Tõendusmaterjali kokkuvõte - EvSu

Kliiniline küsimus nr 14

Kas kroonilise neeruhaigusega patsientidel järgmiste ravimite kasutamise ja annustamise otsustamisel tuleb arvestada neerufunktsiooni (kreatiniin, eGFR) väärtusi vs mitte:

- metformiin
- NSAIDd
- AKEId, ARBd
- spironolaktoon
- aspiriin

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

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

- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. **KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease** (Kidney inter., Suppl. 2013; 3: 1-150; http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf) **(KDIGO)**
- National Clinical Guideline Centre; National Institute for Health and Care Excellence. **Chronic kidney disease (artial update). Early identification and management of chronic kidney disease in adults in primary and secondary care**. Clinical Guideline 182. 2014 (http://www.nice.org.uk/guidance/cg182/evidence/cg182-chronic-kidney-disease-update-full-guideline3) **(NICE)**
- Academy of Medicine of Malaysia: **Management of Chronic Kidney Disease**, 2011 (http://www.acadmed.org.my/index.cfm?&menuid=67) **(Mal)**
- KHA-CARI Guideline: **Early chronic kidney disease: Detection, prevention and management**. 2013 (http://www.cari.org.au/CKD/CKD%20early/ckd_early_ckd.html) **(CARI)**
- Scottish Intercollegiate Guidelines Network**: Diagnosis and management of chronic kidney disease**. A national clinical guideline 103. 2008. (http://www.sign.ac.uk/pdf/sign103.pdf) **(SIGN)**

Teostatud täiendavad otsingud infosüsteemides: täistektidena saadaolevad artiklid alates 2011.a,
Metformiin:
PubMed lihtotsing chronic kidney disease and metformin →piirangud→65 artiklit
Advanced chronic kidney disease (chronic kidney injury, chronic renal failure, chronic renal insufficiency) and metformin + piirangud (systematic review, 5 years, English) 9 artiklit
Advanced search metformin dosage and chronic kidney disease + piirangud 3 artiklit, 2 sobivat
Advanced search: metformin and lactic acidosis and chronic kidney disease 7 artiklit, 5 sobivat
Advanced search: metformin and lactic acidosis and renal failure: 10 artiklit – 6 sobivat

SumSearch2 chronic kidney disease and metformin 13 systematic reviews
Metformin dosage and chronic kidney disease – 5 systematic reviews, 3 sobivat
Kokku leitud 6 sobivat artiklit

CKD and NSAIDs:
PubMed chronic kidney disease and NSAIDs (piirangud: 5 aastat, süstematiline ülevaade) 10 tulemust
PubMed: non-steroidal anti-inflammatory drugs usage and chronic kidney disease + piirangud - 2 artiklit
NSAIDs use and chronic kidney disease + piirangud: 16 artiklit, 2 sobivat
Analgesic therapy and CKD +piirangud – 16 artiklit, 1 sobiv
SumSearch: non-steroidal anti-inflammatory drugs and CKD 5 artiklit – 1 sobiv
NSAIDS dosage and CKD 10 süstemaatilist ülevaadet, 2 sobivat

CKD and spironolactone, CKD ja aspirin
SumSearch2: CKD and spironolactone 2 artiklit
CKD and aldosterone antagonists 5 artiklit
Aldosterone antagonists therapy and CKD: 24 artiklit, neist 3 sobivat
Aldosterone antagonists therapy limitations and CKD: 25 artiklit, 3 sobivat
PubMed: CKD and spironolactone advanced search: 5 y., systematic review 9 artiklit – samad
PubMed: advanced + limitations (5 years, system. Review and meta-analysis): 9 artiklit, sobiv 1 tasuline (Nemerovski CW et al. Aspirin for primary prevention of cardiovascular disease events)
Aspirin use and chronic kidney disease + piirangud: 9 artiklit, 2 sobivat
SumSearch: aspirin use and chronic kidney disease: 19 systematic reviews: neist 3 sobivat

CKD and AKE/ARB
PubMed: advanced (systematic review, 5 years) Angiotensin-converting enzyme drugs use and CKD – 47 artiklit, 3 sobivat
ACE side effects and CKD + filtrid 4 artiklit, 1 sobiv

Süstemaatilised ülevaated

Allpool toodud tabelisse on lisatud nii süstemaatilised ülevaated kui ka üksikud uuringud.

Metformiini kasutamise ja annustamise kohta KNHga patsientidel leitud 4 artiklit. Kaks süstemaatilist ülevaadet (Wenya, Nue) metformiini kõrvaltoimete kohta KNHga patsientidel, üks ülevaade metformiini toimete ja kõrvaltoimete kohta 2. t. DM ja KNHga patsientidel. Üks ülevaade ravijuhenditest metformiini kasutamise kohta. Antud artiklites metformiini mõju ja kõrvaltoimete hindamiseks kasutatud võrdlusuuringuid, vaatlusuuringuid, meta-analüüse, juht-kontroll uuringuid. Kokkuvõtlikult kõigis artiklites tehtud järeldus, et kerge KNH puhul (eGFR ≥ 60ml/min/1,73m2) metformiini kasutamine ei ole seotud kõrgema laktoatsidoosi tekeriski ja hüpoglükeemiaga, keskmise raskusega KNH puhul (eGFRga 45-30 ml/min/1,73m2) soovitatakse vähendada metformiini annust ning raske KNH korral (eGFRga< 30ml/min/1,73m2) lõpetada ravi. Randomiseeritud kontrolluuringuid metformiini ohutuse kohta keskmise ja raske KNH puhul pole tehtud.

Mittesteroidsete põletikuvastaste ravimite kohta leitud üks süstemaatiline ülevaade, mis käsitleb NSAIDide mõju KNH progresseerumisele. 2 uuringuküsimust: Kas pikaajaline

NSAIDide tarvitamine tõstab KNH süvenemise riski? Kas krooniline NSAIDide tarvitamine tõstab mõõduka või raske KNH riski? 7 uuringu tulemused olid töödeldud (5 kohort uuringut, 1 läbilõikeuuring, 1 juht-kontrolluuring). Kõik need uuringud olid kestvusega > 6 kuud, KNH 3-5 staadiumiga nii naised kui mehed, NSAID tablettravi. Nende uuringute tulemuste hindamisel tehti järeldus, et tavadoosis NSAIDide kasutamine pole seotud kiirendatud neerufunktsiooni languse kiirenemisega. Kõrges doosis NSAIDid põhjustavad kiiret neerufunktsiooni langust. Antud süstemaatiline ülevaade ei anna vastust küsimusele kas NSAIDide kasutamine võib põhjustada mõõduka või raske KNH kujunemist. Süstemaatilise ülevaate piirangud: NSAIDide kõrge annus ei olnud standartiseeritud; ei ole selge kui pikk on ohutu periood NSAIDide kasutamiseks.

Spironolaktooni kasutamise kohta KNHga patsientidel leitud 3 süstemaatilist ülevaadet. Esimene ülevaade (Sankar D. Navaneethan et al) käsitleb aldosterooni antagonistide positiivset mõju albuminuuriale ja neerufunktsioonile kooskasutamisel AKE ja/või ARBidega, mineralokortikoidide retseptorite antagonistide (MRA) mõju proteinuuriale ning ravimite kõrvaltoimeid. Ülevaade hõlmab 11 uuringut (991 pts), uuringutesse olid võetud albuminuuria/proteinuuriaga 1-4 staadiumi KNHga patsiendid (diabeetikud ja mittediabeetikud). Uuringutesse ei võetud 5 staadiumi KNHga haigeid, NAR patsiente. Üheksas uuringus võrreldud efekti rühmades: MRA pluss AKE ja/või ARB vs AKE ja/või ARB. Kahes uuringus võrreldi selektiivse aldosterooni antagonisti lisamist raviskeemi. Spironolaktooniga uuringutest tuli välja, et kombinatsioon MRA+AKE ja/või ARB vähendab proteinuuriat, süstoolset ja diastoolset rõhku, positiivset mõju neerufunktsioonile pole leitud. Kõrvaltoimetest hüperkaleemia risk tõusis märkimisväärselt peale spironolaktooni lisamist raviskeemi AKE ja ARBi kõrvale (kolmikravi). Kahe prepraadiga ravi korral (spironolaktoon + AKE või spironolaktoon + ARB) hüperkaleemia risk ei tõusnud võrreldes monoteraapiaga. Kahes uuringus olid kirjeldatud günekomastia juhud, ainult 1 patsient vajas ravi. Selektiivse MRA lisamine raviskeemi (eplererone + AKE) andis positiivset efekti 24-tunni proteinuuriale, süstoolsele vererõhule. Neerufunktsioonile, diastoolsele vererõhle mõju ei leitud. Epleferone rühmas hüperkaleemia süvenemist ei leitud. Günekomastiat selektiivse aldosterooni antagonisti rühmas ei esinenud. Ülevaate piiranguteks oli uuringute lühike kestvus, pikaajalist prognoosi ei olnud võimalik teha, väike osalejate arv, proteinuuria vähenemise tulemuste heteroeensus.
Teise süstemaatilise ülevaate (Khai P Ng et al.) eesmärgiks oli uurida MRA mõju südameveresoonkonnale KNHga patsientidel. Ülevaade hõlmab 29 uuringut. Leitud, et spironolaktoon alandab nii süstoolset kui diastoolset rõhku. Diabeetilise nefropaatiaga haigetel leitud müokardi perfusiooni paranemist selektiivse MRA kasutajate rühmas võrreldes tiasiiddureetikumravil haigetel. Kolmes randomiseeritud uuringus leitud MRA positiivset mõju natriureetilise peptiidi tasemele. Kahes platseebo-kontrollitud uuringus leitud spironolaktooni mõju vasaku vatsakese massi vähenemisele 40 nädalal ja 6 kuul ravi algusest. Mõju kreatiniini ja GFR taseme pole leitud. 21 uuringus oli teada uuringu lõpu kaaliumi tase. 26 uuringus kirjeldati hüperkaleemia episoode, kuid tulemused olid kõrge heterogeensusega. Nii mitteselektiivse kui selektiivse MRA kasutamine oli seotud kõrgema hüperkaleemia riskiga.
Kolmanda süstemaatilise ülevaate (Thomas A. Mavrakanas et al.) eesmärgiks oli uurida kas MBA lisamine AKE/ARBile aeglustab KNH progresseerumist diabeetikutel. Hinnati albuminuuriat, GFRi, vererõhku, hüperkaleemia esinemist. Ülevaade hõlmab 8 uuringut. Uuringute tulemustest selgus, et kombineeritud raviskeem vähendab proteinuuriat, alandab oluliselt vererõhku. Kombineeritud teraapia korral hüperkaleemia risk tõuseb 17% (kirjeldatud kahes uuringus). Olulist positiivset efekti neerufunktsioonile pole kirjeldatud.

