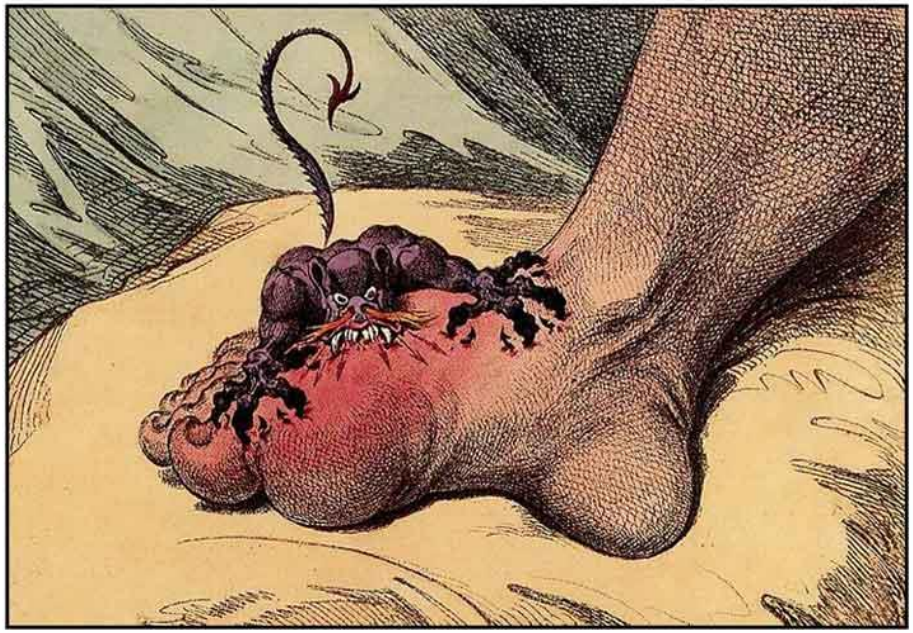
GOUT שגרון



WHAT'S NEW ABOUT AN OLD DISEASE IN OLD PEOPLE

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Jan. 7, 2016

כ"ו טבת תשע"ו

כל התורה על רגל אחת

GOUT

- A metabolic disease characterized by recurrent attacks of acute inflammatory arthritis caused by uric acid crystals in joints.

- The most common rheumatic inflammatory disease of adulthood

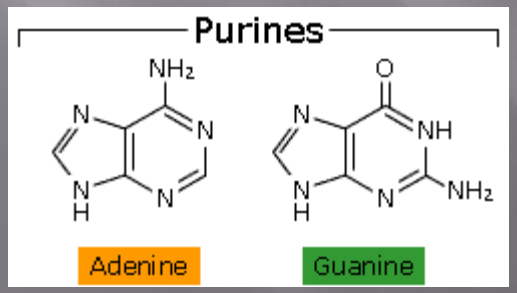
- Hyperuricemia :

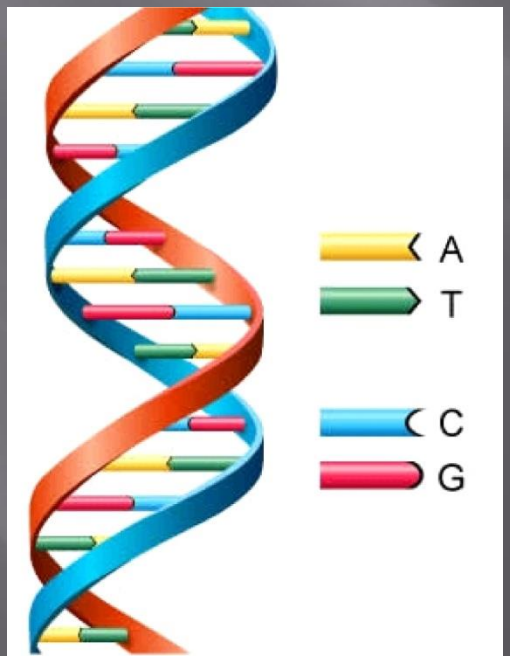
overproduction/under excretion/both

Hyperuricemia ? Gout

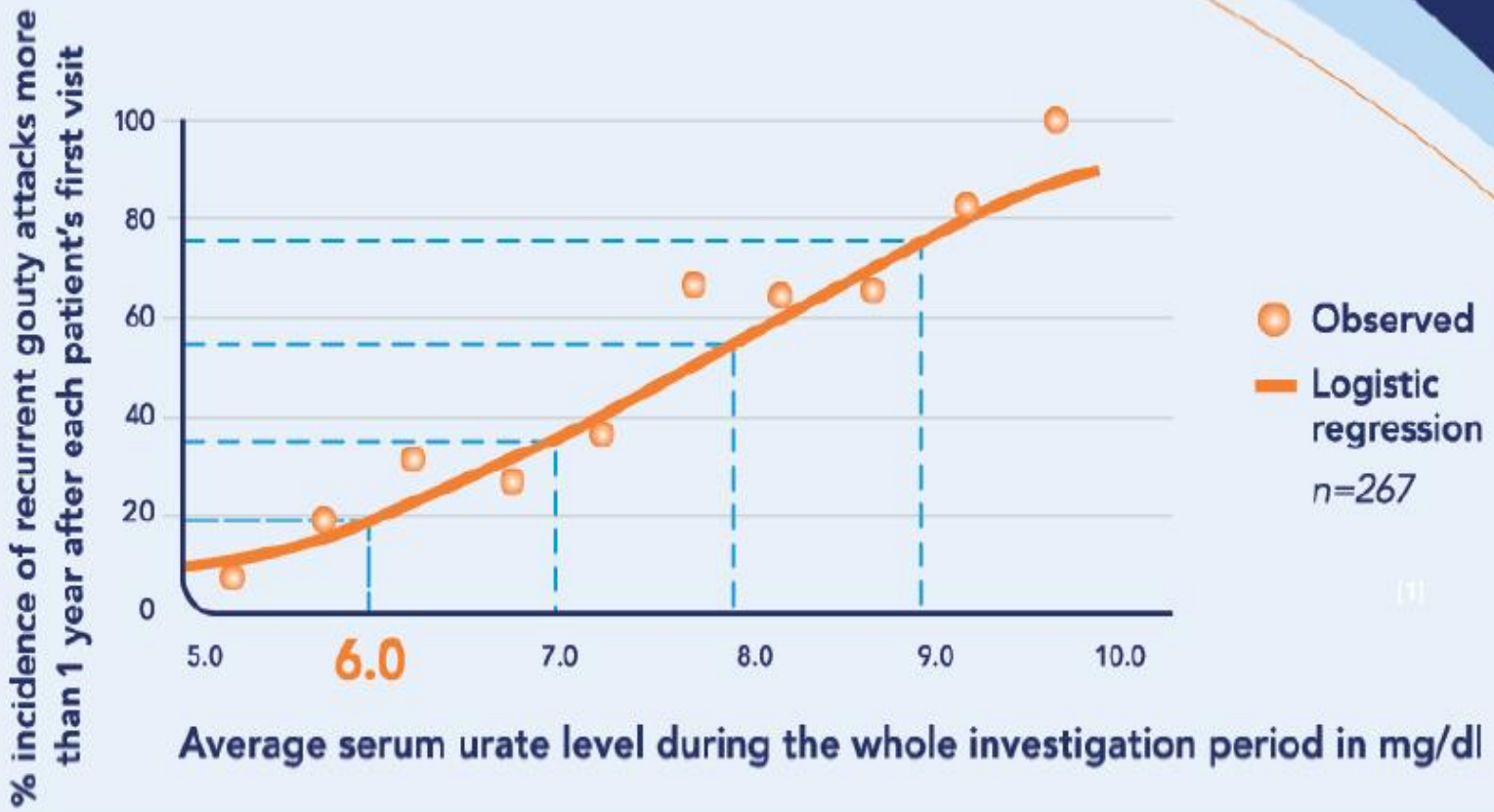
Uric Acid comes from breakdown of Purines

