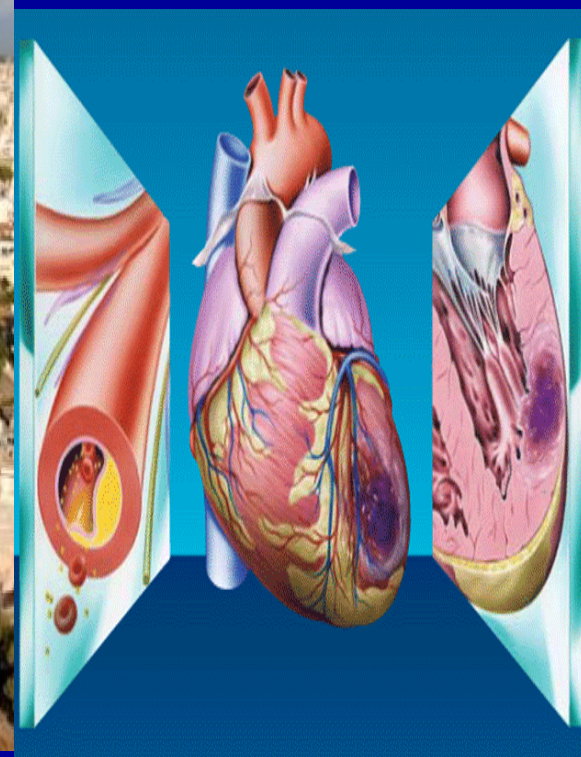
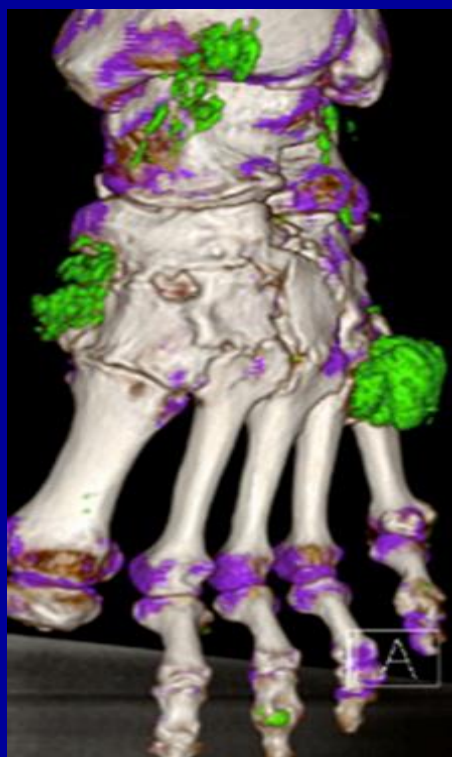


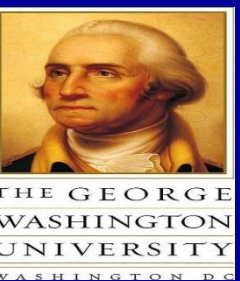


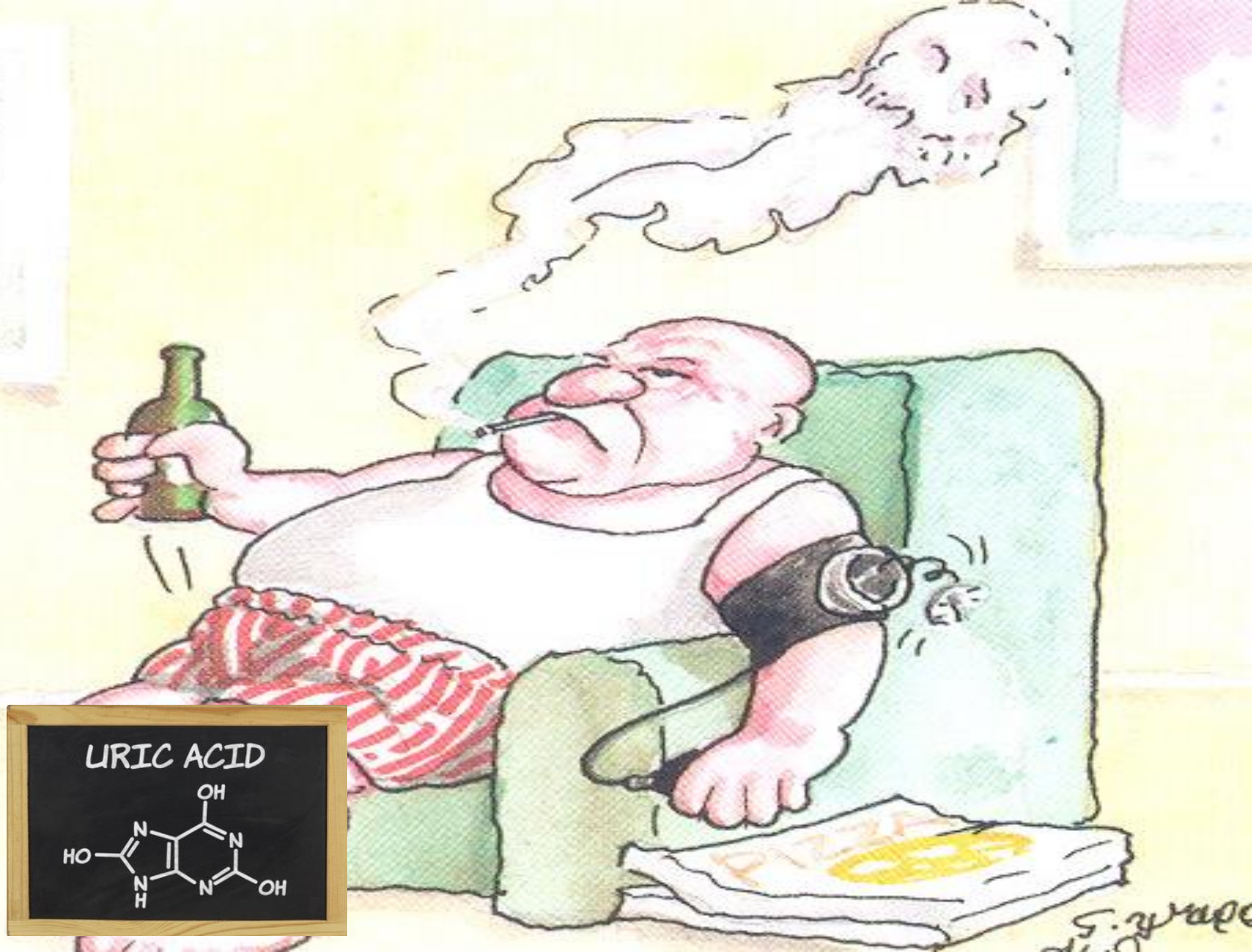
Υπερουριχαιμία και καρδιαγγειακός κίνδυνος. Νεότερα δεδομένα»



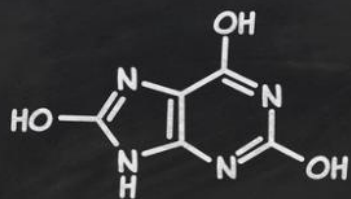
Ανδρέας Πιτταράς

Καρδιολόγος - Hypertension Specialist ESH
Ass. Prof. George Washington University USA
Πρ. Ελλ. Εταιρ. Καρδιαγ/κής Προστασίας
Υπερτασικό ιατρείο Ασκληπιείο Βούλας **MEDITON**





URIC ACID



URIC ACID

AS

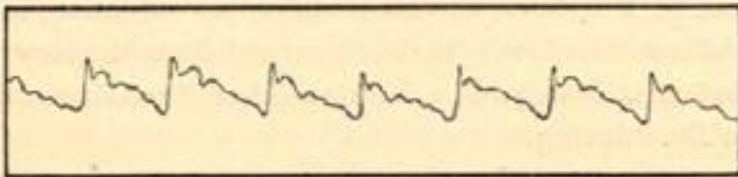
A FACTOR IN THE CAUSATION OF DISEASE.

A CONTRIBUTION TO THE

PATHOLOGY OF HIGH ARTERIAL TENSION,
HEADACHE, EPILEPSY, MENTAL DEPRESSION, GOUT,
RHEUMATISM, DIABETES, BRIGHT'S DISEASE,
AND OTHER DISORDERS.

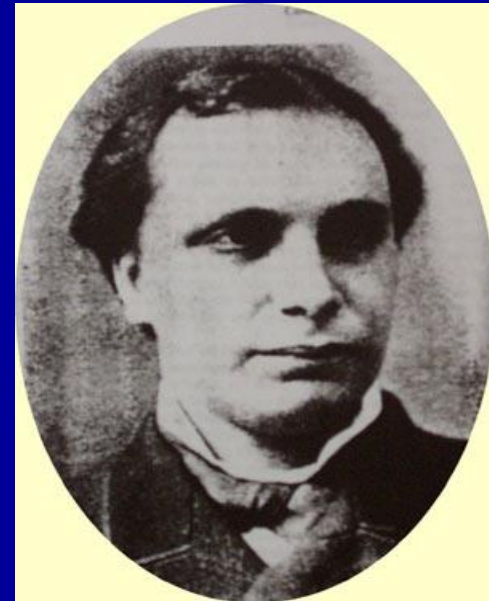
BY

ALEXANDER HAIG, M.A., M.D. OXON., F.R.C.P.



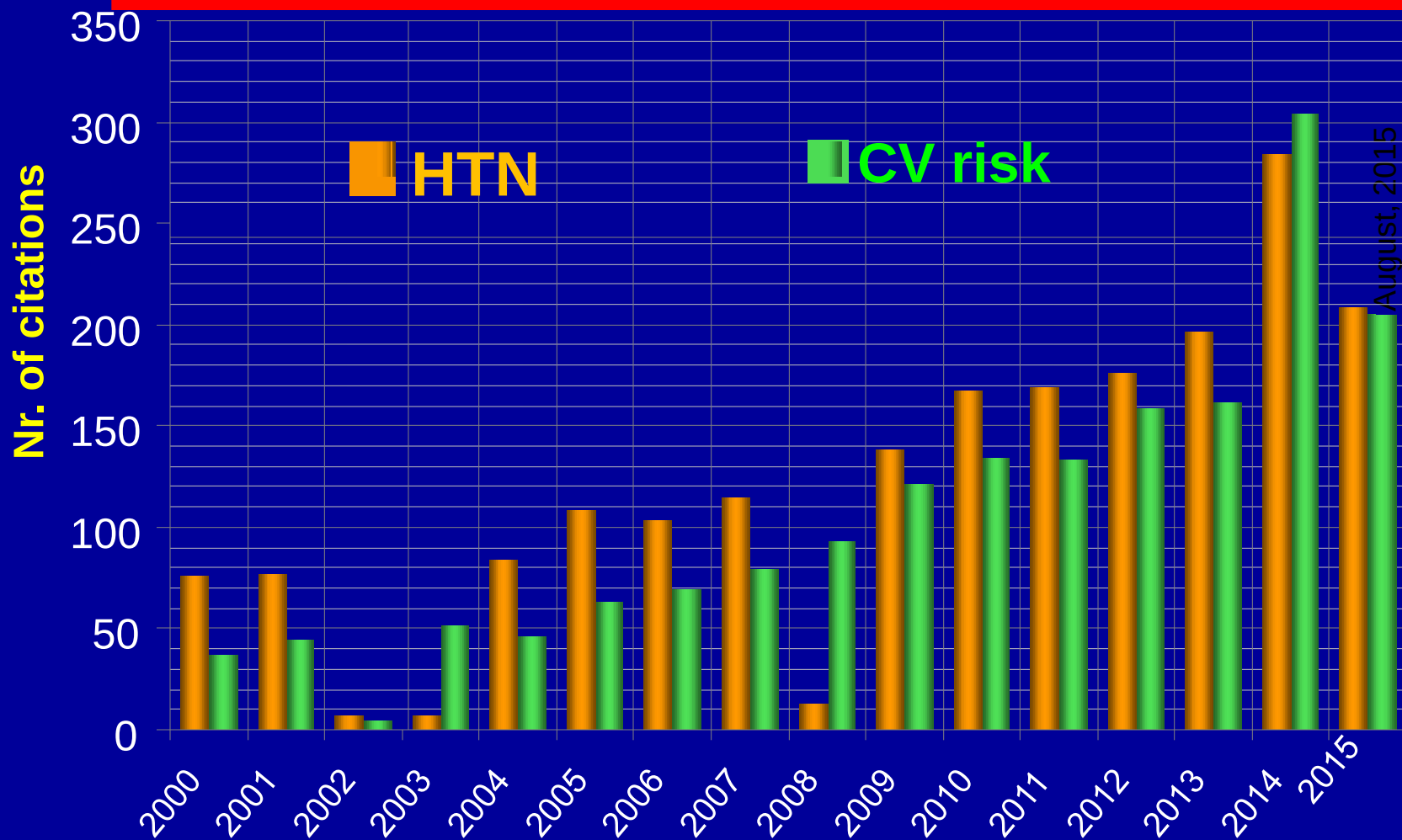
Haig A: Uric Acid as a Factor in the Causation of Disease: A Contribution to the Pathology of High Arterial Tension, Headache, Epilepsy, Mental Depression, Gout, Rheumatism, Diabetes, Bright's Disease, and Other Disorders, edn 1. London: J & A Churchill; 1892.

**Frederick Akbar Mohamed
hypothesized that uric acid
might be integral in the
development of essential
hypertension (1879)**

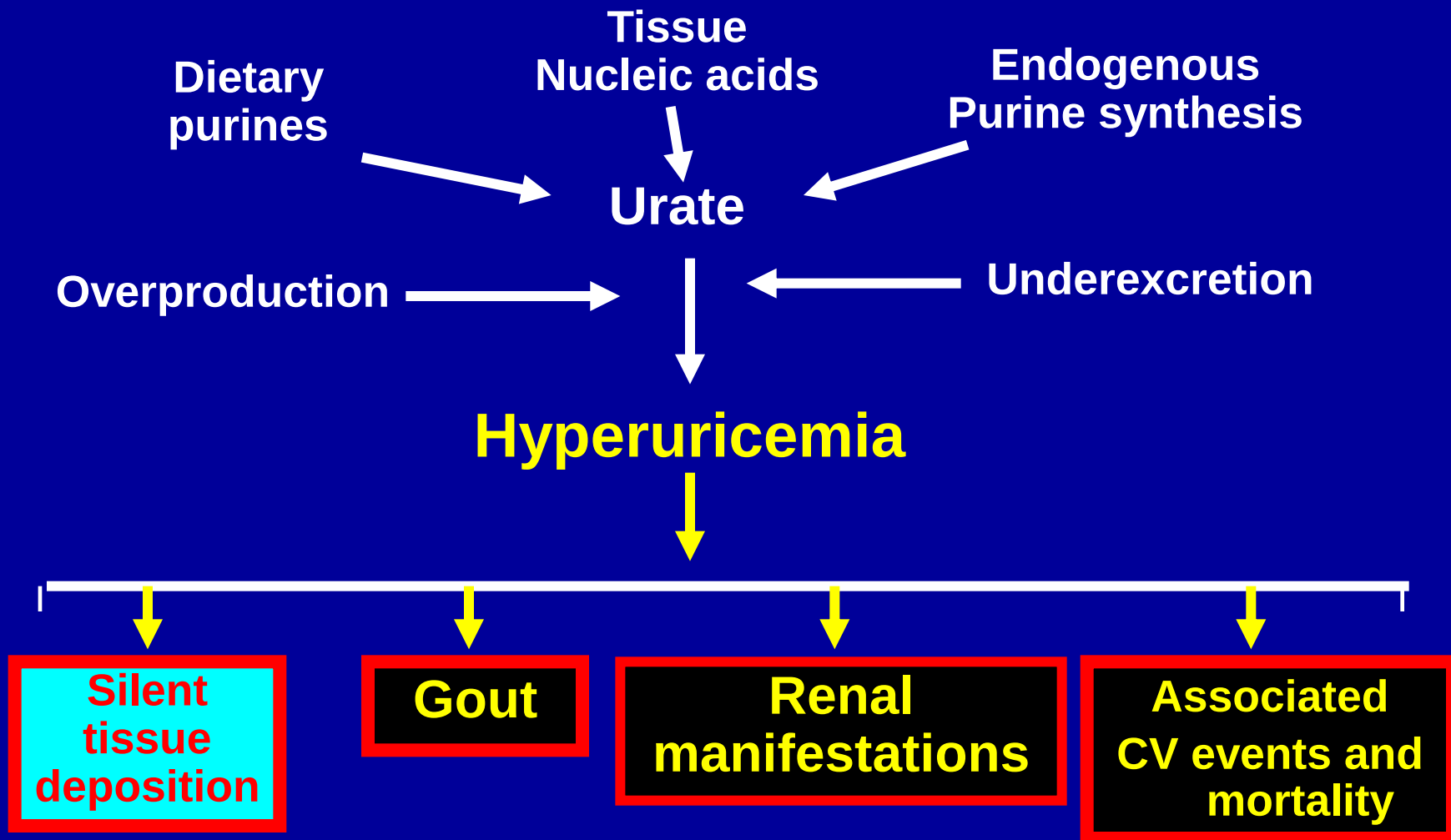


Uric Acid & Hypertension/CV risk

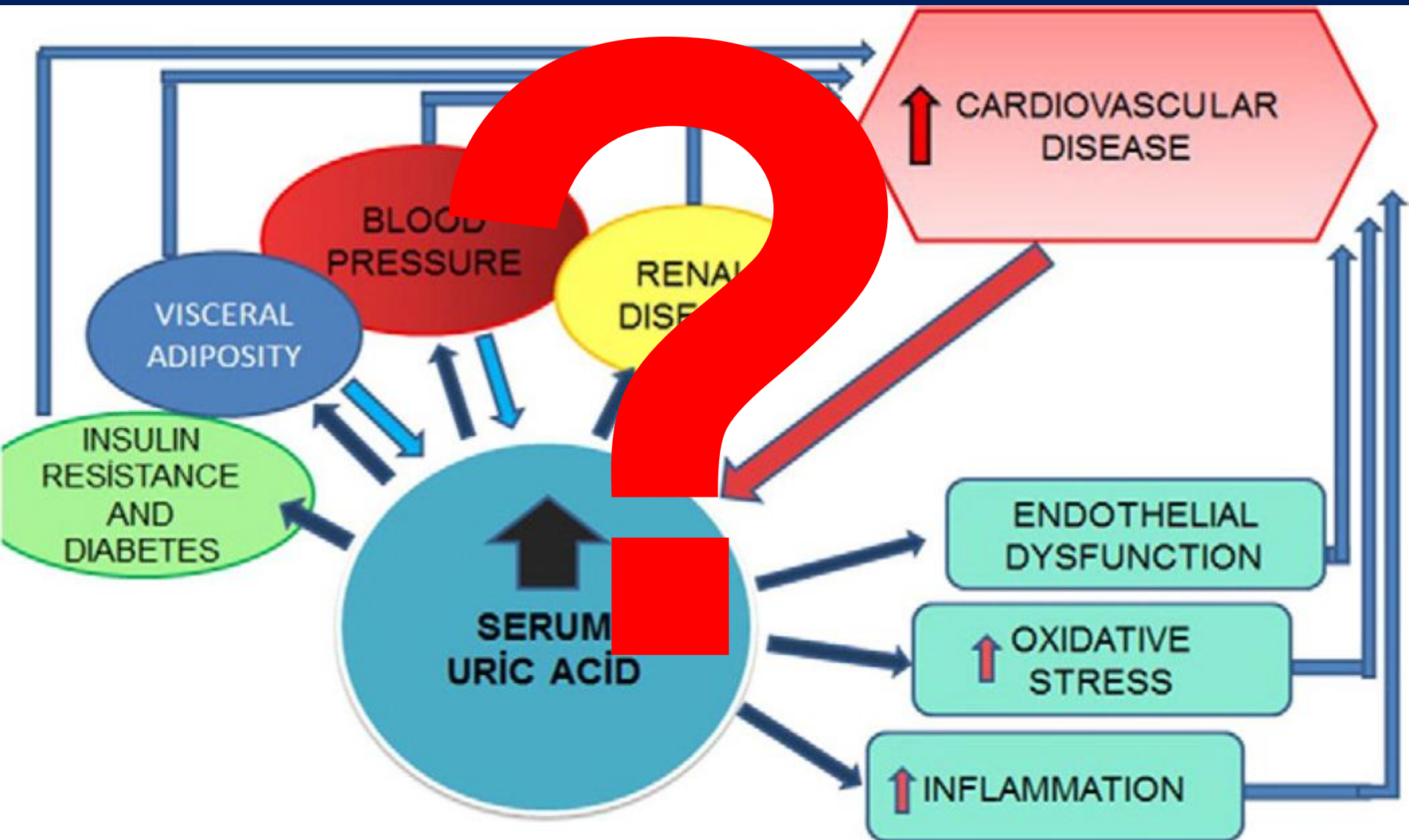
PubMed **SUA**>74.000,
HTN/CVR>40.000 citations



