

SGLT-2 inhibitie: cardiovasculaire risico- interventie bij T2DM?

Cees J. Tack, internist

Radboudumc

Conflict of interest

(potentiële) belangenverstrengeling	zie hieronder
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Onderzoeksondersteuning (grants): AstraZeneca Voordrachten / deelname adviesraad: MSD NovoNordisk

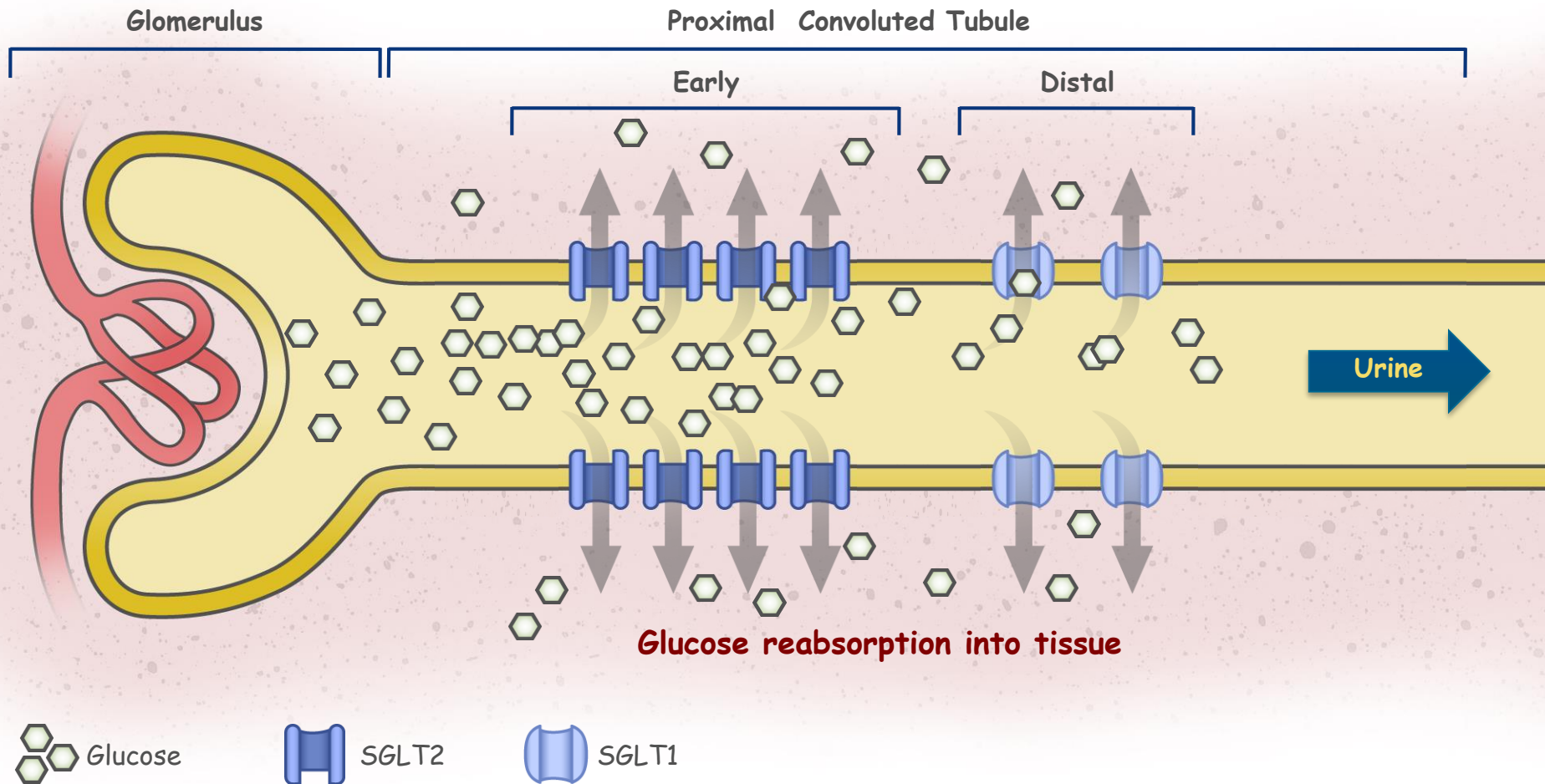
Doelen

- Twee nieuwe klassen: hier - SGLT-2 inhibitors
- Nieuwste studieresultaten
- Effect op CV risico
- Implicaties voor de interne geneeskunde / richtlijnen

Rol van de nieren in het glucosemetabolisme

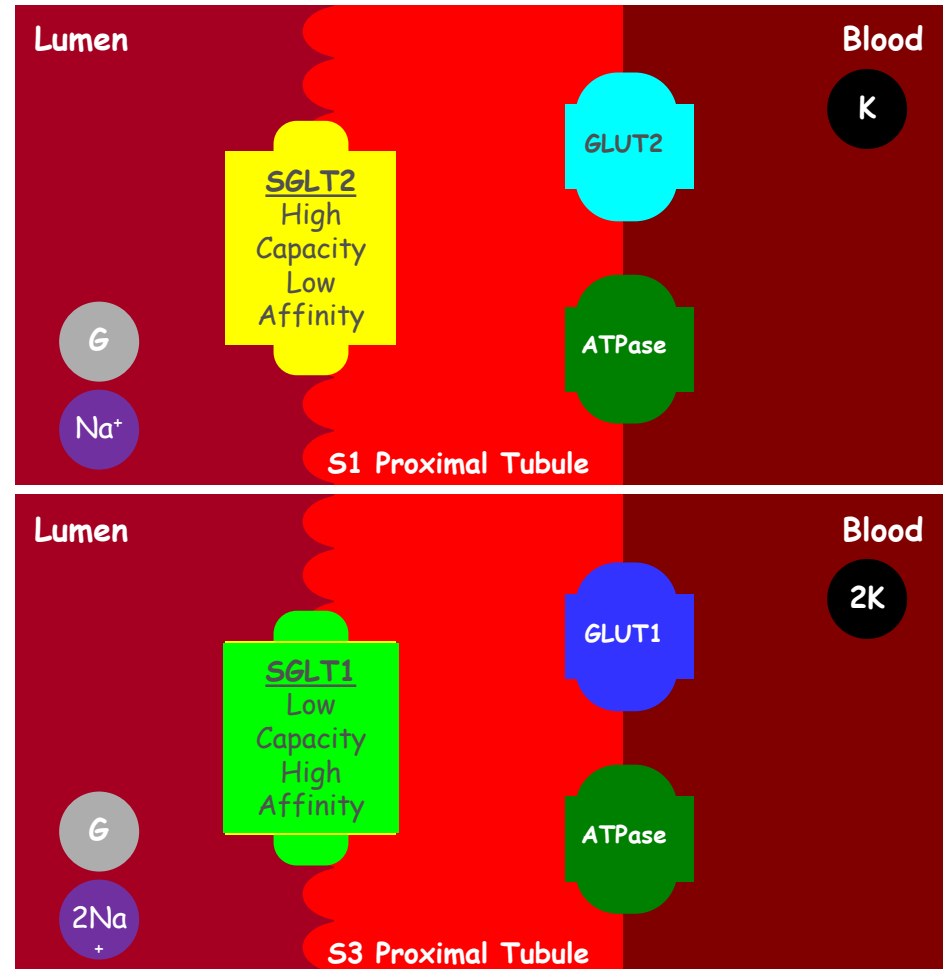
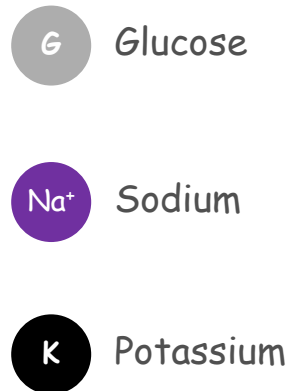
- 180 g glucose dagelijks gefiltreerd
- Vrijwel alle glucose wordt in de proximale tubulus gereabsorbeerd door SGLT2 (~90%) en SGLT1 (~10%)
- Nierdrempel ~10 mmol/L (DM2: hoger)

