Van een antidiabeticum naar een cardiovasculaire en renale behandeling: ***het verbazingwekkende verhaal*** van SGLT2-remmers: stand van zaken

Prof. Robert Hilbrands
Kliniekhoofd Diabeteskliniek UZBrussel
Diabetoloog-Nefroloog

Universitair Ziekenhuis Brussel

Diabeteskliniek

De schepping der Gliflozines……

1835

Het begin van het begin….

1835…. Franse chemici extraheren **Phlorizin** uit de schors van de **appelboom**

Niet-selectieve inhibitor van SGLT1 en 2
Toename urinaire glucose excretie in proefdieren

2003…. **Selectieve** SGLT2 inhibitoren getest in de mens

2012…. Eerste SGLT2i (Dapagliflozine) **goedgekeurd** als medicijn bij de mens

Het begin…..

2010

SGLT2 inhibition — a novel strategy for diabetes treatment

Edward C. Chao and Robert R. Henry

Cardiologen/nefrologen

Collega's/nefrologen

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Chao E and Henry R; Nature Reviews Drug Discovery p551, 2010

2022…. het **VERBAZINGWEKKENDE** verhaal

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SGLT2i

2007….een kritische blik met grote gevolgen

Steven Nissen
Cardioloog

FDA places "black box" warning on antidiabetes drugs

Janice Hopkins Tanne NEW YORK

The US Food and Drug Administration has asked the makers of two antidiabetes drugs—rosiglitazone (marketed as Avandia), made by GlaxoSmithKline, and pioglitazone (Actos), made by Takeda—to place "black box" warnings, the most serious kind, on their labels.

The new labels warn of an increased risk of congestive heart failure. Andrew von Eschenbach, the FDA's commissioner, announced the warning at a hearing of the US House of Representatives' Committee on Oversight and Government Reform last week to examine the FDA's role in evaluating the safety of rosiglitazone.

The new labels do not address the question of whether these drugs pose an increased risk of heart attacks and strokes.

The cardiovascular risk was raised last month by an article and accompanying editorial in the *New England Journal of Medicine* (doi: 10.1056/NEJMoa072761).

John Buse, of the University of North Carolina, and the incoming president of the American Diabetes Association, told the hearing that SmithKlineBeecham (now part of GlaxoSmithKline) had tried to intimidate him when he spoke out with his concerns about rosiglitazone's cardiovascular safety.

Dr Buse said that he had spoken at least twice in June 1999 about "a trend toward increases in serious cardiovascular events and cardiovascular deaths with Avandia as compared to active comparators."

He said that employees of SmithKlineBeecham had told him in telephone calls that "there were some in the company who felt that my actions were scurrilous enough to attempt to hold me liable for a loss in market capitalisation [share value]."

See Editorial, p 1233

Commissioner Andrew von Eschenbach announced the warnings las

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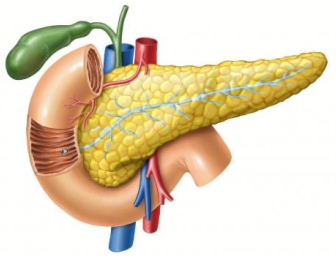
Voor 2008: vereisten voor nieuwe diabetesmedicatie

- Metformine
- Glitazone
- SU/gliniden
- DPP4i
- **SGLT-2i**
- GLP-1
- Insuline

→ **↓ HbA1c**

FDA/EMA



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Voor 2008: te weinig CV outcome studies in diabetespatienten

Diabetes 2

Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes

Rury R Holman, Harald Sourij, Robert M Califf

Lancet 2014; 383: 2008–17

This online publication has been corrected. The corrected

Few trials of glucose-lowering drugs or strategies in people with type 2 diabetes have investigated cardiovascular outcomes, even though most patients die from cardiovascular causes despite the beneficial effects of lipid-reducing and blood pressure-lowering treatments. The evidence-based reduction in risk of microvascular disease with glucose

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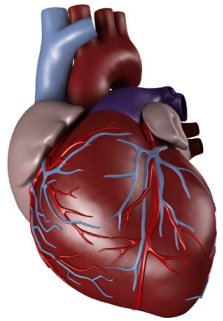
2007



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 14, 2007 VOL. 356 NO. 24

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

42 studies
12.282 patienten

AMI: 86 vs 72 events
CV death: 39 vs 22 events

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analysis. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

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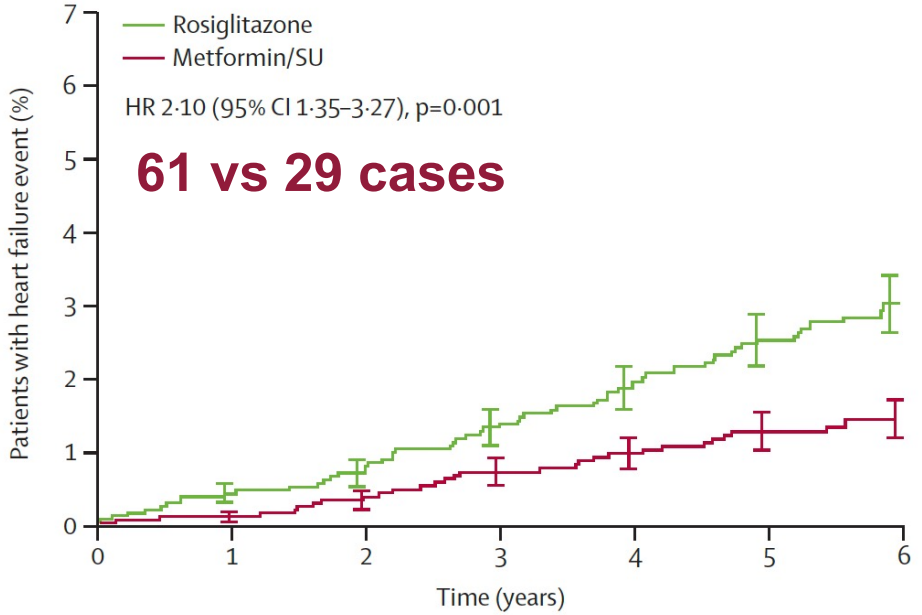
Rosiglitazone increases the risk of heart failure

Several other properties of rosiglitazone may contribute to adverse cardiovascular outcomes. Rosiglitazone and other thiazolidinediones are known to precipitate congestive heart failure in susceptible patients.[26] Congestive heart failure is



RECORD Trial:

N=4440

T2D zonder hartfalen

Pre-specified criteria voor HF

Nissen S and Wolski K NEJM 2007

Gilbert R and Connelly K Lancet Diab Endocrinol 2015, p930

FDA and EMA guidelines 2008

- Approval for new anti-diabetic drugs:

  → Prove HbA1c reduction

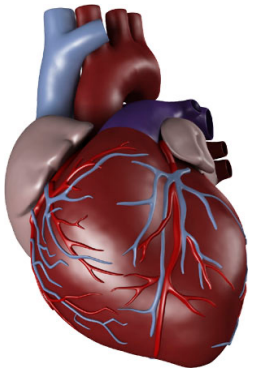
  → Additional evidence for CV safety required! (CV mortality, AMI and stroke and heartfailure)

NA 2008: CV safety first!

- Metformine
- Glitazone
- SU/gliniden
- DPP4i
- SGLT-2i
- GLP-1
- Insuline

↓ HbA1c

+



FDA/EMA

CVOT in type 2 diabetes

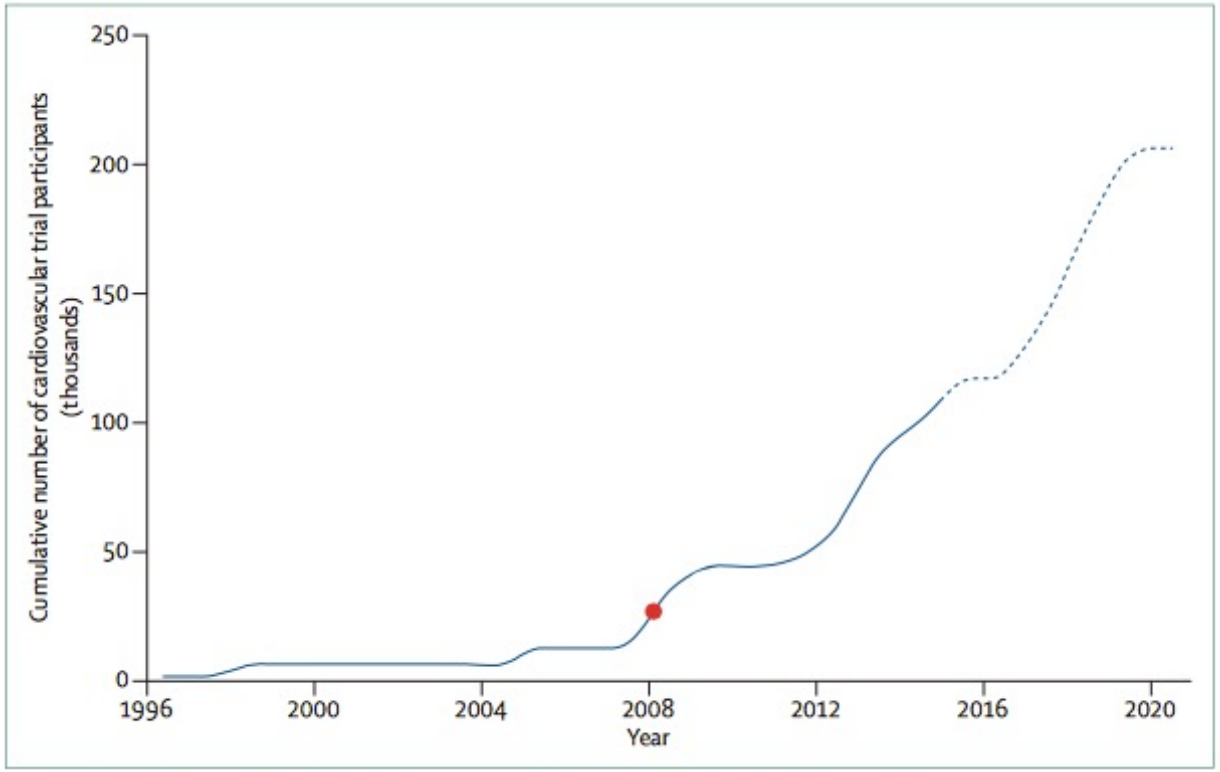


Figure: **Cumulative number of participants in cardiovascular outcome trials over time**
Numbers of trial participants are added at the time of publication for historical trials (solid line) and at the estimated time of reporting for ongoing trials (dotted line). The red circle indicates when the new US Food and Drug Administration guidance for industry was issued.

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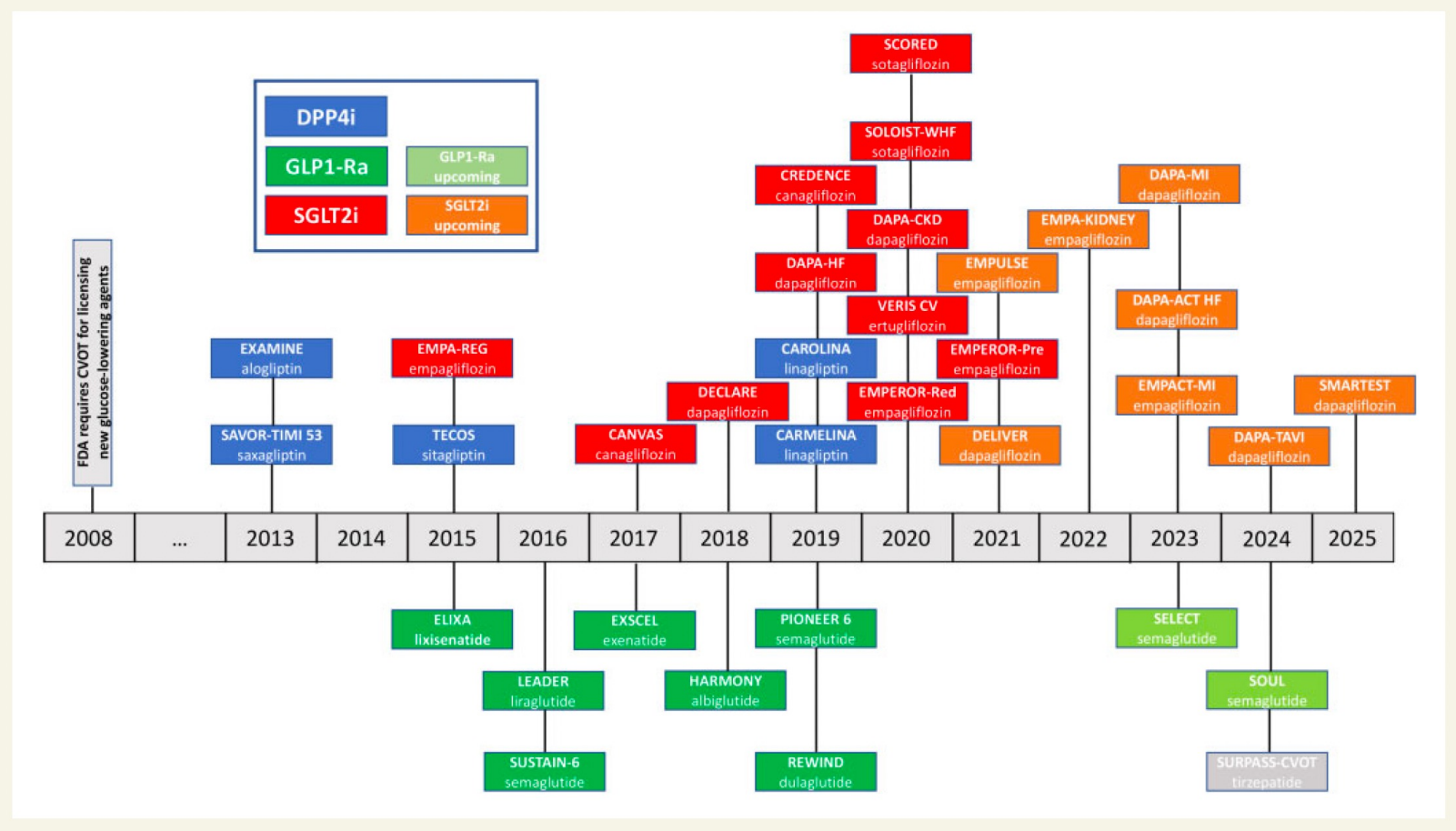
Holmann R et al. Lancet 2014; p2008-17

CVOTs with glucose-lowering agents



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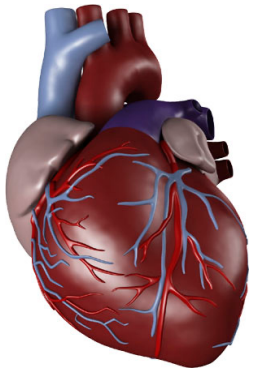
Savarese G et al. Cardiovascular Research 2021

CVOT in anti-diabetic drugs



CV veiligheid

FDA en EMA richtlijnen 2008

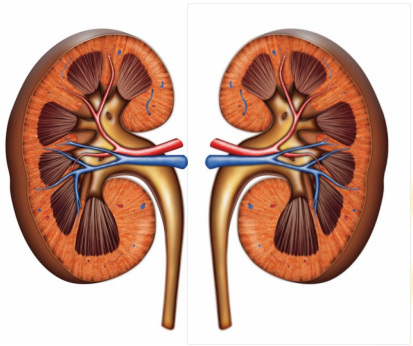
Resultaat

- Design culture of ‘risk-avoidance studies’
- Maximise financial return on pharmaceutical investment

- Most trials: power for non-inferiority, NOT superiority vs placebo
- Event driven studies
- Long-term (CV) effects insufficiently studied

- **<u>Specific ‘high risk’ populations</u>**

2010: SGLT2 inhibitor studies



such as metformin or the insulin secretagogues.

