

KP Hawaii Algorithm for Management of Patients with Chronic Kidney Disease in Primary Care

CHRONIC KIDNEY DISEASE
 Adults with CKD GFR <60mL/min/1.73m² (as estimated by 4-variable MDRD formula) without guideline exclusions (See Box A)

ABBREVIATIONS:
 CKD: Chronic Kidney Disease
 GFR: glomerular filtration rate
 LVH: left ventricular hypertrophy
 uPr/Cr: urinary protein to creatinine ratio

**BOX A
 GUIDELINE EXCLUSIONS**

- Reversible disease (e.g. acute renal failure)
- Terminal illness
- Very advanced age (>85)
- High risk patients needing referral to Nephrology

Cardiovascular risk
 Manage per CMI guidelines

Diabetes
 Manage per CMI guidelines

Update Labs at least annually
 (lytes, Cr and GFR, microAlb/Cr or UPr/Cr, Hgb)

BLOOD PRESSURE

- Target: <130/80 mmHg
- Lowering BP reduces cardiovascular risk, proteinuria and progression of kidney disease.

PROTEINURIA

- Target UPr/Cr ratio <1.0
- If UPr/Cr ≥0.3, use ACEI or ARB, unless nondiabetic normotensive with UPr/Cr <1.0.
- When used, ACEIs and ARBs should be titrated up to moderate to high doses (e.g., lisinopril 40 mg bid, losartan 100 mg q day) and may be combined as needed, if significant proteinuria present

**BOX B
 REFERRAL GUIDELINES**

- Patient at high risk because of decreased GFR or proteinuria:
 - High risk for ESRD*
 - Heavy proteinuria (est. >4 grams/24 h) refractory to intervention by PCP, even if low risk for ESRD
- Unclear diagnosis, especially in young patients.
- Potentially unstable disease, such as lupus nephritis
- Refractory hypertension (failure to achieve goals despite 4-5 drug regimen)
- Clear evidence of rapid progression, with annualized loss of GFR >10mL/min

*Includes:
 1. GFR <20
 2. GFR <40, UPr/Cr ≥ 2

Refer to Nephrology? (See Box B)

Monitor

MICROALBUMINURIA

- For pts with diabetes and CKD with microalbuminuria, the use of an ACEI/ARB delays the appearance of overt proteinuria, but evidence of long-term benefit is limited.

ACEIs or ARBS

- ACEI or ARB can be continued if GFR decline is <30% from baseline or creatinine increase is <30% and serum potassium is ≤5.5 mEq/L.
- When titrating doses, measure electrolytes and Cr/GFR upon initiation or in 2-4 weeks.

DIURETICS

- Diuretics are reasonable antihypertensive meds in many pts with CKD.
- When titrating doses, measure electrolytes and Cr/GFR upon initiation or in 2-4 weeks.
- Use thiazides when GFR ≥30.
- Use loop diuretics when GFR <30.
- Potassium-sparing diuretics should be used with caution when GFR <30 or with ACEIs or ARBs.

**BOX C
 MEDICATIONS**

AVOID IF GFR <30:

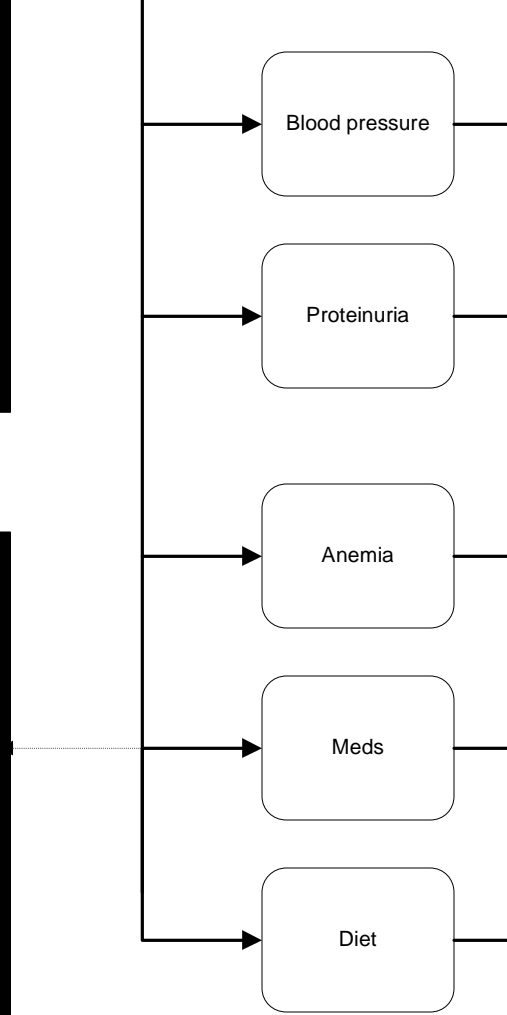
- Biphosphanates (alendronate, risedronate, zoledronic acid)
- Hydrochlorothiazide
- Fondaparinux

AVOID IF GFR <60:

- Glyburide
- Meperidine
- Metformin
- Nitrofurantoin
- Phenazopyridine
- Probenecid

USE WITH CAUTION:
 Morphine sulfate, NSAIDs, Spironolactone

ADJUST FOR CKD:
 Allopurinol, Antibiotics (acyclovir, valacyclovir, imipenem), Digoxin, Enoxaparin, Metoclopramide, Phenytoin



Refer to:
 Anemia Management using EPO for Patients with CKD, Hawaii Clinical Practice Guidelines

See Box C

- Medications to avoid depending on GFR
- Medications to use with caution in CKD
- Medications safe to use but with adjustment for CKD

- NaCl intake <2.4 g/d
- Avoid high protein intake
- Consider modest protein restriction: (0.8-1.0g/kg/day) in consultation with dietician
- May require potassium and/or phosphorus restriction
- Consider referral to dietician, especially with multiple co-morbidities

Allopurinol (GFR <100), significant increase in t1/2 of active metabolite [1 week in ESRD patients], concerns of interstitial nephritis, exfoliative dermatitis, or hepatitis

Cr Cl	Dose (milligrams)/Interval
100	300 mg/day
80	250 mg/day
60	200 mg/day
40	150 mg/day
20	100 mg/day
10	100 mg/every 2 days
0	100 mg/every 2 days

(Hande et al, 1984) – consistent with Lexi-Comp/KP eFormulary

Alternative dosing scheme based on GFR and 300 mg/24 hours for normal renal function:

GFR	% of Normal Dose
> 50	75%
10 to 50	50%
< 10	25%

(Aronoff et al, 1999) – dose adjustment utilized in Drug Prescribing in Renal Failure by Bennett et al.

- 1) The incidence of allopurinol hypersensitivity may be increased in patients with compromised renal function taking a thiazide and allopurinol concomitantly (Prod Info Zylprim(R), 2000)(Prod Info Aloprim(TM), 99b; Yale et al, 1996). However, in a retrospective of 120 patients (adults) with gout and hyperuricemia whose initial doses were adjusted for creatinine clearance, 68 (57%) eventually required higher than recommended dose titrations to reduce serum uric acid concentrations to less than 390 micromole/liter (6.6 mg/dL). Two of these 68 (3%) were judged to have drug-induced adverse reactions compared to 3 of 52 (6%) patients whose doses matched renal function (Vazquez-Mellado, 2001).
- 2) Patients with renal insufficiency have developed hepatic dysfunction and progressive renal failure, which may be enhanced by thiazide diuretic administration (Ohsawa & Ohtsubo, 1985; Raper et al, 1984; Phanichphant & Boonpucknavig, 1980; Lindsey & Evans, 1978; Boyer et al, 1977; Young et al, 1974).
- 3) In the majority of cases reporting hepatic failure, symptoms developed while receiving allopurinol 300 milligrams/day for 1 to 4 weeks. The most common findings include fever, hepatomegaly, elevated liver function tests, left upper quadrant pain, splenomegaly, jaundice, asterixis, fatigue, anorexia, drowsiness, eosinophilia, arthralgias, myalgias, dermatitis, and diplopia. Liver biopsy revealed focal necrosis, fatty changes, noncaseating granulomas, fibrin ring granulomas, and toxic

hepatic centrilobular necrosis. Allopurinol-induced liver injury appears to be enhanced in patients receiving thiazide diuretics or in patients with renal insufficiency. In severe cases pulmonary edema and hypotension developed and proved fatal. However, in the majority of cases, discontinuation of allopurinol lead to prompt improvement (Tam & Carroll, 1989; Vanderstigel et al, 1986; Ohsawa & Ohtsubo, 1985; Raper et al, 1984; Chawla et al, 1977; Simmons et al, 1972; Espiritu et al, 1976; Al-Kawas et al, 1981a).

