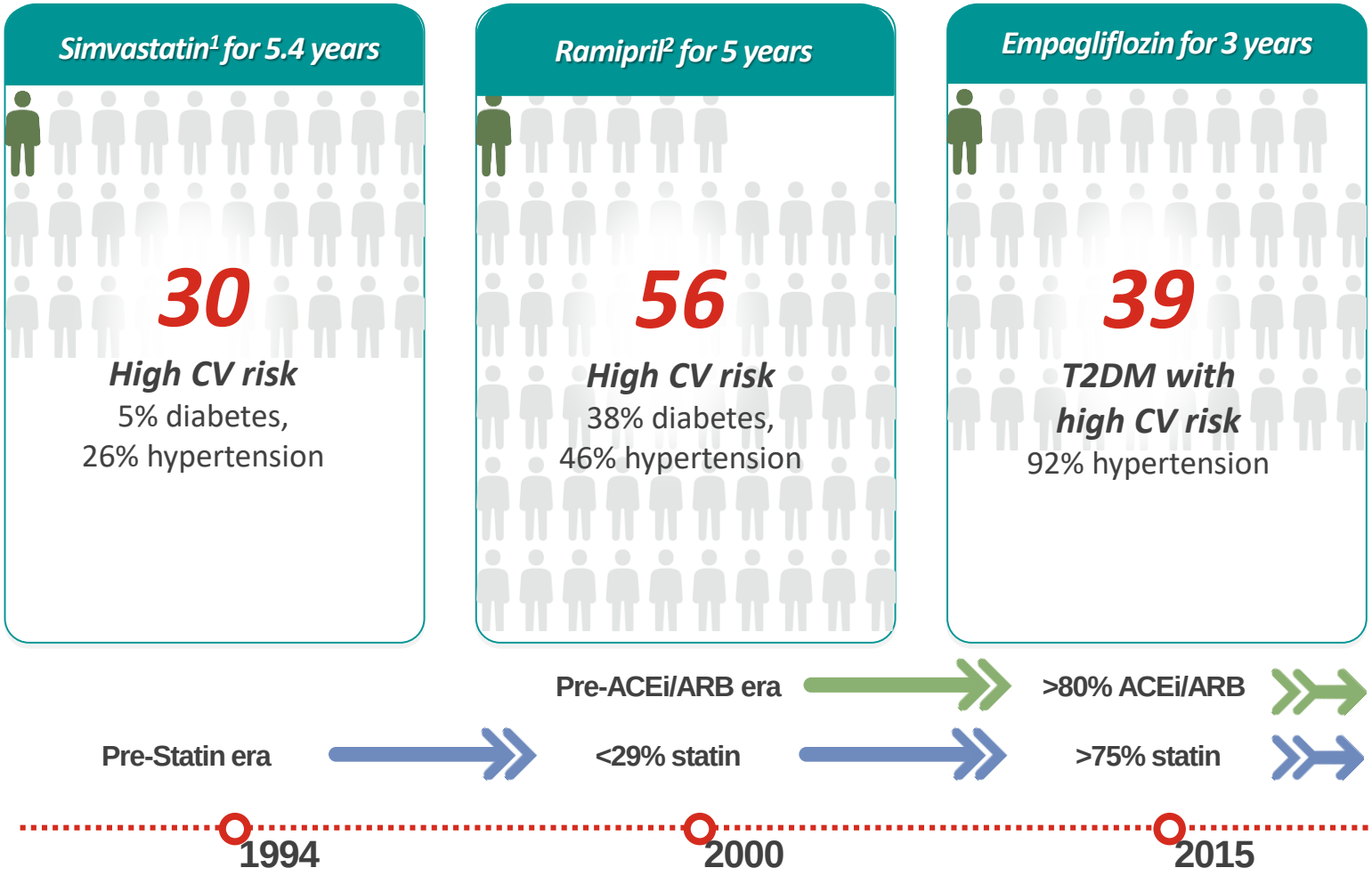


No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Empagliflozin is not indicated for CV risk reduction. Patients treated with ≥1 dose of study drug.
HR and 95% CIs based on Cox regression analysis. *Nominal *p*-value. Cumulative incidence function
van de Borne P *et al. European Society of Cardiology Heart Failure (ESC-HF)* 2016. P2231

Empagliflozin can save 1 live in 39 T2D patients with CV risk

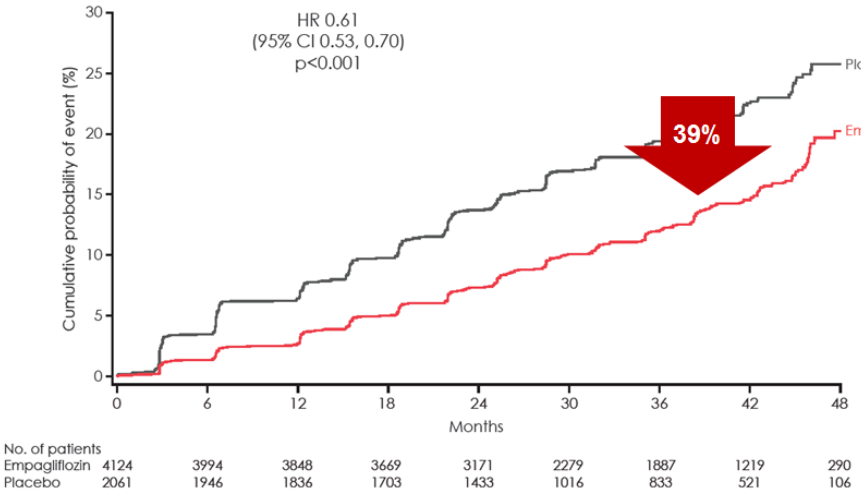
Number needed to treat (NNT) to prevent one death across landmark trials in patients with high CV risk



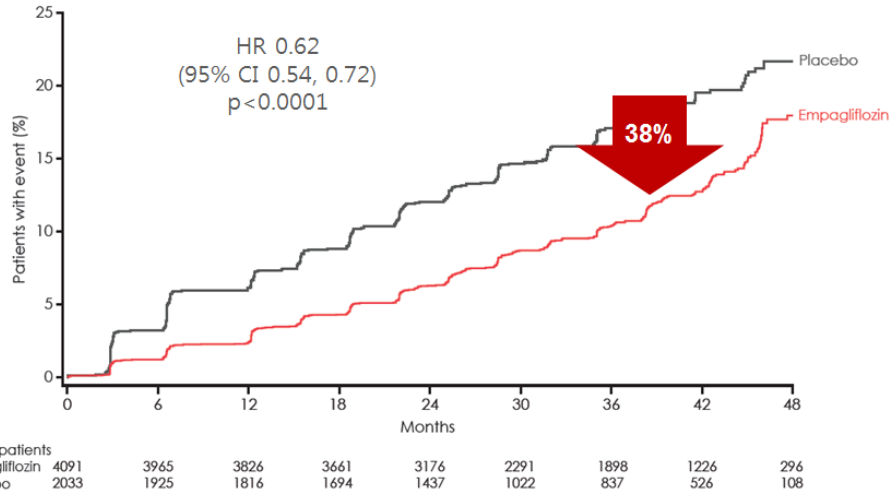
1. 4S investigator. Lancet 1994; 344: 1383-89, http://www.trialresultscenter.org/study2590-4S.htm;
2. HOPE investigator N Engl J Med 2000;342:145-53, http://www.trialresultscenter.org/study2606-HOPE.htm

