Hyperuricémie asymptomatique

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Conflit d’intérêt potentiel

Type d'affiliation	Nom de la compagnie	Période
Consultant	Servier, Merck, Abbott, Sanofi, Takeda, Shire, Forest Lab., Valeant	2010-2015
Conférencier	Merck, Abbott, Sanofi, Takeda, Shire, Boehringer, Janssen, Amgen, Lilly, Servier, Valeant	2010-2015
Subvention de recherche	Novartis, Servier	2010-2015

Cas clinique

- Homme 56 ans, intelligent, prend 7 médicaments
- IRC cl. cr. 35cc/min
- DB2 (HBA1C 6.5%), DLP (LDL 1.6), HTA (118/65)
- Se met à faire de l'exercice, perd du poids, moins de sel, mange mieux, ne fume pas
- Tout est dans les cibles!
- Que faire de plus?
- Acide urique 527 umol/L
- Urates antérieures: 544, 483, 501, 465, 499 umol/L

Objectifs

- Au terme de cette présentation, le participant devrait être en mesure de :

  - Comprendre l'importance de l'acide urique comme facteur de risque rénal et cardiovasculaire
  - Revoir la prise en charge des traitements de l'Hyperuricémie du point de vue du Néphrologue
  - Évaluer le ratio risque/bénéfice de traiter l'hyperuricémie asymptomatique chez un patient donné

Plan

1) Association entre l'acide urique et les maladies rénales et cardiovasculaires

2) Le bénéfice du traitement de l'hyperuricémie asymptomatique: évidences

3) Ratio risque/bénéfice du traitement de l'hyperuricémie asymptomatique

1) Association entre l'acide urique et les maladies rénales et cardiovasculaires

© Med Sci Monit, 2010; 16(10): RA224-230
PMID: 20885365

WWW.MEDSCIMONIT.COM
Review Article

Received: 2010.05.09
Accepted: 2010.06.04
Published:

Uric acid and the development of hypertension

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

MEDICAL PROGRESS

Uric Acid and Cardiovascular Risk

Daniel I. Feig, M.D., Ph.D., Duk-Hee Kang, M.D., and Richard J. Johnson, M.D.

The Journal of Rheumatology Volume 35, no. 5

Asymptomatic hyperuricemia: perhaps not so benign?

Tuhina Neogi

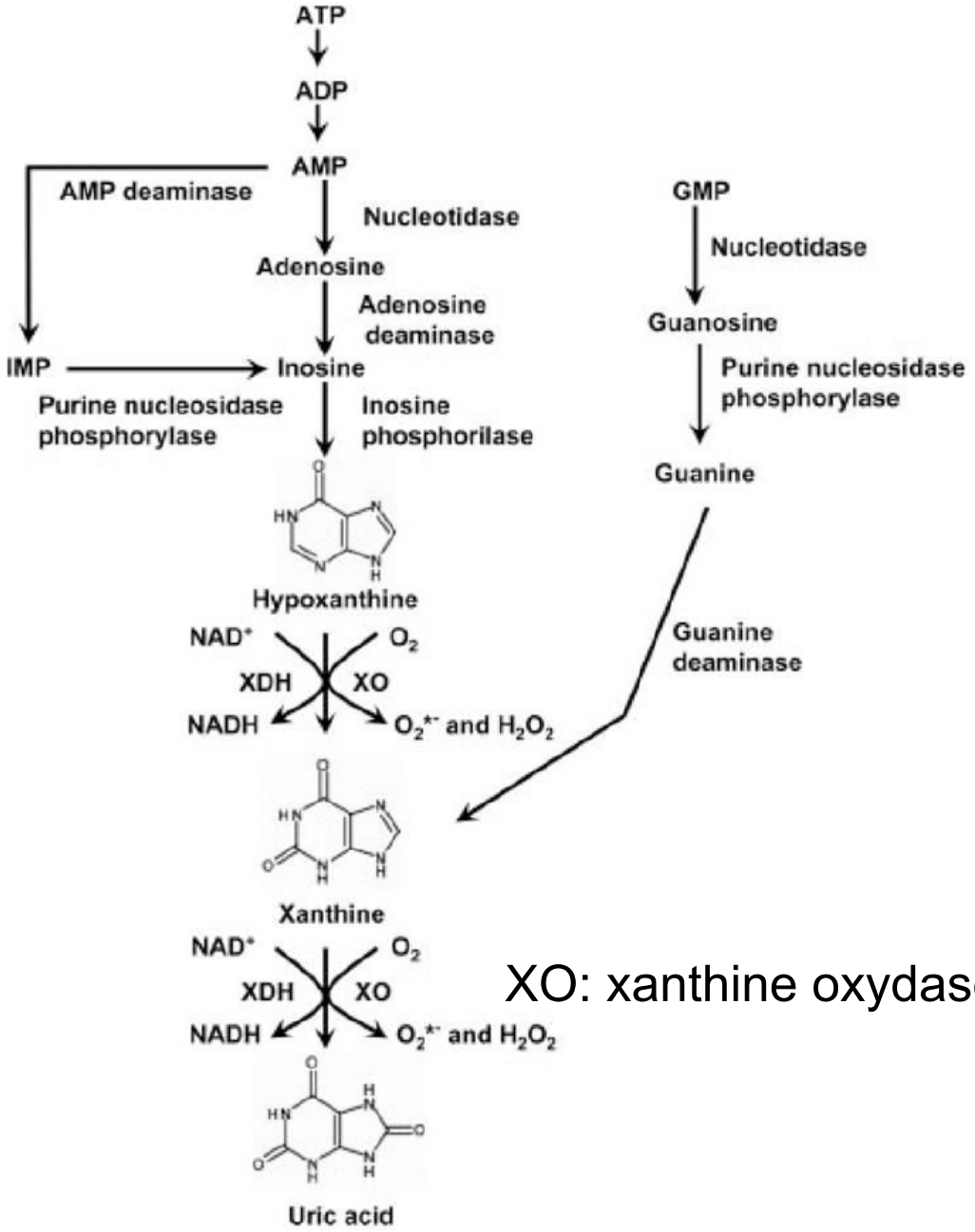
Association indépendante entre l'acide urique et les maladies rénales et cardiovasculaires

- HTA
- Syndrome métabolique
- Diabète
- MCAS / MVAS
- Insuffisance rénale
- Protéinurie / microalbuminurie
- HVG
- AVC
- Démence vasculaire
- Pré-éclampsie
- Etc.

1) Association entre l'acide urique et les maladies rénales et cardiovasculaires

Conclusion: association est très forte et constante

2) Le bénéfice du traitement de l'hyperuricémie asymptomatique: évidences



XO: xanthine oxydase

Fig. 1.
Schematic diagram of the purine degradation pathway.

(*Cardiology in Review* 2011;19: 265–271)

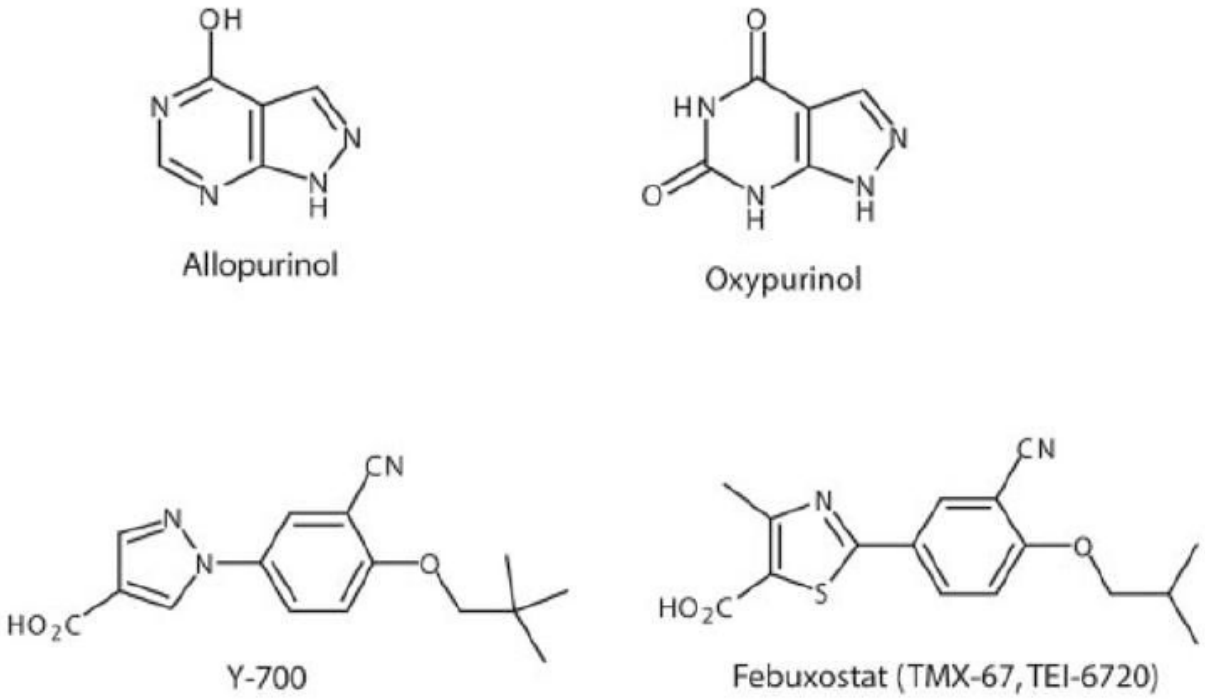


Fig. 3.
Chemical structures of selected xanthine oxidase inhibitors.

Effect of Allopurinol on Blood Pressure of Adolescents With Newly Diagnosed Essential Hypertension: A Randomized Trial

Daniel I. Feig, MD, PhD[1], **Beth Soletsky, RN**[1], and **Richard J. Johnson, MD**[2]

1 *Department of Pediatrics, Renal Section, Baylor College of Medicine, Houston, Texas*

2 *Division of Nephrology, Hypertension and Transplantation, Department of Medicine, University of Florida School of Medicine, Gainesville*

Abstract

Context—Hyperuricemia is a predictor for the development of hypertension and is commonly present in new-onset essential hypertension. Experimentally increasing uric acid levels using a uricase inhibitor causes systemic hypertension in animal models.