Anti-infectives (various)

Acyclovir (GFR <50), significant neurotoxicity, development or worsening of renal impairment due to crystal nephropathy

CrCl	IV		PO	
	% usual dose	dosing interval	normal dosage	adjusted dosage
> 50	100%	q 8 hours	800mg q 4 hours	no adjustment
25 - 50	100%	q 12 hours	800mg q 4 hours	no adjustment
10 - 25	100%	q 24 hours	800mg q 4 hours	800mg q 8 hours
0 - 10	50%	q 24 hours	800mg q 4 hours	800mg q 12 hours
> 10			400mg q 12 hours	no adjustment
0 - 10			400mg q 12 hours	200mg q 12 hours

- 1) Approximately 1% of patients receiving IV acyclovir have manifested lethargy, tremors, confusion, hallucination, agitation, seizures, or coma (Prod Info Zovirax(R) injection, 2002)(Arndt, 1988). Other central nervous system effects reported include disorientation, delusions, myoclonus, slurred speech, hyperacusis, delirium, dysarthria, fatigue and mania (Prod Info Zovirax(R) injection, 2003)(Saral et al, 1981; Fukunishi et al, 1994). Often these symptoms are associated with high doses of acyclovir, or concomitant neurotoxic drugs, or impaired renal function (Wade & Meyers, 1983; Cohen et al, 1984; Jones & Beier-Hanratty, 1986; Thomson et al, 1985; Feldman et al, 1988; Johnson et al, 1994). Also, these side effects may be more marked in older adults or in patients with renal impairment (Prod Info Zovirax(R) Capsules, Tablets, Suspension, 2003). Hemodialysis may be useful for patients with end-stage renal dysfunction, who are experiencing toxicity with acyclovir (Kriebel et al, 1993).
- 2) Neurotoxicity is more common in patients receiving intravenous acyclovir; however, neurotoxicity may occur with oral administration in the presence of severe renal failure (Swan & Bennett, 1989; MacDiarmid-Gordon et al, 1992; Beales et al, 1994). Neurotoxicity progressing to coma has been described in a case report (Rajan et al, 2000).
- 3) Renal dysfunction due to acyclovir is the result of crystal nephropathy, which can occur when the maximum solubility of free drug is exceeded. Acute tubular necrosis, without crystalluria, has also been reported with intravenous acyclovir (Becker et al, 1993). Although renal impairment occurs most frequently with bolus or infused intravenous

acyclovir, oral acyclovir has been reported to cause renal failure (Prod Info Zovirax(R) Capsules, Tablets, Suspension, 2003; Eck et al, 1991; Johnson et al, 1994). Concurrent use of nephrotoxic drugs, preexisting renal disease, and dehydration predispose to the development of renal impairment (Bradley et al, 1997). In most cases renal dysfunction is transient and resolves spontaneously after acyclovir is discontinued (Peterslund et al, 1988). Renal function should be monitored closely in patients receiving intravenous acyclovir, in those predisposed to dysfunction and adequate hydration should be maintained throughout treatment to assure a high urine flow. It appears safe to reinitiate therapy with the drug at lower doses following subsidence of renal dysfunction (Sawyer et al, 1988).

Imipenem (GFR <50), Increased seizure risk and thrombocytopenia have been reported in patients with significant renal dysfunction. Meropenem may be preferred.

DO NOT use concomitantly with ganciclovir: May enhance the adverse/toxic effect of Imipenem. May increase risk of seizures. *Risk X: Avoid combination*

- 1) Seizures have occurred during imipenem/cilastatin therapy (Lane et al, 1996; Calandra et al, 1985a; Solomkin et al, 1985b; Brotherton & Kelber, 1984a). The incidence of seizures appears to be about 1% to 1.5% (Calandra et al, 1985a). However, the manufacturer indicates an incidence of 0.4% (Prod Info PRIMAXIN(R) IM injection, 2006). Risk factors associated with seizures in patients being treated with imipenem/cilastatin include preexisting central nervous system lesions or disorders, renal dysfunction, exceeding the recommended dose, and *Pseudomonas aeruginosa* infection. The average time to onset of seizures is seven days (Calandra et al, 1988). Imipenem/cilastatin should be used cautiously in patients with impaired renal function; adjusting the dose may not be adequate to prevent seizures (Leo & Ballow, 1991a; Tse et al, 1987); (Fitzsimmons et al, 1987)(Drusano, 1986; Park & Parker, 1986).
- 2) The average time of onset of seizures was seven days after the start of therapy. In the retrospective study of 1754 patients receiving imipenem/cilastatin revealed 7% of patients who received a dose in excess of the manufacturer's recommendations seized while 1.6% of patients who were dosed by the recommendations seized. Of the patients who experienced seizures during treatment, 21% (10/48) had a Cl_{cr} of <20 mL/minute, while only 3% of non-seizing patients had low clearance (Calandra et al, 1988).

Valacyclovir (GFR <50), significant neurotoxicity, development or worsening of renal impairment due to crystal nephropathy (see acyclovir for further comments and details)

Biphosphanates (GFR < 35), not well studied → [see specific agent]

Alendronate (GFR < 35), not well-studied

- 1) Dosage adjustment is NOT necessary for patients with a $Cl_{cr} > 35$ mL/min. Alendronate is NOT recommended for patients with a $Cl_{cr} < 35$ mL/min. Since alendronate is eliminated by the kidneys, greater accumulation especially in bone may be expected in patients with impaired renal function (Prod Info FOSAMAX(R) TABLETS AND ORAL SOLUTION, 2005)
- 2) A significant portion of a dose of alendronate is eliminated unchanged in the urine (Fleisch, 1994b; Averbuch, 1993a; Inzerillo, 1994a), and lower doses (or avoidance) of the drug are indicated in patients with renal impairment.

Zoledronic acid (GFR <35), nephrotoxicity

- 1) Zoledronic acid is not recommended in patients with a $Cl_{cr} < 35$ mL/min (Prod Info RECLAST(R) IV injection, 2008).
- 2) Renal dysfunction has been reported following zoledronic administration, especially in patients with preexisting renal conditions or other risk factors (eg, oncology patients receiving chemotherapy, patients receiving concomitant nephrotoxic medications or those who are severely dehydrated). The majority of patients received a 4-mg dose every 3 to 4 weeks. Renal dysfunction has also been observed following a single dose. Renal deterioration was not reported following a single 5-mg intravenous infusion in the Paget's disease clinical trials. Zoledronic acid is not recommended in patients with $Cl_{cr} < 35$ mL/min. Serum creatinine should be monitored before each dose (Prod Info RECLAST(R) IV injection, 2007a).
- 3) In clinical trials involving patients with bone metastases, renal deterioration, defined as an increase of 0.5 mg/dL for patients with normal baseline creatinine (less than 1.4 mg/dL) or an increase of 1.0 mg/dL for patients with an abnormal baseline creatinine (at least 1.4 mg/dL) was reported between 10.7% and 17.4% of patients treated with zoledronic acid 4-mg intravenous infusion compared with 9.3% of patients treated with pamidronate 90 mg intravenous infusion and 6.7% to 12.8% of patients treated with placebo (Prod Info ZOMETA(R) injection for intravenous infusion, 2005).
- 4) With post-marketing use of zoledronic acid, renal deterioration progressing to renal failure and dialysis has been reported (Chang et al, 2003). There have been instances of this occurring after the initial Zometa dose (Prod Info ZOMETA(R) IV injection, 2005).
- 5) No dose adjustment required in patients with $Cl_{cr} \geq 35$ mL/min (Prod Info RECLAST(R) IV injection, 2008).
- 6) Upon treatment initiation for multiple myeloma and metastatic bone lesions from solid tumors, the recommended dose for patients with reduced renal function (mild to moderate renal impairment):(Prod Info Zometa(R), 2004):

Baseline Creatinine Clearance (mL/min)	Zometa Recommended Dose *
> 60	4.0 mg
50-60	3.5 mg

40-49	3.3 mg
30-39	3.0 mg

*Doses calculated assuming target AUC of 0.66 (mg•hr/L) (CrCl=75mL/min)

- 7) Serum creatinine (SCr) should be measured prior to each zoledronic acid dose. Patients with hypercalcemia of malignancy and deterioration of renal function should be evaluated regarding risk versus benefit for continued zoledronic acid therapy. Patients with bone metastases and deterioration of renal function should have zoledronic acid therapy withheld until SCr values return to within 10% of baseline. (Prod Info ZOMETA(R) IV injection, 2008).
- 8) Use of zoledronic acid in patients with hypercalcemia of malignancy and severe renal impairment (serum creatinine (SCr) ≥ 4.5 mg/dL) has not been adequately evaluated; in clinical studies, patients with SCr greater than 4.5 mg/dL were excluded; clinical benefit versus risk of renal failure should be considered in these patients (Prod Info ZOMETA(R) IV injection, 2008).
- 9) When being used for the prevention and/or treatment of lytic bone disease in multiple myeloma, an expert panel from the American Society of Clinical Oncology recommends no change in dosage, infusion time, or interval of zoledronic acid in patients with pre-existing renal disease and a serum creatinine of < 3.0 mg/dL. Use of bisphosphonates in patients with worse renal function has been minimally assessed (Berenson et al, 2002c).

Risedronate (GFR < 30), not well-studied

- 1) No dosage adjustment for risedronate is necessary for patients with $Cl_{cr} \geq 30$ mL/min. Risedronate is NOT recommended in patients with a $Cl_{cr} < 30$ mL/min (Prod Info ACTONEL(R) oral tablets, 2008; Prod Info ACTONEL(R) with Calcium oral tablets, 2006).
- 2) A retrospective analysis of data pooled from 9 randomized, double-blind, placebo-controlled, phase 3 trials (n=9883) showed that oral risedronate 5 milligrams per day for up to 3 years was safe and effective in preserving bone mineral density (BMD) and reducing new vertebral fractures in osteoporotic women with mild, moderate, or severe renal impairment. Patients included in the analysis were those who had age-related renal impairment ($Cl_{cr} < 80$ mL/min). The Cl_{cr} was estimated using the Cockcroft and Gault method, and patients were classified as having mild (Cl_{cr} 50 to 80 mL/min; n=4353), moderate (Cl_{cr} 30 to 49 mL/min; n=4071), and severe (Cl_{cr} less than 30 mL/min; n=572) renal impairment (Miller et al, 2005).
- 3) One study has proposed deferring dose adjustments for patients with Cl_{cr} above 20 mL/min (Mitchell et al, 2000). Renal clearance of risedronate was decreased by about 70% in patients with severe renal impairment.