Given the mechanism of action of SGLT2 inhibitors, other safety issues include the development of urinary tract infections and fungal genitourinary infections, as well as deterioration of renal function. Clinical studies so far on dapagliflozin have found that the rates of urinary tract infections were comparable in treatment and placebo groups. Elevated urine volume of 400–600 ml

nefrologen

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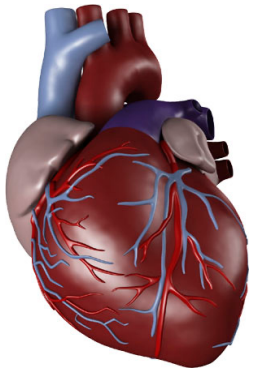
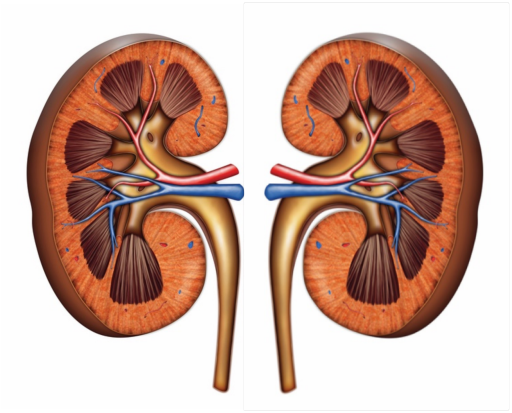
Chao E and Henry R; Nature Reviews Drug Discovery p551, 2010

CVOT in SGLT2-inhibitors

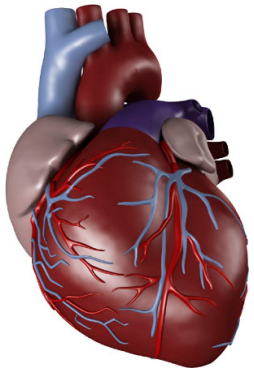


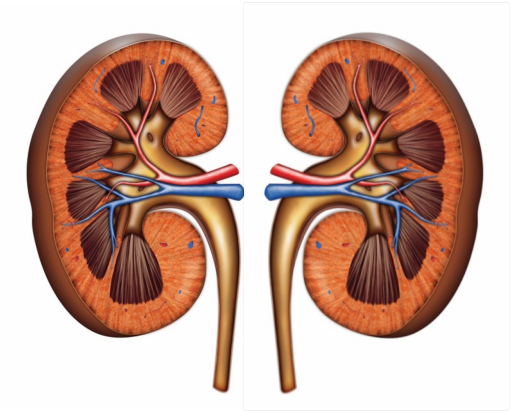
CV veiligheid



Renale veiligheid

CVOT in SGLT2-inhibitors





3-point MACE

= CV mortality, non-fatal AMI, CVA

(primair eindpunt)

Composite Renal Endpoint

(secondair eindpunt)

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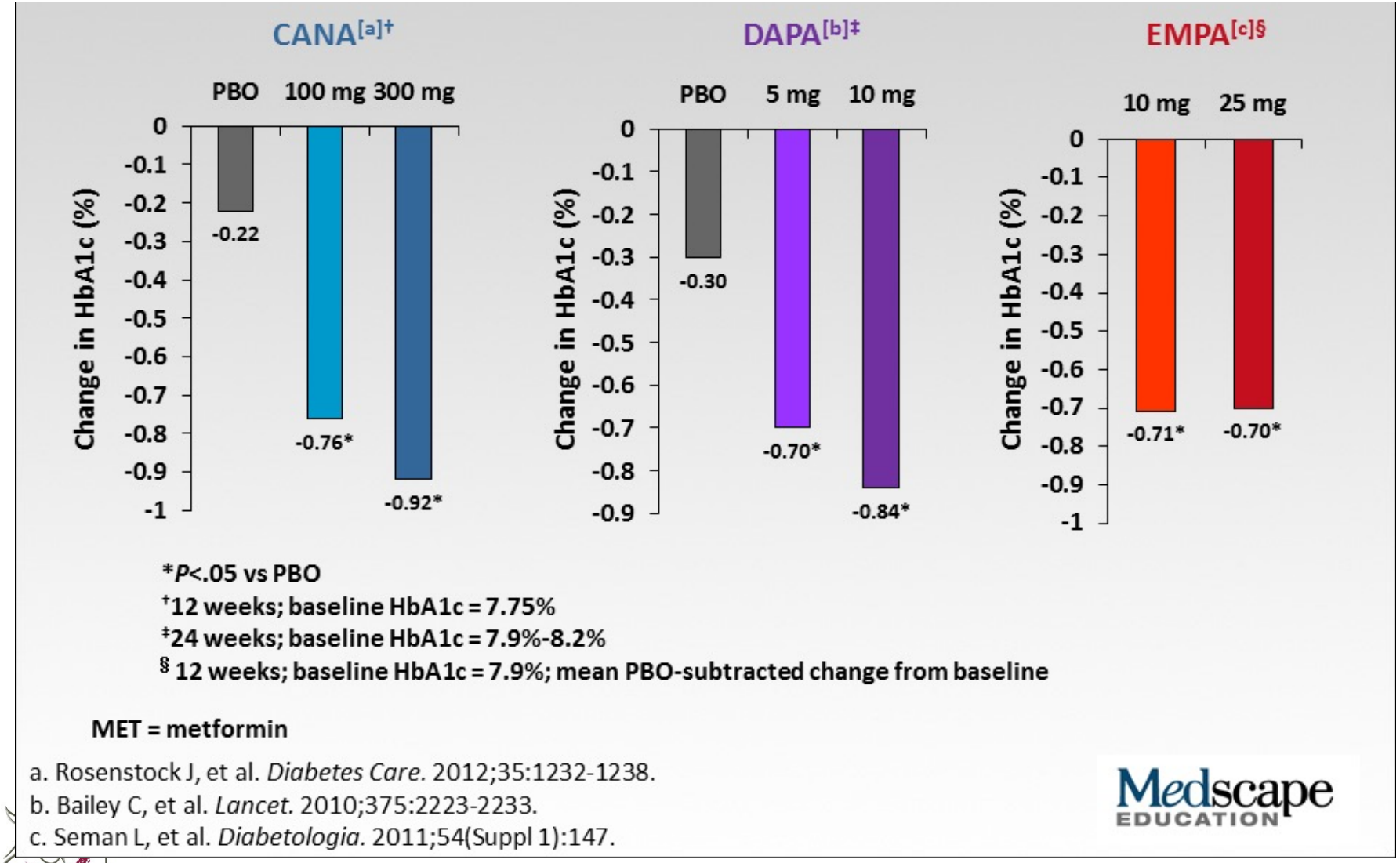
Diabeteskliniek

SGLT2-inhibitoren

Als medicijn voor diabetes

SGLT2 Inhibitoren: Effect op HbA1c wanneer toegevoegd aan metformine (tweede lijn)



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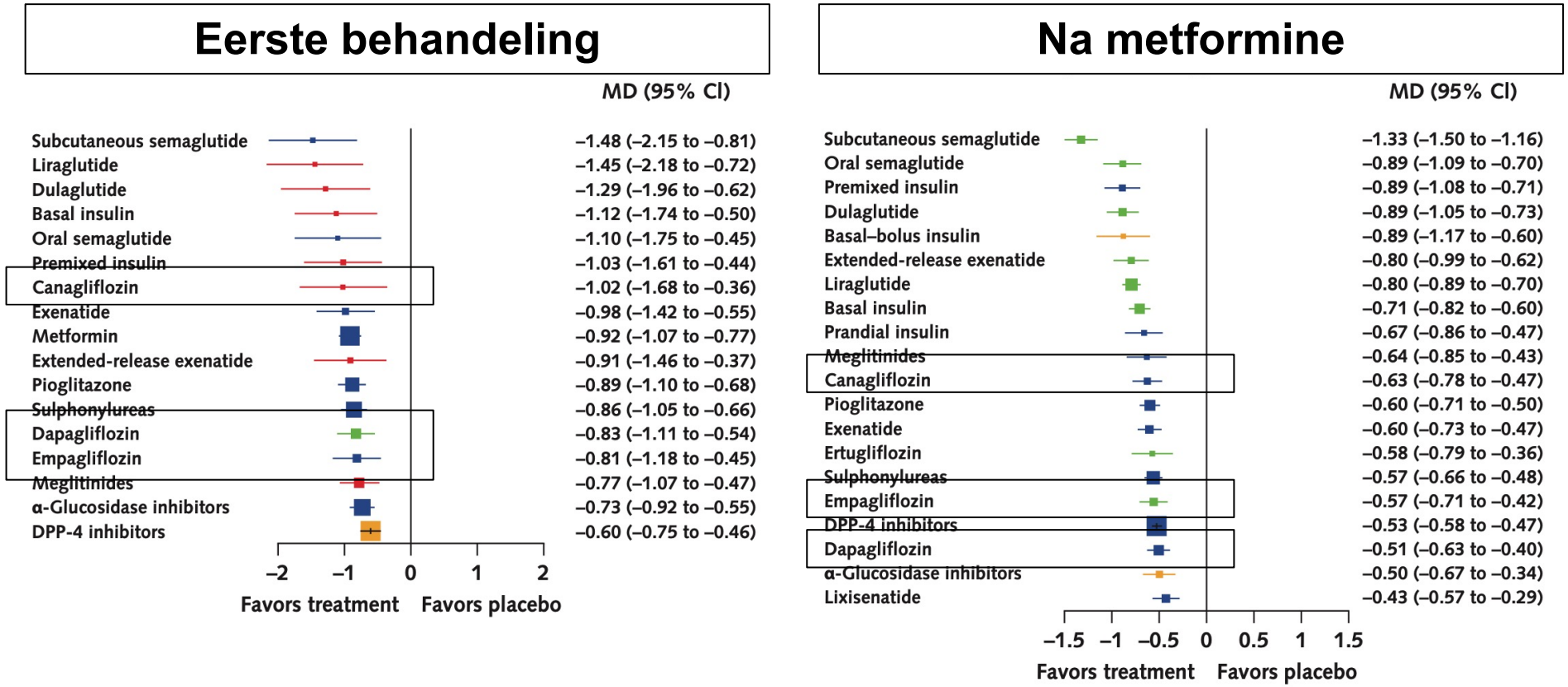
Nihsimura et al. Cardiovasculair Diab 2015, 14:11

Kracht van add-on therapy in Type 2 diabetes

Figure 2. Network meta-analysis results for the primary outcomes compared with placebo.



Bij ‘add-on’ therapie neemt te verwachten HbA1c daling af

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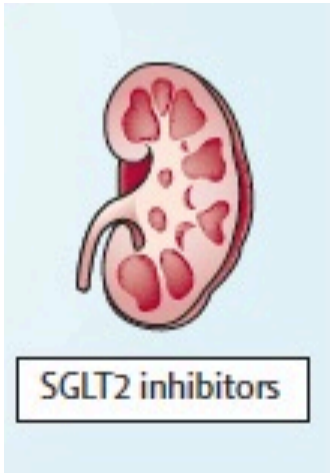
Tsapas et al. Annals of Int Med 2020

Klinisch effect SGLT2 inhibitie



Verhoogde glucose excretie

↓ Nuchtere en post-prandiale glycemie
ZONDER hypo's

↓ HbA1c 0.6-1%

Verlies calorieën

2-3 kg gewichtsverlies

Verhoogde natrium excretie

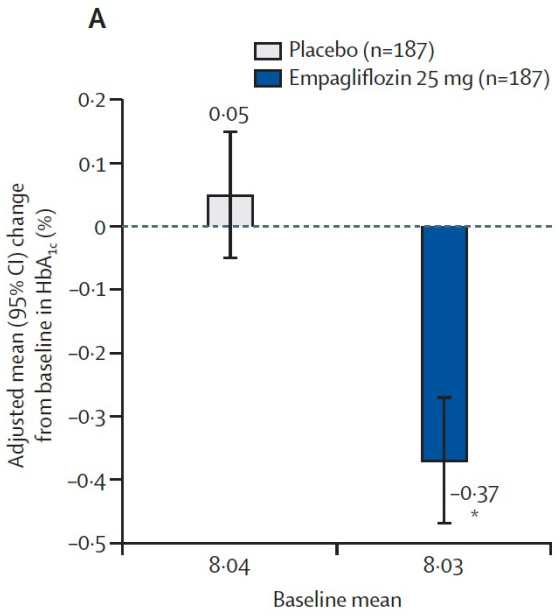
Daling circulerend volume

3-5 mmHg daling BD

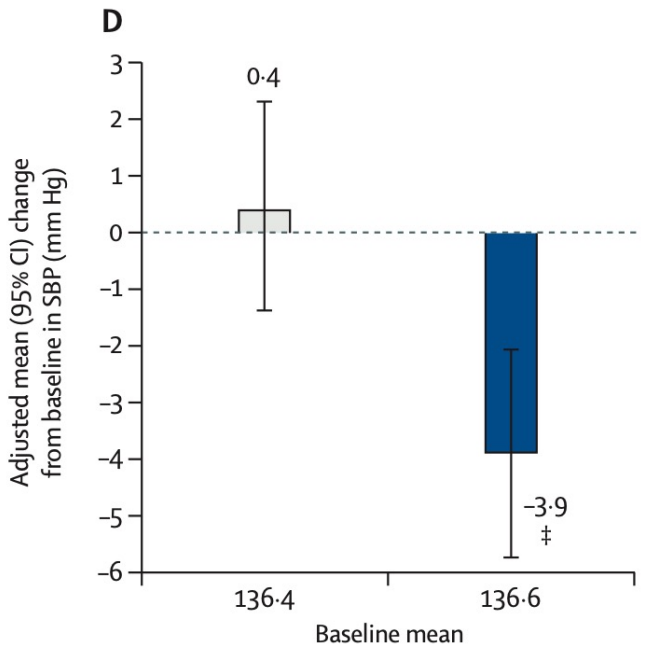
Effect van SGLT-2 inhibitoren op glycemie daalt bij lagere nierfunctie

Stage 3 CKD

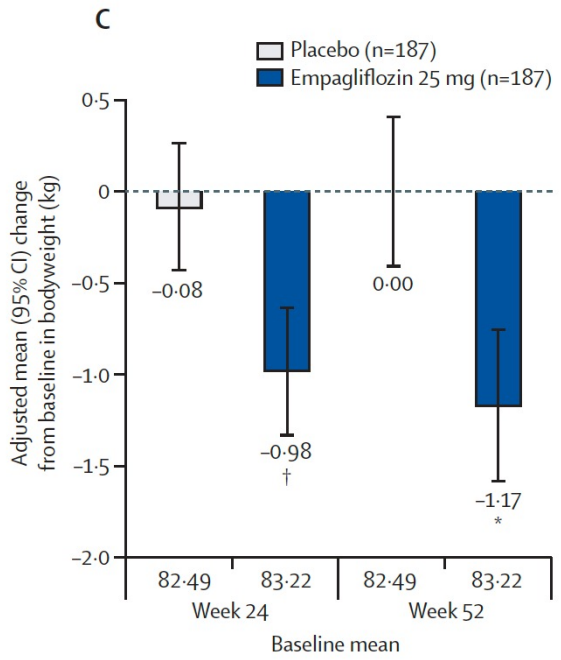
HbA1c



Syst BP



Bodyweight



Stage 4 CKD

<u>no effect on HbA1c</u>

Lower bloodpressure

Lower bodyweight

Terugbetalingscriteria SGLT2i bij introductie op Belgische markt

- HbA1c >7.0% en <9.0%
- eGFR >60 ml/min

Bij renale klaring <60 ml/min neemt effect op glycemie snel af!!

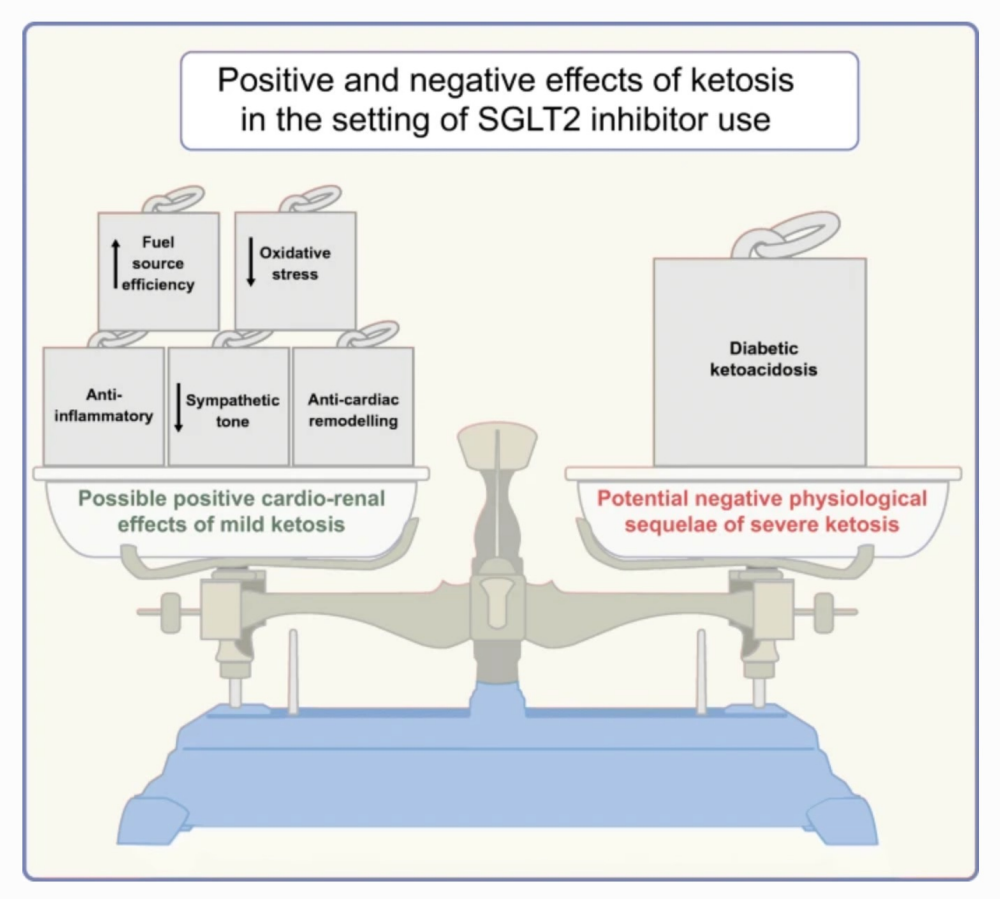
SGLT-2 inhibitoren in België 2022

Compound	Merknaam	Producent	Dosis	Kostprijs/maand (BCFI)
Canagliflozine	Invokana®	Mundipharma	100 mg en 300 mg	€ 61,76 - € 88.64
Empagliflozine	Jardiance®	Boehringer Ingelheim	10 mg en 25 mg	€ 50,06
Dapagliflozine	Forxiga®	AstraZeneca	5 mg en 10 mg	€ 47,00
Ertugliflozine	Steglatro®	MSD	5 mg en 15 mg	Niet meer beschikbaar

Nevenwerkingen en valkuilen

- Zeer goed verdragen
- Verhoogd risico urogenitale (schimmel)infecties
- Toegenomen diurese met laag risico op hypovolemie, vooral bij ouderen en patient onder diuretica
- **Hypoglycemie** wanneer in combinatie met SU of Insuline
- **Euglycemische ketoacidose**

Ketones… 'the double-edged sword' ?



