Kliiniline küsimus nr 4

Kas kõigil kroonilise neeruhaiguse riskigrupi või juba kroonilise neeruhaiguse diagnoosiga patsientidel kasutada täpsemaks albuminuuria(/proteinuuria) hindamiseks **kohest kvantitatiivset albuminuuria (proteinuuria) määramist** vs **albumiini/kreatiniini (proteinuuria/kreatiniini) määramist** vs **ööpäevase albuminuuria (proteinuuria) määramist** või **muud meetodit (albuminuria, proteinuuria testriba)**?
Tulemusnäitajad: haigestumine kroonilisse neeruhaigusesse, patsiendi elukvaliteet, elulemus, üldsuremuse vähenemine, uuringumeetodi tundlikkus ja spetsiifilisus, diagnostiline täpsus

Kliinilisele küsimusele vastates tugenesime sekretariaadi poolt Agree II meetodil hinnatud ravijuhenditele, milledes küsimust oli käsitletud:

- Kidney Disease. Improving Global Outcomes (KDIGO_CKD_2012),
- National Institute for Health and Care Excellence (NICE CKD 2014),
- Scottish Intercollegiate Guidelines Network (SIGN_2008),
- Academy of Medicine of Malaysia (CKD Malaysia 2011),
- Kidney Health Australia CARI Guidelines (KHA-CARI 2013)

Lisaks otsisime PUBMED, OVID Medline andmebaasidest lisaks süstemaatilisi ülevaateid, metaanalüüse ning randomiseeritud kontrollitud uuringuid, kasutades järgmiseid otsinguid:

- PUBMED (("Proteinuria"[Mesh]) AND "Renal Insufficiency, Chronic"[Mesh]) AND "Mass Screening"[Mesh] Filters: published in the last 5 years
- PUBMED proteinuria AND "chronic kidney disease" AND screening Filters: Systematic Reviews; published in the last 5 years
- OVID Medline Proteinuria/ AND Renal Insufficiency, Chronic/ AND Mass Screening/ Limit to last 5 years
- OVID Medline proteinuria.mp. AND chronic kidney disease.mp. AND screening /Limit to systematic reviews and last 5 years

Ravijuhendid:

Kokkuvõte ravijuhendite soovitustest: proteinuuria määramise erinevaid meetodeid ja soovitusi oli käsitletud viies ravijuhendis. (KDIGO_CKD_2012, NICE CKD 2014, SIGN_2008, CKD Malaysia 2011, KHA-CARI 2013)

Kõik ravijuhendid soovitavad kroonilise neeruhaiguse (KNH) riskigrupi patsientidel ja KNH diagnoosiga patsientidel kasutada esmaseks skriinimiseks ja haiguse progressiooni hindamiseks esmasena uriini albumiini-kreatiniini suhet (ACR), soovitatavalt esmasest hommikusest uriinist. Eelistatud on see meetod kindlasti diabeetikutel, et võimalikult varakult diagnoosida diabeetiline neerukahjustus.

Kõrgema proteinuuria taseme puhul sobib proteinuuria määramiseks ja haiguse progressiooni hindamiseks uriini proteiini-kreatiniini suhe (PCR).

Uriini ribatesti võib kasutada esmase meetmena kroonilise neeruhaiguse tuvastamisel, kuna uriini ribatest on mugav, odav ja laialdaselt kasutatav. Uriini ribatestist üksi ei piisa proteinuuria esinemise kinnitamiseks või välistamiseks.

24-tunni uriinist valgu määramine on sama hea kui PCR juhuslikust või hommikusest esmasest uriinist.

NICE CKD 2014:

Mitte *kasutada testribasid proteinuuria määramiseks välja arvatud juhul, kui need on spetsiifilised albumiini mõõtmiseks madalal kontsentratsioonil ja väljendades tulemusi ACR-na. Proteinuuria avastamiseks ja määramiseks kasutada eelistatult ACR (albumiin-kreatiniini suhe) mitte PCR (proteiin-kreatiniini suhe). ACR-l suurem sensitiivsus proteinuuria madala taseme juures. Kvantitatiivseks määramiseks ja kõrge tasemega proteinuuria monitoorimiseks võib PCR –i kasutada kui alternatiivi. <u>ACR on soovitatav meetod diabeedihaigetel.</u>*

ACR 3 mg/mmol või rohkem on kliiniliselt oluline proteinuuria.

Kvantitatiivne albumiini või valgu kadu on soovitatud määrata diabeetikutel ja neil, kellel GFR on vähem kui 60 ml/min/1,73m2.

Kui GFR on 60 ml/min/1,73m2 või rohkem, siis on kvantitatiivne albumiini või valgu kao määramine ainult neil, kellel on tõsine kahtlus kroonilisele neeruhaigusele.

Proteinuria

- Do not use reagent strips to identify proteinuria unless they are capable of specifically measuring albumin at low concentrations and expressing the result as an ACR. [2008]

- To detect and identify proteinuria, use urine ACR in preference to protein:creatinine ratio (PCR), because it has greater sensitivity than PCR for low levels of proteinuria. For quantification and monitoring of high levels of proteinuria (ACR 70 mg/mmol or more), PCR can be used as an alternative. ACR is the recommended method for people with diabetes. [2008, amended 2014]

- For the initial detection of proteinuria, if the ACR is between 3 mg/mmol and 70 mg/mmol, this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol or more, a repeat sample need not be tested. [2008, amended 2014]

- Regard a confirmed ACR of 3 mg/mmol or more as clinically important proteinuria. [2008, amended 2014]

- Quantify urinary albumin or urinary protein loss as in recommendation 18 for:

-people with diabetes

-people without diabetes with a GFR of less than 60 ml/min/1.73 m2. [2008, amended 2014]

- Quantify by laboratory testing the urinary albumin or urinary protein loss of people with a GFR of 60 ml/min/1.73 m2 or more if there is a strong suspicion of CKD (see also recommendation 1.1.28). [2008]

Update 2014

Table 4: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by one level.
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels.

