Tõendusmaterjali kokkuvõte - EvSu

Kliiniline küsimus nr 12

Kas kroonilise neeruhaigusega patsientidele tuleb ravitulemuste parandamiseks teostada sekundaarse hüperurikeemia ravi vs mitte?

Kriitilised tulemusnäitajad:
kroonilise neeruhaiguse ravi tulemuslikkus, kroonilise neeruhaiguse progresseerumine, komplikatsioonide teke, hospitaliseerimine, patsiendi elukvaliteet, ravikulu, elulemus, üldsuremuse vähenemine, suremus südame- ja veresoonkonnahaigustesse

Kliinilise küsimuse vastamiseks otsiti leiti eelnevalt sekretariaadi poolt Agree II meetodil hinnatud ravijuhenditest

- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. **KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease** (Kidney inter., Suppl. 2013; 3: 1-150; http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf) **(KDIGO)**
- National Clinical Guideline Centre; National Institute for Health and Care Excellence. **Chronic kidney disease (partial update). Early identification and management of chronic kidney disease in adults in primary and secondary care**. Clinical Guideline 182. 2014 (http://www.nice.org.uk/guidance/cg182/evidence/cg182-chronic-kidney-disease-update-full-guideline3) **(NICE)**
- KHA-CARI Guideline: **Early chronic kidney disease: Detection, prevention and management**.2013 (http://www.cari.org.au/CKD/CKD%20early/ckd_early_ckd.html) **(CARI)**

Täiendavalt teostati 17.05.2015. otsing PubMed andmebaasis järgmiste otsingusõnadega : *allopurinol, febuxostat, rasburicase, uric acid, hyperuricaemia, chronic kidney disease.* Otsiti viimase viie aasta jookul avaldatud süstemaatilisi ülevaateid ja metanalüüse. Leiti 20 vastet, millest ravijuhendi kliinilise küsimuse tõenduseks sobis 10 artiklit.

* Vt ka KNH_EvSu_K14II

Ravijuhendid

Hüperurikeemia ravi KNH-ga patsientidel on häsitletud kolmes ravijuhendis (NICE, KDIGO, CARI). Kõigis neis mainitakse, et hüperurikeemia ravi võib pidurdada KNH progressiooni. Samas rõhutatakse kõigis ravijuhistes, et hüperurikeemia ravi KNH patsientidel on uuritud vähe, uurngud on väikeste valimitega ja esineb mitmeid vigu uuringute metoodikas. Kaks ravijuhendit (NICE ja KDIGO) seetõttu soovitust ei sõnasta. CARI juhend annab madala tõenduspõhisusega soovituse mitte kasutada kusihapet langetavaid preparaate 1 – 3 staadiumi KNH patsientidel asümptomaatilise hüperurikeemia raviks, põhjendades seda soovitust just siiani ebapiisava kõrvaltoimete riski uurimisega KNH patsientidel.

NICE, 2014
lk 358 – 364

Ravijuhendis viidatakse seostele seerumi kusihappe taseme ja KNH progressiooni vahel ning võimalikule kasule asümptomaatilise hüperurikeemia ravis KNH patsientidel. Ravijuhendi raames on

koostatud süstemaatiline ülevaade hindamaks kusihappe taseme langetamise efekti kroonilistel neeruhaigetel, kuid kuna teemakohaseid uuringuid oli vähe ja need olid madala kvaliteediga, siis soovitusi ei sõnastatud. Samuti oli plaanis teostada ülevaatlik kulutõhususe analüüs, kuid kuna ühtegi sellekohast uuringut ei leitud, siis ka kulutõhususe koha pealt antud ravijuhend soovitusi ei anna.

Review question: What is the clinical and cost effectiveness of uric acid lowering with allopurinol or febuxostat in the management of CKD?

Eesmärk oli analüüsida randomiseeritud kontrollitud uuringuid ja võrrelda KNH patsientidel asümptomaatilise hüperurikeemia ravi allopurinoli, febuksostaadi, platseebo ja tavapärase raviga *(standard care)*. Kriitilisteks tulemusnäitajateks olid KNH progresseerumine, kardiovaskulaarsed sündmused, antihüpertensiivsete ravimite vähendamine, üldsuremus; olulistks tulemusnäitajateks hospitaliseerimine ja elukvaliteet.

Febuksostaadi kasutamise kohta asümptomaatilise hüperurikeemia raviks KNH-ga patsientidel randomiseeritud kontrollitud uuringuid ei leitud.
Süstemaatilisse ülevaatesse kaasati **3 uuringut allopurinoli kasutamisest asümptomaatilise hüperurikeemiaga KNH patsientidel:**

1. Goicoechea M et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol 2010; 5(8):1388-1393;
2. Kao MP et al. Allopurinol benefits left ventricular mass and endothelial dysfunction in chronic kidney disease. J Am Soc Nephrol 2011; 22(7):1382-1389;
3. Siu YP et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. Am J Kidney Dis 2006; 47(1):51-59.