Lupsa B et al. Diabetologia 2022

Euglycemische ketoacidose

- Bij type 2 diabetes patienten
- Weinig frequent (0.1% in EMPA-REG, n=7020)
- **Komt voor bij licht tot niet verhoogde glycemie!!**
- Symptomen: nausea, braken, malaise
- Uitlokkende factoren
  - → Ziekte, stress
  - → Minder vocht en voedsel (KH) inname
  - → Lagere insuline dosis
  - → Alcohol
  - → Heelkundige ingreep
  - → Insulinopenie

- **Detectie** door ketonurie/ketonemie bij patient op SGLT2i en onwel of acute ziekte

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Rosenstock and Ferrannini Diab Care 2015, p1638

Behandeling euglycemische DKA

- STOP SGLT2i
- Check ketonen (bloed of urine)
- Vocht toediening
- Koolhydraat inname om insuline secretie (of toediening) toe te laten

- Indien geen orale intake mogelijk, tachypnoe, braken of hemodynamische instabiliteit → urgentie!

Rosenstock and Ferrannini Diab Care 2015, p1638

Behandeling euglycemische DKA

This card holder takes diabetes medication that can cause diabetic ketoacidosis without high glucose levels

STOP DKA Protocol

Symptomatic (e.g. lethargy, loss of appetite, nausea, abdominal pain) → **STOP** SGLTi

AND

Test ketones* and glucose every 2-4 hours
(even if blood glucose is not elevated)

AND

Oral ingestion of fluid and carbohydrates
(250–500 mL fluid every 2 hours and up to 30–60 g of carbohydrates every 2-4 hours)

AND

Protocol instructions for supplemental insulin and carbohydrates
(see STOP DKA table)

*Ketosis/DKA may occur without an elevated blood glucose

STOP DKA Considerations for Bolus Insulin and Carbohydrates

(for moderate or higher ketones, consider increasing basal insulin by 20%–50% until ketones return to normal)

KETONE level (mmol/L) and category (check every 2–4 h)	BLOOD GLUCOSE* (check every 2–4 h) 4·0–8·0 mmol/L (70–150 mg/dL)	8·1–14·0 mmol/L (151–250 mg/dL)	>14 mmol/L (>250 mg/dL)
<1.0 Normal or Mild	• No extra insulin • Give usual bolus to cover carbohydrates plus usual correction	• No extra insulin • Give usual bolus to cover carbohydrates plus usual correction	• 5–10% TDD supplemental insulin or usual correction bolus plus usual bolus to cover carbohydrates
1·0–1·4 Moderate	• 5% TDD supplemental insulin plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 10% TDD supplemental insulin or 1.5x correction bolus plus usual bolus to cover carbohydrates • 30 g carbohydrates every 2–4 h	• 10% TDD supplemental insulin or 1.5x correction bolus plus usual bolus to cover carbohydrates every 2-4h
1·5–2·9 High	• 10% TDD supplemental insulin plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates every 2-4 h
≥3·0 Extreme	• 10% TDD supplemental insulin plus usual bolus to cover carbohydrates • 45–60 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates • 30–45 g carbohydrates every 2–4 h	• 20% TDD supplemental insulin or 2x correction bolus plus usual bolus to cover carbohydrates every 2-4 h

⚠ DKA is likely if ketones remain ≥3 mmol/L despite supplemental insulin
If symptoms are ongoing and/or you are unable to ingest fluids, go directly to the emergency department ⚠

*Glucose values in mg/dL are not exact conversions from those in mmol/L to allow for round numbers. TDD=total daily insulin dose; usual bolus=usual bolus using insulin:carbohydrate ratio without correction. If supplemental insulin is calculated by both TDD and correction bolus methods, administer the amount that provides the higher dose of insulin.

Sources of 15 g Simple Carbohydrates (Fluid)

- 150 mL (2/3 cup) regular soft drink
- 250 mL (1 cup) of sports drink
- 150 mL (~2/3 cup) of juice
- 125 mL (1/2 cup) of regular gelatin dessert
- 125 mL (1/2 cup) of apple sauce
- 75 mL (1 stick) of popsicle

Sources of Sugar-free Fluids

- Water
- Low or zero calorie drink mix
- Diet soft drink
- Tea
- Clear soup or broth

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Goldenberg R et al. Diabetes Obes Metab. 2019

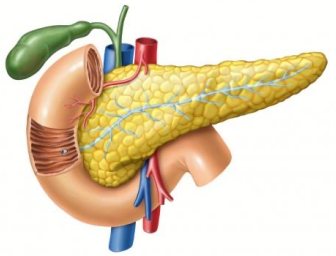
Rosenstock and Ferrannini Diab Care 2015, p1638

Glucocentric approach for treating Type 2 diabetes

- Metformin
- Glitazone
- SU/gliniden
- DPP4i
- **SGLT-2i**
- GLP-1
- Insulin

→ **↓ HbA1c**

FDA/EMA



En toen……

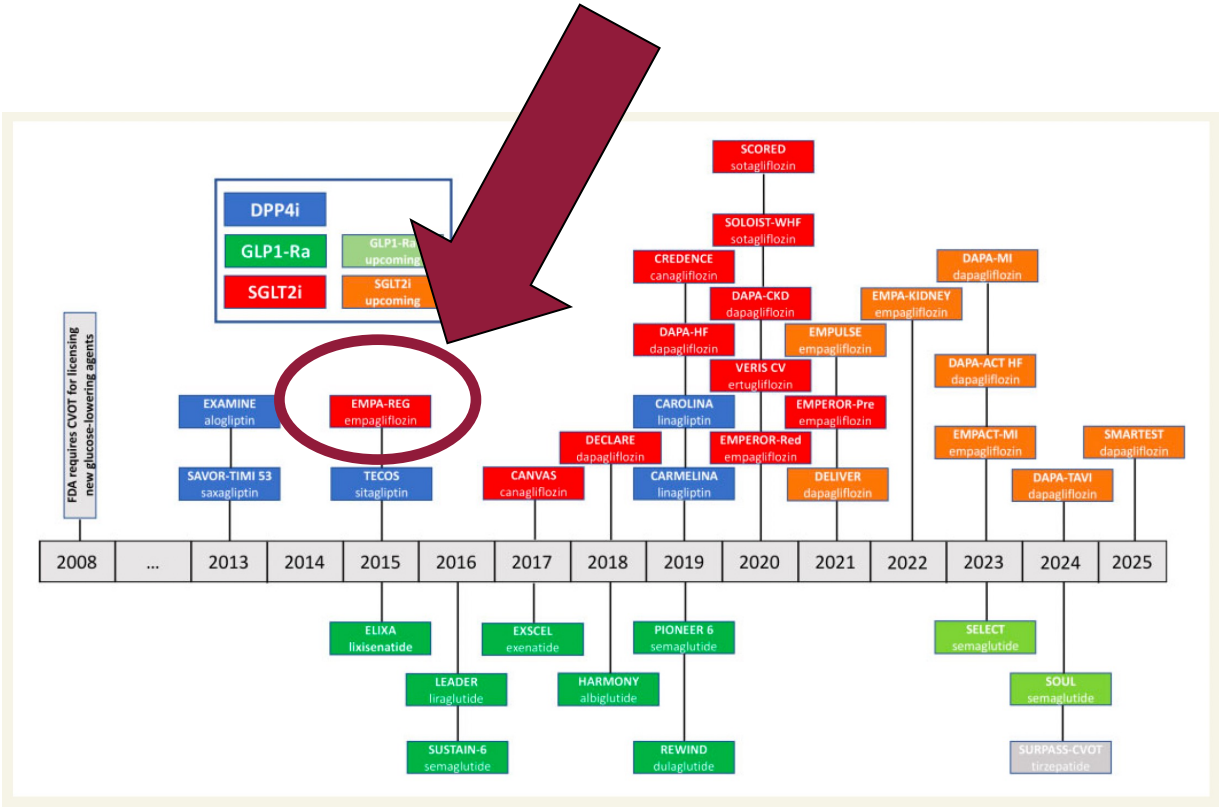
2015….EMPA-REG OUTCOME trial

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



CVOT studies in type 2 diabetes

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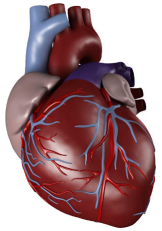
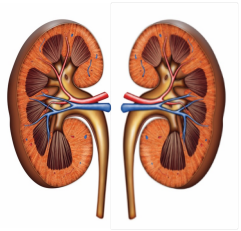
Diabeteskliniek

SGLT2 inhibitoren

Cardio-renale protectie bij diabetespatienten





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Diabeteskliniek

Effect of glucose-lowering drugs on combined primary endpoint (3-point MACE): **CV mortality, non-fatal AMI, CVA**

Trial	Drug	Categorie	Hazard Ratio (HR)	P-waarde
ORIGIN	Glargine	Insuline	1.02 (CI 0.94-1.11)	NS
SAVOR	Saxagliptine	DPP4-inhibitor	1.00 (CI 0.89-1.12)	NS
EXAMINE	Alogliptine	DPP4-inhibitor	0.96 (CI 0.80-1.15)	NS
TECOS	Sitagliptine	DPP4-inhibitor	0.98 (CI 0.89-1.08)	NS
ELIXA	Lixisenatide	GLP-1 analoog	1.02 (CI 0.89-1.17)	NS

=CV safe

*secondary endpoint

Schernthaner G et al. Clin Ther 2016; p 1288
Savarese G et al. Cardiovascular Research 2021

Effect of glucose-lowering drugs on combined primary endpoint (3-point MACE): **CV mortality, non-fatal AMI, CVA**

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ELIXA	Lixisenatide	GLP-1 analoog	1.02 (CI 0.89-1.17)	NS
PROactive*	Pioglitazone	Ppar-gamma agonist	0.84 (CI 0.72-0.98)	0.02*
EMPA-REG	Empagliflozine	**SGLT-2 inhibitor**	0.86 (CI 0.74-0.99)	0.04
LEADER	Liraglutide	**GLP-1 analoog**	0.87 (CI 0.78-0.97)	0.01
SUSTAIN	Semaglutide	**GLP-1 analoog**	0.74 (CI 0.58-0.95)	0.02
CANVAS	Canagliflozine	**SGLT-2 inhibitor**	0.86 (CI 0.75-0.97)	0.02
EXSCEL	Exenatide ER	**GLP-1 analoog**	0.91 (CI 0.83-1.00)	0.06 (superiority)
DECLARE	Dapagliflozine	**SGLT-2 inhibitor**	0.93 (CI 0.84-1.03)	0.17 (superiority)
REWIND	Dulaglutide	**GLP-1 analoog**	0.88 (CI 0.79-0.99)	0.03 (superiority)

SGLT-2 inhibitoren
GLP-1 analogen

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Diabeteskliniek

*secondary endpoint

Schernthaner G et al. Clin Ther 2016; p 1288
Savarese G et al. Cardiovascular Research 2021

Patient population in CVOTs in T2D

Table 1. Summary of GLP1-RA and SGLT2i Cardiovascular Outcomes Trials

	GLP1-RA					SGLT2i		
Trial	**ELIXA**	**LEADER**	**SUSTAIN-6**	**EXSCEL**	**HARMONY**	**EMPA-REG OUTCOME**	**CANVAS Program**	**DECLARE-TIMI 58**
Drug	Lixisenatide	Liraglutide	Semaglutide	Exenatide	Albiglutide	Empagliflozin	Canagliflozin	Dapagliflozin
Median follow-up time, y	2.1	3.8	2.1	3.2	1.6	3.1	2.4	4.2
Trial participants, n	6068	9340	3297	14 752	9463	7020	10 142	17 160
Age, y, mean	60.3	64.3	64.6	62.0	64.1	63.1	63.3	63.9
Female sex, n (%)	2894 (30.7)	3337 (35.7)	1295 (39.3)	5603 (38.0)	2894 (30.6)	2004 (28.5)	3633 (35.8)	6422 (37.4)
Proportion of patients with established atherosclerotic cardiovascular disease, n (%)	6068 (100)	6775 (72.5)	2735 (83.0)	10 782 (73.1)	9463 (100)	7020 (100)	6656 (66)	6974 (41)
History of heart failure, n (%)	1922 (20.3)	1667 (17.8)	777 (23.6)	2389 (16.2)	1922 (20.3)	706 (10.1)	1461 (14.4)	1724 (10.0)
eGFR <60 ml/min per 1.73 m^2, n (%)	1407 (23.2)	2158 (23.1)	939 (28.5)	3191 (21.6)	NA	1819 (25.9)	2039 (20.1)	1265 (7.4)

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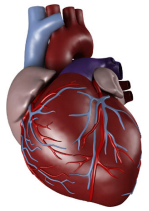
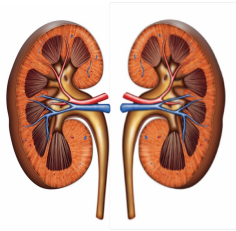
Zelniker et al Circulation 2019, p2022

Meta-analysis SGLT2

Patients WITH CV disease



NIET afhankelijk van HbA1c!



3-MACE -14%

HHF -31%

CV death -15%*

* Heterogeneity between studies

Renal composite -38%

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Zelniker T et al. Circulation 2019 p2022

SGLT2 inhibitoren

Waarom zijn de cardioloog en nefroloog zo enthousiast?

Positieve effecten lijken NIET afhankelijk van HbA1c!

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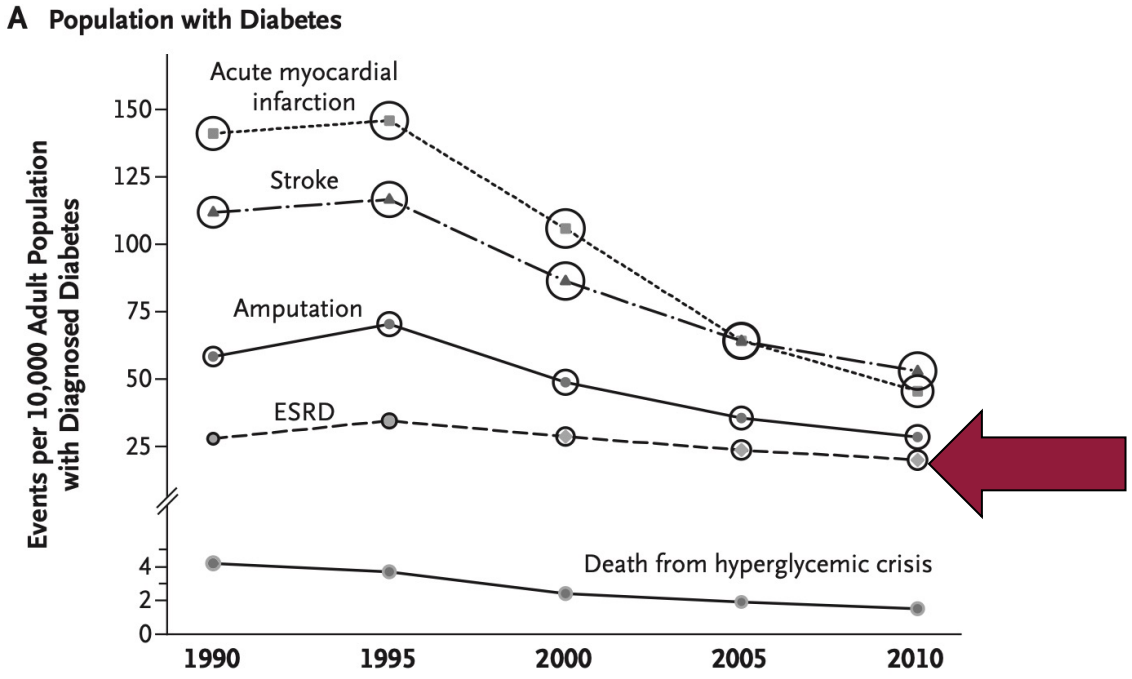
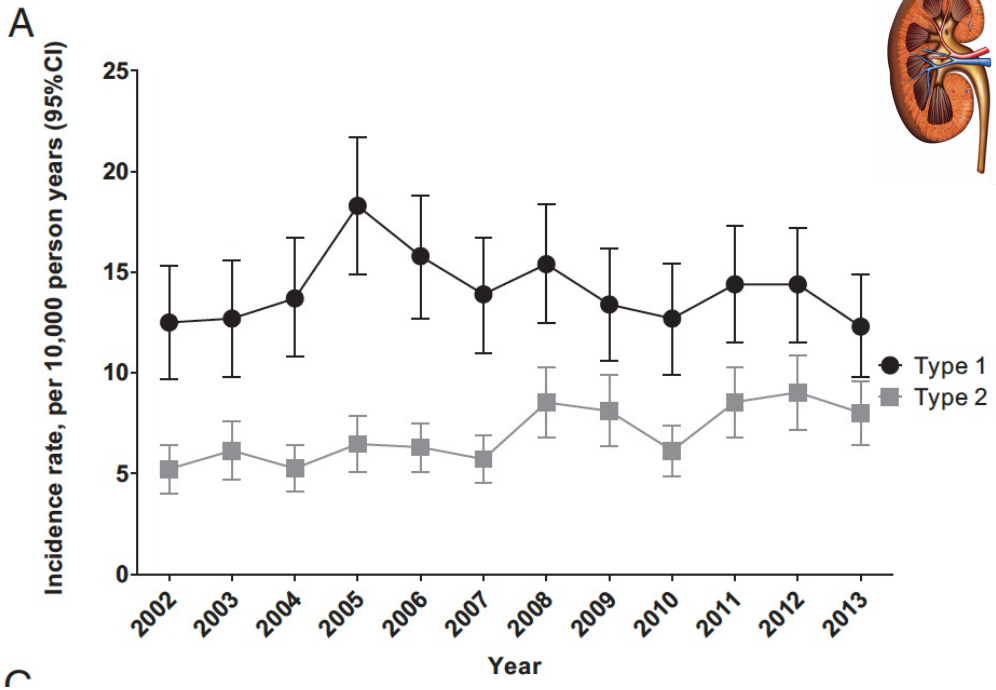
Afname ESRD teleurstellend bij diabetes patienten