Glucose Reabsorption in a Nondiabetic Person (Plasma Glucose <10 mmol/L)

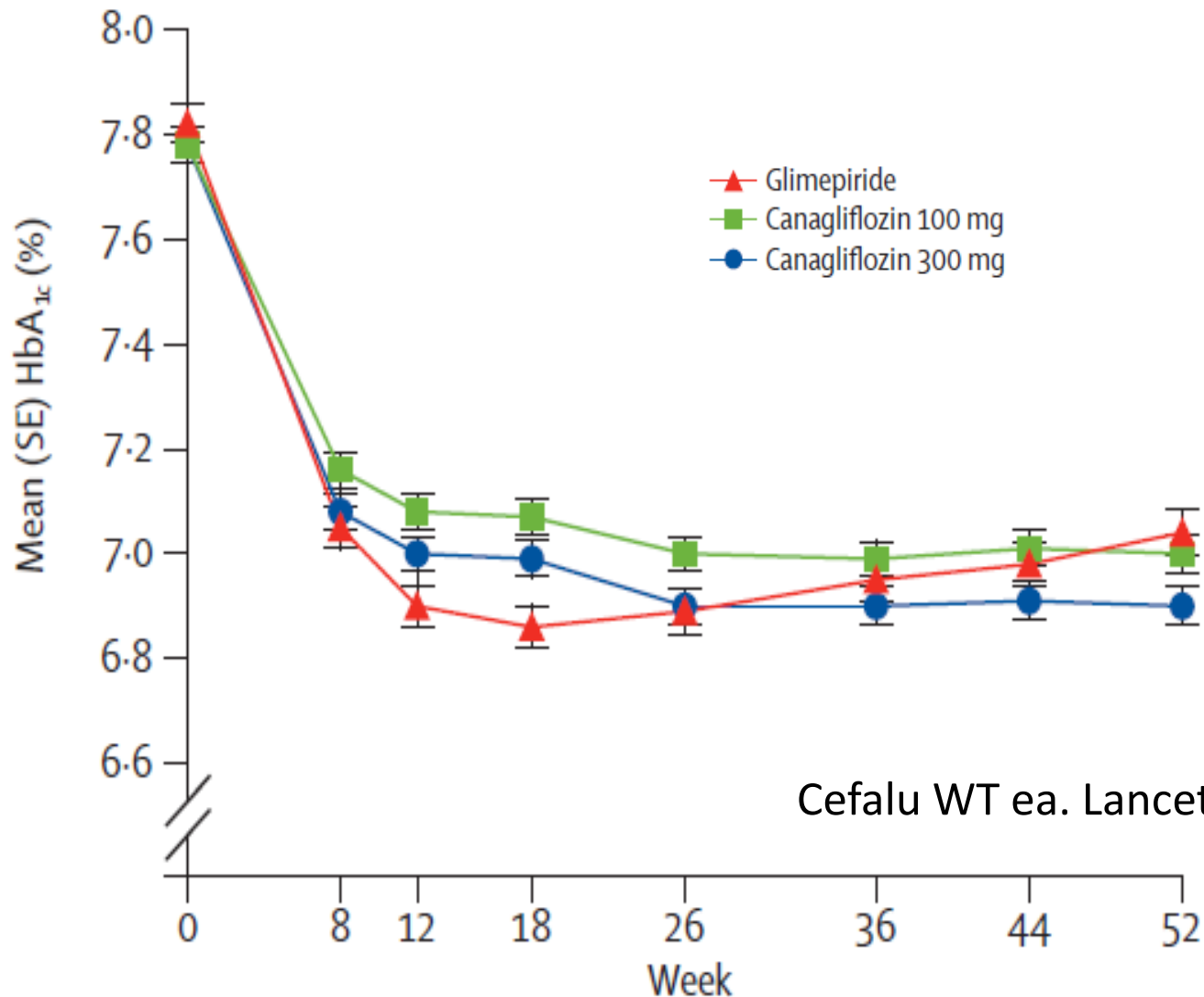


Adapted with permission from Rothenberg PL et al.
SGLT = sodium-glucose linked co-transporter.
Rothenberg PL et al. Poster presented at EASD 2010; Stockholm, Sweden

Glucose Transport in Tubular Epithelial Cells

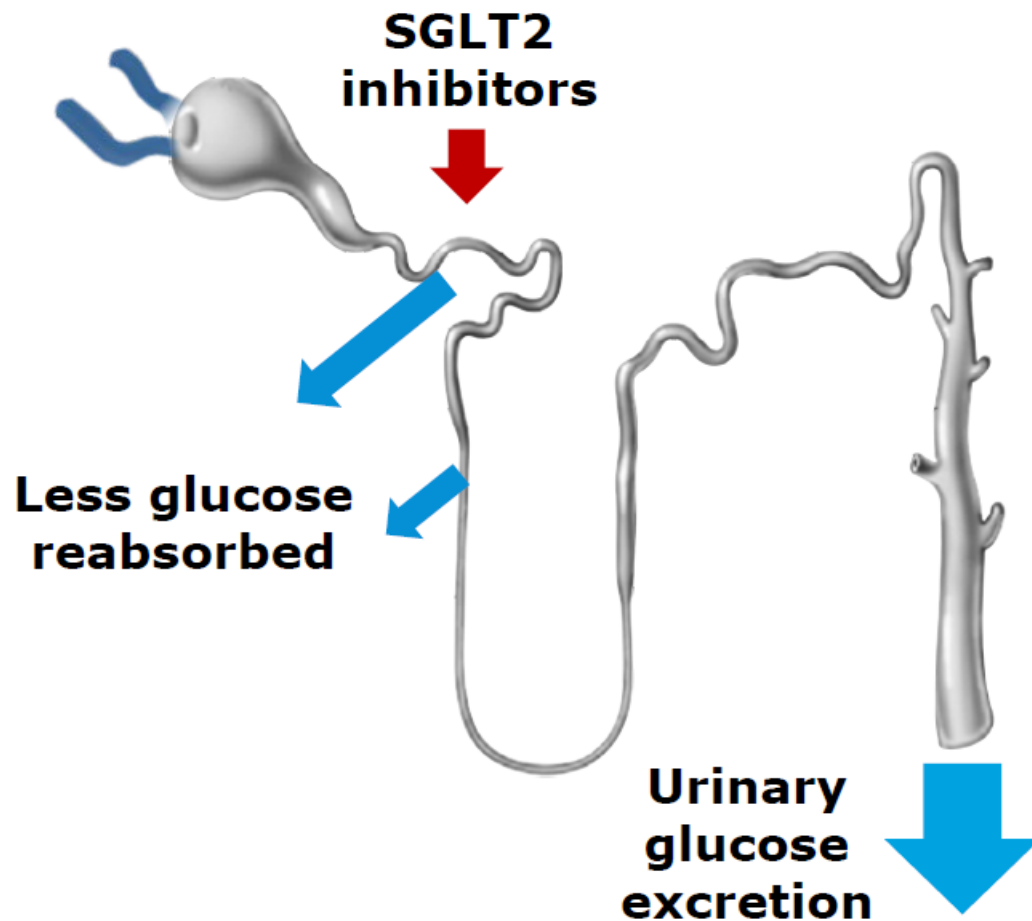


SGLT-2i lower glucose



Cefalu WT ea. Lancet 2013; 382:941-50.

