Een verhoogd urinezuur: wat nu?

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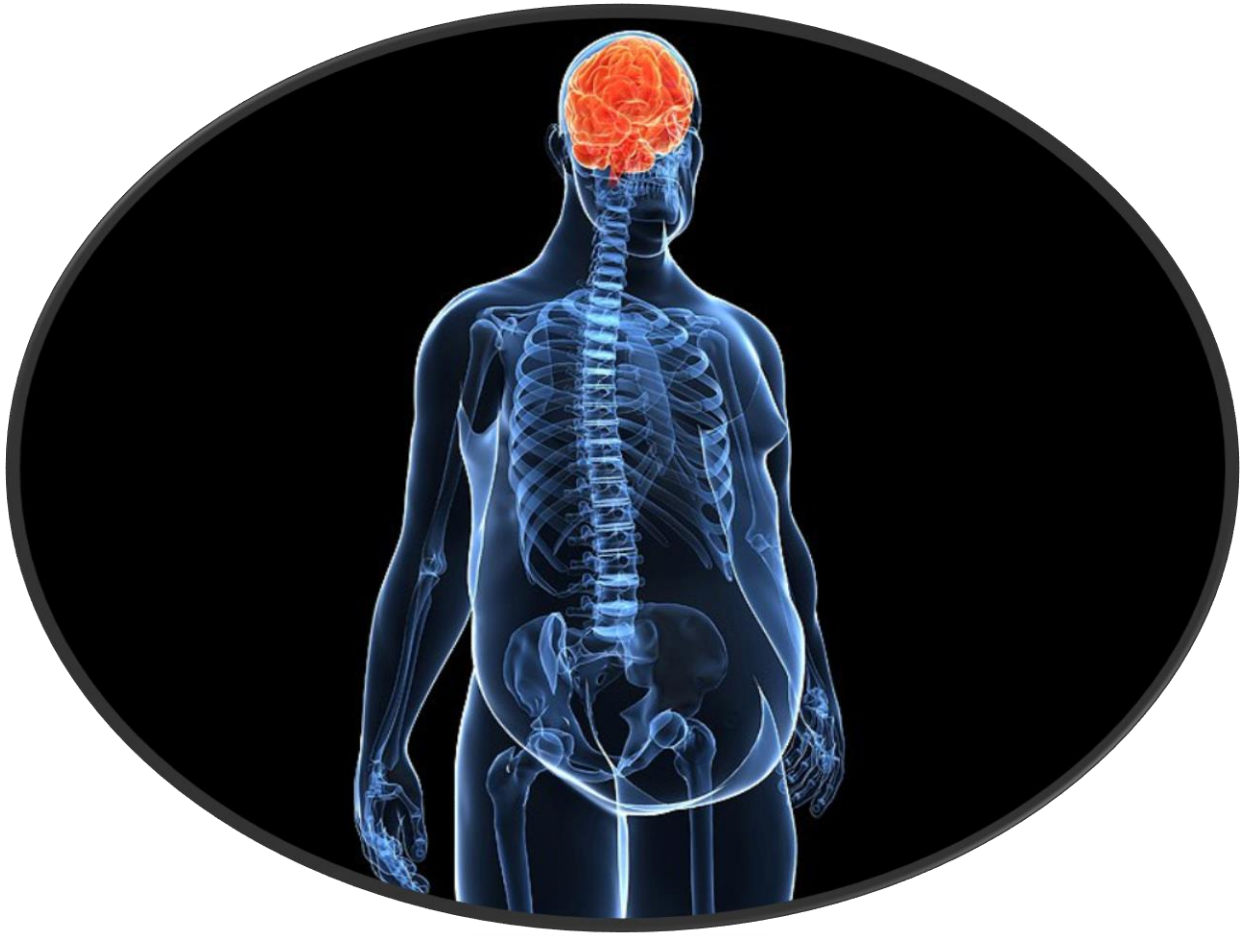
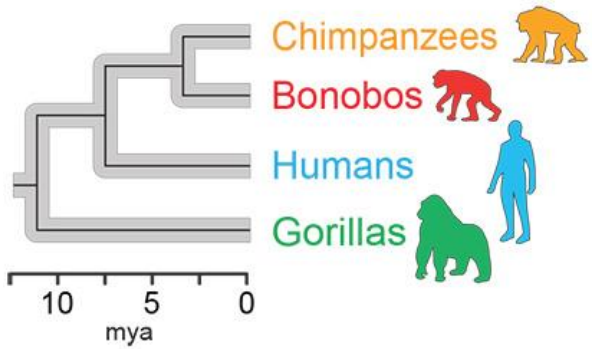
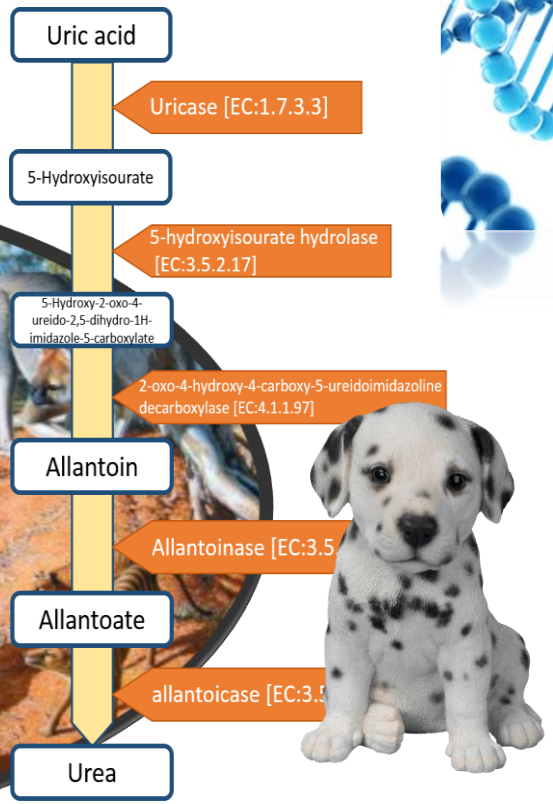
21 februari 2018

Urinezuur en hypertensie: een bewezen relatie



De geschiedenis van urinezuur





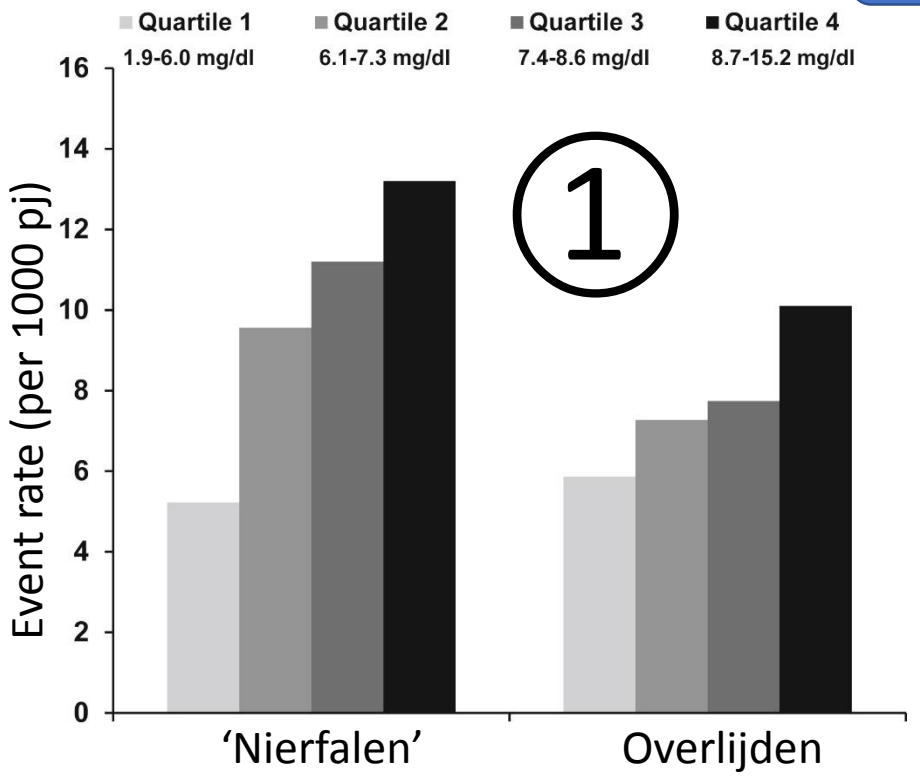
Evolutionair voordeel?

Adapted from Johnson RJ et al. *Seminars in Nephrology* 2011

UZ GENT

Serum urinezuur: *vaak* prognostische merker

Chronisch nierfalen



Srivastava A et al. *AJKD* 2017

UZ GENT

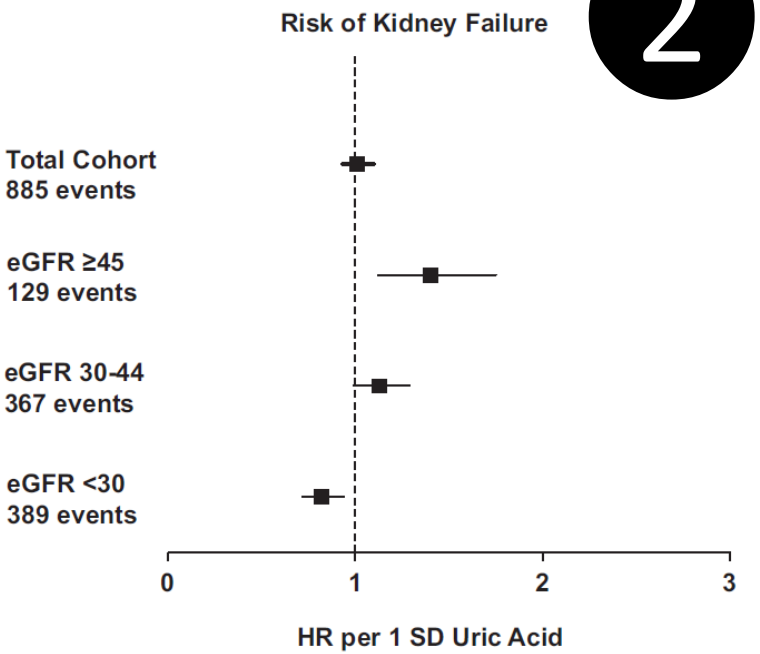
Nierfunctie is de confounder!

1 AHR nierfalen

Uric Acid	No. of Events	Events per 1,000 Person-y	HR (95% CI) Model 1	Model 2	Model 3	Model 4
Continuous[a]	885	39.2	1.42 (1.33-1.51)	1.31 (1.23-1.41)	1.24 (1.15-1.34)	1.01 (0.93-1.10)
Categorical						
Q1	118	5.2	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q2	216	9.6	1.83 (1.47-2.26)	1.72 (1.38-2.14)	1.36 (1.08-1.72)	1.05 (0.84-1.33)
Q3	253	11.2	2.28 (1.85-2.81)	2.03 (1.64-2.52)	1.56 (1.24-1.97)	1.03 (0.82-1.30)
Q4	298	13.2	2.81 (2.29-3.45)	2.35 (1.90-2.92)	1.85 (1.46-2.34)	1.07 (0.84-1.37)

Note: Model 1 is unadjusted; model 2 is stratified by center and adjusts for age, sex, race, systolic blood pressure, diabetes, body mass index, and any cardiovascular disease; model 3 is model 2 plus further adjustment for urate-lowering medicines, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, diuretics, β-blockers, statins, antiplatelet drugs, hemoglobin, serum albumin, and log(urinary albumin-creatinine ratio); and model 4 is model 3 plus further adjustment for baseline estimated glomerular filtration rate.