Table 5: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

KDIGO_CKD_2012:

Esmaseks proteinuuria määramiseks soovitatakse kasutada järgmisi meetodeid (eelistatult esmasest hommikusest uriinist):

1.ACR

2.PCR

3.Testriba analüüs totaalse proteinuuria määramiseks (automatiseeritud lugemine)

4.Testriba analüüs totaalse proteinuuria määramiseks (käsitsi lugemine)

Guide to Frequency of Monitoring (number of times per year) by GFR and Albuminuria Category				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	G1	Normal or high	≥90	1 if CKD	1	2
	G2	Mildly decreased	60–89	1 if CKD	1	2
	G3a	Mildly to moderately decreased	45–59	1	2	3
	G3b	Moderately to severely decreased	30–44	2	3	3
	G4	Severely decreased	15–29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

Figure 17 | GFR and albuminuria grid to reflect the risk of progression by intensity of coloring (green, yellow, orange, red, deep red). The numbers in the boxes are a guide to the frequency of monitoring (number of times per year). Green reflects stable disease, with follow-up measurements annually if CKD is present; yellow requires caution and measurements at least once per year; orange requires measurements twice per year; red requires measurements at 3 times per year while deep red may require closest monitoring approximately 4 times or more per year (at least every 1–3 months). These are general parameters only based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient. CKD, chronic kidney disease; GFR, glomerular filtration rate. Modified with permission from Macmillan Publishers Ltd: *Kidney International*. Levey AS, de Jong PE, Coresh J, et al.[30] The definition, classification, and prognosis of chronic kidney disease: a KDIGO controversies conference report. Kidney Int 2011; 80: 17–28; accessed http://www.nature.com/ki/journal/v80/n1/full/ki2010483a.html

1.4.4 Evaluation of albuminuria

1.4.4.1: We suggest using the following measurements for initial testing of proteinuria (in descending order of preference, in all cases an early morning urine sample is preferred) (2B):

(1) urine albumin-to-creatinine ratio (ACR);

(2) urine protein-to-creatinine ratio (PCR);

(3) reagent strip urinalysis for total protein with automated reading;

(4) reagent strip urinalysis for total protein with manual reading.

1.4.4.2: We recommend that clinical laboratories report ACR and PCR in untimed urine samples in addition to albumin concentration or proteinuria concentrations rather than the concentrations alone. (1B)

1.4.4.2.1: The term microalbuminuria should no longer be used by laboratories. (Not Graded)

1.4.4.3: Clinicians need to understand settings that may affect interpretation of measurements of albuminuria and order confirmatory tests as indicated (Not Graded):

- Confirm reagent strip positive albuminuria and proteinuria by quantitative laboratory measurement and express as a ratio to creatinine wherever possible.

- Confirm ACR ≥30 mg/g (≥3 mg/mmol) on a random untimed urine with a subsequent early morning urine sample.

- If a more accurate estimate of albuminuria or total proteinuria is required, measure albumin excretion rate or total protein excretion rate in a timed urine sample.

1.4.4.4: If significant non-albumin proteinuria is suspected, use assays for specific urine proteins (e.g., a1-microglobulin, monoclonal heavy or light chains, [known in some countries as ‘‘Bence Jones’’ proteins]). (Not Graded)

2.1: DEFINITION AND IDENTIFICATION OF CKD PROGRESSION 2.1.1: Assess GFR and albuminuria at least annually in people with CKD. Assess GFR and albuminuria more often for individuals at higher risk of progression, and/or where measurement will impact therapeutic decisions (see figure below). (Not Graded)

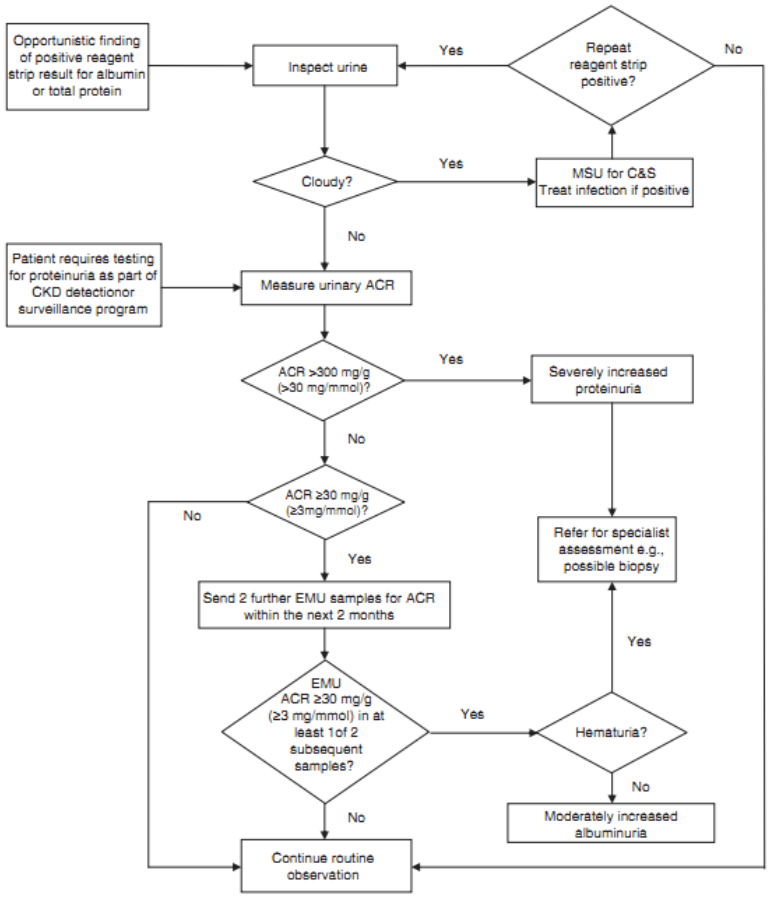


Figure 16 | Suggested protocol for the further investigation of an individual demonstrating a positive reagent strip test for albuminuria/proteinuria or quantitative albuminuria/proteinuria test. Reagent strip device results should be confirmed using laboratory testing of the ACR on at least two further occasions. Patients with two or more positive (≥30 mg/g or ≥3 mg/mmol) tests on early morning samples 1-2 weeks apart should be diagnosed as having persistent albuminuria. The possibility of postural proteinuria should be excluded by the examination of an EMU. PCR measurement can be substituted for the ACR but is insensitive in the detection of moderately increased albuminuria/proteinuria. Approximate PCR equivalent to an ACR of 30 mg/mmol is 50 mg/mmol. ACR, albumin-to-creatinine ratio; C&S, culture and sensitivity; CKD, chronic kidney disease; EMU, early morning urine; MSU, mid-stream urine; PCR, protein-to-creatinine ratio. [a]Consider other causes of increased ACR (e.g., menstrual contamination, uncontrolled hypertension, symptomatic urinary tract infection, heart failure, other transitory illnesses, and strenuous exercise), especially in the case of type 1 diabetes present for less than 5 years. The presence of hematuria may indicate non-diabetic renal disease. This figure was published and adapted from Lamb EJ, Price CP.[122] Kidney function tests, in *Tietz Textbook of Clinical Chemistry and Molecular Diagnostics*, eds Burtis CA, Ashwood E, Bruns DE, 5th edition, pp 669-708, 2012. Copyright Elsevier.

