Cursus SGLT2 remmers

Achtergronden, casuïstiek en klinische implementatie

2020

Nascholing geschreven door:
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- dr PC Oldenburg-Ligtenberg, internist

Beiden uit Meander MC, Amersfoort

Disclosure slide

Dr. Oldenburg

Geen (potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties:	
Sponsoring of onderzoeksgeld	•
Honorarium of andere (financiële) vergoeding	• **Presentaties/webinar NovoN, Boehringer-I** • **Cursus AstraZeneca**
Aandeelhouder	•
Andere relatie, namelijk …	

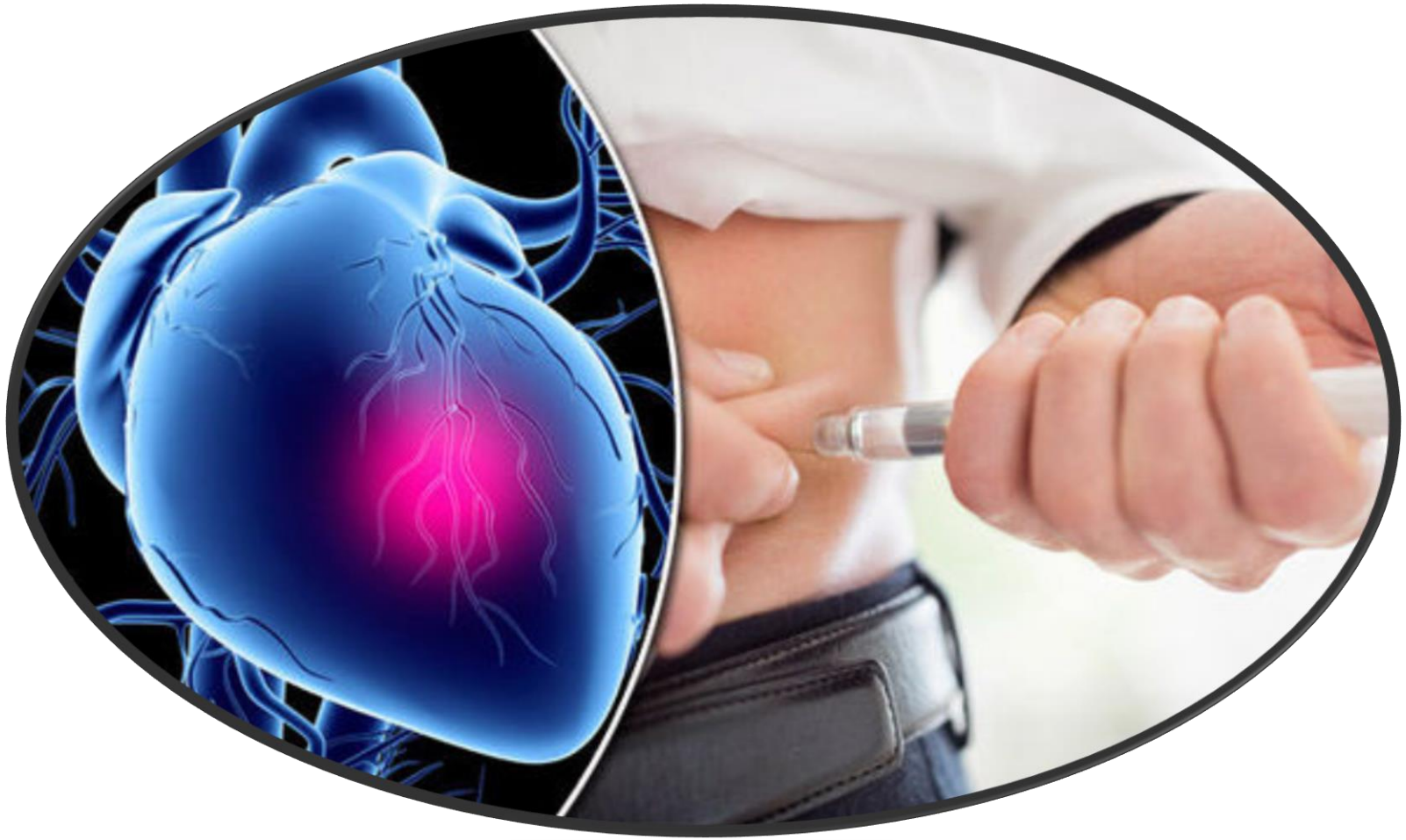
Dr. Mosterd

Geen (potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties:	
Sponsoring of onderzoeksgeld	• **Unrestricted Grant Novartis voor het UMCU.**
Honorarium of andere (financiële) vergoeding	• **Vergoeding voor werkzaamheden als national lead Stand-UP HF trial (BMS) en Victoria Trial (MSD).** • **Cursus Astra Zeneca.**
Aandeelhouder	•
Andere relatie, namelijk …	

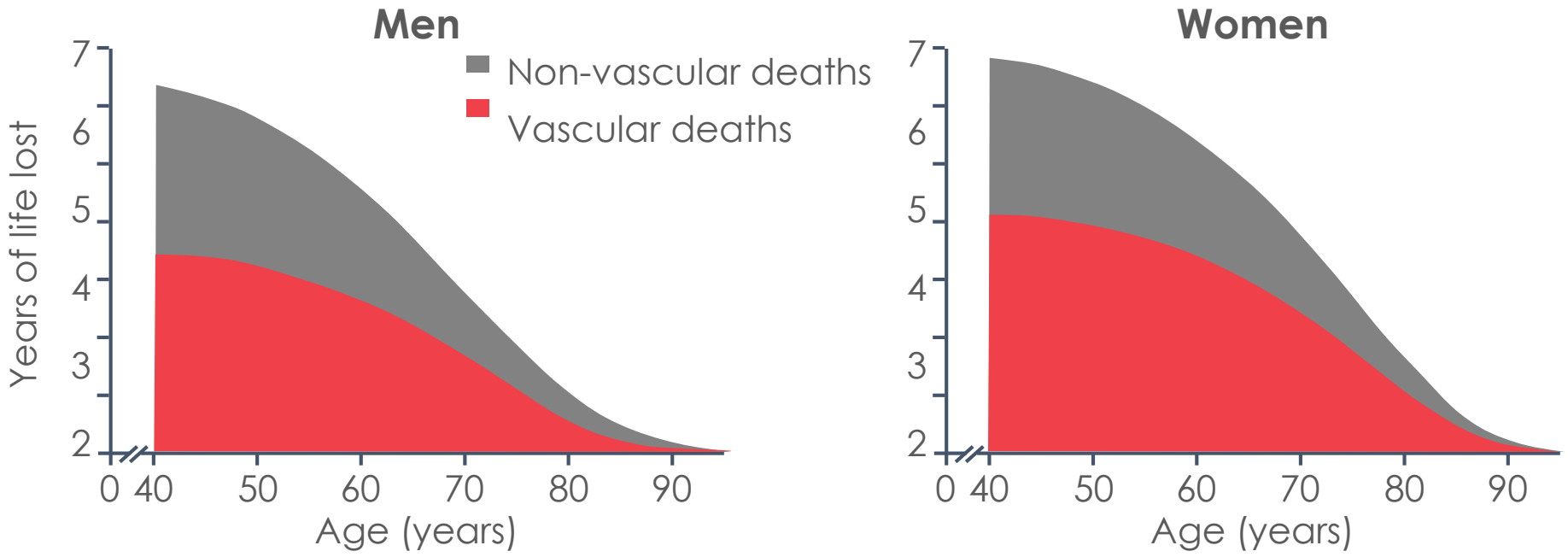
Cursus SGLT2 remmers

- Casus (3 à 4) met tussendoor:
- Werkingsmechanisme SGLT2i
- Wetenschappelijk bewijs tot nu toe
  - Bij diabetes/niet diabetes
  - Bij hartfalen
  - Tav nierinsufficientie

Inleiding



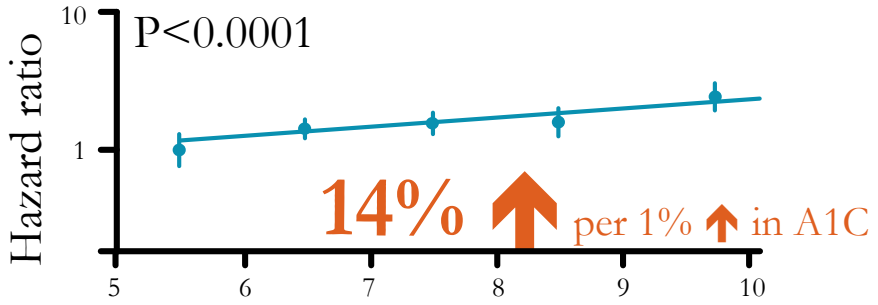
Diabetes: (CV) loss of life years



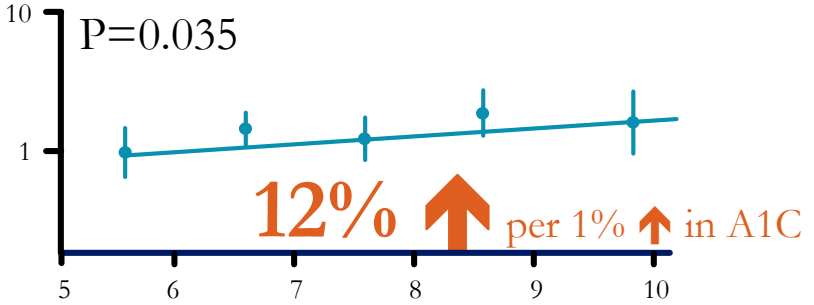
Seshasai et al. N Engl J Med 2011;364:829-41

UKPDS 35: Association of A1C with CV Risk in T2DM

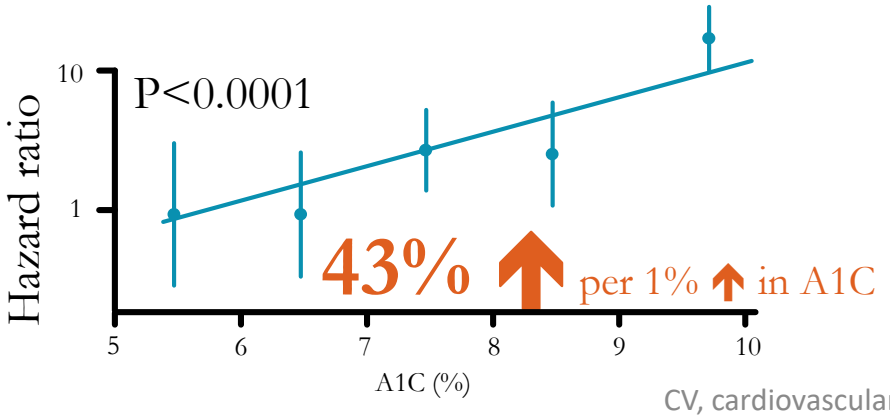
Fatal and Non-fatal MI



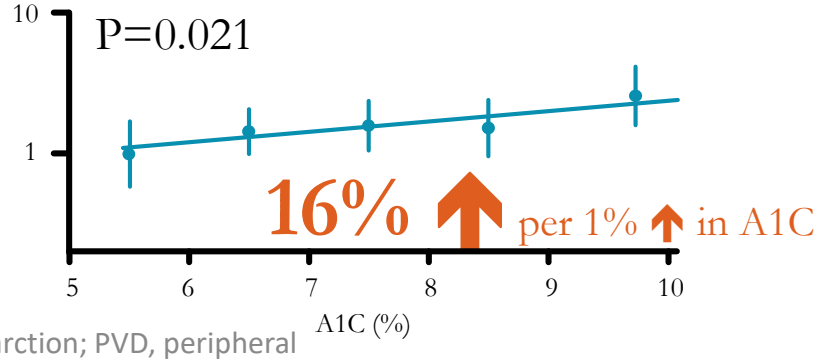
Fatal and No-Fatal Stroke



Amputation/Death from PVD



Heart Failure



CV, cardiovascular; MI, myocardial infarction; PVD, peripheral vascular disease.

Stratton IM et al. BMJ. 2000;321:405-12.

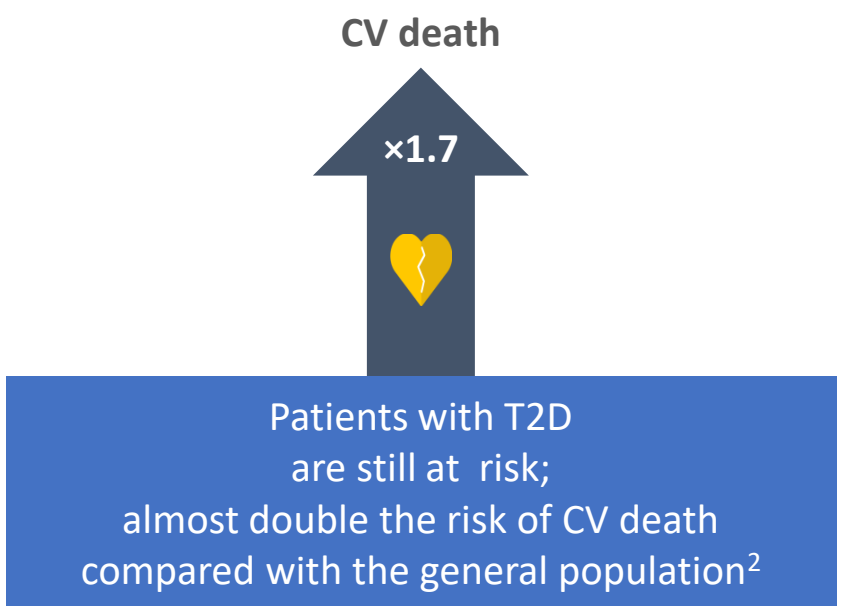
Patients with T2D and established CV disease: still at risk

CV risk management[1]

- Lipid management (e.g. statins)
- Blood pressure control (e.g. ACEi or ARBs)
- Antithrombotic agents (e.g. ASA)

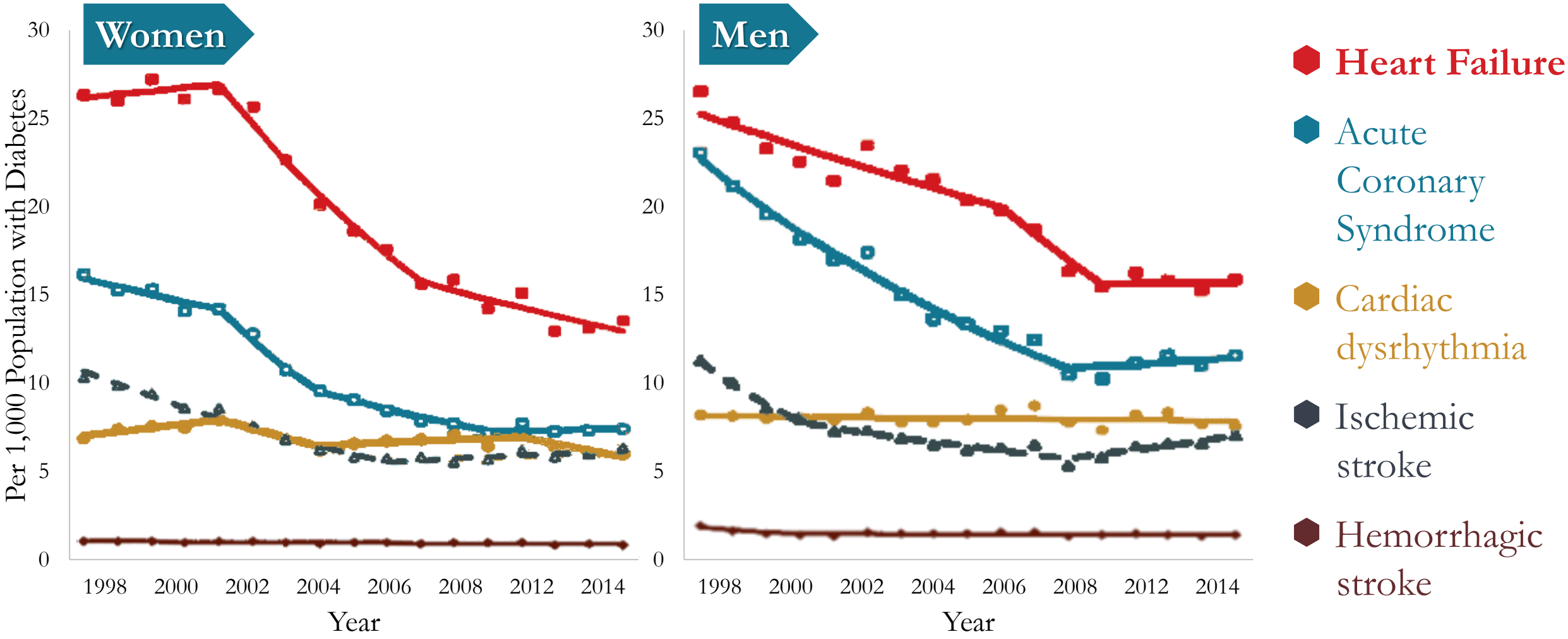
Glucose control[1]

- Achieve blood glucose levels (HbA1c < 53 mmol/mol,



1 American Diabetes Association. Diabetes Care 2016;
2. Centers for Disease Control and Prevention. National Diabetes Statistics Report. 2014. www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf (accessed May 2016)

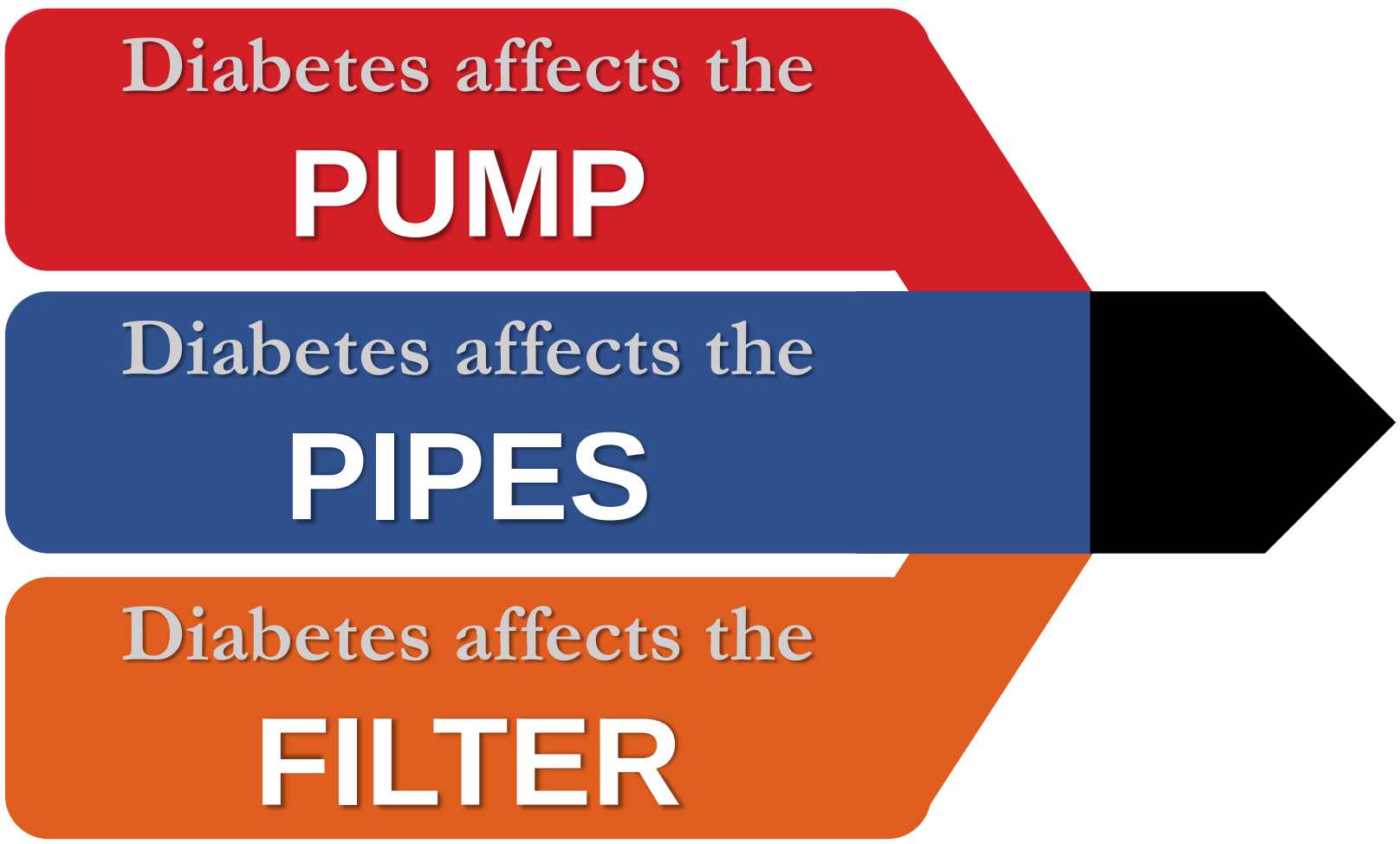
Heart Failure is the Most Common Cause of CV-related Hospitalizations Amongst People with Diabetes



ACS, acute coronary syndrome; CV, cardiovascular.