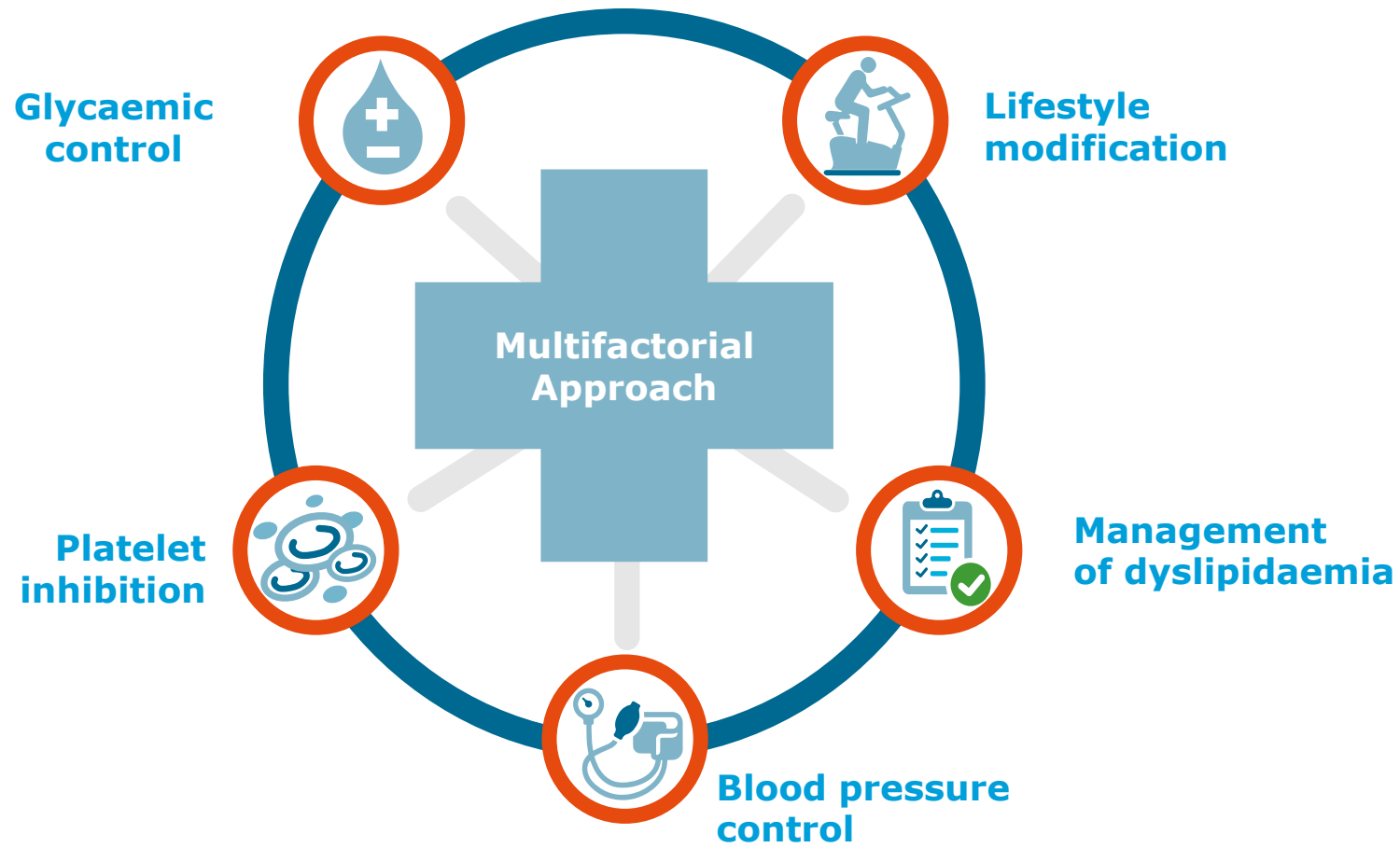
SGLT2 Inhibition



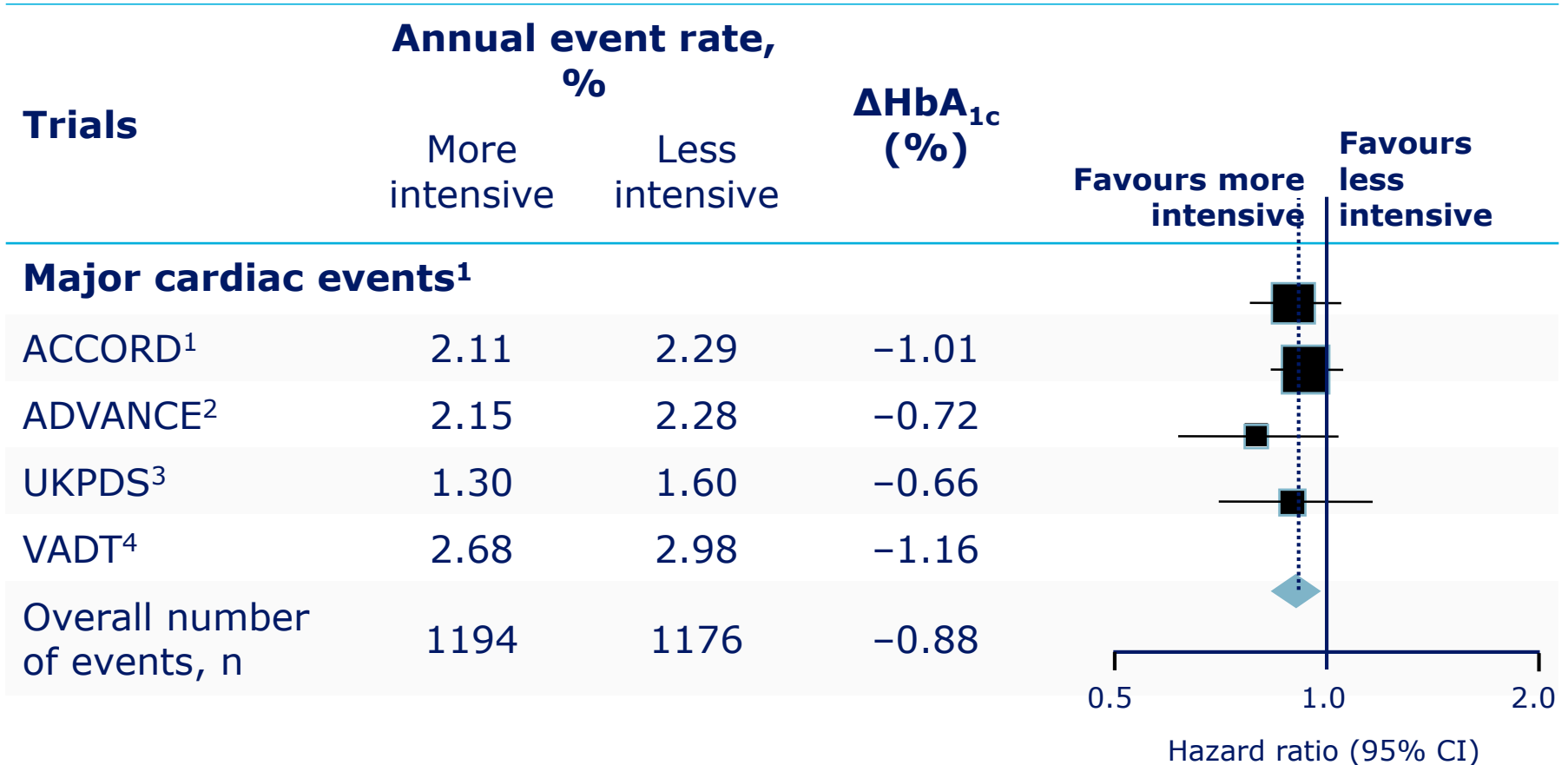
CV Risk Factor Reduction

- Lowers blood glucose levels
- Lowers BP via osmotic diuresis
- Increases urinary caloric loss with reductions in body weight
- Reduces albuminuria possibly due to alterations in tubuloglomerular feedback

How do we modify CV risk in T2DM?



Meta-analysis: Modest reduction in major cardiovascular events with ↓ glycaemia



Een nieuwe trend: cardiovasculaire veiligheid

Cardiovascular outcomes trials

Efficacy vs safety; superiority vs non-inferiority

Efficacy trials

Aim: Demonstrate CV benefit

Initiation of treatment vs comparator