AKE/ARBi ja KNH kohta leitud 1 süstemaatiline ülevaade ja 2 meta-analüüsi.
Süstemaatilises ülevaates (Matthew R. Weir and Mark Rolfe) toodud välja 14 uuringut, milles uuriti RAAS blokaatorite toimet ja kõrvalmõjusid KNHga patsientidel. On leitud, et monoteraapia RAAS blokaatoriga (AKE või ARB) KNH puhul tõstab hüperkaleemia tekkeriski võrredes normaalse neerufunktsiooniga. Samuti on leitud positiivne seos neerufunktsiooni ja hüperkaleemia tekeriski vahel (madala neerufunktsiooniga patsientidel (KNH 4. staadium) risk hüperkaleemia tekkeks on kõrgem, võrreldes nendega, kelle neerufunktsioon on parem). Ravi kahe RAAS blokaatoriga on seotud suurema hüperkaleemia riskiga, kuid risk on mõõdukas ning ravi katkestamise protsent hüperkaleemia tõttu on suhteliselt väike (5%). Kolmikteraapia (AKE, ARB, MRA) kohta on toodud välja 3 uuringu tulemused: kahes uuringus on näidatud olulist kaaliumi taseme tõusu ning ühes oli kaaliumi tase kolmikravi korral sama kui kahe preparaadiga (AKE+ARB).
Teine artikkel (Suetonia C Palmer et al.) on meta-analüüs, ilmunud 2015 aastal. Eesmärgiks oli hinnata antihüpertensiivse ravi efektiivsust ja ohutust diabeedi ja KNHga patsientidel. Tulemused: AKE/ARB ravi aeglustab KNH progresseerumist. Olulist hüperkaleemia ja ägeda neerukahjustuse riski AKE/ARBi ravi puhul pole leitud. Soovitustes on siiski kirjas, et kaksikteraapia valikul peab arvestama nende tüsistuste potentsiaalse riskiga.
Kolmas artikkel on samuti meta-analüüs (2013), hindab RAAS mono- ja topeltteraapia efektiivsust ja ohutust KNHga patsientidel. Töödeldud 59 uuringu tulemused. 31 uuringus GFR => 60ml/min/1,73m2, 7 uuringus GFR <60 ml/min/1,73m2, 21 uuringus pole GFR teada. Tulemustest oluline seos oli kaksikteraapia ja albumiinuuria ja proteinuuria vähenemise vahel, kuid samuti oli kaksikteraapia seotud GFR alanemise, hüperkaleemia ja hüpotoonia riskiga.

Aspiriini kasutamise ja kõrvalmõjude kohta KNHga patsientidel ei leitud süstemaatilisi ülevaateid ega meta-analüüse. Ühes retrospektiivses uuringus (Ae Jin Kim et al., osalejate arv 25340) uuriti aspiriini mõju südameveresoonkonna haiguste tekele (MI, angiograafia, isheemiline insult, perifeerne vaskulaarhaigus). Kõrvaltoimetest hinnati verejooksu ohtu (gastrointestinaalne verejooks, hemorraagiline insult, hingamisteede verejooks). Lisaks hinnati elulemust, kreatiniini tõusu, KNH progresseerumist, NAR alustamist. Peale tulemuste statistilist analüüsi selgus, et verejooksu oht aspiriini tarvitajate rühmas oli sama kui neil, kes aspiriini ei saanud. Kreatiniini taseme kahekordistumine ja risk surra neerupuudulikkusesse olid kõrgemad aspiriini tarvitajate rühmas.
Ravinder K. Wali artiklis välja toodud 2002 aastal publitseeritud meta-analüüsi andmed, kus oli näidatud aspiriini positiivne mõju südameveresoonkonna haiguste progresseerumisele KNH puhul. Verejooksu risk oli aspiriini tarvitajate rühmas kõrgem, kuid statistiliselt mitteoluline. Artiklis on välja toodud ka uuringud (Japanise Primary Prevention of Atherosclerosis with Aspirin for diabetics, POPADAD study), mis pole tõestanud madalas doosis aspiriini kasutamise positiivset efekti südameveresoonkonna haiguste progresseerumisele diabeetikutel.
Meg J. Jardine artiklis kirjeldatud 1998 aastal läbi viidud HOT (Hypertension Optimal Treatment) uuringu (randomiseeritud kontrollitud uuring) post-hoc analüüs aspiriini mõju ja kõrvatoimete kohta KNH puhul. Uuringu tulemustest selgus, et aspiriinil on positivine efekt südameveresoonkonnhaiguste ennetemisel KNHga hüpertooniatõve patsientidel. Verejooksude risk on nendel haigetel kõrgem, kuid kasu siiski ületab riski.

Viited

Kokkuvõtte (abstract või kokkuvõtlikum info)	**Viide kirjandusallikale**
1. Wenya R. Lu et al. **Unleash Metformin: Reconsideration of the Contraindication in Patients with Renal Impairment (2013)** **Abstract Objective:** To evaluate the expanded use of metformin in renal impairment. **Data Sources:** The MEDLINE database via PubMed, Web of Science, and Cumulative Index to Nursing and Allied Health were searched in August 2013 and included studies from 1950 onward. **Study Selection and Data Extraction:** The search included comparative trials, observational cohort studies, and meta-analyses using the terms *diabetes mellitus*, *metformin*, *renal insufficiency*, and *acidosis, lactic*. **Data Synthesis:** One randomized controlled trial, 1 meta-analysis, 1 case-control, and 3 prospective-cohort studies, representing about 150 000 patients, revealed that metformin is safe in patients with stable mild-moderate renal impairment. The incidence of lactic acidosis is low and similar to sulfonylureas. In addition, reduced risks of cardiovascular disease, all-cause mortality, or any acidosis/serious infection were seen with metformin use in mild-to-moderate renal impairment. **Conclusions:** Data over the past decade refute the historical contraindication in patients with renal impairment and suggest that the risk of metformin-associated lactic acidosis is low in stable mild-to-moderate renal impairment and similar to the risk with other type 2 diabetes mellitus (DM2) medications with no renal impairment restrictions. Because of its unique impact on microvascular and macrovascular complications, it is advantageous to utilize metformin as the cornerstone in DM2 treatment for as long as possible, including in those patients with mild to moderate stages of renal impairment with no additional contraindications. A dosage reduction is recommended if estimated glomerular filtration rate (eGFR) is between 30 and 45 mL/min/1.73m^2 and discontinuation if eGFR is <30mL/min/1.73m^2.	http://www.ncbi.nlm.nih.gov/pubmed/24259604

Table 2. Summary of Included Studies.

Study	LOE[a] and Study Design	Study Groups	Baseline Characteristics of Metformin Users	Results
Bodmer et al[18] (2008)	4; Case-control	Cases of lactic acidosis or hypoglycemia were matched with up to 4 controls (total n = 50 048)	Presence of acute heart failure, urosepsis, hypovolemia, seizure, or renal failure	5 Cases of lactic acidosis associated with current metformin and other AHAs use; crude incidence rate of lactic acidosis per 100 000 person-years in metformin was 3.3 and in sulfonylureas, 4.8
Rachmani et al[31] (2002)	1b; Prospective, RCT; 4-year duration	Continued metformin (n = 195) vs discontinued metformin (n = 198)	SCr of 1.5–2.5 mg/dL, NYHA classes 3 or 4, abnormal liver function test, COPD, or acute coronary syndromes	No cases of lactic acidosis; no differences in SCr and serum lactate; significant improvement in BMI, A1c, LDL, and HDL with metformin continued; no differences in all-cause CV events or total mortality
Salpeter et al[32] (2003)	2a; Systemic review of 194 studies[b] (3 received a Jadad score of A; 40, a score of B; 55, a score of C; 28, a score of D; and 68, a score of E (observational studies); mean duration = 2.1 years (1 month to 10.7 years)	Metformin (n = 18 689) vs non–metformin (n = 38 003) groups	80 Studies allowed inclusion of renal insufficiency and 174 allowed inclusion of at least 1 contraindication	No cases of fatal or nonfatal lactic acidosis in both the metformin and non–metformin groups; no differences in serum lactate
Pongwecharak et al[33] (2009)	2b; Retrospective cohort	Metformin users (n = 1458) vs non–biguanide users (n = 172)	Chronic renal impairment 13.9%, chronic liver disease 1.3%, and heart failure 4.5%	No cases of lactic acidosis in both groups; prevalence of prescribing metformin in patients with existing contraindication of renal impairment more than 13.9%
Roussel et al[34] (2010)	2b; Prospective observation cohort; 2-year duration	All-cause mortality in metformin users (n = 7397) vs non–biguanide users (n = 12 156)	eGFR <60 mL/min/1.73 m^2: n = 4442; eGFR 30 to <60 mL/min/1.73 m^2: n = 1572; eGFR <30 mL/min/1.73 m^2: n = 118	All-cause mortality: eGFR <60 mL/min/1.73 m^2: HR = 1.06 (0.47–2.38), P = .89; eGFR 30 to <60 mL/min/1.73 m^2: HR = 0.64 (0.48–0.86), P < .003; eGFR <30 mL/min/1.73 m^2: HR = 0.89 (0.71–1.11), P = .30; no lactic acidosis reported
Ekström et al[35] (2012)	2b; Prospective observation cohort	Metformin (28%) vs metformin + other OAHA (17%) vs metformin + insulin (14%) vs insulin (24%) vs other OAHA (10%) vs insulin + other OAHA (2.6%) vs metformin + insulin + other OAHA (4.3%); total n = 51 675	Mean ± SD age of 65.3 ± 9.8 years, diabetes duration of 9.4 ± 8.0 years, A1c of 7.3% ± 3.3%, and eGFR of 78.1 ± 21.9 mL/min/1.73 m^2; more than 19% of all patients had eGFR ≤60 mL/min/1.73 m^2 and 63.6% of those were metformin users	Reduced risks of acidosis/serious infection and all-cause mortality in patients with eGFR 45–60 mL/min/1.73 m^2 and > 60 mL/min/1.73 m^2 receiving metformin-based treatments

