Kliiniline küsimus nr 13

Kas kõikidel kroonilise neeruhaigusega patsientidel sõltub komplikatsioonide teke:
- neerufunktsiooni muutusest vs mitte
- põhidiagnoosist vs mitte?

Kriitilised tulemusnäitajad: kroonilise neeruhaiguse ravi tulemuslikkus, komplikatsioonide teke, kroonilise neeruhaiguse progresseerumine, neeruasendusravi, südame-vereseoonkonna tüsistused, aneemia, sekundaarne hüperparatüreoidism, hospitaliseerimine, patsiendi elukvaliteet, ravikulu, elulemus, üldsuremuse vähenemine

Otsiti andmebaasidest PubMed, MedLine. Filtriteks kasutati süstemaatilised ülevaated, meta-analüüsid, randomiseeritud-kontrollitud uuringud, viimased 5 aastat, inimesed, tasuta täistekst
Otsingud 16.-21.november 2015
Otsingusõnad: krooniline neeruhaigus, komplikatsioonid, progresseerumine, eGFR
"chronic kidney disease"[All Fields] AND ("complications"[Subheading] OR "complications"[All Fields]) AND egfr[All Fields] AND "disease progression"[MeSH Terms] leitud kokku 1126 selekteerimise käigus sobivateks võetud 5 artiklit
Lisaks andmebaasidest leitud uuringutele kasutati eelnevalt sekretariaadi poolt Agree II meetodil hinnatud ravijuhendeid

Süstemaatilised ülevaated
Leiti viis sobivat uuringut. Autorid hindasid uuringute tugevuseks suurt osalejate hulka. Peamiseks nõrkuseks peeti lühikest järelkontrolli või jälgimisaega. Oluliseks hinnati komplikatsioonide tekkimise ennetamist, mis vähendab lõppstaadiumis neeruhaiguse teket ja suremust ning teisi võimalikke kaasuvaid tüsistusi. Samuti vähendab ravikulusid.
Kuna põhidiagnoosidele uuringuid ei leitud tehti vastavalt töörühma ja sekretariaadi koosoleku otsusele ja kokkulepitud strateegiale uus otsing. Valitud põhidiagnooside (kõrgvererõhktõbi, diabeet, glomerulonefriit, polütsüstoos) ja komplikatsioonide tekke osas (aneemia, hüperparatüreoos, isheemiatõbi jm südame- ja veresoonkonna kahjustused).

Otsingud tehti PubMed ja MEDLINE andmebaasidest. 02.-12. Jaanuar 2016

Otsingusõnad hüpertensioon, diabeet, glomerulonefriit ja polütsüstoos. Otsingusse lisati võimalike komplikatsioonide teke - aneemia, hüperparatüreoos, isheemiatõbi, südame- ja veresoonkonna kahjustused ja atsidoos.

"chronic kidney disease"[All Fields] AND ("disease progression"[MeSH Terms] OR ("disease"[All Fields] AND "progression"[All Fields]) OR "disease progression"[All Fields] OR "progression"[All Fields]) AND ("Diabete"[Journal] OR "diabete"[All Fields])
ckd[All Fields] AND ("anaemia"[All Fields] OR "anemia"[MeSH Terms] OR "anemia"[All Fields]) AND ("complications"[Subheading] OR "complications"[All Fields])
ckd[All Fields] AND ("hypertension"[MeSH Terms] OR "hypertension"[All Fields]) AND ("complications"[Subheading] OR "complications"[All Fields])
("hypertension"[MeSH Terms] OR "hypertension"[All Fields]) AND ("anaemia"[All Fields] OR "anemia"[MeSH Terms] OR "anemia"[All Fields]) AND ("complications"[Subheading] OR "complications"[All Fields])
("hypertension"[MeSH Terms] OR "hypertension"[All Fields]) AND ("complications"[Subheading] OR "complications"[All Fields]) AND cvd[All Fields]

("albuminuria"[MeSH Terms] OR "albuminuria"[All Fields]) AND ("complications"[Subheading] OR "complications"[All Fields]) AND ("renal insufficiency, chronic"[MeSH Terms] OR ("renal"[All Fields] AND "insufficiency"[All Fields] AND "chronic"[All Fields]) OR "chronic renal insufficiency"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields])

Uue otsinguga kõrge kvaliteediga süstemaatilisi ülevaateid ja meta-analüüse ei leitud. Enamus leitud uuringutest olid vähese osalejate arvuga kliinilised uuringud või raviga seotud retrospektiivsed kohortidel põhinevad uuringuid. Käesoleva kliinilise küsimuse jaoks võeti ülevaate tegemiseks 4 läbilõikeuuringut üldrahvastikule, milles uuriti KNH ja aneemia levimust ja komplikatsioonide seoseid, samuti GFRi, proteinuuria, albuminuuria seoseid komplikatsioonide tekkes. Glomerulonefriidi ja polütsüstoosi kohta otsingud tulemusi ei andnud.

Lisaks on võetud ülevaate tegemiseks 2 KDIGO ravijuhendis kasutatud uuringut, millest üks on süstemaatiline ülevaade (Palmer, S.C. et.al;2011), milles hinnati tõendeid KNHga inimeste seerumi fosfori, parathormooni (PTH) ja kaltsiumi seoseid surmajuhtumite, kardiovaskulaarse suremuse ja mitteletaalsete kardiovaskulaarsete haigustega. Teine KDGOs kasutatud uuring (Adeney, K.L. et.al;2009) on tehtud Multi-Ethnic Study of Atherosclerosis (MESA) kohordis, kus uuriti seerumi fosfaadi kontsentratsiooni seoseid veresoonte ja südameklapi lubjastumisel.

Viited esmase otsingu tulemustele

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Retrospektiivses uuringus (Minutolo R et. al; 2014) hinnati 30326 dialüüsivaba täiskasvanud KNHga patsienti (KNH raskusatmetes 1-5). Valim võeti 2002 ja 2003 aasta 700st erinevast Itaalia perearstikeskusest, kes kunagi ei olnud käinud nefroloogi konsultatsioonil. KNH raskusastmeteks loeti: 1 ja 2 (GFR 60 ml / min per 1,73 m2) ja oli ka albuminuuria või oli KNH diagnoositud rahvusvahelise koodi järgi, raskusate 3a (GFR = 59-45), raskusaste 3b (GFR = 44-30), 4. raskusaste (GFR = 29-15) ja 5. raskusaste (GFR 15). Esmane tulemusnäitaja oli risk lõppstaadiumis neerupuudulikkusele (ESRD) (dialüüs või transplantatsioon) või üldisele suremusele. **Tulemustes** leiti, et KNH patsientidel oli risk ESRD ja suremusele suurem KNH raskusastmetes 3b-5. Lisaks leiti, et sõltumatud riskitegurid ESRDle ja suremusele (tabel 4) olid meessugu, diabeet ja koronaararterite haigus. Aneemia ja albuminuuria kahekordistavad ESRDd ja suremuse riski vastavalt 56% ja 12% ulatuses. Ainult hüpertensioon, ilma teiste riskiteguriteta ei suurenda suremuse riski. **Abstract** **Background and objectives.** Rising prevalence of CKDrequires active involvement of general practitioners to limit ESRD and mortality risk. However, the outcomes of patients with CKD exclusively managed by general practitioners are ill defined. Design, setting, participants, &measurements We prospectively evaluated 30,326 adult patientswith nondialysis CKD stages 1–5 who had never received consultation in tertiary nephrology care recruited from 700 general practitioner offices in Italy during 2002 and 2003. CKD stages were classified as stages 1 and 2 (GFR=60 ml/min per 1.73 m2 and either albuminuria or an International Classification of Diseases, Ninth Revision, Clinical Modification code for kidney disease), stage 3a (GFR=59–45), stage 3b (GFR=44–30), stage 4 (GFR=29–15), and stage 5 (GFR,15). Primary outcome was the risk of ESRD (dialysis or transplantation) or all-cause death. **Results** Overall 64% of patients were in stage 3a, and 4.5% of patients were in stages	**Risk of ESRD and death in patients with CKD not referred to a nephrologist: a 7-year prospective study.** **2014** Minutolo R, Lapi F, Chiodini P. **http://cjasn.asnjournals.org/content/9/9/1586.full.pdf+html**

3b–5. Patients with stages 1 and 2 were younger, were predominantly men, more frequently had diabetes, and had lower prevalence of previous cardiovascular disease than patients with stages 3a–5. Hypertension was frequent in all CKD stages (80%–94%), whereas there was a lower prevalence of dyslipidemia, albuminuria, and obesity associated with more advanced CKD. During the follow-up (median=7.2 years; interquartile range=4.7–7.7), 6592 patients died and 295 started ESRD. Compared with stages 1 and 2 (reference), mortality risk (hazard ratio, 95% confidence interval)was higher in stages 3b–5 (1.66, 1.49–1.86, 2.75, 2.41–3.13 and 2.54, 2.01–3.22, respectively) but not stage 3a (1.11, 0.99–1.23). Similarly, ESRD risk (hazard ratio, 95% confidence interval) was not higher at stage 3a (1.44, 0.79–2.64) but was greater in stages 3b–5 (11.0, 6.3–19.5, 91.2, 53.2–156.2 and, 122.8, 67.9–222.0, respectively).
Among modifiable risk factors, anemia and albuminuria significantly predicted either outcome, whereas hypertension only predicted mortality.
Conclusions In patients with CKD not referred to nephrology, risks of ESRD and mortality were higher in those with CKD stages 3b–5.

Table 4. Multivariable Cox model of determinants of ESRD and all-cause death

Variables	ESRD Hazard Ratio (95% Confidence Interval)	All-Cause Death Hazard Ratio (95% Confidence Interval)
Age (1 yr)	0.96 (0.96 to 0.97)[a]	1.10 (1.10 to 1.11)[a]
Women	0.49 (0.39 to 0.63)[a]	0.60 (0.57 to 0.63)[a]
Body mass index≥30 kg/m^2 (yes versus no)	0.71 (0.50 to 1.01)	1.02 (0.94 to 1.11)
Hypertension (yes versus no)	1.60 (0.93 to 2.76)	1.11 (1.02 to 1.21)[a]
Diabetes mellitus (yes versus no)	1.63 (1.26 to 2.11)[a]	1.61 (1.52 to 1.70)[a]
Coronary artery disease (yes versus no)	1.33 (1.03 to 1.71)[a]	1.48 (1.41 to 1.56)[a]
Dyslipidemia (yes versus no)	1.11 (0.86 to 1.44)	0.67 (0.64 to 0.71)[a]
Anemia (yes versus no)	2.08 (1.50 to 2.89)[a]	1.56 (1.44 to 1.69)[a]
Albuminuria (yes versus no)	2.11 (1.57 to 2.84)[a]	1.12 (1.01 to 1.24)[a]
Use of RAS inhibitors (yes versus no)	1.17 (0.89 to 1.53)	1.02 (0.97 to 1.08)
CKD stage		
1 and 2	Reference	Reference
3a	1.44 (0.79 to 2.64)	1.11 (0.99 to 1.23)
3b	11.04 (6.26 to 19.48)[a]	1.66 (1.49 to 1.86)[a]
4	91.2 (53.2 to 156.2)[a]	2.75 (2.41 to 3.13)[a]
5	122.8 (67.9 to 222.0)[a]	2.54 (2.01 to 3.22)[a]

Hazard ratios are adjusted for all variables included into the model. RAS, renin-angiotensin system.
[a]Significant hazard ratio.

Albuminuuria ja madala glomerulaarfiltratsiooni kiiruse (eGFR) täpne mõju kardiovaskulaarsele suremusele, üldsuremusele ja neerude töö halvenemisele diabeeti põdevatel inimestel on ebakindel.
Meta-analüüs (Toyama, T. et.al;2013) viidi läbi andmebaasidest MEDLINE, EMBASE ja CINHAL alates1950 kuni 2010 aastani. Sobivaks peeti ja võeti hindamiseks 31 kohortuuringut diabeeti põdevate inimesetega (148 350 patsienti). Tulemuseks arvutati kohandatud suhteline risk (RR), albuminuuria ja madala eGFR, risk kardiovaskulaarsele suremusele, üldsuremusele ja neerude näitajate muutustele (joonis 3). (Albuminuuria defineeriti vt tabel 2)

Tulemused: Kardiovaskulaarsele suremusele olid mikroalbuminuuria (RR 1,76, 95% CI 1,38-2,25) ja makroalbuminuuria (RR 2,96 95% CI 2,44-3,60) olulised riskitegurid võrreldes normoalbuminuriaga. Sama trendi võis näha mikroalbuminuuria (RR 1,60, 95% CI 1,42-1,81) ja makroalbuminuuria (RR 2,64, 95% CI 2,13-3,27) riskil üldsuremusele ja ka mikroalbuminuuria (RR 3,21, 95% CI 2,05-5,02) ja makroalbuminuuria (RR 11,63, 95% CI 5,68-23,83) riskil neeru näitajate halvenemisele. Suhteline seotud risk madala eGFRi ja albuminuuriaga olid peaaegu võrdsed tõstes iga riski määra.
Järeldused: kõrge albuminuuria ja madal eGFR on olulised riskitegurid diabeeti

The Impacts of Albuminuria and Low eGFR on the Risk of Cardiovascular Death, All-Cause Mortality, and Renal Events in Diabetic Patients: Meta-Analysis

2013

Toyama, T, Furuichi, K, Niniomya,T. et.al.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3797878/

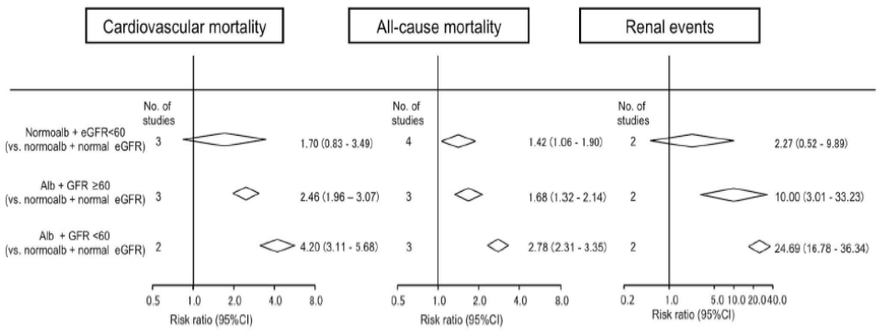
põdevatel inimestel. Albuminuuria ja madal eGFR võivad olla teineteisest sõltumatud.
Kokkuvõte: Kõrge albuminuuria ja madal eGFR on riskiteguriks kardiovaskulaarsele suremusele, üldsuremusele ja neerude kahjustusele diabeeti põdevatel inimestel (vt. joonis 3). Mikro- ja makroalbuminuuria olid olulised riskitegurid kõigile kolmele väljundile. Vähem tõendeid oli ainult madala eGFR mõjust kardiovaskulaarsele suremusele, üldsuremusele ja neerude kahjustusele .

Abstract
Background: Precise effects of albuminuria and low estimated glomerular filtration rate (eGFR) on cardiovascular mortality, all-cause mortality, and renal events in diabetic patients are uncertain.
Materials and Methods: A systematic review was conducted of the literature through MEDLINE, EMBASE, and CINHAL from 1950 to December 2010. Cohort studies of diabetic patients providing adjusted relative risk (RR) of albuminuria and eGFR for risks of cardiovascular mortality, all-cause mortality, and renal events were selected. Two reviewers screened abstracts and full papers of each study using standardized protocol.
Results: We identified 31 studies fulfilling the criteria from 6546 abstracts. With regard to the risk of cardiovascular mortality, microalbuminuria (RR 1.76, 95%CI 1.38–2.25) and macroalbuminuria (RR 2.96 95%CI 2.44–3.60) were significant risk factors compared to normoalbuminuria. The same trends were seen in microalbuminuria (RR 1.60, 95%CI 1.42–1.81), and macroalbuminuria (RR 2.64, 95%CI 2.13–3.27) for the risk of all-cause mortality, and also in microalbuminuria (RR 3.21, 95%CI 2.05–5.02) and macroalbuminuria (RR 11.63, 95%CI 5.68–23.83) for the risk of renal events. The magnitudes of relative risks associated with low eGFR along with albuminuria were almost equal to multiplying each risk rate of low eGFR and albuminuria. No significant factors were found by investigating potential sources of heterogeneity using subgroup analysis.
Conclusions: High albuminuria and low eGFR are relevant risk factors in diabetic patients. Albuminuria and low eGFR may be independent of each other. To evaluate the effects of low eGFR, intervention, or race, appropriately designed studies are needed.

Table 2

Definitions of Albuminuria.