No treatment adjustment

Difference between treatment arms
e.g. biomarkers such as HbA_{1c} or lipids



Significant reduction in CV outcomes
vs active comparator

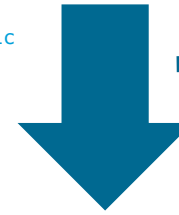
Lower CV risk vs placebo/active comparator

Safety trials

Aim: Demonstrate CV safety

Initiation of treatment vs placebo

Maintain similar HbA_{1c}
in treatment arms



Treatment adjustment

■ ■ ■ (standard of care)

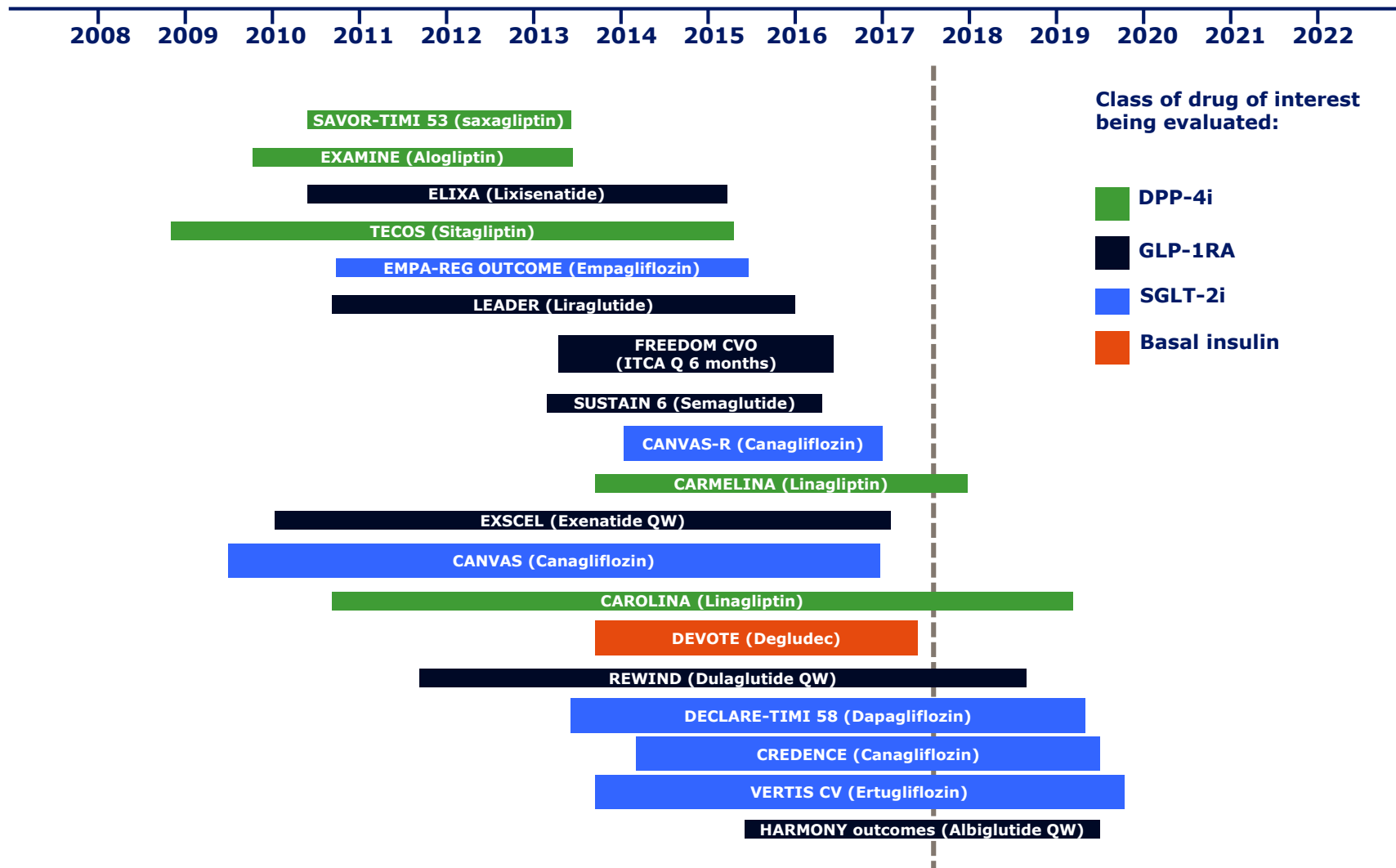
Small/no difference in biomarkers e.g. HbA_{1c}
observed between treatment arms



Non-inferiority vs placebo

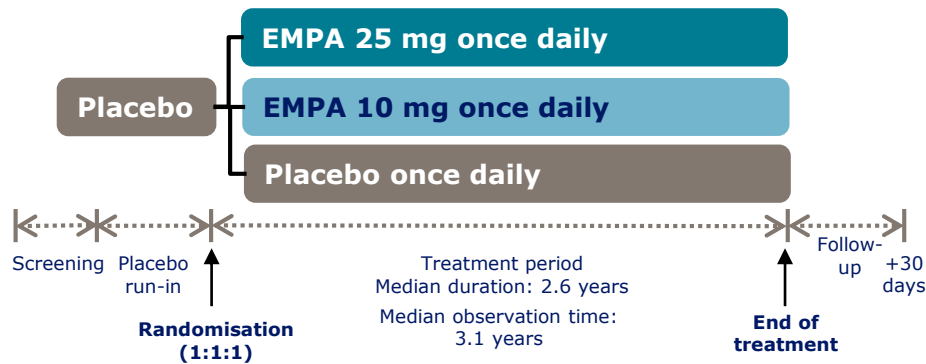
**No unacceptable increase in CV risk vs placebo
as part of standard care**