2



Srivastava A et al. *AJKD* 2017

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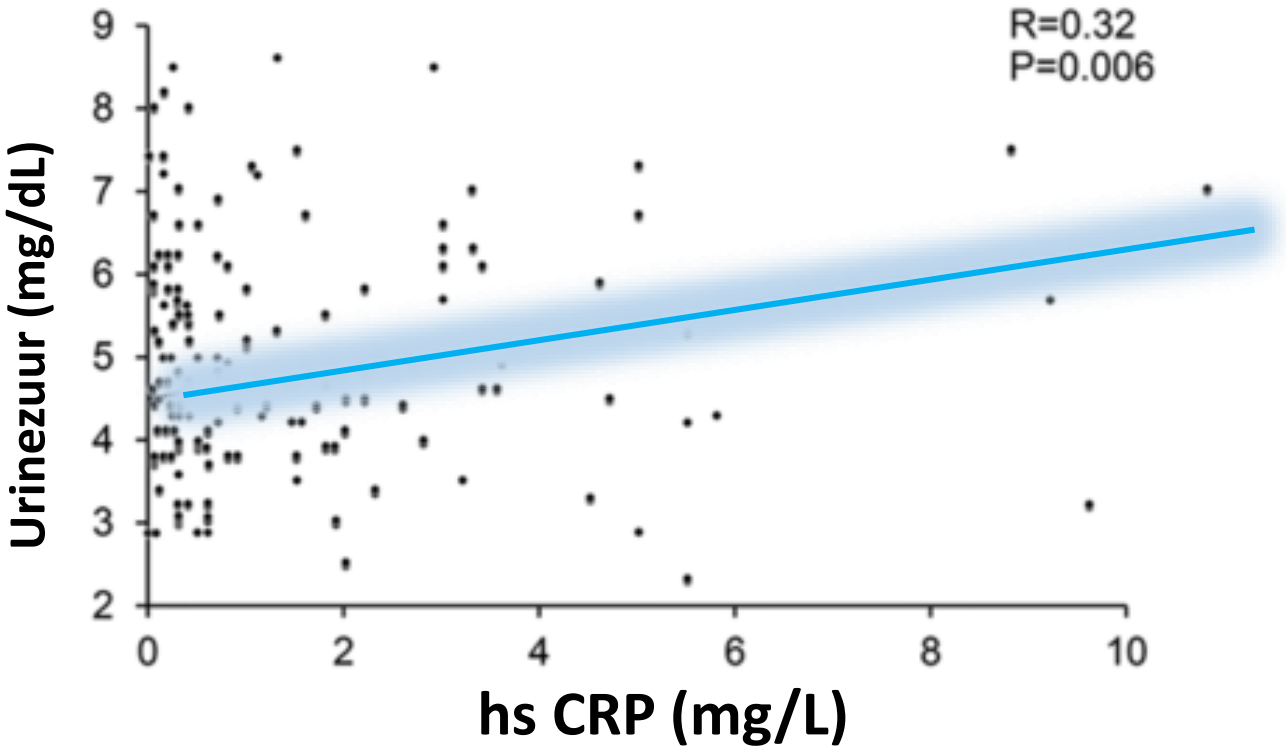
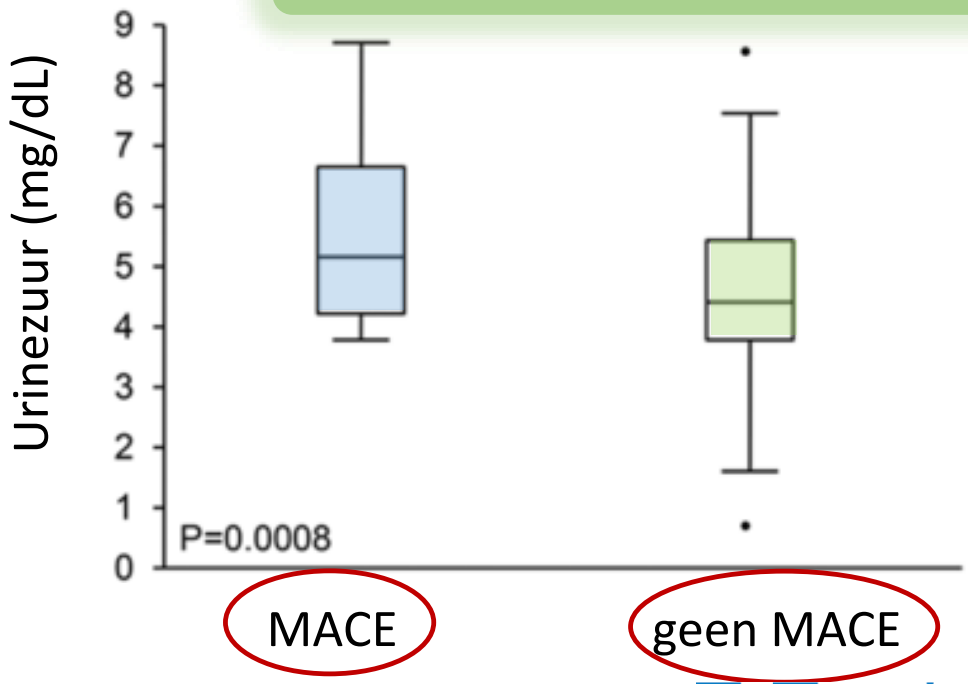
Serum urinezuur: *vaak* associatie CV lijden

Postmenopausale vrouwen MET coronaire endotheeldysfunctie (precursor atherosclerose)



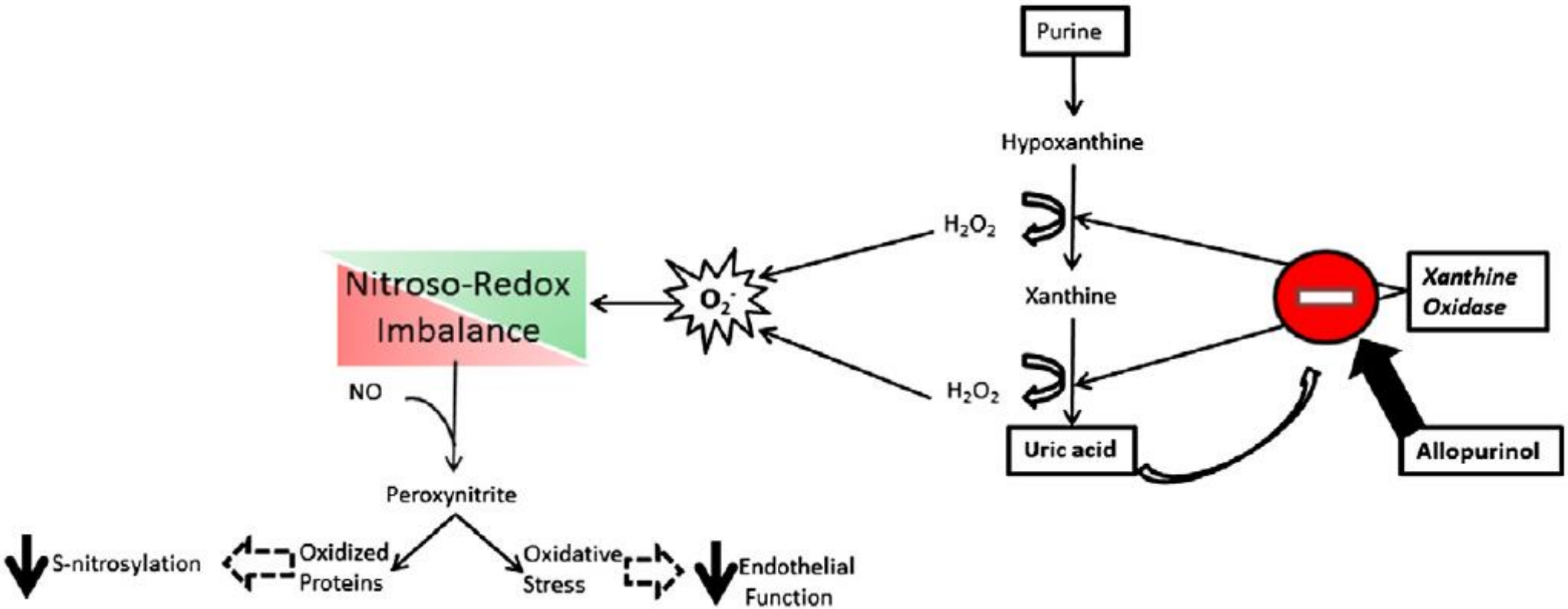
Geen rekening met nierfunctie!