Measurement Method	Microalbuminuria	Macroalbuminuria	Any level of albuminuria
24 hour urine collection	30–300 mg/day or 20–200 µg/min	>300 mg/day or >200 µg/min	>30 mg/day or >20 µg/min
(proteinuria)	N/A	>0.3–0.5 g/day	N/A
Spot urine albumin creatinine ratio	30–300 mg/g or 3.4–34 mg/mmol	>300 mg/g or >34 mg/mmol	>30 mg/g or >3.4 mg/mmol
(proteinuria)	N/A	>0.3–0.5 g/g	N/A
Spot urine albumin concentration	3–30 mg/dl	>30 mg/dl	>3 mg/dl
(proteinuria)	N/A	>0.3–0.5 g/l	N/A
Spot urine dipstick	Specific microalbuminuria dipstick positive	N/A	N/A

 **Figure 3. Risk ratio for the association of low eGFR with the risk of each outcome according to the presence of albuminuria, compared with normal eGFR and normoalbuminuria.** Albuminuria was defined as any level of albuminuria or pooled estimate of microalbuminuria and macroalbuminuria. Abbreviations: normoalb, normoalbuminuria; alb, albuminuria. doi:10.1371/journal.pone.0071810.g003	
Neerupuudulikkus mängib kriitilist rolli südame isheemiatõve patogeneesis. RCT (Dan, K;2012) eesmärk oli uurida neerutalitlusehäirete levimust ja KNH mõju stabiilse stenokardiaga patsientidel kardiovaskulaarsete tüsistuste tekkeks (vasaku pärgarteri haiguse tekkeks (LMCAD)) . Uuringusse kaasati 626 patsienti, mooduststi kaks gruppi, kellel oli LMCAD ja kellel ei olnud LMCAD. Krooniline neeruhaigus defineeriti eGFR <60 ml · min-1 · 1,73 m-2 ja/või esines proteinuuria. Analüüsid olid teostatud enne koronarograafiat. ***Tulemused:*** *Krooniline neeruhaigus oli seotud kardiovaskulaarse tüsistuse LMCADga (kohandatud riskisuhe, 1,74; 95% usaldusvahemik (UI)1,09-2,76, p = 0,01). 1-aastane järelkontroll näitas, et kummulatiivne esinemissagedus raskete kardiovaskulaarsete tüsistuste tekkeks (LMCAD) patsientidel, kelle eGFR oli <30 ml · min-1 · 1,73 m-2 oli suurem kui patsientidel, kelle eGFR oli ≥60 ml · min-1 · 1,73 m-2 (P = 0,03). Riskide suhe kardiovaskulaarsetele tüsistustele oli 9,54 (95% UI: 3,15-28,89, P <0,01) patsientedel, kellel esines LMCAD (eGFR <30 ml · min-1 · 1,73 m-2) vs patsientidel ilma LMCAD (eGFR ≥60 ml · min-1 · 1,73 m-2).* ***Krooniline neeruhaigus on riskiteguriks kardiovaskulaarsete tüsistuste (LMCAD) tekkeks stabiilse stenokardiaga patsientidel ja ennustab halba prognoosi. Seega on vaja tähelepanelik olla KNHga patsientide stabiilse stenokardia ravimisega.*** ***Background:*** *Renal insufficiency plays a critical role in the pathogenesis of ischemic heart disease. The aim of the present study was to investigate the prevalence of renal dysfunction and its impact on prognosis in patients with left main coronary artery disease (LMCAD) and stable angina pectoris.* ***Methods and Results:*** *A total of 626 consecutive patients with significant coronary artery stenosis were enrolled. Renal insufficiency was graded using estimated glomerular filtration rate (eGFR) before coronary angiography. Chronic kidney disease (CKD) was defined as eGFR <60 ml · min–1 · 1.73 m–2 and/or proteinuria. Patients with LMCAD (n=95) had a significantly higher prevalence of CKD than those without LMCAD (P=0.02). Multiple logistic regression analysis showed that CKD was independently associated with LMCAD (adjusted odds ratio, 1.74; 95% confidence interval [CI]: 1.09–2.76, P=0.01). A 1-year follow-up of patients with LMCAD showed that the cumulative incidence of major adverse cardiovascular events among patients with eGFR <30 ml · min–1 · 1.73 m–2 was higher than that among patients with eGFR ≥60 ml · min–1 · 1.73 m–2 (P=0.03). The hazard ratio for a cardiovascular event was 9.54 (95% CI: 3.15–*	***Impact of Chronic Kidney Disease on Left Main Coronary Artery Disease and Prognosis in Japanese Patients 2012*** *Dan, K, MD; Miyoshi, T, MD;Ueeda, M. et.al.* ***https://www.jstage.jst.go.jp/article/circj/76/9/76_CJ-11-1455/_pdf***

28.89, P<0.01) when comparing patients with LMCAD and eGFR <30 ml · min–1 · 1.73 m–2 vs. patients without LMCAD and eGFR ≥60 ml · min–1 · 1.73 m–2. ***Conclusions:*** *Renal insufficiency is a risk factor for LMCAD and predicts poor prognosis in Japanese patients.* **Table 4. Effect of Renal Dysfunction on MACCE vs. Presence of LMCAD** This multivariate logistic analysis was adjusted for PCI and CABG. HR, hazard ratio. Other abbreviations as in Tables 1–3.	
Neerufunktsiooni muutused on kõige tugevam südamepuudulikkuse prognoosija. Neerufunktsioon ja neerufunktsiooni muutused annavad olulist kliinilist informatsiooni südamepuudulikkusega patsientidel. Nii neerufunktsiooni halvenemine kui äge neerupuudulikkus suurendavad suremuse riski ja südamepuudulikkuse süvenemist. Süstemaatilises ülevaates (*Damman K*, et.al;2012) on vaadeldud ja võrreldud erinevaid neerufunktsiooni näitajaid ja markereid, mis näitavad ägeda- ja kroonilise südamepuudulikkuse prognoosi ja suremuse riski (tabelid 1 ja 2). Südamepuudulikkuse ja neerupuudulikkuse vastasmõjud ei ole staatilised vaid võivad olla dünaamilised, mõjutatud seisundi muutustest ja neurohormonaalsetest ja neerufunktsiooni muutustest, samuti mõjutab seda ravi. Seisundi muutused võivad areneda kiiresti ja võivad olla olulised või vastupidi aeglased ja ebaolulised. Paremini, kui ainult kreatiniin võivad anda täpsemat teavet eGFRi muutuste kohta markerid tsüstatiin- C ja uurea (tsüstatiini-C võib kasutada eGFRi määramisel sarnaselt kreatiniini valemiga). Kliinilises praktikas on tsüstatiini-C valemit eGFRi arvutamiseks vähe kasutatud ja seetõttu on väärtuste hindamisel vähe kogemusi. Kreatiniini baasil eGFRi on arvutatud aastaid ning arstid teavad nende normväärtuseid. Igapäevaselt tsüstatiin-C määramine on ka oluliselt kallim võrreldes kreatiniini määramisega. Osad markerid võivad südamepuudulikkusega patsientidel prognoosida ägedaid neerufunktsiooni muutuseid veel enne kreatiniini muutust. **Tabel 1.** annab ülevaate erinevate markerite seosest ägeda- ja kroonilise südamepuudulikkuse prognoosimisel. **Abstract** Renal function is the most important predictor of clinical outcome in heart failure (HF). It is therefore essential to have accurate and reliable measurement of renal function and early specific markers of renal impairment in patients with HF. Several renal functional entities exist, including glomerular filtration (GFR), glomerular permeability, tubulointerstitial damage, and endocrine function. Different markers have been studied that can be used to determine changes and the effect of treatment in these entities. In the present review, we summarize current and novel markers that give an assessment of renal function and prognosis in the setting of acute and chronic HF. **Conclusions.** The interaction between heart failure and renal impairment is not static, but comprises of dynamic changes in volume status, inflammatory response, neurohormonal activation	**Current and novel renal biomarkers in heart failure** **2012** *Damman K1, Voors AA, Navis G* **http://link.springer.com/article/10.1007%2Fs10741-011-9254-2**

eGFR (ml · min⁻¹ · 1.73 m⁻²)	No. patients	MACCE (%)	HR (95%CI)	P value
Non-LMCAD				
≥60	123	7	1.00	
≥30, <60	111	21	2.39 (1.35–4.26)	<0.01
<30	15	40	6.82 (3.21–14.52)	<0.01
LMCAD				
≥60	24	17	2.25 (0.86–5.88)	NS
≥30, <60	28	21	1.86 (0.70–4.93)	NS
<30	4	75	9.54 (3.15–28.89)	<0.01

and changes in renal function, by natural course, or in relation to therapy. These changes may be quick and substantial, but may also be slow and subtle. Finding the right marker to predict renal function in all of these situations may be impossible, but new markers are emerging that seem to perform better than serum creatinine alone. Some of these markers may give a good representation of GFR, such as cystatin C, BUN, while others give information on glomerular permeability (albuminuria) or tubulointerstitial damage (NAG, KIM-1, NGAL, and FABP). Importantly, the latter group (including IL-18) represents markers that may also predict acute changes in renal function, even before changes in creatinine occur. These markers are therefore suitable candidates as markers of treatment effect and as possible targets for therapy. New randomized clinical trials should, therefore, include measurement of these markers and possibly target these markers to preserve or even improve renal function in patients with HF.

Table 1 Properties of different markers

	Detection	"Validation"	Relation with prognosis	Pro's	Cons
Glomerular filtration rate					
Creatinine	Serum[a]	CHF	Strong evidence	Easy	Exponential relationship with GFR
		AHF		Cheap	Dependent on muscle mass
				Interpretable	
(s)MDRD	Serum	CHF	Strong evidence	Valid	Formula (calculation)
		Not in AHF		Accurate	Less reliable in extremes of GFR
BUN	Serum	CHF	Emerging evidence	Easy	Interpretation difficult
		AHF		Cheap	
Cystatin C	Serum[a]	CHF	Evidence in AHF	Unbiased	Interpretation difficult
		AHF		Very reliable	Costs
Glomerular permeability					
Albuminuria	Urine	CHF	Strong evidence CHF	Easy obtainable	Low specificity
		Not in AHF		Cheap	
				Additive to GFR	
Tubulointerstitial damage					
NAG	Urine	CHF	Emerging evidence CHF	Easy obtainable	Low specificity
		Not in AHF		Additive to GFR and UAE	Costs
				Strong marker of AKI	
KIM-1	Urine	CHF	Emerging evidence CHF	Easy obtainable	Costs
		Not in AHF		Additive to GFR and UAE	
				Strong marker of AKI	
NGAL	Urine/ Serum	CHF	Emerging evidence CHF and AHF	Easy obtainable	Low specificity especially in serum and in CHF
		AHF		Additive to GFR and UAE	
				Strong marker of AKI	
IL-18	Urine/ Serum	CHF	Emerging evidence CHF	Easy obtainable	Also strongly increased in inflammation
		Not in AHF		Strong marker of AKI	
FABP-1	Urine/ Serum	Not in CHF	None	Strong marker of AKI	Elevated in sepsis
		Not in AHF			Also found in liver

AHF acute heart failure, *AKI* acute kidney injury, *BUN* blood urea nitrogen, *CHF* chronic heart failure, *FABP* fatty acid binding protein, *GFR* glomerular filtration rate, *IL-18* Interleukin 18, *KIM-1* kidney injury molecule 1, *MDRD* modification of diet in renal disease (formula), *NAG N*-acetyl-beta-D-glucosaminidase, *NGAL* neutrophil gelatinase-associated lipocalin, *UAE* urinary albumin excretion

[a] Can be measured in urine, but then does not resemble GFR

Table 2 Relationship between blood urea nitrogen and outcome in heart failure studies

Study	Year	*N*	Setting	BUN (mg/dL)	Relative risk for mortality
Lee [25]	2003	4031	ADHF	29 ± 19	1.49 (1.39–1.60) per 10 units increase
Aronson [19]	2004	541	ADHF	34 ± 22	2.3 (1.3–4.1) for quartiles
Heywood [24]	2005	680	CHF	29 ± 20	BUN 30–50: 1.9, BUN >50: 2.2
Shenkman [26]	2007	257	ADHF	33 ± 22	3.6 (1.8–7.3) per log unit increase
Filippatos [21]	2007	302	ADHF	31 ± 17	1.03 (1.00–1.05) per unit increase
Cauthen [20]	2008	444	CHF	14 (6–22)	1.04 (1.03–1.06) per unit increase
Klein [27]	2008	949	CHF	25 (14–41)	1.11 (1.07–1.15) per 5 units increase
Lin [22]	2009	243	CHF	27 ± 17	1.24 (1.02–1.51) for BUN-to-creatinine ratio
Gotsman [23]	2010	362	ADHF	23 (17–29)	1.80 (1.30–2.49), per tertile BUN/creatinine

ADHF Acute decompensated heart failure, *BUN* Blood urea nitrogen, *CHF* Chronic heart failure

Retrospektiivsesse uuringusse (Turin TC, et. al;2012) kaasati 598 397 täiskasvanut, kellel

Short-term change in

oli vähemalt kahel ambulatoorsel külastusel mõõdetud eGFR (vähemalt 6 kuud) vähemalt 1 aasta jooksul. (jälgimisaja mediaan 3,5 aastat). Vaadeldi neerufunktsiooni muutust kasutades neerutalitluse muutuse määratlemiseks valemit: eGFR arvutati [(viimane eGFR - esimene eGFR) / esimene eGFR × 100] ja väljendati protsentides (%). Neerufunktsiooni muutused defineeriti järgmiselt: "teatud langus" (kroonilise neeruhaiguse kategooria eGFR langus ≥25%); "ebakindel langus" (kroonilise neeruhaiguse eGFR langus <25%); "stabiilne" (kroonilise neeruhaiguse raskusate ei muutu); "ebakindel tõus (kroonilise neeruhaiguse eGFR tõus <25%) ja" teatud tõus (kroonilise neeruhaiguse eGFR tõus ≥25%). Arvutati lõppstaadiumis neerupuudulikkuse (ESRD) kohandatud määr 1000 inimaastale. **Tulemustes** leiti, et teatud eGFRi langusega patsientidel oli 5 korda suurem risk ESRDle (HR: 5,11; 95% CI: 4,56-5,71) . Ebakindla langusega eGFR patsientidel oli 2 korda suurem risk ESRDle (HR 2,13; 95% CI: 1,84-2,47) võrrelduna stabiilse neerufunktsiooniga patsientidega. Pärast eGFRi kohandamist ühismuutujatele, ei leitud seost suurenenud ESRD riskile ebakindla langusega eGFRi patsientidel. **Riskisuhe ESRDle on seotud viimase eGFR mõõtmisega ja aja suhtega, HR 2,89 (95% CI: 2,35-3,55), 10.98 (95% CI: 8,69-13,87), 35.20 (95% CI: 27,95-44,32) ja 147,96 (116,92-187,23) vastavalt GFRi 2, 3a, 3b ja 4 võrrelduna eGFR 1.** Riske ESSRDle hinnati muutustega neerude funktsioonis ja võrreldi stabiilse neerufunktsiooniga. Patsientidel, kellel tekkisid "teatud muutused" neerude funktsioonis (nii langus kui tõus) olid vanemad, tõenäolisemalt naised ja neil oli suurem kaasuvate haiguste esinemissagedus võrreldes nendega, kellel oli stabiilne neerufunktsioon. **Kokkuvõte:** Muutus eGFR kategooriates ≥25% langus (teatud langus) on seotud suurenenud ESRD riskiga, kuid tuleb arvestada ka patsiendi teisi näitajaid. Usaldusväärsemaks ESRD prognoosimiseks on vajalik määrata enam kui kahe seerumi kreatiniini sisaldust pikema perioodi jooksul kui 1 aasta. **Abstract** **BACKGROUND:** It is unclear what degree of change in the eGFR over a 1-year period indicates clinically significant progression, and whether this change adds additional information beyond that obtained by a single eGFR measure alone. **METHODS:** We included 598 397 adults who had at least two outpatient eGFR measurements (at least 6 months apart) during 1-year accrual period in Alberta, Canada. Change in kidney function (using the first and last eGFR) was defined by change in kidney function category with confirmation based on percent (%) change in eGFR [(last eGFR - first eGFR)/first eGFR × 100]. The groups for change in kidney function were thus defined as: 'certain drop' (drop in CKD category with ≥25% decrease in the eGFR); 'uncertain drop' (drop in CKD category with <25% decrease in the eGFR); 'stable' (no change in CKD category); 'uncertain rise' (rise in CKD category with <25% rise in the eGFR) and 'certain rise' (rise in CKD category with ≥25% increase in the eGFR). Adjusted end-stage renal disease (ESRD) rates (per 1000 person-years) for each group of change in kidney function were calculated using Poisson regression. Adjusted risks of ESRD associated with change in kidney function, in reference to stable kidney function, were estimated. **RESULTS:** Among the 598 397 participants, 74.8% (n = 447 570) had stable (no change in CKD category), 3.3% (n = 19 591) had a certain drop and 3.7% (n = 22 171) had a	**kidney function and risk of end-stage renal disease.** **2012** Turin TC, Coresh J, Tonelli M. et al. http://ndt.oxfordjournals.org/content/27/10/3835.full.pdf+html

certain rise in kidney function. Participants who experienced a certain change in kidney function (both drop and rise) were older, more likely to be female, and had a higher prevalence of comorbidities, in comparison with those with stable kidney function. There were 1966 (0.3%) ESRD events over a median follow-up of 3.5 years. Compared with participants with stable kidney function, after adjustment for covariates, and the first eGFR measurement, those with certain drop had 5-fold increased risk of ESRD (HR: 5.11; 95% CI: 4.56-5.71), whereas those with an uncertain drop had 2-fold increased risk (HR: 2.13; 95% CI: 1.84-2.47). After adjustment for the eGFR and covariates at the last visit, neither a certain nor uncertain drop in the eGFR was associated with an increased ESRD risk. The ESRD risk associated with the last eGFR level, adjusted for the slope over time, were 2.89 (95% CI: 2.35-3.55), 10.98 (95% CI: 8.69-13.87), 35.20 (95% CI: 27.95-44.32) and 147.96 (116.92-187.23) for categories 2, 3a, 3b and 4, respectively, in reference to category 1.

CONCLUSIONS: A change in eGFR category accompanied by ≥25% decline (certain drop) is associated with increased ESRD risk. However, this elevated risk is captured by patient characteristics and eGFR at the last visit, suggesting that eGFR trajectories based on more than two serum creatinine measurements over a period longer than 1 year are required to determine ESRD risk and allow more reliable risk prediction.

