SGLT2 remmers bij CKD zonder proteinurie: Is er genoeg evidence

Nee!

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Papendal December 2022

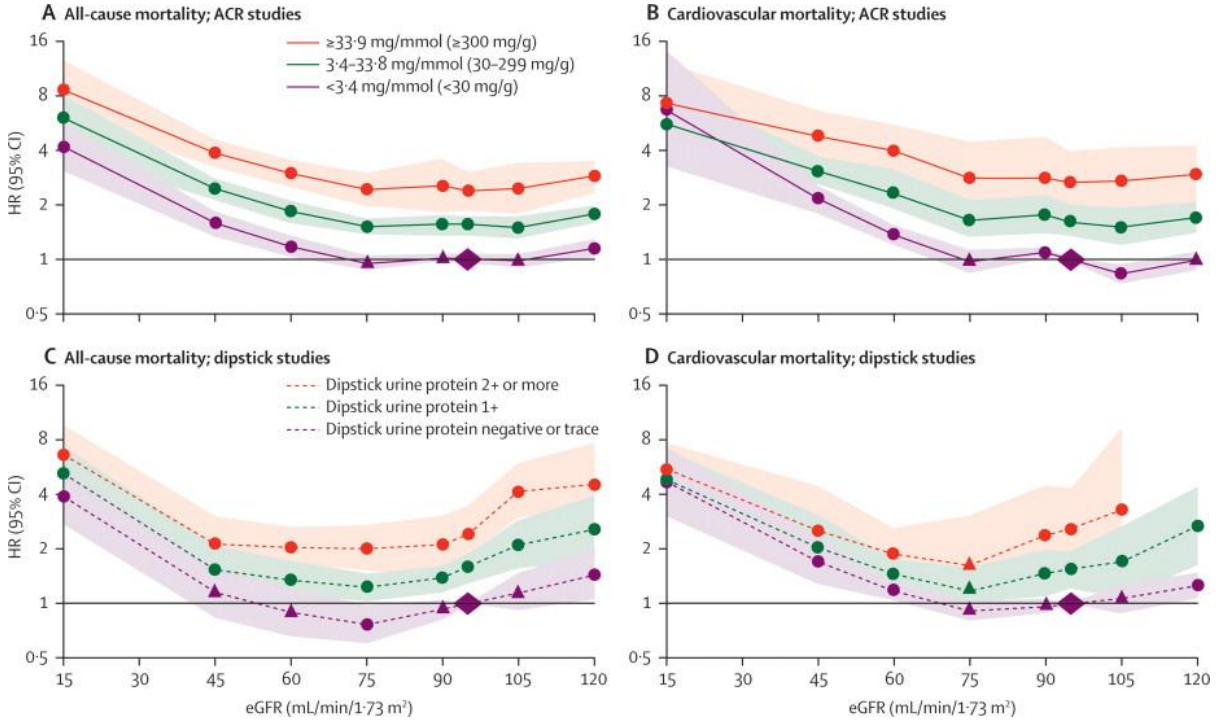
Disclosures

- Pharmaceutical industry
  - Lecture fees (*all to institution*), scientific support and advisor for: VFMCRP and Vifor, Shire, Bayer, Kissei, Cablon Medical; all companies involved in marketing or developing phosphate-lowering drugs
  - Scientific support from: Amgen, NedMag (*all to institution*) and FMC
  - Advisory board of: Otsuka, Astra-Zeneca, Vifor, Unicycive, Inozyme (*fees to institution*)