Pre-specified renal outcome

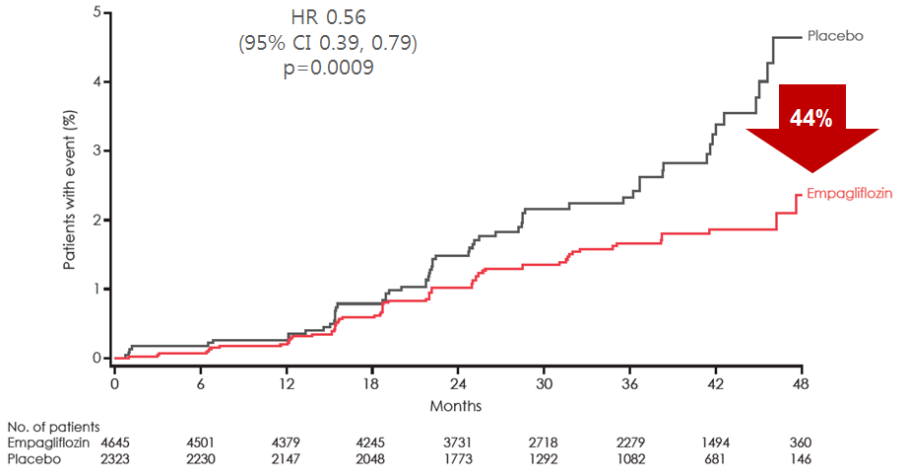
New onset or worsening nephropathy



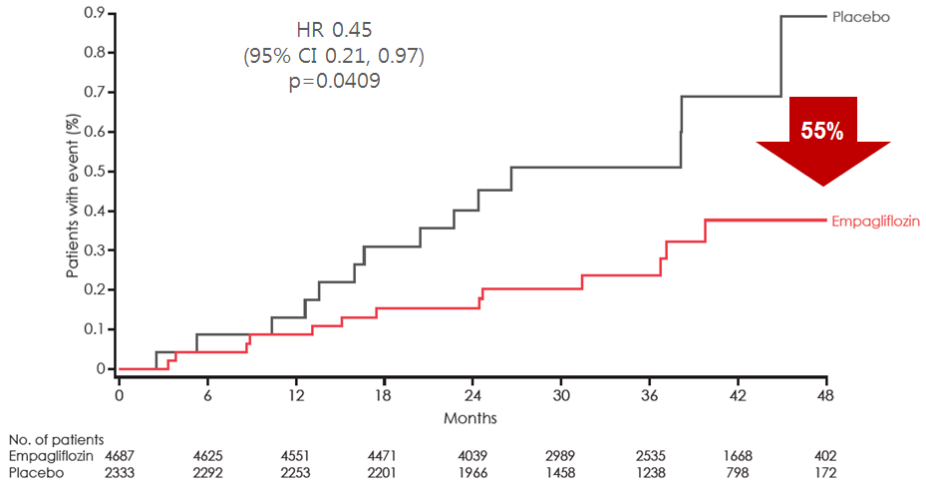
New onset of macroalbuminuria



Doubling of serum creatinine with eGFR ≤45 ml/min/1.73m²

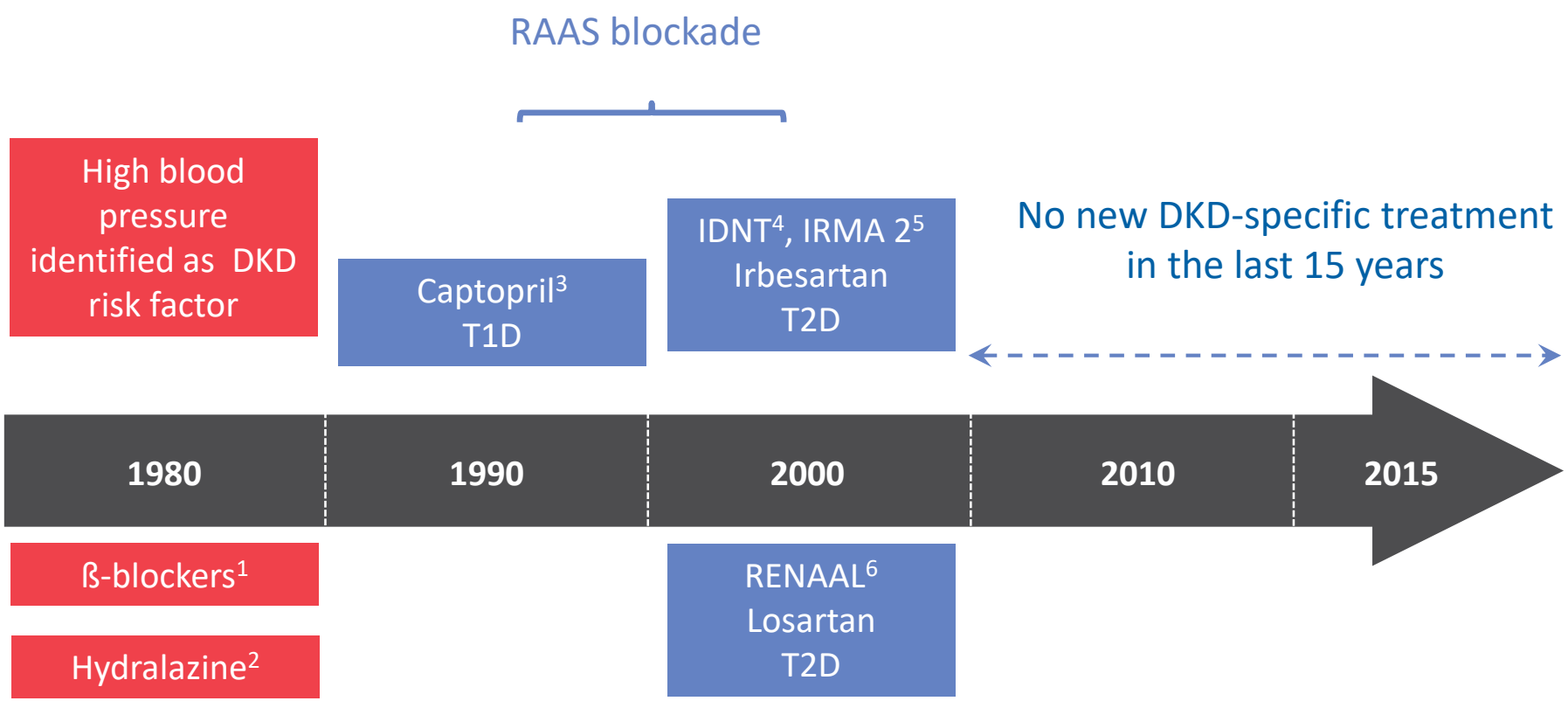


Time to first initiation of continuous renal replacement therapy



Kaplan-Meier estimate. Patients treated with at least one dose of study drug. Hazard ratios are based on Cox regression analyses. HR, hazard ratio; CI, confidence interval.