Burrows NR et al. Diabetes Care. 2018;41:293-302.

Cardiovascular-Renal Spectrum of Diabetes



Heart Failure

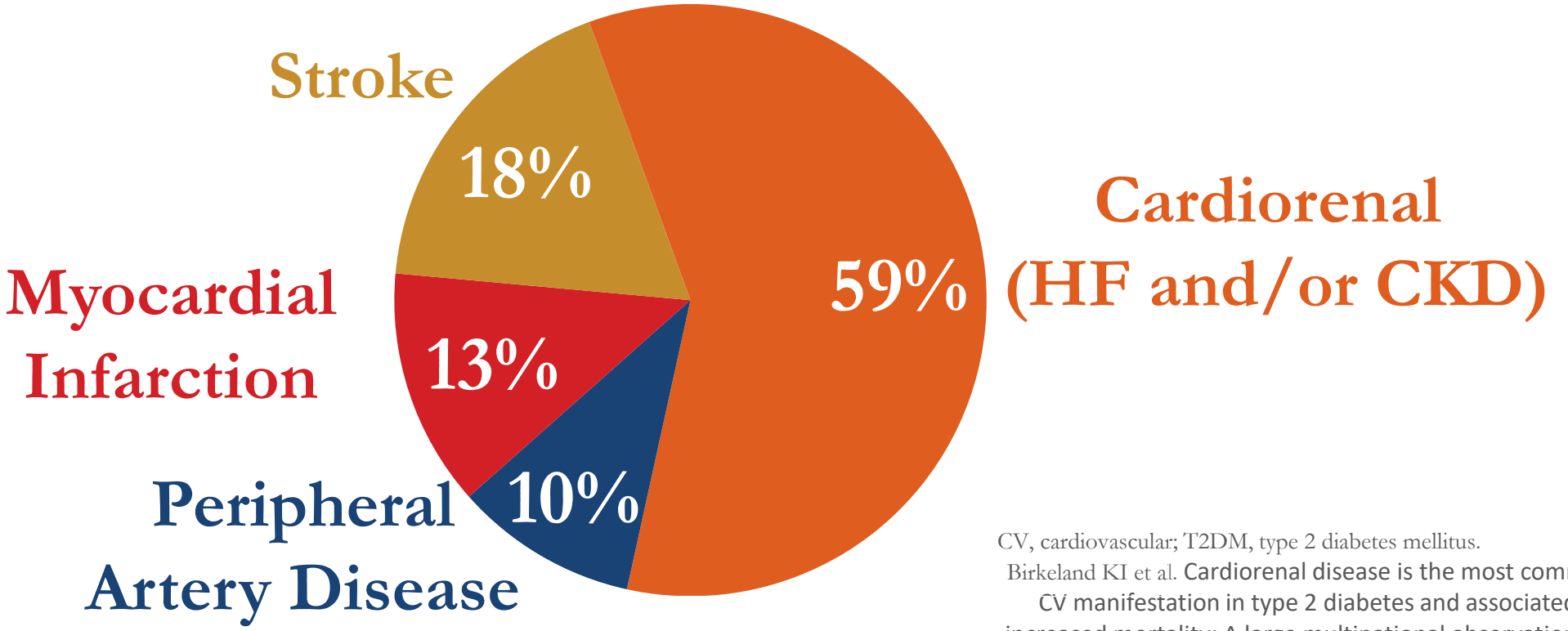
MACE

Renal Disease

MACE, major adverse cardiovascular events (non-fatal stroke, non-fatal myocardial infarction, and cardiovascular death).
Verma S et al. Lancet. 2019;393:3-5.

Recent Registry Data Indicate that Cardiorenal Disease is the Most Common First CV Manifestation inT2DM

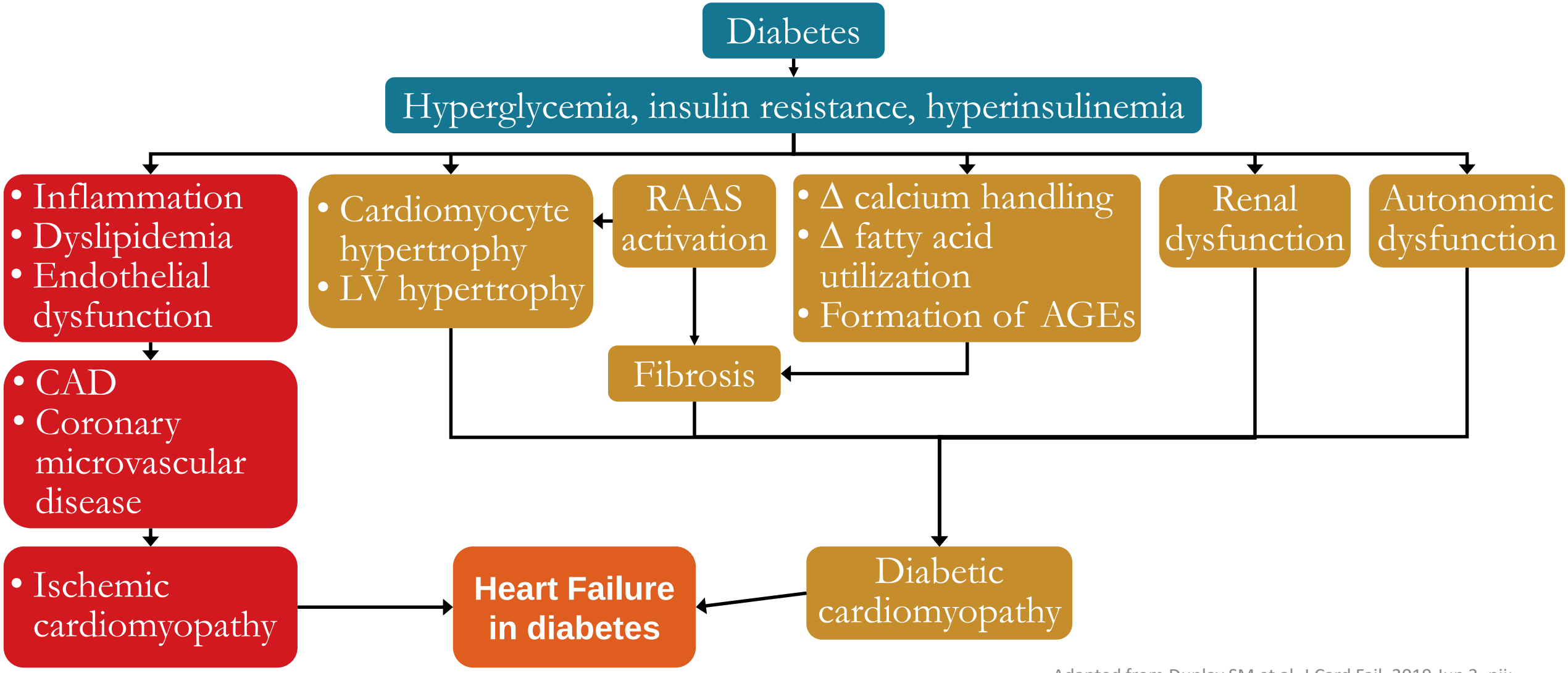
N=645,180 CV free people with T2DM
from registries from Germany, Japan, Norway and Sweden



CV, cardiovascular; T2DM, type 2 diabetes mellitus.

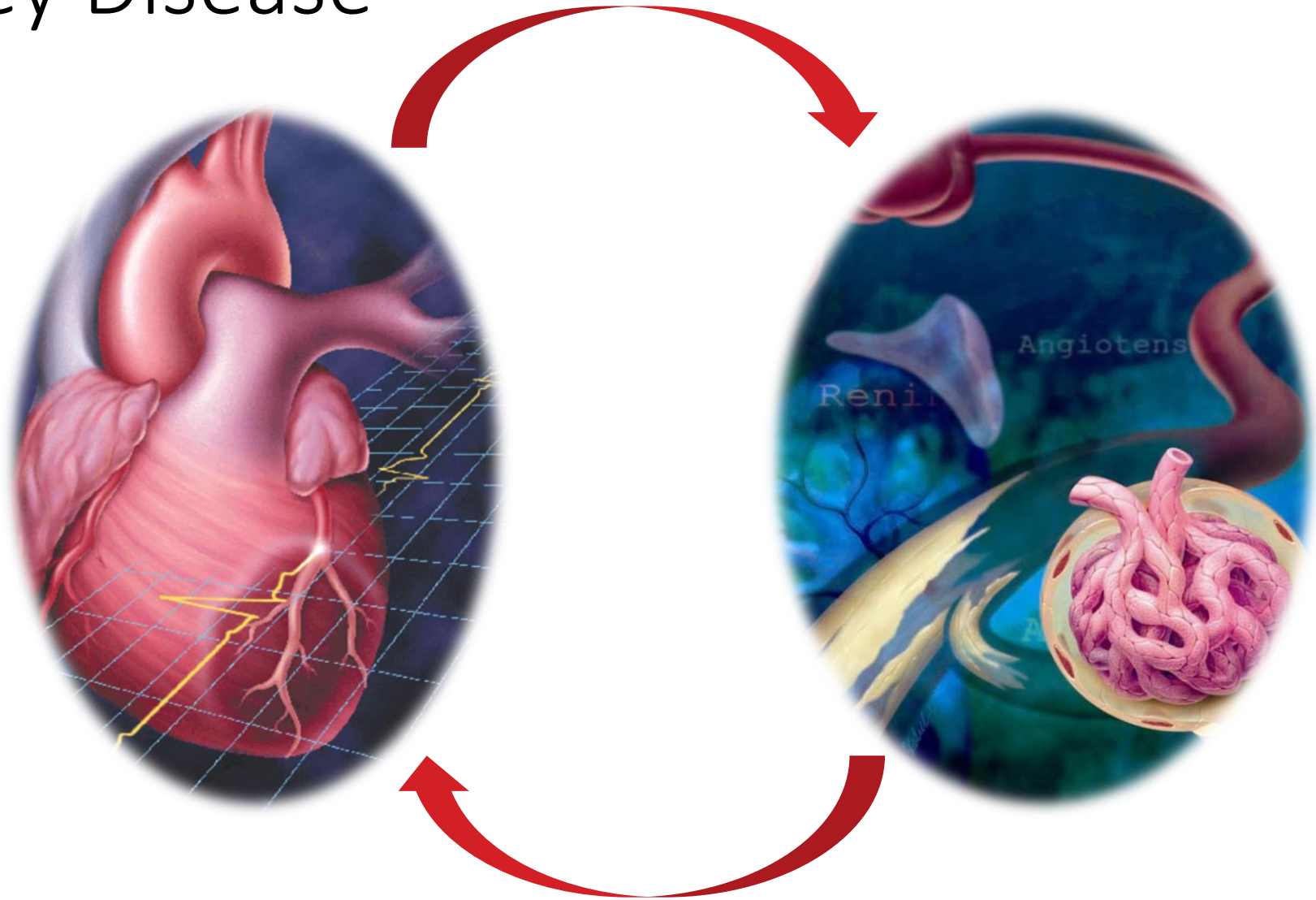
Birkeland KI et al. Cardiorenal disease is the most common first CV manifestation in type 2 diabetes and associated with increased mortality: A large multinational observational study. 206-LB. Presented at the 79th Scientific Sessions of the American Diabetes Association, June 7 to 11, 2019. San Francisco, CA, USA.

Pathophysiology of HF in Diabetes Mellitus

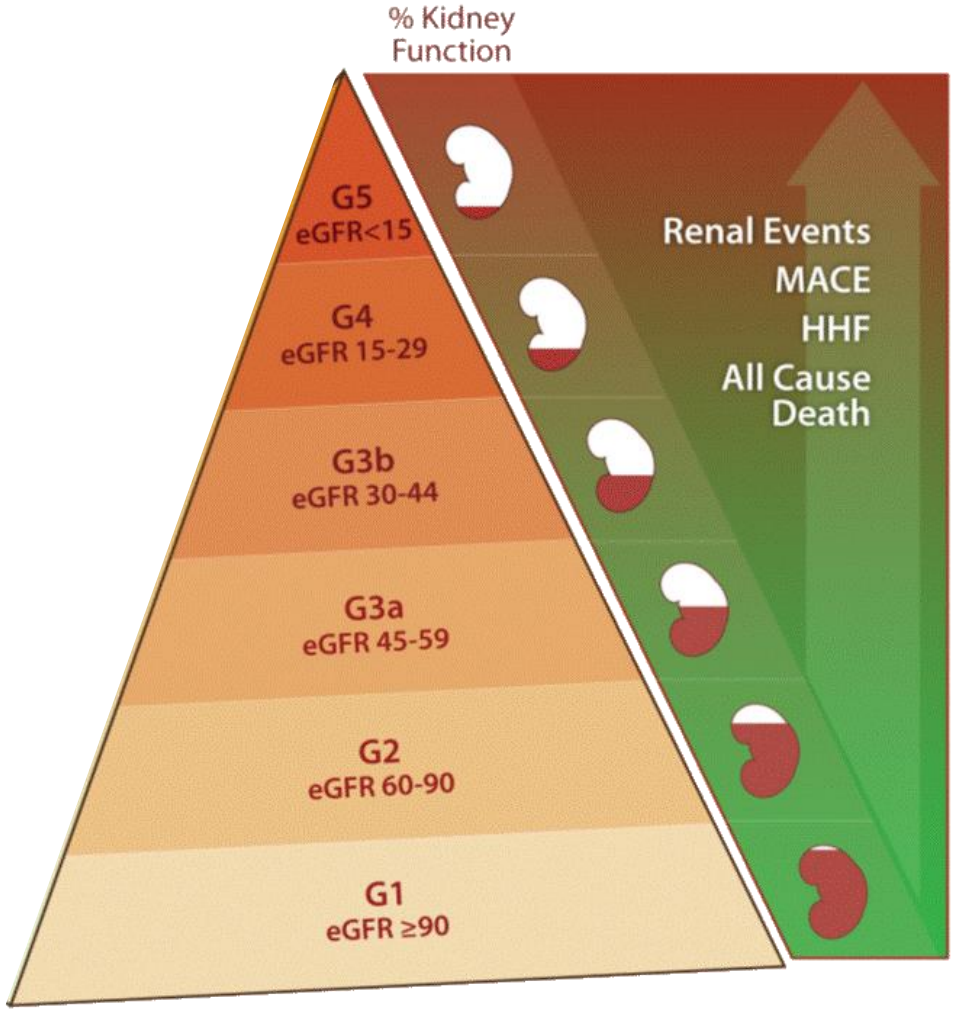


Adapted from Dunlay SM et al. J Card Fail. 2019 Jun 3. pii: S1071-9164(19)30521-4. doi: 10.1016/j.cardfail.2019.05.007.

The Bad Marriage of Diabetes and Chronic Kidney Disease



Cardiorenal Outcomes, Including HF, Increase with Declining Renal Function



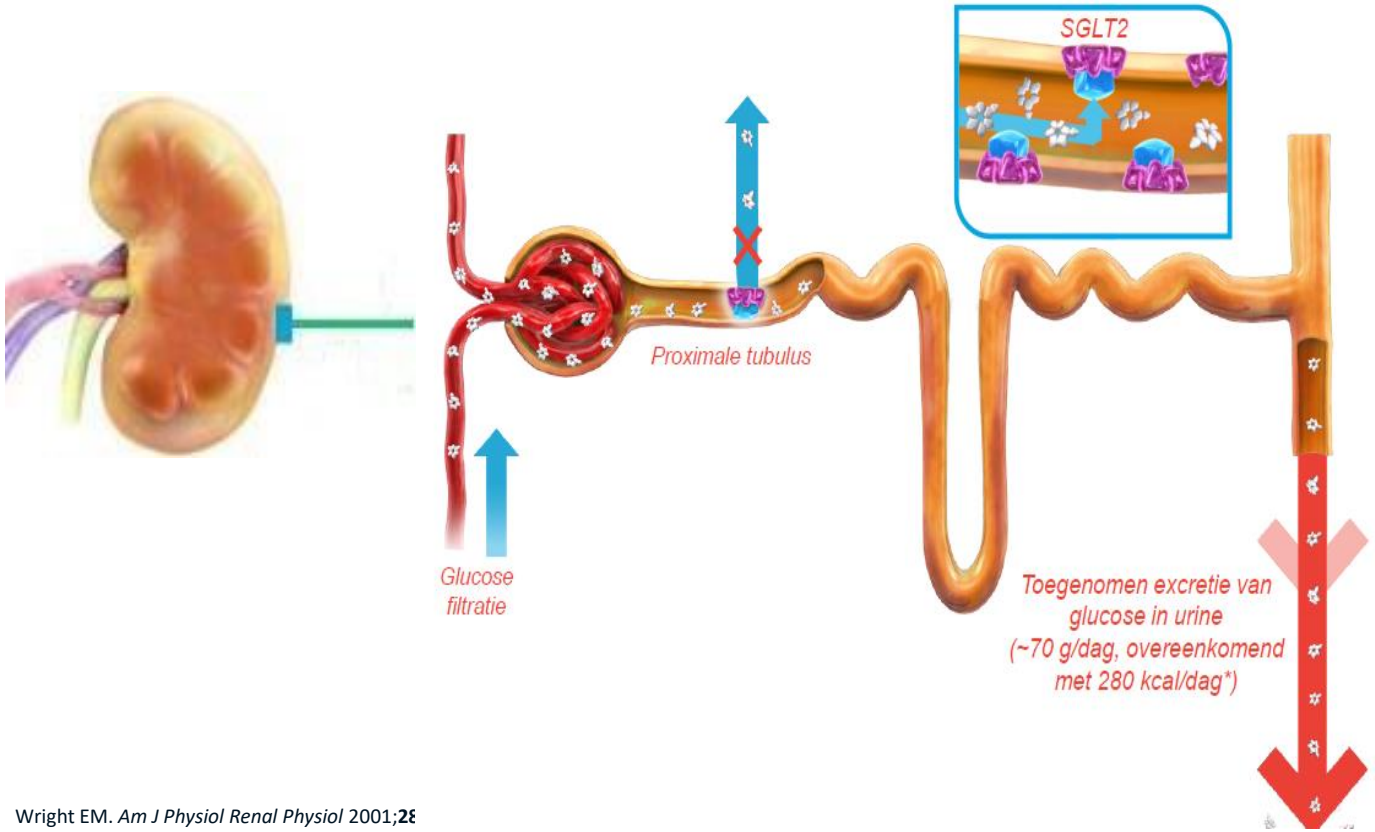
eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; MACE, major adverse cardiovascular events.