Digoxin (GFR < 50), dosage of digoxin must be reduced in renal insufficiency (Marcus, 1966). The most reliable indicator of digoxin excretion is creatinine clearance (Doherty & Kane, 1973)

- 1) The volume of distribution of digoxin can decrease by as much as 50% in patients with renal failure (Doherty et al, 1970a; Anderson et al, 1976a). However, it is not clear whether or not dosage should be reduced corresponding to the

reduced volume of distribution, as tissue uptake (including myocardial uptake) of digoxin is reduced in renal failure (Jusko, 1978). The pharmacologic and clinical effects of this reduced uptake are not clear, but increased digitalis tolerance has been reported in uremic patients (Kramer et al, 1978). Some investigators prefer digitoxin over digoxin in renal failure patients, since digitoxin pharmacokinetics are not as affected by impaired renal function (Rasmussen et al, 1972; Jelliffe et al, 1970; Anderson et al, 1976a; Keller et al, 1980).

- 2) Patients with normal renal function will excrete 35% to 40% of digoxin body stores daily, in contrast to 14% daily elimination of total body stores in anephric patients (Jelliffe, 1968; Anderson et al, 1976a).

Enoxaparin (GFR <50), bleeding complications – DO NOT USE in patients with GFR <30 (Nephrology consensus)

- 1) Enoxaparin has not been FDA approved for use in dialysis patients. Its elimination is primarily via the renal route. Serious bleeding complications have been reported with use in patients who are dialysis dependent or have severe renal failure. LMWH administration at fixed doses without monitoring has greater unpredictable anticoagulant effects in patients with chronic kidney disease. If used, dosages should be reduced and anti-Xa activity frequently monitored, as accumulation may occur with repeated doses. Many clinicians would not use enoxaparin in this population especially without timely anti-Xa activity assay results.
- 2) In subjects with mild to moderate renal impairment (Cl_{cr} 30 to 80 milliliter/minute), anti-factor Xa exposure represented by AUC is marginally increased after repeated doses of enoxaparin 40 mg subcutaneously once daily compared to healthy volunteers. In patients with severe renal impairment ($CrCl$ <30 mL/min), the AUC at steady state is increased by 65% after repeated doses compared to healthy volunteers (Prod Info Lovenox(R), 2003).
- 3) Based on a prospective, non-randomized, open-label study (n=233), anti-Xa concentrations measured 4 hours post-injection were higher and more likely to reach supratherapeutic levels among patients with moderate-to-severe renal impairment compared with individuals with normal renal function; therefore, dosing adjustment of enoxaparin may be necessary for severe renally-impaired individuals to maintain target anti-Xa therapeutic range. Patients were treated with either 1 milligram per kilogram (mg/kg) every 12 hours or 1.5 mg/kg every 24 hours. With twice-daily dosing, the mean anti-Xa levels were 1.06 (95% confidence interval (CI), 0.99 to 1.14) in patients with calculated Cl_{cr} >50 mL/min, 1.25 (95% CI, 1.12 to 1.39) in patients with moderate renal impairment (Cl_{cr} 30 to 50 mL/min), and 1.27 (95% CI, 1.15 to 1.4) in individuals with severe renal impairment (Cl_{cr} 10 to 30 mL/min). Once-daily administration of enoxaparin resulted in similar and overlapping anti-Xa levels: 1.1 (95% CI, 1 to 1.2), 1.21 (95% CI, 1.09 to 1.33), and 1.18 (95% CI, 0.92 to 1.44), respectively. The analysis suggested that anti-Xa levels increased by 0.03 international units/mL for every 10-mL/min decrease in $CrCl$ (Bazinet et al, 2005).
- 4) A study with 532 patients (34% normal renal function, 36% mild renal impairment, 20% moderate renal impairment, and 10% severe renal impairment) found that dosage adjustments for enoxaparin in patients treated for non-ST-segment elevation in acute coronary syndrome with Cl_{cr} <50 mL/min should be considered. All patients, regardless of renal function, should receive 1 mg/kg subcutaneously for the first dose, then dose reductions should be done based on Cl_{cr} . In patients with moderate renal impairment (Cl_{cr} from 30 to 49 mL/min), the subsequent doses should be 0.8 mg/kg subcutaneously every 12 hours. In patients with severe renal impairment (Cl_{cr} <30 mL/min), the subsequent doses

should be 0.66 mg/kg every 12 hours. These dosage adjustments should be considered in order to keep peak anti-Xa activities within the target range of 0.5 to 1.2 international units/milliliter (Hulot et al, 2005).

Fondaparinux (GFR <50), bleeding complications – **DO NOT USE in patients with GFR <30**

- 1) Specific dosing recommendations in patients with renal impairment are not available. The clearance of fondaparinux is approximately 25% lower in patients with mild renal impairment (Cl_{cr} between 50 to 80 mL/min), approximately 40% lower in patients with moderate renal impairment (Cl_{cr} 30 to 50 mL/min), and approximately 55% lower in patients with severe renal impairment (Cl_{cr} <30 mL/min) when compared to patients with normal renal function. Use of fondaparinux in patients with Cl_{cr} <30 mL/min is contraindicated (Prod Info ARIXTRA (R) subcutaneous injection, 2008).
- 2) Increasing renal impairment increases the risk of hemorrhage in patients administered fondaparinux. The occurrence of major bleeding in patients receiving prophylactic fondaparinux in hip fracture, hip replacement, or knee replacement surgery was 1.6%, 2.4%, 3.8% and 4.8% in patients with normal renal function, mild renal impairment, moderate renal impairment, and severe renal impairment, respectively. The occurrence of major bleeding in patients receiving therapeutic fondaparinux for deep vein thrombosis and pulmonary embolism was 0.4%, 1.6%, 2.2% and 7.3%, in patients with normal function, mild, moderate and severe renal impairment, respectively. The use of fondaparinux is therefore contraindicated in patients with a Cl_{cr} <30mL/min. Caution should also be exercised when used in patients with mild to moderate renal impairment (Prod Info ARIXTRA (R) subcutaneous injection, 2008).

Glyburide (GFR <50, per literature, <60 mL/min per KPHI criteria), increased risk of hypoglycemia due to increased duration of active metabolites

- 1) Because glucose homeostasis is impaired and insulin clearance decreased in renal insufficiency, glyburide is relatively contraindicated in the presence of severe renal insufficiency due to the risk of profound and prolonged hypoglycemia (Asmal & Marble, 1984a; Jackson & Bressler, 1981b; Paice et al, 1985a). Conservative initial and maintenance doses should be used in patients with renal failure to avoid hypoglycemia (Prod Info Micronase(R), 1997; Prod Info Glynase(R), 1997).
- 2) Glyburide is NOT recommended in patients with a Cl_{cr} <50 mL/min because as much as 50% of a dose may be eliminated unchanged in the urine (Bennett et al, 1994).

Per KPHI P&T, glyburide use limited to 1) members < 65 years old AND 2) GFR > 60mL/min

Hydrochlorothiazide (GFR<30), ineffective

- 1) Avoid use when Cl_{cr} <10 mL/minute. Usually ineffective with GFR <30 mL/min. May be effective at lower GFR in combination with a loop diuretic.
- 2) Investigators (Bennett et al, 1987) indicate that no specific dosage adjustment is necessary in patients with mild to moderate renal failure.

- 3) Patients with renal failure are usually refractory to hydrochlorothiazide. Hydrochlorothiazide should not be used in patients with a serum creatinine >2.5 mg/dL (Anon, 1993c). Some clinicians do not recommend hydrochlorothiazide if the GFR is <15 to 25 mL/min; other clinicians use furosemide if the GFR is <50 mL/min. Hydrochlorothiazide should be stopped if progressive renal failure is evident by increasing non-protein nitrogen, increasing blood urea nitrogen, and increasing serum creatinine (Anderson & Kepler, 1975a). Hydrochlorothiazide itself decreases GFR; this may aggravate renal failure (Gilman et al, 1990e).

Meperidine (GFR <50), decreased seizure threshold, with accumulation of neurotoxic metabolite

- 1) No dosage adjustment is necessary in patients with mild renal failure (GFR >50 mL/min) (Bennett et al, 1994). However, patients with moderate renal failure (GFR 10 to 50 mL/min) should receive 75% of the normal dose at the usual intervals and patients with severe renal failure (GFR <10 mL/min) should receive 50% of the normal dose at the usual intervals.
- 2) Normeperidine, a metabolite of meperidine, is a CNS excitotoxin which can accumulate with repetitive dosing and can cause anxiety, tremors, myoclonus, and generalized seizures (Kaiko et al, 1983a). Patients using meperidine for more than 2 days, or patients with pre-existing renal impairment, sickle-cell disease, or central nervous system (CNS) disease, or patients receiving meperidine doses of greater than 600 milligrams/24 hours are particularly at high risk for normeperidine toxicity. Naloxone does not reverse, and may even exacerbate, this hyperexcitability (Szeto et al, 1977a; American Pain Society, 2003). Therefore, meperidine use should be avoided in patients with renal impairment. However, if used, meperidine should not be administered for more than 1 to 2 days. Chronic use is not recommended (American Pain Society, 2003).