No new DKD-specific treatment in the last 15 years

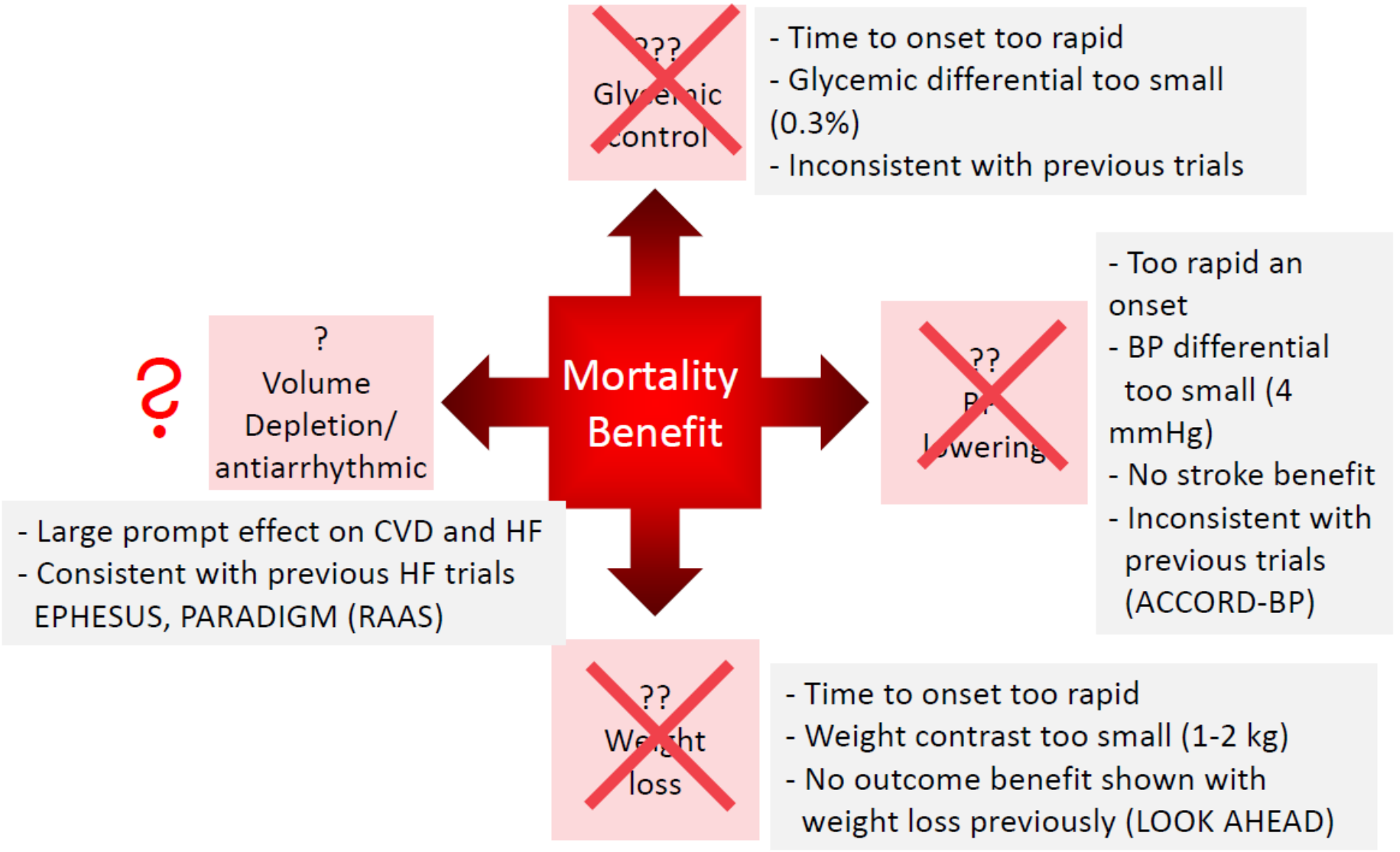


DKD, diabetic kidney disease; T1D, type 1 diabetes; T2D, type 2 diabetes; IDNT, Irbesartan Type 2 Diabetic Nephropathy Trial; RAAS, renin–angiotensin-aldosterone system; RENAAL, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan.

1. Mogensen CE *et al. Br Med J (Clin Res Ed)*1982;285:685; 2. Parving HH *et al. Lancet* 1983;1:1175
3. Lewis EJ *et al. N Engl J Med* 1993;329:1456; 4. Lewis EJ *et al. N Engl J Med* 2001;345:851; 5. Brenner BM *et al. N Engl J Med* 2001;345:861

EMPA-REG OUTCOME®: Explaining Findings

Should We Even Attempt to Explain an 'Unexpected' Outcome?

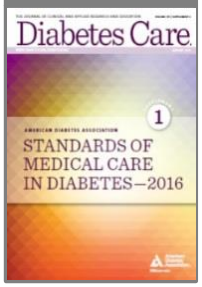


Impact to Various Guidelines

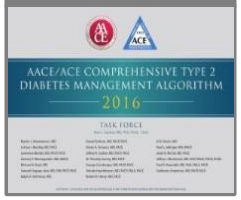
EMPA-REG OUTCOME®

2016

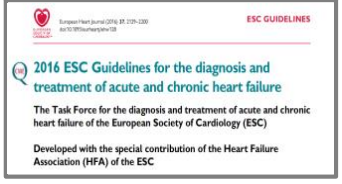
2016 ADA



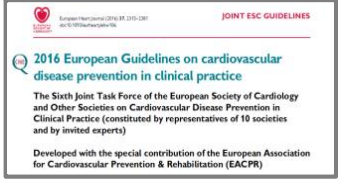
2016 AACE



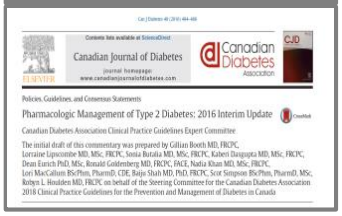
ESC (HF)



ESC (CV)