Table 1. Baseline characteristics of study participants by 1-year change in kidney function

	One-year change in kidney function, *n* (%)				
	Certain drop, 19 591 (3.3)	Uncertain drop, 64 067 (10.7)	Stable, 447 570 (74.8)	Uncertain rise, 44 998 (7.5)	Certain rise, 22 171 (3.7)
Age, mean (SD), year	63.3 (17.4)	58.6 (15.1)	54.6 (17.0)	57.9 (14.8)	59.9 (17.8)
Female gender (%)	61.75	57.59	58.48	56.15	63.27
Aboriginal (%)	2.93	1.88	2.49	1.75	2.59
Diabetes (%)	23.39	15.09	13.05	13.78	16.27
Hypertension (%)	57.20	43.55	36.52	41.24	48.55
Proteinuria (%)					
Normal	41.97	54.42	57.15	55.97	48.25
Mild	9.86	6.35	5.89	6.23	8.69
Heavy	5.43	1.69	1.16	1.12	2.12
Unmeasured	42.74	37.54	35.80	36.68	40.95
Kidney function at baseline (%)					
Category 1	36.14	67.10	45.03	0	0
Category 2	40.84	23.34	45.74	71.47	44.81
Category 3a	13.96	7.58	5.96	21.30	32.11
Category 3b	7.22	1.78	2.48	6.09	16.61
Category 4	1.85	0.20	0.79	1.14	6.47
Cerebrovascular disease (%)	8.05	4.40	3.48	3.84	6.30
Peripheral vascular disease (%)	6.40	2.93	2.16	2.56	4.04
CHF (%)	13.23	5.17	3.61	4.48	9.21
COPD (%)	23.02	17.75	16.42	17.05	20.83
Cancer (%)	10.90	6.92	6.01	6.31	8.93
Dementia (%)	5.12	2.31	1.81	2.26	4.54
Myocardial infarction (%)	8.62	4.38	3.29	3.95	5.99
Mild liver disease (%)	2.04	1.34	1.29	1.19	1.70
Moderate liver disease (%)	0.48	0.15	0.14	0.11	0.28
Paralysis (%)	1.31	0.63	0.60	0.49	0.87
Peptic ulcer disease (%)	4.38	2.83	2.70	2.77	3.83
Rheumatic disease (%)	3.61	2.42	2.09	2.16	2.93
Socioeconomic status (%)					
Pensioner	29.46	45.62	50.42	48.85	39.90
Low	10.52	12.55	12.12	13.07	10.51
With subsidy	4.68	3.28	3.73	3.10	4.62
eGFR, mean (SD), mL/min/1.73 m^2					
First measurement	78.9 (24.1)	84.8 (18.7)	87.8 (21.4)	76.4 (15.7)	59.6 (17.8)
Last measurement	51.4 (18.6)	74.1 (17.0)	87.8 (21.5)	86.1 (17.4)	84.1 (22.2)

CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease.
Data are in %, unless mean (SD). Totals do not always add to 100% because of rounding.

Figure 4. The unadjusted and adjusted (for covariates at the first measurement) risk of ESRD increased in a near exponential fashion with decline in kidney function defined by percent decrease in the eGFR. This association disappeared when adjustment for covariates were done at the last measurement of the eGFR.

Table 2.
ESRD rates, per 1000 person-years, by 1-year change in kidney function

	One-year change in kidney function				
	Certain drop	Uncertain drop	Stable	Uncertain rise	Certain rise
Events, *n*	534	236	1061	62	73
Patients, *n*	19 591	64 067	447 570	44 998	22 171
Adjusted for covariates at first measurement					
Rate (95% CI)	0.77 (0.44–1.10)	0.24 (0.13–0.36)	0.18 (0.12–0.0.24)	0.08 (0.02–0.14)	0.05 (0.01–0.09)
Adjusted for covariates at last measurement					
Rate (95% CI)	0.15 (0.10–0.21)	0.11 (0.07–0.16)	0.21 (0.15–0.26)	0.29 (0.13–0.46)	0.36 (0.16–0.55)

CI, confidence interval.

Rates are adjusted for age, sex, diabetes, hypertension, socioeconomic status, kidney function, proteinuria and history of cancer, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, dementia, metastatic solid tumor, myocardial infarction, mild liver disease, moderate or severe liver disease, paralysis, peptic ulcer disease, peripheral vascular disease and rheumatic disease.

Viited teisele otsingule, valitud põhidiagnooside ja komplikatsioonide tekke osas

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
Läbilõikeuuring (‚Shimizu et.al;2014) teostati neerukahjustuse ja aneemia vaheliste seoste selgitamiseks. N=1105 60-89-aastased mehed, kes ei võtnud aneemia ravimeid ja kellele tehti üldine tervise kontroll. **Tulemused:** Meestel eGFR-ga <60 ml / min / 1,73 m2 leiti oluliselt suurem risk aneemia tekkeks. Risk oli väiksem kerge neerukahjustusega (60 ml / min / 1,73 m2 ≤GFR <90 ml/min/1,73 m2) ja ilma KNH-ta patsientidel. Klassikalised kardiovaskulaarsed riskitegurid kohandati riskisuhtele (OR). Peale kohandamist oli OR aneemiale 1,81 (1,23 - 2,68). Normaalse neerufunktsiooniga (eGFR ≥90 ml/min/1,73m2) meestel võrrelduna kerge neerukahjustusega meestega oli OR vastavalt 0,26 (0,15-0,47) ja 0,60 (0,33-1,09). Riskisuhe ja 95% usaldusvahemikud (UI) aneemia seosed eGFRiga ilma KNHta ja KNHga meestel on toodud tabelis 2. Lisaks oli uuringu üheks osaks täiendav uurimine ateroskleroosi osas. Uuriti mehi, kellel oli teostatud Transcatheter Aortic Heart Valve (TAVI) N=1059 meest. Leiti, et nii eGFR kui hemoglobiin olid oluliselt seotud ateroskleroosiga. Vanuse järgi korrigeeritud riskisuhted ateroskleroosi tekke riski kohta koos standardhälbega (SD) eGFR tõus (17,3 ml/min/1,73 m2) ja hemoglobiini langus (1,3 g / dl) võrra oli OR vastavalt 0,82 (0,71-0,95, P = 0,007) ja 1,31 (1,14-1,50,<0,001. **Kokkuvõte**. Krooniline neeruhaigus kujutab märkimisväärset ohtu aneemia tekkeks vanematel meestel. Kerge neerukahjustusega oli väiksem risk aneemiale, kuid suurem risk oli ateroskleroosi tekkeks.	**1. Associations between renal impairment and anemia in older, rural Japanese men: the Nagasaki Island study** Shimizu, Y, Sato, S, Koyamatsu J. 2014 http://jphysiolanthropol.biomedcentral.com/articles/10.1186/1880-6805-33-7

Table 2 Odds ratios (OR) and 95% confidence intervals (CI) for anemia in relation to glomerular filtration rate (GFR) levels

	Non-chronic kidney disease[d]		Chronic kidney disease[c]	*P*
	Normal renal function[a]	Mild renal impairment[b]		
Number at risk	109	645	351	
Number of cases (percentage)	26 (23.9)	63 (9.8)	73 (20.8)	
Age-adjusted OR	1.00		1.54 (1.08 to 2.20)	0.016
	1.00	0.26 (0.16 to 0.45)	052 (0.30 to 0.89)	0.967
Multivariable OR	1.00		1.81 (1.23 to 2.68)	0.003
	1.00	0.26 (0.15 to 0.47)	0.60 (0.33 to 1.09)	0.644

[a]Normal renal function, [b]mild renal impairment, and [c]chronic kidney disease (CKD) were defined as respectively, GFR ≥90 mL/min/1.73 m^2, 90 mL/min/1.73 m^2 > GFR ≥60 mL/min/1.73 m^2, and GFR <60 mL/min/1.73 m^2. [d]Non-chronic kidney disease includes normal renal function and mild renal impairment. Anemia: hemoglobin in level <13.0 g/dL. Multivariable OR: adjusted further for age, systolic blood pressure, antihypertensive medication use, body mass index, smoking, alcohol intake, diabetes, history of cardiovascular disease, serum HDL cholesterol, serum triglycerides (TG), serum aspartate aminotransferase (AST), and serum γ-glutamyltranspeptidase (γGTP).

Background
Renal impairment is known to be associated with atherosclerosis, which in turn is reported to be positively associated with hemoglobin levels. In addition, renal impairment is known to be associated with a form of anemia known as renal anemia.
Methods
To clarify the associations between renal impairment and anemia, we conducted a cross-sectional study of 1,105 60 to 89-year-old men, who were not taking medication for anemia and were undergoing general health check-ups.
Results
Compared with non-chronic kidney disease, chronic kidney disease (CKD) with a glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 was found to constitute a significant risk of anemia. However, we noted that this risk was lower for mild renal impairment (60 mL/min/1.73 $m^2 \leq$ GFR <90 mL/min/1.73 m^2). Compared with the non-CKD reference group, the classical cardiovascular risk factors adjusted odds ratio (OR) for anemia was 1.81 (1.23 to 2.68) and compared with the normal renal function (GFR ≥90 mL/min/1.73 m^2) reference group, the ORs for mild renal impairment and CKD were 0.26 (0.15 to 0.47) and 0.60 (0.33 to 1.09).
Conclusions
Independent from classical cardiovascular risk factors, CKD, which was identified during general health check-ups, appeared to constitute a significant risk of anemia for older Japanese men. For mild renal impairment, however, this association was a reduced risk of anemia and thus possibly a higher risk of atherosclerosis.

Uuringu andmed on võetud National Health and Nutrition Examination Survey (NHANES) andmebaasist üle 18 aastaste täiskasvnute kohta.
Hinnati kolme aspekti: kroonilise neeruhaiguse levimust, aneemia levimust KNHga patsientidel ja ise raporteeritud aneemia ravi. Krooniline neeruhaigus oli jagatud 5 raskusastmesse ja aneemia defineeriti seerumi hemoglobiinitasemega 120 g/l naistel ja 130 g/l meestel.
Leiti, et hinnanguliselt 14,0% USA täiskasvanud elanikkonnast oli KNH (2007-2010 aastate andmed). Aneemiat esines 2x enam KNHga inimestel (15,4%) võrrelduna üldrahvastikuga (7,6%). Aneemia levimus KNH 1 raskusastmes oli 8,4% ja 53,4% 5 raskusastmes. Kokku 22,8% KNHga patsientidest raporteerisid aneemia ravimist eelneva 3 kuu jooksul.
Aneemia levimus KNH rakusastmete lõikes on toodud tabelis 3.

2. Prevalence of Anemia in Chronic Kidney Disease in the United States
Stauffer,M.E, Fan,T. 2014

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3879360/pdf/pone.0084943.pdf

Table 3. Prevalence of anemia.

	N	Weighted percentage	95% CI	Projected number in US
With CKD	410	15.4	13.1–18.2	4.8×10^6
Stage 1	57	8.4	5.5–12.4	0.6×10^6
Stage 2	68	12.2	9.2–16.0	0.9×10^6
Stage 3	231	17.4	13.7–21.8	2.7×10^6
Stage 4	37	50.3	37.2–63.4	0.5×10^6
Stage 5	17	53.4	34.1–71.7	0.2×10^6
Without CKD	729	6.3	5.3–7.4	11×10^6

The percentages reflect the prevalence of anemia, survey weighted to the US population. The analysis by stage of CKD was limited to subjects with CKD as defined in the Methods section (N = 2,125); data for anemia were missing for a total of 7 CKD patients (<1%), all in stages 1–3. Prevalence of anemia in subjects without CKD was determined in 9,269 subjects with non-missing data on anemia status.

Abstract Anemia is one of the many complications of chronic kidney disease (CKD). However, the current prevalence of anemia in CKD patients in the United States is not known. Data from the National Health and Nutrition Examination Survey (NHANES) in 2007–2008 and 2009–2010 were used to determine the prevalence of anemia in subjects with CKD. The analysis was limited to adults aged .18 who participated in both the interview and exam components of the survey. Three outcomes were assessed: the prevalence of CKD, the prevalence of anemia in subjects with CKD, and the self-reported treatment of anemia. CKD was classified into 5 stages based on the glomerular filtration rate and evidence of kidney damage, in accordance with the guidelines of the National Kidney Foundation. Anemia was defined as serum hemoglobin levels 12 g/ dL in women and 13 g/dL in men. We found that an estimated 14.0% of the US adult population had CKD in 2007–2010. Anemia was twice as prevalent in people with CKD (15.4%) as in the general population (7.6%). The prevalence of anemia increased with stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5. A total of 22.8% of CKD patients with anemia reported being treated for anemia within the previous 3 months–14.6% of patients at CKD stages 1–2 and 26.4% of patients at stages 3–4. These results update our knowledge of the prevalence and treatment of anemia in CKD in the United States

Läbilõikeuuring (Inker,A. et al;2012) üldrahvastikus 30,528 inimesel, US National Health and Nutrition Examination Survey üksuse andmetel, aastatel 1988–1994 ja 1999–2006 (neist n=8,242 oli hüperparatüreoosiga). Kasutati NKF- KDOQI eGFRi ja proteinuuria klassifikatsiooni. Hinnati aneemia, atsidoosi, hüperfosfateemia, hüpoalbumineemia, hüperparatüreoosi ja hüpertensiooni esinemist. Uuringusse võeti vanemad kui 20 aastased patsiendid, kellel olid määratud kõik tulemusnäitajad. Välja jäeti rasedad ja eGFR<15 mL/min/1.73m2 (vähese valimi tõttu).

Osalejad olid jagatud kahte rühma: 1. ainult eGFR taseme määramine vastavalt NKF-KDOQI süsteemile ja 2. alternatiivne klassifikatsioonisüsteem eGFR ja proteinuuria taseme määramine.

Tulemused:

Pärast kohandamist vanusele, rassile-rahvusele, soole, kehamassiindeksile, HDL-kolesteroolile, diabeedile, hüpertensioonile, südame-veresoonkonna haiguste esinemisele olid levimuse suhtarvud aneemia, atsidoos, hüperfosfateemia ja hüperparatüreoosi suuremad NKF KDOQI 3. ja 4. raskusatmes võrreldes 1. ja 2. rakusatmega (tabel 2) võrreldes alternatiivse hindamisega.

Tabelis 2 on toodud korrigeeritud levimuse suhtarvud kroonilise neeruhaiguse tüsistustele kahes rühmas.

Hüpoalbumineemia, hüpertensiooni ja hüperparatüreoosi esinemissagedus oli suurem suuremas kroonilise neeruhaiguse rakusastmes. Hüperparatüreoidismi levimus oli 9,1%,

3. Comparison of Concurrent Complications of CKD by 2 Risk Categorization Systems
Inker, A, Tonelli, M, Hemmelgarn, B.R. et al; 2012

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3288542/pdf/nihms335228.pdf

11,1%, 28,2% ja 72,5% vastavalt KNH raskusastmetes 1, 2, 3 ja 4. Levimus igale tüsistusele oli suurim osalejatel KNH raskusastmetes 3 ja 4 (tabel 4).

Järeldused: NKF-KDOQI süsteem võib paremini tuvastada teatud samaaegsed kroonilise neeruhaiguse tüsistusi võrreldes, alternatiivse eGFRi ja proteinuuria koos kasutamisega.

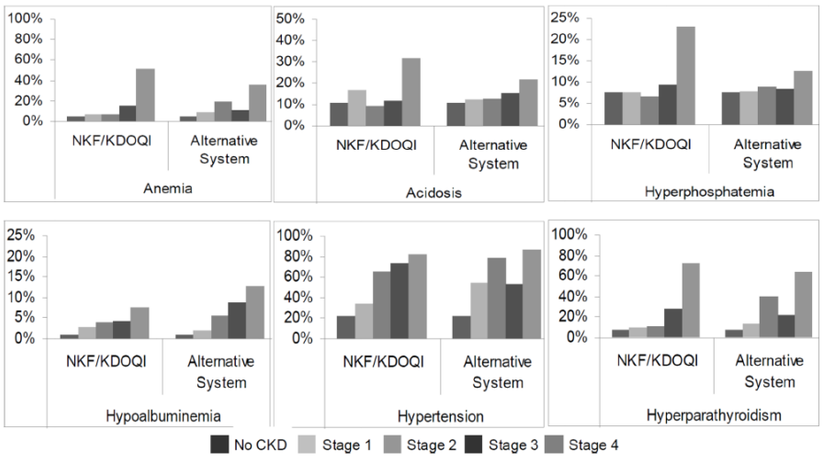


Figure 2.
Prevalence of complications according to the 2 classification systems

Table 2

Multivariable adjusted prevalence ratios for CKD complications by the 2 staging systems.

		No CKD	CKD stage				p-trend
			1	2	3	4	
Anemia							
	NKF-KDOQI	1 (ref)	1.34 (1.04 – 1.74)	1.02 (0.82 – 1.26)	2.06 (1.79 – 2.37)	5.23 (3.99 – 6.86)	<0.001
	Alternative system	1 (ref)	1.33 (1.14 – 1.56)	2.45 (1.99 – 3.01)	1.57 (1.31 – 1.89)	4.37 (3.39 – 5.63)	<0.001
Acidosis							
	NKF-KDOQI	1 (ref)	1.34 (1.12 – 1.61)	1.13 (0.85 – 1.51)	1.70 (1.44 – 2.00)	4.89 (3.43 – 6.96)	<0.001
	Alternative system	1 (ref)	1.33 (1.14 – 1.55)	1.99 (1.51 – 2.62)	1.39 (1.10 – 1.77)	2.95 (2.27 – 3.82)	<0.001
Hyperphosphatemia							
	NKF-KDOQI	1 (ref)	0.91 (0.70 – 1.18)	1.06 (0.75 – 1.50)	1.61 (1.36 – 1.92)	3.64 (2.40 – 5.52)	<0.001
	Alternative system	1 (ref)	1.11 (0.93 – 1.33)	1.57 (1.12 – 2.19)	1.16 (0.81 – 1.67)	2.02 (1.28 – 3.18)	0.003
Hypoalbuminemia							
	NKF-KDOQI	1 (ref)	1.97 (1.36 – 2.85)	2.25 (1.59 – 3.18)	2.07 (1.25 – 3.43)	3.03 (1.31 – 7.04)	<0.001
	Alternative system	1 (ref)	1.11 (0.76 – 1.63)	2.47 (1.27 – 4.78)	5.13 (3.38 – 7.78)	5.61 (3.22 – 9.78)	<0.001
Hypertension							
	NKF-KDOQI	1 (ref)	1.47 (1.34 – 1.60)	1.20 (1.12 – 1.28)	1.01 (0.96 – 1.06)	0.97 (0.83 – 1.14)	0.002
	Alternative system	1 (ref)	1.19 (1.13 – 1.25)	1.05 (0.98 – 1.12)	1.12 (1.03 – 1.23)	1.07 (0.96 – 1.19)	<0.001
Hyperparathyroidism							
	NKF-KDOQI	1 (ref)	1.15 (0.70 – 1.58)	1.00 (0.63 – 1.59)	2.63 (1.97 – 3.51)	6.05 (4.46 – 8.19)	<0.001

Prevalence and prevalence ratios for complications by CKD stage using the 2 staging systems.