2. Helen J. Nye, William G. Herrington **Metformin: The Safest Hypoglycaemic Agent in Chronic Kidney Disease? (2011) Abstract** Metformin is the first-line oral agent in the treatment of type 2 diabetes and has many established benefits, including the reduction of macrovascular complications of diabetes. Its prescription in patients with renal impairment is limited by concerns relating to the theoretical risk of lactic acidosis, a fear which is perpetuated by numerous case reports in which it is implicated. Critical review of this literature calls into question the validity of these claims, with metformin usually acting as an 'innocent bystander' in acutely unwell patients with conditions well recognised to precipitate lactic acidosis such as sepsis or hypovolaemia. In fact, the evidence supports the safe use of

http://www.karger.com/Article/Pdf/323739

appropriate doses of metformin in patients with chronic stable renal impairment, and highlights the important possible greater risks of the alternatives, most notably severe hypoglycaemia in patients taking sulphonylureas and/or insulin and fluid retention in patients taking a thiazolidinedione. Other traditional contraindications to metformin use such as heart failure are also being re-evaluated, as the benefits of metformin in these patients are increasingly recognised. Physicians should weigh this evidence carefully before deciding to withdraw metformin therapy in their patients with stable chronic kidney disease. **Conclusions:** The conclusion of the most recent Cochrane review [7] is clear: there is no evidence from prospective comparative trials or from observational cohort studies that metformin is associated with an increased risk of lactic acidosis, or with increased levels of lactate, compared with other oral hypoglycaemic treatments. Pooled data from 347 comparative trials and cohort studies revealed no cases of fatal or non-fatal lactic acidosis in 70,490 patient-years of metformin use or in 55,451 patient-years in the non-metformin group. This implies an upper limit for true incidence of lactic acidosis of 5 per 100,000 patient-years. Although individual creatinine concentrations were not available in the meta-analysis, 45% of the studies reviewed did not exclude patients with a creatinine >133 mkmol/l. This equates to 37,360 patient-years of metformin use in studies including chronic kidney disease patients with no episodes of lactic acidosis. A recent nested case-control study using the UK-based General Practice Research Database (GPRD) identified over 50,000 patients with type 2 diabetes taking oral antidiabetes drugs with or without concomitant insulin use [8]. All cases of lactic acidosis occurring after first prescription of an oral antidiabetic drug were reviewed. The crude incidence rate of lactic acidosis was calculated as ~3.3 per 100,000 patient-years in metformin users, and ~4.8 per 100,000 patient-years in sulphonylurea users. The incidence of lactic acidosis in patients with diabetes does not appear to be influenced by the use of metformin. This study also investigated the incidence of hypoglycaemia presenting to a physician within the same patient population. It revealed that the crude incidence of hypoglycaemia for those patients prescribed sulphonylureas was 110 per 100,000 patient-years and for metformin users (usually prescribed in combination with oth- er hypoglycaemic agents) 60 per 100,000 patient-years. Of the 73 cases of severe hypoglycaemia (3.6% of the total events) that resulted in hospitalisation or death, only 3 patients were on metformin alone. Compared to pa- tients taking metformin alone the adjusted odds ratios for severe hypoglycaemia with sulphonylureas, insulin and the two in combination were 2.8, 16.5 and 39.9, respectively. Renal failure was the only co-morbidity that was significantly associated with an increased risk of hypoglycaemia. It has therefore been suggested that the risk of death as a result of sulphonylurea- (or insulin-) induced hypoglycaemia in CKD patients is likely to be greater than the risk of death due to metformin-associated lactic acidosis.	
3. Silvio E. Inzucchi et al. **Metformin in Patients With Type 2 Diabetes and Kidney Disease: A Systematic Review (2014)**	http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4427053/pdf/ni

Abstract IMPORTANCE—Metformin is widely viewed as the best initial pharmacological option to lower glucose concentrations in patients with type 2 diabetes mellitus. However, the drug is contraindicated in many individuals with impaired kidney function because of concerns of lactic acidosis. OBJECTIVE—To assess the risk of lactic acidosis associated with metformin use in individuals with impaired kidney function. EVIDENCE ACQUISITION—In July 2014, we searched the MEDLINE and Cochrane databases for English-language articles pertaining to metformin, kidney disease, and lactic acidosis in humans between 1950 and June 2014. We excluded reviews, letters, editorials, case reports, small case series, and manuscripts that did not directly pertain to the topic area or that met other exclusion criteria. Of an original 818 articles, 65 were included in this review, including pharmacokinetic/metabolic studies, large case series, retrospective studies, meta-analyses, and a clinical trial. RESULTS—Although metformin is renally cleared, drug levels generally remain within the therapeutic range and lactate concentrations are not substantially increased when used in patients with mild to moderate chronic kidney disease (estimated glomerular filtration rates, 30-60 mL/min per 1.73 m^2). The overall incidence of lactic acidosis in metformin users varies across studies from approximately 3 per 100 000 person-years to 10 per 100 000 person-years and is generally indistinguishable from the background rate in the overall population with diabetes. Data suggesting an increased risk of lactic acidosis in metformin-treated patients with chronic kidney disease are limited, and no randomized controlled trials have been conducted to test the safety of metformin in patients with significantly impaired kidney function. Population-based studies demonstrate that metformin may be prescribed counter to prevailing guidelines suggesting a renal risk in up to 1 in 4 patients with type 2 diabetes mellitus—use which, in most reports, has not been associated with increased rates of lactic acidosis. Observational studies suggest a potential benefit from metformin on macrovascular outcomes, even in patients with prevalent renal contraindications for its use. CONCLUSIONS AND RELEVANCE—Available evidence supports cautious expansion of metformin use in patients with mild to moderate chronic kidney disease, as defined by estimated glomerular filtration rate, with appropriate dosage reductions and careful follow-up of kidney function.	hms-686487.pdf
4. Farshad Kajbaf, Paul Arnouts, Marc de Broe and Jean-Daniel Lalau. **Metformin therapy and kidney disease: a review of guidelines and proposals for metformin withdrawal around the world (2013)** ABSTRACT **Objective:** We compared and contrasted guidelines on metformin treatment in patients with chronic kidney disease (CKD) around the world, with the aim of helping physicians to refine their analysis of the available evidence before deciding whether to continue or withdraw this drug. **Methods:** We performed a systematic research for metformin contraindications in: (i) official documents from the world's 20 most populated countries and the 20 most scientifically productive countries in the field of diabetology and (ii) publications referenced in electronic databases from 1990 onwards. **Results:** We identified three international guidelines, 31	http://onlinelibrary.wiley.com/doi/10.1002/pds.3501/abstract;jsessionid=F6319C6036A0BB09B099F7C9CD8A06C4.f01t02?systemMessage=Wiley+Online+Library+and+related+systems+will+have+3+hours+of+downtime+on+Saturday+12th+September+2015+from+10%3A00-13%3A00+BST+%2F+05%3A00-08%3A00+EDT+%2F+17%3A0