Table 40 | GRADE system for grading quality of evidence

Step 1: Starting grade for quality of evidence based on study design	Step 2: Reduce grade	Step 3: Raise grade	Final grade for quality of evidence and definition
Randomized trials = High	*Study quality* -1 level if serious limitations -2 levels if very serious limitations *Consistency* -1 level if important inconsistency	*Strength of association* +1 level is strong[a], no plausible confounders +2 levels if very strong[b], no major threats to validity *Other* +1 level if evidence of a dose-response gradient +1 level if all residual plausible confounders would have reduced the observed effect	High = Further research is unlikely to change confidence in the estimate of the effect Moderate = Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate
Observational study = Low	*Directness* -1 level if some uncertainty -2 levels if major uncertainty		Low = Further research is very likely to have an important impact on confidence in the estimate and may change the estimate
Any other evidence = Very low	*Other:* -1 level if sparse or imprecise data[c] -1 level if high probability of reporting bias		Very low = Any estimate of effect is very uncertain

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
[a]Strong evidence of association is defined as 'significant relative risk of >2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders.
[b]Very strong evidence of association is defined as 'significant relative risk of >5 (<0.2)' based on direct evidence with no major threats to validity.
[c]Sparse if there was only one study or if the results include just a few events or observations and were uninformative. Imprecise if the confidence interval spans a range greater than 1 or confidence limits are <0.5 to >2.0
Adapted by permission from Macmillan Publishers Ltd: *Kidney International*. Uhlig K, Macleod A, Craig J et al.[725] Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; 70: 2058–2065; accessed http://www.nature.com/ki/journal/v70/n12/pdf/5001875a.pdf

Table 41 | Final grade for overall quality of evidence

Grade	Quality of evidence	Meaning
A	High	We are confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very low	The estimate of effect is very uncertain, and often will be far from the truth.

Table 42 | Balance of benefits and harm

When there was evidence to determine the balance of medical benefits and harm of an intervention to a patient, conclusions were categorized as follows:

- For statistically significant benefit/harm, report as 'benefit [or harm] of drug X'.
- For non-statistically significant benefit/harm, report as 'possible benefit [or harm] of drug X'.
- In instances where studies are inconsistent, report as 'possible benefit [or harm] of drug X'.
- 'No difference' can only be reported if a study is not imprecise.
- 'Insufficient evidence' is reported if imprecision is a factor.

Table 43 | KDIGO nomenclature and description for grading recommendations

	Implications		
Grade*	Patients	Clinicians	Policy
Level 1 'We recommend'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'We suggest'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require substantial debate and involvement of stakeholders before policy can be determined.

Abbreviation: KDIGO, Kidney Disease: Improving Global Outcomes.
*The additional category "Not Graded" was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

CKD Malaysia 2011

KNH skriining sisaldab proteinuuria, hematuuria ja neerufunktsiooni hindamist. Soovitataksse kasutada uriini testribasid proteinuuria skriinimiseks. Diabeetikutel soovitatakse iga-aastaselt määrata uriini albumiini-kreatiniini suhe mikroalbuminuuria skriinimiseks kui ribatest on negatiivne.

Mikroalbuminuuria on diabeetilise neerukahjustuse esmane sümptom ja ennustab kardiovaskulaarhaigustesse haigestumise ja surevuse tõusu ja lõpp-staadiumi neerukahjustuse kujunemist. Uriini ACR on mikroalbuminuuriast tunduvalt sensitiivsem ja spetsiifilisem meetod.

Screening for CKD should include assessment for proteinuria, haematuria and renal function.

Proteinuria

Recommendation 2:

• Urine dipsticks should be used to screen for proteinuria. (Grade C)

• In patients with diabetes, albumin: creatinine ratio (ACR) on an early morning spot urine sample should be performed at least annually to screen for microalbuminuria if urine dipstick is negative. (Grade C) Refer to Algorithm 1 and 2

Proteinuria has both diagnostic and prognostic value in CKD.27, level II-1 However, it shows considerable biological variation. Therefore, the presence of proteinuria should be confirmed by a repeat test within three months.

Urine dipstick testing is convenient, cheap and widely available. It is often the initial measure used to detect CKD. However its accuracy may be affected by fluctuations in urine concentration. Automated urinalysis has greater predictive values for significant proteinuria

(>0.3 g/24 hours) when compared with urine dipstick28, level II-2 and is the preferred method.

Although 24-hour urinary protein or albumin excretion is considered a 'gold standard' for the quantification of proteinuria, it is cumbersome and error may arise from incomplete collection. In a study involving non-diabetic CKD patients, protein: creatinine ratio (PCR) measured on early morning or random urine sample was as good as 24-hour urine protein estimation at predicting the rate of Glomerular Filtration Rate (GFR) loss. In the same group of patients, measurement of PCR may be used to predict risk of progressive disease.29, level III