	Stage 1 or 2 CKD by NKF-KDOQI		Stage 3 or 4 CKD by NKF-KDOQI	
	Stage 1 or 2 via alternate system	Stage 3 or 4 via alternate system	Stage 1 or 2 via alternate system	Stage 3 or 4 via alternate system
Prevalence of complication				
Anemia	6.8%	5.9%	13.4%	31.4%
Acidosis	13.3%	13.9%	10.8%	20.3%
High phosphorus	6.9%	7.4%	9.5%	11.9%
Hypoalbuminemia	1.8%	9.1%	2.9%	10.8%
Hypertension	47.5%	44.4%	71.5%	83.7%
Hyperparathyroidism	10.4%	6.4%	26.2%	54.7%
Prevalence ratio (95% CI) of complication				
Anemia	1.18 (0.86 – 1.63)	1 (ref)	**2.03 (1.41 – 2.91)**	**4.03 (2.88 – 5.65)**
Acidosis	1.17 (0.79 – 1.74)	1 (ref)	**1.61 (1.10 – 2.34)**	**3.07 (2.09 – 4.50)**
Hyperphosphatemia	0.92 (0.58 – 1.46)	1 (ref)	**1.64 (0.98 – 2.75)**	**1.84 (1.03 – 3.28)**
Hypoalbuminemia	0.22 (0.13 – 0.36)	1 (ref)	0.33 (0.19 – 0.57)	1.15 (0.69 – 1.92)
Hypertension	1.00 (0.96 – 1.04)	1 (ref)	1.00 (0.96 – 1.04)	0.94 (0.90 – 0.98)
Hyperparathyroidism	2.45 (0.73 – 8.22)	1 (ref)	**5.57 (1.60 – 19.4)**	**9.62 (2.89 – 32.0)**

Prevalence ratios are adjusted for age, race-ethnicity, sex, body mass index, total and HDL-cholesterol, diabetes mellitus, hypertension (except for the model with hypertension as the outcome), a history of cardiovascular disease, and NHANES (National Health and Nutrition Examination Survey) survey phase.

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; NKF-KDOQI, National Kidney Foundation's Kidney Disease Outcomes Quality Initiative;

Bolded prevalence ratios represents p-value <0.05 compared to the referent group of individuals with stage 1 or 2 CKD by NKF-KDOQI and stage 3 or 4 via the alternative system.

Tabel 4

Abstract Background—Using both estimated glomerular filtration rate (eGFR) and proteinuria to classify the severity of chronic kidney disease (CKD) has been proposed. The utility of a staging system incorporating both eGFR and proteinuria for guiding evaluation of concurrent CKD complications is not known. **Study design—**Cross-sectional analysis Setting & participants—30,528 participants in the US National Health and Nutrition Examination Survey conducted in 1988–1994 and 1999–2006 (n=8,242 for hyperparathyroidism). **Predictors—Classification** system that uses both eGFR and

proteinuria (alternative) and a system that primarily uses eGFR (NKF-KDOQI; the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative) **Outcomes—Prevalence** of anemia, acidosis, hyperphosphatemia, hypoalbuminemia, hyperparathyroidism and hypertension **Measurements—**GFR estimated from the CKD-Epidemiology Collaboration (CKD-EPI) equation and proteinuria assessed using urine albumin-creatinine ratio (ACR) **Results—**The prevalence of hypoalbuminemia, hypertension and hyperparathyroidism increased with more severe CKD using the NKF-KDOQI system. For example, the prevalence of hyperparathyroidism was 9.1%, 11.1%, 28.2% and 72.5% for Stages 1, 2, 3 and 4, respectively Similarly the prevalence of anemia, acidosis and hyperphosphatemia increased progressively from Stage 2 through 4. With the alternative system, the prevalence of anemia, hyperphosphatemia, hypertension and hyperparathyroidism was lower in Stage 3 compared to Stage 2. For example, the prevalence of hyperparathyroidism was 13.5%, 40.3%, 22.2%, and 63.4% for stages 1, 2, 3 and 4, respectively. Applying the alternative system, participants without each complication were more likely to be appropriately reclassified to lower stages (for example, overall net reclassification index of −6.5% for hyperparathyroidism). However, participants with complications (except for hypoalbuminemia) were more likely to be inappropriately reclassified to lower stages. Limitations—Use of single creatinine to estimate GFR and single measure to assess ACR. Small number of participants with CKD Stage 4. **Conclusions—**The NKF-KDOQI system may better identify patients with certain concurrent CKD complications compared to systems using eGFR and proteinuria,	

Uuring (Inker, A.et.al;2011) on tehtud samadel andmetel, mis eelminegi, kuid uuritud on GFRi ja albuminuuria seoseid erinevate komplikatsioonidega KNH patsientidel. Levimus vanuse järgi korrigeeritud levimuse suhtarvud komplikatsioonidele aneemia, atsidoos, hüperfosfateemia, hüpoalbumineemia, hüperparatüreoosi ja hüpertensiooni seosed albuminuuria tasemega on toodud tabelis 2.
Madal eGFR on seotud kõikide komplikatsioonide suurema esinemissagedusega (suhtarvud).

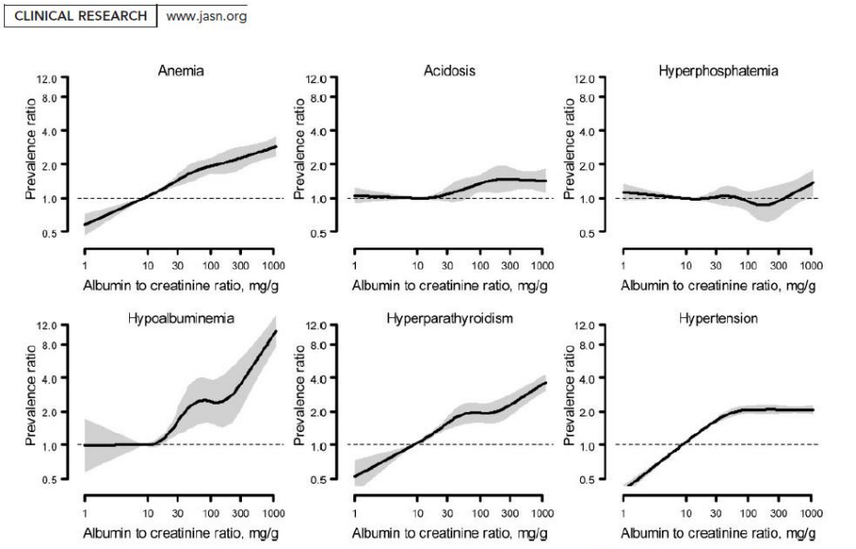


Figure 1. Unadjusted prevalence ratios for anemia, acidosis, hyperphosphatemia, hypoalbuminemia, hyperparathyroidism, and hypertension associated with level of urine albumin-to-creatinine ratio.

4. Estimated GFR, Albuminuria, and Complications of Chronic Kidney Disease
Inker, A, Coresh, J, Levey, A.S. et al; 2011

http://jasn.asnjournals.org/content/22/12/2322.full.pdf+html

Higher levels of albuminuria associate with increased risk for adverse outcomes independent

Table 2. Prevalence rates and age-adjusted and multivariable-adjusted prevalence ratios for anemia, acidosis, hyperphosphatemia, hypoalbuminemia, hyperparathyroidism, and hypertension associated with level of albuminuria

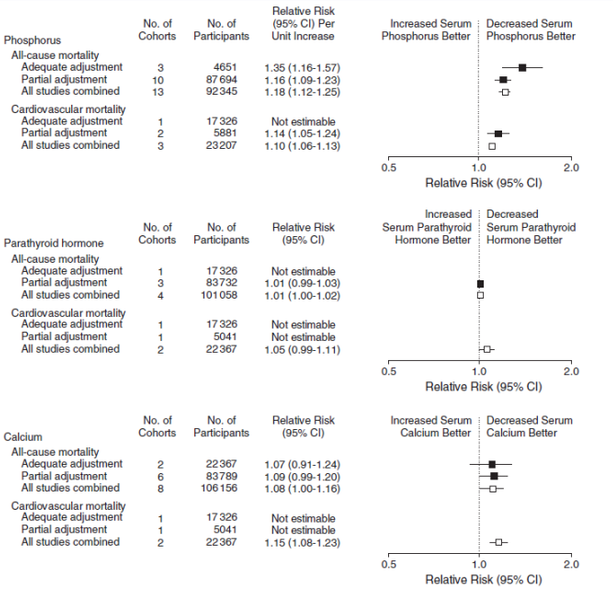
Albuminuria	Anemia	Acidosis	Hyperphosphatemia	Hypoalbuminemia	Hyperparathyroidism	Hypertension
Unadjusted prevalence rates						
<10	4.4%	10.5%	7.5%	1.0%	7.1%	20.3%
10 to 29	6.4%	10.6%	7.9%	1.6%	10.6%	39.0%
30 to 299	8.7%	13.0%	7.2%	2.4%	15.5%	53.0%
≥300	13.5.%	16.0%	8.6%	10.6%	28.9%	55.5%
P trend	<0.001	<0.001	0.295	<0.001	<0.001	<0.001
Age-adjusted prevalence ratios						
<10	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
10 to 29	1.2 (1.1 to 1.5)	1.1 (1.0 to 1.3)	1.1 (0.9 to 1.3)	1.4 (1.0 to 1.9)	1.3 (1.1 to 1.6)	1.3 (1.3 to 1.4)
30 to 299	1.6 (1.3 to 1.9)	1.4 (1.2 to 1.71)	1.0 (0.9 to 1.3)	1.8 (1.2 to 2.7)	1.7 (1.4 to 2.1)	1.5 (1.4 to 1.6)
≥300	2.4 (1.9 to 3.0)	1.5 (1.16 to 1.92)	1.3 (1.0 to 1.8)	7.1 (4.9 to 10.03)	2.9 (2.1 to 4.0)	1.5 (1.3 to 1.6)
P trend	<0.001	<0.001	0.026	<0.001	<0.001	<0.001
Adjusted prevalence ratios: model 1[a]						
<10	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
10 to 29	1.2 (1.0 to 1.4)	1.0 (0.9 to 1.2)	1.1 (0.9 to 1.3)	1.2 (0.9 to 1.7)	1.3 (1.1 to 1.6)	1.3 (1.3 to 1.4)
30 to 299	1.4 (1.2 to 1.6)	1.3 (1.1 to 1.6)	1.0 (0.8 to 1.2)	1.6 (1.1 to 2.4)	1.5 (1.2 to 1.9)	1.5 (1.4 to 1.6)
≥300	1.9 (1.5 to 2.4)	1.4 (1.1 to 1.8)	1.2 (0.9 to 1.6)	6.1 (4.2 to 8.7)	1.6 (1.2 to 2.2)	1.4 (1.3 to 1.5)
P trend	<0.001	<0.001	0.322	<0.001	0.021	<0.001
Adjusted prevalence ratios: model 2[b]						
<10	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
10 to 29	1.2 (1.0 to 1.4)	1.0 (0.9 to 1.2)	1.2 (0.9 to 1.2)	1.1 (0.8 to 1.6)	1.3 (1.0 to 1.7)	1.3 (1.2 to 1.4)
30 to 299	1.4 (1.2 to 1.7)	1.3 (1.1 to 1.5)	1.0 (0.8 to 1.2)	1.1 (0.8 to 1.8)	1.5 (1.2 to 1.9)	1.4 (1.3 to 1.5)
≥300	1.9 (1.5 to 2.4)	1.4 (1.1 to 1.8)	1.1 (0.8 to 1.5)	4.4 (3.1 to 6.1)	1.7 (1.2 to 2.5)	1.3 (1.2 to 1.4)
P trend	<0.001	<0.001	0.675	<0.001	0.012	<0.001

All prevalence ratios include adjustment for NHANES phase (1988–1994, 1999–2000, 2001–2002, 2003–2004, or 2005–2006).

[a]The adjusted prevalence ratio model 1 includes age, race/ethnicity, gender, and estimated GFR.

[b]The adjusted prevalence ratio model 2 includes variables in model 1 and cigarette smoking, body mass index, hypertension, diabetes, and C-reactive protein except in the model for hypertension, where hypertension was not adjusted.

of estimated GFR (eGFR), but whether albuminuria also associates with concurrent complications specific to chronic kidney disease (CKD) is unknown. Here, we assessed the association of spot albumin-tocreatinine ratio with anemia, acidosis, hyperphosphatemia, hypoalbuminemia, hyperparathyroidism, and hypertension among 30,528 adult participants in NHANES 1988–1994 and 1999–2006. After multivariable adjustment including eGFR, higher albumin-to-creatinine ratios associated with anemia, acidosis, hypoalbuminemia, hyperparathyroidism, and hypertension but only weakly associated with acidosis and anemia. Furthermore, the associations between albumin-to-creatinine ratio and both anemia and acidosis were not consistent across eGFR strata. Higher albumin-to-creatinine ratio levels did not associate with hyperphosphatemia. Lower eGFR associated with higher prevalence ratios for all complications, and these associations were stronger than those observed for the albumin-to-creatinine ratio; after multivariable adjustment, however, the associations between eGFR and both hypoalbuminemia and hypertension were NS. In conclusion, albuminuria and eGFR differentially associate with complications of CKD.	
Süstemaatilise ülevaate ja meta-analüüsi (Palmer et.al;2011) eesmärgiks oli hinnata tõendeid KNHga inimeste seerumi fosfori, parathormooni (PTH) ja kaltsiumi seoseid surmajuhtumite, kardiovaskulaarse suremuse ja mitteletaalsete kardiovaskulaarsete haigustega. Andmeid otsiti andmebaasidest MEDLINE (1948 kuni detsember 2010) ja EMBASE (1947 kuni detsember 2010). Uuringu kriteeriumitele vastasid 47 kohortuuringut (N = 327 644 patsienti). **Tulemused**. Surma risk on suurenenud 18% iga 1 mg/dl seerumi fosfori tõusuga (suhteline risk [RR], 1,18 [95% usaldusvahemik {CI} 1,12-1,25]). Puudus oluline seos üldsuremuse ja parathormooni seerumi taseme vahel (RR 100-pg/ml tõus, 1,01 [95% CI, 1,00-1,02]) või seerumi kaltsiumisisalduse vahel (RR per 1 mg/dl tõusul, 1,08 [95% CI, 1,00-1,16]). Uuringut piirasid puudulikud andmed. **Järeldused.** Tugevat tõenduspõhisust ei ole seerumi kaltsiumi- ja parathormooni seosega surma riski ja kardiovaskulaarsete tüsistustega KNH patsientidel. Siiski näib olevat seos tõusnud fosfori taseme ja suremuse vahel, selles kohordis. Seda uuringut on kasutanud ka KDIGO ravijuhend.	**5. Serum Levels of Phosphorus, Parathyroid Hormone, and Calcium and Risks of Death and Cardiovascular Disease in Individuals With Chronic Kidney DiseaseA Systematic Review and Meta-analysis.** Palmer, S.C, Hayen, A, Macaskill, P. et.al; 2011



Risks of all-cause mortality, cardiovascular mortality, and nonfatal cardiovascular events are shown per 1-mg/dL increase in serum levels of phosphorus, 100-pg/mL increase in serum parathyroid hormone, and 1-mg/dL increase in serum calcium. Summary estimates are not reported when only a single cohort contributed data. CI indicates confidence interval.

Figure 19 | Summary estimates for risks of all-cause mortality and cardiovascular mortality associated with levels of serum phosphorus, PTH, and calcium. PTH, parathyroid hormone. Reprinted with permission from Palmer SC, Hayen A, Macaskill P, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. JAMA 2011; 305(11): 1119-1127.[387] Copyright © (2011) American Medical Association. All rights reserved. Accessed http://jama.jamanetwork.com/data/Journals/JAMA/18301/jrv15003_1119_1127.pdf

http://jama.jamanetwork.com/article.aspx?articleid=646157

Abstract

CONTEXT:

Clinical practice guidelines on the management of mineral and bone disorders due to chronic kidney disease recommend specific treatment target levels for serum phosphorus, parathyroid hormone, and calcium.

OBJECTIVE:

To assess the quality of evidence for the association between levels of serum phosphorus, parathyroid hormone, and calcium and risks of death, cardiovascular mortality, and nonfatal cardiovascular events in individuals with chronic kidney disease.

DATA SOURCES:

The databases of MEDLINE (1948 to December 2010) and EMBASE (1947 to December 2010) were searched without language restriction. Hand searches also were conducted of the reference lists of primary studies, review articles, and clinical guidelines along with full-text review of any citation that appeared relevant.

STUDY SELECTION:

Of 8380 citations identified in the original search, 47 cohort studies (N = 327,644 patients) met the inclusion criteria.

DATA EXTRACTION:

The characteristics of study design, participants, exposures, and covariates together with the outcomes of all-cause mortality, cardiovascular mortality, and nonfatal cardiovascular events at different levels of serum phosphorus, parathyroid hormone, and calcium were analyzed within studies. Data were summarized across studies (when possible) using random-effects meta-regression.

