Kliiniline küsimus nr 14

Kas kroonilise neeruhaigusega patsientidel järgmiste ravimite kasutamise ja annustamise otsustamisel tuleb arvestada neerufunktsiooni (kreatiniin, eGFR) väärtusi vs mitte: metformiin, NSAIDd, AKEId, ARBd, spironolaktoon, digoksiin, aminoglükosiidid, statiinid, aspiriin, allopurinol
Lisa: AKE/ARBide renoprotektiivne toime, AKE/ARBi kombinatsiooniteraapia

Kriitilised tulemusnäitajad: kroonilise neeruhaiguse ravi tulemuslikkus, põhihaiguse ravi tulemuslikkus, äge neerukahjustus, kroonilise neeruhaiguse progresseerumine, neeruasendusravi, hospitaliseerimine, patsiendi elukvaliteet, ravikulu, elulemus, üldsuremuse vähenemine

Süstemaatilised ülevaated

AKE/ARBide renoprotektiivset toimet on kirjeldatud nii diabeetikutel kui kroonilise neeruhaigusega haigetel randomiseeritud kontrollitud uuringutes (RCT). Allpool toodud süstemaatilistes ülevaadetes on kirjeldatud RCT tulemusi.
Vejakama et al. süstemaatilises ülevaates (2012) on kirjeldatud AKE/ARBide renoprotektiivset toimet neerukahjustusega 2. tüüpi diabeetikutel (ülevaates on kirjeldatud 28 uuringute tulemusi sealhulgas RENAAL; HOPE; DIAB-HYCAR, SMART; AASK; UKPDS uuringute tulemusi). Wühl'i (2011) ja Casas'e (2005) süstemaatilistes ülevaadetes on kirjeldatud AKE/ARBIde renoprotektiivset toimet kroonilise neeruhaigusega patsientidel ilma suhkurhaigusega. Ülevaadetes on kirjeldatud MDRD, ABCD, AASK REIN-2 randomiseeritud kontrollitud uuringute tulemusi.
AKE ja ARBi kombinatsiooniteraapia kohta leitud 3 süstemaatilist ülevaadet (Malone et al., Palmer et al., Susantitaphong et al.). NB! Wühl'i artiklis on ka infot ONTARGET (AKE/ARB kombinatsiooniteraapia) uuringu tulemuste kohta. Ülevaadetes kirjeldatud RCT tulemused on erinevad, mistõttu hetkel ühist konsensuslikku arvamust kombinatsiooniteraapia kohta ei ole.

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
P.Vejakama et al. **Reno-protective effects of renin–angiotensin system blockade in type 2 diabetic patients: a systematic review and network meta-analysis (2012)** **Abstract:** Aims/hypothesis This meta-analysis aimed to compare the renal outcomes between ACE inhibitor (ACEI)/angiotensin II receptor blocker (ARB) and other antihypertensive drugs or placebo in type 2 diabetes. **Methods:** Publications were identified from Medline and Embase up to July 2011. Only randomised controlled trials comparing ACEI/ARB monotherapy with other active drugs or placebo were eligible. The outcome of end-stage renal disease, doubling of serum creatinine, microvascular complications, microalbuminuria, macroalbuminuria and albuminuria regression were	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3268972/pdf/125_2011_Article_2398.pdf UKPDS study:http://www.bmj.com/content/317/7160/713.full.pdf+html AASK trial: http://onlinelibrary.wiley.com/doi/10.1111/j.1524-6175.2003.01924.x/epdf SMART study: http://care.diabetesjournals.org/content/30/6/1581.long RENAAL study: http://archinte.jamanetwork.com/article.aspx?articleid=215837 HOPE study:

extracted. Risk ratios were pooled using a random-effects model if heterogeneity was present; a fixed-effects model was used in the absence of heterogeneity. **Results:** Of 673 studies identified, 28 were eligible (n 0 13– 4,912). In direct meta-analysis, ACEI/ARB had significantly lower risk of serum creatinine doubling (pooled RR00.66 [95% CI 0.52, 0.83]), macroalbuminuria (pooled RR00.70 [95% CI 0.50, 1.00]) and albuminuria regression (pooled RR 1.16 [95% CI 1.00, 1.39]) than other antihypertensive drugs, mainly calcium channel blockers (CCBs). Although the risks of end-stage renal disease and microalbuminuria were lower in the ACEI/ARB group (pooled RR 0.82 [95% CI 0.64, 1.05] and 0.84 [95% CI 0.61, 1.15], respectively), the differences were not statistically significant. The ACEI/ARB benefit over placebo was significant for all outcomes except microalbuminuria. A network meta-analysis detected significant treatment effects across all outcomes for both active drugs and placebo comparisons. **Conclusions/interpretation:** Our review suggests a consistent renoprotective effect of ACEI/ARB over other antihypertensive drugs, mainly CCBs, and placebo in type 2 diabetes. The lack of any differences in BP decrease between ACEI/ARB and active comparators suggest this benefit is not due simply to the antihypertensive effect. Süstemaatilises ülevaates kasutatud RENAAL study, HOPE study, UKPDS study, DIAB-HYCAR study, SMART study tulemused	http://www.ncbi.nlm.nih.gov/pubmed/11967789 DIAB-HYCAR study: http://www.ncbi.nlm.nih.gov/pubmed/9081852
Wühl E and Franz Schaefer **Managing kidney disease with blood-pressure control. (2011)** **Abstract:** The progression of chronic kidney disease (CKD) is largely independent of the underlying kidney disorder once renal function has fallen below a critical level. Hypertension is an independent risk factor for disease progression in both adult and pediatric patients with kidney disorders. Increasing evidence from clinical trials indicates that the rate of CKD progression can be lowered by pharmacological interventions. Nephroprotective strategies currently focus on the blockade of the renin–angiotensin system. Angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers provide efficient	http://www.ncbi.nlm.nih.gov/pubmed/21691318

control not only of blood pressure, but also of proteinuria, an effect associated with improved long-term nephroprotection compared with other antihypertensive drug classes. In addition, evidence for an additional nephroprotective advantage of tight blood-pressure control towards the low–normal range in young patients and patients with proteinuria is emerging. In this Review, we describe the role of hypertension in CKD and discuss the therapeutic principle of the prevention of CKD progression with antihypertensive agents. Influence on proteinuria: The MDRD, ABCD and AASK trials demonstrated uniformly that effective blood-pressure control also has a proteinuria-lowering effect. A low blood-pressure goal (that is, <125/75 mmHg in adults) either reduced proteinuria absolutely by 50% or prevented the twofold to threefold rise in proteinuria seen in patients with a more 'conventional' blood-pressure target (that is, 140/90 mmHg).Similarly, in the pediatric ESCAPE trial, effective blood-pressure lowering by ACE inhibition was associated with a reduction of proteinuria by 50% at 6 months of treatment.The early antiproteinuric response predicted long-term renal survival, in keeping with previous findings in adult studies. Combination therapy (AKE/ARB ONTARGET study): However, in patients with high cardiovascular risk owing to atherosclerotic disease and diabetes mellitus, ACE inhibitor–ARB combination therapy, despite providing greater proteinuria reduction, resulted in inferior renal outcomes (including death) than ACE inhibitor or ARB monotherapies.	
Juan P Casas et al. **Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis.(2005)** A consensus has emerged that angiotensin-converting-enzyme (ACE) inhibitors and angiotensin-II receptor blockers (ARBs) have specific renoprotective effects. Guidelines specify that these are the drugs of choice for the treatment of hypertension in patients with renal disease. We sought to determine to what extent this consensus is supported by the available evidence. **Methods** Electronic databases were searched up to January,	http://www.ncbi.nlm.nih.gov/pubmed/16338452