- Member of
  - KDIGO committee on CKD-MBD

Ik ben al eens verslagen

Invloed eGFR en albuminurie op (CV) sterfte

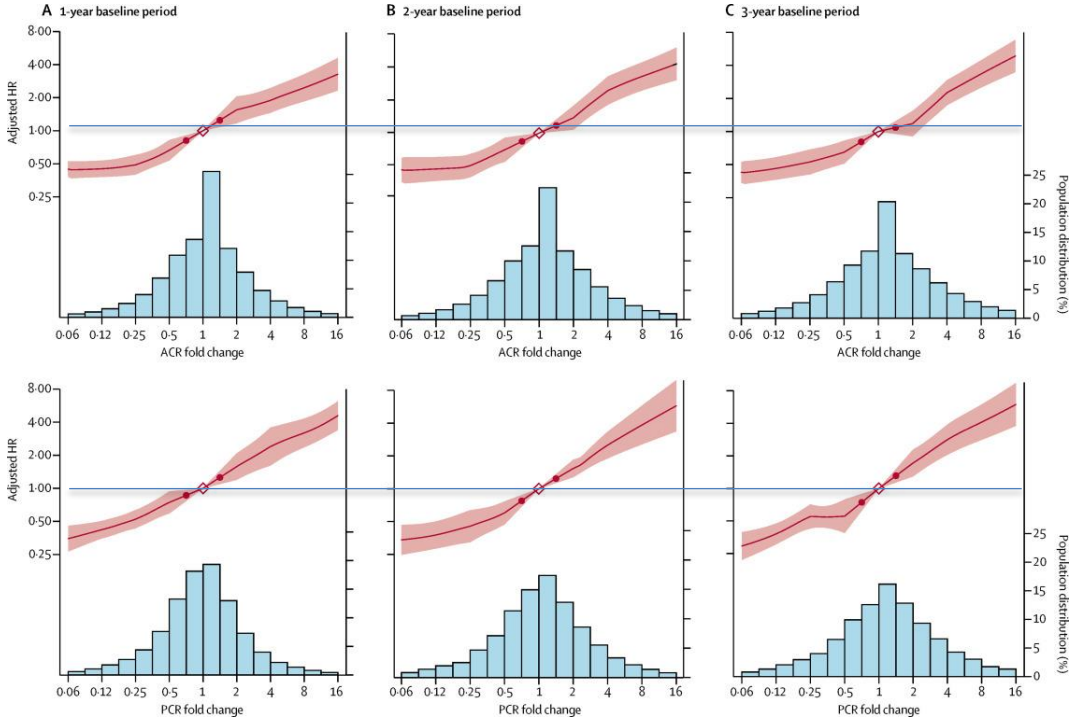


CKD prognosis consortium, Lancet 2010

Risico op ESKD en Δ albuminurie

Beloop albuminurie

Beloop proteinurie



Coresh, Lancet DE 2019

HLH was mede-auteur!

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dapagliflozin in Patients with Chronic Kidney Disease

Hiddo J.L. Heerspink, Ph.D., Bergur V. Stefánsson, M.D., Ricardo Correa-Rotter, M.D., Glenn M. Chertow, M.D., Tom Greene, Ph.D., Fan-Fan Hou, M.D., Johannes F.E. Mann, M.D., John J.V. McMurray, M.D., Magnus Lindberg, M.Sc., Peter Rossing, M.D., C. David Sjöström, M.D., Roberto D. Toto, M.D., Anna-Maria Langkilde, M.D., and David C. Wheeler, M.D., for the DAPA-CKD Trial Committees and Investigators*

Pro-con debat SGLT2 remmers?

Baseline karakteristieken

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Dapagliflozin (N=2152)	Placebo (N=2152)
Age — yr	61.8±12.1	61.9±12.1
Estimated GFR		
Mean — ml/min/1.73 m^2	43.2±12.3	43.0±12.4
Distribution — no. (%)		
≥60 ml/min/1.73 m^2	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m^2	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m^2	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m^2	293 (13.6)	331 (15.4)
Urinary albumin-to-creatinine ratio§		
Median (interquartile range)	965 (472–1903)	934 (482–1868)
>1000 — no. (%)	1048 (48.7)	1031 (47.9)

Dapa-CKD

Prognosis of CKD by GFR and Albuminuria Categories

GFR categories (ml/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012

Inclusie-criterium

Gerecruteerd:

- eGFR: mean ±SD
- Albuminuria: Median ± IQR

Subgroep analyse

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of participants/total no.		
All participants	197/2152	312/2152	0.61 (0.51–0.72)
Urinary albumin-to-creatinine ratio			
≤1000	44/1104	84/1121	0.54 (0.37–0.77)
>1000	153/1048	228/1031	0.62 (0.50–0.76)

Even effectief?