DATA SYNTHESIS:

The risk of death increased 18% for every 1-mg/dL increase in serum phosphorus (relative risk [RR], 1.18 [95% confidence interval {CI}, 1.12-1.25]). There was no significant

association between all-cause mortality and serum level of parathyroid hormone (RR per 100-pg/mL increase, 1.01 [95% CI, 1.00-1.02]) or serum level of calcium (RR per 1-mg/dL increase, 1.08 [95% CI, 1.00-1.16]). Data for the association between serum level of phosphorus, parathyroid hormone, and calcium and cardiovascular death were each available in only 1 adequately adjusted cohort study. Lack of adjustment for confounding variables was not a major limitation of the available studies.

CONCLUSIONS:

The evidentiary basis for a strong, consistent, and independent association between serum levels of calcium and parathyroid hormone and the risk of death and cardiovascular events in chronic kidney disease is poor. There appears to be an association between higher serum levels of phosphorus and mortality in this population.

Normi piiridest, suuremat seerumi fosfaadi kontsentratsiooni seostatakse kardiovaskulaarsete haiguste ja suremusega KNHga inimestel ja ka nendel, kellel on normaalne neerufunktsioon. Eksperimentaalsed mudelid näitavad, et fosfaadil on otsene mõju veresoonte silelihaste lubjastumisele.

KDIGO ravijuhendis kasutatud uuringus (Adeney et.al 2009**)** uuriti seerumi fosfaadi kontsentratsiooni seoseid veresoonte ja südameklapi lubjastumisega. 439 osalejat, kellel oli mõõdukas krooniline neeruhaigus ja südame-veresoonkonna haigused. Fosfaaditaseme kontsentratsioon oli normi piires (2,5-4,5 mg/dl) 95% uuringus osalejal. Levimus koronaararterite, alaneva aordi, aordiklapi ja mitraalklapi lubjastumisele oli vastavalt 67, 49, 25 ja 20%. Pärast korrigeerimist demograafilistele näitajatele ja eGFRile (Tabel 3) iga 1-mg/dl seerumi fosfaadi kontsentratsiooni tõustes leiti lubjastumise tõus 21% (P = 0,002), 33% (P = 0,001), 25% (P = 0,16) ja 62% (P = 0,007) võrra vastavalt koronaararterites, alanevas aordis, aordiklapis ja mitraalklapis. Reguleerimine traditsiooniliste ateroskleroosi riskitegurite, parathormooni või 1,25-dihüdroksüvitamiiniga D tasemele ei muuda neid andmeid.

Uuringu tulemustest järeldati, et suurem seerumi fosfaadi kontsentratsioon, kuigi veel normi piires, on seotud veresoonte ja südameklappide lubjastumisega inimestel, kellel on mõõdukas krooniline neeruhaigus.

Table 3. Associations of 1-mg/dl greater serum phosphate concentrations with prevalent calcification after adjustment for potential mediators

Site	Adjusted for Age, Race, Gender, and Kidney Function			Add Serum PTH Levels			Add Serum 1,25-$(OH)_2$D Levels		
	PR	95% CI	P[a]	PR	95% CI	P[a]	PR	95% CI	P[a]
Coronary artery	1.22	1.08 to 1.37	0.001	1.19	1.05 to 1.35	0.005	1.19	1.05 to 1.35	0.005
Descending aorta	1.33	1.13 to 1.58	0.001	1.32	1.11 to 1.57	0.002	1.33	1.12 to 1.58	0.001
Aortic valve	1.25	0.93 to 1.70	0.140	1.27	0.93 to 1.73	0.130	1.24	0.90 to 1.70	0.190
Mitral valve	1.61	1.14 to 2.31	0.008	1.67	1.17 to 2.38	0.005	1.69	1.18 to 2.41	0.004

[a]P values not adjusted for multiple comparisons.

Abstract

Within the normal range, higher serum phosphate concentrations are associated with cardiovascular events and mortality in individuals with chronic kidney disease (CKD) and in those with normal kidney function. Experimental models suggest that phosphate has a direct calcifying effect on vascular smooth muscle. We examined associations of serum phosphate concentrations with vascular and valvular calcification in 439 participants from the Multi-Ethnic Study of Atherosclerosis who had moderate CKD and no clinical cardiovascular disease. Serum phosphate concentrations were within the normal range (2.5 to 4.5 mg/dl) in 95% of study participants. The prevalence of calcification in the coronary arteries, descending thoracic aorta, aortic valve, and mitral valve was 67, 49, 25, and 20%, respectively, measured by electron-beam or multi-detector row computed tomography. After

6. Association of serum phosphate with vascular and valvular calcification in moderate CKD Adeney, K.L, Siscovick, D.S, Ix, J.H. et.al;2009

http://jasn.asnjournals.org/conten/20/2/381.full.pdf+html

adjustment for demographics and estimated GFR, each 1-mg/dl increment in serum phosphate concentration was associated with a 21% (P = 0.002), 33% (P = 0.001), 25% (P = 0.16), and 62% (P = 0.007) greater prevalence of coronary artery, thoracic, aortic valve, and mitral valve calcification, respectively. Adjustment for traditional risk factors for atherosclerosis, parathyroid hormone, or 1,25-dihydroxyvitamin D levels did not alter these associations. In conclusion, higher serum phosphate concentrations, although still within the normal range, are associated with a greater prevalence of vascular and valvular calcification in people with moderate CKD. It remains to be determined whether lowering phosphate concentrations will impact calcification risk in the setting of kidney disease.	

Ravijuhendid esmase otsinustrateegia kohta

Kokkuvõte ravijuhendites leiduvast
Antud kliinilisele küsimusele leidus ülevaateid kolmes sekretariaadi poolt AGREEga hinnatud ravijuhendis.

KDIGO
Tüsistuste esinemissagedus ja levik sõltub KNH raskusastmest ja määratletakse valdavalt eGFRi kategooriatetele (vt. tabel 27).
Kõikidel ei teki kõiki tüsistusi, samuti tekivad tüsistused erineva kiirusega. Oluline on ühtselt teada võimalikke tüsistusi langeva eGFRi ja tõusva albuminuuria puhul.
KNH patsientidel on levinud tüsistuseks aneemia, kuid õige käsitlusega on võimalik hoida seda kontrolli all (vt. aneemia ravijuhendit, http://www.njur.se/filer/behandlingsriktlinjer/riktlinjer_kdigo-anemia_gl.pdf).

Soovitused
3.2.3: Teha kindlaks aneemia KNH inimestel määrates Hb kontsentratsioon (Not Graded):
*** kui see on kliiniliselt näidustatud inimestele, kelle eGFR on ≥60 ml / min / 1,73 m2 (eGFR G1-G2);**
***vähemalt kord aastas inimestel, kelle eGFR on 30-59 ml / min / 1,73 m2 (eGFR G3A-G3B);**
***vähemalt kaks korda aastas inimestel, kelle eGFR on <30 ml / min / 1,73 m2 (eGFR G4-G5).**

4.1.1:Kõikidel KNH patsientidel on suurenenud risk südame-veresoonkonna haigustele (1A).

4.1.2: Soovitame, et südame isheemiatõvega inimeste ravikäsitlus ei süvendaks kroonilist neeruhaigust. (1A)

4.3.1: Soovitame täiskasvanud KNH patsientidel regulaarselt jälgida perifeersete arterite haiguse ilminguid ja kaaluda tavalist teraapiasuunda. (1B)

4.3.2: Soovitame täiskasvanud KNHga ja diabeediga patsientidele regulaarset podiaatrilist hinnangut. (2 a)

3.2 COMPLICATIONS ASSOCIATED WITH LOSS OF KIDNEY FUNCTION
People with CKD are prone to develop a variety of complications which reflect loss of endocrine or exocrine function **of**the kidneys. The incidence and prevalence of these complications increase with severity of CKD as defined predominantly by GFR categories (Table 27). It is beyond the scope of this guideline to describe each of the complications and the proposed treatment options for them in detail as guidance for these conditions can be found in other documents. However, for the purpose of completeness, the key complications and management recommendations for people with CKD are addressed in this section. In addition to these complications, we have described strategies to delay progression of CKD which are in part predicated on the identification and management of the clinical, metabolic, and hematologic complications. Note that not all people with CKD will have all of the complications and complications may not occur at the same rate or to the same degree in individuals with the same categories of GFR or albuminuria. Nonetheless knowledge of the common complications and treatment options is important in the care of CKD. Management of Complications Anemia in CKD. Anemia is an important complication of CKD because it contributes significantly to the heavy symptom burden of CKD. It has a major impact on the lives of people with CKD but it is potentially reversible with appropriate treatment. The guideline statements included here are those we consider to be the key considerations for people with non-dialysis CKD. Interested readers are referred to the KDIGO Clinical Practice Guideline for Anemia in for comprehensive guidance on this topic.

Definition and identification of anemia in CKD
3.2.1: Diagnose anemia in adults and children ≥15 years
with CKD when the Hb concentration is o13.0 g/ dl (o130 g/l) in males ando12.0 g/dl (o120 g/l) in females. (Not Graded)
Evaluation of anemia in people with CKD

3.2.3: To identify anemia in people with CKD measure Hb concentration (Not Graded): when clinically indicated in people with GFR ≥60 ml/min/1.73 m2 (GFR categories G1-G2); at least annually in people with GFR 30-59 ml/ min/1.73 m2 (GFR categories G3a-G3b); at least twice per year in people with GFR o30 ml/min/1.73 m2 (GFR categories G4-G5).

4.1.1: We recommend that all people with CKD be considered at increased risk for cardiovascular disease. (1A)

In those with an eGFR of 45-59 ml/min/1.73 m2, risk is increased by 43% and in those with eGFR below 15 ml/min/1.73 m2, risk is increased by 343%.58 Although people with GFR category G5 (GFRo15 ml/min/1.73 m2) are at the highest risk of a CVD event, there will be more events in people with GFR categories G3a-G3b (GFR 30–59 ml/min/1.73 m2) because of the much higher prevalence at these categories.420 These events occur at a younger age in people with CKD suggesting that CKD promotes CVD at an accelerated rate.421 The prognosis after an acute event is related to level of GFR with a significant rise
in mortality when eGFR falls below 45 ml/min/1.73 m2.422–424
The Chronic Kidney Disease Prognosis Consortium demonstrated that in general practice cohorts there was an increase in cardiovascular mortality when ACR is higher than 30 mg/g (3 mg/mmol).4 Analysis of data from the Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that any degree of albuminuria is a risk factor for cardiovascular events in individuals with or without diabetes.428

4.1.2: We recommend that the level of care for ischemic heart disease offered to people with CKD should not be prejudiced by their CKD. (1A)

4.3.1: We recommend that adults with CKD be regularlyexamined for signs of peripheral arterial disease and be considered for usual approaches to therapy. (1B)

4.3.2: We suggest that adults with CKD and diabetes are offered regular podiatric assessment. (2A)

Table 31 | Peripheral arterial disease and CKD

Study	Population	PAD definition	Outcome of interest
O'Hare et al.[585]	NHANES age 40+	ABI <0.9	24% prevalence in people with CKD and a CrCl of <60 ml/min (< 1 ml/s) versus 3.7% in those with normal kidney function
O'Hare et al.[587]	HERS study, postmenopausal women with known CHD	PAD event rates (amputation, revascularization, or lumbar sympathectomy)	Incident PAD event rates were 0.55%, 0.92%, and 2.73% per year with CrCl 60, 30-59, and 30 ml/min/1.73 m^2, respectively
O'Hare et al.[586]	Cardiovascular Health Study, adults age 65+	Lower-extremity PAD procedure (bypass surgery, angioplasty, or amputation)	HR for PAD procedure 2.5 (95% CI 1.2-5.1) for highest quintile of cystatin C (≥1.28 mg/l) versus lowest (≤0.9 mg/l)
De Vinuesa et al.[582]	102 adults in a CKD clinic, mean age 70 ± 11 years, GFR 15-60 ml/min/ 1.73 m^2	ABI <0.9	17% signs and symptoms of PAD, which had passed unnoticed; 32% had ABI <0.9 (mean 0.64 ± 0.25)
Liew et al.[584]	6-year follow up of 1027 subjects (ABI index recording and GFR measured within 90 d)	ABI <0.9	6-year mortality rate for CKD and PAD 45% versus 28% CKD alone, 26% PAD alone, and 18% for neither condition
Wattanakit et al.[588]	6760 subjects, aged 45-84 years in the Multi-Ethnic Study of Atherosclerosis	ABI <0.9	Albuminuria was associated with PAD in subjects with diabetes (odds ratio 1.90, 95% CI 1.19–3.04) but not in those without
Lash et al.[583]	3612 subjects age 58.2 ± 11.0 years in the Chronic Renal Insufficiency Cohort study	ABI <0.9	Overall, 16% prevalence of PAD in subjects with GFR<60 ml/min/1.73 m^2, increasing from 4% in those with GFR>60 to 22% in those with GFR<30 ml/min/1.73 m^2
Bello et al.[581]	920,985 subjects with GFR and proteinuria assessment, median follow-up 35 months (IQR 22-44)	Time to first hospitalization with PAD	1891 of subjects (0.2%) hospitalized at least once for PVD, adjusted rates increased with lower GFR

Abbreviations: ABI, ankle-brachial index; CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; CrCl, creatinine clearance; d, day; GFR, glomerular filtration rate; HERS, Heart and Estrogen/Progestin Replacement Study; HR, hazard ratio; IQR, interquartile range; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral arterial disease; PVD, peripheral vascular disease.

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.

NICE

Ravijuhendis kasutatud üks kõrge kvaliteediga IPD meta-analüüs näitab, et on olemas suundumus, et eGFR suurem langus on seotud tõusva albuminuuriaga. Kelle eGFR on 15-29ml / min / 1,73 m2, ainult albuminuuria on suurem kui 10 mg / g ennustab eGFRi langust. Kelle eGFR on suurem kui 90 ml / min / 1,73 m2 on ebaselge, kas albuminuuria lisab sellele ennustatavat väärtust.

Kaks kõrge kvaliteediga IPD meta-analüüsi näitavad, et kõigil eGFR raskusastmetel on trend ESRD (lõppstaadiumis krooniline neeruhaigus) sagenemisele süveneva proteinuuria ja albuminuuria korral

ESRD prognoos ei ole selge üle või alla 65-aasta vanustel eGFR või albuminuuria muutumisel, välja arvatud eGFR 15-29ml / min / 1,73 m2, kus suurenev albuminuuria väärtus võib ennustada ESRD alla 65 aastastel inimestel, kuid usaldusintervall on väga lai.

Puudub ühtne erinevus progresseerumise riskile, erinevatel eGFR raskusastmetel või albuminuuriaga inimestestel:

o koos või ilma diabeetita

o või ilma hüpertensioonita.

Üldsuremus

IPD meta-analüüs ei viita proteinuuria ja üldsuremuse tõusu seosele. Suurem albuminuuria ennustab üldsuremuse tõusu. Kui albuminuuria on suurem kui 30 mg / g ennustab oluliselt suurenenud üldsuremust kõikides eGFR raskusastmetes.

Teine IPD meta-analüüs näitas, et seos vähenenud eGFRi ja suurenenud suremuse riski vahel vähenes vanuse tõustes (üle 54-aastased koos albuminuuriaga).

Hüpertensioonil olid samasuguseid tulemused A1 raskusastmes 10-29mg / g, mis ennustab rohkem üldsuremust hüpertensiooniga inimestel.

Kardiovaskulaarne suremus

IPD meta-analüüs näitas, et kui albuminuuria tase on suurem kui 300 mg / g ennustab see rohkem kardiovaskulaarset suremust kui albuminuuria on 10-29 või 30-299mg / g.

Ei ole selge erinevus kardiovaskulaarse haigestumuse kohta kõigis eGFR või albuminuuria raskusastmetes (alla või üle 65-aastased) või kaasuva diabeedi või hüpertensiooni diagnoosiga inimestel.

ÄNK

IPD meta-analüüs näitas, et progresseeruv albuminuuria ennustab ÄNK (äge neerupuudulikkus).

Soovitused

Liigitada krooniline neeruhaigus kasutades kombinatsiooni eGFR ja albuminuuria (nagu on kirjeldatud tabelis 27).

Pea meeles, et:

Suurenenud albuminuuria on seotud suurenenud riskiga kõrvaltoimete tekkeks.

Langenud eGFR on seotud suurenenud riskiga kõrvaltoimete tekkeks.

Suurenenud albuminuuria ja langenud eGFR kombinatsioonis tõstab kõrvaltoimete riski. Ärge juhinduge kroonilise neeruhaiguse diagnoosimisel ainult vanusest.

Määrake isiku eGFRi ja albuminuuriat (vt tabel 27), mis näitavad nende kõrvaltoimete riski (näiteks kroonilise neeruhaiguse progresseerumist, äge neerukahjustus, üldsuremust ja kardiovaskulaarset haigust).

6.1 The influence of GFR, age, gender, ethnicity and proteinuria on patient outcomes

6.1.1 Introduction

In 2002 the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative published a classification of chronic kidney disease split into five stages defined by glomerular filtration rate (GFR). Although internationally accepted, a classification of CKD based solely on GFR category has been the subject of debate in the intervening years. In 2008 NICE clinical practice guideline CG73 recommended adjusting this classification to sub-divide stage 3 CKD into 3a (GFR 45-59 ml/min/1.73 m^2) and 3b (GFR 30-44 ml/min/1.73 m^2) on the basis of a clear difference in adverse outcomes associated with the 2 different GFR categories. NICE CG73 also recognised the importance of associated proteinuria, recommending the addition of a suffix p for those with significant proteinuria (defined as urinary albumin:creatinine ratio (ACR) >30 mg/mmol), to delineate people at increased risk of adverse outcome. Recent epidemiological studies have focussed on determining the influence of differing levels of proteinuria on outcomes in all categories of GFR. The purpose of this question was to review these new data to determine whether the definition and classification of chronic kidney disease should be further refined.

6.1.2 Review question: For people with suspected CKD, what is the effect of proteinuria at any given eGFR on adverse outcomes?

Update 2014

For full details see review protocol in Appendix C.

