LÉČIT ASYMPTOMATICKOU HYPERURIKÉMII?

NE

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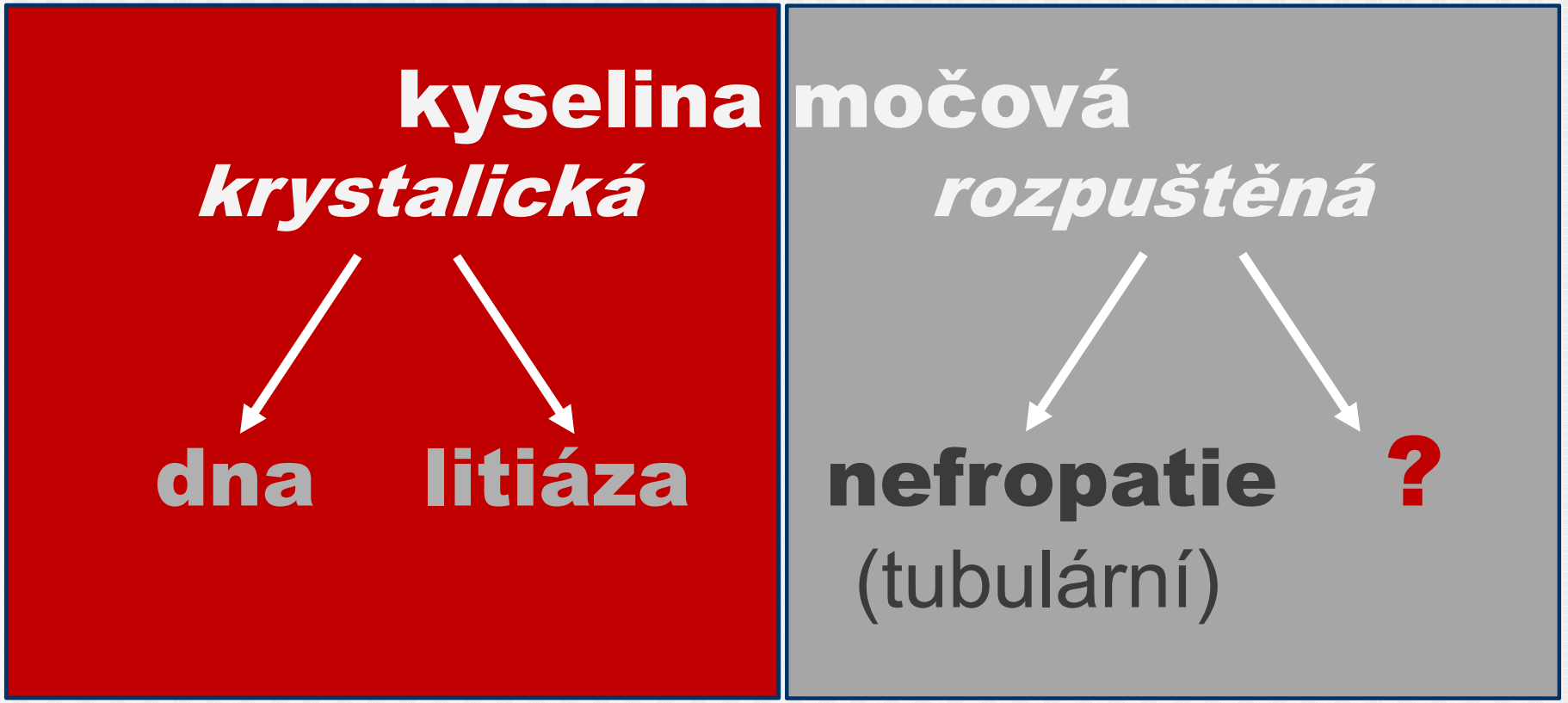
3. LF UK Praha

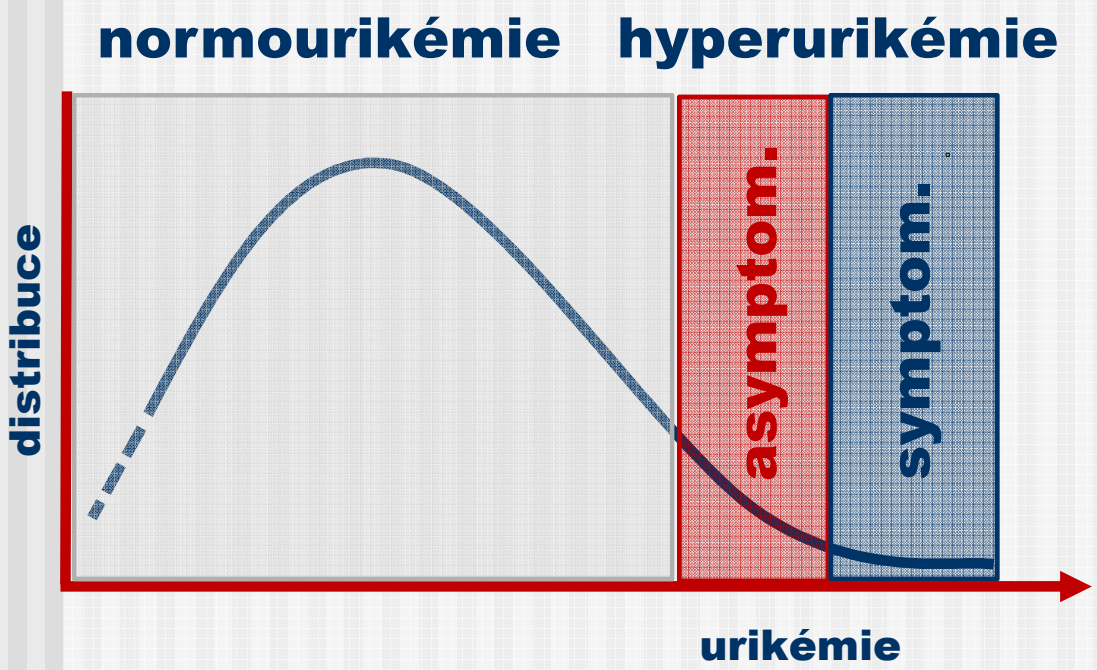
XXV výroční sjezd ČKS,

Brno 2017

Význam kys. močové v etiopatogenezi a konsenzus o indikaci k léčbě

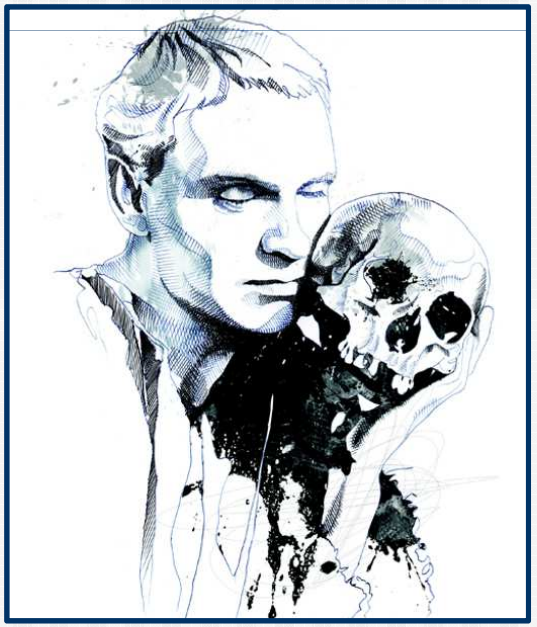


Léčit asymptomatickou hyperurikémii?

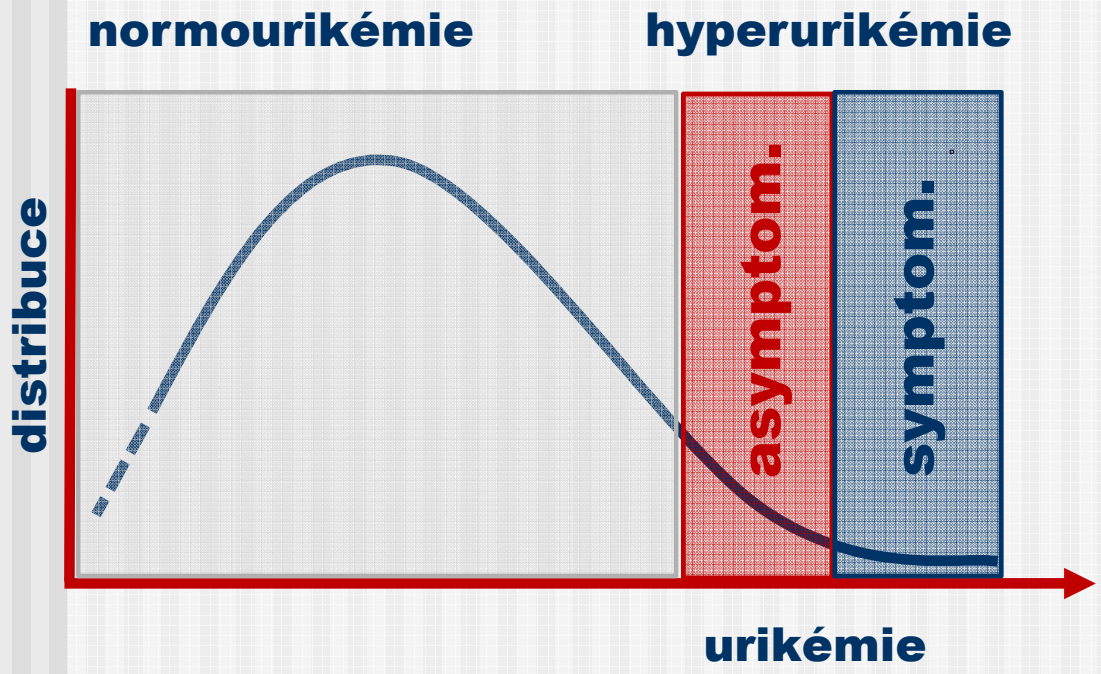


- **otázka hamletovská**

„léčit či neléčit?“



Léčit asymptomatickou hyperurikémii?

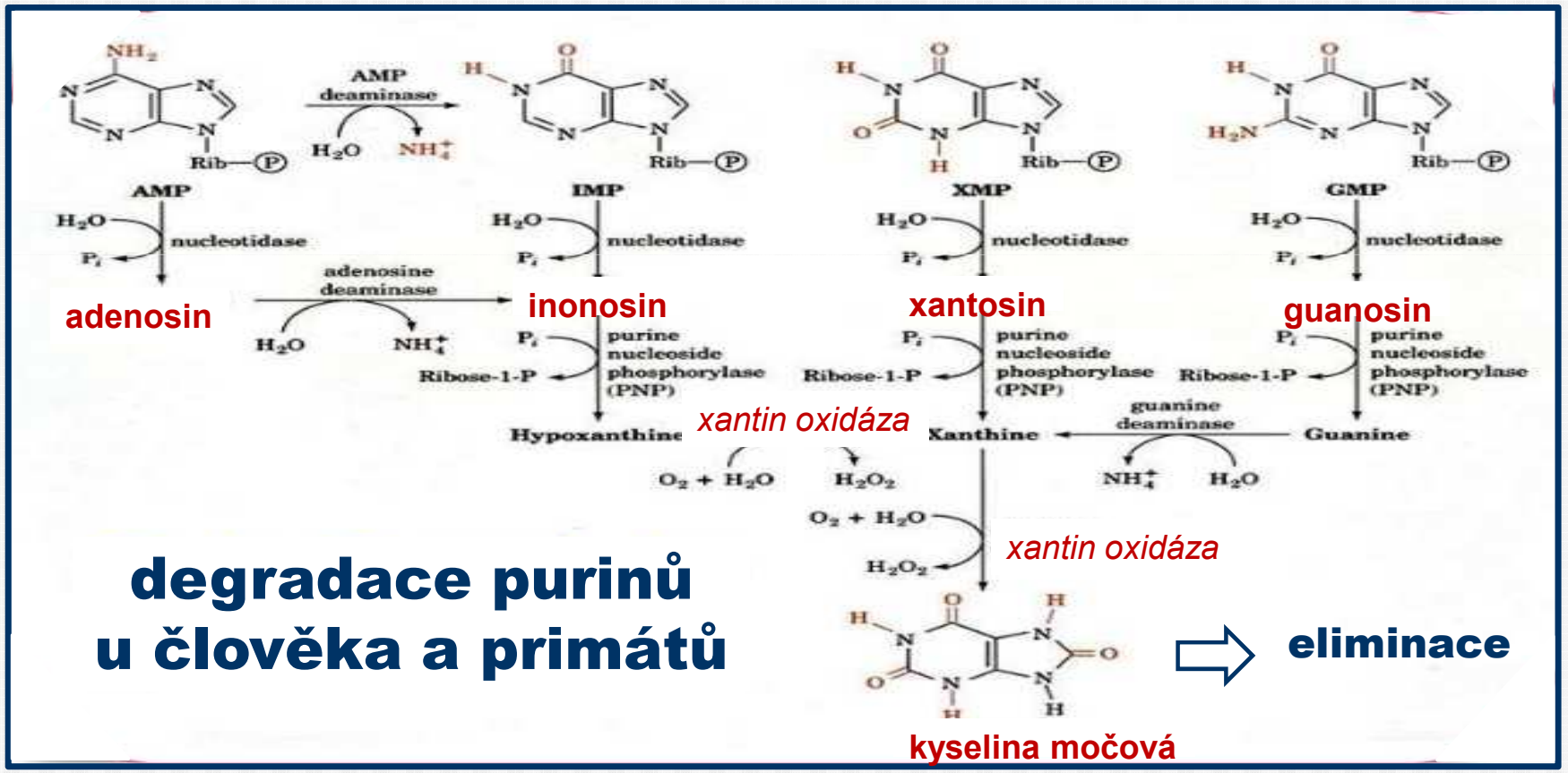


- **otázka odborná**
  - Biol. význam kys. močové?
  - Máme doklady o účinnosti a bezpečnosti léčby?
- **otázka forenzní**
  - Co říkají doporučené postupy?
  - Co uvádí SPC?

