Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care *DRAFT*

Temporary Web Version from the CKD Guideline Group

July 24, 2006

I. Introduction

This draft algorithm and evidence synthesis for this clinical guideline are designed to provide information and decision support for the management of chronic kidney disease in primary care.   The algorithm is part of a larger evidence-based guideline, the entirety of which will be made available as the various components are developed. This chronic kidney disease (CKD) algorithm and evidence synthesis was developed with the support of Kaiser Permanente Hawaii's CME department, Nephrology Department, Kaiser's Care Management Institute (CMI), with stakeholders from Nephrology, Internal Medicine, Family Practice, Clinical Nutrition and Pharmacy, and with facilitation and support by Delfini Group, LLC. See detailed documentation (V.) below.

II. Notes about this draft version of the CKD guideline:
- The guideline was designed to assist in management of stable CKD.
- GFR can be estimated from the MDRD equations which are available from many sources.
- For purposes of the guideline, GFR<60ml/min per 1.73m2 defines CKD.
- Referral from primary care to Nephrology is a judgment call but can be informed by estimated risk which in turn is based on both GFR and proteinuria level. Therefore both GFR and proteinuria levels should be followed in primary care.
- The evidence for Ace Inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) is strongest for patients with significant proteinuria and this guideline is designed to lower urinary protein.
- This CKD guideline is a work in progress and topics such as renal bone disease, renal acidosis, CKD with GFR>60 ml/min per 1.73m2, and other important considerations in CKD have not yet been developed.

III. See Algorithm for 1 page recommendations.

IV. Evidence Synthesis CKD

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 (Grade U: Uncertain) to draw conclusions 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* 2000, 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 May 20, 2005 yielded no additional RCTs.

Angiotensin Converting Enzyme Inhibitors (ACEIs)
- **Diabetics with microalbuminuria**

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

- o In 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 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.
  - ▪ 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 (Grade B: Possibly useful)
    - • Reference: Clinical Evidence summary for Diabetic nephropathy; search date November 2004
- o In normotensive 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 (Grade B: Possibly useful)
    - • Reference: Clinical Evidence summary for Diabetic nephropathy; search date November 2004
  - ▪ Cochrane had a systematic review of ACEIs in normotensive diabetic patients with microalbuminuria. Twelve RCTS were included in the meta-analysis, which included both type 1 and type 2 diabetics.
    - • Methodology: Good Evidence (Grade B: Possibly useful)
    - • Reference: Lovell, HG. Angiotensin converting enzyme inhibitors in normotensive diabetic patients with microalbuminuria. *The Cochrane Database of Systematic Reviews* 2003.

- **Diabetics with macroalbuminuria**
  - o 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.
  - o 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 ≥ 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
    - ▪ Methodology: Good evidence (Grade B: Possibly useful)
    - ▪ Reference: Clinical Evidence summary for Diabetic nephropathy; search date November 2004

- **Non-diabetic patients**
  - o There is sufficient evidence to conclude that ACEIs decrease progression of nephropathy in patients with proteinuria in non-diabetic patients with chronic kidney disease.
    - ▪ Kidney Disease Outcomes Quality Initiative (K/DOQI) found 3 RCTs, the largest of which included 583 patients, comparing ACEIs with placebo on the progression of renal disease.

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

Endpoints in the various studies included doubling of the serum creatinine, dialysis, and loss of glomerular filtration rate.
  - Methodology: Good evidence (Grade B: Possibly useful)
  - Reference: K/DOQI Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease. *American Journal of Kidney Diseases.* S1-S290, 2004 (suppl1).

- **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: Uncertain evidence (Grade U: Uncertain validity); 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.