Prasad M et al. *Hypertension* 2017

UZ GENT

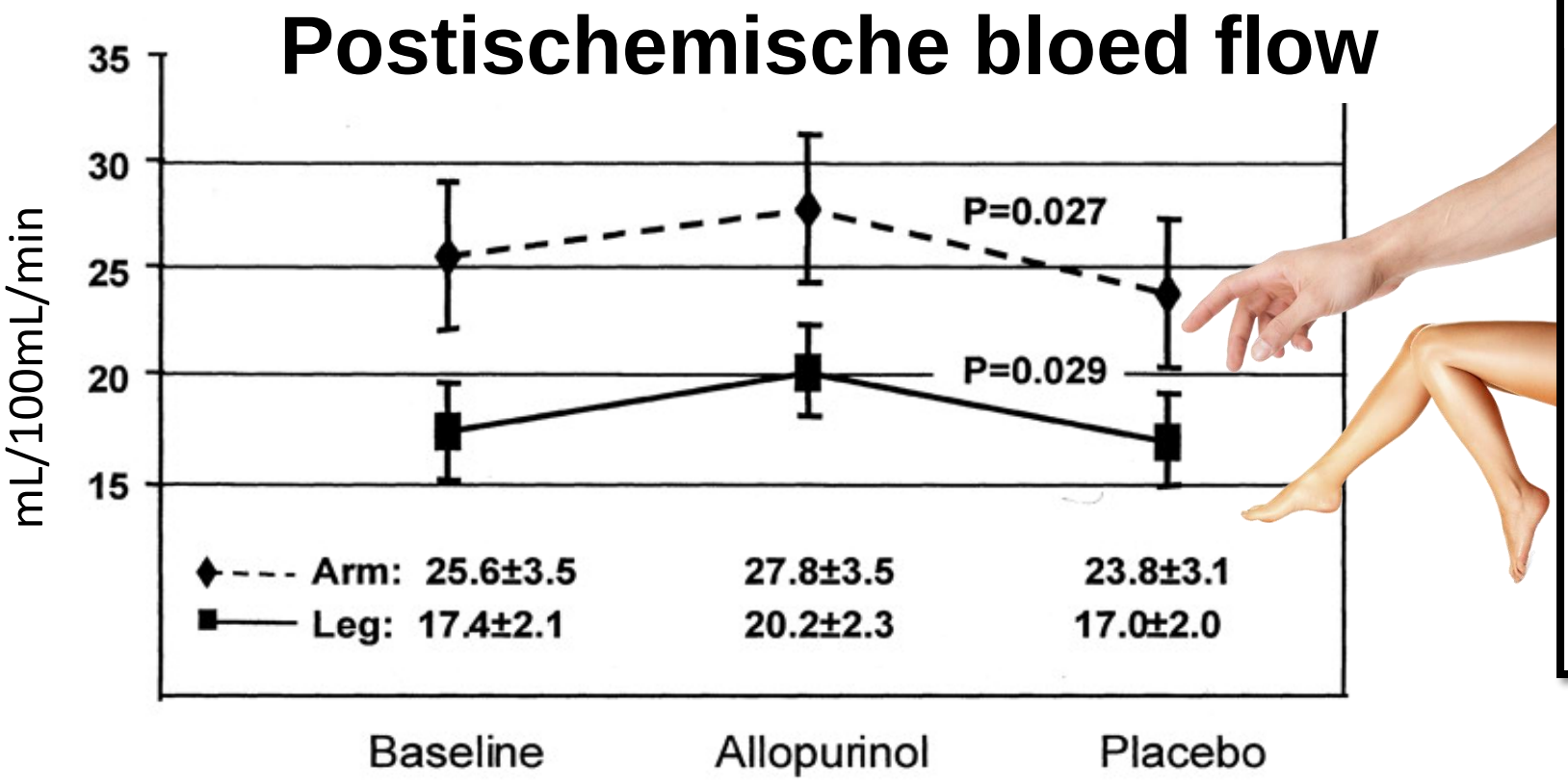
Allopurinol reduceert oxidatieve stress

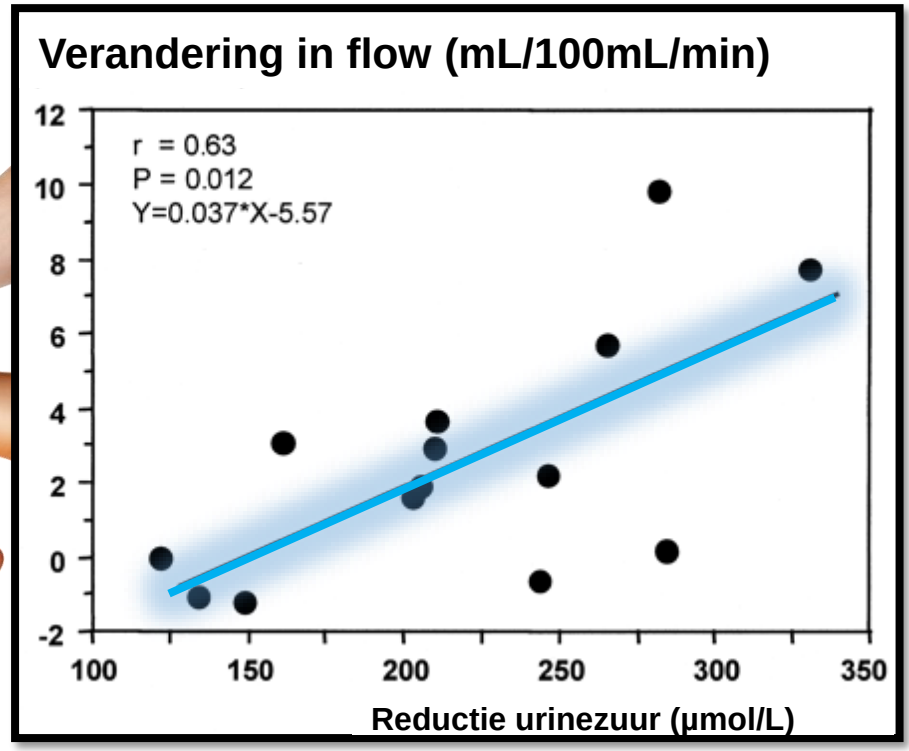


Karantalis V et al. JACC 2013

UZ GENT

Allopurinol en effecten op surrogaat merkers



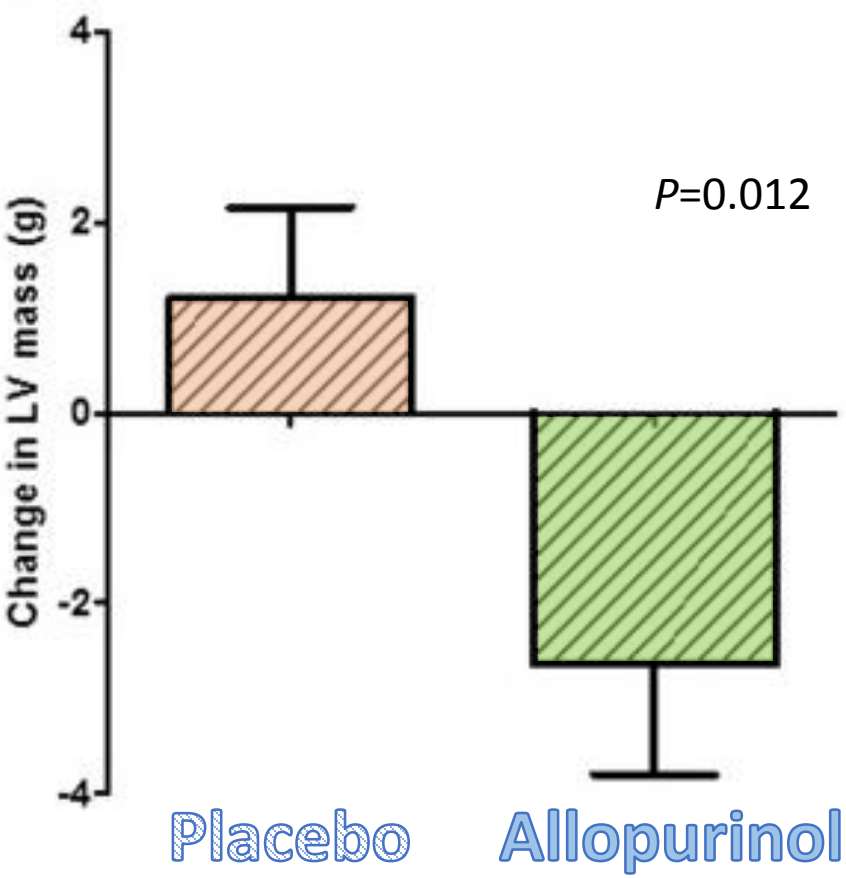


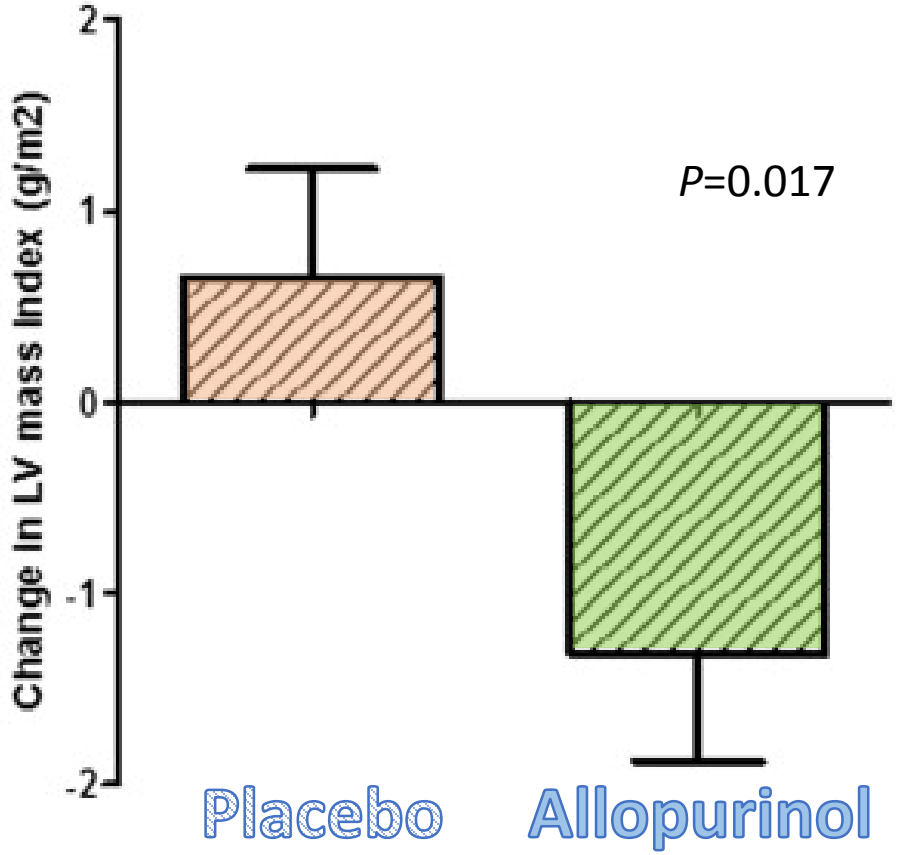
Allopurinol verbetert endotheelfunctie in CHF

Doehner W et al. *Circulation* 2002

UZ GENT

Allopurinol en effecten op surrogaat merkers





Allopurinol reduceert linker ventrikel hypertrofie in type 2 diabetes

Szwejkowski BR et al. JACC 2013

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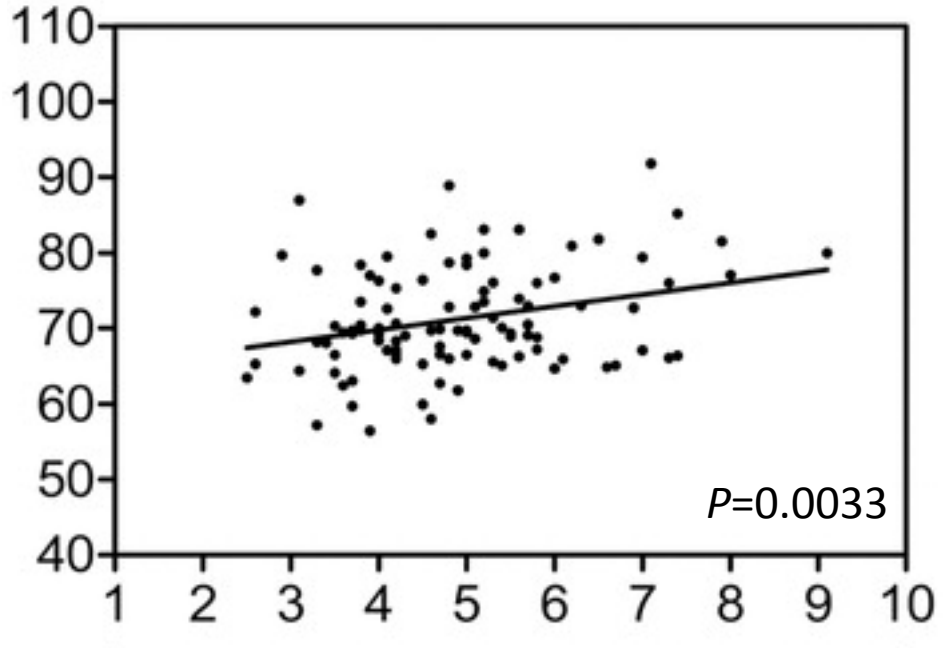
De relatie tussen urinezuur en hypertensie

