CHU Liège

# Prise en charge de l'hyperuricémie, facteur de risque cardiovasculaire?

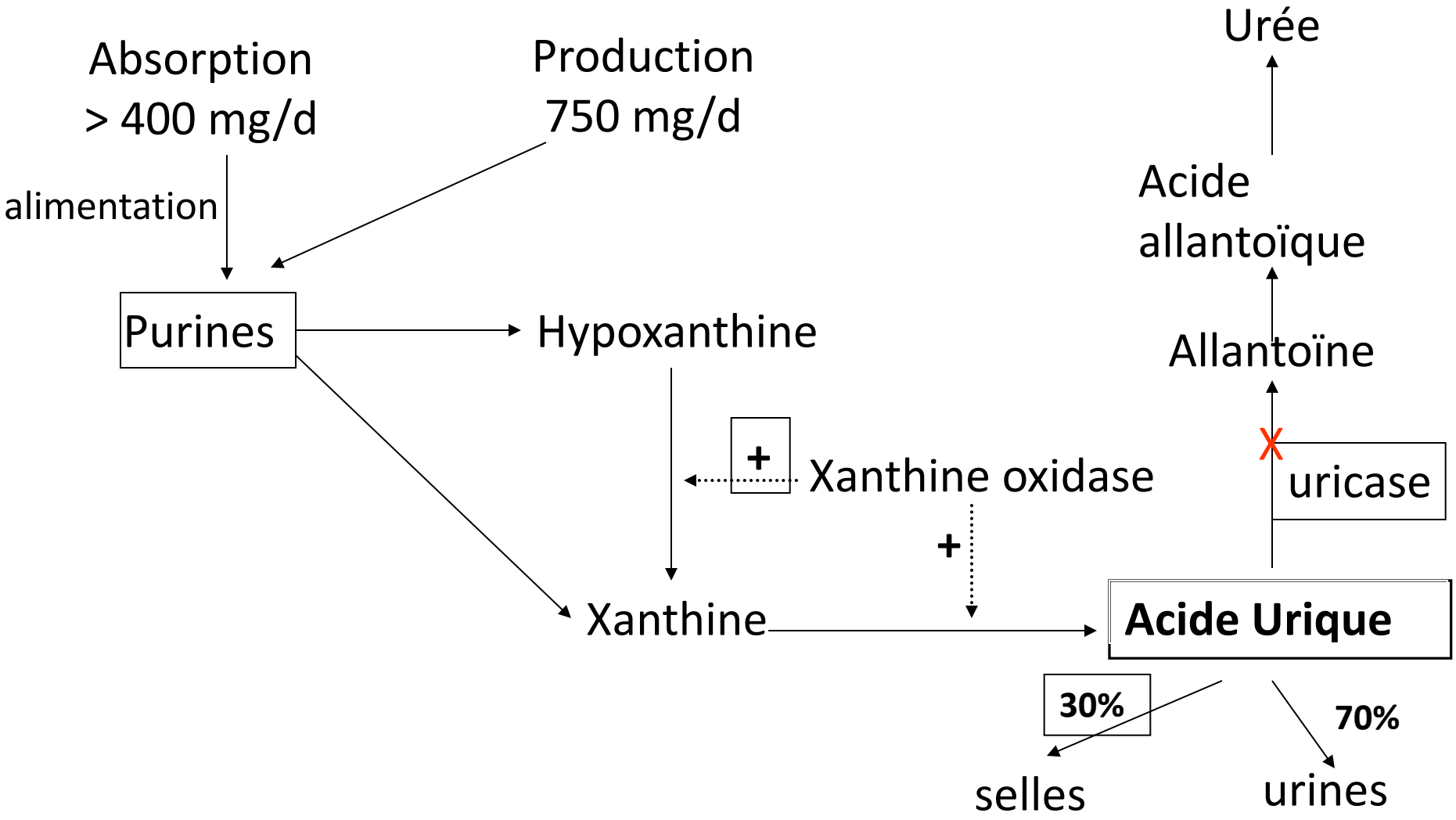
JM Krzesinski

Chef de service de Néphrologie

CHU Liège - ULg

CHU Liège

# Voie métabolique de l'acide urique



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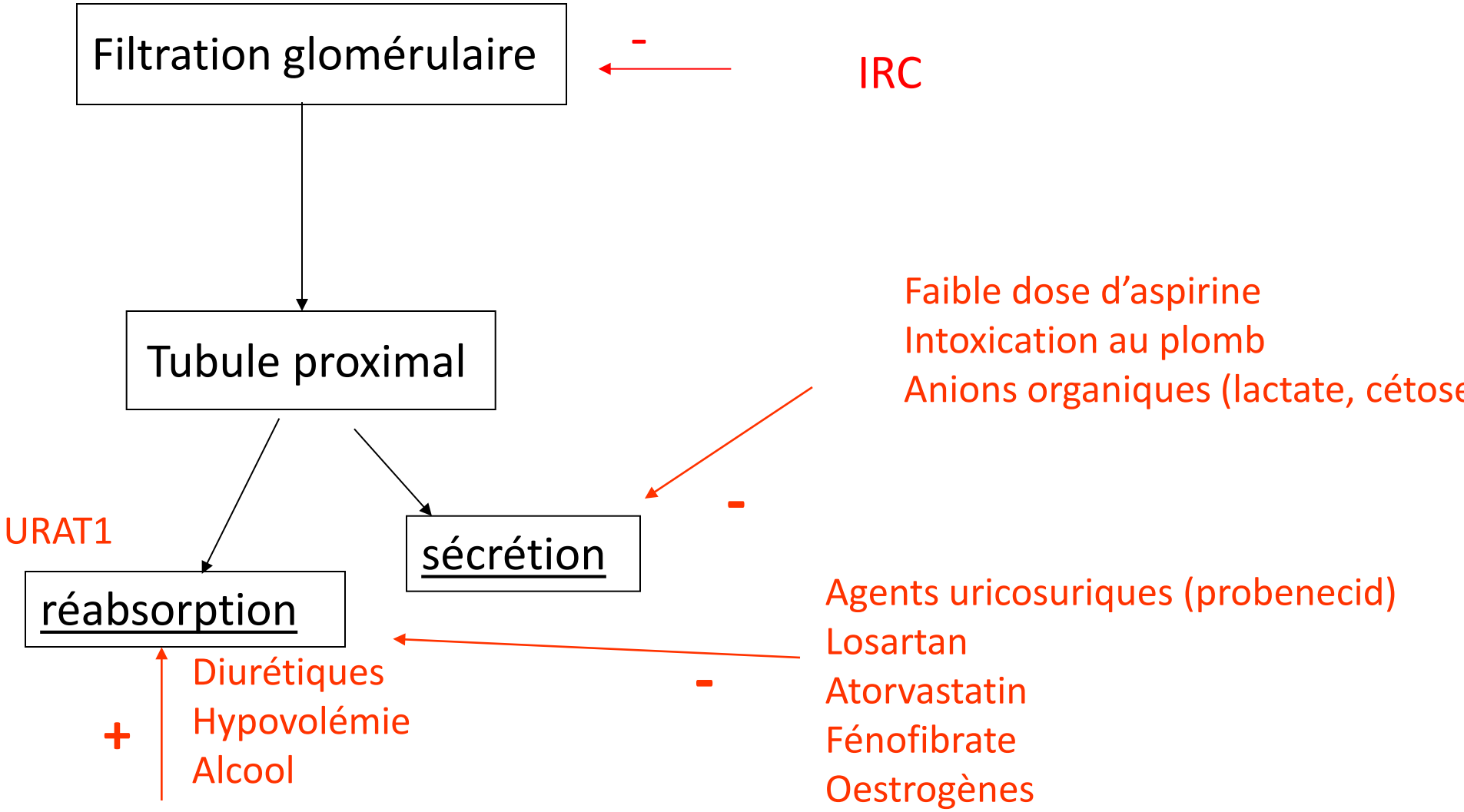
# Régulation de l'excrétion d'acide urique par le rein



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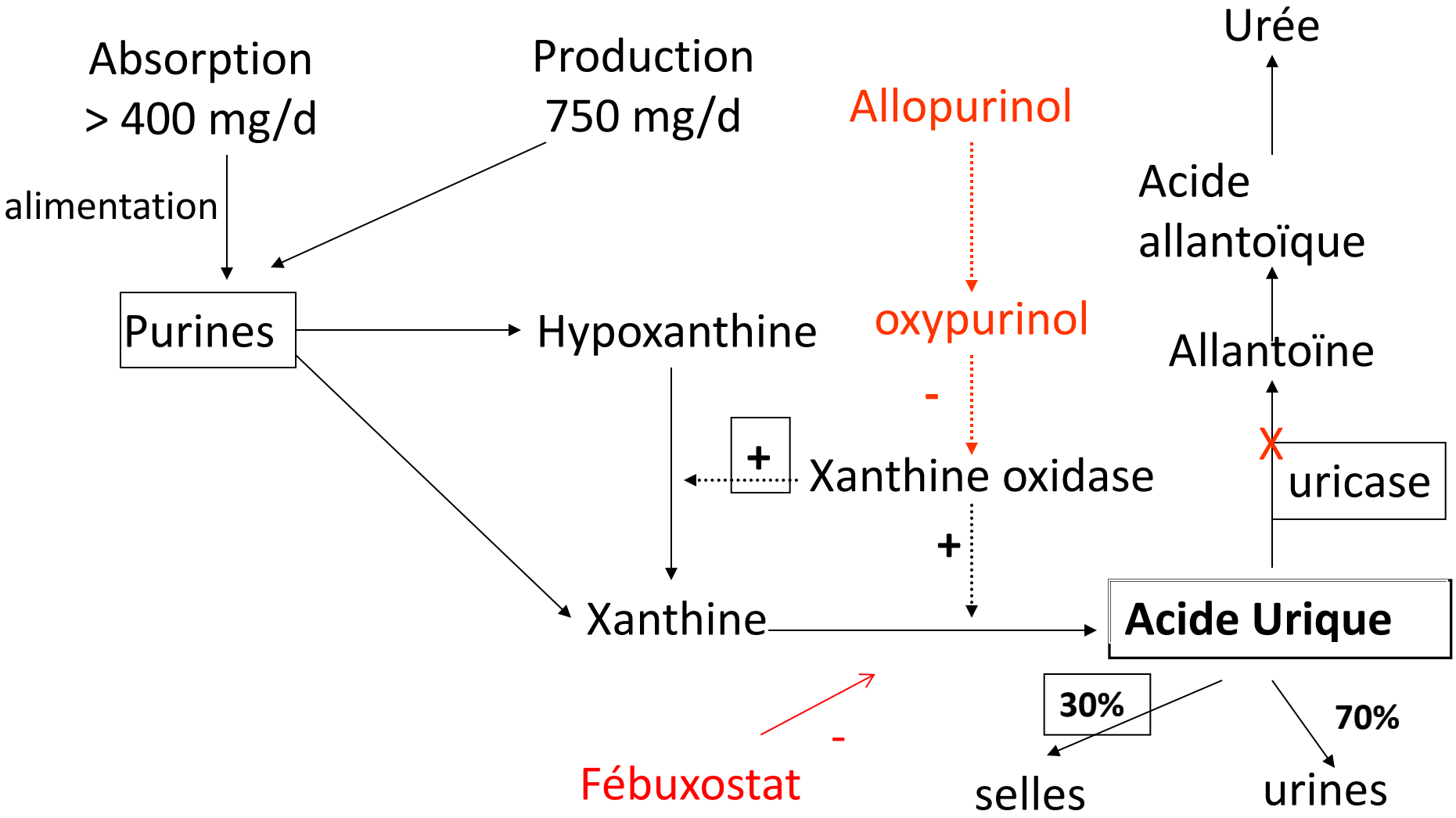
# Voie métabolique de l'acide urique



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# Hyperuricémie symptomatique

N ENGL J MED 350;11 WWW.NEJM.ORG MARCH 11, 2004

**Figure. The Gout, by James Gillray, 1799.**
Courtesy of the Wellcome Library, London.

Goutte
Lithiase d'acide urique
Néphropathie urique aiguë
Néphroangiosclérose

# L'approche du traitement de la goutte

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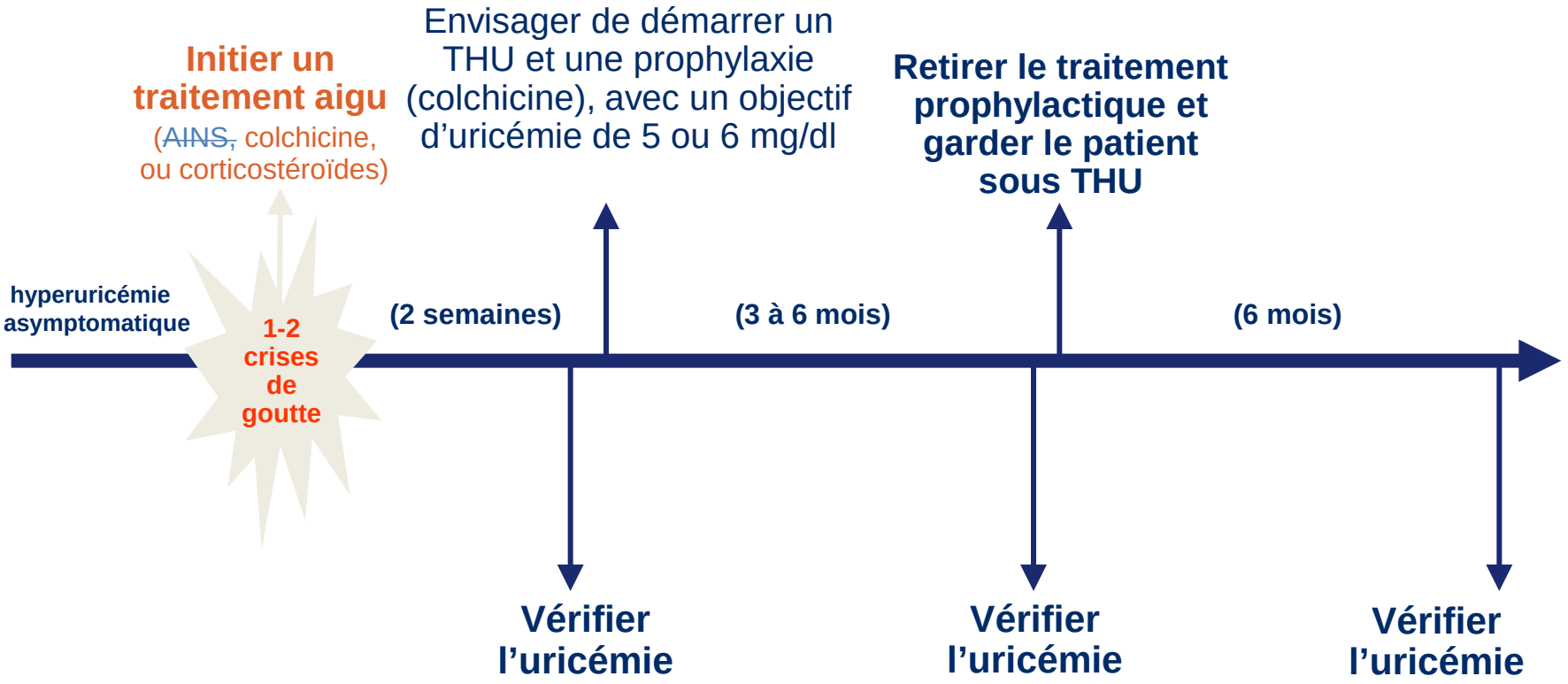
JMK




** Tout comme le taux de cholestérol doit être régulièrement suivi, l'uricémie doit l'être aussi pour assurer un taux d'acide urique en dessous de 5 ou 6 mg/dl.*

# Les comorbidités sont fréquentes chez le patient goutteux

- **Insuffisance rénale**
- **Maladie coronaire**
- **Syndrome métabolique**
  - Obésité
  - Dyslipidémie
  - Hypertension
  - Diabète de type 2

*Agudelo CA. JAMA 2003; 289(21):2857-2860.*

# ACIDE URIQUE, FACTEUR DE RISQUE CARDIOVASCULAIRE?

# Uric Acid and Cardiovascular Risk

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

N Engl J Med 2008;359:1811-21.

**Table 1. Cardiovascular Conditions and Risk Factors Associated with Elevated Uric Acid.**

| |
|---|
| Hypertension and prehypertension |
| Renal disease (including reduced glomerular filtration rate and microalbuminuria) |
| Metabolic syndrome (including abdominal obesity, hypertriglyceridemia, low level of high-density lipoprotein cholesterol, insulin resistance, impaired glucose tolerance, elevated leptin level) |
| Obstructive sleep apnea |
| Vascular disease (carotid, peripheral, coronary artery) |
| Stroke and vascular dementia |
| Preeclampsia |
| Inflammation markers (C-reactive protein, plasminogen activator inhibitor type 1, soluble intercellular adhesion molecule type 1) |
| Endothelial dysfunction |
| Oxidative stress |
| Sex and race (postmenopausal women, blacks) |
| Demographic (movement from rural to urban communities, Westernization, immigration to Western cultures) |

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.

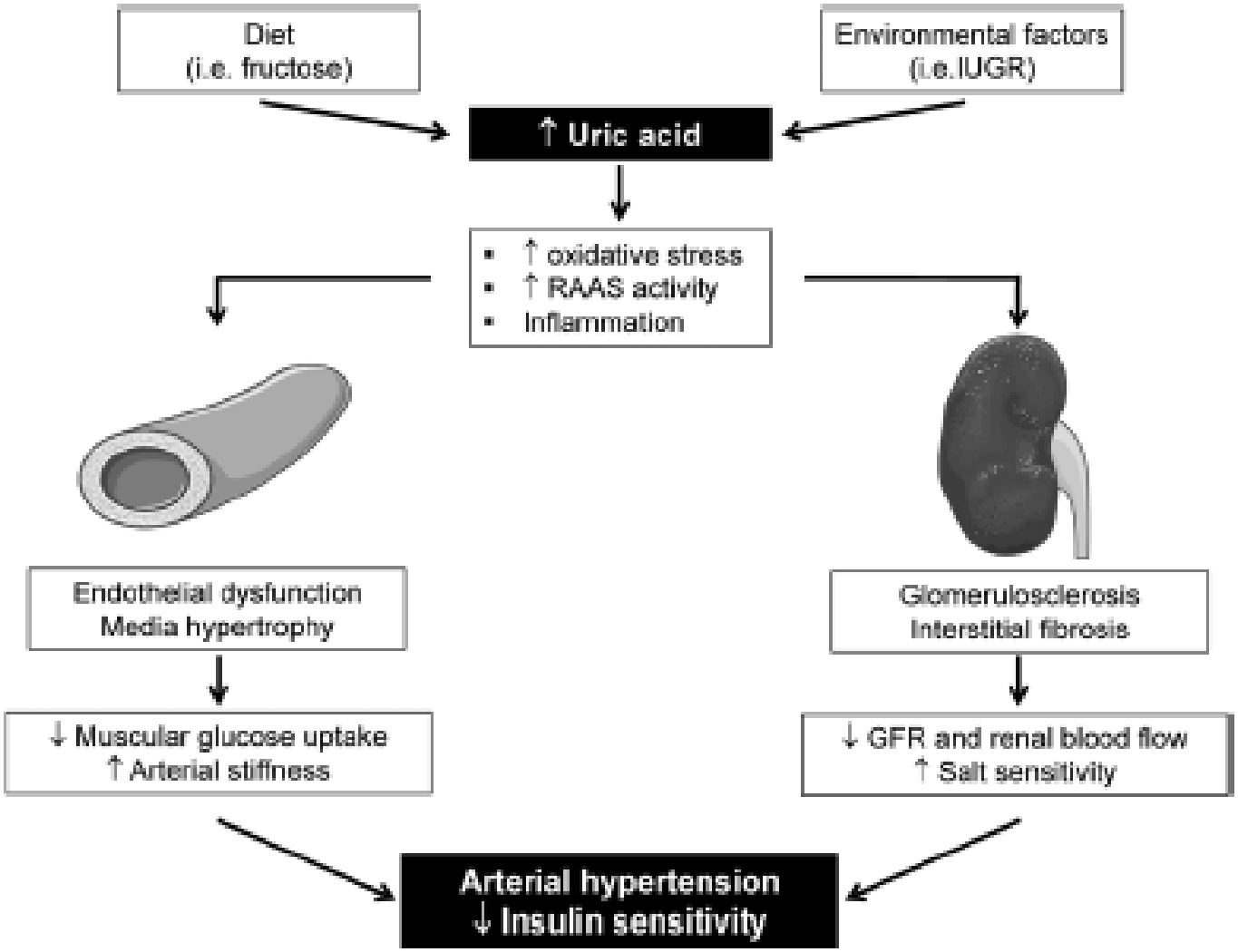
1892：Dr. Davis wrote, “High arterial tension in gout is due in part to uric acid or other toxic substances in the blood which increase the tonus of the [renal] arterioles.”