- Purines are part of the chemical structure of our genes – DNA bases - found in the nuclei of all of the body's cells, and in virtually all foods.





Frequence of gout attacks is strongly related to sUA level [1]



The relationship between sUA and gout flares [1]

(1) Shoji A, et al. Arthritis Rheum 2004; 51:321-325. (2) Schumacher HR, et al. Rheumatology 2009;48:188-194.
(3) Becker MA, et al. N Engl J Med 2005;353:2450-2461. (4) Schumacher HR, et al. Arthritis Rheum 2008;59:1540-1548. (5) Feburic® prescribing information

GOUTY ARTHRITIS

Risk factors for Gout	Comment
Raised serum urate	The higher the urate level, the greater the risk of gout.
Genetics	Mutations in genes for urate transporter URAT1 and fructose transporter GLUT9 are associated with gout.
Age	2% of 45-64 year old men and 6% men >75 years old have gout.
Gender	Male :Female ratio 3:1 in those > 65 years

COMMON GOUT RISK FACTORS

- GENETICS
- OBESITY
- ASPIRIN USE
- DIURETICS
- ALCOHOL USE
- SWEETENED BEVERAGES (FRUCTOSE, CORN SYRUP)

GOUTY ARTHRITIS

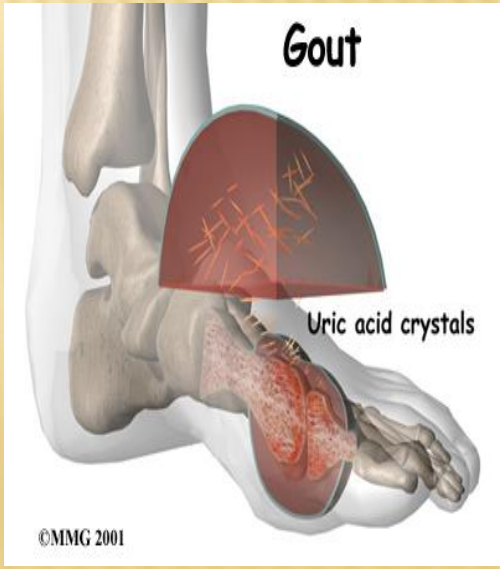
Acute gout

- Acute, self limiting, monoarticular
- Painful, red, hot, swollen
- Usually resolves within 2 weeks if untreated
- May occur even if serum urate is normal

- Commonly affected joints

  1st metatarsophalangeal joint (podagra)

  I. Forefoot/instep
  II. Ankle joint
  III. Knee joint
  IV. DIPs (hands) of elderly women



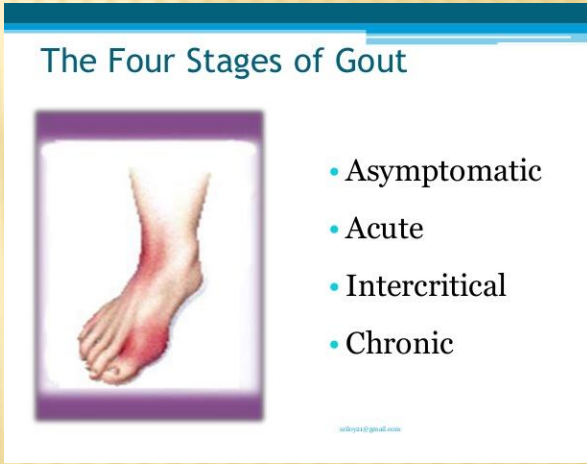
DIP TOPHACEOUS GOUT IN ELDERLY WOMEN

Intercritical gout

- Asymptomatic period between attacks

*** **CARDIOVASCULAR RISK FACTOR**

***** **RENAL RISK FACTOR**

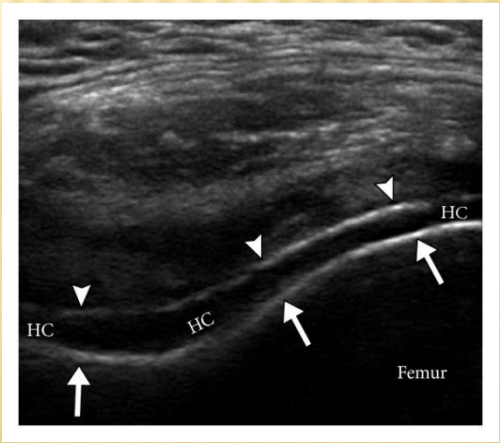


- Sites of tophi:
- Digits of hands and feet (most common)
  - Pinna of ear (classic, less common)
  - Bursa around elbows and knees
  - Achilles tendon

DIAGNOSIS

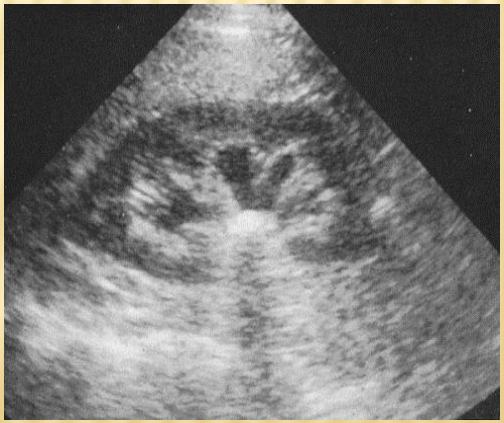
- Definitive diagnosis : presence of monosodium urate crystals seen in synovial fluid/tissues