- Tegemist on väikese valimiga ühe keskuse poolt läbi viidud uuringutega, kus võrreldi allopurinoli kasutamist platseebo või "tavapärase raviga", allopurinoli doos uuringutes oli 100 – 300mg päevas. Täpsemalt ei olnud selgitatud "tavapärase ravi" sisu, lisaks esineb huvide konflikte, võimalikke süstemaatilisi vigu (s.h. vigu pimendamisel) ning uuringutest on palju väljalangejaid. Uuringute kestus on liialt lühike (follow-up 9 – 24 kuud), et hinnata kardiovaskulaarseid sündmusi. **Seega hinnatakse uuringute kvaliteeti madalaks või väga madalaks.**

Kokkuvõtteks järeldati, et:

- **KNH progressiooni aeglustamises (eGFR-i muutusena) võib allopurinol 100mg päevas olla efektiivsem kui platseebo**, samas kui allopurinol 300mg päevas ei erinenud tulemustelt platseebost. Samuti ei olnud statistilist erinevust lõppstaaduimi neerupuudulikkuse ja neeruasendusravi osas uuringu- ja kontrollgrupis. (madal või väga madal tõenduse kvaliteet)
- **Võrreldes platseebo või tavapärase raviga võib allopurinol olla efektiivsem üldsuremuse, kardiovaskulaarsete sündmuste ja hospitaliseerimise vähendamisel**. (väga madal tõenduse kvaliteet)
- **Võrreldes platseebo või tavapärase raviga võib allopurinol omada mõningast antihüpertensiivset efekti** (uuringugrupis enam patsiente, kes uuringu teostamise ajal lõpetasid antihüpertensiivsete ravimite kasutamise ja vähem patsiente, kes vajasid antihüpertensiivse ravi alustamist). (väga madal tõenduse kvaliteet)

Ravijuhendi koostajate arvates on antud järelduste tõendus ebapiisav üldiste soovituste sõnastamiseks.

KDIGO, 2012
lk.79

3.1.20: There is insufficient evidence to support or refute the use of agents to lower serum uric acid concentrations in people with CKD and either symptomatic or asymptomatic hyperuricemia in order to delay progression of CKD. (Not Graded)

KDIGO ravijuhendi töögruppi arvates on oluline teadvustada seoseid KNH-ga kaasneva hüperurikeemia ja kardiovaskulaarsete tüsistuste vahel ning viitavad võimalikule mõjule KNH progresseerumisel, kuid piisava tõenduse puudumise tõttu ei sõnastata soovitusi hüperurikeemia ravi osas.

Small studies using appropriate RCT design have shown reduced left ventricular mass, improved endothelial function, and reduced progression of CKD with uric acid lowering therapy in people with either symptomatic or asymptomatic hyperuricemia and CKD.
**Eelmainitust võib jääda mulje, et tegu on väikest kuid hea kvaliteediga uuringutega. Samas on NICE ravijuhendi süstemaatilises ülevaates kasutatud samu uuringuid (siin viited 316, 317, 320) ja seal hinnatud nende kvaliteeti madalaks või väga madalaks.*

- Published data implicate elevated serum uric acid (SUA) concentrations in the progression of CKD.[311–315] Reduction of SUA by allopurinol has been reported to delay progression of CKD in people with both diabetic and nondiabetic CKD.[316,317]
  Treatment of asymptomatic hyperuricemia has also been reported to improve kidney function even in subjects with normal levels of GFR.[318,319] Both GFR and endothelial function significantly improved in asymptomatic hyperuricemic subjects randomly assigned to 300 mg/day of allopurinol in comparison to placebo.[318]
- A separate doubleblind, placebo-controlled, parallel-group study in 67 people with CKD (GFR 30-60 ml/min/1.73 m2) and left ventricular hypertrophy (LVH) randomly assigned subjects to treatment with allopurinol (300 mg/day) or placebo for 9 months.[320] In comparison to placebo, the allopurinol-treated subjects had significant reductions in left ventricular mass and improvements in endothelial function.
- Another study randomized 70 subjects with SUA ≥420 mcmol/l to treatment with either allopurinol monotherapy (100-200 mg/day) or a combination of allopurinol and a citrate preparation (3 g/day).[321] SUA concentrations were decreased in both groups but to a significantly lower level by combination treatment. GFR assessed by CrCl increased in the combination therapy group but remained unchanged in those treated with allopurinol alone.
- In an 8-week, placebo-controlled group comparison of rasburicase and placebo, a single 4.5 mg dose of rasburicase significantly lowered SUA and resulted in a significant improvement in kidney function assessed by CrCl.[322]
- In a post hoc analysis of 1342 patients with type 2 diabetes mellitus and nephropathy participating in the RENAAL trial, Miao et al. examined the relationship between change in SUA concentration after 6 months of treatment with losartan and doubling of SCr or ESRD.[323] Baseline SUA was 400 mcmol/l. During the first 6 months, losartan lowered SUA by 9.5 mcmol/l [95% CI 0.30-0.01; P¼0.031] as compared with placebo. The risk of doubling of SCr or ESRD was decreased by 6% (95% CI 10%-3%) per 30-mcmol/l decrement in SUA during the first 6 months.

There is insufficient evidence to recommend the use of uric acid lowering agents in asymptomatic individuals for the specific purpose of delaying CKD progression.