US cohort NHIS (6-20x10^6 patients)

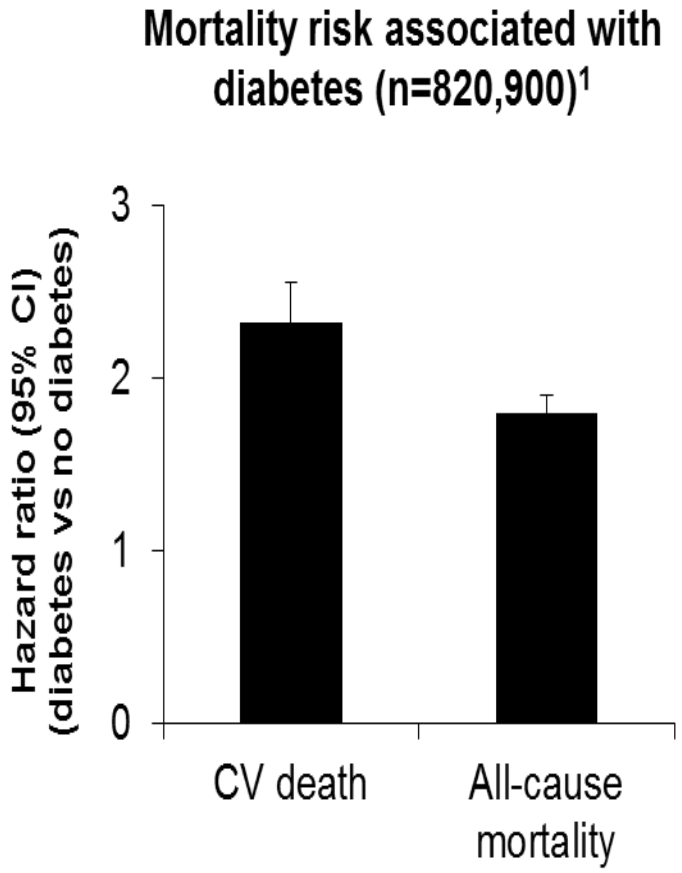


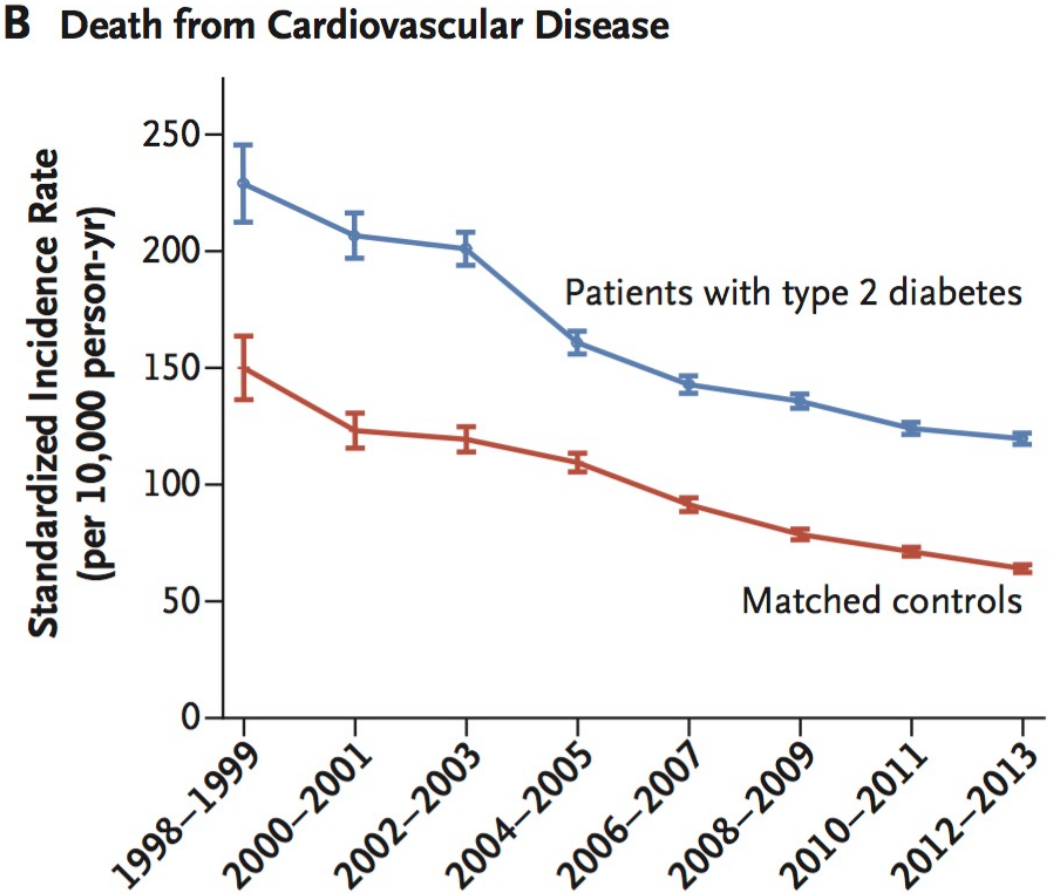
Australian registry (>1x10^6 patients)

Gregg et al. NEJM 2014, p1514, Koye et al. AJKD 2018, p300

CV overlijden belangrijkste doodsoorzaak bij diabetes

40 year old diabetic loses 6-7 years of life





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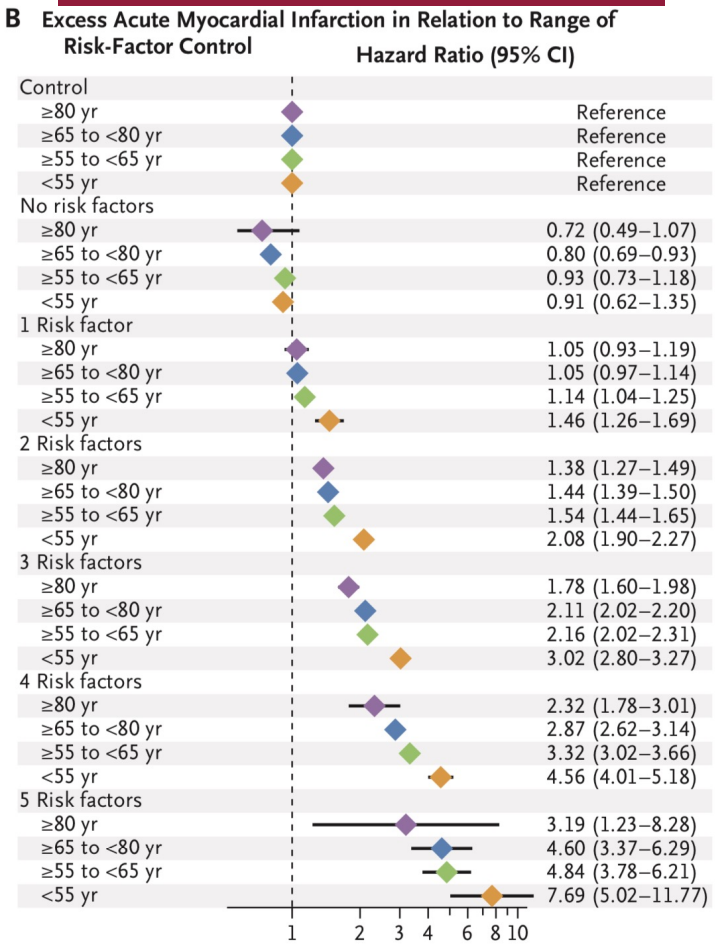
Rawshani A et al. NEJM 2017, p 1407

Excess risk for heartfailure among diabetic patients

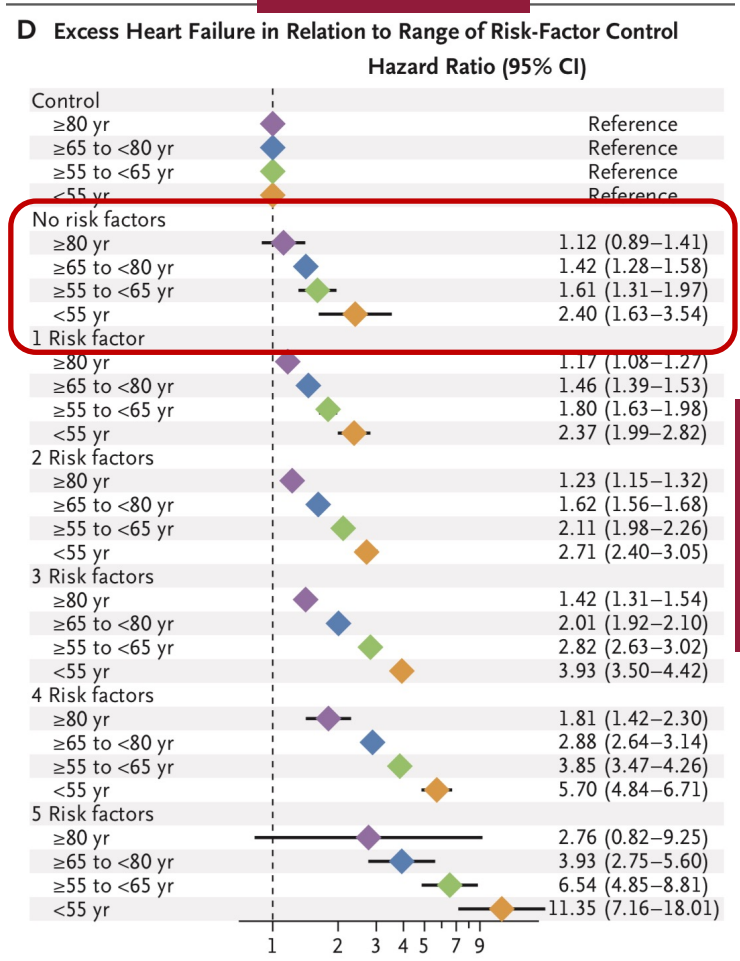
Risk factors

- HbA1c >7.0%
- BP >140/80 mmHg
- Albuminuria
- Smoking
- LDL >97 mg/dL

Acute myocard infarct



Hartfalen



HR 1.45
(95% CI 1.34-1.75)

Hoger risico op hartfalen zelfs <u>zonder</u> additionele risicofactoren!!

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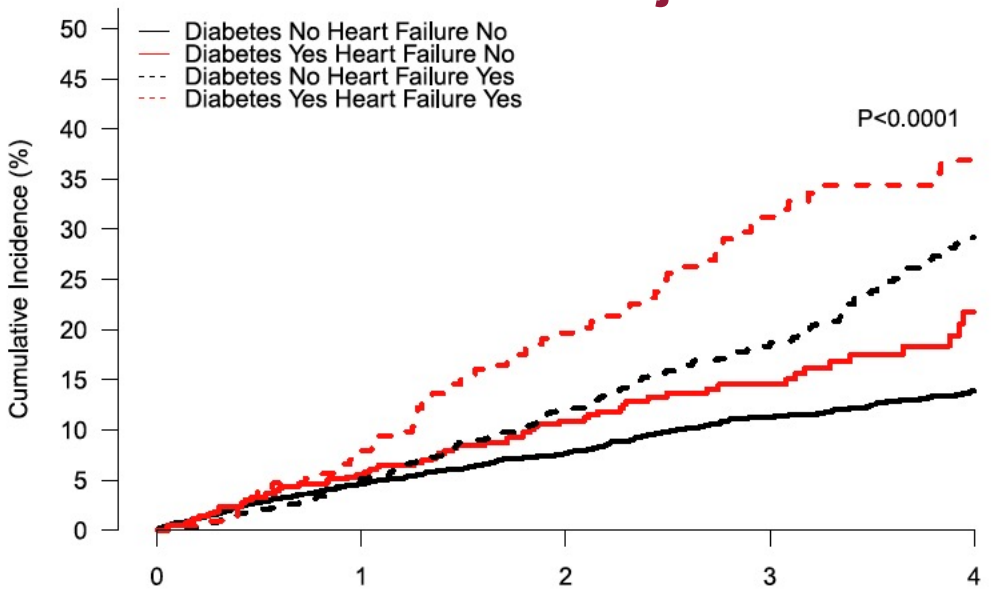
Diabeteskliniek

Rorth R et al. Diab Care 2018

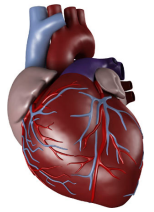
Higher mortality when diabetes + heartfailure

Overlijden



Population					
Diabetes No Heart Failure No:	2715	2588	2038	1188	519
Diabetes Yes Heart Failure No:	433	407	298	162	62
Diabetes No Heart Failure Yes:	861	816	669	450	209
Diabetes Yes Heart Failure Yes:	214	196	143	90	46

Figure 2—Risk of death according to diabetes status and development of HF.



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Diabeteskliniek

Rorth R et al. Diab Care 2018

Volume increase in diabetics increases risk for heartfailure

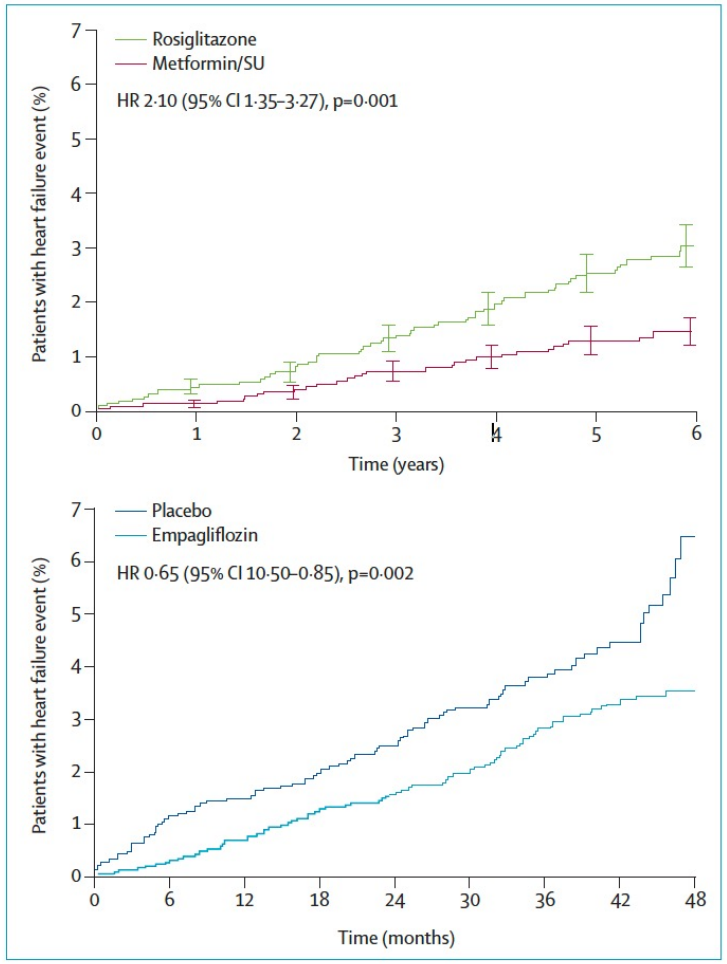

***Figure*: Time to heart failure events in the RECORD (left) and EMPA-REG OUTCOME (right) studies**
Adapted and reproduced from *European Heart Journal* (upper panel)[3] and *New England Journal of Medicine* (lower panel),[4] by permission of Oxford University Press and Massachusetts Medical Society, respectively. HR=hazard ratio.