2005, for randomised trials assessing antihypertensive drugs and progression of renal disease. Effects on primary discrete endpoints (doubling of creatinine and end-stage renal disease) and secondary continuous markers of renal outcomes (creatinine, albuminuria, and glomerular filtration rate) were calculated with random-effect models. The effects of ACE inhibitors or ARBs in placebocontrolled trials were compared with the effects seen in trials that used an active comparator drug. **Findings** Comparisons of ACE inhibitors or ARBs with other antihypertensive drugs yielded a relative risk of 0·71 (95% CI 0·49–1·04) for doubling of creatinine and a small benefit on end-stage renal disease (relative risk 0·87, 0·75–0·99). Analyses of the results by study size showed a smaller benefit in large studies. In patients with diabetic nephropathy, no benefit was seen in comparative trials of ACE inhibitors or ARBs on the doubling of creatinine (1·09, 0·55–2·15), end-stage renal disease (0·89, 0·74–1·07), glomerular filtration rate, or creatinine amounts. Placebo-controlled trials of ACE inhibitors or ARBs showed greater benefits than comparative trials on all renal outcomes, but were accompanied by substantial reductions in blood pressure in favour of ACE inhibitors or ARBs. **Interpretation** The benefits of ACE inhibitors or ARBs on renal outcomes in placebo-controlled trials probably result from a blood-pressure-lowering effect. In patients with diabetes, additional renoprotective actions of these substances beyond lowering blood pressure remain unproven, and there is uncertainty about the greater renoprotection seen in non-diabetic renal disease.	
Ausilia Maione et al. **Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials (2011)** **Abstract: Background.** A recent clinical trial showed harmful renal effects with the combined use of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin-II receptor blockers (ARB) in people with diabetes or vascular disease. We examined the benefits and risks of these agents in people with albuminuria and	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4122498/pdf/pone.0104179.pdf Maione A, Navaneethan SD, Graziano G, Mitchell R, Johnson D, Mann JFE *et al. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and combined therapy in patients with micro- and macroalbuminuria and other cardiovascular risk factors: a systematic review of randomized controlled trials.* Nephrology Dialysis

one or more cardiovascular risk factors. **Methods.** MEDLINE, EMBASE and Renal Health Library were searched for trials comparing ACEI, ARB or their combination with placebo or with one another in people with albuminuria and one or more cardiovascular risk factor. **Results.** Eighty-five trials (21 708 patients) were included. Of the 85 RCTs, 52 (11 125 patients) compared ACEI with placebo, 9 (4550 patients) compared ARB with placebo, 12 (4969 patients) compared combination therapy with each monotherapy and 12 (1064 patients) did a head-to-head comparison between ACEI and ARB. There was no significant reduction in the risk of all-cause mortality or fatal cardiac–cerebrovascular outcomes with ACEI versus placebo, ARB versus placebo, ACEI versus ARB or with combined therapy with ACEI 1 ARB versus monotherapy. There was a significant reduction in the risk of nonfatal cardiovascular events with ACEI versus placebo but not with ARB versus placebo, ACEI versus ARB or with combined therapy with ACEI 1 ARB versus monotherapy. Development of end-stage kidney disease and progression of microalbuminuria to macroalbuminuria were reduced significantly with ACEI versus placebo and ARB versus placebo but not with combined therapy with ACEI 1 ARB versus monotherapy. **Conclusions.** ACEI and ARB exert independent renal and nonfatal cardiovascular benefits while their effects on mortality and fatal cardiovascular disease are uncertain. There is a lack of evidence to support the use of combination therapy. A comparative clinical trial with ACE, ARB and its combination in people with albuminuria and a cardiovascular risk factor is warranted.	Transplantation 2011: 26, 2827–2847
Suetonia C Palmer et al. **Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis (2015)** **Summary** **: Background:** The comparative efficacy and safety of pharmacological agents to lower blood pressure in adults with diabetes and kidney disease remains controversial. We aimed to investigate the benefits and harms of blood pressure- lowering drugs in this population of patients. **Methods** We did a network meta-analysis of randomised trials	http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(14)62459-4.pdf