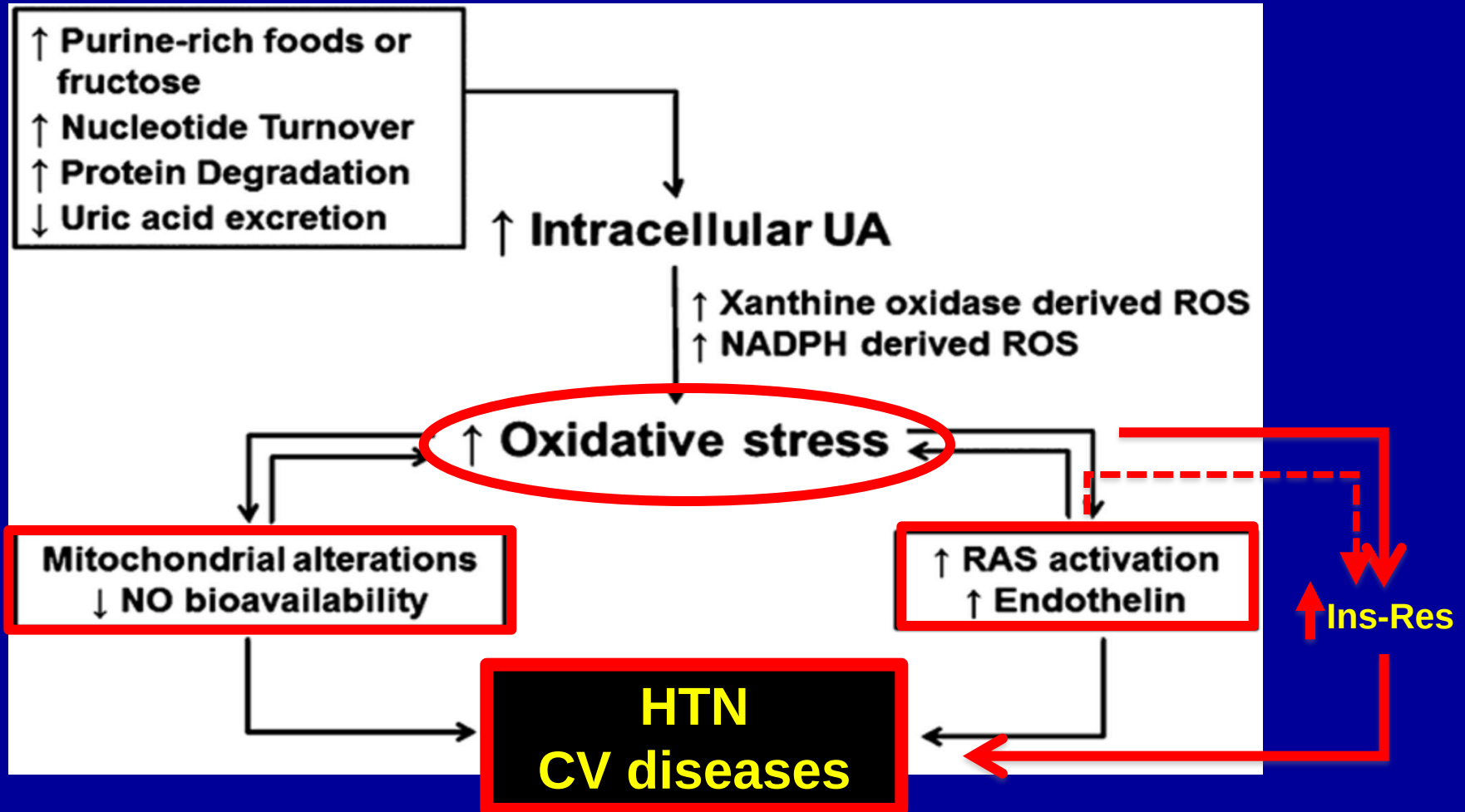
The Hyperuricemia Cascade



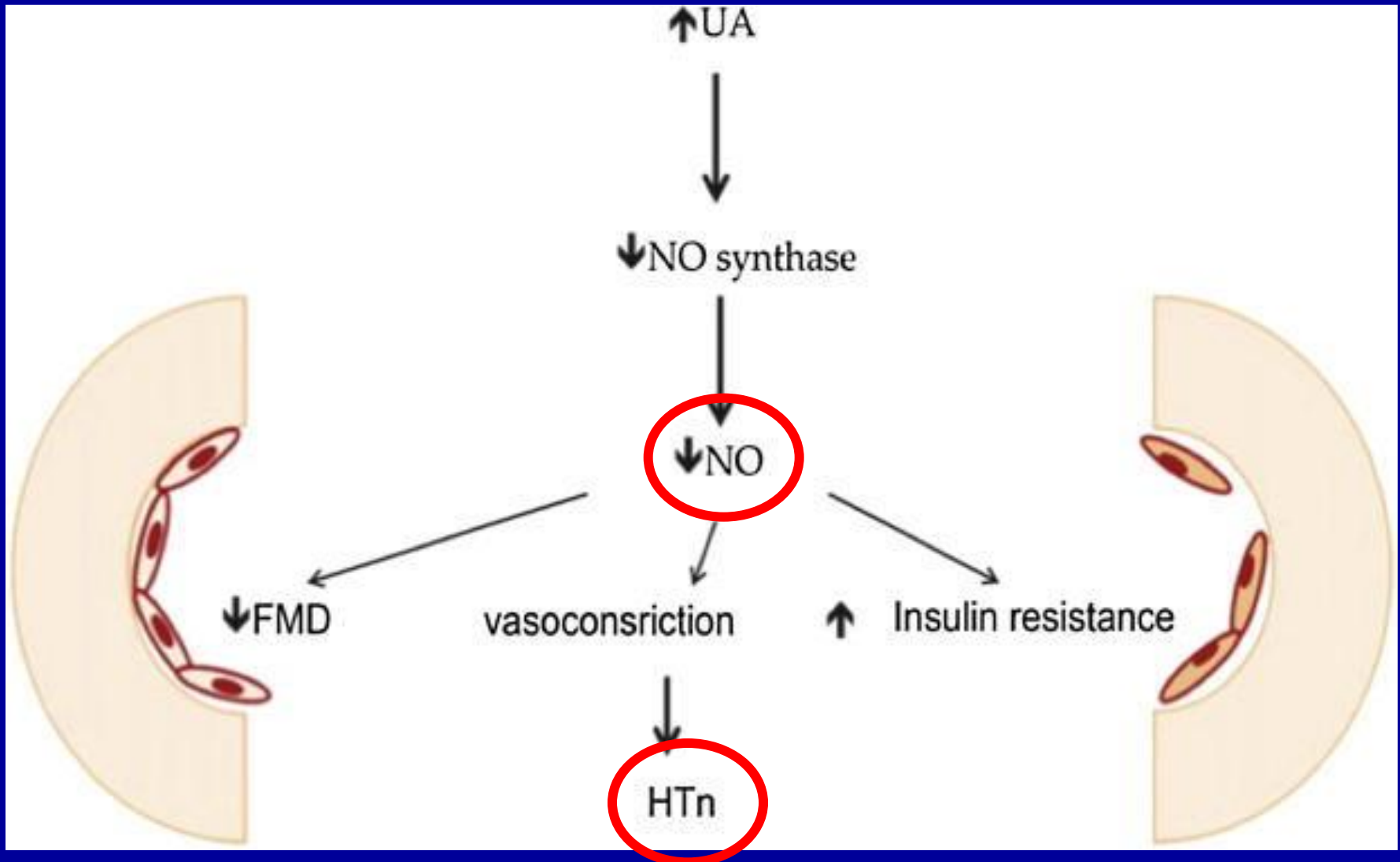
Complex Interaction of Uric Acid, Components of Metabolic Syndrome and CVD

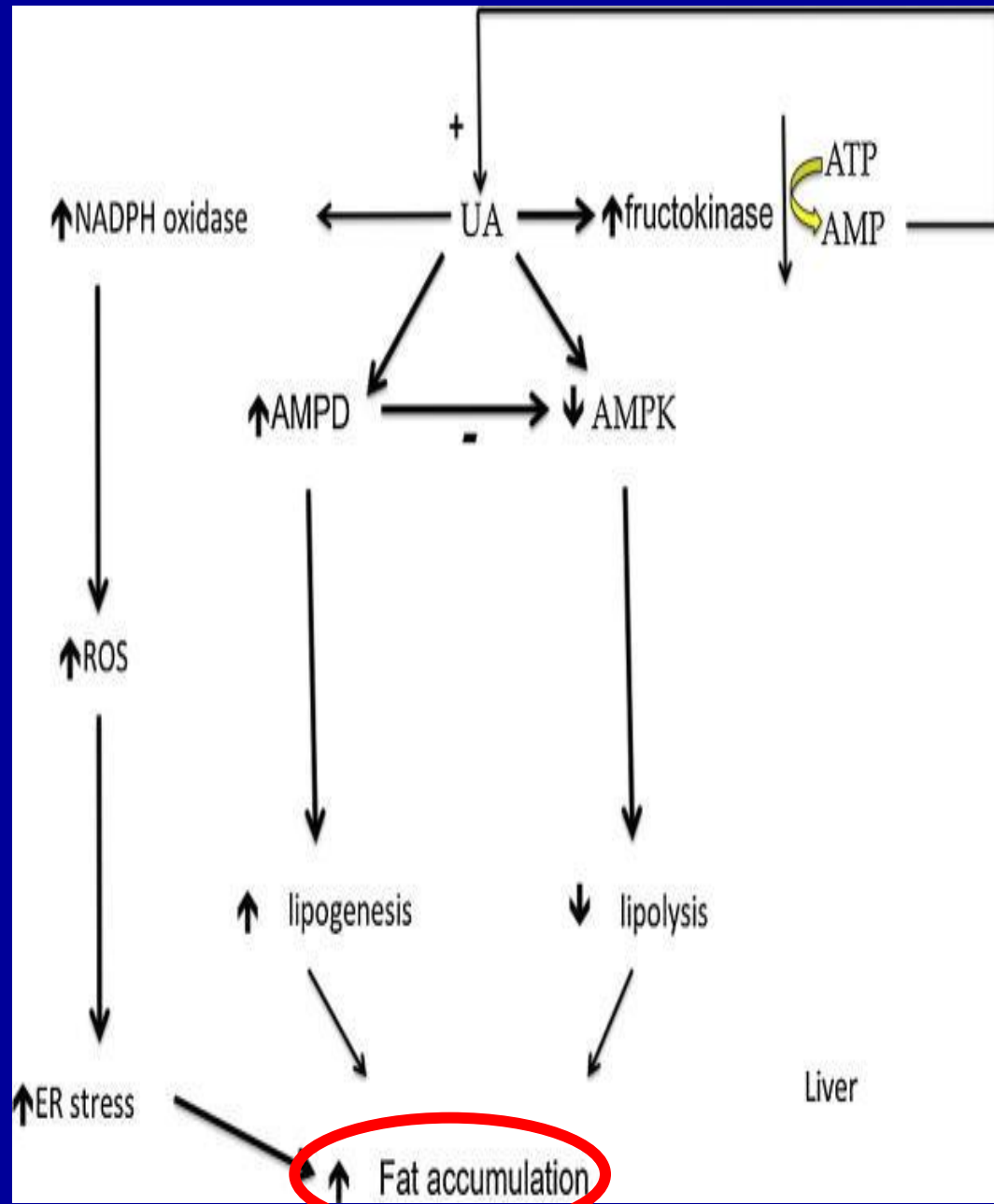
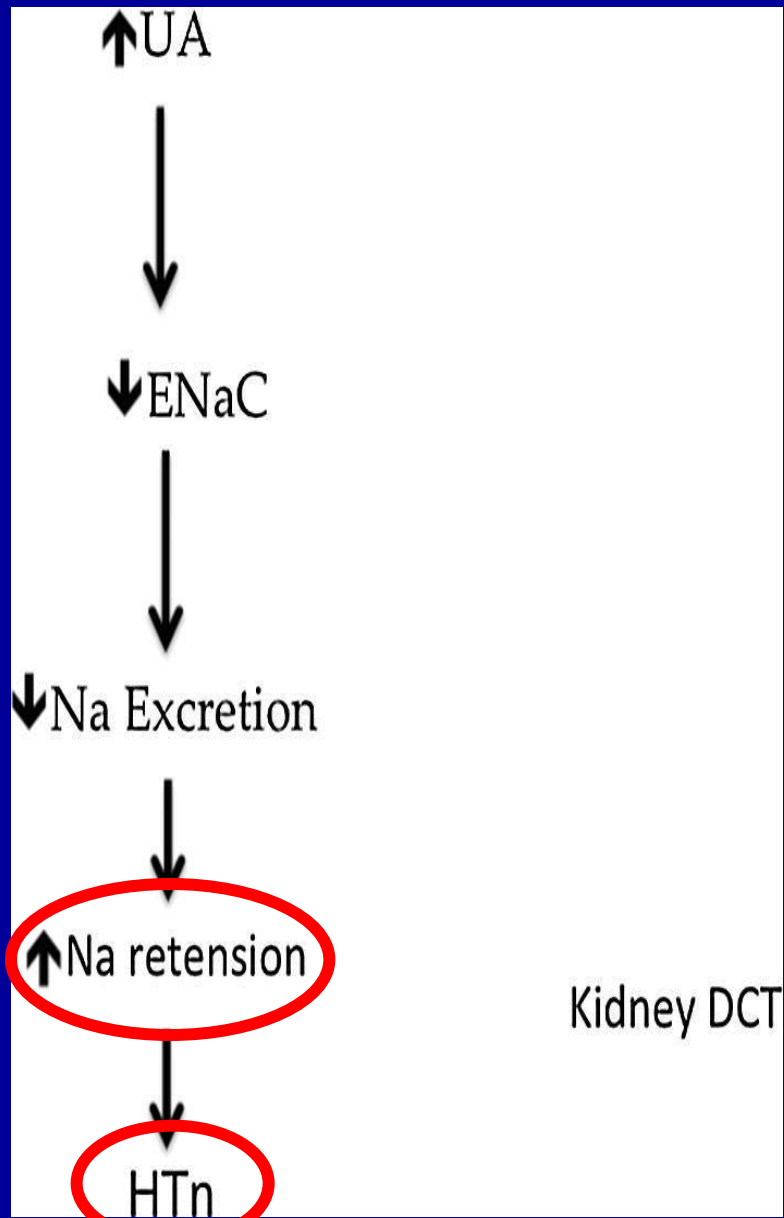