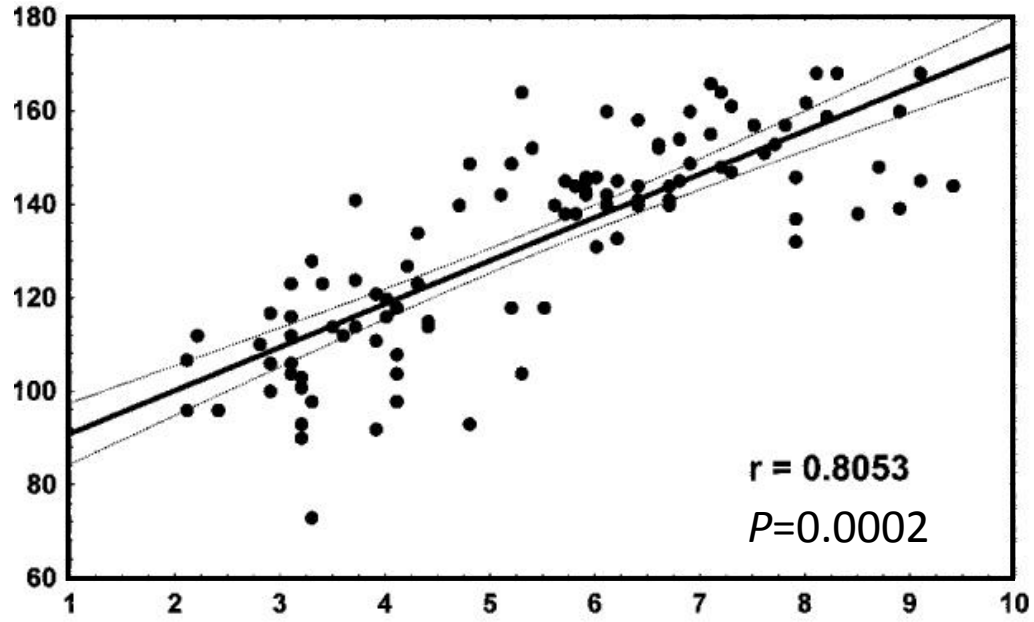
Urinezuur en arteriële hypertensie

24u diastolische bloeddruk (mmHg) (N=104)



serum urinezuur (mg/dL)

Systolische bloeddruk (mmHg) (N=125)



serum urinezuur (mg/dL)

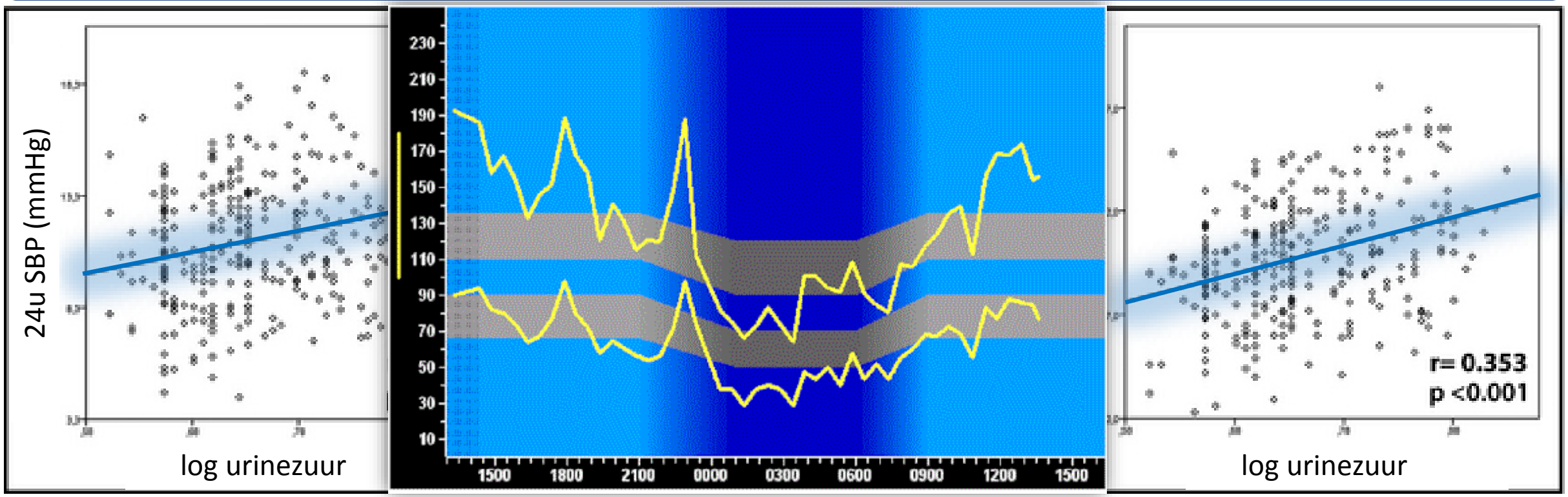
kinderen verwezen voor potentiële hypertensie

Jones DP et al. Pediatr Res 2008-Feig D et al. Hypertension 2003

UZ GENT

Urinezuur en BD variabiliteit

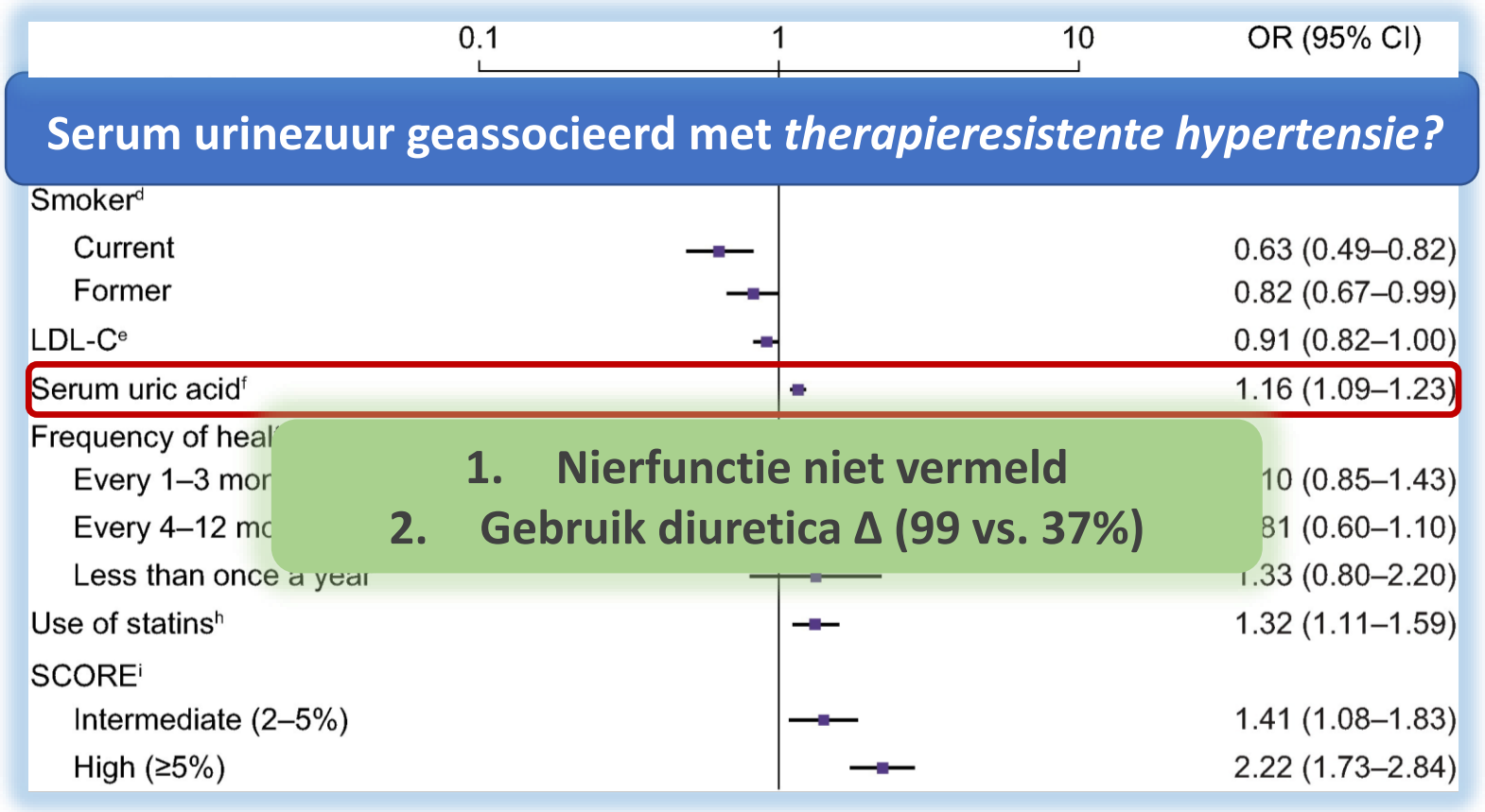
Serum urinezuur is geassocieerd met hoge BD variabiliteit bij hypertensieve patiënten



Cagli K et al. – *J Clin Hypertens* 2015

UZ GENT

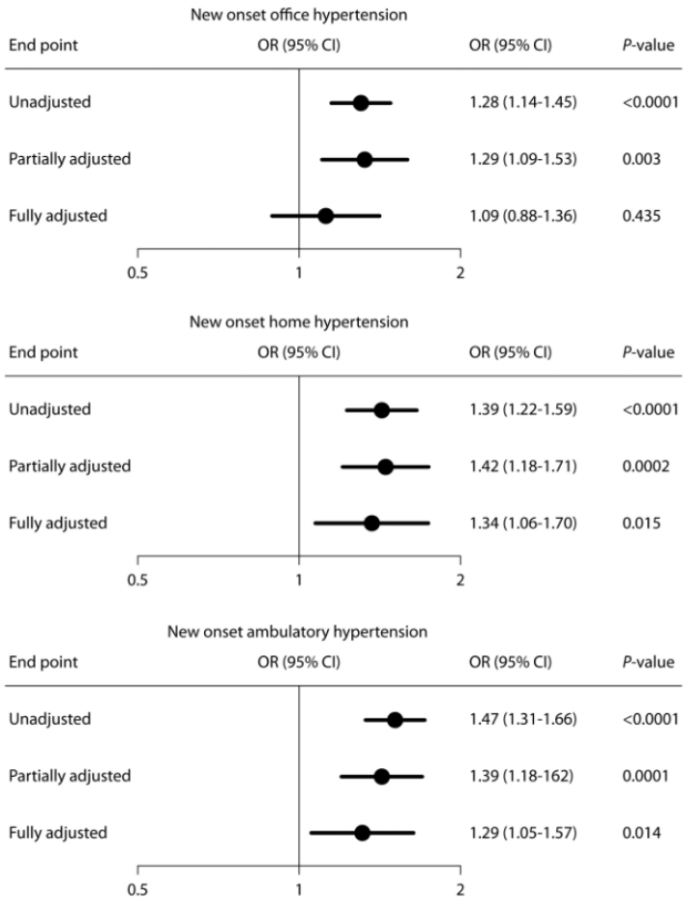
Therapieresistente hypertensie en serum urinezuur



N=5220; EURIKA studie: 14% therapieresistente hypertensie

Borghi et al. *Int J Cardiol* 2016

Urinezuur voorspelt *de novo* hypertensie



Per toename serum urinezuur 1mg/dL

9% hoger risico *de novo* office hypertensie (NS)

34% hoger risico *de novo* hypertensie thuis (*P*=0.015)

29% hoger risico de novo hypertensie portometrie (*P*=0.014)

N=2045; herevaluatie na 10j (PAMELA studie)