national guidelines, and 20 proposals in the scientific literature. The criteria for metformin withdrawal were (i) mainly qualitative in the most populated countries; (ii) mainly quantitative in the most scientifically productive countries (with, in all cases, a suggested threshold for withdrawing metformin); and (iii) quantitative in all, but one of the literature proposals, with a threshold for withdrawal in most cases (n = 17) and/or adjustment of the metformin dose as a function of renal status (n = 8). There was a good degree of consensus on serum creatinine thresholds; whereas guidelines based on estimated glomerular filtration rate thresholds varied from 60 mL/minute/1.73 m2 up to stage 5 CKD. Only one of the proposals has been tested in a prospective study. **Conclusions:** In general, proposals for continuing or stopping metformin therapy in CKD involve a threshold (whether based on serum cre- atinine or estimated glomerular filtration rate) rather than the dose adjustment as a function of renal status (in stable patients) performed for other drugs excreted by the kidney. KEY POINTS The criteria for metformin withdrawal are mainly qualitative in the most populated countries Quantitative criteria for metformin withdrawal are mostly based on serum creatinine values The current contraindications for metformin exclude its use in a large proportion of patients with CKD In contrast to recommendations on other drugs excreted by the kidney, guidelines do not involve adjustment of the metformin dose as a function of renal status.	0-20%3A00+SGT+for+essential+maintenance.++Apologies+for+the+inconvenience.
1. Paul Nderitu, Lucy Doos, Peter W Jones, Simon J Davies and Umesh T Kadam **Non-steroidal anti-inflammatory drugs and chronic kidney disease progression: a systematic review (2013)** **Abstract: Background.** Non-steroidal anti-inflammatory drugs (NSAIDs) are widely regarded as one risk factor, which influences chronic kidney disease (CKD) progression. However, previous literature reviews have not quantified the risk in moderate to severe CKD patients. **Objective.** To estimate the strength of association between chronic NSAID use and CKD progression. **Methods.** We conducted a systematic review and meta-analysis of observational general practice or population studies featuring patients aged 45 years and over. The electronic databases searched were MEDLINE, EMBASE, Cochrane, AMED, BNI and CINAHL until September 2011 without date or language restrictions. Searches included the reference lists of relevant identified studies, WEB of KNOWLEDGE, openSIGLE, specific journals, the British Library and expert networks. For relevant studies, random effects meta-analysis was used to estimate the association between NSAID use and accelerated CKD progression (estimated glomerular filtration rate decline ≥ 15ml/min/1.73 m2). **Results.** From a possible 768 articles, after screening and selection, seven studies were identi- fied (5 cohort, 1 case–control and 1 cross-sectional) and three were included in the meta-analysis. Regular-dose NSAID use did not significantly affect the risk of accelerated CKD progression; pooled odds ratio (OR) = 0.96 (95%CI: 0.86–1.07), but high-dose NSAID use significantly	http://fampra.oxfordjournals.org/content/30/3/247.full.pdf+html

increased the risk of accelerated CKD progression; pooled OR = 1.26 (95%CI: 1.06–1.50). Conclusions. The avoidance of NSAIDs in the medium term is unnecessary in patients with moderate to severe CKD, if not otherwise contraindicated. As the definition of high-dose of NSAID use remains unclear, the lowest effective dose of NSAIDs should be prescribed where indicated. Limitations of our systematic review are the lack of a standardized measure of 'high-dose' NSAID use and the unknown duration of safe NSAID use.	
1. Sankar D. Navaneethan et al. **Aldosterone Antagonists for Preventing the Progression of Chronic Kidney Disease: A Systematic Review and Meta-analysis (2009)** **Background and objectives:** Addition of aldosterone antagonists (AA) might provide renal benefits to proteinuric chronic kidney disease (CKD) patients over and above the inhibition of renin-angiotensin system blockers (RAS). We evaluated the benefits and harms of adding selective and nonselective AA in CKD patients already on RAS. **Design, setting, participants, & measurements:** MEDLINE, EMBASE, and Renal Health Library were searched for relevant randomized clinical trials in adult CKD patients. Results were summarized using the random-effects model. **Results:** Eleven trials (991 patients) were included. In comparison to angiotensin- converting enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARB) plus placebo, nonselective AA along with ACEi and/or ARB significantly reduced 24 h proteinuria (seven trials, 372 patients, weighted mean difference [WMD] -0.80 g, 95% CI -1.27, -0.33) and BP. This did not translate into an improvement in GFR (WMD -0.70 ml/min/1.73m2, 95% CI -4.73, 3.34). There was a significant increase in the risk of hyperkalemia with the addition of nonselective AA to ACEi and/or ARB (relative risk 3.06, 95% CI 1.26, 7.41). In two trials, addition of selective AA to ACEi resulted in an additional reduction in 24 h proteinuria, without any impact on BP and renal function. Data on cardiovascular outcomes, long-term renal outcomes and mortality were not available in any of the trials. **Conclusions:** Aldosterone antagonists reduce proteinuria in CKD patients already on ACEis and ARBs but increase the risk of hyperkalemia. Long-term effects of these agents on renal outcomes, mortality, and safety need to be established. Limitations: The major limitation is the lack of long-term studies ana- lyzing the efficacy of aldosterone antagonists on mortality, progression of CKD, and development of ESKD. The majority of the included studies enrolled few patients and were powered to observe differences in surrogate end-points rather than patient-focused outcomes. Five studies had a cross-over design and most did not adequately report study methods to assess methods and trial quality. There was a significant heterogeneity noted in our analysis of effects of adding an aldosterone antagonist to RAS inhibition on proteinuria. Our subgroup analyses, although limited by a very small number of trials, show that heterogeneity can be partly explained by the differences in the study duration of included studies.	http://cjasn.asnjournals.org/content/4/3/542.full.pdf+html
2. Khai P Ng et al. **Cardiovascular actions of mineralocorticoid receptor antagonists in patients with chronic kidney disease: A systematic review and meta-analysis of randomized trials (2015)** **Abstract : Introduction:** The safety and actions of mineralocorticoid receptor antagonists on surrogate markers of cardiovascular disease as well as	http://cjasn.asnjournals.org/content/4/3/542.full.pdf+html

major patient level cardiovascular end-points in patients with chronic kidney disease are unclear. **Methods**: MEDLINE, EMBASE, Trip Database, Cochrane Central Register of Controlled Trials, Cochrane Renal Group specialized register, Current Controlled Trials and clinicaltrials.gov were searched for relevant trials. **Results:** Twenty-nine trials (1581 patients) were included. Overall, mineralocorticoid receptor antagonists lowered both systolic and diastolic blood pressure (–5.24, 95% confidence interval (CI) –8.65, –1.82 mmHg; *p*=0.003 and –1.96, 95% CI –3.22, –0.69 mmHg; *p*=0.002 respectively). There were insufficient data to perform a meta-analysis of other cardiovascular effects. However, a systematic review of the studies included suggested a consistent improvement in surrogate markers of cardiovascular disease. Overall, the use of mineralocorticoid receptor antagonists was associated with an increased serum potassium (0.23, 95% CI 0.13, 0.33 mmol/l; *p*<0.0001) and higher risk ratio (1.76, 95% CI 1.20, 2.57; *p*=0.001) of hyperkalemia. Data on long-term cardiovascular outcomes and mortality were not available in any of the trials. **Conclusions:** The long-term effects of mineralocorticoid receptor antagonists on cardiovascular events, mortality and safety need to be established.	
3. Thomas A. Mavrakanas et al. **Mineralocorticoid receptor blockade in addition to angiotensin converting enzyme inhibitor or angiotensin II receptor blocker treatment: An emerging paradigm in diabetic nephropathy. A systematic review (2013)** **Abstract:** Blockade of the renin–angiotensin–aldosterone system (RAAS) is a standard therapeutic intervention in diabetic patients with chronic kidney disease (CKD). Concomitant mineralocorticoid receptor blockade has been studied as a novel approach to further slow down CKD progression. We used PubMed and EMBASE databases to search for relevant literature. We included in our review eight studies in patients of at least 18 years of age, with a diagnosis of type 1 or type 2 diabetes mellitus and diabetic nephropathy, under an angiotensin converting enzyme inhibitor (ACEI) and/or an angiotensin II receptor blocker (ARB) as standard treatment. A subset of patients in each study also received a mineralocorticoid receptor blocker (MRB) (either spironolactone or eplerenone) in addition to standard treatment. Combined treatment with a mineralocorticoid receptor blocker further reduced albuminuria by 23 to 61% compared with standard treatment. Estimated glomerular filtration rate values upon study completion slightly decreased under combined treatment. Blood pressure levels upon study completion were significantly lower with combined treatment in three studies. Hyperkalemia prevalence increased in patients under combined treatment raising dropout rate up to 17%. Therefore, combined treatment by an ACEI/ARB and a MRB may further decrease albuminuria in diabetic nephropathy. This effect may be due to the specific properties of the MRB treatment. Clinicians should regularly check potassium levels because of the increased risk of hyperkalemia. Available evidence should be confirmed by an adequately powered comparative trial of the standard treatment (ACEI or ARB) versus combined treatment by an ACEI/ARB and a MRB.	http://www.ejinme.com/article/S0953-6205(13)01000-5/pdf
1. Matthew R. Weir and Mark Rolfe. **Potassium Homeostasis and Renin-Angiotensin-Aldosterone System Inhibitors (2010)** **Abstract:** Inhibition of the renin-angiotensin-aldosterone system (RAAS) is a key strategy in treating hypertension and cardiovascular and renal diseases.	http://cjasn.asnjournals.org/content/5/3/531.full.pdf+html

However, RAAS inhibitors (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, and direct renin inhibitors) increase the risk of hyperkalemia (serum potassium >5.5 mmol/L). This review evaluates the effects on serum potassium levels of RAAS inhibitors. Using PubMed, we searched for clinical trials published up to December 2008 assessing the effects on serum potassium levels of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, and direct renin inhibitors, alone and in combination, in patients with hypertension, heart failure (HF), or chronic kidney disease (CKD); 39 studies were identified. In patients with hypertension without risk factors for hyperkalemia, the incidence of hyperkalemia with RAAS inhibitor monotherapy is low (<2%), whereas rates are higher with dual RAAS inhibition (□5%). The incidence of hyperkalemia is also increased in patients with HF or CKD (5% to 10%). However, increases in serum potassium levels are small (□0.1 to 0.3 mmol/L), and rates of study discontinuation due to hyperkalemia are low, even in high-risk patient groups (1% to 5%). Patients with HF or CKD are at greater risk of hyperkalemia with RAAS inhibitors than those without these conditions. However, the absolute changes in serum potassium are generally small and unlikely to be clinically significant. Moreover, these patients are likely to derive benefit from RAAS inhibition. Rather than denying them an effective treatment, electrolyte levels should be closely monitored in these patients.

