MANAGEMENT OF CHRONIC KIDNEY DISEASE IN SECONDARY LEVEL

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Chronic kidney disease

Prevalence of CKD is increasing

with big morbidity & mortality,progress to ESRD

only 10% of ESRD can afford to proceed RRT

Prevention of ESRD is important at secondary level

Approach

- Stopping & delaying the progression
- Treating the complications
- Timely referral to tertiary level(Nephrology service)

Defining the progression

Decline in eGFR more than 5ml/min in 1 yr (or)

more than 10 ml/min in 5 yr

(in absence of other cause of a/c deterioration)

Early and Effective Treatment Of Cause

1.Glomerular Disease=appropriate &adequate treatment
2.DM=tight glycemic control
3.HT
4.Obstruction(stone)
5.Hyperuricaemia
6.UTI
7.Nephrotoxics

REMOVING THE AGGRAVATING FACTORS

1. Fluid & Electrolyte imbalance
   (a) dehydration a/w/a over hydration
   (b) sodium deficit
   (c) hypokalaemia

2. Haemodynamic disturbance
   (a) Congestive heart failure
   (b) Hypotension
   (c) Shock

3. Hypertension especially malignant
4. Urinary tract infection
5. Urinary tract obstruction

6. Metabolic disorders

(a) Hypercalcaemia

(b) Hyperphosphataemia

(c) Hyperuricaemia

(d) Hyperoxaluria

7. Nephrotoxins

(a) Aminoglycosides

(b) Tetracycline

(c) N.S.A.I.D

(d) Radio contrast material

(e) Some indigenous medicines

(f) Natural products??

BP control

slow the rate of progression

independently of the agents

target BP <140/90 =DM,Non DM(-)proteinuria

<130/80 =DM,Non DM(+)proteinuria

RAS Blockage

ACEI /ARB

reduce intraglomerular pr…….>longterm benefit

GFR correlated to intraglomerular pr

initial small rise of creatinine(up to 20-30%)

monitoring is mandatory

avoid in advanced RF

bilateral RAS

RAS in solitary kidney

Dual RAAS Therapy

generally not recommanded

no significant benefit on overall mortality

additive antiproteinuric effect(+)

ONTARGET…increase hyperK &risk of worsening RF

need tertiary level consultation

Spironolactone

antiproteinuric

together with ACEI/ARB ‘aldosterone escape’

monitor- hyperK

Diabetic Control

- strict glycemic control(HBA1c<7%)

-dose adjustment of OHA as CKD progression to prevent hypo

-ACEI/ARB =DM+HT

-ACEI/ARB=DM+normotensive+microalbuminuria

-No evidence in normotensive,no microalbuminuric DM pt

Dyslipidemia

- ✓ statin prevent CKD progression
- ✓ antiproteinuric effect
- ✓ lipid lowering effect
- ✓ antiinflammatory

SHARP
STUDY OF HEART AND RENAL PROTECTION

Study of Heart and Renal Protection (SHARP): Randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease

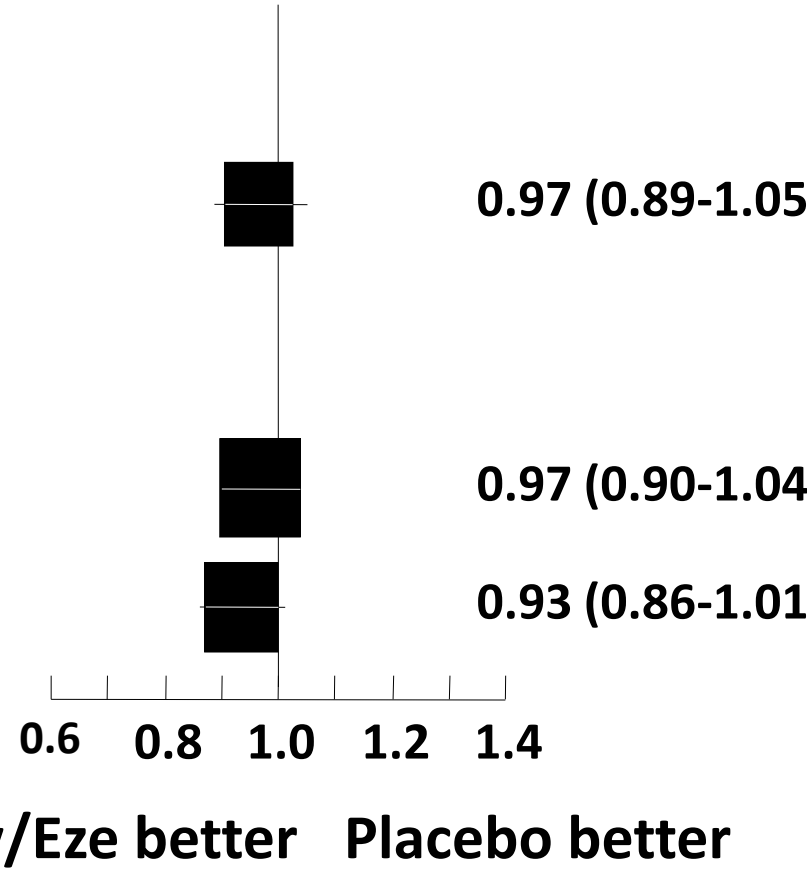
SHARP Collaborative Group

- Randomized, double-blind, placebo-controlled multicenter trial
- Men or women aged at least 40 years without known CHD (prior MI or coronary revascularization) who had CKD (creatinine ≥1.7 mg/dL in men or ≥1.5 mg/dL in women)

Am Heart J 2010; 160(5): 785-794

SHARP: Renal outcomes

Event	Simv/Ezetimibe (n=3117)	vs	Placebo (n=3130)	Risk ratio & 95% CI
Main renal outcome				
ESRD	1057 (33.9%)		1084 (34.6%)	0.97 (0.89-1.05
Tertiary renal outcomes				
ESRD or death	1477 (47.4%)		1513 (48.3%)	0.97 (0.90-1.04
ESRD or 2 x creatinine	1190 (38.2%)		1257 (40.2%)	0.93 (0.86-1.01



Statin/Lipid Treatment in Patients with CKD

CKD Patient Population	Treatment
Age ≥ 50 years with eGFR < 60 ml/min/1.73 m2	Statin or statin +ezetimibe
Age ≥ 50 years with eGFR ≥ 60 ml/min/1.73 m2	Statin
Age 18-49 with eGFR ≥ 60 ml/min/1.73 m2 (G1-G2) and either: known coronary disease (myocardial infarction or coronary revascularization), diabetes mellitus, prior ischemic stroke, or estimated 10-year incidence of coronary death or non-fatal myocardial infarction > 10%	Statin
Hypertriglyceridemia	Therapeutic lifestyle changes

NEPHROTOXIC MEDICATIONS

- a/c or chronic renal deterioration d/o severity
- affect any part of kidney
- reversible if detected & treated early

Nephrotoxins

1. Aminoglycosides
2. NSCID
3. Tetracycline
4. Radiocontrast iodine
5. Some indigenous medicines
6. Some natural products

Key Risk Factors Predisposing Patients to Drug-Induced Nephrotoxicity

- Age greater than 60 years
- Diabetes mellitus
- Drug-drug interactions resulting in synergistic nephrotoxic effects
- Exposure to multiple or high doses of nephrotoxins
- Heart failure
- History of kidney transplant
- Multiple myeloma
- Sepsis
- Underlying kidney dysfunction (e.g., eGFR < 60 mL/min, renal artery stenosis)
- Vascular disease
- Volume depletion