from around the world comparing blood pressure-lowering agents in adults with diabetic kidney disease. Electronic databases (the Cochrane Collaboration, Medline, and Embase) were searched systematically up to January, 2014, for trials in adults with diabetes and kidney disease comparing orally administered blood pressure-lowering drugs. Primary outcomes were all-cause mortality and end- stage kidney disease. We also assessed secondary safety and cardiovascular outcomes. We did random-effects network meta-analysis to obtain estimates for primary and secondary outcomes and we presented these estimates as odds ratios or standardised mean differences with 95% CIs. We ranked the comparative effects of all drugs against placebo with surface under the cumulative ranking (SUCRA) probabilities. Findings 157 studies comprising 43256 participants, mostly with type 2 diabetes and chronic kidney disease, were included in the network meta-analysis. No drug regimen was more effective than placebo for reducing all-cause mortality. However, compared with placebo, end-stage renal disease was significantly less likely after dual treatment with an angiotensin-receptor blocker (ARB) and an angiotensin-converting-enzyme (ACE) inhibitor (odds ratio 0·62, 95% CI 0·43–0·90) and after ARB monotherapy (0·77, 0·65–0·92). No regimen significantly increased hyperkalaemia or acute kidney injury, although combined ACE inhibitor and ARB treatment had the lowest rank among all interventions because of borderline increases in estimated risks of these harms (odds ratio 2·69, 95% CI 0·97–7·47 for hyperkalaemia; 2·69, 0·98–7·38 for acute kidney injury). **Interpretation** No blood pressure-lowering strategy prolonged survival in adults with diabetes and kidney disease. ACE inhibitors and ARBs, alone or in combination, were the most effective strategies against end-stage kidney disease. Any benefits of combined ACE inhibitor and ARB treatment need to be balanced against potential harms of hyperkalaemia and acute kidney injury.	
Paweena Susantitaphong et al. **Efficacy and Safety of Combined vs. Single Renin–Angiotensin–Aldosterone System Blockade in Chronic Kidney Disease: A Meta-Analysis (2013)** **Background:** Although dual blockade of the renin–angiotensin–aldosterone system (RAAS) has gained popularity for the treatment of kidney disease, its	http://ajh.oxfordjournals.org/content/26/3/424.full.pdf+html

benefits and potential risks have not been fully elucidated. We conducted a meta-analysis of all randomized controlled trials comparing the efficacy and safety of combined vs. single RAAS blockade therapy in chronic kidney disease (CKD). **Methods:** We performed a literature search using MEDLINE, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, scientific abstracts from meetings, and bibliographies of retrieved articles. We used random-effects models to compute net changes and rate differences in variables. **Results:** Fifty-nine (25 crossover and 34 parallel-arm) randomized controlled trials (RCTs) comparing the efficacy and safety of combined vs. single RAAS blockade therapy in CKD were identified (4,975 patients). Combined RAAS blockade therapy was associated with a significant net decrease in glomerular filtration rate (GFR) (–1.8 ml/min or ml/min/1.73 m^2; $P = 0.005$), albuminuria (–90mg/g of creatinine; $P = 0.001$ or –32mg/day; $P = 0.03$), and proteinuria (–291mg/g; $P = 0.003$ or –363mg/day; $P < 0.001$). Combined RAAS blockade therapy was associated with a 9.4% higher rate of regression to normoalbuminuria and a 5% higher rate of achieving the blood pressure (BP) goal (as defined in individual trials). However, combined RAAS blockade therapy was associated with a significant net increase in serum potassium level, a 3.4% higher rate of hyperkalemia, and a 4.6% higher rate of hypotension. There was no effect on doubling of the serum creatinine level, hospitalization, or mortality. **Conclusions:** Although combined RAAS blockade therapy in CKD is associated with a decrease in albuminuria and proteinuria, it is associated with a decrease in GFR and a higher incidence of hyperkalemia and hypotension relative to monotherapy. The potential long-term kidney **benefits of combined RAAS blockade therapy require further study.**	
Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events The ONTARGET Investigators (2008) **Background** In patients who have vascular disease or high-risk diabetes without heart failure, angiotensin-converting–enzyme (ACE) inhibitors reduce mortality and morbidity from cardiovascular	http://www.nejm.org/doi/pdf/10.1056/NEJMoa0801317 1. Mann JF, Schmieder RE, McQueen M, Dyal L, Schumacher H, Pogue J *et al. Renal outcomes with*

causes, but the role of angiotensin-receptor blockers (ARBs) in such patients is unknown. We compared the ACE inhibitor ramipril, the ARB telmisartan, and the combination of the two drugs in patients with vascular disease or high-risk diabetes. **Methods** After a 3-week, single-blind run-in period, patients underwent double-blind randomization, with 8576 assigned to receive 10 mg of ramipril per day, 8542 assigned to receive 80 mg of telmisartan per day, and 8502 assigned to receive both drugs (combination therapy). The primary composite outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. **Results** Mean blood pressure was lower in both the telmisartan group (a 0.9/0.6 mm Hg greater reduction) and the combination-therapy group (a 2.4/1.4 mm Hg greater reduction) than in the ramipril group. At a median follow-up of 56 months, the primary outcome had occurred in 1412 patients in the ramipril group (16.5%), as compared with 1423 patients in the telmisartan group (16.7%; relative risk, 1.01; 95% confidence interval [CI], 0.94 to 1.09). As compared with the ramipril group, the telmisartan group had lower rates of cough (1.1% vs. 4.2%, P= 0.01) and a higher rate of hypotensive symptoms (2.6% vs. 1.7%, P= 0.03), and renal dysfunction (13.5% vs. 10.2%, P< 0.001). **Conclusions** Telmisartan was equivalent to ramipril in patients with vascular disease or highrisk diabetes and was associated with less angioedema. The combination of the two drugs was associated with more adverse events without an increase in benefit.	*telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial*. The Lancet 2008: 372, 547–553.