Proposed Mechanisms Leading from SUA to HTN & CVD



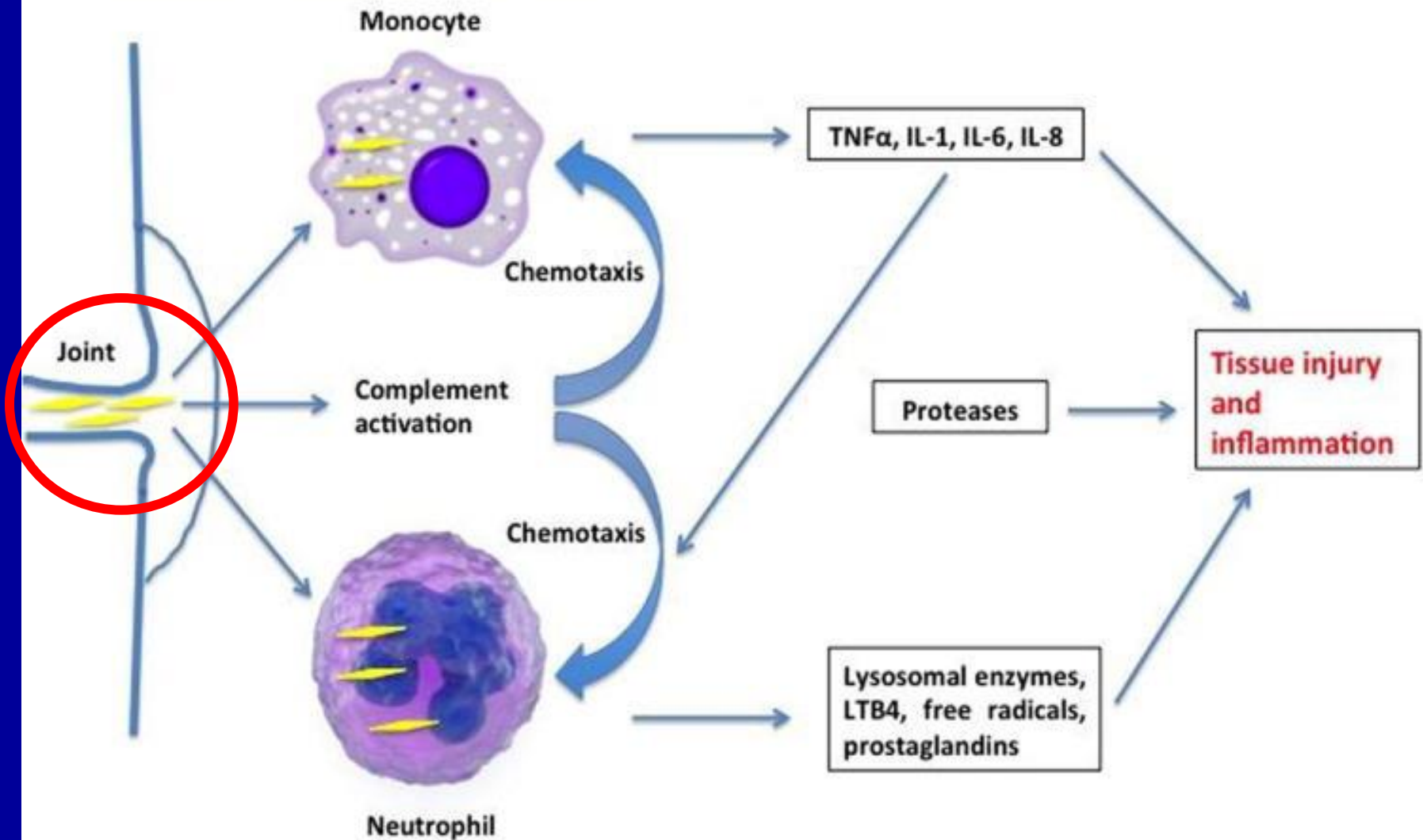
Effect of intra-cellular UA on NO synthesis within vascular endothelium





Pathogenesis of acute gouty inflammation

Pathogenesis of acute gouty arthritis

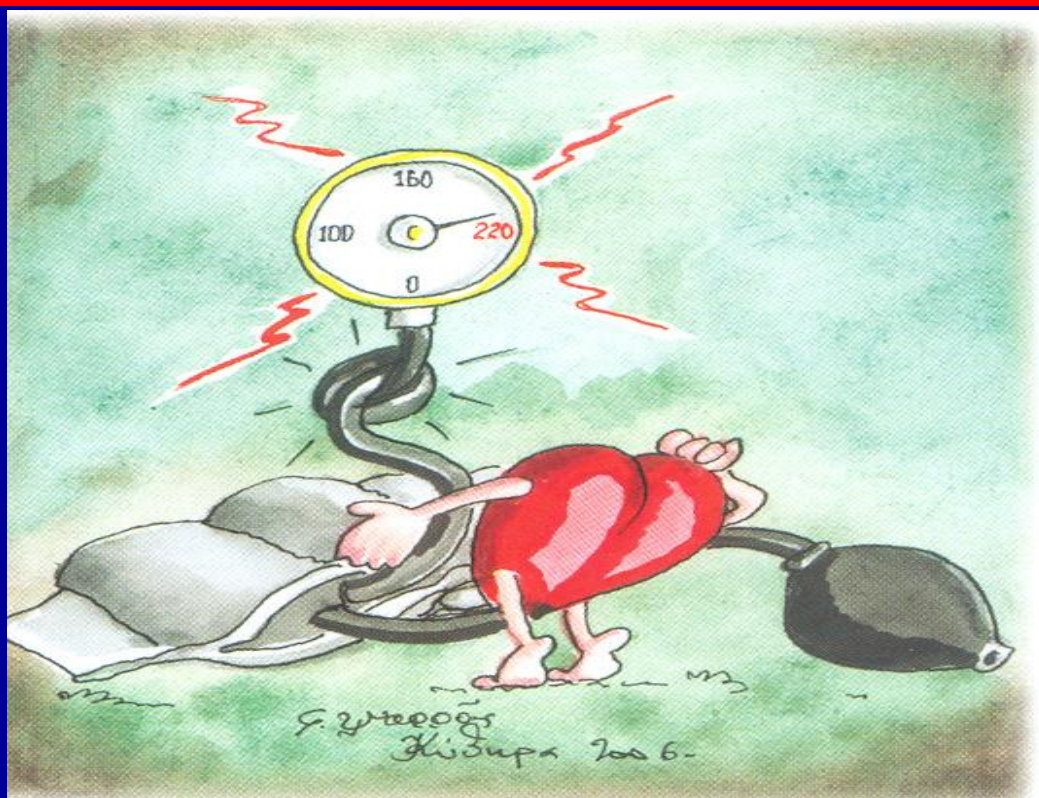


ΣΥΖΗΤΗΣΗ ΠΕΡΙΣΤΑΤΙΚΟΥ



- Ασθενής **58 ετών** μέτριος καπνιστής, μέτριος πότης.
- **Υπέρταση** (ΑΠ 162/100mmHg), Σφύξεις 75/min.
- Α/α θώρακα και ΗΚΓ χωρίς παθολογικά ευρήματα.
- **Γλυκόζη**: 120mg/dl, **Κρεατινίνη**: 1.25 mg/dl,
- **K⁺/Na⁺**: 3.6/138mEq/L, **TC**: 220mg/dl,
- **LDL**: 135mg/dl, **HDL**: 35mg/dl, **TRG**: 260mg/dl,
- **Ουρικό οξύ**: 10.4 mg/dl, ιστορικό ουρικής αρθρίτιδας
- **ΣΒ**: 96Kg, **BMI**: 31Kg/m²
- **Ατενολόλη** (50mg)
- **Ολμεσαρτάνη+HCTZ** (40+25mg)
- **Σιμβαστατίνη** 20mg και
- **Ασπιρίνη** 100 mg

**Πως θα χειρισθούμε συνολικά αυτόν τον
ασθενή και τι θα κάνουμε για τα αυξημένα
επίπεδα του ουρικού οξέος?**



2018 ESC-ESH Guidelines for the Management of Arterial HTN



Factors influencing CV risk in pts with HTN



Demographic characteristics and laboratory parameters

Sex (men > women)

Age

Smoking – current or past history

Total cholesterol and HDL-C

Uric acid

Diabetes

Overweight or obesity

Family history of premature CVD (men: < 55 years and women: < 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 per min)

Uric acid

ESH/ESC HTN Guidelines

**2007
GLs**

↑ SCr (> 1.4-1.5 mg/dl)
↓ eCrCl / GFR
MA
EKG

- LVH (EKG/Echo)
- Concentric LVH
- LA enlargement
- CA thickening / plaques
- Ankle/Brachial ratio
- Arterial stiffening (PWV)*

Routine

Recommended

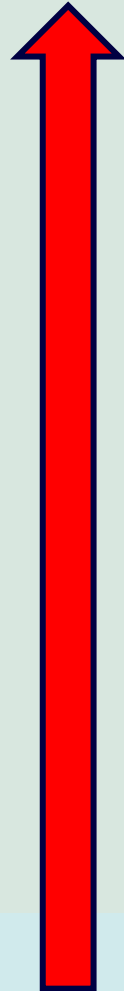
**2013
2018
GLs**

- Hb, Ht
- Glucose
- TC, HDL, LDL, TG
- **Uric Acid**
- SCr, GFR, K, Na
- Γενική ούρων (λεύκωμα)
- EKG

- Echocardiogram
- Carotid U/S
- Ankle/Brachial ratio
- Arterial stiffening (PWV)*
- Holter ECG
- U/S Abdomen, Peripheral arteries
- HbA1c (Gluc > 102mg/dl or DM)
- Urine protein, K, Na, K/Na
- ABPM, HBPM
- Fundoscopy

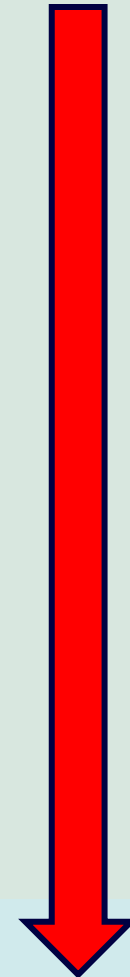
Drugs that raise serum urate concentrations

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

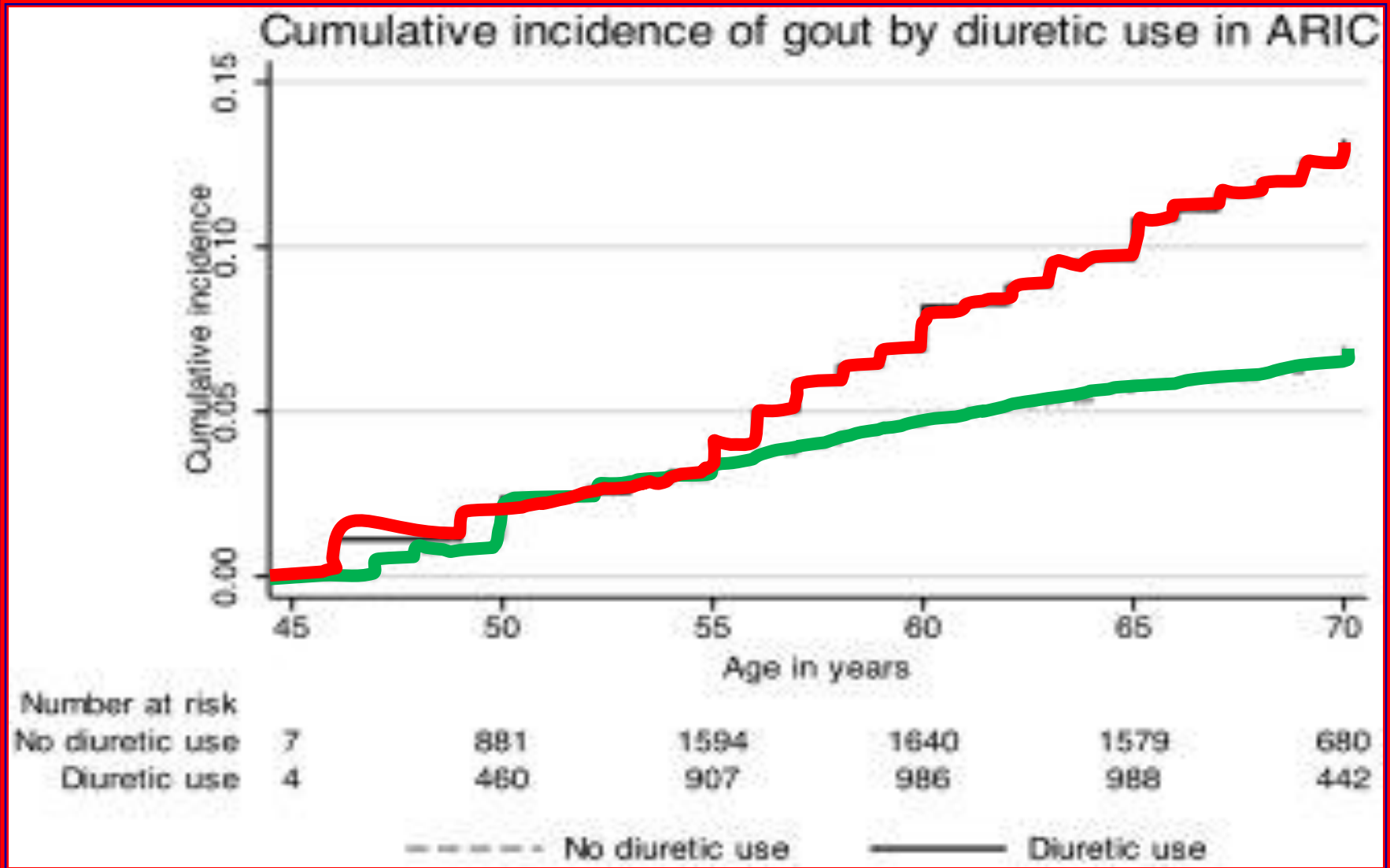


Drugs that lower serum urate concentrations

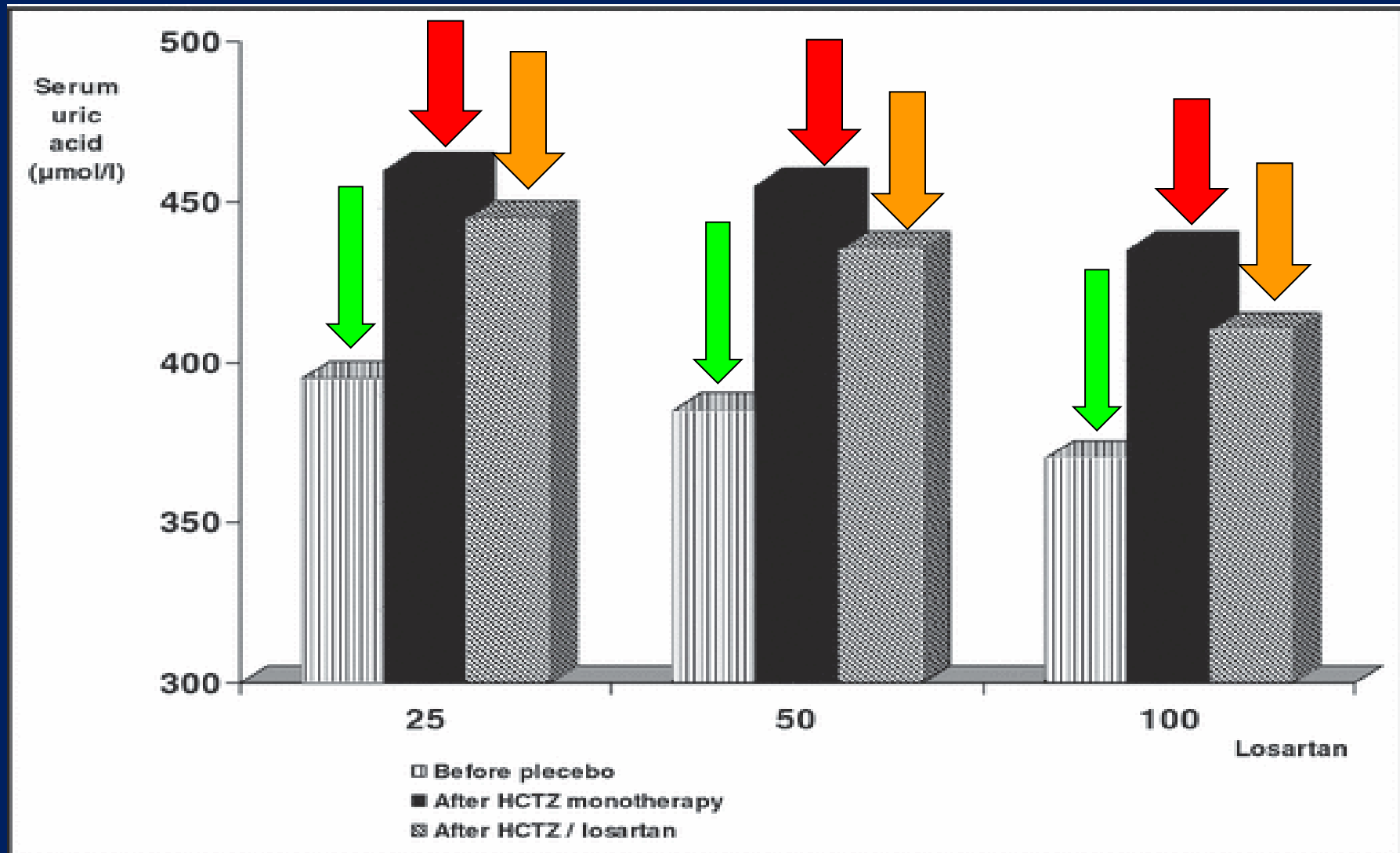
- Ascorbic acid
- Benzbromarone
- Calcitonin
- Citrate
- Oestrogens
- Fenofibrate
- Losartan
- Probenecid
- Salicylates (high dose)
- Sulfipyrazone
- **Amlodipine**
- **SGLT2-i**



Diuretic use, $\uparrow$ UA and risk of gout in a population-based study of adults with HTN



Managing Hypertensive Patients With Gout Who Take Thiazide





- Ασθενής **58 ετών** μέτριος καπνιστής, μέτριος+ πότης.
- **Υπέρταση** (ΑΠ 162/100mmHg), Σφύξεις 75/min.
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- **Ουρικό οξύ**: 10.4 mg/dl, **ιστορικό ουρικής αρθρίτιδας**
- **ΣΒ**: 96Kg, **BMI**: 31Kg/m², **Περίμετρος μέσης**: 104cm.
- **Ατενολόλη** (50mg) και στη συνέχεια προστέθηκε
- **Ολμεσαρτάνη+HCTZ** (40+25mg)
- **Σιμβαστατίνη** 20mg και
- **Ασπιρίνη** 100 mg

ΑΣΘΕΝΗΣ ΜΕ ΥΠΕΡΤΑΣΗ

Εκτίμηση βλάβης οργάνου – στόχου:

- α/α θώρακα (-), ΗΚΓ (-)
- ECHO LVMI: 129 mg/m²
- Νεφρική λειτουργία eGFR: 69ml/min (<60ml/min)
- Ποσοτική εκτίμηση πρωτεϊνουρίας: Λεύκωμα ούρων
24h: 180 & 201 mg/d
- U/S Καρωτίδων: ↑ IMT, Αθηρωματικές πλάκες
- PWV: 13 m/sec
- ΥΠΕΡΤΑΣΙΚΟΣ ΜΕ ΒΛΑΒΕΣ ΟΡΓΑΝΩΝ ΣΤΟΧΩΝ

Cessation of hyperuricemic drugs

- **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.