Per KPHI P&T, meperidine use limited to following indication: shivering, rigors, conscious sedation

Metformin (GFR <60), risk of lactic acidosis

- 1) Metformin is substantially excreted by the kidney. The risk of accumulation and lactic acidosis increases with the degree of impairment of renal function. Patients with renal function below the limit of normal for their age should not receive metformin.
- 2) In elderly patients, renal function should be monitored regularly; should not be used in any patient ≥ 80 years of age unless measurement of creatinine clearance verifies normal renal function.
- 3) Use of concomitant medications that may affect renal function (ie, affect tubular secretion) may also affect metformin disposition. Metformin should be suspended in patients with dehydration and/or prerenal azotemia. Therapy should be suspended for any surgical procedures (resume only after normal intake resumed and normal renal function is verified).

- 4) Do not administer metformin at the time of and for 48 hours after radiologic studies involving intravascular iodinated contrast materials due to the risk of lactic acidosis. Metformin can be reinstated only after confirming renal function is normal (Prod Info GLUCOPHAGE(R), GLUCOPHAGE(R) XR oral tablets, extended-release oral tablets, 2006).
- 5) The plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance. Per the manufacturer, metformin is contraindicated in the presence of renal dysfunction defined as a serum creatinine >1.5 mg/dL in males, or >1.4 mg/dL in females and in patients with abnormal clearance. Clinically, it has been recommended that metformin be avoided in patients with $Cl_{cr} < 60-70$ mL/min (DeFronzo, 1999).

Metoclopramide (GFR <50), increase in EPS adverse effects

- 1) Based on a normal dose of 10 to 15 milligrams four times daily with normal renal function (Aronoff et al, 1999). The pharmacokinetics of metoclopramide were evaluated after intravenous and oral dosing (10 milligrams) in 6 patients with chronic renal failure. The clearance was shown to be approximately 30% of that found in normal subjects. This difference is not accounted for by the change in renal clearance and suggests impaired metabolism or an alteration in enterohepatic circulation of metoclopramide in renal failure. The mean terminal half-life of both after parenteral and oral therapy was approximately 14 hours, suggesting that the dose of metoclopramide in severe renal failure should be reduced by at least 50% of that normally recommended (Bateman et al, 1981).
- 2) The following dosage reductions are recommended in patients with renal failure:

GFR mL/minute	DOSE RECOMMENDATION
10 or less	50% of usual dose
10-50	75% of usual dose
51 or more	100% of usual dose

Morphine sulfate (GFR <50), neurotoxicity and respiratory depression with decreased clearance of putatively active metabolites

- 1) Morphine primarily undergoes hepatic metabolism to inactive metabolites, which are renally excreted. It would be expected that dosage adjustment in renal failure would not be necessary (Gilman et al, 1990). However, it has been recommended that patients with moderate renal failure (GFR 10 to 50 mL/min) receive 75% of the normal dose at the usual intervals, and patients with severe renal failure (GFR <10 mL/min) receive 50% of the normal dose at the usual intervals; no dosage adjustment is necessary for patients with mild renal failure (GFR >50 mL/min) (Aronoff et al, 1999). These recommendations are based on actual reports of decreased morphine clearance in renal failure patients, and the possibility that morphine-6- glucuronide may have some narcotic activity (Portenoy et al, 1991; Ball et al, 1985). Epidural

administration should be done cautiously, since high morphine levels, due to decreased clearance, may take several days to develop (Prod Info Duramorph(R), 1994a).

- 2) Morphine plasma concentrations following intravenous infusion in intensive care patients, as well as morphine clearance, depends on renal function with dose-related plasma levels increasing as renal function deteriorated. Plasma morphine levels were linearly related to plasma creatinine and creatinine clearance; morphine clearance was linearly related to creatinine clearance. The authors emphasize that a reduction in morphine clearance in intensive care patients with impaired renal function can lead to increased elimination half-lives of the drug and neurological impairment (Ball et al, 1985).
- 3) It has been suggested that accumulation of morphine-6-glucuronide might cause toxicity with renal insufficiency. All of the metabolites (ie, morphine-3-glucuronide, morphine-6-glucuronide, and normorphine) have been suggested as possible causes of neurotoxicity (eg, myoclonus).

Nitrofurantoin (GFR <60), ineffective and risk of pulmonary toxicity; peripheral sensory neuropathy

- 1) Use with caution in patients with G6PD deficiency or in patients with anemia. Therapeutic concentrations of nitrofurantoin are not attained in urine of patients with $Cl_{cr} < 60$ mL/minute. Use with caution if prolonged therapy is anticipated due to possible pulmonary toxicity. Acute, subacute, or chronic (usually after 6 months of therapy) pulmonary reactions have been observed in patients treated with nitrofurantoin; if these occur, discontinue therapy immediately; monitor closely for malaise, dyspnea, cough, fever, radiologic evidence of diffuse interstitial pneumonitis or fibrosis.
- 2) Normal nitrofurantoin doses in patients with mild renal failure (GFR more than 50 mL/min) is recommended, but in patients with moderate to severe renal failure (GFR less than 50 mL/min), the use of nitrofurantoin should be avoided (Bennett et al, 1987).

Patients with moderate to severe renal failure should not receive nitrofurantoin since it is ineffective with GFR below 20 to 30 mL/min and peripheral sensory neuropathy may occur with a GFR of 10 to 50 mL/min due to metabolites (Felts et al, 1971; Goff et al, 1968; Sachs et al, 1968; Sullivan et al, 1975; Bennett et al, 1987).

NSAIDs, nephrotoxicity, due to dose-dependent decrease in prostaglandin synthesis

- 1) Analgesics, including NSAIDs and COX-2 inhibitors, have the potential for causing nephrotoxicity, especially in high risk patients (eg, congestive heart failure, hepatic cirrhosis, the nephrotic syndrome, hypertension, sepsis, diabetes mellitus, hypovolemia, chronic renal insufficiency). Although case reports of sulindac-induced nephrotoxicity are available, it may be a better choice for use in high risk patients due to a favorable metabolic pathway. Regardless of the agent selected, early and frequent monitoring of the patient's serum creatinine is suggested to detect changes in renal function as soon as possible. Randomized controlled trials have demonstrated that the selective COX-2 inhibitors celecoxib and rofecoxib can impair renal function in healthy patients. Therefore, it appears that celecoxib and rofecoxib have similar effects on renal function as traditional NSAIDs. Drug discontinuation is the recommended treatment. Upon discontinuation of

analgesic therapy, analgesic-induced renal insufficiency usually reverses, regardless of whether a nonspecific COX inhibitor or COX-2 specific inhibitor is used.

- 2) NSAID use may compromise existing renal function; dose-dependent decreases in prostaglandin synthesis may result from NSAID use, reducing renal blood flow which may cause renal decompensation. Patients with impaired renal function, dehydration, heart failure, liver dysfunction, those taking diuretics, and ACE inhibitors, and the elderly are at greater risk of renal toxicity. Rehydrate patient before starting therapy; monitor renal function closely. Not recommended for use in patients with advanced renal disease. Long-term NSAID use may result in renal papillary necrosis.
- 3) Ibuprofen may precipitate acute renal failure in patients, who are dependent on renal prostaglandins for maintenance of renal blood flow (FDA, 2005; Prod Info Motrin(R), 1999g; Fong & Cohen, 1982; Kimberly et al, 1979); (Kovesi et al, 1998)(Adams et al, 1967); (Van Biljon, 1989). A case of acute renal failure occurring in a preterm infant who received ibuprofen for closure of Patent ductus arteriosus has also been identified (Erdeve et al, 2008).
- 4) Ibuprofen use has been associated with interstitial nephritis, and papillary necrosis (Prod Info Motrin(R), 1999g); (DuBose & Molony, 1994)(Schlondorff, 1993; Spierto et al, 1992; Whelton & Hamilton, 1991; Piepho et al, 1991; Kleinknecht et al, 1986; Shah et al, 1981). Reactions of this type may also occur in children (Primack et al, 1997).
- 5) Ibuprofen use has also been associated with nephrotic syndrome, and membranous nephropathy (Prod Info Motrin(R), 1999g); (DuBose & Molony, 1994)(Schlondorff, 1993; Spierto et al, 1992; Whelton & Hamilton, 1991; Piepho et al, 1991; Kleinknecht et al, 1986; Shah et al, 1981). Reactions of this type may also occur in children (Primack et al, 1997). (Radford et al, 1996); (Morgenstern, 1989; Justiniani, 1986).
- 6) Ibuprofen use has also been associated papillary necrosis (FDA, 2005; Prod Info Motrin(R), 1999g); (DuBose & Molony, 1994)(Schlondorff, 1993; Spierto et al, 1992; Whelton & Hamilton, 1991; Piepho et al, 1991; Kleinknecht et al, 1986; Shah et al, 1981). Reactions of this type may also occur in children (Primack et al, 1997).
- 7) All NSAIDs inhibit cyclooxygenase, the enzyme required for conversion of arachidonic acid to prostaglandins. Renal prostaglandins are produced as needed in response to vasoactive hormones (eg, angiotensin II, vasopressin, norepinephrine, endothelin), cytokines, hypoxia, ischemia, or cellular disturbances. All of these stimuli cause release of arachidonic acid with subsequent synthesis of PGI₂, PGE₂, and PGF_{2a}, the predominant renal prostaglandins. Renal prostaglandins attenuate the effects of vasoconstrictors (eg, angiotensin II, norepinephrine, vasopressin, endothelin) by causing vasodilation. This ultimately maintains renal blood flow and glomerular filtration. The other major effects of renal prostaglandins include increased renin release and increased diuresis and natriuresis. Alterations in the pharmacokinetics of NSAIDs may contribute to nephrotoxicity. Elderly patients have a decrease in total body water and a lower serum albumin, which increases the free NSAID serum concentration and possibly the drug effect. Impaired liver function potentially decreases metabolism of an NSAID to inactive metabolites, which increases the half-life of the active drug. Since up to 50% of unchanged drug and the metabolites are eliminated by the kidney, decreased renal function increases the duration of effect of the active drug.