Chronic Kidney Disease. The incidence of serum potassium elevations with single RAAS inhibition in patients with CKD has been assessed in a number of clinical trials (Table 3). The data show that although patients with CKD are at an increased risk of serum potassium elevations, the observed absolute increases are typically small (<0.3 mmol/L) and generally are not associated with clinically relevant adverse effects or study discontinuations (1% to 2%). Monotherapy with an ACEI or an ARB is associated with an increased risk of hyperkalemia in patients with CKD. A long- term study by Hou et al. (25) in patients with nondiabetic CKD (proteinuria >300 mg/d) showed that in those with baseline serum creatinine 3.1 to 5.0 mg/dl, serum potassium levels at follow-up were significantly higher for those receiving the ACEI benazepril than for those on placebo ($P < 0.001$). How- ever, the rate of serum potassium >6.0 mmol/L with benazepril was similar to that with placebo (5.4% versus 4.5%). It should be noted that mean estimated GFR (eGFR) in this group was 25.8 to 26.3 ml/min per 1.73 m2 (i.e., stage 4 CKD), and these patients were therefore at particularly high risk of hyperkalemia. In the subgroup of the patients with baseline serum creatinine 1.5 to 3.0 mg/dl, rates of serum potassium >6.0 mmol/L were low (Table 3). Monotherapy with lisinopril (10 mg/d) or valsartan (80 mg/d) caused small increases from baseline in serum potassium (0.12 mmol/L) in a 10-week, randomized, double-blind, crossover study by Bakris et al. (26) in patients with CKD (renal insufficiency with creatinine clearance 30 to 80 ml/min). Larger increases in serum potassium were observed in the subgroup of patients with eGFR <60 ml/min per 1.73 m2 (Table 3). An analysis by Takaichi *et al.* (2) of data from more than 9000 patients with diabetes or CKD (serum creatinine □5 mg/dl) in clinical practice showed significantly higher serum potassium levels in patients receiving ACEI (4.59 mmol/L) or ARB (4.58 mmol/L) treatment than in patients not receiving a RAAS agent (4.45 mmol/L; both P □ 0.001). In the Irbesartan

Diabetic Nephropathy Trial (IDNT) in 1715 patients with diabetes-associated CKD (with proteinuria 900 mg/d), rates of discontinuation due to hyperkalemia were significantly higher with the ARB irbesartan (300 mg/d) than with the calcium channel blocker amlodipine (10 mg/d) or placebo (Table 3; *P* 0.01 for both comparisons) (27). **Dual therapy:** analysis of the data reveals that the magnitude of the serum potassium increases is modest (typically <0.5 mmol/L), and the rates of hyperkalemia requiring discontinuation of dual RAAS inhibition are generally low (<5%). Moderate-dose ACEI/ARB combination therapy is associated with small increases in serum potassium levels in patients with CKD, according to the data from two meta-analyses (Table 3). In the meta-analysis by Jennings *et al*. (42) of 10 clinical trials in 315 patients with CKD (diabetic nephropathy), serum potassium increased by 0.2 mmol/L with combination therapy compared with ACEI monotherapy. Similar increases in serum potassium were also observed in the meta-analysis by MacKinnon *et al*. (9) of 14 crossover studies in 373 patients with CKD. **Tripple therapy:** in a long-term study by Tylicki and col- leagues in patients with nondiabetic CKD (proteinuria>300 mg/d), combination therapy with spironolactone (25 mg), telmisartan (80 mg), and the ACEI cilazapril (5 mg) was associated with a statistically significant increase in serum potassium levels compared with the combination of telmis- artan and cilazapril (0.31 *versus* 0.16 mmol/L; *P* 0.02; Table 3) (50). In a separate study in patients with nondiabetic CKD (proteinuria 500 mg/d), spironolactone/losartan/enalapril (25/50/5 mg) combination therapy increased serum potassium by 0.15 mmol/L from baseline, whereas losartan/ enalapril therapy slightly reduced serum potassium (0.06 mmol/L; Table 3) (49). Finally, in the study by Chrysostomou *et al*. (48) in patients with CKD (proteinuria 1500 mg/d), increases in serum potassium with triple RAAS inhibition (spironolactone 25 mg, ramipril 5 mg, and irbesartan 150 mg) were similar to those with dual RAAS inhibition (Table 3).	
2. Suetonia C Palmer et al. **Comparative efficacy and safety of blood pressure-lowering agents in adults with diabetes and kidney disease: a network meta-analysis (2015)** **Summary : Background:** The comparative efficacy and safety of pharmacological agents to lower blood pressure in adults with diabetes and kidney disease remains controversial. We aimed to investigate the benefits and harms of blood pressure- lowering drugs in this population of patients. **Methods** We did a network meta-analysis of randomised trials from around the world comparing blood pressure- lowering agents in adults with diabetic kidney disease. Electronic databases (the Cochrane Collaboration, Medline, and Embase) were searched systematically up to January, 2014, for trials in adults with diabetes and kidney disease comparing orally administered blood pressure-lowering drugs. Primary outcomes were all-cause mortality and end-stage kidney disease. We also assessed secondary safety and cardiovascular outcomes. We did random-effects network meta-analysis to obtain estimates for primary and secondary outcomes and we presented these estimates as odds ratios or standardised mean differences with 95% CIs. We ranked the comparative effects of all drugs against placebo with surface under the cumulative ranking (SUCRA) probabilities. Findings 157 studies comprising 43256 participants, mostly with type 2 diabetes and chronic kidney disease,	http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(14)62459-4.pdf

were included in the network meta-analysis. No drug regimen was more effective than placebo for reducing all-cause mortality. However, compared with placebo, end-stage renal disease was significantly less likely after dual treatment with an angiotensin-receptor blocker (ARB) and an angiotensin-converting-enzyme (ACE) inhibitor (odds ratio 0·62, 95% CI 0·43–0·90) and after ARB monotherapy (0·77, 0·65–0·92). No regimen significantly increased hyperkalaemia or acute kidney injury, although combined ACE inhibitor and ARB treatment had the lowest rank among all interventions because of borderline increases in estimated risks of these harms (odds ratio 2·69, 95% CI 0·97–7·47 for hyperkalaemia; 2·69, 0·98–7·38 for acute kidney injury). **Interpretation** No blood pressure-lowering strategy prolonged survival in adults with diabetes and kidney disease. ACE inhibitors and ARBs, alone or in combination, were the most effective strategies against end-stage kidney disease. Any benefits of combined ACE inhibitor and ARB treatment need to be balanced against potential harms of hyperkalaemia and acute kidney injury.	
3. Paweena Susantitaphong et al. **Efficacy and Safety of Combined vs. Single Renin–Angiotensin–Aldosterone System Blockade in Chronic Kidney Disease: A Meta-Analysis (2013)** **Background:** Although dual blockade of the renin–angiotensin–aldosterone system (RAAS) has gained popularity for the treatment of kidney disease, its benefits and potential risks have not been fully elucidated. We conducted a meta-analysis of all randomized controlled trials comparing the efficacy and safety of combined vs. single RAAS blockade therapy in chronic kidney disease (CKD). **Methods:** We performed a literature search using MEDLINE, the Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, scientific abstracts from meetings, and bibliographies of retrieved articles. We used random-effects models to compute net changes and rate differences in variables. **Results:** Fifty-nine (25 crossover and 34 parallel-arm) randomized controlled trials (RCTs) comparing the efficacy and safety of combined vs. single RAAS blockade therapy in CKD were identified (4,975 patients). Combined RAAS blockade therapy was associated with a significant net decrease in glomerular filtration rate (GFR) (–1.8 ml/min or ml/min/1.73 m^2; P = 0.005), albuminuria (–90mg/g of creatinine; P = 0.001 or –32mg/day; P = 0.03), and proteinuria (–291mg/g; P = 0.003 or –363mg/day; P < 0.001). Combined RAAS blockade therapy was associated with a 9.4% higher rate of regression to normoalbuminuria and a 5% higher rate of achieving the blood pressure (BP) goal (as defined in individual trials). However, combined RAAS blockade therapy was associated with a significant net increase in serum potassium level, a 3.4% higher rate of hyperkalemia, and a 4.6% higher rate of hypotension. There was no effect on doubling of the serum creatinine level, hospitalization, or mortality. **Conclusions:** Although combined RAAS blockade therapy in CKD is associated with a decrease in albuminuria and proteinuria, it is associated with a decrease in GFR and a higher incidence of hyperkalemia and hypotension relative to monotherapy. The potential long-term kidney **benefits of combined RAAS blockade therapy require further study.**	http://ajh.oxfordjournals.org/content/26/3/424.full.pdf+html
1. Ae Jin Kim et al. **Low-Dose Aspirin for Prevention of Cardiovascular**	http://www.ncbi.nlm.nih.gov/pm