Table 23: PICO characteristics of classification review question

Population	Adults (aged 18 and over) with suspected CKD
Prognostic factor	Proteinuria: • ACR <3 mg/mmol (<30mg/g) • ACR 3-29 mg/mmol (30-299mg/g) • ACR >30 mg/mmol (>300mg/g) (or equivalent PCR and reagent strip result
Outcomes	Critical • CKD progression: change in eGFR • CKD progression: occurrence of end stage kidney disease (ESRD or ESKD as reported by the study)All-cause mortality • Cardiovascular mortality • AKI Important • Cardiovascular events • Hospitalisation
Study design	Prospective cohort studies, meta-analysis (retrospective cohort studies if prospective studies not identified)

6.1.3 Clinical evidence

Six individual patient data (IPD) meta-analyses were included in the review.[21,108,117,134,237,408] Evidence from these are summarised below in Table 25, and a narrative summary of results in the evidence statements. See also the study selection flow chart in Appendix D, forest plots in Appendix I and study evidence tables in Appendix G.

As these studies are all IPD meta-analysis, quality was assessed per-study using a customised methodology checklist for quality assessment of systematic reviews of prognostic studies adapted from Hayden 2006[138] rather than by using the GRADE profile. The study quality rating is given in the final column of Table 25. A narrative summary of results is provided in place of the GRADE summary of findings table.

The included IPD meta-analyses addressed the review question directly and covered all subgroups in the review protocol, therefore individual cohort studies were excluded from this review (Appendix J).

No evidence was identified reporting hospitalisation or cardiovascular events.

The IPD meta-analyses included study populations of people with CKD,[21] populations at high risk of chronic kidney disease,[117,408] those with and without diabetes[108] and those with and without hypertension[237]. Gansevoort et al.[117] also included data from general population cohorts, but data from high risk cohorts was presented separately in the analysis due to important baseline differences between the groups, and only the high risk data are included in this review. Hallan et al.[134] included general population, high risk and CKD cohorts. Although CKD cohorts were separated for analysis of mortality and ESRD, hazard ratios could not be calculated from the data presented. The overall data has therefore been presented as this also separates by eGFR and ACR categories. Although these three studies included populations that could be considered indirect to the review target population (both included data from general population cohorts as well as high risk and CKD cohorts), they were included as they addressed subgroups of interest and provided data on eGFR and proteinuria levels from which CKD status could be derived.

Update 2014

References to the individual cohorts included in each of the meta-analyses are provided in the evidence tables in Appendix G.

All ACR and PCR data in this review are in mg/g as reported in the papers. The equivalent mg/mmol values are given in Table 24 below. Reagent strip category has also been reported from some studies. It is important to note that the evidence does not differentiate ACR category by sex and thus what was previously termed microalbuminuria is equivalent to an ACR of less than 3mg/mmol in both men and women.

Table 24: Unit conversion for albuminuria and proteinuria

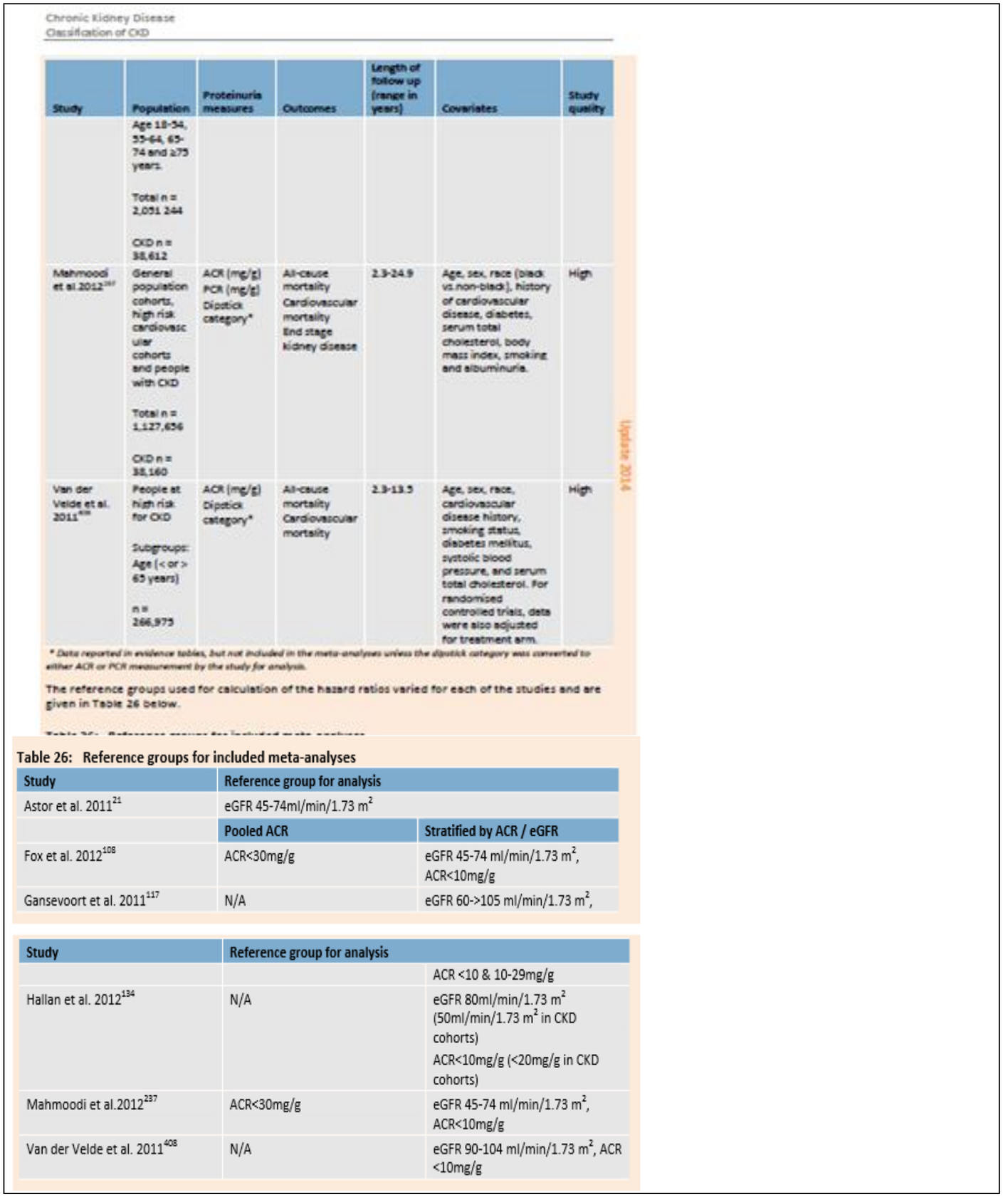
Measure	Units	Normal to mildly increased	Moderately increased	Severely increased
ACR	mg/g	<30	30-300	>300
	mg/mmol	<3	3-30	>30
PCR	mg/g	<150	150-500	>500
	mg/mmol	<15	15-50	>50

Summary of included studies

Table 25: Summary of studies included in the review

Study	Population	Proteinuria measures	Outcomes	Length of follow up (range in years)	Covariates	Study quality
Astor et al. 2011[75]	People with CKD (of diverse clinical diagnoses) n = 21,688	ACR (mg/g) PCR (mg/g) Dipstick category*	End stage kidney disease All-cause mortality	2.3-9.5	Age, sex, race, previous cardiovascular disease, smoking status, diabetes mellitus, systolic blood pressure and serum total cholesterol concentration.	High
Fox et al. 2012[106]	General population cohorts, high risk cardiovascular cohorts and people with CKD Total n = 1,024,977 CKD n = 38,612	ACR (mg/g) PCR (mg/g) Dipstick category*	All-cause mortality Cardiovascular mortality End stage kidney disease	2.3-24.9	Age, sex, race (black vs.non-black), smoking, systolic blood pressure, total cholesterol, body-mass index, history of cardiovascular disease, and albuminuria.	High
Gansevoort et al. 2011[113]	People at high risk for CKD Subgroups: Age (< or > 65 years) n = 173,892	ACR (mg/g) Dipstick category*	Progression of CKD (change in eGFR) End stage kidney disease AKI	2.3-21.6	Age, sex, race and cardiovascular risk factors (including cardiovascular disease history, smoking status, diabetes mellitus, systolic blood pressure and serum total cholesterol).	High
Hallan et al. 2012[144]	General population cohorts, high risk cardiovascular cohorts and cohorts of people with CKD. Subgroups:	ACR (mg/g) PCR (mg/g) Dipstick category*	All-cause mortality. End stage kidney disease.	2.3-24.9	Sex, race (black versus non-black) history of cardiovascular disease history, smoking status, diabetes mellitus, systolic blood pressure, serum total cholesterol, BMI, albuminuria and the randomized intervention (for clinical trials).	High

Update 2014



Chronic Kidney Disease
Classification of CKD

Study	Population	Proteinuria measures	Outcomes	Length of follow up (range in years)	Covariates	Study quality
	Age 18-34, 35-64, 65-74 and ≥75 years. Total n = 2,051 244 CKD n = 38,612					
Mahmoodi et al.2012[237]	General population cohorts, high risk cardiovascular cohorts and people with CKD Total n = 1,127,656 CKD n = 38,160	ACR (mg/g) PCR (mg/g) Dipstick category*	All-cause mortality Cardiovascular mortality End stage kidney disease	2.3-24.9	Age, sex, race (black vs.non-black), history of cardiovascular disease, diabetes, serum total cholesterol, body mass index, smoking and albuminuria.	High
Van der Velde et al. 2011[408]	People at high risk for CKD Subgroups: Age (< or > 65 years) n = 266,975	ACR (mg/g) Dipstick category*	All-cause mortality Cardiovascular mortality	2.3-13.5	Age, sex, race, cardiovascular disease history, smoking status, diabetes mellitus, systolic blood pressure, and serum total cholesterol. For randomised controlled trials, data were also adjusted for treatment arm.	High

(Update 2014)

* Data reported in evidence tables, but not included in the meta-analyses unless the dipstick category was converted to either ACR or PCR measurement by the study for analysis.

The reference groups used for calculation of the hazard ratios varied for each of the studies and are given in Table 26 below.

Table 26: Reference groups for included meta-analyses

Study	Reference group for analysis	
Astor et al. 2011[21]	eGFR 45-74ml/min/1.73 m^2	
	Pooled ACR	Stratified by ACR / eGFR
Fox et al. 2012[108]	ACR<30mg/g	eGFR 45-74 ml/min/1.73 m^2, ACR<10mg/g
Gansevoort et al. 2011[117]	N/A	eGFR 60->105 ml/min/1.73 m^2, ACR <10 & 10-29mg/g
Hallan et al. 2012[134]	N/A	eGFR 80ml/min/1.73 m^2 (50ml/min/1.73 m^2 in CKD cohorts) ACR<10mg/g (<20mg/g in CKD cohorts)
Mahmoodi et al.2012[237]	ACR<30mg/g	eGFR 45-74 ml/min/1.73 m^2, ACR<10mg/g
Van der Velde et al. 2011[408]	N/A	eGFR 90-104 ml/min/1.73 m^2, ACR <10mg/g

6.1.4 Economic evidence

Published literature

No relevant economic evaluations were identified

6.1.5 Evidence statements

Clinical

Progression of CKD

- Evidence from one high quality IPD meta-analysis[117] indicates that there is a trend for worse decline in eGFR with increasing ACR. At eGFR of 15-29ml/min/1.73 m^2, only ACR greater than 10mg/g predicts decline in eGFR, although all categories are predictive for eGFR 30-59ml/min/1.73 m^2. At eGFR greater than 90ml/min/1.73 m^2 there is uncertainty as to whether ACR adds any predictive value.
- Evidence from two high quality IPD meta-analyses[21,117] shows that for all eGFR categories there is a trend for increased occurrence of ESRD with increasing PCR and ACR, however for PCR measures, confidence intervals at each stratification of eGFR overlap. The association is clearer with measures of ACR. When stratified by eGFR, ACR significantly predicts increased risk of ESRD for eGFR 15-29, 30-44 and 45-59ml/min/1.73 m^2, but the trend declines at higher eGFRs.
- There is no clear difference between those aged over or under 65 years at any eGFR or ACR, except at eGFR 15-29ml/min/1.73 m^2 where increased ACR may be to be more predictive of ESRD for people aged under 65, although confidence intervals are very wide.[408] However, another IPD meta-analysis demonstrated that the association between reduced eGFR and increased risk of progression was decreased with increasing age (greater than 54 years of age), but this was less evident for ACR.[134]
- There is no consistent difference in risk of progression, and confidence intervals are wide for all effect sizes at varying eGFR category or ACR, in people:
  - with or without diabetes,[108] or
  - with or without hypertension.[237]

Update 2014

All-cause mortality

- Evidence from one high quality IPD meta-analysis[21] does not indicate an association with PCR level and incidence of all-cause mortality. Increasing ACR predicts increased all-cause mortality, but differentiation by ACR category is uncertain due to overlapping confidence intervals. When stratified by eGFR[408], the trend decreases as with increasing eGFR category. However, an ACR greater than 30mg/g significantly predicts increased all-cause mortality at all eGFR categories.

- There is no clear difference in risk of all-cause mortality at any category of eGFR or ACR when stratified by either age (over or under 65 years) or presence of diabetes.[108,408] However, another IPD meta-analysis demonstrated that the association between reduced eGFR and increased mortality risk was decreased with increasing age (greater than 54 years of age), but this was less evident for ACR.
- Stratifying by hypertension showed identical results,[237] except for the ACR category 10-29mg/g which appeared to be more predictive of all-cause mortality for people with hypertension, although confidence intervals are very wide. When stratified by eGFR, this difference between populations is no longer apparent.

Cardiovascular mortality

- Evidence from one high quality IPD meta-analysis[408] shows that ACR levels greater than 300mg/g are more predictive of cardiovascular mortality than ACR 10-29 or 30-299mg/g, but all are significant. When stratified by eGFR the trend is indicated at all eGFR levels, but decreases with increasing eGFR.
- There is no clear difference in risk of cardiovascular mortality at any category of eGFR or ACR when stratified by age (over or under 65 years) or presence of diabetes or hypertension.

AKI

- Evidence from one high quality IPD meta-analysis[117] shows that increasing ACR predicts AKI.

Economic

- No relevant economic evaluations were identified.

6.1.6 Recommendations and link to evidence

Jpdate 2014

Recommendations	• **Classify CKD using a combination of GFR and ACR categories (as described in Table 27). Be aware that:** o **increased ACR is associated with increased risk of adverse outcomes** o **decreased GFR is associated with increased risk of adverse outcomes** o **increased ACR and decreased GFR in combination multiply the risk ofadverse outcomes. [new 2014]** • **Do not determine management of CKD solely by age. [new 2014]** • **Use the person's GFR and ACR categories (see Table 27) to indicate their risk of adverse outcomes (for example, CKD progression, acute kidney injury, all-cause mortality and cardiovascular events) and discuss this with them. [new 2014]**
Relative values of different outcomes	The GDG considered that the critical outcomes for decision making were CKD progression (measured by change in eGFR and occurrence of end stage kidney disease), all-cause mortality, cardiovascular mortality and acute kidney injury (AKI). Cardiovascular events and hospitalisation were considered as important outcomes, but no information was available in this review for these outcomes.
Trade off between clinical benefits and harms	The GDG considered that in terms of risk of progression, mortality or risk of developing AKI, there was no difference between CKD stages 1 and 2 in the existing classification system. After careful consideration, it was agreed that in view of the risks of changing this classification system in terms of the confusion it may cause to people that had already been diagnosed, and for clinicians, it would be inappropriate to combine these. However, this is reflected in the classification table demonstating the comparable level of risk by the shading.

Economic considerations	Economic evaluations for the classification of CKD were not applicable given the purely clinical nature of this topic. The GDG considered that an accurate and clear classification of CKD is imperative to facilitate appropriate treatment and management of CKD. The inclusion of risk factors that increase the risk of CKD progression and/or associated adverse outcomes within the classification of CKD does not in itself increase the costs of CKD management for a person. Rather, doing so facilitates more appropriate CKD treatment which can help reduce downstream cost and health consequences. Furthermore, the GDG also considered the negative consequences of stress associated with CKD disease labelling and felt it appropriate to ensure patients with insignificant reduction in kidney function (eGFR >90 ml/min/1.73 m^2) did not experience a reduction in their quality of life from a diagnosis of CKD.
Quality of evidence	The evidence reviewed was from 5 large high quality IPD meta-analyses. However, it was noted that all of the data were estimated GFR rather than measured GFR values. In addition, the GDG acknowledged the difficulties of interpreting the evidence for adverse outcomes in people who were 'hyperfiltering' (see glossary) and the inability to distinguish those with spuriously high GFRs as a consequence of abnormally low serum creatinine levels (for example due to severe malnutrition or loss of muscle) from those who were truly hyperfiltering. The GDG considered that itwas unlikely that people with high GFRs who were truly hyperfiltering were older (and therefore those who would most likely have severe malnutrition or muscle loss), and it was more likely that these were younger people.
Other considerations	There was no evidence that the risk differed in people with hypertension or diabetes, or between males and females, and therefore the GDG agreed that separate recommendations for these populations were not indicated. The GDG were aware that the evidence considered reported ACR as mg/g. When discussing the evidence (in this LETR), for reasons of clarity the GDG refer to the mg/mmol equivalent to conform with UK standard units of measurement for ACR (See Table 24). All outcomes were significantly worse in people with ACR>3 mg/mmol (reported in the evidence as 30 mg/g), this held true for those aged both >65 and <65. Similarly in those with ACR<3 mg/mmol all outcomes were significantly worse for those with eGFR<60 ml/min/1.73 m^2, again this was irrespective of age. However, Hallan et al. reported risk of all-cause mortality and end stage kidney disease according to age subgroup. This evidence demonstrated that the risk at any point in time was lower in people aged over 75 than those aged 55-64.[134] The GDG debated the term 'microalbuminuria' in relation to people with diabetes and agreed it was unhelpful to include this term in any classification. The ACR value should be stated specifically to prevent confusion in terminology of what constitutes 'significant proteinuria' and 'microalbuminuria'. Using ACR >3mg/mmol was considered to be more appropriate. The GDG agreed that the data from the CKD prognosis consortia (see classification evidence review, chapter 6.1) indicated that the risk associated with albuminuria rises with increasing albumin creatinine ratio and is evident at levels of ACR below 3mg/mmol. ACR is an independent risk factor for adverse outcomes in people both with and without diabetes mellitus and hypertension. It was noted that a classification incorporating eGFR and ACR categories is rarely used for prescribing, and in this situation GFR category is preferred. The BNF acknowledges that kidney function in adults is reported on the basis of eGFR derived from prediction equations. In the context of drug nephrotoxicity, creatinine clearance is frequently used as a surrogate for GFR. (See recommendation 16) Classification by eGFR and ACR category is more useful in the clinic and for people diagnosed with CKD. The GDG agreed that it was important that people with CKD were made aware that both the eGFR and ACR levels were important, and that this should be highlighted when the classification was explained. The GDG voted to make recommendation 27 a key priority for implementation as

Update 2014

they agreed it would have a high impact on outcomes that are important to patient and set challenging but achievable expectations of health services.