Phenazopyridine (GFR <50), toxicity [hematologic, renal] due to decreased clearance

- 1) It has been recommended that the dosage interval for phenazopyridine dosage interval be increased in patients with mild renal failure (GFR >50 mL/min) to every 8 to 16 hours. The drug should not be used in patients with moderate to severe renal failure (GFR <50 mL/min) (Bennett et al, 1980).
- 2) A yellow discoloration of the skin or sclera may indicate an accumulation of phenazopyridine due to impaired renal excretion and may require discontinuation of the agent (Prod Info Pyridium(R), 1997a).
- 3) Hemolytic anemia has been observed during therapy with normal doses and following overdoses of phenazopyridine (Greenberg, 1976; Loughner & Bennett, 1980; Jeffery et al, 1982; Green et al, 1979). Hemolysis has been associated with some cases of methemoglobinemia due to phenazopyridine toxicity (Greenberg & Wong, 1964; Greenberg, 1976; Jeffery et al, 1982; Cohen & Bovasso, 1971).
- 4) Methemoglobinemia has been reported during phenazopyridine therapy. Most cases are secondary to overdose or in patients with renal failure. However, methemoglobinemia has been observed in patients with normal renal function taking therapeutic doses (Terrell et al, 1988; Cohen & Bovasso, 1971; Randazzo et al, 1975; Green et al, 1979; Jeffery et al, 1982; Zimmerman et al, 1980). Methemoglobinemia usually occurs within 2 to 3 hours after ingestion of phenazopyridine, but may be delayed. (Wieland et al, 1983).
- 5) Several cases of acute renal failure with transient elevations of creatinine and BUN have been reported with phenazopyridine. Drug withdrawal is associated with clinical improvement (Alano & Webster, 1970; Eybel et al, 1974; Green et al, 1979; Engle & Schoolwerth, 1981). Patients should receive phenazopyridine cautiously and in reduced dosage in the presence of renal impairment. Transient acute renal failure may result from large doses or prolonged use (Tomlinson et al, 1983; Sharon et al, 1986).

Phenytoin Sedation, confusional states, or cerebellar dysfunction (loss of motor coordination) may occur at higher total serum concentrations, or at lower total serum concentrations when the free fraction of phenytoin is increased (↓ protein binding + ↑ volume of distribution). Closely monitor free phenytoin levels.

- 1) No specific dose adjustment is recommended (Bennett et al, 1994). However, serum phenytoin protein binding is altered in uremia which can effect proper interpretation/evaluation of serum phenytoin concentrations (Blum et al, 1972; Letteri et al, 1971; Reidenberg et al, 1971). The fraction of unbound phenytoin increases as renal function decreased, partially due to decreases in serum albumin (Liponi et al, 1984). In patients with renal disease, the following equation has been used to relate the measured, or observed, phenytoin concentration to the phenytoin concentration one would expect to measure if there was normal protein binding (Evans et al, 1992):

$$C(\text{normal}) = \frac{C(\text{observed})}{(0.1 \times \text{albumin}) + 0.1}$$

C (normal) = normal serum phenytoin concentration in nonuremic patients

C (observed) = observed serum phenytoin concentration in uremic patients

Probenecid (GFR <50), ineffective

- 1) In chronic renal impairment probenecid may not be effective when the GFR is <30 mL/min. However, in moderate renal insufficiency to maintain normal serum uric acid levels or uric acid excretion rates above 700 milligrams/24 hours, the dosage may require increasing in increments of 500 milligrams every 4 weeks to a maximum recommended dose of 2 grams/day in 4 divided doses (Prod Info Benemid(R), 1998c).
- 2) Practitioners recommend that probenecid be avoided in patients with moderate to severe renal failure (GFR <50 mL/min) due to inefficacy in this condition (Bennett et al, 1987a). No dosage adjustment is necessary for patients with mild renal failure (GFR >50 mL/min).
- 3) Probenecid is not effective and therefore not recommended for the reduction of uric acid levels in patients with moderate to severe renal failure (Cl_{cr} <50 mL/min) (Hawkins, 1989).

Spiroinolactone (dose adjust in GFR <50, avoid in GFR <10), hyperkalemia

- 1) Increasing the dosing interval to every 6 to 12 hours in patients with mild renal failure (GFR >50 mL/min) and every 12 to 24 hours in patients with moderate renal failure (GFR 10 to 50 mL/min) has been recommended (Bennett et al, 1987). It is recommended that patients with severe renal failure (GFR <10 mL/min) avoid the use of drug.
- 2) Severe hyperkalemia (serum potassium levels greater than 7) may result in paralysis, flaccid paraplegia and cardiac arrhythmias with subsequent cardiovascular collapse (Rado et al, 1968a; Rado et al, 1968b; Herman & Rado, 1966; Pongpaew et al, 1973). In most cases serious hyperkalemia with potentially fatal consequences occur in patients receiving spiroinolactone with impaired renal function.
- 3) Spiroinolactone is frequently reported to cause hyperkalemia particularly when used in patients with impaired renal function, those receiving potassium chloride therapy, elderly patients, or patients with diabetes (McGeown, 1987). An incidence as high as 40% of all patients experiencing adverse reactions to spiroinolactone has been reported for hyperkalemia (Greenblatt & Koch-Weser, 1973b). Severe hyperkalemia (serum potassium levels greater than 7) may result in paralysis, flaccid paraplegia and cardiac arrhythmias with subsequent cardiovascular collapse (Rado et al, 1968a & b)(Herman & Rado, 1966; Pongpaew et al, 1973). In most cases serious hyperkalemia with potentially fatal consequences occur in patients receiving spiroinolactone with impaired renal function.

2008 Update Search Strategy and Evidence Synthesis: Management of Patients with Chronic Kidney Disease in Primary Care

Population

- Adults with GFR under 60 ml/min/1.73m²

Sponsors

- Knowledge Management Hawaii
- Continuing Medical Education
- Nephrology Division

Date of Development

- 1/3/06 Approved by Quality Council
- Last Updated: 10/08

Search Strategy and Results for DARE, Cochrane, Clinical Evidence, and KDOQI

Search terms: "Chronic kidney disease"

Date: New articles published since last search date 5/17/05

Search Date: 9/9/08

- DARE:
 - 38 citations – 2 saved after excluding non-relevant reviews and articles published before last search date.
- Cochrane Database of Systematic Reviews:
 - Search terms: kidney disease
 - 92 citations – 2 additional citations added
- Clinical Evidence:
 - 2 relevant citations related to chronic kidney disease with associated updates
- KDOQI
 - 1 relevant citation

Search Strategy and Results for PubMed Chronic Kidney Disease

- Search date: 9/20/08
- Search terms: prevention, chronic kidney disease from 5/17/2005 through 9/20/08. Limit to English Language
- PubMed Translation: ("kidney failure, chronic"[MeSH Terms] OR ("kidney"[All Fields] AND "failure"[All Fields] AND "chronic"[All Fields]) OR "chronic kidney failure"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields] AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]) AND (("2005/05/01"[PDAT] : "2008/09/20"[PDAT]) AND English[lang] AND Meta-Analysis[ptyp])
- Yield: 18 meta-analyses
- No additional relevant meta-analyses added

- PubMed Translation: ("kidney failure, chronic"[MeSH Terms] OR ("kidney"[All Fields] AND "failure"[All Fields] AND "chronic"[All Fields]) OR "chronic kidney failure"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields] AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]) AND (("2005/01/01"[PDAT] : "2008/09/20"[PDAT]) AND Randomized Controlled Trial[ptyp])
- Yield: 150 articles
- 7 articles relevant for further review

Search Strategy and Results for PubMed Diabetic Kidney Disease

- Search date: 9/21/08

- Search terms: prevention, diabetic kidney disease from 5/1/05 through 9/21/08. (to update K/DOQI). Limit to English Language
- PubMed Translation: ("diabetic nephropathies"[MeSH Terms] OR ("diabetic"[All Fields] AND "nephropathies"[All Fields]) OR "diabetic nephropathies"[All Fields] OR ("diabetic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "diabetic kidney disease"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]) AND (("2005/05/01"[PDAT] : "2008/09/22"[PDAT]) AND English[lang] AND Meta-Analysis[ptyp])
- Yield: 8 meta-analyses
- 1 additional meta-analysis relevant
- PubMed Translation: ("diabetic nephropathies"[MeSH Terms] OR ("diabetic"[All Fields] AND "nephropathies"[All Fields]) OR "diabetic nephropathies"[All Fields] OR ("diabetic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "diabetic kidney disease"[All Fields]) AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prevention"[All Fields]) AND (("2005/05/01"[PDAT] : "2008/09/21"[PDAT]) AND English[lang] AND Randomized Controlled Trial[ptyp])
- Yield: 53 articles
- 8 additional relevant articles found.