Disease in Patients with Chronic Kidney Disease (2014) **Abstract Background:** Chronic kidney disease (CKD) is a major risk factor for the development of cardiovascular disease (CVD). Previous trials have investigated the effects of low-dose aspirin on CVD prevention in patients with diabetes; however, patients with CKD were not examined. The role of aspirin in diabetics is controversial, and the available literature is contradictory. Therefore, we studied whether low-dose aspirin would be beneficial for patients with CKD, a group that is at high risk for CVD. **Method:** From a total of 25340 patients with CKD, 1884 recipients of low-dose aspirin (100 mg/day) were paired 1:1 with non-recipients for analysis using propensity score matching. The primary endpoint was the development of atherosclerotic CVD, including coronary arterial disease, stroke, and peripheral arterial disease. Secondary endpoints included death from any cause, bleeding events, doubling of serum creatinine, and renal death. **Results:** The incidence of a primary endpoint of any atherosclerotic CVD was significantly higher in the aspirin users than in the non-users (P,0.001). Secondary endpoints, including all-cause mortality and composite bleeding events, were not significantly different between the aspirin users and the non-users. However, the doubling of serum creatinine levels (P = 0.001) and renal death (P = 0.042) were significantly associated with the use of aspirin. **Conclusion:** These results suggest that the use of low-dose aspirin in patients with CKD may have harmful consequences related to the development of CVD and renal progression.	c/articles/PMC4122498/pdf/pone.0104179.pdf
2. Ravinder K. Wali. **Aspirin and the Prevention of Cardiovascular Disease in Chronic Kidney Disease Time to Move Forward?(2010)** A meta-analysis of randomized clinical trials (15) and observational studies in high-risk patients (with established CVD) have demonstrated that long-term treatment with a single daily dose of aspirin typically prevents at least 10 to 20 fatal and nonfatal vascular events for every 1,000 patients during a 1-year treatment period. Conversely, the risk of major bleeding complications with low-dose aspirin therapy was 1 to 2 per 1,000 patients for 1 year, and with the absolute number of hemorrhagic strokes being 1 to 2 per 10,000 patients. Hence, on balance, the benefits outweigh the risks. It is well known that the presence of diabetes mellitus (types 1 and 2) is considered to be a "CAD equivalent." At present, the American Diabetic Association and the Ameican Heart Association recommend aspirin therapy for all diabetic patients older than 40 years of age. Ogawa et al., in the JPAD (Japanese Primary Prevention of Athero- sclerosis With Aspirin for Diabetics) study, randomized type 2 diabetic patients without a history of atherosclerotic disease to low-dose aspirin therapy (80 to 100 mg/day) versus placebo. During a median follow-up of >4 years, aspirin therapy did not confer benefit for any CVD events or for total mortality. Only the subgroup analysis of patients 65 years of age or older showed a trend toward a benefit with low-dose aspirin therapy for the primary end point (hazard ratio: 0.68; 95% confidence interval: 0.46 to 0.99) compared with the control group of a similar age. An important and notable finding of this study was that aspirin therapy was associated with	http://content.onlinejacc.org/article.aspx?articleid=1143151

an increased risk of gastrointestinal and retinal bleeding as well as the need for blood transfusions. One important caveat of this trial was that the study may have been underpowered. However, another study, the POPADAD (Prevention of Progression of Arterial Disease and Diabetes) trial comparing low-dose aspirin with placebo for type 2 diabetic patients with asymptomatic peripheral vascular disease again demonstrated no benefit associ- ated with low-dose aspirin.	
3. Meg J. Jardine et al. **Aspirin Is Beneficial in Hypertensive Patients With Chronic Kidney Disease. A Post-Hoc Subgroup Analysis of a Randomized Controlled Trial (2010)** **Objectives** The purpose of this study was to determine the benefit and risk associated with antiplatelet therapy in the chronic kidney disease (CKD) population. **Background** Cardiovascular and possibly bleeding risks are elevated in patients with CKD. The balance of benefit and harm associated with antiplatelet therapy remains uncertain. **Methods** The HOT (Hypertension Optimal Treatment) study randomly assigned participants with diastolic hypertension to aspirin (75 mg) or placebo. Study treatment effects were calculated using univariate proportional hazards regression models stratified by baseline estimated glomerular filtration rate (eGFR) with trends tested by adding interaction terms. End points included major cardiovascular events, total mortality, and major bleeding. **Results** The study included 18,597 participants treated for 3.8 years. Baseline eGFR was =>60 ml/min/1.73 m2 in 3,619 participants. Major cardiovascular events were reduced by 9% (95% confidence interval [CI]: - 9% to 24%), 15% (95% CI: -17% to 39%), and 66% (95% CI: 33% to 83%) for patients with baseline eGFR of =>60, 45 to 59, and <45 ml/min/1.73 m2, respectively (p trend = 0.03). Total mortality was reduced by 0% (95% CI: -20% to 17%), 11% (95% CI: -31% to 40%), and 49% (95% CI: 6% to 73%), respectively (p trend = 0.04). Major bleed- ing events were nonsignificantly greater with lower eGFR (hazard ratio [HR]: 1.52 [95% CI: 1.11 to 2.08], HR: 1.70 [95% CI: 0.74 to 3.88], and HR: 2.81 [95% CI: 0.92 to 8.84], respectively; p trend = 0.30). Among every 1,000 persons with eGFR <45 ml/min/1.73m2 treated for 3.8 years, 76 major cardiovascular events and 54 all-cause deaths will be prevented while 27 excess major bleeds will occur. **Conclusions** Aspirin therapy produces greater absolute reduction in major cardiovascular events and mortality in hypertensive patients with CKD than with normal kidney function. An increased risk of major bleeding appears to be out-weighed by the substantial benefits.	http://ac.els-cdn.com/S0735109710024666/1-s2.0-S0735109710024666-main.pdf?_tid=edbd9052-5a5d-11e5-a8fb-00000aacb361&acdnat=1442179697_bdc55d4370373fa8feba0612034c842c

Ravijuhendid

Neljas ravijuhendis (KDIGO, NICE, MALAYSIA CKD MANAGEMENT, SIGN) leidub infot ravimite kasutamise ja annuse korrigeerimise kohta sõltuvalt neerufunktsioonist.

***KDIGO (RAAS blokaatorid, metformiin, NSAIDid)**

ravijuhendis on soovitatud ravimite valikul arvestada neerufuntsiooniga (kreatiniin, GFR) (1A), kui kreatiniini ja GFRi määramine pole mingil põhjusel adekvaatne, siis kasutada neerufunktsiooni hindamiseks tsüstatiin C või kreatiniinikliirensit (1C).

Soovitatud ajutiselt lõpetada nefrotoksiliste ravimite manustamine kui GFR on< 60 ml/min/1.73m2 (G3a-G5) ja kaasuva raske haiguse tõttu on ÄNK risk kõrgem. Nende ravimite hulka kuuluvad RAAS süsteemi blokaatorid, diureetikumid, NSAIDid, metformiin, litium, digoksiin (1C).

Soovitatud kasutada metformiini tavadoosis kui GFR >45ml/min/1,73m2 (G1-G3a), annust peab vähendama kui GFR 30-44 ml/min/1,73m2 (G3b) ning metformiin ravi lõpetama kui GFR on < 30ml/min/1,73m2 (G4-G5) (1C).

Tabelist 32:

RAAS süsteemi blokaatoreid soovitatud mitte kasutada neeruarteri stenoosi puhul, alustada ravi madamas doosis neil, kellel GFR <45 ml/min/1,73m2. Määrata GFR ja kaaliumi 1 nädal peale ravi alustamist või doosi tõstmist. Ajutiselt lõpetada raske haiguse korral, enne i/v kontrastaine manustamist, koloskoopiat, kirurgilist operatsiooni. Rutiinselt mitte lõpetada ravi nende preparaatidega kui GFR <30ml/min/1,73m2 – renoprotektiivne toime.

Metformiini soovitatud lõpetada kui GFR <30ml/min/1,73m2, kaaluda kasutamist kui GFR <45ml/min/1,73m2, kasutada edasi kui GFR >=45ml/min/1,73m2, peatama raske ägeda haiguse korral.

NSAIDid: vältida kui GFR<30ml/min/1,73m2, pikaajaline kasutamine pole näidustatud kui GFR <60ml/min/1,73m2, soovitav mitte tarvitada koos liitiumiga, vältida kasutamist koos RAAS blokaatoritega.

***Malaysia (AKE/ARB, aspiriin, NSAIDid)**

Neerufunktsiooni peab hindama kahe nädala jooksul peale AKE/ARBiga ravi alustamist või nende ravimite doosi tõstmist (B).

Kui esineb püsiv kreatiniini tõus > 30% (või eGFR langus > 25% algväärtusest) või kaaliumi tase on kõrgem kui 5,6 mmol/l 2 kuu jooksul peale ARBi/AKE ravi alustamist ning teised neerufunktsiooni alanemise ja hüperkaleemia põhjused on välistatud, peab doosi vähendama või ravi lõpetama ning suunama pt nefroloogi konsultatsioonile (B).

AKE/ARBi peab kasutama ettevaatlikult või ravi nende preparaatidega lõpetama:

- Neeruarteri stenoosi puhul

- Vanematel patsientidel

- Koos NSAIDidega

- Kooskasutamine ravimitega, mis tõstavad kaaliumi taset (beeta-blokaatorid, aldosterooni antagonistid)

- Kudede hüpoperfusiooni korral (kongestiivne südamepuudulikkus, dehüdratatsioon, sepsis).

Aspiriini peab kasutama KNH ga haigetel südame-veresoonkonna haiguste sekundaarseks prevensiooniks (B).

Aspiriini ja klopidogreeli kombinatsiooni peab vältima KNHga patsientidel, kui selleks pole kaalukaid põhjusi (B).

Tuleb vältida NSAIDide ja COX-2 inhibiitorite kasutamist (mefenamic acid, diclofenac, ibuprofen, naproxen, indomethacin, ketoprofen, salicylic acid [high dose], meloxicam, celecoxib, etoricoxib).

***NICE CKD (AKE/ARB, aspiriin)**

RAAS antagonistid

Enne AKE/ARBi ravi alustamist peab määrama kaaliumi taset ja GFRi. Korrata neid 1-2 nädala pärast ravi alustamist ja iga kord kui nende näitajate tase muutub.