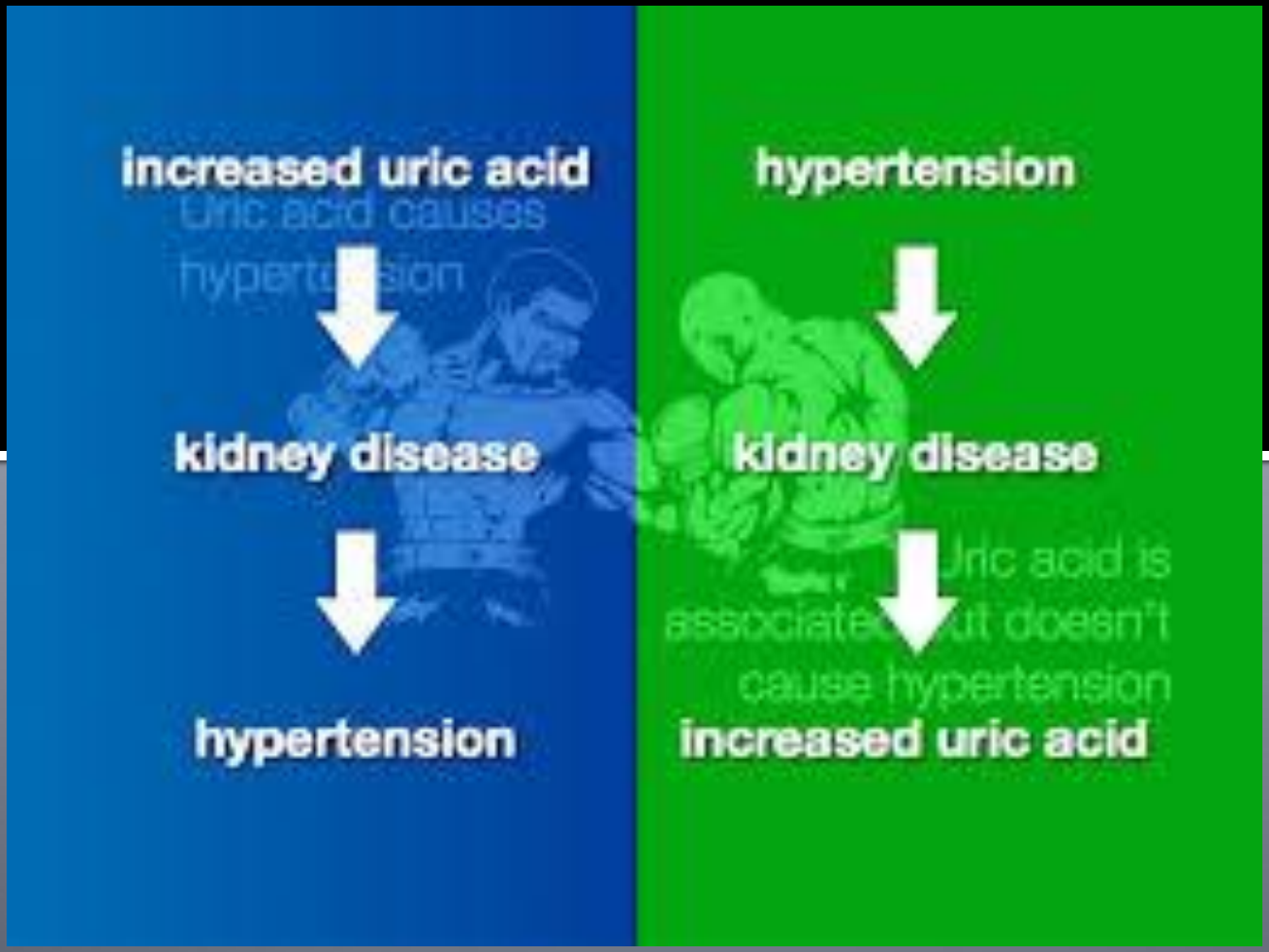
- Imaging



URATE/GOUTY NEPHROPATHY

- Acute urate nephropathy
- **Chronic urate nephropathy - INTERSTITIAL**
- Urate nephrolithiasis





Metabolic syndrome cardiovascular disease

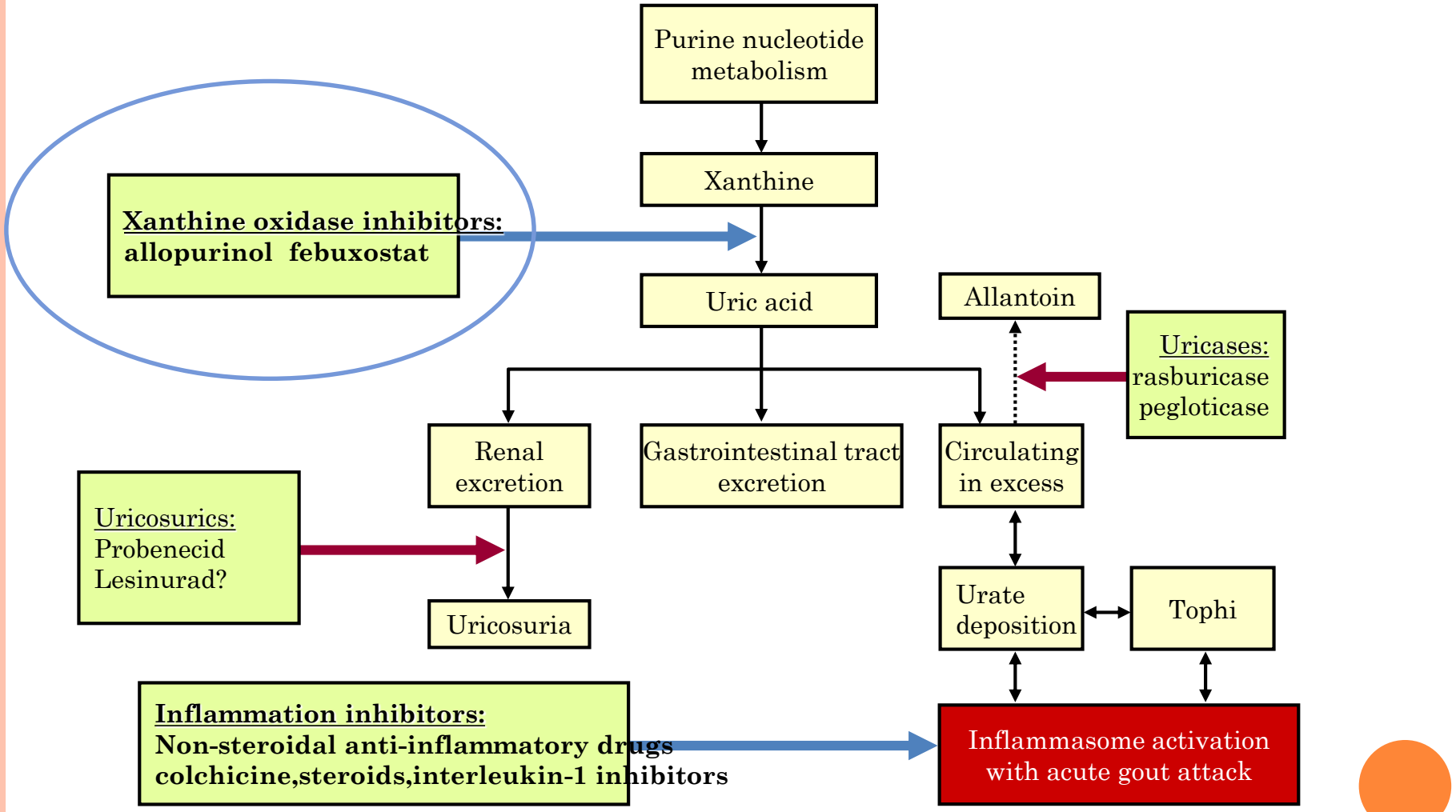
Treating Acute Gout

- Ice Pack
- COLCHICINE
- NSAIDs
- STEROIDS
- COMBINATION!

- Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 ACR Guidelines for Management of Gout. Arth Care & Res 2012; 64 (10): 1447-61.

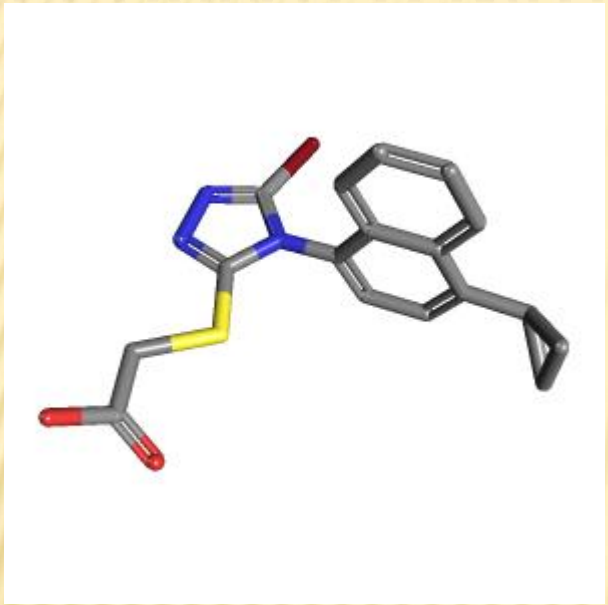
- Anti IL1

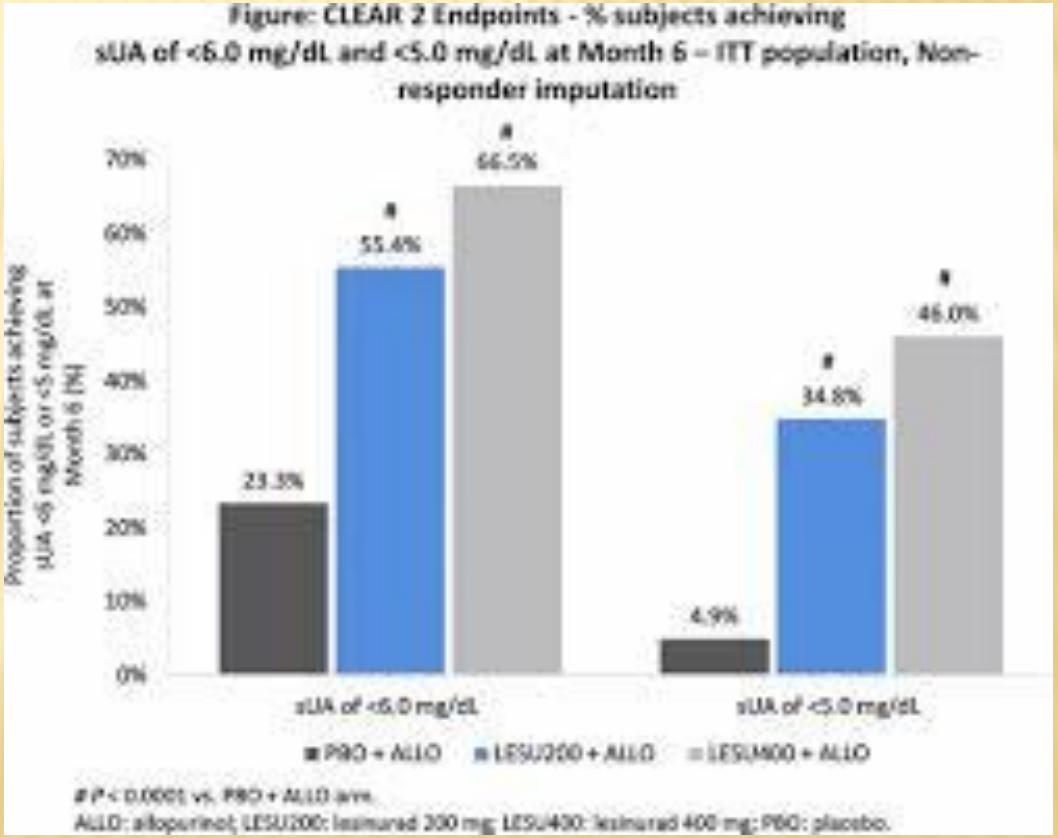
Targets for intervention in the treatment and prophylaxis of gout