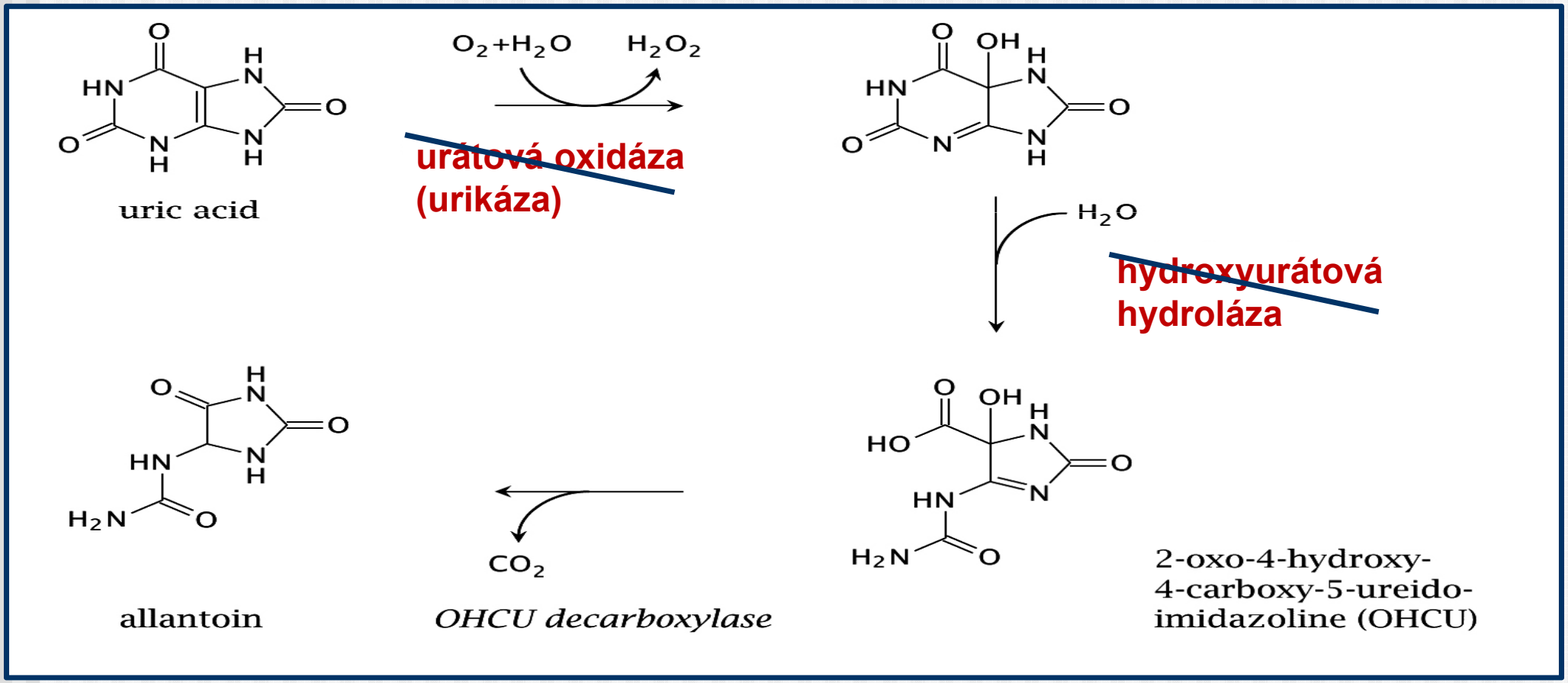
Má kyselina močová biologickou funkci či je pouze toxickým degradačním produktem?

- **nálezy evoluční biologie**
  - defekt konverze kyseliny močové na alantoin s následným zvýšením její hladiny nevznikl náhodně a může být evoluční výhodou
- **důvody fyziologické**
  - organizmus většinu (90%) kyseliny močové z primární moče v nefronu reabsorbuje

Biodegradace nukleotidů na kys. močovou



Biodegradace nukleotidů na alantoin – defekt genů na dvou místech před 15 mil. let

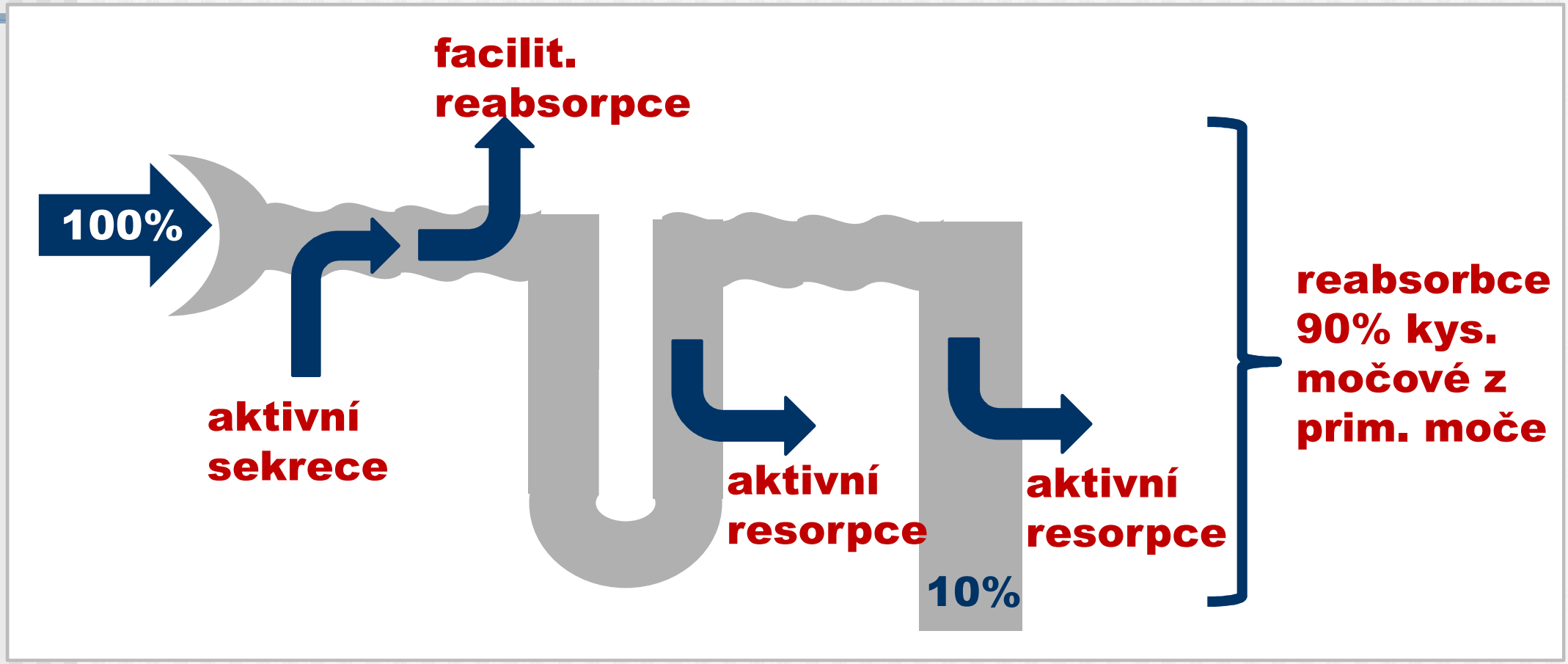


Závěr evoluční biologie

- „Vzhledem k tomu, že k vyřazení funkčního genu proběhlo během evoluce před 15 mil. lety souběžně na dvou místech, je nepravděpodobné, že by se tomu stalo náhodně. Data podporují hypotézu, že ztráta enzymů může být evoluční výhodou“

Wu, X., Muzny, D.M., Chi Lee, C. et al. J Mol Evol (1992) 34: 78. doi:10.1007/BF00163854

Renální eliminace kys. močové - souhra 7 transportních proteinů



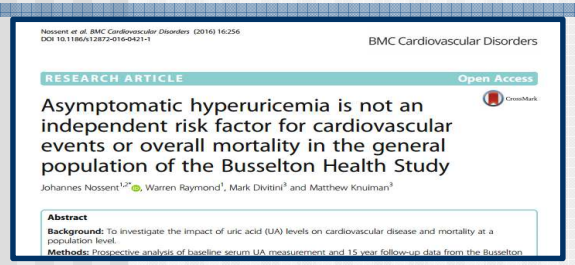
Nature Clinical Practice Oncology (2006) **3**, 438-447, doi:10.1038/ncponc0581

Odborné důvody pro/proti léčbě asymptomatické hyperurikémie

- Řada studií dokládá asociaci hyperurikémie s hypertenzí, dyslipidemií, ICHS i srdečním selháním.
- Není jasné, zda se jedná o vztah kausální. Pro příčinnou souvislost mezi hyperurikémií a hypertenzí či KVO jsou výsledky kontraverzní.
- Pro léčbu asymptomatické hyperurikémie nejsou validní data.

Asociační studie pro ICHS

(u asymptomatické a symptomatické hyperurikémie)



Nossent *et al. BMC Cardiovascular Disorders* (2016) 16:256
DOI 10.1186/s12872-016-0421-1

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

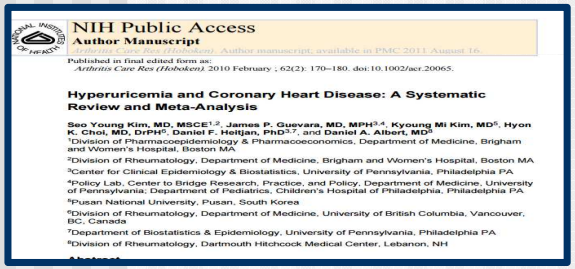
Asymptomatic hyperuricemia is not an independent risk factor for cardiovascular events or overall mortality in the general population of the Busselton Health Study

Johannes Nossent[1,2*], Warren Raymond[1], Mark Divitini[3] and Matthew Knuiman[3]

Abstract

Background: To investigate the impact of uric acid (UA) levels on cardiovascular disease and mortality at a population level.

Methods: Prospective analysis of baseline serum UA measurement and 15 year follow-up data from the Busselton



NIH Public Access
Author Manuscript
Arthritis Care Res (Hoboken). Author manuscript; available in PMC 2011 August 16.

Published in final edited form as:
Arthritis Care Res (Hoboken). 2010 February ; 62(2): 170–180. doi:10.1002/acr.20065.

Hyperuricemia and Coronary Heart Disease: A Systematic Review and Meta-Analysis

Seo Young Kim, MD, MSCE[1,2], James P. Guevara, MD, MPH[3,4], Kyoung Mi Kim, MD[5], Hyon K. Choi, MD, DrPH[6], Daniel F. Heitjan, PhD[3,7], and Daniel A. Albert, MD[8]

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[4]Policy Lab, Center to Bridge Research, Practice, and Policy, Department of Medicine, University of Pennsylvania; Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia PA

[5]Pusan National University, Pusan, South Korea

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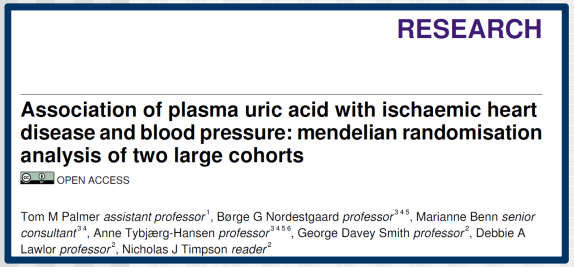