**TABLE 3. Studies assessing the relationship between hyperuricemia and the risk of new onset hypertension**

| Author | Patients (*n*) | Cut-off point | Follow-up | Adjusted risk ratio |
|---|---|---|---|---|
| Krishnan *et al.*, 2007 [24] | 3073 Normotensive men, age 35–57 yrs, nondiabetic, without metabolic syndrome | >7.0 mg/dl | 6 years | HR 1.81 (95% CI, 1.59–2.07) |
| Grayson *et al.*, 2011 [21] | 55 607 Meta-analysis | 1 SD higher serum uric acid | 3 to 21.5 years | RR 1.13 (95% CI, 1.06–1.20) |
| Perlstein *et al.*, 2006 [25] | 2062 Healthy men | >7.0 mg/dl | 21.5 years | RR 1.1 (95% CI, 1.06–1.15) |
| Forman *et al.*, 2009 [26] | 1496 Healthy women aged 32–52 yrs | >4.6 mg/dl | 8 years | OR 1.89 (95% CI, 1.26–2.82). |
| Mellen *et al.*, 2006 [27] | 9104 Healthy, mean (range) age 53.3 (45–64) yrs | >7.0 mg/dl | 9 years | HR 1.1 (95% CI, 1.04–1.15) |
| Zhang *et al.*, 2009 [28] | 7220 General population | 5.7 (men) | 4 years | RR 1.55 (95% CI, 1.10–2.19) for men |
| | | 4.8 (women) | | RR 1.91 (95% CI, 1.12–3.25) for women |
| Shankar *et al.*, 2006 [29] | 2520 General population | 6.6 mg/dl | 10 years | RR 1.65 (95% CI, 1.41–1.93) |
| Sundström *et al.*, 2005 [30] | 3329 General population | 1 SD increase in serum uric acid | 4 years | OR 1.17 (95% CI, 1.02–1.33) |
| Bombelli *et al.*, 2014 [22] | 2051 General population | 1-mg/dl increase in serum uric acid | 16 years | HR 1.34 (95% CI 1.06–1.70) home hypertension |
| | | | | HR 1.29 (95% CI 1.05–1,70) ambulatory hypertension |

l, confidence interval; HR, hazard ratio; NC, not calculated; OR, odds ratio; RR, relative risk.

# Serum Uric Acid in Primary Hypertension




(*Hypertension*. 2016;67:845-847.

# Relation Between Serum Uric Acid and Risk of Cardiovascular Disease in Essential Hypertension

## The PIUMA Study

Paolo Verdecchia, Giuseppe Schillaci, GianPaolo Reboldi, Fausto Santeusanio, Carlo Porcellati, Paolo Brunetti

*Hypertension* December 2000

**TABLE 3. Multivariate Survival Analysis**

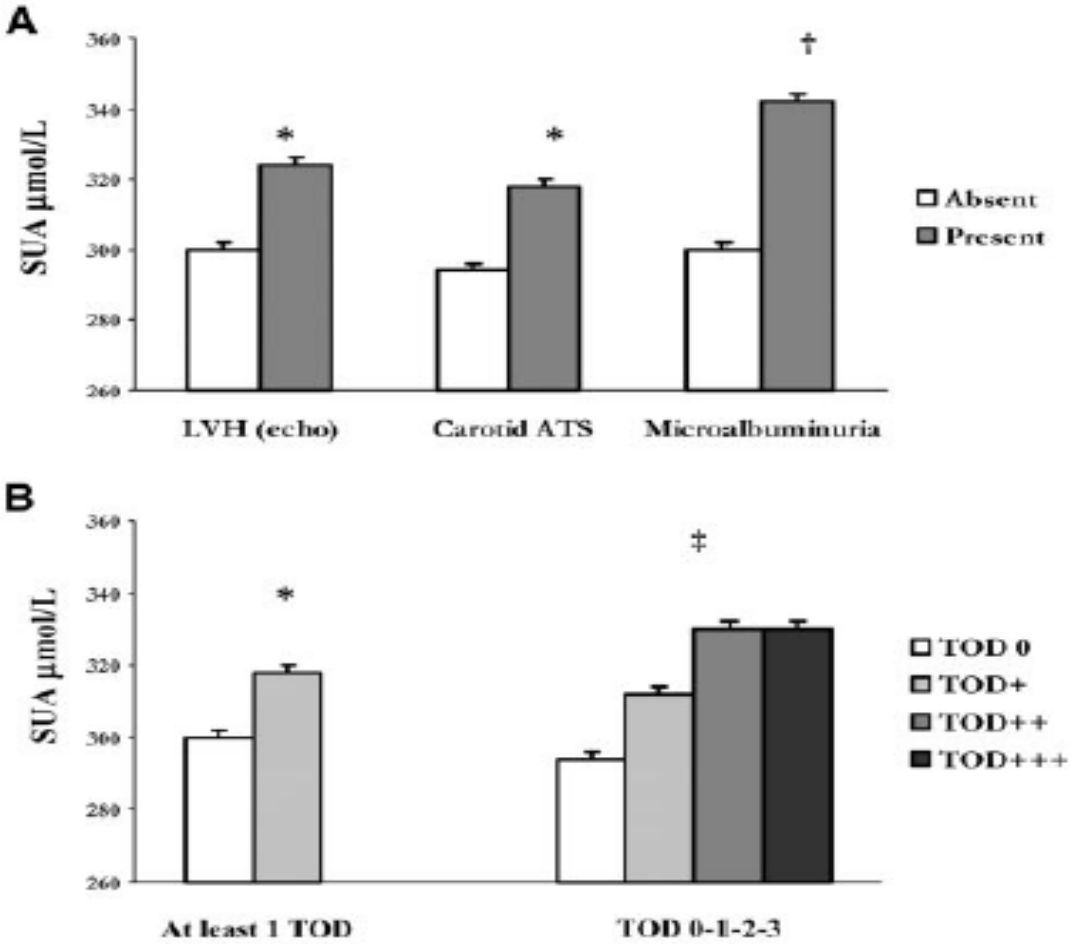
| Variable | Comparison | Relative Risk (95% CI) | *P* |
|---|---|---|---|
| Cardiovascular morbidity | | | |
| Age | (5 y) | 1.23 (1.12–1.34) | 0.00001 |
| Sex | (men vs women) | 1.71 (1.17–2.50) | 0.0055 |
| Diabetes | (yes vs no) | 1.91 (1.21–2.99) | 0.0050 |
| LV hypertrophy | (yes vs no) | 1.74 (1.18–2.57) | 0.0052 |
| 24-h PP | (10 mm Hg) | 1.37 (1.17–1.62) | 0.0002 |
| TC/HDL-C | (1 U) | 1.24 (1.10–1.40) | 0.0006 |
| SUA | Quartile 1 vs 2 | 1.14 (0.62–2.06) | 0.66 |
| | Quartile 3 vs 2 | 1.46 (0.84–2.52) | 0.17 |
| | Quartile 4 vs 2 | 1.73 (1.01–3.00) | 0.0492 |
| Cardiovascular mortality | | | |
| Age | (5 y) | 1.81 (1.49–2.21) | 0.00001 |
| Sex | (men vs women) | 1.94 (0.96–3.93) | 0.060 |
| Diabetes | (yes vs no) | 1.92 (0.96–3.85) | 0.066 |
| 24-h PP | (10 mm Hg) | 1.41 (1.11–1.79) | 0.0046 |
| SUA | Quartile 1 vs 2 | 2.03 (0.61–6.81) | 0.86 |
| | Quartile 3 vs 2 | 1.03 (0.30–3.62) | 0.85 |
| | Quartile 4 vs 2 | 1.96 (1.02–3.79) | 0.042 |
| All-cause mortality | | | |
| Age | (5 y) | 1.68 (1.48–1.91) | 0.00001 |
| Sex | (men vs women) | 2.66 (1.64–4.34) | 0.0001 |
| Diabetes | (yes vs no) | 1.67 (1.02–2.72) | 0.0401 |
| 24-h PP | (10 mm Hg) | 1.28 (1.08–1.50) | 0.0034 |
| SUA | Quartile 1 vs 2 | 1.73 (0.77–3.89) | 0.18 |
| | Quartile 3 vs 2 | 1.43 (0.64–3.20) | 0.38 |
| | Quartile 4 vs 2 | 1.63 (1.02–2.57) | 0.037 |

# Serum Uric Acid and Target Organ Damage in Primary Hypertension

*Hypertension*. 2005;45:991-996.)

Francesca Viazzi, Denise Parodi, Giovanna Leoncini, Angelica Parodi, Valeria Falqui, Elena Ratto, Simone Vettoretti, Gian Paolo Bezante, Massimo Del Sette, Giacomo Deferrari, Roberto Pontremoli

*Abstract*—The role of serum uric acid as an independent risk factor for cardiovascular and renal morbidity is controversial. A better understanding of its relationship with preclinical organ damage may help clarify the mechanism(s) implicated in the development of early cardiovascular disease. We evaluated the association between uric acid and the presence and degree of target organ damage in 425 (265 males, 160 females) middle-aged, untreated patients with essential hypertension. Left ventricular mass index and carotid intima-media thickness were assessed by ultrasound scan. Albuminuria was measured as the albumin to creatinine ratio in 3 nonconsecutive first morning urine samples. Overall, patients with target organ damage had significantly higher levels of serum uric acid as compared with those without it (presence versus absence of left ventricular hypertrophy, $P=0.04$; carotid abnormalities, $P<0.05$; microalbuminuria,



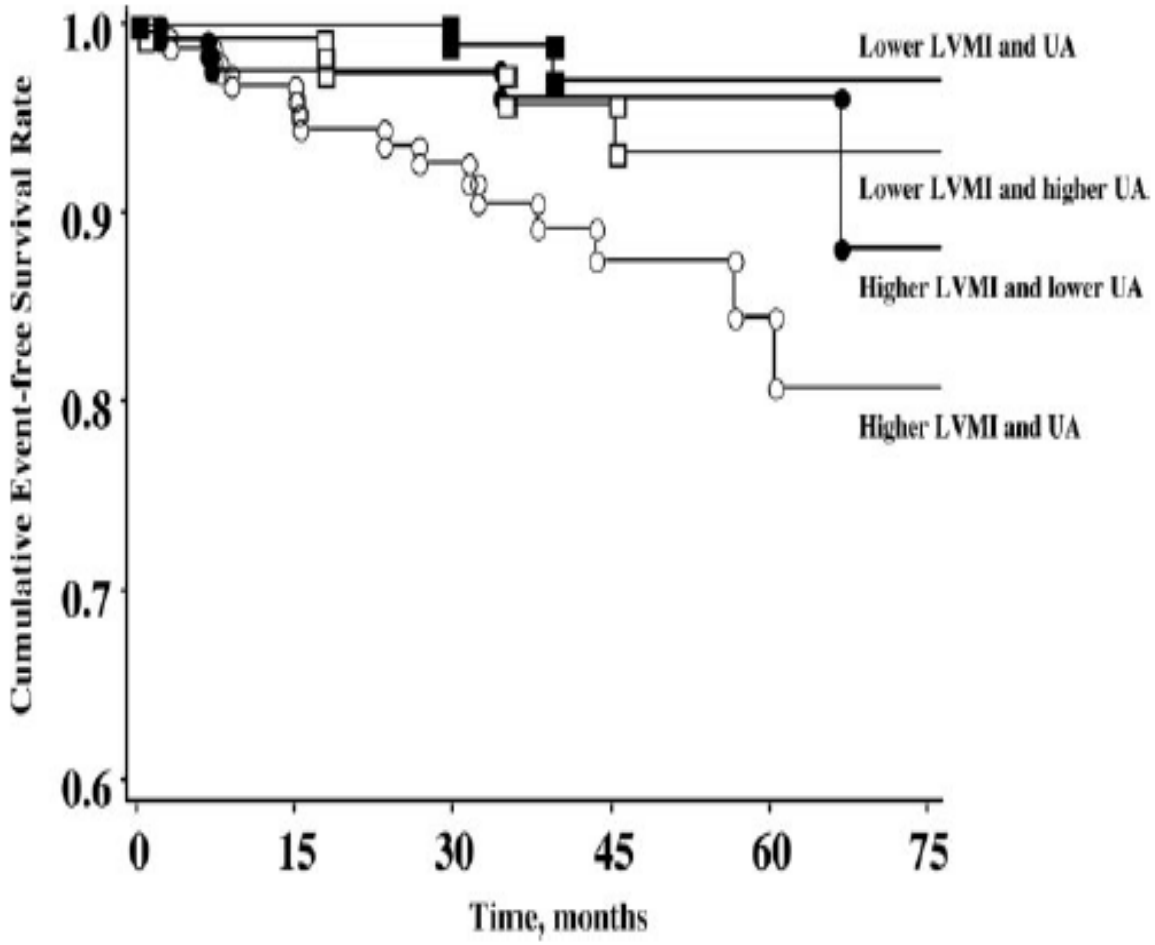

*Hypertension*. 2005;45:991-996.)

**Figure 1.** Serum uric acid and target organ damage in patients with essential hypertension (n=425). SUA levels are analyzed on the basis of the presence/absence of different signs of TOD (1a) and on the basis of the severity of TOD involvement (1b). SUA indicates serum uric acid; LVH(echo), left ventricular hypertrophy by echocardiography; Carotid ATS, carotid atherosclerosis by US carotid scan; TOD 0, patients without signs of organ damage; TOD+, subgroup of patients with either LVH or carotid abnormalities or microalbuminuria; TOD++, patients with a combination of any two signs of TOD; TOD+++, those with all three signs of the TOD we examined. *$P<0.05$ and †$P<0.01$ vs patients without damage; ‡ $P<0.01$ refers to inter-group comparison.

# Uric Acid, Left Ventricular Mass Index, and Risk of Cardiovascular Disease in Essential Hypertension

Yoshio Iwashima, Takeshi Horio, Kei Kamide, Hiromi Rakugi, Toshio Ogihara, Yuhei Kawano

(*Hypertension*. 2006;47:195-202.)




Kaplan–Meier plots showing cumulative CVD-free survival in subjects according to 4 groups divided by median values of UA and LVMI (log-rank $\chi^2$=13.18; $P$=0.0042). Marker groups for LVMI (g/m$^2$): lower-LVMI, ≤126.9 for men and ≤112.0 for women; higher-LVMI, >126.9 for men and >112.0 for women. Marker groups for UA (μmol/L): lower-UA, ≤374.7 for men and ≤303.3 for women; higher-UA, >374.7 for men and >303.3 for women.

# Prognostic value of serum uric acid: new-onset in and out-of-office hypertension and long-term mortality

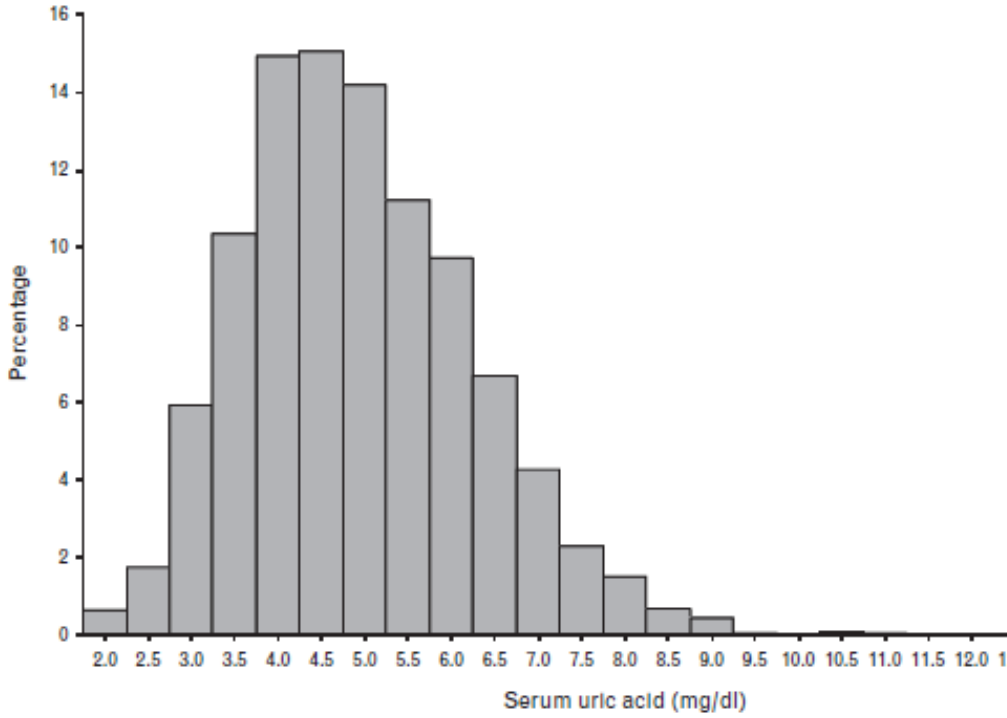
Michele Bombelli[a,b], Irene Ronchi[a], Marco Volpe[a], Rita Facchetti[a], Stefano Carugo[b], Raffaella Dell'Oro[a], Cesare Cuspidi[b,c], Guido Grassi[a,b,d], and Giuseppe Mancia[b,c]

Journal of Hypertension 2014, .