Bombelli et al. J *Hypertension* 2014

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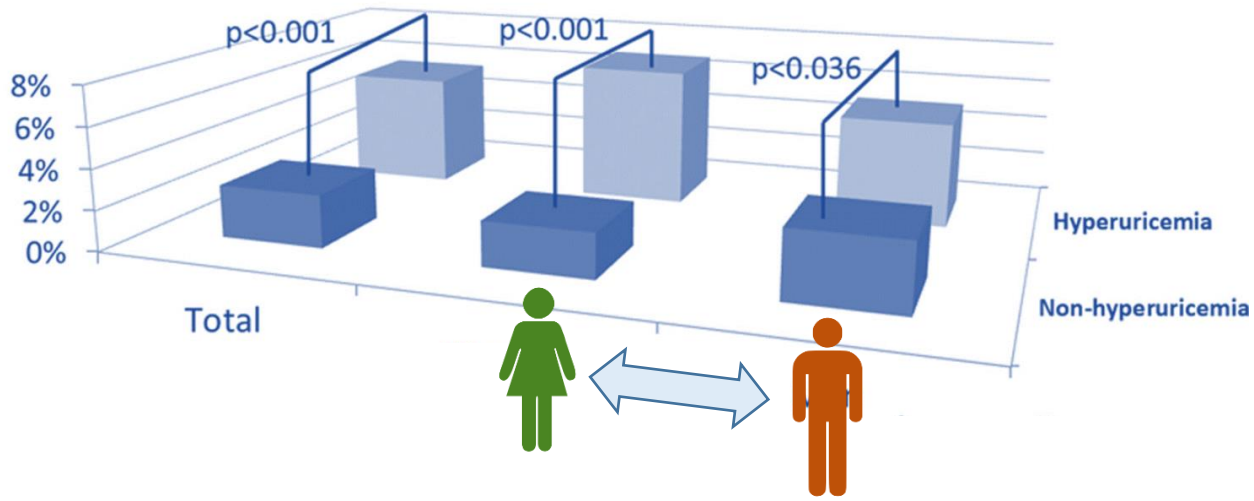
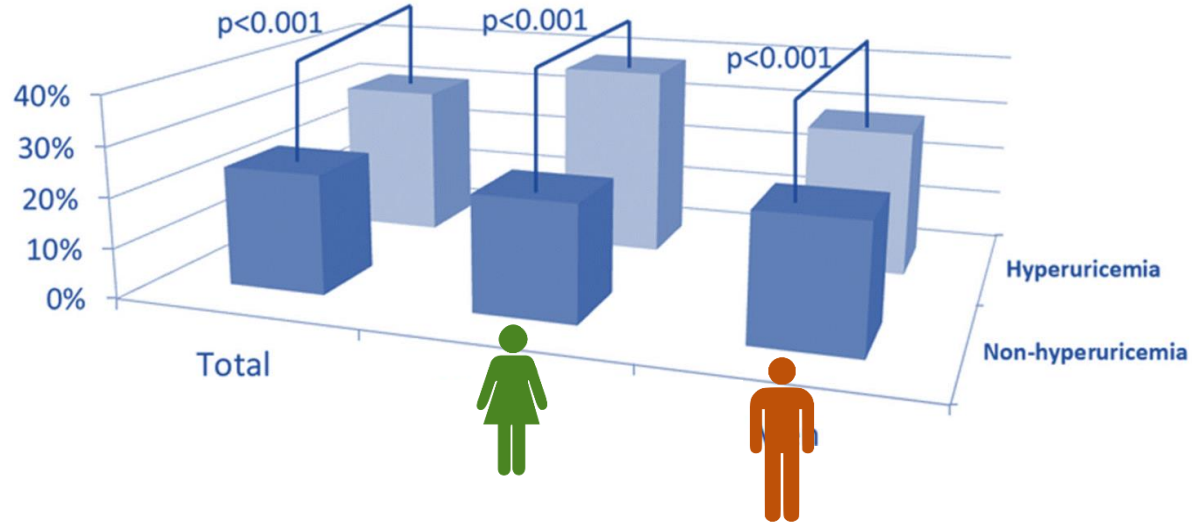
Urinezuur voorspelt hypertensie of BD controle

