Amsterdam UMC
Universitair Medische Centra

Type 2 Diabetes Mellitus & Chronische Nierschade

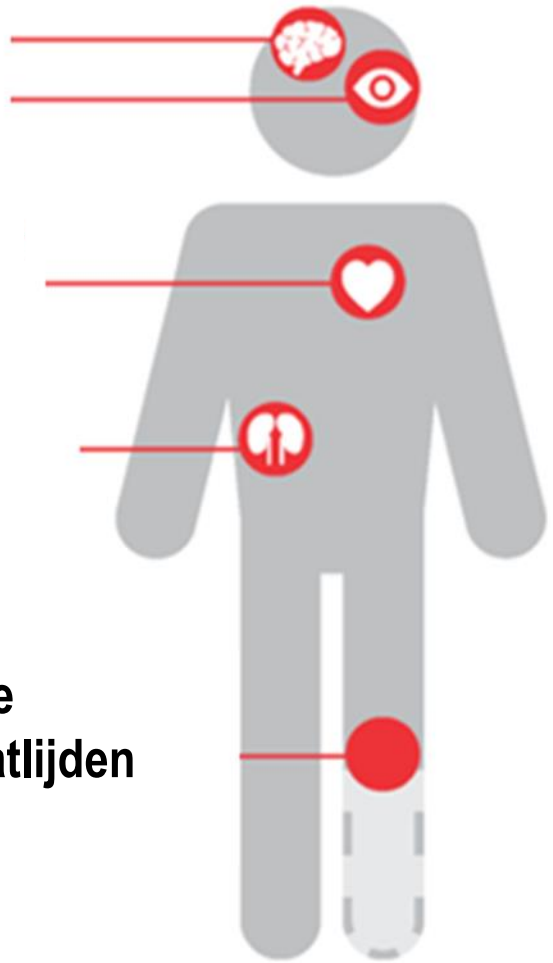
SGLT2-remmers, GLP1-RA en Finerenon: de één, de ander of een combinatie?

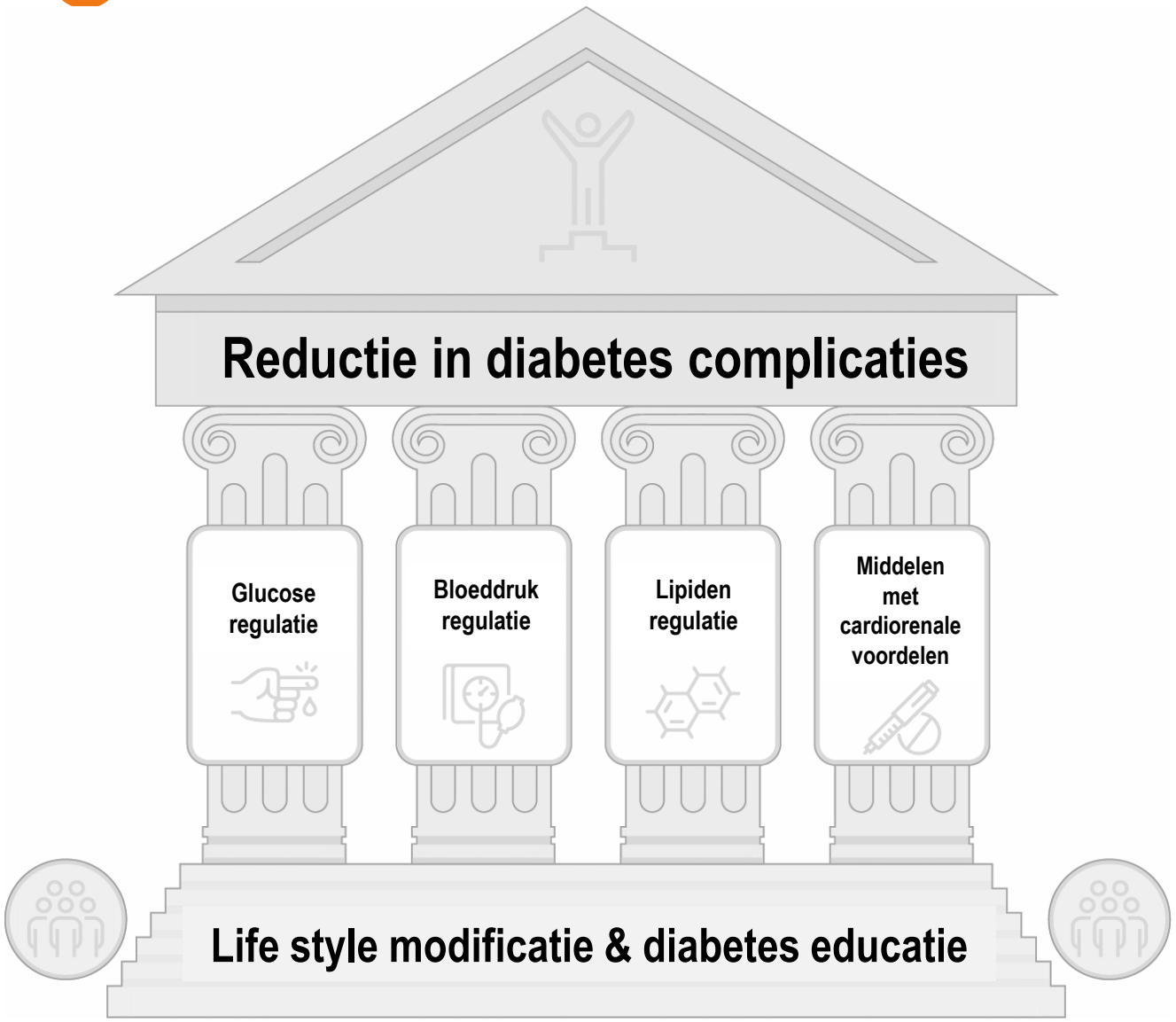
Erik Serné

Disclosures

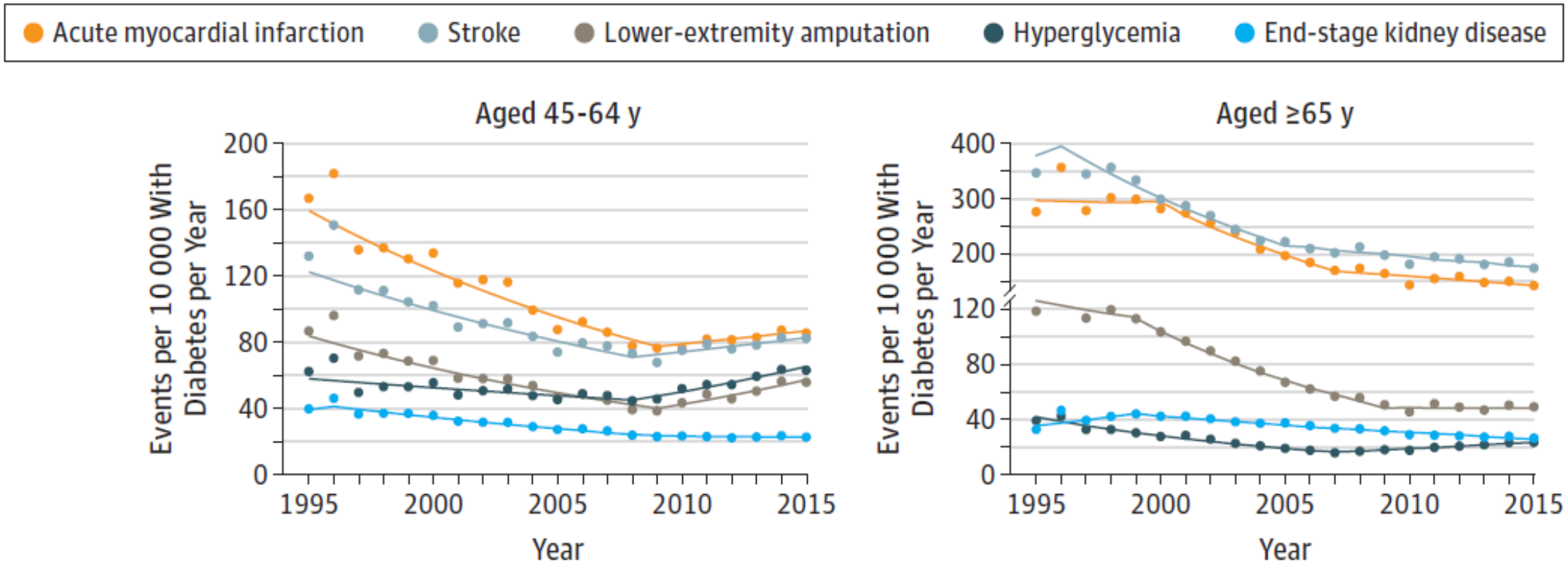
(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	**NVT**
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	• ZonMW (2x) • NVT • NVT • NVT

Diabetes Mellitus Type 2





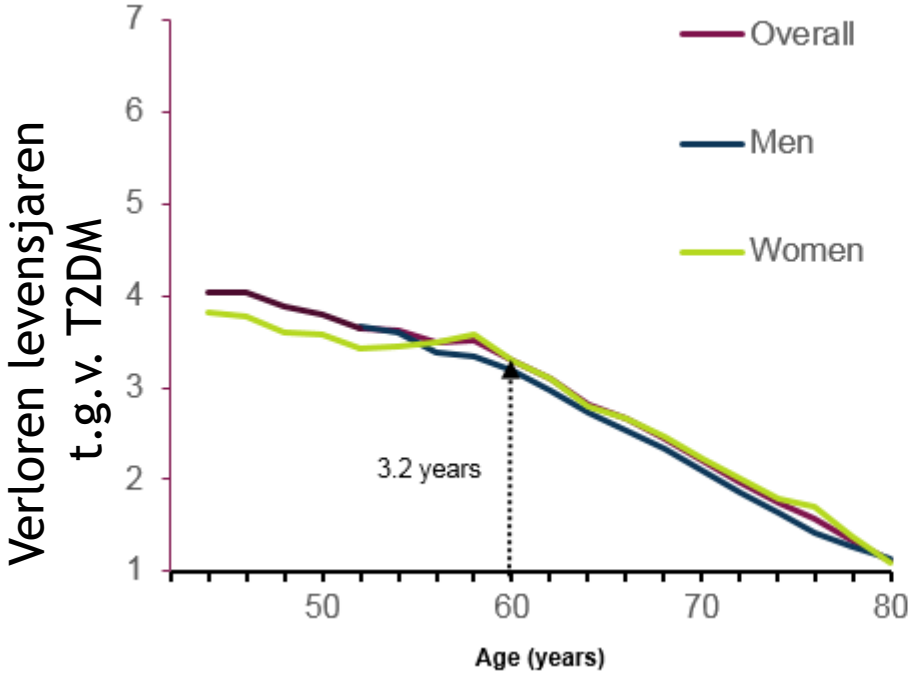
CVRM succesvol
Maar….stabilisatie diabetescomplicaties