Mitte kasutada RAAS antagoniste KNHga patsientidele kui enne ravi alustamist kaaliumi tase on kõrgem kui 5,0 mmol/l (uuendatud 2014)

Mitmete kaaliumi tõstvate preparaatide samaaegse kasutamise puhul peab kaaliumi taset kontrollima sagedamini (2008)

Lõpetage ära ravi RAAS blokatoriga siis kui kaaliumi tase on 6,0 mmol/l või kõrgem ning teised hüperkaleemia põhjustavad preparaadid on jäetud ära (2008)

Peale ravi alustamist või doosi tõstmist ärge muutke RAAS antagonistide annust kui GFR langus on vähem kui 25% võrreldes GFRga enne ravi alustamist ja kreatiniini taseme tõus on vähem kui 30% (2008)

Kui peale ravi alustamist esineb eGFR langus vähem kui 25% või kreatiniini taseme tõus vähem kui 30% peab kordama analüüsi 1-2 nädala jooksul. Ärge muutke RAAS antagonistide annust kui eGFR langus on vähem kui 25% ja kreatiniini tõus on vähem kui 30% (2008)

Kui eGFR langus on enam kui 25% või kreatiniini taseme tõus > 30%:

Selgitage välja teised neerufunktsiooni halvenemise põhjused (nt. hüpovoleemia, teised ravimid (NSAIDid))

Kui muud neerufunktsiooni halvenemise põhjused on välistatud, lõpetage ära ravi RAAS antagonistidega või vähendage nende ravimite annust, vajadusel lisage preparaate teistest ravimite rühmadest (2008)

Antiagregantravi

Antiagregantravi on näidustatud KNHga patsientidele südame-veresoonkonna haiguste ennetamiseks, kuid peab arvestama verejooksu riski tõusuga (2014)

***SIGN (RAAS antagonistid, aspiriin)**

RAAS antagonistide kõrvaltoimed

Hüperkaleemiat (>5,5 mmol/l) on täheldatud AKE/ARBi ravi foonil KNH erinevates staadiumides. RAAS blokaatorid võivad põhjustada ka GFR alanemist. Pole alati vajalik lõpetada ravi AKE/ARBiga kui esineb GFR vähenemine peale ravi alustamist või doosi tõstmist, kui GFR alaneb vähem kui 20% võrra ja neerufunktsioon on stabiilne. Kaaliumi taset ja neerufunktsiooni peab kontrollima peale AKE/ARBi ravi alustamist ja annuste muutmist.

Antiagregantravi

Madalas doosis antiagregantravi on näidustatud kõigile patsientidele KNH staadiumiga 1-3, kelle arvutuslik 10-aastane kardiovaskulaarne risk on => 20% (B).

Kokkuvõte:

Nefrotoksiliste ravimite ja nende annuste valikul peab arvestama

neerufunktsiooniga **(KDIGO 1A).** Nefrotoksiliste ravimite maustamist on soovitav ajutiselt lõpetada kaasuva raske haiguse ajaks kui GFR < 60ml/min/1,73m2 ja ÄNK risk on kõrge **(KDIGO 1C).**

	KDIGO	Malaysia	NICE	SIGN
AKE/ARB	+	+	+	+
metformiin	+		+	
spironolaktoon	+		+	+
NSAIDid	+	+	+	
aspiriin		+	+	+

RAAS antagonistid:

KDIGO

RAAS süsteemi blokaatoreid soovitatud mitte kasutada neeruarteri stenoosi puhul, alustada ravi madamas doosis neil, kellel GFR <45 ml/min/1,73m2. Määrata GFR ja kaaliumi 1 nädal peale ravi alustamist või doosi tõstmist. Ajutiselt lõpetada raske haiguse korral, enne i/v kontrastaine manustamist, koloskoopiat, kirurgilist operatsiooni. Rutiinselt mitte lõpetada ravi nende preparaatidega kui GFR <30ml/min/1,73m2 – renoprotektiinve toime.

Malaysia

Neerufunktsiooni peab hindama kahe nädala jooskul peale AKE/ARBiga ravi alustamist või nende ravimite doosi tõstmist (B).

Kui esineb püsiv kreatiniini tõus > 30% (või eGFR langus > 25% algväärtusest) või kaaliumi tase on kõrgem kui 5,6 mmol/l 2 kuu jooksul peale ARBi/AKE ravi alustamist ning teised neerufunktsiooni alanemise ja hüperkaleemia põhjused on välistatud, peab doosi vähendama või ravi lõpetama ning suunama pt nefroloogi konsultatsioonile (B).

AKE/ARBi peab kasutama ettevaatlikult või ravi nende preparaatidega lõpetama:

- Neeruarteri stenoosi puhul

- Vanematel patsientidel

- Koos NSAIDidega

- Kooskasutamine ravimitega, mis tõstavad kaaliumi taset (beeta-blokaatorid, aldosterooni antagonistid)

- Kudede hüpoperfusiooni korral (kongestiivne südamepuudulikkus, dehüdratatsioon, sepsis).

NICE

Enne AKE/ARBi ravi alustamist peab määrama kaaliumi taset ja GFRi. Korrata neid 1-2 nädala pärast ravi alustamist ja iga kord kui nende näitajate tase muutub.

Mitte kasutada RAAS antagoniste KNHga patsientidele kui enne ravi alustamist kaaliumi tase on kõrgem kui 5,0 mmol/l (uuendatud 2014)

Mitmete kaaliumi tõstvate preparaatide samaaegse kasutamise puhul peab kaaliumi taset kontrollima sagedamini (2008)

Lõpetage ära ravi RAAS blokatoriga siis kui kaaliumi tsa on 6,0 mmol/l või kõrgem ning teised hüperkaleemia põhjustavad preparaadid on jäetud ära (2008)

Peale ravi alustamist või doosi tõstmist ärge muutke RAAS antagonistide annust kui GFR lanus on vähem kui 25% võrreldes GFRga enne ravi alustamist ja kreatiniini taseme tõus on vähem kui 30% (2008)

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Kui eGFR langus on enam kui 25% või kreatiniini taseme tõus > 30%:

Selgitage välja teised neerufunktsiooni halvenemise põhjused (nt. hüpovoleemia, teised ravimid (NSAIDid))

Kui muud neerufunktsiooni halvenemise põhjused on välistatud, lõpetage ära ravi RAAS antagonistidega või vähendage nende ravimite annust, vajadusel lisage preparaate teistest ravimite rühmadest (2008)

SIGN

Hüperkaleemiat (>5,5 mmol/l) on täheldatud AKE/ARBi ravi foonil KNH erinevates staadiumides. RAAS blokaatorid võivad põhjustada ka GFR alanemist. Pole alati vajalik lõpetada ravi AKE/ARBiga kui esineb GFR vähenemine peale ravi alustamist või doosi tõstmist, kui GFR alaneb vähem kui 20% võrra ja neerufunktsioon on stabiilne. Kaaliumi taset ja neerufunktsiooni peab kontrollima peale AKE/ARBi ravi alustamist ja annuse muutmist.

Metformiin:

KDIGO

Soovitatud kasutada metformiini tavadoosis kui GFR >45ml/min/1,73m2 (G1-G3a), annust peab vähendama kui GFR 30-44 ml/min/1,73m2 (G3b) ning ravi metformiiniga lõpetada kui GFR on < 30ml/min/1,73m2 (G4-G5) (1C).

NICE (Type 2 diabetes: national clinical guideline for management in primary and secondary care (Update) 2009

Vaadata üle metformiini annust kui kreatiniini tase > 1.5 mg/dL (150mkmol/l) või eGFR < 45 ml/min/1.73m2

Lõpetada ravi metformiiniga kui seerumi kreatiniini tase >1.7 mg/dL (170mkmol/l) või eGFR < 30 ml/ min/1.73m2

Kasutada metformiini ettevaatusega kui on risk neerufunktsiooni halvenemiseks või eGFRi languseks < 45 ml/min/1,73m2

NSAIDid:

KDIGO

Vältida NSAIDide kasutamist kui GFR<30ml/min/1,73m2, pikaajaline kasutamine pole näidustatud kui GFR <60ml/min/1,73m2, soovitav mitte tarvitada koos liitiumiga, vältida kasutamist koos RAAS blokaatoritega.

Malaysia

Tuleb vältida NSAIDide ja COX-2 inhibiitorite kasutamist (mefenamic acid, diclofenac, ibuprofen, naproxen, indomethacin, ketoprofen, salicylic acid [high dose], meloxicam, celecoxib, etoricoxib).

NICE

Nendel, kes regulaarselt tarvitab nefrotoksilisi ravimeid (sh. NSAIDid) peab kontrollima GFR vähemalt 1 kord aastas.

KNHga patsientidel pikaajaline NSAIDide kasutamine võib olla seotud neerufunktsiooni langusega ning lühiajaline kasutamine võib põhjustada taaspöörduvat neerufunktsiooni langust. Nendel patsientidel tuleb kasutada NSAIDe ettevaatusega, kontrollima regulaarselt GFRi eriti madala GFRi ja lisa riskifaktoritega haigetel.

Aspiriin:

Malaysia

Aspiriini peab kasutama KNH ga haigetel südame-veresoonkonna haiguste sekundaarseks prevensiooniks (B).

Aspiriini ja klopidogreeli kombinatsiooni peab vältima KNHga patsientidel, kui selleks pole kaalukaid põhjusi (B).