SGLT2 inhibition – a new mechanism in the treatment of T2D

Rationale and evidence for SGLT2 inhibition to prevent CVD in T2D

SGLT-2 inhibitors

- Reduction of resorption of glucose
- Glucose-excretion in urine increases
- Slight increase of urinary sodium loss – not affecting its serum levels
- Bloodglucose level reduces



Wright EM. *Am J Physiol Renal Physiol* 2001;**28**
Hummel CS, *et al. Am J Physiol Cell Physiol* 2011;**300**:C14–21;

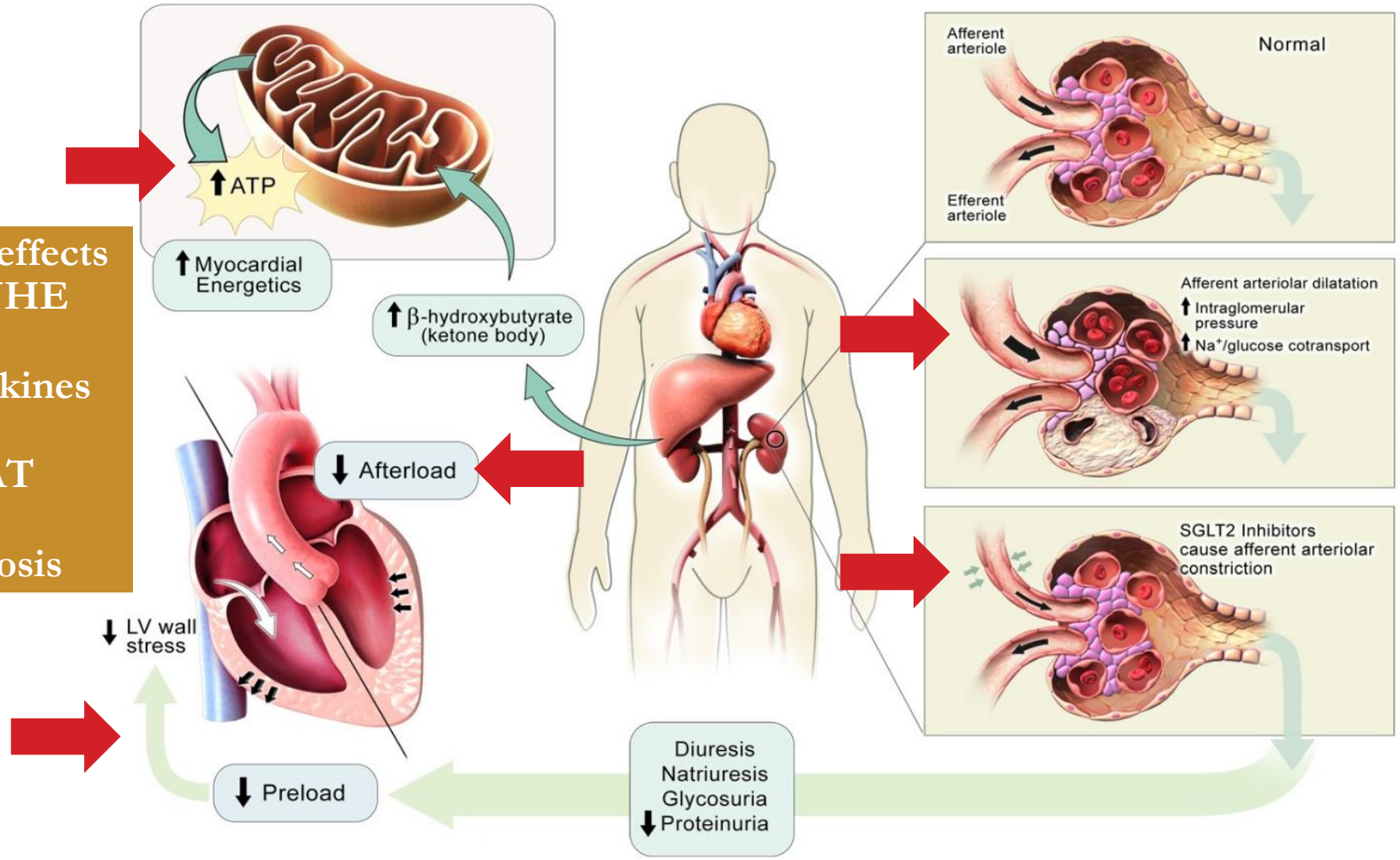
SGLT2 Inhibition and Cardiorenal Protection

Direct effects on NHE

Adipokines

EAT

Fibrosis



Potential mechanisms

- Improve ventricular loading conditions
  - Diuresis
  - Natriuresis
  - Afterload reduction
- Myocardial energetics and metabolomics
- Direct effects on myocardium
- TGF and reduction in IGH

EAT, epicardial adipose tissue; IGF, insulin-like growth factor; NHE, sodium–hydrogen exchanger; TGF, transforming growth factor.

Verma S et al. JAMA Cardiol. 2017;2:939-940.

Casus 1: Meneer B, 80 jaar

Voorgeschiedenis:

2005 – Onderwandinfarct waarvoor PCI

2009 – DM2

2016 – HFrEF met een ejectiefractie van 25%

Medicatie:

Acenocoumarol op geleide INR

Spironolacton 25mg 1dd1

Sacubitril/valsartan 2dd1

Atorvastatine 40mg 1dd1

Furosemide 40mg 1dd1

Metformine 1000mg 2dd1

Pantoprazol 40mg 1dd1

Gliclazide 30mg 1dd2

Nog meer aanvullende informatie nodig?

Aanvullend onderzoek

Laboratoriumonderzoek:

- Glucose 8.0 mmol/l
- HbA1c 54 mmol/mol
- eGFR 89 ml/min
- Cholesterol 4.1
- Triglyceriden 1.8
- HDL-cholesterol 1.0
- LDL-cholesterol 2.5

Wat zijn normaalwaarden van het HbA1c?

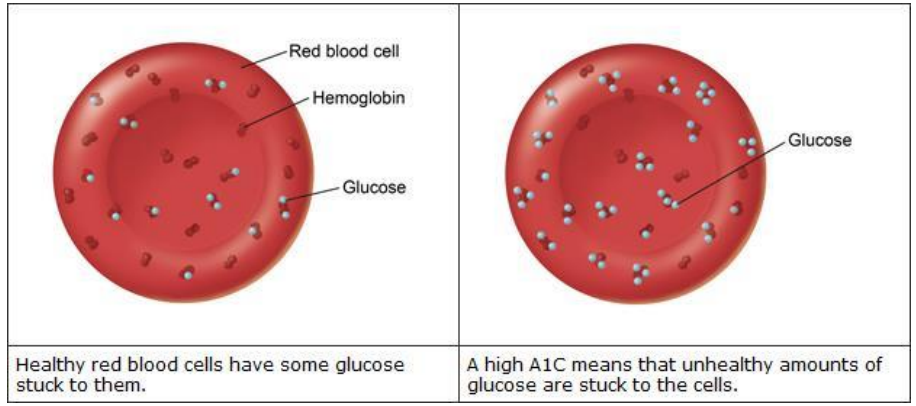
Over welke periode geeft het HbA1c de regulatie weer?

Achtergrond HbA1c

Normaalwaarden en streefwaarden
Normaalwaarde HbA1c (indien geen DM2): ≤42
Streefwaarde HbA1c bij DM2 met leeftijd <70 jaar: ≤53
Streefwaarde HbA1c bij DM2 met hoge leeftijd of >10 jaar DM2: ≤64

Periode regulatie
Levensduur van een erytrocyt is ongeveer 120 dagen.

HbA1c geeft regulatie van de DM2 over laatste 8-12 weken weer



Bron: https://richtlijnen.nhg.org/standaarden/diabetes-mellitus-type-2#volledige-tekst-streefwaarden-bloedglucose-en-hba1c

Behandeling diabetes mellitus type 2

Stap 1: Leefstijladviezen!

- Gewichtsreductie
- Niet roken
- Goede voeding
- Veel bewegen

Stap 2: Medicamenteus

Medicamenteuze behandeling DM2

Behandeling onderverdeeld in grote groepen

- Biguaniden: Metformine
- Sulfonylureumderivaten (SU): Gliclazide, glimepiride (-ide)
- DPP4-remmers: Linagliptine, sitagliptine (-gliptine)
- GLP-1 agonisten: Dulaglutide, liraglutide (-glutide)
- SGLT-2 remmers: Dapagliflozine, empagliflozine (-gliflozine)
- Insuline
  - Kortwerkend bijv aspart, humalog
  - Langwerkend bijv glargine, levemir, degludec

Welke middelen geven meer kans op hypoglycemieen?

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Welke middelen geven meer kans op hypoglycemieen?

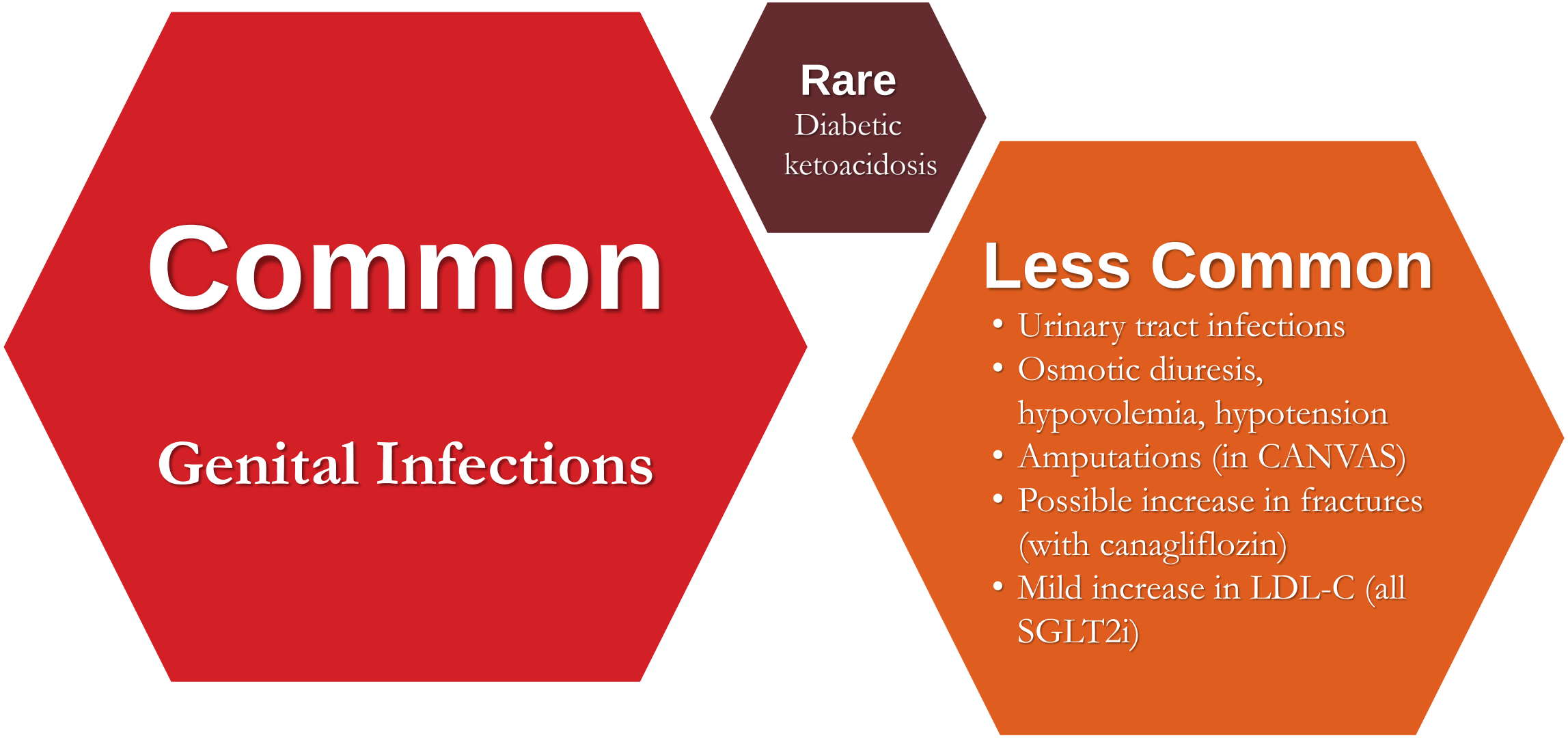
SGLT-2 remmers geven dus niet meer kans op hypoglycemieen!

Wat moet worden opgelet bij het voorschrijven van SGLT-2 remmers?

Hypoglycemie (alleen indien gecombineerd met SU of insuline)

Bijwerkingen

SGLT2i-Associated Side Effects



DAPA-HF: Urinary Tract and Genital Infections

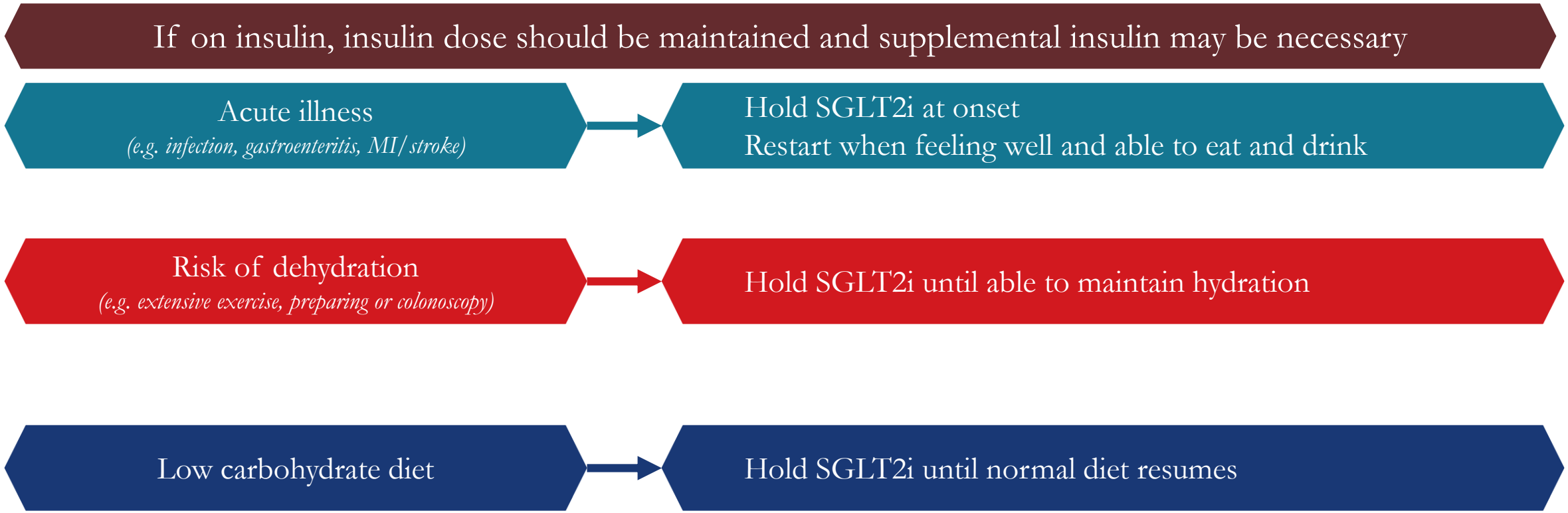
Participants exposed to ≥1 dose of study drug (%)	Dapagliflozin (n=2368)	Placebo (n=2368)	P
UTI serious AEs, n (%)	15 (0.6)	19 (0.8)	0.61
UTI AEs leading to discontinuation, n (%)	5 (0.2)	5 (0.2)	-
Urosepsis reported by the investigator, n (%)	4 (0.2)	7 (0.3)	-

Participants exposed to ≥1 dose of study drug (%)	Dapagliflozin (n=2368)	Placebo (n=2368)	P
Genital infection serious AEs, n (%)	0 (0.0)	1 (0.0)	-
Genital infections leading to discontinuation, n (%)	7 (0.3)	0 (0.0)	-

AE, adverse event; UTIs, urinary tract infections.

Adapted from McMurray JJV et al. 55th Annual Meeting of the European Association for the Study of Diabetes 2019, September 19, 2019. Barcelona, Spain.

Precipitants for and Measures to Avoid SGLT2 Inhibitor-Associated Diabetic Ketoacidosis



*Empirical based on 5 half-lives.
MI, myocardial infarction.
Goldenberg RM et al. Clin Ther. 2016;38:2654-2664

Safety

Favorable effects SGLT-2 inhibitors
Reduction of pre-load (diuretic effects)
Reduction of afterload (blood pressure, arterial stiffness)
Delay of decline in eGFR
Delay of micro- and macroalbuminuria
Weight loss
Improvement in glycemia
Reduction in uric acid

Unfavorable effects SGLT-2 inhibitors
Urinary and genital infections
Volume depletion/hypotension
Diabetic ketoacidosis
Fractures?
Amputations (in particular toe, metatarsal)?
Fourniers gangrene?

Zelniker TA, Braunwald E. Cardiac and Renal Effects of Sodium-Glucose Co-Transporter 2 Inhibitors in Diabetes. J Am Coll Cardiol. 2018;1–11. (adjusted)

Contra-indications SGLT2-i

- recurrent genital (mycotic) infections
- augmented risk of ketoacidosis (alcoholism/malnutrition)
- symptomatic peripheral vascular disease
- discuss risk and symptoms of diabetic keto-acidosis

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Gliclazide 30mg 1dd2

Laboratoriumonderzoek:

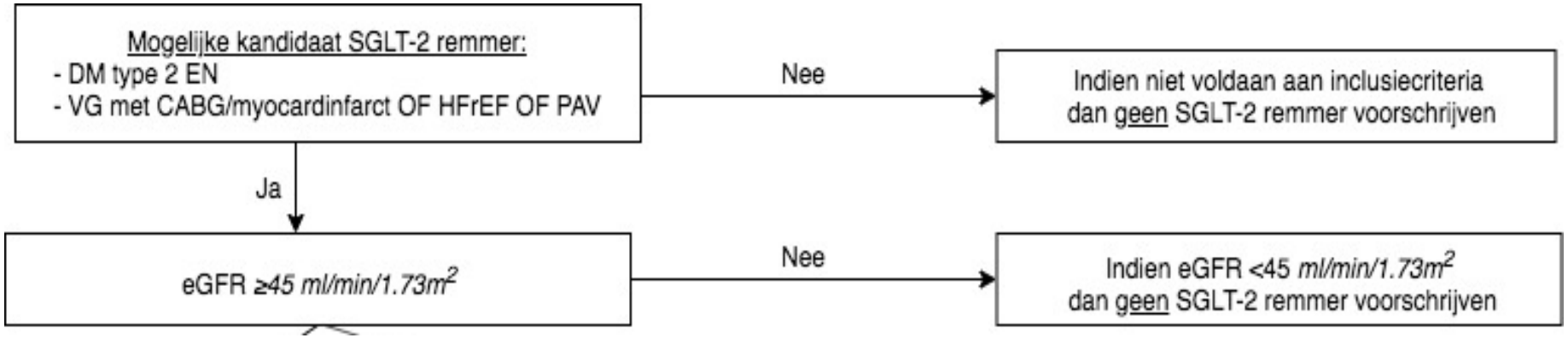
- Glucose 8.0 mmol/l
- HbA1c 54 mmol/mol
- eGFR 89 ml/min

Terug naar de casus:

SGLT-2 remmer toevoegen?

Stroomschema voor de cardiologie polikliniek

1. Is er sprake van DM2?
2. Is er sprake van CABG/myocardinfarct EN/OF HFrEF EN/OF perifeer arterieel vaatlijden
3. Nierfunctie met eGFR>30 mL/min/1.73m^2



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- eGFR 89 ml/min

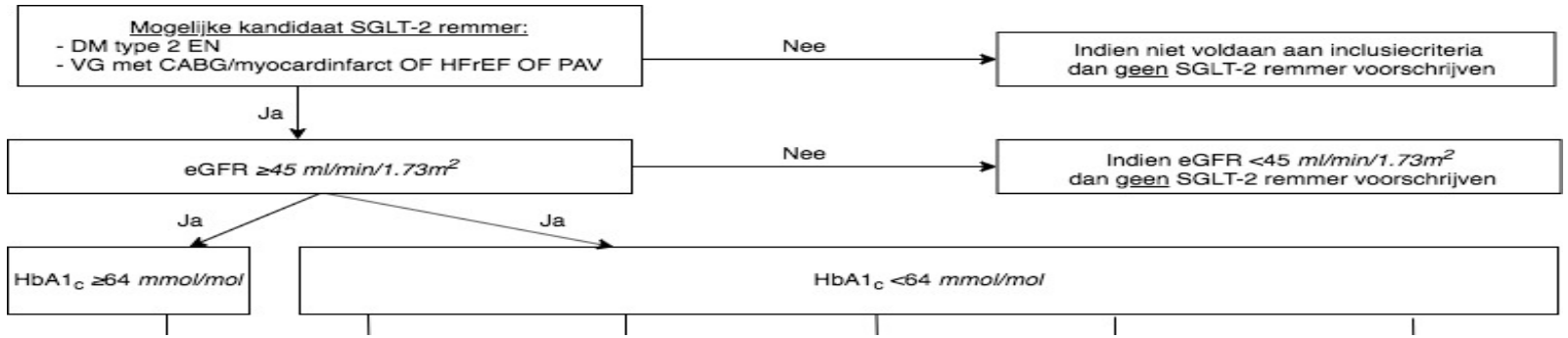
Komt in aanmerking

SGLT-2 remmer toevoegen!
Aanpassen andere medicatie?