Search Strategy and Results for PubMed ACEI

- Search date: 9/21/08
- Search terms: angiotensin-converting enzyme inhibitor, chronic kidney disease from 5/30/05 to 9/21/08. Limit to English Language
- PubMed Translation: ("kidney failure, chronic"[MeSH Terms] OR ("kidney"[All Fields] AND "failure"[All Fields] AND "chronic"[All Fields]) OR "chronic kidney failure"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields]) AND (angiotensin converting enzyme inhibitor[All Fields] OR angiotensin converting enzyme inhibitor/angiotensin[All Fields] OR angiotensin converting enzyme inhibitors[All Fields] OR angiotensin converting enzyme inhibitors/agonists[All Fields] OR angiotensin converting enzyme inhibitors/analysis[All Fields] OR angiotensin converting enzyme inhibitors/biosynthesis[All Fields] OR angiotensin converting enzyme inhibitors/blood[All Fields] OR angiotensin converting enzyme inhibitors/chemistry[All Fields] OR angiotensin converting enzyme inhibitors/classification[All Fields] OR angiotensin converting enzyme inhibitors/contraindications[All Fields] OR angiotensin converting enzyme inhibitors/economics[All Fields] OR angiotensin converting enzyme inhibitors/history[All Fields] OR angiotensin converting enzyme inhibitors/immunology[All Fields] OR angiotensin converting enzyme inhibitors/metabolism[All Fields] OR angiotensin converting enzyme inhibitors/pharmacokinetics[All Fields] OR angiotensin converting enzyme inhibitors/pharmacology[All Fields] OR angiotensin converting enzyme inhibitors/physiology[All Fields] OR angiotensin converting enzyme inhibitors/poisoning[All Fields] OR angiotensin converting enzyme inhibitors/standards[All Fields] OR angiotensin converting enzyme inhibitors/toxicity[All Fields] OR angiotensin converting enzyme inhibitors/urine[All Fields] OR angiotensin converting enzyme inhibitory[All Fields]) AND (("2005/05/01"[PDAT] : "2008/09/21"[PDAT]) AND English[lang] AND Meta-Analysis[ptyp])
- Yield: 7 meta-analyses
- 2 meta-analyses relevant for further review
- Search date: 9/21/08
- Search terms: angiotensin-converting enzyme inhibitor, diabetic kidney disease from 5/01/05 to 9/21/08. (to update K/DOQI). Limit to English Language
- Pubmed Translation: (angiotensin converting enzyme inhibitor[All Fields] OR angiotensin converting enzyme inhibitor/angiotensin[All Fields] OR angiotensin converting enzyme inhibitors[All Fields] OR angiotensin converting enzyme inhibitors/agonists[All Fields] OR angiotensin converting enzyme inhibitors/analysis[All Fields] OR angiotensin converting enzyme inhibitors/biosynthesis[All Fields] OR angiotensin converting enzyme inhibitors/blood[All Fields] OR angiotensin converting enzyme inhibitors/chemistry[All Fields] OR angiotensin converting enzyme inhibitors/classification[All Fields] OR angiotensin converting enzyme inhibitors/contraindications[All Fields] OR angiotensin converting

- enzyme inhibitors/economics[All Fields] OR angiotensin converting enzyme inhibitors/history[All Fields] OR angiotensin converting enzyme inhibitors/immunology[All Fields] OR angiotensin converting enzyme inhibitors/metabolism[All Fields] OR angiotensin converting enzyme inhibitors/pharmacokinetics[All Fields] OR angiotensin converting enzyme inhibitors/pharmacology[All Fields] OR angiotensin converting enzyme inhibitors/physiology[All Fields] OR angiotensin converting enzyme inhibitors/poisoning[All Fields] OR angiotensin converting enzyme inhibitors/standards[All Fields] OR angiotensin converting enzyme inhibitors/toxicity[All Fields] OR angiotensin converting enzyme inhibitors/urine[All Fields] OR angiotensin converting enzyme inhibitory[All Fields]) AND ("diabetic nephropathies"[MeSH Terms] OR ("diabetic"[All Fields] AND "nephropathies"[All Fields]) OR "diabetic nephropathies"[All Fields] OR ("diabetic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "diabetic kidney disease"[All Fields]) AND (("2005/05/01"[PDAT] : "2008/09/21"[PDAT]) AND English[lang] AND Meta-Analysis[ptyp])
- Yield: 7 meta-analyses
 - 1 additional meta-analysis relevant

Search Strategy and Results for PubMed ARB

- Search Date: 9/21/08
 - Search terms: angiotensin receptor blocker, chronic kidney disease from 5/31/05 to 9/21/08. Limit English Language
 - PubMed Translation: ("kidney failure, chronic"[MeSH Terms] OR ("kidney"[All Fields] AND "failure"[All Fields] AND "chronic"[All Fields]) OR "chronic kidney failure"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields]) AND (("receptors, angiotensin"[MeSH Terms] OR ("receptors"[All Fields] AND "angiotensin"[All Fields]) OR "angiotensin receptors"[All Fields] OR ("angiotensin"[All Fields] AND "receptor"[All Fields]) OR "angiotensin receptor"[All Fields]) AND blocker[All Fields] AND (("2005/05/01"[PDAT] : "2008/09/21"[PDAT]) AND English[lang] AND Meta-Analysis[ptyp])
 - Yield: 3 meta-analyses
 - No additional meta-analyses added.
- Search Date: 9/21/08
 - Search terms: angiotensin receptor blocker, diabetic kidney disease from 5/1/05 to 9/21/08 (to update K/DOQI). Limit to English Language.
 - PubMed Translation: (angiotensin receptor blocker[All Fields] OR angiotensin receptor blockers[All Fields]) AND ("diabetic nephropathies"[MeSH Terms] OR ("diabetic"[All Fields] AND "nephropathies"[All Fields]) OR "diabetic nephropathies"[All Fields] OR ("diabetic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "diabetic kidney disease"[All Fields]) AND (("2005/05/01"[PDAT] : "2008/09/21"[PDAT]) AND English[lang] AND Meta-Analysis[ptyp])
 - Yield: 4 meta-analyses
 - No additional meta-analyses added

Search Strategy and Results for PubMed Diet

- Search Date: 9/21/08
- Search terms: dietary protein, chronic kidney disease from 5/1/05 to 9/21/08. Limit English Language
- PubMed Translation: ("kidney failure, chronic"[MeSH Terms] OR ("kidney"[All Fields] AND "failure"[All Fields] AND "chronic"[All Fields]) OR "chronic kidney failure"[All Fields] OR ("chronic"[All Fields] AND "kidney"[All Fields] AND "disease"[All Fields]) OR "chronic kidney disease"[All Fields]) AND ("diet"[MeSH Terms] OR "diet"[All Fields]) AND (("2005/05/01"[PDAT] : "2008/09/21"[PDAT]) AND English[lang] AND Meta-Analysis[ptyp])
- Yield: 5 meta-analyses
- No additional meta-analyses added.

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1. Robertson L et al. Protein restriction for diabetic renal disease. 2007.
2. Strippoli GFM et al. Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease. 2006
3. Strippoli GFM et al. Antihypertensive agents for preventing diabetic kidney disease. Cochrane Database Syst Rev. 2005 Oct 19;(4):CD004136. Review. PMID: 16235351

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KDOQI

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1. Appel LJ et al. Long-term effects of renin-angiotensin system-blocking therapy and a low blood pressure goal on progression of hypertensive chronic kidney disease in African Americans. Arch Intern Med. 2008 Apr 28; 168(8):832-9. PMID: 18443258
2. Mohanram A et al. The effect of losartan on hemoglobin concentration and renal outcome in diabetic nephropathy of type 2 diabetes. Kidney Int. 2008 Mar; 73(5):630-6. Epub 2007 Dec 19. PMID: 18094675
3. Schaeffner et al. Blood pressure measures and risk of chronic kidney disease in men. Nephrol Dial Transplant. 2008 Apr; 23(4):1246-51. Epub 2007 Nov 5. PMID: 17984108
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5. Hou FF et al. Efficacy and safety of benazepril for advanced chronic renal insufficiency. N Engl J Med. 2006 Jan 12; 354(2):131-40. PMID: 16407508
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PubMed Diabetic Kidney Disease Prevention MAs

1. Jennings DL. Combination therapy with an ACE inhibitor and an angiotensin receptor blocker for diabetic nephropathy: a meta-analysis. Diabet Med. 2007 May; 24(5):486-93. Epub 2007 Mar 15. PMID: 17367311