Objective—To determine whether lowering uric acid lowers blood pressure (BP) in hyperuricemic adolescents with newly diagnosed hypertension.

Design, Setting, and Patients—Randomized, double-blind, placebo-controlled, crossover trial (September 2004-March 2007) involving 30 adolescents (aged 11–17 years) who had newly diagnosed, never-treated stage 1 essential hypertension and serum uric acid levels ≥6 mg/dL. Participants were treated at the Pediatric Hypertension Clinic at Texas Children's Hospital in Houston. Patients were excluded if they had stage 2 hypertension or known renal, cardiovascular, gastrointestinal tract, hepatic, or endocrine disease.

356umol/L

Allopurinol 400mg vs placebo sur 4 sem.

JAMA. 2008 August 27; 300(8): 924–932. doi:10.1001/jama.300.8.924.

Table 2

Blood Pressure (BP) Response to Placebo and Allopurinol (Posttreatment Values)

Parameter	Mean (95% Confidence Interval) Placebo	Allopurinol	*P* Value
Change in casual systolic BP, mm Hg	−2.0 (0.3 to −4.3)	−6.9 (−4.5 to −9.3)	.009[a]
Change in casual diastolic BP, mm Hg	−2.4 (0.2 to −4.1)	−5.1 (−2.5 to −7.8)	.05
Change in 24-h ambulatory systolic BP, mm Hg	0.8 (3.4 to −2.9)	−6.3 (−3.8 to −8.9)	.001[a]
Change in 24-h ambulatory diastolic BP, mm Hg	−0.3 (2.3 to −2.1)	−4.6 (−2.4 to −6.8)	.004[b]
Systolic BP load, %[c]	48.6 (34.0 to 50.2)	23.3 (15.8 to 30.9)	.01[a]
Diastolic BP load, %[c]	29.2 (25.6 to 37.1)	18.1 (12.3 to 23.8)	.01[b]
Hypertensive, No./total (%)[d]	29/30 (97)	10/30 (33)	.001[b]

Table 3

Effect of Placebo and Allopurinol on Non–Blood Pressure End Points

Parameter	Pretreatment[a]	Mean (95% Confidence Interval) Placebo	Allopurinol	*P* Value
Heart rate, beats/min	72 (67–78)	74 (69–80)	75 (69–80)	.87
Cardiac output, L/min	6.4 (5.6–7.1)	6.2 (5.4–7.0)	6.6 (5.9–7.2)	.56
Systemic vascular resistance index, (dyne s/cm^5)/m^2	2478 (2223–2731)	2473 (2232–2615)	2136 (2056–2228)	.03[b]
Total body water, L	27.8 (26.0–29.7)	28.0 (26.1–30.1)	28.1 (26.0–29.9)	.86
Plasma renin activity, ng/mL/h	1.9 (1.7–2.2)	2.1 (1.8–2.4)	1.4 (0.8–2.1)	.02[b]

Conclusions: Baisse de TA

JAMA. 2008 August 27; 300(8): 924–932. doi:10.1001/jama.300.8.924.

Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: 3-year randomized parallel-controlled study

Peng Liu*, Yingying Chen*, Bin Wang†, Fengmei Zhang*, Debao Wang* and Yangang Wang†

Table 2. Post-treatment changes of indexes between two groups

	Post-treatment (mean ± SD)			Changing values		
	Allopurinol group (n = 82)	Conventional group (n = 70)	P value	Allopurinol group (n = 82)	Conventional group (n = 70)	P value
Body mass index, kg/m^2	25·3 ± 1·1	25·4 ± 1·0	0·436	0·3 ± 0·2	0·3 ± 0·2	0·088
Systolic blood pressure, mm Hg	124 ± 7[b]	127 ± 8	*0·014*	2 ± 3[a]	6 ± 2	*<0·001*
Diastolic blood pressure, mm Hg	75 ± 5[a]	78 ± 7	*0·003*	1 ± 3[a]	4 ± 2	*<0·001*
Fasting plasma glucose, mmol/l	6·24 ± 0·62	6·22 ± 0·52	0·792	0·02 ± 0·45	0·01 ± 0·28	0·893
2 h postprandial plasma glucose, mmol/l	9·80 ± 0·64	9·84 ± 0·61	0·674	−0·01 ± 1·05	0·01 ± 0·84	0·894
HbA_1c, %	7·0 ± 0·5	6·9 ± 0·5	0·775	0·1 ± 0·7	0·0 ± 0·3	0·586
HOMA-IR	3·49 ± 1·01	3·57 ± 0·72	0·584	0·10 ± 0·15[a]	0·21 ± 0·18	*<0·001*
Total cholesterol, mmol/l	4·17 ± 0·22	4·16 ± 0·27	0·828	−0·91 ± 0·78	−0·90 ± 0·79	0·946
LDL-C, mmol/l	2·27 ± 0·25	2·25 ± 0·24	0·703	−0·71 ± 0·67	−0·69 ± 0·54	0·816
HDL-C, mmol/l	1·04 ± 0·17	1·03 ± 0·13	0·666	−0·02 ± 0·03[a]	−0·04 ± 0·03	*0·001*
Triglyceride, mmol/l	2·10 ± 0·47	2·23 ± 0·43	0·073	0·12 ± 0·12[a]	0·29 ± 0·16	*<0·001*
Serum uric acid, μmol/l	329 ± 18[a]	455 ± 12	<0·001	−104 ± 19[a]	23 ± 11	*<0·001*
UAER, μg/min	13·7 ± 5·2[a]	17·6 ± 7·7	*0·002*	1·4 ± 2·9[a]	5·6 ± 6·1	*<0·001*
Serum creatinine, μmol/l	74·8 ± 11·5	78·4 ± 12·8	0·075	−0·8 ± 3·3[a]	3·4 ± 5·4	*<0·001*
GFR, ml/min/1·73 m^2	89·3 ± 17·8	85·2 ± 18·8	0·178	−0·8 ± 3·9[a]	−4·9 ± 5·0	*<0·001*
Smoking (%)	14 (17·1)	10 (14·3)	0·639	−15 (−18·3)	−13 (−18·6)	0·965
Drug use						
Oral hypoglycaemic drugs (%)	25 (30·5)	17 (24·3)	0·394	−13 (−15·9)	−13 (−18·6)	0·657
Insulin combined with oral hypoglycaemic drugs (%)	57 (69·5)	53 (75·7)	0·394	13 (15·9)	13 (18·6)	0·657
Lipid lowering drugs (%)	69 (84·1)	60 (85·7)	0·788	32 (39·0)	30 (42·9)	0·632
Antihypertensive drugs (%)	3 (3·7)	6 (8·6)	0·201	3 (3·7)	6 (8·6)	0·201
Aspirin (%)	74 (90·4)	64 (91·4)	0·801	33 (40·2)	31 (44·3)	0·615

vs Conventional group, [a]$P < 0.01$, [b]$P < 0.05$.

Conclusions: Baisse de TA et protection rénal

Effect of Allopurinol in Chronic Kidney Disease Progression and Cardiovascular Risk

Marian Goicoechea, Soledad García de Vinuesa, Ursula Verdalles, Caridad Ruiz-Caro, Jara Ampuero, Abraham Rincón, David Arroyo, and José Luño

Servicio de Nefrología, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Background and objectives: Hyperuricemia is associated with hypertension, inflammation, renal disease progression, and cardiovascular disease. However, no data are available regarding the effect of allopurinol in patients with chronic kidney disease.

Design, setting, participants, & measurements: We conducted a prospective, randomized trial of 113 patients with estimated GFR (eGFR) <60 ml/min. Patients were randomly assigned to treatment with allopurinol 100 mg/d ($n = 57$) or to continue the usual therapy ($n = 56$). Clinical, biochemical, and inflammatory parameters were measured at baseline and at 6, 12, and 24 months of treatment. The objectives of study were: (*1*) renal disease progression; (*2*) cardiovascular events; and (*3*) hospitalizations of any causes.

Avec hyperuricémie asymptomatique, sans goutte

Results: Serum uric acid and C-reactive protein levels were significantly decreased in subjects treated with allopurinol. In the control group, eGFR decreased 3.3 ± 1.2 ml/min per 1.73 m^2, and in the allopurinol group, eGFR increased 1.3 ± 1.3 ml/min per 1.73 m^2 after 24 months. Allopurinol treatment slowed down renal disease progression independently of age, gender, diabetes, C-reactive protein, albuminuria, and renin-angiotensin system blockers use. After a mean follow-up time of 23.4 ± 7.8 months, 22 patients suffered a cardiovascular event. Diabetes mellitus, previous coronary heart disease, and C-reactive protein levels increased cardiovascular risk. Allopurinol treatment reduces risk of cardiovascular events in 71% compared with standard therapy.

Conclusions: Allopurinol decreases C-reactive protein and slows down the progression of renal disease in patients with chronic kidney disease. In addition, allopurinol reduces cardiovascular and hospitalization risk in these subjects.