- **Ατενολόλη** 50mg/d: Διακοπή (αύξηση TG, Gluc) και στη συνέχεια αντικατάσταση με **Νεμπιβολόλη** 5 mg
- **Ολμεσαρτάνη+HCTZ** 40+25mg → **40+12.5mg**
(Μείωση διουρητικού για Ουρικό οξύ & Κάλιο)
(Σε επίτευξη στόχου ΑΠ σκέψη για **Λοσαρτάνη**)
- **Προσθήκη Αμλοδιπίνης** 5mg, λόγω ουρικοζουρητικής δράσης το βράδυ για ↓οιδημάτων (Σε δεύτερο χρόνο σε σταθεροποίηση **SPC τριπλός συνδυασμός?**).
- Επιπρόσθετη χορήγηση **Επλερενόνης** σε ανθεκτική υπέρταση ή εναλλακτική αντικατάσταση διουρητικού.
- Επιπρόσθετη χορήγηση **Μοξονιδίνης** σε ανθεκτική υπέρταση.

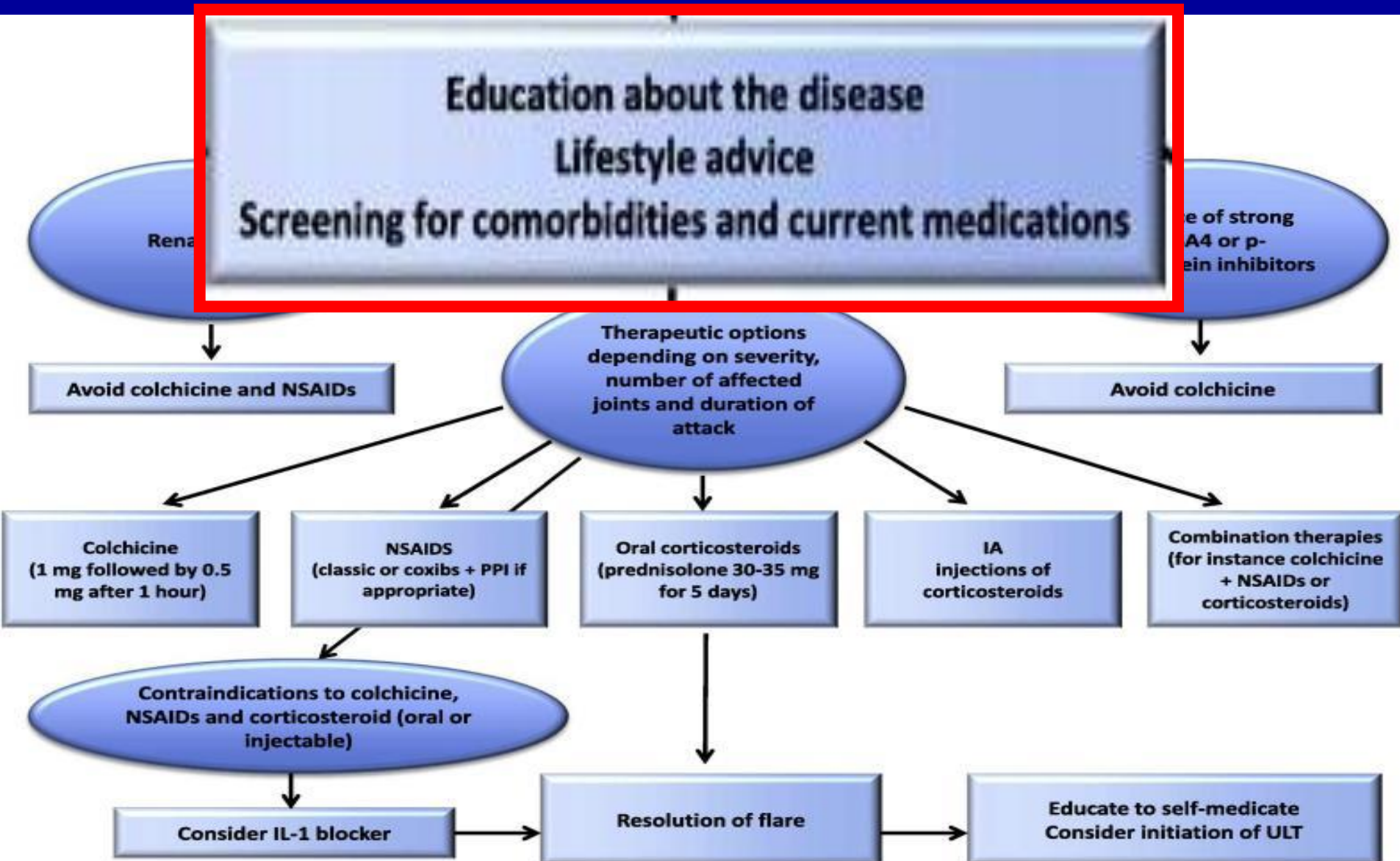
- **Σιμβαστατίνη** 20mg: Διακοπή → **Ροσουβαστατίνη** 20mg.
- Δίαιτα–άσκηση-↓αλκοόλ για TG - UA και πιθανή προσθήκη **Φενοφιμπράτης** 145 mg (↓UA) ή **Ω3**.
- Σε συνεχιζόμενη διαταραχή μεταβολισμού γλυκόζης (↑HbA1c) πιθανή χορήγηση **SGLT2-I (Dapagliflozine)**
- Διακοπή **Ασπιρίνης** μέχρι τουλάχιστον ρύθμιση ΑΠ και επαναξιολόγηση της ένδειξης χορήγησης της.

**Πως θα χειρισθούμε αυτόν τον ασθενή
για τα αυξημένα επίπεδα του ουρικού
οξέος?**

Έστω ότι μετά την παρέμβαση

UA: 8.9mg/dl

EULAR recommendation for the management of flares in patients with gout



Υπάρχουν και τροφές

που μειώνουν το ουρικό οξύ όπως

Νερό, πράσινο τσαι, τα light γαλακτερά

τα κεράσια, μπανάνα, φράουλες, blueberries,

Μήλο, αχλάδι, μπρόκολο, σέλερι, αγγούρι,

νερό καρύδας, φρέσκια ντομάτα

και η βιταμίνη C.

Μη φαρμακευτική θεραπεία

Όχι οινοπνευματώδη ποτά και κυρίως μπύρα.

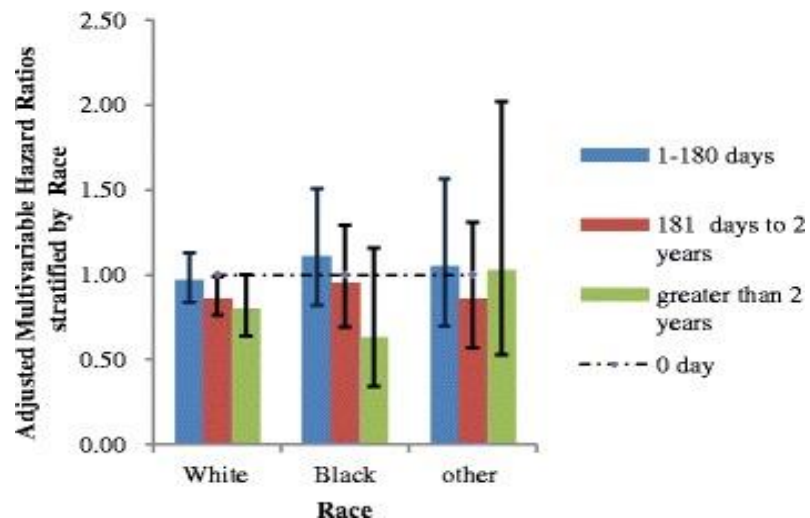
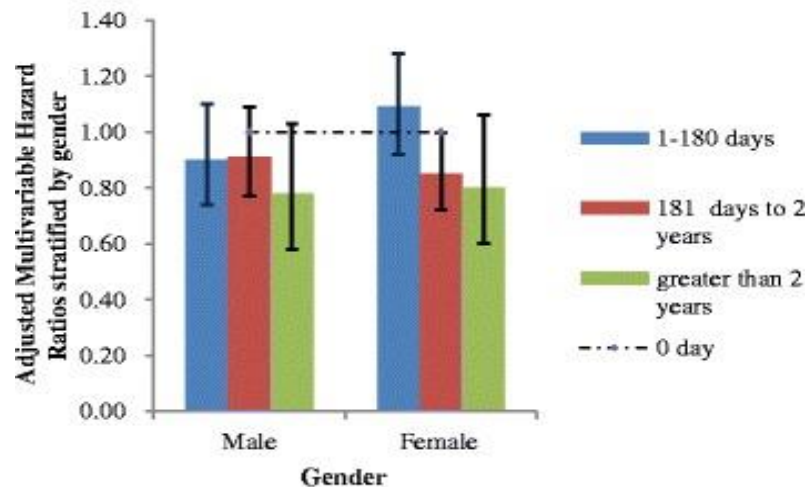
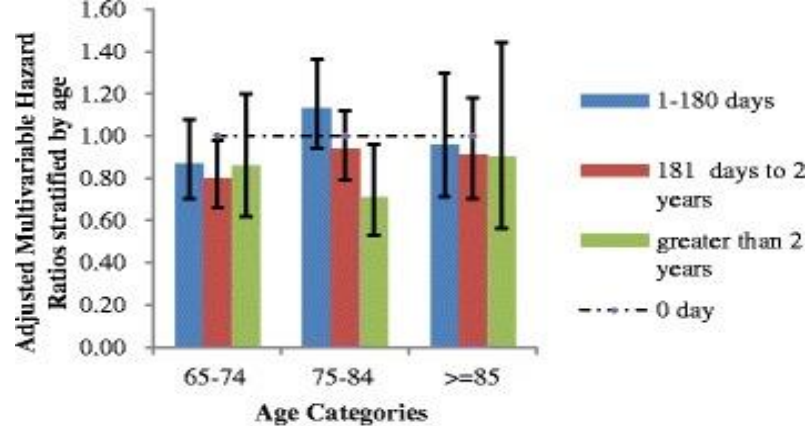
Όχι κρεατικά και θαλασσινά

Όχι παχυσαρκία

Όχι σακχαρώδη ποτά

**Εάν τα κάνετε όλα αυτά θα μειώσετε
το ουρικό οξύ του αίματός σας το πολύ κατά 10-15%.**

**Αρα η μόνη λύση για τη θεραπεία
της υπερουριχαιμίας είναι τα φάρμακα!!!**



UA Therapy and the risk of Stroke in older adults receiving medicare

Multivariable-adjusted* HRs of duration of UA Therapy with incident stroke by

Age

Gender

Race

Multivariable-adjusted HRs of MI by duration of UA Therapy

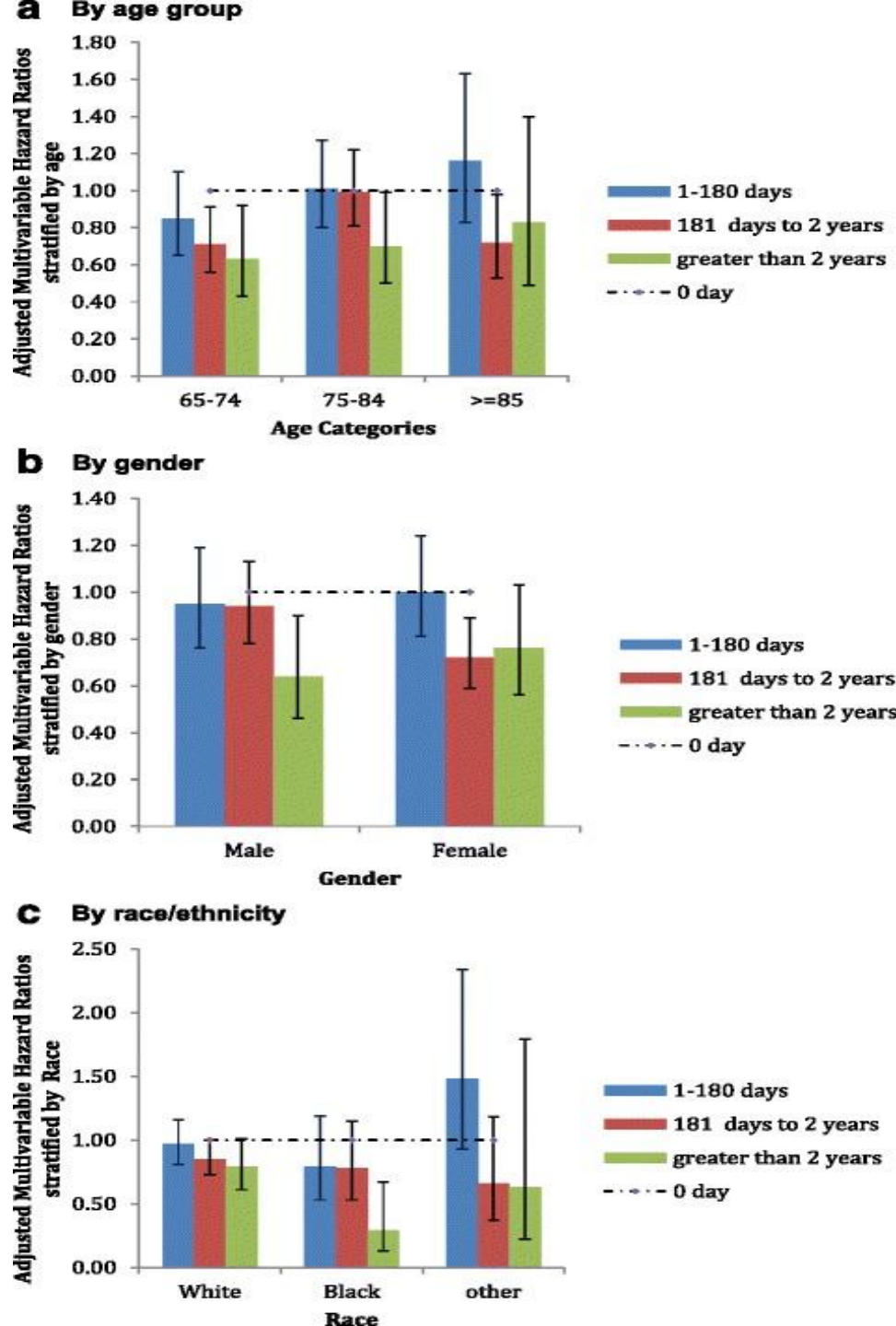
by

a Age group,

b Gender

c Race

in the elderly

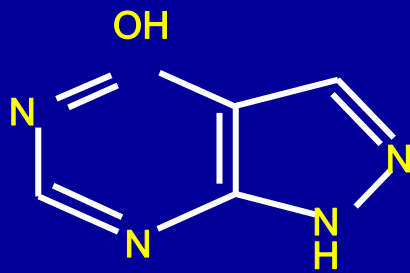


Singh JA et al
Arthritis Res Ther. 2016

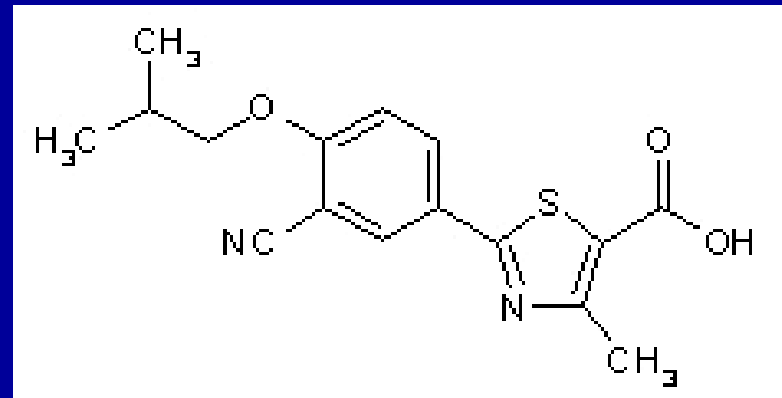
Φάρμακα που αναστέλλουν την παραγωγή ουρικού οξέος Θυρικοστατικά

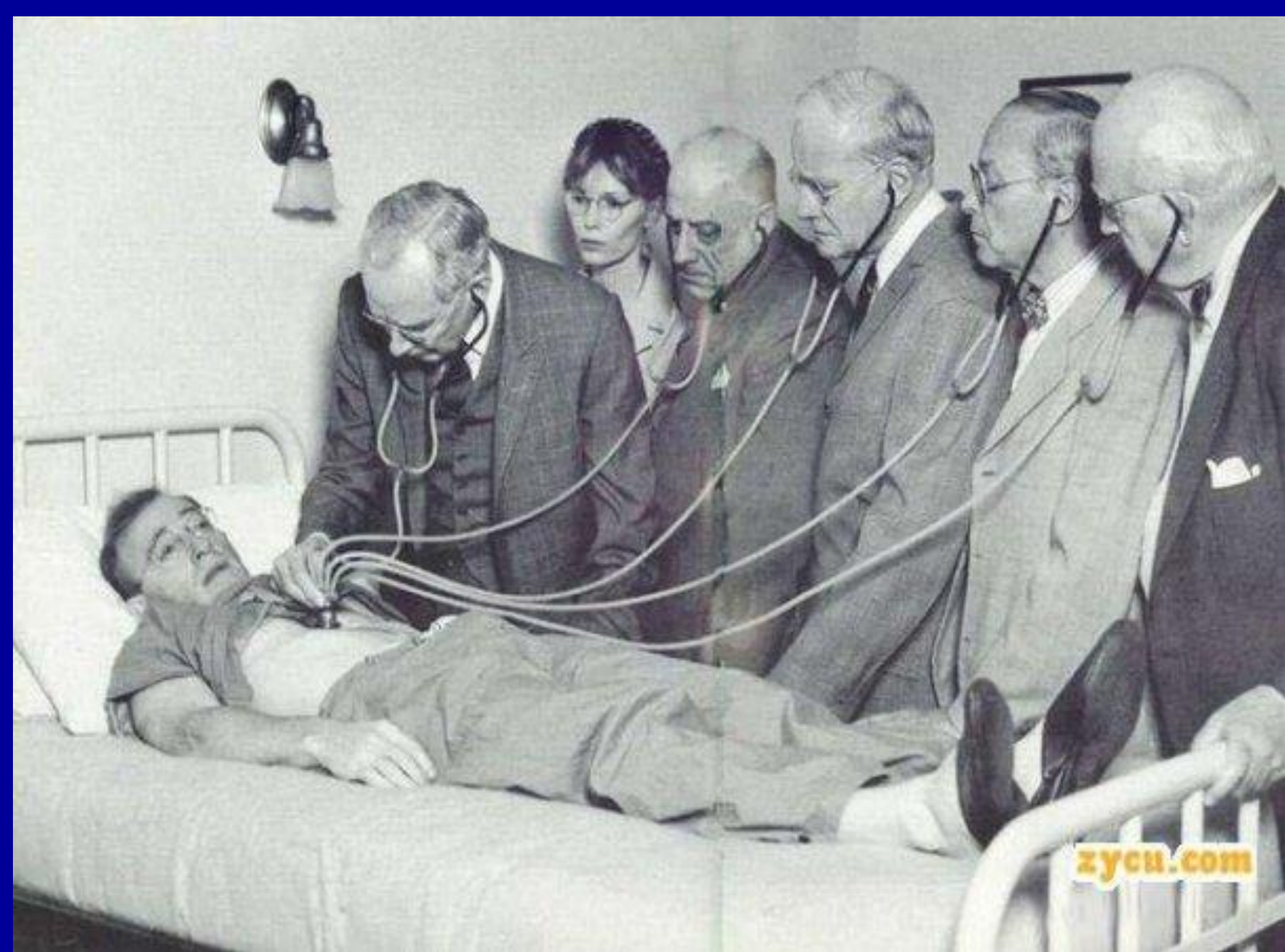
Αναστολείς της οξειδάσης της ξανθίνης

Αλλοπουρινόλη



Φεμπουξοστάτη





Urate lowering drugs: *Indications* EULAR

- **Severe gout** or
- When associated with **UA lithiasis** as traditionally,
- In pts with **Cardio-Vascular or Renal comorbidities**,
- or with high (**>8 mg/dL**) uricemia
- or young age (**<40 years**),

As these are likely to have frequent attacks(>2/year).