PubMed Diabetic Kidney Disease Prevention RCTs

1. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med. 2008 Jun 2; 358(24):2560-72. Epub 2008 Jun 6. PMID: 18539916
2. Parving HH et al. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med. 2008 Jun 5; 358(23):2433-46. PMID: 18525041
3. Furumatsu Y et al. Effect of renin-angiotensin-aldosterone system triple blockade on non-diabetic renal disease: addition of an aldosterone blocker, spironolactone, to combination treatment with an angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker. Hypertens Res. 2008 Jan;31(1):59-67. PMID: 18360019
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 8. Sengul Am et al. Beneficial effect of lisinopril plus telmisartan in patients with type 2 diabetes, microalbuminuria and hypertension. *Diabetes Res Clin Pract.* 2006 Feb; 71(2):210-9. Epub 2005 Aug 19. PMID: 16112244

PubMed ACEI/chronic kidney disease

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2. Casas JP et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet.* 2005 Dec 10; 366(9502):2026-33. PMID: 16338452

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Evidence Synthesis

Angiotensin Converting Enzyme Inhibitors (ACEIs)

• Diabetics with microalbuminuria

- In type I diabetics with microalbuminuria, there is sufficient evidence to conclude that ACEIs reduce progression from microalbuminuria to macroalbuminuria.
 - Clinical Evidence found one systematic review evaluating the effects of ACEIs vs. placebo on microalbuminuria in type 1 diabetics. Individual patient data from 12 trials (698 patients) were included. The review found that, compared with placebo or controls, angiotensin converting enzyme inhibitors (captopril, lisinopril, enalapril, perindopril, and ramipril) reduced progression to macroalbuminuria in type 1 diabetics with microalbuminuria.
 - Methodology: Good Evidence
 - Reference Clinical Evidence summary for Diabetic Nephropathy; search date November 2006
- In normotensive type 1 diabetics with microalbuminuria, there is sufficient evidence to conclude that ACEIs can arrest or cause regression of albumin excretion.
 - Clinical Evidence found one systematic review evaluating the effects of ACEIs on microalbuminuria in type I diabetics. Individual patient data from 12 trials (698 patients) were included. The review found that, compared with placebo or controls, angiotensin converting enzyme inhibitors (captopril, lisinopril, enalapril, perindopril, and ramipril) increased regression to normoalbuminuria in type 1 diabetics with microalbuminuria.

- Methodology: Good Evidence
 - Reference: Clinical Evidence summary for Diabetic nephropathy; search date November 2006
 - In type 2 diabetics with microalbuminuria, there is sufficient evidence to conclude that ACEIs reduce progression from microalbuminuria to macroalbuminuria.
 - Clinical Evidence found one systematic review evaluating the effects of ACEIs on microalbuminuria in type 2 diabetics. The review included 642 patients from 9 RCTs. Three subsequent RCTs were also found, the largest of which included 4912 patients.
 - Methodology: Good Evidence
 - Reference: Clinical Evidence summary for Diabetic nephropathy; search date November 2006
- **Diabetics with macroalbuminuria**
 - In type 1 diabetics with macroalbuminuria, there is sufficient evidence to conclude that captopril reduce progression to end-stage renal disease, death, or renal transplantation over 3 years.
 - No RCT has compared angiotensin II receptor blocker (ARB) against ACEI in type I diabetics with advanced nephropathy.
 - Clinical Evidence found 1 RCT of 409 type I diabetics with macroalbuminuria (urine protein excretion \geq 500 mg per day). Captopril reduced the risk of a doubling of the serum creatinine as well as the combined endpoint of death, dialysis, and renal transplantation (23/207 [11%] with captopril v 42/202 [21%] with placebo; RR 0/50, [CI 0.19-0.70]).
 - Methodology: Good evidence
 - Reference: Clinical Evidence summary for Diabetic nephropathy; search date November 2004
- **Non-diabetic patients**
 - There is insufficient evidence to conclude that ACEIs decrease progression of nephropathy in non-diabetic patients with chronic kidney disease.
 - .
 - Clinical Evidence found one systematic review. The systematic review identified 11 RCTs of 1860 people (mean serum creatinine 203 mcmmol/L, SD 106 mcmmol/L, mean proteinuria 1.8g/d SD 2.3 g/d). Fewer people reached ESRD with ACEI compared with the control group (ESRD 70/941 [7%] with ACEI v 106/919 [12%] with controls, RR 0.69, CI 0.51-0.94). There was no significant difference in mortality. Systolic blood pressure was 4.5 mm HG greater in ACEI compared with controls and decline in diastolic blood pressure was 2.3 mmHg greater with ACEI compared with controls.
 - Methodology: Fair Evidence
 - Reference: Clinical Evidence Summary on Chronic Renal Failure; search date April 2006.
- **Harms/Risks**
 - Spironolactone is associated with an increased risk of hyperkalemia in patients with chronic kidney disease, especially in combination with an ACEI/ARB.

- One population-based study of 1.3 million patients published after the Randomized Aldactone Evaluation Study associated an abrupt increase in spironolactone prescription rate with rates of hyperkalemia-associated hospitalizations and deaths.
- Methodology: Insufficient evidence. Cause and effect can only be concluded from randomized controlled trials (RCTs). The above harms data is not from RCTs pre-specifying hyperkalemia as an outcome measure. Harms are rare events requiring many people to show statistically significant differences but when additional studies confirm harms, clinicians and patients should be made aware of the potential harms patients along with a thorough discussion of an agent's benefits and potential harms.
- Reference: Juurlink ND et al. Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study. *NEJM*. 351:543, 2004.

▪

Angiotensin II Receptor Blockers

- **Diabetics with microalbuminuria**

- There is sufficient evidence to conclude that ARBs reduce the progression from microalbuminuria to macroalbuminuria in type 2 diabetics.
- No RCTs were found comparing ARBs versus placebo in type I diabetics with microalbuminuria.
 - Clinical Evidence found one RCT of 590 type 2 diabetics with microalbuminuria, given either irbesartan or placebo. Irbesartan 300 mg reduced progression from microalbuminuria to macroalbuminuria over 2 years vs. placebo. However, no significant decrease was observed with irbesartan 150 mg (10/194[5%] with irbesartan 300 mg v 30/201 [15%] with placebo; HR 0.30, 95 % CI 0.14-0.61; p< 0.001; 19/195 [10%] with irbesartan 150 mg vs 30/201 [15%] with placebo; HR 0.61, 95% CI 0.34-1.08; p=0.08).. One RCT of 250 people with type 2 diabetes and microalbuminuria found to significant change in the glomerular filtration rate, mortality, stroke, heart failure, or MI between an ARB and ACEI enalapril over 5 years.
 - Methodology: Good Evidence
 - Reference: Clinical Evidence summary for Diabetic nephropathy; search date November 2006.

- **Diabetics with macroalbuminuria**

- There is sufficient evidence to conclude that ARBs reduce progression to end stage renal disease in type 2 diabetics with macroalbuminuria.
 - Clinical evidence found one systematic review comparing angiotensin II receptor antagonists with placebo for end stage renal disease and all cause mortality. Most patients had late nephropathy although it combined RCTs of early and late nephropathy. Angiotensin II receptor antagonists significantly reduced end stage renal disease compared with placebo (3 RCTs, 3251 patients; 229/1719 [13.7%] with angiotensin II receptor antagonists v 195/1532 [12.7%] with placebo; RR 0/78, 95% CI 0.67-0.91) Most people from the review were from two RCTs comparing the effects of ARBs versus placebo in type 2 diabetics with

macroalbuminuria, on the outcomes of progression to end stage renal disease, cardiovascular events, and all cause mortality. The first RCT of 1513 people with moderate renal insufficiency (creatinine 1.3 to 3 mg/dl) and urine albumin/creatinine ratio ≥ 300 mg/g, showed that losartan reduced progression to end-stage renal disease over 3.4 years versus placebo (147/751 [20%] with losartan v 194/762 [26%] with placebo RR 0.72, 95% CI 0.58-0.89; ARR 2.3/100 person years). The second RCT of 1715 patients with type 2 diabetes, mild-moderate renal insufficiency (creatinine 1 to 3 mg/dl), and proteinuria > 900 mg compared irbesartan and placebo. Irbesartan was associated with a significant reduction in the doubling of the serum creatinine. There was no significant difference, however, between the groups in progression to end-stage renal disease or death from any cause over 2.6 years (82/579 [14%] with irbesartan v 113/569 [20%] with placebo; RR 0.77, 95% CI 0.57-1.03; $p = 0.07$; death from any cause RR 0.92 95% CI 0.69-1.23).

- Methodology: Fair Evidence
- Reference: Clinical Evidence summary for Diabetic nephropathy; search date November 2006

Combination ACEI and ARBs

- Diabetics
 - There is insufficient evidence to conclude that combination ACEI and ARB in reduce renal outcomes in type I or type II diabetes.
 - Methodology: Insufficient Evidence
 - Reference: Clinical Evidence Summary for Diabetic Nephropathy; search date November 2006, Cochrane Systematic Review Angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists for preventing the progression of diabetic kidney disease 2006 (search date December 2005; 2008 CKD update search
- Nondiabetics
 - There is insufficient evidence to conclude that compared with ACEIs or with ARBs alone, ACEIs plus ARBs is more effective at reducing disease progression or end-stage renal disease in people with chronic renal failure.
 - One RCT (263 people with > 0.3 g proteinuria/day, serum creatinine 265-271 μ mol/L, SD 9.5 to 10.2 μ mol/L, EGFR 37.5-38.4 ml/min/1.73 m², SD 3.7-4 ml/min/1.73m²) compared trandolapril 3 mg daily, losartan 100 mg daily, and trandolapril 3mg + losartan 100 mg. At 3.3 years follow-up, trandolapril + losartan significantly reduced the number of people with doubling of the serum creatinine or ESRD compared with trandolapril alone or losartan alone (10/85 [11%] trandolapril + losartan vs 20/85 [23%] trandolapril alone; HR 0.38, 95% CI 0.18-0.63, $p = 0.018$; 10/85 [11%] trandolapril +losartan v 20/86 [23%] with losartan alone; HR 0.40, 95% CI 0.17-0.69, $p=0.016$).
 - A second RCT (25620 high vascular risk people mean age 66 yrs old with BMI 28, mean bp 141.8/82.1 compared telmisartan 80 mg + ramipril 10 mg with ramipril 10 mg alone. No specific criteria used for starting HD. 56 month median follow-up. The primary composite endpoint (all dialysis, doubling of the serum creatinine) was higher with telmisartan+ramipril group than with either telmisartan or ramipril alone (telmisartan 1147 [13.4%], ramipril 1150 [13.5%]).