The GDG commented that the recommendation will hopefully facilitate the introduction of international classification and risk-based approach to care. They agreed that this recommendation underpinned the rest of the guideline and represents a step forwards in CKD management, although it will need support in implementation. Examples of how this classification would be used are as follows:

- A person with an eGFR of 25 ml/min/1.73 m^2 and an ACR of 15 mg/mmol has CKD G4A2.
- A person with an eGFR of 50 ml/min/1.73 m^2 and an ACR of 35 mg/mmol has CKD G3aA3.
- An eGFR of less than 15 ml/min/1.73 m^2 (GFR category G5) is referred to as kidney failure.

Table 27: Classification of chronic kidney disease: GFR and ACR categories

GFR and ACR categories and risk of adverse outcomes			ACR categories (mg/mmol), description and range		
			<3 Normal to mildly increased	3–30 Moderately increased	>30 Severely increased
			A1	A2	A3
GFR categories (ml/min/173 m^2), description and range	≥90 Normal and high	G1	No CKD in the absence of markers of kidney damage		
	60–89 Mild reduction related to normal range for a young adult	G2			
	45–59 Mild–moderate reduction	G3a[1]			
	30–44 Moderate–severe reduction	G3b			
	15–29 Severe reduction	G4			
	<15 Kidney failure	G5			

Increasing risk (GFR categories)

Increasing risk (ACR categories)

Update 2014

[1] Consider using eGFRcystatinC for people with CKD G3aA1 (see recommendations 14 and 15)

Abbreviations: ACR, albumin:creatinine ratio; CKD, chronic kidney disease; GFR, glomerular filtration rate

Adapted with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2013) KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International (Suppl. 3): 1–150

Malaysia

Iga KNH raskusaste koos proteinuuriaga oli seotud kahekordse kardiovaskulaarse haigestumise riski ja suremusega. Uuring viidi läbi diabeeti põdevate inimeste kohordis, kaasati ka need kelle eGFR on ≥90 ml / min / 1,73.

Patsientidel koos albuminuuriaga oli tunduvalt (85%) suurem risk kardiovaskulaarsesse haigusesse haigestumisel võrreldes ilma albuminuuriata. Samuti näitas uuring, et albuminuuria suurendab kardiovaskulaarset haigestumust 89% teises raskusastmes.

Igas KNH raskusastmes proteinuuria püsimine ennustab selle progresseerumist ja arengut lõppstaadiumis neeruhaiguseks.Ühes Jaapani kohortuuringus, suurendas proteinuuria riski ESRDle rohkem kui neli korda. Elanikkonna kestvusuuringute ja meta-analüüside järgi uuritud progresseerumise riski ja proteinuuria taseme põhjal on leitud, et albuminuuria ≥30 mg / mmol tuleks kasutada markerina, sest näitab suurenenud risk KNH progressioonile (võrdub PCR ≥50 mg /mmol või proteinuuria väärtused ≥0.5 g / päevas).

KNH diagnoos eakatel ei tohiks tugineda üksnes eGFR hindamisel. NKF-KDOQI klassifikatsioon võib põhjustada KNH ülediagnoosimist, eriti eakatel. Eakatel patsientidel (vanus> 70 aastat) stabiilse 3a neeruhaigusega ei ole tõenäoline, et neil areneb kroonilise neeruhaigusega seotud komplikatsioone.

At any stage of CKD, the presence of proteinuria was associated with doubling of CV risk and mortality. In a study conducted in the diabetes population, despite eGFR of ≥90 ml/min/1.73m2, patients with albuminuria had a significantly 85% increased risk of CV events compared to those without albuminuria. Similarly, the study showed that albuminuria increased CV events by 89% in patients with stage 2 disease.50, level II-2

At any stage of CKD, persistence of proteinuria predicts its progression and development of ESRD. In a Japanese cohort study, proteinuria significantly increased the risk of ESRD by more than four times. The 7-year cumulative incidence per 1,000 subjects of ESRD gradually increases with declining renal function in stage 3 and 4 ofCKD.51, level II-2

A study by Hallan Sl et al. demonstrated that combining the effect of GFR and albuminuria for classifying CKD significantly improved prediction of ESRD. The hazard ratio (HR) was 13 if the patient had microalbuminuria compared to 47.2 if the patient had macroalbuminuria.52, level II-2

Evidence from longitudinal population studies and meta-analysis of progression risk and level of proteinuria suggested that an ACR ≥30 mg/mmol should be used as a marker for increased risk for progression of CKD (equivalent to a PCR ≥50 mg/mmol or proteinuria values ≥0.5 g/day).53, level II-2; 54, level I

Therefore, the suffix (p) is important to be added to denote the presence of proteinuria when staging CKD.A suffix (d) should be added if the patient is on dialysis and (t) should be added if the patient has been transplanted.55, level II

The diagnosis of CKD in the elderly should not solely rely on eGFR estimation. The NKF-KDOQI classification may lead to overdiagnosis of CKD particularly in the elderly. Elderly patients (age >70 years old) with stable stage 3A of kidney disease are not likely to develop CKD-related complications.[56, level III]

Clinical audit indicators for quality management proposed are:

- Percentage of diabetes patients screened for proteinuria/ microalbuminuria = $\frac{\text{Number of diabetes patients screened for proteinuria within a year}}{\text{Total number of diabetes patients on follow-up in the same period}} \times 100\%$
- Percentage of diabetes patients screened for proteinuria = $\frac{\text{Number of hypertensive patients screened for proteinuria within a year}}{\text{Total number of hypertensive patients on follow-up in the same period}} \times 100\%$
- Percentage of diabetic CKD patients with BP <130/80 = $\frac{\text{Number of diabetic CKD patients with BP <130/80 within a year}}{\text{Total number. of diabetic CKD patients in the same period}} \times 100\%$
- Percentage of non-diabetic CKD patients with BP <140/90 = $\frac{\text{Number of non-diabetic CKD patients with BP <140/90 within a year}}{\text{Total number of non-diabetic CKD patients in the same period}} \times 100\%$
- Percentage of patients with hypertension and proteinuria receiving treatment with ACEi or ARB = $\frac{\text{Number of patients with hypertension and proteinuria receiving treatment with ACEi or ARB within a year}}{\text{Total number of hypertension and proteinuria in the same period}} \times 100\%$
- Percentage of patients with diabetes and proteinuria receiving treatment with ACEi or ARB = $\frac{\text{Number of patients with diabetes and proteinuria receiving treatment with ACEi or ARB within a year}}{\text{Total number of diabetes and proteinuria in the same period}} \times 100\%$

Ravijuhendid (lisamaterjal)

Sekretariaadi poolt AGREEga hinnatud ravijuhenditest leiti lisamaterjale kahest ravijuhendist. Soovitused on tehtud pigem nõrgad, kuna puudub hea tõenduspõhisus. Mõnel juhul ei tehtud ka konsensusel soovitust madala kvaliteedi ja ebakindlate järelduste tõttu.

KDIGO

Kroonilise neeruhaigusega inimestel on kalduvus erinevate komplikatsioonide tekkeks, mis peegeldavad endokriinsüsteemi või eksokriinnäärme funktsiooni langust neerude kaudu. Nende komplikatsioonide esinemissagedus ja levik on toodud tabelis 27 vastavalt eGFRi raskusastmele.

Table 27 | Prevalence of CKD complications by GFR category* derived from CKD cohorts

Complication	GFR category (ml/min/1.73 m^2)					Reference
	≥90	60-89	45-59	30-44	<30	
Anemia[1]	4.0%	4.7%	12.3%	22.7%	51.5%	366
Hypertension[2]	18.3%	41.0%	71.8%	78.3%	82.1%	366
25(OH) Vit D deficiency[3]	14.1%	9.1%	10.7%		27.2%	367
Acidosis[4]	11.2%	8.4%	9.4%	18.1%	31.5%	366
Hyperphosphatemia[5]	7.2%	7.4%	9.2%	9.3%	23.0%	366
Hypoalbuminemia[6]	1.0%	1.3%	2.8%	9.0%	7.5%	366
Hyperparathyroidism[7]	5.5%	9.4%	23.0%	44.0%	72.5%	366

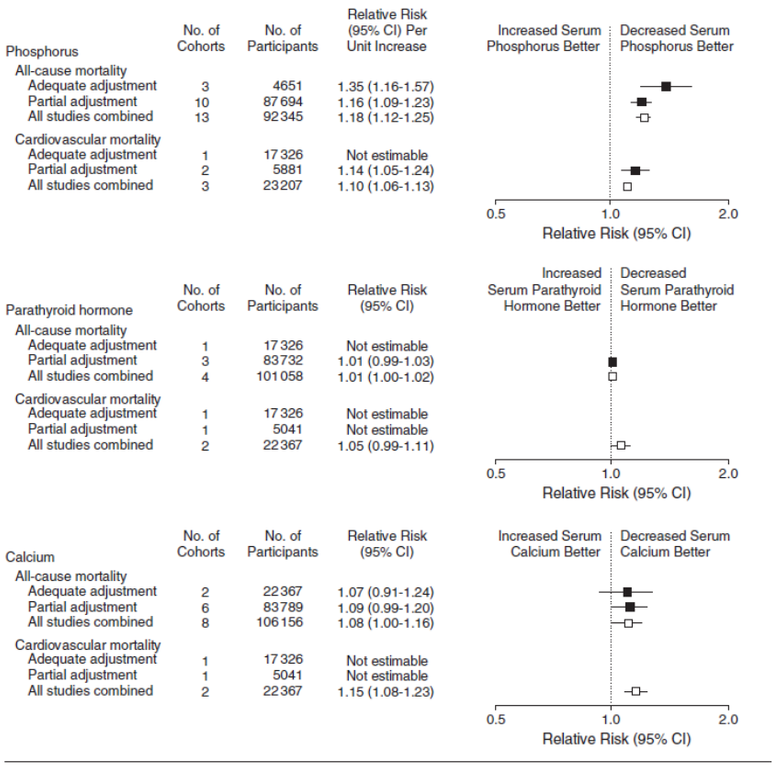
Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate.
*Note that modification of prevalence according to albuminuria categories data is not yet available to inform this table adequately, though there are limited data to suggest increasing prevalence of hypoalbuminemia, hypertension, anemia, and acidosis as albuminuria category increases
[1]Defined as hemoglobin levels <12 g/dl (120 g/l) for women; <13.5 g/dl (135 g/l) for men
[2]Defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or self-reported use of antihypertensive medication
[3]Less than 15 ng/ml [37 nmol/l] (as defined in Study for the Evaluation of Early Kidney disease [SEEK])
[4]Defined as serum bicarbonate less than 21 mEq/l
[5]Defined as serum phosphate ≥4.5 mg/dl (≥1.5 mmol/l)
[6]Defined as serum albumin less than 3.5 g/dl (35 g/l)
[7]Defined as PTH levels ≥70 pg/ml; (≥7.4 pmol/l)

Kõrgemat seerumi fosfaadi kontsentratsiooni seostatakse suurenenud suremusega ja andmed näitavad, et seerumi fosfaadi kontsentratsioon on otseselt seotud luu haiguse, veresoonte lubjastumise ja veresoonkonnahaigustega. KNHga patsientidel on fosfaaditase, kaltsiumi ja parathormooni (PTH) kontsentratsioon kõik omavahel seotud. Randomiseeritud uuringud puuduvad, kuid süstemaatilised ülevaated näitavad, et varasem fosfaadi kontrollimine võib aidata vähendada varakult KNHga seotud tüsistusi.

Süstemaatiline ülevaade kaltsiumi, fosfaadi ja PTH kontsentratsioon seerumis ja suremuse risk südame-veresoonkonna haigustesse, KNHga inimestel näitas, et surma risk suurenes iga 1 mg /dl (0,33 mmol/l) seerumi fosfaadi kontsentratsiooni tõusuga 18% (RR 1,18; 95% CI 1,12-1,25).

Kaltsiumi ja PTH konsentratsioonile seerumis ei leitud seost üldsuremusele. Uuritavatesst N=327644 ainult 16247 ei saanud dialüüsi ja neist vaid 8990 oli eGFR <60 ml/min/1,73 m2 ja ei saanud neeruasendusravi. Nende inimeste risk üldsuremusele iga 1 mg/dl (0,33/l) seerumi fosfaadi kontsentratsiooni tõusuga oli väga sarnane (RR 1,29; 95% CI 1,12-1,48). Andmed kardiovaskulaarse suremuse ja kaltsiumi, fosfaadi ja PTH seose kohta olid kättesaadavad ainult ühes uuringus.

Multi-Ethnic Study of Atherosclerosis (MESA) uuris 439 inimest seerumi fosfaadi kontsentratsiooni seost veresoonte ja südameklapi lubjastumisele, kelle eGFR oli <60 ml/min/1,73 m2. Iga 1 mg/dl. Suurenenud (0,33/l) seerumi fosfaadi kontsentratsiooni seostati 21% (P=0.002), 33% (P=0.001), 25% (P= 0.16) ja 62% (P=0.007) suurema levimusega vastavalt pärgarteri-, aordi, aordiklapi ja mitraalklapi lubjastumisega. Seoste tugevus ei sõltunud vanusest, rassist ega diabeedi diagnoosist.



Risks of all-cause mortality, cardiovascular mortality, and nonfatal cardiovascular events are shown per 1-mg/dL increase in serum levels of phosphorus, 100-pg/mL increase in serum parathyroid hormone, and 1-mg/dL increase in serum calcium. Summary estimates are not reported when only a single cohort contributed data. CI indicates confidence interval.

Figure 19|Summary estimates for risks of all-cause mortality and cardiovascular mortality associated with levels of serum phosphorus, PTH, and calcium. PTH, parathyroid hormone. Reprinted with permission from Palmer SC, Hayen A, Macaskill P, et al. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. JAMA 2011; 305(11): 1119-1127.[387] Copyright © (2011) American Medical Association. All rights reserved. Accessed http://jama.jamanetwork.com/data/Journals/JAMA/18301/jrv15003_1119_1127.pdf

3.3.3: Inimestel, kelle e GFR on <45 ml / min / 1,73m2 (eGFR G3B-G5), soovitame säilitada seerumi fosfaadi kontsentratsiooni normi piires, vastavalt kohalikele laborinormide väärtustele. (2C)

3.3.4: Inimestel, kelle eGFR on <45 ml / min / 1,73m2 (eGFR G3B-G5), nende optimaalne PTH tase ei ole teada. Soovitame jätta selle esialgu määramata ja esmalt hinnata hüperfosfateemia, hüpokaltseemia,ja D-vitamiini puudust. (2C)

3.3.3: In people with GFR < 45 ml/min/1.73m2 (GFR categories G3b-G5), we suggest maintaining serum phosphate concentrations in the normal range according to local laboratory reference values. (2C)

3.3.4: In people with GFR <45 ml/min/1.73m2 (GFR categories G3b-G5) the optimal PTH level is not known. We suggest that people with levels of intact PTH above the upper normal limit of the assay are first evaluated for hyperphosphatemia, hypocalcemia, and vitamin D deficiency. (2C)

Kardiovaskulaarhaigus ja neerupuudulikkus

Population-based studies have demonstrated an increased risk of death and cardiovascular mortality as GFR falls below 60
ml/min/1.73 m2 or when albumin is detected on urinalysis. This is not explained by an increase in traditional risk factors.

There are CKD-specific risk factors associated with more advanced CKD which drive the high rates of mortality and morbidity even at young ages. People with CKD are more likely to experience a cardiovascular event than to progress to ESRD, have a worse prognosis with higher mortality after acute myocardial infarction (MI), and have a higher risk of recurrent MI, heart failure and sudden cardiac death. Management of modifiable cardiovascular risk factors, such as improved BP and diabetes control, also reduces CKD progression.