CARI, 2013

Guideline grade. (1A, 1B, 1C, 1D, 2A, 2B, 2C, 2D)	Benefit vs. harms	Overall evidence grade (A, B, C, D)	Interpretation	Implications
1A – recommendation with a high quality of evidence.	Benefits clearly outweigh harms or vice versa	A. RCTs without important limitations or overwhelming evidence from high quality observational studies. Confident that the true effect lies close to that of the estimate of the effect.	Applicable to most patients in most circumstances.	Patients: Most would want the recommended course of action and only a small proportion would not. Clinicians: Most patients should receive the course of action. Policy: The recommendation can be adopted as a policy in most situations.
1B – recommendation with a moderate quality of evidence.		B. RCTs with some limitations (methodological, imprecision, indirectness, etc.) or strong evidence from high quality observational studies. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.		
1C – recommendation with a low quality of evidence		C. RCTs with serious limitations (methodological, imprecision, indirectness, etc.) or observational studies with some limitations. The true effect may be substantially different from the estimate of the effect.	Applicable to most patients in most circumstances, that: • may warrant review when higher quality evidence becomes available or • is an obvious course of action irrespective of the evidence (no further research warranted).	
1D – recommendation with a very low quality of evidence		D. Observational studies with limitations or case series. The estimate of the effect is very uncertain, and often will be far from the truth.		
2A – suggestion with a high quality of evidence	Benefits closely balanced harms	A. RCTs without important limitations or overwhelming evidence from high quality observational studies. Confident that the true effect lies close to that of the estimate of the effect.	The best action may differ depending on circumstances or patients' or societal values and other alternatives may be equally reasonable.	Patients: Most would want the recommended course of action, but some would not depending on individual circumstances and values. Clinicians: Different choices will be appropriate for different patients, and a management decision consistent with patients' values, preferences and circumstances should be reached. Policy: would require substantial debate and involvement of many stakeholders.
2B – suggestion with a moderate quality of evidence		B. RCTs with some limitations (methodological, imprecision, indirectness, etc.) or strong evidence from high quality observational studies. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.		
2C – suggestion with a low quality of evidence		C. RCTs with serious limitations (methodological, imprecision, indirectness, etc.) or observational studies with some limitations. The true effect may be substantially different from the estimate of the effect.	The best action may differ depending on circumstances or patients' or societal values and: • other alternatives may be equally reasonable. • suggestion may change when higher quality evidence is obtained.	
2D – suggestion with a very low quality of evidence		D. Observational studies with limitations or case series. The estimate of the effect is very uncertain, and often will be far from the truth.		

Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: uric acid-lowering agents

- **We suggest that use of uric acid lowering agents (such as allopurinol, rasburicase or febuxostat) should not be routinely recommended in people with early (stages 1–3) CKD who have asymptomatic hyperuricaemia (2C).**

Recent small, single-centre, short-duration trials of suboptimal methodologic quality have provided suggestive signals of a benefit of uric acid-lowering agents on surrogate markers of CKD progression. However, there are no adequately powered, high quality randomised controlled trials examining patient-level outcomes to permit recommendation of the routine use of uric acid lowering agents in patients with early (stages 1-3) CKD with asymptomatic hyperuricaemia. There has also not been an adequate assessment of the safety of allopurinol therapy under such circumstances.

Indirect evidence (2 cohort studies) suggests that allopurinol may be beneficial in retarding CKD progression.

- Kanbay et al. [29] performed a 3-month study of 41 patients who were treated with allopurinol 300 mg/d and compared them with 18 healthy controls. In the allopurinol group, there was an improvement of creatinine clearance from 79.2 ± 31.9 to 92.9 ± 36.8 ml/min ($P < 0.05$).
- Talaat et al. [30] examined the effect of allopurinol withdrawal from 50, stage 3-4 CKD patients who had been on chronic allopurinol therapy for mild hyperuricaemia. Allopurinol withdrawal was associated with significant worsening of hypertension and acceleration of the rate of loss of kidney function.

Four RCTs have examined the effect of allopurinol on CKD progression.

- Siu et al. [31] compared 12 months of allopurinol therapy with "usual therapy" and found that allopurinol was safe and helped preserve kidney function. 4 of 25 patients (16%) in the allopurinol group experienced deteriorating renal function or became dialysis-dependent,

compared to 12 of 26 patients (46.1%) in the control group (P < 0.05).

- Gicoechea et al[32] conducted a prospective, randomized trial of 113 patients with eGFR <60 ml/min randomised to treatment with allopurinol 100 mg/d (n = 57) or to continue usual therapy (n = 56) for a period of 24 months. eGFR decreased by 3.3 ± 1.2 ml/min/1.73 m2 in the control group and increased by 1.3 ± 1.3 ml/min/1.73 m2 in the allopurinol group after 24 months (p=0.018). Allopurinol treatment slowed renal disease progression (defined as an eGFR decrease >0.2 ml/min/ 1.73 m2 per month) compared with controls (HR 0.53, 95% CI 0.28-0.99, p=0.048).
- Momeni et al[33] conducted a double-blind RCT of allopurinol 100 mg daily versus placebo for 4 months in 40 CKD patients with type 2 diabetes mellitus, proteinuria >0.5 g/d and serum creatinine <229 µmol/L. After 4 months of treatment, proteinuria was significantly reduced in the allopurinol group compared with controls (1011±767 vs 1609±1071 mg/d, p=0.049).
- A randomised, double-blind, placebo-controlled, parallel-group study of allopurinol 300 mg daily versus placebo in 53 patients with stage 3 CKD and left ventricular hypertrophy for 9 months found that allopurinol significantly reduced left ventricular hypertrophy (p=0.036), improved endothelial function (p=0.009), and improved the central augmentation index (p=0.015)[34]

The advent of two novel, urate-lowering agents, febuxostat (a selective xanthine oxidase inhibitor) and rasburicase (recombinant urate oxidase) may provide alternative approaches in patients with CKD. Both agents have demonstrated better efficacy than allopurinol in lowering uric acid with a more favourable safety profile, particularly in patients with impaired renal function. [35, 36]

- No studies have evaluated the effect of febuxostat on CKD progression.
- One recent RCT compared rasburicase with placebo in elderly (65 – 85 yrs) patients with CKD and hyperuricaemia. [37] In this small (38 patients), 8-week study, patients managed with rasburicase + diet treatment had a decrease in serum creatinine of 60 µmol/L vs an increase of 14 µmol/L in the placebo group, (P < 0.001). The treatment group had an increase in creatinine clearance of 12.7 vs a decrease of 1.10 ml/min/24 h for the placebo group, (P < 0.001).

Süstemaatilised ülevaated

Kokku leiti 10 süstemaatilist ülevaadet või metaanalüüsi, kus käsitletakse hüperurikeemiaga seotud riske ja hüperurikeemia ravi kroonilistel neeruhaigetel. Andmed on saadud nii randomiseeritud kontrollitud uuringutest (6 uuringut) kui ka kohortuuringutest (6 uuringut).