In patients with a definite diagnosis of gout, the EULAR advises to **discuss with the patient** the indication of ULD as soon as **after the first flare**.

EULAR Recommendations for Treating to Target

SUA Targets

< 0.36 mmol/L (< 6 mg/dL)
in all patients with gout

< 0.30 mmol/L (< 5 mg/dL)
in patients with severe gout

ULT

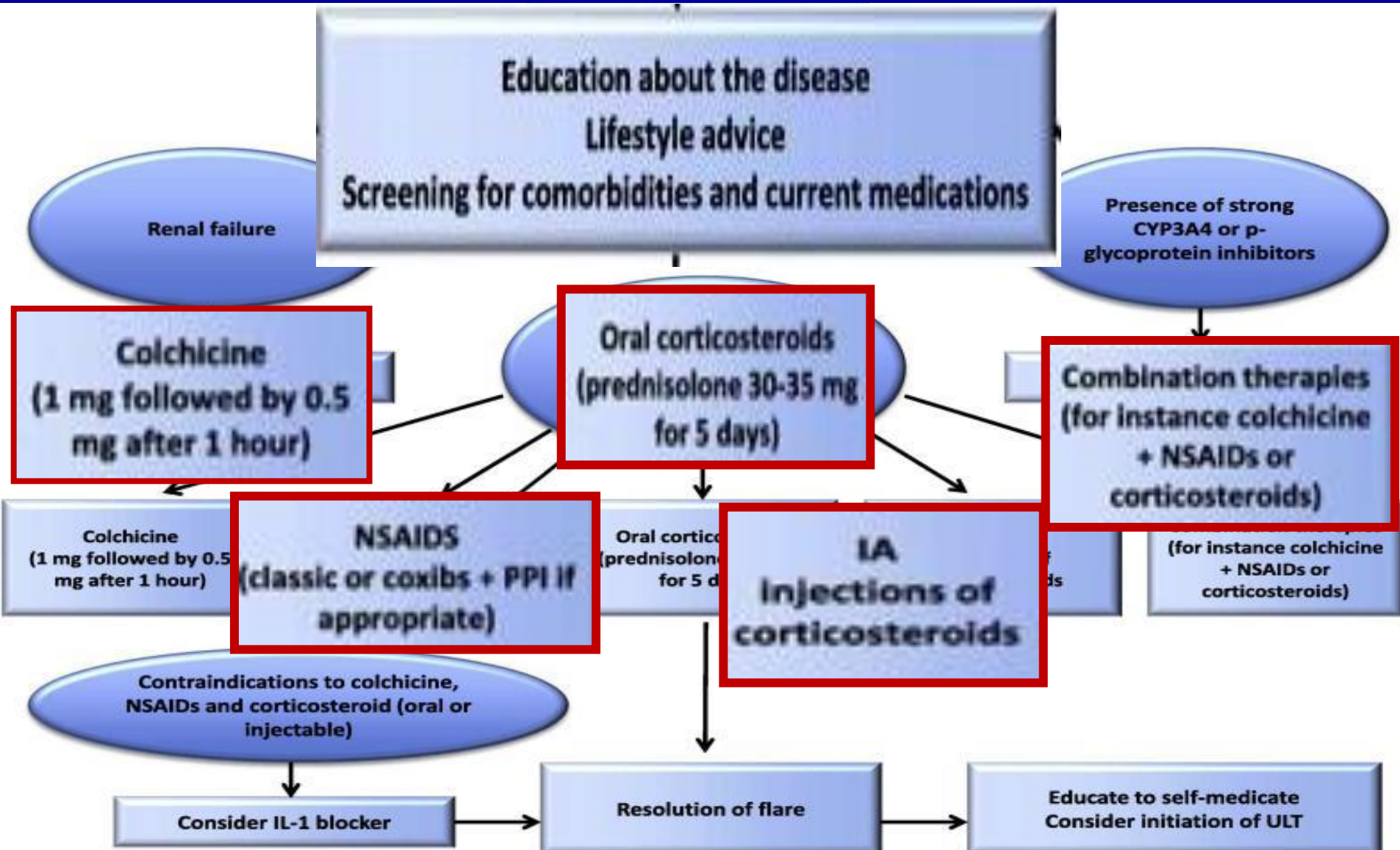
First Line: Allopurinol

- First-line therapy for patients with normal renal function
- Adjust dosage in patients with impaired renal function

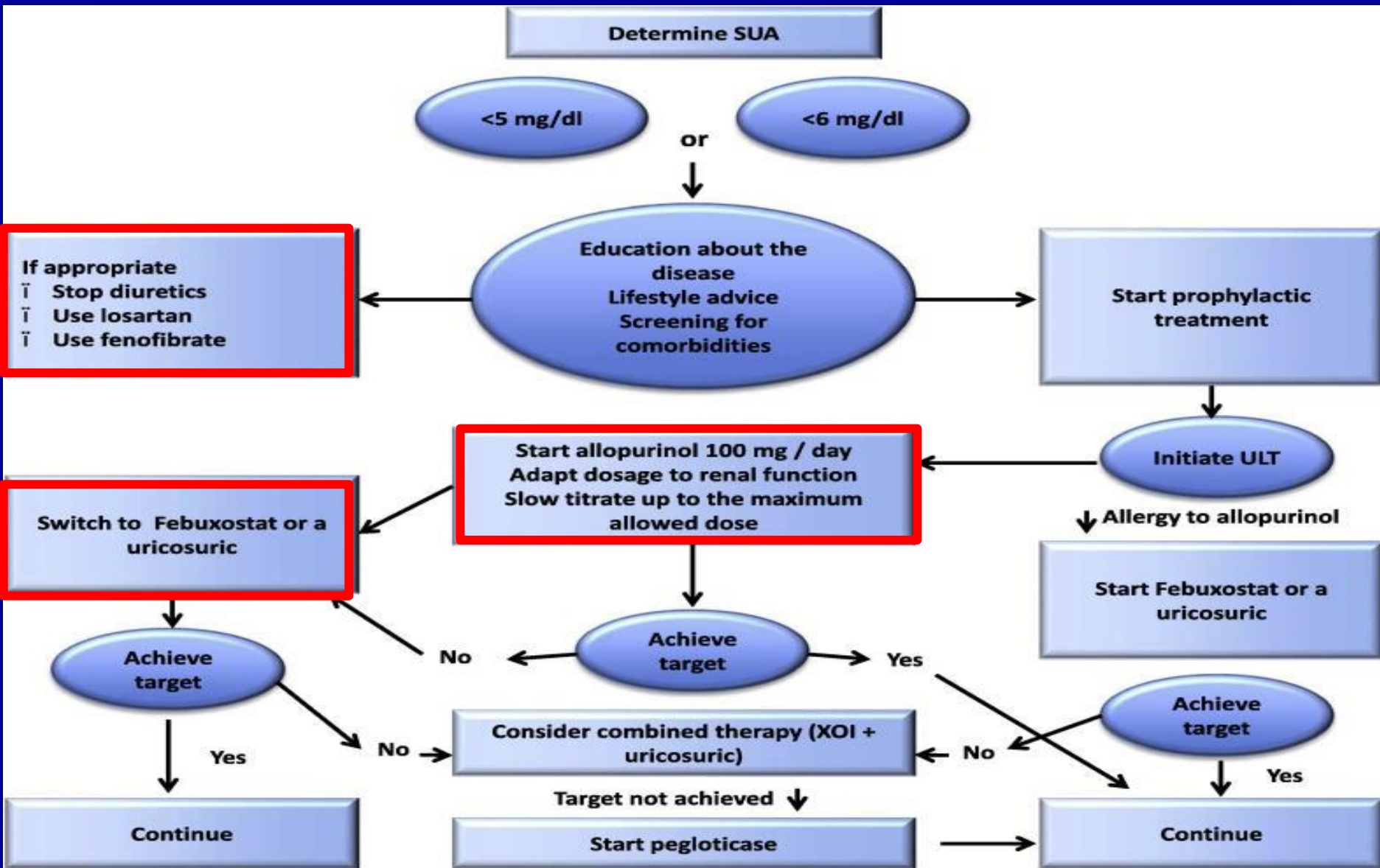
Second Line: Febuxostat and/or Uricosuric

- If SUA target cannot be achieved with allopurinol, substitute with:
 - Febuxostat or a uricosuric
 - XO inhibitor and a uricosuric

EULAR recommendation for the management of flares in patients with gout



EULAR recommendation for the management of hyperuricemia in patients with gout



2020 American College of Rheumatology Guideline for the Management of Gout

Pts with 1 or more subcutaneous tophi, we strongly recommend initiating ULT over no ULT. Pts with radiographic damage (any modality) attributable to gout, we strongly recommend initiating ULT over no ULT. Pts with frequent gout flares (>2/year), we strongly recommend initiating ULT over no ULT.	High Moderate
Pts experienced >1 flare but infrequent flares <2/year, conditionally recommend initiating ULT over no ULT.	High Moderate
Pts experiencing first flare, we conditionally recommend <i>against</i> initiating ULT over no ULT, with the following exceptions.	Moderate
For patients experiencing their first flare and CKD stage >3, SU >9 mg/dl, or urolithiasis, we conditionally recommend initiating ULT	Very Low
Patients with asymptomatic hyperuricemia (SU >6.8 mg/dl with no prior gout flares or subcutaneous tophi), we conditionally recommend <i>against</i> initiating any pharmacologic ULT (allopurinol, febuxostat, probenecid) over initiation of pharmacologic ULT.	High

Μεγάλες μελέτες.....

- **CARES**
- **FAST**
- **ALL-HEART**
- **XILO-FIST**
- **PRIZE**
- **FREED**
- **CKD**
- **METANAΛΥΣΕΙΣ**

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

William B. White, M.D. et al.

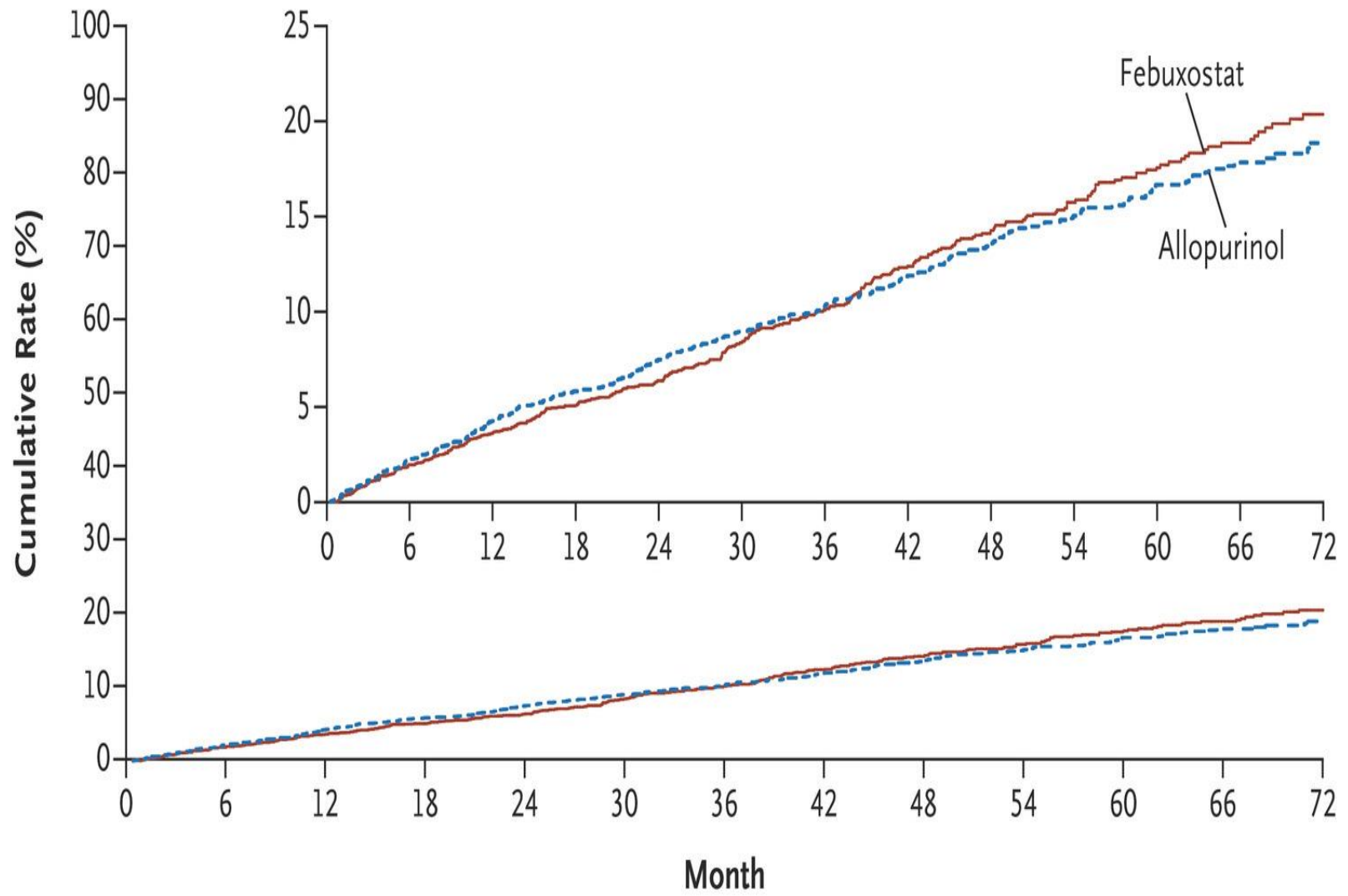
CARES Study

NEJM March 12, 2018

Table 2. Major Safety End Points (Modified Intention-to-Treat Analysis).*

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

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

GRADE

Evaluation

CARES

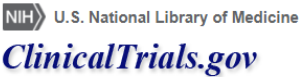
Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

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*

Article **Figures/Media**

Metrics **March 29, 2018**
N Engl J Med 2018; 378:1200-1210
DOI: 10.1056/NEJMoa1710895

22 References 192 Citing Articles Letters



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[Home](#) > [Search Results](#) > Study Record Detail Save this study

Cardiovascular Safety of Febuxostat and Allopurinol in Participants With Gout and Cardiovascular Comorbidities (CARES) (CARES)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our [disclaimer](#) for details.

ClinicalTrials.gov Identifier: NCT01101035

Recruitment Status : Completed
First Posted : April 9, 2010
Results First Posted : June 14, 2018
Last Update Posted : June 14, 2018

Sponsor:
Takeda

Information provided by (Responsible Party):
Takeda

Study Details **Tabular View** **Study Results** [Disclaimer](#) [How to Read a Study Record](#)

Study Type	Interventional
Study Design	Allocation: Randomized; Intervention Model: Parallel Assignment; Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor); Primary Purpose: Treatment
Condition	Cardiovascular Disease
Interventions	Drug: Febuxostat Drug: Allopurinol
Enrollment	6198

Recruitment Details	Participants took part in the study at 320 investigative sites in Canada, Mexico and United States from 23 April 2010 to 18 July 2017.
Pre-assignment Details	Participants with a diagnosis of gout and significant cardiovascular comorbidities were enrolled in a 1:1 ratio to receive either febuxostat or allopurinol.

Arm/Group Title	Febuxostat	Allopurinol
▼ Arm/Group Description	Febuxostat 40 mg (or 80 mg beginning on week 4 if serum uric acid level was ≥6.0 mg/dL), tablets, orally, once daily for up to approximately 82 months.	Allopurinol 300 mg to 600 mg (increased in 100 mg increments each month until serum uric acid was <6.0 mg/dL), tablets, orally, once daily for up to approximately 83 months to participants with mildly impaired renal function or normal renal function (estimated creatinine clearance [eCLcr] ≥60 mL/min) or allopurinol 200 mg to 400 mg (increased in 100 mg increments each month until serum uric acid was <6.0 mg/dL), tablets, orally, once daily for up to approximately 83 months to participants with moderately impaired renal function (eCLcr ≥30 but <60 mL/min).

