

Υπερουριχαιμία και Καρδιαγγειακός κίνδυνος Νεότερα δεδομένα

Καπερνόπουλος Χ. Χαράλαμπος

Ειδικός παθολόγος

Εξειδικευθείς στον Σακχαρώδη διαβήτη

Δήλωση σύγκρουσης συμφερόντων



- Η ομιλία αντανακλά τις απόψεις του ομιλητή
- Ο ομιλητής έχει λάβει τιμητικές αμοιβές για διαλέξεις σε συνέδρια, επιστημονικές ημερίδες/ εκδηλώσεις και συμβουλευτική από τις εταιρείες: Abbott, AstraZeneca, Novo Nordisk, Boehringer Ingelheim, Servier, InterMed, Menarini, Φαρμασερβ-Lilly.



Future →

← Past



Μετάλλαξη της ουρικής άσης προ 13 εκατομμυρίων ετών



Υπερουριχαιμία



Richette P, Bardin T. Gout. Lancet 2010;375:318–28.
Riches PL, et al., Hum Mol Genet 2009;18:R177–84

Η προοδευτική άνοδος του ουρικού οξέος στον οργανισμό του ανθρώπου είχε 3 θετικά αποτελέσματα

**1. Αύξηση του μέσου όρου ζωής
(αντιοξειδωτικό)**

**2. Βελτίωση του νοητικού επιπέδου
(νευροδιεγερτικό)**

**3. Επίτευξη της όρθιας στάσης του ανθρώπου
(αλατοπροστατευτικό)**

Επίτευξη της όρθιας στάσης του ανθρώπου

Διατροφή με ελάχιστο αλάτι και προσαρμογή της αρτηριακής πίεσης στην τετράποδη στάση



Η μεταβολή της στάσης θα προκαλούσε
ορθοστατική υπόταση

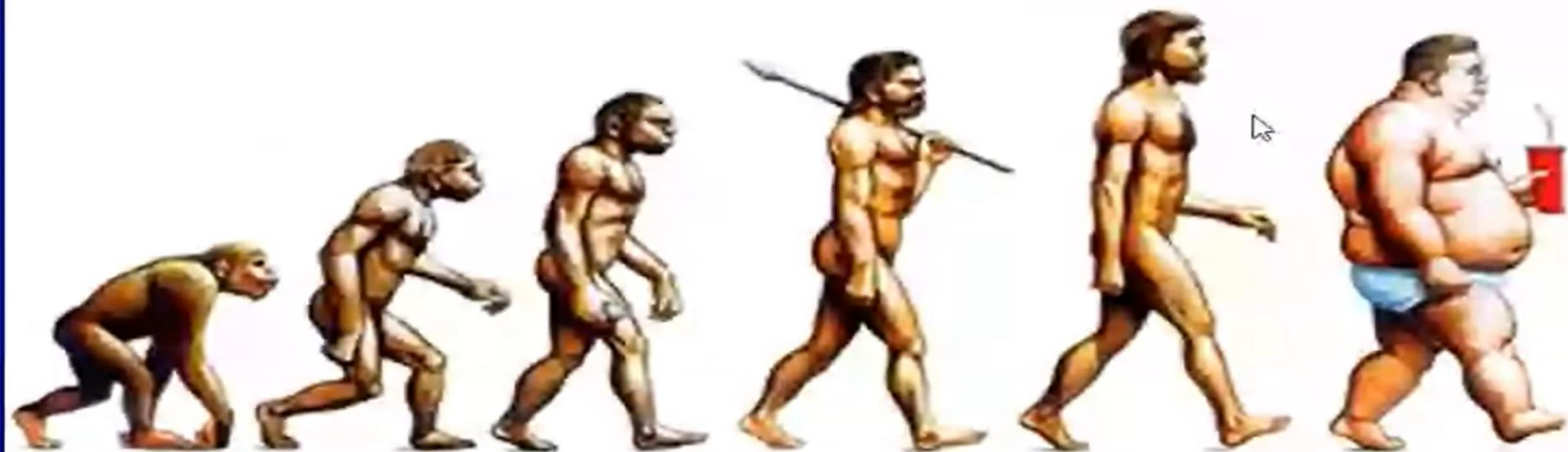


Το ουρικό οξύ ενεργοποιεί τον άξονα ρενίνης-αγγειοτασίνης και
είναι αλατοπροστατευτικό στα νεφρικά σωληνάκια



- α) Χέρια - εργαλεία
- β) Οπτικό πεδίο
- γ) Βάδιση σε φόρτιση
- δ) Αύξηση εγκεφάλου

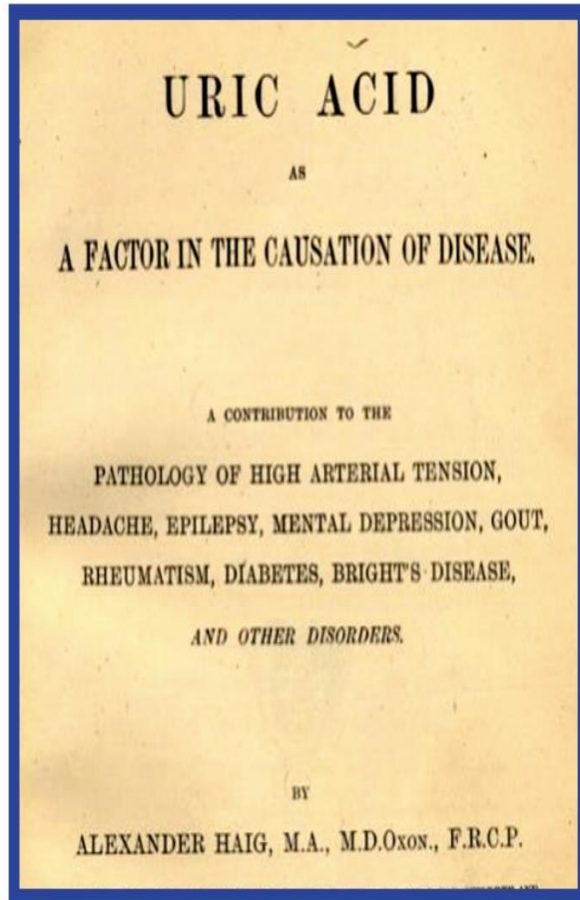




Η εξέλιξη του ανθρώπου προκάλεσε έντονες διατροφικές αλλαγές και από ρίζες, καρπούς και ελάχιστο κρέας ο άνθρωπος άρχισε να τρώει πολλές πρωτεΐνες, λίπη και σάκχαρα. με αποτέλεσμα την άνοδο του ουρικού οξέος και την βλαπτική υπερουριχαιμία

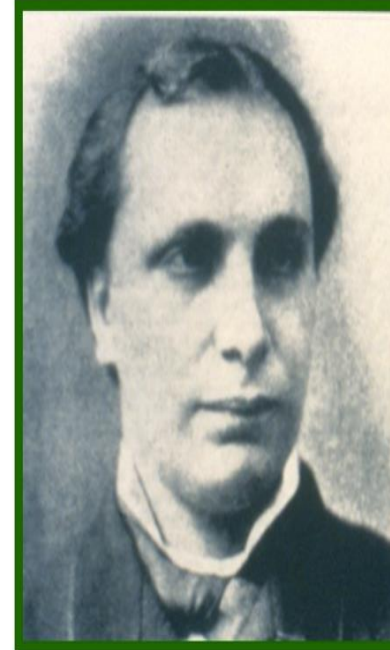
Uric Acid and Disease

Uric Acid and Hypertension



Alexander Haig 1896

In a 572 page treatise, described that elevated serum uric acid was detectable in many patients with chronic, non-infectious disease

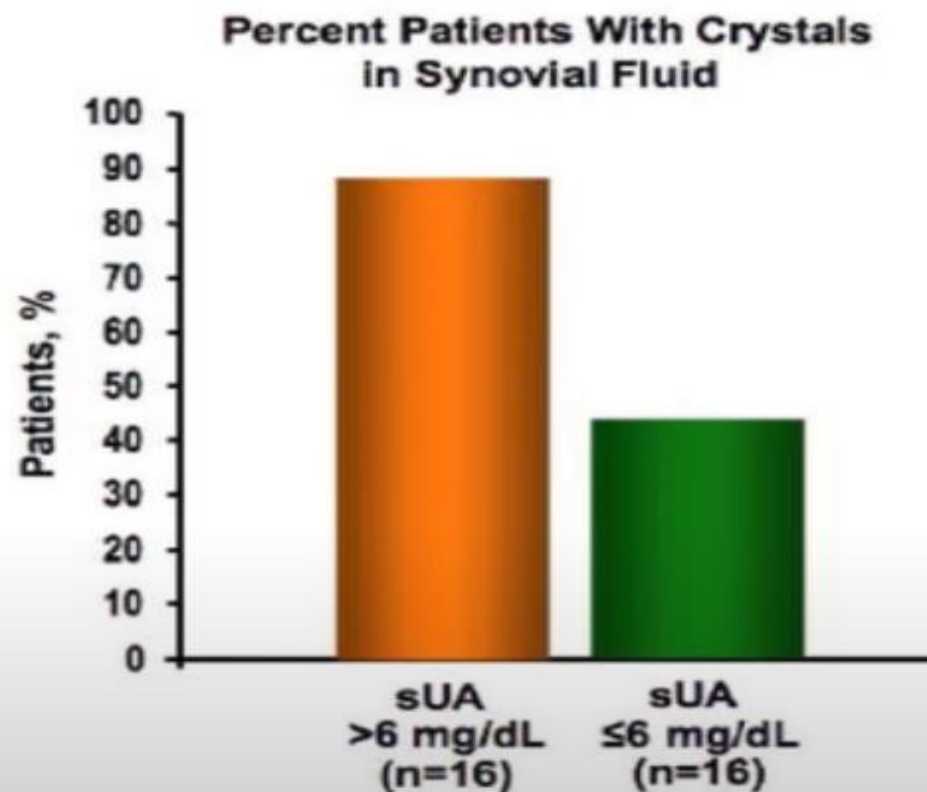


"People who are subject to this high blood pressure diathesis frequently belong to gouty families, or have themselves suffered from the symptoms of this disease"

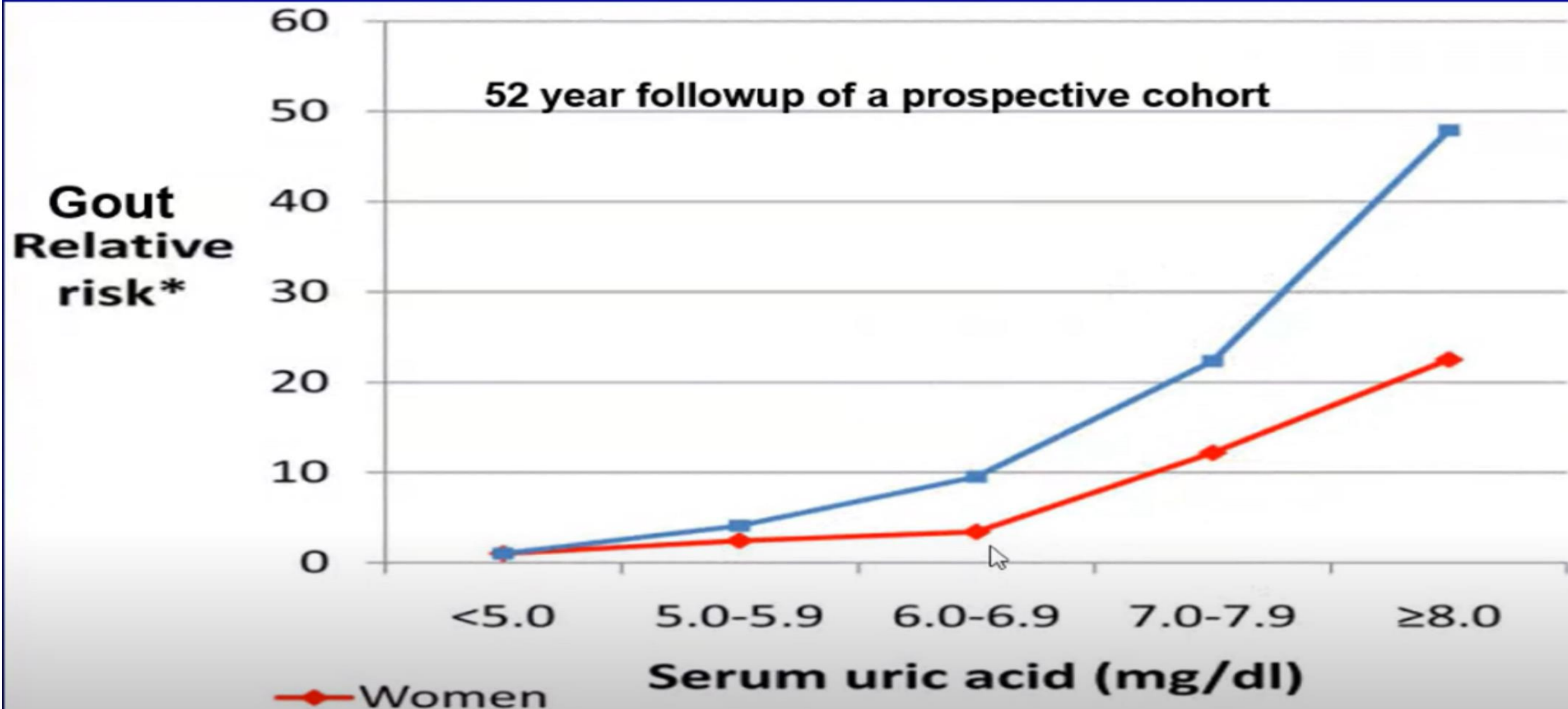
**Frederick Mahomed.
Lancet i:400, 1879**

Ουρικό οξύ ορού και κρύσταλλοι στις αρθρώσεις

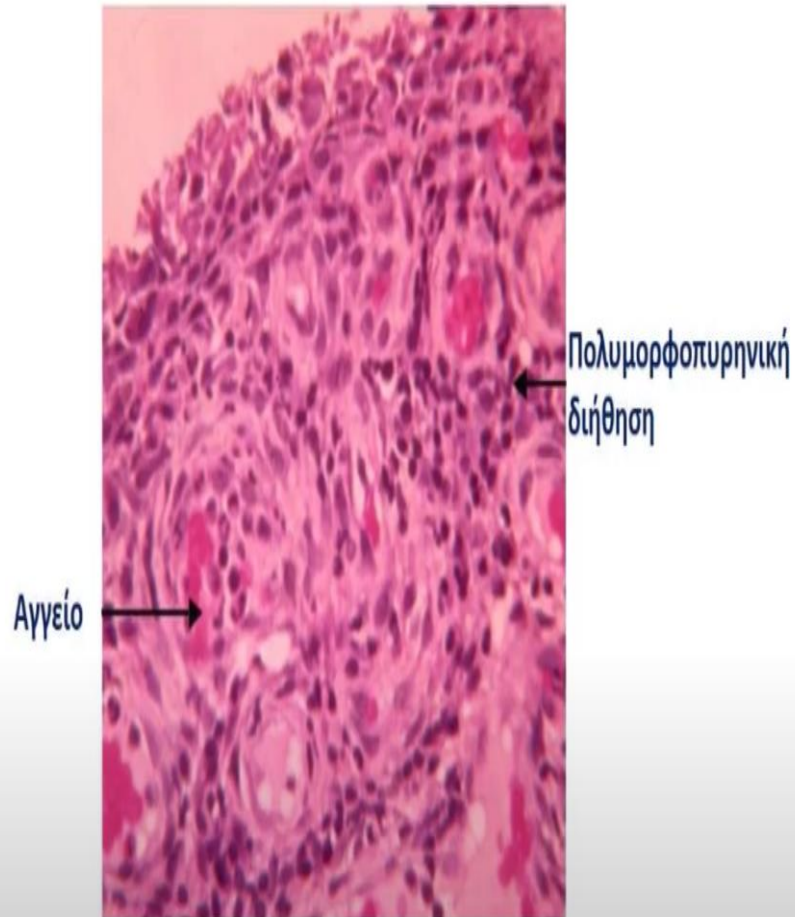
- Κρύσταλλοι στις αρθρώσεις όταν κορεστεί η διαλυτότητα του ουρικού στον ορό (~6.8mg/dl)
- Αντίστροφα, σε ασθενείς με ουρική αρθρίτιδα ελαττώνονται οι κρύσταλλοι στο αρθρικό υγρό επί διατήρησης ουρικού οξέος στον ορό <6mg/dl
- Η καθίζηση των κρυστάλλων και η φλεγμονή σε κάποια άρθρωση επηρεάζονται από παράγοντες όπως τραύμα, τοπική θερμοκρασία και προηγούμενη νόσος, όπως ΟΑ των ΑΜΦ



Relative risk of developing gout according to SUA level in men and women in the Framingham Heart Study

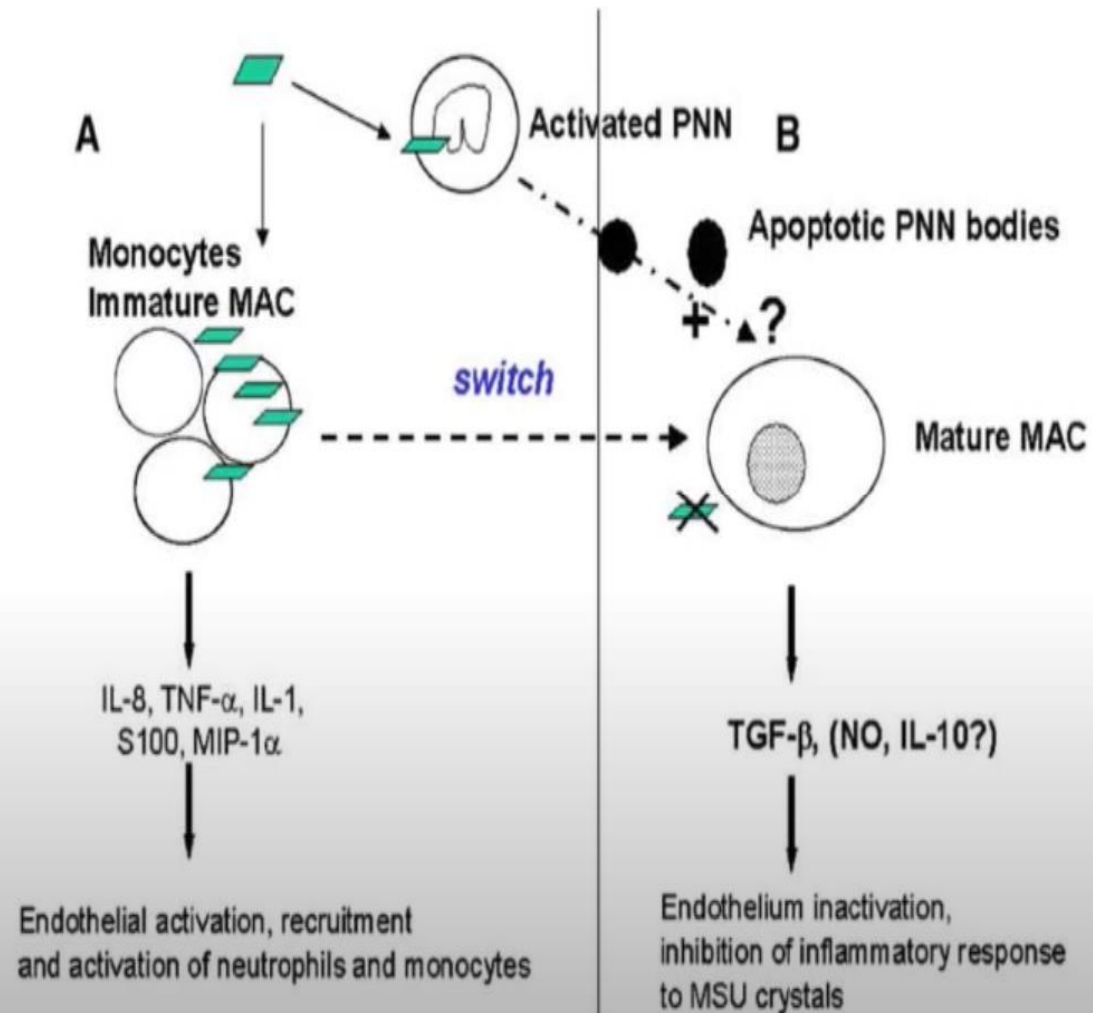


Κρίση ουρικής αρθρίτιδας



Πολυμορφοπυρηνικά διηθήματα και αγγειακή συμφόρηση στον αρθρικό υμένα

Τα ανώριμα μακροφάγα ξεκινούν την ουρική φλεγμονή και τα ώριμα σταματούν την κρίση με την απελευθέρωση TGF-β