Stroomschema voor de cardiologie polikliniek (2)

Vervolgens:

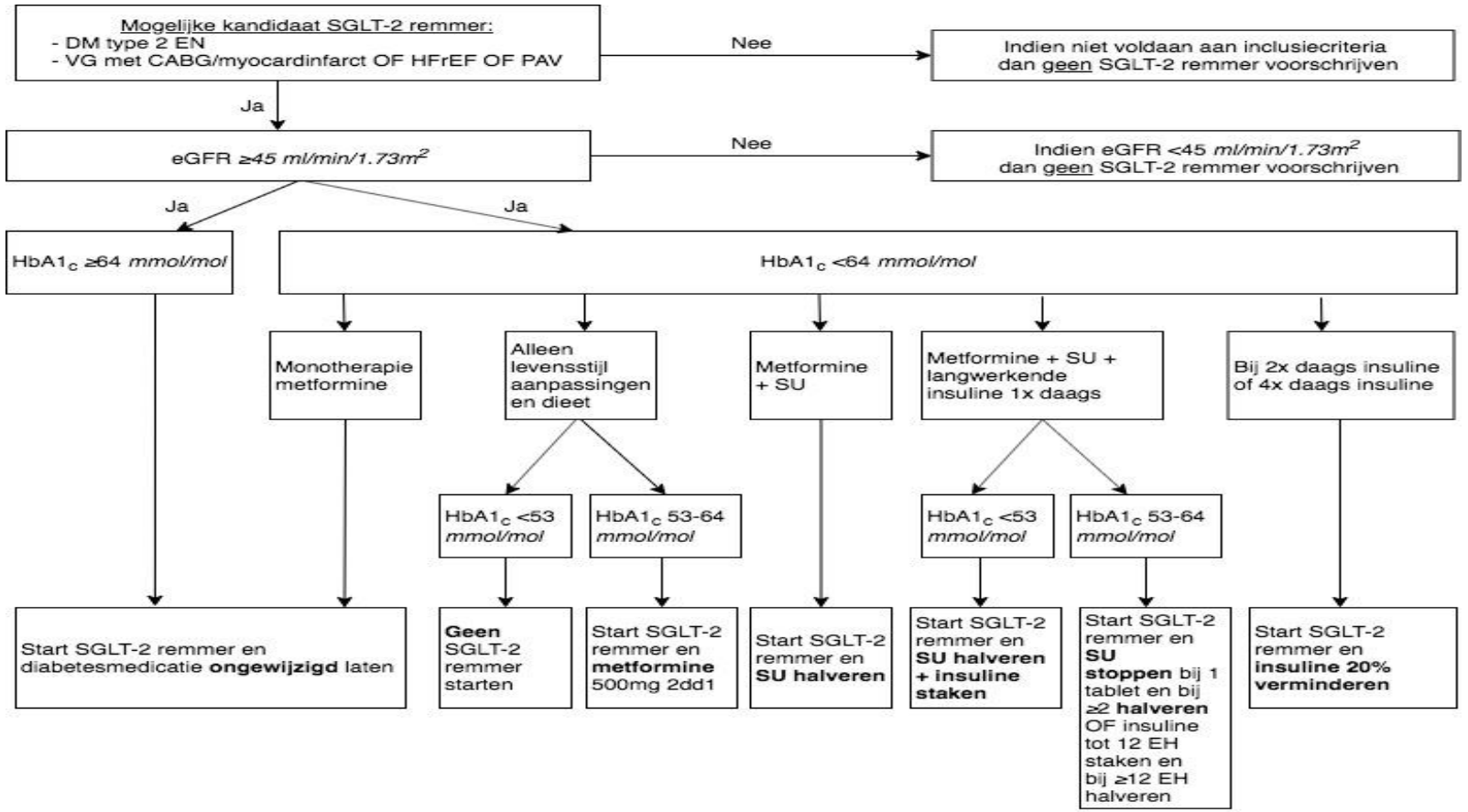
1. Sprake van een ‘slecht’ of ’goed’ gereguleerde patiënt met diabetes mellitus middels waarde van HbA1c
2. Op basis hiervan aanpassen van SU of insuline (ter voorkomen hypoglycemie)



Stroomschema voor de cardiologie polikliniek (3)

Vervolgens:

1. Medicatie eventueel aanpassen middels stroomschema



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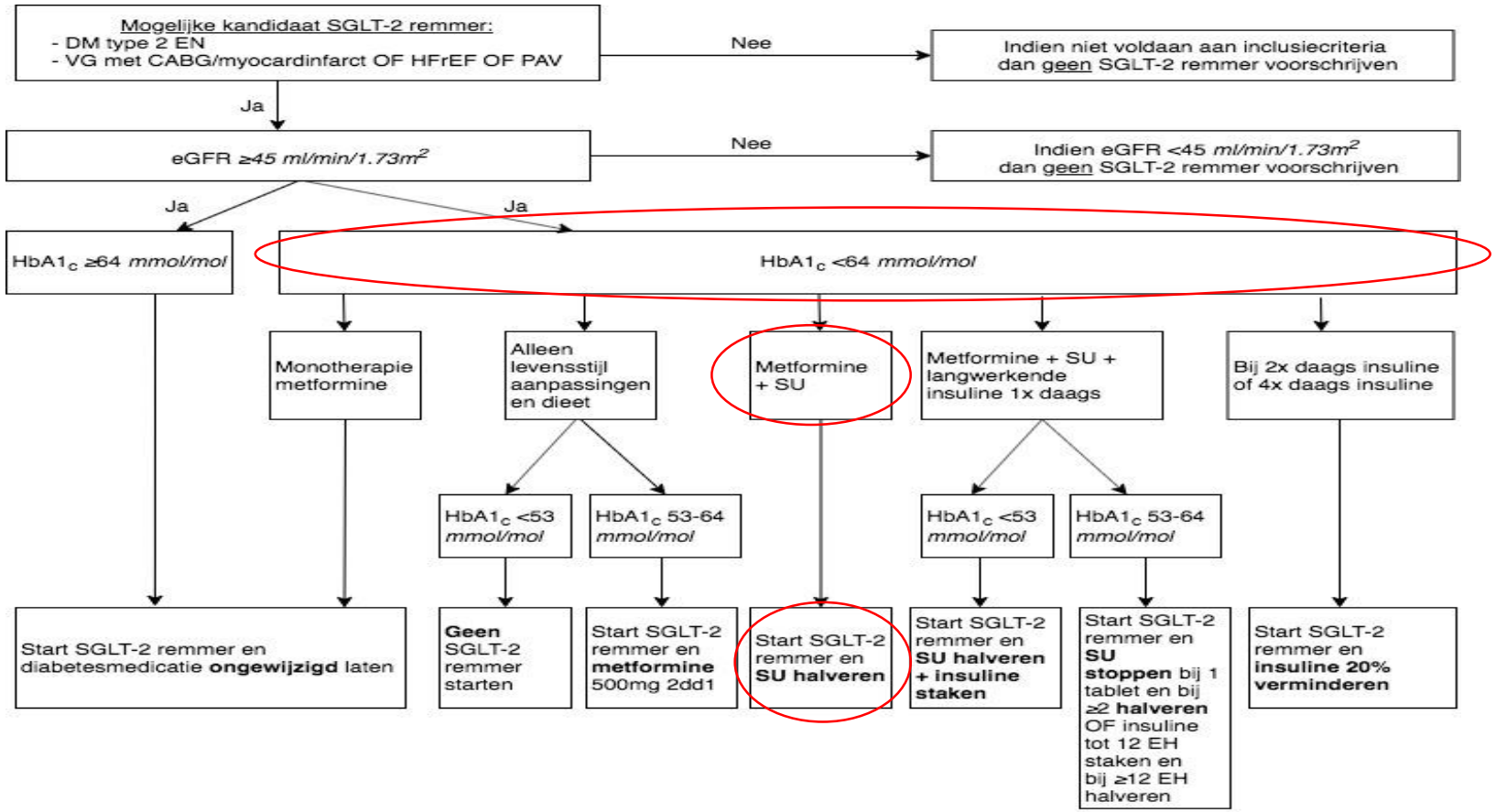
Terug naar de casus:

Welke medicatie aan te passen?

Stroomschema voor de cardiologie polikliniek (3)

Vervolgens:

1. Medicatie eventueel aanpassen middels stroomschema



Casus 1: Beleid

- Toevoegen SGLT-2 remmer
- Aanpassen sulfonylureumderivaat ter voorkomen van hypoglycemie bij goede waarde HbA1c 54
- Gliclazide halveren van 1dd60mg naar 1dd30mg

Follow-up casus 1

Na 1 maand

- HbA1c 48
- eGFR >90

Na 4 maanden

- HbA1c 50 (bij volledig staken SU)
- eGFR 87

“Patiënt heeft voor zover bekend geen hypo’s. Het gaat op dit moment heel goed met zijn hart. Controleert eens in de twee weken met een vingerprik zijn bloedglucose”

PIPES

MACE Outcomes

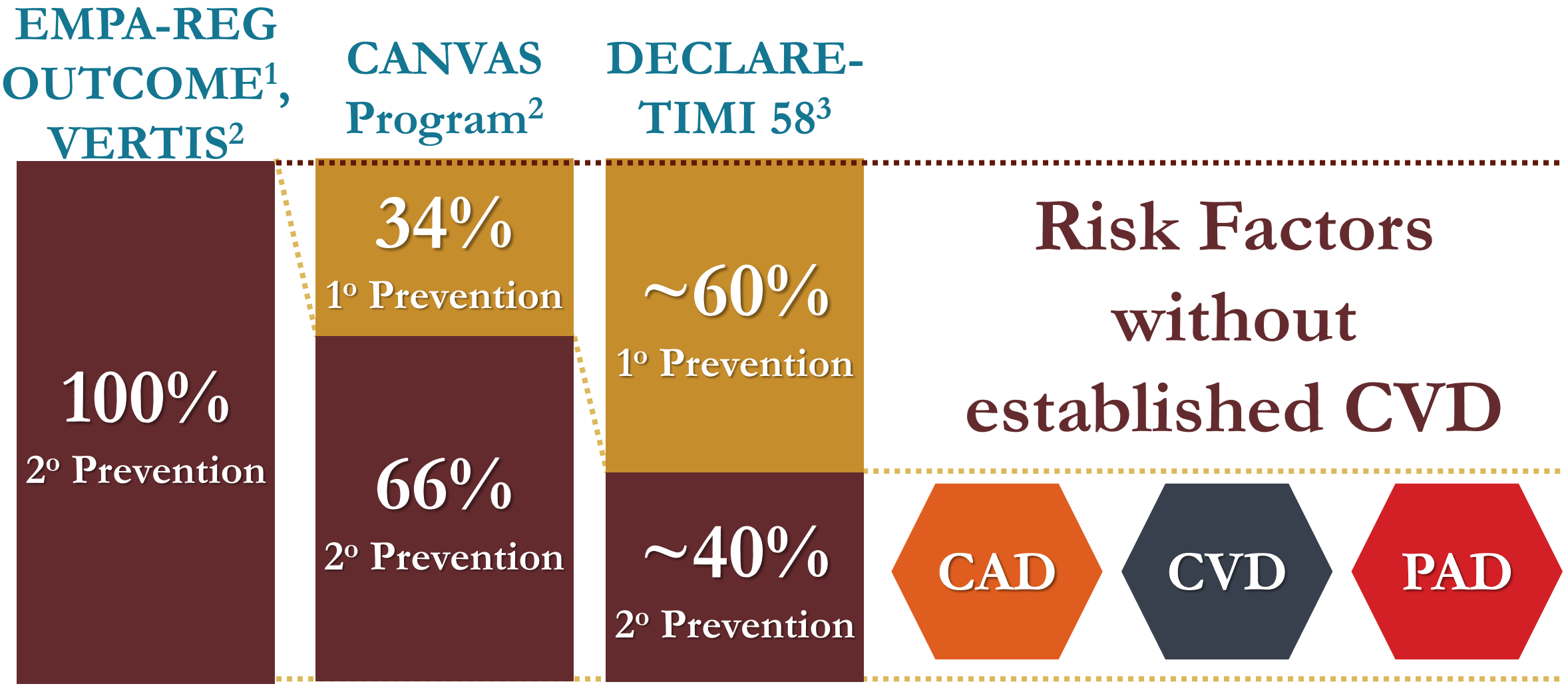
Evidence SGLT2-i on MACE anno 2020?

SGLT2-i and MACE

Four RCT's on major cardiovascular events (primary outcome):

1. EMPA-REG (Empaglifozin; N=7020)
2. CANVAS (Canaglifozin; N=9734)
3. DECLARE-TIMI58 (Dapaglifozin; N=17160)
4. VERTIS (Ertugliflozin; n=8246)

Differences Among the Study Cohorts of the Completed SGLT2i Cardiovascular Outcome Trials

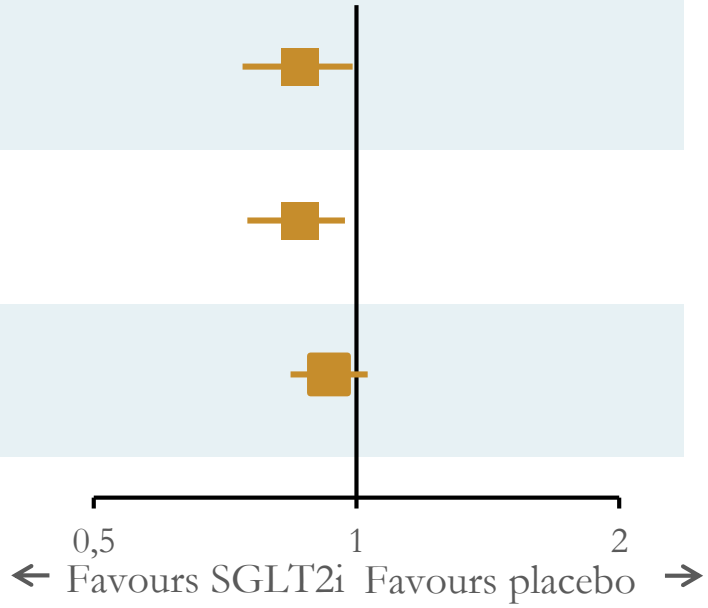


CAD, coronary artery disease; CVD, cardiovascular disease; PAD, peripheral artery disease.

1. Zinman B et al. N Engl J Med. 2015;373:2117-28. 2. American Diabetes Association 2020 Virtual Scientific Sessions – Published on: June 16, 2020. 3 Neal B et al. N Engl J Med. 2017;377:644-657. 4. Wiviott SD et al. Am Heart J. 2018;200:83-89.

MACE Reduction Across the SGLT2i CVOTs

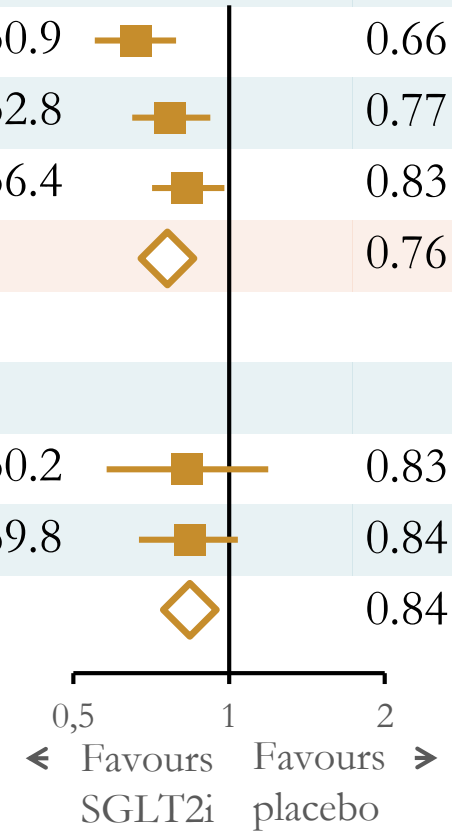
Trial	Primary endpoint	Number of events, /1,000 PY		HR (95% CI)
		SGLT2i	Placebo	
EMPA-REG OUTCOME (empagliflozin)	3P-MACE	37.4	43.9	0.86 (0.74, 0.99)
CANVAS Program (canagliflozin)	3P-MACE	26.9	31.5	0.86 (0.75, 0.97)
DECLARE-TIMI 58 (dapagliflozin)	3P-MACE	22.6	24.2	0.93 (0.84, 1.03)



CVOTs, cardiovascular outcome trials; MACE, major adverse cardiovascular events; PY, patient years.
Adapted from Zelniker TA et al. Lancet. 2019;393:31-39.

CV Death/HHF Benefit According to the Presence or Absence of ASCVD

	Patients		Events	Events per 1,000 patient years		Weight (%)	Hazard Ratio (95% CI)
	Treatment n/N	Placebo n/N		Treatment	Placebo		
Patients with ASCVD							
EMPA-REG OUTCOME	4,687/7,020	2,333/7,020	463	19.7	30.1	30.9	0.66 (0.55, 0.79)
CANVAS Program	3,756/6,656	2,900/6,656	524	21.0	27.4	32.8	0.77 (0.65, 0.92)
DECLARE-TIMI 58	3,474/6,974	3,500/6,974	597	19.9	23.9	36.4	0.83 (0.71, 0.98)
Fixed effects model for ASCVD (P<0.0001)							0.76 (0.69, 0.84)
Patients with multiple risk factors							
CANVAS Program	2,039/3,486	1,447/3,486	128	8.9	9.8	30.2	0.83 (0.58, 1.19)
DECLARE-TIMI 58	5,108/10,186	5,078/10,186	316	7.0	8.4	69.8	0.84 (0.67, 1.04)
Fixed effects model for multiple risk factors (P=0.0634)							0.84 (0.69, 1.01)



ASCVD, atherosclerotic cardiovascular disease; HHF, hospitalization for heart failure.
Adapted from Zelniker TA et al. Lancet. 2019;393:31-39.