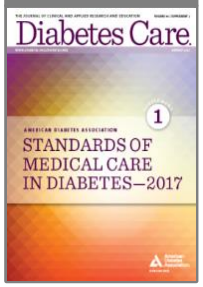


2016 CAD

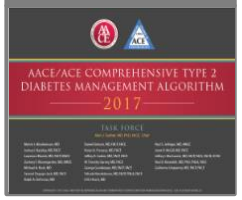


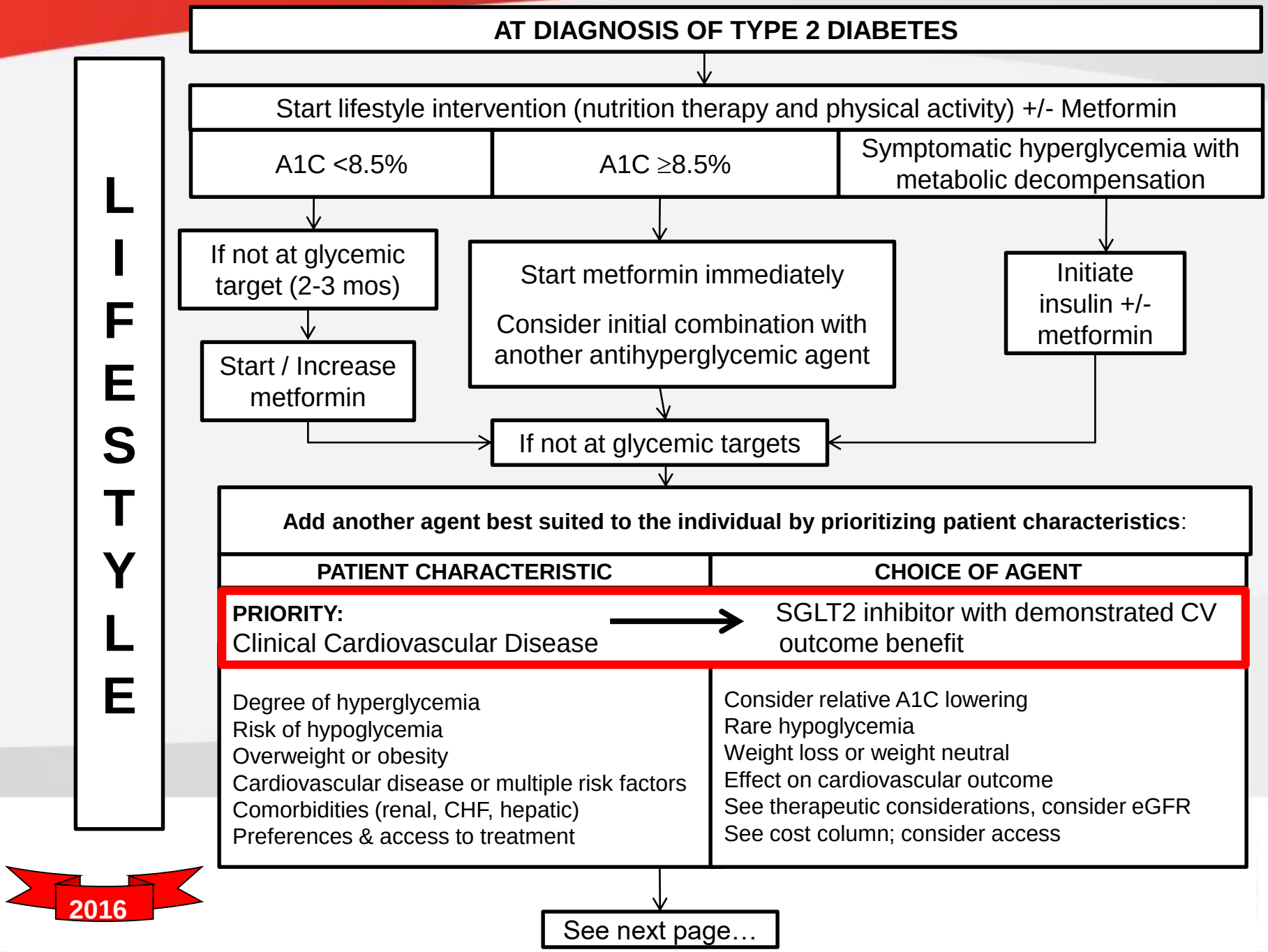
2017

2017 ADA



2017 AACE




AT DIAGNOSIS OF TYPE 2 DIABETES
LIFESTYLE
Start lifestyle intervention (nutrition therapy and physical activity) +/- Metformin
A1C <8.5%
A1C ≥8.5%
Symptomatic hyperglycemia with metabolic decompensation
If not at glycemic target (2-3 mos)
Start / Increase metformin
Start metformin immediately
Consider initial combination with another antihyperglycemic agent
Initiate insulin +/- metformin
If not at glycemic targets
Add another agent best suited to the individual by prioritizing patient characteristics:
PATIENT CHARACTERISTIC
CHOICE OF AGENT
PRIORITY:
Clinical Cardiovascular Disease
SGLT2 inhibitor with demonstrated CV outcome benefit
Degree of hyperglycemia
Risk of hypoglycemia
Overweight or obesity
Cardiovascular disease or multiple risk factors
Comorbidities (renal, CHF, hepatic)
Preferences & access to treatment
Consider relative A1C lowering
Rare hypoglycemia
Weight loss or weight neutral
Effect on cardiovascular outcome
See therapeutic considerations, consider eGFR
See cost column; consider access
2016
See next page…

European Heart Journal Advance Access published June 8, 2016

European Heart Journal
doi:10.1093/eurheartj/ehw106

JOINT ESC GUIDELINES

2016 European Guidelines on cardiovascular disease prevention in clinical practice

In patients with type 2 DM and CVD, the use of an SGLT2 inhibitor should be considered early in the course of the disease to reduce CV and total mortality.	IIa	B	394
Lipid lowering agents (principally statins) are recommended to reduce CV risk in all patients with type 2 or type 1 DM above the age of 40 years.	I	A	371, 372
Lipid lowering agents (principally statins) may be considered also in individuals below 40 years of age if at significantly elevated risk, based on the presence of micro-vascular complications or of multiple CV risk factors.	IIb	A	371, 372
In DM patients at very high-risk (see table 5), a LDL-C target <1.8 mmol/L (<70 mg/dL), or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL), is recommended.[d] In DM patients with high-risk (see table 5), LDL-C target <2.6 mmol/L (<100mg/dL) or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) is recommended.[d]	I	B	395
BP targets in type 2 DM are generally recommended to be <140/85 mmHg, but a lower target of <130/80 mmHg is recommended in selected patients (e.g. younger patients at elevated risk for specific complications) for additional gains on stroke, retinopathy and albuminuria risk. Renin-angiotensin-aldosterone system blocker is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro- albuminuria. Recommended BP target in patients with type 1 DM is <130/80 mmHg.	I	B	396, 397
The use of drugs that increase HDL-C to prevent CVD in type 2 DM is not recommended.	III	A	386
Antiplatelet therapy (e.g. with aspirin) is not recommended for people with DM who do not have CVD.	III	A	398

New Recommendation: Pharmacologic Therapy For T2DM

- In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, empagliflozin or liraglutide should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care. Ongoing studies are investigating the cardiovascular benefits of other agents in these drug classes. B

American Diabetes Association Standards of Medical Care in Diabetes. Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ! TZD
- ! Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ! TZD
- ! Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ! SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

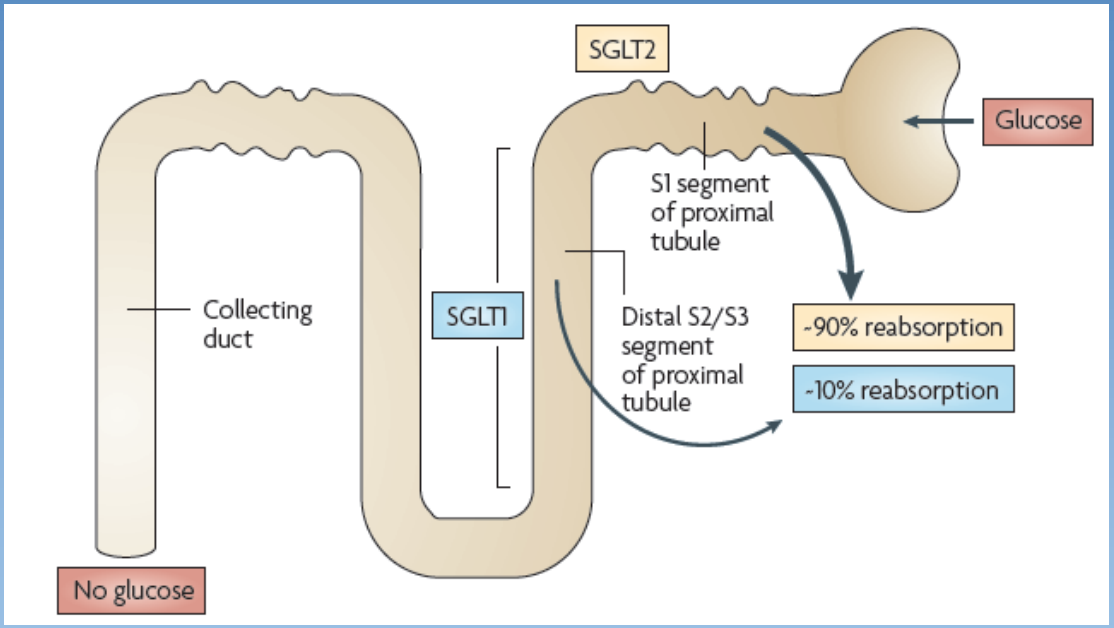
- ✓ Few adverse events and/or possible benefits
- ! Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE

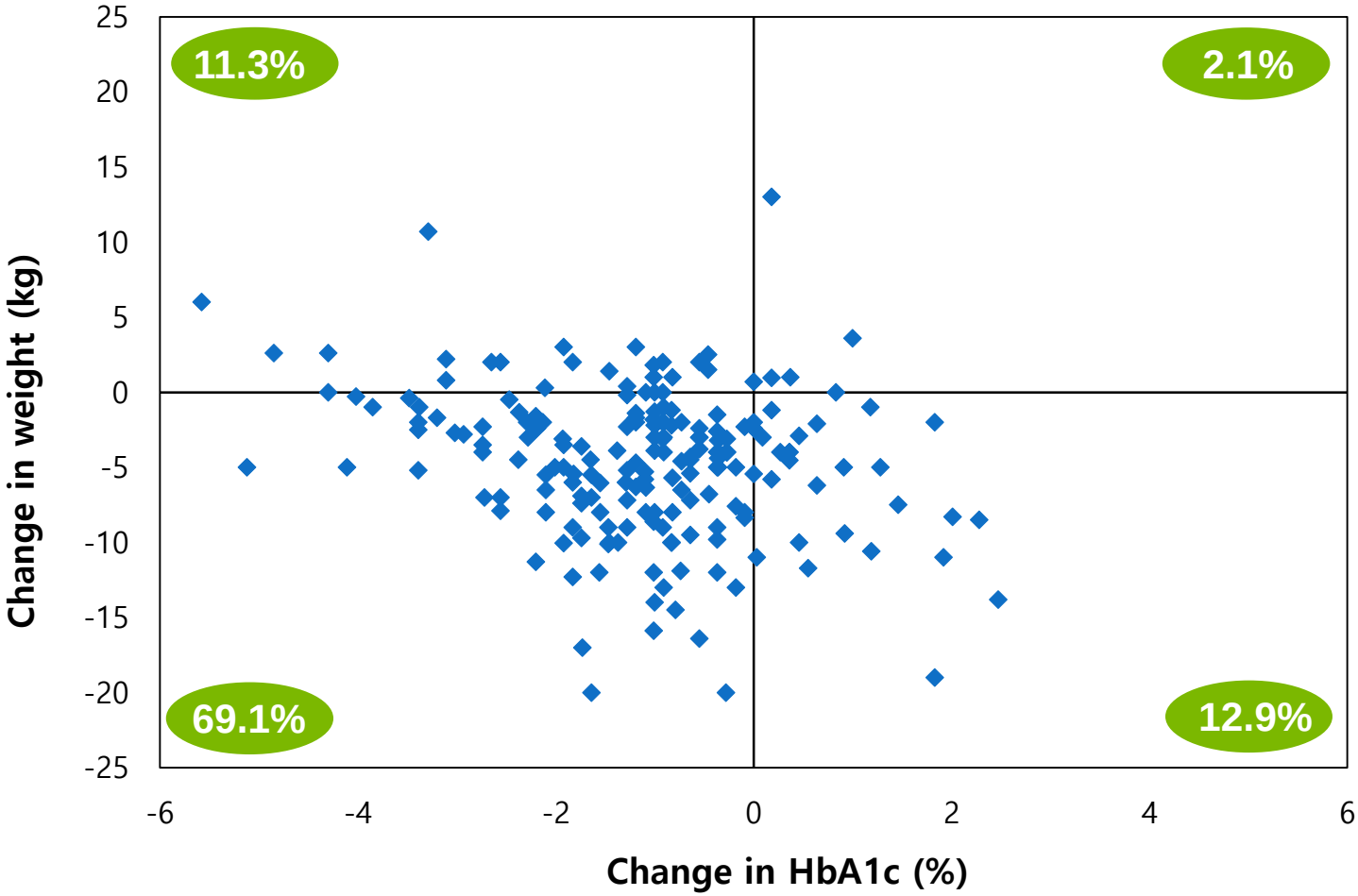
 DOI 10.4158/EP161682.CS

Recent Clinical Issues in SGLT2 inihibitors



Change in HbA1c (%) and weight (kg) at >180 days in the 3 most common combination groups

Change in HbA1c (%) and weight (kg) at >180 days from patients in the most common treatment groups: Dual (add-on to MET), triple and add-on to insulin (n=194)



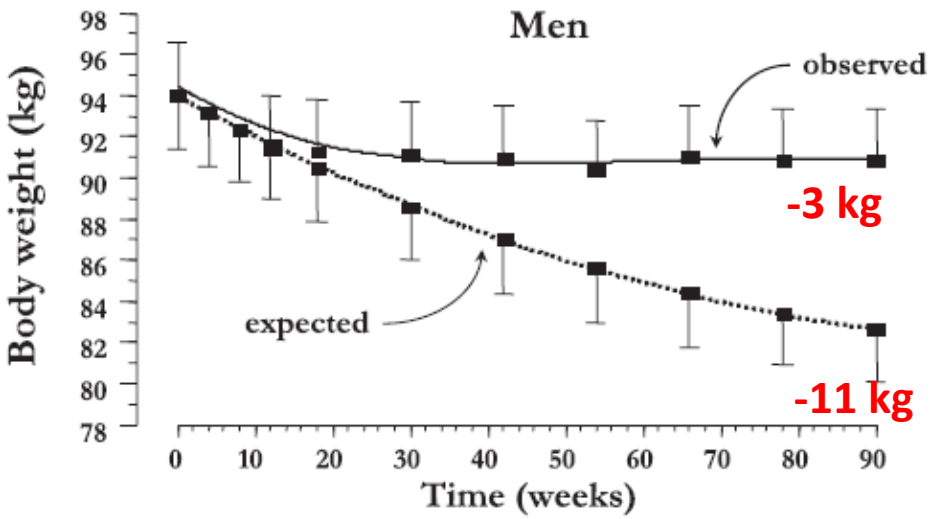
(°) Only patients with changes in both parameters are included for the calculations of the percentages for each quadrant. Data not shown for 1 patient with ΔHbA1c –9.06%, ΔWeight +2.0 kg.

Dapagliflozin is not indicated for the management of obesity . Weight change was a secondary endpoint in clinical trials

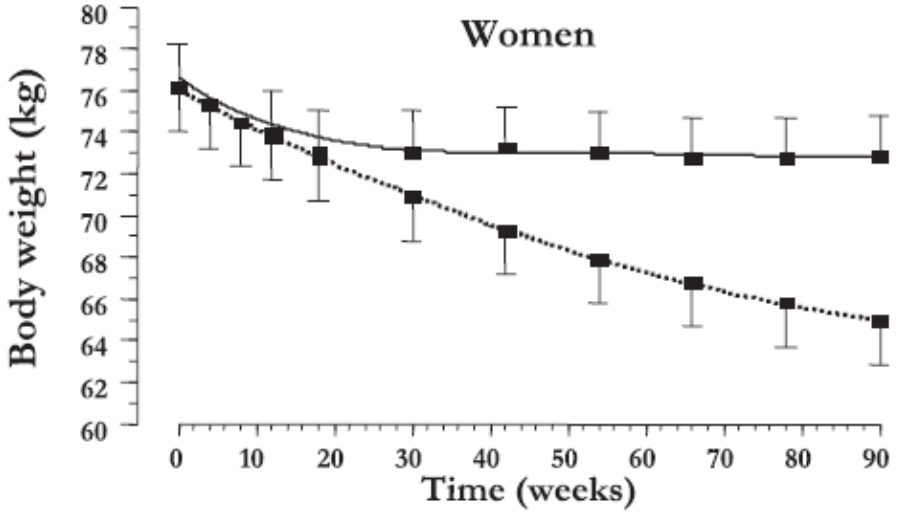
Wilding et al., Diabetes Ther. 2016 Dec;7(4):695-711

Energy Balance after SGLT2 inhibition

- Time course of observed and predicted weight loss (by glycosuria) with Empagliflozin



Modified from ref.



Modified from ref.

Predicted weight loss: -11.3 ± 3.1 kg
Observed weight loss: -3.2 ± 4.2 kg

Diabetes Care 2015 38 1730-1735.,http://webcasts.diabetes.org/netadmin/Preview_redirect.aspx?lid=39344

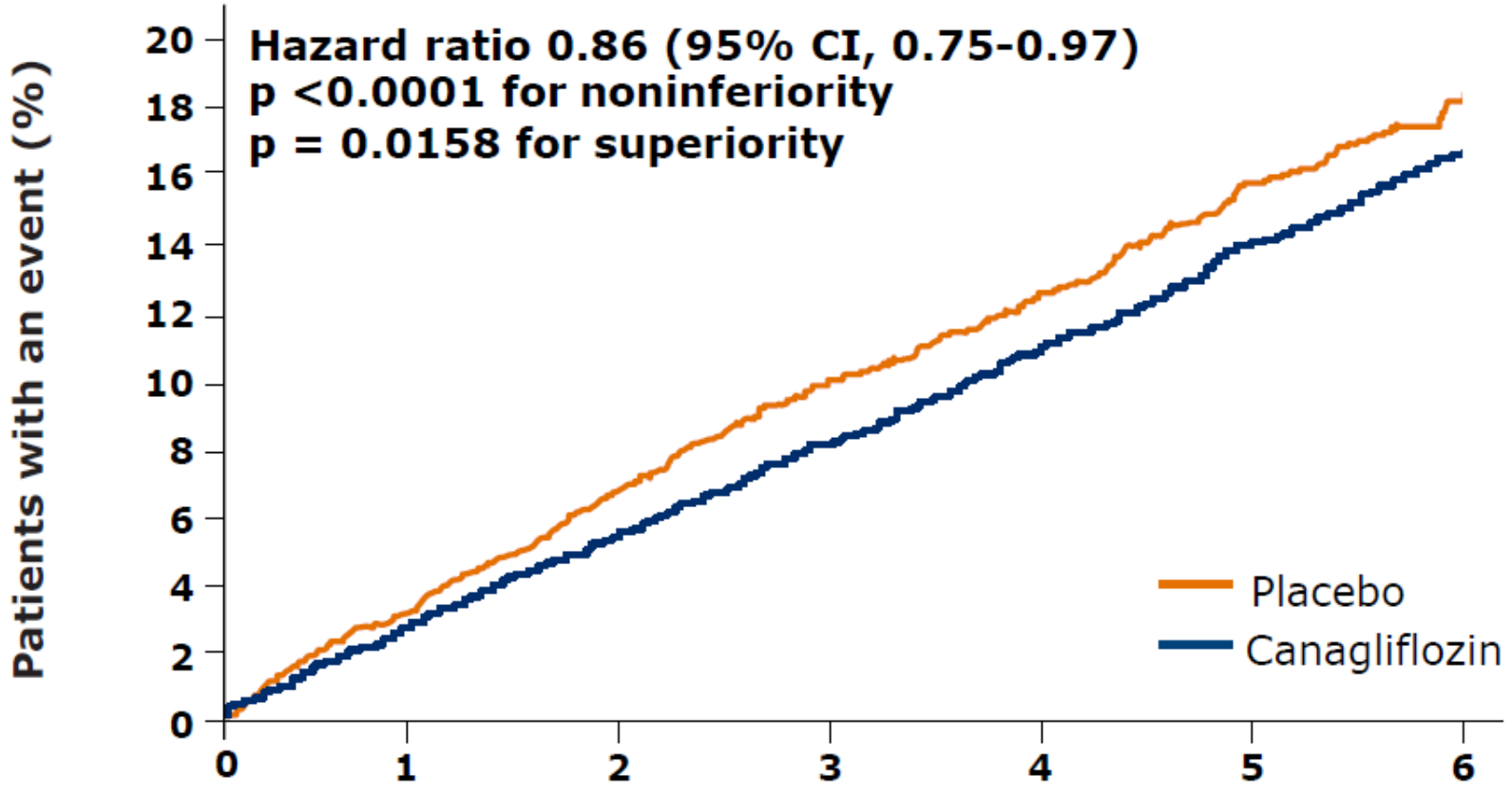
Postulated Adaptive Metabolic Mechanisms after SGLT2 inhibitor Therapy