2016 EULAR RECOMMENDATION FOR THE MANAGEMENT OF FLARES IN PATIENTS WITH GOUT

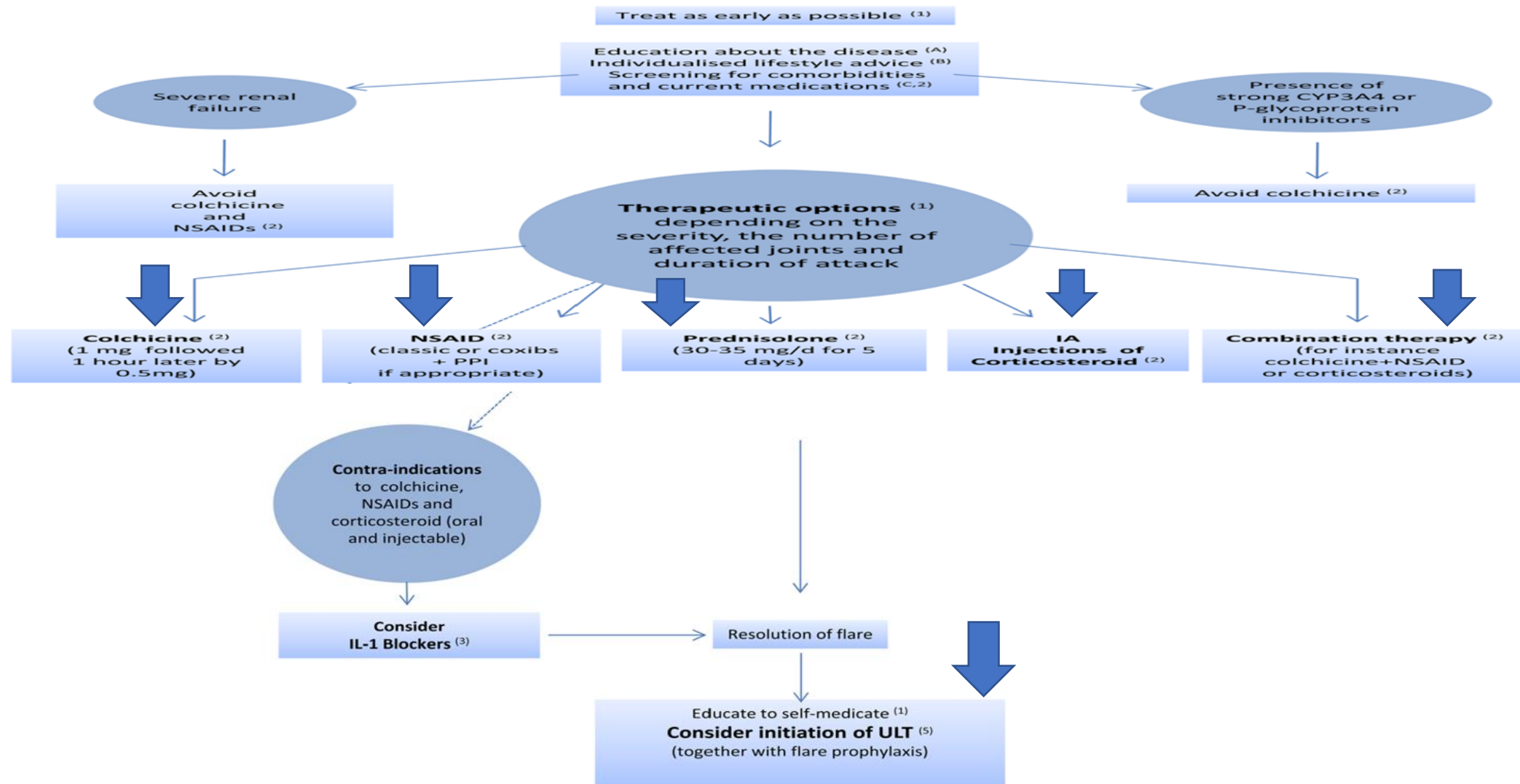


Figure 1 Management of acute flare according to the European League Against Rheumatism recommendations. Letters and numbers in parentheses indicate the items of the recommendations presented in [table 1](#). Strong P-glycoprotein or CYP3A4 inhibitors are cyclosporin, clarithromycin, ketoconazole and ritonavir. IL, interleukin; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; ULT, urate-lowering therapy.

2016 EULAR RECOMMENDATION FOR THE MANAGEMENT OF HYPERURICEMIA IN PATIENTS WITH GOUT

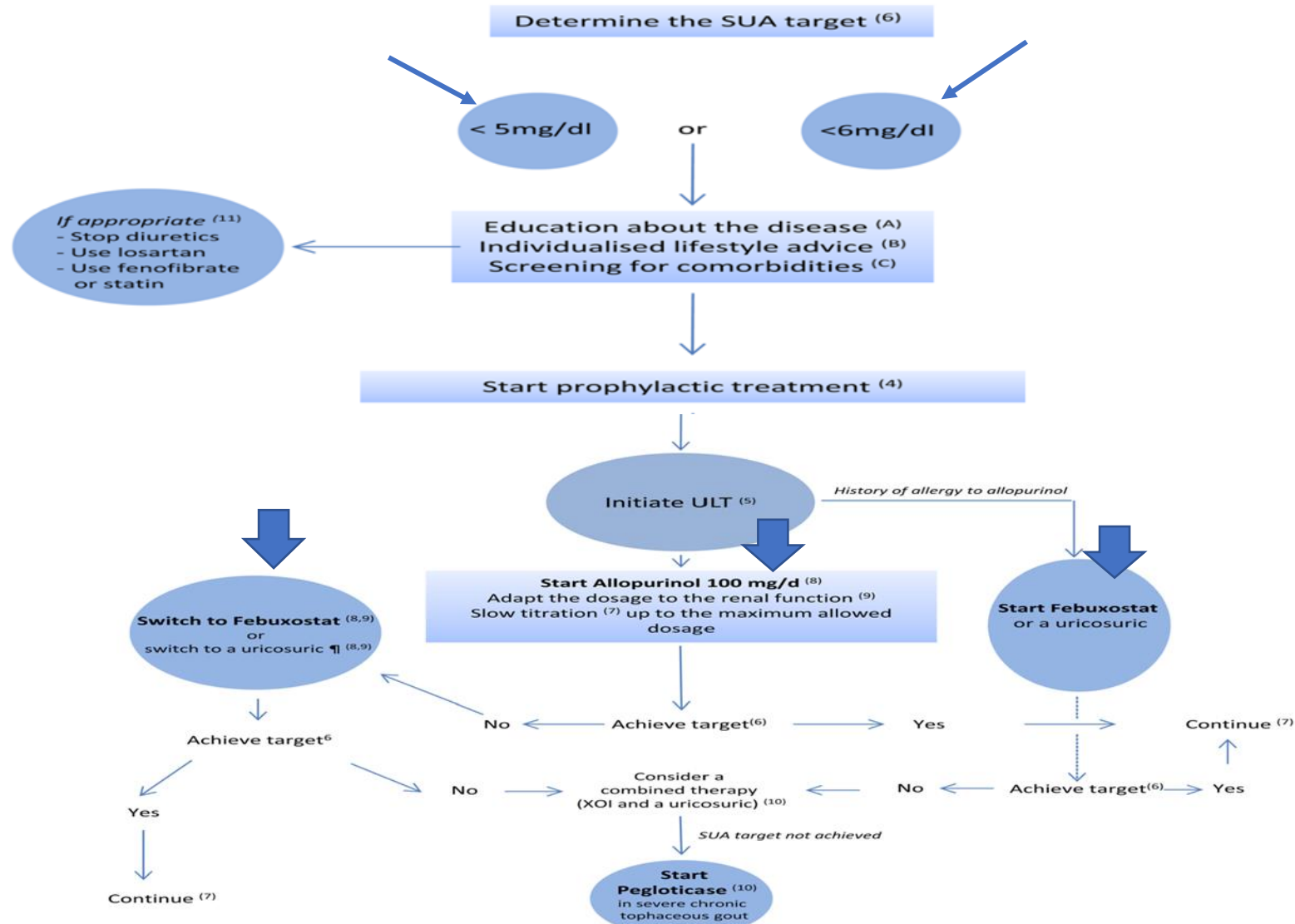
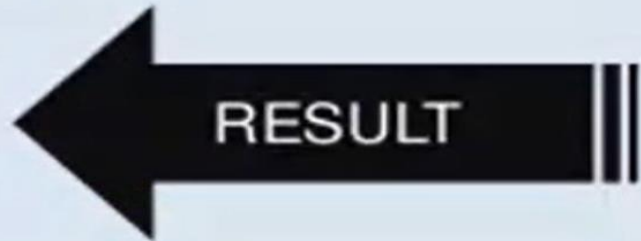
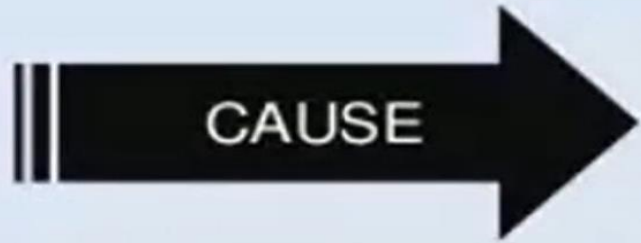


Figure 2 Management of hyperuricaemia in patients with gout according to the European League Against Rheumatism recommendations. Letters and numbers in parentheses refer to the items of the recommendations presented in table 1. SUA, serum uric acid; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor. ¶At this stage, combined allopurinol and a uricosuric is also recommended.

Asymptomatic Hyperuricemia

>7mg/dl (M)
>6mg/dl (F)



Hypertension

CV Disease

Stroke

Renal Disease

**Metabolic
Syndrome**

Πότε χορηγούμε αγωγή στην ασυμπτωματική υπερουριχαιμία;

ΕΟΦ:

«Για την ασυμπτωματική υπερουριχαιμία δεν υπάρχει ομοφωνία για την ανάγκη θεραπείας. Χορηγείται σε ειδικές περιπτώσεις όπως η χημειοθεραπεία και η ακτινοβολία (φαινόμενο λύσεως όγκου), τα πολύ υψηλά επίπεδα ουρικού οξέος στο αίμα (>12 mg/dL στους άντρες και >10 mg/dL στις γυναίκες) κ.λπ.»

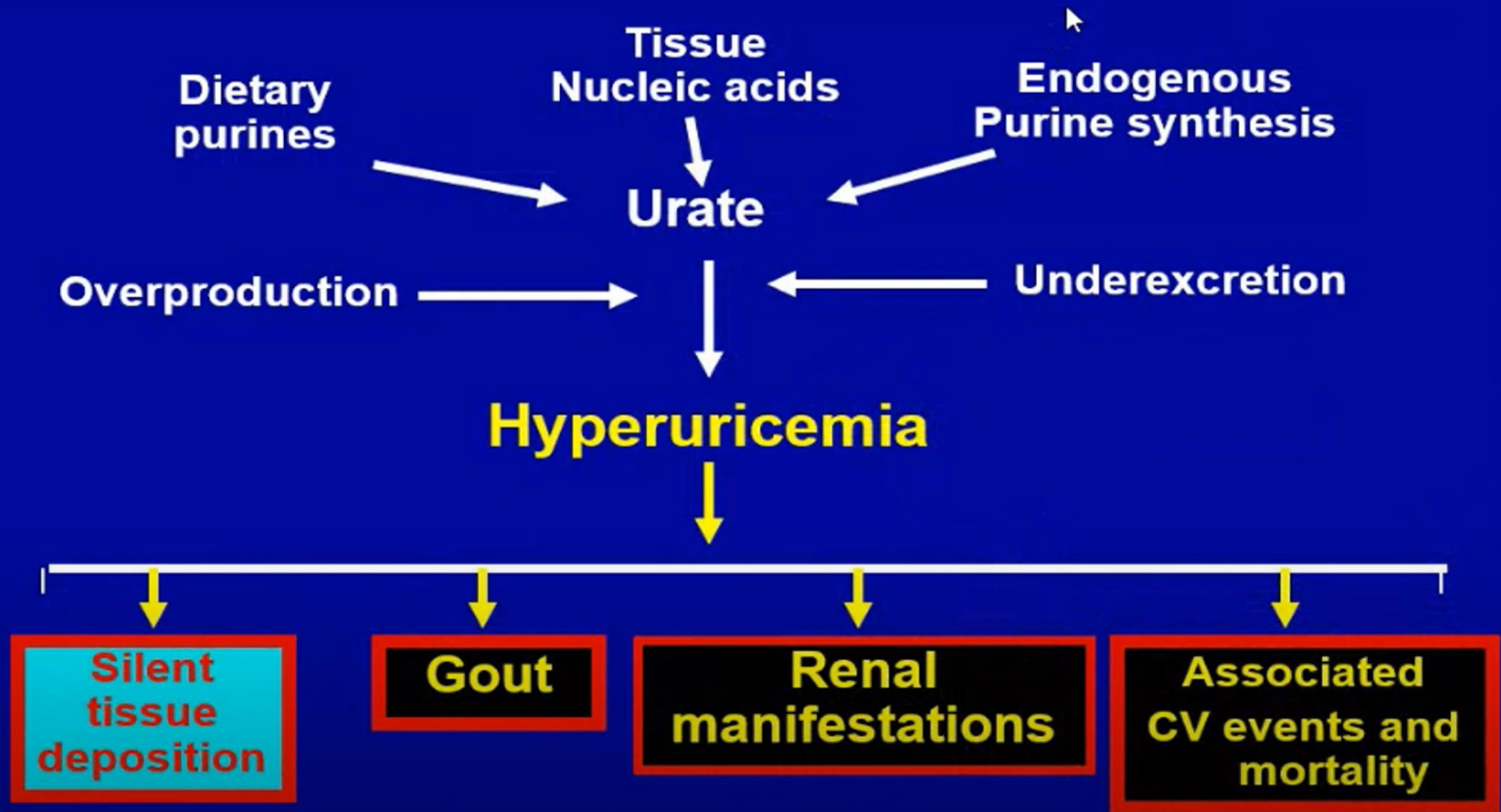
- Diuretics
- Tacrolimus
- Ciclosporin
- Ethambutol
- Pyrazinamide
- Cytotoxic chemotherapy
- Ethanol
- Salicylates (low dose)
- Levodopa
- Ribavirin and interferon
- Teriparatide
-



- Ascorbic acid
- Benzbromarone
- Calcitonin
- Citrate
- Oestrogens
- Fenofibrate
- Losartan
- Probenecid
- Salicylates (high dose)
- Sulfipyrazone
- **Amlodipine**
- **SGLT2-i**



- **Thiazide and loop diuretics** increase uricemia by an average of 0.65 and 0.96 mg/dL respectively.
- **Beta-blockers, non-Losartan ARBs and ACE inhibitors** increase risk of gout and increased uricemia.
- **CCBs and Losartan** should be privileged.
- In cardiac failure, **Spironolactone-Eplerenone** which have no effect on uric acid can be advised when possible.
- Cardio-protective **Aspirin** modestly increases uricemia and **replacement by Clopidogrel** can be considered.



Υπερουριχαιμία ως πολυσυστηματική νόσος

Οι ασθενείς με ουρική νόσο (gout) πάσχουν από πολλαπλά συνοδά νοσήματα

Μεταβολικό Σύνδρομο^{1,4}
63-87%

Υπερλιπιδαιμία²
63%

Χρόνια Νεφρική Νόσος²
47%

Νεφρολιθίαση⁵
39%

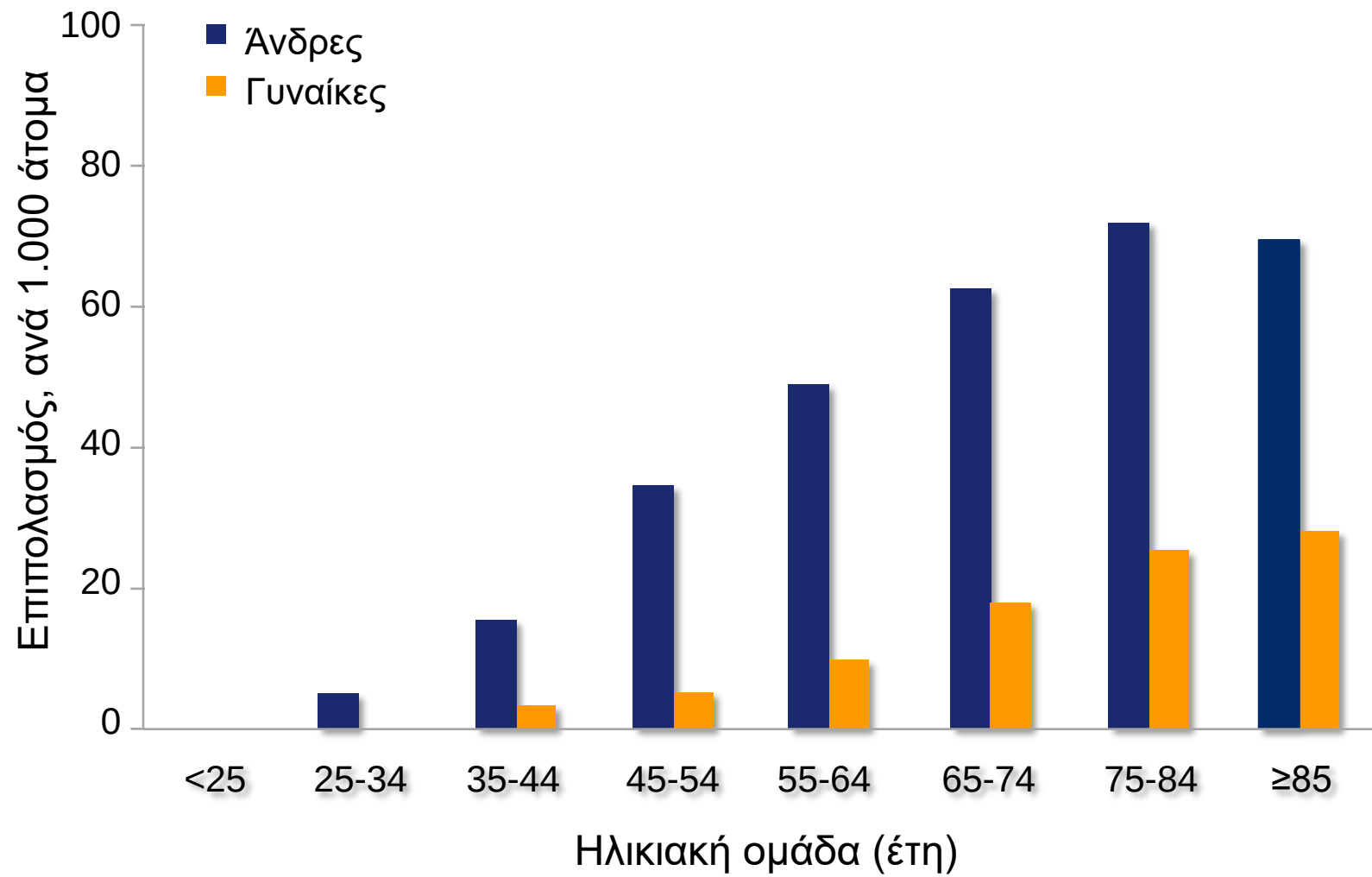
Αρτηριακή Υπέρταση²
89%

Στεφανιαία Νόσος²
37%

Διαβήτης^{3,4}
29-33%

Καρδιακή Ανεπάρκεια³
12%

Ο επιπολασμός της ουρικής αρθρίτιδας αυξάνεται με την ηλικία



In a US population-based study, the prevalence of CKD (stage ≥ 2) in patients with SUA level ≥ 10 mg/dL ($594.9 \mu\text{mol/L}$) and in patients with gout was 86% and 53%, respectively. CKD appears to be a major risk factor for gout and, conversely, gout might cause renal dysfunction.^{53 54} The task force agreed that identifying CKD in patients with gout was of major importance because of the therapeutic implications, as discussed in items 1, 2, 4, 5, 8 and 9. Therefore, estimated glomerular filtration rate (eGFR) should be calculated at the time of diagnosis for CKD classification and monitored regularly in parallel with SUA measurement. This item also emphasises the need to search for other important associated comorbidities, especially coronary heart disease, heart failure, stroke, peripheral arterial disease and diabetes because large epidemiological studies have suggested that hyperuricaemia and/or gout are independent risk factors for these conditions^{55–63} and for death due to cardiovascular causes.^{17 58}

Uric Acid and Diabetes: Is there a Link?