PUMP

Heart Failure Outcomes

Potential effects by which SGLT2 inhibition improves heart failure outcomes

SGLT2 INHIBITION

Reduce Preload/Afterload[1,2]
↓Plasma volume
↓Vascular resistance

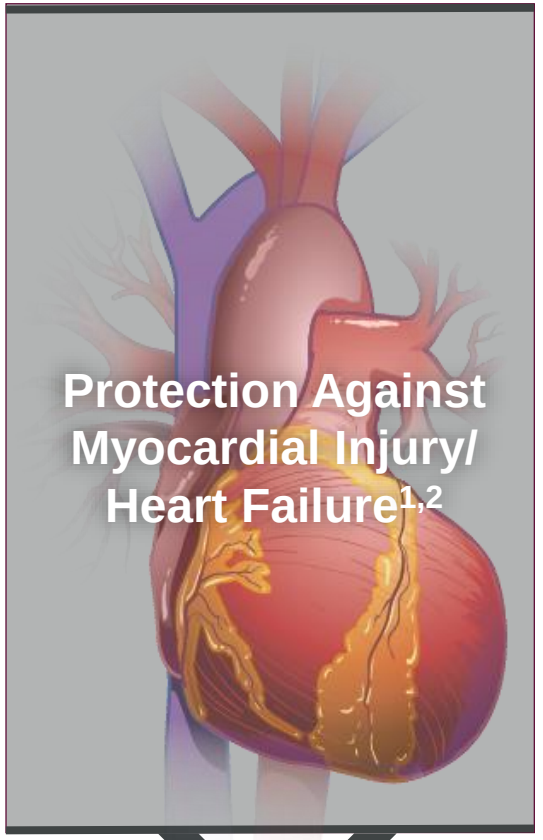
Improved Myocardial[2] **Energetics**
↓ Reliance on fatty acids
↑Ketone body formation
↓Cardiac NHE1

Cardiac Remodeling[1,2]
↓Inflammation/fibrosis
↓Cardiac wall stress

CLINICAL EFFECTS

BP Reduction[1]

Improved Cardiac Contractility
↓LV mass[3,4]
↑Diastolic function[2]



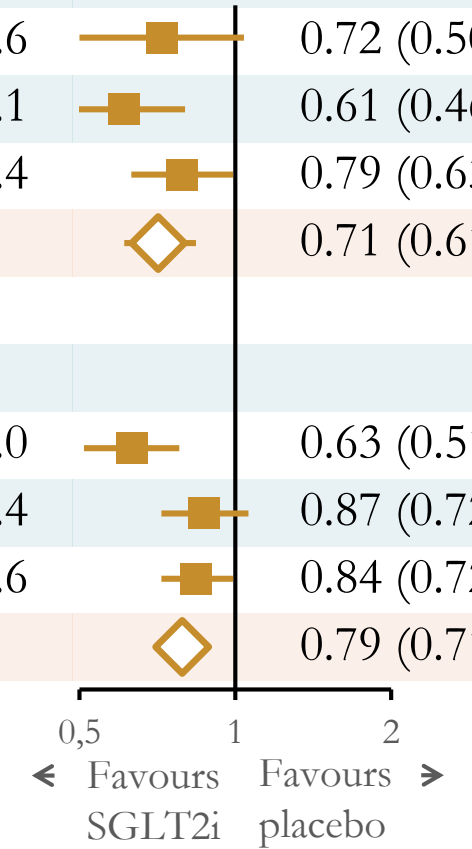
Improved Cardiac Function Reduced Heart Failure[1,2]

BP = blood pressure; LV=left ventricular; NHE1=sodium-hydrogen exchanger 1; SGLT2 = sodium-glucose cotransporter-2;

1. Heerspink HJL, et al. *Kidney Int*. 2018;94(1):26-39. 2. Tamargo J. *Eur Cardiol*. 2019;14(1):23-32. 3. Verma S, et al. *Diabetes Care*. 2016;39(12):e212-e213. 4. Verma S. Presented at: American Heart Association Scientific Sessions; Nov. 10-12, 2018; Chicago.

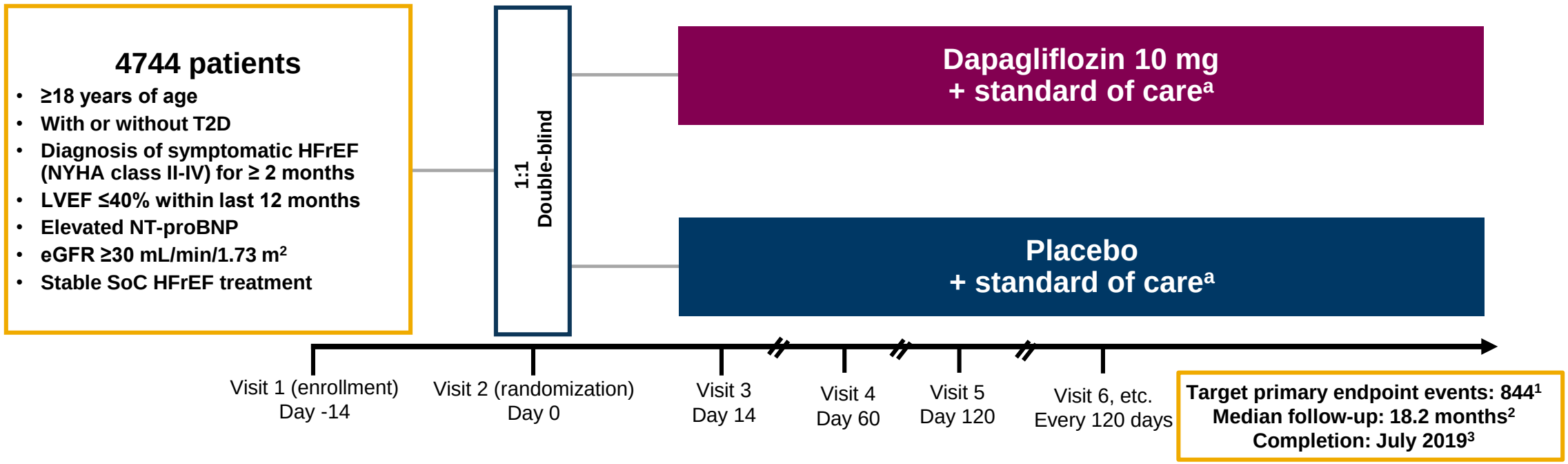
CV Death/HHF Benefit According to the Presence or Absence of a Heart Failure History

	Patients		Events	Events per 1,000 patient years		Weight (%)	Hazard Ratio (95% CI)
	Treatment n/N	Placebo n/N		Treatment	Placebo		
Patients with a history of heart failure							
EMPA-REG OUTCOME	462/706	244/706	124	63.6	85.5	23.6	0.72 (0.50, 1.04)
CANVAS Program	803/1,461	658/1,461	203	35.4	56.8	34.1	0.61 (0.46, 0.80)
DECLARE-TIMI 58	852/1,724	872/1,724	314	45.1	55.5	42.4	0.79 (0.63, 0.99)
Fixed effects model for a history of heart failure (P<0.0001)							0.71 (0.61, 0.84)
Patients with no history of heart failure							
EMPA-REG OUTCOME	4,225/6,314	2,089/6,314	339	15.5	24.9	30.0	0.63 (0.51, 0.78)
CANVAS Program	4,992/8,681	3,689/8,681	449	13.6	15.2	32.4	0.87 (0.72, 1.06)
DECLARE-TIMI 58	7,730/15,436	7,706/15,436	599	8.9	10.5	37.6	0.84 (0.72, 0.99)
Fixed effects model for no history of heart failure (P<0.0001))							0.79 (0.71, 0.88)



CVOTs, cardiovascular outcome trials; HHF, hospitalization for heart failure.
Adapted from Zelniker TA et al. Lancet. 2019;393:31-39.

Assessing Dapagliflozin in Patients with Chronic HFrEF With or Without T2D[1-4]



Composite Primary Endpoint: CV death or hHF or an urgent HF visit

[a]Patients were treated according to regional standard of care for HF. Dose reduction or discontinuation of standard of care therapy was discouraged unless all other measures failed. Changes in standard of care medications was at the discretion of the investigator; [b]Defined as sustained eGFR <15 mL/min/1.73m², chronic dialysis treatment, or receiving a renal transplant.

1. McMurray JJV et al. Article and supplementary appendix. *Eur J Heart Fail.* 2019;21:665-675; 2. McMurray JJV et al. *N Engl J Med*. 2019; 381:1995-2008; 3. Study NCT03036124. ClinicalTrials.gov website; 4. McMurray JJV et al. *Eur J Heart Fail*. 2019. http://dx.doi/org/10.1002/ejhf.1548. Accessed July 16, 2019.

DAPA-HF: Key Baseline Characteristics

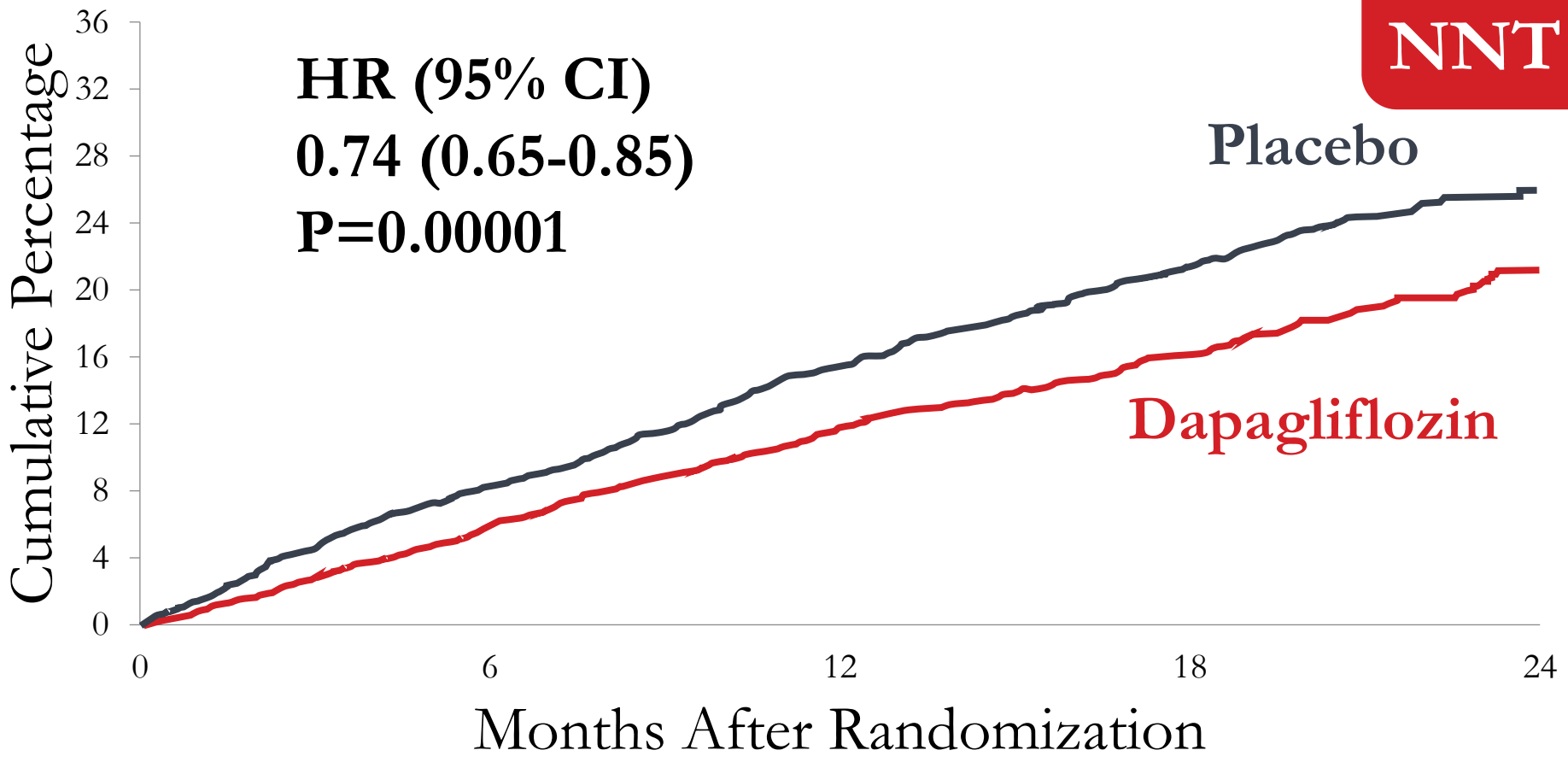
Characteristic	Dapagliflozin (n=2373)	Placebo (n=2371)
Mean age (years)	66	67
Male (%)	76	77
NYHA class II/III/IV (%)	68/31/1	67/32/1
Mean LVEF (%)	31	31
Median NT pro BNP (pg/mL)	1428	1446
Mean systolic BP (mmHg)	122	122
Ischemic etiology (%)	55	57
Mean eGFR (mL/min/1.73m^2)	66	66
Prior diagnosis T2DM (%)	42	42

BP, blood pressure; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B type natriuretic peptide; T2DM, type 2 diabetes mellitus.

Adapted from McMurray JJV. European Society of Cardiology Congress 2019, September 1, 2019. Paris, France.

DAPA-HF: Primary Endpoint
CV Death or HHF or an Urgent HF Visit

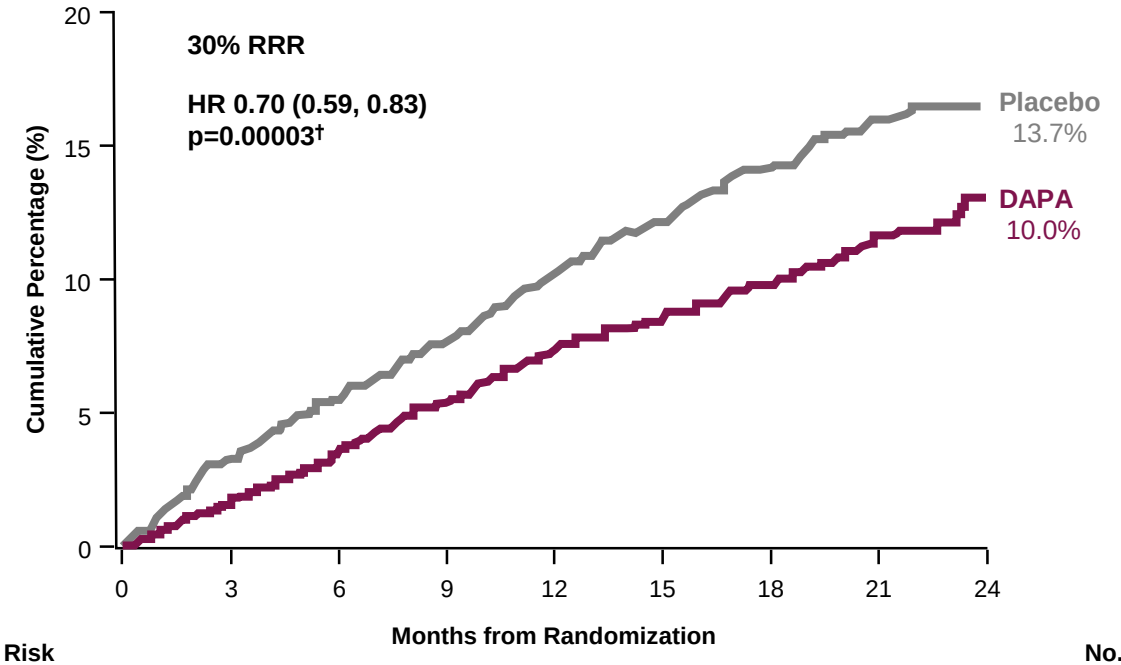
RRR = 26%
NNT = 21



CV, cardiovascular; HF, heart failure; HHF, hospitalization for heart failure.
Adapted from McMurray JJV. European Society of Cardiology Congress 2019, September 1, 2019. Paris, France.

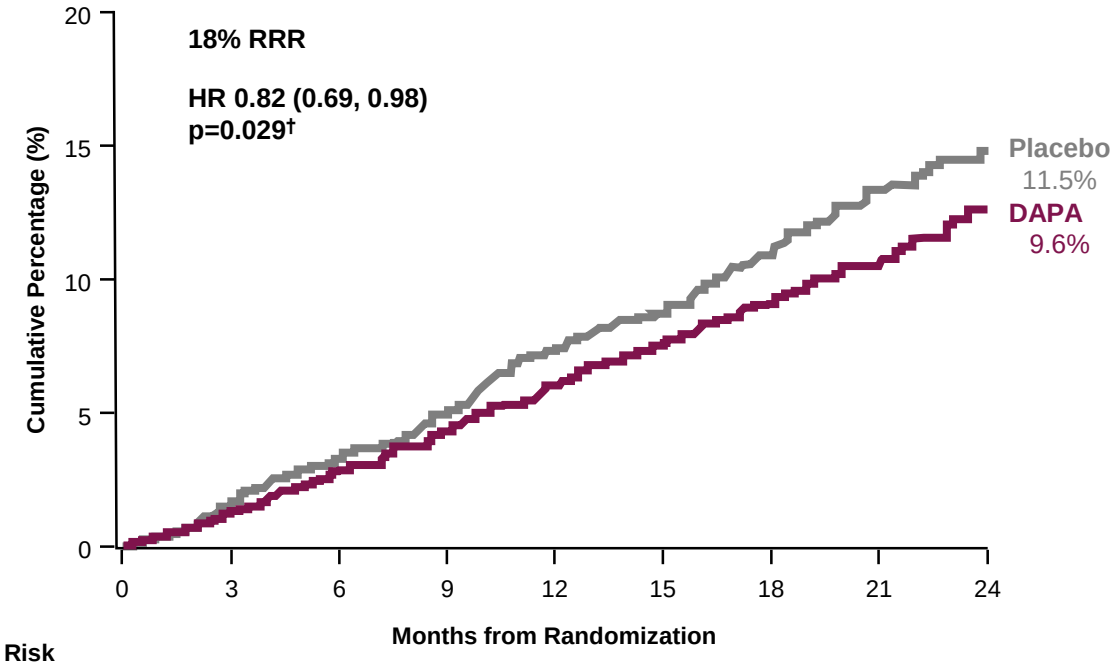
Components of the Primary Endpoint[1]

Worsening HF Event*



No. at Risk									
DAPA	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

CV Death



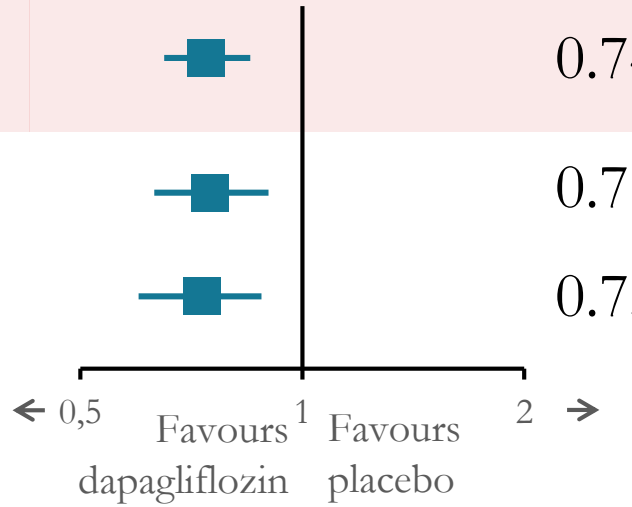
No. at Risk									
DAPA	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo	2371	2330	2279	2230	2091	1636	1219	664	234

*Defined as unplanned hospitalization for HF or urgent HF visit requiring intravenous therapy. †Nominal P-value
CV = cardiovascular; DAPA = Dapagliflozin; HF = Heart failure; HR = Hazard ratio; RRR = relative risk reduction.

1. McMurray JJV et al. *N Engl J Med*. 2019. https://doi.org/10.1056/NEJMoa1911303.

DAPA-HF: Primary Endpoint Stratified by Baseline T2DM Status

Characteristics		Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All Patients		386/2373	502/2371	0.74 (0.65, 0.85)
T2DM at baseline	Yes	215/1075	271/1064	0.75 (0.63, 0.90)
	No	171/1298	231/1307	0.73 (0.60, 0.88)



T2DM, type 2 diabetes mellitus.
Adapted from McMurray JJV. European Society of Cardiology Congress 2019, September 1, 2019. Paris, France.

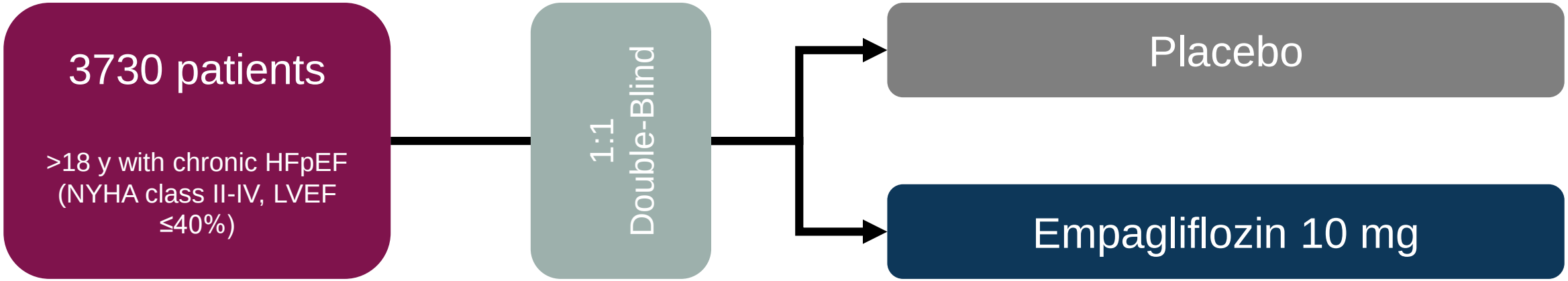
Safety/Adverse Events

Patients exposed to at least one dose of study drug	Dapagliflozin (n=2368)	Placebo (n=2368)	p-value
Adverse events (AE) of interest (%)			
Volume depletion[+]	7.5	6.8	0.40
Renal AE[‡]	6.5	7.2	0.36
Fracture	2.1	2.1	1.00
Amputation	0.5	0.5	1.00
Major hypoglycaemia	0.2	0.2	-
Diabetic ketoacidosis	0.1	0.0	-
AE leading to treatment discontinuation (%)	4.7	4.9	0.79
Any serious adverse event (incl. death) (%)	38	42	<0.01

[+]Volume depletion serious AEs in 29 dapagliflozin patients (1.2%) and 40 placebo patients (1.7%), p=0.23
[‡]Renal serious AEs in 38 dapagliflozin patients (1.6%) and 65 placebo patients (2.7%), p=0.009

McMurray JJV et al. *N Engl J Med*. 2019;381:1995-2008.