Rosiglitazone (Avandia)
Volume 3% <u>expansion</u>

Empagliflozin
Volume 3% <u>contraction</u>

Gilbert R and Connelly K Lancet Diab Endo 2015, p930

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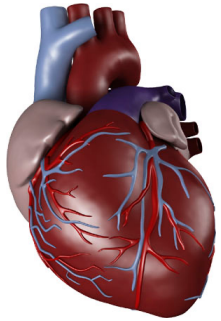
Diabetes

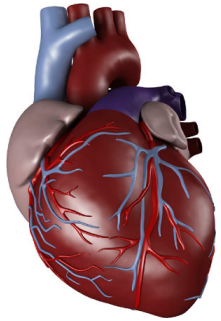
SGLT2 inhibitoren

en de cardioloog

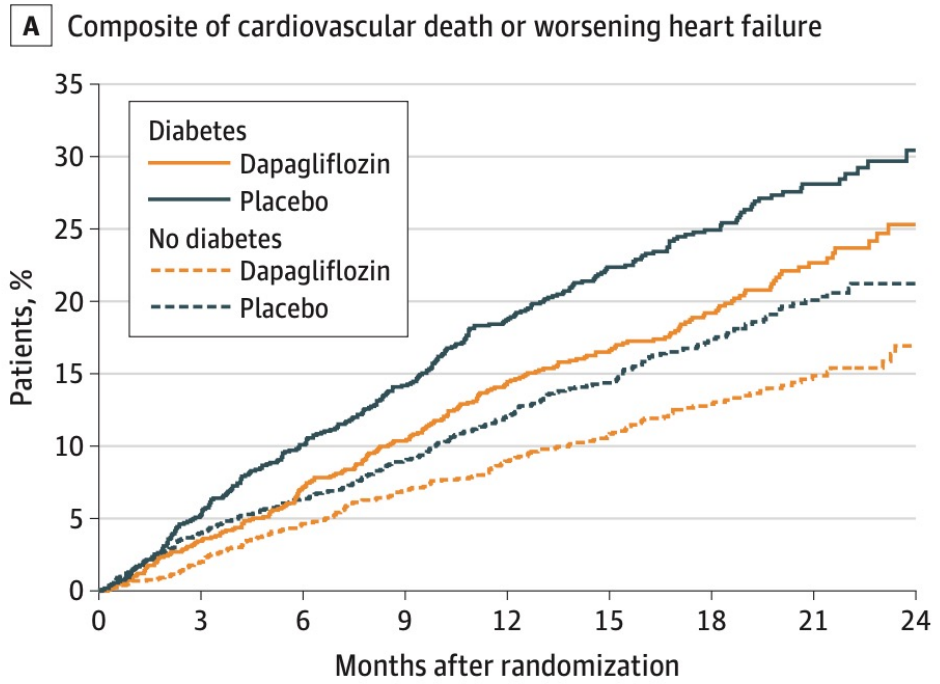


SGLT2 inhibitoren

*Bij patienten **ZONDER** diabetes*



DAPA-HF trial – HFrEF (≤40%)



No. at risk									
No diabetes									
Dapagliflozin	1298	1268	1227	1192	1126	882	646	353	122
Placebo	1307	1253	1214	1176	1101	848	627	340	121
Diabetes									
Dapagliflozin	1075	1037	994	955	876	678	500	259	88
Placebo	1064	1005	949	899	816	630	469	253	89

Independent of diabetes

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Diabeteskliniek

Petrie M et al. JAMA 2020, p1353

SGLT-2i trials bij patienten met hartfalen (met en zonder diabetes)

Table 2. **Results of SGLT2i trials focusing on Heart Failure and Renal disease outcomes.**

Trial	Drug	Population	Primary outcome (CV death or HHF)	All-cause death	CV death	First HHF	Total HHF
A. Heart Failure							
DAPA-HF[200]	Dapagliflozin vs.Placebo	HF with EF ≤ 40% with/without T2DM	0.74 (0.65-0.85)[a]	0.83 (0.71-0.97)	0.82 (0.69-0.98)	0.70 (0.59-0.83)	0.71 (0.61-0.82)[202]
EMPEROR-Reduced[218]	Empagliflozin vs. Placebo	HF with EF ≤ 40% with/without T2DM	0.75 (0.65-0-86)	0.92 (0.77-1.10)	0.92 (0.75-1.12)	0.69 (0.59-0.81)	0.70 (0.58-0.85)
EMPEROR-Preserved[228]	Empagliflozin vs. Placebo	HF with EF >40% with/without T2DM	0.79 (0.69-0.90)	1.00 (0.87-1.15)	0.91 (0.76-1.09)	0.71 (0.60-0.83)	0.73 (0.61-0.88)
SOLOIST-WHF[229]	Sotagliflozin vs. Placebo	T2DM with a recent hospitalization for WHF	0.67 (0.52-0.85)[b]	0.82 (0.59-1.14)	0.84 (0.58-1.22)	-	0.64 (0.49-0.83)[c]

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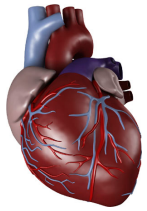
Savarese G et al. Cardiovascular Research 2021

Meta-analysis SGLT2 in hartfalen (HFrEF)



All-cause mortality

-13%

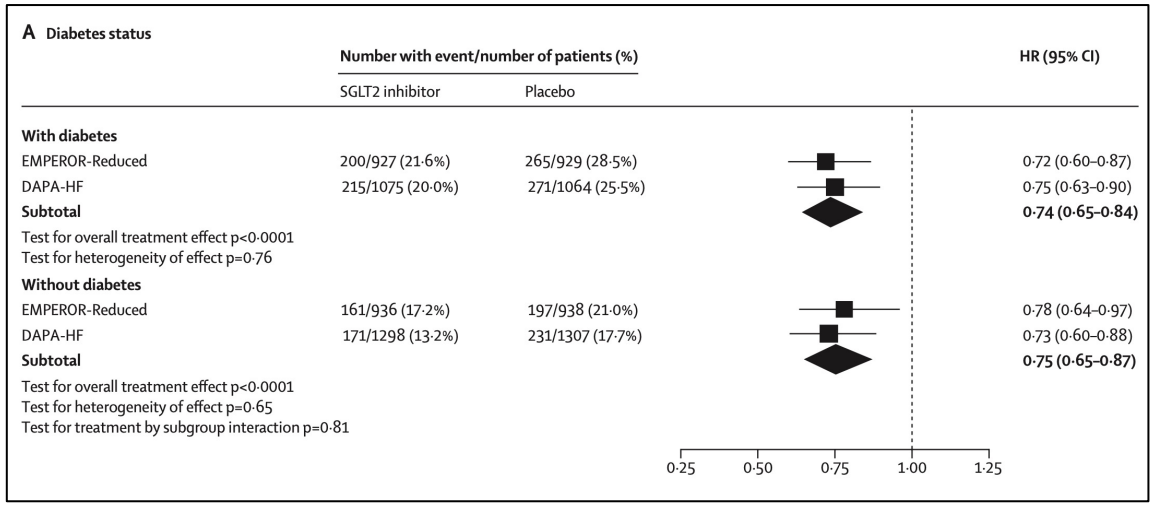
HHF

-31%

CV death

-14%

HHF or CV death
Idem met of zonder diabetes



A Diabetes status	Number with event/number of patients (%)		HR (95% CI)
	SGLT2 inhibitor	Placebo	
With diabetes			
EMPEROR-Reduced	200/927 (21·6%)	265/929 (28·5%)	0·72 (0·60–0·87)
DAPA-HF	215/1075 (20·0%)	271/1064 (25·5%)	0·75 (0·63–0·90)
Subtotal			**0·74 (0·65–0·84)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·76			
Without diabetes			
EMPEROR-Reduced	161/936 (17·2%)	197/938 (21·0%)	0·78 (0·64–0·97)
DAPA-HF	171/1298 (13·2%)	231/1307 (17·7%)	0·73 (0·60–0·88)
Subtotal			**0·75 (0·65–0·87)**
Test for overall treatment effect p<0·0001			
Test for heterogeneity of effect p=0·65			
Test for treatment by subgroup interaction p=0·81			

0·25 0·50 0·75 1·00 1·25

renal endpoint -38%

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Diabeteskliniek

Zannad F. et al. Lancet 2020

SGLT-2i in HFpEF - reduced CV death and HHF

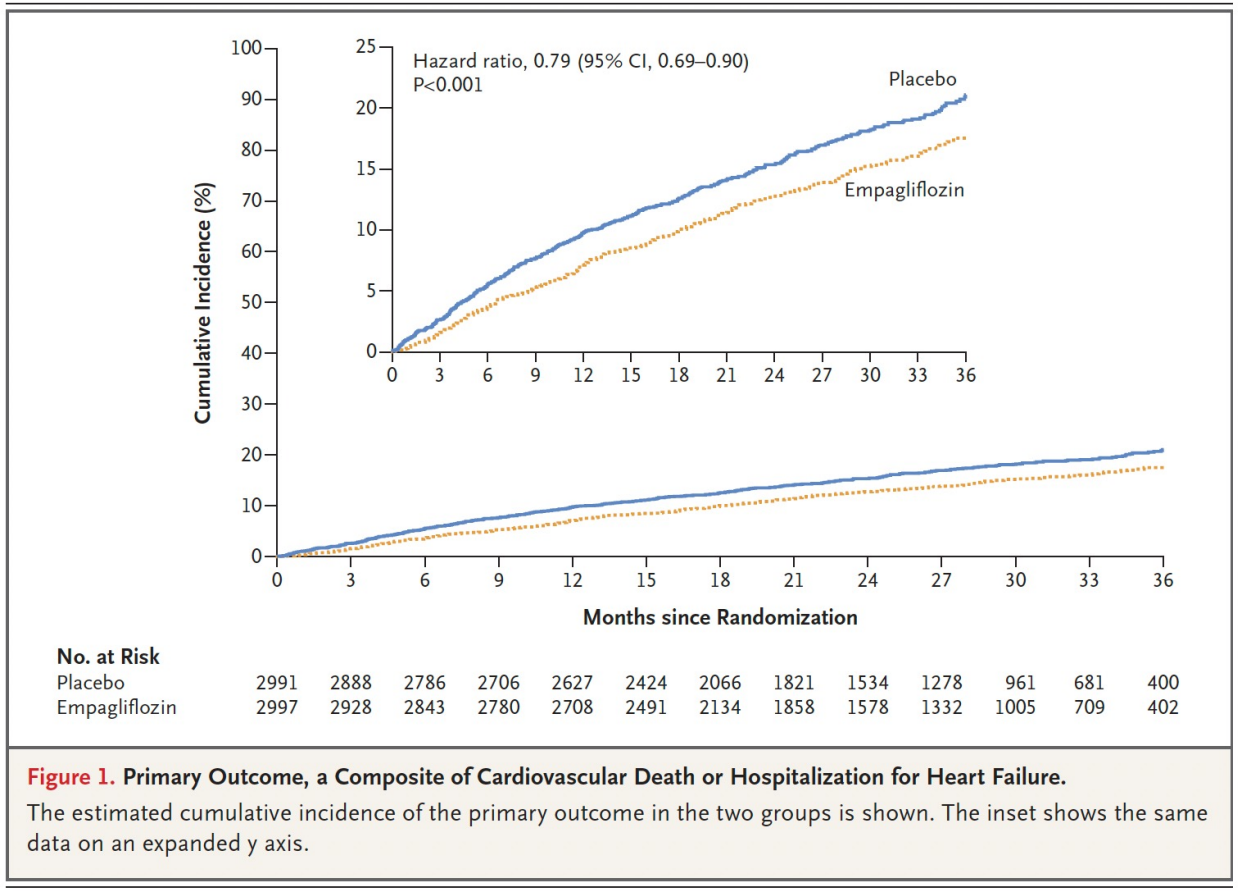

Figure 1. Primary Outcome, a Composite of Cardiovascular Death or Hospitalization for Heart Failure.
The estimated cumulative incidence of the primary outcome in the two groups is shown. The inset shows the same data on an expanded y axis.

Independent of diabetes

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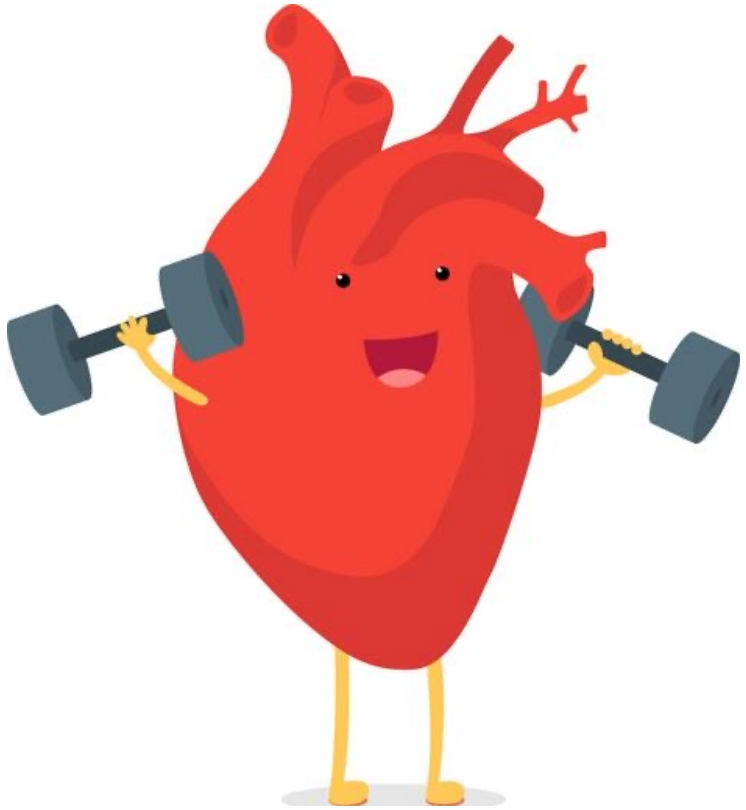
Anker et al. NEJM 2021, p1451



Guidelines recommendations

- 1e lijn bij T2D en CV ziekte (**samen met GLP-1 analogen**)
- Opgenomen in behandeling HFrEF (ongeacht diabetes)
- Succesvol bij HFpEF (weinig alternatief)

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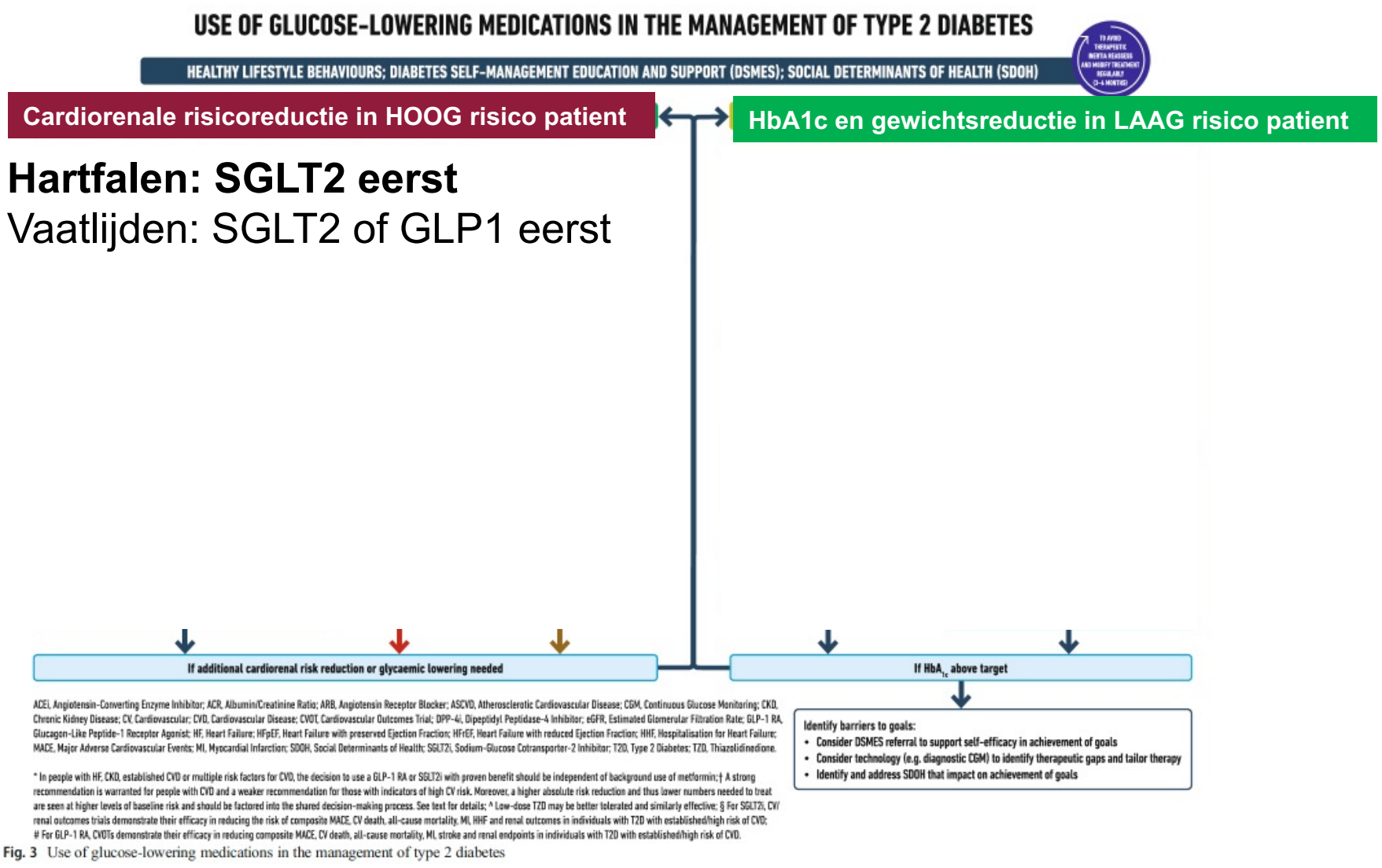
EASD guidelines 2022