Niki Katsiki¹, Nikolaos Papanas², Vivian A. Fonseca³, Efstratios Maltezos² and Dimitri P. Mikhailidis^{1,*}

Ινσουλinoαντίσταση



Υπερινσουλιναιμία



**Αυξημένη νεφρική
επαναρρόφηση ουρικού οξέος**



Υπερουριχαιμία

Υπεργλυκαιμία



Γλυκοζουρία



**Αυξημένη νεφρική απέκκριση
ουρικού οξέος**

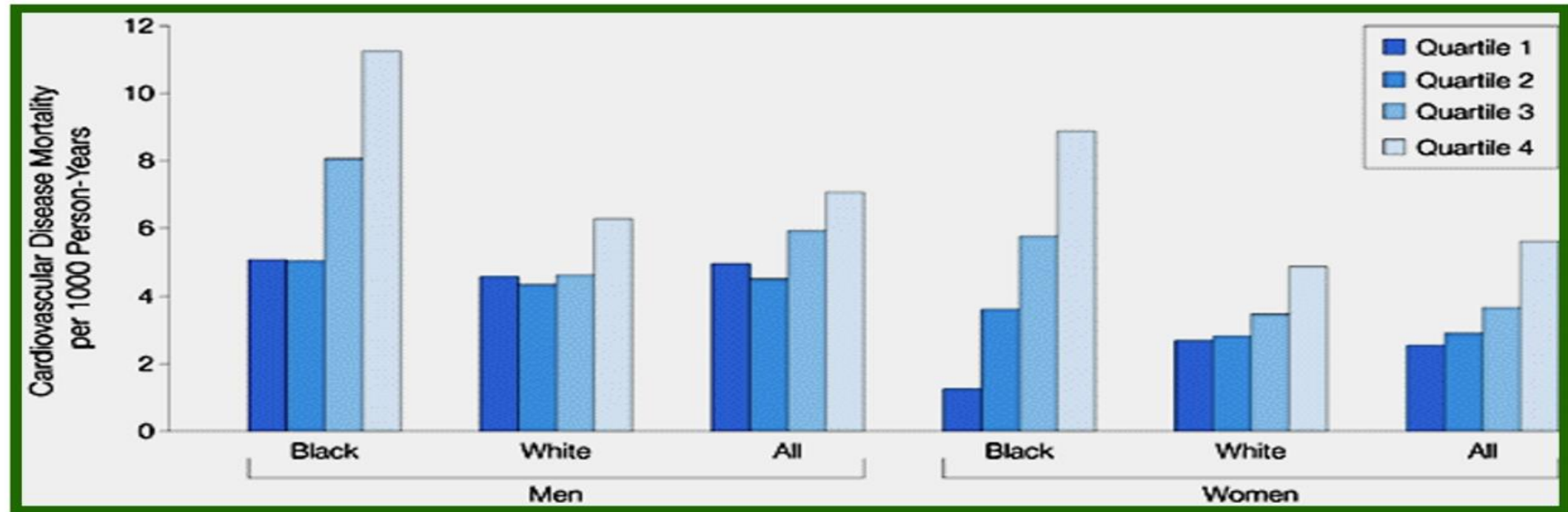


**Μείωση επιπέδων ουρικού
οξέος στο αίμα**

C. *Every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidaemia, hypertension, diabetes and smoking, which should be addressed as an integral part of the management of gout.*

Age-Adjusted CV Mortality Rates by Serum Uric Acid Quartile

NHANES



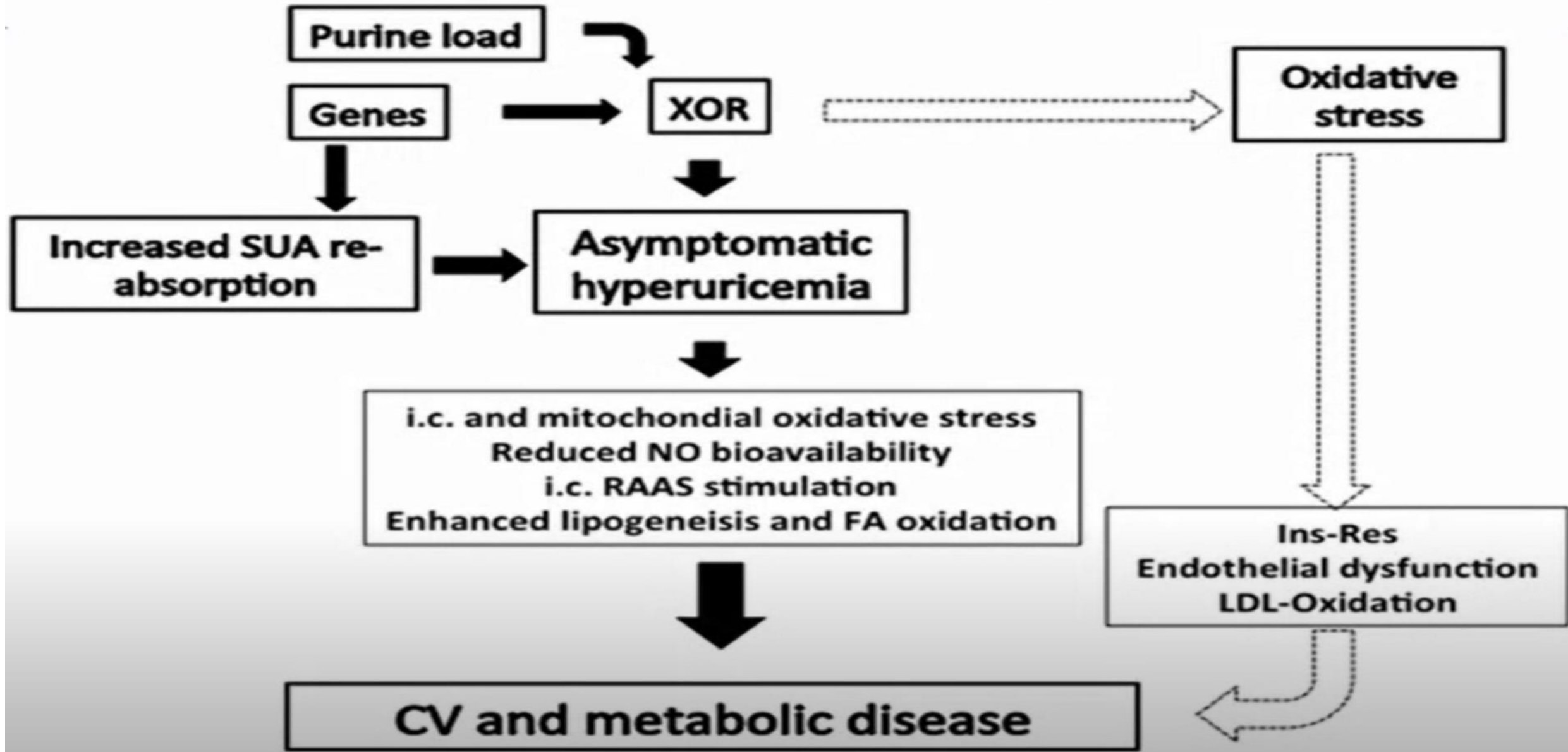
Fang, J. et al. JAMA 2000;283:2404-2410.



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UAB MEDICINE
PEDIATRIC NEPHROLOGY

Παθοφυσιολογικοί μηχανισμοί



Treatment Options for type 2 Diabetes in Adolescents and Youth

Post-intervention Follow-up



**Serum uric acid, urinary albumin excretion
and hypertension in adolescents with type 2
diabetes in the TODAY Study**

Methods 3: TODAY + T2P1

- N=539 (77.1%) of participants were followed annually through year 7 for an average of 5.7 ± 1.7 years (TODAY + T2P1).**
- SUA, urine albumin-to-creatinine (UACR), eGFR by Zappitelli (Cys C and Cr), and BP collected at baseline and annually up to year 7.**
- SUA measured by colorimetric method on Roche Modular P autoanalyzer assay.**

Methods 4: Post-hoc analysis

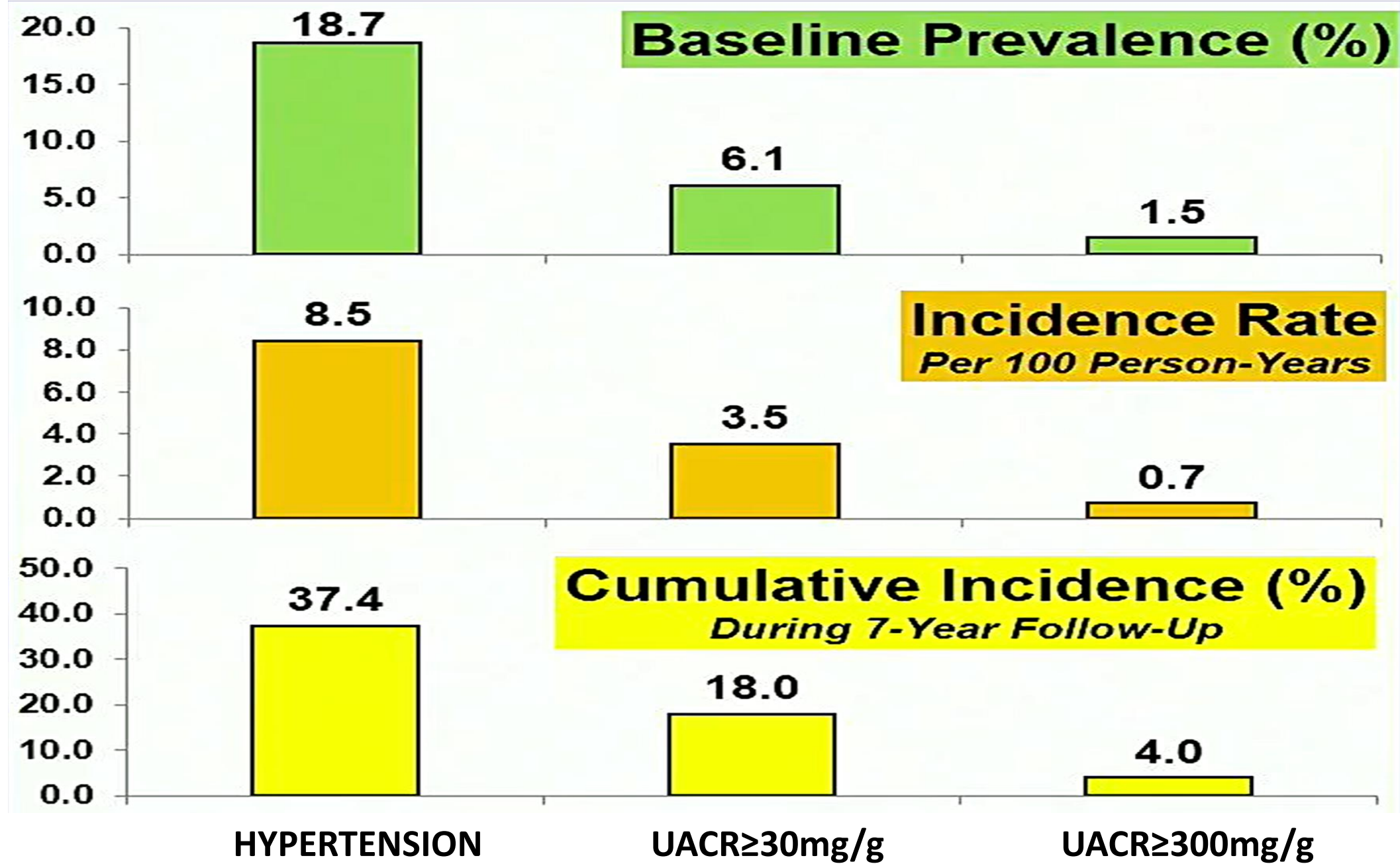
- **Hyperuricemia*:**
 - ≥ 6.8 mg/dL
- **DKD:**
 - **Elevated albumin excretion**
 - **UACR ≥ 30 mg/g**
 - **UACR ≥ 300 mg/g**
- **CVD:**
 - **Hypertension $\geq 130/80$ mm Hg**

** Richette et al. Lancet 2010.*

	Overall (n=539)	Female (n=344)	Male (n=195)	P-value
Sex (%)		64	36	--
Age (years)	13.9 ± 2.0	13.6 ± 2.0	14.4 ± 1.9	<.0001
Diabetes duration (months)	7.9 ± 5.9	8.1 ± 6.0	7.5 ± 5.7	ns
Race/ethnicity (%)				
Black non-Hispanic	34	36	29	ns
Hispanic	43	41	46	
White non-Hispanic	20	18	23	
Other	3	5	2	
Tanner stage 4-5 (%)	89	91	87	ns
BMI (kg/m ²)	34.6 ± 7.8	34.3 ± 7.5	35.2 ± 8.3	ns
HbA1c (%)	6.0 ± 0.7	6.0 ± 0.7	5.9 ± 0.7	ns

Results 2: Baseline CVD and DKD

	Overall (n=539)	Female (n=344)	Male (n=195)	P-value
SUA (mg/dL)	5.8 ± 1.4	5.4 ± 1.2	6.6 ± 1.4	<.0001
Hyperuricemia (%)	26%	12%	50%	<.0001
SBP (mm Hg)	113 ± 11	111 ± 10	117 ± 11	<.0001
DBP (mm Hg)	66 ± 8	66 ± 8	67 ± 8	.03
UACR (µg/mg) [§]	7 (5-13)	7 (5-15)	6 (4-12)	.04
eGFR (mL/min/1.73m ²)	117 ± 19	122 ± 19	108 ± 17	<.0001
ACEi/ARB therapy (%)	5%	5%	4%	ns



Risk of incident hypertension over 7 yrs

OVERALL
(# cases=164)

Baseline SUA
(per 1 mg/dL) ==>

HR = 1.2 (1.1, 1.4); $p=0.01$

Baseline hyperuricemia
(≥ 6.8 mg/dL) ==>

HR = 1.9 (1.2, 2.9); $p=0.003$



Risk of incident UACR ≥ 30 mg/g over 7 yrs

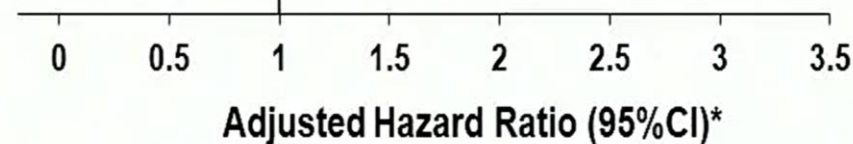
OVERALL
(# cases=91)

Baseline SUA
(per 1 mg/dL) ==>

HR = 1.2 (1.1, 1.5); $p=0.02$

Baseline hyperuricemia
(≥ 6.8 mg/dL) ==>

HR = 1.1 (0.6, 1.9); $p=0.75$



Rat Model of Hyperuricemia



**Normal Rat
Uric Acid
(0.5-1.4 mg/dl)**

**Uricase
inhibitor**
→
**Oxonic acid
(OA)**



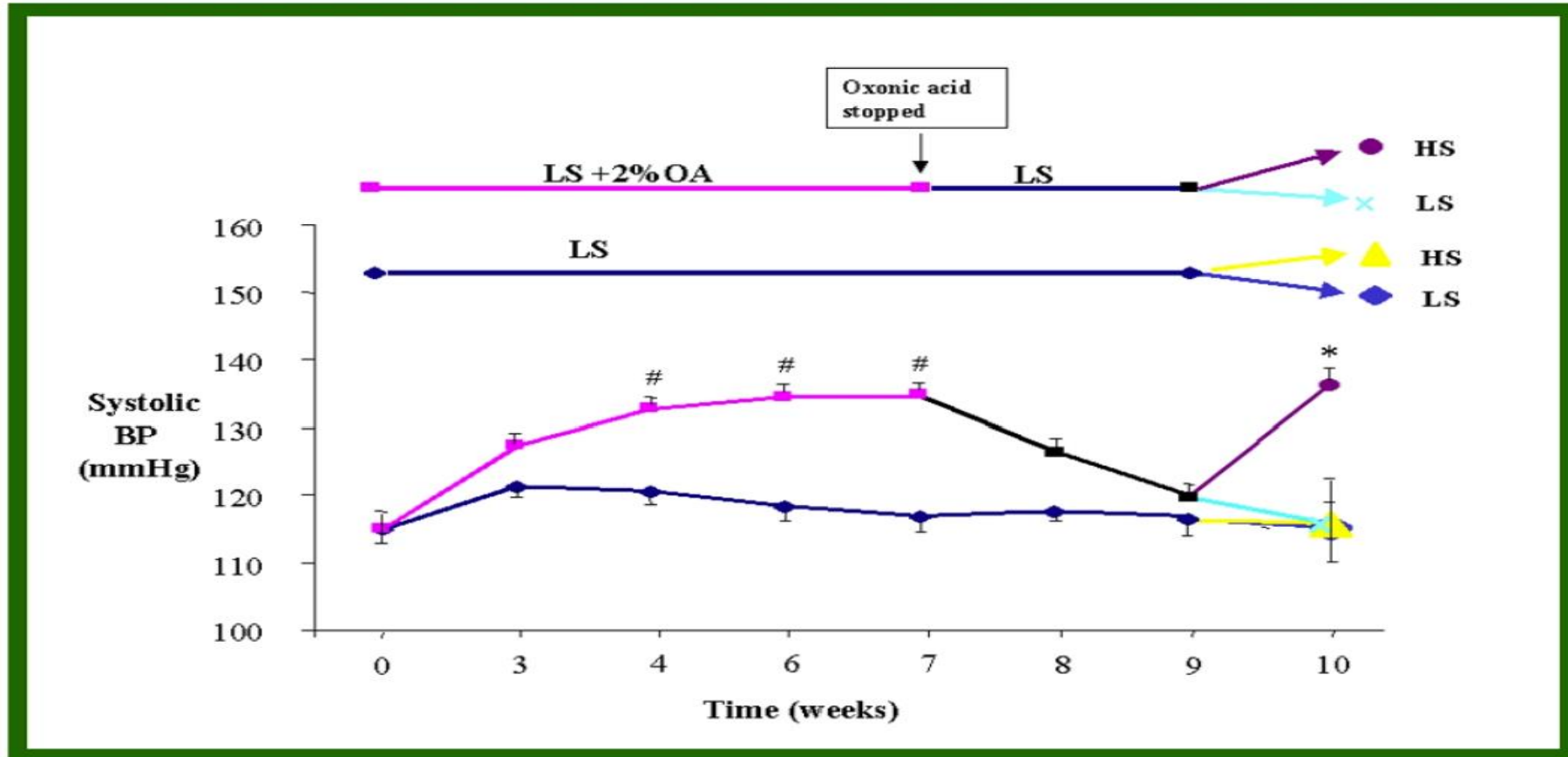
**Hyperuricemic Rat
Uric Acid
(2.7-4.0 mg/dl)**



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Hyperuricemia Induces Hypertension



Watanabe S et al., *Hypertension* 2002; 40:355-360

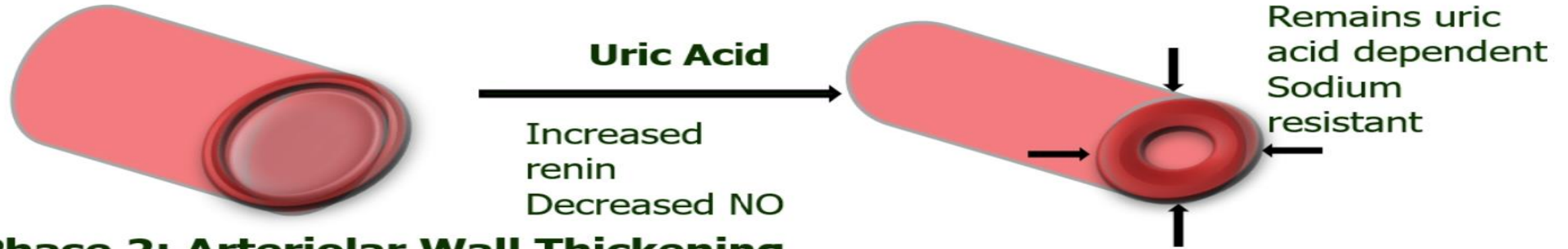


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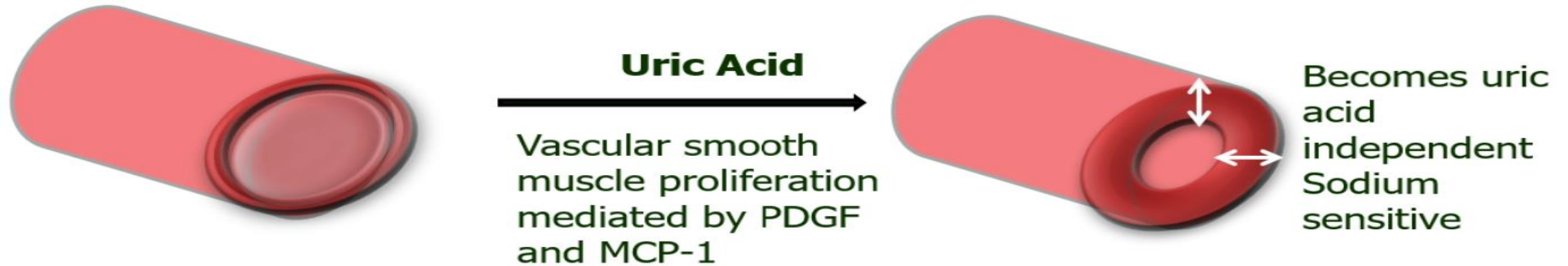
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Vascular model of Uric Acid Mediated Hypertension

Phase 1: Reversible Vasoconstriction



Phase 2: Arteriolar Wall Thickening



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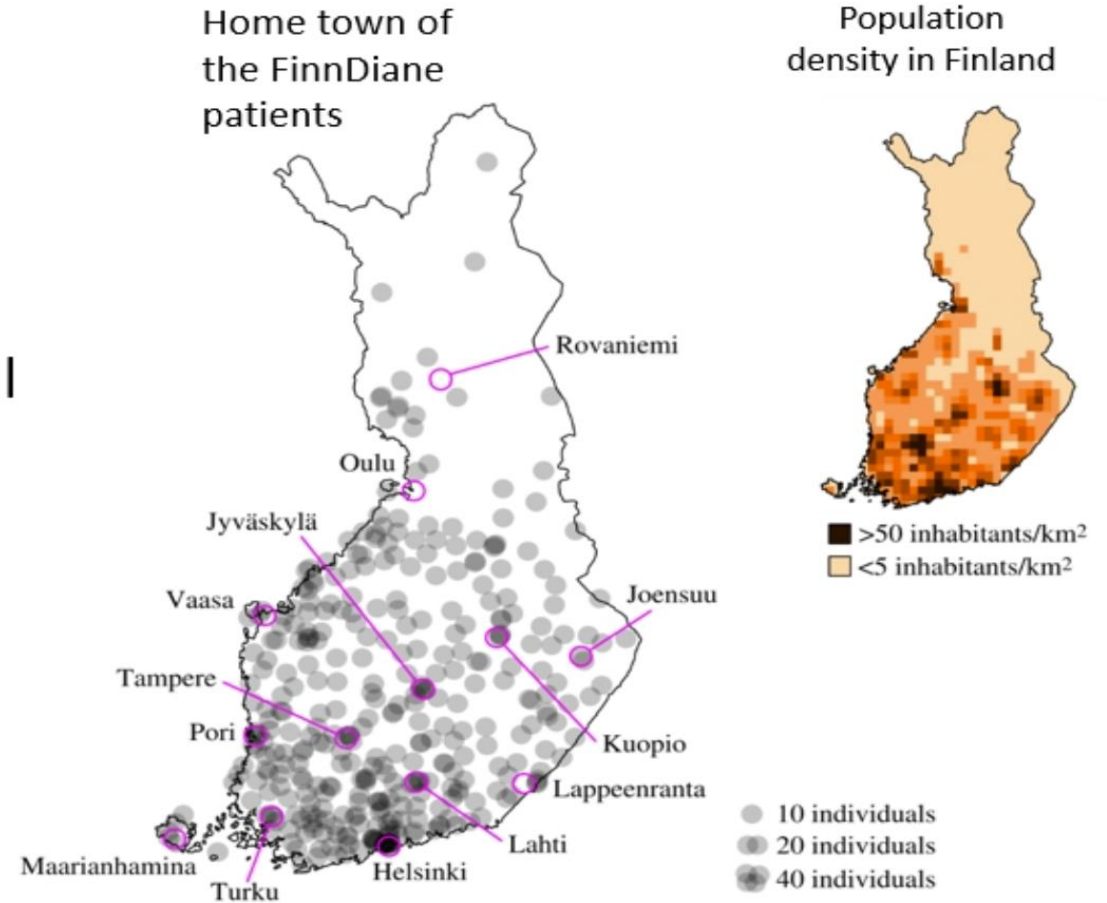
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The Finnish Diabetic Nephropathy Study (FinnDiane) 1997-

“...to identify clinical, biochemical, environmental and genetic markers for diabetic complications with special emphasis on diabetic nephropathy.”