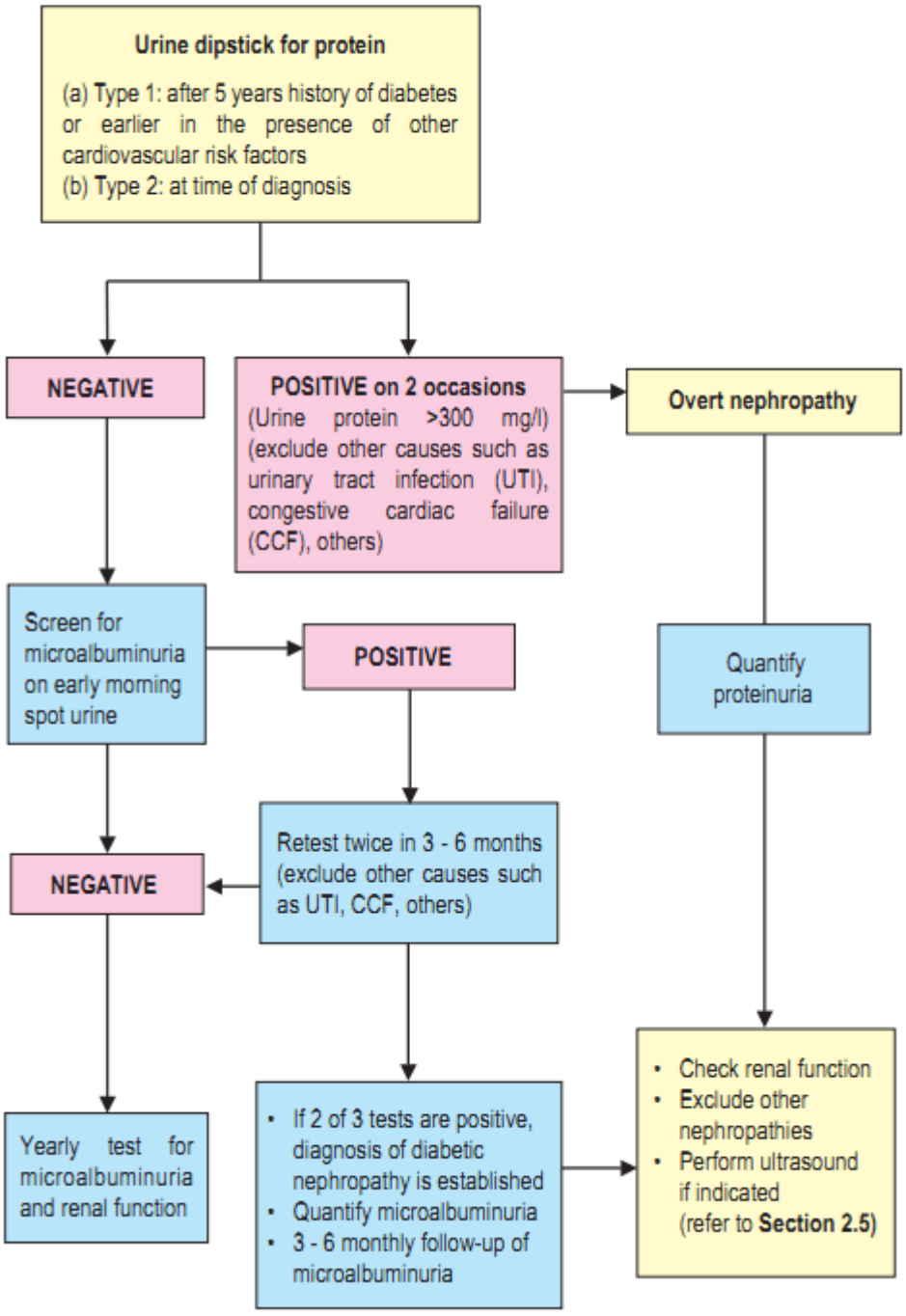
Microalbuminuria refers to the presence of a small amount of albumin in the urine, which cannot be detected with the usual urine dipstick. It is defined as urinary albumin excretion rate 20 - 200 µg/min/24 hour or 30 - 300 mg/24 hour. Overt proteinuria (macroalbuminuria) is defined as albumin excretion rate of >200 µg/min/24 hour or >300 mg/24 hour. Further classification of proteinuria by method of screening is shown in Table 2.

Microalbuminuria is the earliest sign of DKD and predicts increased cardiovascular (CV) mortality and morbidity, and ESRD. Diabetes patients should be screened for microalbuminuria at least annually (refer to Algorithm for Screening of Microalbuminuria in Diabetes Patients). It is also a marker of renal insufficiency in non-diabetes subjects.30, level III

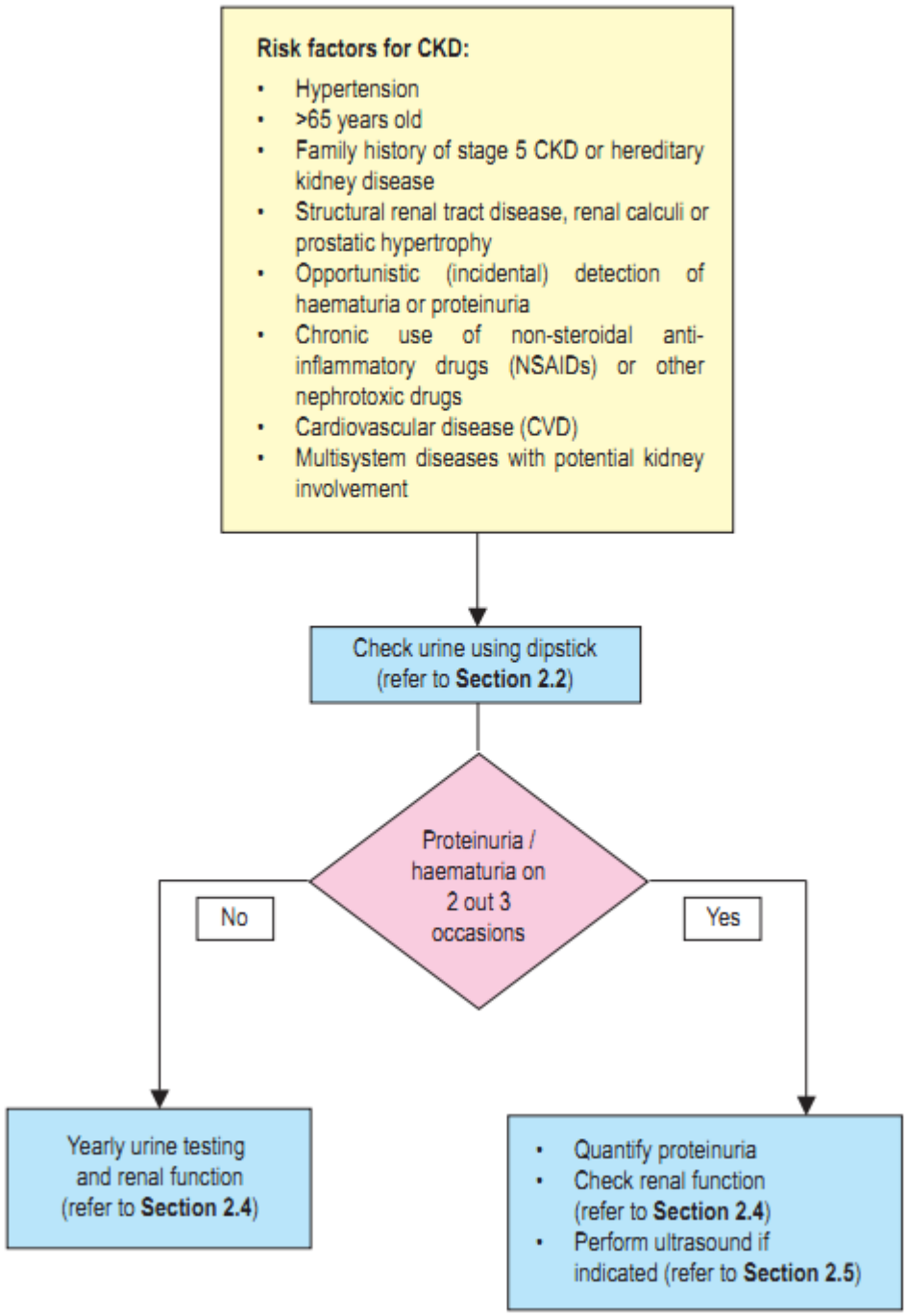
Urine ACR is highly sensitive and specific for microalbuminuria.31, level III This should be performed on an early morning urine sample to minimise the effect of posture and exercise on urine albumin excretion