EMPEROR-R



The study population was enriched for patients with an ejection fraction of ≤30%. If the ejection fraction was >30% eligible patients were required to show very high levels of NTproBNP or a hospitalization for HF within 12 months of randomization.

Primary endpoint Time to first event of CV death or hospitalization for HF
1st Secondary endpoint Total number of hospitalizations
2nd Seconday endpoint Slope of decline in eGFR over time

M. Packer et al. NEJM 2020. DOI:10.1056/NEJMoa2022190

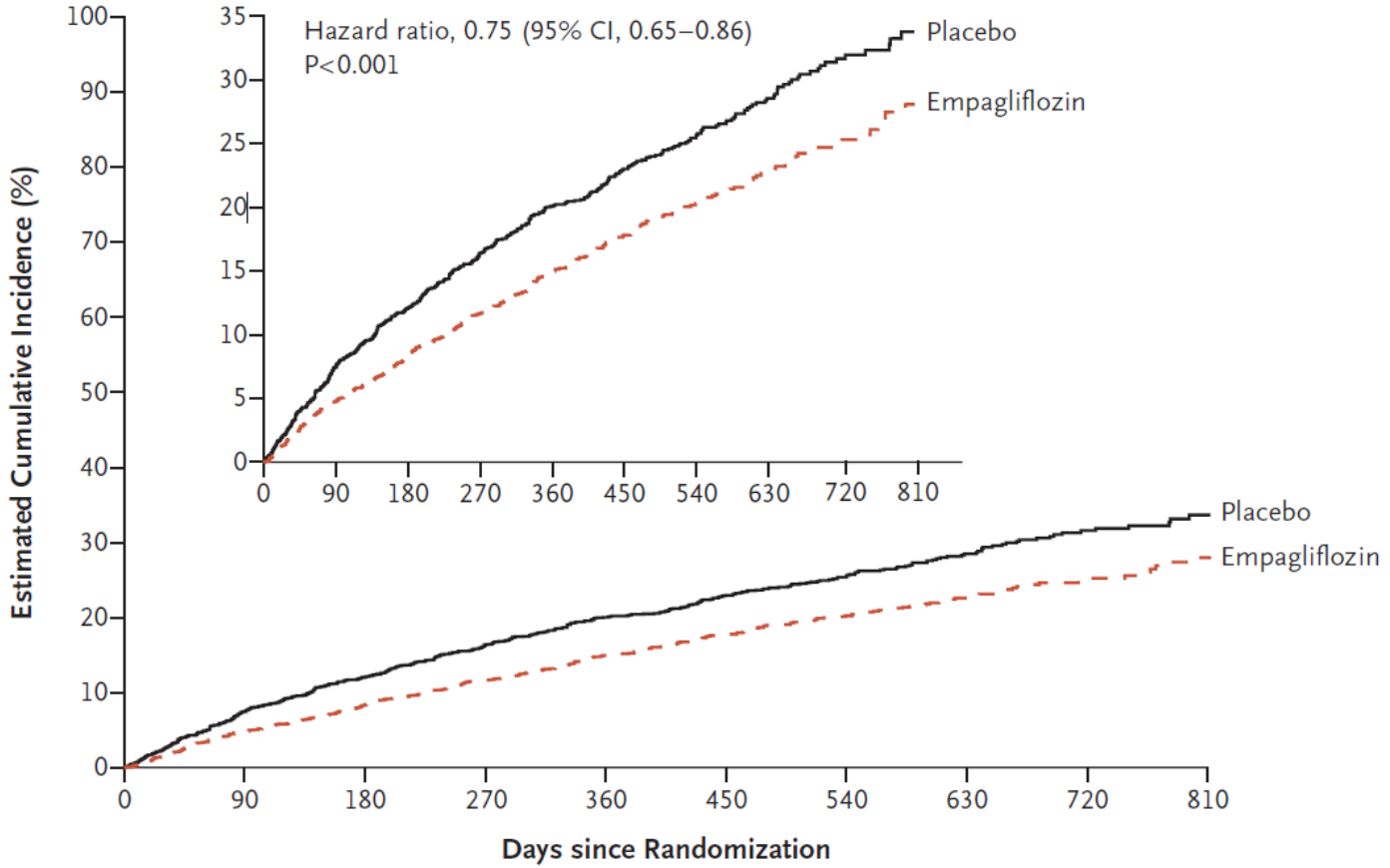
Key Baseline Characteristics

Characteristic	Empagliflozin (n=1863)	Placebo (n=1867)
Mean age (yr)	67.2 ± 10.8	66.5 ± 11.2
Female (%)	23.5	24.4
NYHA class II/III/IV (%)	75/24/1	75/24/1
Mean LVEF (%)	27.7 ± 6.1	27.2 ± 6.1
Median NT pro BNP (pg/mL)	1887	1926
Mean systolic BP (mmHg)	122.6	121.4
Ischaemic aetiology (%)	52.8	50.7
Mean eGFR (mL/min/1.73m^2)	61.8	62.2
Prior diagnosis T2D (%)	49.8	49.8

BP = blood pressure; eGFR = estimated glomerular filtration rate; NT pro BNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; LVEF = left ventricular ejection fraction; T2D = type 2 diabetes.

M. Packer et al. NEJM 2020. DOI:10.1056/NEJMoa2022190

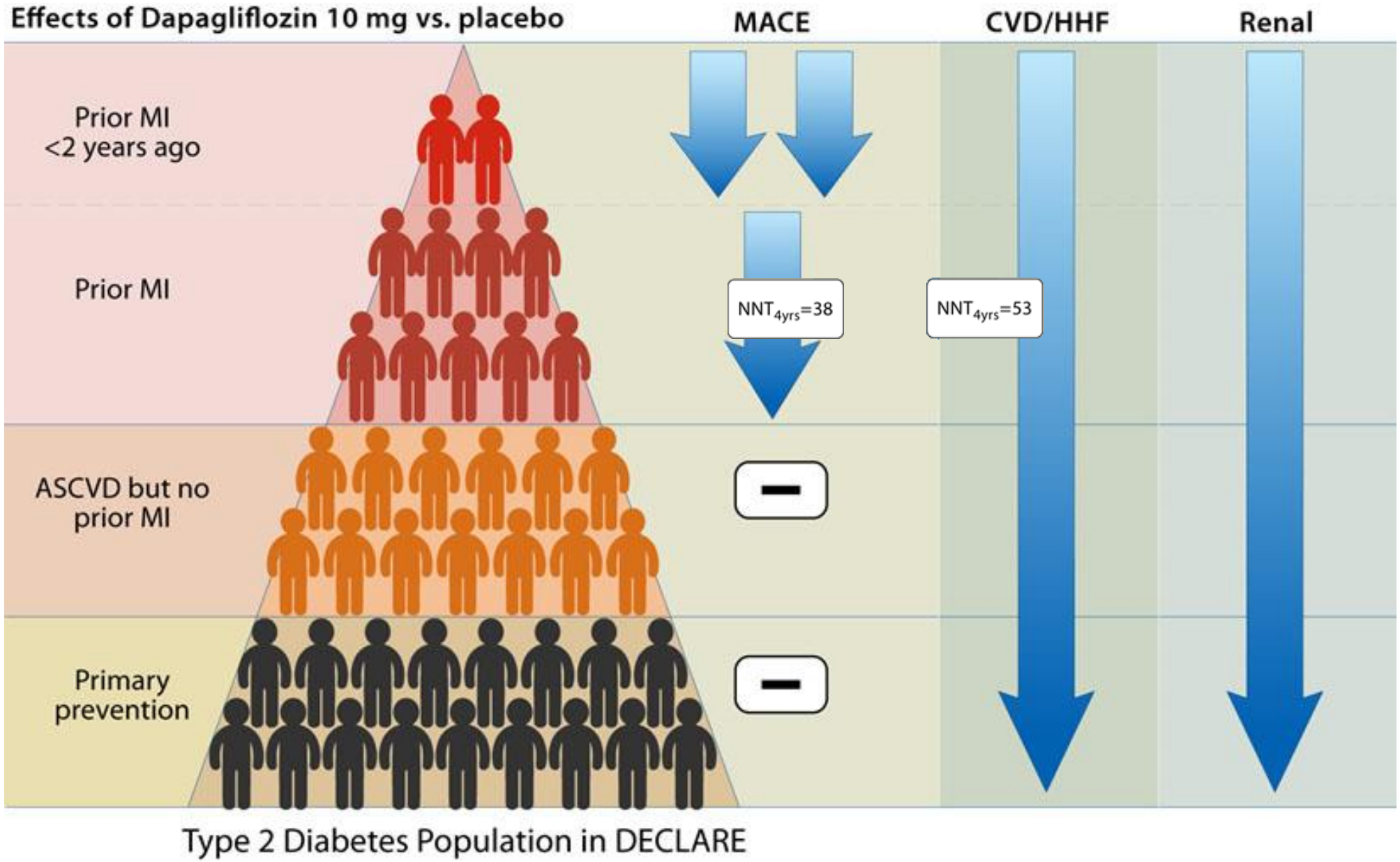
Primaire eindpunt
hHF & CV Death



No. at Risk										
Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

Subgroup	Empagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of patients with events/total no.		
Overall	361/1863	462/1867	0.75 (0.65–0.86)
Baseline diabetes status			
Diabetes	200/927	265/929	0.72 (0.60–0.87)
No diabetes	161/936	197/938	0.78 (0.64–0.97)

1. M Packer et al. *N Engl J Med*. 2020 doi:10,1056NEJMoa2022190



Verma S, McMurray JJV. Circulation. 2019;139:2537-2541.

Casus 2: meneer de J, 74 jaar

Voorgeschiedenis

2002 – Onderwandinfarct

2011 – DM2

2017 – Perifeer vaatlijden

Medicatie:

Fosinopril 20mg 1dd1

Rivaroxaban 20mg 1dd1

Spironolacton 25mg 1dd1

Metformine 500mg 2dd1

Novorapid volgens schema

Lantus volgens schema

Pantoprazol 40mg 1dd1

Metoprolol 50mg 1dd1

Aanvullend onderzoek

eGFR 45

HbA1c 66

EAI rechts: 0.68 monofasisch

EAI links: 1.32 trifasisch

Zou u bij deze nierfunctie een SGLT2 remmer starten?

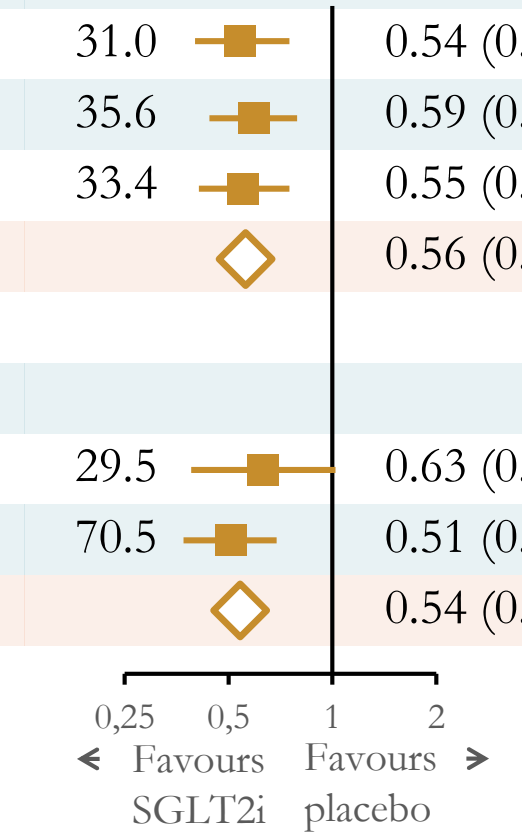
En bij perifeer vaatlijden?

FILTER

Renal Outcomes

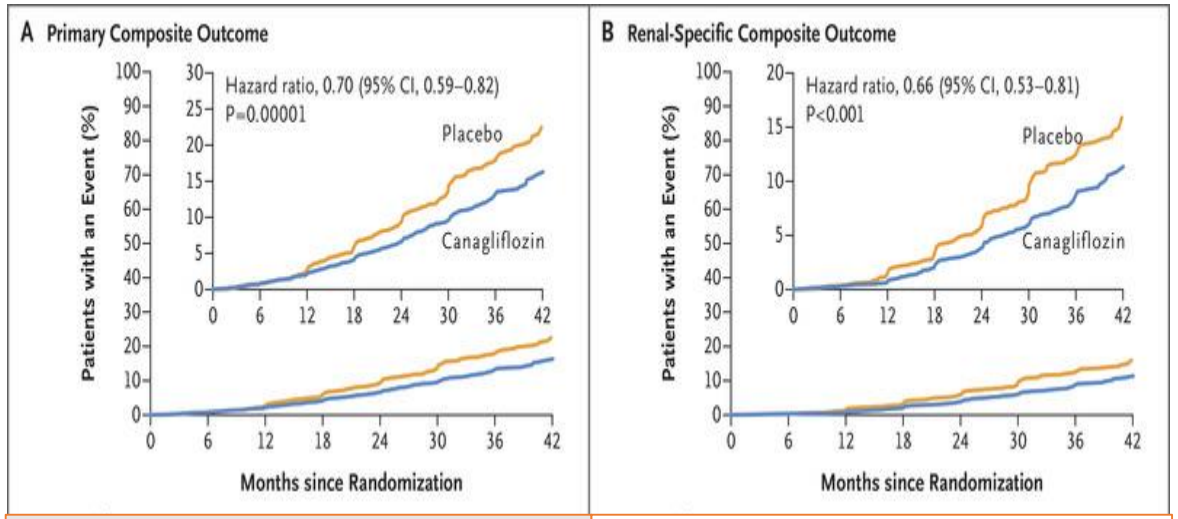
Delayed Decline in Renal Function Across the SGLT2i CVOTs

	Patients		Events	Events per 1,000 patient years		Weight (%)	Hazard Ratio (95% CI)
	Treatment n/N	Placebo n/N		Treatment	Placebo		
Patients with ASCVD							
EMPA-REG OUTCOME	4,645/6,968	2,323/6,968	152	6.3	11.5	31.0	0.54 (0.40, 0.75)
CANVAS Program	3,756/6,656	2,900/6,656	179	6.4	10.5	35.6	0.59 (0.44, 0.79)
DECLARE-TIMI 58	3,474/6,974	3,500/6,974	183	4.7	8.6	33.4	0.55 (0.41, 0.75)
Fixed effects model for ASCVD (P<0.0001)							0.56 (0.47, 0.67)
Patients with multiple risk factors							
CANVAS Program	2,039/3,486	1,447/3,486	70	4.1	6.6	29.5	0.63 (0.39, 1.02)
DECLARE-TIMI 58	5,108/10,186	5,078/10,186	182	3.0	5.9	70.5	0.51 (0.37, 0.69)
Fixed effects model for multiple risk factors (P<0.0001)							0.54 (0.42, 0.71)



ASCVD, atherosclerotic cardiovascular disease; CVOTs, cardiovascular outcome trials.
Adapted from Zelniker TA et al. Lancet. 2019;393:31-39.

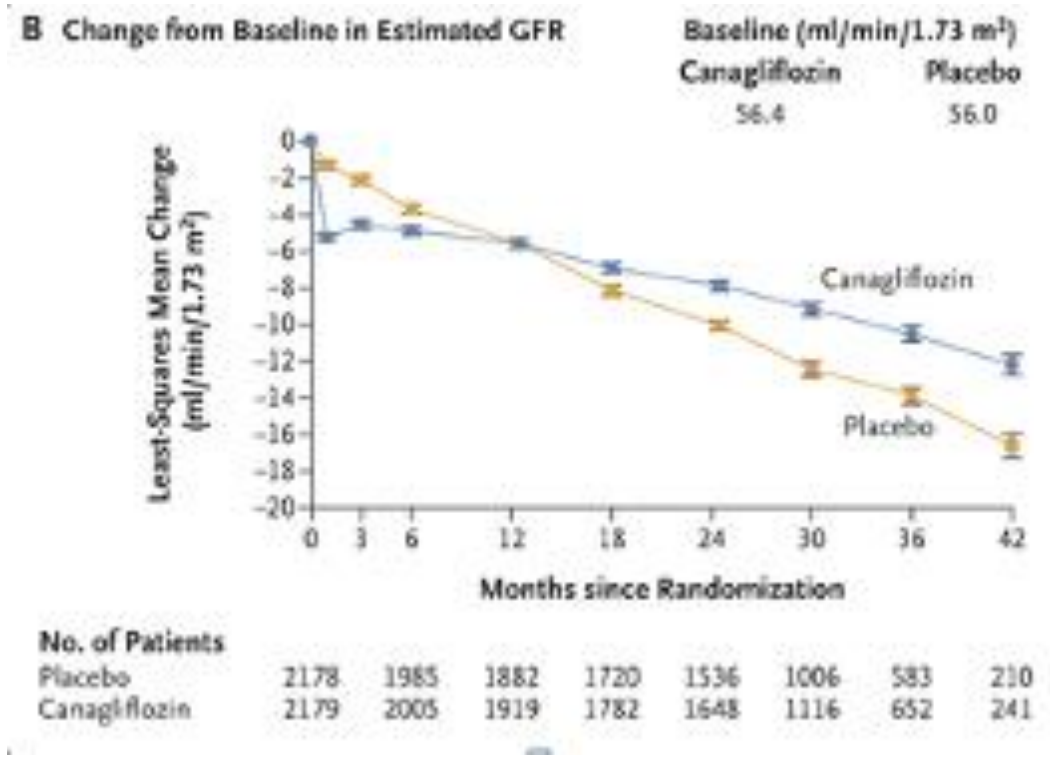
Primary Composite, Renal,and Mortality Outcomes – The CREDENCE trial



primary composite outcome of end- stage kidney disease, doubling of the serum creatinine level, or renal or cardiovascular death

renal-specific composite outcome of endstage kidney disease, doubling of serum creatinine level,
or renal death.