RESEARCH

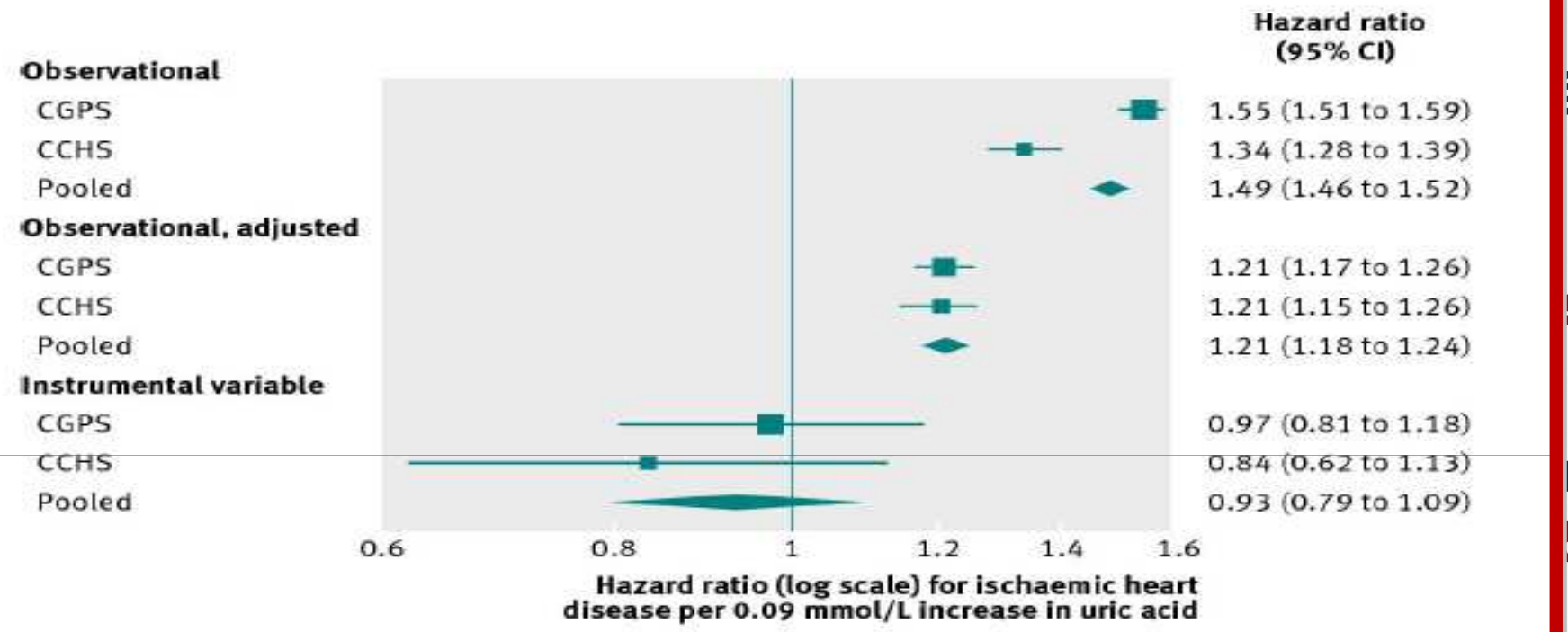
Association of plasma uric acid with ischaemic heart disease and blood pressure: mendelian randomisation analysis of two large cohorts

OPEN ACCESS

Tom M Palmer *assistant professor*[1], Børge G Nordestgaard *professor*[3 4 5], Marianne Benn *senior consultant*[3 4], Anne Tybjærg-Hansen *professor*[3 4 5 6], George Davey Smith *professor*[2], Debbie A Lawlor *professor*[2], Nicholas J Timpson *reader*[2]

- **Hyperurikémie je asociována s rizikem KV mortality pouze u probandů se dnou a s přítomnými KV chorobami.**
- **Po adjustaci bylo sdružené RR symptomatické i asymptomatické hyperurikémie 1,09 (95% CI: 1,03-1,16) pro výskyt KV onemocnění.**
- **Avšak, při užití genotypizace příčin hyperurikémie, přestala být causální asociace mezi urikémií, ICHS a TK přítomna.**

1) BMC Cardiovascular Disorders (2016) 16:256 DOI 10.1186/s12872-016-0421-1, 2) Arthritis Care Res (Hoboken). 2010; 62(2): 170–180. doi:10.1002/acr.20065, 3) *BMJ* 2013;347:f4262 doi: 10.1136/bmj.f4262 (2013)



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KV

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5% CI:

RESEARCH

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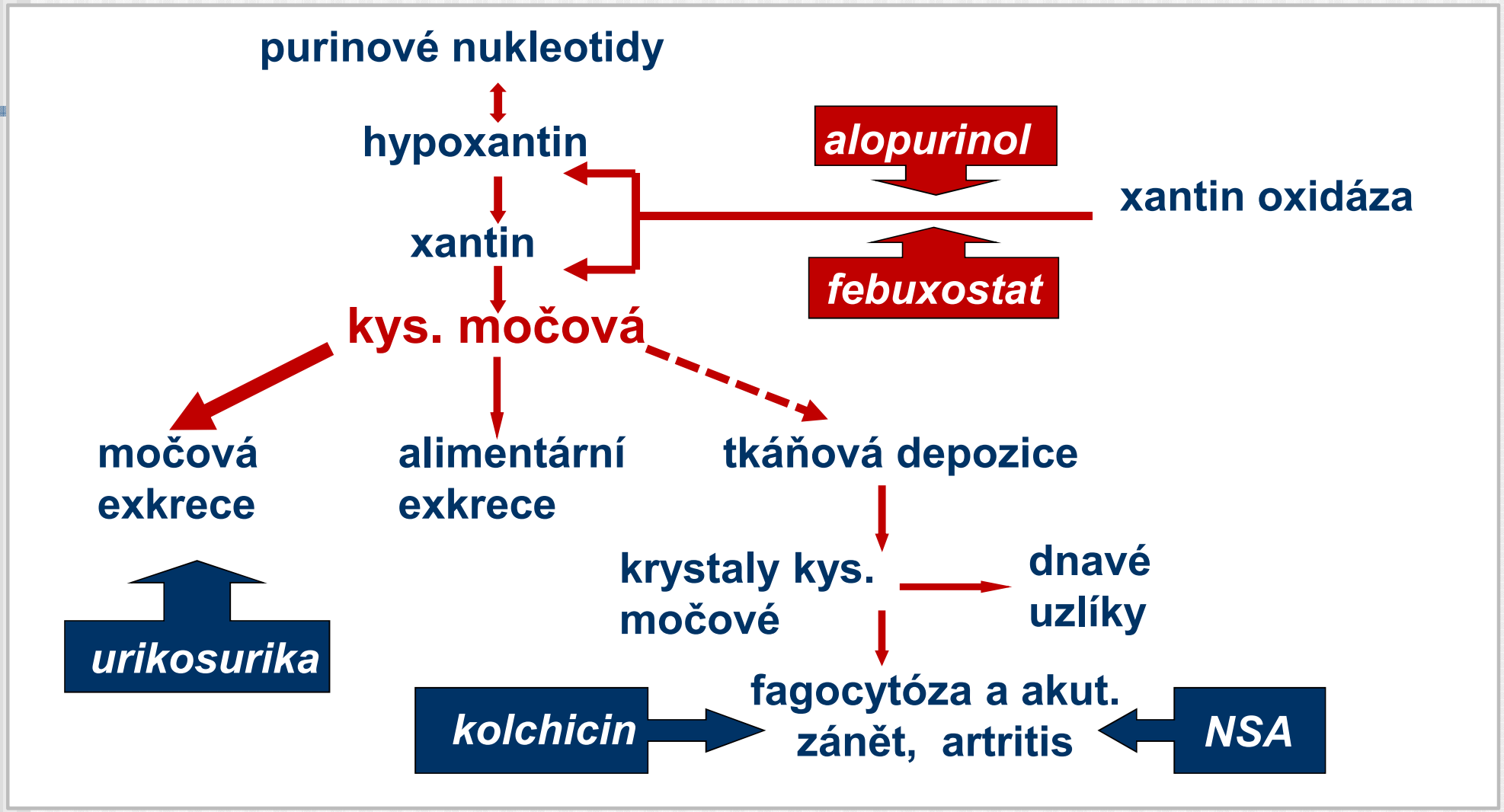
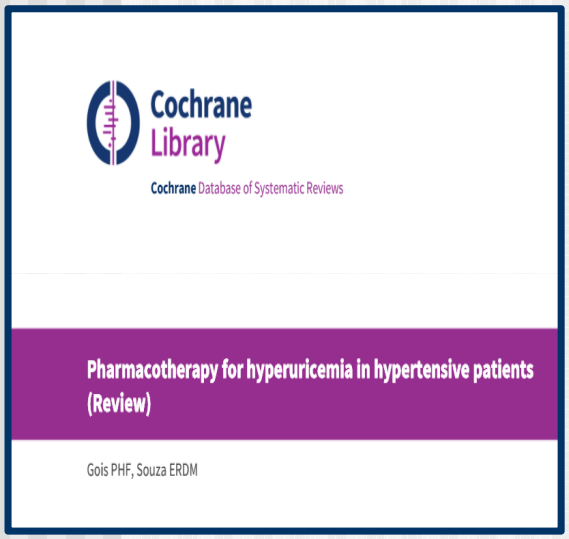
Léčba hyperurikemie a dny



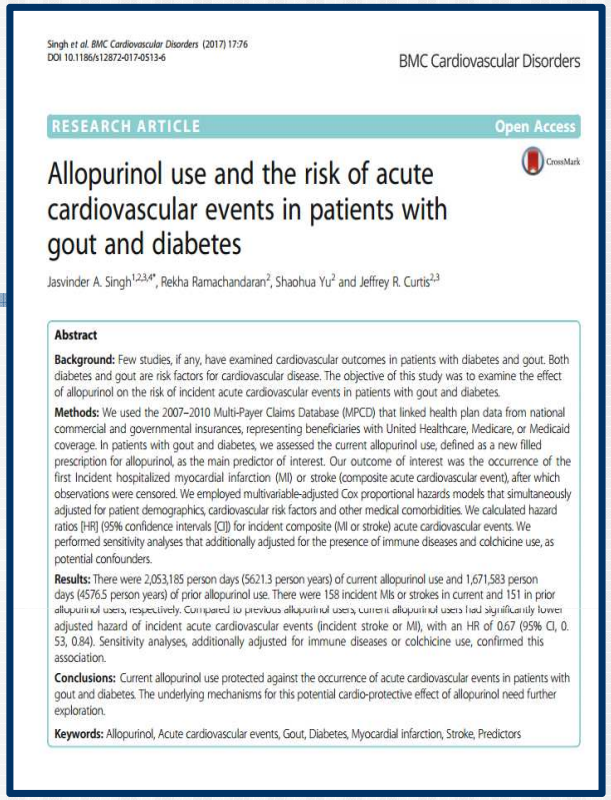
Prospektivní studie pro léčbu hyperurikémie u hypertenze



- „Meta-analýzu nebylo v tomto přehledu možno provést. Pouze jedna studie z 11 splnila vstupní kritéria studií validních. V této práci alopurinol snížil TK v ordinaci i při domácím měření. Ale vzhledem k tomu, že tato jediná randomizovaná studie byla stran počtu nemocných malá a navíc omezená na adolescenty s čerstvě odhalenou primární hypertenzí, je přínos pro zodpovězení otázky efektu léčby hyperurikémie alopurinolem malý.“

Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD008652. DOI: 10.1002/14651858.CD008652.pub3.

Efekt alopurinolu v léčbě symptomat. hyperurikémie



Singh et al. BMC Cardiovascular Disorders (2017) 17:76
DOI 10.1186/s12872-017-0513-6

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Allopurinol use and the risk of acute cardiovascular events in patients with gout and diabetes

Jasvinder A. Singh[1,2,3,4*], Rekha Ramachandaran[2], Shaohua Yu[2] and Jeffrey R. Curtis[2,3]

Abstract

Background: Few studies, if any, have examined cardiovascular outcomes in patients with diabetes and gout. Both diabetes and gout are risk factors for cardiovascular disease. The objective of this study was to examine the effect of allopurinol on the risk of incident acute cardiovascular events in patients with gout and diabetes.

Methods: We used the 2007–2010 Multi-Payer Claims Database (MPCD) that linked health plan data from national commercial and governmental insurances, representing beneficiaries with United Healthcare, Medicare, or Medicaid coverage. In patients with gout and diabetes, we assessed the current allopurinol use, defined as a new filled prescription for allopurinol, as the main predictor of interest. Our outcome of interest was the occurrence of the first Incident hospitalized myocardial infarction (MI) or stroke (composite acute cardiovascular event), after which observations were censored. We employed multivariable-adjusted Cox proportional hazards models that simultaneously adjusted for patient demographics, cardiovascular risk factors and other medical comorbidities. We calculated hazard ratios [HR] (95% confidence intervals [CI]) for incident composite (MI or stroke) acute cardiovascular events. We performed sensitivity analyses that additionally adjusted for the presence of immune diseases and colchicine use, as potential confounders.

Results: There were 2,053,185 person days (5621.3 person years) of current allopurinol use and 1,671,583 person days (4576.5 person years) of prior allopurinol use. There were 158 incident MIs or strokes in current and 151 in prior allopurinol users, respectively. Compared to previous allopurinol users, current allopurinol users had significantly lower adjusted hazard of incident acute cardiovascular events (incident stroke or MI), with an HR of 0.67 (95% CI, 0.53, 0.84). Sensitivity analyses, additionally adjusted for immune diseases or colchicine use, confirmed this association.

Conclusions: Current allopurinol use protected against the occurrence of acute cardiovascular events in patients with gout and diabetes. The underlying mechanisms for this potential cardio-protective effect of allopurinol need further exploration.