ALGORITHM 1: SCREENING AND INVESTIGATIONS FOR CKD IN PATIENTS WITH DIABETES

(Adapted: Ministry of Health Malaysia. Diabetic Nephropathy: Putrajaya: MOH; 2004)



ALGORITHM 2: SCREENING AND INVESTIGATIONS FOR CKD IN PATIENTS WITHOUT DIABETES



LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

Note: The grades of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

KHA-CARI 2013

KNH skriinimiseks soovitatakse uriini analüüsi albuminuuria määramiseks ja vere analüüsist kreatiniini eGFR määramiseks. Soovitatakse uriini albumiini : kreatiniini suhet (UACR) esimesest hommikusest uriinist nii diabeetikutel kui ka mitte-diabeetikutel. Kui esmasest hommikusest uriinist pole võimalik määrata, siis soovitatakse UACR määrata juhuslikust uriinist. Positiivset UACR analüüsi tuleks 1-2 korda 3 kuu jooksul korrata. Kui esmane positiivne UACR on juhuslikust analüüsist, siis soovitatakse korrata UACR-i esmasest hommikusest uriinist.

a. We recommend screening for CKD as it is an effective strategy to allow earlier detection and management to reduce the increasing CKD burden (1C).

b. We recommend that screening for CKD be targeted and performed in individuals at increased risk of developing CKD, including those with diabetes mellitus, hypertension, and established CVD (1B).

c. We recommend screening in those with additional CKD risk factors identified in Guideline 2a (obesity, cigarette smoking, Aboriginal and Torres Strait Islander peoples, family history of stage 5 CKD or hereditary kidney disease in a first or second degree relative and severe socioeconomic disadvantage) (1D).

d. We recommend screening every 1–2 years in adults depending on their risk factor profile as per Table 1 (1D).

e. The tests recommended for CKD screening should include both a urine test for albuminuria and a blood test for serum creatinine to determine an eGFR (1C).

f. We recommend a urinary albumin : creatinine ratio (UACR) measurement in a first void specimen for the detection of proteinuria in both diabetic and non-diabetic patients (1C).

i. Where a first void specimen is not possible or practical, a ‘spot’ (random) urine specimen for UACR is recommended (1C).

g. We recommend that a positive UACR screening test should be repeated on 1–2 occasions over a period of three months to confirm persistence of albuminuria. If the first positive UACR is a random spot (as it may be for opportunistic screening), then repeat tests should ideally be first morning void specimens (1D)

i.We recommend following the algorithm depicted in Figure 1 (1D)

Appendix 6: Evidence Grading

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.		

Table 12: Interpretation of grading of guideline statements (recommendations and suggestions) Adapted from Institute of Medicine and KDIGO

SIGN 2008:

Proteinuuria assotsieerub kardiovaskulaar- ja neeruhaigustega ja on organkahjustusele viitav hüpertensiooni patsientidel. Proteinuurial on nii diagnostiline kui ka prognostiline tähtsus. ACR on soovitatav kasutada diabeetilise nefropaatia kinnitamiseks ja monitoorimiseks.KNH-ga mittediabeetikutel võib kasutada PCR haiguse progresseerumise hindamiseks.Uriini ribatest on mugav, odav ja laialdaselt kätte saadav. Uriini ribatestist üksi ei piisa proteinuuria esinemise kinnitamiseks või välistamiseks.

B In patients with diabetes, albumin/creatinine ratio may be used to exclude diabetic nephropathy.

C Albumin/creatinine ratio is recommended for detecting and monitoring diabetic nephropathy.

B In patient groups with a high prevalence of proteinuria without diabetes protein/creatinine ratio may be used to exclude chronic kidney disease.

D In patients with established chronic kidney disease and without diabetes, measurement of protein/creatinine ratio may be used to predict risk of progressive disease.

- Dipstick proteinuria (≥1+) can be used to identify patients at risk of subsequent endstage renal disease and cardiovascular disease.

- Urine dipstick testing cannot be used reliably in isolation to diagnose the presence or absence of proteinuria

Summary of evidence and other considerations.

Overall, the evidence suggests that urine dipstick testing cannot reliably be used to diagnose the presence or absence of proteinuria although there is evidence that dipstick proteinuria (≥1+) predicts ESRD and cardiovascular disease. There is no evidence that isolated asymptomatic UTI causes proteinuria/albuminuria. PCR and ACR are accurate rule-out tests in populations with a high probability of proteinuria. PCR and ACR predict subsequent progression of renal disease. ACR has also been shown to predict cardiovascular disease, although similar evidence for PCR was not identified.7 4 3 2+ 3 3 2++ 4 The measure of protein excretion that is used in a particular context will be influenced by other considerations. For example, because of its widespread availability, convenience and relatively low cost, urine dipstick testing will often be the initial measure used. Where confirmation is required for diagnostic purposes, the lower cost of PCR should be weighed against the superior accuracy of ACR at low concentrations. The role of microalbuminuria in the detection and management of diabetic nephropathy means that ACR will be preferred in patients with diabetes.

KEY TO EVIDENCE STATEMENTS AND GRADES OF RECOMMENDATIONS

LEVELS OF EVIDENCE

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Ravijuhendite allikatest kasutasime järgmiseid artikleid:

1. Gilg J, Rao A, and Fogarty D. UK Renal Registry 16th annual report: chapter 1 UK renal replacement therapy incidence in 2012: national and centre-specific analyses, 2013.
2. Hallan SI, Ritz E, Lydersen S *et al. Combining GFR and albuminuria to classify CKD improves prediction of ESRD.* J Am Soc Nephrol 2009; 20: 1069–1077.
3. Brantsma AH, Bakker SJ, Hillege HL *et al. Cardiovascular and renal outcome in subjects with K/DOQI stage 1–3 chronic kidney disease: the importance of urinary albumin excretion.* Nephrol Dial Transplant 2008; 23: 3851–3858.
4. Waugh J, Bell SC, Kilby M *et al. Effect of concentration and biochemical assay on*

Kokkuvõtte (abstract või kokkuvõtlikum info)	Viide kirjandusallikale

the accuracy of urine dipsticks in hypertensive pregnancies. Hypertens Pregnancy 2001; 20: 205–217.