Clin J Am Soc Nephrol 5: 1388–1393, 2010. doi: 10.2215/CJN.01580210

Clin J Am Soc Nephrol 5: 1388–1393, 2010. doi: 10.2215/CJN.01580210

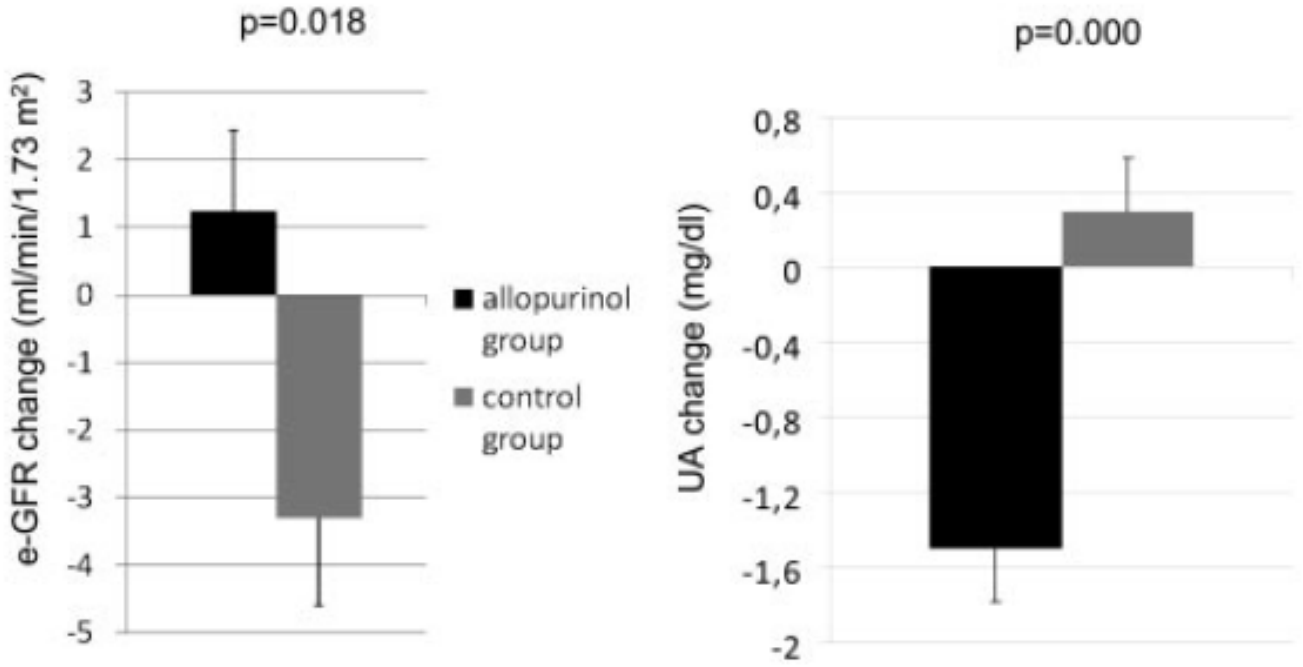


Figure 2. Change in UA levels and change in eGFR at the end of study. Values are expressed as mean ± SEM.

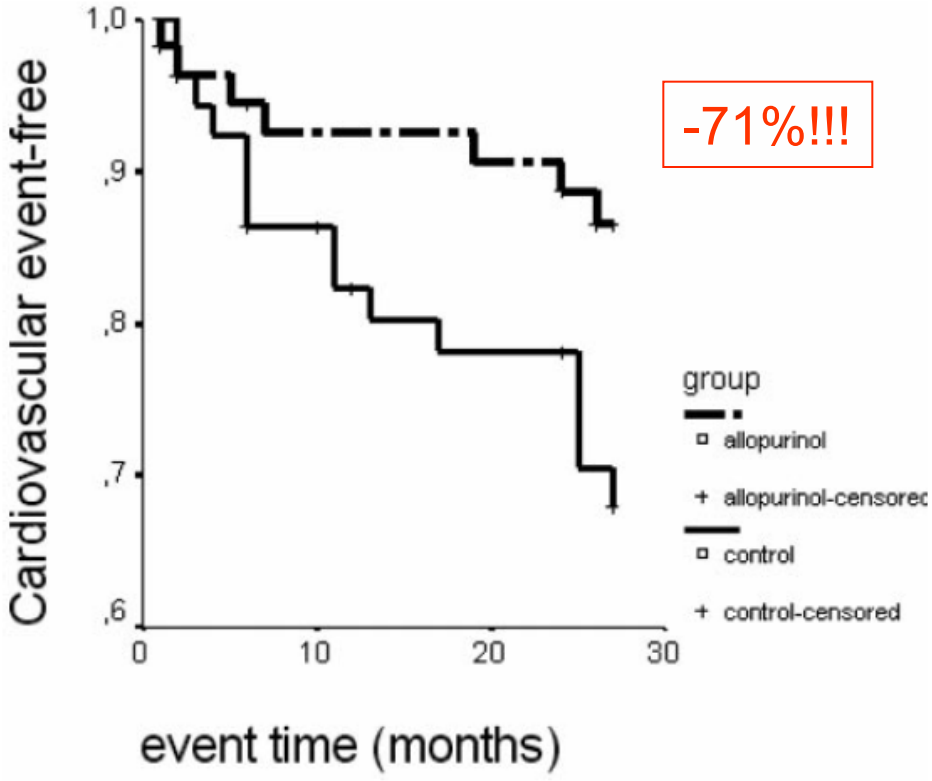
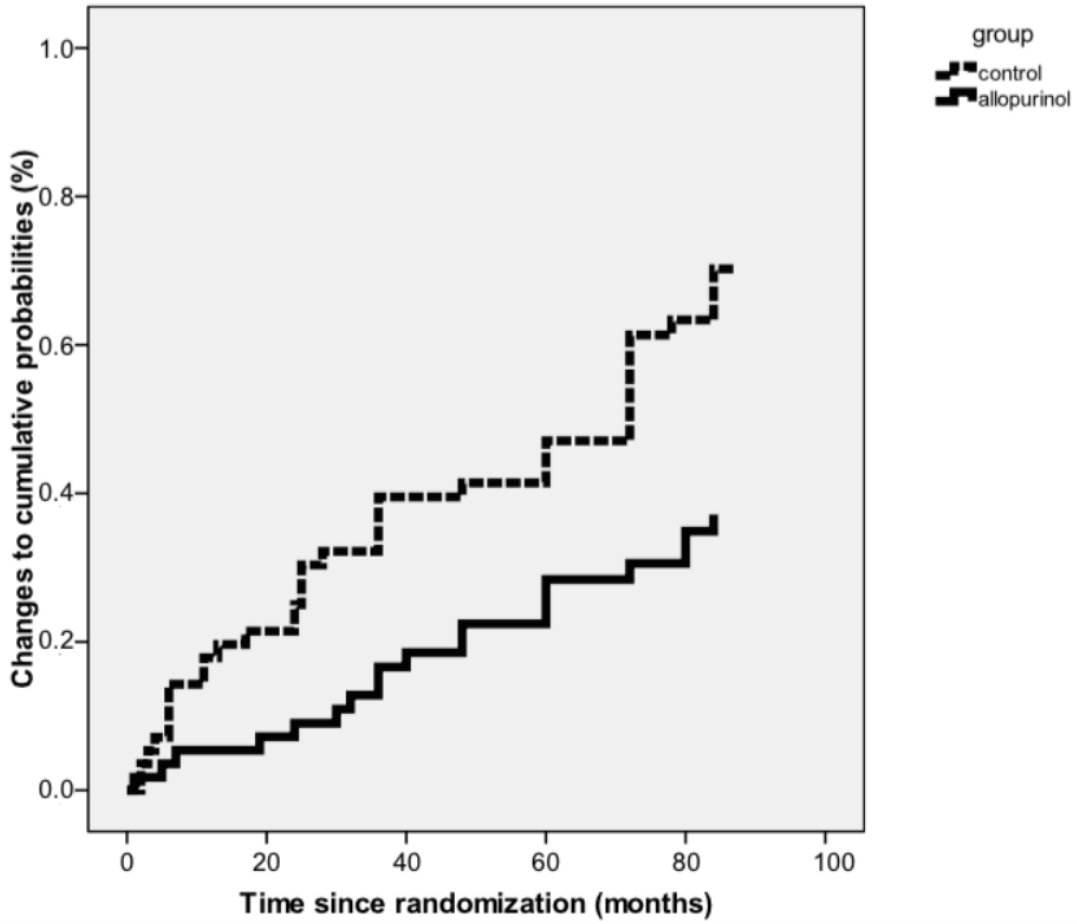


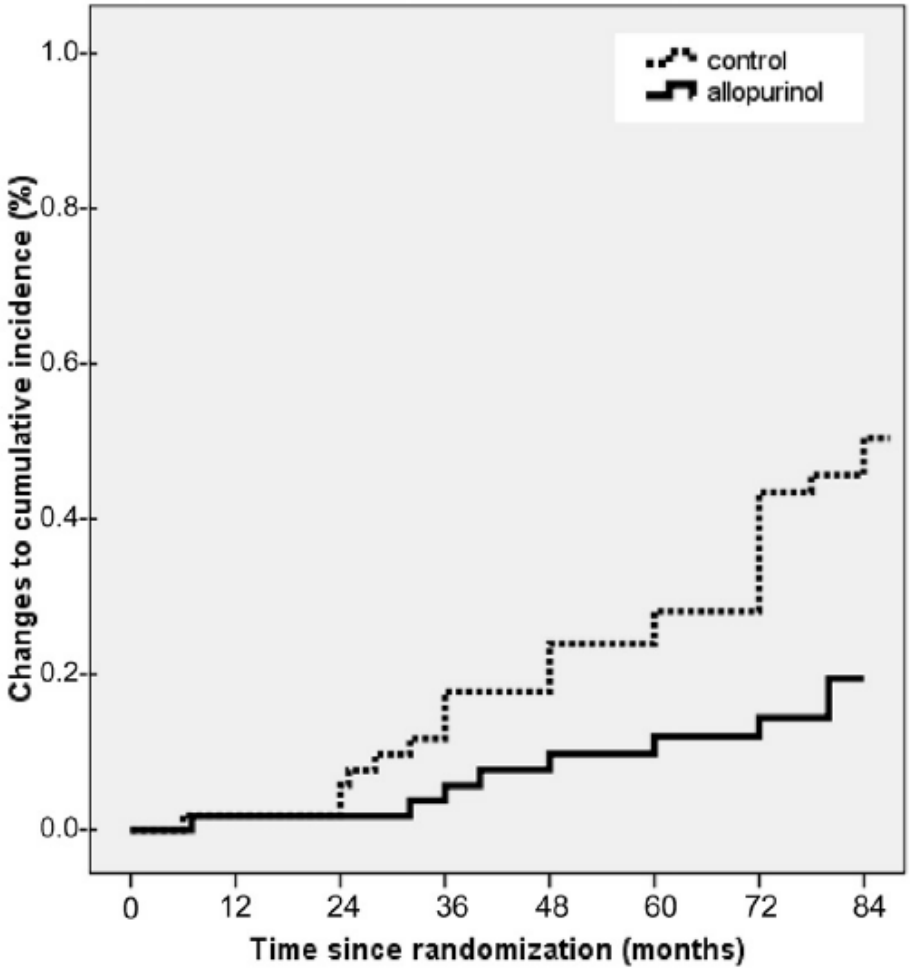
Figure 3. Effect of allopurinol treatment in cardiovascular events. Log rank: 4.25; $P = 0.039$.