- ↑ Glucose reabsorption by SGLT1 downstream to limit urinary glucose loss
- ↑ Endogenous glucose production (EGP) in part via an increase in glucagon and decrease in insulin levels
- ↑ Carbohydrate consumption in the setting of lower glycemia, lower insulin doses and lower body weight

Diabetes Care 2015 38 1730-1735.,http://webcasts.diabetes.org/netadmin/Preview_redirect.aspx?lid=39344

Primary MACE Outcome

CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

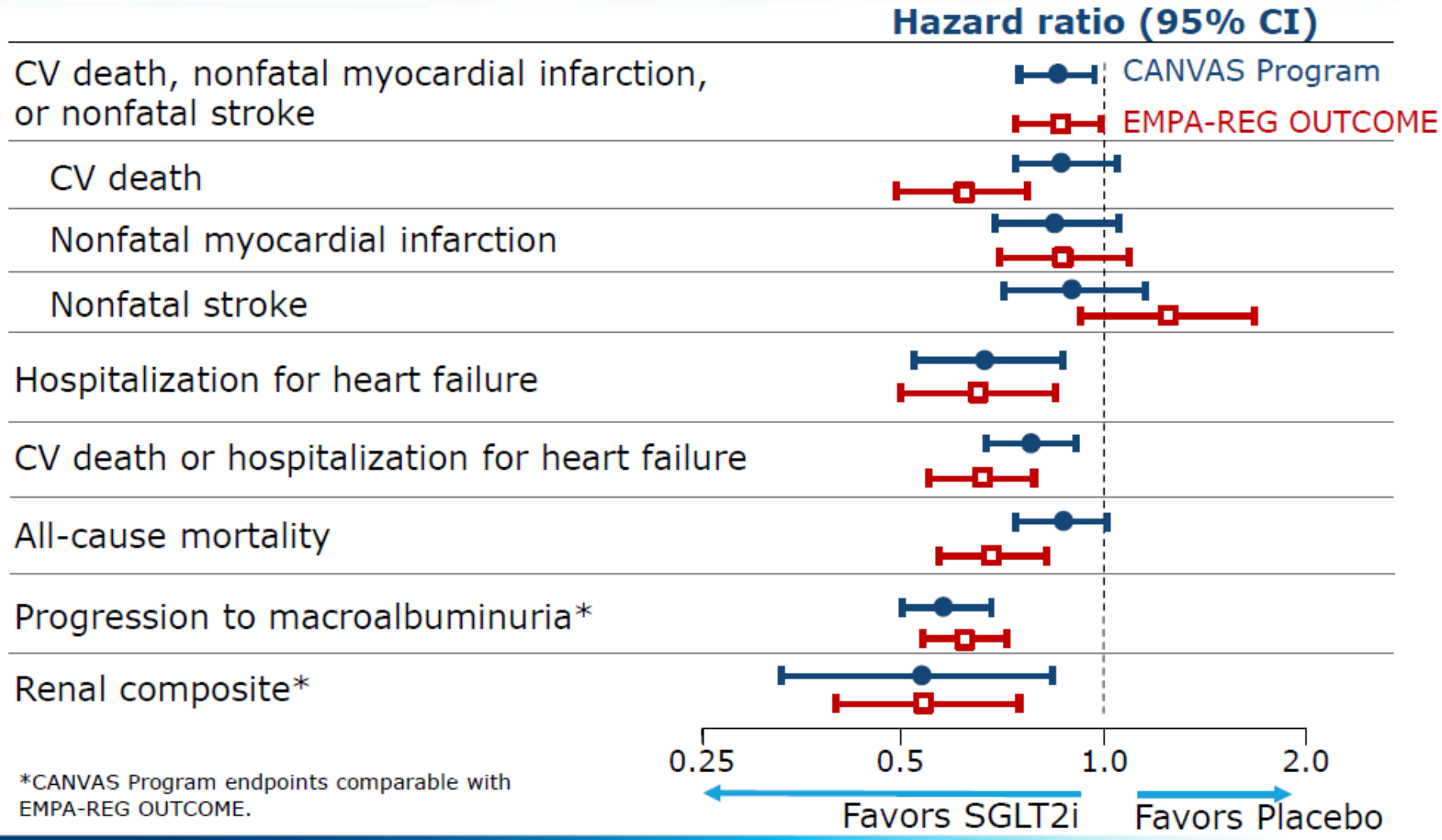


No. of patients							
Placebo	4347	4153	2942	1240	1187	1120	789
Canagliflozin	5795	5566	4343	2555	2460	2363	1661

Intent-to-treat analysis

CANVAS Program

Key Outcomes in the CANVAS Program and EMPA-REG OUTCOME



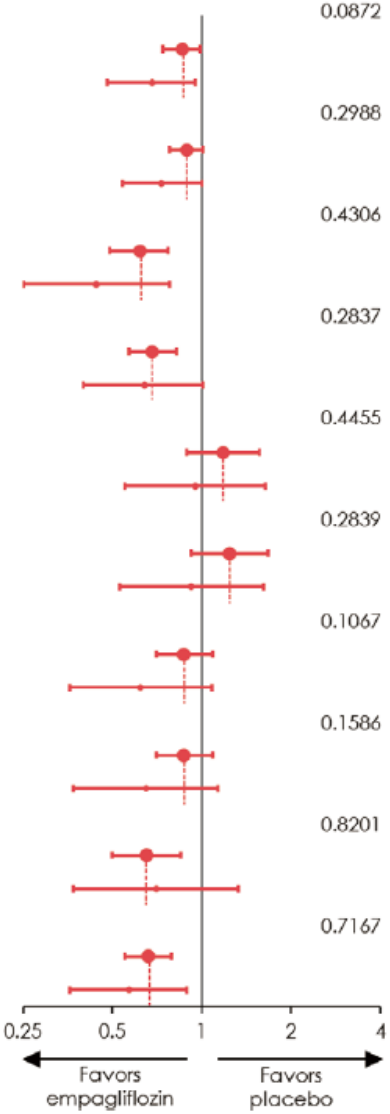
*CANVAS Program endpoints comparable with EMPA-REG OUTCOME.

Zinman Bet al. N Engl J Med. 2015 ;373(22):2117-2128.
Wanner K et al. N Engl J Med. 2016;375(4):323-334.