Hartfalen: SGLT2 eerst

Vaatlijden: SGLT2 of GLP1 eerst

Fig. 3 Use of glucose-lowering medications in the management of type 2 diabetes

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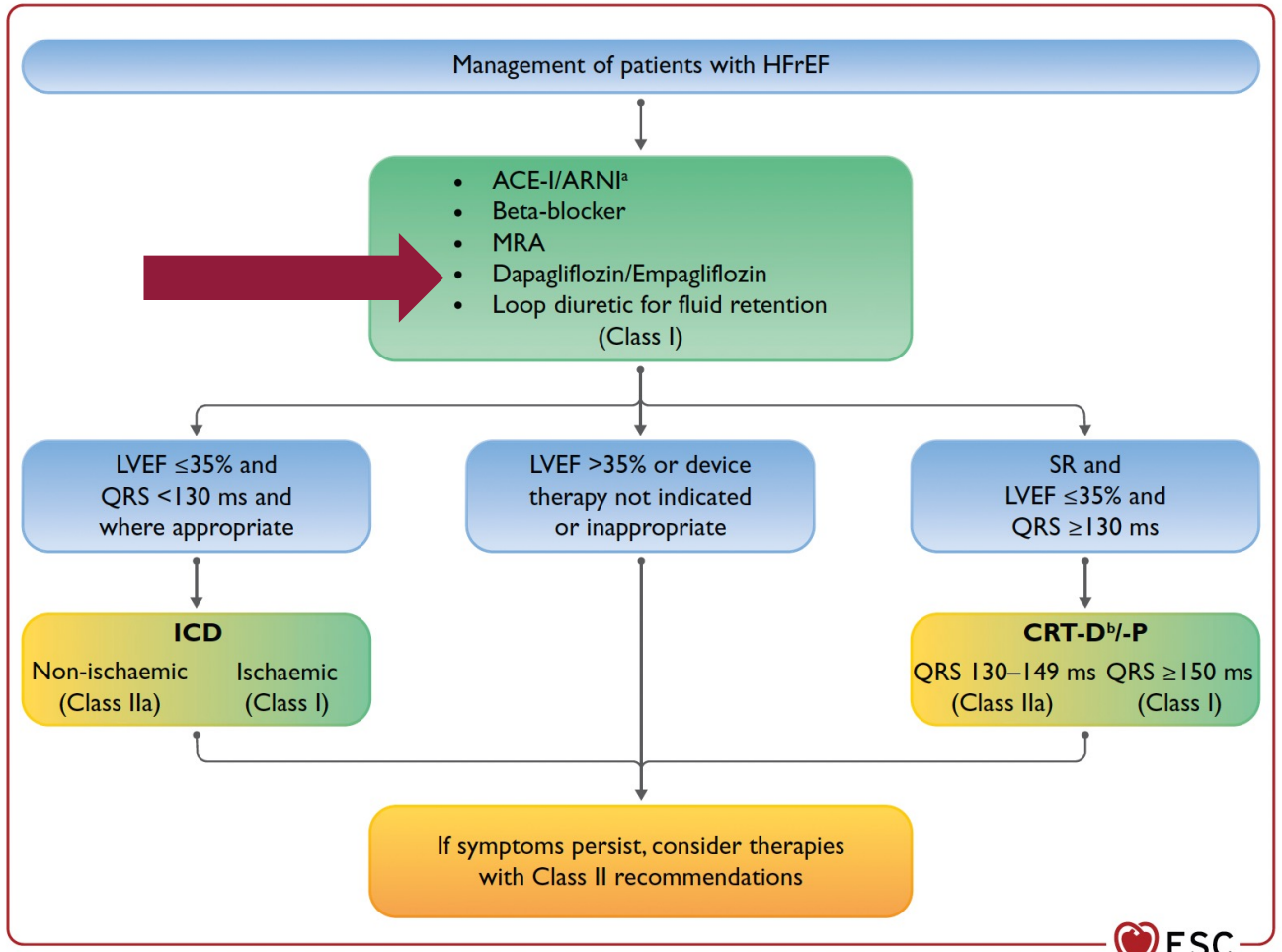
ESC Guidelines voor HFrEF



Onafhankelijk van diabetes

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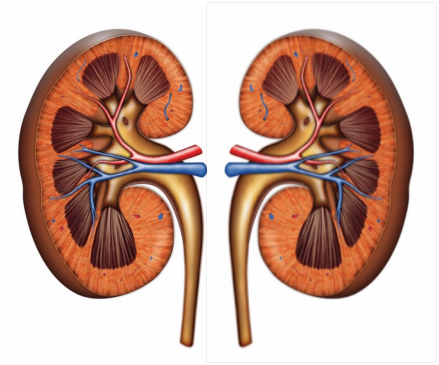
European Heart Journal 2021, p3599

SGLT2 inhibitoren

Nefroloog



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SGLT-2 inhibitors slow renal progression

	Renal-related endpoint	HR (95% CI)
	Secondary endpoint	
EMPA-REG OUTCOME	Doubling serum creatinine, initiation of RRT or death from renal disease	**0.54 (0.40-0.75)**
CANVAS program	Sustains 40% reduction in eGFR, RRT, or death from renal causes	**0.60 (0.47-0.77)**
DELCLARE-TIMI 58	Sustained ≥40% reduction in eGFR to <60 ml/min/1.73m^2 and/or ESRD and/or renal or CV death	**0.53 (0.43-0.66)**
VERTIS CV	Renal death, dialysis/transplant or doubling of serum creatinine from baseline	**0.81 (0.64-1.03)***
	Primary endpoint	
CREDENCE	Sustained doubling of serum creatinine level and/or ESRD and/or renal or CV death	**0.70 (0.59-0.82)**
DAPA-CKD	Sustained ≥50% reduction in eGFR and/or ESRD and/or renal or CV death	**0.61 (0.51-0.72)**
EMPA-KIDNEY	Sustained ≥40% reduction in eGFR, eGFR<10 ml/min/1.73m^2, ESRD or renal death or CV death	**0.72 (0.64-0.82)**

* ns

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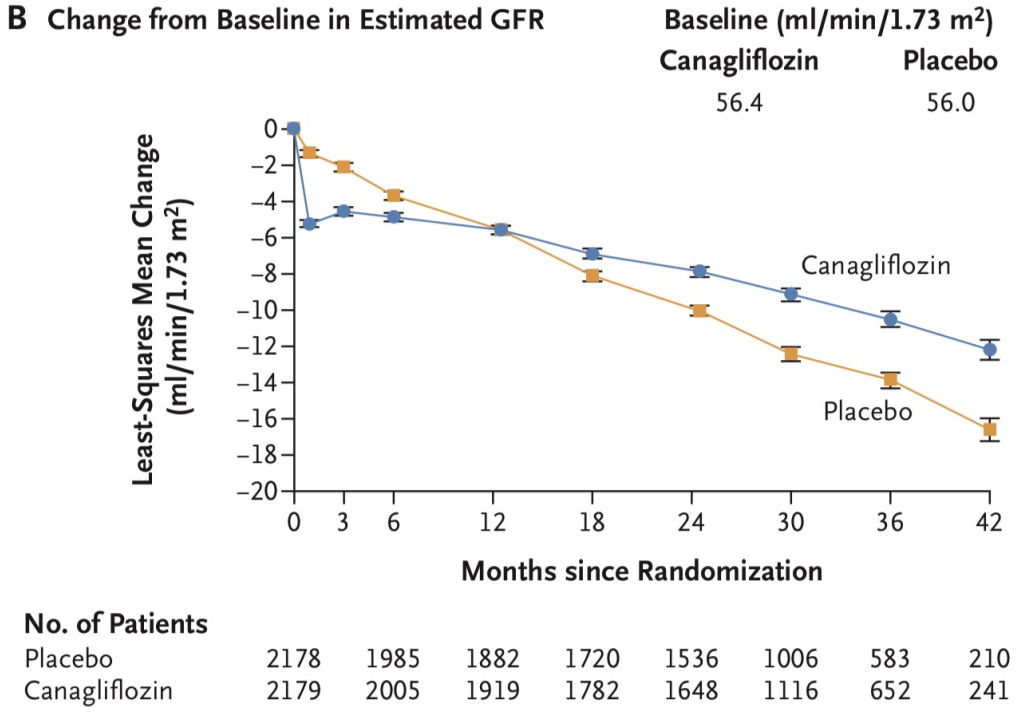
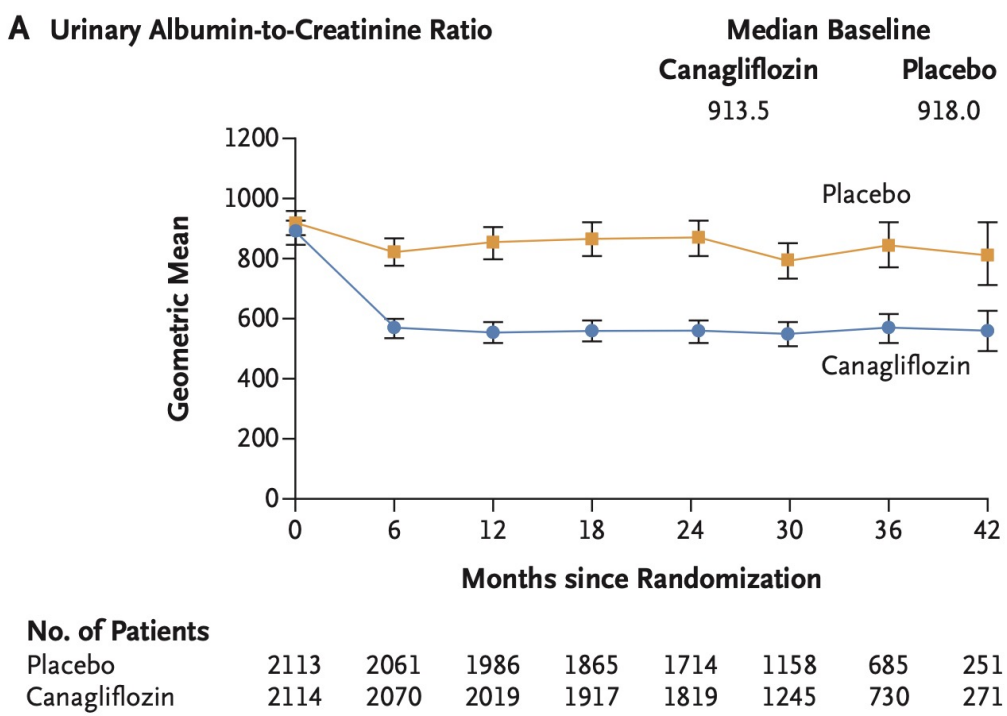
Diabeteskliniek

Canagliflozin 100mg/d in **DKD patients** (CREDENCE)





Perkovic V et al. NEJM 2019 p2295

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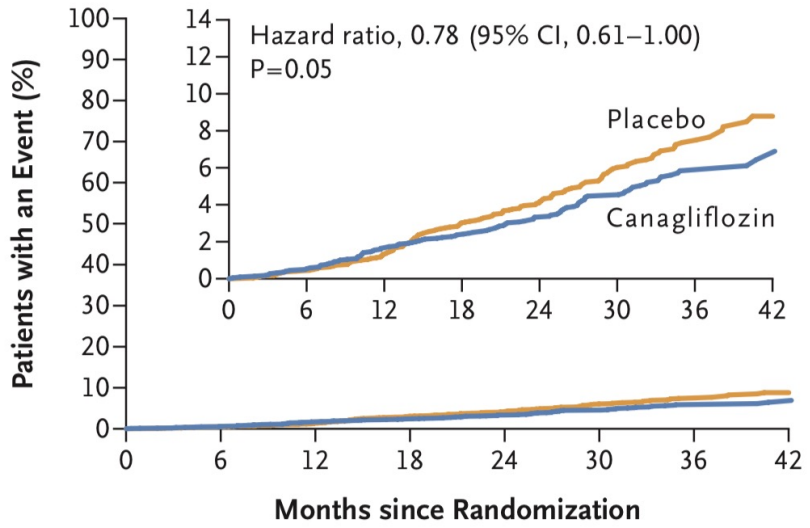
Diabeteskliniek

Mortality benefit of Canagliflozin and Dapagliflozin in DKD/CKD patients

E **Death from Cardiovascular Cause**



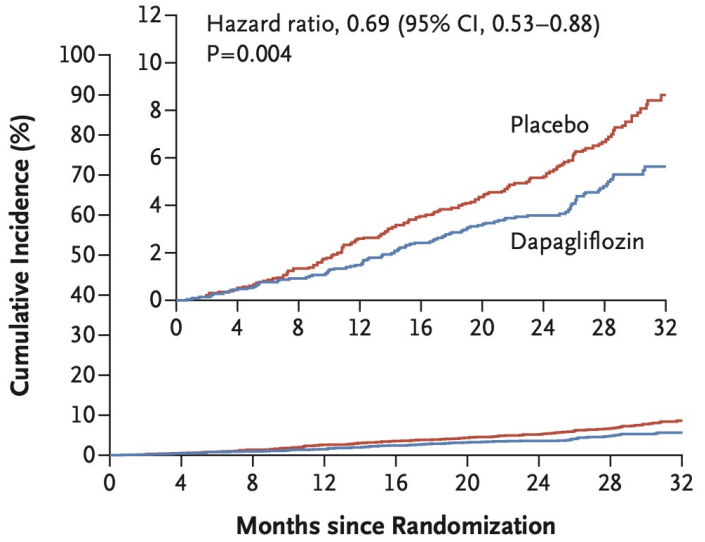
No. at Risk

Placebo	2199	2185	2160	2106	1818	1220	688	189
Canagliflozin	2202	2187	2155	2120	1835	1263	687	212

22%*

*not significant

D **Death from Any Cause**



No. at Risk

Placebo	2152	2035	2018	1993	1972	1902	1502	1009	379
Dapagliflozin	2152	2039	2029	2017	1998	1925	1531	1028	398

31%

Perkovic V et al. NEJM 2019 p2295

Heerspink et al.. NEJM 2020

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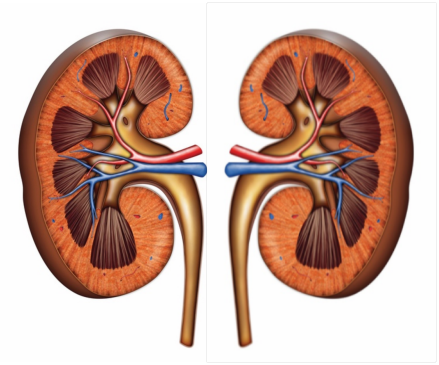
Diabeteskliniek

SGLT2 inhibitoren

*Bij patienten **ZONDER** diabetes*



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Diabeteskliniek

Dapagliflozin in non-diabetic CKD (DAPA-CKD trial)

- **Population** *(biopsy in 20%)*
  - Type 2 diabetes: n=2906 (68%) → 14% NDKD
  - No Diabetes: n= 1398 (32%)

DKD	2510 (58%)
Glomerulonephritis	695 (16%)
Ischeamic or hypertensive	687 (16%)
Other or uncertain	412 (10%)

Investigator reported!
(20% biopsy)

Exclusion criteria:
Type 1 diabetes, polycystic kidney disease, lupus nephritis, ANCA vasculitis, patients receiving immunosuppressive treatment for primary or secondary kidney disease <6 months of enrolment

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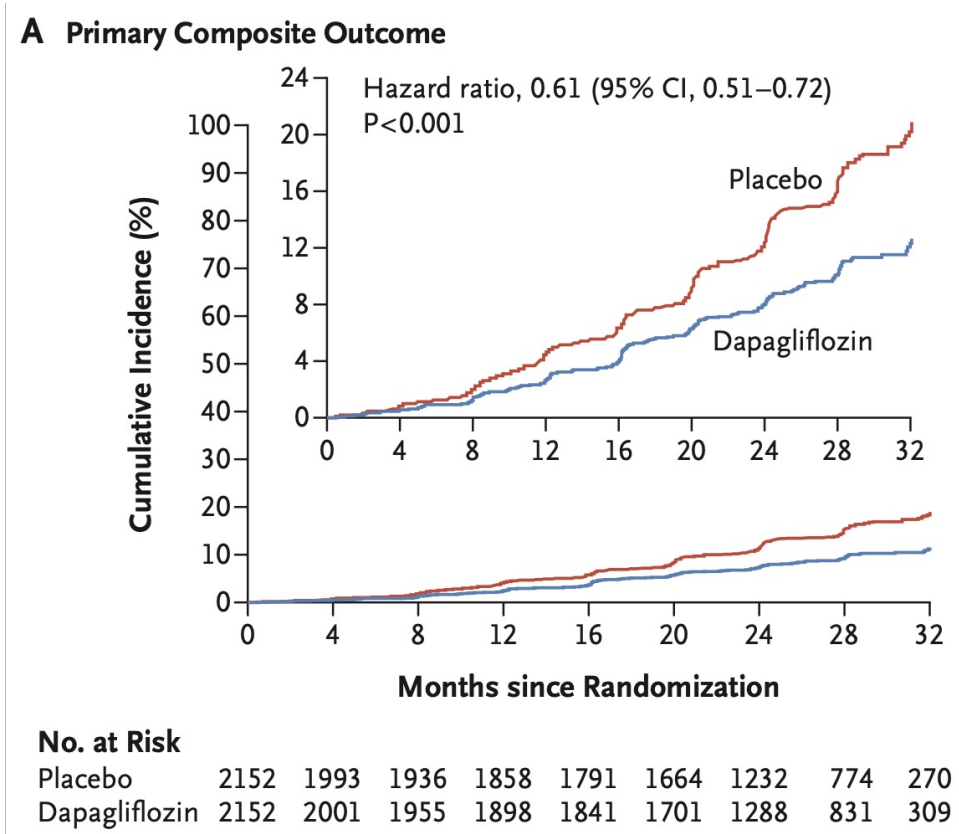
Diabeteskliniek