General Strategies to Prevent Drug-Induced Nephrotoxicity

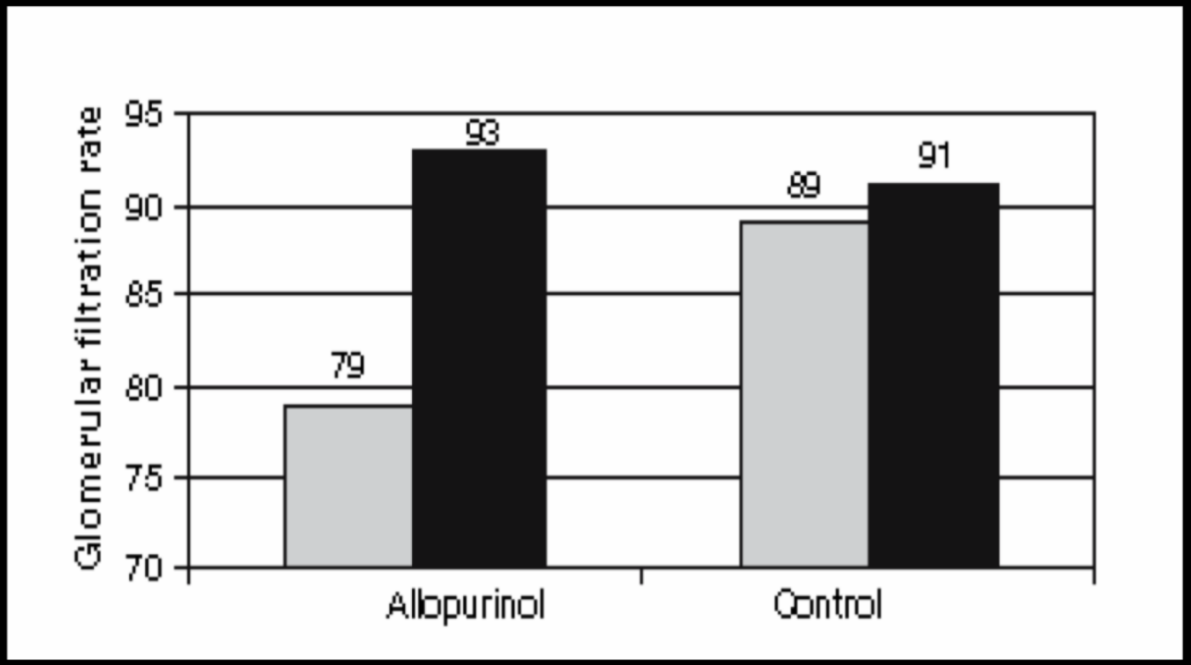
-Assess baseline renal function prior to initiating potentially nephrotoxic drugs
-Adjust medication dosages based on renal function as needed
-Avoid nephrotoxic drug combinations
-Use non-nephrotoxic alternatives whenever possible
-Correct risk factors for nephrotoxicity before initiating drug therapy whenever possible
-Ensure adequate hydration before and during therapy with potential nephrotoxic drugs
-Limit dose and duration of therapy when possible

Hyperuricemia / Allopurinol

- Mechanisms = hypertension with RAAS activation, renal afferent arteriolopathy, increased glomerular hypertension, and fibrosis.

- Allopurinol could be protective by reducing not only serum uric acid but also, oxidative stress by inhibition of xanthine oxidase. A

Allopurinol Increases Glomerular Filtration Rate



and helps preserve kidney function during 12 months of therapy compared with controls