Recent and ongoing CVOTs



EMPA-REG OUTCOME

Study design and inclusion criteria



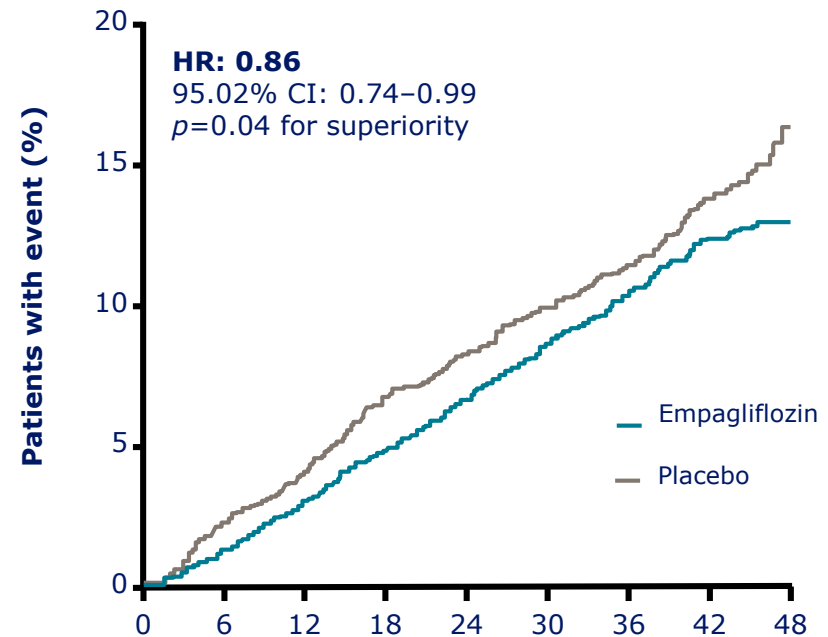
N=7028

- T2DM with established CV disease
- Age: ≥ 18 years; ≥ 20 years in Japan; ≤ 65 years in India
- Drug-naïve and $\text{HbA}_{1c} \geq 7.0$ to $\leq 9.0\%$ or stable background antidiabetes therapy* and $\text{HbA}_{1c} \geq 7.0$ to $\leq 10.0\%$
- BMI $\leq 45.0 \text{ kg/m}^2$ and $\text{eGFR} \geq 30 \text{ mL/min/1.73m}^2$

Primary endpoint

- Three-point MACE – time to first occurrence of:
 - CV death, non-fatal MI[†], or non-fatal stroke