Incidentie van hypertensie na normotensie



Incidentie van hypertensie na prehypertensie

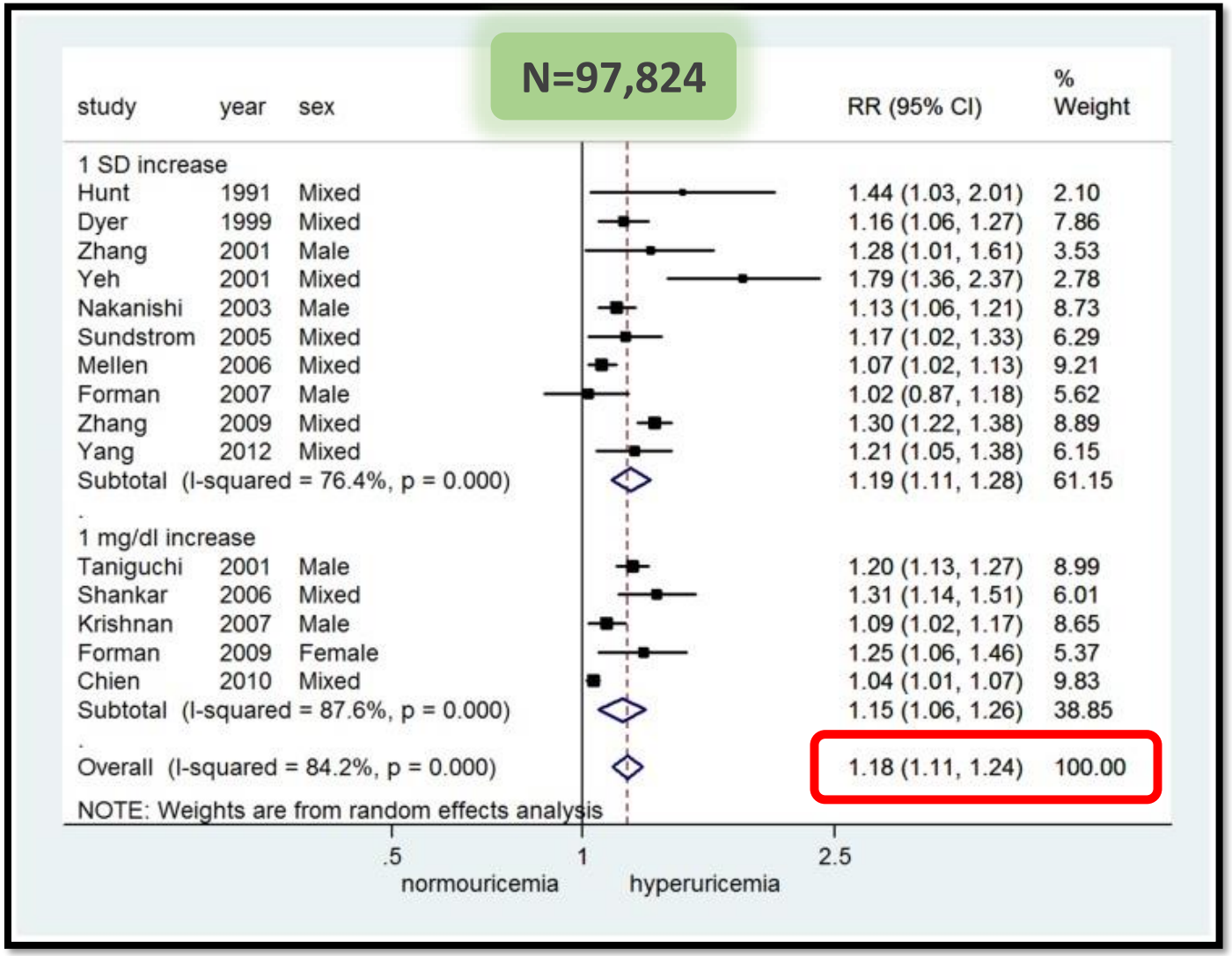


N=3584; 5y FU

Kuwabara M et al. *Hypertension* 2018

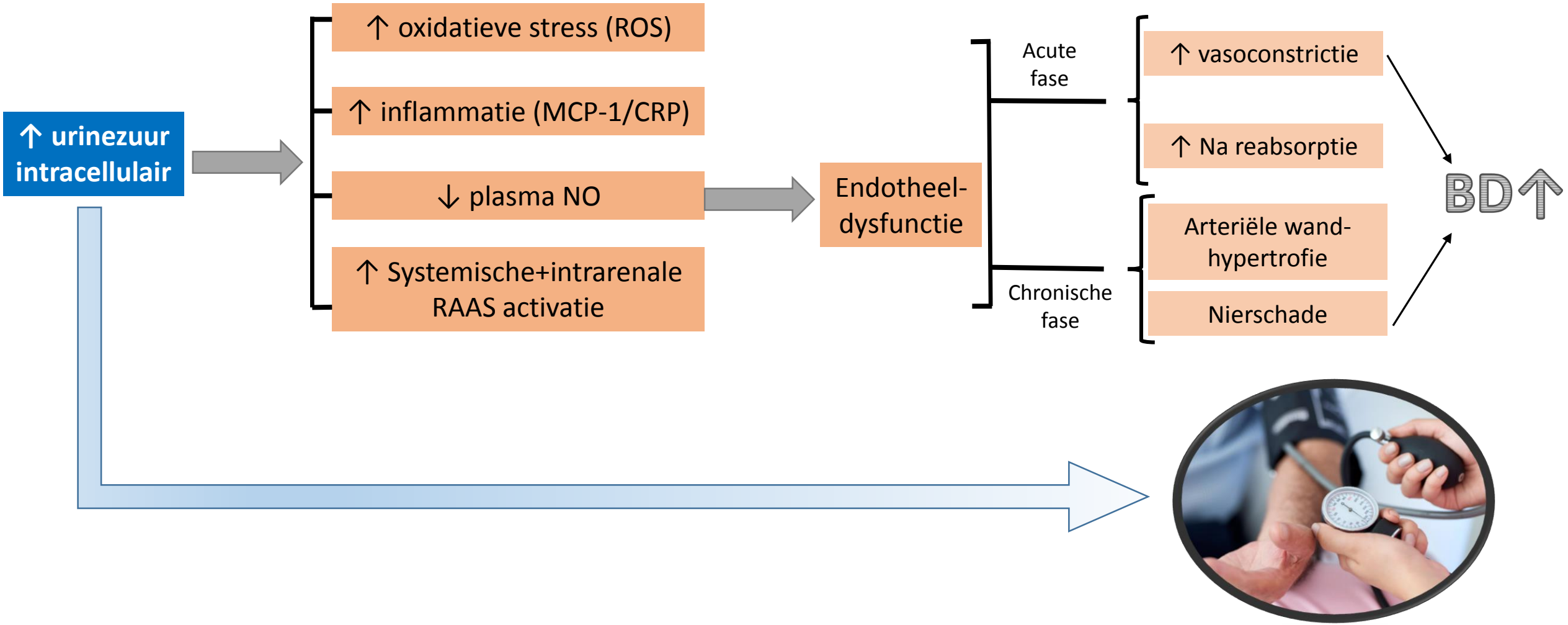
UZ GENT

Serum urinezuur en *de novo* hypertensie



Wang J et al. Plos One 2014

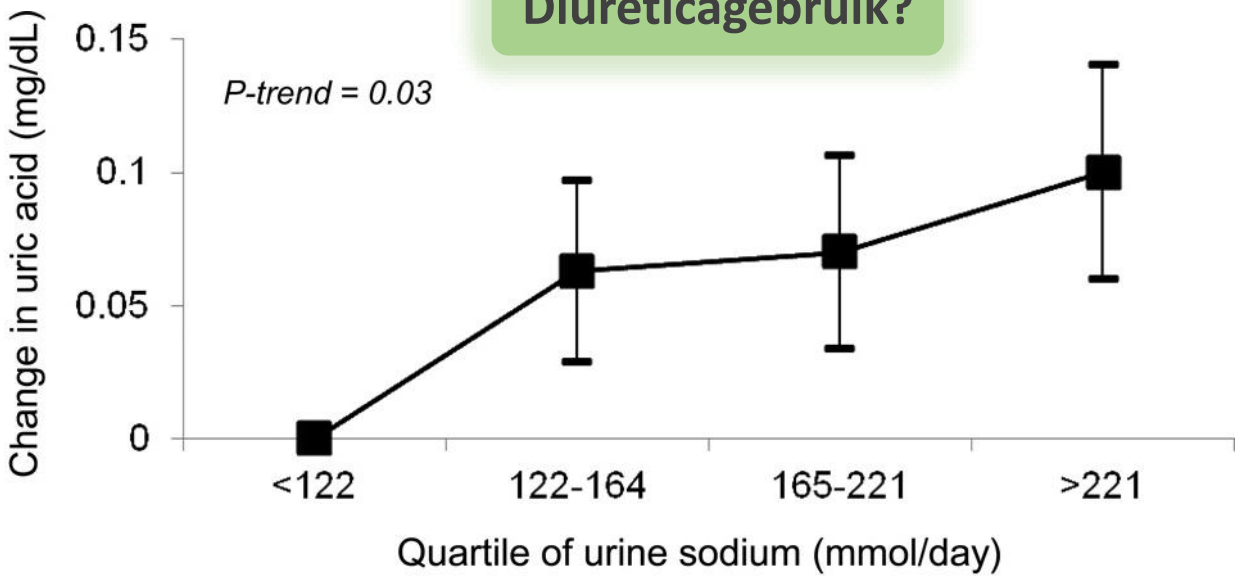
Urinezuur en de ontwikkeling van hypertensie



Cheng YB *Hypertension* 2018

De relatie tussen urinezuur en zoutinname

Diureticagebruik?



1

N=5556 (PREVEND studie-normotens)

Serum urinezuur is geassocieerd met hogere zoutinname (excretie urine) en vooral geassocieerd met ontwikkeling hypertensie bij hogere zoutinname

Forman JP et al. *Circulation* 2012

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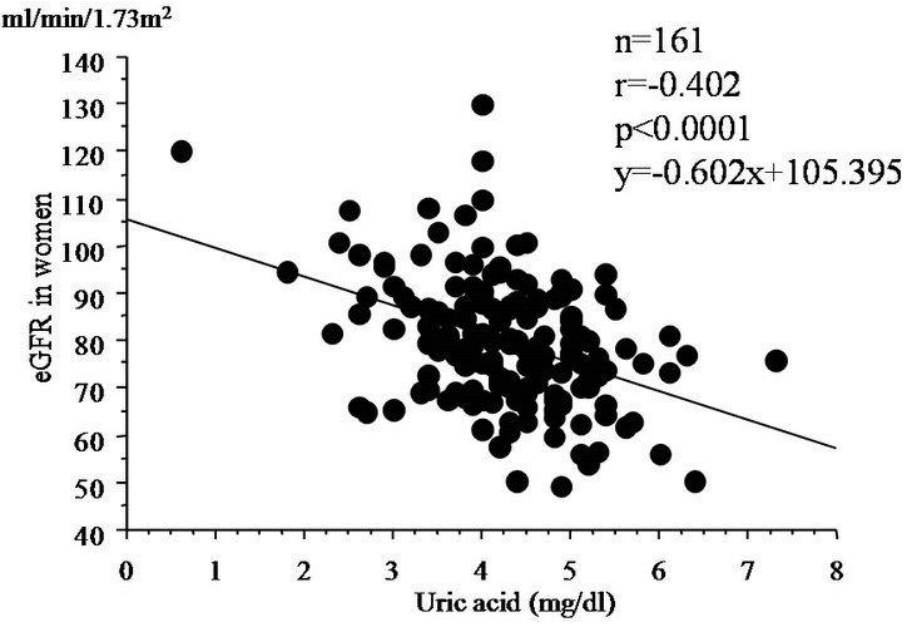
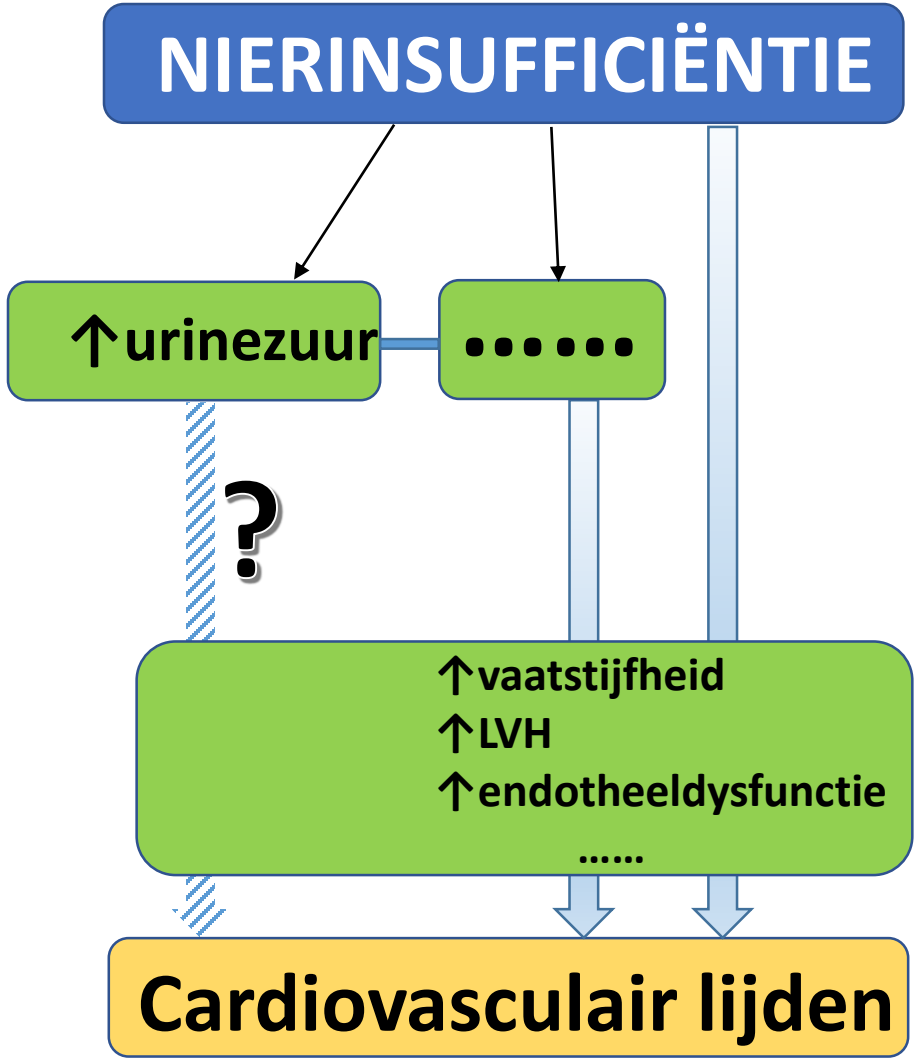
De invloed van dieet op serum urinezuur

URINEZUUR

CONFOUNDING?

Is urinezuur misschien een bystander?





Innocent bystanders

Genetische studies urinezuur: dissonant!

Multiple Genetic Loci Influence Serum Urate Levels and Their Relationship With Gout and Cardiovascular Disease Risk Factors

Qiong Yang, PhD; Anna Köttgen, MD, MPH; Abbas Dehghan, MD, DSc; Albert V. Smith, PhD; Nicole L. Glazer, PhD; Ming-Huei Chen, PhD; Daniel I. Chasman, PhD; Thor Aspelund, PhD; Gudny Eiriksdottir, MSc; Tamara B. Harris, MD; Lenore Launer, PhD; Michael Nalls, PhD; Dena Hernandez, MS; Dan E. Arking, PhD; Eric Boerwinkle, PhD; Megan L. Grove, MS; Man Li, MS; W.H. Linda Kao, PhD, MHS; Michel Chonchol, MD; Talin Haritunians, PhD; Guo Li, MS; Thomas Lumley, PhD; Bruce M. Psaty, MD, PhD; Michael Shlipak, MD, MPH; Shih-Jen Hwang, PhD; Martin G. Larson, ScD; Christopher J. O'Donnell, MD, MPH; Ashish Upadhyay, MD; Cornelia M. van Duijn, PhD; Albert Hofman, MD, PhD; Fernando Rivadeneira, MD, PhD; Bruno Stricker, MB, PhD; Andre G. Uitterlinden, PhD; Guillaume Paré, MD, MSc; Alex N. Parker, PhD; Paul M. Ridker, MD; David S. Siscovick, MD; Vilmundur Gudnason, MD, PhD; Jacqueline C. Witteman, PhD; Caroline S. Fox, MD, MPH; Josef Coresh, MD, PhD

Relatie genetische 'urinezuur score' en jicht overweldigend doch afwezig voor CV risk+outcome

		Age and Sex Adjusted*		Multivariable Adjusted†		Multivariable Adjusted†			Detectable at 80% Power‡
Phenotype§	N/n Events	β, OR‖	*P*	β, OR‖	*P*	β, OR‖	95% CI	*P*	β, OR‖
Serum urate and gout									
Serum urate, μmol/L	28 220	100	. . .	100	. . .	99.3	95.0, 103.7	<5E-308	6.3
Gout (OR)	25 982/1033	(2.4)	<0.001	(2.1)	<0.001	(12.4)	8.5, 18.0	3E-39	(1.7)
CVD risk factors									
SBP, mm Hg¶	28 199	3.44	<0.001	1.89	<0.001	−1.01	−2.10, 0.09	0.07	1.57
SBP (not treated), mm Hg#	20 673	2.82	<0.001	1.26	<0.001	−0.83	−1.96, 0.30	0.15	1.61
DBP, mm Hg¶	28 194	1.84	<0.001	1.03	<0.001	−0.15	−0.80, 0.49	0.64	0.92
DBP (not treated), mm Hg#	20 669	1.67	<0.001	0.78	<0.001	−0.34	−1.04, 0.35	0.33	0.99
Fasting glucose, mmol/L	25 877	0.12	<0.001	−0.002	0.80	−0.058	−0.13, 0.02	0.13	0.11
Fasting glucose (diabetes excluded), mmol/L	23 726	0.14	<0.001	0.09	<0.001	−0.0001	−0.036, 0.036	1.00	0.05
Fasting insulin (no DM)**	19 899	35.84	<0.001	20.22	<0.001	−0.015	. . .	0.99	. . .
Log eGFR, mL/min per 1.73m^2	23 884	−0.08	<0.001	−0.08	<0.001	0.001	−0.01, 0.02	0.91	−0.02
CKD	23 387/3092	(2.31)	<0.001	(2.18)	<0.001	(1.20)	0.96, 1.50	0.12	(1.38)
Incident CHD	23 362/3050	(1.23)	<0.001	(1.09)	<0.001	(1.03)	0.85, 1.25	0.76	(1.32)