Clin J Am Soc Nephrol 5: 1388–1393, 2010. doi: 10.2215/CJN.01580210

Figure S1. Kaplan Meier curves for composite outcome: renal and cardiovascular events. Log rank: 11.040, p=0.001



Am J Kidney Dis. 2015;65(4):543-549



Time (mo)	0	12	24	36	48	60	72	84
Allopurinol (n)	57	55	54	46	41	37	35	32
Control (n)	56	52	49	41	37	34	27	21

Figure 2. Kaplan-Meier curves for renal events. Differences were evaluated using log-rank test.

Renal events: débuter la dialyse, doubler la créatinine ou > 50% baisse de DFG

Conclusions: Protection rénale et cardiovasculaire

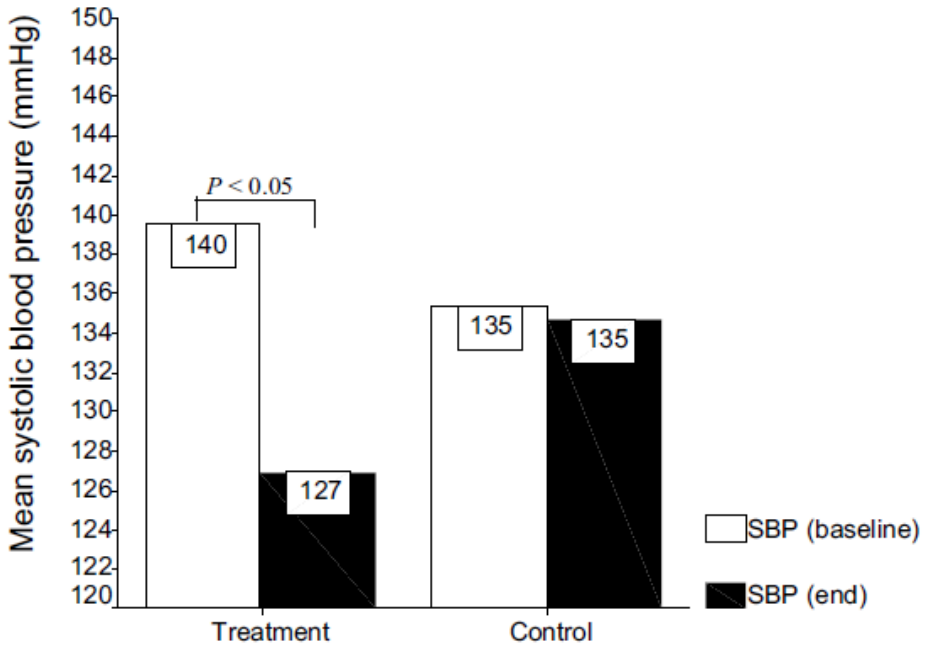
Am J Kidney Dis. 2015;65(4):543-549

Use of Allopurinol in Slowing the Progression of Renal Disease Through Its Ability to Lower Serum Uric Acid Level

Yui-Pong Siu, MRCP, Kay-Tai Leung, MRCP, Matthew Ka-Hang Tong, MRCP, and Tze-Hoi Kwan, FRCP

- Étude randomisée
- 51 patients sur 12 mois
- IRC stade 3
- Hyperuricémie asymptomatique
- Allopurinol 100-300 mg/j selon *cible d'acide urique < 360 umol/L

2006 *Am J Kidney Dis* 47:51-59.



2006 *Am J Kidney Dis* 47:51-59.

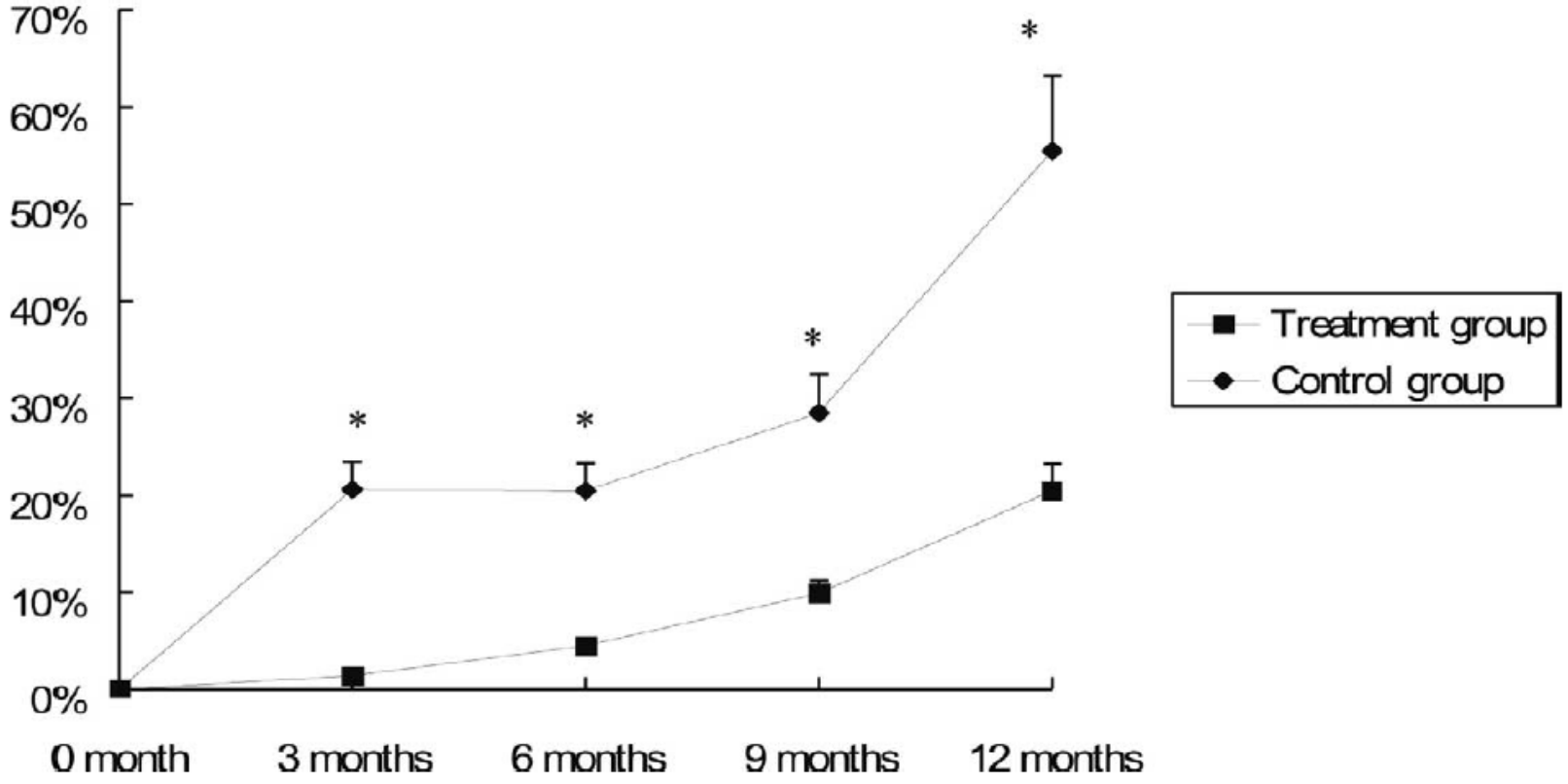


Fig 5. Mean percentage of change in Cr levels in the treatment and control groups. *$P < 0.05$ compared with baseline.

Conclusions: Baisse de TA et protection rénale

2006 *Am J Kidney Dis* 47:51-59.

IJKD KIDNEY DISEASES

Effect of Allopurinol in Decreasing Proteinuria in Type 2 Diabetic Patients

Ali Momeni,[1] Shahrzad Shahidi,[2] Shiva Seirafian,[3] Shahram Taheri,[3] Soleiman Kheiri[4]

- RCT
- 40 patients sur 4 mois
- DB2 et protéinurique: NDB
- *Sans hyperuricémie nécessairement!
- Allopurinol 100 mg /j vs placebo

IJKD 2010;4:128-32

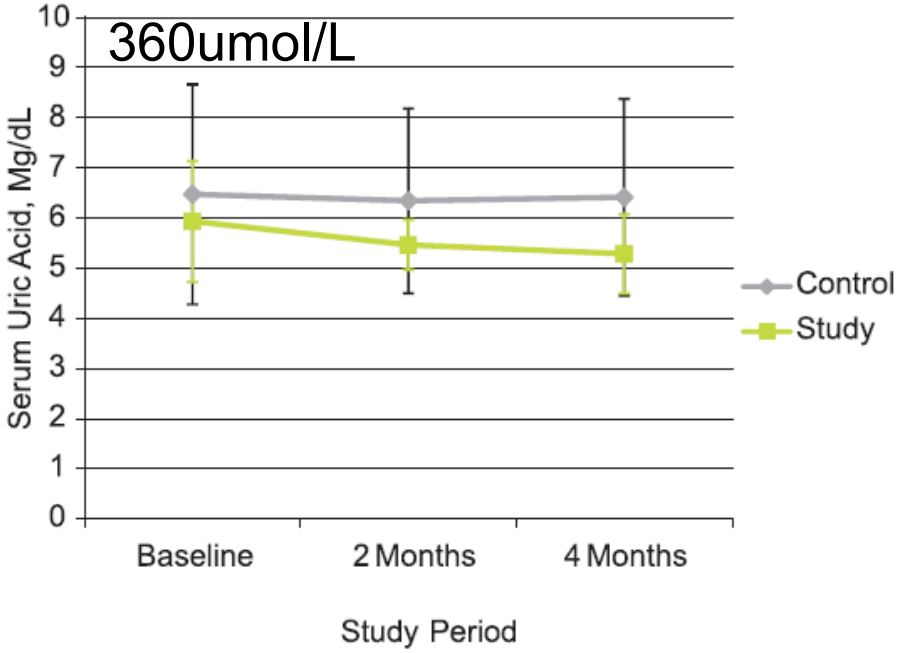


Figure 1. Mean serum levels of uric acid during the study in patients receiving allopurinol (study group) and placebo (control group).