Wheeler et al. Lancet Diab Endocrinol 2021, p22

Dapagliflozin 10 mg/d in CKD patients (DAPA-CKD)



DKD: eGFR 25-75 ml/min + albuminurie 200-5000 mg/g creatinine
Met (2/3) EN ZONDER diabetes (1/3)

Composite renal end-point

- *>50% decrease in eGFR*
- *ESRD*
- *Renaal of CV overlijden*

39%

Heerspink et al.. NEJM 2020

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Dapagliflozin in non-diabetic CKD (DAPA-CKD trial)

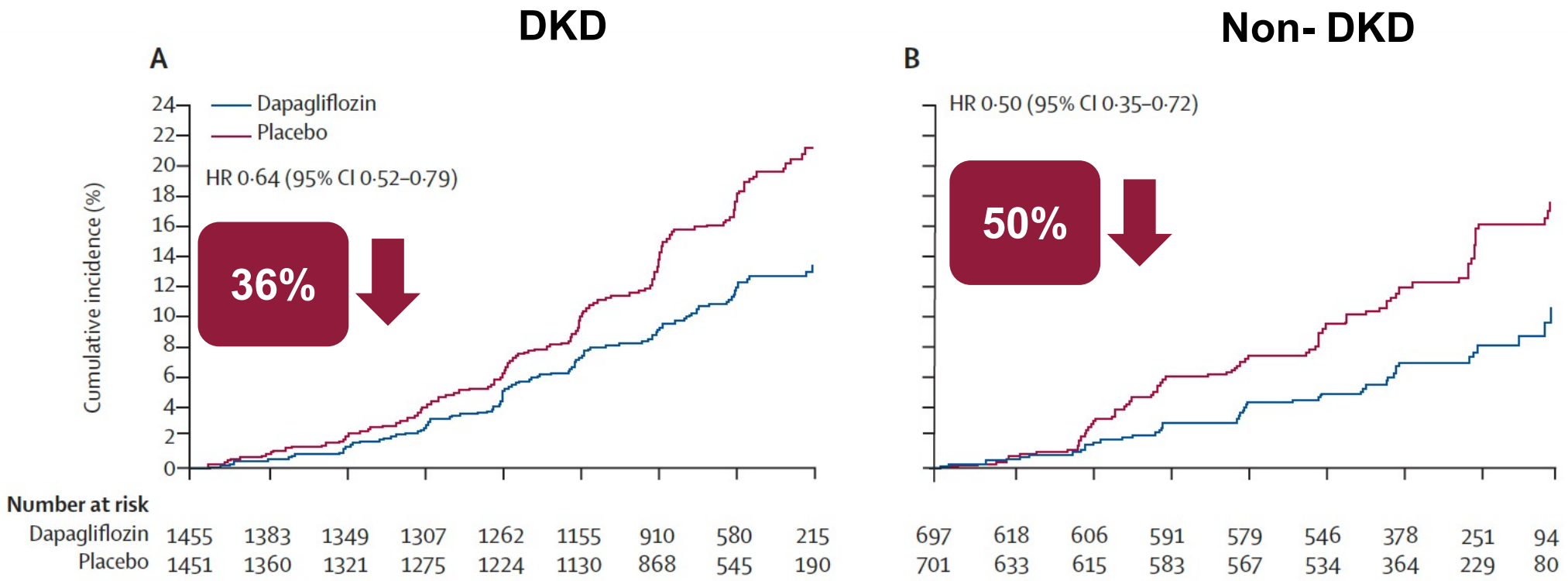

Figure 1: **Kaplan-Meier curves of the primary composite outcome in participants (A) with type 2 diabetes and (B) without diabetes and the kidney-specific composite secondary outcome in participants (C) with type 2 diabetes and (D) without diabetes**
HR=hazard ratio.

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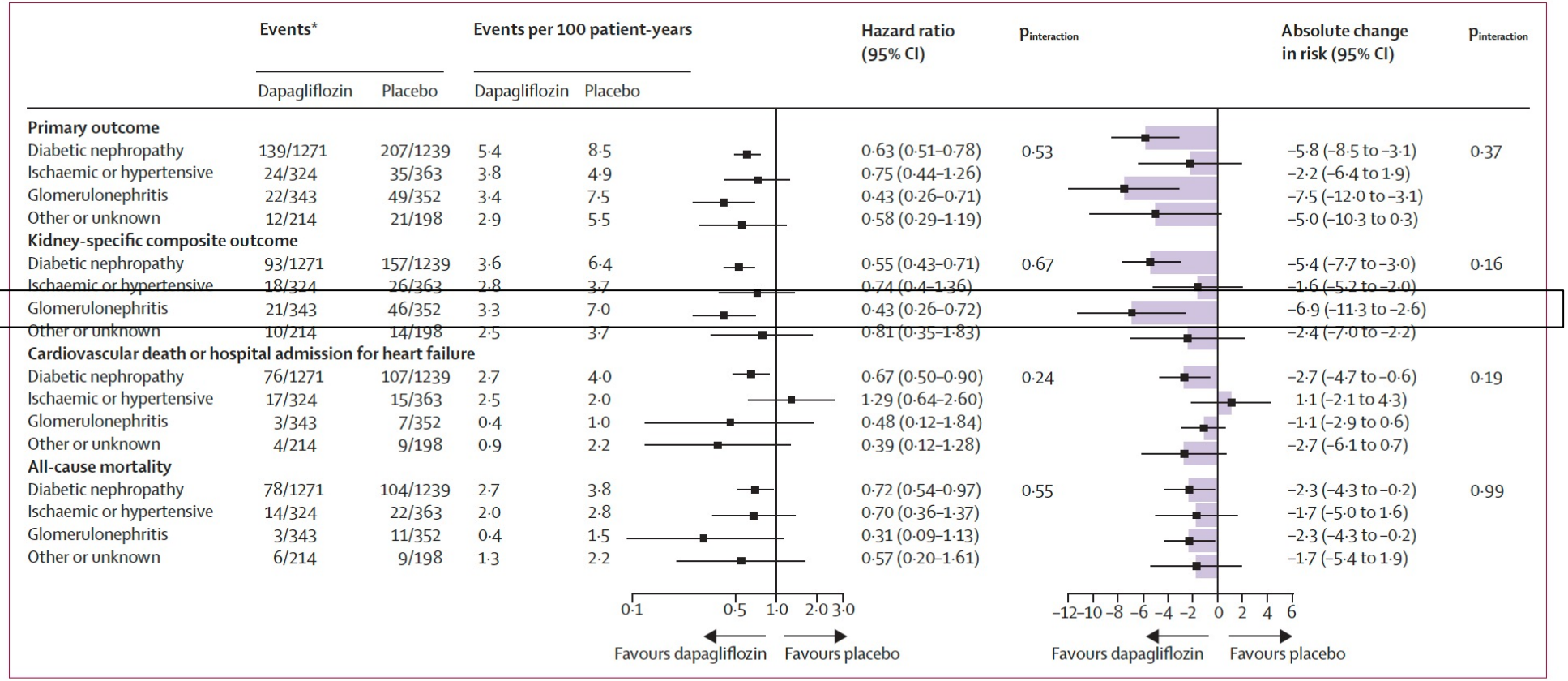
Diabeteskliniek

Wheeler et al. Lancet Diab Endocrinol 2021, p22

Dapagliflozin in non-diabetic CKD (DAPA-CKD trial)



	Events*		Events per 100 patient-years		Hazard ratio (95% CI)	$p_{interaction}$	Absolute change in risk (95% CI)	$p_{interaction}$
	Dapagliflozin	Placebo	Dapagliflozin	Placebo				
Primary outcome								
Diabetic nephropathy	139/1271	207/1239	5·4	8·5	0·63 (0·51–0·78)	0·53	−5·8 (−8·5 to −3·1)	0·37
Ischaemic or hypertensive	24/324	35/363	3·8	4·9	0·75 (0·44–1·26)		−2·2 (−6·4 to 1·9)	
Glomerulonephritis	22/343	49/352	3·4	7·5	0·43 (0·26–0·71)		−7·5 (−12·0 to −3·1)	
Other or unknown	12/214	21/198	2·9	5·5	0·58 (0·29–1·19)		−5·0 (−10·3 to 0·3)	
Kidney-specific composite outcome								
Diabetic nephropathy	93/1271	157/1239	3·6	6·4	0·55 (0·43–0·71)	0·67	−5·4 (−7·7 to −3·0)	0·16
Ischaemic or hypertensive	18/324	26/363	2·8	3·7	0·74 (0·4–1·36)		−1·6 (−5·2 to −2·0)	
Glomerulonephritis	21/343	46/352	3·3	7·0	0·43 (0·26–0·72)		−6·9 (−11·3 to −2·6)	
Other or unknown	10/214	14/198	2·5	3·7	0·81 (0·35–1·83)		−2·4 (−7·0 to −2·2)	
Cardiovascular death or hospital admission for heart failure								
Diabetic nephropathy	76/1271	107/1239	2·7	4·0	0·67 (0·50–0·90)	0·24	−2·7 (−4·7 to −0·6)	0·19
Ischaemic or hypertensive	17/324	15/363	2·5	2·0	1·29 (0·64–2·60)		1·1 (−2·1 to 4·3)	
Glomerulonephritis	3/343	7/352	0·4	1·0	0·48 (0·12–1·84)		−1·1 (−2·9 to 0·6)	
Other or unknown	4/214	9/198	0·9	2·2	0·39 (0·12–1·28)		−2·7 (−6·1 to 0·7)	
All-cause mortality								
Diabetic nephropathy	78/1271	104/1239	2·7	3·8	0·72 (0·54–0·97)	0·55	−2·3 (−4·3 to −0·2)	0·99
Ischaemic or hypertensive	14/324	22/363	2·0	2·8	0·70 (0·36–1·37)		−1·7 (−5·0 to 1·6)	
Glomerulonephritis	3/343	11/352	0·4	1·5	0·31 (0·09–1·13)		−2·3 (−4·3 to −0·2)	
Other or unknown	6/214	9/198	1·3	2·2	0·57 (0·20–1·61)		−1·7 (−5·4 to 1·9)	

Figure 4: **Forest plot of primary and secondary outcomes by kidney disease diagnosis at baseline**
Participants with type 2 diabetes who had a reported cause of kidney disease other than diabetic nephropathy were analysed on the basis of the investigator-reported underlying aetiology. *Event data are numbers of participants with an outcome event/total participants.

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Wheeler et al. Lancet Diab Endocrinol 2021, p22

SGLT-2 inhibitoren en nefroprotectie

- Minder progressie albuminurie
- Minder snelle daling eGFR
- Minder ESRD
- **Gedaalde mortaliteit indien reeds CKD/DKD!**
- **Niet enkel bij diabetici:** Lijkt ook te bestaan bij non-DKD nefropathie zoals glomerulonefritis

- Mechanismen:
  - → **Onafhankelijk van HbA1c! (cfr guidelines)**
  - → Herstel tubuloglomerulaire feedback
  - → Minder glomerulaire hyperfiltratie/hypertensie
  - → Minder hypoxie
  - → ….

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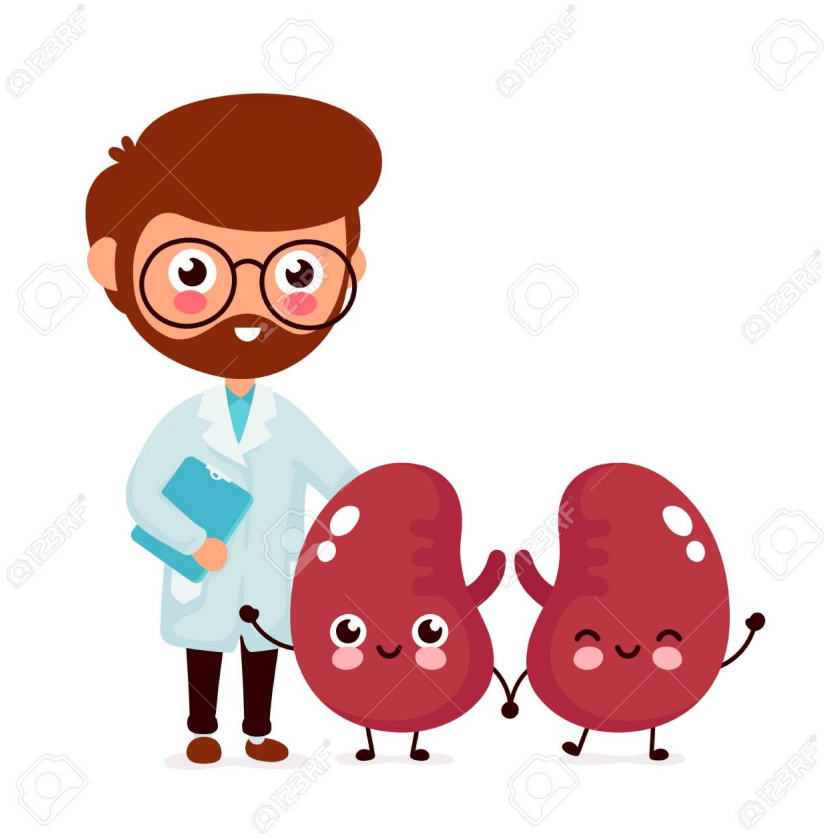


Clinical practice

- Minder achteruitgang nierfunctie ongeacht diabetes
- Zeer goede resultaten bij bijv. IgA nefropathie
- Klasse-effect met brede toepassing ?