**TABLE 1. Demographic, anthropometric, hemodynamic and metabolic characteristics of the population sample (*N* = 2045)**

| | Patients (*N* = 2045) |
|---|---|
| Age (years) | 50.9 ± 13.7 |
| Male/female (*N*) | 1037/1008 |
| BMI (kg/m$^2$) | 25.6 ± 4.4 |
| WC (cm) | 85.7 ± 12.4 |
| Office SBP (mmHg) | 132.8 ± 21.3 |
| Office DBP (mmHg) | 83.9 ± 10.7 |
| Home SBP (mmHg) | 124.6 ± 19.2 |
| Home DBP (mmHg) | 76.5 ± 10.6 |
| 24-h SBP (mmHg) | 120.3 ± 11.9 |
| 24-h DBP (mmHg) | 74.4 ± 7.6 |
| LVMI (g/m$^2$) | 86.7 ± 21.0 |
| Total serum cholesterol (mg/dl) | 224 ± 42.8 |
| Total HDL cholesterol (mg/mg) | 4.32 ± 1.46 |
| Serum glucose (mg/dl) | 90.8 ± 21.0 |
| Serum triglycerides (mg/dl) | 116.1 ± 76.6 |
| Serum creatinine (mg/dl) | 0.88 ± 0.19 |
| Serum uric acid (mg/dl) | 4.94 ± 1.34 |
| Treated hypertension | 395 (19.3%) |

LVMI, left-ventricular mass index; WC, waist circumference.
Data are shown as mean ± SD or in percentage.




Distribution of serum uric acid value in the study population.

# Prognostic value of serum uric acid: new-onset in and out-of-office hypertension and long-term mortality

Journal of Hypertension 2014, 32:000–000

**Methods:** In 2045 participants of the Pressioni Arteriose Monitorate E Loro Associazioni study, we measured, along with SUA, metabolic, renal, and anthropometric variables, left-ventricular mass index, and office, home and ambulatory BP. Cardiovascular and all-cause mortality was assessed over a 16-year follow-up period, and measurements were repeated 10 years after the initial data collection.

Développement HTA

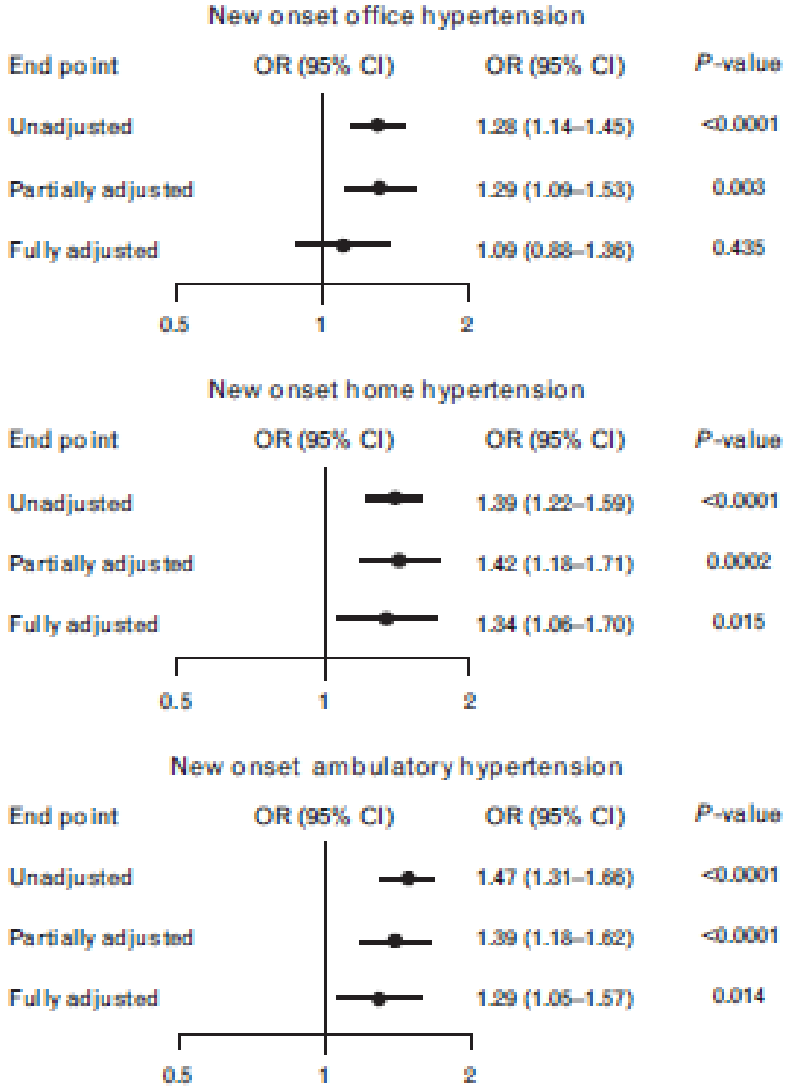



**FIGURE 2** Odd ratio (OR) and 95% confidence interval (95% CI) of developing office, home and ambulatory hypertension, associated to a 1 mg/dl increase of serum uric acid. Data are shown unadjusted, partially adjusted (age and sex), and fully adjusted (age, sex, the ratio between serum total and HDL-cholesterol, serum triglycerides, smoking, serum glucose, BMI, serum creatinine, LVMI, baseline office, home or ambulatory SBP) confounders. HDL, high-density lipoprotein; LVMI, left-ventricular mass index.

Bombelli *et al.*

Mortalité

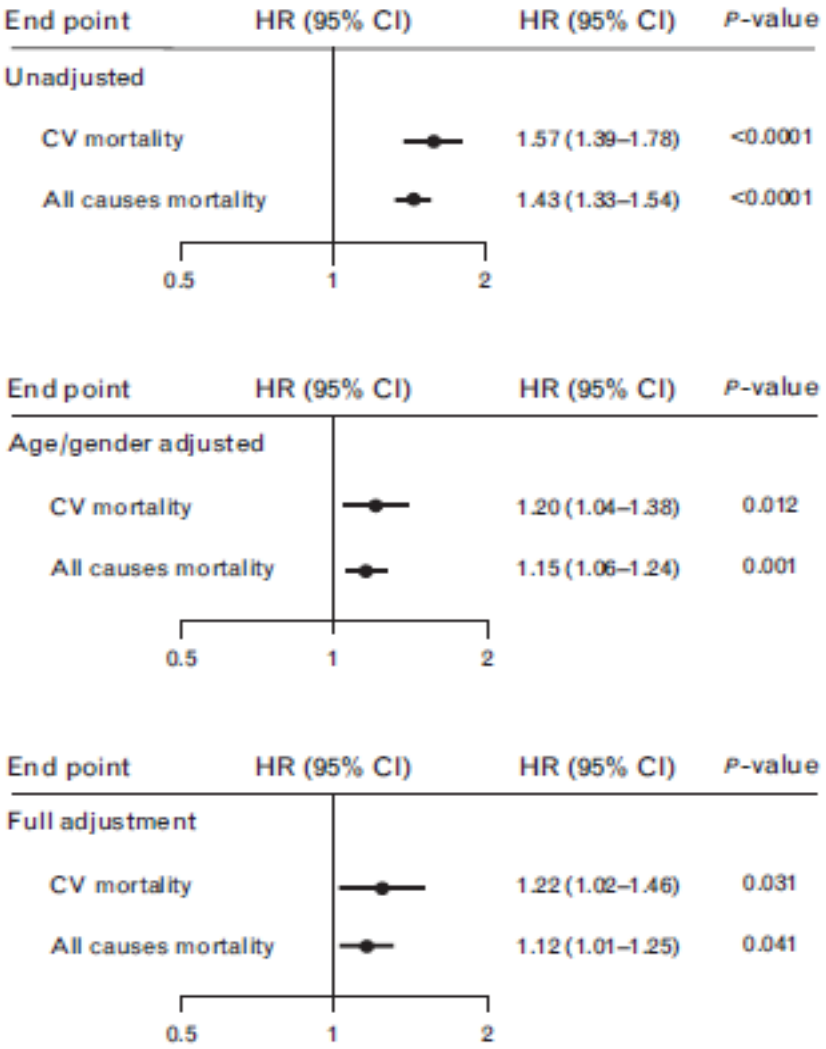
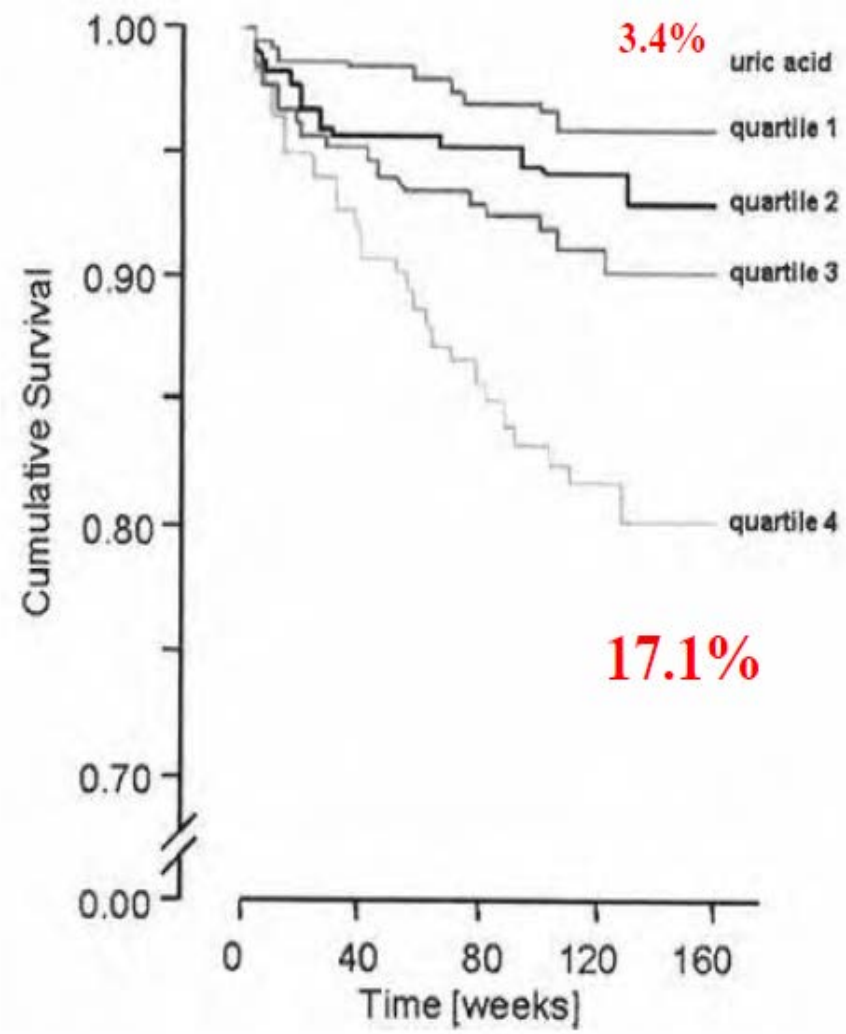



**FIGURE 3** Hazard ratio (HR) and 95% confidence intervals (95% CIs) of CV and all-cause mortality associated to a 1 mg/dl increase of serum uric acid. Data are shown unadjusted, partially adjusted (age and sex), and fully adjusted (age, sex, smoking, BMI, baseline ambulatory SBP, left-ventricular mass index, serum glucose, the ratio between total and HDL cholesterol, triglycerides, serum creatinine, previous CV event and diuretic therapy). CV, cardiovascular; HDL, high-density lipoprotein.

# Survie chez 1017 coronariens (prouvés) selon le niveau d'acide urique divisé en quartiles (<5,1 mg/dl Q1 et > 7,1mg/dl Q4)




Mortalité 5X> qd AU élevé Relation persiste après ajustement

Bickel et al, Am J Cardiol 89:12, 2002

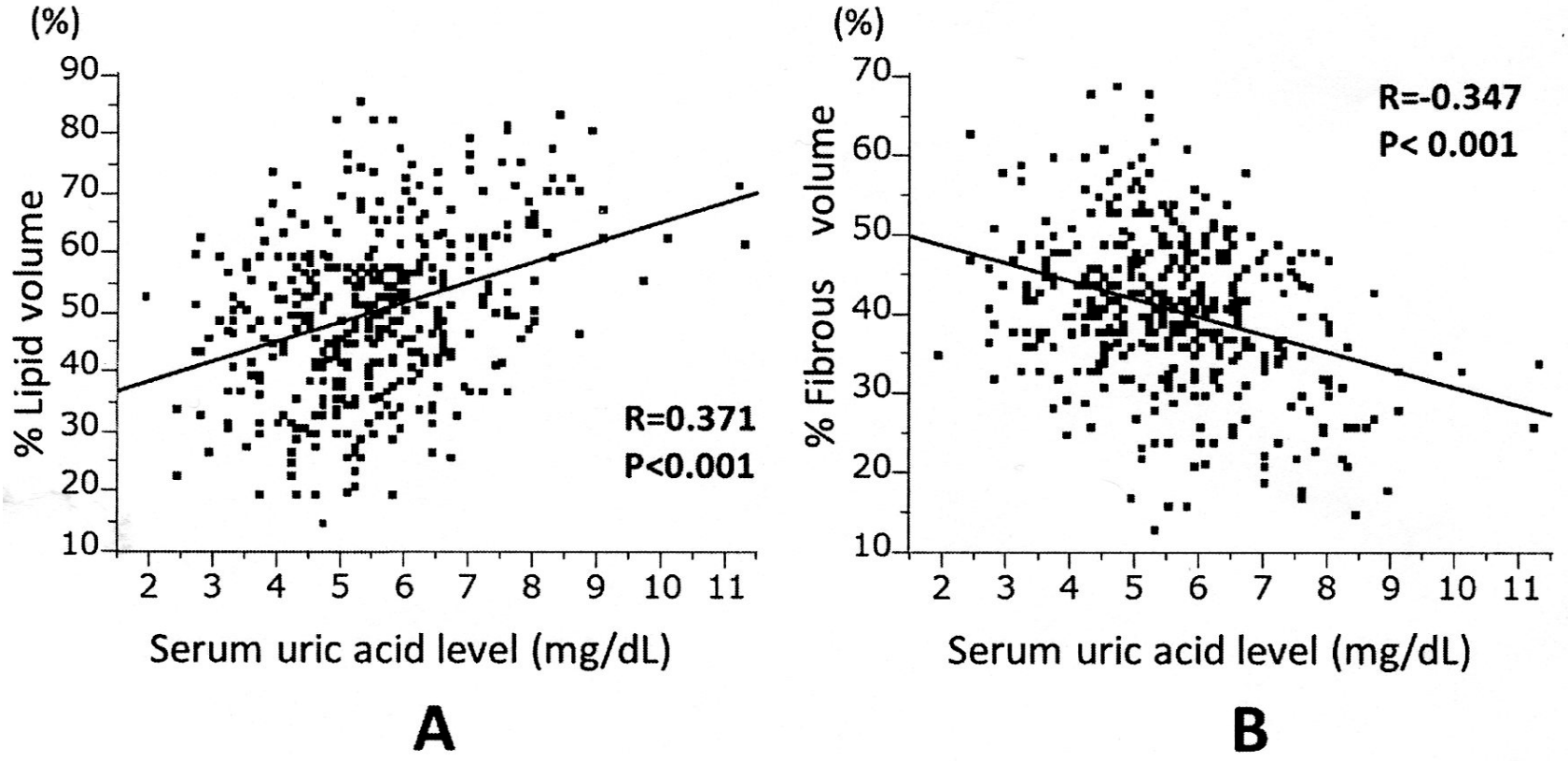
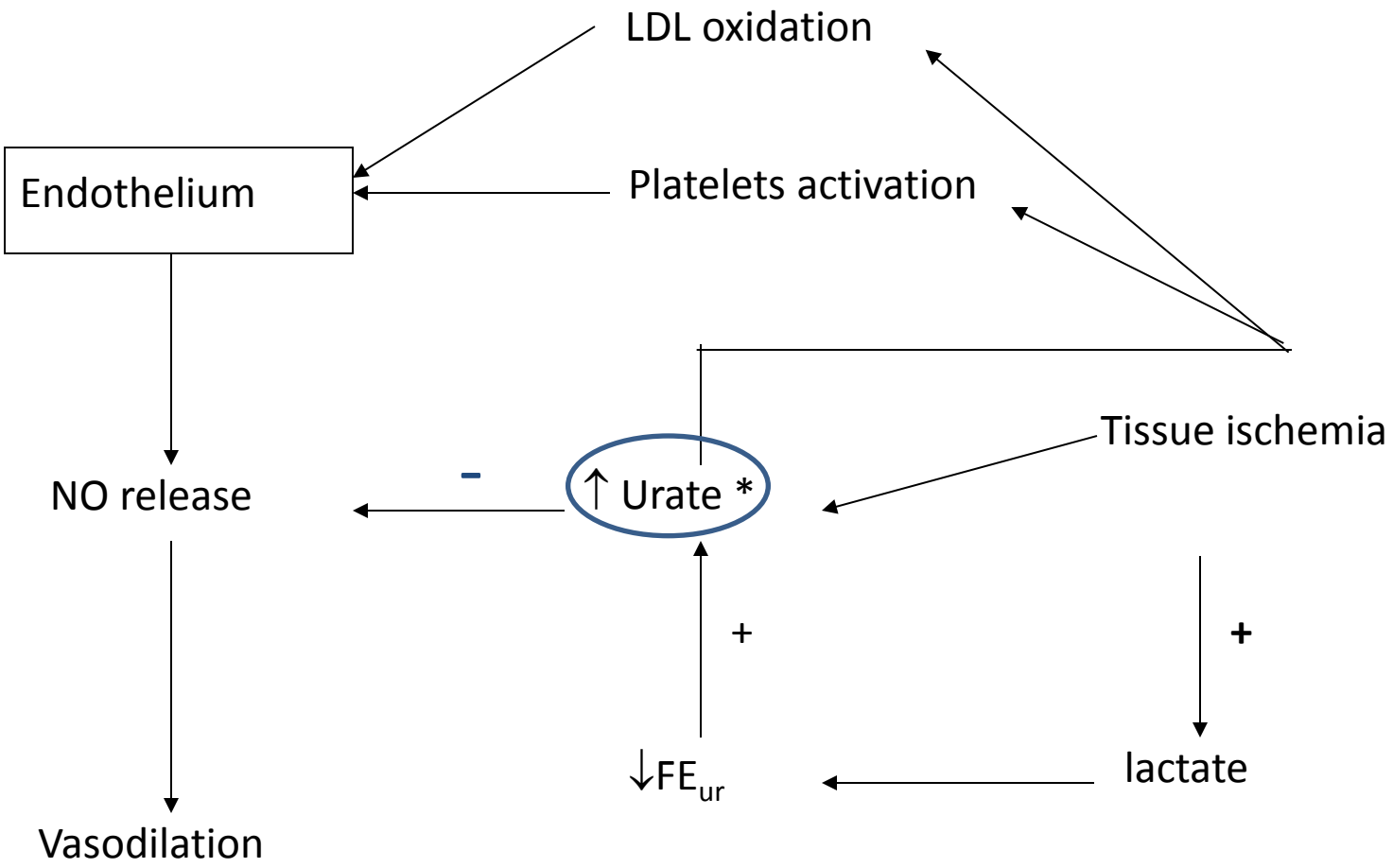



**Fig. 1.** Simple linear regression analysis showing the relationship between serum uric acid levels and coronary plaque components: (A) % lipid volume and (B) % fibrous volume.