CANVAS Program

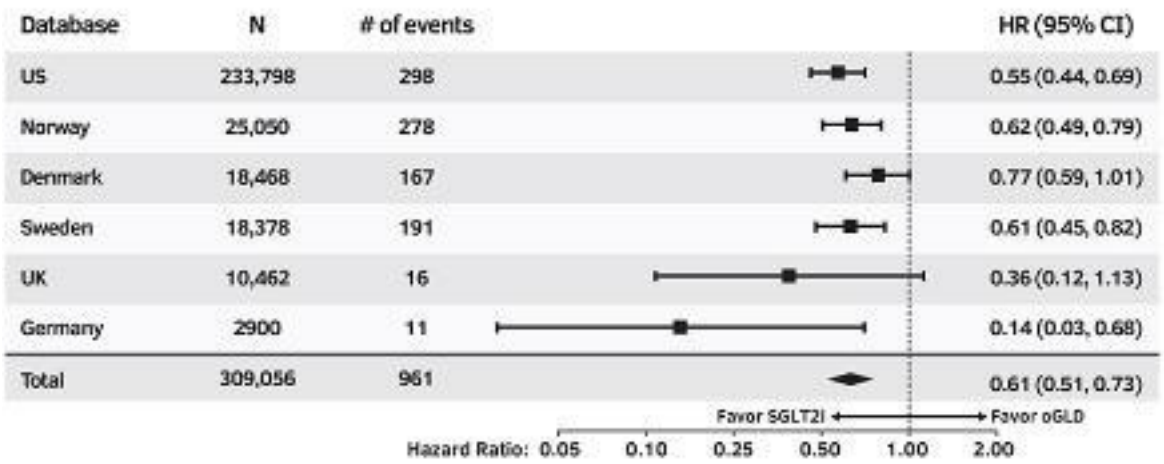
EMPA-REG OUTCOME: Asian Subgroup Analysis

	Empagliflozin *n with events/N (%)*	Placebo *n with events/N (%)*	Hazard ratio (95% CI)	p-value for race by treatment interaction
3-point MACE				0.0872
Overall	490/4687 (10.5)	282/2333 (12.1)	0.86 (0.74–0.99)	
Asian	79/1006 (7.9)	58/511 (11.4)	0.68 (0.48–0.95)	
4-point MACE				0.2988
Overall	599/4687 (12.8)	333/2333 (14.3)	0.89 (0.78–1.01)	
Asian	101/1006 (10.0)	69/511 (13.5)	0.73 (0.54–1.00)	
CV death				0.4306
Overall	172/4687 (3.7)	137/2333 (5.9)	0.62 (0.49–0.77)	
Asian	22/1006 (2.2)	25/511 (4.9)	0.44 (0.25–0.78)	
All-cause mortality				0.2837
Overall	269/4687 (5.7)	194/2333 (8.3)	0.68 (0.57–0.82)	
Asian	41/1006 (4.1)	32/511 (6.3)	0.64 (0.40–1.01)	
Fatal or non-fatal stroke				0.4455
Overall	164/4687 (3.5)	69/2333 (3.0)	1.18 (0.89–1.56)	
Asian	38/1006 (3.8)	20/511 (3.9)	0.95 (0.55–1.64)	
Non-fatal stroke				0.2839
Overall	150/4687 (3.2)	60/2333 (2.6)	1.24 (0.92–1.67)	
Asian	35/1006 (3.5)	19/511 (3.7)	0.92 (0.53–1.62)	
Fatal or non-fatal myocardial infarction				0.1067
Overall	223/4687 (4.8)	126/2333 (5.4)	0.87 (0.70–1.09)	
Asian	29/1006 (2.9)	23/511 (4.5)	0.62 (0.36–1.08)	
Non-fatal myocardial infarction				0.1586
Overall	213/4687 (4.5)	121/2333 (5.2)	0.87 (0.70–1.09)	
Asian	29/1006 (2.9)	22/511 (4.3)	0.65 (0.37–1.13)	
Hospitalization for heart failure				0.8201
Overall	126/4687 (2.7)	95/2333 (4.1)	0.65 (0.50–0.85)	
Asian	22/1006 (2.2)	16/511 (3.1)	0.70 (0.37–1.33)	
Heart failure hospitalization or CV death				0.7167
Overall	265/4687 (5.7)	198/2333 (8.5)	0.66 (0.55–0.79)	
Asian	39/1006 (3.9)	35/511 (6.8)	0.57 (0.36–0.89)	



SGLT-2i CV Safety Real World Evidence : CVD-REAL presented at 66th ACC (2017)

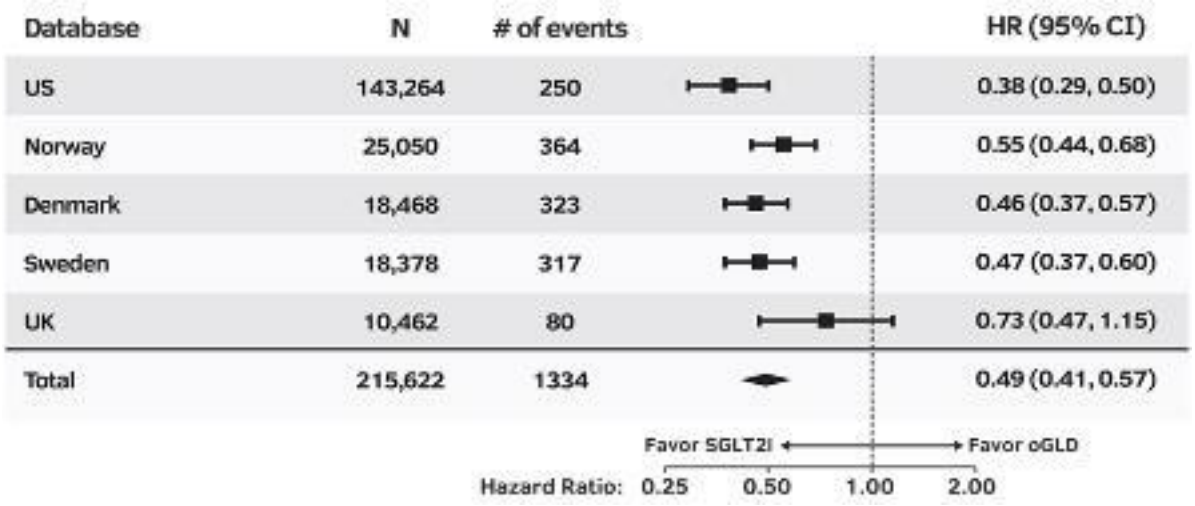
Primary endpoint: hospitalisation from heart failure