Period Title: **Overall Study**

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

Started	3101	3097
Completed	1704	1706
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<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

GRADE TOOL REFINED

RISK OF BIAS			Yes/No	Grading
A. Randomized			YES	0
B. Double blind			YES	0
C. Dropouts/Withdrawals			YES	-1
D. Loss of follow-up			YES	-1
E. Discussion of effect studies			YES	0
F. Early termination			YES	-1
G. Failure to report outcomes			NO	0
OVERALL RISK OF BIAS SCORE				-3
INCONSISTENCY				
Population Heterogeneity			NO	0
Intervention Heterogeneity			YES	-1
Outcome heterogeneity			NO	0
OVERALL INCONSISTENCY SCORE				-1
INDIRECTNESS				
Indirect comparison (ie. comparison to placebo)			NO	0
Study population differs from target population			NO	0
Comparator differs among studies			NO	0
Study outcomes differ from outcomes of interest			NO	0
OVERALL INDIRECTNESS SCORE			NO INDIRECTNESS	0
IMPRECISION				
Optimal information size requirement			NO	-1
Mean difference 95%CI includes 0			NO	0
Mean 95%CI ranges overlap			NO	0
RR 95%CI includes 1			YES	-1
OVERALL IMPRECISION SCORE				-2
PUBLICATION BIAS				
Failure to report studies espec those showing no effect			NO	0
Evidence arises from small trials funded by the drug company			NO	0
Author affiliations on the study include the drug company			YES	-1
OVERALL PUBLICATION BIAS SCORE				-1
TOTAL SCORE				-7
GRADE EVALUATION				
			VERY LOW	

GRADE TOOL REFINED

RISK OF BIAS	Yes/No	Grading
A. Randomized	YES	0
B. Double blind	YES	0
C. Dropouts/Withdrawals	YES	-1
D. Loss of Follow-up	YES	-1
E. Discussion of effect studies	YES	0
F. Early termination	YES	-1
G. Failure to report outcomes	NO	0
OVERALL RISK OF BIAS SCORE		-3
INCONSISTENCY		
Population Heterogeneity	NO	0
Intervention Heterogeneity	YES	-1
Outcome heterogeneity	NO	0
OVERALL INCONSISTENCY SCORE		-1
INDIRECTNESS		
Indirect comparison (ie., comparison to placebo)	NO	0
Study population differs from target population	NO	0
Comparator differs among studies	NO	0
Study outcomes differ from outcomes of interest	NO	0
OVERALL INDIRECTNESS SCORE	NO INDIRECTNESS	0
IMPRECISION		
Optimal information size requirement	NO	-1
Mean difference 95%CI includes 0	NO	0
Mean 95%CI ranges overlap	NO	0
RR 95%CI includes 1	YES	-1
OVERALL IMPRECISION SCORE		-2
PUBLICATION BIAS		
Failure to report studies esp. those showing no effect	NO	0
Evidence arises from small trials funded by the drug company	NO	0
Author affiliations on the study include the drug company	YES	-1
OVERALL PUBLICATION BIAS SCORE		-1
TOTAL SCORE		-7
GRADE EVALUATION		
	VERY LOW	

45% μ 16% lose of follow up

Different doses for Allop

Percentage of Participants With Primary MACE Composite
10,8% for Febux vs. 10,4% for Allop, (0.87-1.23, 97%CI)

Inference for Means: Comparing Two Independent Samples

(To use this page, your browser must recognize JavaScript.)

Choose which calculation you desire, enter the relevant population values for μ_1 (mean of population 1), μ_2 (mean of population 2), and σ (common standard deviation) and, if calculating power, a sample size (assumed the same for each sample). You may also modify α (type I error rate) and the power, if relevant. After making your entries, hit the calculate button at the bottom.

- * Calculate Sample Size (for specified Power)
- Calculate Power (for specified Sample Size)

Enter a value for μ_1 : 0.104

Enter a value for μ_2 : 0.108

Enter a value for σ : 0.1

- 1 Sided Test
- * 2 Sided Test

Enter a value for α (default is .05): .05

Enter a value for desired power (default is .80): .97

The sample size (for each sample separately) is: 18440

Table 2. Major Safety End Points (Modified Intention-to-Treat Analysis).^a

End Point	Febuxostat (N = 3098)	Allopurinol (N = 3092)	Hazard Ratio (95% CI)	P Value ^c
no. of patients (%)				
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

Author Affiliations

From the University of Connecticut School of Medicine, Farmington (W.B.W.); the University of Alabama, Birmingham (K.G.S.); University of Chicago Medicine, Chicago (M.A.B.), and Takeda Development Center Americas, Deerfield (B.H., M.C., L.G.) — both in Illinois; the State University of New York, Downstate Medical Center, Brooklyn (J.S.B.); Michigan State University College of Human Medicine, Grand Rapids (P.B.G.); and Johns Hopkins University School of Medicine, Baltimore (A.W.).

FUTURE STUDIES
ARE VERY LIKELY TO
CHANGE
THE ESTIMATE

4. Secondary Outcome

Title	Percentage of Participants With Cardiovascular (CV) Death
▼ Description	Events were adjudicated by an independent cardiovascular endpoints committee as CV death.
Time Frame	Up to last dose of study drug (approximately 83 months)

Overall Number of Participants Analyzed	3098	3092
Measure Type: Number		
Unit of Measure: percentage of participants		
	4.3	3.2

Inference for Proportions: Comparing Two Independent Samples

(To use this page, your browser must recognize JavaScript.)

Choose which calculation you desire, enter the relevant population values (as decimal fractions) for p_1 (proportion in population 1) and p_2 (proportion in population 2) and, if calculating power, a sample size (assumed the same for each sample). You may also modify α (type I error rate) and the power, if relevant. After making your entries, hit the **calculate** button at the bottom.

- ☒ Calculate Sample Size (for specified Power)
- ☐ Calculate Power (for specified Sample Size)

Enter a value for p_1 :

Enter a value for p_2 :

- ☐ 1 Sided Test
- ☒ 2 Sided Test

Enter a value for α (default is .05):

Enter a value for desired power (default is .80):

The sample size (for each sample separately) is:

Post-CARES EMA REQUIREMENTS

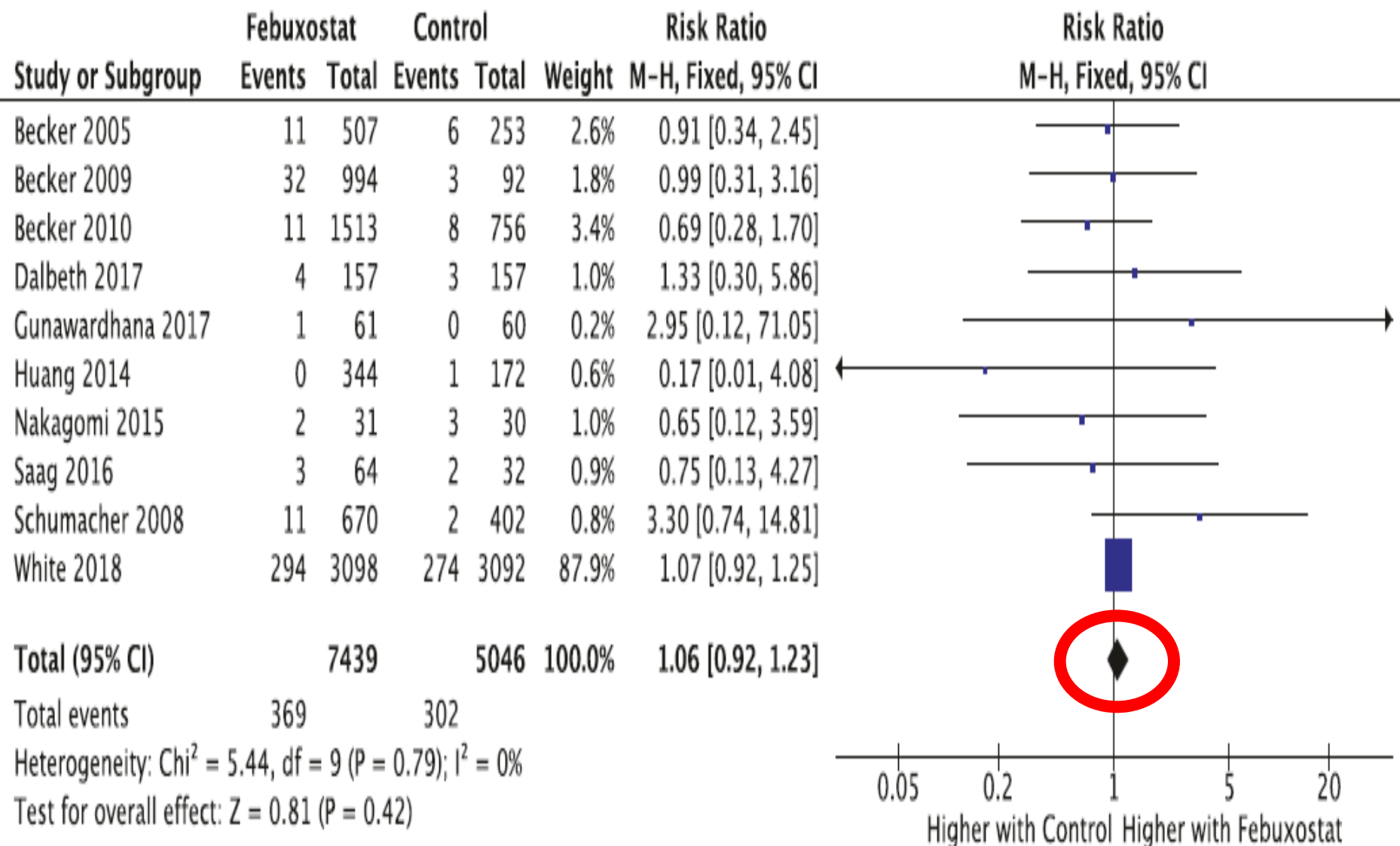
Dear Doctor Letter

- In the CARES study Febuxostat **increased risk of CV death** and **all-cause mortality**.

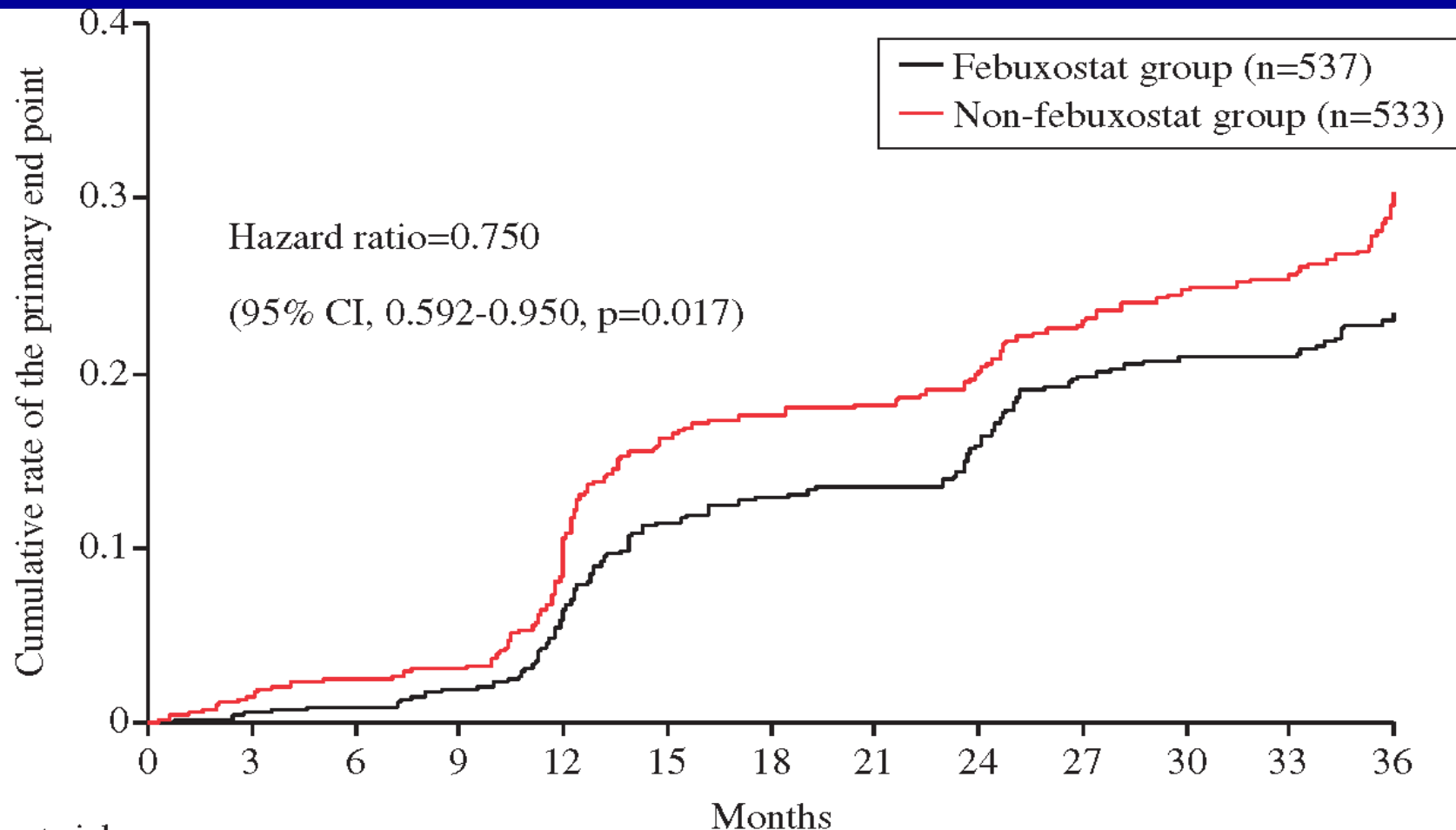
Updated CV warning in the SPC: (July 2019)

- Treatment with Febuxostat **in pts with pre-existing major CVD** (e.g. MI, stroke or unstable angina) **should be avoided**, unless no other therapy options are appropriate

Febuxostat and CV Events: Review and Meta-Analysis



Febuxostat for Cerebral and Cardiovascular Events Prevention Study (FREED)