Numbers needed to treat

UACR	Absolute risico dapa	Absolute risico placebo	NNT
≤1000	4,0%	7,5%	29
>1000	14,6%	22,1%	18

NNT om welke events te voorkomen?

Gedurende 2,4 jaar (IQR 2,0-2,7)

Outcome	Dapagliflozin		Placebo	
	no./total no. (%)	*events/100 patient-yr*	*no./total no. (%)*	
Primary outcome				
Primary composite outcome	197/2152 (9.2)	4.6	312/2152 (14.5)	
Decline in estimated GFR of ≥50%	112/2152 (5.2)	2.6	201/2152 (9.3)	89
End-stage kidney disease	109/2152 (5.1)	2.5	161/2152 (7.5)	
Estimated GFR of <15 ml/min/1.73 m^2	84/2152 (3.9)	1.9	120/2152 (5.6)	36
Long-term dialysis†	68/2152 (3.2)	1.5	99/2152 (4.6)	31
Kidney transplantation†	3/2152 (0.1)	0.1	8/2152 (0.4)	
Death from renal causes	2/2152 (<0.1)	0.0	6/2152 (0.3)	
Death from cardiovascular causes	65/2152 (3.0)	1.4	80/2152 (3.7)	15

Heerspink, N Engl J Med 2021

Zorginstituut Nederland

kleiner is en de follow-up duur korter. De EMA geeft hierbij aan dat het de verwachting is dat dapagliflozine ook werkzaam is bij patiënten met een lagere UACR. Uit subgroepanalyses van de DAPA-CKD studie blijkt in ieder geval dat het effect van dapagliflozine op de samengestelde, primaire, renale uitkomstmaat consistent is ongeacht het wel/niet hebben van DM2, het wel/niet hebben van hartfalen, de nierfunctie (<45 of ≥45 ml/min/1,73m^2), de UACR (≤1000 of >1000) en de etiologie van de nierziekte. Tevens blijkt uit subgroepanalyses van de

Onderdeel van de beoordeling van geneesmiddelen voor
opname in het geneesmiddelenvergoedingssysteem (GVS)

Datum Maart 2022
Status Definitief

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin in Patients with Chronic Kidney Disease

The EMPA-KIDNEY Collaborative Group*

EMPA-Kidney

Prognosis of CKD by GFR and Albuminuria Categories

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Inclusie-criterium

Gerecruteerd:

- eGFR: mean ±SD
- Albuminuria: Median ± IQR

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Primaire eindpunt

Samengesteld: Eerste optreden van:

- Cardiovasculaire sterfte
- Bijvende eGFR<10
- Start dialyse of niertransplantatie
- Blijvende achteruitgang eGFR van minstens 40%
- (“renal death”)

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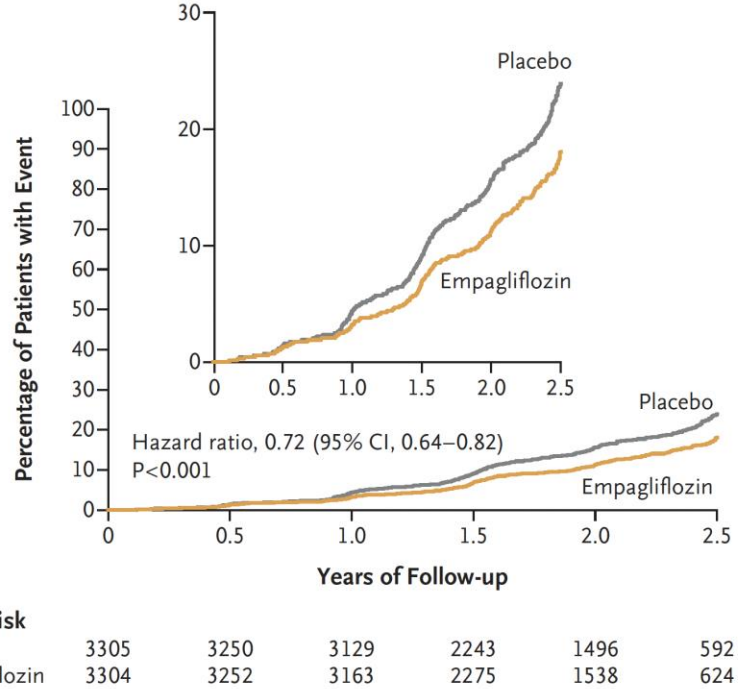
Primaire uitkomst