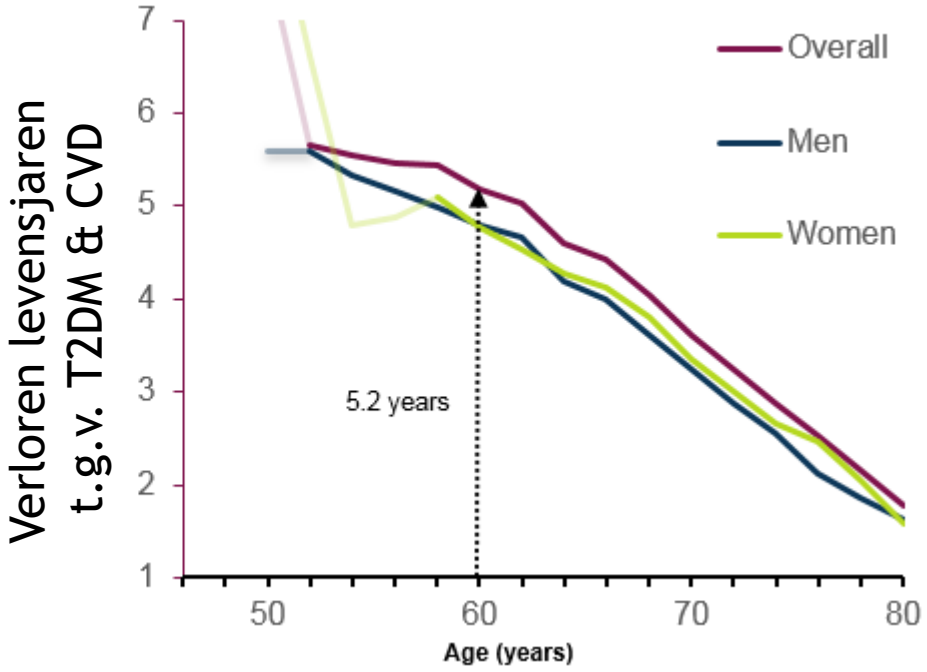
JAMA. 2019 Apr 15. doi: 10.1001/jama.2019.3471

Diabetes in Nederland

Verloren levensjaren PHARMO database 2018



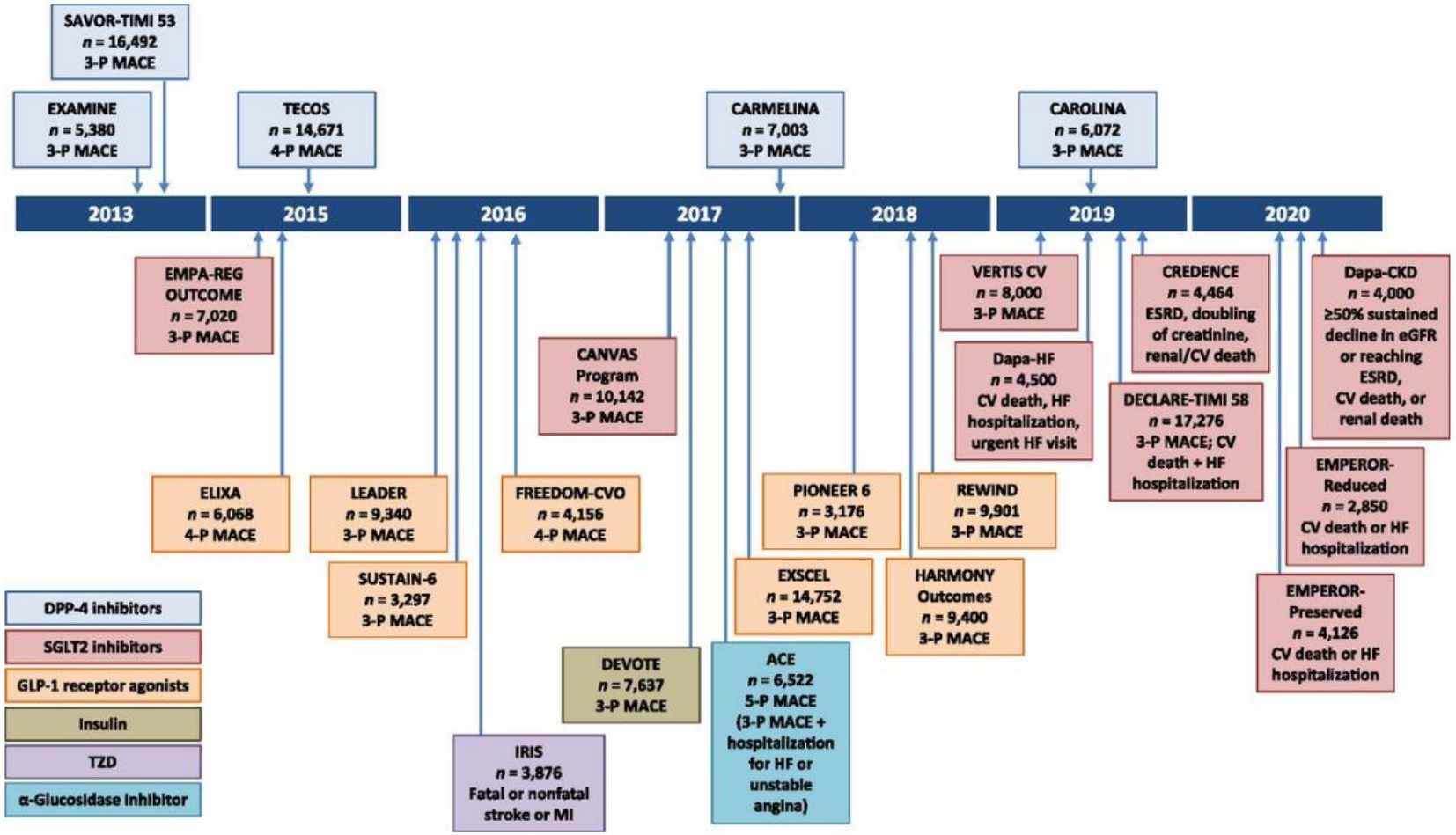
Gemiddeld zal een 60-jaar-oud individu met diabetes, zonder hart- en vaatziekten **3,2** jaar eerder overlijden vergeleken met iemand zonder diabetes



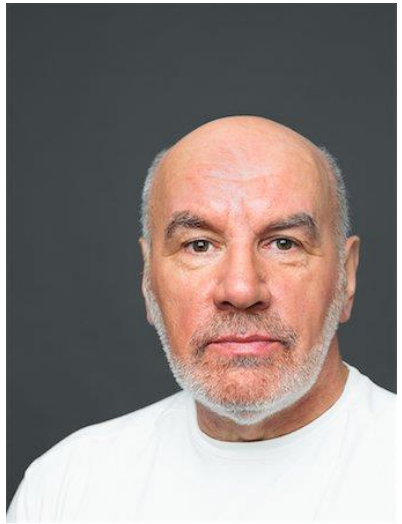
Gemiddeld zal een 60-jaar-oud individu met diabetes, met hart- en vaatziekten **5,2** jaar eerder overlijden vergeleken met iemand zonder diabetes

Value in Health 2018;21:S6-S7

Cardiovasculaire uitkomst studies nieuwe geneesmiddelen (CVOTs)



Dhr. Janssen



- 64 jaar
- Type 2 diabetes, diabetesduur 12 jaar
- Achtergrond diabetische retinopathie
- Microalbuminurie genormaliseerd bij Lisinopril gebruik
- Hartinfarct, 2 jaar geleden
- Metformine 1000 mg 2dd, gliclazide 80 mg 3dd, Lisinopril 20 mg, Rosuvastatine 20 mg, acetylsalicylzuur 80 mg
- Hba1c 8.7 % (64 mmol/mol)
- LDL-cholesterol 1.8 mmol/l
- eGFR 79 ml/min/1,73 m2
- Albumine-Creatinine ratio < 3 mg/mmol Kreat
- Bloeddruk 135/77 mmHg
- BMI 32,0 kg/m2

CVOTs
Persisterend hoog risico ondanks CVRM in placebogroep

CVRM

- Syst RR 135
  - >80% ACE/ARB
- LDL-Cholesterol < 2,5
  - 77% statine
- Hba1c 8.2%
  - >75% metformine
  - >40% SU
  - >45% insuline
- BMI > 30
- eGFR 76, ACR <3

Residual Risk MACE

- **1-year MACE: 4.5%**

*MACE: niet-fataal hartinfarct, niet-fatale beroerte, sterfte aan hart- en vaatziekten

Lancet Diabetes Endocrinol 2017

Dhr. De Vries

- 62 jaar
- Type 2 diabetes, diabetesduur 15 jaar
- Achtergrond diabetische retinopathie
- Hypertensie
- Metformine 1000 mg 2dd, gliclazide 80 mg 3dd, NPH insuline 22 E, Lisinopril/HCT 20/12,5 mg, Simvastatine 40 mg
- Hba1c 8.3 % (64 mmol/mol)
- LDL-cholesterol 2.5 mmol/l
- eGFR 50 ml/min/1,73 m2
- Albumine-Creatinine ratio 90 mg/mmol Kreat
- Bloeddruk 136/78 mmHg
- BMI 31,0 kg/m2