Hüperurikeemiat kui kroonilise neeruhaiguse riskifaktorit ning seoseid hüperurikeemia ja sagedasema KNH esmashaigestumise vahel on kirjeldatud kolmes süstemaatilises ülevaates (**3,5,6**). Ühes neist (**6**) viidatakse lisaks ka hüpertensioonile kui võimalikule hüperurikeemia negatiivse mõju vahendajale neerufunktsiooni langusel. Seega neerufunktsioon võib kõrge kusihappe taseme korral halveneda, suurem on see risk kaasuva hüpertensiooni korral.

Viies süstemaatilises ülevaates (**1,2,4,8,9**) on analüüsitud hüperurikeemia ravi mõju neerufunktsioonile ja jõutud järeldustele, et kusihappe taseme langetamine seostub madalama kreatiniini ja kõrgema eGFR-i väärtustega, stabiilsema neerufunktsiooni ning aeglasema KNH progressiooniga. Lisaks võib hüperurikeemia ravi olla ka antihüpertensiivse efektiga: kahes ülevaates (**1,2**) kirjeldati hüperurikeema ravi ajal süstoolse vererõhu langust, ja ühes (**1**) diastoolse vererõhu langust. Samas ühes artiklis (**4**) ei leitud statistiliselt olulist seost hüperurikeemia ravi ja vererõhu muutuste vahel.

Hüperurikeemia raviga seotud kõrvaltoimetele on viidatud kahes artiklis (**4,10**) – rasked kõrvaltoimed ja hüpersensitiivsusreaktsioonid on küll harvad, kuid KNH patsientidel vähe uuritud ja seetõttu tuleb KNH patsientide ravimisel kusihapet langetavate ravimite (eriti allopurinooliga) olla ettevaatlik. Tähtis on dooside korrigeerimine vastavalt neerufunktsioonile.

Kokkuvõtteks võib öelda, et kuigi on leitud hüperurikeemia ravi positiivne mõju KNH-le, on uuringute kvaliteet siiski madal, mistõttu KNH patsientide sekundaarse hüperurikeemia ravisoovituste osas jäävad autorid tagasihoidlikuks. Hüperurikeemia ravi KNH ennetamise eesmärgil ei ole praegu veel soovitatav (**1**). Samuti ei soovitata ravida asümptomaatilist hüperurikeemiat juba välja kujunenud kroonilise neeruhaigusega patsientidel (**7,9,10**).

Viited

Kokkuvõtte	**Viide kirjandusallikale**
Süstemaatiline ülevaade ja metaanalüüs hindamaks asümptomaatilise hüperurikeemia ravi kasu ja riske KNH 3-5 staadiumi patsientidel**.** - 19 randomiseeritud kontrollitud uuringut, 992 patsienti - Enamik uuringutest olid ühe keskuse põhised ja võrdlemisi väikese valimi (13 – 140 patsienti) ja lühikese jälgimisperioodiga (2 päeva - 24 kuud). Statistilisse analüüsi kaasati lõpuks uuringud (11), kus võrreldi **allopurinoli** inaktiivse kontrolliga (patseebo või mitte ravimine) ja mille pikkus oli vähemalt 3 kuud. **Results:** - Pooled estimate for eGFR was in favour of allopurinol with a mean difference (MD) of 3.2 ml/min/1.73 m2, 95% CI 0.16-6.2 ml/min/1.73 m2, p=0.039. - Pooling of serum creatinine also favoured allopurinol with a mean difference of 0.63 mg/dL (55,7 mcmol/l), 95% CI 0.43-0.83 mg/dL (38 – 73,4 mcmol/l). p=0,003 - Notably reductions were found for both pooled estimates of systolic (MD 6.6 mmHg, 95% CI 2.0-11.1 mmHg) and diastolic blood pressure (MD 2.1 mmHg, 95% CI 0.50-3.7 mmHg). - Proteinuria showed a tendency towards benefit, again favouring allopurinol. **(p = 0.579)** - No serious adverse events were noted in any of the included studies, specifically allopurinol hypersensitivity syndrome, toxic epidermal necrolysis or Steven-Johnson syndrome. **In our meta-analysis of RCTs of treatments to lower serum urate, we observed a small but potentially clinically important and statistically significant improvement in eGFR and serum creatinine, favouring allopurinol. There were also statistically significant reductions in systolic and diastolic blood pressure, and serum uric acid, as expected. A tendency towards benefit for proteinuria was shown as**	**1. Urate lowering therapy to improve renal outcomes in patients with chronic kidney disease:systematic review and meta-analysis**. Kanji T, Gandhi M, Clase CM, Yang R. BMC Nephrol. 2015 Apr 19;16(1):58 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4431373/pdf/12882_2015_Article_47.pdf