From Circ Cardiovasc Genet 2010

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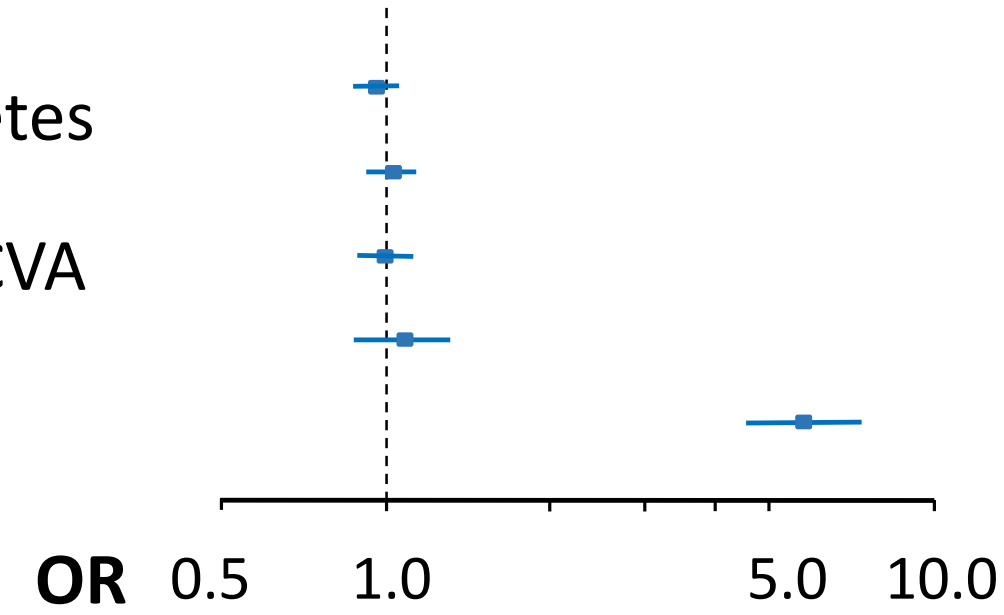
Associaties met ‘genetisch verhoogd urinezuur’

Uitkomst	OR	95%CI	p value
Type 2 Diabetes	0.95	(0.86-1.05)	0.28
CHD	1.02	(0.92-1.12)	0.73
Ischemisch CVA	0.99	(0.88-1.12)	0.93
Hartfalen	1.07	(0.88-1.30)	0.51
Jicht	5.84	(4.56-7.49)	4.2^{E}-44



OR (95%CI) per SD toename in serum urinezuur volgens ‘genetica score’

Relatie genetische ‘urinezuur score’ en jicht overweldigend doch afwezig voor CV risk+outcome

Keenan T et al. *JACC* 2016

Urinezuur verlaging voor tensiecontrole?

Cochrane Library

Cochrane Database of Systematic Reviews

Pharmacotherapy for hyperuricemia in hypertensive patients (Review)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with placebo	Risk with Uric acid (UA) lowering drug			
24h-Systolic Blood Pressure	-	MD 6.19 lower (12.82 lower to 0.45 higher)	MD -6.2 (-12.8, 0.5)	229 (3 RCTs)	⨁⨁◯◯ LOW [12]
24h-Diastolic Blood Pressure	-	MD 3.92 lower (9.19 lower to 1.36 higher)	MD -3.9 (-9.2, 1.4)	229 (3 RCTs)	⨁⨁◯◯ LOW [12]
Clinic Systolic Blood Pressure	-	MD 8.43 lower (15.24 lower to 1.62 lower)	MD -8.4 (-15.2, -1.6)	120 (2 RCTs)	⨁⨁◯◯ LOW [12]
Clinic Diastolic Blood Pressure	-	MD 6.45 lower (13.6 lower to 0.7 higher)	MD -6.5 (-13.6, 0.7)	120 (2 RCTs)	⨁⨁◯◯ LOW [12]
Serum uric acid	-	MD 3.09 lower (3.76 lower to 2.43 lower)	MD -3.1 (-3.8, -2.4)	223 (3 RCTs)	⨁⨁⨁⨁ HIGH

Gois et al. *Cochrane Database Syst Rev* 2017

UZ GENT

Urinezuur verlaging voor tensiecontrole?

Cochrane Library

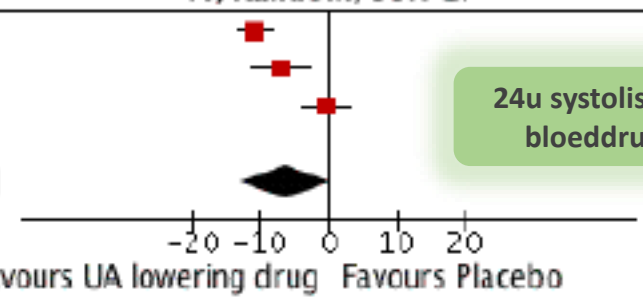
Cochrane Database of Systematic Reviews

Pharmacotherapy for hyperuricemia in hypertensive patients (Review)

Study or Subgroup	Mean Difference	SE	UA lowering drug Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Soletsky 2012	-10.95	1.2856	40			-10.95 [-13.47, -8.43]
Feig 2008	-7.1	2.1833				7.10 [-11.38, -2.82]
NCT01496469	-0.3	1.8246				, 3.28]
Total (95% CI)						, 0.45]

Heterogeneity: Tau² = 31.18; Chi² = 22.78, df = 2 (P < 0.

Test for overall effect: Z = 1.83 (P = 0.07)

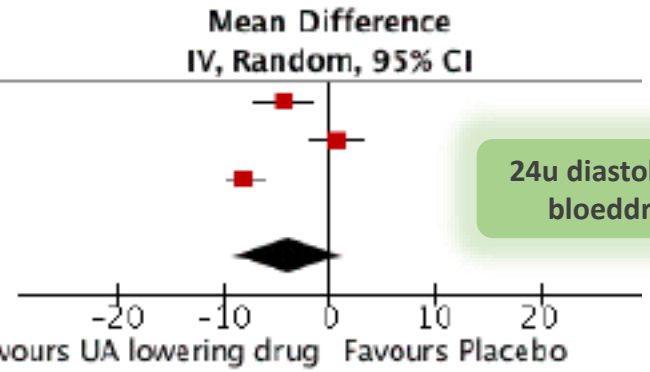


24u systolische bloeddruk

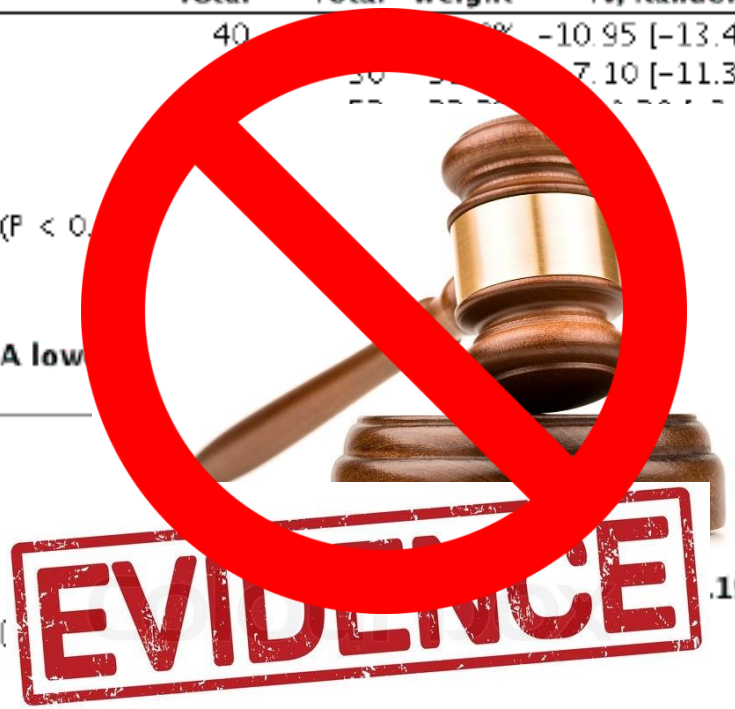
Study or Subgroup	Mean Difference	SE	UA low…	…ce …% CI
Feig 2008	-4.3	1.3898		1.58]
NCT01496469	0.7	1.2659		3.18]
Soletsky 2012	-8	0.9052		5.23]
Total (95% CI)				.19, 1.36]

Heterogeneity: Tau² = 20.29; Chi² = 31.48, df = 2 (

Test for overall effect: Z = 1.45 (P = 0.15)



24u diastolische bloeddruk



Gois et al. *Cochrane Database Syst Rev* 2017

UZ GENT

Urinezuur verlaging voor nefroprotectie?

Cochrane Library

Cochrane Database of Systematic Reviews

Uric acid lowering therapies for preventing or delaying the progression of chronic kidney disease (Review)

There is insufficient evidence to support an effect on blood pressure, proteinuria or other cardiovascular markers by uric acid lowering therapy. It should be noted that the apparent benefits of treatment were not apparent at all time points, introducing the potential for bias.

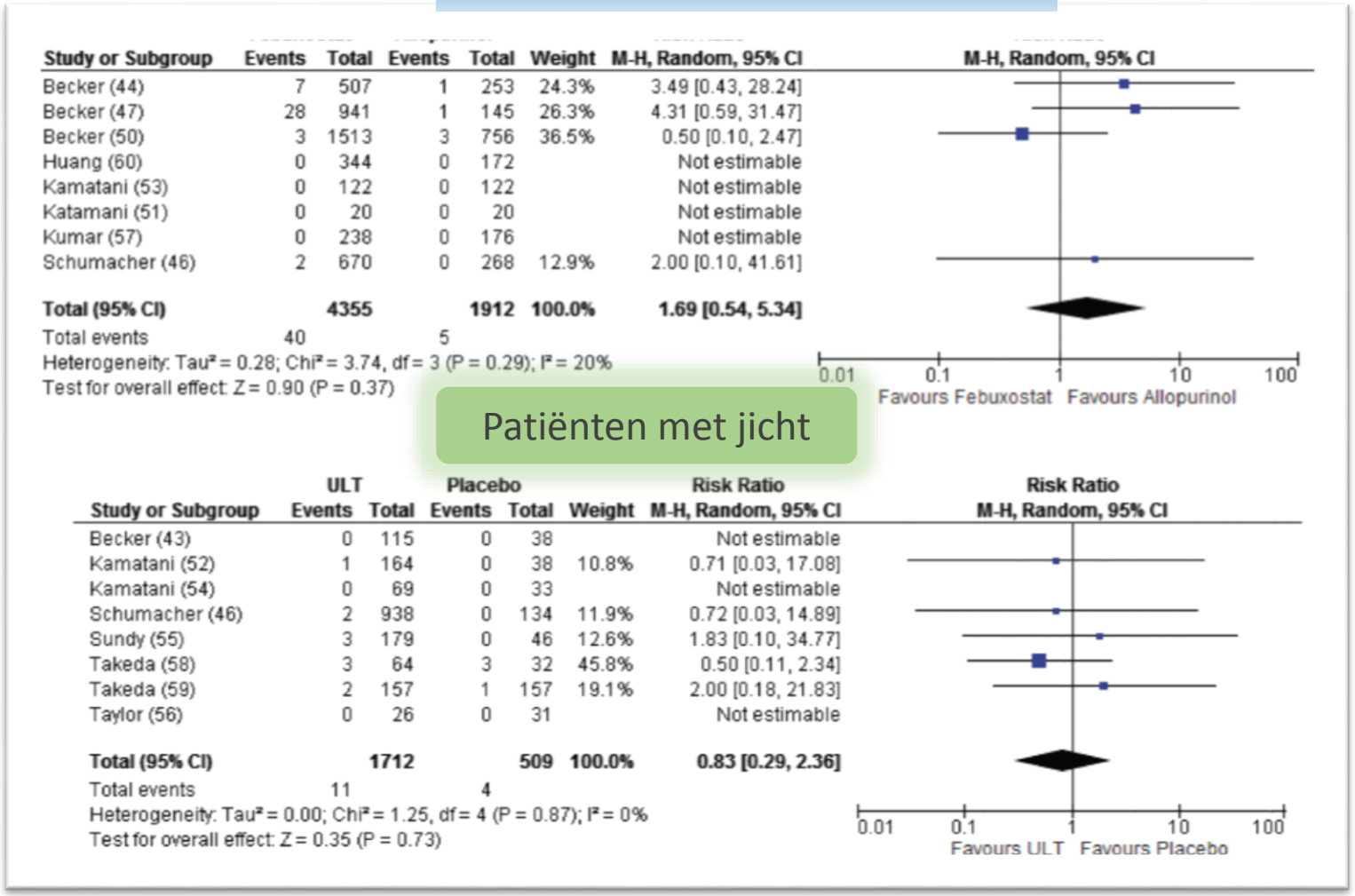
Nefroprotectie hoogst onzeker in afwachting van RCT van adequate methodologische kwaliteit