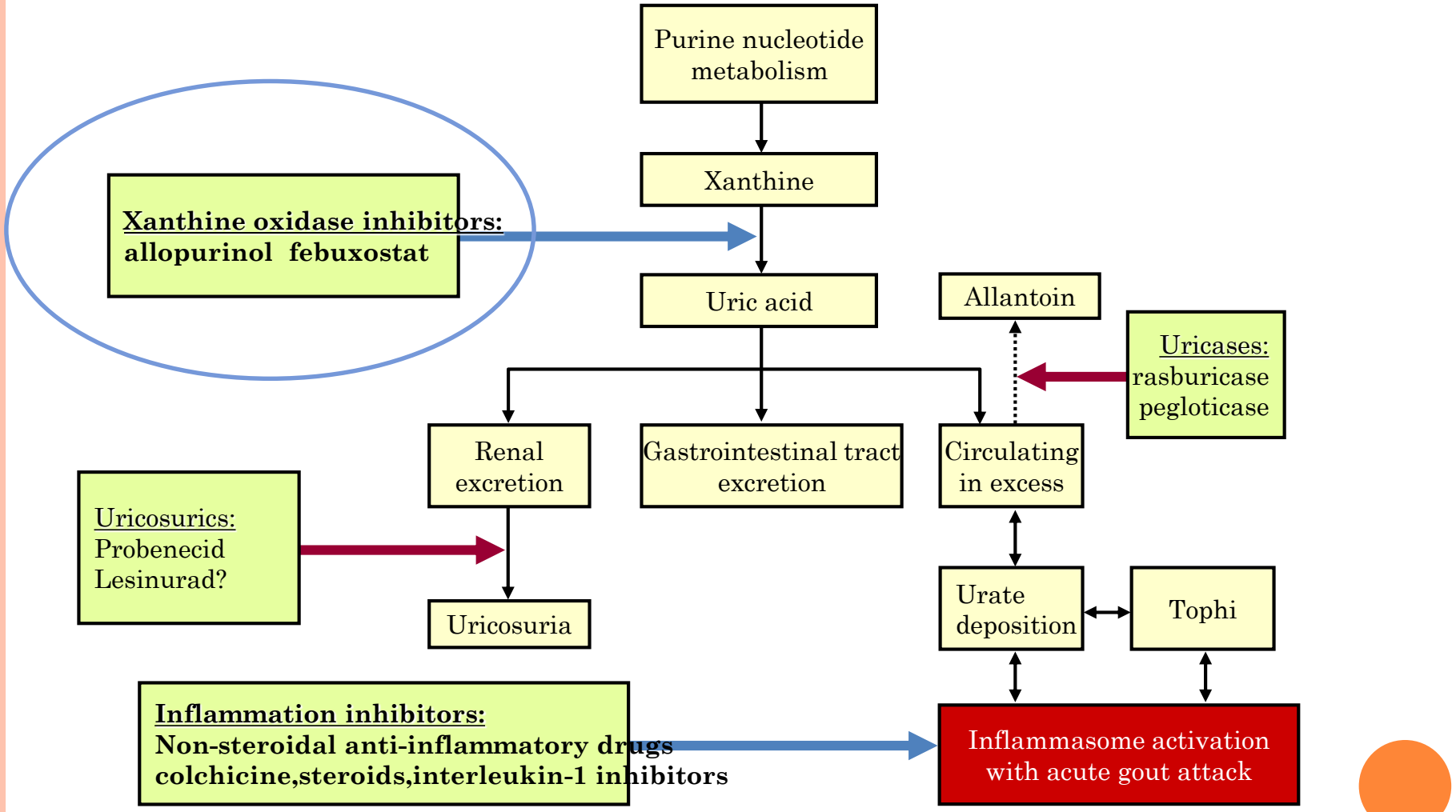
Christopher M Burns et al.: Lancet 2011:377:165-77

FDA APPROVES ZURAMPIC (LESINURAD) TO TREAT HIGH BLOOD URIC ACID LEVELS ASSOCIATED WITH GOUT



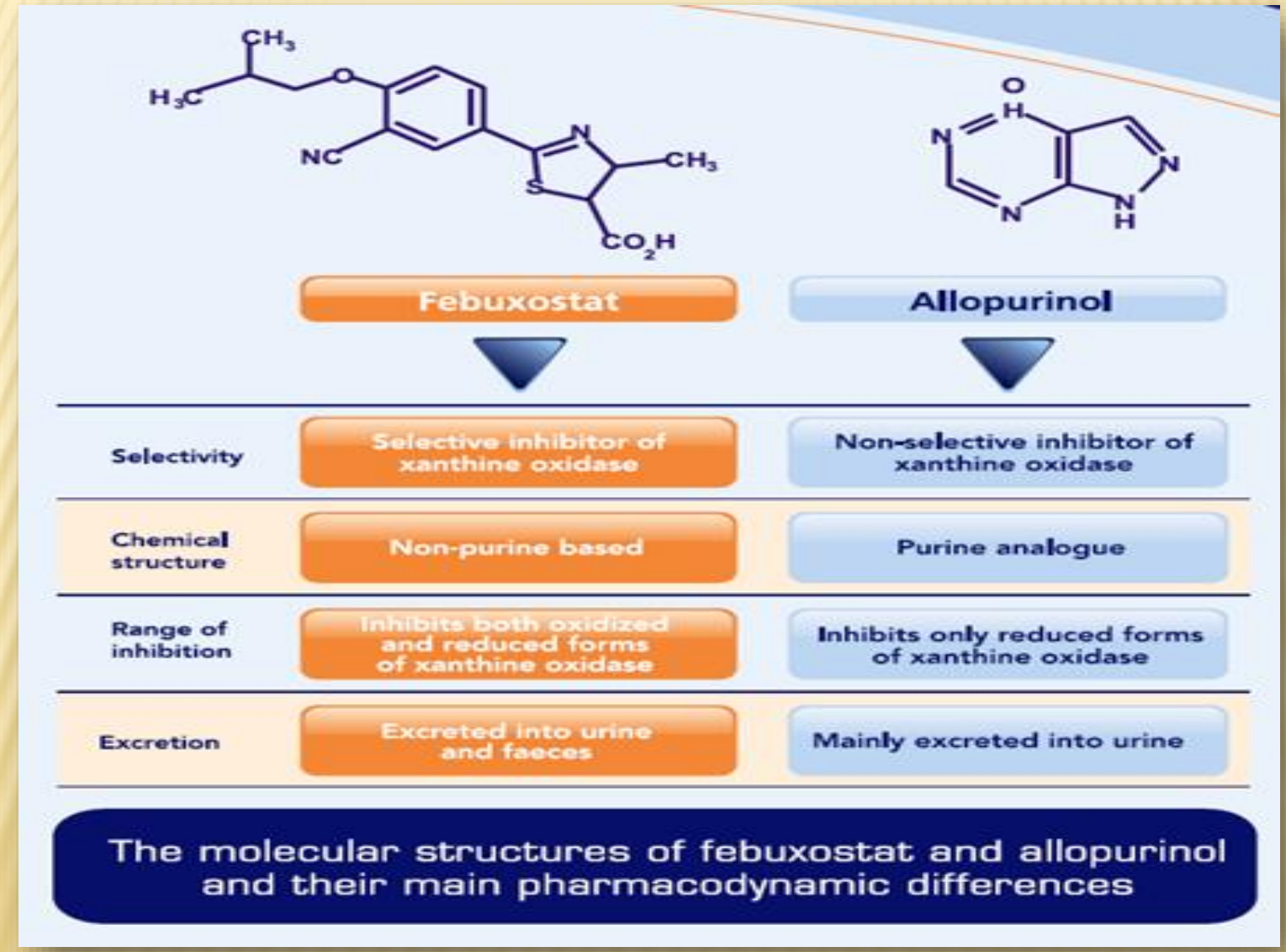


Targets for intervention in the treatment and prophylaxis of gout



Christopher M Burns et al.: Lancet 2011:377:165-77

Feburic® and Alloril – The Pharmacodynamics Difference



The molecular structures of febuxostat and allopurinol and their main pharmacodynamic differences

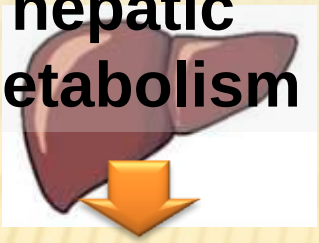
Main Differences in the Elimination Pathways between Febuxostat and Allopurinol

SmPC FEBURIC®.

Febuxostat

↓

hepatic metabolism



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Metabolites

↓

Biliary excretion

Urinary excretion

After inactivated in the liver, Febuxostat is eliminated via multiple pathways including bile and the kidneys.