- 13,1% Empagliflozine
- 16,9% Placebo
- NNT: 26, gedurende 2,0 jaar (mediaan)

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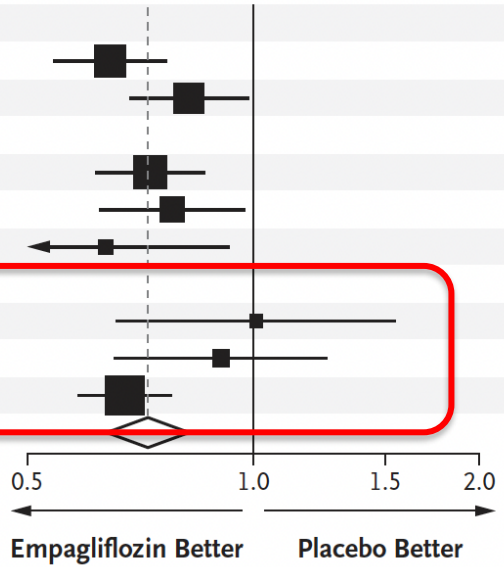
Empa-Kidney: subgroep analyse primaire eindpunt

Subgroup	Empagliflozin (no. of patients with event/total no.)	Placebo (no. of patients with event/total no.)	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
Diabetes mellitus			
Present	218/1525	306/1515	0.64 (0.54–0.77)
Absent	214/1779	252/1790	0.82 (0.68–0.99)
Estimated GFR			
<30 ml/min/1.73 m^2	247/1131	317/1151	0.73 (0.62–0.86)
≥30 to <45 ml/min/1.73 m^2	140/1467	175/1461	0.78 (0.62–0.97)
≥45 ml/min/1.73 m^2	45/706	66/693	0.64 (0.44–0.93)
Urinary albumin-to-creatinine ratio			
<30	42/665	42/663	1.01 (0.66–1.55)
≥30 to ≤300	67/927	78/937	0.91 (0.65–1.26)
>300	323/1712	438/1705	0.67 (0.58–0.78)
All patients	432/3304	558/3305	0.72 (0.64–0.82)



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Secundaire uitkomsten

Table 2. Primary, Secondary, and Safety Outcomes.

Outcome	Empagliflozin (N = 3304)		Placebo (N = 3305)		Hazard Ratio (95% CI)*	P Value
	no. (%)	*no. of events/100 patient-yr*	*no. (%)*	*no. of events/100 patient-yr*		
Key secondary outcomes†						
Hospitalization for heart failure or death from cardiovascular causes	131 (4.0)	2.04	152 (4.6)	2.37	0.84 (0.67–1.07)	0.15
Hospitalization for any cause‡	—	24.8	—	29.2	0.86 (0.78–0.95)	0.003
Death from any cause	148 (4.5)	2.28	167 (5.1)	2.58	0.87 (0.70–1.08)	0.21

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CKD progressie en CV sterfte