- **Cardiovascular Outcomes**
  - There is sufficient evidence to conclude that ACE Inhibitors prevent cardiovascular events in patients with diabetes age ≥ 55 years with one or more cardiovascular factors (Total cholesterol >200 mg/l, HDL-cholesterol ≤ 35 mg/l, hypertension, microalbuminuria, or current smoking) or a history of CVD (CAD, stroke, or peripheral vascular disease).
    - One large multicenter RCT was found that compared an ACE Inhibitor to placebo in the prevention of cardiovascular events. 3577 people with diabetes over age 55 with a history of cardiovascular disease (CAD, stroke, or PVD) or diabetes plus at least one other CV risk factor (total cholesterol >5.2 mmol/l, HDL-C =0.9 mmol/l, hypertension, known microalbuminuria, or current smoking) were randomized to either placebo or an ACE Inhibitor (10 mg ramipril daily). The study ran for 4.5 years and was stopped 6 months early due to the beneficial effect of ramipril. There were significantly fewer MIs in the treatment group (RRR 22%; 95% CI 6, 36; p=0.01), as well as fewer strokes (RRR 33%; 95% CI 10, 50; p=0.0074), and CV deaths (RRR 37%; 95% CI 21, 51; p=0.0001). The relative risk reduction for total mortality with an ACE Inhibitor was 24% (95% CI 8, 37; p=0.004).
    - There is evidence that an ACE Inhibitor can prevent MI, stroke, and mortality in people with diabetes with and without a history of CVD. Intensive therapy lowered the risk of CV disease [HR 0.46 (0.24-0.73)], nephropathy [HR 0.39(0.17-0.87)], retinopathy [HR 0.42 (0.21 to 0.86)], and autonomic neuropathy [HR 0.37 (0.18-0.79)].
    - Methodology: **
    - Reference: CMI Guidelines Published: 5/2002, Review/Revised: 2/2004

<u>Angiotensin II Receptor Blockers</u>
- **Diabetics with microalbuminuria**
  - There is sufficient evidence to conclude that ARBs reduce the progression from microalbuminuria to macroalbuminuria in type 2 diabetics.

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

- o 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. However, no significant decrease was observed with irbesartan 150 mg. 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 (Grade B: Possibly Useful)
  - Reference: Clinical Evidence summary for Diabetic nephropathy; search date November 2004

- **Diabetics with macroalbuminuria**
  - o There is sufficient evidence to conclude that ARBs reduce progression to end stage renal disease in type 2 diabetics with macroalbuminuria.
    - Clinical evidence found 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 (creat 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. The second RCT of 1715 patients with type 2 diabetes, mild-moderate renal insufficiency (creatinine 1to 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.
    - Methodology: Good Evidence (Grade B: Possibly Useful)
    - Reference: Clinical Evidence summary for Diabetic nephropathy; search date November 2004

- **Cardiovascular Outcomes**
  - o There is sufficient evidence to conclude that ARB therapy reduces cardiovascular outcomes for the following patients with CAD who are intolerant to ACE Inhibitors:
    - A. Patients with CAD and diabetes with hypertension and microalbuminuria (or albuminuria),
    - B. Patients with CAD and left ventricular systolic dysfunction (LVSD),
    - C. For patients with CAD and hypertension (without either LVSD or diabetes) who are intolerant to ACE Inhibitors ARB therapy is an option equal to other antihypertensive medications..

  - o For all other patients with CAD who are intolerant to ACEIs, there is insufficient evidence to recommend for or against ARB therapy.
    - ARBs in ACEI intolerant patients

      One new RCT that added to the evidence for these recommendations was found since the 2002 CMI Heart Failure Guidelines were published. The CHARM randomized, controlled trials compared the ARB candesartan to placebo in three distinct populations: patients taking ACEI and BB (CHARM-Added); patients who were ACEI-intolerant (CHARM-Alternative); and patients with preserved LV function (CHARM-Preserved). The CHARM-Alternative study compared candesartan to placebo in 2,028 patients with LVSD who were ACEI-intolerant. Results showed that candesartan significantly reduced cardiovascular death and hospitalization, [HR 0.80 (0.66 to 0.96) for CV death] and [0.70 (0.60 to 0.81) for hospitalization]. The CHARM-Preserved trial enrolled 3,029 patients with LVSD (EF > 40%). Of these, 1,514 patients were

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

assigned to 32 mg candesartan daily and 1509 to placebo. The primary endpoint was CV death or unplanned admission to hospital for management of worsening heart failure. The hazard ratio showed a non-statistical difference between the treatment and placebo groups 0.89 (0.77 to 1.03), $p = 0.118$. The CHARM-Added trial of 2,548 patients compared the addition of candesartan or placebo to standard heart failure treatment of ACEI and beta-blockers. (Fifty-five percent of participants were on beta-blockers.) The overall Hazard Ratio for CV death or Heart Failure hospitalization was 0.85 (0.75 to 0.96). The interaction of outcomes for patients on beta-blockers and those not on beta-blockers was not significant, $p = 0.14$. Thus, results were similar whether or not participants were taking beta-blockers.