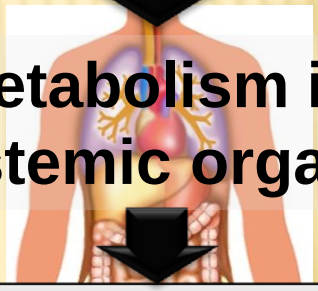
↓

No dose adjustments for patients **with mild to moderate renal impairment**

Allopurinol

↓

Metabolism in systemic organs



↓

Metabolite (Oxyprinol)

↓

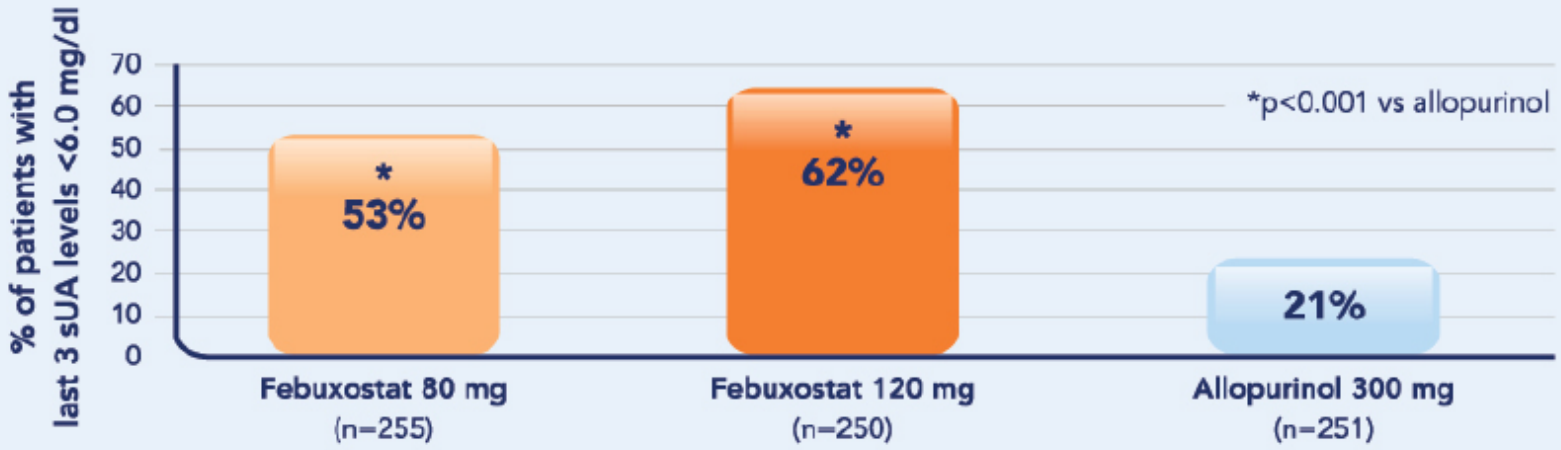
Urinary excretion

Active metabolite, oxyprinol is excreted primarily by the kidneys (Single excretion pathway)

↓

Dose adjustment is required for patients with renal impairment.

- **FACT: a randomised, double-blind, 52-week, multicentre trial to compare the efficacy and safety of Feburic® 80 mg or 120 mg qd with allopurinol 300 mg qd in adult subjects with gout and sUA ≥8 mg/dl (480 µmol/l)**



ITT population: subjects with serum urate level ≥8.0 mg/dl on day -2.

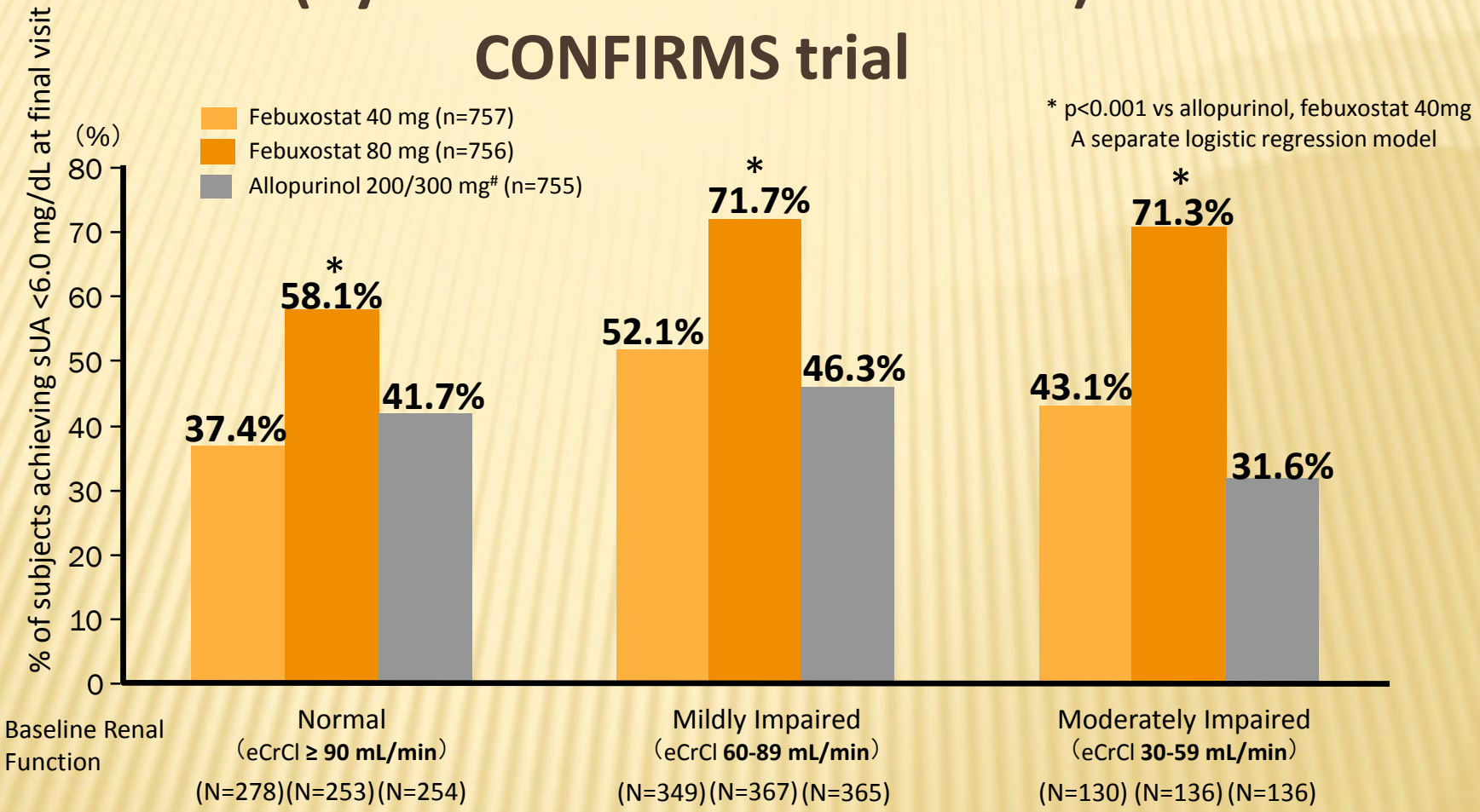
Comparison of the efficacy of recommended doses of Feburic® and allopurinol in the **FACT study** [3]