well. There were insufficient data on adverse events, incidence of ESRD and cardiovascular disease for analysis. **Conclusions:** Though the data we summarize here are suggestive and encouraging, **using allopurinol in clinical practice to delay progression of CKD would be premature.**	
Süstemaatiline ülevaade ja metaanalüüs, kus hinnati kusihapet langetava ravi tõhusust ja ohutust KNH-st tingitud sekundaarse hüperurikeemiaga patsientidel edasise KNH progresseerumise pidurdamiseks. *UALT = uric acid lowering therapy* - 7 randomiseeritud kontrollitud uuringut 451 uuritavat, 228 uuringugrupis ja 223 kontrollgrupis - uuringud ei olnud pimendatud, enamikel uuringutel randomiseerimise põhimõtted ebaselged, uuringute kvaliteet GRADE järgi C. - väikese valimiga uuringud (47 – 98), uuritavate vanuse mediaan 45,6 – 72,4 aastat, uuringute kestus 6 – 12 kuud - kõik uuritavad KNH ja hüperurikeemiaga, *kuid KNH ei olnud progresseerunud ureemiani (autorid ei täpsusta, mida konkreetselt selle all mõeldakse)* - allopurinoli annus 100 – 300 mg/p - Articles meeting any one of the following would be excluded: (1) Subjects were patients with primary hyperuricemia, or patients with a history of gouty arthritis, renal stones, tumor, allopurinol hypersensitivity or intolerance; (2) Subjects had received UALT in the latest 3 months before screening. **Results** - For the treatment group, SUA was decreased from (501.4±97.8) to (357.3±69.4) μmol/L, (P<0.05). The control group showed no significant difference. - UALT delayed the increase of serum creatinine (mean difference, MD=–62.55 μmol/L, 95% CI: –98.10 to –26.99) and blood urea nitrogen (MD= –6.15 mmol/L, 95% CI: –8.17 to –4.13) as well as the decrease of glomerular filtration rate [MD=5.65 mL/min/1.73 m2), 95% CI: 1.88 to 9.41]. - Compared with control group, UALT was associated with a higher rate of stable renal function (RR=1.73, 95% CI: 1.44 to 2.09) and a lower risk of worsening renal function and ESRD (RR=0.30, 95% CI: 0.19 to 0.46) - UALT decreased systolic blood pressure (SBP) (MD= –6.08 mmHg, 95% CI: –11.67 to –0.49) - UALT reduced the risk of the renal disease progression (RR=0.30, 95% CI: 0.19 to 0.46). - There was no statistically significant difference in 24-h urinary protein quantity and diastolic blood pressure (P>0.05).	**2. Effect of uric-acid-lowering therapy on progression of chronic kidney disease: a meta-analysis.** Zhang YF, He F, Ding HH, Dai W, Zhang Q, Luan H, Lv YM, Zeng HB. J Huazhong Univ Sci Technolog Med Sci. 2014 Aug;34(4):476-81. http://link.springer.com/article/10.1007%2Fs11596-014-1302-4

Conclusion **We identified that UALT could delay the progression of CKD with secondary hyperuricemia. And this also indirectly proved that hyperuricemia was a risk factor for the CKD progression.**	
Süstemaatiline ülevaade ja metaanalüüs hindamaks hüperurikeemia ja KNH vahelisi seoseid. - 13 uuringut, 190 718 uuritavat KNH-ga - enamik kaasatud uuringutest prospektiivsed kohortuuringud, valimis 324 - 94 422 patsienti, jälgimisaeg 2,5 – 18 aastat. - Ei kaasatud uuringuid, kus käsitleti ägeda neerupuudulikkusega, lõppstaadiumis neeruhaigusega või dialüüsravil olevaid patsiente. **Results:** - A significant positive association was found between elevated serum uric acid levels and new-onset CKD at follow-up (summary OR, 1.15; 95% CI, 1.05–1.25). - Hyperuricemia was found to be an independent predictor for the development of newly diagnosed CKD in non-CKD patients (summary OR, 2.35; 95% CI, 1.59–3.46). This association increased with increasing length of follow-up. The present meta-analysis and systematic review found that elevated SUA was significantly positively associated with new-onset CKD in populations with normal renal function: **individuals with hyperuricemia had an increased risk of new-onset CKD compared with those without hyperuricemia.** The association between elevated SUA and the development of new-onset CKD was found to be independent of sex, age, body mass index, alcohol intake, smoking, hypertension, metabolic syndrome, hypertriglyceridemia, diabetes and medication. The summary OR for the association between elevated SUA and development of new-onset CKD increased with increasing length of follow-up time, indicating **hyperuricemia may play a role in the long-term progression of renal function.** Subgroup analysis showed a **stronger association between elevated SUA and CKD development in Western countries** compared with Asian populations. The results of our subgroup analysis found that **males and females had similar risks of CKD and new-onset CKD associated with hyperuricemia.** **We found that hyperuricemia could be a risk factor for CKD**. For patients with subclinical kidney disease, hyperuricemia can be the consequence of decreased renal uric acid excretion, which could in turn further exacerbate kidney function. Therefore, the causal relationship between hyperuricemia and CKD is far more complicated than a simple cause-and-effect relationship. This means that the results of the	**3. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease?: Asystematic review and meta-analysis based on observational cohort studies.** Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P. BMC Nephrol. 2014 Jul 7;15:122. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4132278/

current study should be interpreted with caution. **Our study emphasizes the need to identify individuals with hyperuricemia, as early intervention that decreases SUA levels may lower the risk of developing CKD.** **Conclusions:** With long-term follow-up of **non-CKD individuals, elevated serum uric acid levels showed an increased risk for the development of chronic renal dysfunction.**	
Süstemaatiline ülevaade ja metaanalüüs, milles uuriti, kas allopurinol vähendab KNH patsientide suremust, KNH progresseerumist või kardiovaskulaarset riski. Täiendavalt uuriti materjali allopurinoli kõrvaltoimete ning allopurinoli kasutamise ja elukvaliteedi kohta KNH patsientidel. - 4 randomiseeritud kontrollitud uuringut, kus võrreldi allopurinoli tavapärase raviga, hõlmasid 257 patsienti. Rahuldava kvaliteediga uuringud, valimid võrdlemisi väikesed (40 – 113 patseinti), suur vanuselise koosseisu erinevus uuringute vahel, info randomiseerimise kohta ebapiisav. Jälgimisperiood 6 – 24 kuud. Kardiovaskulaarseid sündmusi oli hinnatud ainult ühes uuringus. - 21 vaatlusuuringut, milles kokku 2372 patsienti **Results**: - Efficacy evidence was derived solely from four randomised controlled trials (RCTs). - Adverse event (AE) data were derived from the RCTs and 21 observational studies. - Progression of CKD was measured by estimated glomerular filtration rate (eGFR) in three trials and by changes in serum creatinine in the other. No significant differences in eGFR over time were reported. The only significant difference between groups was reported in one trial at 24 months favouring allopurinol [eGFR: 42.2 ml/minute/1.73m2, standard deviation (SD) 13.2 vs. 35.9 ml/minute/1.73m2, SD 12.3 ml/minute/1.73m2; p<0.001]. In this same trial, there were twice as many cardiovascular events in the control arm (27%) as in the allopurinol arm (12%). Another trial reported an improvement in CKD progression as measured by serum creatinine in the allopurinol arm. - No significant differences were reported in blood pressure between treatment groups in the meta-analyses. - The incidence of adverse events (AEs) was estimated to be around 9% from all studies. The incidence of severe cutaneous adverse reactions (SCARs), which typically occurred within the first 2 months after allopurinol commencement, was reported to be 2% in two studies. Evidence for whether or not AEs and SCARs were dose related was conflicting. Not all patients had CKD in these studies.	**4. Allopurinol for the treatment of chronic kidney disease: a systematic review.** Fleeman N, Pilkington G, Dundar Y, Dwan K, Boland A, Dickson R, Anijeet H, Kennedy T, Pyatt J. Health Technol Assess. 2014 Jun;18(40):1-77 http://www.ncbi.nlm.nih.gov/books/NBK242342/pdf/TOC.pdf