Combination 1233 [14.5%] HR 1.09, CI 1.01-1.18, p=0.037). Much of the change was due to acute dialysis in the combination group vs ramipril alone (combination 28 [33%] combination vs 13 [15%] ramipril alone, HR 2.19. CI 1.13-4.22, p=0.020). Risk for renal outcomes was higher in low renal risk groups (no microalbuminuria/macroalbuminuria, no diabetes, and no hypertension).

- Methodology: Insufficient Evidence for therapy, Fair Evidence for harms
- References: Nakao et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomized controlled trial. *Lancet* 2003; 361:117-124. Mann et al. Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multi-centre, randomized, double-blind, controlled trial. *Lancet* 2008; 372: 547-53.

Glycemic Control in Diabetics

- There is sufficient evidence to conclude that intensive glucose control reduces progression of early nephropathy in type 1 diabetics.
 - Clinical Evidence found one systematic review (search date 1991, 16 RCT's) which compared conventional control and intensive glycemic control. It found that intensive glycemic control reduced progression of nephropathy in people with type 1 diabetes and either normal albumin excretion or microalbumin.
 - Methodology: Good Evidence
 - Reference: Clinical Evidence summary for Diabetic nephropathy. Search date November 2006, Michael Shlipak.
- There is fair evidence that intensive glucose control reduces the incidence of microvascular complications in type 2 diabetics.
 - One RCT of 11140 high risk type 2 diabetics to intensive glucose control compared a Hb A1C target of $\leq 6.5\%$ vs standard HB A1C targets. Microvascular events (new or worsening nephropathy (macroalbuminuria, doubling of the serum creatinine to at least 2.26 mg/dl, need for RRT, or death from renal disease; or retinopathy) were lower in the intensive control group (hazard ratio 0.86, CI 0.77-0.97; p = 0.01). There were significantly more hospitalizations for any cause and for hypoglycemia in the intensively treated group.
 - Methodology: Fair Evidence
 - Reference: ADVANCE Collaborative Group. Intensive Blood glucose control and vascular outcomes in type 2 diabetes. *N Engl J Med.* 2008 Jun 2; 358(24): 2560-72.
- There is insufficient evidence to conclude that intensive glucose control reduces the incidence of end stage renal disease in diabetics.
 - Clinical Evidence found no RCT's on glycemic control in people with type 2 diabetes and late nephropathy on the incidence of end-stage renal disease
 - Methodology: Insufficient Evidence (Grade U: Uncertain)
 - Reference: Clinical Evidence summary for Diabetic nephropathy. Search date November 2004, Michael Shlipak.

Blood Pressure Control

- **Diabetics**
 - Higher levels of blood pressure are associated with more rapid progression of diabetic kidney disease.

- Target blood pressure in diabetic kidney disease should be < 130/80 mm Hg.
 - Methodology: Good Evidence
 - Reference: Reference: K/DOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Diabetes and Chronic Kidney Disease.. *Am J Kidney Dis.* 2007 Feb; 49(2 Suppl 2):S12-154. CMI Guidelines.
- **Nondiabetics**
 - Higher levels of blood pressure are associated with more rapid progression of nondiabetic kidney disease.
 - Target blood pressure in nondiabetic kidney disease should be < 130/80 mm Hg.
 - Methodology: Good Evidence
 - Reference: Reference: K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. *American Journal of Kidney Diseases.* S1-S290, 2004 (suppl1).

Diet

- There is insufficient evidence to conclude that low protein diets reduce the progression of CKD
 - Cochrane Database of Systematic Reviews (Cochrane) found seven trials which evaluated the effect of low protein diets on the time to dialysis in non diabetics with moderate to severe nephropathy. No quality assessment of the studies was performed.
 - Methodology: Insufficient Evidence regarding efficacy/effectiveness—Judgment of CKD Guideline Team.
 - Reference: Fouque D, Wang P, Laville M, Boissei JP. Low protein diets for chronic renal failure in nondiabetic adults. *The Cochrane Database of Systematic Reviews* 2006, Issue 2.
 - Cochrane also evaluated 12 studies of modified or restricted protein diets in type 1 or type 2 diabetics. There was no significant benefit noted of a low protein diet in type I diabetics. No quality assessment of the studies was performed
 - Methodology: Insufficient Evidence
 - Reference: Robertson L et al. Protein restriction for diabetic renal disease. *The Cochrane Database of Systematic Reviews* 2007, Issue 4.
 - Clinical Evidence found one small, non-blinded RCT comparing the effects on end stage renal disease of usual protein intake vs. a low protein diet in type 1 diabetics with early nephropathy and no RCTs in type 2 diabetics.
 - Methodology: Insufficient Evidence (Grade U: Uncertain) to draw conclusions regarding efficacy/effectiveness—Judgment of CKD Guideline Team.
 - Reference: Clinical Evidence summary for Diabetic nephropathy; search date November 2004
 - A search of PubMed through September 21, 2008 yielded no additional RCTs.

Evidence Grading

CMI	Delfini
Evidence	
Good	Grade B
Fair	Grade BU? Uncertain about comparability
Insufficient	Grade U
Synthesis & Recommendations	
Evidence-based	B (BU?)
Consensus-based	U or lacking
NEW: Consensus-based w/o Review	Where the team has not conducted an evidence review

The *Delfini Validity & Usability Grading Scale for Summarizing the Evidence for Interventions* was used to grade all relevant studies published after the search dates of the trusted sources. Details of the grading scale are presented below:

Grade of Usability	Strength of Evidence
<ul style="list-style-type: none"> • Grade A: Useful 	<p>The evidence is strong and appears sufficient to use in making health care decisions – it is both valid and useful (e.g., clinical significance, of sufficient magnitude, physician and patient acceptability, etc.)</p> <ul style="list-style-type: none"> • Evidence from well-designed and conducted systematic reviews might fall into this category or they might be considered Grade B. Suggestion is to do a careful analysis of the review and the studies included. • Several well-designed and conducted studies that consistently show similar results <ul style="list-style-type: none"> ○ For therapy, screening, prevention and diagnostic studies: RCTs. In some cases a single, large well-designed and conducted RCT may be sufficient. ○ For natural history and prognosis: Cohort studies
<ul style="list-style-type: none"> ⊙ Grade B: Possibly Useful 	<p>The evidence is potentially strong and might be sufficient to use in making health care decisions.</p> <p>The evidence is strong enough to conclude that the results are probably valid and useful (see above); however, study results from multiple studies are inconsistent or the studies may have some (but not lethal) threats to validity.</p> <ul style="list-style-type: none"> • Evidence from well-designed and conducted systematic reviews might fall into this category or they might be considered Grade A. Suggestion is to do a careful analysis of the review and the studies included. • Evidence from at least one well-designed and conducted RCT (cohort studies for natural history and prognosis; for diagnosis, valid studies assessing test accuracy for detecting a condition when there is evidence of effectiveness from valid, applicable RCTs.)
<ul style="list-style-type: none"> ○ Grade UV: Uncertain Validity ○ Grade UU: Uncertain Usefulness 	<p>There is sufficient uncertainty so that caution is urged regarding its use in making health care decisions.</p> <ul style="list-style-type: none"> • Uncertain Validity: This may be due to uncertain validity due to methodology (enough threats to validity to raise concern – our suggestion would be to not use such a study in most circumstances) or may be due to

<ul style="list-style-type: none"> ○ Grade UVU: Uncertain Validity and Usefulness ○ Grade UA: Uncertainty of Author 	<p>conflicting results.</p> <ul style="list-style-type: none"> • Uncertain Usefulness: Or this may be due to uncertain applicability due to results (good methodology, but questions due to effect size, applicability of results when relating to biologic markers, or other issues). These latter studies may be useful and should be viewed in the context of the weight of the evidence. • Uncertain Validity and Usefulness: This is a combination of the above. • Uncertainty of Author: If the author has reached a conclusion that the findings are uncertain, doing a critical appraisal is unlikely to result in a different conclusion. The evidence leaves us uncertain regardless of whether the study is valid or not. Critical appraisal is at the discretion of the reviewer.
<p>X Grade X: (Optional) Not Useful</p>	<p>Evidence which has lethal threats to validity or other egregious problems fits into the U category. However, there may be instances in which a study is so poorly done and so potentially misleading that the reviewer may wish to provide a stronger caution about the quality of the study than “Grade U.” Grade X is optional for this purpose.</p>