(1) Shoji A, et al. Arthritis Rheum 2004; 51:321-325. (2) Schumacher HR, et al. Rheumatology 2009;48:188-194.
(3) Becker MA, et al. N Engl J Med 2005;353:2450-2461. (4) Schumacher HR, et al. Arthritis Rheum 2008;59:1540-1548. (5) Feburic® prescribing information

Confidential / legally privileged information

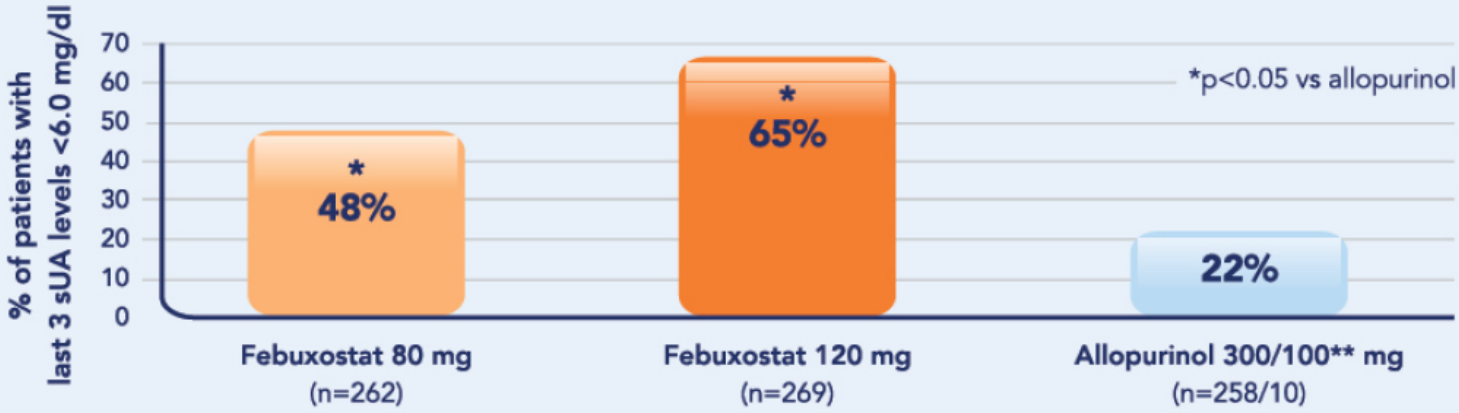
ניאופרם ישראל
קבוצת ניאופרם

% Subjects Achieving sUA <6.0 mg/dL (By Baseline Renal Function) CONFIRMS trial



Becker MA. et al.: Arthritis Res Ther.: 12(2): R63, 2010

APEX: a randomised, double-blind, 28-week, multicentre trial to compare the urate-lowering efficacy of Feburic®, allopurinol and placebo in adult subjects with gout and sUA ≥8 mg/dl (480 µmol/l) with normal or impaired renal function



** Patients treated with allopurinol 100 mg had serum creatinine levels >1.5 - ≤2 mg/dl.
ITT population: subjects with serum urate level ≥8.0 mg/dl on day -2.

Comparison of the efficacy of recommended doses of Feburic® and allopurinol in the **APEX study** [4]

(1) Shoji A, et al. Arthritis Rheum 2004; 51:321-325. (2) Schumacher HR, et al. Rheumatology 2009;48:188-194.
(3) Becker MA, et al. N Engl J Med 2005;353:2450-2461. (4) Schumacher HR, et al. Arthritis Rheum 2008;59:1540-1548. (5) Feburic® prescribing information