Keywords: Allopurinol, Acute cardiovascular events, Gout, Diabetes, Myocardial infarction, Stroke, Predictors

Table 4 Multivariable-adjusted associations of allopurinol use with incident composite outcome (MI and stroke)

	Incident MI or stroke	
	Hazard ratio (95% CI)	*p*-value
Allopurinol User		
Current	**0.67 (0.53, 0.84)**	**0.0006**
Previous	Ref	

Table 2 New Allopurinol use and Incident MI[a] or incident stroke[b] outcome

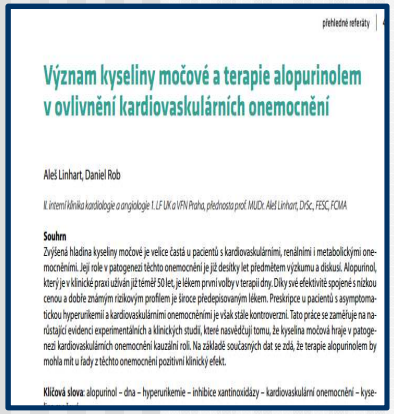
Allopurinol use	Total Person days (total person years)	Incident MI or Stroke	Per 100,000 PD (per 100 PY)
Current	2,053,185 person days (5621.3 person years)	158	7.70 (2.81 per 100 PY)
Previous	1,671,583 person days (4576.5 person years)	151	9.03 (3.30 per 100 PY)

PD person-days; *PY* person years

absolutní pokles AKS o <0,5 příhod/100 léč./rok u diabetiků se dnou

Singh et al. BMC Cardiovascular Disorders (2017) 17:76 DOI 10.1186/s12872-017-0513-6

Co říkají názory expertů o léčbě asymptomatické hyperurikémie?


přehledné referáty

Význam kyseliny močové a terapie alopurinolem v ovlivnění kardiovaskulárních onemocnění

Aleš Linhart, Daniel Rob

II. interní klinika kardiologie a angiologie 1. LF UK a VFN Praha, přednosta prof. MUDr. Aleš Linhart, DSc, FESC, FCMA

Souhrn

Zvýšená hladina kyseliny močové je velice častá u pacientů s kardiovaskulárními, renálními i metabolickými onemocněními. Její role v patogenezi těchto onemocnění je již desítky let předmětem výzkumu a diskusí. Alopurinol, který je v klinické praxi užíván již téměř 50 let, je lékem první volby v terapii dny. Díky své efektivitě spojené s nízkou cenou a dobře známým rizikovým profilem je široce předepisovaným lékem. Preskripce u pacientů s asymptomatickou hyperurikemií a kardiovaskulárními onemocněními je však stále kontroverzní. Tato práce se zaměřuje na narůstající evidenci experimentálních a klinických studií, které nasvědčují tomu, že kyselina močová hraje v patogenezi kardiovaskulárních onemocnění kauzální roli. Na základě současných dat se zdá, že terapie alopurinolem by mohla mít u řady z těchto onemocnění pozitivní klinický efekt.

Klíčová slova: alopurinol – dna – hyperurikemie – inhibice xantinoxidázy – kardiovaskulární onemocnění – kyse-

- „U většiny nemocných s asymptomat. hyperurikémií se nikdy nevyvine dna či litiáza. Léčba přináší rizika a nepovažuje se být přínosná a cost-efektivní, není proto doporučena.“
- „Podání alopurinolu u pacientů s asymptomatickou hyperurikemií nelze na základě současných dat doporučit. Pro změnu těchto doporučení chybí prospektivní randomizované studie adekvátního uspořádání, rozsahu a trvání.“

Borghi C. Curr Med Res Opin. 2015; 31 Suppl 2:21-6, A.Linhart, D.Rob: Vnitř Lék 2015; 61(5): 421-430

Co říkají doporučené postupy o léčbě asymptomatické hyperurikémie?

ACP American College of Physicians™ Leading Internal Medicine, Improving Lives

CLINICAL GUIDELINE

Management of Acute and Recurrent Gout: A Clinical Practice Guideline From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Russell P. Harris, MD, MPH; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians*

Description: The American College of Physicians (ACP) developed this guideline to present the evidence and provide clinical recommendations on the management of gout.

Methods: Using the ACP grading system, the committee based these recommendations on a systematic review of randomized, controlled trials; systematic reviews; and large observational studies published between January 2010 and March 2016. Clinical outcomes evaluated included pain, joint swelling and tenderness, activities of daily living, patient global assessment, recurrence, intermediate outcomes of serum urate levels, and harms.

Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes adults with acute or recurrent gout.

Recommendation 1: *ACP recommends that clinicians choose corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine to treat patients with acute gout. (Grade: strong recommendation, high-quality evidence)*

Recommendation 2: *ACP recommends that clinicians use low-dose colchicine when using colchicine to treat acute gout. (Grade: strong recommendation, moderate-quality evidence)*

Recommendation 3: *ACP recommends against initiating long-term urate-lowering therapy in most patients after a first gout attack or in patients with infrequent attacks. (Grade: strong recommendation, moderate-quality evidence)*

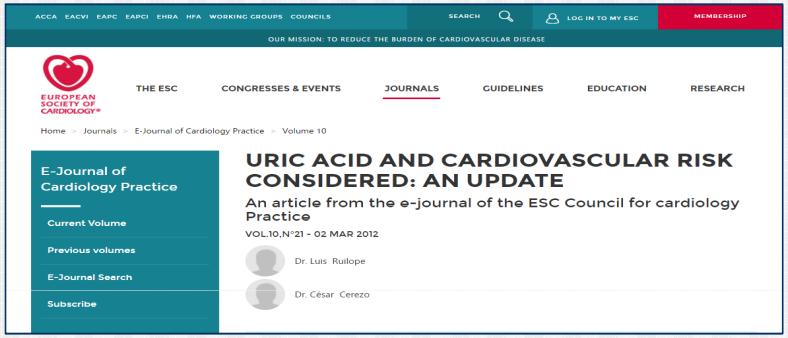
Recommendation 4: *ACP recommends that clinicians discuss benefits, harms, costs, and individual preferences with patients before initiating urate-lowering therapy, including concomitant prophylaxis, in patients with recurrent gout attacks. (Grade: strong recommendation, moderate-quality evidence)*

Ann Intern Med. doi:10.7326/M16-0570 www.annals.org
For author affiliations, see end of text.
This article was published at www.annals.org on 1 November 2016.

- **ACP doporučení se staví proti dlouhodobé léčbě snižující hladinu kyseliny močové u většiny pacientů po prvé atace dny či u nemocných s málo častými atakami.**
- **Význam snížení hladiny kyseliny močové v prevenci ostatních zdravotních rizik je nejasné.**

Ann Intern Med., 2016, doi:10.7326/M16-0461

Co říkají doporučené postupy o léčbě asymptomatické hyperurikémie?



- „Je příliš brzo dělat klinické závěry o přínosu inhibitorů xantin-oxidázy - alopurinolu či febuxostatu - u nemocných s asymptomatickým zvýšením kyseliny močové a vysokým KV rizikem.“
- …výhodné jsou BKK a některé sartany snižující urikémii…

E-JOURNAL OF CARDIOLOGY PRACTICE, 2012

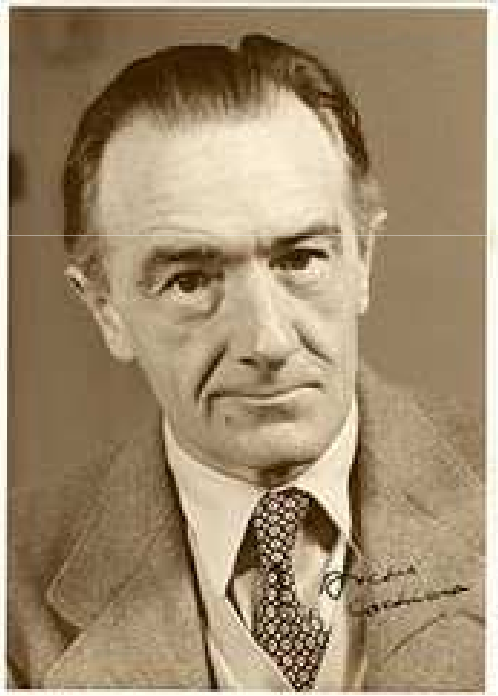
Léčit asymptomatickou hyperurikémii?

Otázka forenzní - co uvádí SPC?

K indikacím alopurinolu patří pouze:

- ***idiopatická dna***
- ***litiáza způsobená kyselinou močovou***
- ***akutní nefropatie způsobená kyselinou močovou***
- ***nádorové a myeloproliferativní onemocnění s vysokou mírou tvorby a zániku buněk***

Děkuji za pozornost



„…bez respektování kritických analýz velkých randomizovaných studií, bude naše povolání i nadále podrobováno oprávněné kritice…“

Archie Cochrane, 1988

Děkuji za pozornost

„…ne sit medica gravior ipso morbo“

„…aby léčba nebyla nebezpečnější nežli nemoc“

J.E.Purkyně, 1858

- Hyperuricem
associated w
increased ris
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1.19-1.49) a
(unadjusted
95% CI 1.20
- When adjust
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CHD inciden
(95% CI: 1.0
mortality.

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Hyperuricemia and Coronary Heart Disease: A Systematic Review and Meta-Analysis

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[7]Department of Biostatistics & Epidemiology, University of Pennsylvania, Philadelphia PA

[8]Division of Rheumatology, Dartmouth Hitchcock Medical Center, Lebanon, NH

Abstract

BACKGROUND—The role of serum uric acid as an independent risk factor for cardiovascular disease remains unclear although hyperuricemia is associated with cardiovascular disease such as coronary heart disease (CHD), stroke and hypertension.

METHODS—A systematic review and meta-analysis using a random-effects model was conducted to determine the risk of CHD associated with hyperuricemia in adults. Studies of hyperuricemia and CHD were identified by searching major electronic databases using the Medical Subject Headings and keywords without language restriction (through February 2009). Only prospective cohort studies were included if they had data on CHD incidences or mortalities related to serum uric acid levels in adults.

RESULTS—26 eligible studies of 402,997 adults were identified. Hyperuricemia was associated with an increased risk of CHD incidence (unadjusted risk ratio (RR) 1.34; 95% confidence interval (CI) 1.19-1.49) and mortality (unadjusted RR 1.46; 95% CI 1.20-1.73). When adjusted for potential confounding, the pooled RR was 1.09 (95% CI: 1.03-1.16) for CHD incidence and 1.16 (95% CI: 0.91-1.30) for mortality. For each increase of 1 mg/dL in uric acid level, the pooled multivariate RR for CHD mortality was 1.12 (95% CI: 1.05-1.19). Subgroup analyses showed no

Arthritis Care Res (Hoboken). 2010 February ; 62(2): 170–180. doi:10.1002/acr.20065.

Koho léčit?

- dnavé uzlíky
- dnavá artropatie – klinický či RTG průkaz
- urolitiáza či nefrolitiáza

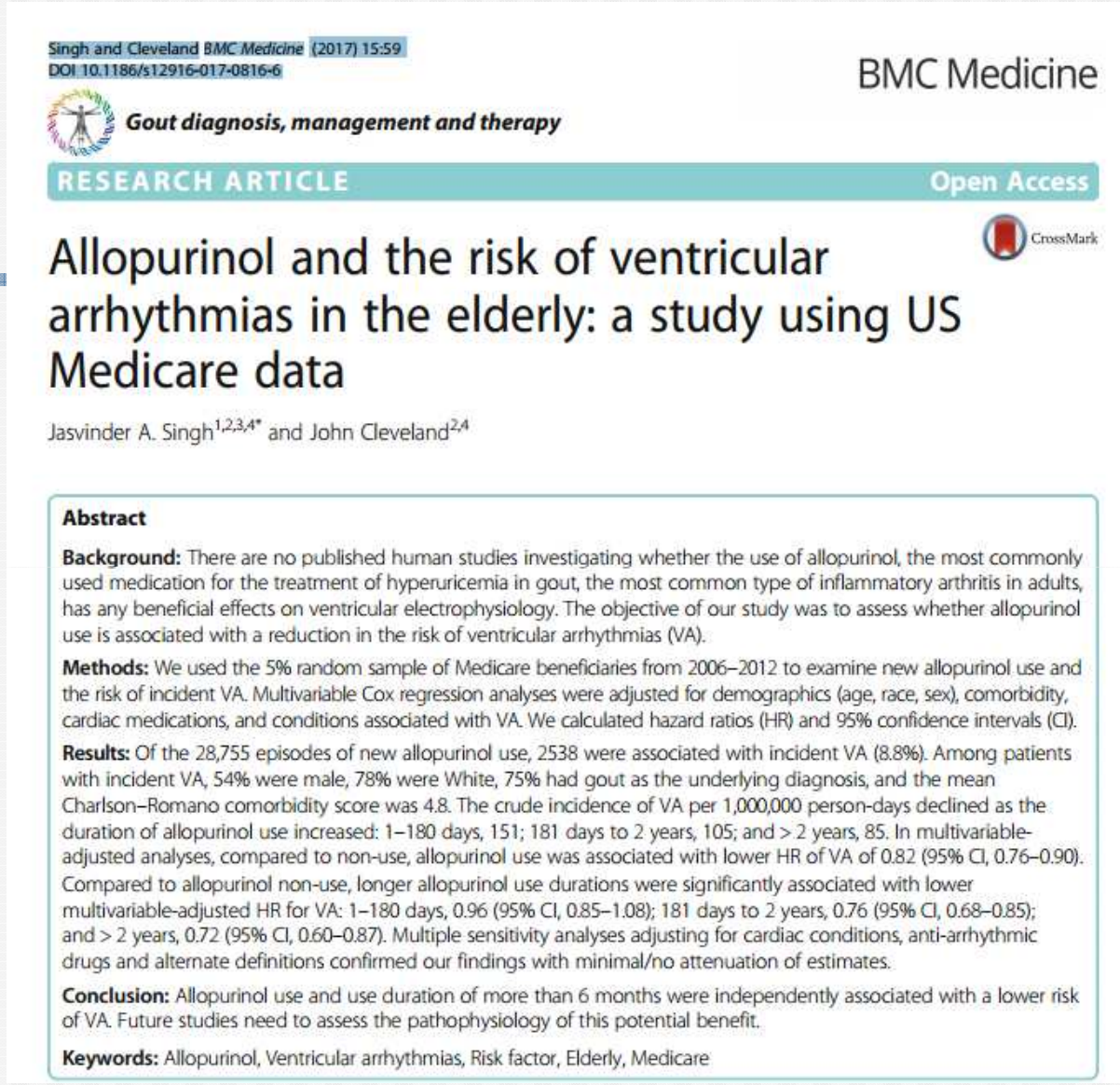
- pravděpodobně není nutné (vhodné?) léčit hyperurikemii preventivně
- kyselina močová může být účinným antioxidans

- A positive association has been found between urate levels and a number of important disorders, including hypertension, CKD, CHF, the metabolic syndrome, T2DM, endothelial cell dysfunction, cardiovascular events, and fatty liver disease. The strength of these associations will be discussed below. There are also a few intervention studies, mostly with allopurinol, but these are small and may not be representative of the effects of lowering urate by different mechanisms.