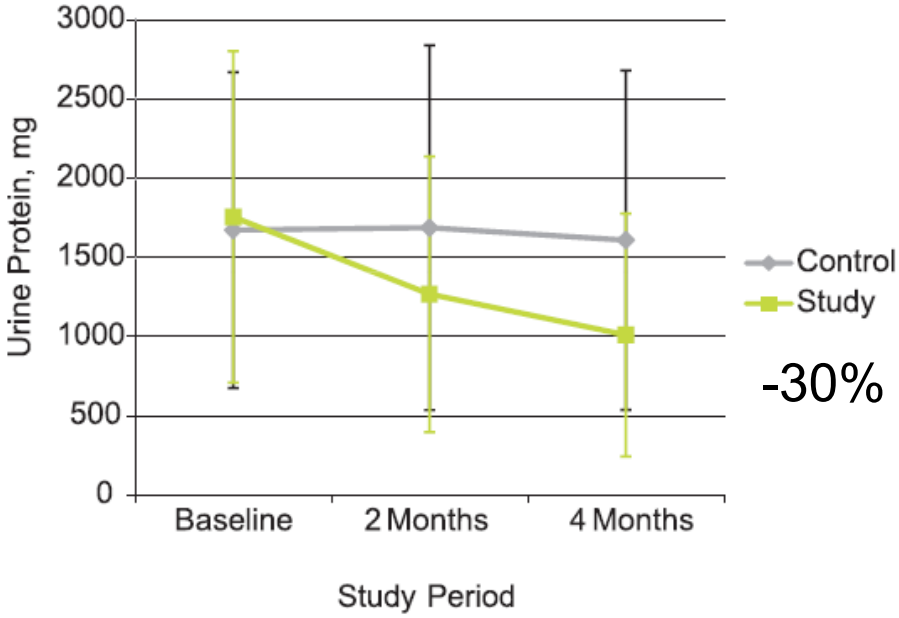


Figure 2. Mean 24-hour urine levels of protein during the study in patients receiving allopurinol (study group) and placebo (control group).

Mais aussi baisse de TA de 7/3 mmHg dans le groupe allopurinol, insuffisant pour expliquer toute la baisse de protéinurie??

Conclusions: Baisse de TA et baisse de protéinurie

IJKD 2010;4:128-32

Études en cours: Allopurinol (24/134 CVD)
(6 en psy, une en MII, 5 infections, 30 cancers, …)

Effects of Allopurinol on Diastolic Function in Chronic Heart Failure Patients

Condition: Chronic Heart Failure

Intervention: Drug: allopurinol

Using Allopurinol to Relieve Symptoms in Patients With Heart Failure and High Uric Acid Levels

Conditions: Heart Failure; Elevated Serum Uric Acid

Interventions: Drug: allopurinol; Drug: sugar pill

Uric Acid in Essential Hypertension in Children

Condition: Essential Hypertension

Intervention: Drug: Allopurinol

Uric Acid and Hypertension in African Americans

Conditions: Cardiovascular Diseases; Heart Diseases; Hypertension

Interventions: Drug: Allopurinol; Drug: Placebo

Uric Acid and the Endothelium is CKD

Condition: Kidney Disease

Interventions: Drug: Allopurinol; Other: Placebo

Clinicaltrials.gouv

Études en cours: Febuxostat (9/29 CVD)

Effects of Febuxostat on Adipokines and Kidney Disease in Diabetic Chronic Kidney Disease

Conditions: Chronic Kidney Disease; Diabetes

Interventions: Drug: Febuxostat; Drug: Sugar pill

Effect of Febuxostat on Renal Function in Patients With Gout and Moderate to Severe Renal Impairment

Condition: Renal Impairment

Interventions: Drug: Febuxostat; Drug: Placebo

The Influence of Febuxostat on Coronary Artery Endothelial Dysfunction in Participants With Chronic Stable Angina

Condition: Coronary Artery Disease

Interventions: Drug: Febuxostat; Drug: Febuxostat placebo

Effect of Febuxostat on Blood Pressure

Condition: Hypertension

Interventions: Drug: Febuxostat; Drug: Placebo

Effect of Febuxostat Compared to Placebo on Exercise Tolerance in Participants With Chronic Stable Angina

Condition: Angina

Interventions: Drug: Febuxostat; Drug: Placebo

Febuxostat, Blood Pressure and the Intrarenal Renin-Angiotensin System (RAS)

Condition: Hypertension

Intervention: Drug: Febuxostat

Cardiovascular Safety of Febuxostat and Allopurinol in Patients With Gout and Cardiovascular Comorbidities

Condition: Cardiovascular Disease

Interventions: Drug: Febuxostat; Drug: Allopurinol

Study of Febuxostat Effect on Blood Pressure in Patients With High Normal Blood Pressure

Conditions: Prehypertension; Gout; Pulse Wave Velocity; Hypertension; 24 Hour Blood Pressure

Intervention: Drug: Febuxostat

Effects of Hyperuricemia Reversal on Features of the Metabolic Syndrome

Condition: Gout

Intervention: Drug: Febuxostat

Clinicaltrials.gouv

Effets démontrés du traitement de l'hyperuricémie asymptomatique

- Protection rénale
- Réduction de le TA
- Effet antiprotéinurique
- Protection contre les événements cardiovasculaires

2) Le bénéfice du traitement de l'hyperuricémie asymptomatique: évidences

Les évidences sont très nombreuses et toutes positives, mais sur un petit nombre de patients.

Explication / plausibilité physiopathologique?

À traiter l'hyperuricémie asymptomatique avec de si grands bienfaits?