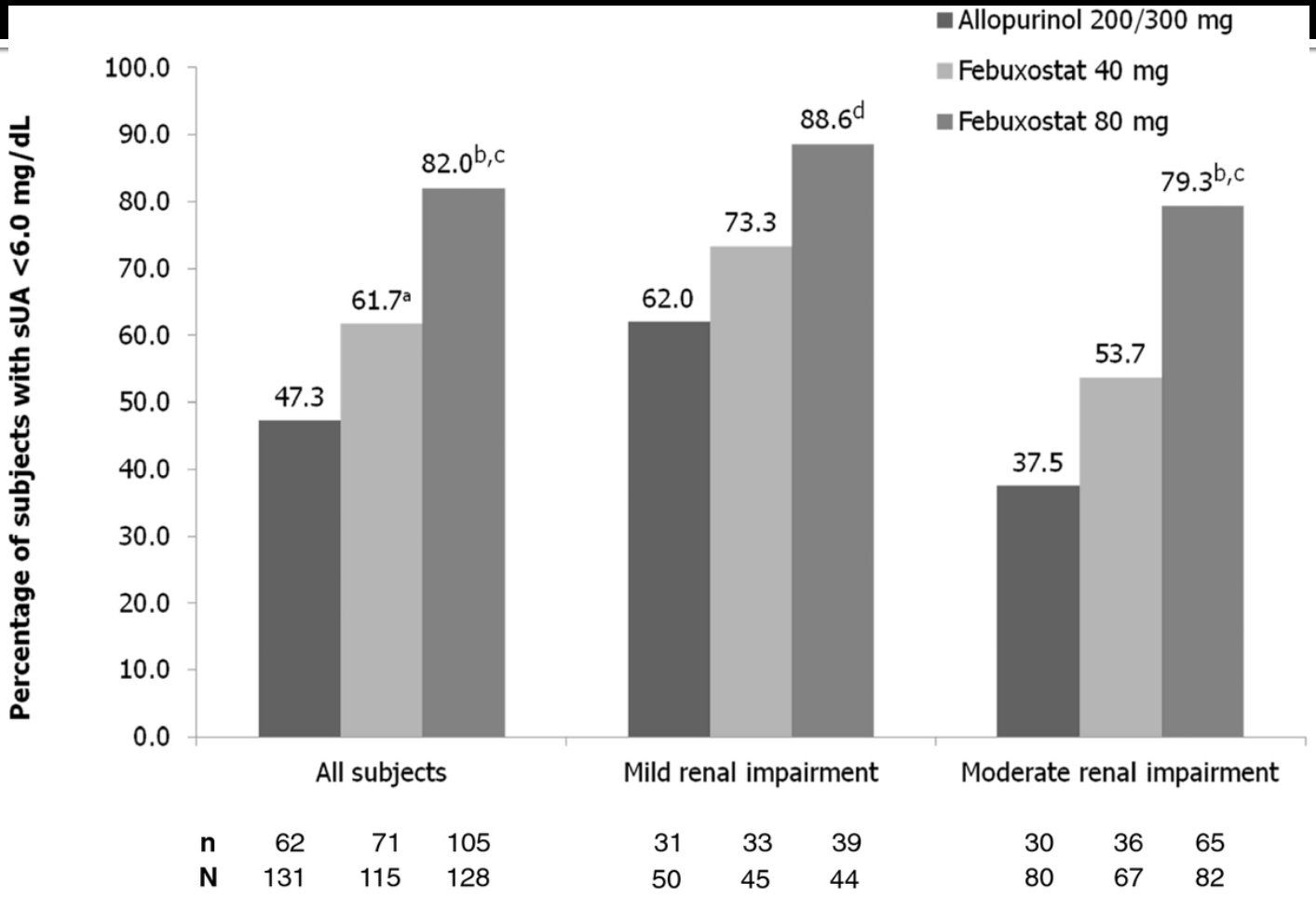
Febuxostat Studies Conclusions

Febuxostat 80 /120mg/day is more effective than allopurinol 300 mg/day in achieving the recommended target by EULAR: sUA levels ≤6.0 mg/dL

- Febuxostat is more effective than allopurinol in patients with sUA levels ≥10 mg/dL
- Febuxostat is more effective than allopurinol in patients with mild to moderate renal insufficiency, without the need to adjust the dosage
- Long term studies have shown that febuxostat is effective in the reduction of acute attacks and tophi

FEBURIC® PI as approved by the Israeli MOH/
Becker MA. et all. N Engl J Med. 2005 Dec 8;353(23):2450-61./ Schumacher HR Jr. et al. Arthritis Rheum. 2008 Nov 15;59(11):1540-8./ Becker MA. et all. J Rheumatol. 2009 Jun;36(6):1273-82.
Epub 2009 Mar 13. /Schumacher HR. et all. Rheumatology (Oxford).2009 Feb;48(2):188-94.

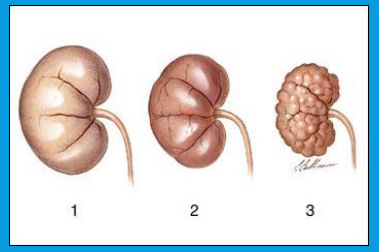
Treatment of gout in the elderly



TREATMENT OF HYPERURICEMIA

- 1. Hypertension

- 2. renal disease



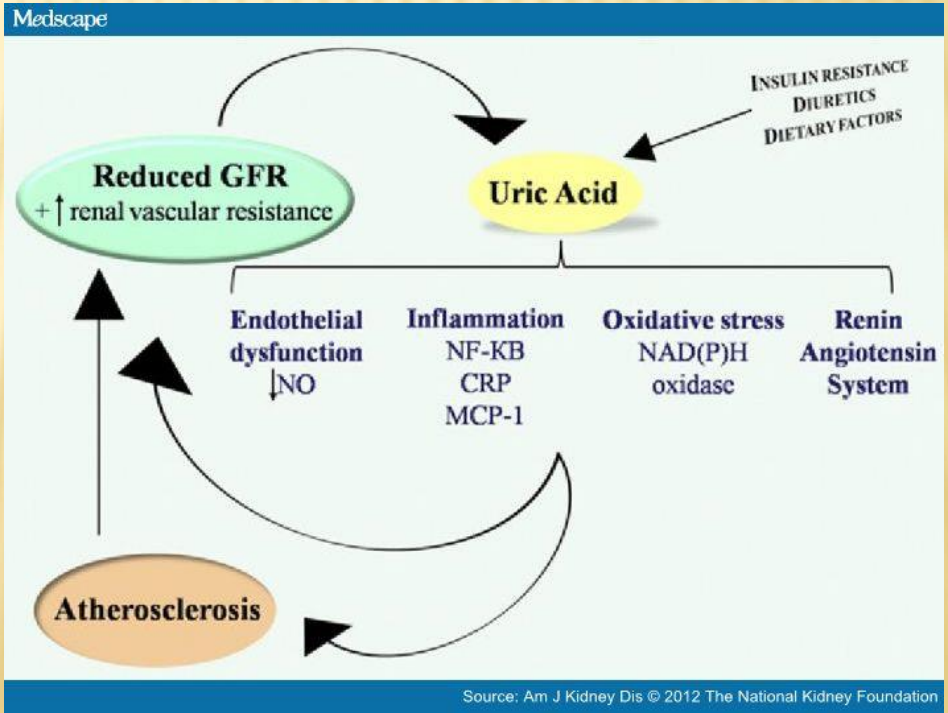
- 3. cardiovascular morbidity

CLIN J AM SOC NEPHROL. 2015 NOV 6;10(11):1921-9.

SERUM URIC ACID AND RISK OF CKD IN TYPE 2 DIABETES.

DE COSMO S, ET AL

- **CONCLUSIONS:**
- Mild hyperuricemia is strongly associated with the risk of CKD in patients with type 2 diabetes.

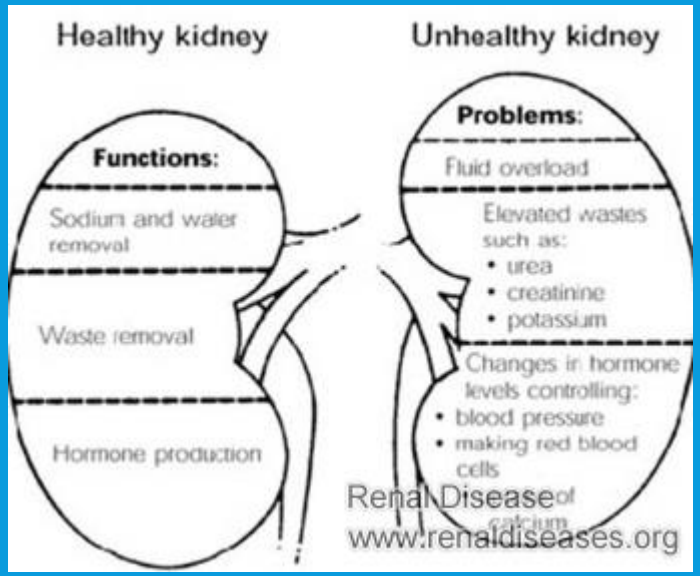


AM J KIDNEY DIS. 2015 DEC;66(6):945-50. EPUB 2015 JUL 30.

EFFICACY OF FEBUXOSTAT FOR SLOWING THE GFR DECLINE IN PATIENTS WITH CKD AND ASYMPTOMATIC HYPERURICEMIA: A 6-MONTH, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL.

SIRCAR D, CHATTERJEE S, WAIKHOM R, GOLAY V, RAYCHAUDHURY A, CHATTERJEE S, PANDEY R

- Conclusions: Febuxostat slowed the decline in eGFR in CKD stages 3 and 4 compared to placebo.



THANK YOU