Figure S2a. Kidney Disease Progression

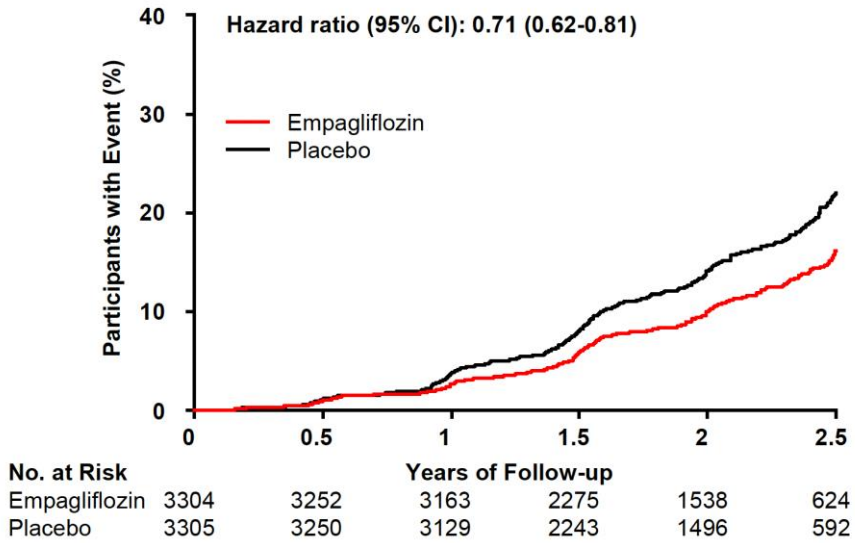
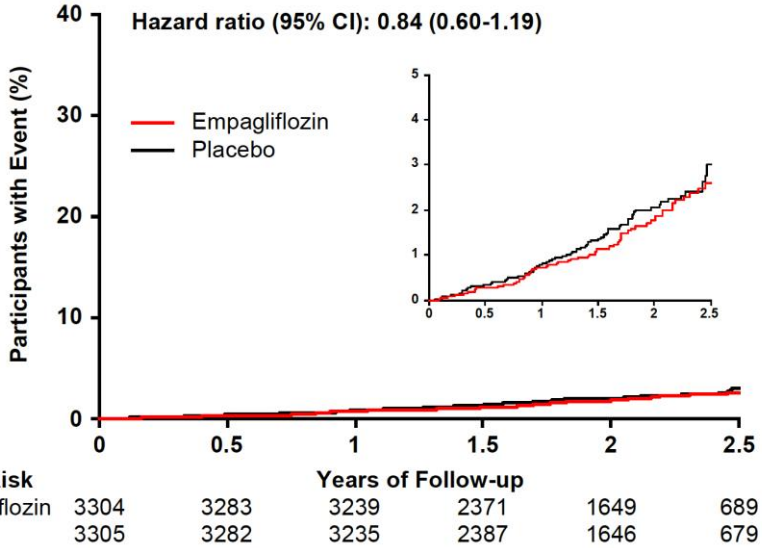


Figure S2b. Death from Cardiovascular Causes



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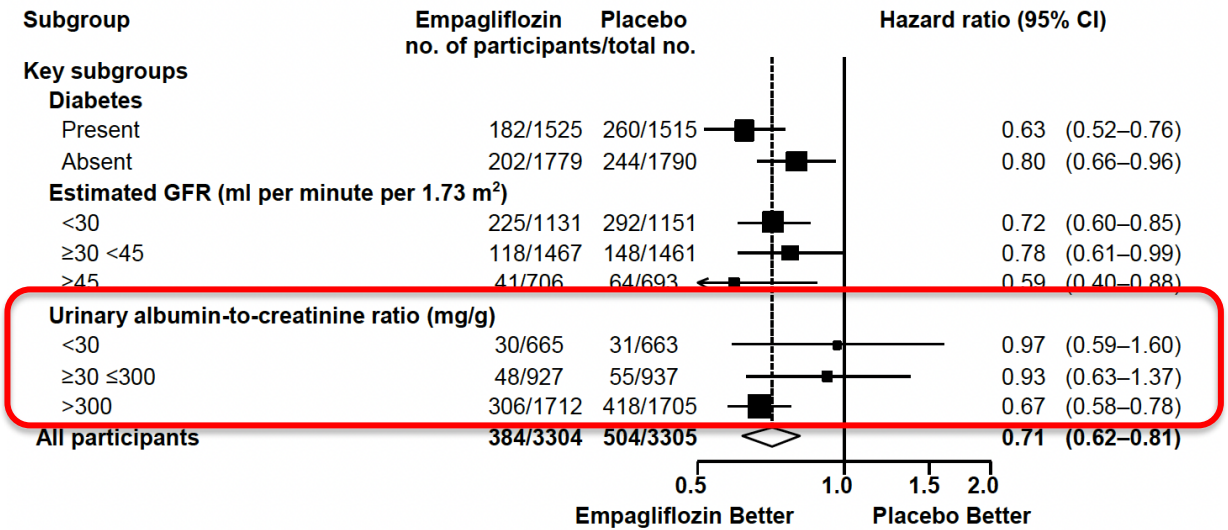
CKD progressie in subgroepen