Conclusions: **There was limited evidence that allopurinol slows down the progression of chronic kidney disease or reduces the occurrence of heart disease.** However, this evidence was not convincing as it was derived from studies with small numbers of patients and similar findings were not reported from more than one study. **No evidence for a significant change in blood pressure, a risk factor for both CKD and CVD, was reported** from any of the trials or from our meta-analysis. **It appears that AEs and in particular serious adverse events attributable to allopurinol are rare**. However, this estimate is derived from evidence of patients treated with allopurinol for any indication and not for CKD. We cannot say whether or not patients with kidney disease taking allopurinol have the same side effects as patients taking the drug for other conditions such as gout. **Direct evidence for the impact of allopurinol on quality of life is lacking.**	
Metaanalüüs, milles uuriti, milline kusihappe tase seostub kroonilise neeruhaiguse esmashaigestumisega. - 15, uuringut 99205 uuritavat, kellest KNH esmashaigestunuid oli 3492. - kaasati uuringud, kus oli mõõdetud kusihappe baastase ja dokumenteeritud KNH esmashaigestumus. KNH esmashaigestunuteks loeti uuritavaid, kelle eGFR uuringu alguses oli >60 mL/min/1.73 m2, kuid langes uuringu lõpuks <60 mL/min/1.73 m2. - longitudinaalsed kohortuuringud, valimid suured (519 – 18778 uuritavat); keskmine vanus 40,5 – 74,5 aastat; keskmine kusihappe tase 238 – 410 mcmol/l (4 - 6,9 mg/dl). Jälgimisperiood 2,2 -26 aastat. Enamikus uuringutes ei olnud infot ravimite tarvitamise kohta (s.h. allopurinol ja diureetikumid). **Results:** - The relative risk of CKD was 1.22 (95% CI 1.16–1.28) per 59,5 mcmol/l (1 mg/dL) serum uric level increment, however, significant heterogeneity was observed (I2 =65.9%, P,0.001). - The observed positive association was more pronounced among group with a mean age <60 years (RR 1.26, 95% CI 1.21–1.31), and low-level heterogeneity was observed in the findings for this age group (I2 = 46.4%, P = 0.022). - No association was observed among studies with a mean age≥60 years (RR 1.04, 95% CI 0.96–1.13), and no evidence of heterogeneity was evident among the studies (I2 = 0%, P = 0.409). - This mean age-related difference in the association between serum uric acid levels and CKD was significant (P = 0.004). **Conclusions:**	**5. Serum uric acid is associated with incident chronic kidney disease in middle-aged populations: a meta-analysis of 15 cohort studies.** Zhu P, Liu Y, Han L, Xu G, Ran JM. PLoS One. 2014 Jun 24;9(6):e100801. http://www.plosone.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pone.0100801&representation=PDF

In the current meta-analysis of 15 cohort studies, **we observed a significant positive association between serum uric acid levels and the incidence of CKD in middle-aged patients. For each 1 mg/dL (59,5 mcmol/l) increment in the serum uric acid level, a 22% increase in the risk of CKD was observed**. This finding was consistent and did not differ appreciably according to the study location, follow-up length, mean serum uric acid level, source of subjects, and adjustment for metabolic syndrome components or proteinuria. In conclusion, **our meta-analysis of cohort studies provides strong evidence that high serum uric acid levels increase the risk of CKD independent of conventional metabolic risk factors. Age may be a potential confounding factor in the risk estimates.**	
Prospektiivne kohortuuring (Rotterdam Study) ja metaanalüüs. Uuriti seerumi kusihappe taseme ja eGFR-i languse ning KNH esmashaigestumise vahelist seost. Andmeid analüüsiti koos teiste sarnaste uuringute tulemustega metaanalüüsis, et hinnata hüperurikeemiast tingitud KNH riski ja võrrelda saadud tulemusi hüper- ja normotensiivsetel patsientidel. - **Rotterdam study**: prospektiivne kohortuuring, 2061 uuritavat, vanus ≥ 55a, uurimisperiood 6,5 aastat. Valimisse ei kaasatud kusihapet langetavate ravimite tarvitajaid. KNH esmashaigestumise analüüsis jäeti valimist välja veel 196 varasemalt teadaoleva KNH-ga patsienti. - Keskmine vanus 70.4 aastat, seerumi kusihape keskmiselt 5.38 mg/dL (314 mcmol/l) ja eGFR keskmiselt 77.15 ml/min/1.73 m2. - **Metaanalüüs**: 12 uuringut, 700 – 14399 uuritavat, enamik populatsioonipõhised kohortuuringud **Results:** - Average annual eGFR decline was 0.92 ml/min per 1.73 m2 (SD = 2.21) for all participants. Each unit (1mg/dL = 59,5 mcmol/l) increase in serum uric acid level was associated with 0.19 ml/min per 1.73 m2 faster annual decline in eGFR (95% confidence interval [CI]: 0.13–0.26) in the age and sex adjusted model. - While the association between serum uric acid and incidence of CKD was not significant in our study population (Hazard Ratio: 1.12, 95% confidence interval [CI]: 0.98–1.28), incorporating our results in a meta-analysis with eleven published studies revealed a significant association (Relative Risk: 1.18, 95%CI: 1.15–1.22; (moderate heterogeneity I2 = 57.7% [19.7%–77.7%]).). - We further examined the association between serum uric acid and CKD separately in hypertensive and normotensive participants. In both models, the association was present in hypertensive subjects (HR: 1.29, 95%CI: 1.14–1.46) but	**6. Serum uric acid and chronic kidney disease: the role of hypertension.** Sedaghat S, Hoorn EJ, van Rooij FJ, Hofman A, Franco OH, Witteman JC, Dehghan A. PLoS One. 2013 Nov 12;8(11):e76827. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3827035/