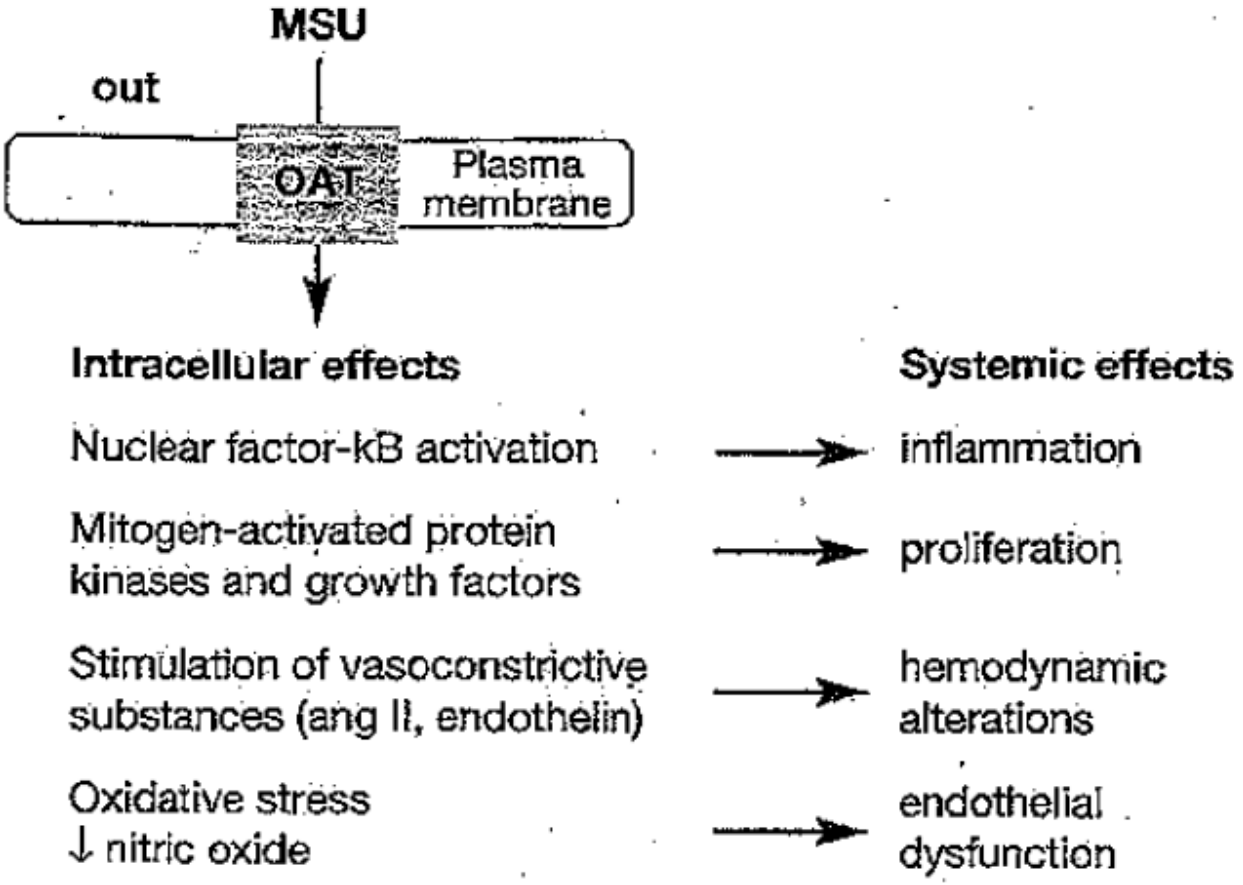
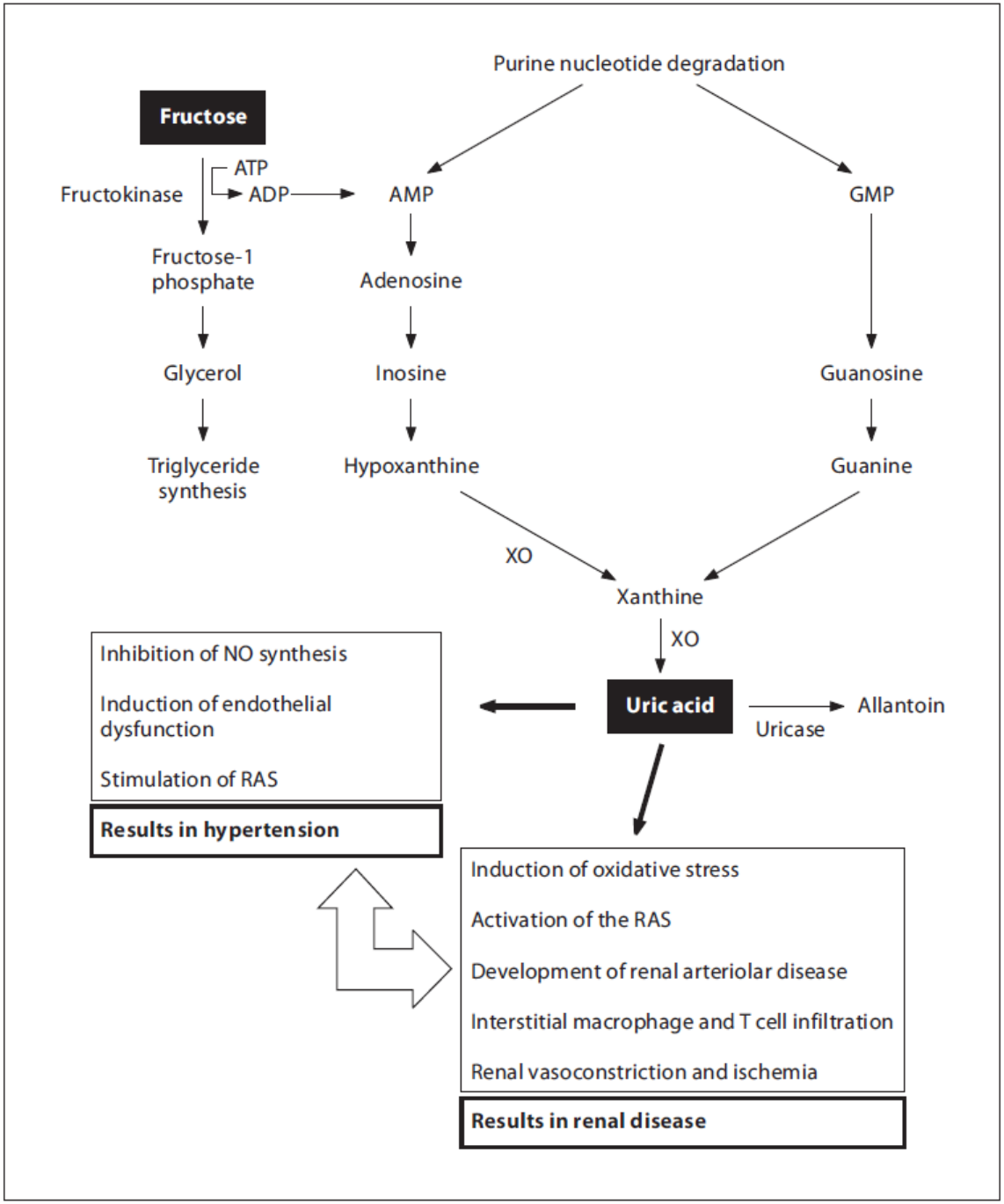


Fig. 1 - *Monosodium urate (MSU) can enter the cells trough a specific carrier (OAT: organic anion transporter). Once inside the cells, MSU activates several pathways that ultimately can lead to systemic effects.*

(J. Endocrinol. Invest. 34: 881-886, 2011)


Purine nucleotide degradation
Fructose
ATP
Fructokinase
ADP
AMP
GMP
Fructose-1 phosphate
Adenosine
Glycerol
Inosine
Guanosine
Triglyceride synthesis
Hypoxanthine
Guanine
XO
Xanthine
XO
Inhibition of NO synthesis
Induction of endothelial dysfunction
Stimulation of RAS
Uric acid
Allantoin
Uricase
Results in hypertension
Induction of oxidative stress
Activation of the RAS
Development of renal arteriolar disease
Interstitial macrophage and T cell infiltration
Renal vasoconstriction and ischemia
Results in renal disease

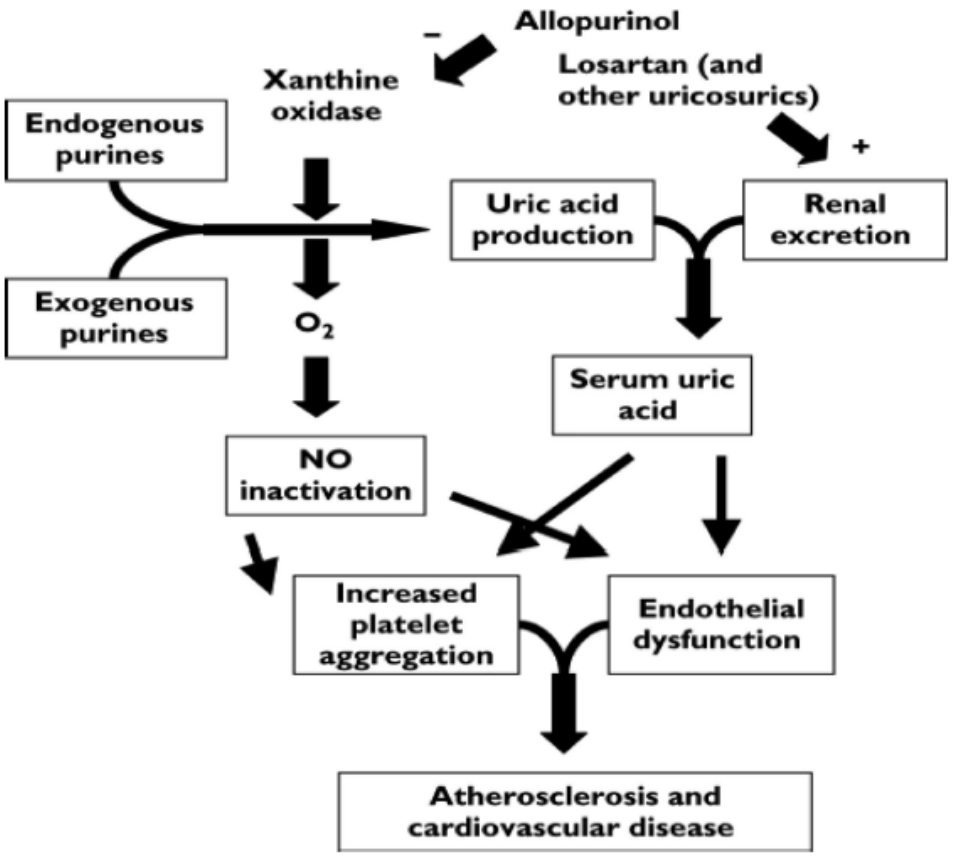
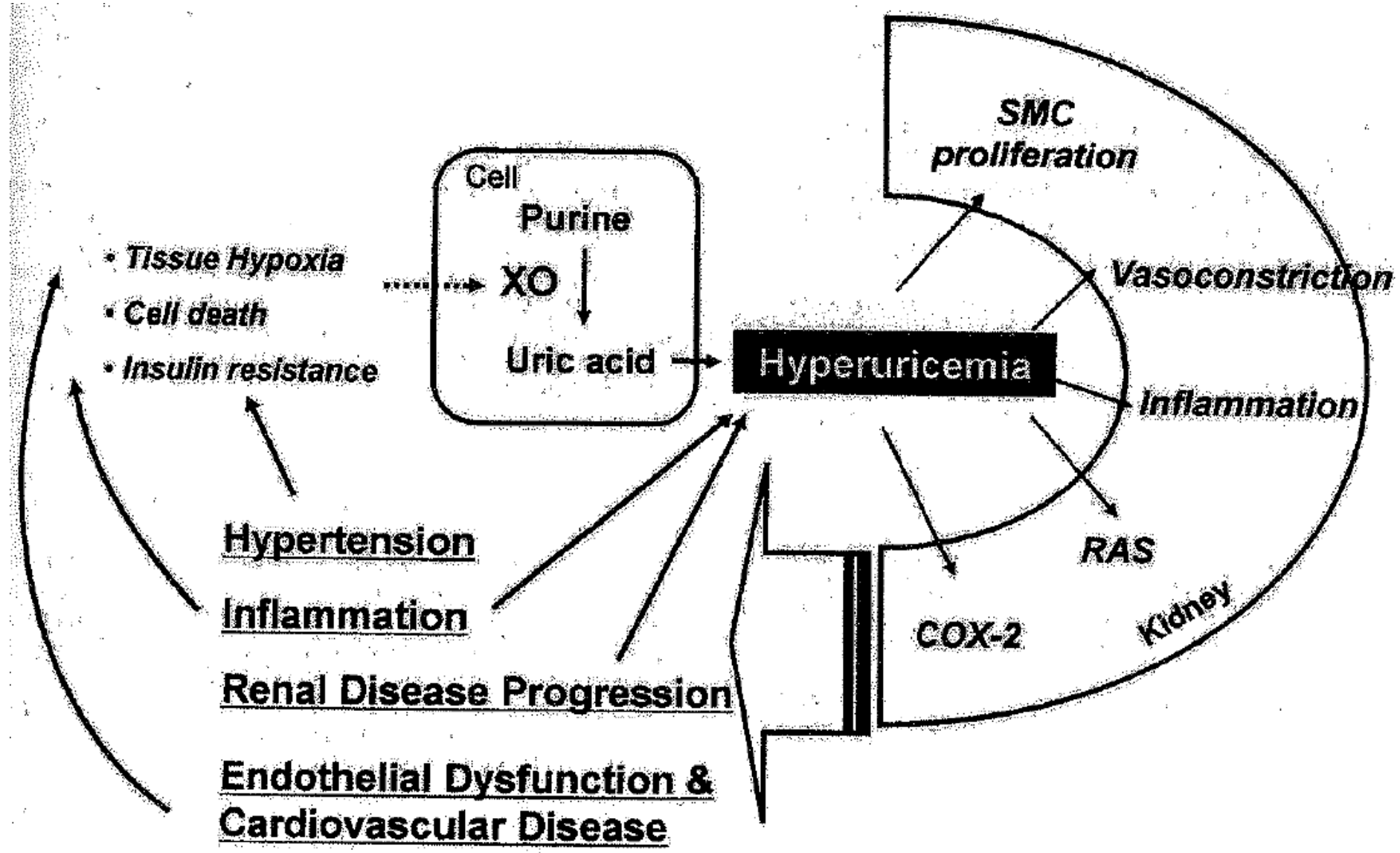