5. Waugh J, Bell SC, Kilby MD *et al*. *Urine protein estimation in hypertensive pregnancy: which thresholds and laboratory assay best predict clinical outcome?* Hypertens Pregnancy 2005; 24: 291–302.
6. White SL, Yu R, Craig JC *et al*. *Diagnostic accuracy of urine dipsticks for detection of albuminuria in the general community*. Am J Kidney Dis 2011; 58: 19–28.
7. Medicines and Healthcare products Regulatory Agency. MHRA 04086 Point of care devices for the quantitation of microalbuminuria. 2004.
8. Medicines and Healthcare products Regulatory Agency. MHRA 04098. Point of care devices for the detection and semi-quantitation of microalbuminuria. 2004.
9. Chitalia VC, Kothari J, Wells EJ, Livesey JH, Robson RA, Searle M, Lynn KL. *Cost-benefit analysis and prediction of 24-hour proteinuria from the spot urine proteincreatinine ratio.* Clin Nephrol. 2001 Jun;55(6):436-47.
10. Kondo M, Yamagata K, Hoshi S *et. al*. *Cost-effectiveness of chronic kidney disease mass screening test in Japan.* Clin Exp Nephrol. 2012 Apr; 16(2): 279–291.

Süstemaatilistes otsingutes vastas ülaltoodud otsingukriteeriumitele 84 tulemit, milledest kliinilisele küsimusele vastamiseks lisas lisaks ravijuhendites ilmnenud soovitustele lisaks 9 artiklit. Kolmes artiklist käsitleti proteinuuria uurimise kulutõhusust Uus-Meremaal, Jaapanis, Belgias ning Šveitsis.

Kõik neli kulutuluanalüüsi jõudsid järeldusele, et proteinuuria hindamine on põhjendatud kulutõhususe aspektist. Ribatesti hinnati kättesaadavuse osas heaks uuringuks, ent meetod ei täida hea skriinimismeetodi kriteeriume, üldpopulatsiooni skriinimiseks oli see Jaapanipõhisel uuringul kulutõhus, ent sellele lisaks on põhjendatud ja kulutõhus ka kreatiniini määramine. Belgia uuringul keskenduti just ilma riskiteguriteta patsientide skriinimisele, sealne tulem oli, et mõttekas on siiski skriinida riskitegurite patsiente.

*NHS EED kriteeriumitele vastav **kulutuluanalüüs** Uus-Meremaal: proteinuuria hindamine 24 tunni uriinianalüüsi ning valk/kreatiniini suhtena uriinis. Uuringusse kaasati ambulatoorsed patsiendid (170), kel glomeurlonefriit (ööpäevane proteinuuria pidi olema rohkem kui 200 mg 1,73 m^2 kohta. Uuringusse ei kaasatud tubulaarse proteinuuriaga ega UTI patsiente. Maksumus ei arvutatud mitte koguvalimilt vaid haigestunute hindamisel, suhtelisel maksumusanalüüsil. Otsuse analüüsimise mudelis arvestati meditsiinilisi tulemeid, mis on seotud iga diagnostilise meetodiga. Sensitiivsusanalüüsi ei teostatud. Uuringu patsiendipõhist maksumust ei arvutatud. Uuringu tulemus: hoolimata neerufunktsioonist on 24 tunni proteinuuria ning uriinis valgu kreatiniini suhte (ribatestil) vahel hea korrelatsioon, topeltanalüüs ei parandanud ribatesti usaldusväärsust.* *Uuringu puuduseks on väike patsientide arv, samuti olid patsiendid eelselekteeritud – nende diagnoosiks oli glomerulonefriit (kroonilise neerupuudulikkuse põhjuseid on oluliselt hulgim)*	**Cost-benefit analysis and prediction of 24-hour proteinuria from the spot urine proteincreatinine ratio** *Chitalia V C, Kothari J, Wells E J, Livesey J H, Robson R A, Searle M, Lynn K L* https://www.ncbi.nlm.nih.gov/pubmed/11434354 *Tulemusnäitajad: diagnostiline täpsus*
Kuluefektiivsuse analüüs võrdlevate skriiningtestide alusel Jaapanis iga-aastase tervisekontrolli käigus: võrdluses kõikide patsientide skriinimine vs üldse mitte. *¥1,139,399/QALY (US $12,660/QALY) üksnes ribatest määramine on kuluefektiivne* *¥8,122,492/QALY (US $90,250/QALY) kreatiniini määramine on kuluefektiivne* *8,235,431/QALY (US $91,505/QALY) ribatest + kreatiniini määramine võiksid kuuluda üldpopulatsiooni skriinimisse* *Tegemist on metodoloogiliselt hea analüüsiga, mis on olustikukohane; käsitleb üldelanikkonna vanuses 40 – 74 eluaastat skriinimist, hoolimata sellest, kas esineb riskitegureid või mitte.*	***Cost-effectiveness of chronic kidney disease mass screening test in Japan*** *Masahide Kondo, Kunihiro Yamagata, Shu-Ling Hoshi, Chie Saito, Koichi Asahi, Toshiki Moriyama, Kazuhiko Tsuruya, Hideaki Yoshida, Kunitoshi Iseki, Tsuyoshi Watanabe* https://www.ncbi.nlm.nih.gov/pubmed/11434354 *Tulemusnäitajad: patsiendi elukvaliteet*
URI Study – cross-sectional study Belgia tööealistest inimestest, kel on iga-aastane vabatahtlik tervisekontroll jaanuaris 2007.a – detsembris 2009.a. Ravimkoormatud patsiendid, kel hüpertooniatõbi, diabeet, düslipideema, kardiovaskulaarhaigus, neeruhaigus arvati välja. *1191 patsienti, kel oli diagnoosimata riskifaktor – skriiniti. Teadaolevalt terve populatsiooni skriinimine toob kaasa suure valepositiivsete tulemuste arvu. Uuringu eesmärk oli leida skriinimiseks ratsionaalne meetod. Uuringu tulemused avaldatid protsentide või standarddeviatsoonidena. 98% uuritavatest oli eGFR üle 60 ml/min/1,73m^2 ning ühelgi uuringus osalejast polnud eGFR alla 50 ml/min/1,73m^2, keskmine vanus oli 38,3. 4.2% valimist võis diagnoosida mikroalbuminuura, 0,04% makroalbuminuuria. Tulemustele*	***Towards a Rational Screening Strategy for Albuminuria: Results from the Unreferred Renal Insufficiency Trial*** *Arjan van der Tol1*, Wim Van Biesen1, Francis Verbeke1, Guy De Groote2, Frans Vermeiren3, Kathleen Eeckhaut3, Raymond Vanholder1* http://journals.plos.org/plosone/article/asset?id=10.1371%2Fjournal.pone.0013328.PDF *Tulemusnäitajad: diagnostiline täpsus*