Time to first occurrence of CV death, non-fatal MI[†], or non-fatal stroke

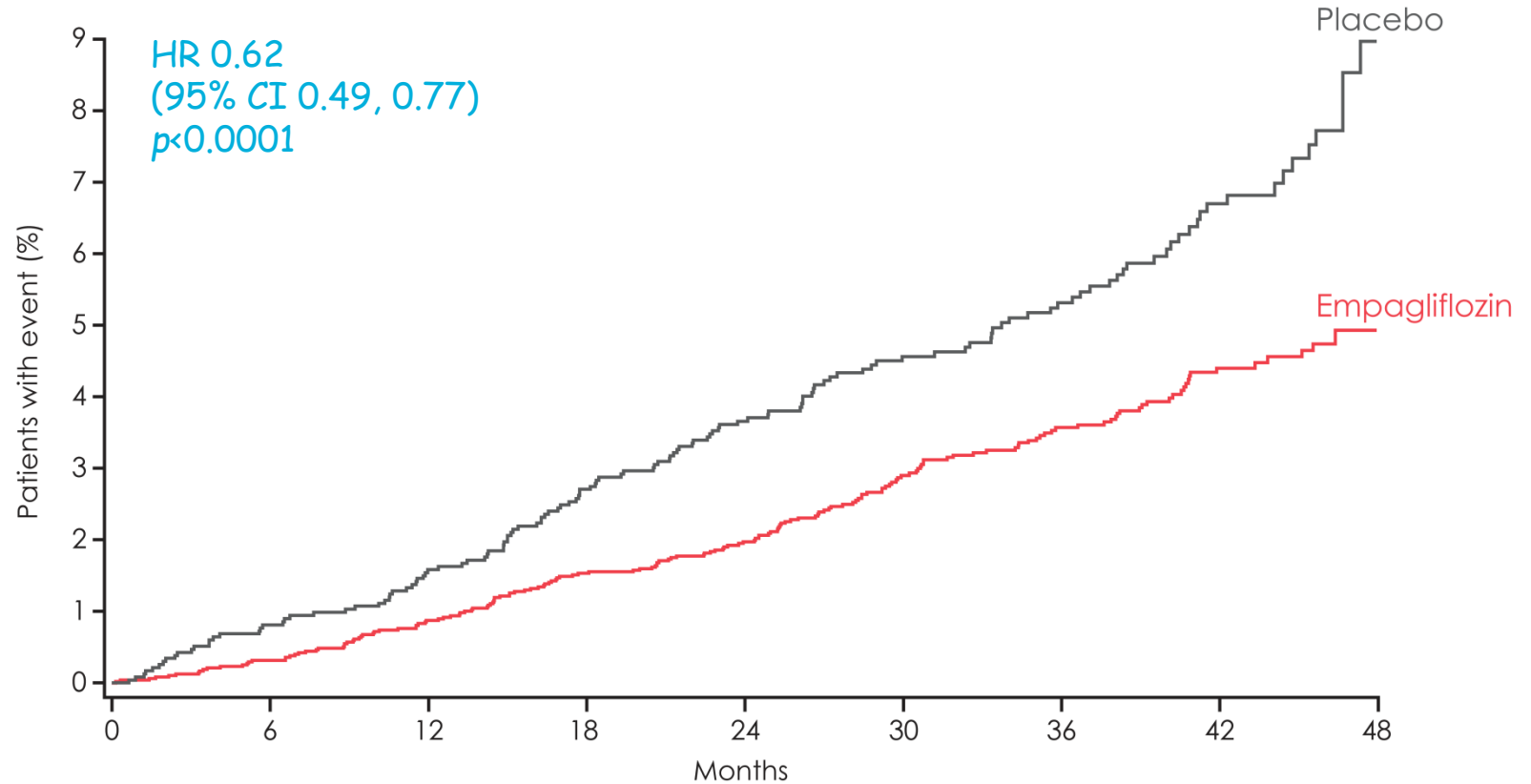


Month

Patients at risk

Empagliflo	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

CV death



No. of patients

Empagliflozin 4687

Placebo 2333

4651

2303

4608

2280

4556

2243

4128

2012

3079

1503

2617

1281

1722

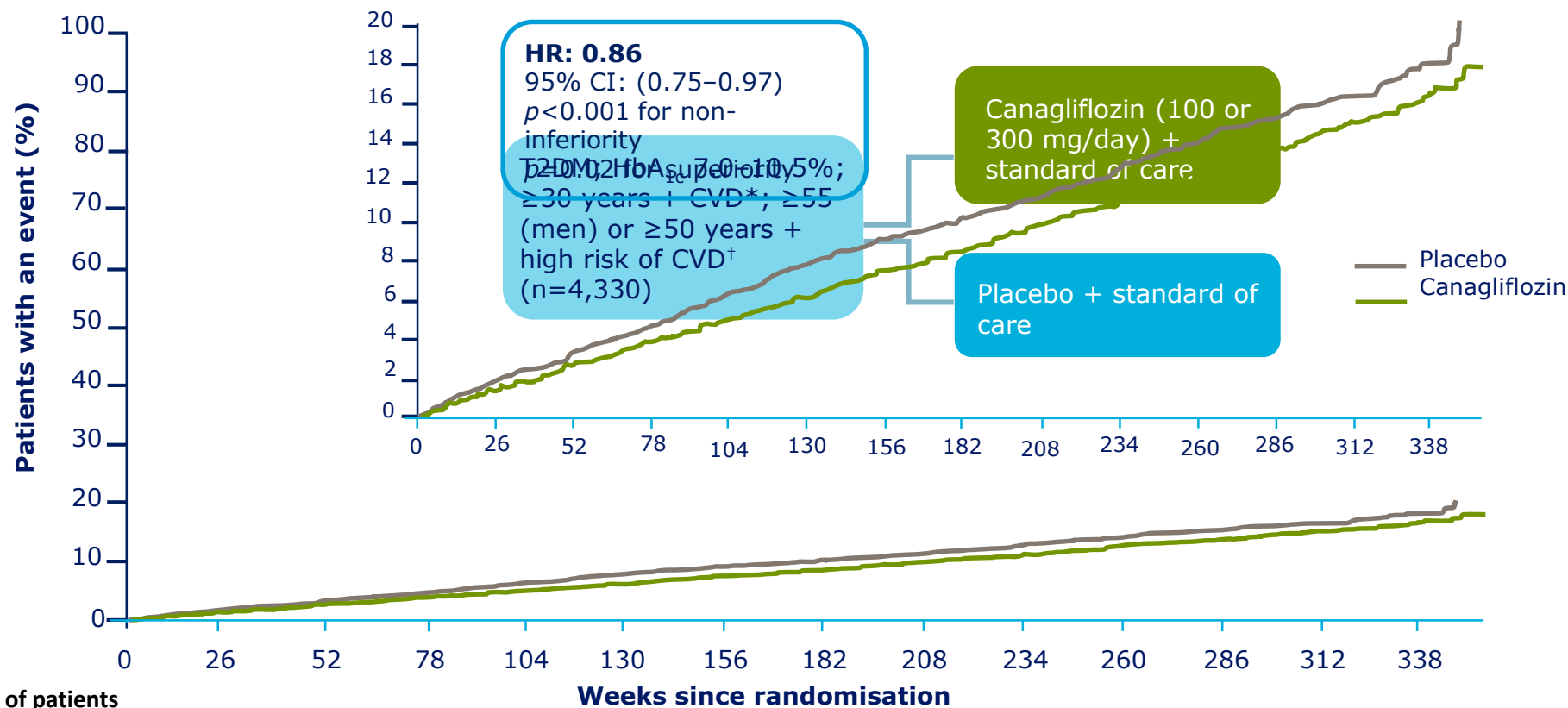
825

414

177

CANVAS Program: Primary outcome

Death from CV causes, non-fatal MI or non-fatal stroke



No. of patients

Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216
Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448

HR and 95% CI were estimated with the use of Cox regression models with stratification according to trial and history of CV disease for all canagliflozin groups combined versus placebo. Analyses are based upon the full integrated data set comprising all participants who underwent randomisation

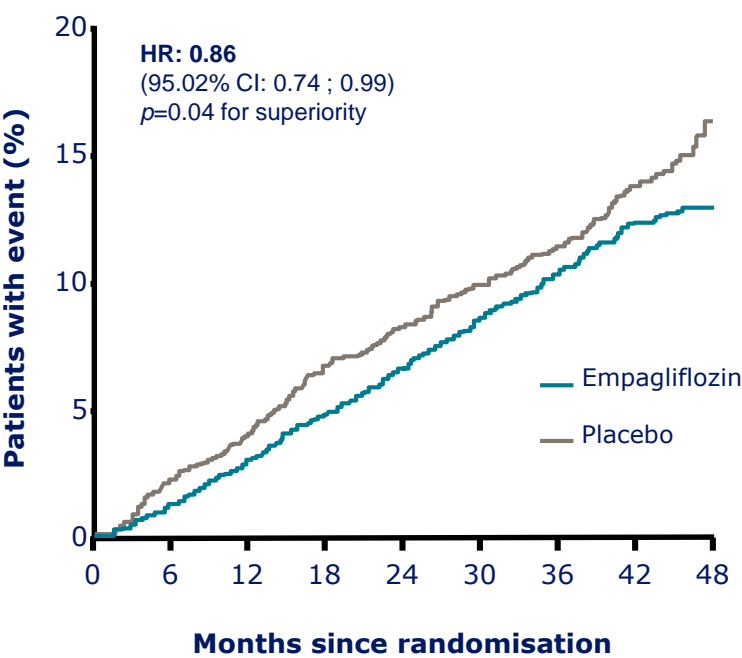
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; T2DM, type 2 diabetes mellitus