This evidence is supported by the subgroup analysis from the Val-HeFT, which found a significant reduction in combined endpoints when ARBs were compared to placebo in small group of patients who were ACEI-intolerant.

- ARBS in CAD and HTN or CAD alone

  For patients with CAD and hypertension (without either LVSD or diabetes), and for those with CAD alone, the CAD Guidelines Workgroup examined the following evidence comparing ARBs to ACE Inhibitors:

  The OPTIMAAL Study compared Losartan with Captopril in patients with acute MI and signs or symptoms of heart failure during the acute phase (n = 5,477). Over 50% of study subjects had ischemic heart disease and 36% had hypertension, equally distributed between intervention groups. Although there were small differences in total mortality (18.2% in Losartan; 16.4% in Captopril; RR = 1.13, 95% CI 0.99 to 1.28, $p = 0.069$), and in CV mortality (15.3% in losartan and 13.3% in captopril; RR = 1.17, 95% CI 1.01 to 1.34, $p = 0.032$) in favor of captopril (ACE-I), losartan (ARB) was better tolerated and associated with significantly fewer discontinuations than captopril. Because of this, the study investigators concluded that losartan can be considered in patients intolerant of ACE inhibition even though the role of losartan in patients intolerant of ACE inhibition was not clearly defined in this study.

  The VALIANT trial compared the effect of valsartan (ARB), captopril (ACE Inhibitor) and the combination of the two on mortality in patients with MI complicated by left ventricular systolic dysfunction, heart failure or both (n = 14,703). Over 50% of study subjects, equally distributed among intervention groups, had hypertension. After 24.7 months of follow-up, all-cause and cause-specific mortality were similar in the three treatment groups (valsartan-treated = 19.9%; captopril-treated = 19.3%; valsartan+captopril-treated = 19.5%). Combining valsartan with captopril increased the rate of adverse events without improving survival. The study investigators concluded that valsartan met the trial criterion of non-inferiority and thus may be considered a clinically effective alternative to ACE Inhibitor therapy.

- Methodology: **
- Reference: CMI Guidelines Published: 5/2002, Review/Revised: 2/2004

Glycemic Control in Diabetics
- There is sufficient evidence to conclude that intensive glucose control reduces progression of early nephropathy in type I diabetics.

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

- o 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.
  - o Methodology: Good Evidence (Grade B: Possibly Useful)
  - o Reference: Clinical Evidence summary for Diabetic nephropathy. Search date November 2004, Michael Shlipak.

- There is insufficient evidence to conclude that intensive glucose control reduces the incidence of end stage renal disease in diabetics.
  - o 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
  - o Methodology: Insufficient Evidence (Grade U: Uncertain)
  - o Reference: Clinical Evidence summary for Diabetic nephropathy. Search date November 2004, Michael Shlipak.

- There is sufficient evidence to conclude that intensive glucose control is recommended in patients with diabetes, if not contraindicated, to reduce the incidence of adverse cardiovascular outcomes.
  - o Three systematic reviews within Clinical Evidence were found that looked at the effect of glycemic control on cardiovascular outcomes.

    Herman's systematic review in Clinical Evidence looked at the effect of intensive glucose control on cardiovascular outcomes, microvascular and neuropathic outcomes, and adverse effects of intensive glucose control. One Meta-analysis and two subsequent RCTs within Herman's systematic review studied the effect of intensive glucose control on CV outcomes. The Meta-analysis and one of the RCTs also looked at the microvascular outcomes. The Lawson Meta-analysis included 6 RCTs that compared intensive insulin therapy to placebo in people with type 1 diabetes (n=1731 for all study populations combined). The studies ranged from 2-8 years. No significant impact on macrovascular mortality was found for intensive glucose control (OR 0.91; 95% CI 0.31, 2.65). UKPDS 33 included 951 newly diagnosed patients with type 2 diabetes (mean age 54, age 48-60) who were randomized to either conventional therapy (diet) or intensive therapy (insulin or sulphonylurea). After 10 years, intensive therapy did not statistically reduce MI (RRR 13; 95% CI -2, 27) or the combined endpoint of amputation or death from peripheral vascular disease (RRR 33; 95% CI -20, 63). Ohkubo compared conventional insulin therapy to intensive insulin therapy in people with type 2 diabetes <70 years old (mean age 49). 110 participants were followed for 6 years. No statistically significant differences were seen for CVD, but the study was small and not powered to give significant results for CV events.