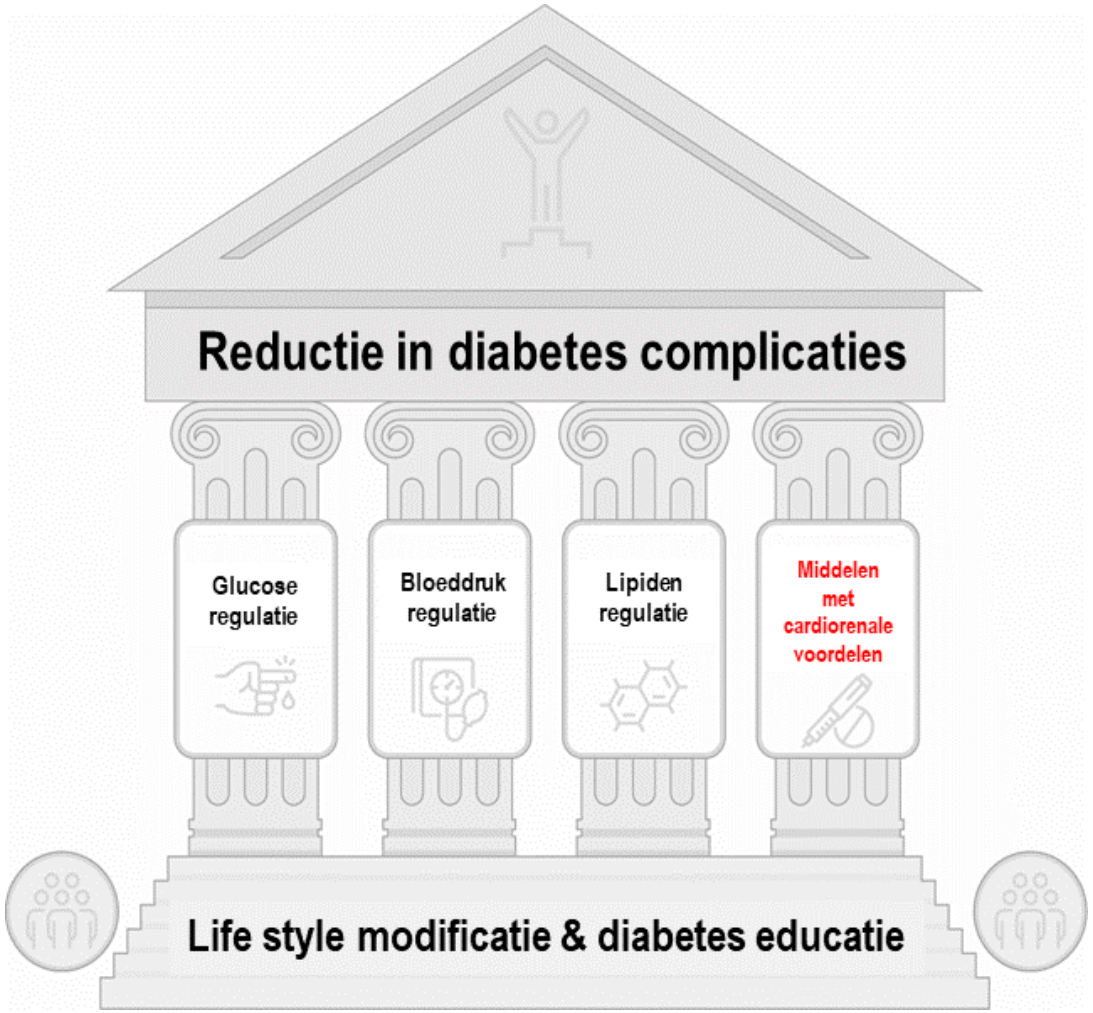
CVOTs
Persisterend hoog risico ondanks CVRM in placebogroep

CVRM

- Syst RR 136
  - 100% ACE/ARB
- LDL-Cholesterol < 2,5
  - 65% statine
- Hba1c 8.2%
  - 57% metformine
  - 29% SU
  - 65% insuline
- BMI > 30
- eGFR 55, ACR >30

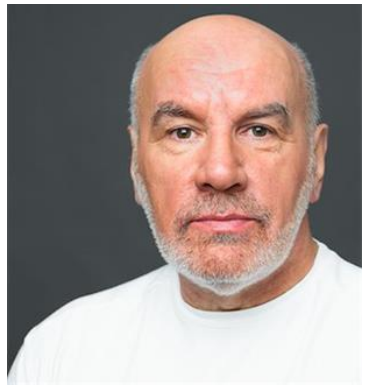
Residual Risk

- **1-year MACE: 6.1%**
- **1-year ESRD/renal death: 1.8%**



- SGLT2-remmers
- GLP1-RA

Absolute winst Dhr. Janssen



Eerder aangetoonde hart- en vaatziekten

Among a 1000 people

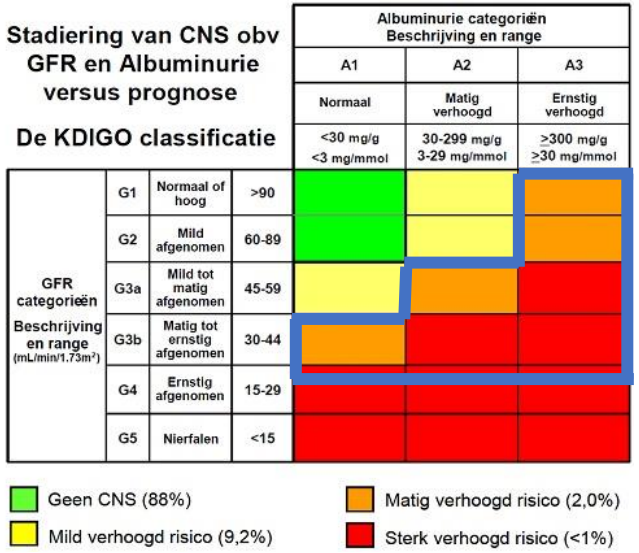
	Usual care	SGLT 2-I	GLP-1 RA
All Cause Mortality 5 years	120 per 1000	16 fewer	13 fewer
	certainty →	⊘⊘⊘○	⊘⊘⊘○
Cardiovascular mortality 5 years	79 per 1000	13 fewer	9 fewer
	certainty →	⊘⊘⊘○	⊘⊘⊘○
Non fatal myocardial infarction 5 years	108 per 1000	13 fewer	8 fewer
	certainty →	⊘⊘⊘○	⊘⊘⊘○
Non fatal stroke 5 years	108 per 1000	1 more	16 fewer
	certainty →	⊘⊘⊘○	⊘⊘⊘○
End stage kidney disease 5 years	20 per 1000	6 fewer	4 fewer
	certainty →	⊘⊘⊘⊘	⊘⊘⊘⊘
Heart failure 5 years	80 per 1000	23 fewer	5 fewer
	certainty →	⊘⊘⊘⊘	⊘⊘⊘○

NNT 17 NNT 23

BMJ. 2021 Jan 13;372:m4573. doi: 10.1136/bmj.m4573.

Absolute winst Dhr. De Vries

Chronische nierschade



Among a 1000 people

	Usual care	SGLT 2-I	GLP-1 RA
All Cause Mortality 5 years	170 per 1000	22 fewer	17 fewer
	certainty →	⊘⊘⊘⊘	⊘⊘⊘○
Cardiovascular mortality 5 years	112 per 1000	17 fewer	12 fewer
	certainty →	⊘⊘⊘○	⊘⊘⊘○
Non fatal myocardial infarction 5 years	120 per 1000	14 fewer	9 fewer
	certainty →	⊘⊘⊘○	⊘⊘⊘○
Non fatal stroke 5 years	120 per 1000	1 more	17 fewer
	certainty →	⊘⊘⊘○	⊘⊘⊘○
End stage kidney disease 5 years	92 per 1000	26 fewer	19 fewer
	certainty →	⊘⊘⊘○	⊘⊘⊘○
Heart failure 5 years	105 per 1000	30 fewer	7 fewer
	certainty →	⊘⊘⊘⊘	⊘⊘⊘○

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NNT 11 NNT 15

Absolute winst Dhr. Huisman: the double whammy

Eerder aangetoonde hart- en vaatziekten
& Chronische nierschade

Among a 1000 people

	Usual care	SGLT 2-I	GLP-1 RA
All Cause Mortality 5 years	265 per 1000	30 fewer	24 fewer
	certainty →	⊘⊘⊘⊘	⊘⊘⊘⊘
Cardiovascular mortality 5 years	175 per 1000	25 fewer	18 fewer
	certainty →	⊘⊘⊘⊘	⊘⊘⊘○
Non fatal myocardial infarction 5 years	190 per 1000	21 fewer	13 fewer
	certainty →	⊘⊘⊘○	⊘⊘⊘○
Non fatal stroke 5 years	190 per 1000	2 more	25 fewer
	certainty →	⊘⊘⊘○	⊘⊘⊘⊘
End stage kidney disease 5 years	148 per 1000	40 fewer	29 fewer
	certainty →	⊘⊘⊘⊘	⊘⊘⊘⊘
Heart failure 5 years	235 per 1000	60 fewer	13 fewer
	certainty →	⊘⊘⊘⊘	⊘⊘⊘○

BMJ. 2021 Jan 13;372:m4573. doi: 10.1136/bmj.m4573.