Neal B et al. *N Engl J Med* 2017;376:1644–657

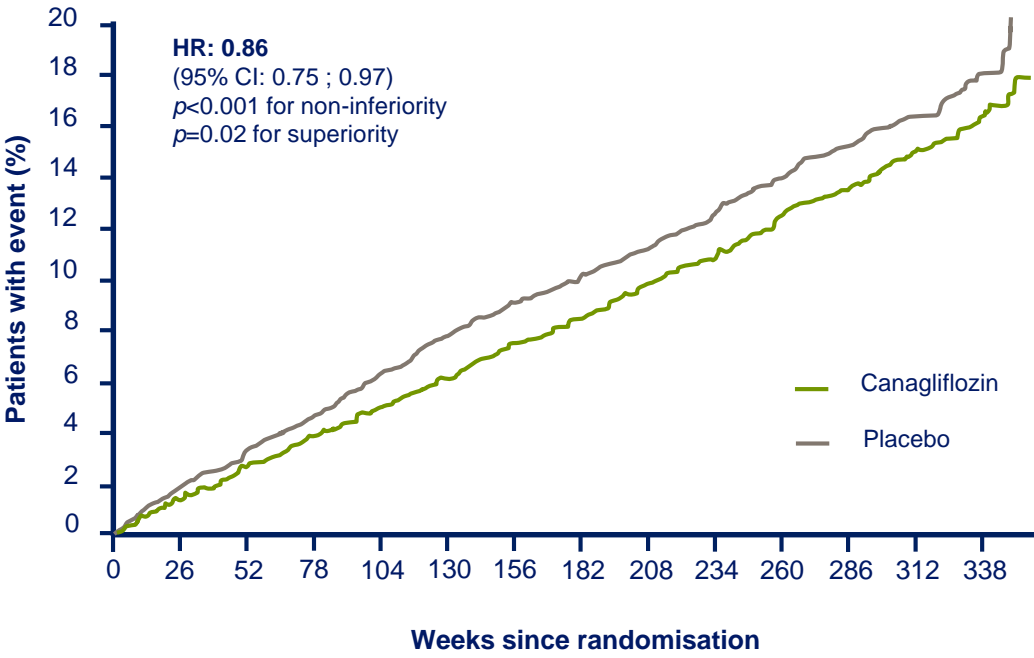
SGLT-2i CVOTs

Time to first occurrence of CV death, non-fatal MI*, or non-fatal stroke

EMPA-REG OUTCOME¹



CANVAS Program²

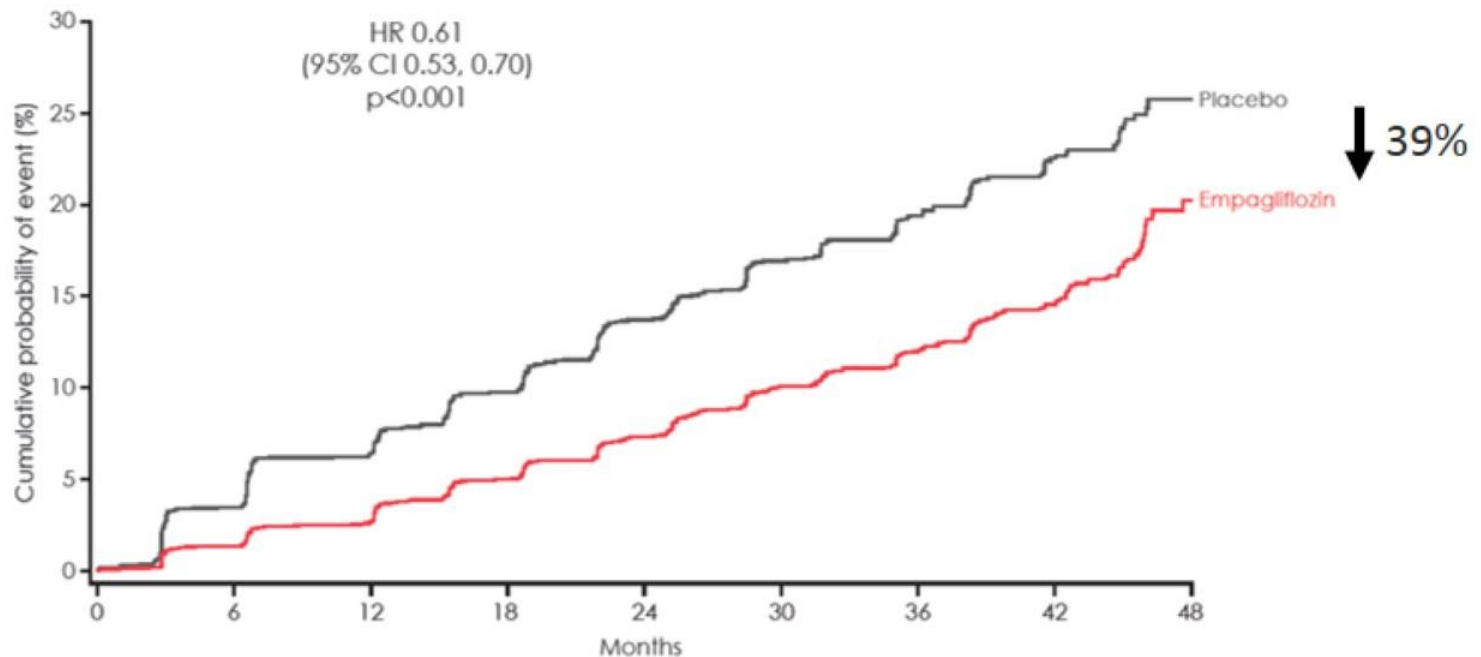


No. at risk

Empa	4687	4580	4455	4328	3851	2821	2359	1534	370
PBO	2333	2256	2194	2112	1875	1380	1161	741	166

Cana	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448
PBO	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216

EMPA REG OUTCOME: New Onset or Worsening DKD*



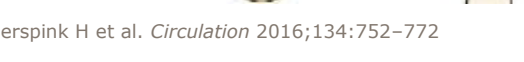
No. of Patients

Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

*Treated set (≥ 1 dose of study drug).

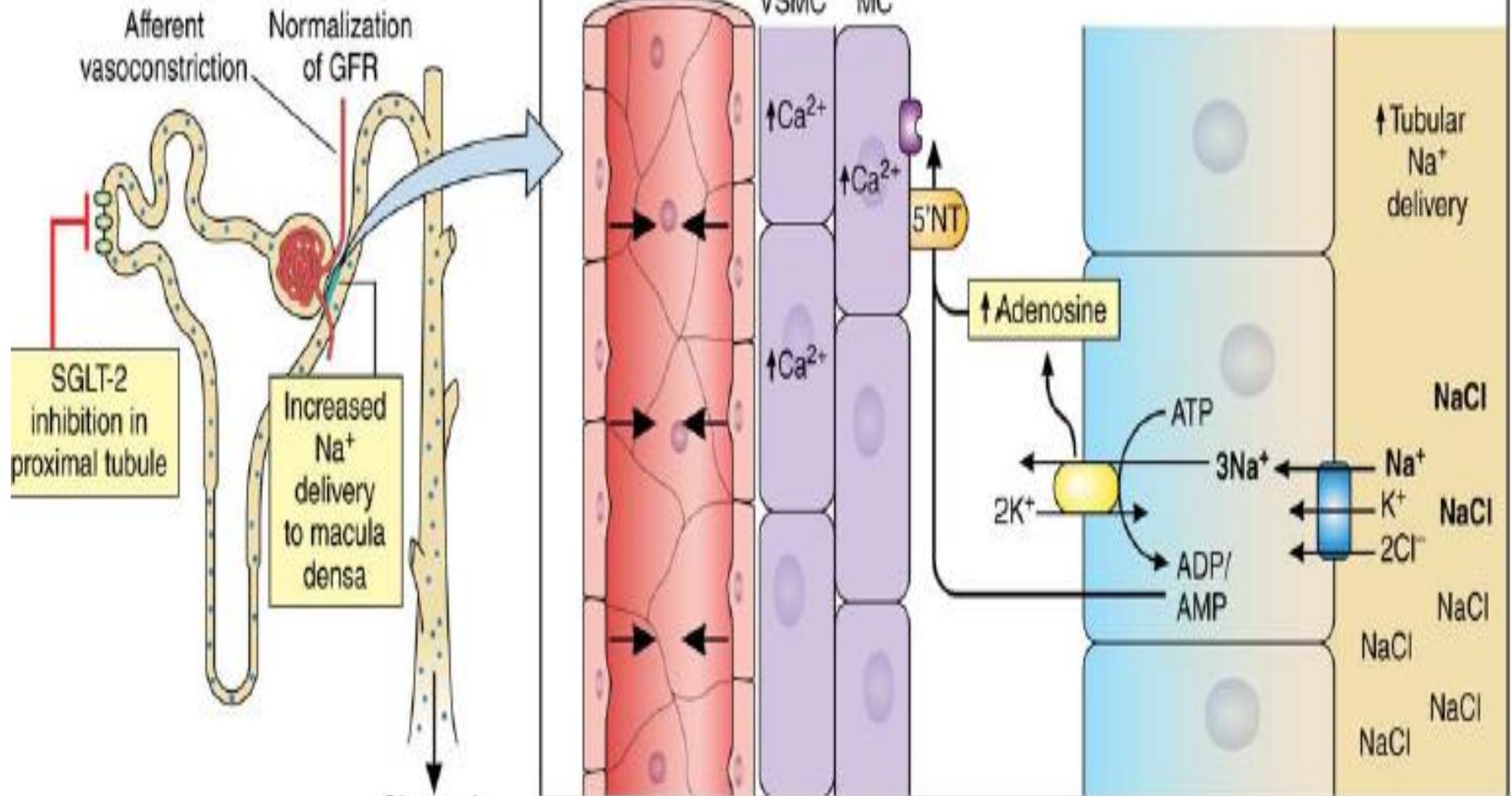
Normal	Normal afferent arteriole	Extra-glomerular VSMC	Macula densa cells	Distal tubule lumen
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Afferent Efferent