Nierfunctiebeloop na start SGLT2remmer



Casus 2: meneer de J, 74 jaar

Voorgeschiedenis

2002 – Onderwandinfarct

2011 – DM2

2017 – Perifeer vaatlijden

Medicatie:

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Metformine 500mg 2dd1

Novorapid volgens schema

Lantus volgens schema

Pantoprazol 40mg 1dd1

Metoprolol 50mg 1dd1

Aanvullend onderzoek

eGFR 45

HbA1c 66

EAI rechts: 0.68 monofasisch

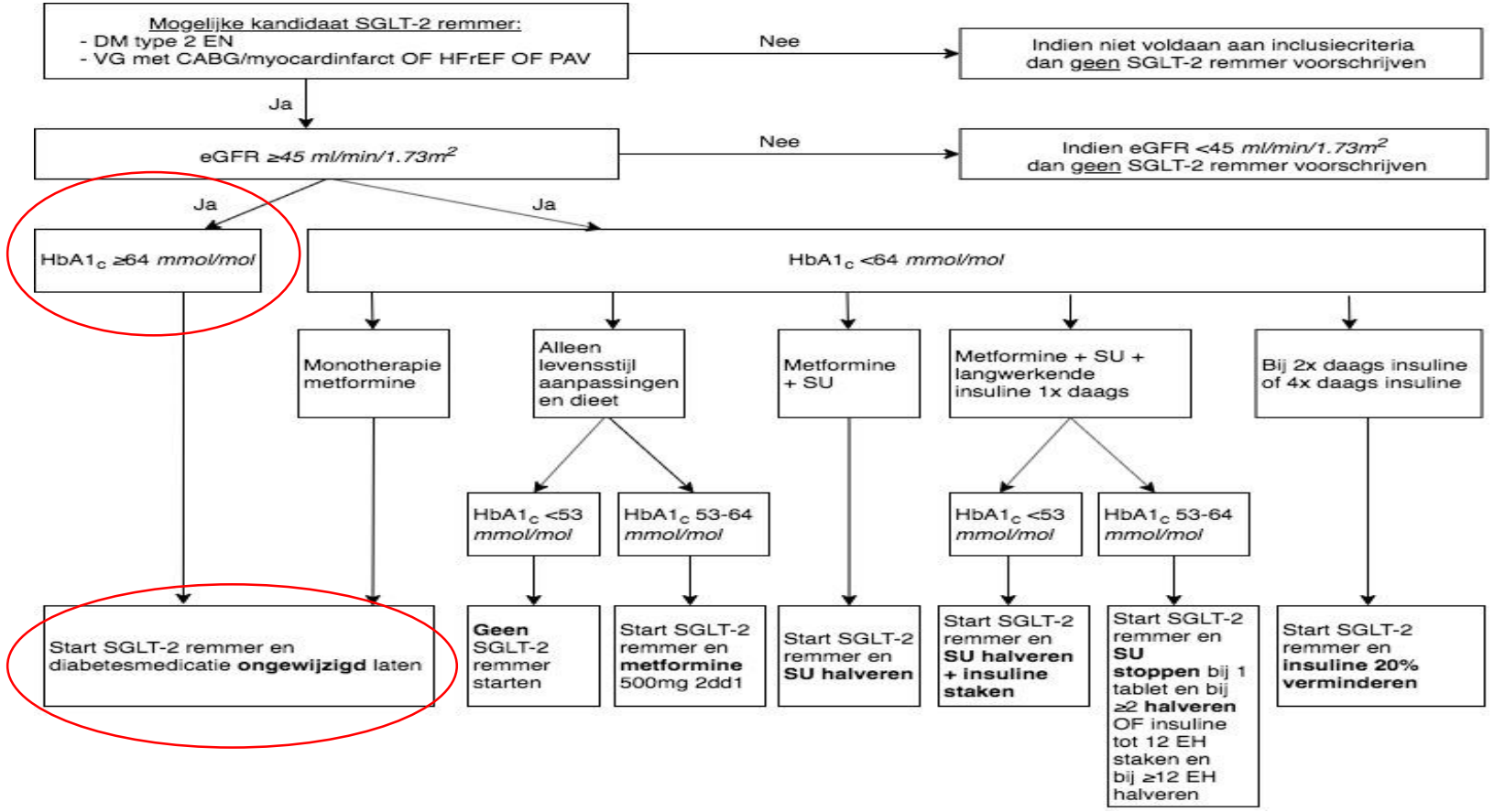
EAI links: 1.32 trifasisch

Toevoegen SGLT-2 remmer!

Medicatie aanpassen?

Stroomschema voor de cardiologie polikliniek

Medicatie eventueel aanpassen middels stroomschema



Conclusie:
Aanpassen diabetesmedicatie niet nodig!

Casus 3: Meneer K van 57 jaar

Voorgeschiedenis:

2006 – NSTEMI

2010 – CAG RCx bij stent restenose

DM2

Medicatie:

Pantoprazol 40mg 1dd1

Clopidogrel 75mg 1dd1

Perindopril 8mg 1dd1

Ascal 80mg 1dd1

Mirtazepine 15mg 1dd1

Gliclazide retard 80mg 1dd1

Atorvastatine 40mg 1dd1

Metoprolol 50mg 1dd1

Metformine 1000mg 2dd1

Linagliptine 5mg 1dd1

Aanvullend onderzoek

HbA1c van 67

eGFR>90

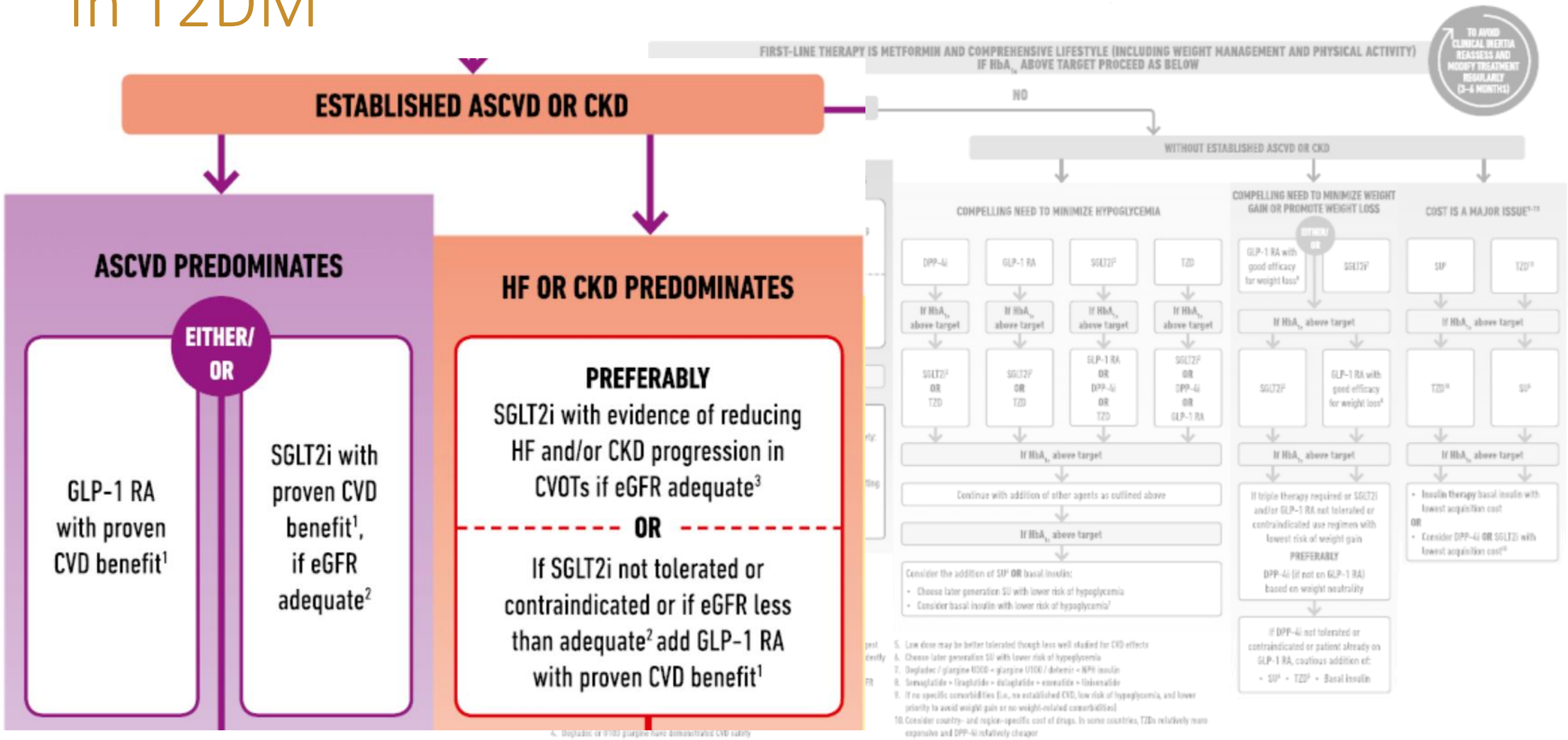
Voorschrijven SGLT-2 remmer

Medicatiewijziging? DPP4-remmer linagliptine?

Wat te doen bij eventuele aanwezigheid GLP-1 analoog?

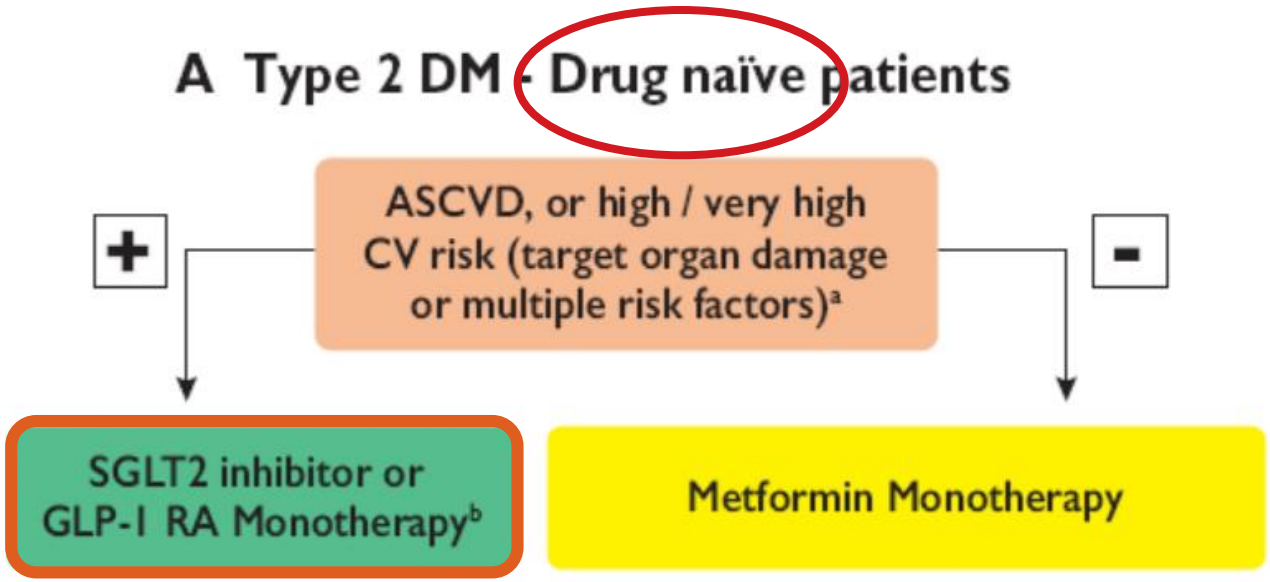
Richtlijnen

2019 Consensus Report by the ADA/EASD on the Overall Approach of Glucose-lowering Medication in T2DM



ACC, American College of Cardiology; AHA, American Heart Association.
Arnett DK et al. J Am Coll Cardiol. 2019 Mar 17. pii: S0735-1097(19)33876-8.

2019 ESC Guidelines on Diabetes, Pre-Diabetes, and CVD Developed in Collaboration with the EASD



SGLT2is or GLP-1RAs are recommended in drug-naïve patients with ASCVD or high/very high CV risk as first-line therapy

ESC GUIDELINES

on diabetes, pre-diabetes, seases developed in e EASD

re-diabetes, and cardiovascular ety of Cardiology (ESC) and the Study of Diabetes (EASD)

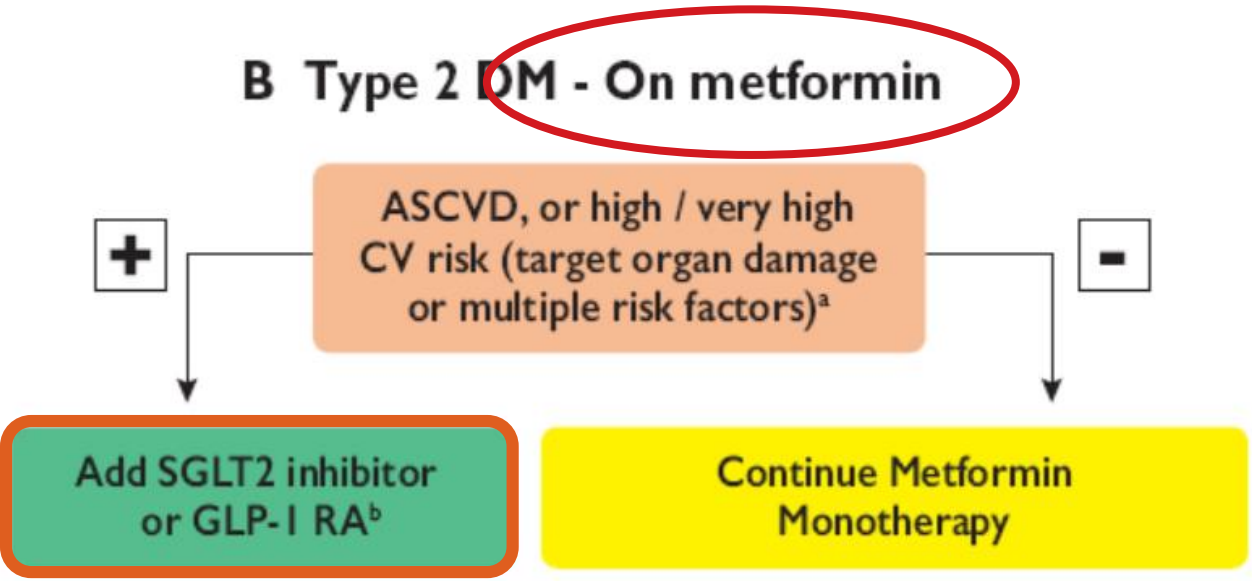
esco Cosentino* (ESC Chairperson) (Sweden), (United Kingdom), Victor Aboyans (France), Antonio Ceriello[1] (Italy), simo Federici[1] (Italy), Gerasimos Filippatos herlands), Tina Birgitte Hansen (Denmark), ohansson (Sweden), Peter Jüni (Canada), Marx (Germany), Linda G. Mellbin (Sweden), ca (Italy), Marco Roffi (Switzerland), etar M. Seferović (Serbia), Miguel Sousa-Uva id C. Wheeler[1] (United Kingdom)

CVD, carc

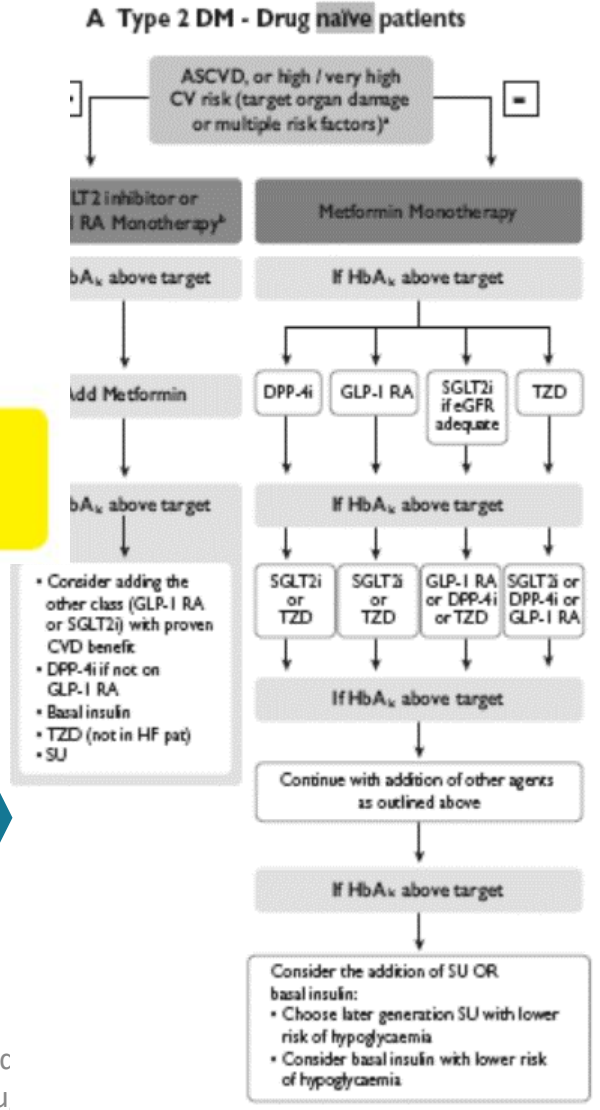
Cosentino F et al. Eur Heart J. 2019 Au

86.

2019 ESC Guidelines on Diabetes, Pre-Diabetes, and CVD Developed in Collaboration with the EASD



SGLT2is or GLP-1RAs are recommended in patients on metformin with ASCVD or high/very high CV risk, irrespective of A1C



ESC GUIDELINES

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CVD, carc

Cosentino F et al. Eur Heart J. 2019 Au

86.

ESC guidelines recommend use of SGLT2 inhibitors for prevention of hHF in patients with HF and T2D

Guideline	Class / LoE	Recommendations
Diabetes, pre-diabetes and CVD (2019)[1]	1/A	SGLT2i are recommended to lower risk of hHF in patients with T2D
Clinical Practice Update on HF guideline (2019)[2]	2A/A	The expert consensus was that canagliflozin and dapagliflozin should also be considered for patients with T2DM and either established cardiovascular (CV) disease or at high CV risk in order to prevent or delay the onset of and hospitalizations for HF
CVD prevention in clinical practice (2016)[3]	2A/B	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.

SGLT2 = sodium-glucose cotransporter 2; hHF = hospitalization for heart failure; T2D = Type 2 Diabetes Mellitus; HF = heart failure; LoE = Level of Evidence; CVD = cardiovascular disease

1. Cosentino F et al. *Eur Heart J* 2019 doi:10.1093/eurheartj/ehz486 2. Severovic PM et al *Eur J HF* 2019 doi:10.1002/ejhf.1531 3. Piepoli MP et al. *Eur Heart J* 2016 doi:10.1093/eurheartj/ehw106

Placeholder behouden voor mogelijk nieuwe NHG richtlijn T2DM.

Indien deze voor december gepubliceerd is dan zal deze nog extra worden toegevoegd in de nascholing

Casus 3: Meneer K van 57 jaar

Voorgeschiedenis:

2006 – NSTEMI

2010 – CAG RCx bij stent restenose

DM2

Medicatie:

Pantoprazol 40mg 1dd1

Clopidogrel 75mg 1dd1

Perindopril 8mg 1dd1

Ascal 80mg 1dd1

Mirtazepine 15mg 1dd1

Gliclazide retard 80mg 1dd1

Atorvastatine 40mg 1dd1

Metoprolol 50mg 1dd1

Metformine 1000mg 2dd1

Linagliptine 5mg 1dd1

Aanvullend onderzoek

HbA1c van 67

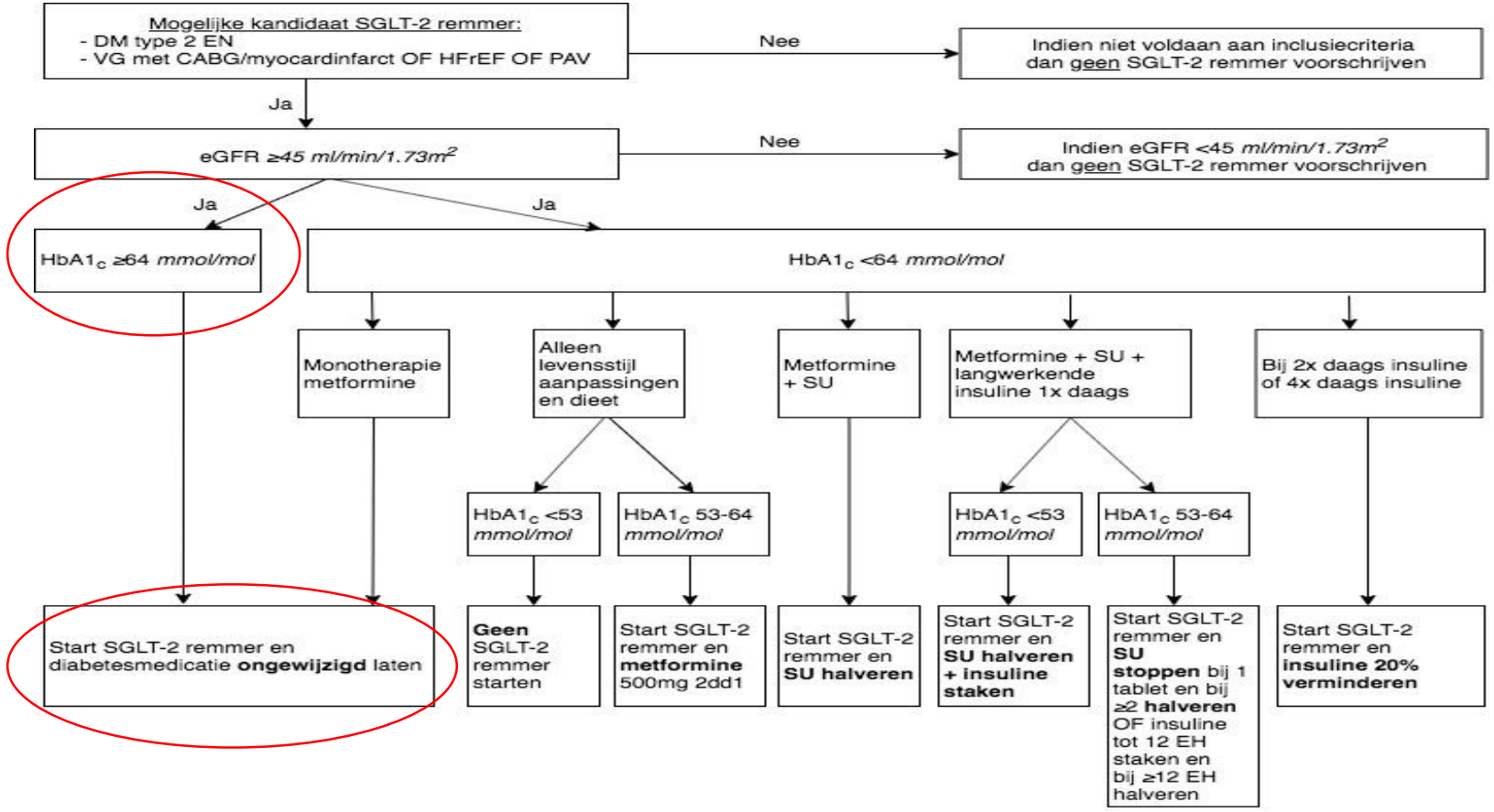
eGFR>90

Voorschrijven SGLT-2 remmer

Nog andere medicatie aanpassen volgens stroomschema?