Sampson AL et al *Cochrane Database Syst Rev* 2017

UZ GENT

Urinezuur verlaging voor cardiovasculaire protectie?

Cardiovasculaire events in RCT



Geen meerwaarde febuxostat tov. allopurinol

Urinezuurverlaging: geen cardiovasculaire baat

Enkel een 'power' probleem?

Zhang T et al. *Rheumatology* 2017

BMJ 2017;357:j2376 doi: 10.1136/bmj.j2376 (Published 7 June 2017)

thebmj

RESEARCH

Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies

OPEN ACCESS

Concordant evidence between observational studies and randomised controlled trials existed for hypertension and chronic kidney disease, but a potential causal role of SUA level for these outcomes has not been verified by current Mendelian randomisation studies and even for these two outcomes not all meta-analyses of randomised controlled trials are concordant among themselves and with observational evidence. Therefore, the available evidence does not support any change in the existing clinical recommendations in relation to hyperuricemia.

Conclusion Despite a few hundred systematic reviews, meta-analyses, and Mendelian randomisation studies exploring 136 unique health outcomes, convincing evidence of a clear role of SUA level only exists for gout and nephrolithiasis.

Xue Li et al. *BMJ* 2017

Urinezuurverlaging voor hypertensie-de conclusie?

Outcomes	Meta-analysis of observational studies	Meta-analysis of randomised controlled trials*	Mendelian randomisation studies
Hypertension†	Class II	Systolic blood pressure: P=0.001, 95% PI included null; diastolic blood pressure: P=0.03, 95% PI included null	Hypertension: n=3060, P=0.56, power=0.05

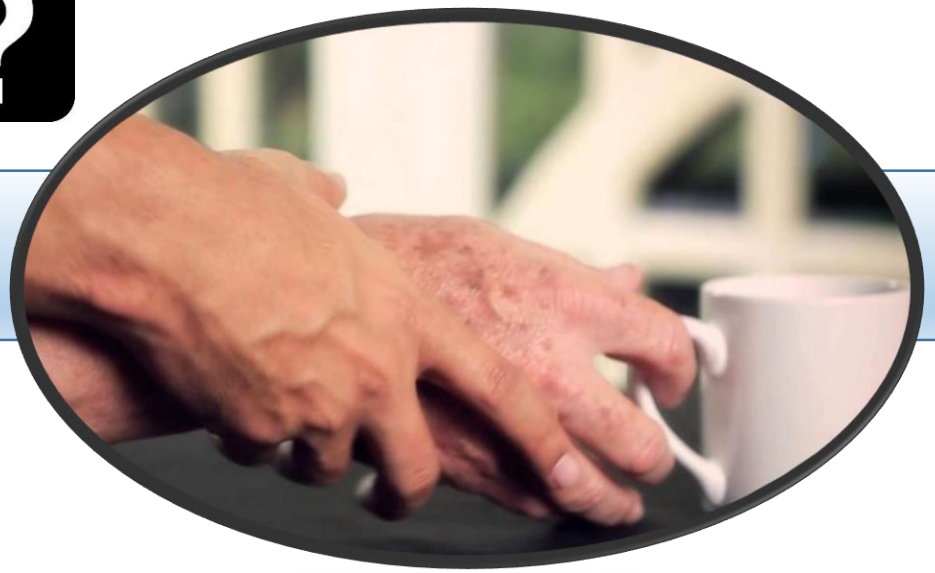
Outcomes	Population	SUA lowering treatment	No of studies	No of participants	Type of metric	Relative risk (95% CI)	P value	I^2 (95% CI)	P value for Egger's test	P value for excess significance test	95% prediction interval
Systolic blood pressure‡[93]	Patients with increased SUA or kidney dysfunction	Allopurinol	10	738	MD (mm Hg)	−3.33 (−5.25 to −1.42)	0.001	87 (79 to 91)	0.60	NP	−13.61 to 6.94
Diastolic blood pressure‡[93]	Patients with increased SUA or kidney dysfunction	Allopurinol	10	738	MD (mm Hg)	−1.29 (−2.48 to −0.10)	0.03	82 (68 to 88)	0.38	NP	−8.22 to 5.65

Xue Li et al. *BMJ* 2017

UZ GENT

Potentiële gevaren (te) liberale urinezuurverlaging?

?



?

Alzheimer

Parkinson

ALS

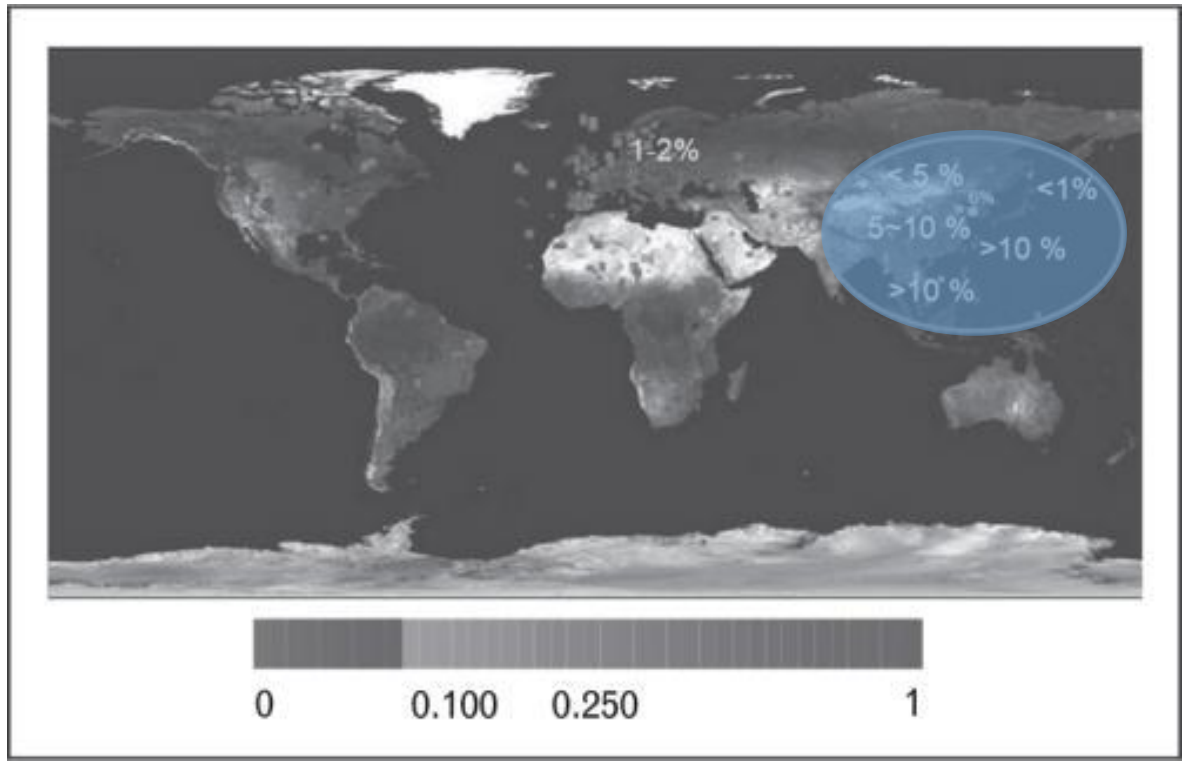
Bij langdurig gebruik (meerdere jaren) serum urinezuur boven 3mg/dL houden

Richette P et al. *Ann Rheum Dis* 2017-2016 UPDATE EULAR GUIDELINES (*)

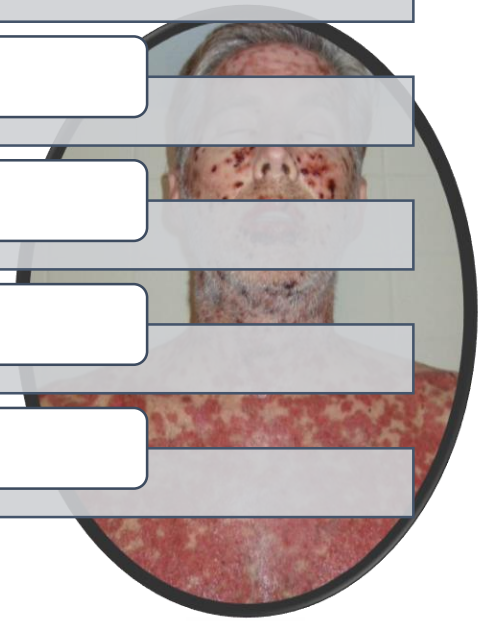
UZ GENT

Potentiële gevaren (te) liberale urinezuurverlaging?

Hypersensitiviteit: 0.1-1% (CAVE no. 1 oorzaak TEN/SJS)



- Geografische regio's: HLAB*5801 testing waar?
- Oudere leeftijd
- Comorbiditeit (nierfalen)
- Asymptomatische hyperuricemie
- Vrouwen



Wang CW et al. Curr Opinion in Allergology and Clin Immunology 2016/ Chang JY et al. JAMA Int Med 2015

Conclusie urinezuurverlaging hypertensie

- Residuele confounding in observationele data (nierfunctie, diuretica)
- Effect op tensiecontrole hoogstens beperkt (1-3mmHg)
- Effecten op harde eindpunten nog niet bewezen
- Geen meerwaarde potenter febuxostat tov. allopurinol
- Geen evidentie allopurinol voor asymptomatische hyperuricemie (CAVEAT uitzonderingen)
- Hypersensitiviteit 0.5-1% met wisselende ernst: aandachtspunt!

Gois PHF et al. Cochrane Database Syst Rev 2017

UZ GENT