8,000 patients with T1D



The Finnish Diabetic Nephropathy Study (FinnDiane) 1997-

Serum Uric Acid measurements in FinnDiane

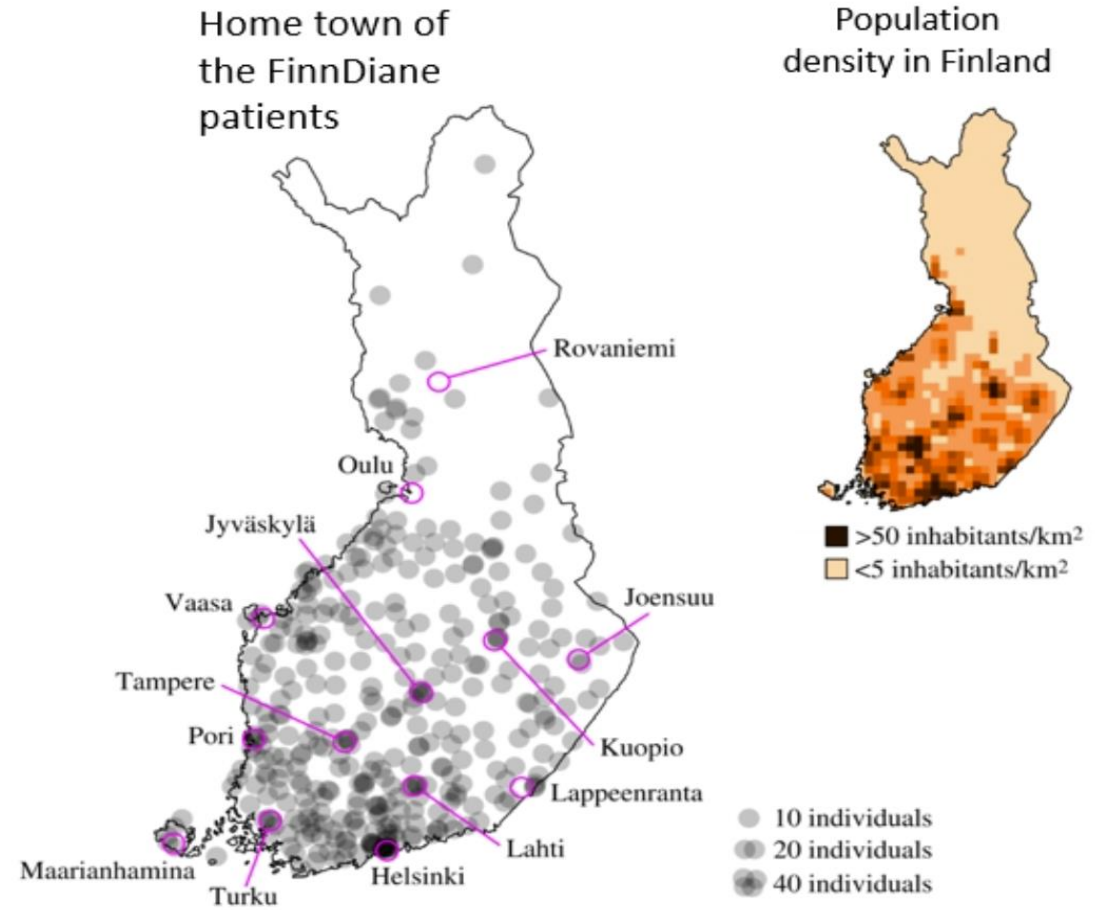
Measured for 94% of participants with follow-up data (7 ± 4 years follow-up)

Follow-up AER data (n = 3,384)

	Nonprogressors	Progressors
Kidney disease (AER)		
Normal AER	n = 2,159	n = 202
Microalbuminuria	n = 393	n = 95
Macroalbuminuria	n = 311	n = 224

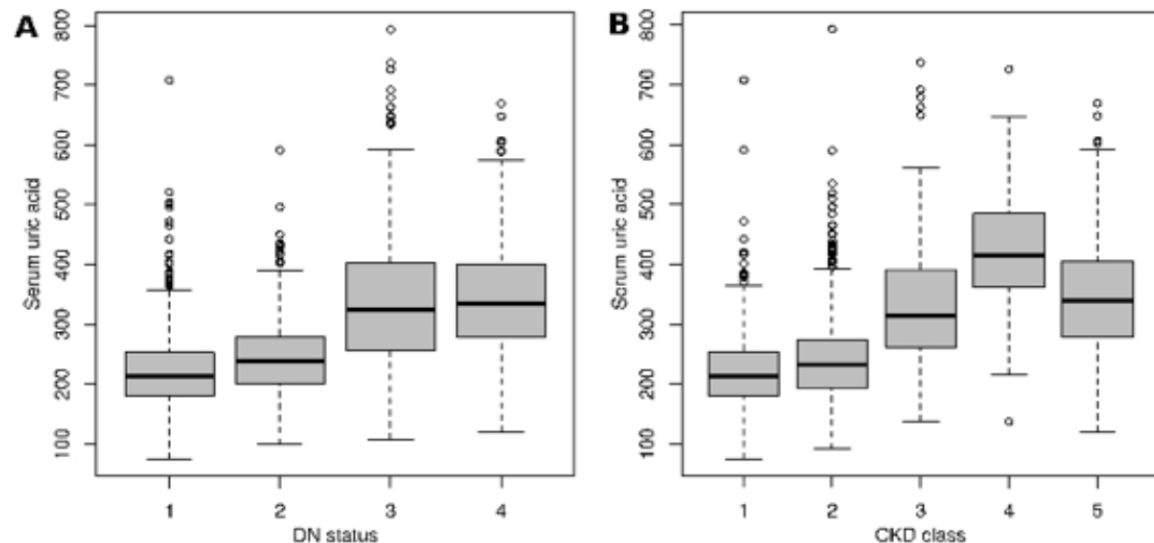
Follow-up eGFR data (n = 2,755)

Renal status (eGFR)		
Stage 1	n = 1,329	n = 196
Stage 2	n = 825	n = 117
Stage 3	n = 106	n = 98
Stage 4	n = 5	n = 64
Stage 5	n = 15	n = NA



Uric acid predicts progression of DKD

- Uric acid associated with DKD status and CKD groups at the baseline
- Predicts progression of DKD and CKD

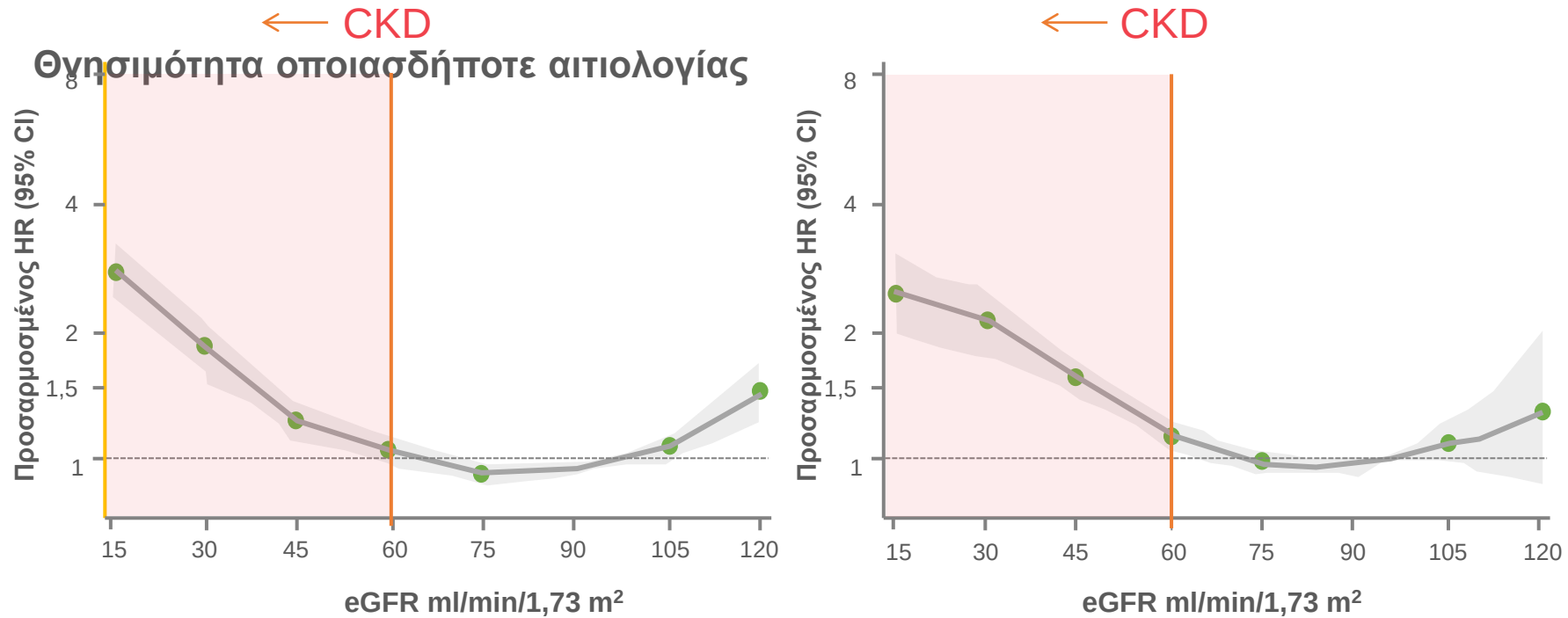


Progression (7 ± 4 years follow-up)	N	Unadjusted Cox PH		Adjusted Cox PH	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Albuminuria based comparisons					
Normal AER → Microalbuminuria	2 361	1.48 (1.00 – 2.18)	0.047	1.11 (0.71 - 1.74)	0.648
Microalbuminuria → Macroalbuminuria	488	1.85 (1.06 – 3.24)	0.03	1.59 (0.87 - 2.93)	0.133
Macroalbuminuria → ESRD	535	4.43 (3.24 – 6.07)	<0.001	1.54 (0.99 - 2.38)	0.054
eGFR based comparisons					
CKD group1/2 → group 3/4/5	2 455	7.58 (4.97 – 11.58)	<0.001	2.79 (1.75 - 4.46)	<0.001
CKD group1/2/3 → group 4/5	2 659	18.80 (13.37 – 26.44)	<0.001	18.80 (13.37 - 26.44)	<0.001
CKD group 3 → group 4/5	204	4.65 (2.83 – 7.65)	<0.001	2.23 (1.22 - 4.08)	0.009
Macroalbuminuria and CKD group 1/2/3 → group 4/5	257	3.37 (2.25 – 5.05)	<0.001	2.47 (1.62 - 3.78)	<0.001

Η μείωση του e-GFR είναι παράγοντας κινδύνου για ΚΔ θάνατο & για θνησιμότητα οποιασδήποτε αιτιολογίας

347.256 υπερτασικά άτομα
2.970.318 ανθρωποέτη

Καρδιαγγειακή θνησιμότητα



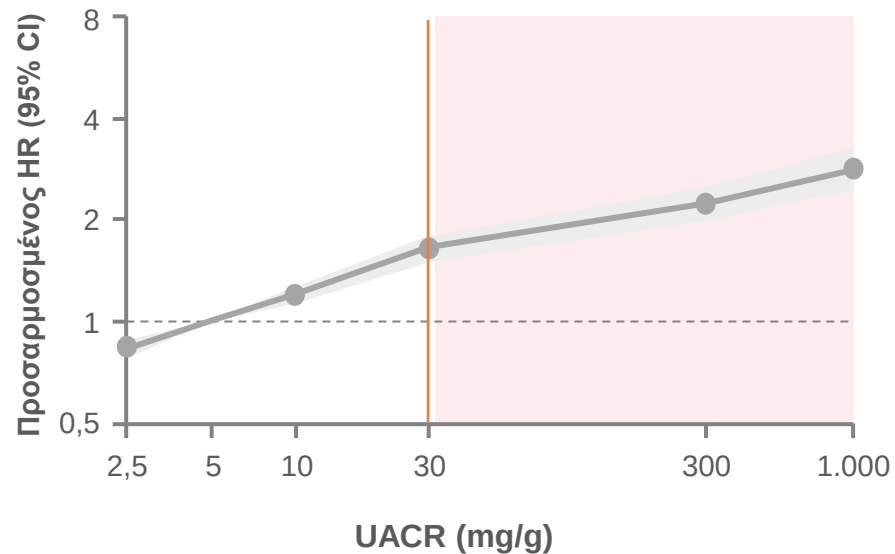
Οι HR προσαρμόστηκαν ως προς την ηλικία, το φύλο, τη φυλή, το κάπνισμα, το ιστορικό καρδιαγγειακής νόσου, τον διαβήτη, τη συγκέντρωση της ολικής χοληστερόλης στον ορό, τον δείκτη μάζας σώματος και τη λευκωματινουρία
CKD = χρόνια νεφρική νόσος, ΚΔ = καρδιαγγειακός, eGFR = εκτιμώμενος ρυθμός σπειραματικής διήθησης, HR = λόγος κινδύνου
Mahmoodi BK et al. *Lancet* 2012;380:1649

Η αύξηση του UACR είναι παράγοντας κινδύνου για ΚΔ θάνατο & για θνησιμότητα οποιασδήποτε αιτιολογίας

347.256 υπερτασικά άτομα
2.970.318 ανθρωποέτη

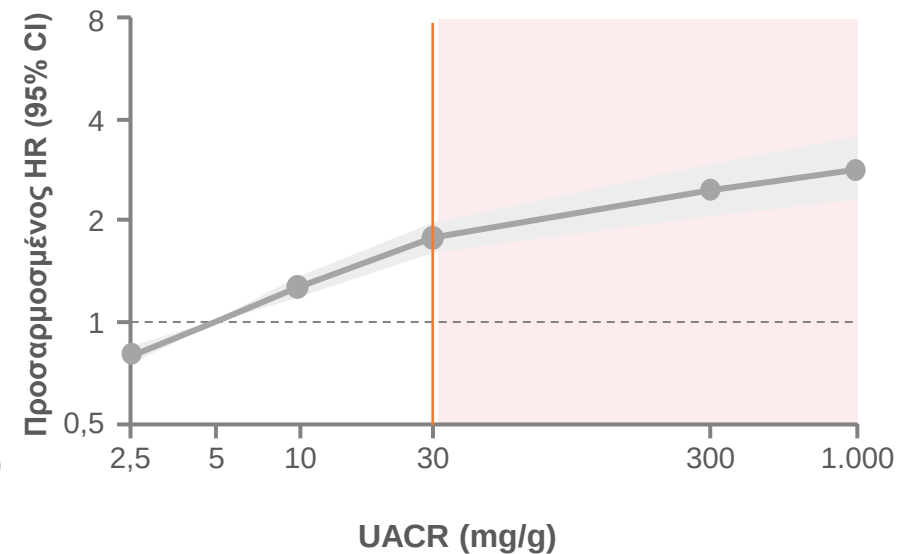
Θνησιμότητα οποιασδήποτε αιτιολογίας

CKD →



Καρδιαγγειακή θνησιμότητα

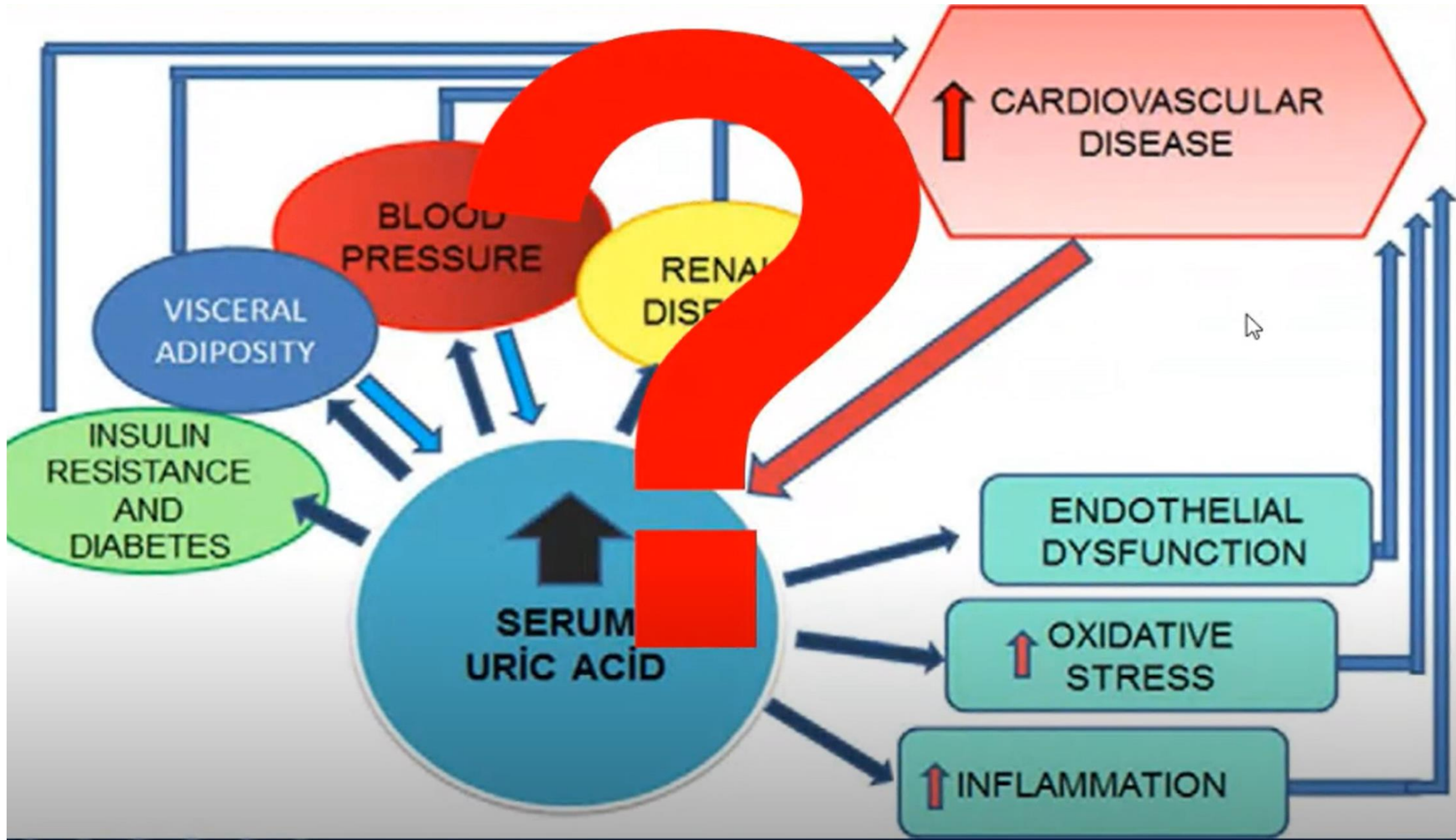
CKD →



Οι HR προσαρμόστηκαν ως προς την ηλικία, το φύλο, τη φυλή, το κάπνισμα, το ιστορικό καρδιαγγειακής νόσου, τον διαβήτη, τη συγκέντρωση της ολικής χοληστερόλης στον ορό, τον δείκτη μάζας σώματος και τα spline eGFR