Kanbay , Covic, Int Urol Nephrol, 2007

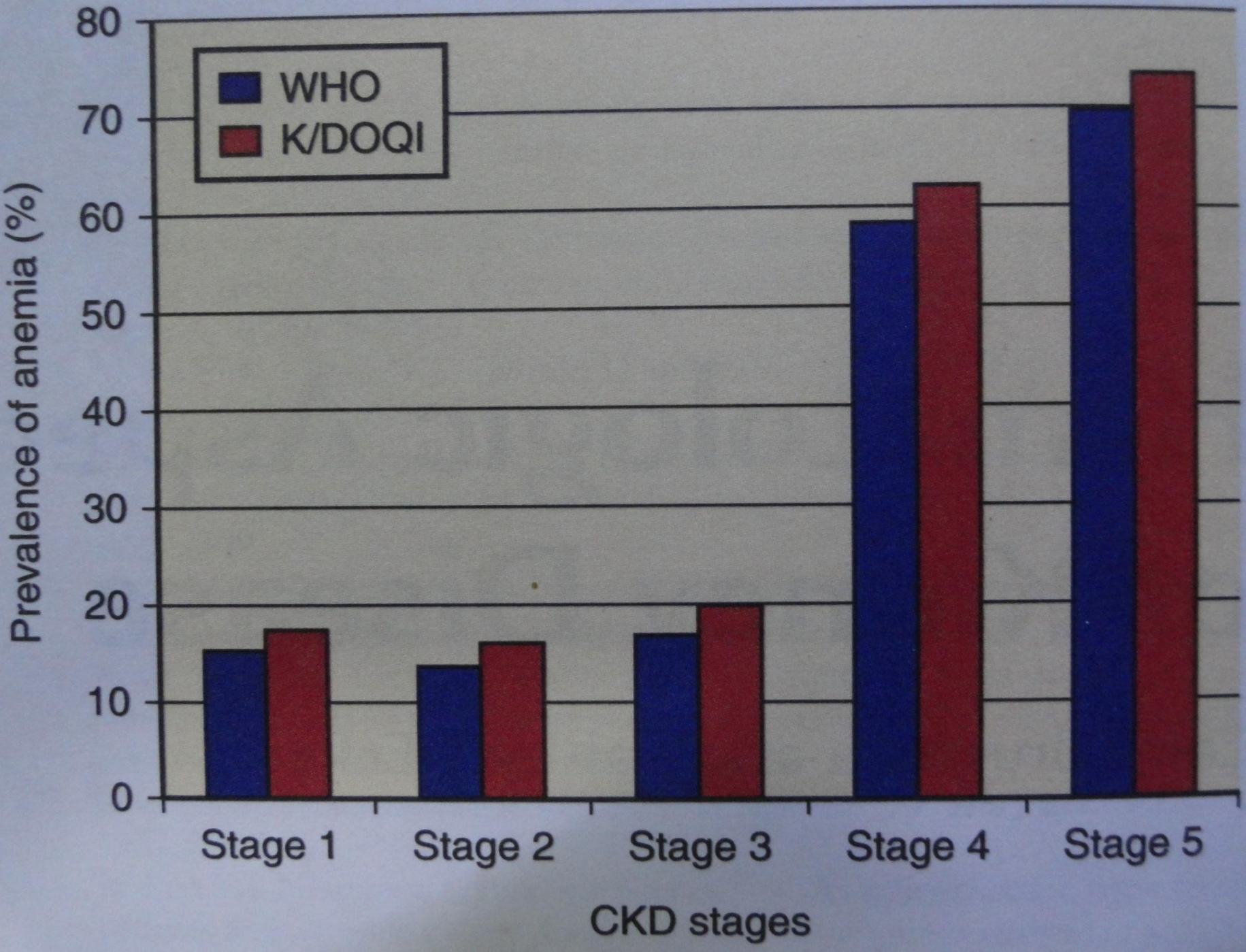
Treating The Complications Of CKD

ANAEMIA

Common complication

More frequent as renal function declines

Independently associated with morbidity &mortality


80
70
60
50
40
30
20
10
0
WHO
K/DOQI
Prevalence of anemia (%)
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
CKD stages

Causes of Anaemia in CKD are multi-factorial

1. Relative EPO deficiency(major cause)
2. Fe deficiency
3. Blood loss
4. Significant reduction in circulating RBC lifespan secondary to uraemia
5. Haemolysis
6. Chronic inflammation
7. Other substrate deficiencies(B12 and folic acid)
8. Bone marrow suppression

Diagnosis of anemia

1.2.1: Adults and children >15 years with CKD

- when the Hb concentration is <13.0 g/dl in males and
- <12.0 g/dl in females. (Not Graded)

Investigation of anemia

1.3: In pats with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of anemia (Not Graded):

- CBC which should include Hb concentration, RBC indices, WBC, and platelet count
- Absolute reticulocyte count
- Serum ferritin level
- Serum transferrin saturation (TSAT)
- Serum vitamin B12 and folate levels

KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease:*Kidney International Supplements :VOL 2 | ISSUE 4 | AUGUST (2) 2012*

Diagnosis and evaluation of anemia in CKD

TESTING FOR ANEMIA: ***Frequency of testing for anemia***

1.1.1: For CKD patients without anemia measure Hb when clinically indicated and (Not Graded):

- at least annually in patients with CKD 3
- at least twice per year in patients with CKD 4–5ND
- at least every 3 months in patients with CKD 5HD and CKD 5PD

1.1.2: For CKD patients with anemia not being treated with an ESA, measure Hb when clinically indicated and (Not Graded):