absent in normotensive subjects (HR: 1.03, 95%CI: 0.85–1.24) (P-value for interaction = 0.030). - In the stratified analyses, we observed that the associations of serum uric acid with eGFR decline and incident CKD were stronger in hypertensive subjects (P for interaction = 0.046 and 0.024, respectively). **Limitations** - Esialgsest valimist langesid välja need, kes jälgimisperioodi jooksul (enne kordusvisiiti) surid. Kuna neist enamik olid vanemad inimesed, kellel kõrgem kusihappe tase ja seega suurem risk KNH tekkeks, võib antud uuring hüperurikeemiaga seotud KNH riski alahinnata. **Conclusions:** **Our findings suggest that hyperuricemia is independently associated with a decline in renal function and CKD incidence. Stronger association in hypertensive individuals may indicate that hypertension mediates the association between serum uric acid and CKD.**	
Süstemaatiline kirjanduse ülevaade hindamaks allopurinoli tõhusust kusihappe langetamisel ja selle ravimi kõrvaltoimete riski KNH patsientidel. - enamik võrdlemisi väikese valimiga retrospektiivsed kohortuuringud ja vaatlusuuringud - KNH patsiendid olid enamikus uuringutes kogu kohordi üks alagruppidest - neerupuudulikkuse raskusastme võrdlemine eri uuringute vahel keeruline, kuna klassifikatsioonid/KNH kriteeriumid erinevad **Results** - Several studies found no significant increases in allopurinol-related adverse effects in patients with CKD when compared with patients without CKD.[19,25,27] However, 1 study did find a higher rate of adverse effects in patients with CKD at baseline.[24] - Age, genetics, and other concomitant medications such as diuretics have been noted to contribute to the risk of adverse events and allopurinol hypersensitivity, but the presence of such medications was not evaluated in all studies presented. - HLA-B*5801 can serve as a valuable screening tool for allopurinol hypersensitivity risk assessment, especially for people of certain nationalities *(asiaadid)* , who may also have renal impairment and carry a greater risk of developing adverse reactions.[20-23] - In general, allopurinol was not effective in reaching the target SUA level when the dose was not titrated.[6] - However, in studies that used doses higher than those recommended and/or allopurinol titration, the number of patients who reached their SUA goal compared with minimal or no titration was improved, without evidence of	**7. Safety and efficacy of allopurinol in chronic kidney disease.** Thurston MM, Phillips BB, Bourg CA. Ann Pharmacother. 2013 Nov;47(11):1507-16.

increase in the risk of serious adverse events.[19,27,28] - Findings from Stamp et al[18] in 2012, led to a recommended starting dose of 1.5 mg of allopurinol per unit of eGFR, with monthly titrations. This aligns with guidelines to limit the starting dose of allopurinol in patients with renal insufficiency. Furthermore, an upper dose limit for increased risk of AHS *(allopurinol hypersensitivity syndrome)* has not been identified.[11,13,18] - In accordance with the clinical practice guidelines for patients with and without renal impairment, allopurinol may be initiated with a dose no greater than 50 to 100 mg/d in CKD. Then, it can be titrated by 50 to 100 mg every 2 to 5 weeks with monitoring of the SUA level prior to the next dose increase. - **When considering allopurinol use in patients with CKD, clinicians should first ensure that patients meet criteria for ULT based on guideline-driven indications because many cases of AHS have occurred in patients with asymptomatic hyperuricemia**. - It is crucial to target a goal SUA of at least <6 mg/dL (357 mcmol/l) with ULT to minimize the risk of acute gouty attacks and subsequent complications. **Conclusions:** Studies evaluating allopurinol use in patients with CKD have reported inconsistent findings relative to safety and efficacy. **Providers should be aware of the potential risk of allopurinol hypersensitivity syndrome as well as the need for reducing the initiation dose and gradual titration of allopurinol to safely achieve a target serum urate level in this population.**	
Metaanalüüs selgitamaks, kas kusihappe taseme langetamine asümptomaatilise hüperurikeemia korral pidurdab neerufunktsiooni langust. - 11 randomiseeritud kontrollitud uuringut, 753 patsienti. **Results** The results showed that ULT was associated with a decrease in serum creatinine and an increase in eGFR. **Our study further confirms that ULT may have beneficial effects on slowing the progression of renal function.**	**8.** Effects of urate-lowering therapy in hyperuricemia on slowing the progression of renal function: a metaanalysis. Wang H, Wei Y, Xianglei K, Xu D. J Ren Nutr. 2013;23(5):389–96.
Süstemaatiline ülevaade kusihapet langetava ravi kasudest ja riskidest neeruga seotud tulemusnäitajate osas (neerufunktsiooni muutus võrreldes baastasemega, lõppstaadiumi neerupuudulikkuse kujunemine, seerumi kreatiniini taseme kahekordistumine, proteinuria muutus, vererõhu muutus, seerumi kusihappe taseme muutus, suremus, kardiovaskulaarsed sündmused, hospitaliseerimine, kõrvaltoimed). - 8 randomiseeritud kontrollitud uuringut, 476 uuritavat. Valimite mediaan 57 uuritavat (36–113); jälgimisaja	**9. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis.** Bose B, Badve SV, Hiremath SS, Boudville N, Brown FG, Cass A, de Zoysa JR, Fassett RG, Faull R, Harris DC, Hawley CM, Kanellis J,