Stroomschema voor de cardiologie polikliniek

Medicatie eventueel aanpassen middels stroomschema



Conclusie:
Aanpassen diabetesmedicatie niet nodig!

Casus 4: Meneer L van 81 jaar

Voorgeschiedenis:

2004 – CABG

pAF

DM2

Medicatie:

Perindopril 5mg 1dd1

Rosuvastatine 20mg 1dd1

Acenocoumarol volgens schema

Furosemide 40mg 2dd1

Metformine 500mg 1dd1

Sotalol 80mg 2dd1

Ezetrol 10mg 1dd1

Aanvullend onderzoek

HbA1c van 41

eGFR 59

Voorschrijven SGLT-2 remmer

Mogelijk met laag HbA1c?

Medicatieveranderingen?

Stroomschema voor de cardiologie polikliniek

Vervolgens:

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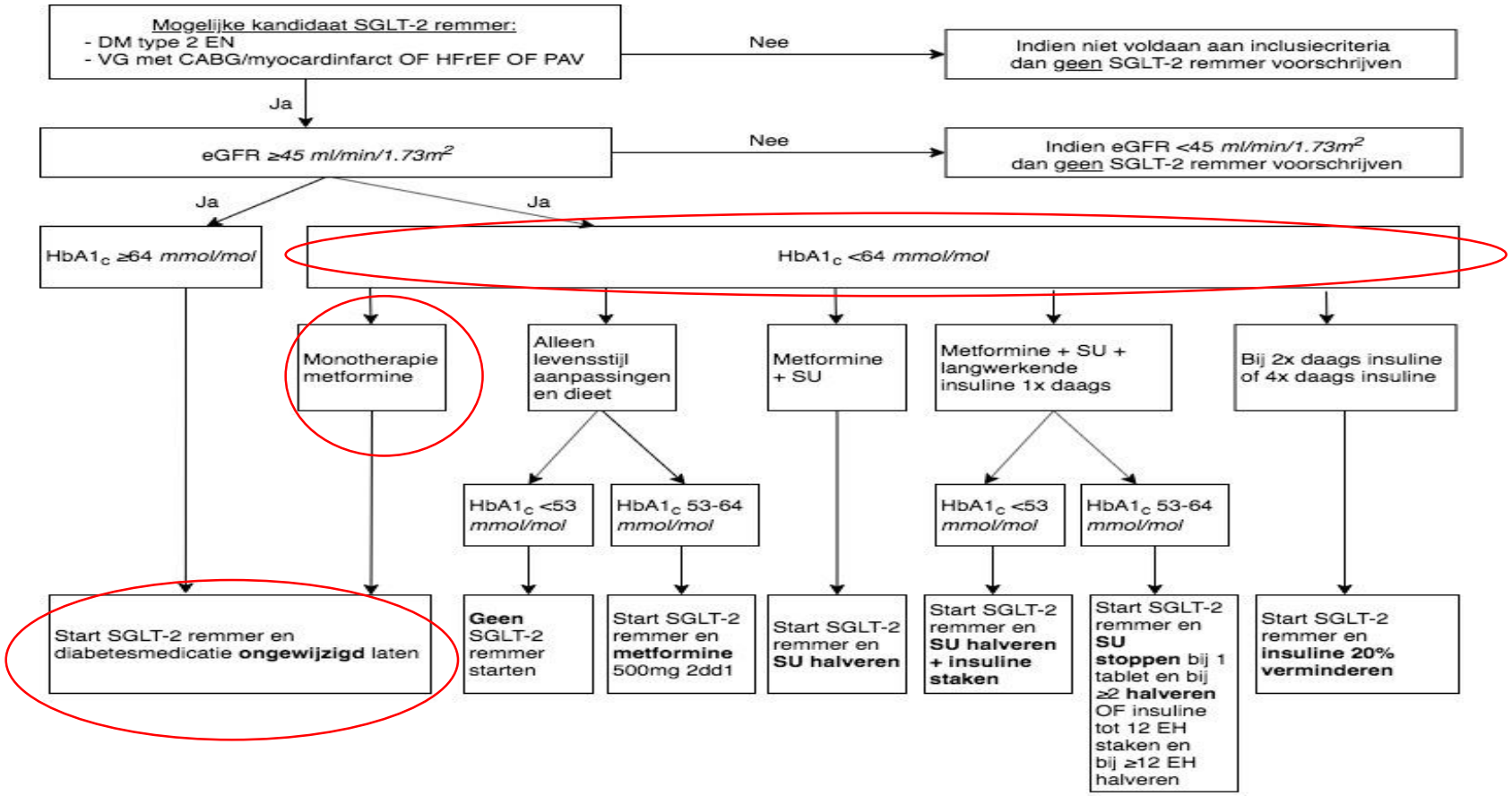

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Voorschrijven SGLT-2 remmer

Geen andere medicatie aanpassen

Onderzoek/implementatie

- Samenwerking tussen interne geneeskunde en cardiologie
  - Veilige zorg
  - Hetzelfde beleid tussen alle specialisten
- Cardiologen mogelijk maken SGLT-2 remmers voor te schrijven – implementatie in klinische praktijk
- ‘Real-world’ evidence verzamelen

Inhoud

- Alle patiënten opgenomen op cardiologie afdeling of CCU en via de polikliniek met DM type 2 en:
  - Myocardinfarct en/of CABG
  - OF coronaire stenose aangetoond door CAG van meer dan 70%
  - OF hartfalen met in de voorgeschiedenis MI/CABG
  - OF perifeer arterieel vaatlijden
- Wordt informed consent gevraagd
- Daarna start SGLT-2 remmers

Baseline tabel

20 mei 2020

In totaal 84 patiënten gestart

Patiënt karakeristieken:

- Gemiddeld 70-jarige man met BMI 28,5
- Grootste deel via de poli (60/40)
- Grootste deel myocardinfarct (>50%)
- DM2 vnl onder behandeling huisarts

Baseline characteristics			
Patient characteristics	N = 84 (100%)	Diabetic medication	
Male	62 (73,8%)	Metformin	73 (86,9%)
Age, mean in years	69.5	Sulfonylurea	35 (41,7%)
BMI, mean	28,6	DPP-4	5 (6,0%)
		GLP-1 RA	4 (4,8%)
Location start SGLT-2 inhibitor		Short-acting insulin	16 (19,0%)
Hospital admission	35 (41,7%)	Long-acting insulin	23 (27,4%)
Outpatient appointment	49 (58,3%)		
		CV medication	
Type of SGLT-2 inhibitor		Beta-blockers	63 (75,0%)
Empagliflozin	67 (79,8%)	Diuretics	41 (48,8%)
Dapagliflozin	17 (20,2%)	Calcium channel blockers	26 (31,0%)
		ACE inhibitors	34 (40,5%)
CV disease*	84 (100%)	Angiotensin II receptor blockers	14 (16,7%)
Myocardial infarction	53 (63,1%)	Alpha blockers	3 (3,6%)
CABG	27 (33,3%)	ARNI	7 (8,3%)
Coronary stenosis >70%	73 (86,7%)		
PAD	12 (14,3%)	Anticoagulants	
HF	20 (23,4%)	Platelet aggregation inhibitors	61 (72,6%)
Ischemic	13 (15,5%)	Direct oral anticoagulants	22 (26,2%)
Non-ischemic	5 (6,0%)	Vitamin K antagonists	10 (11,9%)
Unknown etiology	2 (2,4%)		
		Cholesterol-lowering drugs	
Diabetes mellitus	84 (100%)	HMG-CoA-reductase inhibitors	73 (86,9%)
DM de novo	3 (3,6%)	Cholesterol absorption inhibitors	11 (13,1%)
DM treatment (previously) done by GP	72 (85,8%)	PCSK-9 inhibitors	2 (2,4%)
		None	7 (8,3%)

Table 3. Baseline characteristics.
BMI= body mass index; SGLT-2= sodium-glucose transport protein 2; CV= cardiovascular; CABG= coronary artery bypass graft procedure; PAD= peripheral arterial disease; HF= heart failure; DM= diabetes mellitus; GP= general practitioner. DPP-4= dipeptidyl-peptidase-4; GLP-1 RA= glucagon-like peptide-1 receptor agonist; CV= cardiovascular; ACE= angiotensin-converting-enzyme; ARNI= angiotensin receptor-neprilysin inhibitor; HMG-COA-reductase = 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase; PCKS-9 = proprotein convertase subtilisin/kexin type 9
* Patients could have multiple CV comorbidities in their medical history

Baseline medicatie

Patiënt medicatie:

- Grootste deel metformine (85%) in combinatie met SU (40%) en insuline (20%)
- Cardiovasculair grootste deel bèta-blokkers (75%) en diuretica (50%)
- Groot deel plaatjesremmer (70%)
- Veel hebben een statine (85%)

Resultaten follow-up en eGFR/HbA1c

Resultaten:
- Verlaging van HbA1c
- Verlaging van eGFR

Overig:
- Insuline gestaakt bij 3 patiënten

	Baseline	At 1st OA	At 2nd OA	At 3rd OA
Follow-up				
Time, mean	T=0	47 days	101 days	147 days
Total, n		77	40	13
Specialist		62	24	6
Diabetic nurse		15	16	7
Laboratory result in means				
HbA1c mmol/mol	61.9 (n=75)	57.9 (n=40)	56.9 (n=27)	N/A
eGFR ml/min/1,73m*	72.9 (n=80)	66.5 (n=40)	66.4 (n=27)	N/A

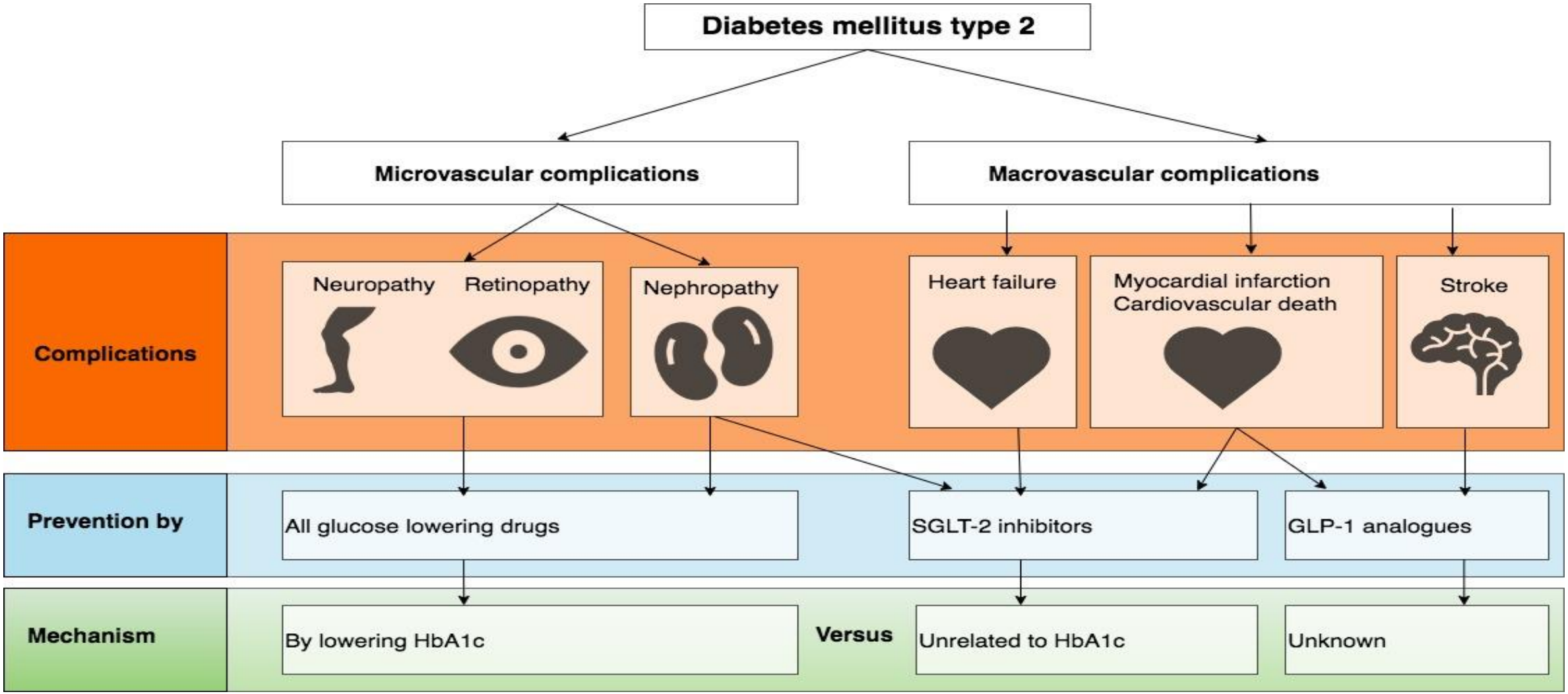
Bijwerkingen

Resultaten:

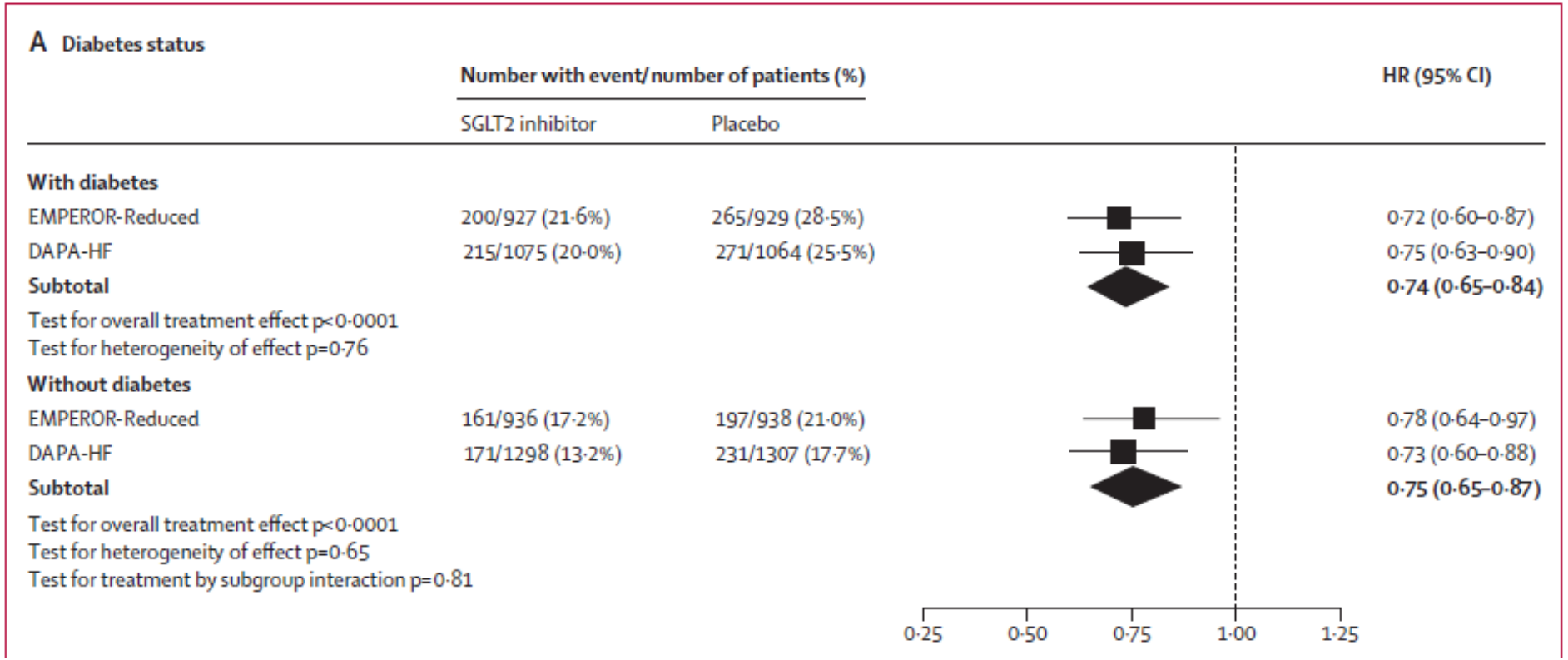
- In totaal 16 bijwerkingen gemeld van n=84
- Hierbij zijn 9 patiënten permanent gestaakt met SGLT-2 remmer

Adverse events	
Total amount adverse events	**16 (17,9%)**
Urogenital infection	6 (7,1%)
Genital	5
Urinary tract	1
Pruritus	3 (3,6%)
Polyuria and polydipsia	3 (3,6%)
General discomfort	1 (1,2%)
Severe obstipation	1 (1,2%)
Foot amputation	1 (1,2%)
Mild hypoglycemia	1 (1,2%)
Consequences	
Permanent discontinuation of SGLT-2 inhibitor	9 (10,7%)
Temporary discontinuation	1 (1,2%)
Reduction in dosage of SGLT-2 inhibitor	2 (2,4%)
Continuation	4 (4,8%)

Nieuwe behandeling diabetes mellitus type 2



SGLT2 remming bij hartfalers 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			

Zannad F. et al. Lancet 2020;396:819-29.

Key Take Home Messages on the Cardiorenal Impact of SGLT2i

Profoundly *prevent* heart failure and also prevent and treat renal disease in T2DM

Several mechanisms, including hemodynamic and metabolic alterations, may underlie these outcomes

Benefits are independent of A1C lowering and are observed across a broad spectrum of eGFR (≥30 ml/min/1.73m^2)

Take home message (1)

- SGLT2-i: protective in case of type 2 DM and established cardiovascular history on atherosclerotic major adverse CV events (EASD+ADA[1] and ESC [2])

- Somewhat beneficial in case of type 2 DM and a high CV risk profile (EASD+ADA[1] and ESC [2])

- There are robust benefits on reducing hospitalisation for heart failure and progression of renal disease regardless of existing atherosclerotic cardiovascular disease or a history of heart failure, independent of glucose control

[1]Davies MJ, et al. Management of Hyperglycemia in Type 2 Diabetes, A Consensus Report (ADA) and EASD. Diabetologia; 2018

[2]Seferović PM, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(5):853–72.

Take home message (2)

- The main adverse events are genital infections, risk of (diabetic) keto-acidosis
- Starting SGLT2i in the cardiology out-patient clinic may be safe provided that certain precautionary measures are taken into account
- Near-future: SGLT2-i in non-diabetic patients with a high cardiovascular risk profile / heart failure?

[1]Davies MJ, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report (ADA) and EASD. Diabetologia; 2018

[2]Seferović PM, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2018;20(5):853-872.