SGLT-2 inhibitors: Decrease in glomerular hyperfiltration

(C) SGLT-2 inhibition reduces hyperfiltration via TGF

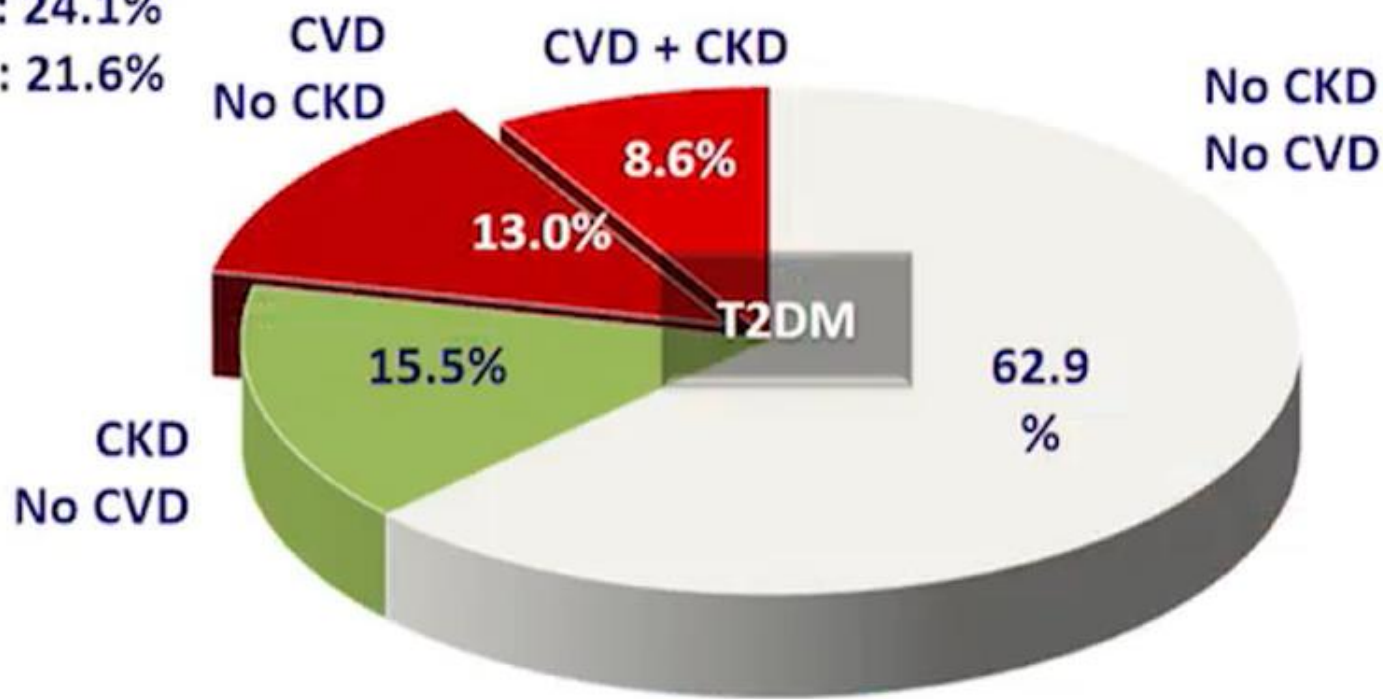


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Prevalence and Co-prevalence of Comorbidities in T2DM (Q-EMR) (N=1.39 million)

Total CKD: 24.1%
Total CVD: 21.6%



CKD was defined based on the presence of an ICD-9-CM diagnosis code or, if a code was not present, an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m² using the most recent measurement prior to the index date. If not already estimated in the database, eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) study equation.

Glycemic Control Algorithm



INDIVIDUALIZE GOALS

A1C ≤ 6.5% For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5% For patients with concurrent serious illness and at risk for hypoglycemia

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

Profiles of Antidiabetic Medications



	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD (moderate dose)	SU GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL / GU	Contra- indicated if eGFR < 30 mL/min/ 1.73 m ²	Exenatide Not Indicated CrCl < 30 Possible Benefit of Liraglutide	Not Indicated for eGFR < 45 mL/ min/1.73 m ² Genital Mycotic Infections Possible Benefit of Empagliflozin	Dose Adjustment Necessary (Except Linagliptin) Effective in Reducing Albuminuria	Neutral	Neutral	More Hypo Risk	Neutral	Neutral	More Hypo Risk	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	See #1	See #2	See #3	Neutral	Moderate	Neutral	Neutral	Neutral	CHF Risk	Neutral
CARDIAC ASCVD						May Reduce Stroke Risk	Possible ASCVD Risk	Benefit	Safe	Neutral	
BONE	Neutral	Neutral	Mild Fracture Risk	Neutral	Neutral	Moderate Fracture Risk	Neutral	Neutral	Neutral	Neutral	Neutral
KETOACIDOSIS	Neutral	Neutral	DKA Can Occur in Various Stress Settings	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral

- Few adverse events or possible benefits
- Likelihood of adverse effects
- Use with caution

1. Liraglutide—FDA approved for prevention of MACE events.
2. Empagliflozin—FDA approved to reduce CV mortality. Canagliflozin shown to reduce MACE events.
3. Possible increased hospitalizations for heart failure with alogliptin and saxagliptin.

Klinische implicaties

- SGLT-2 remmers (m.n. empagliflozin), glucoseverlagers met CV-bonus
- Bijwerkingen: (uro)genitale infectie, keto-acidose, distale amputaties, skelet?, theor: dehydratie
- Internationale richtlijnen: voorkeur bij patiënten met cardiovasculaire ziekte (renaal?)
- Patiënten zonder diabetes?
- NHG standaard – wordt herzien – (zeer) beperkte plaats – nadruk op veiligheid
- Leidraad voor internisten – combinatie met insuline te overwegen



Onze missie

- Innovatieve, duurzame en betaalbare gezondheidszorg
- Vanuit drijfveer, traditie en visie mensgerichte zorg leveren

‘To have a significant impact on healthcare’