FIGURE 1. Mechanisms of uric acid-lowering drugs, and the mechanisms by which increased serum acid levels are related to cardiovascular disease.[25]



Semin Nephrol 25:43-49 © 2005

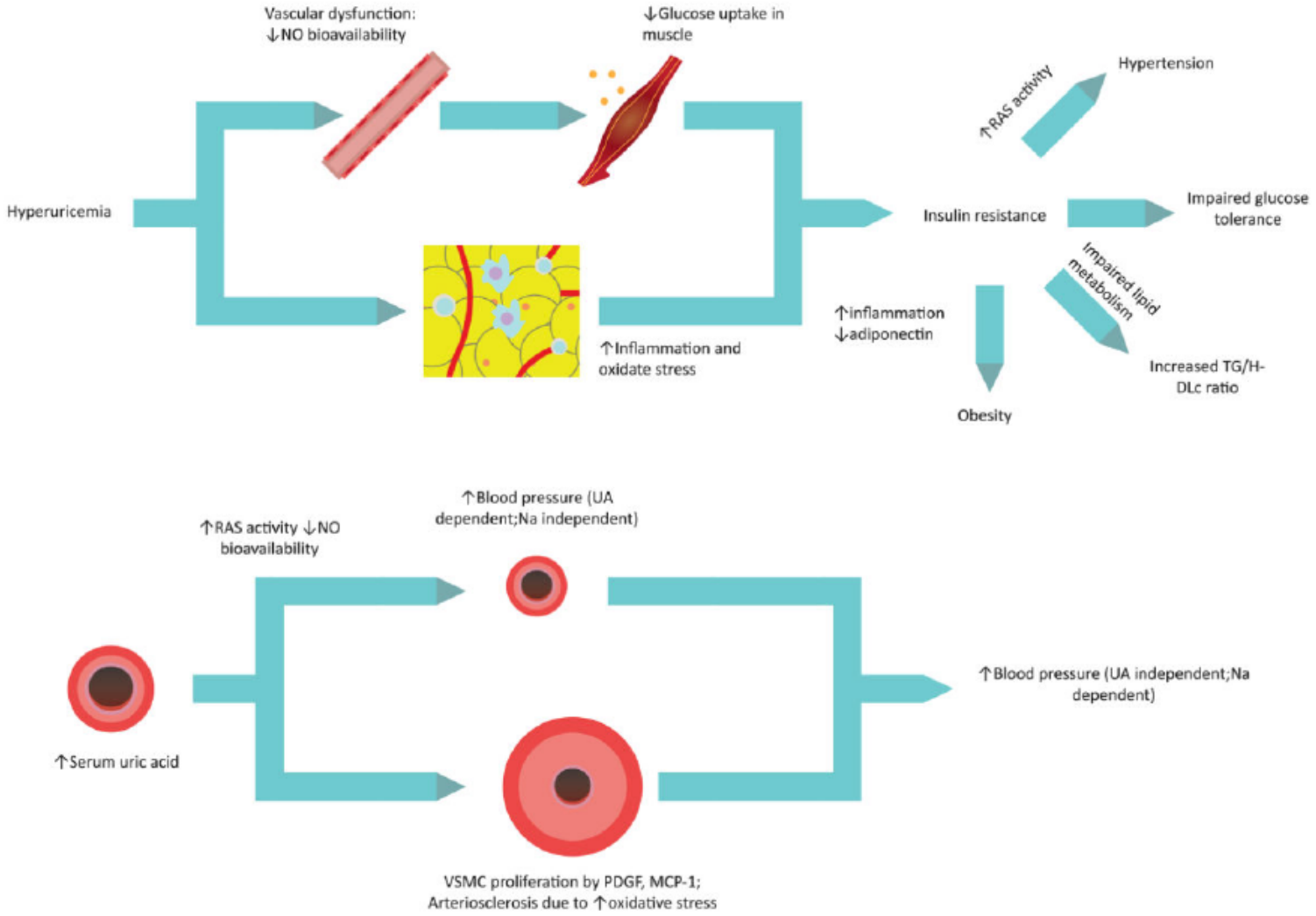


Figure 1.
Proposed two-stage Urate-mediated hypertension

Rheum Dis Clin North Am. 2014 May ; 40(2): 251–278.

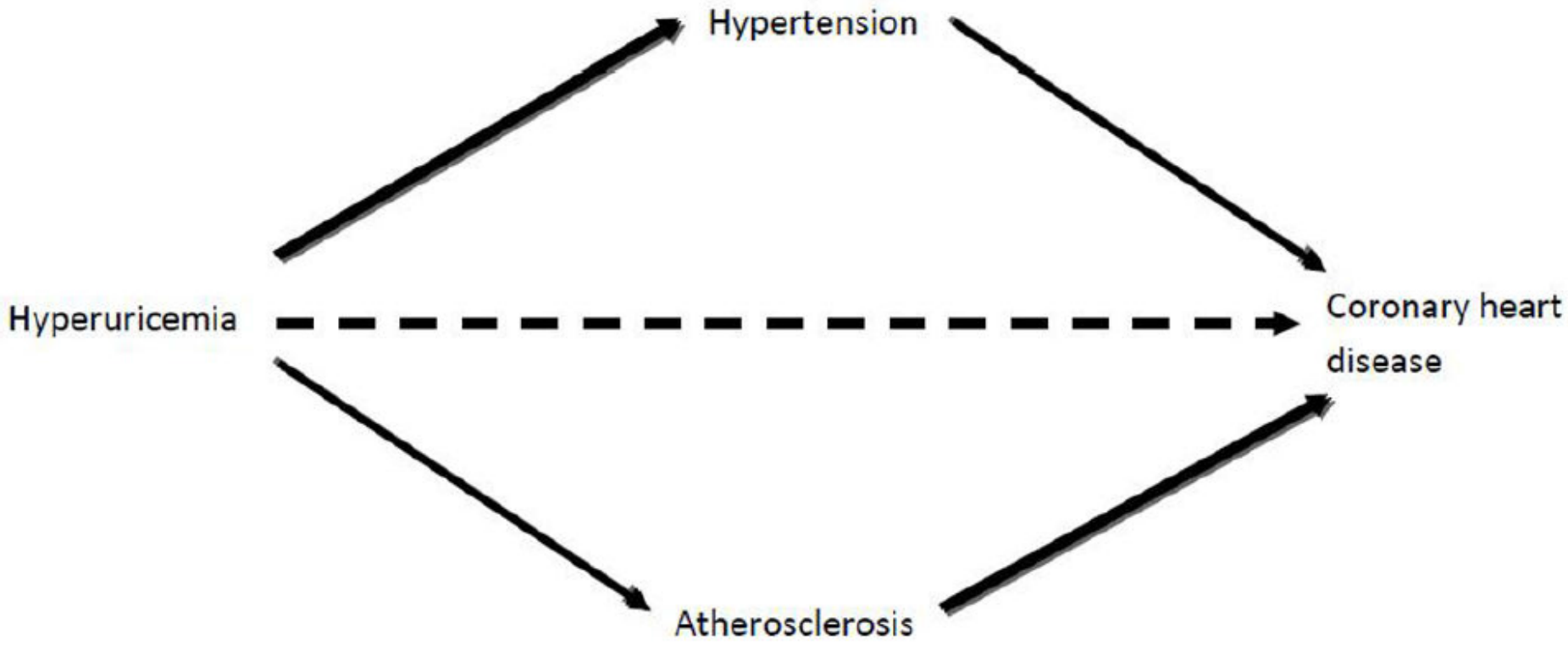


Figure 2.
Association and causality between hyperuricemia and coronary heart disease

Explication / plausibilité physiopathologique?

À traiter l'hyperuricémie asymptomatique avec de si grands bienfaits?

OUI!

3) Ratio risque/bénéfice du traitement de l'hyperuricémie asymptomatique

Est-ce qu'on doit traiter l'hyperuricémie asymptomatique??

OUI selon la Japanese Society of Gout and Nucleic Acid Metabolism

Japanese Guideline for the Management of Hyperuricemia and Gout: Second Edition

Hisashi Yamanaka [a]

[a] Institute of Rheumatology, Tokyo Women's Medical University, Shinjuku-Ku, Tokyo, Japan

Published online: 01 Dec 2011.