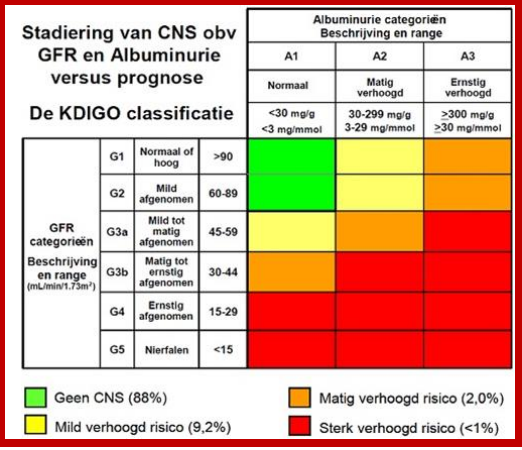
NNT 6 NNT 10

Herziene richtlijn 2021
Farmacotherapie van zeer hoogrisicopatiënten met diabetes mellitus type 2

Patiënten met eerder doorgemaakte hart- en vaatziekten

- Acuut coronair syndroom
- Angina pectoris
- Coronaire revascularisatie
- TIA of beroerte
- Symptomatische aorta-iliofemorale atherosclerose
- Aorta-aneurysma
- Claudicatio intermittens of perifere revascularisatie
- Bij beeldvorming aangetoonde atherosclerotische stenose of ischemie

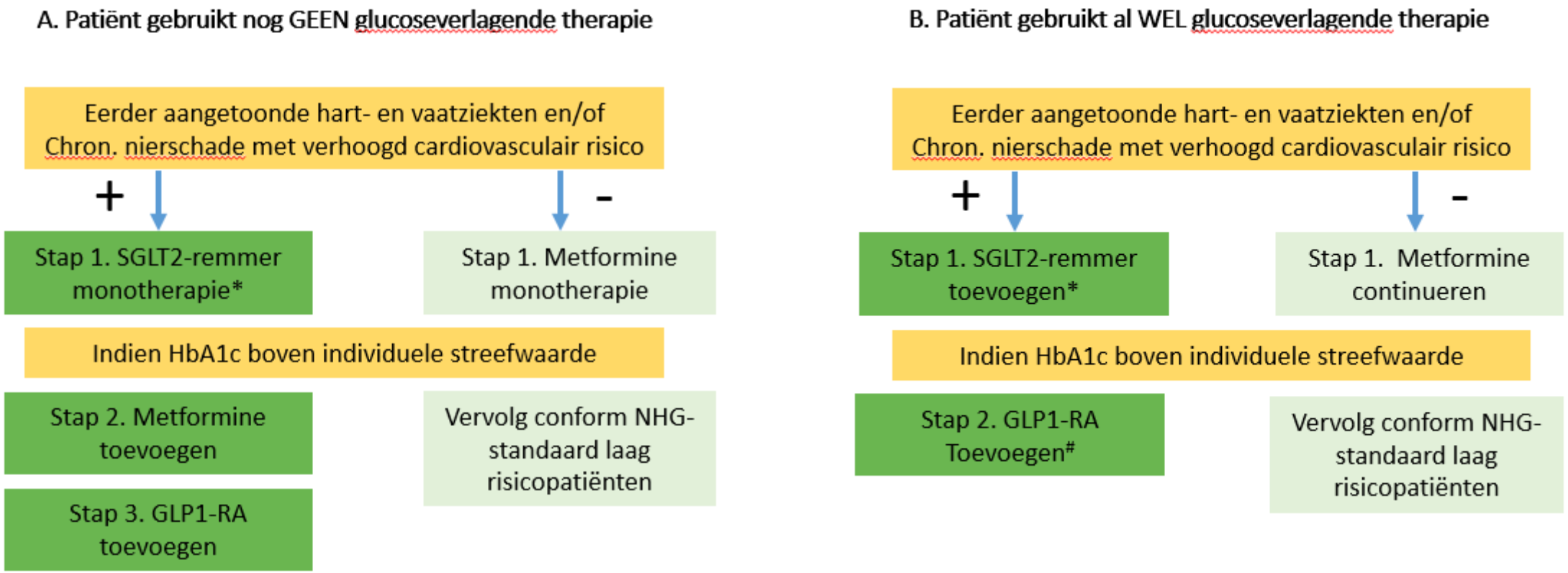
Patiënten met chronische nierschade



Patiënten met eerder doorgemaakte hart- en vaatziekten & Chronische nierschade

Patiënten met hartfalen en EF < 40%

Stappenplan



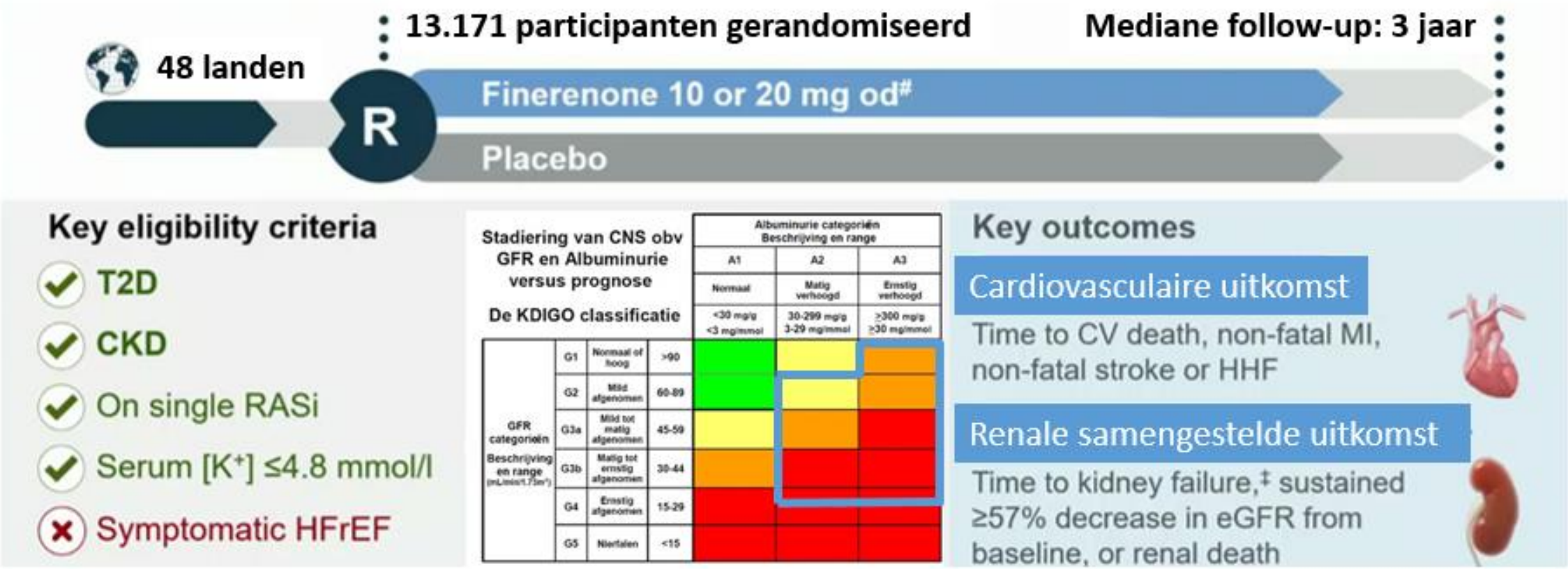
Voeg een GLP1-receptoragonist toe bij contra-indicatie SGLT2-remmer
*Bij de zeer hoog risicopatiënten vervalt het criterium BMI > 30 kg/m^2

Mineralocorticoid receptor antagonisten

	Spironolactone	Eplerenone	Finerenone
Chemistry	Steroidal		Non – steroidal, Dihydropyridine
Distribution	Higher concentrations in renal tissue in comparison to cardiac tissue.		Distributed relatively equally between the heart and the kidney.
Mineralocorticoid receptor	24	990	18
Glucocorticoid receptor	2400	22,000	>10,000
Androgen receptor	77	21,200	>10,000
Progesterone receptor	740	31,200	>10,000

*lagere waardes: sterkere remming

Finerenon, T2DM & CNS: FIDELITY gepoolde analyse



European Heart Journal (2022) 43, 474–484

CVRM optimaal op baseline

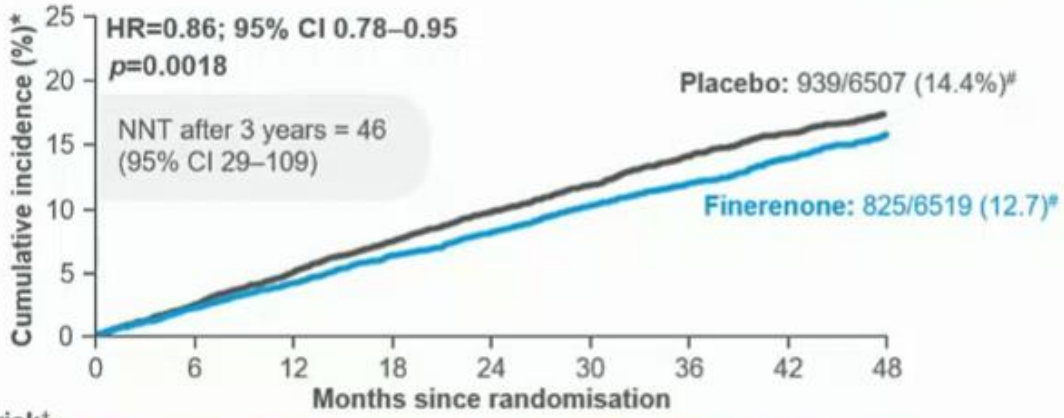
Characteristic	Total (N=13,026)
Age, years	64.8
Male, %	69.8
Duration of T2D, years	15.4
HbA1c, %	7.7
SBP/DBP, mmHg	137/76
History of CV disease, n (%)	5935 (45.6)
History of HF, n (%)	1007 (7.7)
Serum [K^+], mmol/l	4.4

Medications, n (%)	Total (N=13,026)
CV medications	
RASis	13,003 (100)
Statins	9399 (72.2)
Beta blockers	6504 (49.9)
Calcium antagonists	7358 (56.5)
Diuretics	6710 (51.5)
Glucose-lowering therapies	12,720 (97.7)
Metformin	7557 (58.0)
Insulin	7630 (58.6)
GLP-1RAs	944 (7.2)
SGLT-2is	877 (6.7)