Ando *et al.*, J Atheroscler Thromb, 2016; **23**, 932

# Uric acid and endothelial dysfunction




**** Waring WS Br J Clin Pharmacol 2000***

# Relation entre AU et risque

## revue de Dawson et Walters  Br J Clin Pharmacol 2006

- Chez l'HT  observation d'un risque CV, de mortalité, d'AVC fatal accru quand hyperU
- Chez le DM  risque d'AVC et d'atteinte de type PAD quand hyperU
- Chez le coronarien , risque de mortalité accru

Mais lien direct (facteur de risque) ou simple reflet (marqueur de risque) de la présence d'autres FR importants?

# Baseline serum uric acid level as a predictor of cardiovascular disease related mortality and all-cause mortality: A meta-analysis of prospective studies

Atherosclerosis 231 (2013) 61–68

Gang Zhao, Lan Huang, Mingbao Song, Yaoming Song*

*Conclusions:* Baseline SUA level is an independent predictor for future cardiovascular mortality. Elevated SUA appears to significantly increase the risk of all-cause mortality in men, but not in women. Whether low SUA levels are predictors of mortality is still inconclusive.

Elevated SUA increased risk of all-cause mortality (RR 1.24; 95% CI 1.09–1.42) and cardiovascular mortality (RR 1.37; 95% CI 1.19–1.57). Subgroup analyses showed that elevated SUA significantly increase the risk of all-cause mortality among men (RR 1.23; 95% CI 1.08–1.42), but not in women (RR 1.05; 95% CI 0.79–1.39). Risk of cardiovascular mortality appeared to be more pronounced among women (RR 1.35; 95% CI 1.06–1.72). The association between extremely low SUA and mortality was reported in three studies; we did not perform a pooled analysis because of high degree of heterogeneity in these studies.

# Serum Uric Acid and Risk for Cardiovascular Disease and Death: The Framingham Heart Study

Bruce F. Culleton, MD; Martin G. Larson, ScD; William B. Kannel, MD; and Daniel Levy, MD

*Ann Intern Med.* 1999;131:7-13.

Suivi de 20 ans

**Table 1. Baseline Clinical Characteristics***

| Characteristic | Men ($n$ = 3075) | Women ($n$ = 3688) |
|---|---|---|
| Age, *y* | 46 ± 15 | 48 ± 16 |
| Serum uric acid level, *µmol/L* | 379 ± 76 | 285 ± 69 |
| Body mass index, *kg/m²* | 26.7 ± 3.6 | 24.8 ± 4.7 |
| Systolic blood pressure, *mm Hg* | 130 ± 17 | 126 ± 21 |
| Diastolic blood pressure, *mm Hg* | 82 ± 11 | 77 ± 10 |
| Hypertension, % | 32.6 | 28.7 |
| Antihypertensive use, % | 8.0 | 11.6 |
| Diuretic use, % | 4.9 | 9.7 |
| Left ventricular hypertrophy, % | 0.7 | 0.4 |
| Diabetes, % | 3.9 | 2.5 |
| Total serum cholesterol level, *mmol/L* | 5.35 ± 1.02 | 5.40 ± 1.17 |
| Weekly alcohol use, *oz* | 5.5 ± 6.4 | 2.2 ± 3.1 |
| Smoker, % | 45.9 | 37.8 |
| Postmenopausal, % | – | 49.4 |

* Values with plus/minus sign are the mean ± SD.

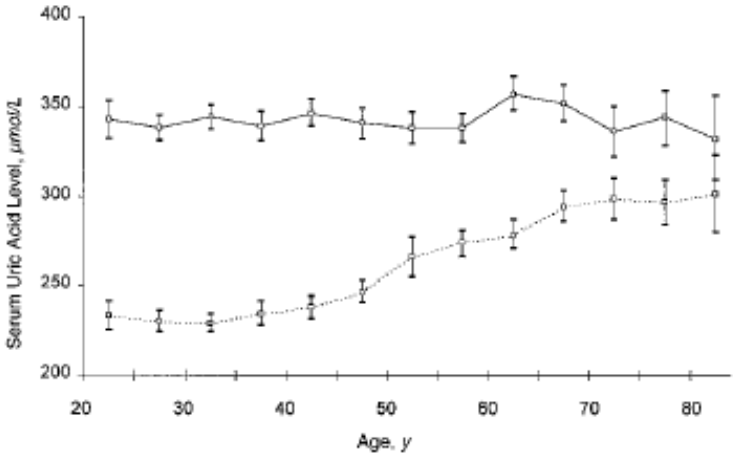



**Figure. Mean serum uric acid level by sex and 5-year age group.** Solid line represents men; dashed line represents women; squares represent values at midpoint of 5-year age group; and vertical bars represent 95% CIs.

Our findings from a community-based prospective study of 6763 adult men and women suggest that an elevated serum uric acid level is not causally associated with increased risk for coronary heart disease, death from cardiovascular disease, or death from all causes. Associations reported in age-adjusted models are probably due to confounding,

# Plasma urate concentration and risk of coronary heart disease: a Mendelian randomisation analysis

*Lancet Diabetes Endocrinol* 2016; 4: 327–36
Published Online January 15, 2016

## Summary

**Background** Increased circulating plasma urate concentration is associated with an increased risk of coronary heart disease, but the extent of any causative effect of urate on risk of coronary heart disease is still unclear. In this study, we aimed to clarify any causal role of urate on coronary heart disease risk using Mendelian randomisation analysis.

**Methods** We first did a fixed-effects meta-analysis of the observational association of plasma urate and risk of coronary heart disease. We then used a conventional Mendelian randomisation approach to investigate the causal relevance using a genetic instrument based on 31 urate-associated single nucleotide polymorphisms (SNPs). To account for potential pleiotropic associations of certain SNPs with risk factors other than urate, we additionally did both a multivariable Mendelian randomisation analysis, in which the genetic associations of SNPs with systolic and diastolic blood pressure, HDL cholesterol, and triglycerides were included as covariates, and an Egger Mendelian randomisation (MR-Egger) analysis to estimate a causal effect accounting for unmeasured pleiotropy.

**Findings** In the meta-analysis of 17 prospective observational studies (166 486 individuals; 9784 coronary heart disease events) a 1 SD higher urate concentration was associated with an odds ratio (OR) for coronary heart disease of 1·07 (95% CI 1·04–1·10). The corresponding OR estimates from the conventional, multivariable adjusted, and Egger Mendelian randomisation analysis (58 studies; 198 598 individuals; 65 877 events) were 1·18 (95% CI 1·08–1·29), 1·10 (1·00–1·22), and 1·05 (0·92–1·20), respectively, per 1 SD increment in plasma urate.

**Interpretation** Conventional and multivariate Mendelian randomisation analysis implicates a causal role for urate in the development of coronary heart disease, but these estimates might be inflated by hidden pleiotropy. Egger Mendelian randomisation analysis, which accounts for pleiotropy but has less statistical power, suggests there might be no causal effect. These results might help investigators to determine the priority of trials of urate lowering for the prevention of coronary heart disease compared with other potential interventions.

**Funding** UK National Institute for Health Research, British Heart Foundation, and UK Medical Research Council.

| | Studies (n)* | N or n:n | Difference in risk factor for a 1 SD higher plasma urate (95% CI) | p value |
|---|---|---|---|---|
| **Continuous variables** | | | | |
| HDL cholesterol (mmol/L) | 4 | 22 669 | −0·08 (−0·087 to −0·065) | <0·0001 |
| LDL cholesterol (mmol/L) | 2 | 19 195 | 0·07 (−0·019 to 0·163) | 0·121 |
| Total cholesterol (mmol/L) | 5 | 68 446 | 0·14 (0·07 to 0·213) | 0·0001 |
| Triglycerides (mmol/L) | 3 | 25 606 | 0·31 (0·216 to 0·393) | <0·0001 |
| Fasting glucose (mmol/L) | 3 | 14 571 | −0·08 (−0·23 to 0·066) | 0·276 |
| Creatinine (mg/L) | 2 | 6696 | 4·43 (1·235 to 7·634) | 0·0066 |
| BMI (kg/m$^2$) | 7 | 84 419 | 1·29 (0·879 to 1·694) | <0·0001 |
| SBP (mm Hg) | 7 | 84 419 | 3·31 (2·498 to 4·128) | <0·0001 |
| DBP (mm Hg) | 4 | 19 033 | 1·95 (0·926 to 2·977) | 0·0002 |
| Age (years) | 3 | 5713 | 0·21 (0·045 to 0·383) | 0·013 |
| eGFR (mL/min/1·73m$^2$) | 2 | 4393 | −4·59 (−4·905 to −4·269) | <0·0001 |
| **Binary traits** | | | | |
| Sex (female *vs* male) | 3 | 3738:1975 | 0·80 (0·746 to 0·865) | <0·0001 |
| Smoking (ever *vs* never) | 2 | 2678:1615 | 1·11 (1·041 to 1·185) | 0·0015 |
| Diabetes (present *vs* absent) | 2 | 517:3877 | 1·07 (0·976 to 1·162) | 0·157 |

SBP=systolic blood pressure. DBP=diastolic blood pressure. eGFR=estimated glomerular filtration rate. *Sources of data are reported in the appendix (p 2).

***Table 1:*** **Observational associations of plasma urate concentration with cardiovascular risk factors**

## Research in context

### Evidence before this study

The observational association between plasma urate and coronary heart disease is well established. However it remains in doubt whether this association is causal. Mendelian randomisation uses naturally occurring genetic variants that are allocated at random and associated with the risk factor of interest as an instrument to infer the causal role of a risk factor in a disease or outcome of interest. Previous Mendelian randomisation studies of plasma urate and risk of coronary heart disease have used single variants that affect plasma urate and reported discrepant findings.

### Added value of this study

Using 31 independent single nucleotide polymorphisms (SNPs) identified as associated with plasma urate concentration from genome-wide association studies, we did a Mendelian randomisation analysis using three complementary approaches. Results from our conventional Mendelian randomisation analysis suggested that plasma urate might have a causal role in coronary heart disease; however, pleiotropic associations of the genetic instrument with several traits including blood pressure, triglycerides, and HDL cholesterol meant that the instrumental variable estimate from conventional Mendelian randomisation could be biased. Results from multivariate and Egger Mendelian randomisation analyses, which account for pleiotropy, both provided weaker evidence for a causal assoication of urate with coronary heart disease, with 95% CIs for both estimates including the null.

### Implications of all the available evidence

Our findings suggest that the causal association, if any, between plasma urate and risk of coronary heart disease is likely to be modest. These data suggest that the observed association between plasma urate and coronary heart disease is probably affected by confounding by risk factors such as blood pressure and LDL cholesterol, HDL cholesterol, and triglycerides. Results of ongoing phase 3 randomised controlled trials will help to clarify this causal association, but any such trials could be underpowered if the predicted efficacy of the therapeutic modification of plasma urate has been based on effect estimates derived from existing observational data.

# Dawson et Walters Br J Clin Pharmacol 2006

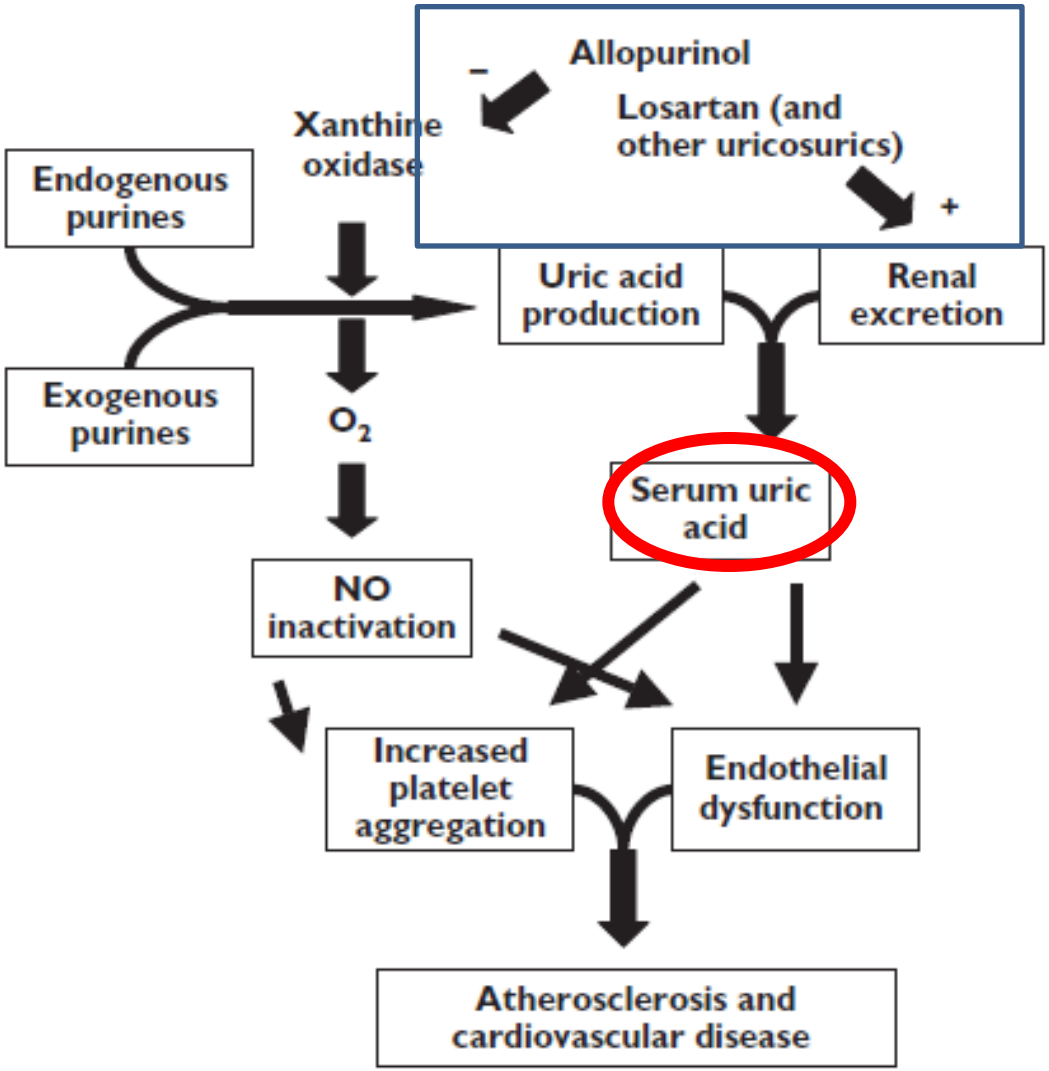


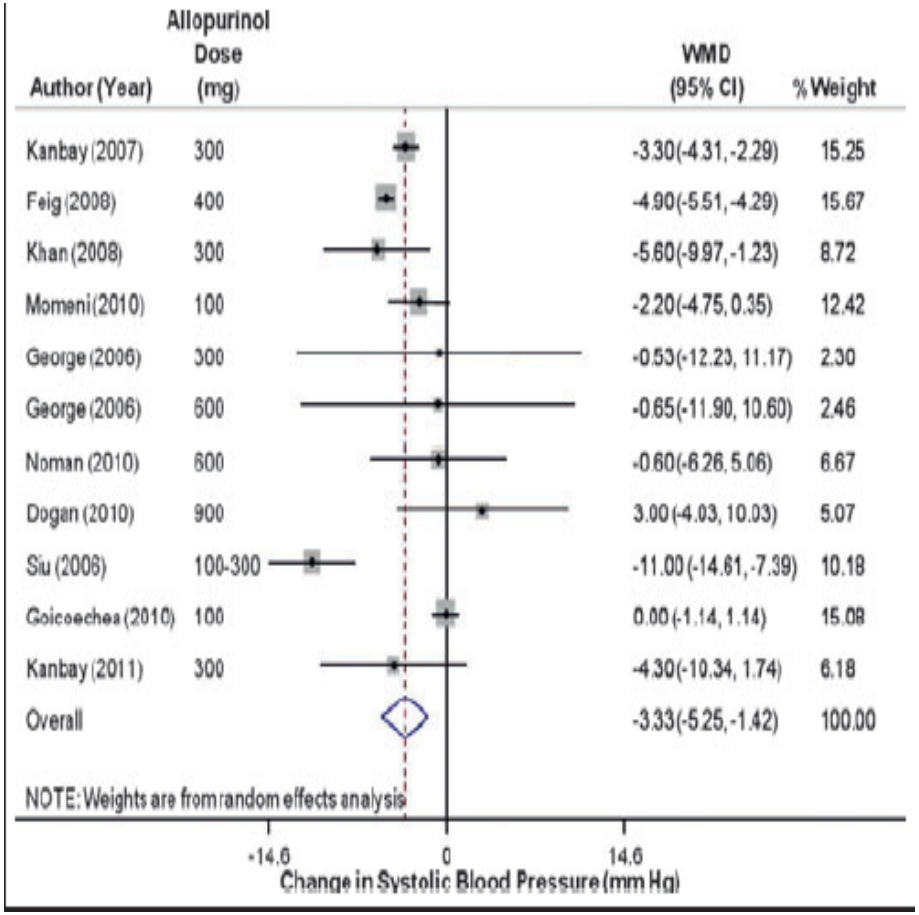

**Figure 1**

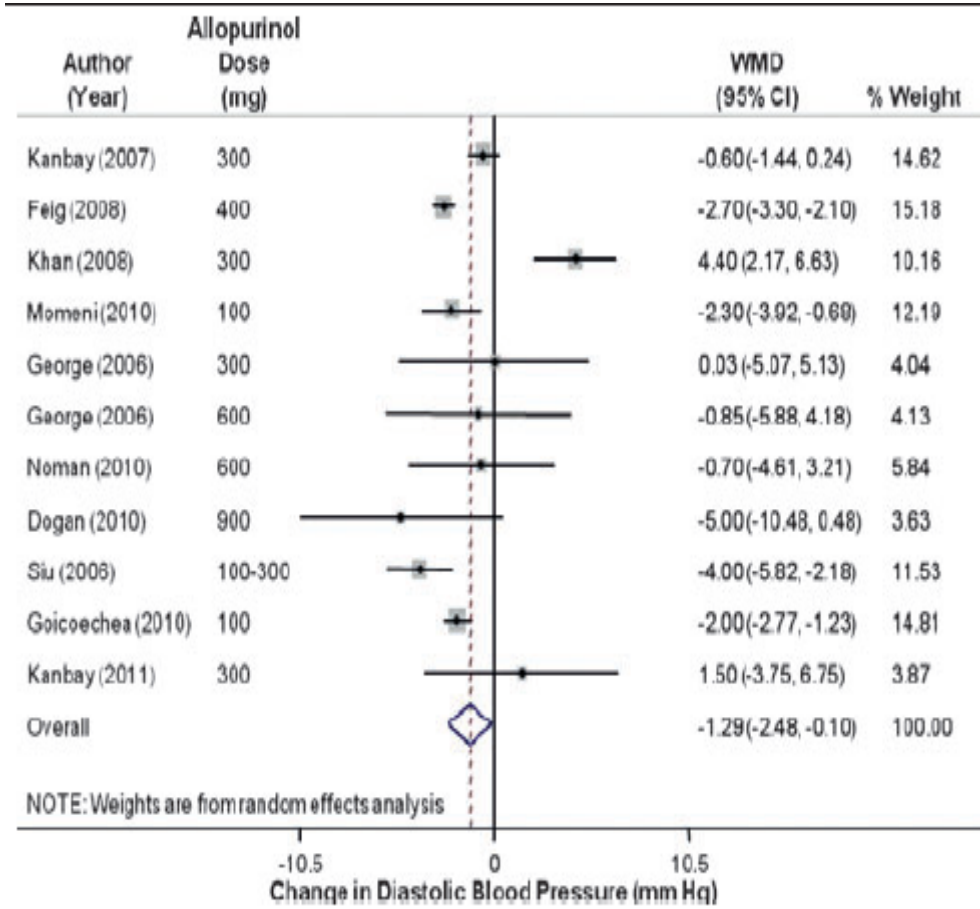
Potential mechanisms by which elevated serum uric acid is related to cardiovascular disease and potential methods of risk reduction

# Effect of Allopurinol on Blood Pressure: A Systematic Review and Meta-Analysis

Vikram Agarwal, MD, MPH;[1] Nidhi Hans, MD, MPH;[2] Franz H. Messerli, MD[1]

*J Clin Hypertens (Greenwich).* 2013;15:435–442.