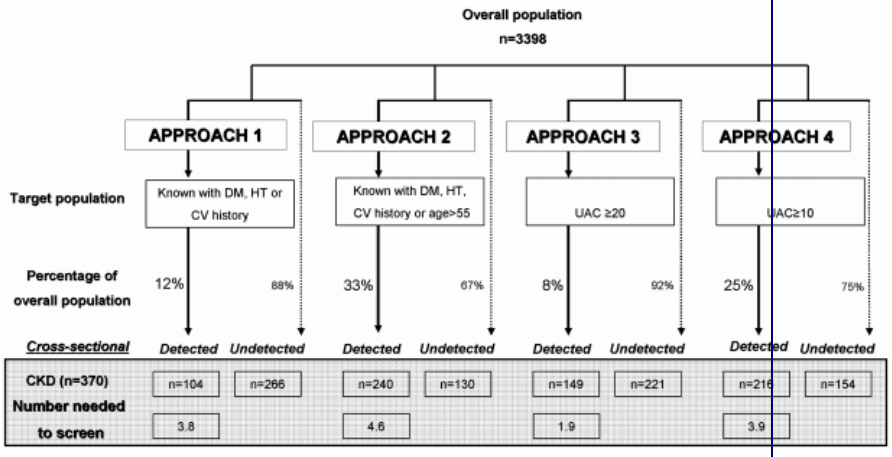
lisati riskifaktorid. *Kokkuvõte: mõttekas on skriinida, kui on riskifaktorid.*	
Skriinima peaks riskigruppi kuuluvaid patsiente. *Uuring on osa prospektiivsest kohortuuringust PREVEND, mille põhieesmärgiks on selgitada albuminuuria osa neeruhaiguse ja südame-veresoonkonna haiguste tulemusnäitajatesse ülepopulatsioonis.* *Kroonilise neeruhaiguse skriinimine riskigruppides nelja lähenemisvõttega* *1) anamneesis südame-veresoonkonnahaigus, suhkurtõbi, kõrgvererõhuhaigus* *2) kõrge südame-veresoonkonna haiguse risk või vanus üle 55 eluaasta* *3) albumiini uriinis rohkem kui 20 mg/L* *4) albumiini uriinis rohkem kui 10 mg/L skriinimise eelselt* *Valimis 3398 patsienti, krooniline neeruhaigus diagnoositi 370 patsiendil, kõige tulemuslikum 2) lähenemisvõte (sensitiivsus 66%), kõige vähem avastas skriinitavaid 3) lähenemisvõte. Samas olid albumiini määramisega meetodid seitsmeaastase jälgimisperioodi vältel need, mis suutsid ennustada neerufunktsiooni langust ning suurenenud kardiovaskulaarset riski võrreldes normaalse neerufunktsiooniga patsientidega. Kokkuvõtvalt leiti, et albumiini kontsentratsiooni määramine uriinis on eelistatud meetod kroonilise neeruhaigusega patsiendi neerufunktsiooni languse ning südame-veresoonkonna riskide hindamiseks.*  **Fig. 2.** Cross-sectional and longitudinal outcome of different screening approaches; *P < 0.05 compared to no CKD. *(mitu patsient on vajalik antud lähenemisvõttel skriinida, et avastada üks patsiet kroonilise neeruhaigusega)*	***Comparison of the yield of different screening approaches to detect chronic kidney disease*** *Marije van der Velde, Paul E. de Jong and Ronald T. Gansevoort* *NDT 2010.a* *http://ndt.oxfordjournals.org/content/25/10/3222.full* *Tulemusnäitajad: haigestumine kroonilisse neeruhaigusesse, üldsuremuse vähenemine, uuringumeetodi tundlikkus ja spetsiifilisus*

Table 3. Screening approach test characteristics to detect CKD

	Approach 1: CV risk	Approach 2: CV risk or age >55 years	Approach 3: UAC ≥20 mg/L	Approach 4: UAC ≥10 mg/L
Sensitivity (%)	28	65	40	58
Specificity (%)	90	71	96	81
Positive predictive value (%)	26	22	55	28
Negative predictive value (%)	91	94	93	94
Likelihood ratio positive test	2.95	2.25	10.08	3.12
Likelihood ratio negative test	0.79	0.49	0.62	0.51

UAC, urinary albumin concentration; CV, cardiovascular.

Lähenemisviis 2) selgitab kindlasti patsiendid, kel on ühtviisi neeruhaiguse kui kardiovaskulaarhaiguse risk!

Uuringu kokkuvõte: kroonilise neerupuudulikkuse uuringud peaksid lähtuma pigem eelskriiningust ööpäevase albumiini erituse kui vaid riskitegurite alusel, sest see võimaldab lisaks neeruhaigusele hinnata ka südame-veresoonkonna haiguste osas.

Mikroalbuminuuria skriinimise kulutõhusus üle 50-aastastel patisentidel Šveitsis 1-, 2-, 5- ja 10-aastase intervalliga. Patsiendi on jaotatud
1) suhkurtõbi
2) kõrgvererõhutõbi (suhkurtõbe ei ole!)
3) ei ole kõrgvererõhutõbe ega suhkruhaigust.
Tulemus: suhkrutõvehaigete skriinimine mikroalbuminuuria osas 2-aastase intervalliga on kulutõhus, kõrgvererõhuhaigete skriinimine 5-aastase intervalliga on kulutõhus; muu rahvastiku osas 10-aastase intervalliga.

PREVEND uuringu alusel (8592 patsienti) skriinimine (ühekordne test mikroalbuminuuriale) 8-aastase intervalliga tähendab 22 000 naelast võitu ühe kvaliteetse eluaasta kohta.

Uuringus oli skriinimismeetodiks albumiin-kreatiniini suhe, mis on ravijuhendite poolt soositud meetod.