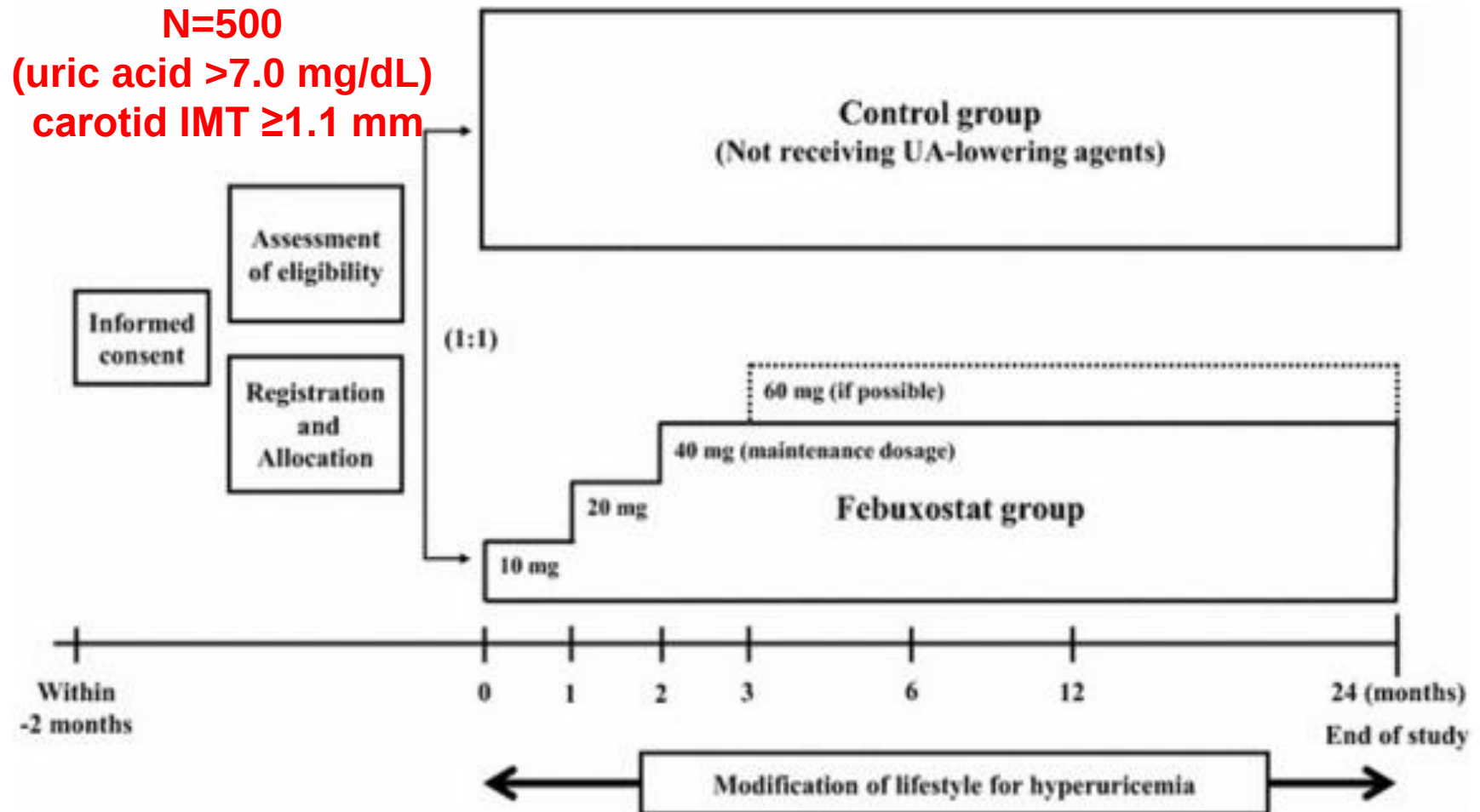
No. at risk

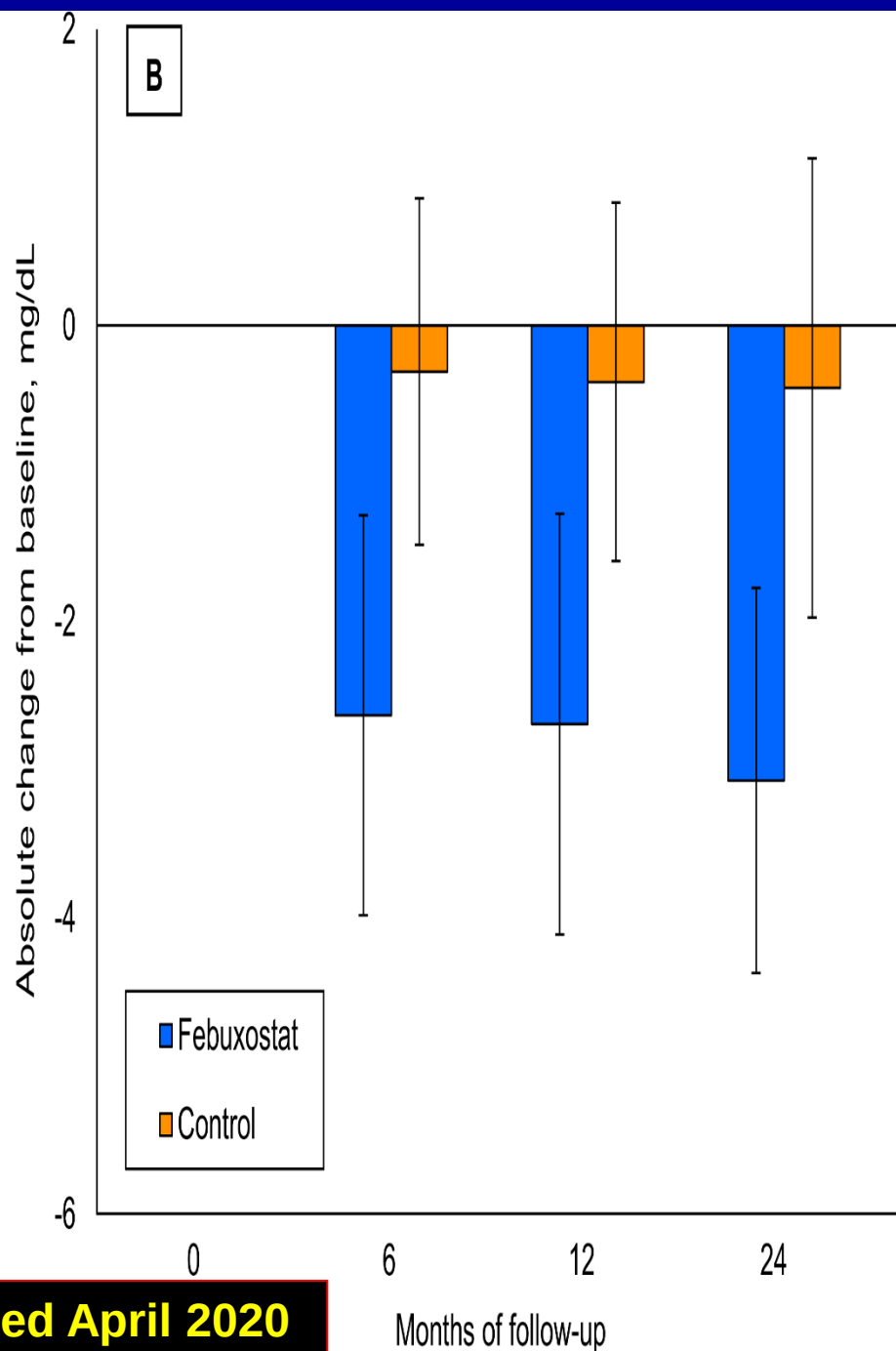
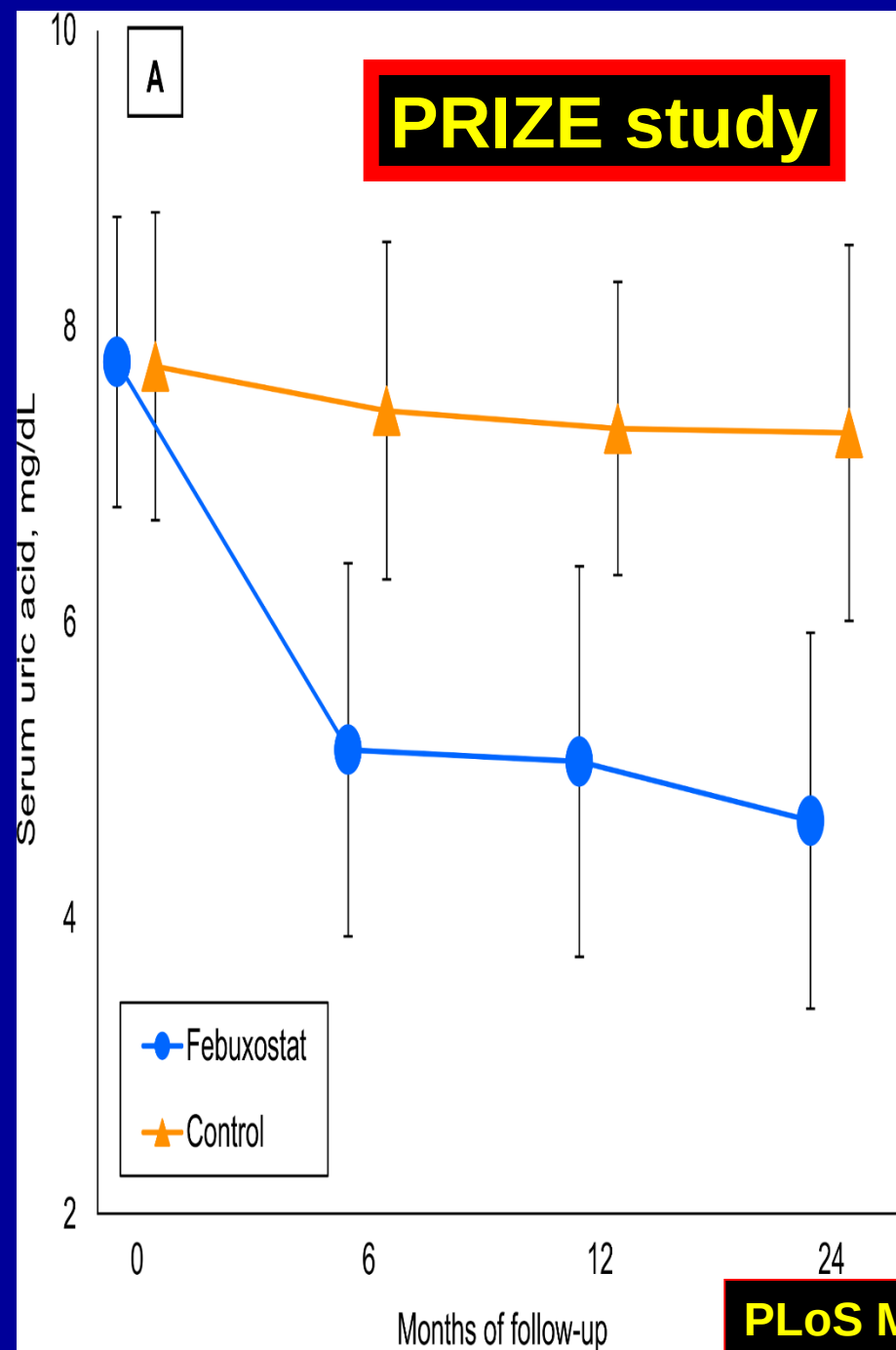
Febuxostat	537	515	473	429	399	372	209
Non-febuxostat	533	501	451	391	370	341	188

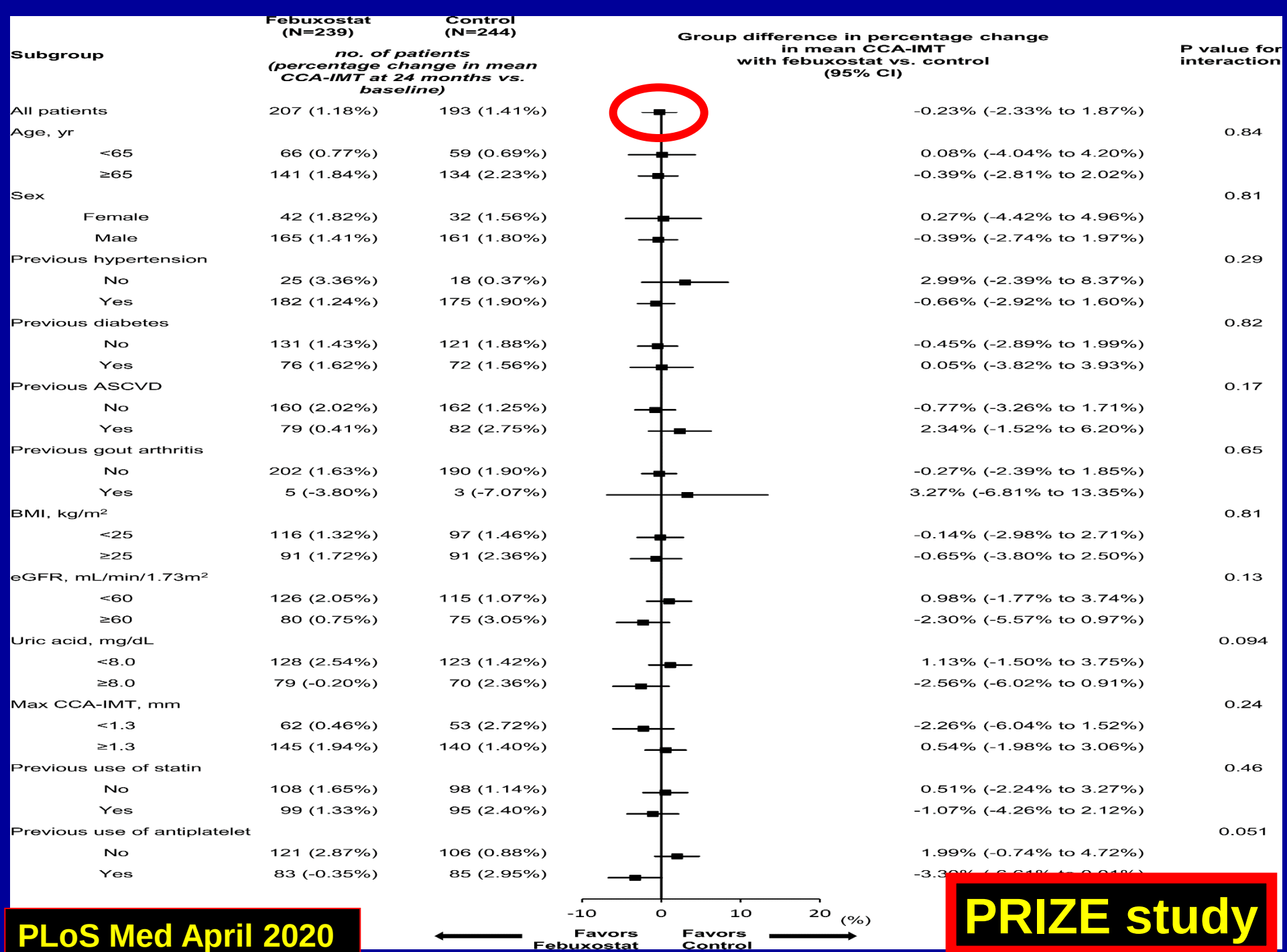
PRIZE study

Effects of febuxostat on atherosclerosis

asymptomatic hyperuricemia



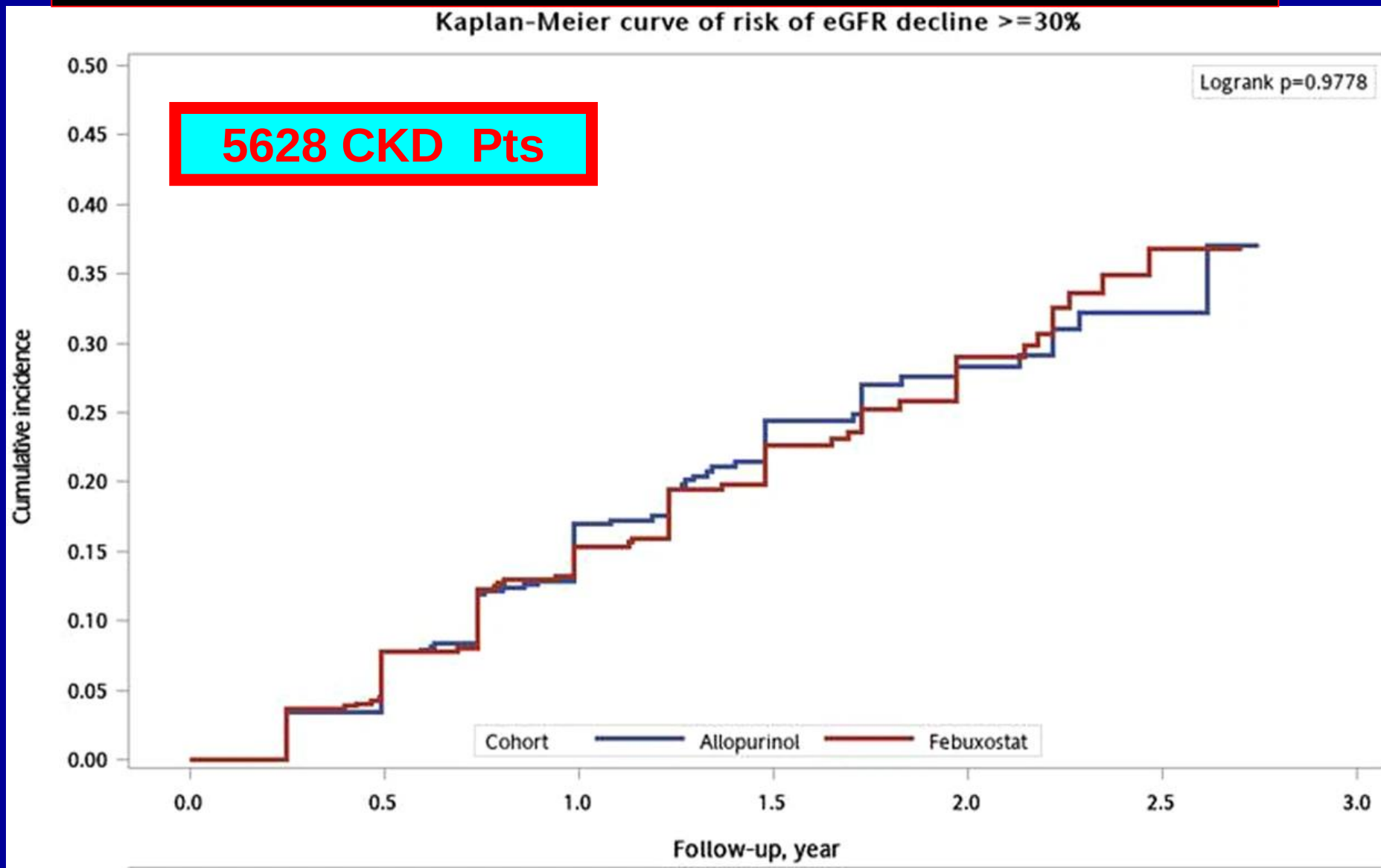




PRIZE study

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)

Comparison of UA reduction and renal outcomes of febuxostat vs allopurinol in patients with CKD



FAST

EMA required a safety clinical trial

Allopurinol
100-900mg*

Febuxostat
80-120mg *

treatment

169 withdrew consent for
all follow up

OUT

6128
were randomized

3065
Allopurinol Arm

3065
Included in the efficacy analysis

2633
completed the trial
263 died

3063
Febuxostat Arm

3063
Included in the efficacy analysis

2652
completed the trial
222 died

3001 started treatment
973 discontinued
treatment

189 withdrew consent for
all follow up

OUT

LANCET
Nov 2020

FAST - ENDPOINTS

Primary endpoint:

- Hospitalisation for non-fatal MI/biomarker positive ACS
- Non-fatal stroke
- Death due to a CV event

Secondary endpoints:

- Hospitalization for non-fatal MI/biomarker positive ACS
- Non-fatal stroke
- CV death
- All cause mortality
- Hospitalization: CHF, Angina, PCI, CABG, Cardiac arrest, Cerebral revascularisation, TIA, thrombotic event, arrhythmia.

Exploratory efficacy endpoint:

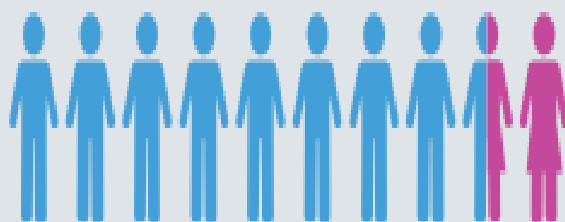
- Proportion of pts whose UA is ≥ 6.0 mg/dL, < 6.0 mg/dL and < 5.0 mg/dL after each year of treatment

FAST- INCLUSION CRITERIA

- Male/Female **gouty pts ≥ 60 yrs with at least one CV risk factor**
- Age ≥ 70 years (male) or ≥ 75 years (female)
- Smoking (current or within the last 2 years)
- Diabetes mellitus or Impaired glucose tolerance
- HTN (BP $> 140/90$ mmHg) or receiving treatment to lower BP
- Dyslipidaemia (investigator assessment)
- CKD Microalbuminuria or proteinuria
- Family history of CAD or stroke in first degree relative at age < 55 yrs
- Inflammatory arthritis (Investigator assessment)
- Chronic NSAID therapy (investigator assessment)
- Previous CV event (MI, CVA or TIA)
- PVD (investigator/clinical assessment)
- Body mass index > 30 kg/m²
- COPD
- Pts who have received ≥ 60 days treatment with Allopurinol or ≥ 2 Allopurinol prescriptions, within the previous 6 months.