    Sigal's systematic review in Clinical Evidence looked at primary and secondary prevention of CVD in people with diabetes. Three RCTs were included in Sigal's systematic review that studied intensive glucose control in **primary prevention** of CVD. UKPDS 33 is described above (included in the Clinical Evidence systematic review by Herman). UKPDS 34 randomized 1704 newly diagnosed people with type 2 diabetes to conventional control (diet), intensive control with metformin, or intensive control with insulin or sulphonylurea. When compared to conventional therapy, metformin was associated with a 32% risk reduction (95% CI 13, 47; p=0.002) of diabetes-related end points (sudden death, hyperglycemia, hypoglycemia, fatal/non-fatal MI, angina, HF, stroke, renal failure, amputation, vitreous hemorrhage, retinopathy, blindness in one eye, or cataract extraction). Metformin was also linked with fewer MIs (NNT 16; 95% CI 10-71) in type 2 diabetes. There was a risk reduction in diabetes related deaths

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

associated with metformin of 0.58 (95% CI 0.37, 0.91; NNT 19). The DCCT randomized 1441 people with type 1 diabetes, age 13-39, to intensive therapy (external insulin pump or ≥3 injections/day) or conventional therapy (1-2 insulin injections/day). Participants were followed for 6.5 years. There was a decrease in CV events in the intensive therapy group, but the results were not statistically significant.

Sigal's systematic review in Clinical Evidence looked at primary and secondary prevention of CVD in people with diabetes. Two RCTs were included in Sigal's systematic review that studied intensive glucose control in **secondary prevention** of CVD, but only one fit our inclusion criteria. Abraira randomized 40-69 year old men with type 2 diabetes to intensive (step therapy insulin injections) versus conventional glucose lowering therapy (once daily insulin injections) on primary cardiovascular disease on men with type 2 diabetes. This was a small study (n=151) with a relatively short follow-up period (27 months). There was no difference in cardiovascular mortality and the difference in new CV events was not statistically different.

Intensive glucose control appears to have little effect on cardiovascular outcomes. Sigal concluded that there is modest support for intensive glucose control for primary prevention of CVD.

o   Supporting Evidence of the Effect on Microvascular and Neuropathic Outcomes

Herman's systematic review in Clinical Evidence looked at the effect of intensive glucose control on cardiovascular outcomes, microvascular and neuropathic outcomes, and adverse effects of intensive glucose control. Two Meta-analyses and three subsequent RCTs were included in Herman's systematic review that looked at the effect of intensive glucose control on **microvascular and neuropathic outcomes**. Wang found 16 small RCTs that included people with type 1 diabetes. Follow-up ranged from 8-60 months. Intensive glucose control was associated with a decrease in progression of retinopathy (OR 0.49: 95% CI 0.28, 0.85) and development or progression of nephropathy (OR 0.34; 95% CI 0.20, 0.58). The Lawson Meta-analysis, described in the cardiovascular section, found a positive decrease in microvascular events associated with intensive therapy (OR 0.55; 95%CI 0.35, 0.88). UKPDS 33 included 951 newly diagnosed patients with type 2 diabetes (mean age 54, age 48-60). Participants were randomized to conventional therapy (diet) or intensive therapy (insulin or sulphonylurea) and followed for 10 years. Intensive therapy was associated with a decrease in progression of retinopathy (NNT 10), and development of neuropathy (NNT 5). The DCCT randomized 1441 people with type 1 diabetes, age 13-39, to intensive therapy (external insulin pump or ≥3 injections/day) or conventional therapy (1-2 insulin injections/day). Participants were followed for 6.5 years. Intensive control was associated with a decrease in development of retinopathy (NNT 6), progression of retinopathy (NNT 5), progression or development of nephropathy (NNT 7), and development or progression of neuropathy (NNT 13). Ohkubo compared conventional insulin therapy to intensive insulin therapy in people with type 2 diabetes. Participants were followed for 6 years (n=110). Intensive therapy was associated with a decrease in progression of retinopathy (NNT 4) and a decrease in progression or development of nephropathy (NNT 5).