CKD = χρόνια νεφρική νόσος, ΚΔ = καρδιαγγειακός, eGFR = εκτιμώμενος ρυθμός σπειραματικής διήθησης, HR = λόγος κινδύνου, UACR = λόγος λευκωματίνης προς κρεατινίνη ούρων

Mahmoodi BK *et al. Lancet* 2012;380:1649



Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis

N=958,410 adults
29 studies

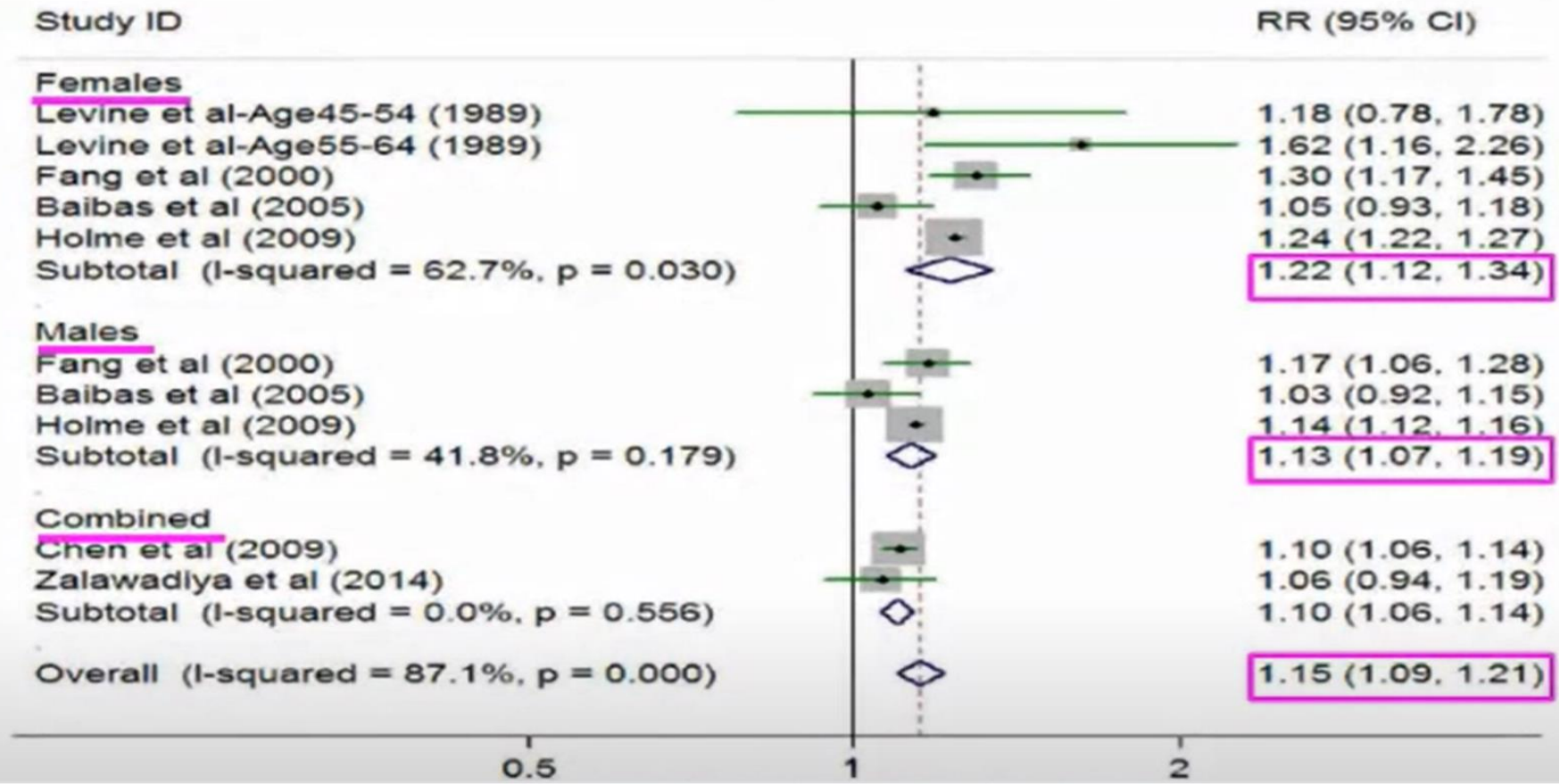


Figure 4. Random effects analysis of multivariate risks of coronary heart disease mortality associated with an increase of 1 mg/dl in serum uric acid level. Combined: studies which did not have sex specific data

Hyperuricemia as an Independent Predictor of Vascular Complications and Mortality in Type 2 Diabetes Patients: A Meta-Analysis

Results: Our search yielded 9 eligible articles (16 ORs and HRs) including 20,891 T2DM patients. Pooled estimates for the relationship suggested that each 0.1 mmol/L increase in SUA resulted in a 28% increase in the risk of diabetic vascular complications and a 9% increase in the risk of diabetic mortality. In stratification-analysis, the positive relationship between SUA and vascular complications remained significant irrespective of mean age, adjustment for metabolic variables and medications. However, it was inconsistent in different populations (significantly positive in the Asian but not in Australian and Italian population) and sample sizes (significantly positive in the relatively large sample size [≥ 1000] but non-significant in the small sample size [< 1000]).

0.1 mmol/L = 1.68 mg/dL

Elevated serum uric acid and risk of cardiovascular or all-cause mortality in people with suspected or definite coronary artery disease: A meta-analysis

Methods: The Pubmed and Embase databases were searched up to April 1, 2016 for the longitudinal studies that investigated the association between the elevated SUA and cardiovascular or all-cause mortality risk in people with suspected or definite CAD. Pooled adjusted risk ratio (RR) and corresponding 95% confidence interval (CI) were calculated for the highest vs. the lowest SUA category or each 1 mg/ml SUA rise.

Results: Nine studies enrolling 25,229 participants were included in the analyses. The highest vs. lowest SUA category was associated with greater risk of cardiovascular mortality (RR 2.09; 95% CI: 1.45–3.02) and all-cause mortality (RR 1.80; 95% CI: 1.39–2.34) after adjustment for potential confounders in a random effects model. Moreover, each 1 mg/ml SUA rise significantly increased by 12% cardiovascular mortality and by 20% all-cause mortality.

Conclusions: Elevated SUA levels are strongly and independently associated with greater risk of cardiovascular and all-cause mortality in people with suspected or definite CAD.

Serum uric acid and cardiovascular mortality in chronic kidney disease: a meta-analysis

N=27,081 CKD patients
11 studies

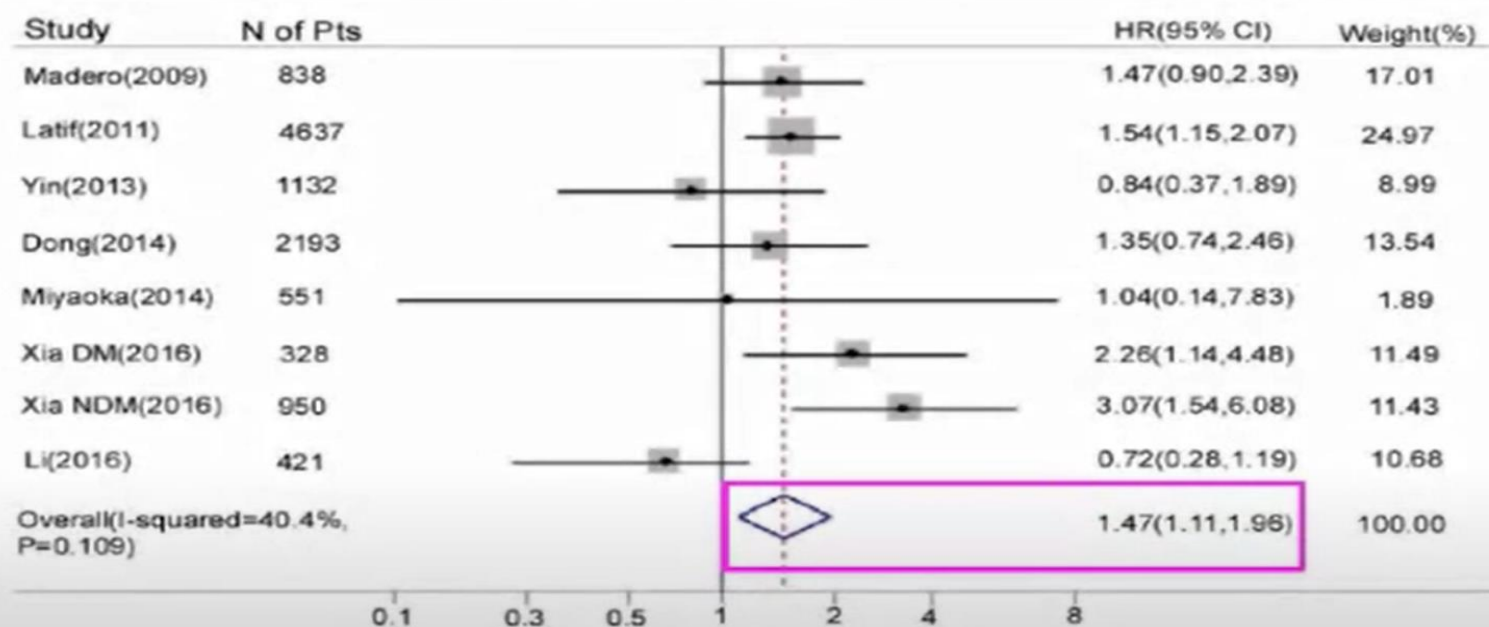


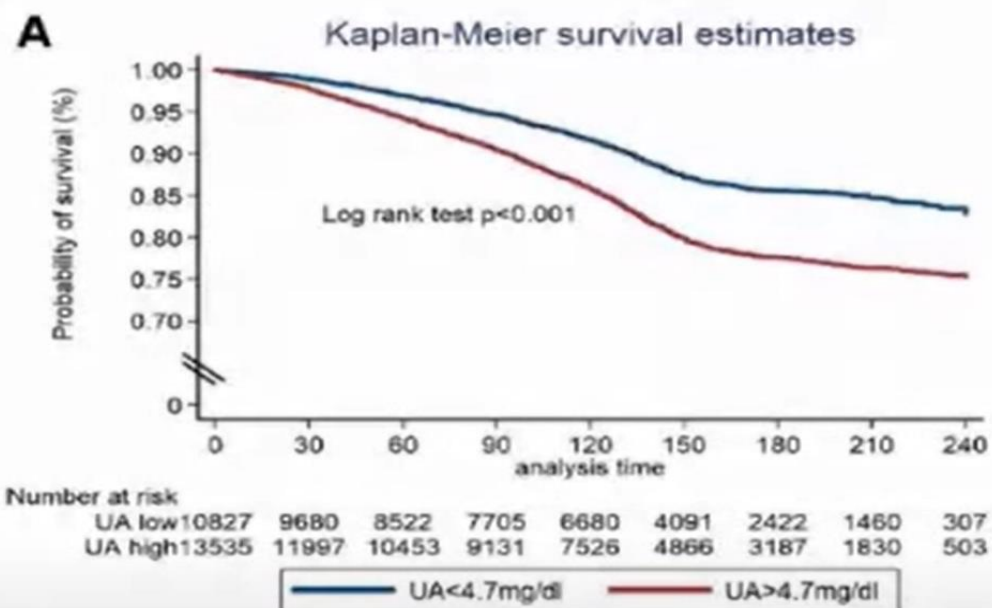
Fig. 2 Forest plot and summary hazard ratio for the association of serum uric acid as a category variable and cardiovascular mortality in patients with chronic kidney disease. Abbreviations: CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; NDM, non-diabetes mellitus

Hyperuricemia and Risk of Cardiovascular Outcomes: The Experience of the URRAH (Uric Acid Right for Heart Health) Project

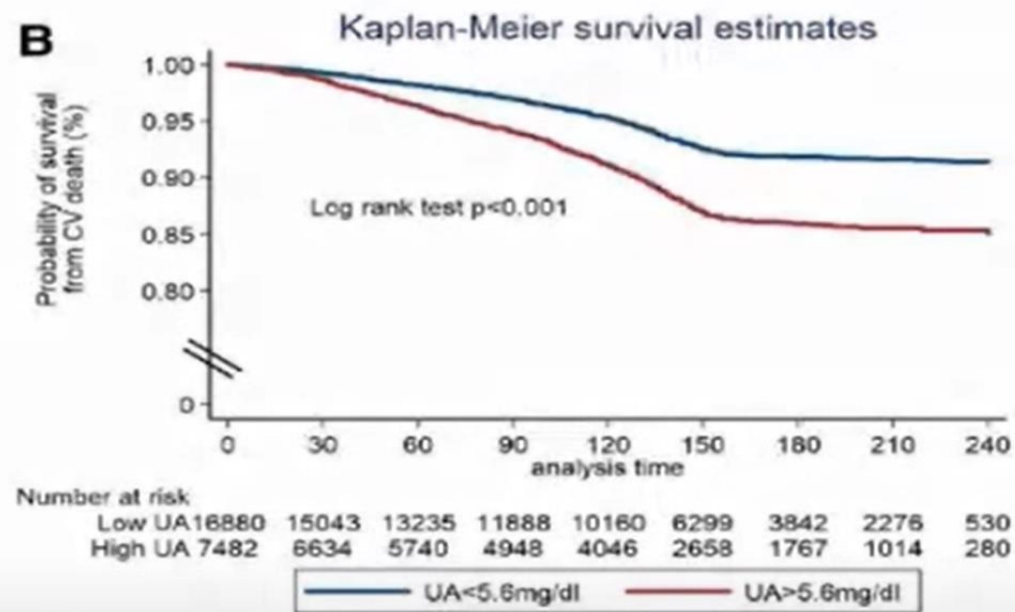
N=22,714 general population + hypertensives

All-cause mortality

CVD mortality



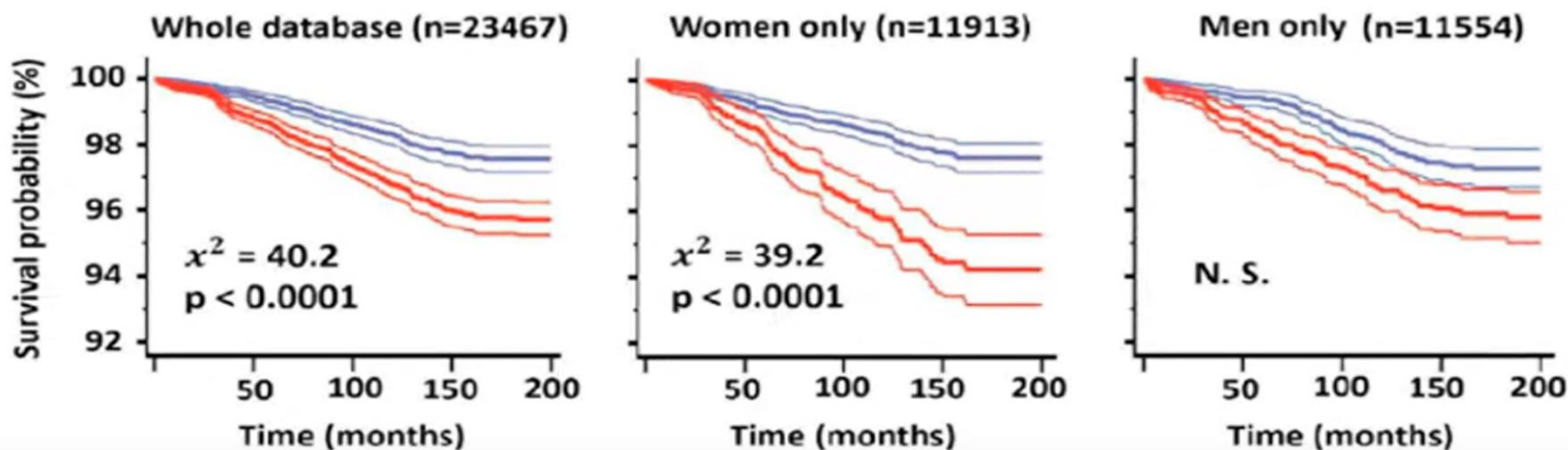
best cut-off value was 4.7 mg/dL
HR of 1.51 (95% CI 1.40–1.63, $p < 0.001$)



optimal cut point for CV mortality was 5.6 mg/dL
HR of 1.59 (95% CI 1.43–1.76, $p < 0.001$)

Hyperuricemia and Risk of Cardiovascular Outcomes: The Experience of the URRAH (Uric Acid Right for Heart Health) Project

Fatal MI: HR 1.146, 95% CI 1.060-1.239; $p=0.0007$
Best SUA cut off point: 5.7 mg/dL



Two cut-offs with little differences were found: 5.26 mg/dL in women and 5.49 mg/dL in men.

THIS IS
THE SIGN
YOU'VE BEEN
LOOKING FOR



NOSE JEWELRY

5. ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation. ULT is indicated in all patients with recurrent flare (≥ 2 /year), tophi, urate arthropathy and/or renal stones. Initiation of ULT is recommended close to the time of first diagnosis in patients presenting at a young age (< 40 years), or with a very high SUA level (> 8 mg/dL; 480 μ mol/L) and/or comorbidities (renal impairment, hypertension, ischaemic heart disease, heart failure). Patients with gout should receive full information and be fully involved in decision-making concerning the use of ULT.