NICE

Antiagregantravi on näidustatud KNHga patsientidele südame-veresoonikonna haiguste ennetamiseks, kuid peab arvestama verejooksu riski tõusuga (2014)

SIGN

Madalas doosis antiagregantravi on näidustatud kõigile patsientidele KNH staadiumiga 1-3, kelle arvutuslik 10-aastane kardiovaskulaarne risk on => 20% (B) (http://www.sign.ac.uk/pdf/sign97.pdf)

KDIGO CKD evaluation and management (lk. 101)

4.4.1: We recommend that prescribers should take GFR into account when drug dosing. (1A)
4.4.2: Where precision is required for dosing (due to narrow therapeutic or toxic range) and/or estimates may be unreliable (e.g., due to low muscle mass), we recommend methods based upon cystatin C or direct measurement of GFR. (1C)
4.4.3: We recommend temporary discontinuation of potentially nephrotoxic and renally excreted drugs in people with a GFR < 60 ml/min/1.73 m2 (GFR categories G3a-G5) who have serious intercurrent illness that increases the risk of AKI. These agents include, but are not limited to: RAAS blockers (including ACE-Is, ARBs, aldosterone inhibitors, direct renin inhibitors), diuretics, NSAIDs, metformin, lithium, and digoxin. (1C)
4.4.4: We recommend that adults with CKD seek medical or pharmacist advice before using over-the-counter medicines or nutritional protein supplements. (1B)
4.4.5: We recommend not using herbal remedies in people with CKD. (1B)
4.4.6: We recommend that metformin be continued in people with GFR>45 ml/min/1.73 m2 (GFR categories G1-G3a); its use should be reviewed in those with GFR 30–44 ml/min/1.73 m2 (GFR category G3b); and it should be discontinued in people with GFR <30 ml/min/1.73 m2 (GFR categories G4-G5). (1C)
4.4.7: We recommend that all people taking potentially nephrotoxic agents such as lithium and calcineurin inhibitors should have their GFR, electrolytes and drug levels regularly monitored. (1A)
4.4.8: People with CKD should not be denied therapies for other conditions such as cancer but there should be appropriate dose adjustment of cytotoxic drugs according to knowledge of GFR. (Not Graded)

Table 32 | Cautionary notes for prescribing in people with CKD

Agents	Cautionary notes
1. Antihypertensives/cardiac medications	
RAAS antagonists (ACE-Is, ARBs, aldosterone antagonists, direct renin inhibitors)	• Avoid in people with suspected functional renal artery stenosis • Start at lower dose in people with GFR <45 ml/min/1.73 m^2 • Assess GFR and measure serum potassium within 1 week of starting or following any dose escalation • Temporarily suspend during intercurrent illness, planned IV radiocontrast administration, bowel preparation prior to colonoscopy, or prior to major surgery • Do not routinely discontinue in people with GFR <30 ml/min/1.73 m^2 as they remain nephroprotective

Metformin	• Suggest avoid when GFR <30 ml/min/1.73 m², but consider risk-benefit if GFR is stable • Review use when GFR <45 ml/min/1.73 m² • Probably safe when GFR ⩾45 ml/min/1.73 m² • Suspend in people who become acutely unwell
2. Analgesics NSAIDS	• Avoid in people with GFR <30 ml/min/1.73 m² • Prolonged therapy is not recommended in people with GFR <60 ml/min/1.73 m² • Should not be used in people taking lithium • Avoid in people taking RAAS blocking agents

CKD Malaysia (lk. 20-23, 27) (AKE/ARB, aspirin, NSAIDid)
Recommendation 8:

- Renal profile should be reassessed within two weeks upon initiation or escalation of Angiotensin-Converting Enzyme Inhibitor (ACEi)/ Angiotensin Receptor Blocker (ARB) therapy. The interval should be determined by baseline renal function. **(Grade B)**

- If there is a sustained rise in creatinine levels above 30% (or estimated glomerular filtration rate reduces >25%) from the baseline or serum potassium is >5.6 mmol/l during the first two months after commencement of ACEi/ARB therapy, reduce or discontinue the ACEi/ARB after excluding other precipitating factors and refer to a nephrologist/physician. **(Grade B)**

ACEi/ARB should be avoided or used with caution in patients with conditions which predispose to worsening of renal function or hyperkalaemia. These conditions include:[110; 111, level I]

- renal artery stenosis
- elderly
- concomitant NSAIDs use
- concomitant medications predisposing to hyperkalaemia (such as beta blockers and aldosterone antagonists)
- hypoperfusion states (such as congestive cardiac failure, dehydration and sepsis) **These patients should be monitored more frequently.**

Recommendation 11:

- Aspirin should be used in patients with chronic kidney disease (CKD) for secondary prevention of cardiovascular disease. **(Grade B)**
- Combination of clopidogrel with aspirin should be avoided in patients with CKD unless compelling indications are present. **(Grade B)**

- Avoid NSAIDs including COX-2 Inhibitors (such as mefenamic acid, diclofenac, ibuprofen, naproxen, indomethacin, ketoprofen, salicylic acid [high dose], meloxicam, celecoxib and

etoricoxib).

NICE

Recommendations

RAAS antagonistid

- In people with CKD, measure serum potassium concentrations and estimate the GFR before starting renin–angiotensin system antagonists. Repeat these measurements between 1 and 2 weeks after starting renin–angiotensin system antagonists and after each dose increase. [2008]

- When hyperkalaemia precludes use of renin-angiotensin system antagonists, assessment, investigation and treatment of other factors known to promote hyperkalaemia should be undertaken and the serum potassium concentration rechecked. [2008]

- Do not routinely offer a renin–angiotensin system antagonist to people with CKD if their pretreatment serum potassium concentration is greater than 5.0 mmol/litre. [2008, amended 2014]

- Concurrent prescription of drugs known to promote hyperkalaemia is not a contraindication to the use of renin-angiotensin system antagonists, but be aware that more frequent monitoring of serum potassium concentration may be required. [2008]

- Stop renin-angiotensin system antagonists if the serum potassium concentration increases to 6.0 mmol/litre or more and other drugs known to promote hyperkalaemia have been discontinued. [2008]

- Following the introduction or dose increase of renin-angiotensin system antagonists, do not modify the dose if either the GFR decrease from pretreatment baseline is less than 25% or the serum creatinine increase from baseline is less than 30%. [2008]

- If there is a decrease in eGFR or increase in serum creatinine after starting or increasing the dose of renin-angiotensin system antagonists, but it is less than 25% (eGFR) or 30% (serum creatinine) of baseline, repeat the test in 1–2 weeks. Do not modify the renin-angiotensin system antagonist dose if the change in eGFR is less than 25% or the change in serum creatinine is less than 30%. [2008]

- If the eGFR change is 25% or more, or the change in serum creatinine is 30% or more:

o investigate other causes of a deterioration in renal function, such as volume depletion or

concurrent medication (for example, NSAIDs)

o if no other cause for the deterioration in renal function is found, stop the renin-angiotensin system antagonist or reduce the dose to a previously tolerated lower dose, and add an alternative antihypertensive medication if required. [2008]

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

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

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

Antiplatelets

- Offer antiplatelet drugs to people with CKD for the secondary prevention of cardiovascular disease, but be aware of the increased risk of bleeding. [new 2014]

Metformin

(NICE (Type 2 diabetes: national clinical guideline for management in primary and secondary care (Update) 2009)

Review the dose of metformin if SCr > 1.5 mg/dL or eGFR < 45 ml/min/1.73m2 Stop metformin if SCr >1.7 mg/dL or eGFR < 30 ml/ min/1.73m2

Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those risk of eGFR falling < 45 ml/min/1,73m2

NSAIDid

Monitor GFR at least annually in people prescribed drugs known to be nephrotoxic, such as calcineurin inhibitors (for example cyclosporin or tacrolimus), lithium and non-steroidal anti- inflammatory drugs (NSAIDs). [2008, amended 2014]

In people with CKD the chronic use of NSAIDs may be associated with progression and acute use is associated with a reversible decrease in GFR. Exercise caution when treating people with CKD with NSAIDs over prolonged periods of time. Monitor the effects on GFR, particularly in people with a low baseline GFR and/or in the presence of other risks for progression. [2008]

SIGN

- ADVERSE EFFECTS OF RENIN ANGIOTENSIN SYSTEM BLOCKADE

- Hyperkalaemia (>5.5 mmol/l) is a recognised consequence of ACE inhibitor and ARb therapy and can occur independently at various stages of CKD. Renin angiotensin system blockade can cause a decline in GFR in the context of low renal perfusion. Low renal perfusion can occur acutely, eg volume depletion, or chronically, eg renovascular disease or low cardiac output states (severe heart failure or outflow tract obstruction). It is not always necessary to discontinue ACE inhibitor/ARb therapy if GFR declines following initiation or dose increase, providing the fall in GFR is less than 20% and renal function stabilises. Similarly, modest, stable hyperkalaemia may be preferable to discontinuing a useful treatment. Potassium and renal function should be checked after commencing and changing the dose of angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers. (lk. 19)

Antiplatelet therapy

3.6.1 REDUCING THE RISK OF CARDIOvASCULAR DISEASE

Aspirin (or other antiplatelet therapy) reduces cardiovascular events by 25% in patients at increased

cardiovascular risk in the general population.[178] Aspirin is indicated both for patients with established cardiovascular disease and, as primary prevention, in individuals at high estimated risk of cardiovascular disease.[172] There are no data from large scale RCTs specifically in patients with stage 1-3 CKD. In the UK-HARP-1 study, aspirin therapy was associated with a threefold increased risk of minor, although not major bleeding in a heterogeneous group of patients with advanced CKD (242 pre-dialysis patients with serum creatinine ≥150 micromol/l; 73 patients on dialysis and 133 post-transplant patients).[179] The substantial benefit of aspirin therapy in terms of cardiovascular disease risk reduction must be weighed against the risk of potential adverse effects.

Low-dose antiplatelet therapy should be considered in all patients with stage 1-3 chronic kidney disease, whose estimated 10-year cardiovascular risk is ≥20% (B).