Intensive glucose control appears to reduce the development and progression of microvascular and neuropathic complications.

o   Methodology: **
o   Reference: CMI Guidelines Published: 5/2002, Review/Revised: 2/2004

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

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.
    - One systematic review in Clinical Evidence included two RCTs that compared varying target blood pressures. UKPDS 38 included patients with type 2 diabetes and hypertension, with and without microalbuminuria. 758 patients were randomized to tight control (=150/≤85 mmHg) and 390 patients to less tight control (=180/≤105 mmHg). Follow-up was 8.4 years. Tight control was associated with fewer MIs (NNT 14; 95%CI 9, 35) and strokes (NNT 27; 95%CI 18, 116). The HOT trial focused on lowering diastolic blood pressure in patients with hypertension. 1503 patients with type 1 or type 2 diabetes were included and followed for 3.8 years. The target for tight control was ≤80 mmHg and the less tight control was ≤90 mmHg. Tight control was associated with fewer MIs, stroke, and other CV death (NNT 22; 95%CI 16, 57).
    - Methodology: Good Evidence (Grade B: Possibly Useful)
    - 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). 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 (Grade B: Possibly Useful)
    - 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).

Erythropoetin
Evidence review in development

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

V. Detailed Documentation

Guideline Web *Draft* Publication Date: July 24, 2006

Background/Process of Guideline Development

Project History

- In January 2005, William Ahuna MD, Continuing Medical Education, and Grant Okawa MD, representing the Kaiser Permanente (KP) Evidence-based Working Group, invited Kaiser Hawaii staff to propose evidence-based clinical improvement projects for KP Hawaii with the understanding that a guideline team would develop clinical recommendations and other tools for the use of appropriate target audiences. The process was to incorporate an evidence-based approach to quality improvement. The approach included identifying questions to be answered by the medical literature, a literature search, critical appraisal of the medical literature, evidence synthesis, development of an algorithm, clinical recommendations and a 1 page document containing key guideline points.
- Brian Lee MD, Dept of Nephrology, Kaiser Permanente Hawaii, proposed Chronic Kidney Disease (CKD) as a work project and volunteered to act as guideline "owner", with responsibility being co-shared with co-owner, Karen Ching, MD.
- Staff from KP Hawaii Nephrology, Renal Nutrition, Primary Care, Pharmacy, The EBM Working Group, and The Kaiser Permanente Care Management Institute (CMI) were recruited as guideline team members.
- The project was facilitated by Michael Stuart MD and Sheri Ann Strite, who compose Delfini Group, LLC.

Relevant studies were distributed to team members for critical appraisal and evidence grading. Dyads of team members reviewed the selected studies with an experienced literature reviewer participating in each dyad. Each group summarized their work in Delfini templates and presented/discussed their reviews at an in-person team meeting in October 26, 2005. The following evidence synthesis and clinical recommendations were created by the team members. Evidence statements and recommendations are "tagged" by evidence-grades developed by Delfini Group.

Guideline Team Members	
Team Member	**Role**
Ahuna, Bill MD	CME Director & Sponsor
Camara, Lisa, MD	Primary Care Champion – Family Medicine
Ching, Karen, MD	Guideline Co-owner & Nephrology
Chiu, Charles PharmD	Pharmacy
Galbraith, Geoff MD	Leadership
Gilbert, Joyce	EBM Working Group
Gonsalves, Johannah	CME
Hong, Steven MD	EBM Working Group
Lee, Brian MD	Guideline Co-owner & Nephrology
Mukaida, Carrie RD	Renal Nutritionist
Okawa, Grant MD	EBM Working Group
Patel, Samir MD	CMI and Family Medicine
Strite, Sheri	Delfini advisor/facilitator
Stuart, Mike MD	Delfini advisor/facilitator

Guideline meetings were conducted by teleconference along with two in-person meetings in Honolulu. The in-person meetings also included educational session covering searching, critical appraisal, evidence grading, evidence synthesis and other clinical guideline issues.