mediaan 11 kuud (4–24 kuud). Märgatav heterogeensus erinevate uuringute vahel neerufunktsiooni baastasemete, KNH põhjuste ja jälgimisperioodi osas. - Kõigis uuringutes sekkumine allopurinoliga, doos 100 – 300mg/päevas. - Kaasatud uuringutest ainult 2 olid platseebokontrollitud. - Võimalikud valikunihked, probleemid pimendamisega **Results** - In five trials, there was no significant difference in change in glomerular filtration rate from baseline between the allopurinol and control arms [mean difference (MD) 3.1 mL/min/1.73 m2, 95% confidence intervals (CI) −0.9, 7.1; heterogeneity $\chi 2 = 1.9$, $I^2 = 0\%$, P =0.75]. - Meta-analysis of the three trials (all in participants with CKD) reporting creatinine data showed that the change in serum creatinine concentration from baseline was in favor of allopurinol (MD −0.4 mg/dL (23,8 mcmol/l), 95% CI −0.8, −0.0 mg/dL; heterogeneity $\chi 2 = 3$, I2 = 34%, P = 0.22). See seos oli seda tugvam, mida pikem oli jälgimisperiood. - Allopurinoli mõju lõppstaadiumi neerupuudulikkuse kujunemise ennetamises oli hinnatud ainult kahes uuringus: allopurinol treatment did not significantly alter the risk of ESRD (RR 1.01, 95% CI 0.15, 6.98, heterogeneity $\chi 2$= 0,I2 = 0%, P = 0.9) - Allopurinol had no effect on proteinuria and blood pressure. - Treatment with allopurinol significantly reduced serum uric acid concentration (8 trials, MD −2.5 mg/dL (149 mcmol/l), 95% CI −3.3, −1.7 mg/dL, P < 0.001). However, this summary statistic should be interpreted with caution due to the presence of a high-level of heterogeneity in treatment estimates between trials ($\chi 2 = 32$, I2 = 78%, P < 0.001). - Allopurinol had uncertain effects on the risks of adverse events. **Conclusions.** Compared with placebo or no treatment, the effects of allopurinol treatment on GFR, proteinuria, progression to ESRD and blood pressure were unclear. Data on the effects of allopurinol on total mortality, major cardiovascular events, hospitalization and adverse effects were insufficient to reliably inform medical practice. While allopurinol therapy lowered serum creatinine concentration (based on 3 trials with 130 participants), effects on GFR, proteinuria and risks of ESKD were uncertain. **Uric acid-lowering therapy with allopurinol may retard the progression of CKD.** **The available RCT evidence evaluating the safety and efficacy of allopurinol as a renoprotective agent in patients with CKD is limited to a small number of single center**	Palmer SC, Perkovic V, Pascoe EM, Rangan GK, Walker RJ, Walters G, Johnson DW. Nephrol Dial Transplant. 2014 Feb;29(2):406-13. http://ndt.oxfordjournals.org/content/29/2/406.long

studies with suboptimal methodology. There is therefore insufficient evidence to currently recommend widespread u se of uric acid-lowering therapy to slow the progression of CKD.	
Süstemaatiline kirjanduse ülevaade hindamaks podagra ravivõimalusi kroonilise neeruhaigusega patsientidel. - Artikkel hõlmab vähe randomiseeritud kontrollitud uuringuid. - Publications were deemed relevant if they reported results from clinical studies, case reports, or prescribing practices of the drug of interest in patients with gouty arthritis and CKD. Articles were not evaluated for risk of bias. **Results:** - Artiklis tuuakse välja, et nii allopurinoli kui ka febuksostaadi kusihapet langetav toime võib lisaks pidurdada ka KNH progresseerumist. Samas ei esine selle väite kinnitamiseks piisavalt tõenduspõhist materjali. - **Asümptomaatilist hüperurikeemiat ravida ei soovitata – puudub piisav tõendusmaterjal, mis sellist ravi toetaks.** - Probleemina viidatakse kroonilistel neeruhaigetel oluliselt sagedamini esinevatele (rasketele) hüpersensitiivsusreaktsioonidele. - Mõeldud on kasutamist diagnoositud podagra korral säilitusravis: Allopurinol can be used for the prophylactic management of chronic hyperuricemia in patients with CKD, but the recommended decreased dosage may limit efficacy and serious hypersensitivity reactions may preclude its use. Febuxostat and pegloticase are new treatment options for chronic urate-lowering prophylaxis; however, the safety of these drugs in patients with advanced CKD has not yet been reported. **Conclusions:** There is currently an unmet need for additional treatment options for the management of gouty arthritis in patients with CKD.	**10. Challenges associated with the management of gouty arthritis in patients with chronic kidney disease: a systematic review.** Curiel RV, Guzman NJ. Semin Arthritis Rheum. 2012 Oct;42(2):166-78.