EASD guidelines 2022

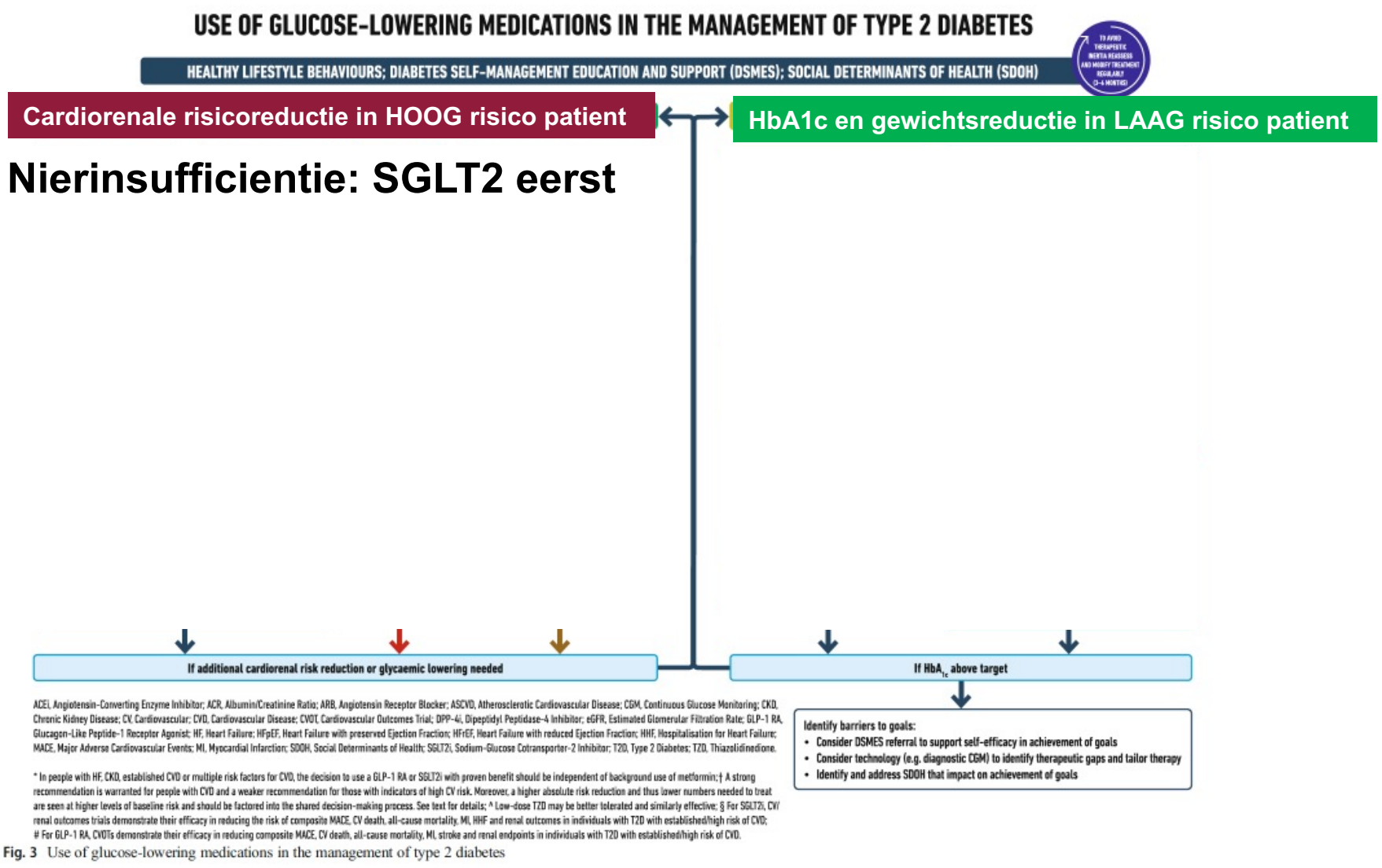
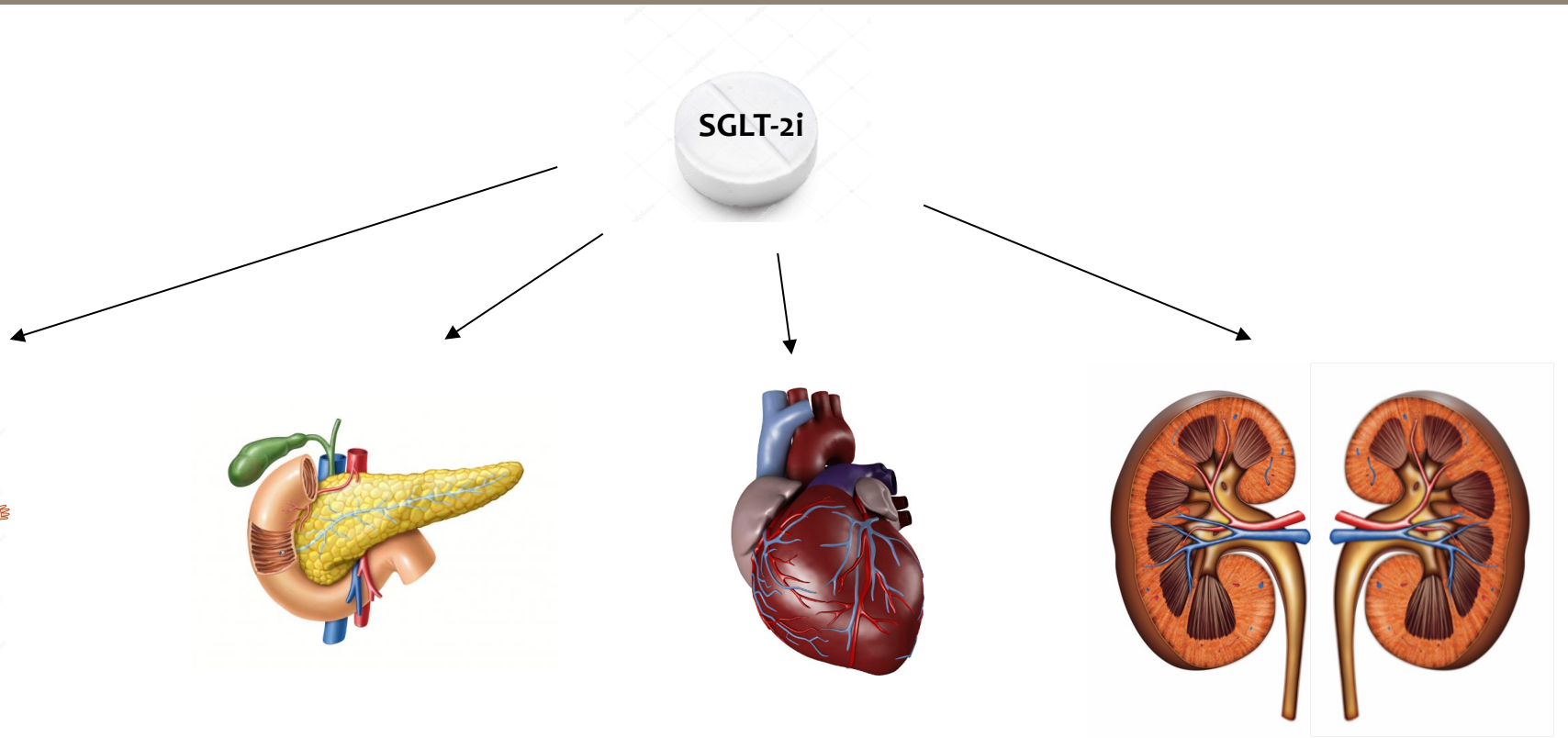


Fig. 3 Use of glucose-lowering medications in the management of type 2 diabetes

One for all…

One for all……



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Type 2 diabetes

cardioloog

ASCVD
Heartfailure
CV mortality

nefroloog

(Diabetes) nephropathy

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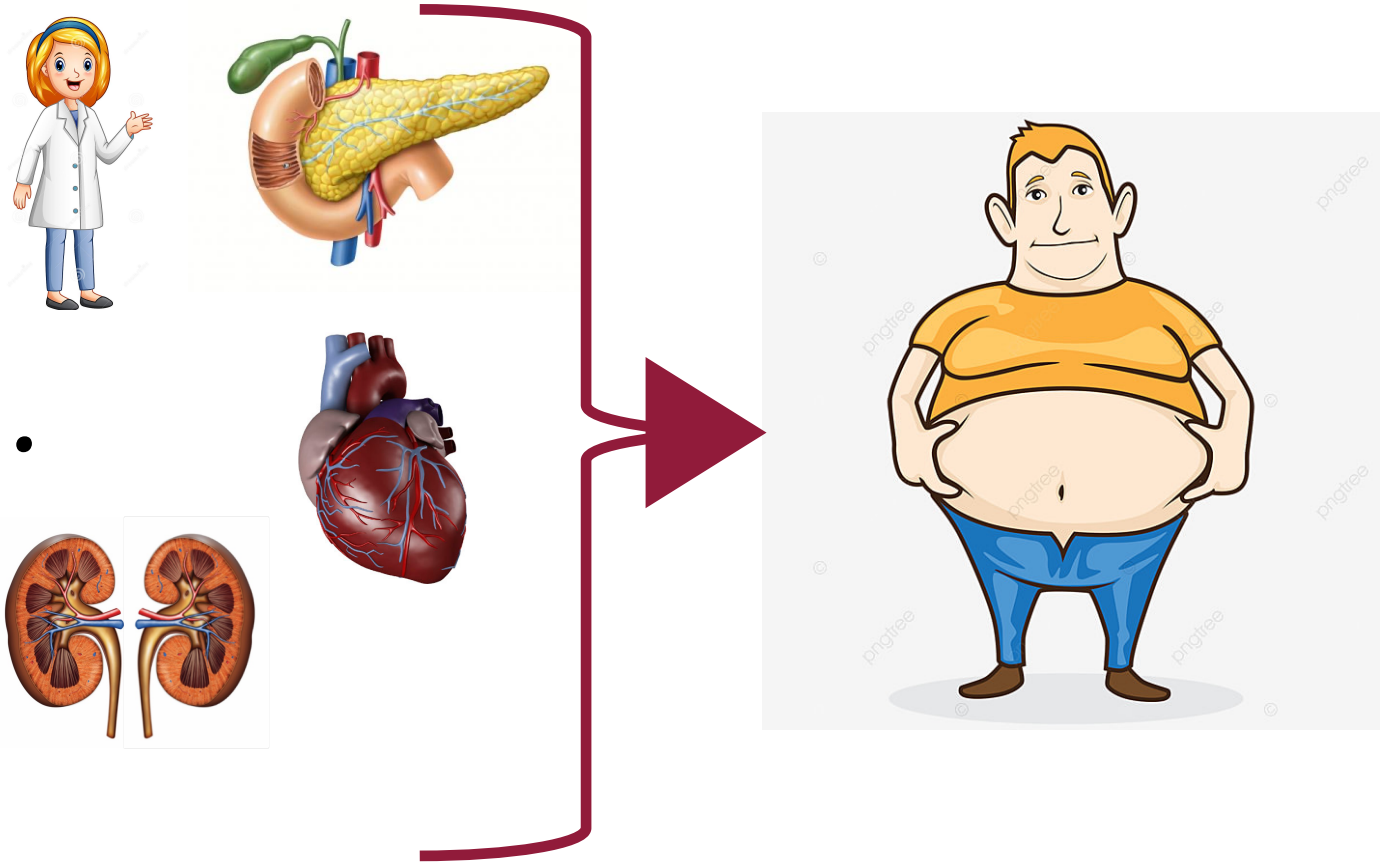
Diabeteskliniek

All for one……



Multidisciplinaire aanpak van Type 2 diabetes

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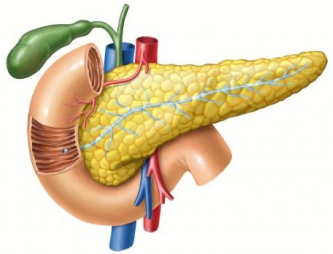
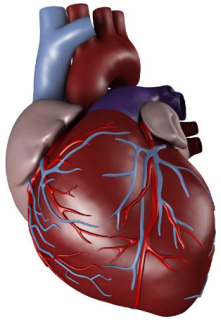


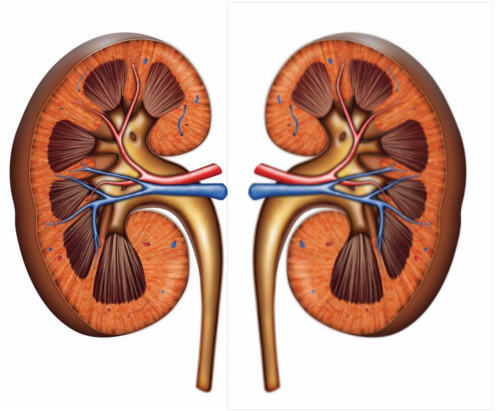
endocrinoloog

Type 2 diabetes



cardioloog

ASCVD
Heartfailure
CV mortality



nefroloog

(Diabetes) nephropathy

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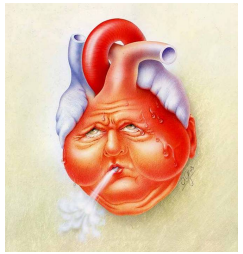
Diabeteskliniek

A new dawn for indications for SGLT-2 inhibitors

- SGLT-2 inhibitors in patients **without diabetes**

  → Hartfalen

  → Chronische nierinsufficientie



Hypoglycemie bij SGLT-2i in de praktijk

- CVOT studies tonen geen hogere risico op hypoglycemie wanneer toegevoegd aan behandeling vs placebo

- Patient **onder insuline** met goede glycemie controle: hypoglycemie mogelijk en vaak noodzaak tot **reductie insulinedosis** → **overleg met diabetoloog noodzakelijk!**

- Patient onder orale medicatie met kans op hypo (**Sulfonylurea**): hypo's mogelijk

  CAVE: SU is veel krachtiger dan SGLT2i in daling glycemie!

Terugbetaling SGLT-2 inhibitoren voor DIABETES

GLUCOCENTRISCH

Na metformine
Mag in combinatie met insuline, NIET met GLP-1

Dapagliflozine
- eGFR >60 ml/min
- HbA1c >7.0 en <9.0%
- >45 ml/min/1.73m2
- >30-44 ml/min MET albuminurie >300 mg/g creatinine

Empagliflozine
- eGFR>30 ml/min/1.73m2
- HbA1c >7.0 en <9.0%

NIET BIJ TYPE 1 DIABETES!!

Hypoglycemierend effect neemt af met GFR!

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DiabetesKliniek

Terugbetaling SGLT-2 inhibitoren voor HARTFALEN en CKD

GLUCOCENTRISCH

Cardio-renale protectie onafhankelijk van HbA1c

- **Hartfalen zonder diabetes bij HFrEF (enkel voor Dapa en Empa)**
- **Reno-protectie zonder diabetes vanaf december 2022 (enkel voor Dapagliflozine)**

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Diabeteskliniek

Terugbetaling SGLT-2 inhibitoren voor HARTFALEN en CKD

Cardio-renale protectie ZONDER diabetes

- **Hartfalen**
  - NYHA klasse II, III of IV
  - **EN** EF <40% op echo
  - **EN** eGFR >20 ml/min/1.73m²
  - **EN** GEEN type 1 diabetes

ENKEL door cardioloog aan te vragen

Dapagliflozine of Empagliflozine

- **Nierinsufficientie (1 dec 2022)**
  - eGFR <60 ml/min/1.73m²
  - **EN** UACR>200 mg/g creatinine
  - **EN** GEEN type 1 diabetes

Dapagliflozine

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Take home message

- SGLT-2 inhibitoren hebben **toepassing** binnen
  - → Type 2 diabetes
  - → Hartfalen en preventie CV risico
  - → Chronische nierziekten

- **T2D patient** is meest **gebaat** bij SGLT2i indien:
  - → Hartfalen
  - → Nierinsufficientie
  - → Hoog CV risico

- BMI>30 en HbA1c>7.5 met **hoog CV risico zonder hartfalen: denk eerst aan GLP-1 analoog!**

- Pas op met risico op hypoglycemie/hyperglycemie **bij diabetespatienten → overleg**

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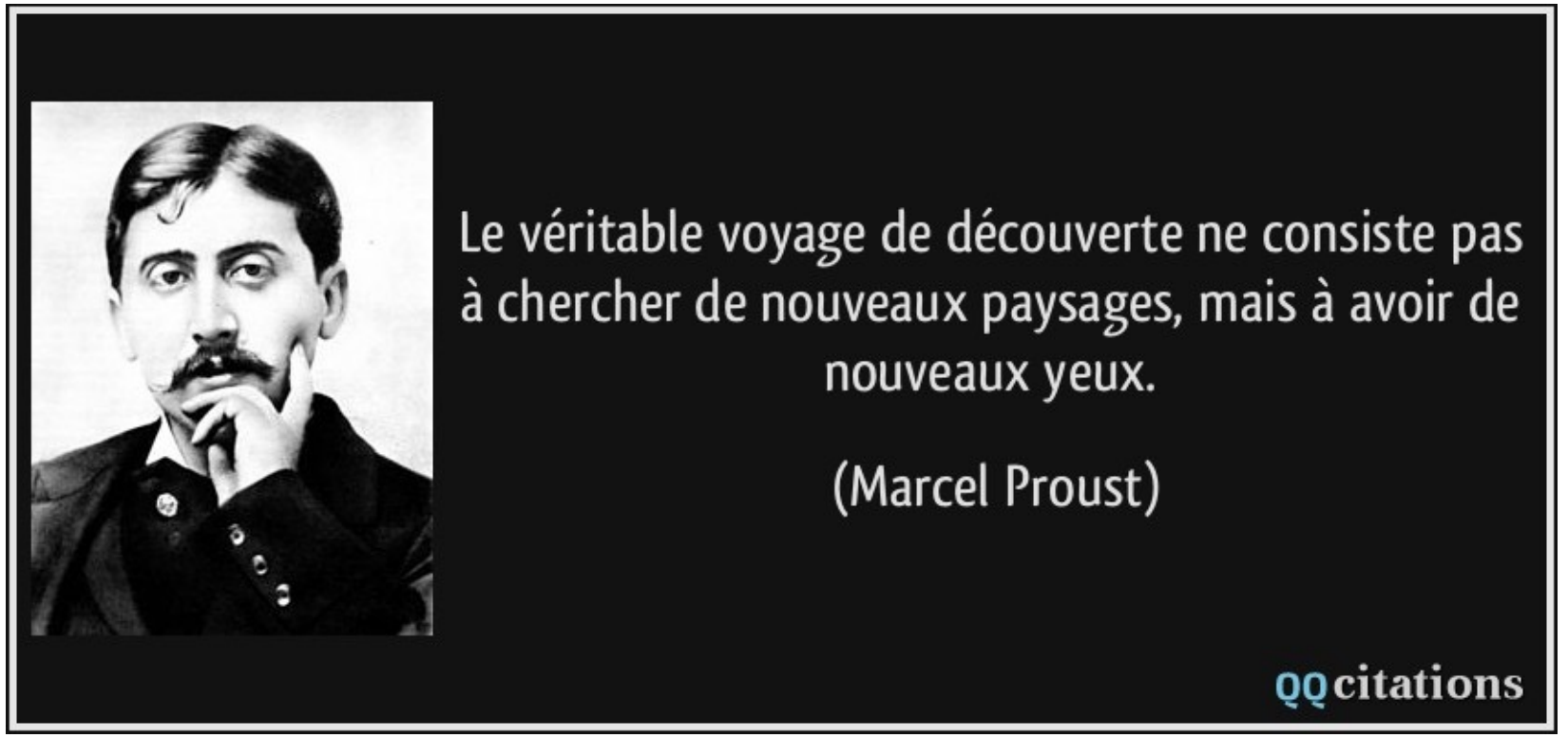
Wijze lessen uit dit '**VERBAZINGWEKKENDE**' verhaal…..

1. Sta open voor kritiek
2. Heb oog voor pathofysiologie in brede zin en vanaf het begin
3. Samenwerken is key


Le véritable voyage de découverte ne consiste pas à chercher de nouveaux paysages, mais à avoir de nouveaux yeux.
(Marcel Proust)
QQ citations