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

Guideline products included:
o   Evidence summary critiques for each study reviewed
o   Evidence synthesis statement
o   Clinical recommendations
o   Guideline recommendations and notes
o   1 pager of key points
o   Documentation of the process
o   References

Review of the Medical Evidence
Questions were posed to the medical literature and the literature was critically appraised, graded and summarized as detailed below. In order to avoid confusion with CMI's evidence labeling, the team created unique statements to tag recommendations with strength of the evidence statements.

Criteria for Study/Evidence Inclusion
For efficacy, effectiveness and adverse events we included valid and useful systematic reviews and meta-analyses, and randomized controlled trials dealing with clinically meaningful health and health care outcomes.

We excluded observational studies dealing with therapy, prevention or screening, editorials, opinion pieces, narrative reviews, animal studies, studies with clinically non-useful outcomes, open-label studies, subgroup analyses, non-relevant studies (e.g., intermediate markers not causally proven to affect meaningful patient outcomes in the areas of quality of life, mortality, morbidity, functioning, symptom relief).

The guideline team made a decision to rely upon evidence from the following guidelines and other sources without critically appraising the original sources for validity --

-K/DOQI Guideline—Search dates through July 2002, references added by experts after 2002. References included are through 2003.
-CMI guidelines
-Cochrane Collaboration
-Clinical Evidence
-DARE

Search Strategy and Results for Dare, Cochrane, and Clinical Evidence
Search terms: "Chronic kidney disease"
  ▪   DARE: Search date: 5/17/05. Search terms: Chronic kidney disease
  ▪   24 hits—saved 10 after excluding non-relevant reviews
  ▪   Cochrane Systematic Reviews: Search date: 5/20/05 Search terms: Chronic kidney disease
      o   187 hits—saved 6 after excluding non-relevant reviews
  ▪   Cochrane Central Register of Controlled Trials. Search date May 30, 2005: Search terms: Chronic Kidney Disease.
      o   58 hits
      o   No additional studies were added from Cochrane Central Register
  ▪   Clinical Evidence: Search date: 5/17/05: Search terms: Chronic Kidney Disease—6 relevant hits reviewing hypertension primary prevention, diabetes nephropathy, prevention secondary complications in CKD, prevention acute renal failure in high risk patients.

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

Search Strategy and Results for PubMed Chronic kidney disease RCT
- Search date: May 20, 2005
- Search terms: prevention chronic kidney disease-- from 2003 through 5/20/2005
- PubMed Translation: (chronic[All Fields] AND (("kidney diseases"[TIAB] NOT Medline[SB]) OR "kidney diseases"[MeSH Terms] OR kidney disease[Text Word]) AND ("prevention and control"[Subheading] OR prevention[Text Word])) AND Randomized Controlled Trial[ptyp]
- Yield: 1398 hits; the team reviewed only citations 2004-2005 since 2003 studies were reviewed by K/DOQI.
- 74 relevant studies were selected for futher review

Search Strategy and Results for PubMed ACEI RCT
- Search date: 5/30/05
- Search terms: angiotensin converting enzyme inhibitor with RCT limit; PubMed
- Yield: 204 hits: selected BP and kidney titles PubMed Translation: (("angiotensin-converting enzyme inhibitors"[TIAB] NOT Medline[SB]) OR "angiotensin-converting enzyme inhibitors"[MeSH Terms] OR "angiotensin-converting enzyme inhibitors"[Pharmacological Action] OR angiotensin converting enzyme inhibitor[Text Word]) AND Randomized Controlled Trial[ptyp]
- 20 relevant studies were selected for further review

Search Strategy and Results for PubMed ARB RCT
- Search date: 5/31/05
- Search terms: angiotensin receptor blocker WITH RCT limit; PubMed
- PubMed Translation: (("angiotensin receptors"[Text Word] OR "receptors, angiotensin"[MeSH Terms] OR angiotensin receptor[Text Word]) AND blocker[All Fields]) AND Randomized Controlled Trial[ptyp]
- Yield: 119 hits: selected BP and kidney titles back to Jan 2004. Only one additional citation found and selected for further review