Health economic modelling of the costeffectiveness of microalbuminuria screening in Switzerland
Reto Kesslera, Gérald Keuschb, Thomas D. Szucsc, John S. Wittenbornd, Thomas J. Hoergerd, Urs Brüggere, Simon Wiesere
The European Journal of Medical Sciences, veebruar 2012.a
https://www.ncbi.nlm.nih.gov/pubmed/20335273?dopt=Abstract
Tulemusnäitajad: patsiendi eluk valiteet ?

Tegemist on heale andmestikule ja analüüsile põhineva kokkuvõttega, mis väidab, et uriini ribaanalüüs ei täida hea skriiningmeetodi kõiki kriteeriume – on palju valepositiivseid tulemusi, mis nõuavad lisaanalüüse ning tõstavad seeläbi kulutusi. Rutiinne skriinimine ei ole kuluefektiivne ($200,000/QALY).

Table 1.
Accuracy of a dipstick result ≥1+ to identify patients with ≥300 mg/g albuminuria

	≥300 mg/g Albuminuria Present by ACR[a]	***<300 mg/g Albuminuria Pres by ACR[b]***

The Primary Care Perspective on Routine Urine Dipstick Screening to Identify Patients with Albuminuria Clin J Am Soc Nephrol. 2013 Jan;8(1):131-5. doi: 10.2215/CJN.12681211. Epub 2012 Aug 23.
https://www.ncbi.nlm.nih.gov/pubmed/22917702
Lipika Samal and Jeffrey A. Linder

Tulemusnäitajad: haigestumine kroonilisse neeruhaigusesse, üldsuremuse vähenemine, uuringumeetodi tundlikkus ja spetsiifilisus, diagnostiline täpsus

Urine dipstick test-positive[c]	*90 (true positives)*	*798 (false positives)*	*888*
Urine dipstick test-negative[d]	*1 (false negative)*	*9947 (true negatives)*	*9948*
Total	*91*	*10,745*	

- *ACR, albumin to creatinine ratio. Modified from ref. 1, with permission.*
- *[a] Sensitivity = (number of true positives)/(number of true positives + number of false negatives)=99%.*
- *[b] Specificity = (number of true negatives)/(number of true negatives + number of false positives)=93%.*
- *[c] Positive predictive value = (number of true positives)/(number of true positives + number of false positives)=10%.*
- *[d] Negative predictive value = (number of true negatives)/(number of true negatives + number of false negatives)=100%.*

Table 2.

Accuracy of a dipstick result ≥1+ to identify patients with ≥30 mg/g albuminuria

	≥30 mg/g Albuminuria Present by ACR[a]	***<30 mg/g Albumin Present by ACR[b]***
Urine dipstick test-positive[c]	*419 (true positives)*	*469 (false positive*
Urine dipstick test-negative[d]	*306 (false negatives)*	*9642 (true negativ*
Total	*725*	*10,111*

- *ACR, albumin to creatinine ratio. Modified from ref. 1, with permission.*
- *[a] Sensitivity = (number of true positives)/(number of true positives + number of false negatives)=58%.*
- *[b] Specificity = (number of true negatives)/(number of true negatives + number of false positives)=95%.*
- *[c] Positive predictive value = (number of true positives)/(number of true positives + number of false positives)=47%.*
- *[d] Negative predictive value = (number of true negatives)/(number of true negatives + number of false negatives)=97%.*

KEEP uuring, kõrge riskiga valim – patsiendid, kel kõrgem vererõhk (süstoolne), diabeet, madalam eGFR, must rass. Riskitegurid on iseenesest sõltumatud ennustajad kroonilise meeruhaiguse tekkeks. Samas albuminuuria puudumine tähendab, et progresseerumise tõenäosus terminaalse neerupuudulikkuseni on madal. *Patsientidelt koguti analüüside seerumi kreatiniini hindamiseks, albuminuuriahindamiseks; eGFR arvutamiseks kasutatu EPI valemit. Alates aprillist 2002.a hakati lisaks määramat albumiin/kreatiniini suhet (<30, 30–300).* *KEEP kohortuuring, eGFR üle 60 mL/min/1,73 m, jälgimiseks keskmiselt 4,8 aastat.* 1) *126 of 13,923 patsienti albuminuuriaga (16/10,000 patient-years)* 2) *56 of 109,135 patsient, kel ei ole albuminuuriat (1.1/10,000 patient-years)* *Mõlema grupi puhul oli tõenäosus kroonilise neerupuudulikkuse progresseerumiseks kõrgem, kui kaasuvaks haiguseks oli diabeet*	***Risk Factors for ESRD in Individuals With Preserved Estimated GFR With and Without Albuminuria: Results From the Kidney Early Evaluation Program (KEEP)*** *Tara I. Chang, MD, MS1, Suying Li, PhD2, Shu-Cheng Chen, MPH, MS2, Carmen A. Peralta, MD, MAS3, Michael G. Shlipak, MD, MPH4, Linda F. Fried, MD, MPH5, Adam T. Whaley-Connell, DO, MSPH6, Peter A. McCullough, MD, MPH7, Manjula Kurella Tamura, MD, MPH1, and on behalf of the KEEP Investigators** https://www.ncbi.nlm.nih.gov/pubmed/23507268 *Tulemusnäitajad: haigestumine kroonilisse neeruhaigusesse, patsiendi elukvaliteet, elulemus, uuringumeetodi tundlikkus ja spetsiifilisus, diagnostiline täpsus*
Prospektiivne kohortuuring, osales 2754 patsienti – uuringu alusel suudab skriiningstrateegia selgitada ~90,8 % patsientidest õigesti kroonilise neeruhaiguse esinemise osas, 1,5% on ekslikult trakteeritud krooniliseks neeruhaiguseks ning 7,7% jäi ekslikult kroonilise neeruhaiguse diagnoosita. Suur osakaal on riskitegurite arvestamisel, eGFR määramine on hea valik, et skriinigmeetodile ribaanalüüsi lisamine tõstis kroonilise neeruhaiguse diagnoosimise tõenäosuse 13%lt 44%ni.	***Dipstick Proteinuria as a screening Strategy to Identify Rapid Renal Decline 2010*** ***William F. Clark,*† Jennifer J. Macnab,‡ Jessica M. Sontrop,*†‡ Arsh K. Jain,*† Louise Moist,*†‡ Marina Salvadori,§ Rita Suri,*† and Amit X. Garg*†‡*** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3171943/ *Tulemusnäitajad: haigestumine kroonilisse neeruhaigusesse, uuringumeetodi tundlikkus ja spetsiifilisus, diagnostiline täpsus*