Diminution de la PA de 3,3 et 1,3 mmHg pour PAS et D

# Allopurinol and Cardiovascular Outcomes in Adults With Hypertension

Rachael L. MacIsaac, Janek Salatzki, Peter Higgins, Matthew R. Walters, Sandosh Padmanabhan, Anna F. Dominiczak, Rhian M. Touyz, Jesse Dawson

*Hypertension*. 2016;67:535-540.

# Allopurinol and Cardiovascular Outcomes in Adults With Hypertension

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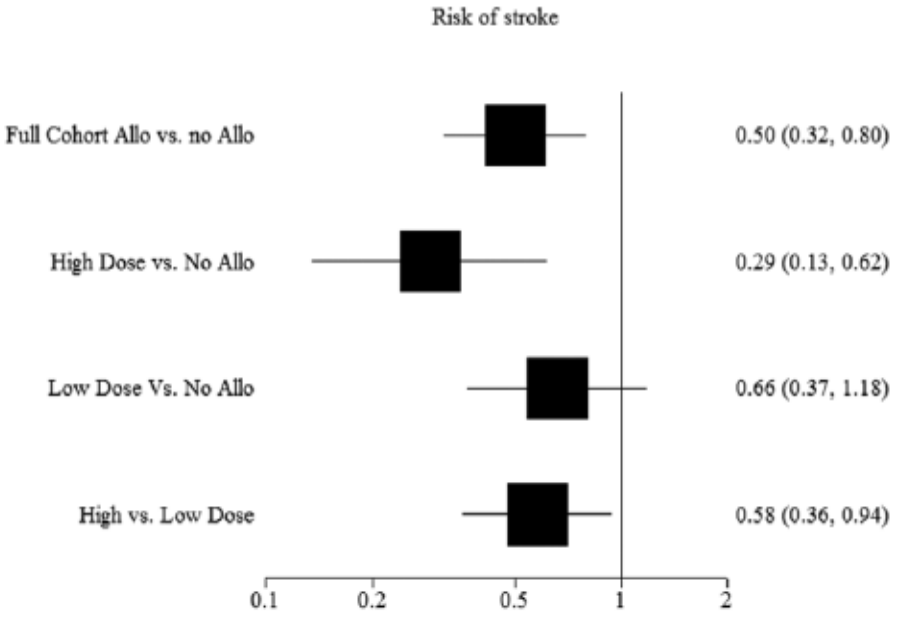
[*Hypertension*. 2016;67:535-540.

Multivariate Cox-proportional hazard models were applied to estimate hazard ratios for stroke and cardiac events (defined as myocardial infarction or acute coronary syndrome) associated with allopurinol use over a 10-year period in adults aged >65 years with hypertension. A propensity-matched design was used to reduce potential for confounding. Allopurinol exposure was a time-dependent variable and was defined as any exposure and then as high (≥300 mg daily) or low-dose exposure. A total of 2032 allopurinol-exposed patients and 2032 matched nonexposed patients were studied. Allopurinol use was associated with a significantly lower risk of both stroke (hazard ratio, 0.50; 95% confidence interval, 0.32–0.80) and cardiac events (hazard ratio, 0.61; 95% confidence interval, 0.43–0.87) than nonexposed control patients.



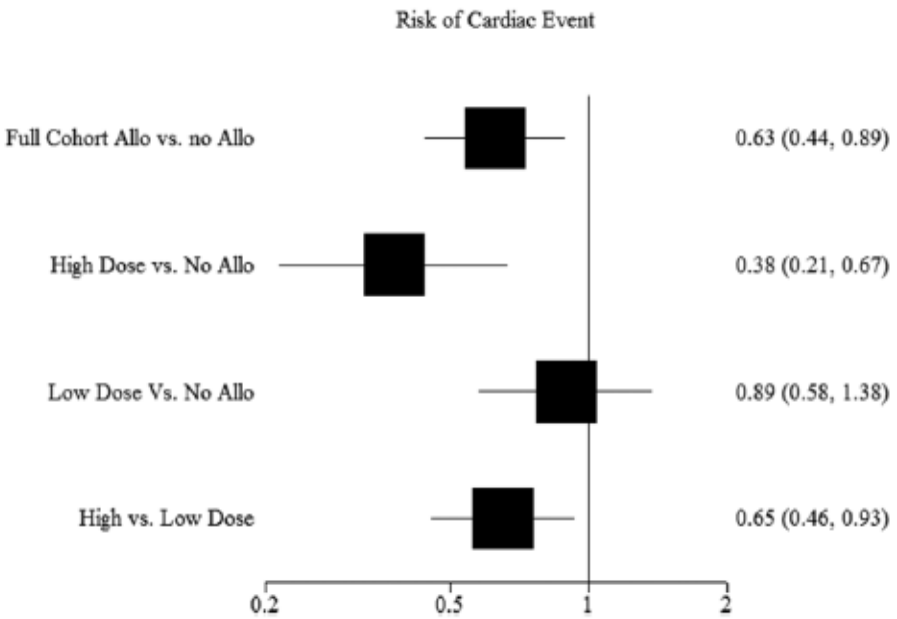




**Figure 2.** Forest plots illustrating the effect of different allopurinol cohorts on outcome. COPD indicates chronic obstructive pulmonary disease; and CPRD, Clinical Practice Research Database.

# Effect of Allopurinol on Cardiovascular Outcomes in Hyperuricemic Patients: A Cohort Study

Kasper Søltoft Larsen, MD, PhD,[a,b,c] Anton Pottegård, MSc Pharm, PhD,[b] Hanne M. Lindegaard, MD, PhD
Jesper Hallas, MD, PhD[a,b]

*The American Journal of Medicine (2016) 129, 299-306*

**OBJECTIVE:** Our objective was to investigate the effect of allopurinol on cardiovascular outcomes in hyperuricemic patients in an observational setting.

**METHODS:** We had access to a study population consisting of all patients from Funen County, Denmark with high urate levels (≥6 mg/dL) from 1992 to 2010. We linked 4 registries; all blood samples, all in- and outpatient contacts in hospitals, all reimbursed prescriptions and causes of death. We identified all incident allopurinol users and matched them 1:1 to nonusers of urate-lowering therapy, with similar urate levels, by using propensity scores. Hazard ratios were calculated using competing risk regression model, with respect to Antiplatelet Trialists' Collaboration composite outcome (myocardial infarction, stroke, or cardiovascular death) and all-cause mortality.

**RESULTS:** Among 65,971 patients with hyperuricemia, we found 7127 patients on allopurinol treatment. In the propensity score-matched cohort we found a hazard ratio of 0.89 (95% confidence interval, 0.81-0.97) for the main outcome among allopurinol treated compared with nonusers of allopurinol. The corresponding hazard ratio for all-cause mortality was 0.68 (95% confidence interval, 0.62-0.74).

**CONCLUSION:** Allopurinol treatment is associated with a decreased cardiovascular risk among hyperuricemic patients.

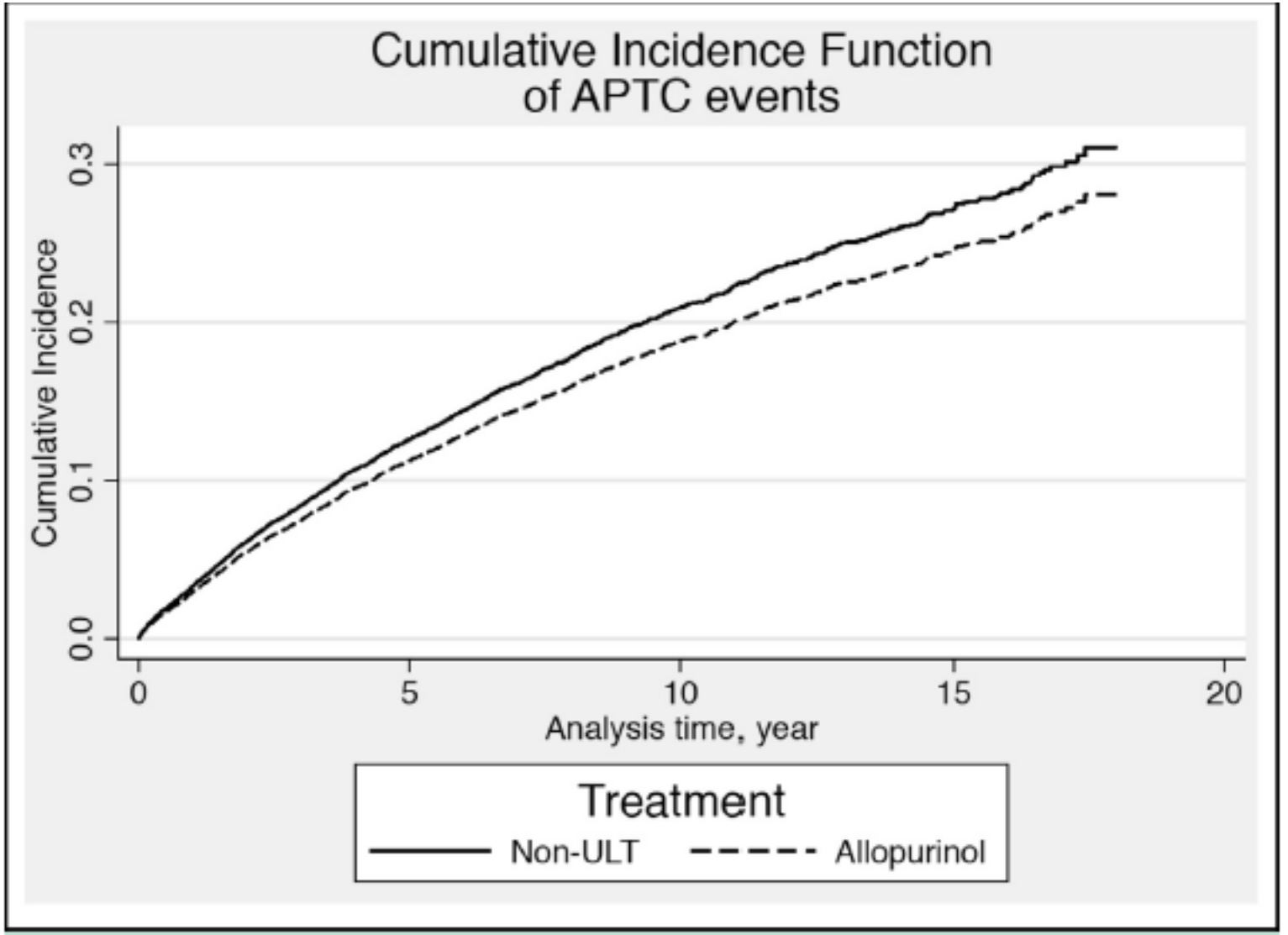
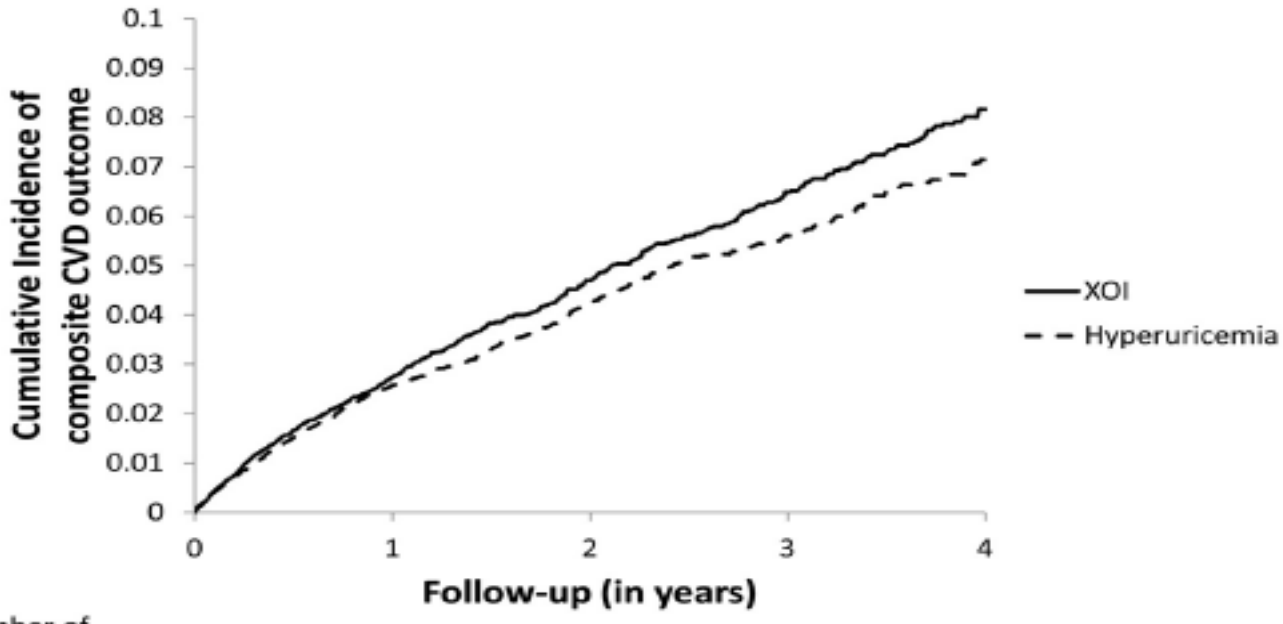



**Figure 2** Cumulative incidence function of main composite cardiovascular outcomes in users and nonusers of allopurinol. APTC = Antiplatelet Trialists' Collaboration; ULT = urate-lowering therapy.

# Effects of Xanthine Oxidase Inhibitors on Cardiovascular Disease in Patients with Gout: A Cohort Study

The American Journal of Medicine, Vol 128, No 6, June 2015




| Number of Patients at Risk | | | | | |
|---|---|---|---|---|---|
| XOI | 22,273 | 1,409 | 260 | 70 | 15 |
| Hyperuricemia | 22,273 | 1,409 | 260 | 70 | 15 |

**Figure 2** Kaplan-Meier curves for cumulative incidence of cardiovascular disease: primary as-treated analysis. CVD = cardiovascular disease; XOI = xanthine oxidase inhibitor. The groups are matched on the propensity score.

A 1 an , 58% seulement sont encore sous IXO

**CONCLUSIONS:** Among patients with gout, initiation of XOI was not associated with an increased or decreased cardiovascular risk compared with those with untreated hyperuricemia. Subgroup analyses adjusting for baseline uric acid levels also showed no association between XOI and cardiovascular risk.

# Impact of allopurinol use on urate concentration and cardiovascular outcome

Li Wei,[1] Isla S. Mackenzie,[1] Yang Chen,[2] Allan D. Struthers[3] & Thomas M. MacDonald[1]

British Journal of Clinical Pharmacology © 2011

A cohort study using a record-linkage database. The study included 7135 patients aged ≥60 years with urate measurements between 2000 and 2002 followed up until 2007. A Cox regression model was used. The association between urate levels, dispensed allopurinol and cardiovascular hospitalization and mortality was determined.

1035 prennent de l'allopurinol

## Table 3

Distribution of urate concentration (mg dl$^{-1}$) in patients aged 60 years and over by allopurinol daily dose

| Daily dose (mg) | Urate concentration (mg dl$^{-1}$) *n* (%) | | | | | Percentage of patients reaching target (≤6 mg dl$^{-1}$) |
|---|---|---|---|---|---|---|
| | ≤6 | 6.01–7 | 7.01–8 | 8.01–9 | >9 | |
| **Men (*n* = 647)** | | | | | | |
| **100** | 60 (20.34) | 60 (43.48) | 50 (60.24) | 41 (63.08) | 37 (56.06) | 24.19 |
| **200** | 39 (13.22) | 33 (23.91) | 9 (10.84) | 13 (20.00) | 2 (3.03) | 40.63 |
| **≥300** | 196 (66.44) | 45 (32.60) | 24 (28.91) | 11 (16.92) | 27 (40.91) | 64.69 |
| **Total** | 295 (100.00) | 138 (100.00) | 83 (100.00) | 65 (100.00) | 66 (100.00) | 45.60 |
| **Average dose** | 253 mg | 191 mg | 172 mg | 153 mg | 184 mg | |
| **Women (*n* = 388)** | | | | | | |
| **100** | 49 (29.17) | 44 (70.97) | 41 (71.93) | 25 (64.10) | 42 (67.74) | 24.38 |
| **200** | 33 (19.64) | 9 (14.52) | 4 (7.02) | 5 (12.82) | 7 (11.29) | 56.90 |
| **≥300** | 860 (51.19) | 9 (14.52) | 12 (21.05) | 9 (23.08) | 13 (20.97) | 66.67 |
| **Total** | 168 (100.00) | 62 (100.00) | 57 (100.00) | 39 (100.00) | 62 (100.00) | 43.30 |
| **Average dose** | 226 mg | 144 mg | 149 mg | 158 mg | 152 mg | |

Univariate and multivariate hazard ratios (HR) for cardiovascular disease and all-cause mortality in patients who had urate concentration measurement

| Allopurinol daily dose | Univariate | | Multivariate† | |
|---|---|---|---|---|
| | HR | 95% Confidence interval | HR | 95% Confidence interval |
| **Cardiovascular outcome** | | | | |
| 100 mg | 1.00 | – | 1.00 | – |
| 200 mg | 0.94 | 0.67–1.33 | 1.01 | 0.70–1.45 |
| ≥300 mg | 0.66 | 0.51–0.86** | 0.69 | 0.50–0.94** |
| **All-cause mortality** | | | | |
| 100 mg | 1.00 | – | 1.00 | – |
| 200 mg | 0.92 | 0.71–1.20 | 0.92 | 0.70–1.21 |
| ≥300 mg | 0.63 | 0.52–0.77** | 0.75 | 0.59–0.94* |

*$P < 0.05$; **$P < 0.01$. †Adjusted for age, gender, social deprivation, urate concentration, gout/hyperuricaemia, renal disease, cardiovascular disease, diabetes mellitus, concurrent use of colchicine, nonsteroidal anti-inflammatory drugs, diabetic medication and cardiovascular drugs during the follow-up and number of cardiovascular prescriptions.