Search Strategy and Results for PubMed Systematic Reviews Using Clinical Queries
- Search Date: May 18, 2005
- Search Engine Used: PubMed Clinical Queries→Systematic Reviews
- Search terms: chronic kidney disease prevention
- PubMed Translation: (Chronic[All Fields] AND (("kidney diseases"[TIAB] NOT Medline[SB]) OR "kidney diseases"[MeSH Terms] OR kidney disease[Text Word]) AND ("prevention and control"[Subheading] OR prevention[Text Word])) AND systematic[sb]
- Yield: 97 hits--39 relevant hits published after 2003 (most recent references fromKDOQI) were selected for further review

Search Strategy and Results for PubMed Meta-Analysis
- Search date: 5/17/05
- Search terms: chronic renal disease prevention AND limit "meta-analysis"
- PubMed Translation: (chronic[All Fields] AND (("kidney diseases"[TIAB] NOT Medline[SB]) OR "kidney diseases"[MeSH Terms]
- OR kidney disease[Text Word])
- AND ("prevention and control"[Subheading] OR prevention[Text Word])) AND Meta-Analysis[ptyp]
- Yield: 16 hits all included in other searches

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

Evidence Grading

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

● **Grade A:** **Useful**	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.)
	
	• 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
	
	    o For therapy, screening, prevention and diagnostic studies: RCTs. In some cases a single, large well-designed and conducted RCT may be sufficient.
	
	    o For natural history and prognosis: Cohort studies

⊙ **Grade B:** **Possibly Useful**	The evidence is potentially strong and might be sufficient to use in making health care decisions. 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. • 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.)
○ **Grade UV:** **Uncertain Validity** ○ **Grade UU:** **Uncertain Usefulness** ○ **Grade UVU:** **Uncertain Validity and Usefulness** ○ **Grade UA:** **Uncertainty of Author**	There is sufficient uncertainty so that caution is urged regarding its use in making health care decisions. • 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 conflicting results. • 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.

Kaiser Permanente Hawaii Evidence-based Clinical Guideline for Management of Patients with Chronic Kidney Disease in Primary Care DRAFT

Temporary Web Version from the CKD Guideline Group

July 24, 2006

Evidence Synthesis and Clinical Recommendations

Relevant studies were distributed to team members for critical appraisal and evidence grading. Dyads of team members reviewed the selected studies with an experienced literature reviewer participating in each dyad. Each group summarized their work in Delfini templates and presented their reviews at an in-person team meeting in October 26, 2005.

Guideline Specific Products Developed for Meeting	Team Process	Actions/Assignments
Draft Evidence Synthesis (Delfini)	Reviewed draft evidence statements, in conjunction with Clinical Evidence and Cochrane, and edited as needed.	o Made at meeting o Emailed edited draft including assignments to each team member after the meeting for approval.
Primary Studies: Included and Excluded Studies Summary Tables (Team)	Reviewed included studies and discussed. Voted on grades for validity and usability.	
Numbered Listing of K/DOQI Guidelines Statements Voted on by Team Members (Team)	Reviewed, in conjunction with Draft Clinical Recommendations, to modify the Draft Clinical Recommendations. Review was conducted item by item by all team members, toggling back to Draft Clinical Recommendations.	Edited statements emailed to team members after the meeting for approval.
Draft Clinical Recommendations (Delfini)	See above	Edited statements emailed to team members after the meeting for approval.
Draft Evidence and Recommendations Tagging Statements (Delfini)	Reviewed. Made suggestions. Discussed translation between tags. Team decided to make tags more consistent with CMI language	Edited statements emailed to team members after the meeting for approval.
Draft Algorithm (Delfini, Brian Lee)	Reviewed by team. Agreed to produce algorithm	Draft algorithm produced

Team members created an evidence synthesis from the trusted sources and literature review. Clinical recommendations were created from the evidence synthesis, with consensus being substituted for evidence when the evidence grade was U (uncertain validity and/or usefulness) or when a clinical recommendation was made without critical appraisal of the medical literature.