Nucleosides, Nucleotides and Nucleic Acids, 30:1018–1029, 2011

Statements:

1) The most important aim of treatment of hyperuricemia is to improve lifestyle changes that are related to the onset of hyperuricemia, in which prognosis-related complications, such as obesity, hypertension, glucose intolerance, and dyslipidemia, are prone to occur—Evidence level 2a, Consensus level 1, and Recommendation level A.
2) Urate-lowering therapy is indicated in patients with recurrent gouty arthritis or gouty tophi; thereby, it is desirable to maintain serum urate at a level of not more than 6.0 mg/dL—Evidence level 2a, Consensus level 1, and Recommendation level A.
3) Urate-lowering therapy may be indicated for asymptomatic hyperuricemia showing a serum urate level of not less than 8.0 mg/dL as a guide; however, it should be applied with caution—Evidence level 3, Consensus level 2, and Recommendation level C.

475umol/L

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Management of asymptomatic hyperuricaemia in patients with chronic kidney disease by Japanese nephrologists: A questionnaire survey

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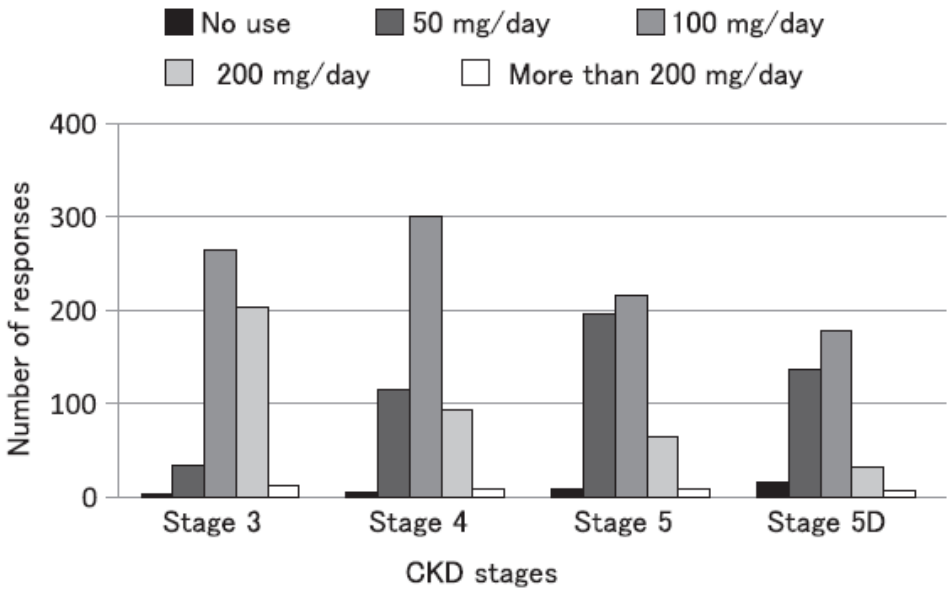

Fig. 2 The maximal dosage of allopurinol used to treat asymptomatic hyperuricaemia in patients with chronic kidney disease (CKD) stages 3–5 and 5D. The most frequently used maximal dosage of allopurinol was 100 mg/day for each stage. The rate of allopurinol usage at a dosage of 200 mg/day decreased and that at a dosage of 50 mg/day increased as the CKD stage progressed into stages 3–5 ($P < 0.001$ by the χ^2-test of independence).

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important reasons for nephrologists to treat AHU at CKD stages 3–5 were prevention of CKD progression (45%), cardiovascular events (CVE) (33%), gout (18%) and urolithiasis (3%), whereas at CKD stage 5D the reasons for treating AHU were prevention of CVE (75%) and gout (25%). In addition, initial and target serum urate levels to start urate-lowering therapy when the most important reason for treating AHU was prevention of CKD progression or CVE tended to be lower compared to those when the reason for treating AHU was prevention of gout or urolithiasis in CKD 5 and CKD 5D, respectively (Table 1).

Recommandations: traitement de l'hyperuricémie asymptomatique.

- Recommandé par **Japanese Society of Gout and Nucleic Acid Metabolism** (uniquement) Débuter un traitement pharmacologique si acide urique:
  - > 475 umol/L avec facteurs de risque cardiovasculaire ou
  - > 535 umol/L pour tous

- UPTODATE : on peut considérer un traitement hypo-uricémiant avec un taux d'acide urique très élevé (niveau ou le risque de néphropathie à l'acide urique existe):
  - Homme: 773 umol/L
  - Femme: 595 umol/L

- Dans un programme éducatif approuvé par le Canadian Heart Research Centre 2014:
  - Viser acide urique < 360 umol/L chez un patient:
    - DB/HTA/IRC<60cc/min et hyperuricémie asymptomatique

Alors pourquoi on n'utilise pas plus d'allopurinol pour traiter l'hyperuricémie asymptomatique??

-Ce n'est pas dans les recommandations Américaine, Canadienne ni Européenne

-Peur des effets secondaires de l'allopurinol!

Allopurinol: risque

- Un des plus vieux RX: > 50 ans d'utilisation!!
- Un des médicaments les mieux toléré de la médecine: 5% d'effets secondaires.
  - HTA: RX les mieux toléré: aliskiren et ARA: 10% d'effets secondaires.
- Effets adverses:
  - 2% rash bénin
  - Rare nausée et céphalée
  - < 1%: hépatites, agranulocytose, SJ, DRESS
- Interactions: azathioprine, mercaptopurine
  - Car la xanthine oxidase participe au métabolisme de ces médicaments, la combinaison doit être évitée! (risque de pancytopénie)
- S'accumule en IRC

Rheum Dis Clin N Am 38 (2012) 663–680

Allopurinol: risque

- Mais ce qu'on craint: le syndrome d'hypersensibilité à l'allopurinol: (DRESS)
  - *Drug Reaction* (ou *Rash*) *with Eosinophilia and Systemic Symptoms*
  - IRA/Hépatite/Steven-Johnson/fièvre/leucocytose/ éosinophilie
  - 0.1-0.4% incidence
  - 5-30% de mortalité
  - Plus décrit avec antibiotiques et anticonvulsivants
- Évitable si on respecte une dose de départ basse selon le niveau d'IRC
  - Start low and go slow
- Alternative: Febuxostat

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Table 3
Proposed allopurinol dosing guidelines: old versus new

Hande et al,[42] 1984 Maximum Dosage Based on Renal Function		Stamp et al,[30] 2012 Starting Dosage Based on Renal Function	
Renal Function (mL/min)	Maximum Dosage	Starting Dosage	Renal Function (mg/mL/min)
0	100 mg 3 × per week	50 mg per week	<5
10	100 mg alternate days	50 mg twice per week	5–15
20	100 mg daily	50 mg every 2 d	16–30
40	150 mg daily	50 mg daily	31–45
60	200 mg daily	100 mg alternate days	46–60
100	300 mg daily	100 mg daily	61–90
		150 mg daily	91–130
		200 mg daily	>130

50mg die

100mg die

On peut aller plus haut selon les recommandations

Recommandations Américaines

Significance & Innovations

- Patient education on diet, lifestyle, treatment objectives, and management of comorbidities is a recommended core therapeutic measure in gout.
- Xanthine oxidase inhibitor (XOI) therapy with either allopurinol or febuxostat is recommended as the first-line pharmacologic urate-lowering therapy (ULT) approach in gout.
- Serum urate level should be lowered sufficiently to durably improve signs and symptoms of gout, with the target <6 mg/dl at a minimum, and often <5 mg/dl. **356umol/L**
- The starting dosage of allopurinol should be no greater than 100 mg/day and less than that in moderate to severe chronic kidney disease (CKD), followed by gradual upward titration of the maintenance dose, which can exceed 300 mg daily even in patients with CKD.

Arthritis Care & Research
Vol. 64, No. 10, October 2012, pp 1431–1446
DOI 10.1002/acr.21772

Conclusions: Allopurinol dans le traitement de l'hyperuricémie asymptomatique

- Suivi des recommandations Japonaises, sauf:
  - Prioriser les patients avec IRC
  - Préférence pour patients hypertendus
  - Exclusions:
    - Priorisation des interventions: HTA, DLP et DB2 non contrôlé. Début de dialyse imminent.
    - Incapacité de comprendre les enjeux (ratio risques/bénéfices)
- Start low (allopurinol 50-100 mg par jour), go slow (augmentation de 50-100 mg par 3-4 mois)
- Viser cible acide urique <360umol/L
- Rash: présenté comme étant un signal d'alarme: patients avisés de cesser l'allopurinol dès l'apparition de la première plaque rouge!! Transféré au febuxostat.

- Clinique de Pré-dialyse Dr Vallée:
- ~90% des patients éligibles sont à l'allopurinol
- ~10%: abandon pour rash (2% rash dans la littérature!): Alternative: Febuxostat (Uloric)
- Mieux d'avoir plus d'abandon mais aucun Steven-Johnson!

3) Ratio risque/bénéfice du traitement de l'hyperuricémie asymptomatique

OUI !

-Minimiser les Risques: Respecter une dose de départ basse (50-100 mg/j) et utilisation chez des patients intelligents

-Maximiser les Bénéfices: Prioriser les patients IRC / HTA / DB

Cas clinique

- Homme 56 ans, intelligent, prend 7 médicaments
- IRC cl. cr. 35cc/min
- DB2 (HBA1C 6.5%), DLP (LDL 1.6), HTA (118/65)
- Se met à faire de l'exercice, perd du poids, moins de sel, mange mieux, ne fume pas
- Tout est dans les cibles!
- Que faire de plus?
- Acide urique 527 umol/L
- Urates antérieures: 544, 483, 501, 465, 499 umol/L
- Discussion sur ratio risques/bénéfices de l'allopurinol dans son cas: patient accepte!
- Mis sous allopurinol 50 mg PO die, ad 250 mg PO die pour acide urique en bas de 360 umol/L

Merci pour votre attention!!

Questions? Commentaires?