P-value for SLGT2 inhibitor vs oGLD: <0.001

Heterogeneity p-value 0.17

Secondary endpoint: all-cause mortality



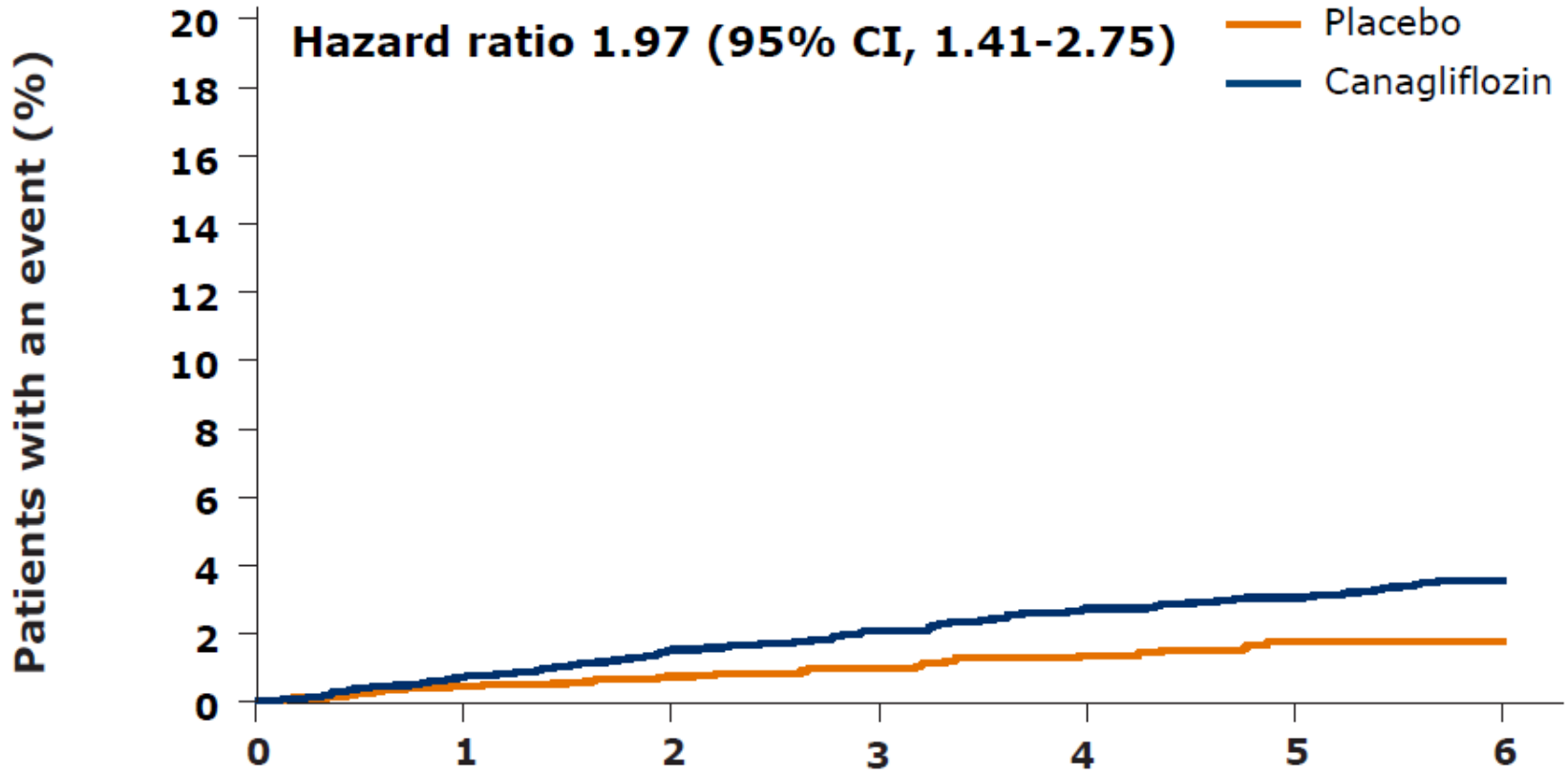
P-value for SLGT2 inhibitor vs oGLD: <0.001

Heterogeneity p-value 0.09

Result from RWE studies may not necessarily relate to the effect of the intervention/treatment alone and results should be still be interpreted in the context of RCT findings. Forxiga is not indicated for CV risk reduction by MFDS.

Data presented at the 66th Annual Scientific Session of the American College of Cardiology, Washington, DC, March 17–19, 2017

Lower-extremity Amputations



No. at risk							
Placebo	4344	4217	3037	1289	1247	1194	844
Canagliflozin	5790	5634	4420	2618	2536	2460	1765

Increased risk communicated to health authorities, investigators, and providers in 2016 based on IDMC letter.

CANVAS Program

Amputation Risk Factors - Multivariate Analysis

Risk Factor at Baseline	Hazard Ratio	95% CI
Amputation	20.9	(14.2-30.8)
Peripheral vascular disease*	3.1	(2.2-4.5)
Male	2.4	(1.6-3.5)
Neuropathy	2.1	(1.6-2.9)
HbA1c >8%	1.9	(1.4-2.6)
Canagliflozin treatment	1.8	(1.3-2.5)
Presence of CV disease	1.5	(1.0-2.3)

- Predictors of amputation risk are similar in both arms
- Canagliflozin treatment, independent of the risk factors, increased amputation risk

Predictive on univariate analysis: nephropathy, insulin use, retinopathy, loop diuretic, eGFR, diabetes duration
Factors assessed but not significantly predictive: non-loop diuretic, smoking, SBP, hemoglobin, age

* Excludes amputations

SGLT2 inhibitors and risk of lower limb amputation (mainly toe)

Advice to Healthcare Professionals

* All patients taking an SGLT2 inhibitor should be counselled on the importance of routine preventative foot care.
* Patients taking canagliflozin, with risk factors for amputation events, such as previous amputation, existing peripheral vascular disease or neuropathy, should be monitored carefully and counselled on the importance of maintaining adequate hydration.
* Patients should be counselled to notify their healthcare professional if they develop ulceration, discolouration, new pain or tenderness in their feet.
* Treatment discontinuation should be considered for patients taking canagliflozin who develop amputation preceding events, for example, lower extremity skin ulcer, infection, osteomyelitis or gangrene.

Euglycemic DKA

Assessment and Precipitating Factors

Assess for DKA when symptoms are present, even if glucose <250 mg/dL

- Nausea/vomiting
- Abdominal pain
- Generalized malaise
- Shortness of breath

Consider factors that predispose to DKA before and during treatment with an SGLT2 inhibitor

- Reduced caloric intake
- Pancreatic insulin deficiency
- Alcohol abuse
- Insulin dose reduction

SGLT2 inhibitors are currently not approved for the treatment of type 1 diabetes.

Rosenstock J, et al. *Diabetes Care*. 2015;38:1638-1642; Erondu N, et al. *Diabetes Care*. 2015;38:1680-1686; Peters AL, et al. *Diabetes Care*. 2015;38:1687-1693.

AACE/ACE Position Statement on SGLT-2 inhibitors and DKA risk

To minimize the risk of DKA associated with SGLT-2 inhibitors

1. Consider stopping the SGLT-2 inhibitor at least 24 hours prior to elective surgery, planned invasive procedures, or anticipated severe stressful physical activity such as running a marathon. As noted above, urinary glucose loss due to SGLT-2 inhibition may persist after the drug is stopped.
2. Avoid stopping insulin or decreasing the dose excessively.
3. For emergency surgery or any extreme stress event, the drug should be stopped immediately, and appropriate clinical care should be provided.
4. Patients taking SGLT-2 inhibitors should avoid excess alcohol intake and very-low-carbohydrate/ketogenic diets.
5. SGLT-2 inhibitors are not approved for use in T1D.

FDA Drug Safety Communication

Acute Kidney Injury

- FDA strengthened existing warnings about acute kidney injury for canagliflozin and dapagliflozin (May 18, 2016)
  - 101 cases* reported from 3/29/2013 to 10/19/2015
  - Most cases are reversible

Meanwhile, with this possibility in mind, we propose avoidance of the concomitant administration of agents that lead to iatrogenic hypoxic medullary injury: avoidance of NSAIDs in patients on SGLT2 inhibitors and cessation of SGLT2 inhibitors prior to radiocontrast studies.

Diabetes Care Publish Ahead of Print, published online January 27, 2017

*Cases were reported to FAERS.
FDA website.

Take-Home Messages: To Date - Summary about SGLT2 inhibitors

* Modest glycemic lowering efficacy (HbA1c 0.5-1.0%)
  * The higher at baseline, the larger reduction in HbA1c
  * Insulin independent mechanism
* Weight reduction by 2-3kg (Fat mass >> Lean mass)
  * The heavier at baseline, the larger reduction in body weight
* BP lowering effect (SBP ~4mmHg, DBP ~ 2mmHg)
* CV benefit (as secondary prevention with previous CVD history)
* Reno-protective effect with potential microvascular Cx prevention
* No data to support the use in early diabetes or as a primary prevention
* Increased risk of lower limb amputation in CANVAS

Take-Home Messages: Good Candidates for SGLT2 inhibitors?

GOOD for T2DM with

* eGFR ≥ 60 ml/min/1.73m^2
* Mild hypertension (SBP 4mmHg↓, DPB 2mmHg↓)
* Overweight or obese
* Frequent HYPO and/or Wt gain on another antidiabetic agents
* GI side-effects on another antidiabetic agents
* Poor control of PPG on another antidiabetic agents

NOT GOOD for T2DM with

* eGFR < 45~60 ml/min/1.73m^2
* Prone to develop ketosis (T1DM or LADA, Dehydration)
* Previous history of UTI or genital infection, old ages (>75yrs old)

Thank you for your attention!!