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

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NON-INFERIORITY - ON TREATMENT POPULATION

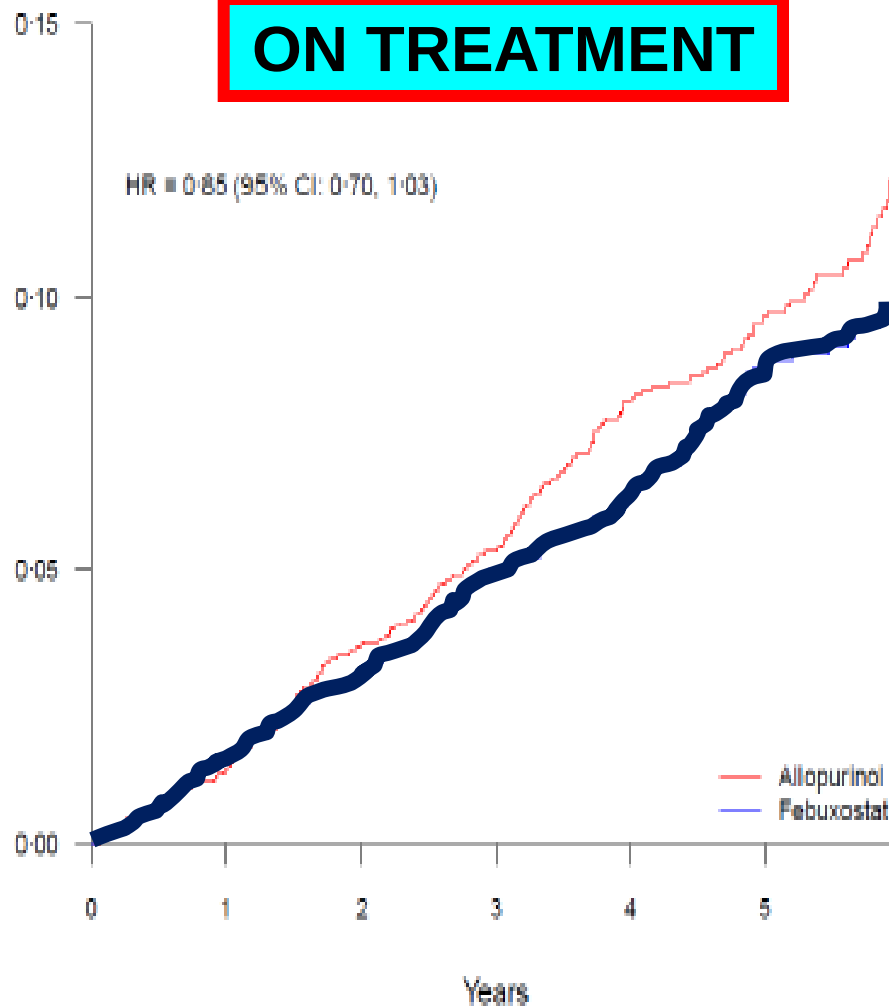
Allopurinol (N=3065)		Febuxostat (N=3063)			
n (%)	Rate	n (%)	Rate	HR (95% CI)	P _{NI}
241 (7·86%)	2·054	172 (5·62%)	1·723	0·85 (0·70, 1·03)	<0·001

NON-INFERIORITY - ITT POPULATION

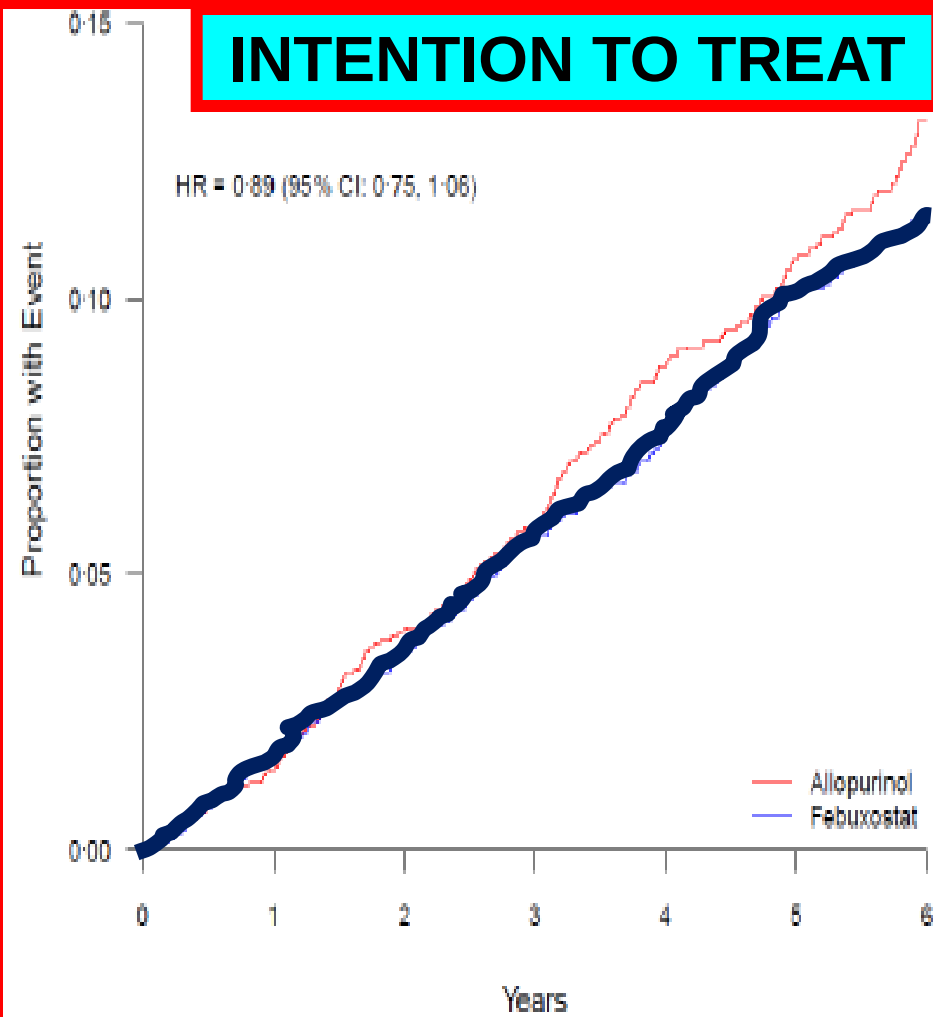
Allopurinol (N=3065)		Febuxostat (N=3063)			
n (%)	Rate	n (%)	Rate	HR (95%CI)	P _{NI}
285 (9·30%)	2·295	256 (8·36%)	2·047	0·89 (0·75, 1·06)	<0·001

FAST- PRIMARY ENDPOINT RESULT

ON TREATMENT



INTENTION TO TREAT



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FAST- SECONDARY ENDPOINT RESULT

	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

FAST- SECONDARY ENDPOINT RESULT

ON TREATMENT

	Allopurinol		Febuxostat			
	N(%)	Rate	N(%)	Rate	HR (95%CI)	Pni
All-cause mortality	174 (5.68%)	1.438	108 (3.53%)	1.062	0.75 (0.59, 0.95)	<0.001

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FAST- SECONDARY ENDPOINT RESULT

INTENTION TO TREAT

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	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	110 (3.59%)	0.873	102 (3.33%)	0.808	0.93 (0.71, 1.21)	0.007
Non-fatal stroke	87 (2.84%)	0.687	80 (2.61%)	0.629	0.92 (0.68, 1.25)	0.013
Cardiovascular death	122 (3.98%)	0.949	117 (3.82%)	0.911	0.96 (0.74, 1.23)	0.009
All-cause mortality	263 (8.58%)	2.045	222 (7.25%)	1.728	0.84 (0.71, 1.01)	<0.001
Hospitalisation for heart failure	102 (3.33%)	0.805	92 (3.00%)	0.724	0.90 (0.68, 1.19)	0.005
Hospitalisation for unstable new or worsening angina	12 (0.39%)	0.094	5 (0.16%)	0.039	0.41 (0.14, 1.16)	0.015

FAST- SECONDARY ENDPOINT RESULT

INTENTION TO TREAT

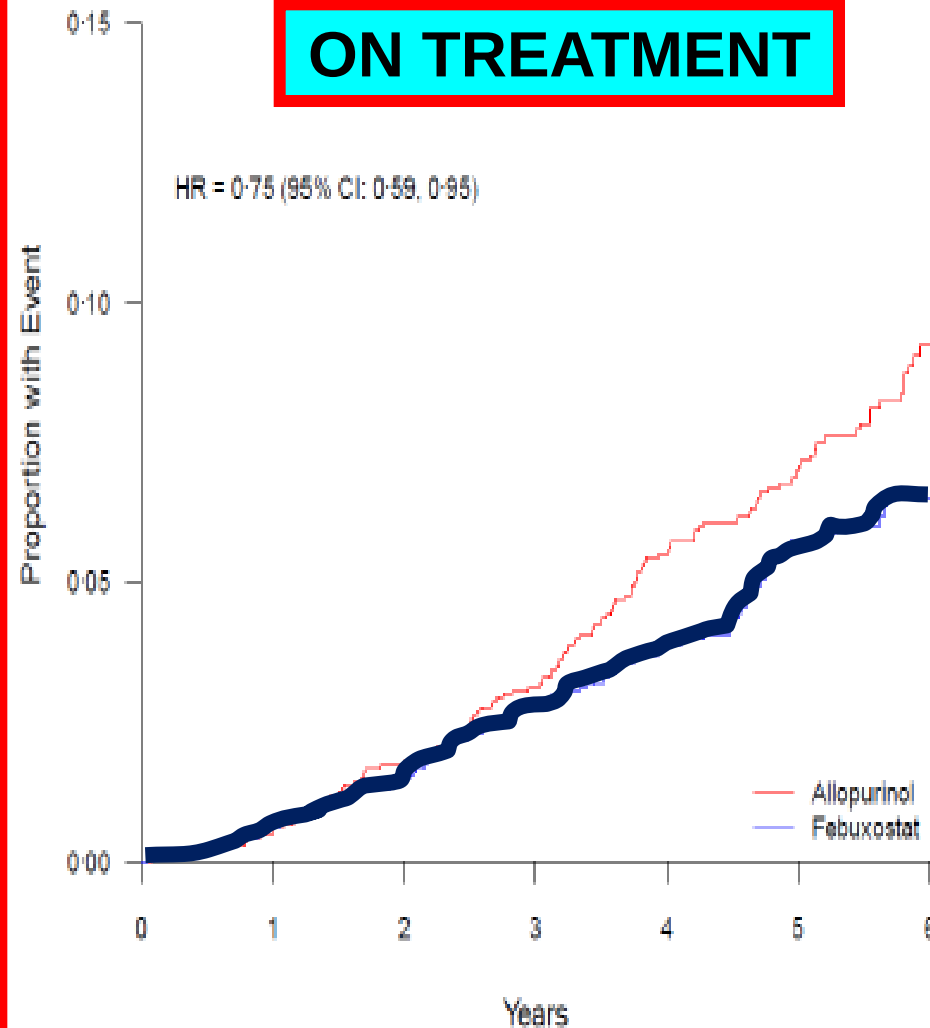
	Allopurinol		Febouxostat			
	n(%)	Rate	N(%)	Rate	HR (95%CI)	Pni
All-cause mortality	263 (8·58%)	2·045	222 (7·25%)	1·728	0·84 (0·71, 1·01)	<0.001

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Nov 2020

FAST- SECONDARY ENDPOINT RESULT

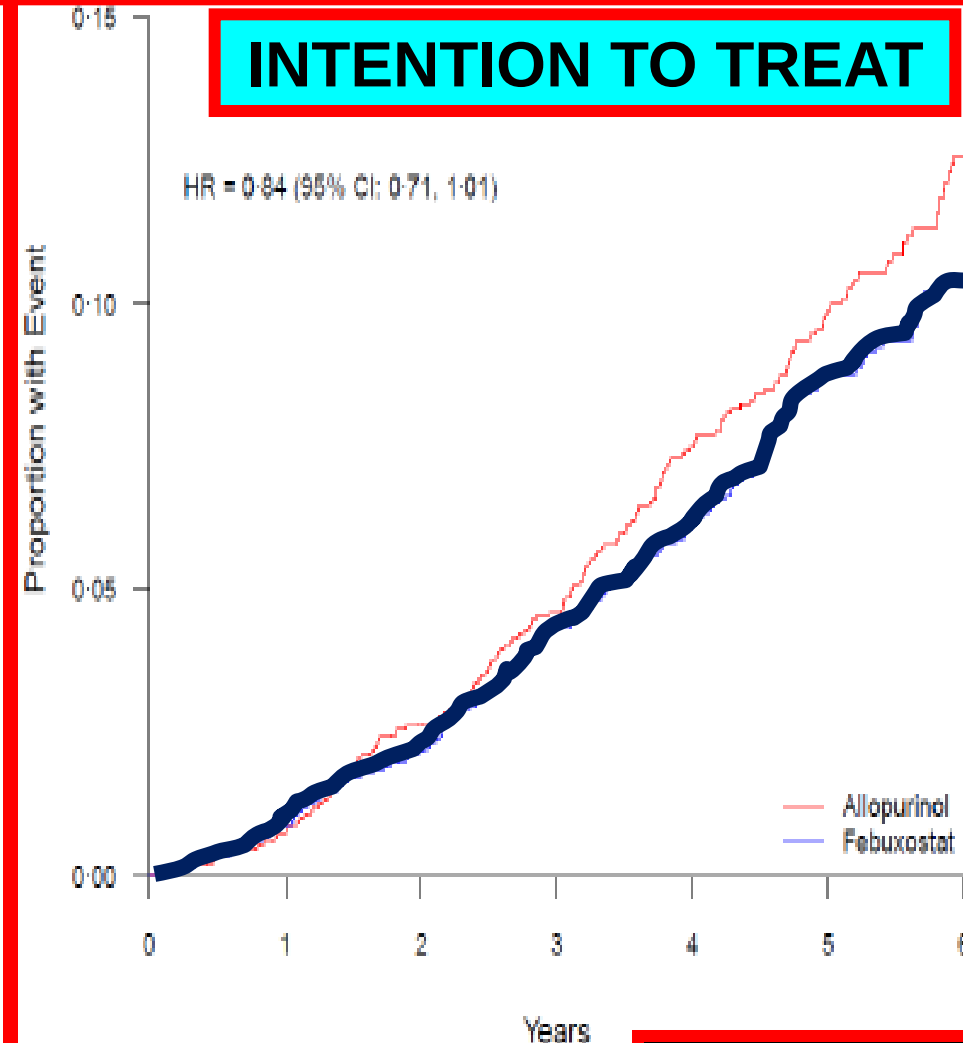
ON TREATMENT

HR = 0.75 (95% CI: 0.59, 0.95)



INTENTION TO TREAT

HR = 0.84 (95% CI: 0.71, 1.01)



All-cause mortality

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FAST EXPLORATORY EFFICACY ENDPOINT

Analysis	Estimate	P-value	Uric acid	Allopurinol	number (%)	P-value
SUA at 12 months	-82.919 umol/L	<0.0001	Year 1 less than 5 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
SUA at 24 months	-82.919 umol/L	<0.0001	Year 2 less than 5 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
SUA at 36 months	-82.919 umol/L	<0.0001	Year 3 less than 5 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
SUA at 48 months	-82.919 umol/L	<0.0001	Year 4 less than 5 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
SUA at 60 months	-82.919 umol/L	<0.0001	Year 5 less than 5 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
SUA at 72 months	-82.919 umol/L	<0.0001	Year 6 less than 5 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
SUA at 84 months	-82.919 umol/L	<0.0001	Year 7 less than 5 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 1 less than 6 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 2 less than 6 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 3 less than 6 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 4 less than 6 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 5 less than 6 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 6 less than 6 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 7 less than 6 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 1 less than 7 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 2 less than 7 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 3 less than 7 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 4 less than 7 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 5 less than 7 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 6 less than 7 mg/dL	635 (91.37%)	635 (91.37%)	<0.001
			Year 7 less than 7 mg/dL	635 (91.37%)	635 (91.37%)	<0.001

**Febuxostat
demonstrated superiority
vs Allopurinol
in SUA reduction
with statistical significance
starting from year 1 to 7
(P<0.0001)**

FAST- SUBSET ANALYSIS

- Following a **request by EMA**, it was performed an **analysis** on a subset of FAST patients **similar** to the ones recruited **in CARES**.

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



	CARES (n=6190)	FAST (n=6128)
Patients	All Established CV event	33% CV event at baseline
SUA Treatment	Newly treated and uncontrolled gouty patient	Already established therapy with Allopurinol
Allopurinol dose	200-600 mg/ die	100-900 mg/ die
Febuxostat dose	40-80 mg/ die	80-120 mg/ die
Therapy discontinuation	56%	16,5% Allopurinol 32,4% Febuxostat
Lost follow-up	45%	5.8%
Primary end point (Type of the analysis)	ITT	OT

FAST- SAFETY ANALYSIS

	Allopurinol	Febuxostat
Serious adverse events (SAE)	1812 (59,4%)	1720 (57.3%)
SAE related to the study drugs	9	15
SAE gastro-intestinal related to the study drugs	1	8
Gout flares in post randomization period	1044	1017

FAST - CONCLUSION

- Febuxostat 80-120mg, in term of CV safety, is not inferior to Allopurinol 100-900mg.
- In Febuxostat arm all-cause of death and CV-death rates were lower than in Allopurinol one
- FAST confirmed the superiority of Febuxostat vs Allopurinol in reaching the SUA target
- No increased risk of CV outcome has been shown in patients with MI, stroke or ACS (subset of patients more similar to the one included in the CARES).

- **Φεμπουξοστάτη 80mg**
- **3 μήνες μετά**
- **UA: 5.8 mg/dl**
- **Κρεατινίνη: 1.12 mg/dl**
- **ΑΠ: 136/86 mmHg**
- **Απώλεια 4 κιλών**

Τι γνωρίζουμε?

- Το UA έχει σημαντικό ρόλο στην αλληλουχία της ΚΑΝ
- Μέχρι σήμερα έχουμε δεί ότι μειώνοντας το UA:
 - 1) Μειώνεται η **ΑΠ**
 - Σε εφήβους και ενήλικες
 - 2) Μειώνεται η **LVMass**
 - 3) Μειώνεται η εξέλιξη **IMT**
 - 4) Βελτιώνεται η λειτουργικότητα των **μικρών αγγείων** στον εγκέφαλο
 - 5) Μειώνεται το **μεταφορτίο**
 - 6) Βελτιώνεται η **ενδοθηλιακή λειτουργία**

Asymptomatic Hyperuricemia

>7mg/dl (M)

>6mg/dl (F)



Hypertension

CV Disease

Stroke

Renal Disease

**Metabolic
Syndrome**

**Υπάρχει πραγματικό κλινικό όφελος να
θεραπεύουμε το ουρικό οξύ στον
καρδιαγγειακό ασθενή??**

Απάντηση

- **Φαίνεται πολλά υποσχόμενο**
- **Έχουμε κατευθυντήριες ενδείξεις θεραπείας**
- **Το αν θα γίνουμε περισσότερο επιθετικοί στην θεραπεία, μελέτες σε εξέλιξη !**

Therapeutic Target in HTN & UA

130/80 mmHg

<6mg/dl



Therapeutic Target in HTN & UA

130/60