European Heart Journal (2022) 43, 474–484

Cardiovasculaire uitkomst

Time to CV death, nonfatal MI, nonfatal stroke, or HHF

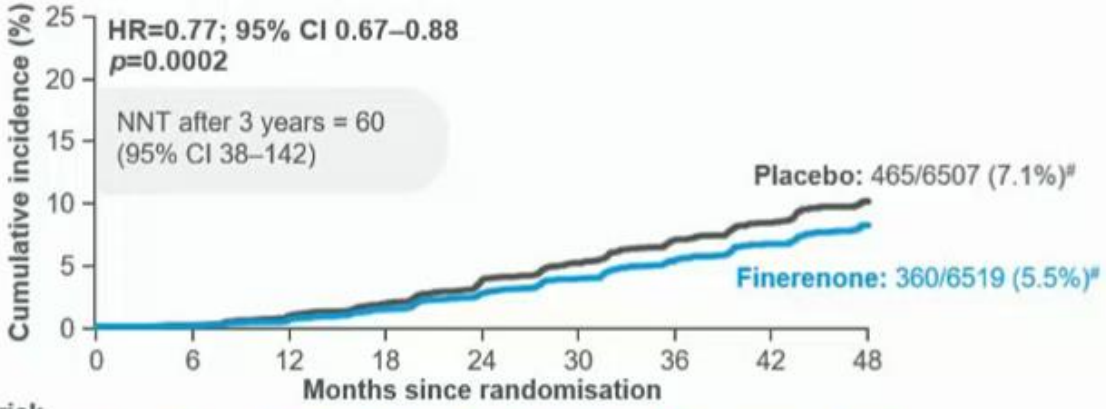


No. at risk‡									
Finerenone	6519	6360	6202	6009	5273	4207	3065	2187	1087
Placebo	6507	6330	6125	5938	5184	4147	2969	2135	1082

14% reduced **risk of CV morbidity and mortality** versus placebo

Renale samengestelde uitkomst

Time to kidney failure,* sustained ≥57% decrease in eGFR from baseline, or kidney-related death



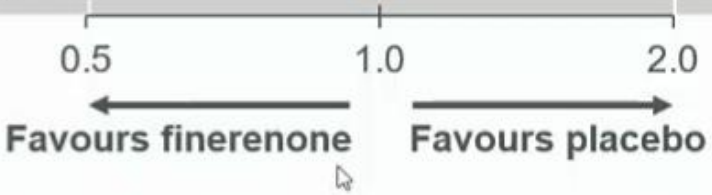
No. at risk									
Finerenone	6519	6291	6107	5848	5027	3973	2815	2024	959
Placebo	6507	6292	6071	5815	4949	3932	2798	1988	962

23% reduced **risk of CKD progression** § versus placebo

European Heart Journal (2022) 43, 474–484

Cardiovasculaire voordeel gedreven door hospitalisatie voor hartfalen en enigszins sterfte door hart- en vaatziekten

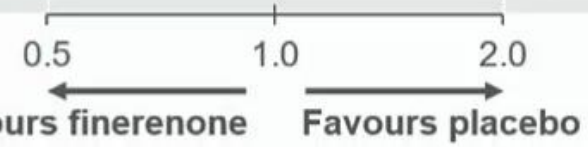
Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	p-value
Composite CV outcome	825 (12.7)	939 (14.4)	0.86 (0.78–0.95)	0.0018
HHF	256 (3.9)	325 (5.0)	0.78 (0.66–0.92)	0.0030
CV death	322 (4.9)	364 (5.6)	0.88 (0.76–1.02)	0.092
Non-fatal MI	173 (2.7)	189 (2.9)	0.91 (0.74–1.12)	0.36
Non-fatal stroke	198 (3.0)	198 (3.0)	0.99 (0.82–1.21)	0.95



European Heart Journal (2022) 43, 474–484

Renale voordeel gedreven door alle niet fatale uitkomsten

Outcome	Finerenone (n=6519) n (%)	Placebo (n=6507) n (%)	HR (95% CI)	p-value
eGFR 57% composite kidney outcome	360 (5.5)	465 (7.1)	0.77 (0.67–0.88)	0.0002
Kidney failure	254 (3.9)	297 (4.6)	0.84 (0.71–0.99)	0.039
ESKD*	151 (2.3)	188 (2.9)	0.80 (0.64–0.99)	0.040#
eGFR <15 ml/min/1.73 m^2‡	195 (3.0)	237 (3.6)	0.81 (0.67–0.98)	0.026#
≥57% decrease in eGFR from baseline‡	257 (3.9)	361 (5.5)	0.70 (0.60–0.83)	<0.0001
Renal death	2 (<0.1)	4 (<0.1)	0.53 (0.10–2.91)	0.46#



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≥57% afname in eGFR = verdubbeling van kreatinine
ESKD = dialyse of transplantatie

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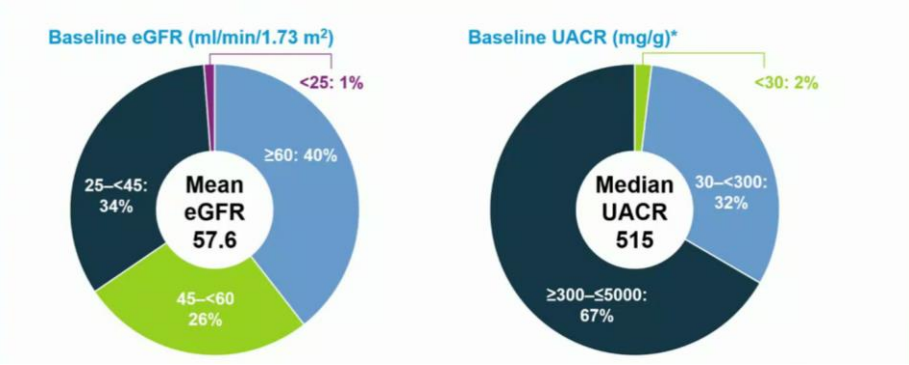
Datum 4 april 2022
Betreft GVS-advies finerenon (Kerendia®)

Onze referentie
2022012185

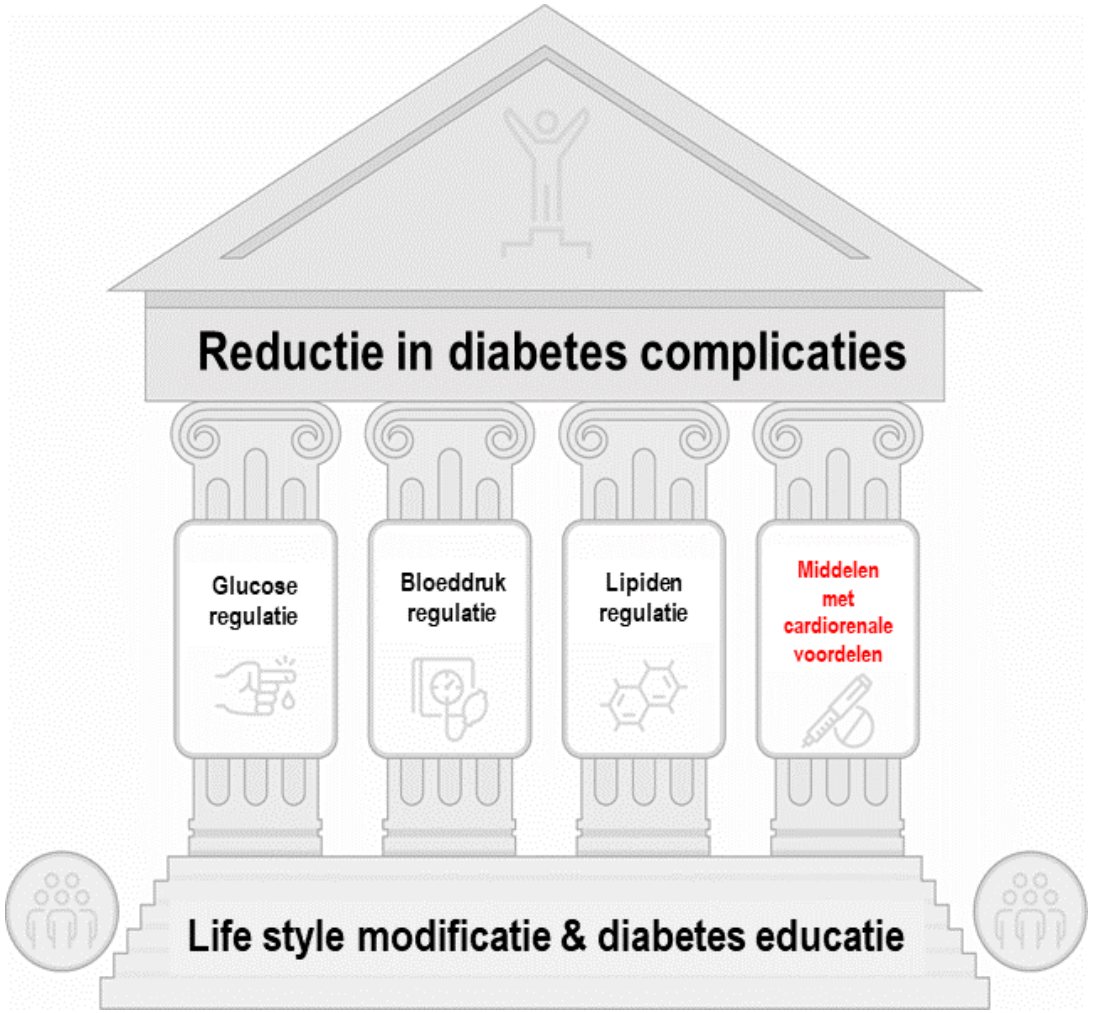
Geachte heer Kuipers,

40% had albuminurie met een normale nierfunctie (eGFR ≥ 60 ml/min/1.73m2)



Ondergetekende heeft finerenon voorgeschreven aan een verzekerde			Kolom 1*	Kolom 2*
1	van 18 jaar of ouder	☐ JA, ga naar 2 ☐ NEE		XO
2	met diabetes mellitus type 2	☐ JA, ga naar 3 ☐ NEE		XO
3	en bij wie sprake is van chronische nierschade (CNS stadium 3 en 4 met albuminurie)	☐ JA ☐ NEE	36	XO