## WHAT THIS STUDY ADDS

- Less than 50% of patients taking allopurinol reached target urate concentration.
- Higher doses of allopurinol were associated with better control of urate and lower risks of both cardiovascular events and mortality in all patients on allopurinol treatment.

British Journal of Clinical Pharmacology © 2011

# Effects of Xanthine Oxidase Inhibition in Hyperuricemic Heart Failure Patients

## The Xanthine Oxidase Inhibition for Hyperuricemic Heart Failure Patient (EXACT-HF) Study

*Circulation*. 2015;131:1763-1771

***Methods and Results***—We randomly assigned 253 patients with symptomatic HF, left ventricular ejection fraction ≤40%, and serum uric acid levels ≥9.5 mg/dL to receive allopurinol (target dose, 600 mg daily) or placebo in a double-blind, multicenter trial. The primary composite end point at 24 weeks was based on survival, worsening HF, and patient global assessment. Secondary end points included change in quality of life, submaximal exercise capacity, and left ventricular ejection fraction.

**Table 4. Clinical Events**

| Event | Allopurinol (n=128) | Placebo (n=125) |
|---|---|---|
| Death | 8 (6) | 7 (6) |
| Cardiovascular death | 5 (4) | 7 (6) |
| Unscheduled outpatient visit | 39 (30) | 38 (30) |
| All-cause hospitalization | 47 (37) | 48 (38) |
| Cardiovascular hospitalization | 30 (23) | 37 (30) |
| HF hospitalization | 22 (17) | 30 (24) |

Data are presented as n (%). All *P* values are >0.05 for comparisons between the groups. HF indicates heart failure.

***Conclusions***—In high-risk HF patients with reduced ejection fraction and elevated uric acid levels, xanthine oxidase inhibition with allopurinol failed to improve clinical status, exercise capacity, quality of life, or left ventricular ejection fraction at 24 weeks.

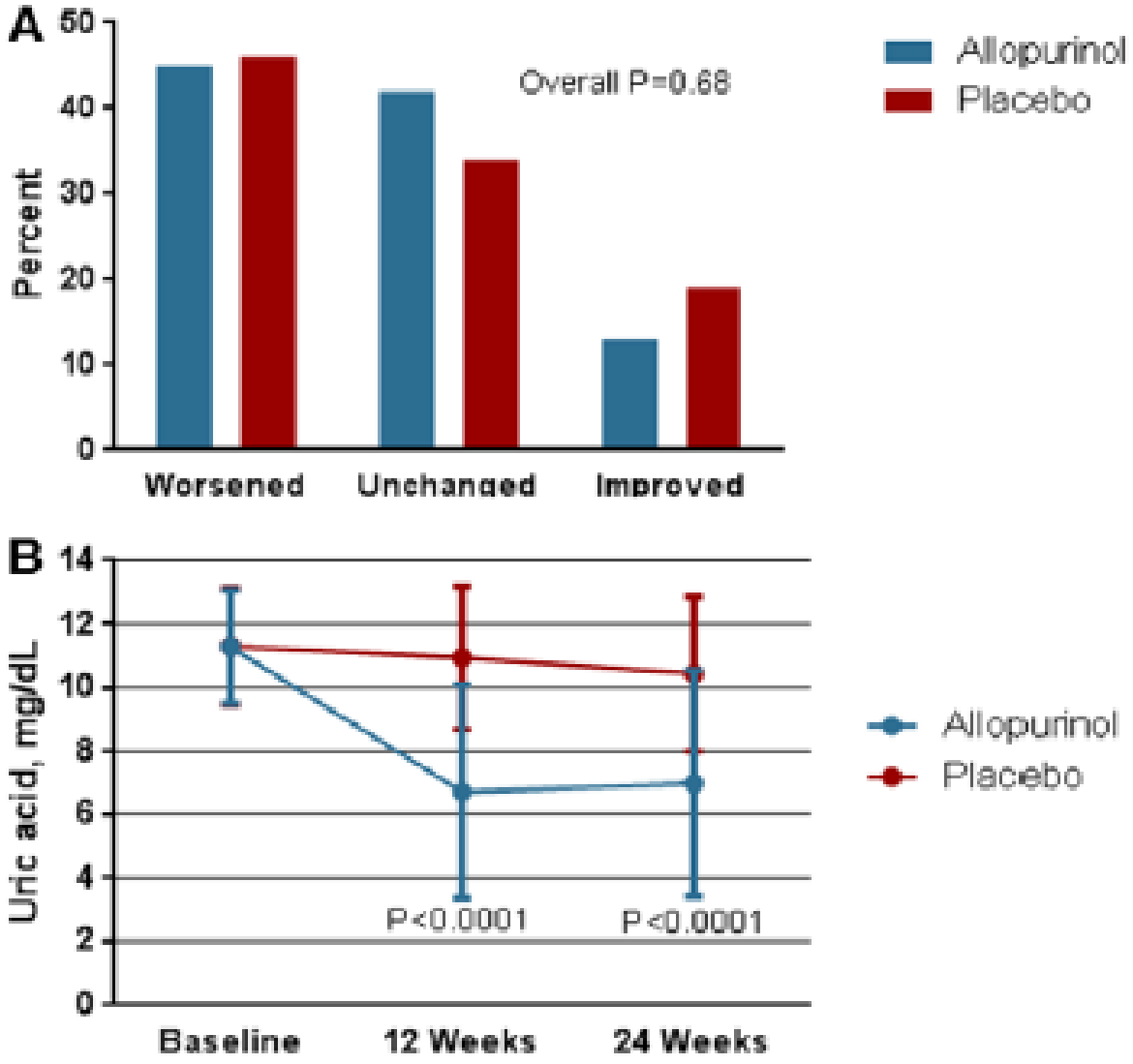
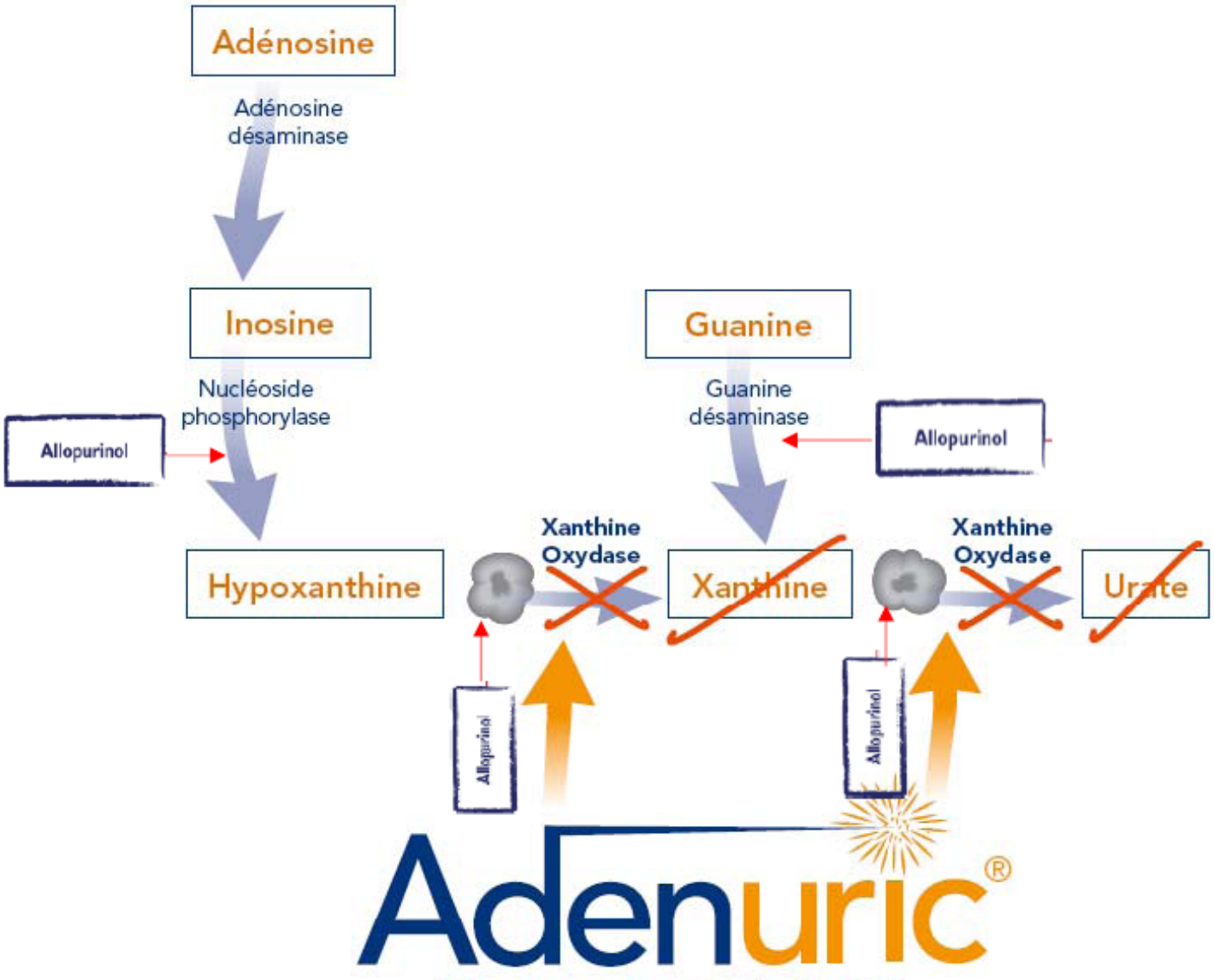



**Figure 2.** Primary composite clinical end point (**A**) and changes in uric acid levels at 12 and 24 weeks (**B**). The *P* value in **A** is

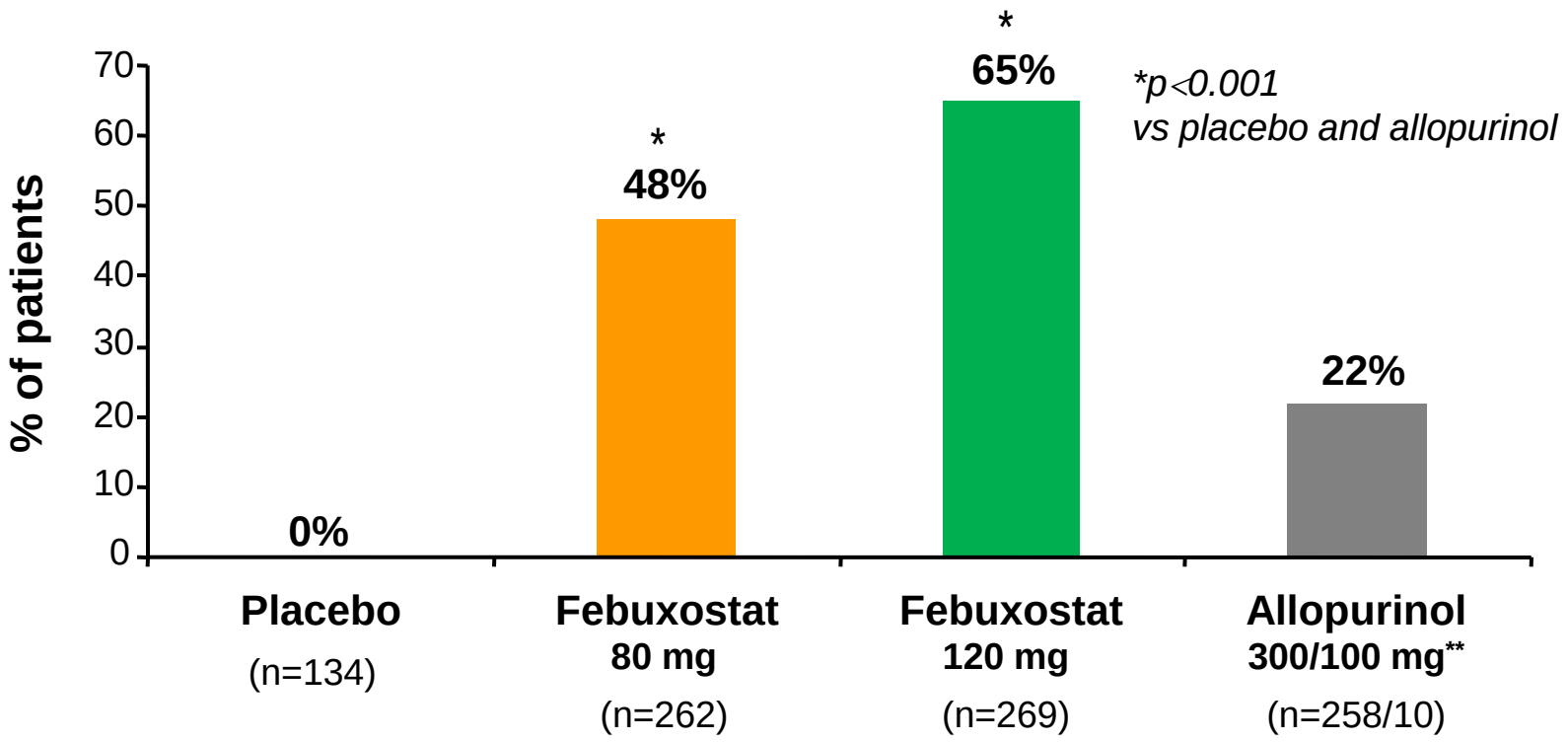
# Mécanisme d'action : blocage puissant de la XO



# Fébuxostat réduit significativement l'uricémie par rapport à l'allopurinol

**APEX study (6 months):**

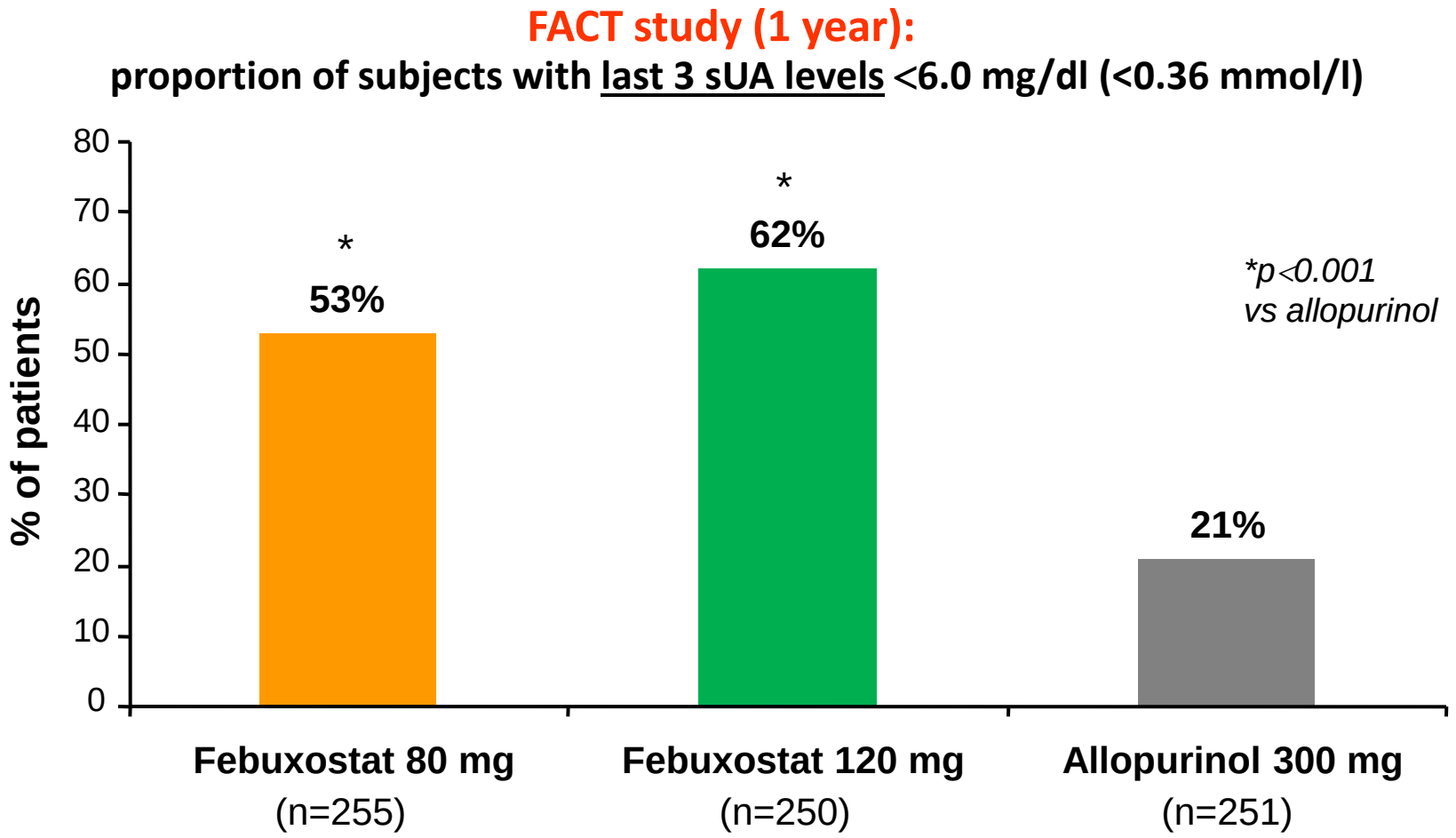
**proportion of subjects with last 3 sUA levels <6.0 mg/dl (<0.36 mmol/l)**




**Within combined allopurinol 300/100 group, allopurinol 100 mg efficacy: 0%; allopurinol 300 mg efficacy: 23%. ITT population: subjects with serum urate level ≥8.0 mg/dl on day -2.