Ravijuhendid

Neljas ravijuhendis (KDIGO, MALAYSIA CKD MANAGEMENT, NICE, SIGN) leidub infot AKE/ARBide näidustuste kohta.

KDIGO

3.1.6: We suggest that an ARB or ACE-I be used in diabetic adults with CKD and urine albumin excretion 30-300 mg/24 hours (or equivalent*). (2D)

3.1.7: We recommend that an ARB or ACE-I be used in both diabetic and non-diabetic adults with CKD and urine albumin excretion more than 300mg/24 hours (or equivalent*). (1B)

3.1.8: There is insufficient evidence to recommend combining an ACE-I with ARBs to prevent progression of CKD. (Not Graded)

Lisamaterjalina otsiti infot ka KDIGO KNH patsientide vererõhuravi käsitlevast juhendist. Soovitused kattusid KDIGO KNH juhendiga.

Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney inter., Suppl. 2012; 2:337–414.

Malaysia

4.1 TREATMENT OF HYPERTENSION AND PROTEINURIA

Recommendation 6:

• Any class of antihypertensive agents can be used to treat hypertension in chronic kidney disease (CKD) patients without proteinuria **(Grade C)** The choice will depend on the patient's co-morbidity.

• Angiotensin-Converting Enzyme Inhibitor (ACEi)/Angiotensin Receptor Blocker (ARB) should be used as first-line agent in:

o non-diabetic CKD with urinary protein excretion ≥0.5 g/day in the presence of hypertension. **(Grade A)**

o non-diabetic CKD when urinary protein excretion ≥1.0 g/day irrespective of the presence of hypertension. **(Grade A)**

o all diabetes patients with albuminuria (micro- or macroalbuminuria) irrespective of the CKD stage and presence of hypertension. **(Grade A)**

Renal profile should be carefully monitored following introduction of ACEi/ARB (refer to **Recommendations in Section 4.4**)

NICE

9.3.6. (lk.318):

Offer a low-cost renin-angiotensin system antagonist to people with CKD and:

o diabetes and an ACR of 3 mg/mmol or more (ACR category A2 or A3)

o hypertension and an ACR of 30 mg/mmol or more (ACR category A3)

o an ACR of 70 mg/mmol or more (irrespective of hypertension or cardiovascular disease).[m] [new 2014]

- Do not offer a combination of renin-angiotensin system antagonists to people with CKD. [new 2014]

- Follow the treatment recommendations in Hypertension (NICE clinical guideline 127) for people with CKD, hypertension and an ACR of less than 30 mg/mmol (ACR categories A1 and A2), if they do not have diabetes. [new 2014]

To improve concordance, inform people who are prescribed renin-angiotensin system antagonists about the importance of:

o achieving the optimal tolerated dose of renin-angiotensin system antagonists and

o monitoring eGFR and serum potassium in achieving this safely. [2008]

SIGN

Patients with chronic kidney disease and type 1 diabetes with microalbuminuria should be treated with an angiotensin converting enzyme inhibitor irrespective of blood pressure. (A)

Patients with chronic kidney disease and type 2 diabetes with microalbuminuria should be treated with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker irrespective of blood pressure. (A)

Angiotensin converting enzyme inhibitors and angiotensin receptor blockers are the agents of choice to reduce proteinuria in patients without diabetes but who have chronic kidney disease and proteinuria. (A)

Angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers should be used as agents of choice in patients *(with or without diabetes)* with chronic kidney disease and proteinuria *(≥0.5 g/day, approximately equivalent to a protein/creatinine ratio of 50 mg/mmol)* in order to reduce the rate of progression of chronic kidney disease. (A)