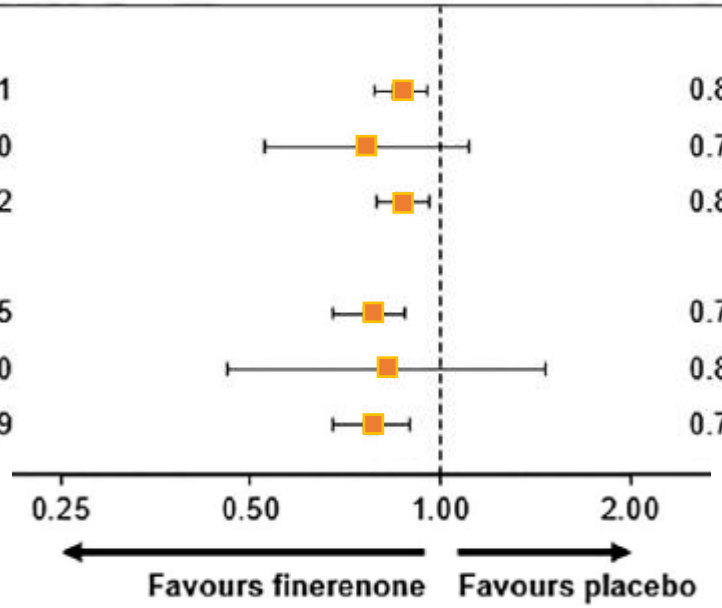
https://www.zorginstituutnederland.nl/publicaties/adviezen/2022/04/04/gvs-advies-finerenon-kerendia



- SGLT2-remmers
- GLP1-RA
- Finerenon

Finerenon reduceert het risico op cardiovasculaire en renale uitkomsten, onafhankelijk van GLP1-RA gebruik

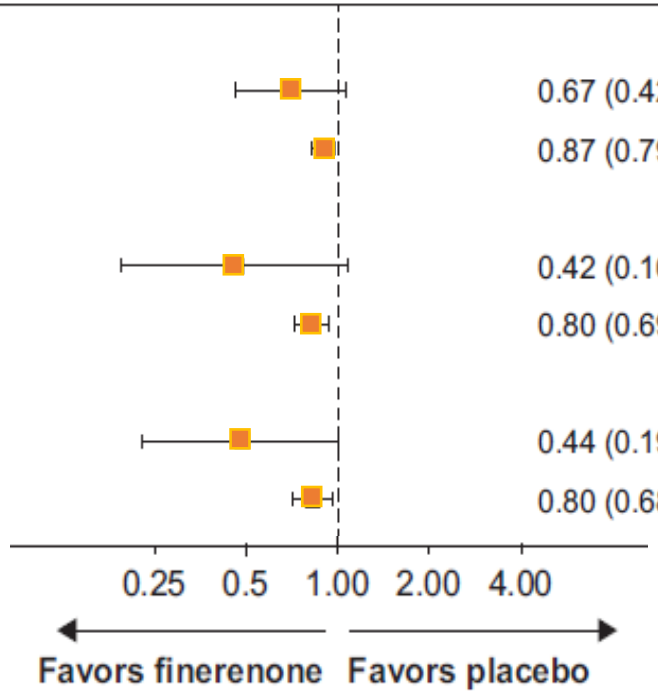
	Finerenone	Placebo	Finerenone	Placebo	Hazard ratio (95% CI)	$p_{interaction}$
	n/N (%)		n per 100 PY			
Cardiovascular composite						
Overall	825/6519 (12.6)	939/6507 (14.4)	4.34	5.01	0.86 (0.78, 0.95)	
GLP-1RA use at baseline	58/497 (11.7)	64/447 (14.3)	3.79	4.90	0.76 (0.52, 1.11)	0.63
No GLP-1RA use at baseline	767/6022 (12.7)	875/6060 (14.4)	4.38	5.02	0.87 (0.79, 0.96)	
Kidney composite (eGFR ≥ 57%)						
Overall	360/6519 (5.5)	465/6507 (7.1)	1.96	2.55	0.77 (0.67, 0.88)	
GLP-1RA use at baseline	22/497 (4.4)	27/447 (6.0)	1.47	2.10	0.82 (0.45, 1.48)	0.79
No GLP-1RA use at baseline	338/6022 (5.6)	438/6060 (7.2)	2.01	2.59	0.77 (0.67, 0.89)	



Diabetes Obes Metab. 2022 Oct 4. doi: 10.1111/dom.14883. Online ahead of print.

Finerenon reduceert het risico op cardiovasculaire en renale uitkomsten, onafhankelijk van SGLT2-remmer gebruik

	Finerenone	Placebo	Finerenone	Placebo	HR (95% CI)	$P_{interaction}$
	n/*N* (%)		*n* per 100 PY			
Analysis for outcomes in patients receiving/not receiving an SGLT2i at baseline						
Cardiovascular composite						
SGLT2i at baseline	39/438 (8.9)	52/439 (11.8)	2.95	4.08	0.67 (0.42–1.07)*	0.46†
No SGLT2i at baseline	786/6,081 (12.9)	887/6,068 (14.6)	4.44	5.08	0.87 (0.79–0.96)*	
Kidney composite						
SGLT2i at baseline	9/438 (2.1)	17/439 (3.9)	0.70	1.37	0.42 (0.16–1.08)*	0.29†
No SGLT2i at baseline	351/6,081 (5.8)	448/6,068 (7.4)	2.06	2.64	0.80 (0.69–0.92)*	
Hospitalization for heart failure						
SGLT2i at baseline	10/438 (2.3)	22/439 (5.0)	0.74	1.68	0.44 (0.19–0.99)*	0.18†
No SGLT2i at baseline	246/6,081 (4.0)	303/6,068 (5.0)	1.35	1.68	0.80 (0.68–0.95)*	



Diabetes Care. 2022 Aug 15;dc220294. doi: 10.2337/dc22-0294. Online ahead of print.

Combinatie SGLT2-remmer & MRA/Finerenon beter?

MIRACLE[1]

MIRACLE is a **phase II dose–response** study that aims to evaluate the efficacy and safety of an **MRA in combination with dapagliflozin** compared with **dapagliflozin alone** on **reducing UACR** in patients with **HF** (LVEF <60%) and **CKD** (eGFR ≥20–≤60 ml/min/1.73 m^2)

Estimated primary completion: June 2023

CONFIDENCE[2]

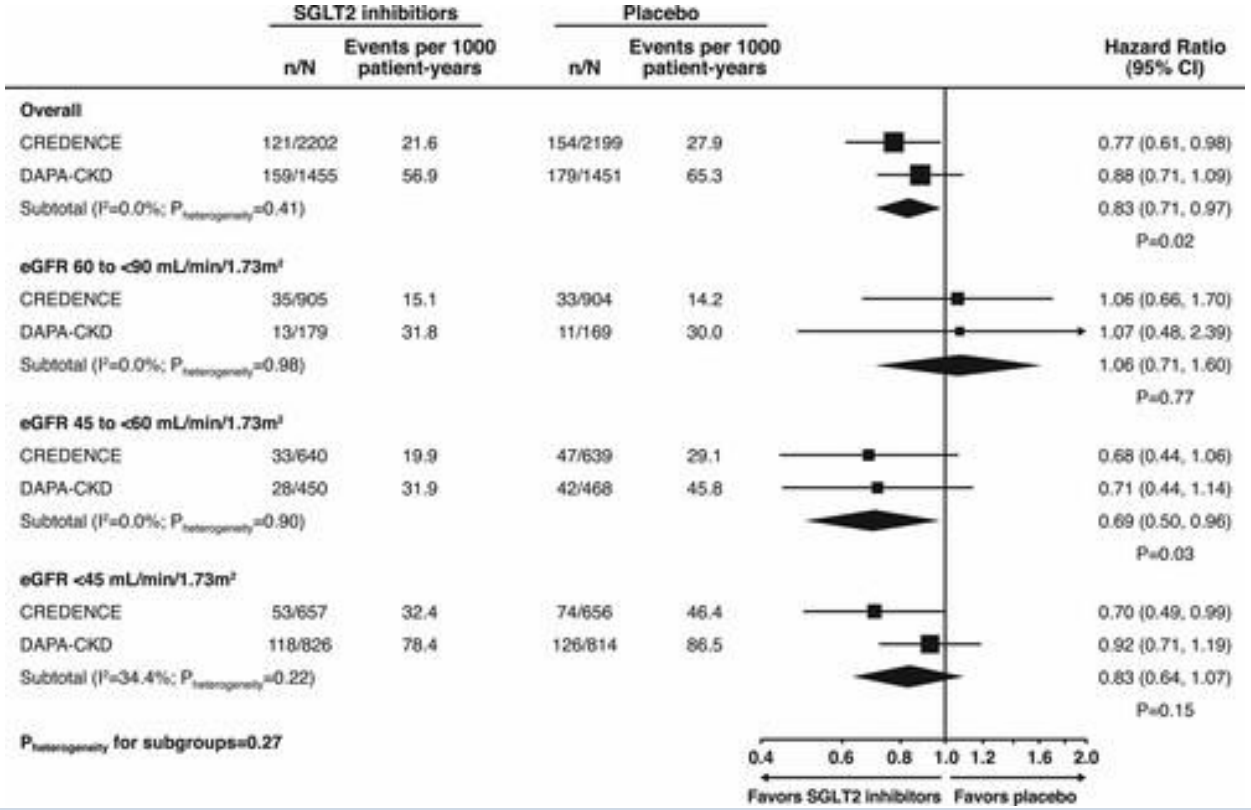
CONFIDENCE is a **phase II study** that aims to assess the effect of **combination of finerenone and empagliflozin** on **reducing UACR** compared with **empagliflozin alone or finerenone alone** in patients with **CKD and T2D** (eGFR 40–90 ml/min/1.73 m^2 and UACR ≥300–<5000 mg/g)

Estimated primary completion: December 2023

Combinatie SGLT2-remmer & Finerenon veiliger?
SGLT2-remmer vermindert hyperkaliëmie

HyperK+	Treatment discontinuation due to HyperK+
14.0%	1.7%
6.9%	0.6%

Serious hyperkalemia
(central laboratory-determined serum potassium ≥6.0 mmol/L)



European Heart Journal (2022) 43, 474–484
Circulation. 2022;145:1460–1470

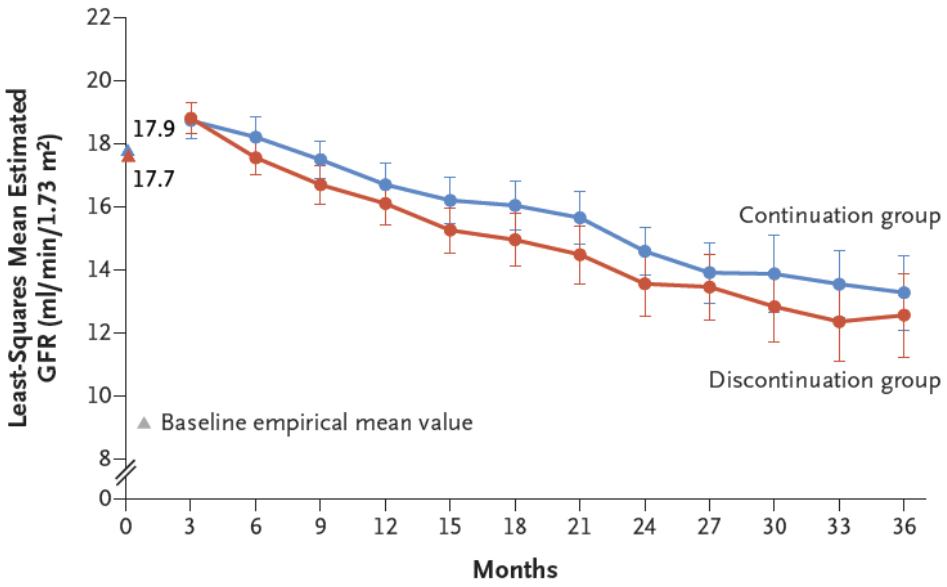
Hyperkaliëmie een probleem?