*Adapted from Schumacher HR, et al. Arthritis Rheum 2008; 59:1540-1548.*

# Fébuxostat réduit significativement l'uricémie par rapport à l'allopurinol




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

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

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Cardiovascular Surgery

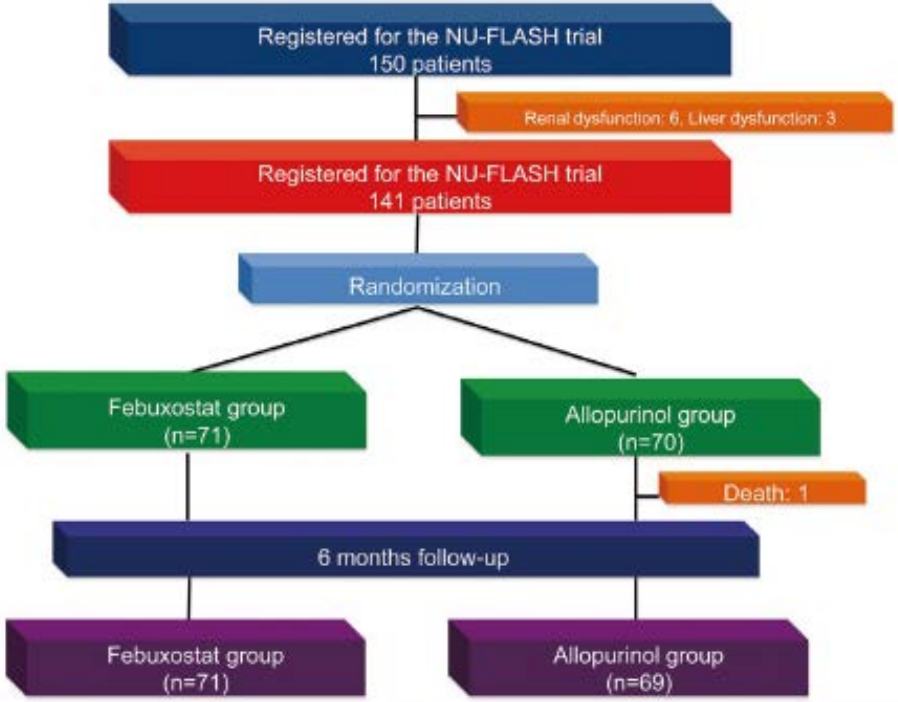
# Comparison of Febuxostat and Allopurinol for Hyperuricemia in Cardiac Surgery Patients (NU-FLASH Trial)

Akira Sezai, MD, PhD; Masayoshi Soma, MD, PhD; Kin-ichi Nakata, MD, PhD; Mitsumasa Hata, MD, PhD; Isamu Yoshitake, MD, PhD; Shinji Wakui, MD, PhD; Hiroaki Hata, MD, PhD; Motomi Shiono, MD, PhD

***Background:*** Febuxostat has been reported to have a stronger effect on hyperuricemia than allopurinol.

***Methods and Results:*** Cardiac surgery patients with hyperuricemia (n=141) were randomized to a febuxostat group or an allopurinol group. The study was single-blind, so the treatment was not known by the investigators. The primary endpoint was serum uric acid (UA) level. Secondary endpoints included serum creatinine, urinary albumin, cystatin-C, oxidized low-density lipoprotein (LDL), eicosapentaenoic acid/arachidonic acid ratio, total cholesterol, triglycerides, LDL, high-density lipoprotein, high-sensitivity C-reactive protein, blood pressure, heart rate, pulse wave velocity (PWV), ejection fraction, left ventricular mass index (LVMI), and adverse reactions. UA level was significantly lower in the febuxostat group than the allopurinol group from 1 month of treatment onward. Serum creatinine, urinary albumin, cystatin-C and oxidized LDL were also significantly lower in the febuxostat group. There were no significant changes in systolic blood pressure, PWV, and LVMI in the allopurinol group, but these parameters all had a significant decrease in the febuxostat group.

***Conclusions:*** Febuxostat was effective for high-risk cardiac surgery patients with hyperuricemia because it reduced UA more markedly than allopurinol. Febuxostat also had a renoprotective effect, inhibited oxidative stress, showed anti-atherogenic activity, reduced blood pressure, and decreased PWV and LVMI. (*Circ J* 2013; **77:** 2043–2049)



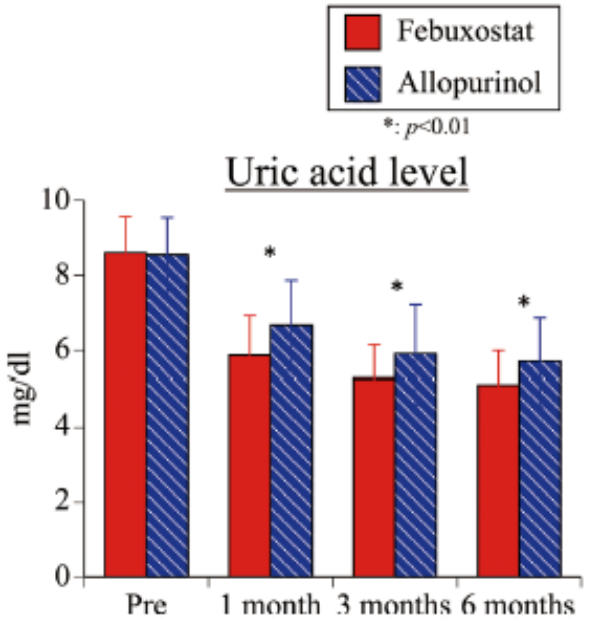




**Figure 2.** Change in uric acid level.

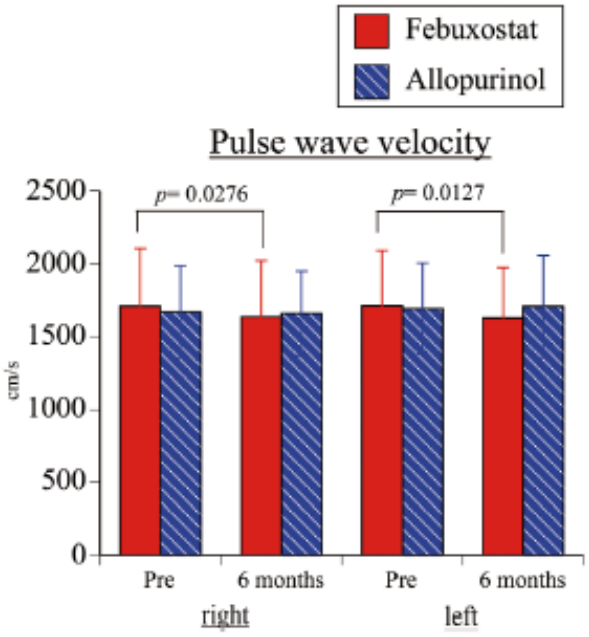



**Figure 4.** Change in pulse wave velocity.

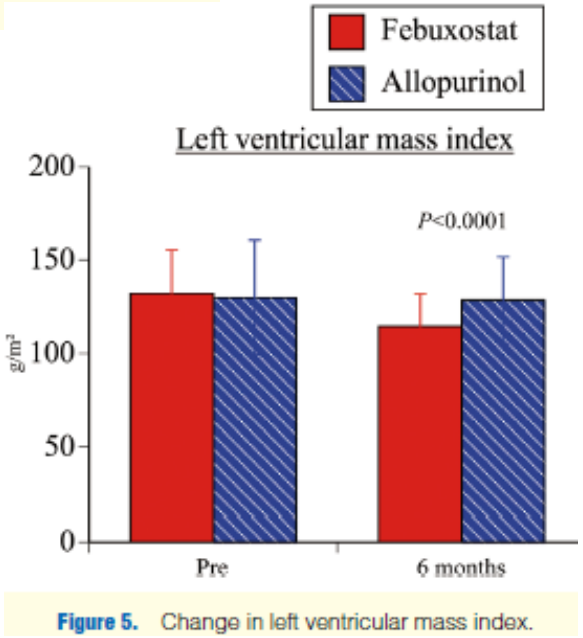
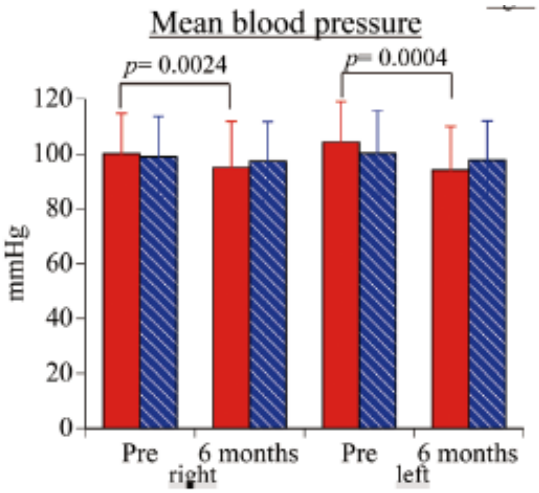



**Figure 5.** Change in left ventricular mass index.



# Stratégies de prise en charge de l'hyperuricémie

- réduire les apports en viandes rouge, en abats, en fruits de mer, sardines
-limiter l'alcool et la consommation de fructose,
- contrôler le poids (correction du Syndrome Métabolique),
- s'hydrater abondamment (eau)
-Revoir les médicaments

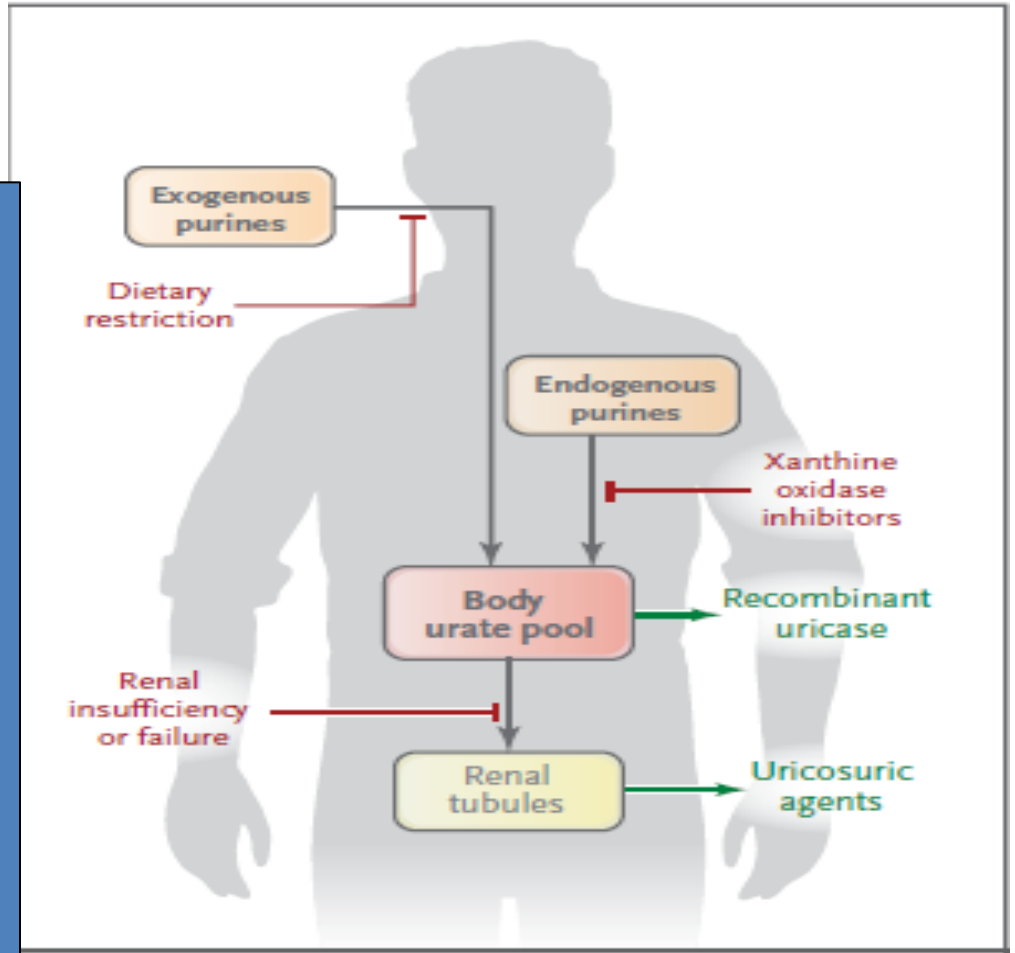



**Figure 2. Management Strategies in Patients with Hyperuricemia.**

N Engl J Med 2011;364:443-52.

# Prise en charge de l'hyperuricémie chez le goutteux

- Suivre l'uricémie qui doit être <6 mg/dl
- SN usage d'un IXO, avec prophylaxie sous colchicine max 1 mg/j pendant au moins 2 à 3 mois,
- En Belgique, IXO: d'abord l'allopurinol puis si EII, C/I ou inefficacité, Fébuxostat.
- Suivi biologique.

# Allopurinol, Febuxostat?

P Delanaye et al RMLg 2012

| | |
|---|---|
| **Précautions d'emploi** | - Pas recommandé chez les patients avec cardiopathie ischémique ou décompensée<br>- Contre-indiqué avec un traitement par mercaptopurine/azathioprine<br>- Contre-indiqué si hypersensibilité à la substance active ou à l'un des excipients<br>- Pas recommandé chez le patient dialysé ou en cas de clairance de créatinine en deçà de 30 ml/min<br>- Prudence avec traitement concomitant par théophylline |

- Pas de preuve absolue actuelle d'une protection CV ou rénale des IXO malgré une tendance
- Fébuxostat: Plus efficace sur l'AU mais plus coûteux, donc plutôt 2$^{ième}$ choix en Belgique
- Prescription d'un IXO si taux UA>> ou risque CV élevé. (expert opinion), Si C/I allopurinol ou inefficacité, Adénuric!

# Faut-il traiter l'hyperuricémie asymptomatique?

- Actuellement non officiellement recommandé mais … peut se discuter vu méfaits potentiels d'une hyperuricémie non traitée
- Ac urique, anti-oxydant à faible dose mais pro-oxydant à forte dose.
- Pas de preuve formelle d'un lien fort entre AU et risque
- Rôle direct de l'acide urique ou plus lié à l'activation de la XO, avec stimulation du stress oxydant ?

# Prendre en charge
# L'ACIDE URIQUE:
# OUI OU NON?

**Il faut croire**
**ceux qui se questionnent**
**et douter de ceux**
**qui croient avoir raison**

**André Gide**

# The Emerging Role of Xanthine Oxidase Inhibition

Claudio Borghi, Giovambattista Desideri

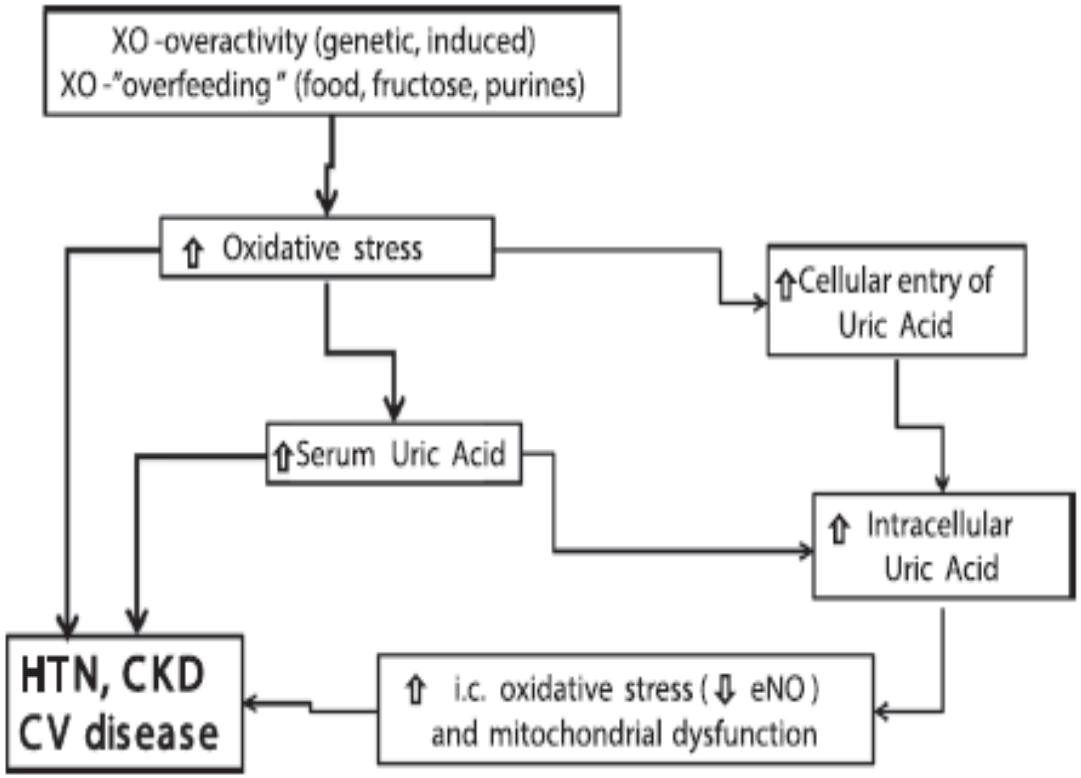



**Figure.** Serum uric acid, oxidative stress, and cardiovascular (CV) disease: a reassessment of an hypothesis. CKD indicates chronic kidney disease; HTN, hypertension; NO, nitric oxide; and XO, xanthine oxidase.

*Hypertension*. 2016;67:496-498.

Table 2
Dose adjustment of allopurinol in patients with chronic renal failure

| Creatinine clearance (ml/min) | Dose |
|---|---|
| 0 | 100 mg every third day |
| 10 | 100 mg every other day |
| 20 | 100 mg/day |
| 40 | 150 mg/day |
| 60 | 200 mg/day |
| 80 | 250 mg/day |
| ≥100 | 300 mg/day |

Modified after Cameron and Simmonds [106].

# Prescription d'adénuric en Belgique

- Si intolérance à l'allopurinol (rash, troubles hémato, hépatite, néphrite T/I)
- Si atteinte hépatique
- Si Insuf rénale (30-60 ml/min) et maintien d'un acide urique élevé sous dose adaptée d'allopurinol
- Si échec de normalisation d'AU (< 6 mg/dl) malgré dose maximale d'allopurinol pendant 10 semaines au moins

Editor's choice
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# Cardiovascular effects and safety of long-term colchicine treatment: Cochrane review and meta-analysis

Lars G Hemkens,[1] Hannah Ewald,[1] Viktoria L Gloy,[1] Armon Arpagaus,[1] Kelechi K Olu,[1] Mark Nidorf,[2] Dominik Glinz,[1] Alain J Nordmann,[1] Matthias Briel[1,3,4]

Hemkens LG, *et al*. *Heart* 2016;**102**:590–596. doi:10.1136/heartjnl-2015-308542

found no evidence supporting colchicine doses above 1 mg/day. Colchicine may have substantial cardiovascular benefits; however, there is sufficient uncertainty about its benefit and harm to indicate the need for large-scale trials to further evaluate this inexpensive, promising treatment in cardiovascular disease.

**Table 3** Results for patients with high cardiovascular risk

| Outcome | Studies (n) | Events (n) | Patients (n) | Summary effect (95% CI) | Heterogeneity ($I^2$), % | Subgroup effect (p Value) |
|---|---|---|---|---|---|---|
| Patients with high cardiovascular risk | | | | | | |
| All-cause mortality | 4 | 29 | 1230 | RR 0.54 (0.26 to 1.14) | 0% | 0.13 |
| Cardiovascular mortality | 2 | 13 | 754 | RR 0.25 (0.02 to 2.66) | 49% | n.c. |
| Myocardial infarction | | | | | | |
| Fatal or non-fatal | 1 | 22 | 532 | RR 0.20 (0.07 to 0.57) | – | n.c. |
| Fatal | 1 | 1 | 532 | RR 0.30 (0.01 to 7.22) | – | n.c. |
| Non-fatal | 1 | 21 | 532 | RR 0.21 (0.07 to 0.61) | – | n.c. |
| Stroke | | | | | | |
| Fatal or non-fatal | 2 | 7 | 754 | OR 0.38 (0.09 to 1.70) | 0% | n.c. |
| Fatal | 2 | 1 | 754 | OR 7.26 (0.14 to 365.85) | – | n.c. |
| Non-fatal | 2 | 6 | 754 | OR 0.23 (0.05 to 1.17) | 0% | n.c. |
| Heart failure | | | | | | |
| Fatal or non-fatal | 1 | 3 | 222 | RR 0.14 (0.01 to 2.69) | – | n.c. |
| Fatal | 1 | 1 | 222 | RR 0.33 (0.01 to 7.95) | – | n.c. |
| Non-fatal | 1 | 2 | 222 | RR 0.20 (0.01 to 4.05) | – | n.c. |
| Hospitalisation | 0 | – | – | – | – | – |
| Cardiovascular intervention | 1 | 9 | 222 | RR 0.79 (0.22 to 2.85) | – | n.c. |
| Adverse event, any | 0 | – | – | – | – | – |
| Adverse event, gastrointestinal | 2 | 62 | 501 | RR 2.41 (1.43 to 4.06) | 0% | n.c. |

n.c., not calculated; OR, Peto's OR; RR, relative risk.