4.1.1: We recommend that all people with CKD be considered at increased risk for cardiovascular disease. (1A)

Evidence Base
Large cohort studies have demonstrated the strong and independent associations between CVD (acute coronary syndrome
[ACS], stroke, heart failure and sudden cardiac death) and CKD by category of eGFR, after adjusting for known CVD risk factors, history of CVD events, and proteinuria. In those with an eGFR of 45-59 ml/min/1.73 m2, risk is increased by 43%
and in those with eGFR below 15 ml/min/1.73 m2, risk is increased by 343%.58 Although people with GFR category G5
(GFRo15 ml/min/1.73 m2) are at the highest risk of a CVD event, there will be more events in people with GFR categories
G3a-G3b (GFR 30–59 ml/min/1.73 m2) because of the much higher prevalence at these categories.420 These events occur at a younger age in people with CKD suggesting that CKD promotes CVD at an accelerated rate.421 The prognosis after
an acute event is related to level of GFR with a significant rise in mortality when eGFR falls below 45 ml/min/1.73 m2.422–424 Albuminuria is associated with duration and severity of hypertension; an adverse lipid profile with higher levels of
total cholesterol, triglycerides and lipoprotein(a) and low HDL-C levels;425 and abnormalities of coagulation. The presence of higher levels of proteinuria increases the risk of mortality and MI independently of level of eGFR.426 Many
studies have demonstrated low levels of urinary albumin to be associated with the increased risk of CVD in people with diabetes independent of renal function; however population studies of non-diabetic individuals have confirmed that even
small amounts of albuminuria are associated with increased CVD risk. In the Third Copenhagen study, in people with microalbuminuria, risk of coronary heart disease was increased independently of age, sex, renal function, diabetes, hypertension, and plasma lipids.427 The Chronic Kidney Disease Prognosis Consortium demonstrated that in general practice cohorts there was an increase in cardiovascular mortality when ACR is higher than 30 mg/g (3 mg/mmol).4
Analysis of data from the Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that any degree of albuminuria is a risk factor for cardiovascular events in individuals with or without diabetes.428 The lack of a threshold of albuminuria for cardiac risk was also confirmed in the HUNT 2 Study429 and the Losartan Intervention For
Endpoint Reduction in Hypertension (LIFE) study in patients with LVH.430 Albuminuria and low eGFR were synergistic cardiovascular mortality risk factors in the HUNT 2 study and using both ACR and eGFR improved cardiovascular risk stratification at all age levels, but particularly in persons 70 years and over.429 In the MDRD Study cohort of patients with GFR categories G3a-G4 (GFR 15–59 ml/min/1.73 m2), cystatin C level was strongly associated with all-cause and cardiovascular mortality particularly in the elderly.431 Analysis of data from MESA and the Cardiovascular Health Study (CHS) demonstrated that the worst prognosis of CVD, heart failure, and progressive CKD was found in those subjects with CKD diagnosed using the cystatin C-based equation.432
LVH is common with CKD, is known to reflect target organ damage, and is associated with increased cardiovascular mortality in CKD.360 It is also important to consider the role of CKD-specific risk factors particularly in patients

with more severe CKD (GFR o30 ml/min/1.73 m2) and correct them where possible. Anemia has been thought to have a particular role in the early development of CVD in people with CKD. Although treatment of anemia is associated with improved well-being and greater exercise capacity, the results of several RCTs of anemia correction have suggested that complete correction of anemia is not advisable in people with lower GFR (o60 ml/min/1.73 m2). A meta-analysis of 9 RCTs comparing different target Hb levels suggests an increase in mortality and worse BP control with the higher treatment targets, independent of the GFR category.433,434 Those patients with LVH at baseline, a sign of
target organ damage and which was present in 47% of the Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta Trial (CREATE) cohort, had significantly worse cardiovascular outcomes when treated to the higher targets.435 Abnormalities of mineral metabolism with low 1,25- dihydroxyvitamin D and PTH were found to occur early in
CKD in the Study for the Evaluation of Early Kidney disease [SEEK] study, however serum calcium and phosphate were
usually normal until eGFR fell below 40 ml/min/1.73 m2.367 An association between elevated serum phosphate and cardiovascular mortality was demonstrated in a prospective study of people with CKD and this was also thought to be associated with low vitamin D levels.436

4.1.2: We recommend that the level of care for ischemic heart disease offered to people with CKD should not be prejudiced by their CKD. (1A)

4.1.3: We suggest that adults with CKD at risk for atherosclerotic events be offered treatment with antiplatelet agents unless there is an increased bleeding risk that needs to be balanced against the possible cardiovascular benefits. (2B)

Atsidoos ja neerupuudulikkus

3.4 ACIDOSIS
The prevalence and severity of metabolic acidosis in peoplewith CKD progressively rises as GFR falls (Table 27). Adaptations in acid excretion by the kidneys initially preventa fall in serum bicarbonate concentration but as GFR continues to decline below 40 ml/min/1.73 m2, metabolic acidosis commonly develops.

3.4.1: Soovitame kroonilise neeruhaigusega inimesi, kelle seerumi vesinikkarbonaadi kontsentratsioon on < 22 mmol/l ravida suukaudse vesinikkarbonaadiga, et säilitada seerumi vesinikkarbonaad normi piires, kui ei ole vastunäidustatud. (2B)

3.4.1: We suggest that in people with CKD and seerum bicarbonate concentrations o22 mmol/l treatment with oral bicarbonate supplementation be given to maintain serum bicarbonate within the normal range, unless contraindicated. (2B)

Serum bicarbonate concentrations less than 22 mmol/l are associated with increased risk of CKD progression and increased risk of death. Conversely, high serum bicarbonate concentrations greater than 32 mmol/l are associated with increased risk of death irrespective of the level of kidney function. Small studies of alkali supplementation have shown reduction in progression of CKD and improved nutritional status in people with CKD.
Chronic metabolic acidosis is associated with increased protein catabolism, uremic bone disease, muscle wasting, chronic inflammation, impaired glucose homeostasis, impaired cardiac function, progression of CKD, and increased mortality.401–410

NICE
Other complications of chronic kidney disease

12. Bone Metabolism and Osteoporosis

12.1Monitoring of calcium, phosphate, vitamin D and parathyroid hormone levels in people with CKD

Viis uuringut näitasid, et vähenenud seerumi kaltsiumisisaldus ainult süvendab neeruhaigust. Kaks neist uuringutest leidsid, et hüpokaltseemia on kroonilise neeruhaigusega inimeste seas levinud.

Tabelis 122 on toodud kokkuvõte kaltsiumi, fosfori, iPTH, 1,25- dihydroxsyvitamiini D ja 25- D-vitamiini tasemed vastavalt neerufunktsiooni tasemetega (95% CI).

12.1.4 Evidence statements

Serum calcium

Five studies showed that serum calcium levels decreased only in advanced kidney disease. Two of these studies reported the prevalence of hypocalcaemia in a CKD population. Of people with GFR <20 ml/min/1.73 m2, 15% had abnormal Ca levels (Ca <2.1 mmol/l).219(Level 3) 43% of people with stage 3 CKD and 71% of people with stage 4 CKD had serum Ca <2.37 mmol/l.206 (Level 3)

Two studies showed that people with stage 4 CKD had significantly lower serum calcium than people with stage 3 CKD.77,206(Level 3). People with moderate CRF (GFR 20-39 ml/min/1.73m2) had significantly lower Ca levels than people with mildCRF (GFR 40-90 ml/min/1.73m2).382 (Level 3).Compared to men with CrCl > 80 ml/min, men with CrCl < 20 ml/min had a significant decrease in ionised serum Ca. 158 (Level 3)

Serum phosphate

Five studies showed that serum phosphate levels increased with advanced kidneydisease. Three of these studies showed that abnormal phosphate levels were highly prevalent when eGFR was <20 ml/min/1.73 m2. Of people with eGFR 20–29 ml/min/1.73 m2, 15% had abnormal phosphorus levels (P >1.49 mmol/l). Of people with GFR < 20 ml/min/1.73 m2, 40% had abnormal phosphorus levels.219 (Level 3). The prevalence of hyperphosphataemia (serum P >1.45 mmol/l) increased with declining CrCl: 7% of people with CrCl 20–30 ml/min/1.73 m2, and 30% of people with CrCl <20 ml/min/1.73 m2had hyperphosphataemia.158 (Level 3). 3% of people with stage 3 CKD and 22% of people with stage 4 CKD had serum P >1.52 mmol/l.206 (Level 3). Two studies showed that people with stage 4 CKD had significantly higher serum phosphate levels than people with stage 3 CKD. 77,206 (Level 3). People with stage 5 CKD had significantly higher serum phosphate than people with stage 4 CKD.77 (Level 3).

Serum intact parathyroid hormone (iPTH)

Four studies showed that iPTH increased in early stages of CKD. One of these studies reported the prevalence of hyperparathyroidism in the CKD population. Levin et al. showed hyperparathyroidism (iPTH >65 ng/ml) was prevalent in approximately 20%, 30%, 40%, 55%, and 70% of people with eGFR 69–60, 59–50, 49–40, 39–30, and 29–20 ml/min/1.73 m2, respectively.382 The increase in iPTH above reference values began at GFR <60 ml/min/1.73 m2. People with mild CRF (GFR 40–90 ml/min/1.73 m2) had significantly higher levels of iPTH than healthy people. People with moderate CRF (GFR 20–39 ml/min/1.73 m2) had significantly higher iPTH levels than people with mild CRF. (Level 3) Craver et al. showed that serum iPTH increased across all stages of CKD. (Level 3)

Table 122: Summary of serum calcium, phosphate, iPTH, 1,25-dihydroxyvitamin D, and 25-hydroxyvitamin D levels according to level of renal function (95% CI)

Reference	n	Serum parameter	CKD stage 3a (GFR 59-45 ml/min/1.73 m^2)	CKD stage 3b (GFR 44-30 ml/min/1.73 m^2)	CKD stage 4 GFR (29-15 ml/min/1.73 m^2)	CKD stage 5 (GFR < 15 ml/min/1.73 m^2)
[77]	1836	Mean Ca	2.39 mmol/l; n=856		2.34 mmol/l; n=354, p<0.05	
[206]	201	Mean Ca	2.37 mmol/l; n=65		2.30 mmol/l, n=113, p not stated but significant	2.25 mmol/l, n=22, p not stated but significant
[382]	51	Mean Ca	2.31 mmol/l; GFR 40-90 ml/min/1.73m ^{2}, n=27	2.24 mmol/l ; GFR 20-39 ml/min/1.73m^2, n=12, p<0.05		
[158]	14,722	Change Ca			-0.03 mmol/l (95% CI -0.05 to -0.01 mmol/l), p=0.002 ; CrCl <20 ml/min, n=20 vs. CrCl >80 ml/min, n=4347	
[219]	1814	% Abnormal Ca (Ca <2.1 mmol/l)			< 10 %, GFR 20-29 ml/min n=204	15%, GFR < 20 ml/min, n=93
[206]	201	% Abnormal Ca (Ca <2.37 mmol/l)	43%, n=65		71%, n=113	
[382]	51	Mean phosphate	1.0 mmol/l ;GFR 40-90 ml/min/1.73 m^2, n=27	1.2 mmol/l; GFR 20-39 ml/min/1.73m^2, n=12, p <0.05		
[77]	1836	Mean phosphate	1.16 mmol/l; n=856		1.27 mmol/l, n=354, p <0.05 vs. stage 3	1.58 mmol/l, n=111, p <0.05 vs. stage4
[206]	201	Mean phosphate	1.13 mmol/l, n=65		1.32 mmol/l, n=113, p not stated but significant	1.42 mmol/, n=22, p not stated but significant
[206]	201	% Hyperphosphataemia (P > 1.52 mmol/l)	3%, n=65		22%, n=113	
[219]	1814	% Hyperphosphataemia (P> 1.49 mmol/l)			15%, GFR 20-29 ml/min, n=204	40%, GFR < 20 ml/min, n=93
[158]	14722	% Hyperphosphataemia (P> 1.45 mmol/l)		3% (95% CI 1-6%), CrCl 30-40 ml/min, n=614	7% (95% CI 1-12%), CrCl 20-30 ml/min, n=224	30% (95% CI 0-62%), CrCl <20 ml/min , n=47

Reference	n	Serum parameter	CKD stage 3a (GFR 59-45 ml/min/1.73 m^2)	CKD stage 3b (GFR 44-30 ml/min/1.73 m^2)	CKD stage 4 GFR (29-15 ml/min/1.73 m^2)	CKD stage 5 (GFR < 15 ml/min/1.73 m^2)
[582]	51	Mean iPTH	57.5 pg/ml, GFR 40-90 ml/min/1.73 m^2, n=27 vs. 25.4 pg/ml, healthy people, n=12, p <0.05	139 pg/ml, GFR 20-39 ml/min/1.73 m^2, n=12, p <0.05		
[77]	1836	Mean iPTH	8.96 pmol/l, n=856 vs. 5.97 pmol/l , stage 2, n=341, p <0.05		16.47 pmol/l, n=354, p <0.05	24.29 pmol/l , n=111, p <0.05
[206]	201	Mean iPTH	114 pg/ml, n=65		235 pg/ml, n=113, p not stated but significant	310 pg/ml, n=22, p not stated but significant
[219]	1814	% Hyperparathyroidism (iPTH >65 ng/ml)	30%, GFR 50-59, n= 396	55%, GFR 30-39, n=358	70%, GFR 20-29, n=204	85%, GFR < 20, n=93
[582]	51	Mean 1,25-dihydroxyvitamin D	42.1 pg/ml , GFR 40-90 ml/min/1.73 m^2, n=27 vs. 54.6 pg/ml healthy people, n=12, p <0.05	39.2 pg/ml, GFR 20-39 ml/min/1.73 m^2, n=12 vs. 54.6 pg/ml healthy people, n=12, p <0.05		
[77]	1836	Mean 1,25-dihydroxyvitamin D	25.7 pg/ml, n=221 vs. 33.9 pg/ml stage 2, n=87, p<0.05		16.8 pg/ml, n=156, p <0.05 vs. stage 3	13.2 pg/ml, n=43, p <0.05 vs. stage 4
[206]	201	Mean 1,25-dihydroxyvitamin D	79.6 pmol/l , n=63		62.3 pmol/l, n=108, p not stated but significant	54.3 pmol/l, n=20, p not stated but significant
[219]	1814	% 1,25-dihydroxyvitamin D deficiency (< 22 pg/ml)	20%, GFR 50-59, n= 396	45%, GFR 30-39, n=358	50%, GFR 20-29, n=204	65%, GFR <20, n=93
[82]	14679	Mean 25-hydroxyvitamin D	75.8 nmol/l, n= 854 vs. 73.3 nmol/l, GFR ≥ 90 ml/min/1.73m^2, n= 9687, NS		61.1 nmol/l, n=44 vs. 73.3 nmol/l, GFR ≥90 ml/min/1.73 m^2, n=9687, p=0.0002	
[77]	1836	Mean 25-hydroxyvitamin D	29.6 ng/ml, n=43		26.2 ng/ml, n=115, NS	23.4 ng/ml, n=35, NS

Chronic Kidney Disease
Bone Metabolism and Osteoporosis

Reference	n	Serum parameter	CKD stage 3a (GFR 59-45 ml/min/1.73 m^2)	CKD stage 3b (GFR 44-30 ml/min/1.73 m^2)	CKD stage 4 GFR (29-15 ml/min/1.73 m^2)	CKD stage 5 (GFR < 15 ml/min/1.73 m^2)
382	51	Mean 25-hydroxyvitamin D	63.3 nmol/lGFR 40-90 ml/min/1.73 m^2, n=27	47.1 nmol/l, GFR 20-39 ml/min/1.73 m^2, n=12, NS		
219	1814	% 25-hydroxyvitamin D deficiency (< 15 ng/ml)		15%, GFR 30-39, n=358	20%, GFR 20-29, n=204	25%, GFR <20, n=93
208	201	% 25-hydroxyvitamin D insufficiency (10-30 ng/ml).	57%, n=65		58%, n=113	
208	201	% 25-hydroxyvitamin D deficiency (< 15 ng/ml)	14%, n=65		26%, n=113	

Soovitused

- **Ärge mõõtke rutiinselt kaltsiumi, fosfaati, PTH hormooni ja D vitamiini taset kui eGFR on 30 ml/min/1.73 m2 või suurem (eGFR G1, G2 or G3)**
- **Mõõtke kaltsiumi, fosfaati ja PTH inimestel, kelle eGFR on alla 30 ml/min/1.73 m2 (eGFR G4 or G5). Määra järgnevate mõõtmiste sagedus, kui tekib kahtlus konsulteeri spetsialistiga.**

12.1.6 Recommendations

- **Do not routinely measure calcium, phosphate, parathyroid hormone (PTH) and vitamin D levels in people with a GFR of 30 ml/min/1.73 m^2 or more (GFR category G1, G2 or G3). [2008]**

- **Measure serum calcium, phosphate and PTH concentrations in people with a GFR of less than 30 ml/min/1.73 m^2 (GFR category G4 or G5). Determine the subsequent frequency of testing by the measured values and the clinical circumstances. Where doubt exists seek specialist opinion. [2008]**

14. Oral bicarbonate supplements

14.1. Oral bicarbonate supplements in the management of metabolic acidosis in people with CKD.

Tõenduspõhisus oli madala kvaliteediga selleks, et teha kindlaid soovitusi vesinikkarbonaadi kasutamisele.

- **Tuleb mõelda suukaudse naatriumvesinikkarbonaadi kasutamisele inimestel, kelle eGFR on madalam kui 30 ml/min/1,73 m2 (eGFR G4 või G5) ja seerumi vesinikkarbonaadi sisaldus on väiksem kui 20 mmol/l.**

14.1.6 Recommendations and link to evidence

Recommendations	• Consider oral sodium bicarbonate supplementation for people with both: o a GFR less than 30 ml/min/1.73 m^2 (GFR category G4 or G5)and o a serum bicarbonate concentration of less than 20 mmol/litre. [new 2014]

Tabelis 131 on toodud KNH komplikatsioonide levimus GFR kategooriate järgi.

Table 131: Prevalence of CKD Complications by GFR Category (modified from KDIGO CKD 2012)[91,166,194,219,387]

Complication	GFR Category (ml/min/1.73m^2)					Reference
	≥90	60-89	45-59	30-44	<30	
Haemoglobin ≤110g/l	4.5	2.8	5.3	17.1	35.7	1[91]
Hypertension	47.1		71.4	86.6	87.8	2[387]
25(OH) D <15 µg/l (<37nmol/l)	14.1	9.1	10.7	27.2		3[219]
Serum bicarbonate <21 mmol/l	11.2	8.4	9.4	18.1	31.5	4[166]
Serum phosphate >1.5 mmol/l	7.2	7.4	9.2	9.3	23.0	4[166]
Serum albumin <35 g/l	1.0	1.3	2.8	9.0	7.5	4[166]
Parathyroid hormone >7.6 pmol/l	5.5	9.4	23.0	44.0	72.5	4[166]

Source: Reprinted with permission from 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'