ORIGINAL ARTICLE

Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease

Sunil Bhandari, Ph.D., Samir Mehta, M.Sc., Arif Khwaja, Ph.D., John G.F. Cleland, M.D., Natalie Ives, M.Sc., Elizabeth Brettell, B.Sc., Marie Chadburn, Ph.D., and Paul Cockwell, Ph.D., for the STOP ACEi Trial Investigators*

A Primary Outcome



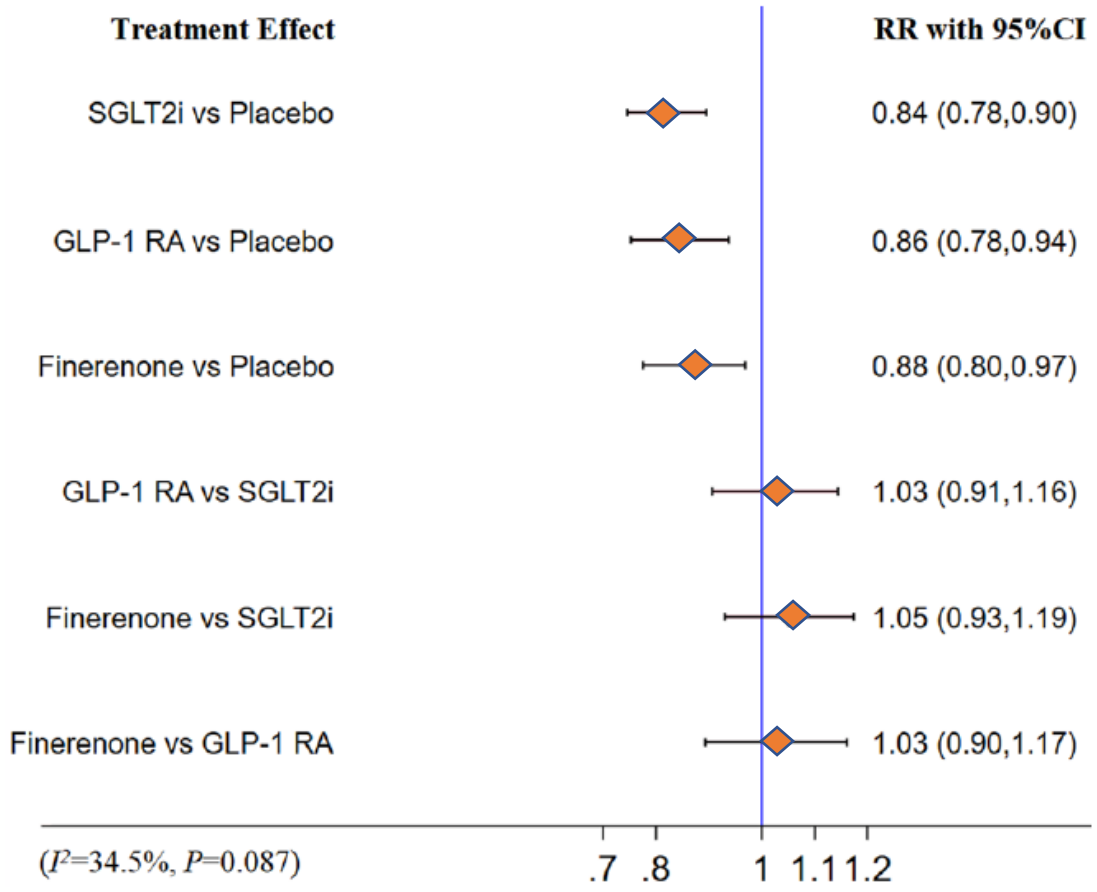
B Subgroup Analysis of the Primary Outcome at Yr 3

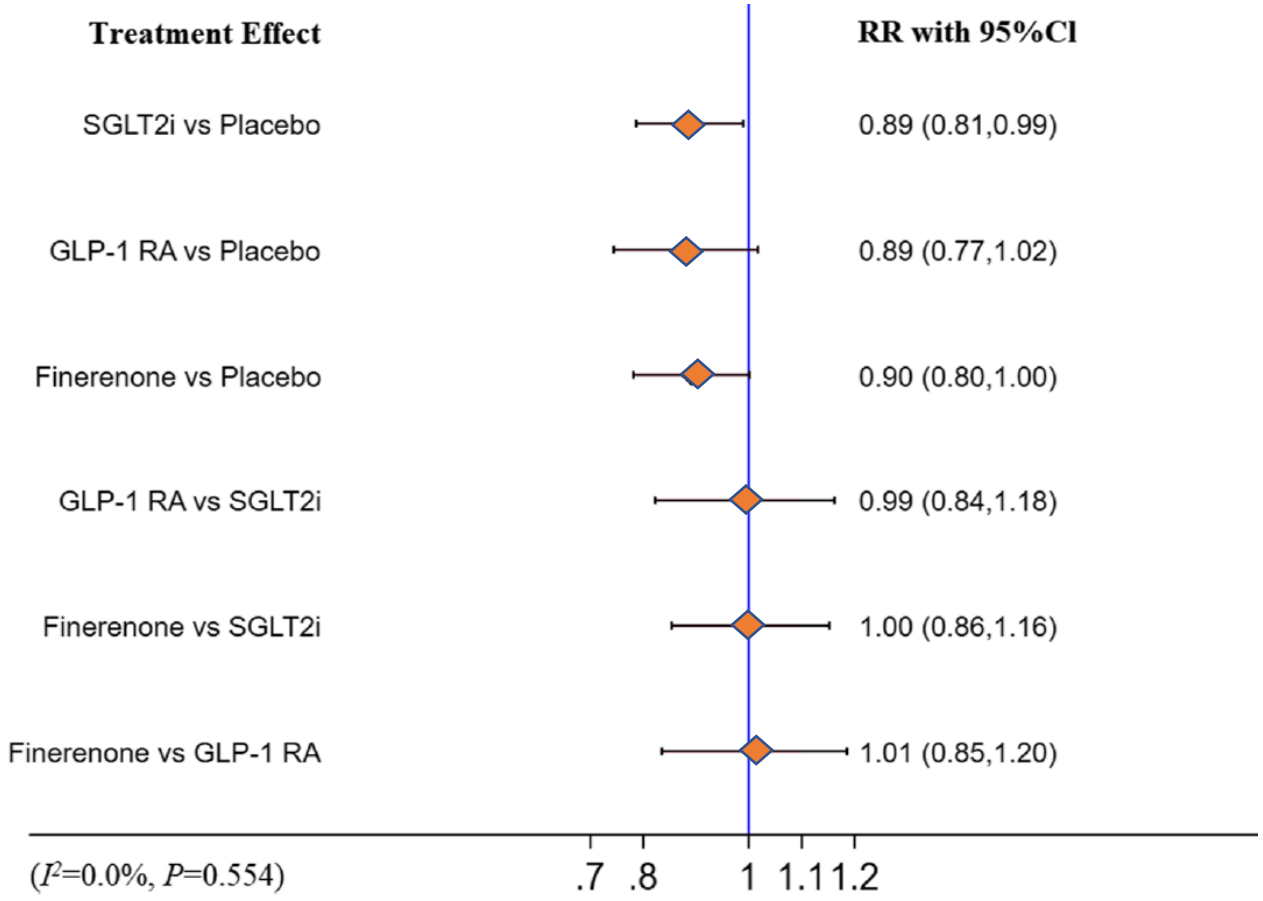
Subgroup	Discontinuation Group	Continuation Group	Mean Difference in Estimated GFR at 3 Yr (95% CI)
	no. of patients		
Diabetes			
Type 1	9	11	2.89 (−1.22 to 6.99)
Type 2	66	67	−0.24 (−3.33 to 2.84)
None	131	127	−1.36 (−3.57 to 0.84)

N Engl J Med. 2022 Dec 1;387(22):2021-2032.