- review of the available literature shows that there is an association between serum urate levels and hypertension, CKD, heart failure, the metabolic syndrome, obesity and cardiovascular events. However, as is often the case in the published literature, support is not unanimous. Understanding in the field is hampered by the difference in urate metabolism between laboratory animals and man, which makes animal studies difficult to interpret. Thus, there is limited evidence for a causal relationship. The interventional studies in man can be considered more as hypothesis-generating, since design quality, duration, and sample size are often insufficient to clarify the role of urate in cardiovascular disease. In addition, most interventional studies are with allopurinol, which is lowering urate via inhibition of XO, leading to decreased production of ROS, which may have contributed to any apparent beneficial effect.

- A definitive answer to the question of whether urate-lowering therapy can reduce cardiovascular morbidity and mortality will, in the end, require large interventional trials, but it is doubtful that the safety profile of allopurinol is sufficient for such large-scale studies.

- pokles o 23 episod komorových arytmií při léčbě alopurinolem ročně/ 1 mil. pacient/den (75% pacientů mělo dnu)



Singh and Cleveland *BMC Medicine* (2017) 15:59
DOI 10.1186/s12916-017-0816-6

BMC Medicine

Gout diagnosis, management and therapy

RESEARCH ARTICLE Open Access

Allopurinol and the risk of ventricular arrhythmias in the elderly: a study using US Medicare data

Jasvinder A. Singh[1,2,3,4*] and John Cleveland[2,4]

Abstract

Background: There are no published human studies investigating whether the use of allopurinol, the most commonly used medication for the treatment of hyperuricemia in gout, the most common type of inflammatory arthritis in adults, has any beneficial effects on ventricular electrophysiology. The objective of our study was to assess whether allopurinol use is associated with a reduction in the risk of ventricular arrhythmias (VA).

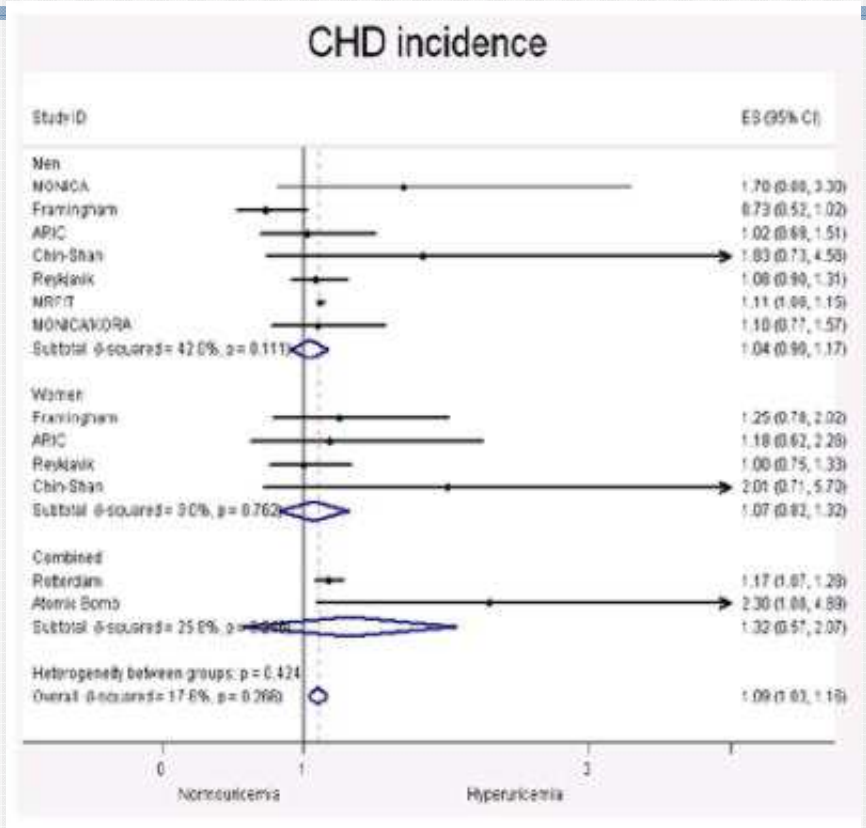
Methods: We used the 5% random sample of Medicare beneficiaries from 2006–2012 to examine new allopurinol use and the risk of incident VA. Multivariable Cox regression analyses were adjusted for demographics (age, race, sex), comorbidity, cardiac medications, and conditions associated with VA. We calculated hazard ratios (HR) and 95% confidence intervals (CI).

Results: Of the 28,755 episodes of new allopurinol use, 2538 were associated with incident VA (8.8%). Among patients with incident VA, 54% were male, 78% were White, 75% had gout as the underlying diagnosis, and the mean Charlson–Romano comorbidity score was 4.8. The crude incidence of VA per 1,000,000 person-days declined as the duration of allopurinol use increased: 1–180 days, 151; 181 days to 2 years, 105; and > 2 years, 85. In multivariable-adjusted analyses, compared to non-use, allopurinol use was associated with lower HR of VA of 0.82 (95% CI, 0.76–0.90). Compared to allopurinol non-use, longer allopurinol use durations were significantly associated with lower multivariable-adjusted HR for VA: 1–180 days, 0.96 (95% CI, 0.85–1.08); 181 days to 2 years, 0.76 (95% CI, 0.68–0.85); and > 2 years, 0.72 (95% CI, 0.60–0.87). Multiple sensitivity analyses adjusting for cardiac conditions, anti-arrhythmic drugs and alternate definitions confirmed our findings with minimal/no attenuation of estimates.

Conclusion: Allopurinol use and use duration of more than 6 months were independently associated with a lower risk of VA. Future studies need to assess the pathophysiology of this potential benefit.

Keywords: Allopurinol, Ventricular arrhythmias, Risk factor, Elderly, Medicare

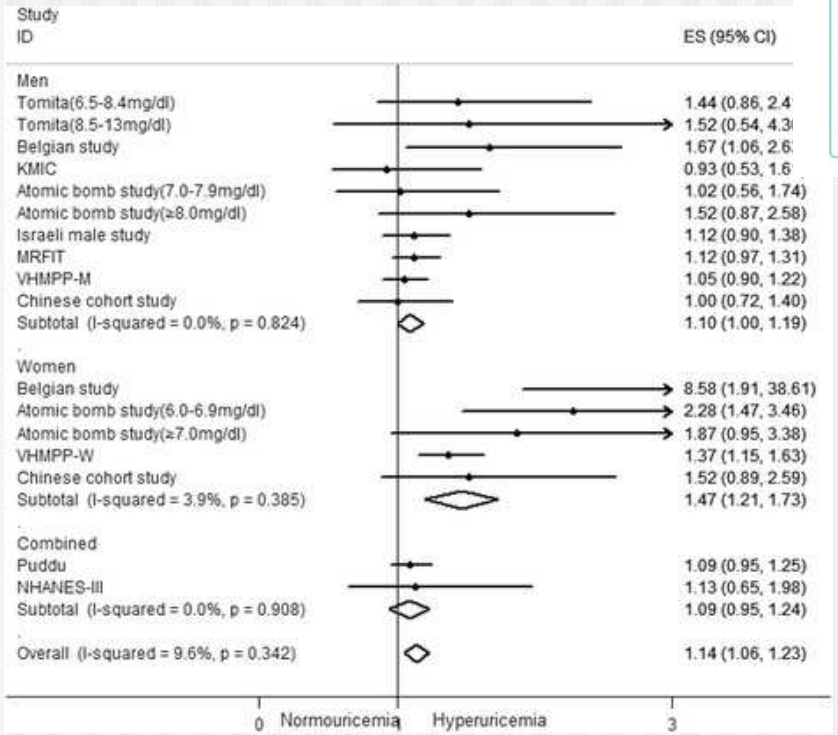
Singh and Cleveland BMC Medicine (2017) 15:59 DOI 10.1186/s12916-017-0816-6

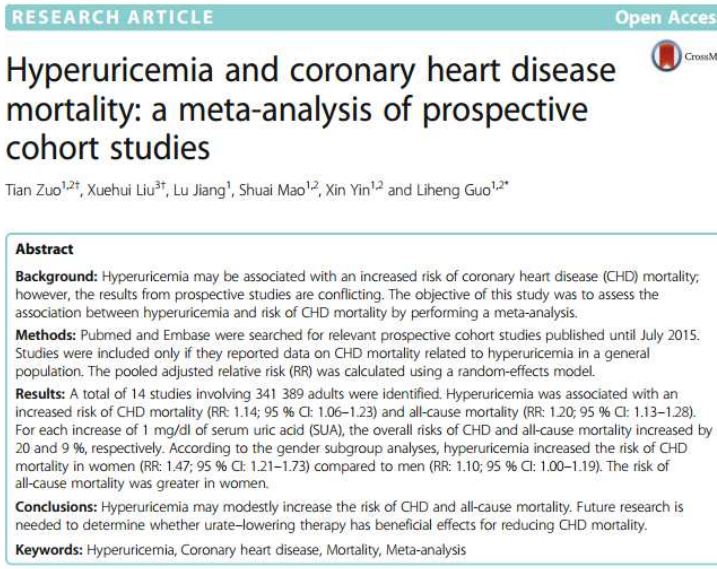


Arthritis Care Res (Hoboken). 2010 February ; 62(2): 170–180. doi:10.1002/acr.20065.

Hyperuricemia and coronary he mortality: a meta-analysis of pr studies

- Hyperuricemia was associated with an increased risk of CHD mortality (RR: 1.14; 95 % CI: 1.06–1.23)




RESEARCH ARTICLE Open Acces

Hyperuricemia and coronary heart disease mortality: a meta-analysis of prospective cohort studies

Tian Zuo[1,2†], Xuehui Liu[3†], Lu Jiang[1], Shuai Mao[1,2], Xin Yin[1,2] and Liheng Guo[1,2*]

Abstract

Background: Hyperuricemia may be associated with an increased risk of coronary heart disease (CHD) mortality; however, the results from prospective studies are conflicting. The objective of this study was to assess the association between hyperuricemia and risk of CHD mortality by performing a meta-analysis.

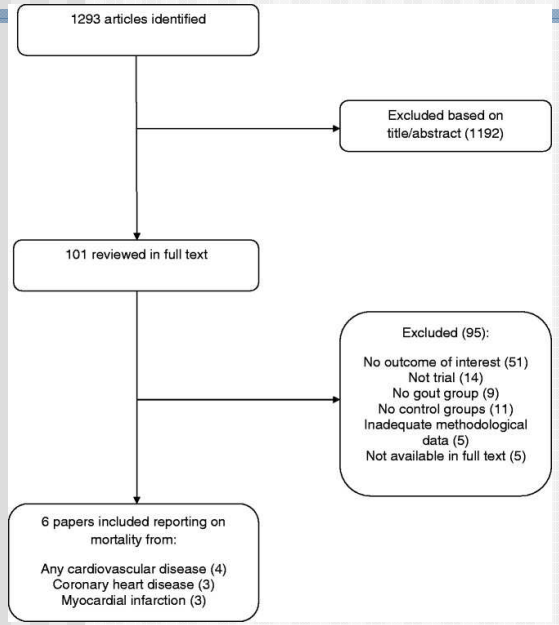
Methods: Pubmed and Embase were searched for relevant prospective cohort studies published until July 2015. Studies were included only if they reported data on CHD mortality related to hyperuricemia in a general population. The pooled adjusted relative risk (RR) was calculated using a random-effects model.

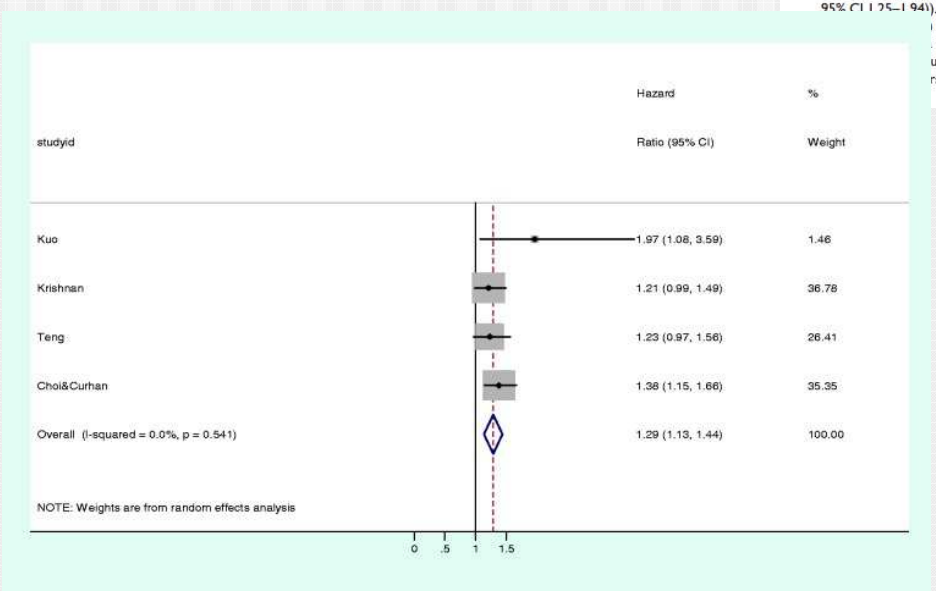
Results: A total of 14 studies involving 341 389 adults were identified. Hyperuricemia was associated with an increased risk of CHD mortality (RR: 1.14; 95 % CI: 1.06–1.23) and all-cause mortality (RR: 1.20; 95 % CI: 1.13–1.28). For each increase of 1 mg/dl of serum uric acid (SUA), the overall risks of CHD and all-cause mortality increased by 20 and 9 %, respectively. According to the gender subgroup analyses, hyperuricemia increased the risk of CHD mortality in women (RR: 1.47; 95 % CI: 1.21–1.73) compared to men (RR: 1.10; 95 % CI: 1.00–1.19). The risk of all-cause mortality was greater in women.