Figure S5. Kidney Disease Progression by Key Prespecified Subgroups (Prespecified Exploratory Outcome)



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Pre-specified analyse DECLARE-TIMI

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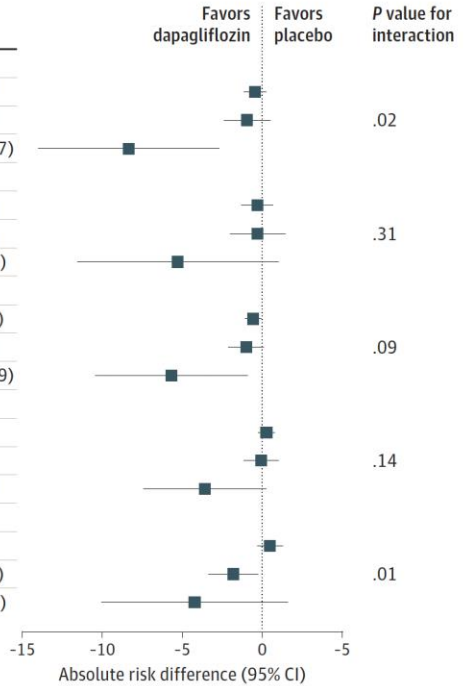
Subgroup	Dapagliflozin (n=8429) Events, No.	Dapagliflozin (n=8429) Events/ 1000 patient-years	Placebo (n=8413) Events, No.	Placebo (n=8413) Events/ 1000 patient-years	Absolute risk difference (95% CI)	P value for interaction
CV death plus HHF						
eGFR ≥60 and UACR <30	186	8.4	211	9.6	-0.5 (-1.2 to 0.2)	
eGFR <60 or UACR ≥30	202	19.2	224	21.9	-1.0 (-2.4 to 0.5)	.02
eGFR <60 and UACR ≥30	24	24.8	52	48.8	-8.3 (-14.0 to -2.7)	
MACE						
eGFR ≥60 and UACR <30	397	18.3	413	19.2	-0.3 (-1.3 to 0.7)	
eGFR <60 or UACR ≥30	310	30.3	313	31.3	-0.3 (-2.0 to 1.4)	.31
eGFR <60 and UACR ≥30	37	39.4	58	56.2	-5.3 (-11.6 to 1.0)	
HHF						
eGFR ≥60 and UACR <30	85	3.8	116	5.3	-0.6 (-1.1 to -0.1)	
eGFR <60 or UACR ≥30	106	10.1	131	12.8	-1.0 (-2.1 to 0.1)	.09
eGFR <60 and UACR ≥30	16	16.5	35	33.0	-5.7 (-10.4 to -0.9)	
CV death						
eGFR ≥60 and UACR <30	119	5.3	104	4.6	0.3 (-0.3 to 0.8)	
eGFR <60 or UACR ≥30	116	10.7	116	10.9	-0.1 (-1.2 to 1.0)	.14
eGFR <60 and UACR ≥30	10	9.8	22	19.2	-3.6 (-7.4 to 0.3)	
ACM						
eGFR ≥60 and UACR <30	270	12.0	243	10.8	0.5 (-0.3 to 1.3)	
eGFR <60 or UACR ≥30	223	20.6	267	25.1	-1.8 (-3.3 to -0.2)	.01
eGFR <60 and UACR ≥30	31	30.4	48	41.8	-4.2 (-10.1 to 1.6)	



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SGLT2 remmers bij CKD zonder proteinurie:

- De evidence zegt: NEE!

- Benefit in DECLARE-TIMI (zonder proteinurie) komt door het hogere background CV risico: DM met established CV ziekte of hoog risico

Voor wie SGLT2 remmers?
opinie

- CKD (60-20) met albuminurie (ACR >200) of proteinurie>500 mg/dag (ná optimaliseren ACEi/ARB)
- CKD (eGFR en/of UACR criterium) met DM2 (volgende presentatie: Erik Serné)
- CKD met hartfalen (al dan niet preserved EF)

Het woord is aan Hiddo