Advanced and progressive chronic kidney disease
(eGFR <30 ml per minute per 1.73 m2)

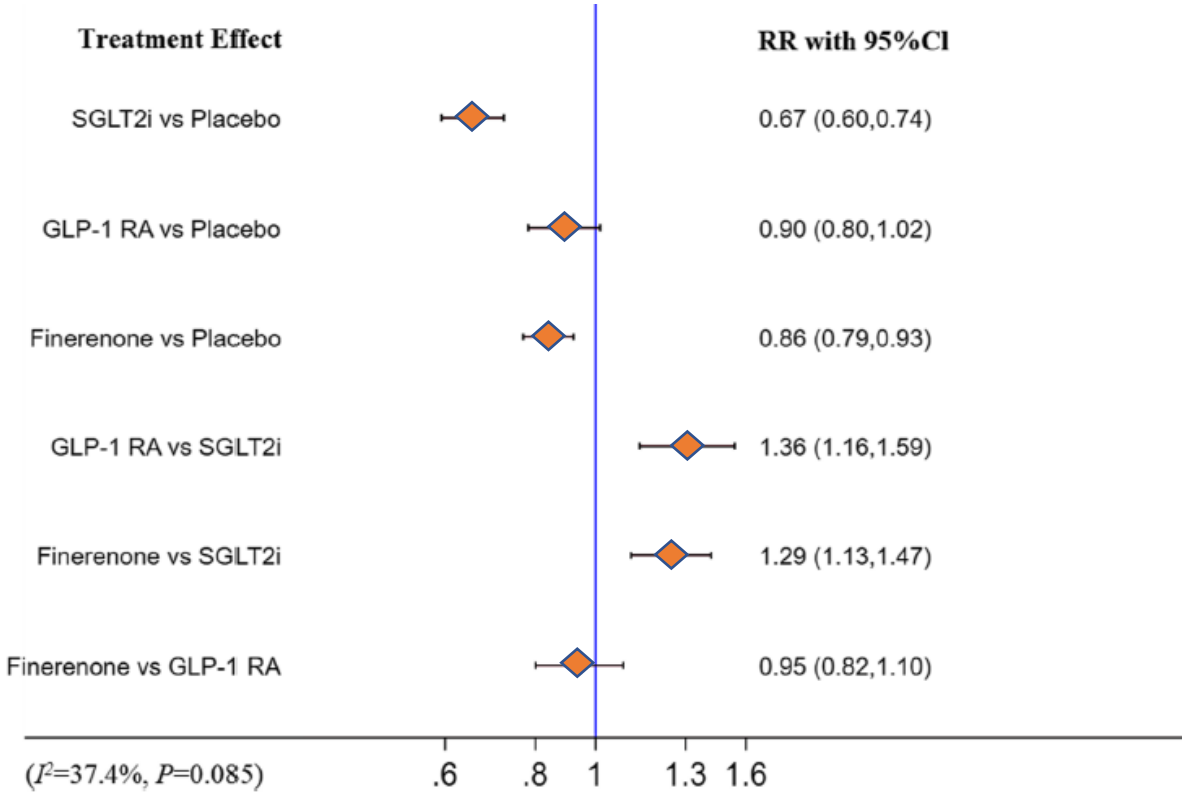
Vergelijkbaar in MACE & Totale Sterfte bij Patiënten met T2DM en Chronische Nierschade

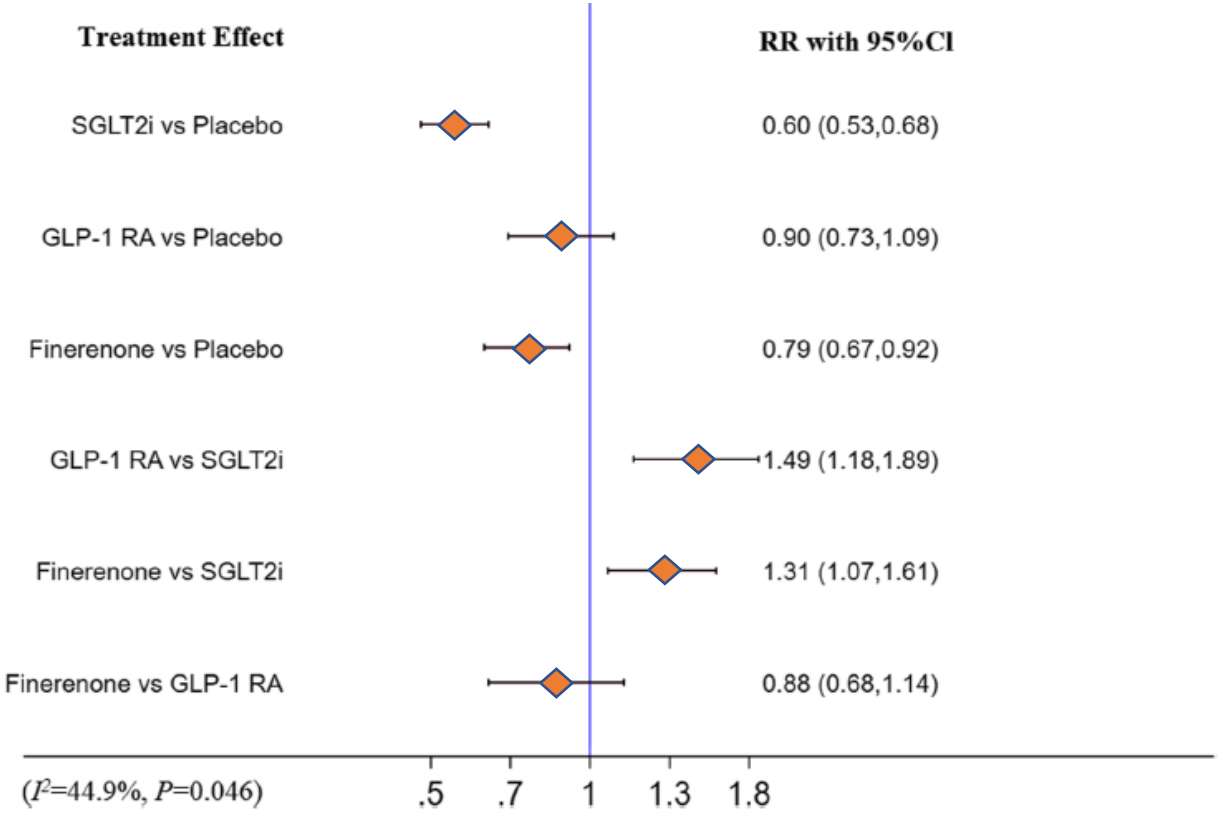




Cardiovasc Diabetol. 2022 Nov 5;21(1):232. doi: 10.1186/s12933-022-01676-5.

SGLT2-remmer Beter in Voorkomen Renale Uitkomsten & Hospitalisatie voor Hartfalen bij Patiënten met T2DM en Chronische Nierschade



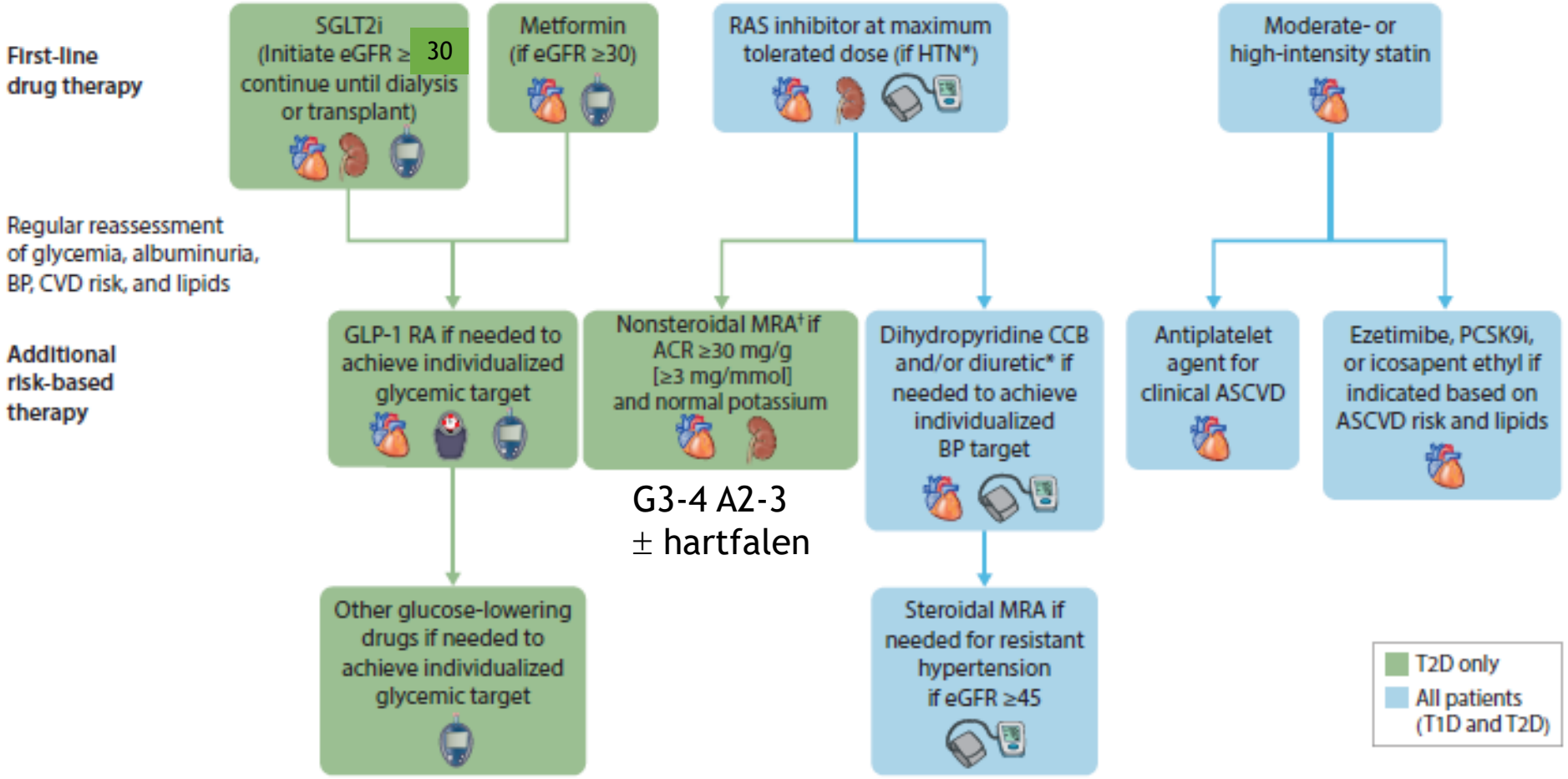


Cardiovasc Diabetol. 2022 Nov 5;21(1):232. doi: 10.1186/s12933-022-01676-5.

Renal outcome: a composite of a sustained decrease of at least 40% in the eGFR from the baseline or a doubling of the serum creatinine level, kidney failure (a composite of end-stage kidney disease or sustained decrease in eGFR to < 15 ml/min/1.73 m2),or renal death

Conclusie KDIGO-guideline

Eerder aangetoonde hart- en vaatziekten en/of
Chron. nierschade met verhoogd cardiovasculair risico



Kidney Int. 2022 Nov;102(5):990-999