Conclusions: Hyperuricemia may modestly increase the risk of CHD and all-cause mortality. Future research is needed to determine whether urate–lowering therapy has beneficial effects for reducing CHD mortality.

Keywords: Hyperuricemia, Coronary heart disease, Mortality, Meta-analysis

Zuo et al. BMC Cardiovascular Disorders (2016) 16:207 DOI 10.1186/s12872-016-0379-z





European Journal of Preventive Cardiology

Original scientific paper

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Increased cardiovascular mortality associated with gout: a systematic review and meta-analysis

LE Clarson[1], P Chandratre[1], SL Hider[1], J Belcher[1], C Heneghan[2], E Roddy[1] and CD Mallen[1]

Abstract

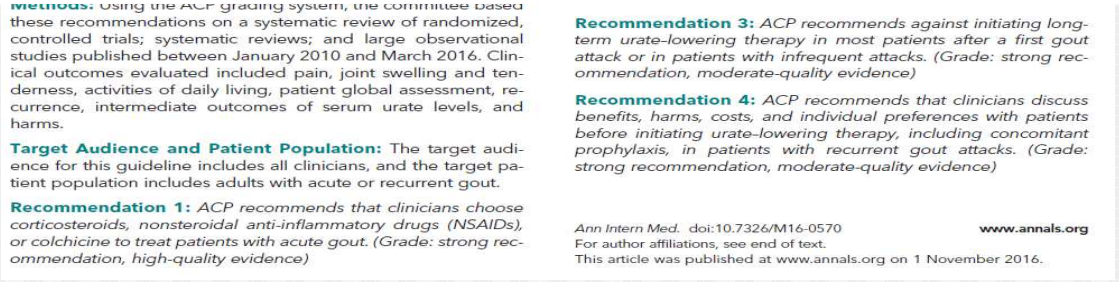
Background: Hyperuricaemia, the biochemical precursor to gout, has been shown to be an independent risk factor for mortality from cardiovascular disease (CVD), although studies examining the clinical phenomenon of gout and risk of CVD mortality report conflicting results. This study aimed to produce a pooled estimate of risk of mortality from cardiovascular disease in patients with gout.

Design: Systematic review and meta-analysis.

Methods: Electronic bibliographic databases were searched from inception to November 2012, with results reviewed by two independent reviewers. Studies were included if they reported data on CVD mortality in adults with gout who were free of CVD at time of entry into the study. Pooled hazard ratios (HRs) for this association were calculated both unadjusted and adjusted for traditional vascular risk factors.

Results: Six papers, including 223,448 patients, were eligible for inclusion (all (CVD) mortality $n=4$, coronary heart disease (CHD) mortality $n=3$, and myocardial infarction mortality $n=3$). Gout was associated with an excess risk of CVD mortality (unadjusted HR 1.51 (95% confidence interval, CI, 1.17–1.84)) and CHD mortality (unadjusted HR 1.59, 95% CI 1.25–1.94)). After adjusting for traditional vascular risk factors, the pooled HR for both CVD mortality (HR 1.29, and CHD mortality (HR 1.42, 95% CI 1.22–1.63) remained statistically significant, but none of the significant association with myocardial infarction.

ut increases the risk of mortality from CVD and CHD, but not myocardial infarction, independently of rs.



Methods: Using the ACP grading system, the committee based these recommendations on a systematic review of randomized, controlled trials; systematic reviews; and large observational studies published between January 2010 and March 2016. Clinical outcomes evaluated included pain, joint swelling and tenderness, activities of daily living, patient global assessment, recurrence, intermediate outcomes of serum urate levels, and harms.

Target Audience and Patient Population: The target audience for this guideline includes all clinicians, and the target patient population includes adults with acute or recurrent gout.

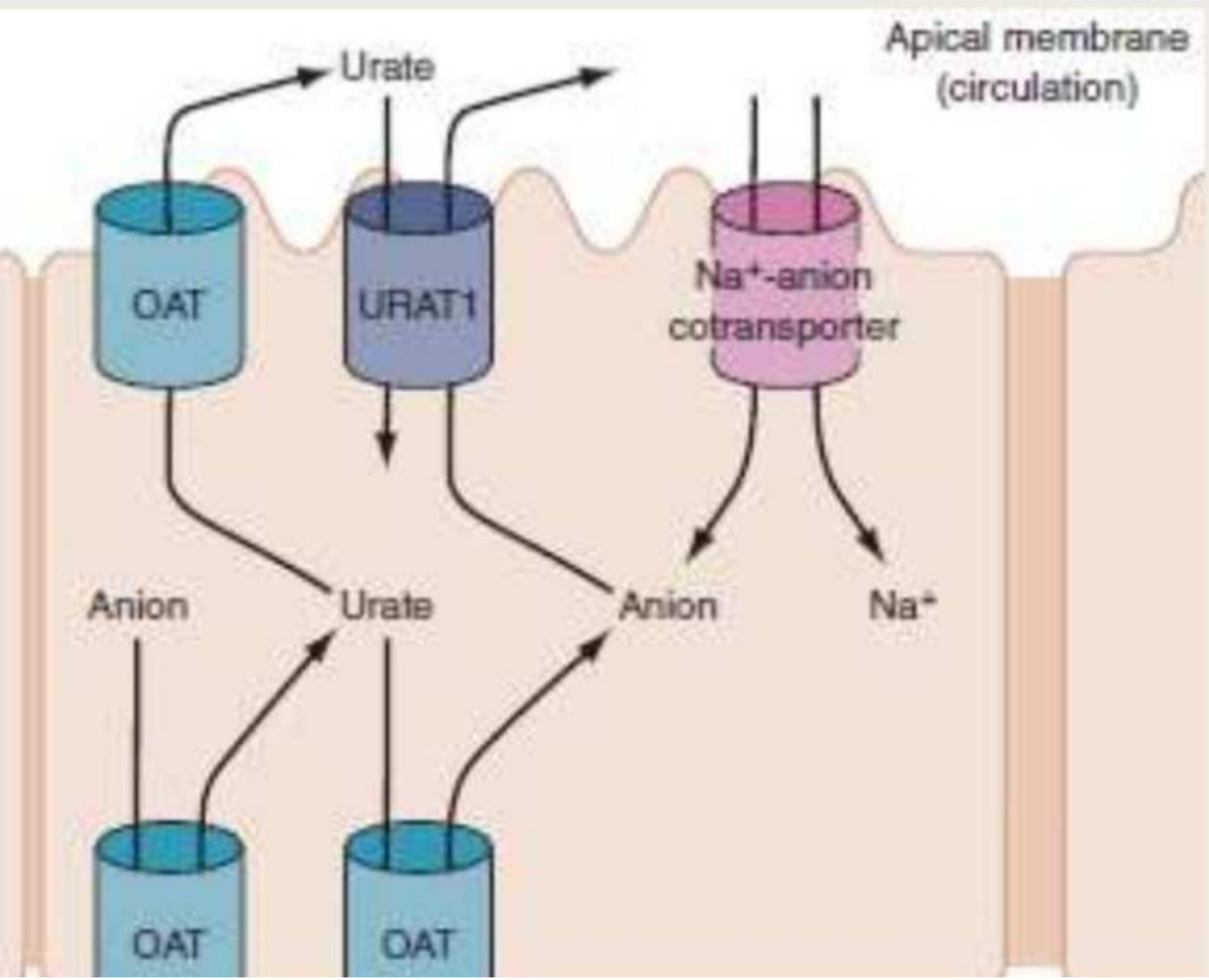
Recommendation 1: *ACP recommends that clinicians choose corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine to treat patients with acute gout. (Grade: strong recommendation, high-quality evidence)*

Recommendation 3: *ACP recommends against initiating long-term urate–lowering therapy in most patients after a first gout attack or in patients with infrequent attacks. (Grade: strong recommendation, moderate-quality evidence)*

Recommendation 4: *ACP recommends that clinicians discuss benefits, harms, costs, and individual preferences with patients before initiating urate-lowering therapy, including concomitant prophylaxis, in patients with recurrent gout attacks. (Grade: strong recommendation, moderate-quality evidence)*

Ann Intern Med. doi:10.7326/M16-0570 **www.annals.org**
For author affiliations, see end of text.
This article was published at www.annals.org on 1 November 2016.

- Evidence was insufficient for gout-specific dietary advice or therapies (such as reduced intake of red meat, fructose, and alcohol) to improve symptomatic outcomes.
- ACP recommends against initiating long-term urate–lowering therapy in most patients after a first gout attack or in patients with infrequent attacks.
- The importance of decreasing urate levels to prevent adverse health outcomes beyond acute gout is uncertain.