2018 ESC/ESH Guidelines for the management of arterial hypertension

Table 14 Routine workup for evaluation of hypertensive patients

Routine laboratory tests
Haemoglobin and/or haematocrit
Fasting blood glucose and glycated HbA _{1c}
Blood lipids: total cholesterol, LDL cholesterol, HDL cholesterol
Blood triglycerides
Blood potassium and sodium
Blood uric acid
Blood creatinine and eGFR
Blood liver function tests
Urine analysis: microscopic examination; urinary protein by dipstick test or, ideally, albumin:creatinine ratio

ESC/ESH 2018

Table 4 Factors influencing cardiovascular risk in patients with hypertension

Demographic characteristics and laboratory parameters
Sex ^a (men > women)
Age ^a
Smoking (current or past history) ^a
Total cholesterol ^a and HDL-C
Uric acid
Diabetes ^a
Overweight or obesity
Family history of premature CVD (men aged <55 years and women aged <65 years)
Family or parental history of early-onset hypertension
Early-onset menopause
Sedentary lifestyle
Psychosocial and socioeconomic factors
Heart rate (resting values >80 beats/min)

Πόσο επικίνδυνη είναι η υπερουριχαιμία;

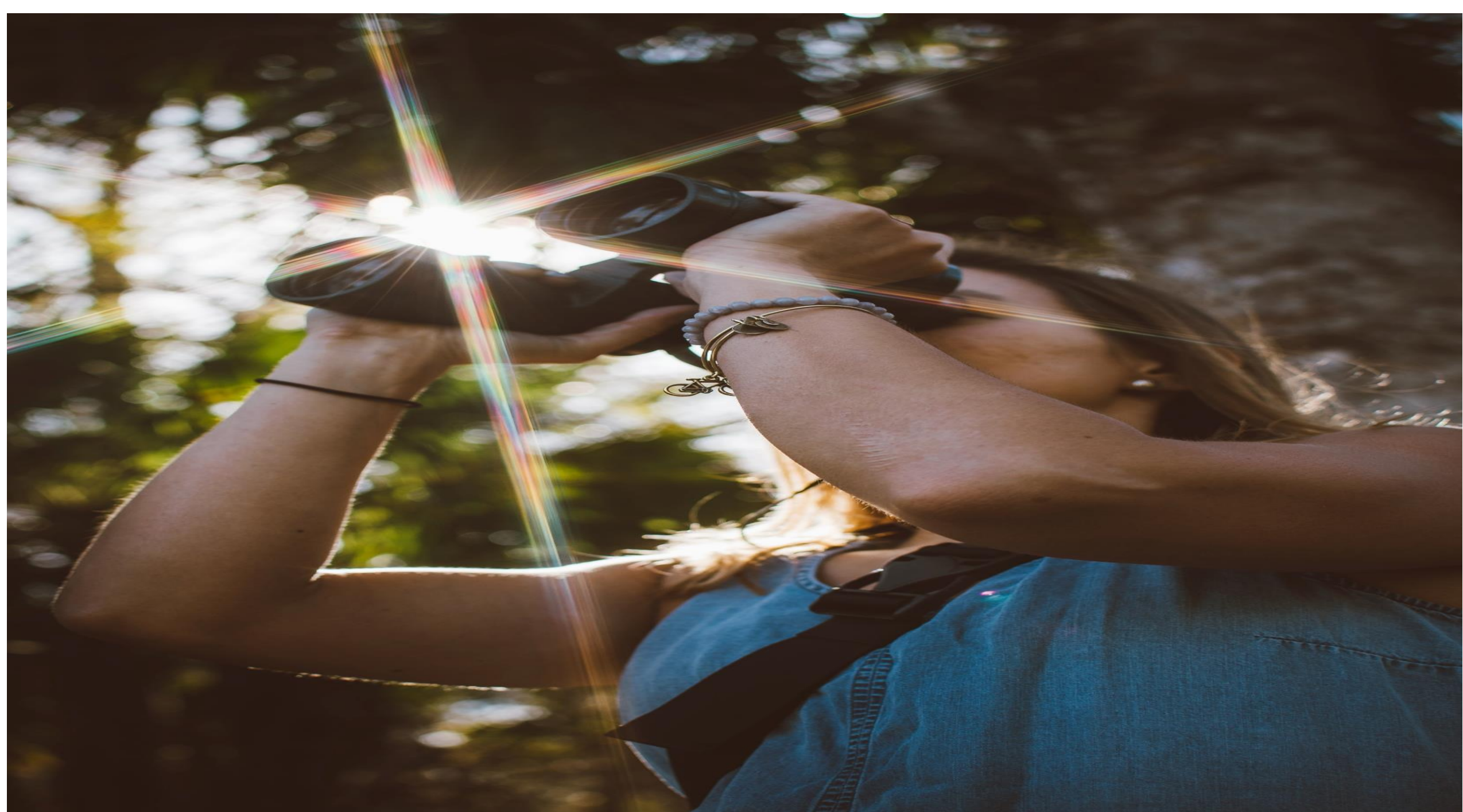
Serum uric acid levels and multiple health outcomes: umbrella review of evidence from observational studies, randomised controlled trials, and Mendelian randomisation studies



OPEN ACCESS

Xue Li *PhD student*¹, Xiangrui Meng *PhD student*¹, Maria Timofeeva *statistical geneticist*², Ioanna Tzoulaki *senior lecturer*³, Konstantinos K Tsilidis *assistant professor*^{3 4}, John PA Ioannidis *professor*^{4 6 7}, Harry Campbell *professor*¹, Evropi Theodoratou *chancellor's fellow*^{1 2}

Συμπέρασμα. Παρά τις εκατοντάδες ανασκοπήσεις, μετα-αναλύσεις, και τυχαιοποιημένες μελέτες με 136 διαφορετικές εκβάσεις, πειστικές αποδείξεις για τον παθολογικό ρόλο των επιπέδων του ουρικού οξέος στο αίμα, υπάρχουν μόνο για την ουρική αρθρίτιδα και την νεφρολιθίαση.





- **600mg allopurinol** daily to the medication of **pts with IHD**, will reduce their risk of having a stroke, heart attack or of dying due to cardiovascular disease.
- We will also measure quality of life and the cost-effectiveness of allopurinol treatment in IHD.
- **5,215 pts** across Scotland and England aged **≥60 yo** with ischaemic heart disease

Xanthine oxidase inhibition for the improvement of long-term outcomes following ischaemic stroke and transient ischaemic attack (XILO-FIST) – Protocol for a randomised double blind placebo-controlled clinical trial

- **N=464** , **>50** years,
- Ischaemic **stroke within the past month**, on a 1:1 basis,
- **2 years allopurinol 300 mg** bid or placebo.
- Brain MRI, cognitive assessment, ABPM & blood sampling.
- Primary outcome: white matter hyperintensity progression.
- Secondary outcomes: change in white matter hyperintensity volume, mean day-time SBP & cognitive function.
- 100 additional cardiac MRI in a sub-study of LVM

Κλινικές διαφορές μεταξύ φεβουξοστάτης και αλλοπουρινόλης

	Φεβουξοστάτη	Αλλοπουρινόλη
Χημική δομή	Μη πουρινικό	Ανάλογο πουρίνης
Αναστολή της οξειδάσης της ξανθίνης	Εκλεκτική αναστολή	Μη εκλεκτική αναστολή
Οδός χορήγησης	Από του στόματος	Από του στόματος
Δοσολογία	80-120 mg	100-900 mg (συνήθως 300 mg)
Ημίσεια ζωή	1,3 έως 15,8 ώρες	Αλλοπουρινόλη: 1 έως 3 ώρες Οξιπουρινόλη: 17 έως 40 ώρες**
Απέκκριση	Ηπατική και νεφρική*	Νεφροί
Προσαρμογή της δόσης σε ήπια έως μέτρια νεφρική δυσλειτουργία	Όχι	Ναι
Φαρμακευτικές αλληλεπιδράσεις	Δεν έχουν καταγραφεί μείζονες φαρμακευτικές αλληλεπιδράσεις με τη φεβουξοστάτη	Αζαθειοπρίνη, 6-μερκαπτοπουρίνη, κυκλοφωσφαμίδη
Σοβαρή ανεπιθύμητη ενέργεια	Άγνωστο	Σύνδρομο υπερευαισθησίας

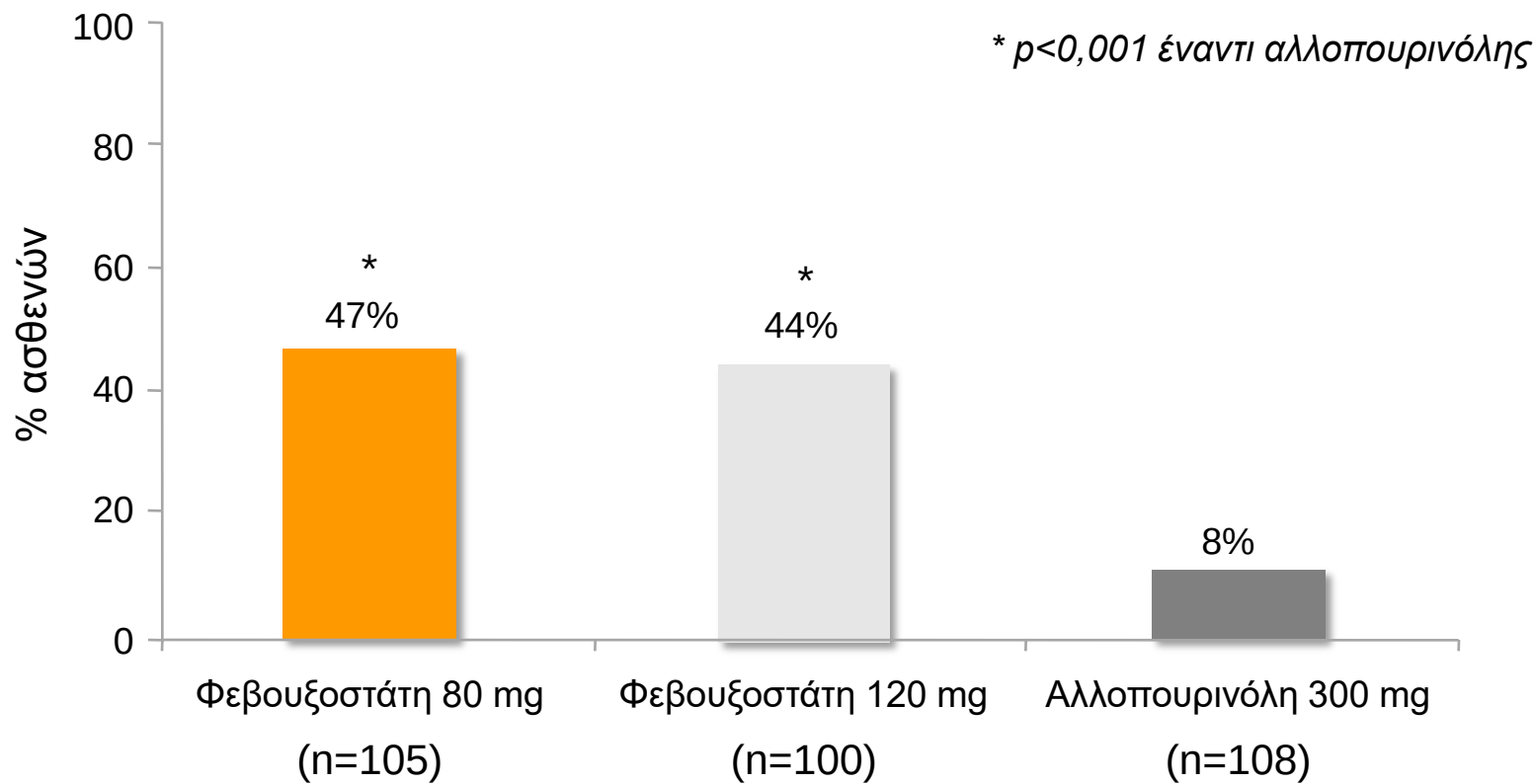
Yu KH. Recent Pat Inflamm Allergy Drug Discov. 2007;1(1):69-75.

* EU SmPC Febuxostat: revised 07/2019.

Η φεβουξοστάτη μειώνει αποτελεσματικά τα επίπεδα του sUA σε ασθενείς με ουρική αρθρίτιδα με υψηλότερα αρχικά επίπεδα

Μελέτη FACT (1 έτος):

Περίπου το 40% των ασθενών διέθετε αρχικά επίπεδα sUA ≥ 10 mg/dl
Ποσοστό ασθενών με ουρική αρθρίτιδα με αρχικά επίπεδα sUA ≥ 10.0 mg/dl που επιτυγχάνει τα τελευταία 3 επίπεδα sUA $< 6,0$ mg/dl



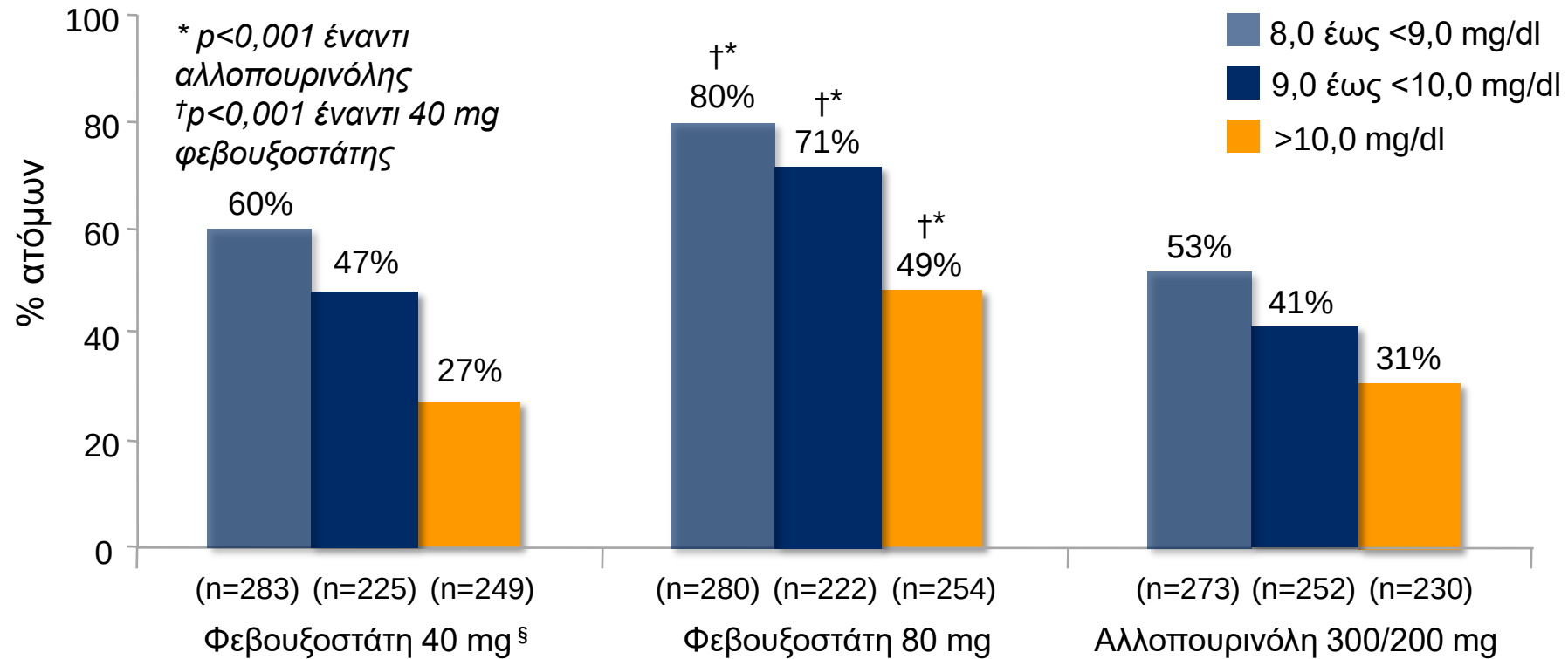
Πληθυσμός ITT: άτομα με ουρική αρθρίτιδα και επίπεδο ουρικού στον ορό $\geq 8,0$ mg/dl την ημέρα -2.

Becker MA, et al. N Engl J Med 2005; 353:2450-2461.

Η φεβουξοστάτη μειώνει αποτελεσματικά τα επίπεδα του sUA (ανάλυση υπο-ομάδας ανά αρχικό sUA)

Μελέτη CONFIRMS:

Ποσοστό των ατόμων με ουρική αρθρίτιδα και sUA <6,0 mg/dl στην τελική επίσκεψη
ανά αρχικό sUA



Πληθυσμός ITT: άτομα με ουρική αρθρίτιδα και επίπεδο ουρικού στον ορό $\geq 8,0$ mg/dl την ημέρα -4.

^s Τα 40 mg φεβουξοστάτης δεν κυκλοφορούν στην Ευρώπη.

Προφίλ ασφάλειας

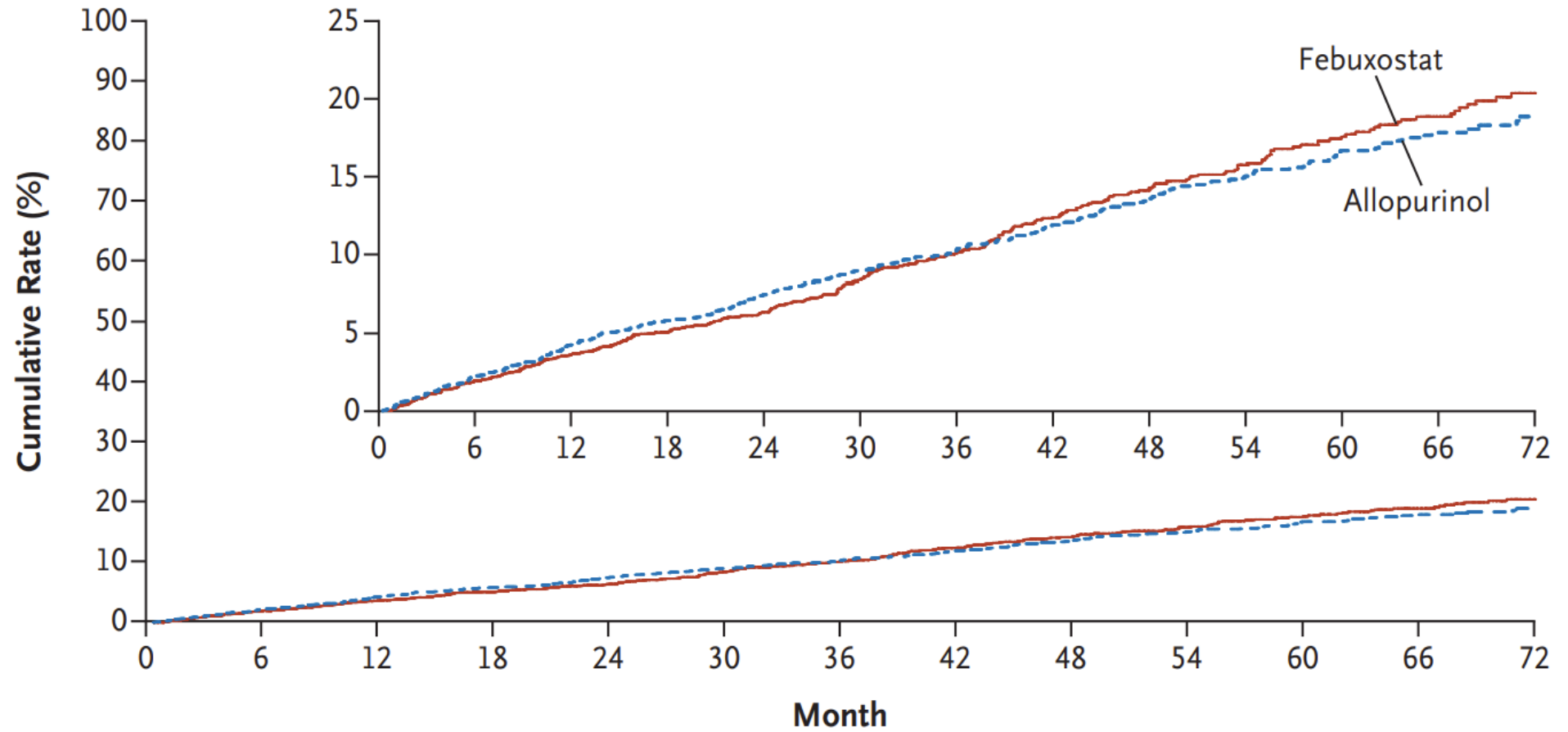
- **Καμία σημαντική φαρμακευτική αλληλεπίδραση με**
 - Κολχικίνη, ινδομεθακίνη, ναπροξένη, υδροχλωροθειαζίδη, βαρφαρίνη ή δεσιπραμίνη
- **Δεν απαιτείται προσαρμογή της δόσης**
 - Σε ασθενείς με ήπια έως μέτρια νεφρική δυσλειτουργία
 - Σε ασθενείς με ήπια ηπατική δυσλειτουργία (αλλά παρακολούθηση των ηπατικών ενζύμων και χρήση μόνο της δόσης των 80 mg)
 - Για ηλικιωμένους ασθενείς
 - Με αναφορά στο φύλο
- **Απαιτείται προσοχή όταν η φεβουξοστάτη χρησιμοποιείται σε ασθενείς με διαταραχή της λειτουργίας του θυρεοειδούς**
- **Η θεραπεία με φεβουξοστάτη σε ασθενείς με προϋπάρχουσα μείζονα καρδιαγγειακή νόσο (π.χ. έμφραγμα του μυοκαρδίου, εγκεφαλικό επεισόδιο ή ασταθής στηθάγχη) θα πρέπει να αποφεύγεται, εκτός εάν δεν υπάρχουν άλλες κατάλληλες επιλογές θεραπείας**

ORIGINAL ARTICLE

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

William B. White, M.D., Kenneth G. Saag, M.D., Michael A. Becker, M.D.,
Jeffrey S. Borer, M.D., Philip B. Gorelick, M.D., Andrew Whelton, M.D.,
Barbara Hunt, M.S., Majin Castillo, M.D., and Lhanoo Gunawardhana, M.D., Ph.D.,
for the CARES Investigators*

A Primary End Point



No. at Risk

Febuxostat	3098	2784	2493	2111	1854	1589	1369	1165	955	778	573	441	264
Allopurinol	3092	2764	2465	2080	1815	1560	1361	1132	933	767	589	437	258

End Point	Febuxostat (N=3098)	Allopurinol (N=3092)	Hazard Ratio (95% CI)	P Value†
	<i>no. of patients (%)</i>			
Primary end point: composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or urgent revascularization due to unstable angina	335 (10.8)	321 (10.4)	1.03 (0.87–1.23)‡	0.66 (0.002)
Secondary end points				
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 (1.03–1.73)	0.03
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 (0.72–1.21)	0.61
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73–1.41)	0.94
Urgent revascularization for unstable angina	49 (1.6)	56 (1.8)	0.86 (0.59–1.26)	0.44
Composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke	296 (9.6)	271 (8.8)	1.09 (0.92–1.28)	0.33
Death from any cause	243 (7.8)	199 (6.4)	1.22 (1.01–1.47)	0.04



The future of Febuxostat after the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial: who CARES?