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BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

# Colchicine in cardiac disease: a systematic review and meta-analysis of randomized controlled trials

Subodh Verma[1,4,7*], John W. Eikelboom[9], Stefan M. Nidorf[10], Mohammed Al-Omran[2,4,7], Nandini Gupta[9], Hwee Teoh[1,3,4,5] and Jan O. Friedrich[5,6,8*]

**Conclusions:** Current RCT data suggests that colchicine may reduce the composite rate of cardiovascular adverse outcomes in a range of patients with established cardiovascular disease. Furthermore, colchicine reduces rates of recurrent pericarditis, post-pericardiotomy syndrome, and peri-procedural atrial fibrillation following cardiac surgery. Further RCTs evaluating the potential of colchicine for secondary prevention of cardiovascular events would be of interest.

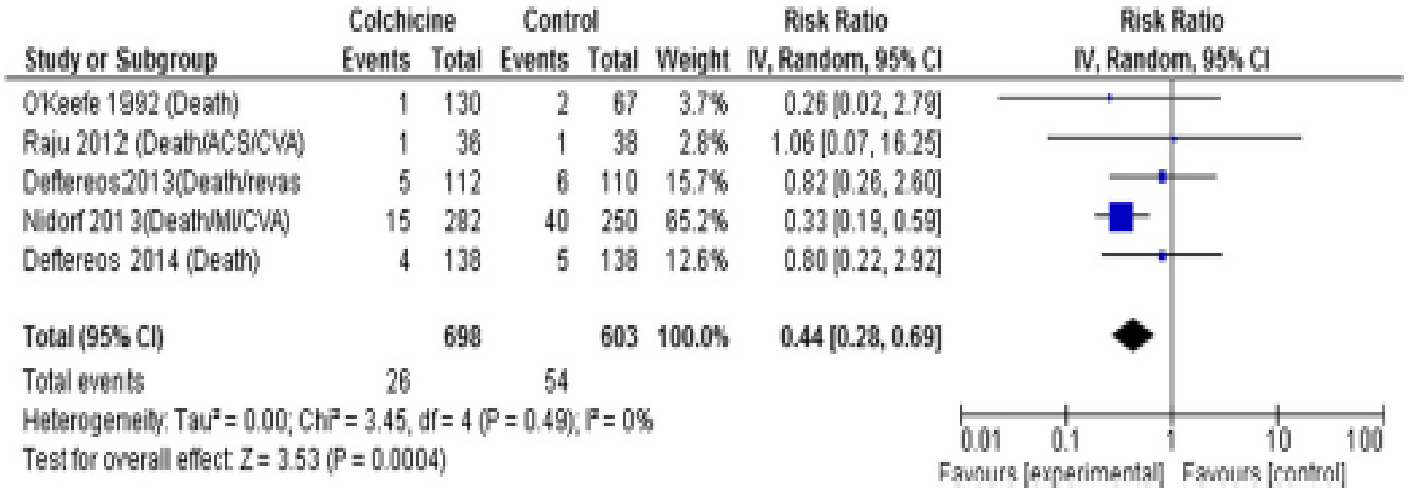



**Fig. 2** Forest Plot for Composite Cardiovascular Outcome. Individual and pooled risk ratios (RR) with 95 % confidence intervals (CI) for randomized controlled trials (RCTs) enrolling patients with cardiovascular diseases comparing colchicine to placebo or control. The pooled RRs with 95 % CI were calculated using random-effects models. Weight refers to the contribution of each study to the overall pooled estimate of treatment effect. Each square and horizontal line denotes the point estimate and 95 % CI for each trial's RR. The diamonds signify the pooled RR; the diamond's centre denotes the point estimate and width denotes the 95 % CI. The composite cardiovascular outcome includes the components indicated for each RCT, except for Nidorf 2013 [14] also includes cardiac arrests. Abbreviations: ACS, acute coronary syndrome; CI, confidence interval; CVA, cerebrovascular attack; IV, inverse variance; MI, myocardial infarction; revasc, revascularization

# The Effect of Fructose on Renal Biology and Disease

Richard J. Johnson,* L. Gabriela Sanchez-Lozada,† and Takahiko Nakagawa*

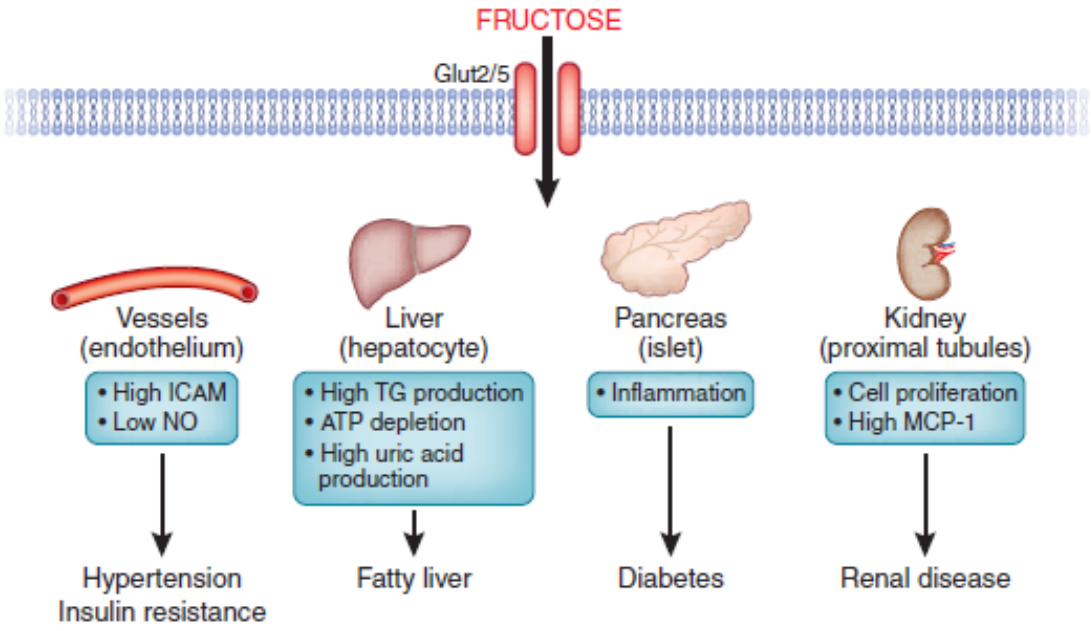



**Figure 2.** Effects of fructose in the development of hypertension, fatty liver, diabetes, and renal disease.

# Febuxostat

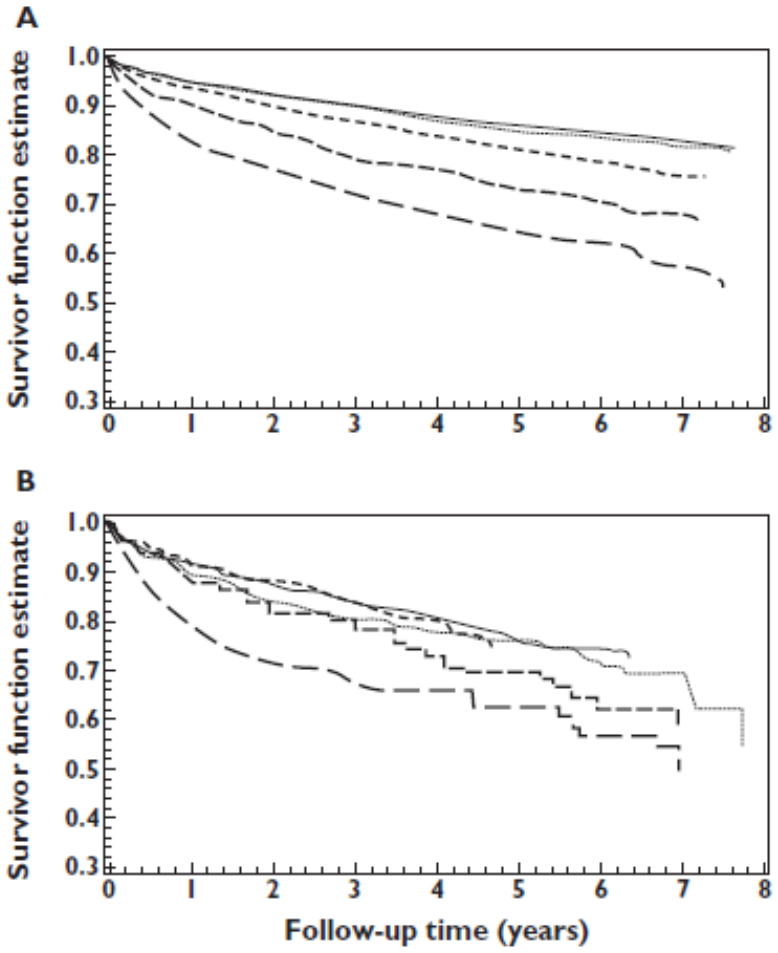
| | Adenuric® Febuxostat |
|---|---|
| **POSOLOGIE** | 1 comprimé par jour |
| **DOSE RECOMMANDÉE** | 80 mg une fois/jour<br>Augmenter la dose à 120 mg si l'objectif thérapeutique d'une uricémie ≤ 6mg/dl n'est pas atteint après 2-4 semaines de traitement. |
| **PAS D'AJUSTEMENT DE LA DOSE** | Insuffisance rénale légère à modérée |
| | Insuffisance hépatique légère (80mg) |
| | Les personnes âgées |
| **PAS D'INTERACTION MEDICAMENTEUSE** | Diurétiques (1) |
| | Warfarine (2) |

(1) Grabowski et al, British Journal of Clinical Pharmacology,2010 mar: 1365-2125
(2) Xenobiotica 2008 May; 38(5):496-510

# Table 1

Characteristics of patients by allopurinol use status

| | Allopurinol group *n* (%) | Non-ULT group *n* (%) | *P*-value |
|---|---|---|---|
| Number | 1035 | 6042 | – |
| Gender | | | |
| Men | 647 (62.5) | 2843 (47.1) | <0.01 |
| Women | 388 (37.5) | 3199 (52.9) | – |
| Age (mean, SD) | 72.6 (7.8) | 72.4 (7.1) | 0.43 |
| Urate concentration (mg dl$^{-1}$) | | | |
| ≤6 | 463 (44.7) | 2774 (45.9) | 0.65 |
| 6.01–7 | 200 (19.3) | 1162 (19.2) | – |
| 7.01–8 | 140 (13.5) | 871 (14.4) | – |
| 8.01–9 | 104 (10.1) | 544 (9.0) | – |
| >9 | 128 (12.4) | 691 (11.4) | – |
| Previous hospitalization | | | |
| Diabetes mellitus | 6 (0.6) | 17 (0.3) | 0.12 |
| Gout or hyperuricaemia | 19 (1.8) | 26 (0.4) | <0.01 |
| Renal disease | 77 (7.4) | 209 (3.5) | <0.01 |
| Cardiovascular disease | 100 (9.7) | 437 (7.2) | <0.01 |
| Hypertension | 8 (0.8) | 38 (0.6) | 0.59 |




## Figure 1

Kaplan–Meier plot of the Antiplatelet Trialists' Collaboration (APTC) event rate by urate concentration in non-users of urate-lowering therapy (non-ULT users; A) and in allopurinol users (B). ≤6 mg dl$^{-1}$ (——); 6.01–7 mg dl$^{-1}$ (——); 7.01–8 mg dl$^{-1}$ (– – –); 8.01–9 mg dl$^{-1}$ (— —); >9 mg dl$^{-1}$ (— ·)

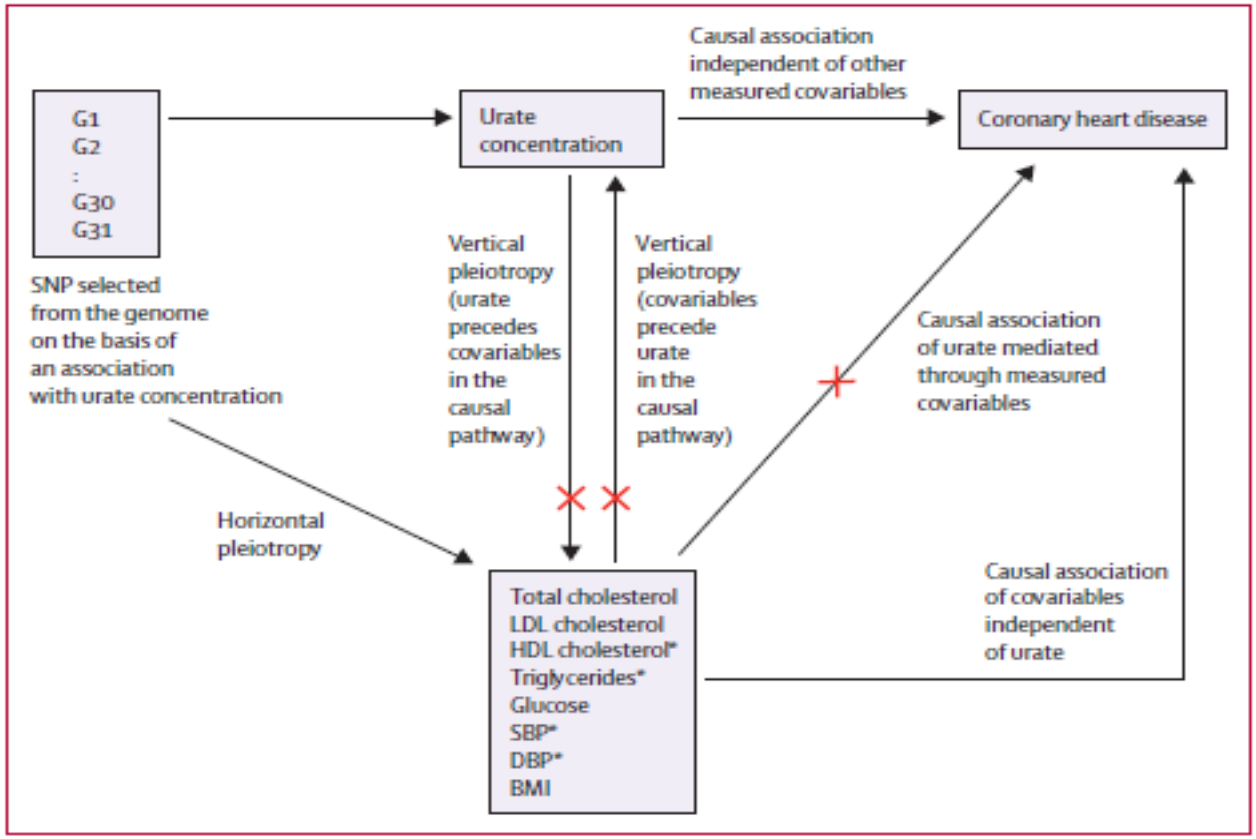



***Figure 1:*** **Conceptual framework for the Mendelian randomisation analysis of urate concentration and risk of coronary heart disease**

G1–31 are genes containing urate variants that together form the multilocus instrument for urate concentration. Horizontal pleiotropy occurs when the instrument associates with traits other than urate that become confounders if also associated with coronary heart disease. Vertical pleiotropy occurs if their level is affected by urate, and does not invalidate Mendelian randomisation analysis. SNP=single nucleotide polymorphism. SBP=systolic blood pressure. DBP=diastolic blood pressure. *Multivariable Mendelian randomisation, including DBP, SBP, HDL cholesterol, and triglycerides as covariates was used to account for possible horizontal pleiotropy arising from association of the instrument with these variables. The effect of the adjustment is to block the paths indicated with red crosses. Egger Mendelian randomisation analysis was used to account for unknown or unmeasured pleiotropic confounders.

**Table. Baseline Demographics for Initial Matched Cohort**

| Variable | Any Allopurinol Exposure | | *P* Value | All (n=4064) |
|---|---|---|---|---|
| | No (n=2032) | Yes (n=2032) | | |
| Age, y, mean (SD) | 73.04 (5.78) | 73.13 (5.74) | 0.624 | 73.08 (5.76) |
| BMI, mean (SD)* | 26.60 (4.03) | 28.25 (4.33) | <0.001 | 27.43 (4.27) |
| SBP base, mean (SD) | 156.27 (20.03) | 156.53 (21.17) | 0.683 | 156.40 (20.60) |
| DBP base, mean (SD) | 85.98 (10.12) | 85.90 (10.16) | 0.815 | 85.94 (10.14) |
| Weight, kg, mean (SD)† | 74.34 (15.19) | 79.33 (15.28) | <0.001 | 76.84 (15.43) |
| Creatinine, mean (SD)‡ | 105.77 (34.90) | 130.41 (41.77) | <0.001 | 113.27 (38.81) |
| Sex (women), n (%) | 782 (38.48%) | 781 (38.44%) | 0.974 | 1653 (38.46%) |
| Smoking status (yes), n (%) | 206 (10.14%) | 207 (10.19%) | 0.959 | 413 (10.16%) |
| Diabetes mellitus (yes), n (%) | 483 (23.77%) | 592 (29.13%) | <0.001 | 1075 (26.45%) |
| IHD (yes), n (%) | 569 (28.00%) | 603 (29.68%) | 0.239 | 1172 (28.84%) |
| Relevant statin exposure (yes), n (%) | 565 (27.81%) | 574 (28.25%) | 0.753 | 1139 (28.03%) |
| NSAID exposure (yes), n (%) | 1615 (79.48%) | 1616 (79.53%) | 0.970 | 3231 (79.50%) |
| Aspirin exposure (yes), n (%) | 1087 (53.49%) | 1070 (52.66%) | 0.593 | 2157 (53.08%) |
| ACEI exposure (yes); n (%) | 999 (49.16%) | 1113 (54.77%) | <0.001 | 2112 (51.97%) |
| β-Blocker exposure (yes), n (%) | 1047 (51.53%) | 1001 (49.26%) | 0.149 | 2048 (50.39%) |
| Calcium channel blocker exposure (yes), n (%) | 1150 (56.59%) | 1014 (49.90%) | <0.001 | 2164 (53.25%) |
| Diuretic exposure (yes), n (%) | 1600 (78.74%) | 1642 (80.81%) | 0.101 | 3242 (79.77%) |
| ARB exposure (yes), n (%) | 231 (11.37%) | 231 (11.37%) | 1.00 | 462 (11.37%) |
| α-Blocker exposure (yes), n (%) | 403 (19.83%) | 425 (20.92%) | 0.392 | 828 (20.37%) |

*Hypertension*. 2016;67:535-540.