TRANSPORTERS

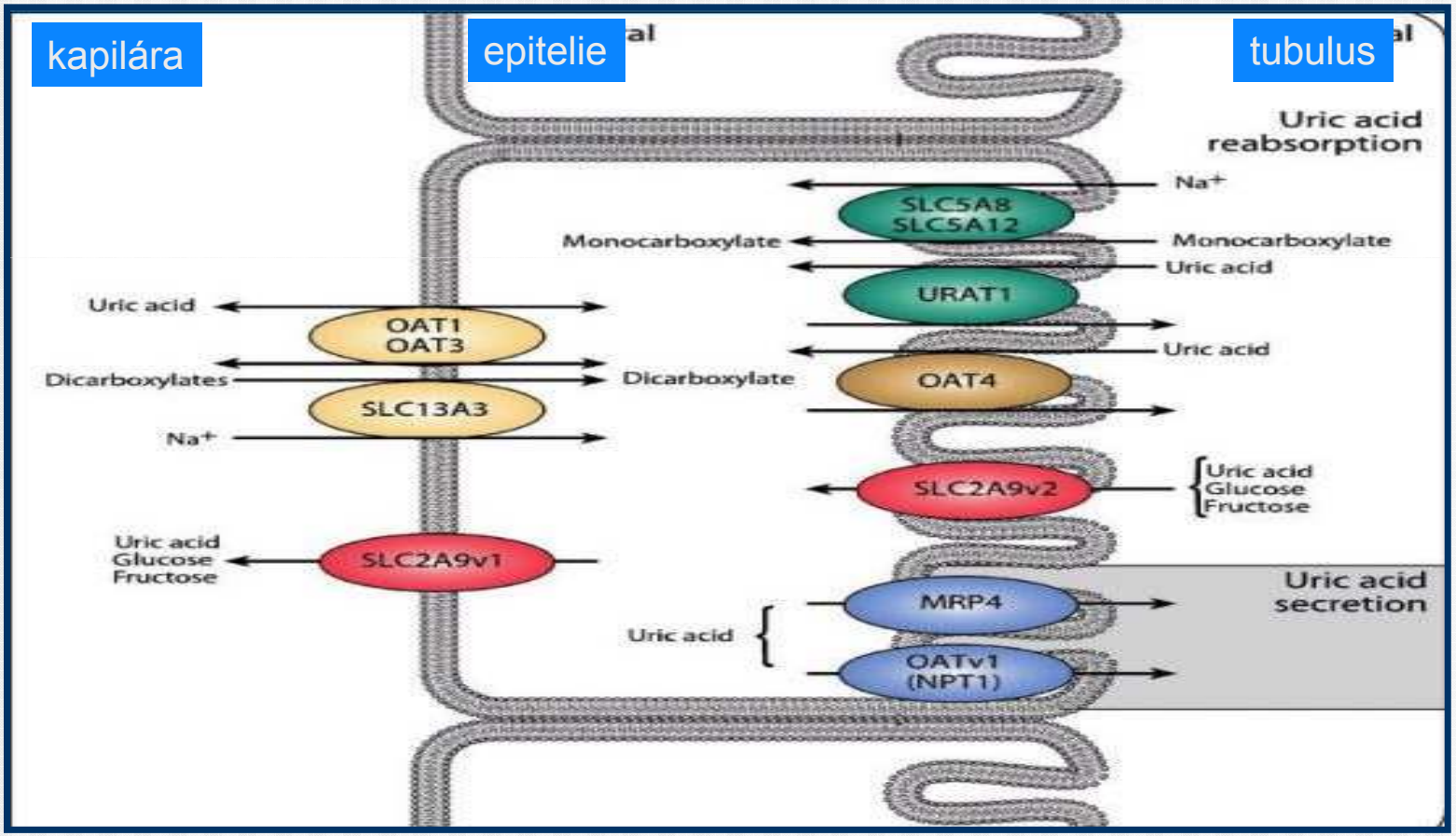
Reabsorption

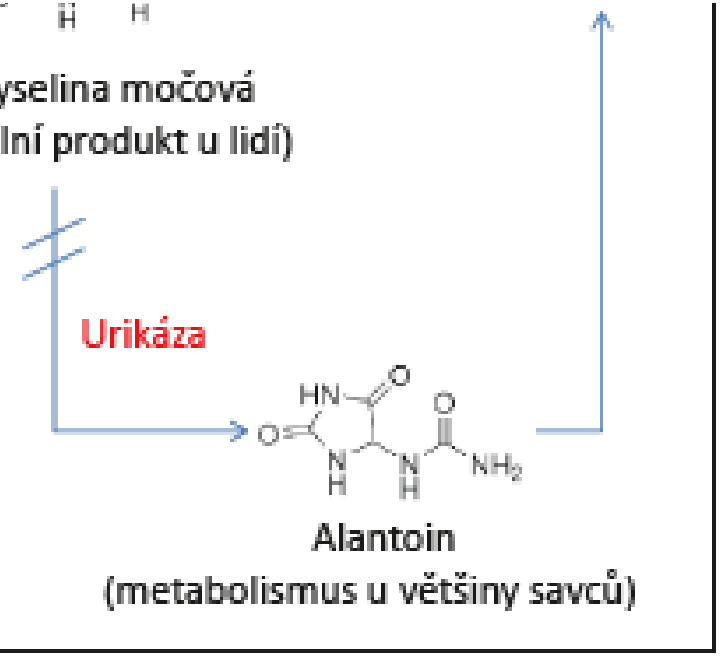
- SLC2A9v1
- SLC2A9v2
- OAT1, 3 and 4

Secretion

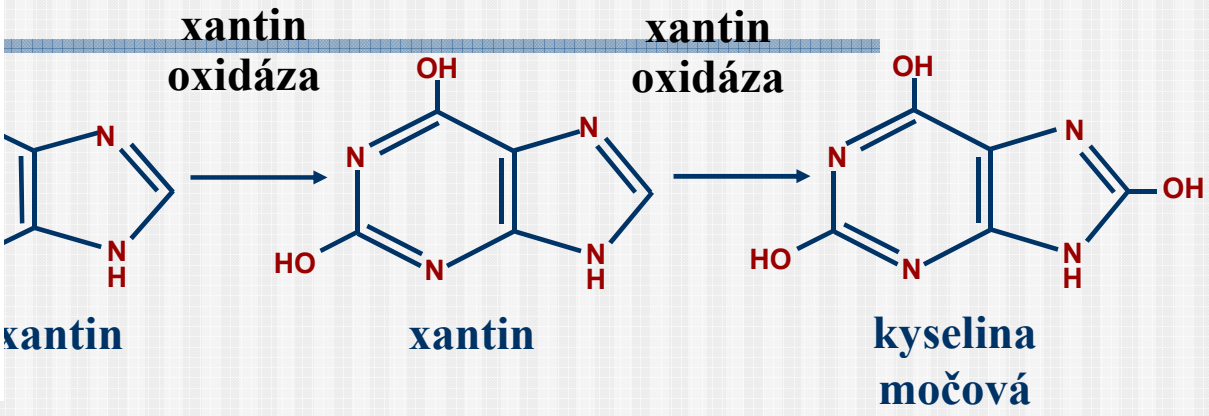
- MRP4
- OATv1

Eliminace kyseliny močové v renálním tubulu – příklad komplexního transportu





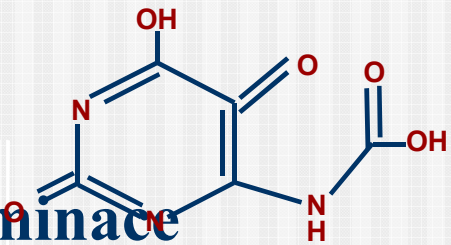
Hyperurikemie



zvýšená syntéza
(metab. odchylka či rozpad NK)

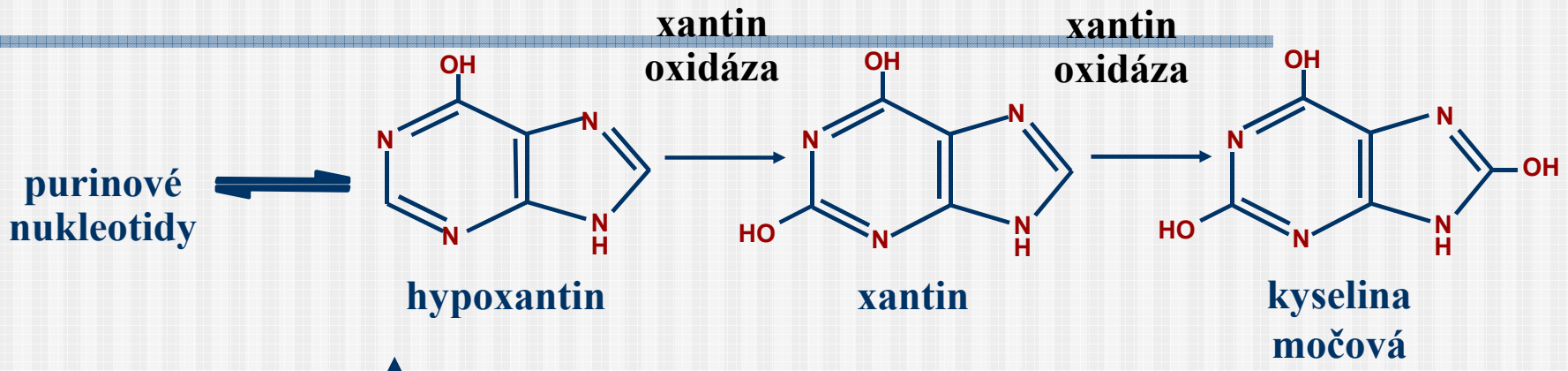
hyperurikémie

snížená exkrece
(inhibice tubul. sekrece, snížení ren. funkcí)



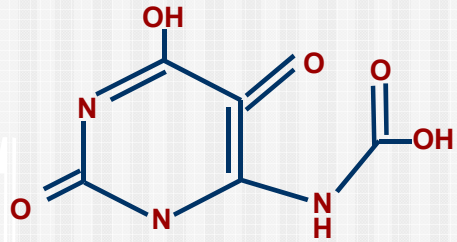
eliminace zejm. tubulární sekrecí

Hyperurikemie



zvýšená syntéza
(metab. odchylka či rozpad NK)

hyperurikémie



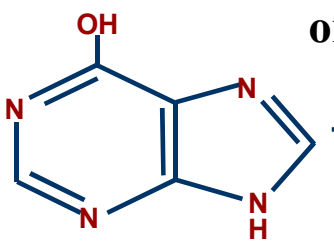
alantoin

snížená exkrece
(inhibice tubul. sekrece, snížení ren. funkcí)

eliminace

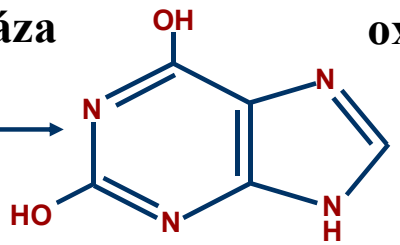
Hyperurikemie

purinové nukleotidy



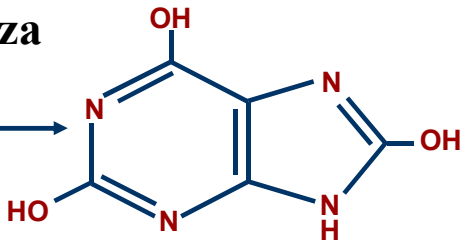
hypoxantin

xantin oxidáza



xantin

xantin oxidáza

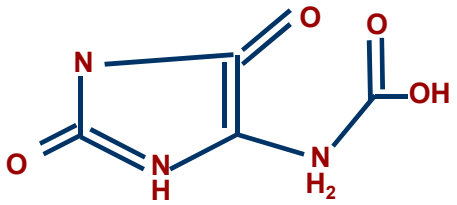


kyselina močová

zvýšená syntéza
(metab. odchylka či rozpad NK)

hyperurikémie

snížená exkrece
(inhibice tubul. sekrece, snížení ren. funkcí)

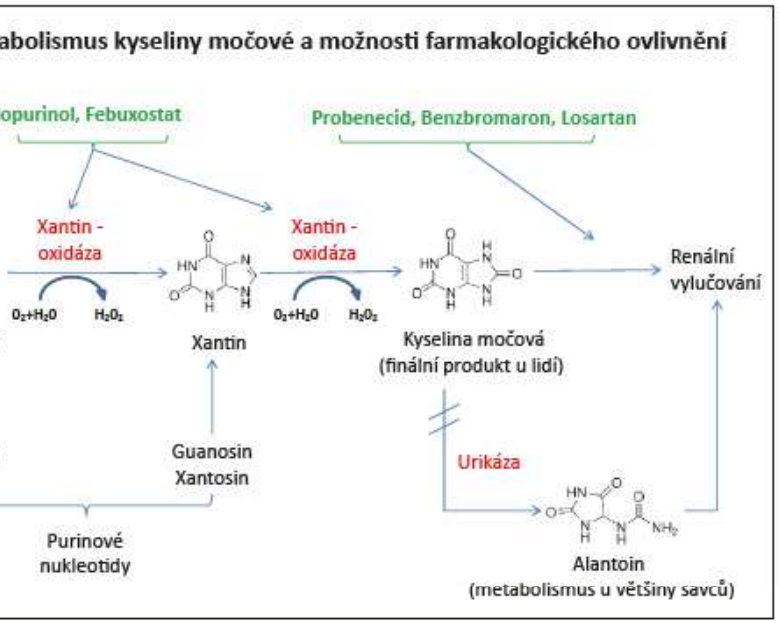


alantoin

eliminace

Inhibitory xantin-oxidázy – *allopurinol, febuxostat*

- **blokáda syntézy kyseliny močové**
- **účinně snižují hladinu kys. močové**
- **řada NÚ - dyspepsie (u 20% léčených), exantém**
  - **- myelosuprese (až agranulocytóza)**
  - - hepatitis, vaskulitis
- **v praxi pravděpodobně léčba nadužívána**
  - **– nevíme, zda každou hyperurikemii nutno léčit**
- **febuxostat účinnější, stejný výskyt NÚ, ale dražší**


abolismus kyseliny močové a možnosti farmakologického ovlivnění
opurinol, Febuxostat
Probenecid, Benzbromaron, Losartan
Xantin - oxidáza
Xantin - oxidáza
Renální vylučování
O_2+H_2O
H_2O_2
O_2+H_2O
H_2O_2
Xantin
Kyselina močová (finální produkt u lidí)
Guanosin
Xantosin
Urikáza
Purinové nukleotidy
Alantoin
(metabolismus u většiny savců)

Gout and Hyperuricemia

Review

1

Gout and Hyperuricemia. 2014; 1(1): 1-7
Access publication Mar. 2014

Treatment of gout and hyperuricemia, an update

Naoyuki Kamatani

- Treatment of asymptomatic hyperuricemia Asymptomatic hyperuricemia is not usually the target of urate-lowering therapy, unless the urate concentration is very high. Hyperuricemia increases the risk of acute gouty arthritis and renal stones. As the need for a urate-lowering drug is likely to be life-long, the advantages and disadvantages of its administration should be carefully compared. The benefits of urate-lowering therapy include the prevention of acute gouty attacks, inhibition of disease progression to chronic tophaceous gout, and prevention of the development of urolithiasis and renal insufficiency. The disadvantages include the occurrence of adverse events caused by the drugs and the necessity to attend clinics and hospitals. Whether asymptomatic hyperuricemia should be treated with drugs differs between different countries. In US and Europe, treatment of asymptomatic hyperuricemia with drugs is not recommended. In Japan, however, the use of febuxostat to treat high-level hyperuricemia is approved.

International Journal of Cardiology 213 (2016) 28–32

Contents lists available at ScienceDirect

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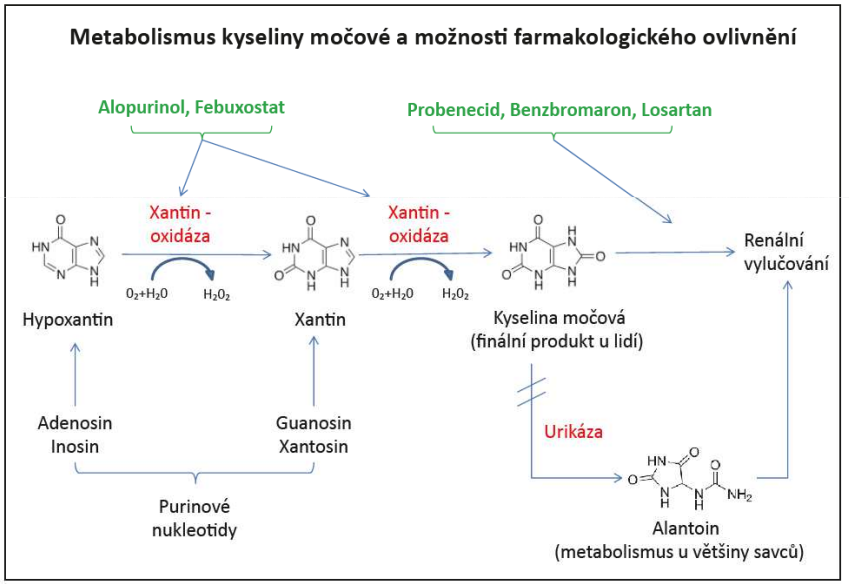
journal homepage: www.elsevier.com/locate/ijcard

Uric acid and coronary artery disease: An elusive link deserving further attention

Simone Biscaglia [a], Claudio Ceconi [a,b], Michele Malagù [a], Rita Pavasini [a], Roberto Ferrari [a,b,c,*]

[a] Department of Cardiology, University Hospital of Ferrara, Italy
[b] LTTA Centre, University Hospital of Ferrara, Italy
[c] Maria Cecilia Hospital, GVM Care & Research, E.S.: Health Science Foundation, Cotignola, Italy

- . Many studies suggest that uric acid could be a CAD risk factor [14], others reached the opposite conclusion [15]. Even meta-analyses are contradictory [16, 17]. The overall risk of cardiovascular mortality has shown to increase by 12% for each increase of 1 mg/dl of uric acid serum levels, and hyperuricemia increases the risk of death in women, as recently confirmed bya cross-sectional retrospective study, which included 607 premenopausal women [18]. Other studies evaluated the correlation between coronary artery calcifications (an early marker of CAD) and uric acid levels, but again with opposite results. Neogi et al. reported a clear association [19], while Krishnan et al. could not confirm it [20]. In a retrospective study involving 1901 patients, De Luca et al. showed that uric acid level was not associated both with platelet aggregation and the extent of coronary artery disease [21].