Niki Katsiki & Claudio Borghi

In addition to the limitations of the CARES trial mentioned by Robinson et al. [1], it should be noted that the majority of the patients (i.e. 56.6%) discontinued the trial drug prematurely; the discontinuation rates were similar in the allopurinol and febuxostat groups, i.e. 55.9 and 57.3%, respectively [2]. This may influence the validity and clinical implications of the results. Furthermore, almost 74% of the patients were on lipid-lowering therapy but low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels were not reported [2]. Statins and fenofibrate may lower SUA levels [4,5]. In the CARES trial, the authors do not clarify how many patients were on statins, fenofibrate or other lipid-lowering therapies. Similarly, several antihypertensive drugs, including angiotensin II receptor antagonists (i.e. losartan), angiotensin-converting enzyme (ACE) inhibitors (i.e. captopril, enalapril and ramipril) and calcium channel blockers (i.e. amlodipine) can decrease SUA [6,7]. In the CARES trial, approximately 70% of the patients in each study group were on renin-angiotensin blocking agents [2]. However, the CARES authors do not mention which renin-

 **43.4%**

Started	3101	3097
Completed	1704	1706
Not Completed	1397	1391
<u>Reason Not Completed</u>		
Adverse Event	191	172
Major Protocol Deviation	52	46
Lost to Follow-up	226	223
Voluntary Withdrawal	595	587
Reason not Specified	333	363

Table S9. Safety End Points On Drug at the Time of the Endpoint*

End Point	Febuxostat (n = 3098)	Allopurinol (n = 3092)	Hazard Ratio for Febuxostat Group (95% CI)	P value
Primary end point: CV death, nonfatal MI, nonfatal stroke or urgent revascularization due to unstable angina — no. (%)	191 (6.2)	199 (6.4)	0.94 (97% , 0.76, 1.17)	0.558
CV death	23 (0.7)	14 (0.5)	1.62 (0.84, 3.15)	0.152
Nonfatal MI	84 (2.7)	96 (3.1)	0.86 (0.65, 1.16)	0.328
Nonfatal stroke	53 (1.7)	57 (1.8)	0.92 (0.63, 1.33)	0.645
Urgent revascularization due to unstable angina	42 (1.4)	44 (1.4)	0.93 (0.61, 1.43)	0.754
Secondary end point: CV death, nonfatal MI, nonfatal stroke - no. (%)	156 (5.0)	161 (5.2)	0.95 (0.77, 1.19)	0.670
Death from any cause	36 (1.2)	27 (0.9)	1.31 (0.80, 2.17)	0.285

*Post hoc analysis

Implications of the cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular morbidities (CARES) trial and associated FDA public safety alert

Strengths of the study

- Large, double-blinded, and randomized study of relevant population (i.e., patients with gout and established CV disease), powered for cardiovascular events
- State-of-the-art adjudication process for relevant CV disease endpoints
- Direct comparison of allopurinol and febuxostat dose titration, including allopurinol dosing above 300 mg/day
- Use of initial gout flare prophylaxis (preferably with colchicine)

Uncertainties arising from the results

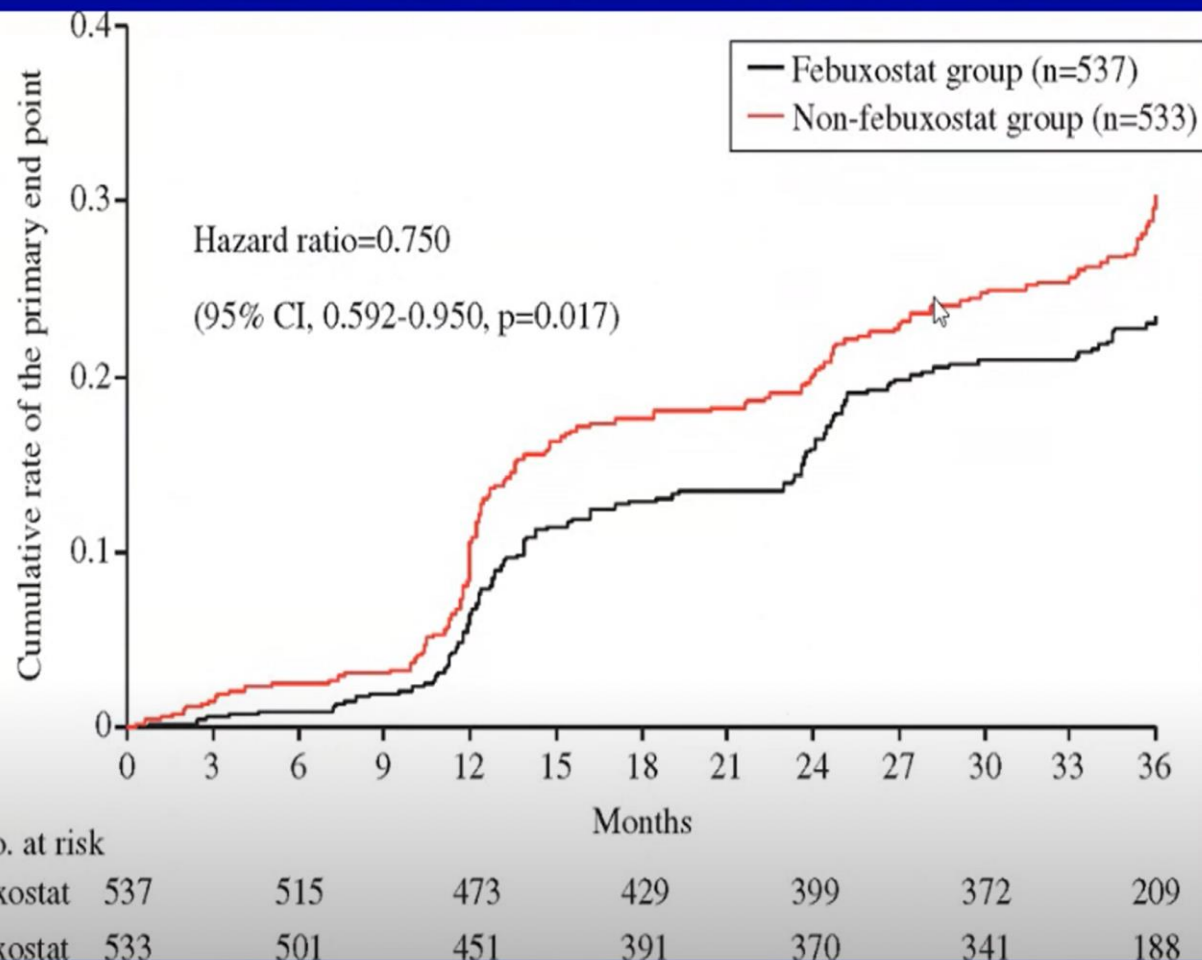
- Particularly high dropout rate of ~50% on average (45–57%) in the treatment groups
- Inconsistent findings between fatal and non-fatal CV endpoints
- ~85% of deaths occurred off study drugs
- Without a placebo comparator, the study design does not answer the question whether allopurinol or febuxostat independently carry an increased risk of CV disease and mortality
- Questions about biologic plausibility, due to anti-inflammatory and anti-atherogenic effects of XOIs, and comparable primary mechanism of action of allopurinol and febuxostat on xanthine oxidoreductase
- Lack of data on temporal course and severity of gout flares, which can exert systemic effects potentially pertinent to CV mortality

The future of Febuxostat after the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial: who CARES?

Niki Katsiki & Claudio Borghi

Almost 39% of the patients in the CARES trial had type 2 diabetes mellitus with small vessel disease; however, antidiabetic treatment was not reported [2]. Metformin has been reported to lower SUA [6]. The sodium-glucose co-transporter 2 (SGLT2) inhibitors empagliflozin and canagliflozin as well as liraglutide (a glucagon-like peptide-1 receptor agonist) can significantly reduce CV morbidity and mortality [8-10]. Empagliflozin and liraglutide were also reported to decrease all-cause death [8,10]. Of note, SGLT2 inhibitors can lower SUA [11,12]. However, it is not known if their SUA-reducing effects are synergistic with XO inhibitors. In this context, it would be interesting to know if antidiabetic therapy differed between the febuxostat and allopurinol group in the CARES trial.

Febuxostat for Cerebral and CaRdiorenovascular Events PrEvEntion StuDY (FREED)



FREED Study

N=1,070 elderly patients with SUA >7 to ≤9 mg/dL

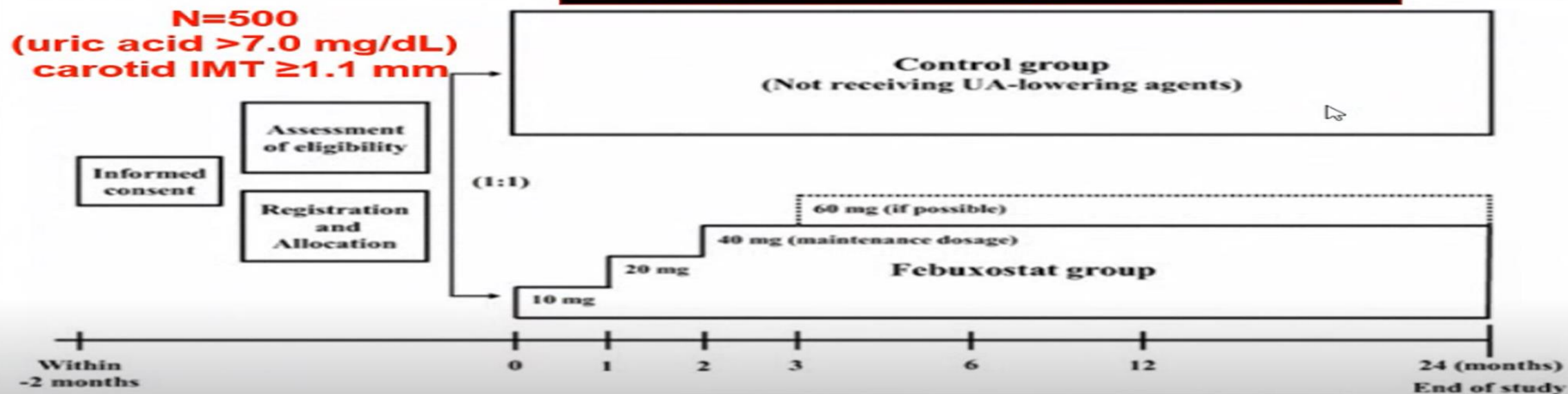
Table 2 Hazard ratio and 95% CIs for component of the primary and secondary endpoints

	Febuxostat group (n = 537)	Non-febuxostat group (n = 533)	Hazard ratio (95% confidence interval)	P-value
Primary endpoint				
Composite of death due to any cause, cerebrovascular disease, non-fatal coronary artery disease, heart failure requiring hospitalization, arteriosclerotic disease requiring treatment, renal impairment, and atrial fibrillation	125 (23.3)	153 (28.7)	0.750 (0.592–0.950)	0.017
			↓ 25%	
Secondary endpoints				
Death due to cerebral, cardiovascular, or renal disease	6 (1.1)	6 (1.1)	0.958 (0.314–2.926)	0.940
Cerebrovascular disease	9 (1.7)	7 (1.3)	1.271 (0.479–3.371)	0.630
Non-fatal coronary artery disease	4 (0.7)	7 (1.3)	0.559 (0.167–1.869)	0.345
Heart failure requiring hospitalization	9 (1.7)	12 (2.3)	0.699 (0.290–1.689)	0.427
Arteriosclerotic disease requiring treatment	2 (0.4)	3 (0.6)	0.644 (0.107–3.873)	0.631
Renal impairment	87 (16.2)	109 (20.5)	0.745 (0.562–0.987)	0.041
Atrial fibrillation	4 (0.7)	3 (0.6)	1.320 (0.292–5.968)	0.719
Death due to other causes	4 (0.7)	6 (1.1)	0.635 (0.179–2.253)	0.482
Hard endpoint: composite of death due to any cause, cerebrovascular disease, or non-fatal coronary artery disease	23 (4.3)	26 (4.9)	0.861 (0.492–1.506)	0.600

PRIZE study

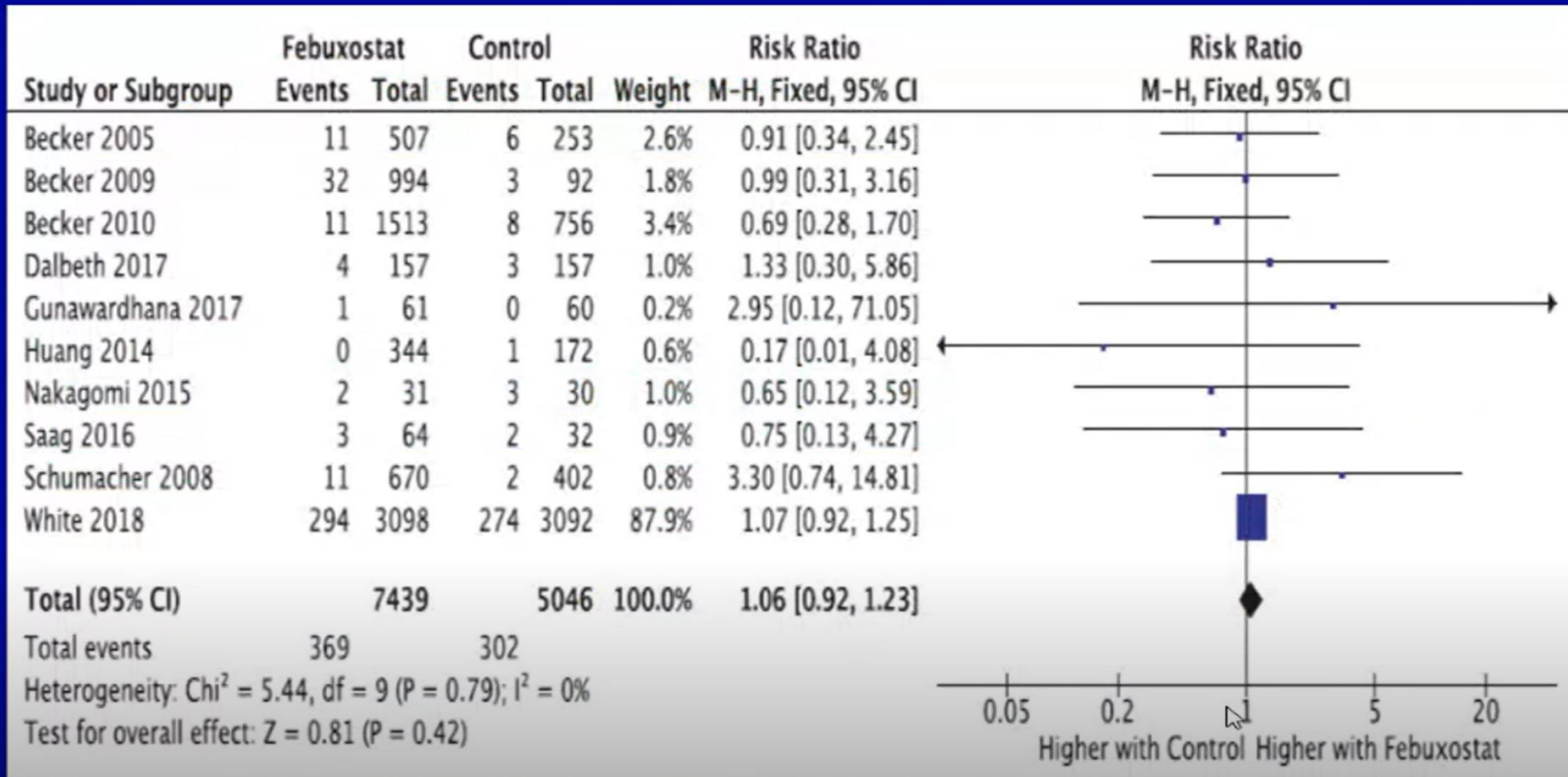
Effects of febuxostat on atherosclerosis

asymptomatic hyperuricemia



Adjudicated clinical event	Febuxostat (<i>n</i> = 241)	Control (<i>n</i> = 247)
Total, number (%)	9 (3.7)	16 (6.5)
Cardiovascular death	1 (0.4)	3 (1.2)
Nonfatal myocardial infarction	0 (0.0)	1 (0.4)
Nonfatal stroke	3 (1.2)	5 (2.0)
Composite renal events ^a	3 (1.2)	4 (1.6)
Non-cardiovascular death	2 (0.8)	4 (1.6)
All-cause death	3 (1.2)	7 (2.8)

Febuxostat and CV Events: Review and Meta-Analysis



A graphic featuring a world map in dark blue on a purple-to-blue gradient background. Overlaid on the map is a large red banner with the word 'BREAKING' in white, bold, italicized capital letters. Below this, a white banner with the word 'NEWS' in red, bold, italicized capital letters is positioned. To the right of the main banner, a smaller red banner with the word 'LIVE' in white, bold, italicized capital letters is visible. The entire graphic is accented with several horizontal red lines of varying lengths.

BREAKING

NEWS

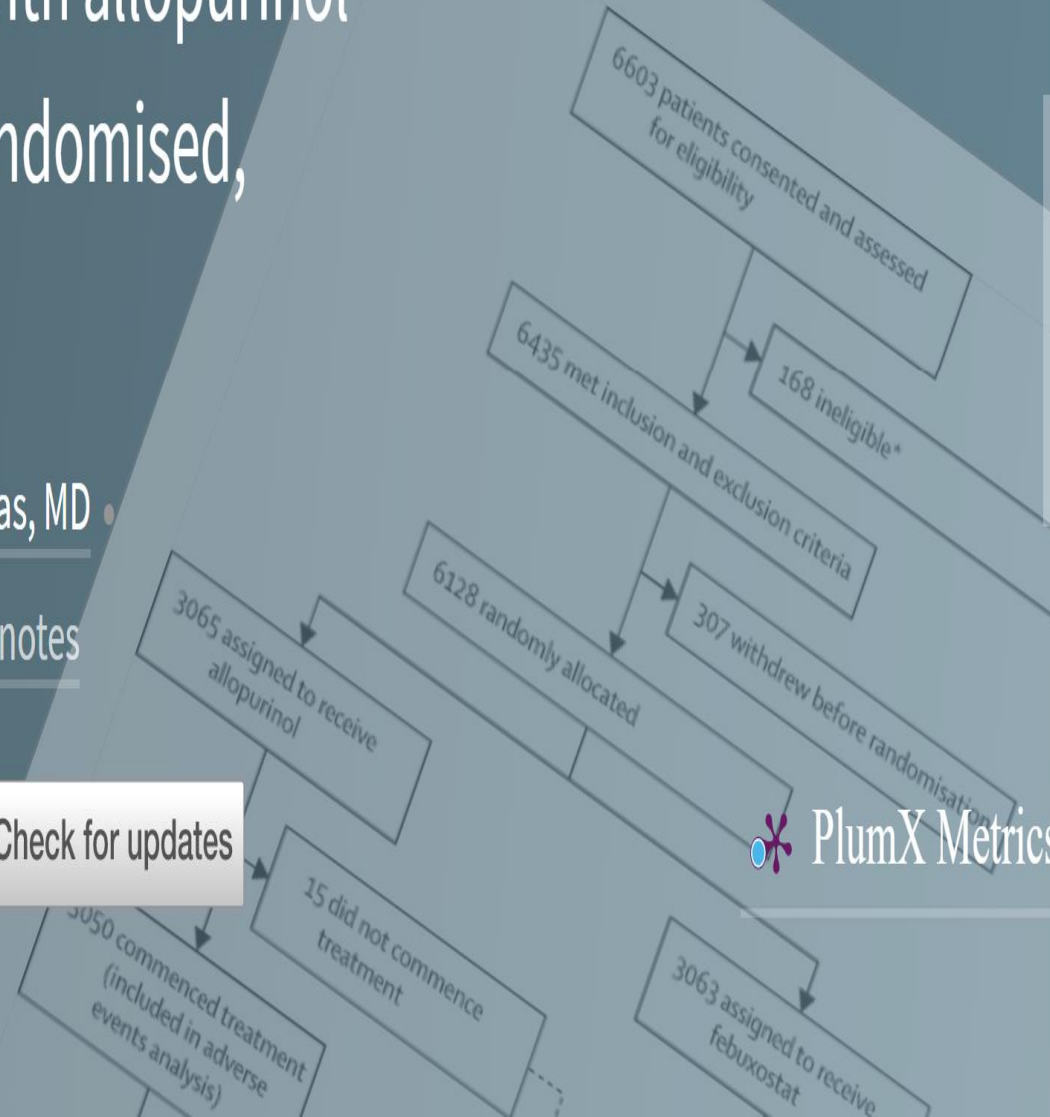
LIVE

Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial

[Prof Isla S Mackenzie, MBChB](#) • [Prof Ian Ford, PhD](#) • [Prof George Nuki, MBBS](#) • [Prof Jesper Hallas, MD](#) •

[Prof Christopher J Hawkey, MD](#) • [Prof John Webster, MD](#) • et al. [Show all authors](#) • [Show footnotes](#)

Published: November 09, 2020 • DOI: [https://doi.org/10.1016/S0140-6736\(20\)32234-0](https://doi.org/10.1016/S0140-6736(20)32234-0) •



EMA required to perform a safety clinical trial

FAST (Febuxostat vs Allopurinol Streamline Trial).