Obr. 2 Metabolismus kyseliny močové a možnosti farmakologického ovlivnění

allopurinol effect on pulse wave velocity.

MEDICAL SCIENCE MONITOR

META-ANALYSIS

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Effects of Allopurinol on Arterial Stiffness: A Meta-Analysis of Randomized Controlled Trials

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Gang Deng
BCF Zhandong Qiu
BCF Dayong Li
BCF Yu Fang
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Department of Neurology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, P.R. China

Corresponding Author: Suming Zhang, e-mail: sumingzhang123@163.com
Source of support: This work was supported by the Fund of National Natural Science Foundation of China (NSFC 81271407)

Background: Several studies have tested the effects of allopurinol on arterial stiffness, but the results have been inconclusive. We aimed to conduct a meta-analysis to investigate the impacts of allopurinol treatment on arterial stiffness, as measured by pulse wave velocity (PWV) and augmentation index (AIx).

Material/Methods: Randomized controlled trials (RCTs) assessing the effects of allopurinol on arterial stiffness were identified through searching PubMed, Web of Science, EMBASE, the Cochrane Library for Central Register of Clinical Trials, and China National Knowledge Infrastructure up to December 2015. The primary endpoints were the change of PWV and AIx after allopurinol treatment. The weighted mean difference (WMD) or standardized mean difference (SMD) and the 95% confidence interval (CI) of each study were pooled for meta-analysis.

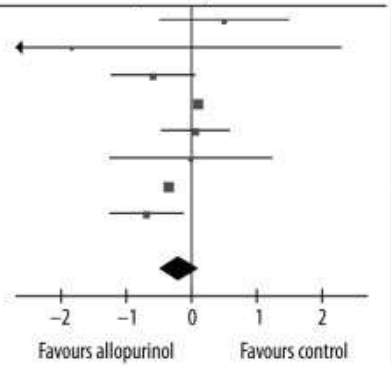
Results: A total of 11 RCTs met the inclusion criteria and were included in the final meta-analysis. Eight RCTs with 1,111 patients were pooled for PWV; eight RCTs with 397 patients were pooled for PWV. Allopurinol administration did not significantly change PWV (WMD=−0.19 m/s, 95% CI: −0.49 to 0.12, Z=1.21, p=0.23), but significantly reduced AIx (SMD=−0.34, 95% CI: −0.54 to −0.14, Z=3.35, p=0.0008).

Conclusions: Although our meta-analysis showed some favorable effects of allopurinol treatment on improving AIx, its impact on arterial stiffness must be tested in more large-scale RCTs.

MeSH Keywords: Allopurinol • Meta-Analysis • Vascular Stiffness

Study or subgroup	Allopurinol Mean	SD	Total	Control Mean	SD	Total	Weight	Me IV, random, 95% CI
Dawson 2009a	0.09	1.63	17	−0.41	1.5	22	6.8%	0.50 [−0.50, 1.50]
Dawson 2009b	0.74	2.255	10	2.58	6.29	10	0.5%	−1.84 [−5.98, 2.30]
Kao 2011	−0.39	1.13	27	0.2	1.28	26	11.6%	−0.59 [−1.24, 0.06]
Mao 2015	0.14	0.1	29	0.039	0.086	30	24.4%	0.10 [0.05, 0.15]
Rekhraj 2013	−0.14	0.82	31	−0.2	1.22	29	14.1%	0.06 [−0.47, 0.59]
Szwejkowski 2013	−0.71	2.65	29	−0.7	2.22	30	4.8%	−0.01 [−1.26, 1.24]
Wang 2012	−0.053	0.231	366	0.297	0.31	366	24.4%	−0.35 [−0.39, −031]
Wang 2015	−1.59	1.33	43	−0.9	1.34	42	13.3%	−0.69 [−1.26, −0.12]
Total (95% CI)			**552**			**555**	**100.0%**	**−0.19 [−0.49, 0.12]**

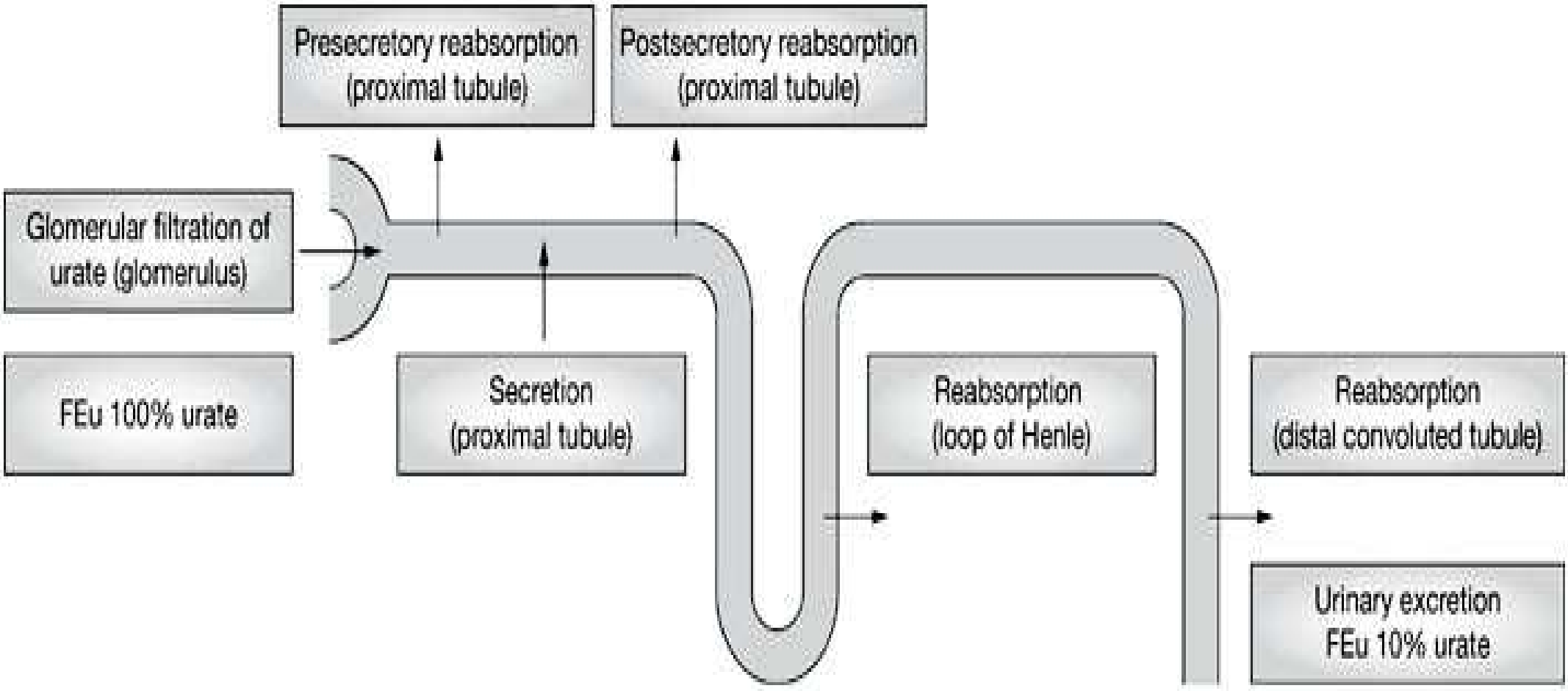
Heterogeneity: Tau^2=0.10; Chi^2=211.46, df=7 (P<0.00001); I^2=97%
Test for overall effect: Z=1.21 (P=0.23)



„Biologická léčba“

léčebné užití tělu vlastních molekul či tkání

- **substituce proteinů** (nejen defektních)
  - enzymů, hormonů, apolipoproteinů, transkripčních faktorů, …
- **buněčná léčba** – kmenovými bb.,…
- **genová léčba** – inhibice, substituce, aktivace
- **inhibice/aktivace regulačních systémů**
  - monoklonálními protilátkami
  - interferující RNA



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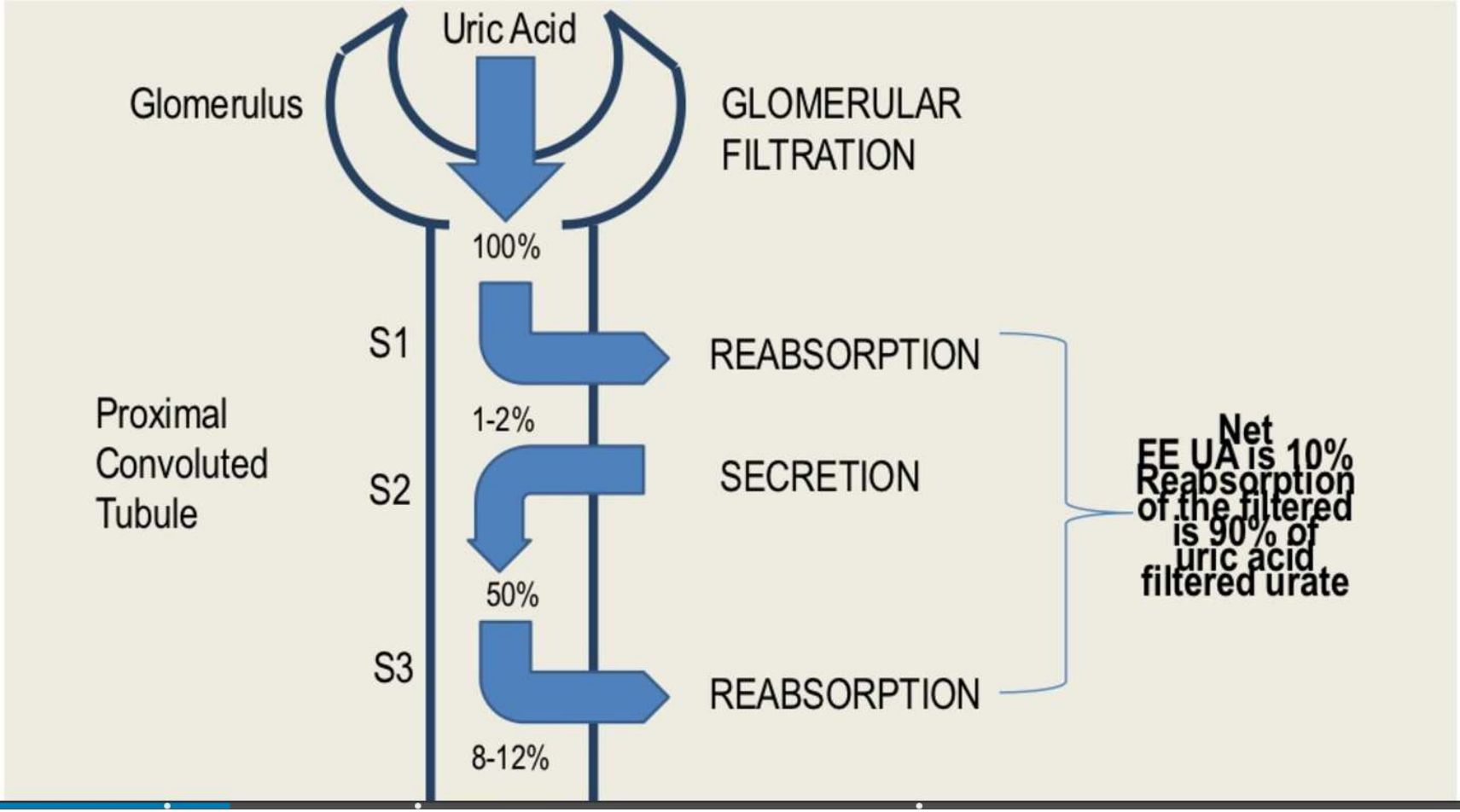

Gois PHF, Souza ERDM. Pharmacotherapy for hyperuricemia in hypertensive patients. Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD008652. DOI: 10.1002/14651858.CD008652.pub3.

- Authors' conclusions
- Meta-analysis was not possible in this systematic review. In the one study that matched the inclusion criteria allopurinol decreased "in office" and ambulatory systolic and diastolic BP. Because there was only one included RCT, the number of patients providing data on pharmacotherapy for hyperuricemia in hypertension is small and restricted to adolescents with recently diagnosed mild essential hypertension. Hence, there is insufficient evidence to recommend the use of allopurinol