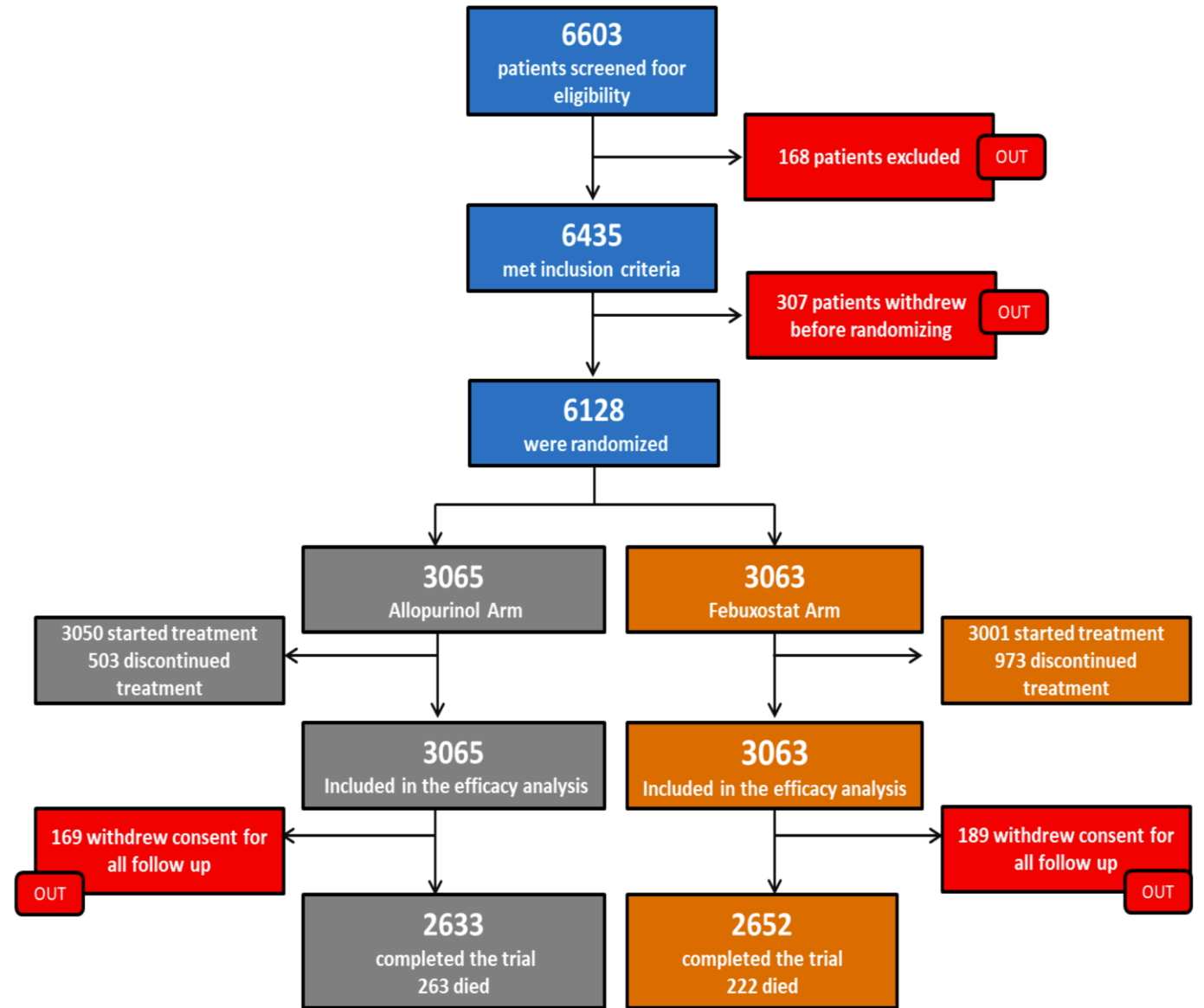
Prospective, randomised, open-label, blinded endpoint (PROBE)

AIM : to demonstrate the non-inferiority of Febuxostat in reaching the Anti-Platelet Trialists' Collaboration (APTC) cardiovascular endpoint as a **composite of** :

- hospitalisation for non-fatal MI/biomarker positive acute coronary syndrome (ACS)
- non-fatal stroke
- cardiovascular death

Trial countries:

Scotland, England, Sweden and Denmark





FAST- INCLUSION CRITERIA

Male or female **gouty patients aged 60 years or older** with at least **one additional cardiovascular risk factor**

- Age ≥ 70 years (male) or ≥ 75 years (female)
- Smoking (current or within the last 2 years)
- Diabetes mellitus or Impaired glucose tolerance
- Hypertension (SBP >140 mmHg and/or DBP >90 mmHg) or receiving treatment to lower blood pressure
- Dyslipidaemia (investigator assessment)
- Chronic kidney disease (CKD), Microalbuminuria or proteinuria
- Family history of coronary heart disease or stroke in first degree relative at age <55 years
- Inflammatory arthritis (Investigator assessment)
- Chronic NSAID therapy (investigator assessment)
- Previous cardiovascular (CV) event (MI, cerebrovascular accident [CVA] or transient ischaemic attack [TIA])
- Peripheral vascular disease (investigator/clinical assessment)
- Body mass index >30 kg/m²
- Chronic obstructive pulmonary disease

Gender ratio

85% male and 15% female



Mean age

71
years



Mean SBP/DBP

138/75 mmHg

Mean BMI

31 kg/m²

Total cholesterol and LDL

4.55 and **2.85** mmol/L respectively

Pre-existing

CV disease 33.4%

Mean age of symptoms of gout appearance

56.1 years old

Median duration of Allopurinol treatment at inclusion

6 years

Any episode of acute gout in past 12 months

26%

Diabetes Mellitus 23,5% in Allopurinol arm and **21,6%** in Febuxostat arm

FAST- PRIMARY ENDPOINT RESULT

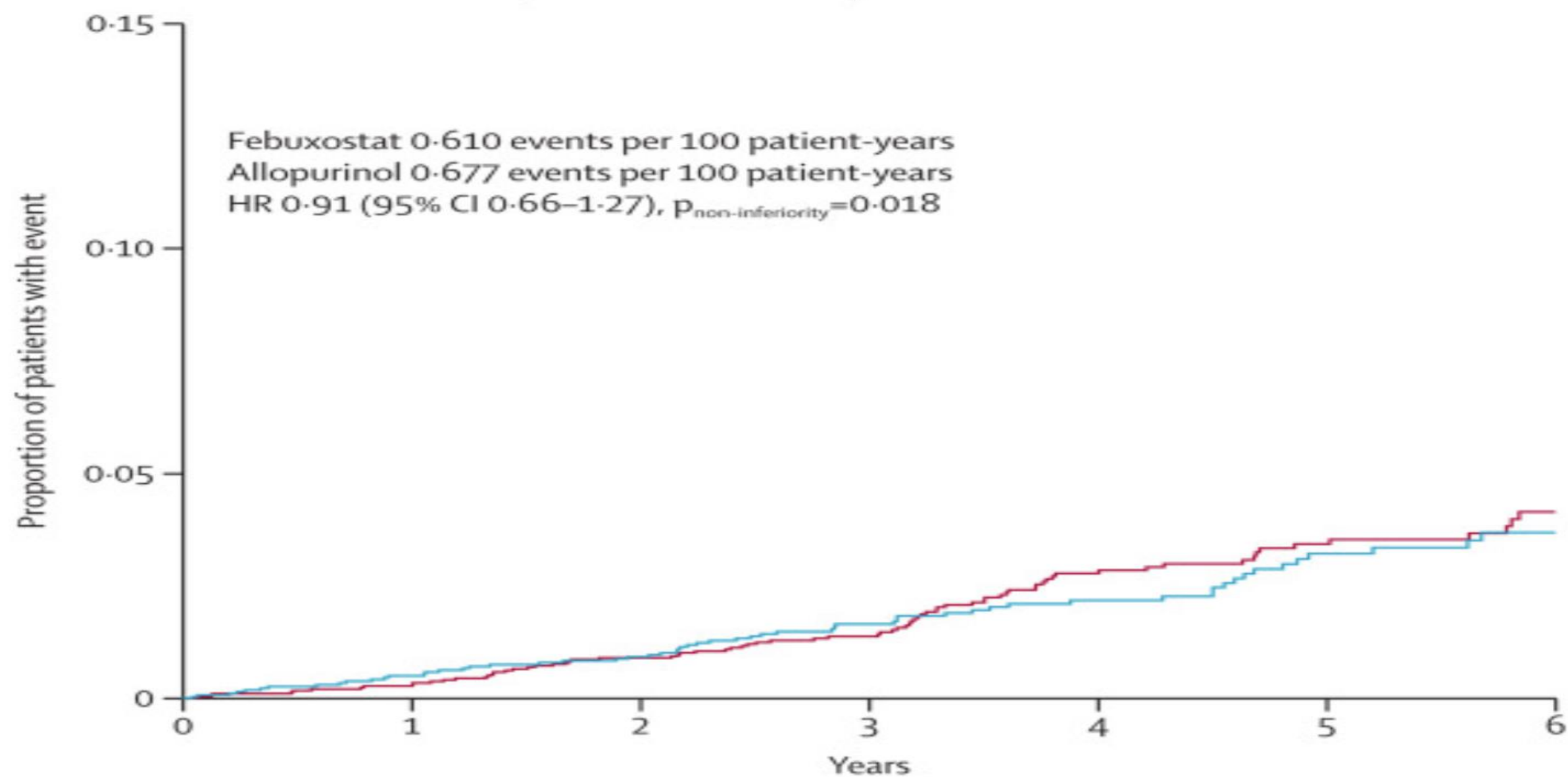


THE STUDY ACHIEVES THE PRIMARY ENDPOINT OF NON-INFERIORITY OF FEBUXOSTAT COMPARED TO ALLOPURINOL FOR THE PRIMARY ENDPOINT IN THE OT POPULATION.

On treatment analysis (OT)

Endpoint	Allopurinol (N=3065)		Febuxostat (N=3063)		HR (95% CI)	P _{NI}
	n (%)	Rate	n (%)	Rate		
Primary Endpoint - cardiovascular death or hospitalisation for non-fatal myocardial infarction/biomarker positive acute coronary syndrome or non-fatal stroke	241 (7.86%)	2.054	172 (5.62%)	1.723	0.85 (0.70, 1.03)	<0.001

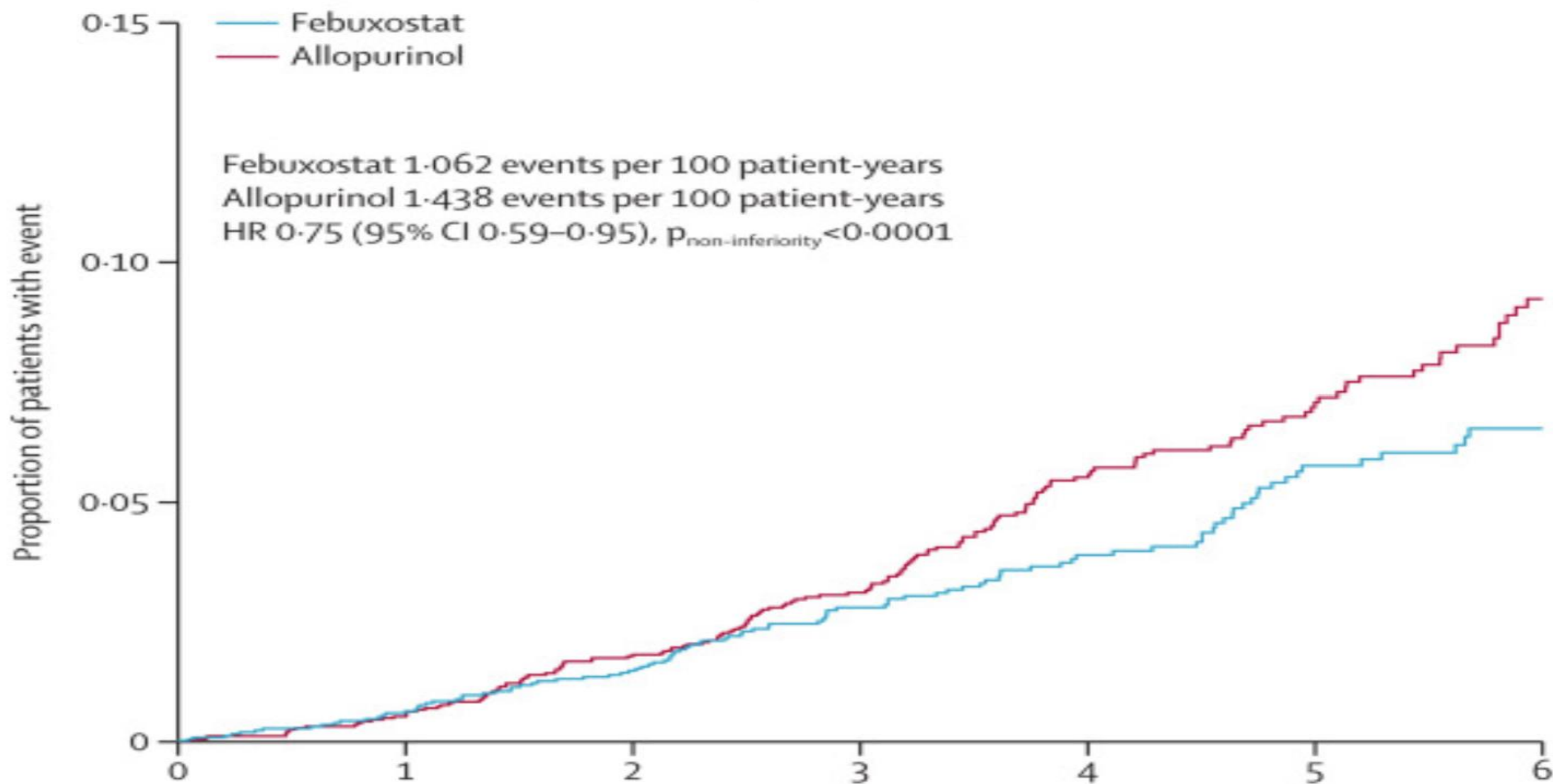
C Cardiovascular death, on-treatment analysis



Secondary outcomes in the on-treatment analysis (n=6128).

	Allopurinol (N=3065)		Febuxostat (N=3063)			
	n (%)	Rate	n (%)	Rate	HR (95% CI)	P _{NI}
Secondary Endpoints						
Hospitalisation for non-fatal myocardial infarction/ biomarker positive acute coronary syndrome	98 (3.20%)	0.824	77 (2.51%)	0.767	0.94 (0.70, 1.27)	0.016
Non-fatal stroke	80 (2.61%)	0.670	58 (1.89%)	0.574	0.87 (0.62, 1.21)	0.009
Cardiovascular death	82 (2.68%)	0.677	62 (2.02%)	0.610	0.91 (0.66, 1.27)	0.018
All-cause mortality	174 (5.68%)	1.438	108 (3.53%)	1.062	0.75 (0.59, 0.95)	<0.001
Hospitalisation for heart failure	89 (2.90%)	0.745	65 (2.12%)	0.645	0.88 (0.64, 1.21)	0.008
Hospitalisation for unstable new or worsening angina	12 (0.39%)	0.099	4 (0.13%)	0.039	0.39 (0.13, 1.22)	0.019
Hospitalisation for coronary revascularisation	78 (2.54%)	0.654	65 (2.12%)	0.648	1.00 (0.72, 1.39)	0.059
Hospitalisation for cerebrovascular revascularisation	8 (0.26%)	0.066	2 (0.07%)	0.020	0.30 (0.06, 1.42)	0.032
Hospitalisation for transient ischaemic attack	23 (0.75%)	0.191	18 (0.59%)	0.177	0.94 (0.51, 1.74)	0.15
Hospitalisation for non-fatal cardiac arrest	6 (0.20%)	0.050	2 (0.07%)	0.020	N/A	0.29
Hospitalisation for venous and peripheral arterial vascular thrombotic event	35 (1.14%)	0.291	29 (0.95%)	0.287	0.99 (0.61, 1.62)	0.14
Hospitalisation for arrhythmia with no evidence of ischaemia	45 (1.47%)	0.375	55 (1.80%)	0.546	1.47 (0.99, 2.18)	0.73

A All-cause death, on-treatment analysis



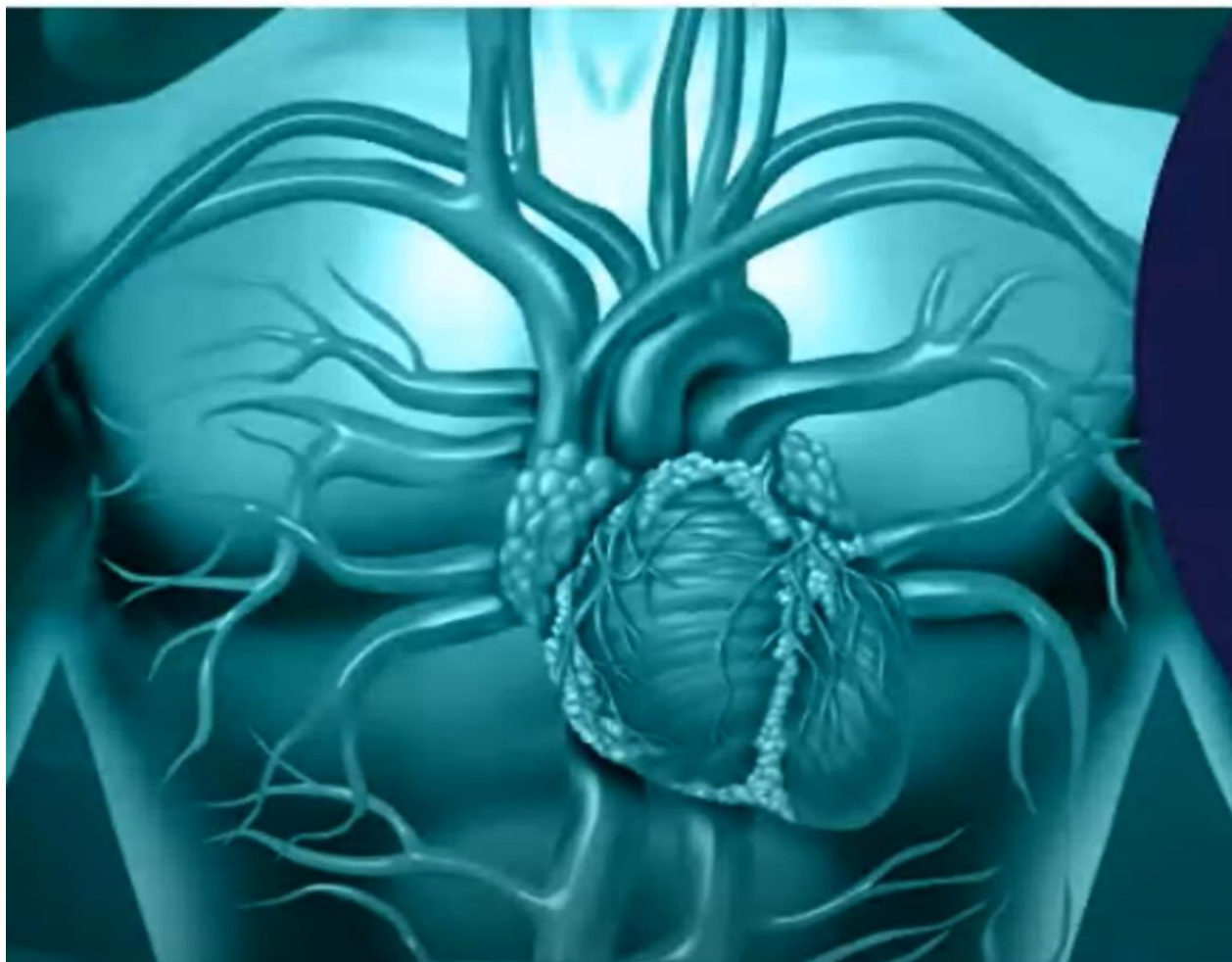
FAST- SUBSET ANALYSIS

Following a request by EMA, after CARES study result (Nov.2017), it was performed an analysis on a subset of FAST patients similar to the ones recruited in CARES.

The analysis did not show an increased risk of CV outcome in patients with a baseline history of MI, stroke or acute coronary syndrome.

FAST

Subset analysis



Notably,
**no increased
risk of adverse
cardiovascular
events was found in
the FAST subgroup
of patients** with
previous myocardial
infarction, stroke,
or acute coronary
syndrome



❑ Συμπεράσματα

- Συχνή είναι η επίπτωση της υπερουριχαιμίας στη σύγχρονη εποχή
- Φαίνεται να υπάρχει συσχέτιση μεταξύ της αύξησης του ουρικού οξέος και του καρδιαγγειακού κινδύνου και την έκπτωση της νεφρικής λειτουργίας
- Η φεβουξοστάτη είναι πιο αποτελεσματική στη μείωση του ουρικού οξέος από την αλλοπουρινόλη
- Δε συνίσταται η χρησιμοποίησή της σε ασθενείς με ισχαιμική καρδιοπάθεια και καρδιακή ανεπάρκεια