- at least every 3 months in patients with CKD 3–5ND and CKD 5PD
- at least monthly in patients with CKD 5HD

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TREATMENT WITH IRON AGENTS

- ✓ For adult CKD patients with anaemia NOT on iron or ESA therapy we suggest a trial of IV iron (or in CKD ND patients alternatively a 1-3 month trial of oral iron therapy)if (2C):

- ✓ an increase in HB concentration without starting ESA treatment is desired AND

- ✓ TSAT=<30% AND
- ✓ Ferritin=<500ng/ml

TSAT(Transferrin Saturation)=Iron/TIBC X 100

CAUTIONS REGARDING IRON THERAPY

- .When the initial dose of IV iron dextran or non dextran is administered,we recommend that patient be monitored for 60 minutes after the infusion(2C)

- Resuscitative facilities(including medications) and personnel trained to evaluate and treat serious adverse reactions be available.(2C)

CAUTIONS REGARDING IRON THERAPY

- ✓ The symptoms of most concern are hypotention and dyspnoea,which may be catastrophic with features of anaphylaxis

- ✓ The rate of such reaction is estimated to occur in 0.6 to 0.7%

IV iron during infection

- ✓ Avoid administering IV iron to patients with active systemic infection (Not Graded)

Use of ESAs to treat anemia in CKD

ESA INITIATION

3.1: Address all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy. (Not Graded)

3.2: In initiating and maintaining ESA therapy, recommend balancing

Potential benefits	Against	Potential Risks
▪ reducing blood transfusions & ▪ anemia-related symptoms		▪ stroke, ▪ vascular access loss, ▪ hypertension (1B)

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Use of ESAs to treat anemia in CKD: ESA INITIATION

3.3: We recommend using ESA therapy with great caution, if at all, in:

1) active malignancy—in particular when cure is the anticipated outcome (1B),
2) a history of stroke (1B), or
3) a history of malignancy (2C).

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Use of ESAs to treat anemia in CKD: ESA INITIATION

3.4.1: For adult CKD ND patients with Hb ≥10 g/dl,

- suggest that ESA therapy not be initiated. (2D)

3.4.2: For adult CKD ND patients with Hb <10 g/dl,

- the decision whether to initiate ESA therapy be individualized based on
  - the rate of fall of Hb concentration,
  - prior response to iron therapy,
  - the risk of needing a transfusion,
  - the risks related to ESA therapy and
  - the presence of symptoms attributable to anemia. (2C)

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ESA MAINTENANCE THERAPY

3.5.1: In general, ESAs not be used to maintain Hb > 11.5 g/dl in adult patients with CKD. (2C)

3.5.2: Some patients may have improvements in quality of life at Hb above 11.5 g/dl and will be prepared to accept the risks.
(Not Graded)

3.6: In adult, we recommend that not be used to intentionally increase the Hb >13 g/dl. (1A)

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ESA DOSING

- Epoetin alfa/beta =20-50 IU/Kg 3x/wk
- Darbepoetin alfa =0.45mg/kg 1x/wk by sc or iv
  =0.75mg/Kg 1x/2 wk by sc
- CERA =0.6mg/kg 1x/2wk by sc or iv CKD ND&CKD 5D or
  =1.2 mg/kg 1x/4 wk by sc

Red cell transfusion to treat anemia in CKD

USE OF RED CELL TRANSFUSION IN CHRONIC ANEMIA

4.1.1: When managing chronic anemia, we recommend avoiding, when possible, red cell transfusions to minimize the general risks related to their use. (1B)

4.1.2: In patients eligible for organ transplantation, we specifically recommend avoiding, when possible, red cell transfusions to minimize the risk of allosensitization. (1C)

4.1.3: When managing chronic anemia, we suggest that the benefits of red cell transfusions may outweigh the risks in patients in whom (2C):

- ESA therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA resistance)
- The risks of ESA therapy may outweigh its benefits (e.g., previous or current malignancy, previous stroke)

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URGENT TREATMENT OF ANEMIA

4.2: In certain acute clinical situations, we suggest patients are transfused when the benefits of red cell transfusions outweigh the risks; these include (2C):

- When rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage, unstable coronary artery disease)
- When rapid pre-operative Hb correction is required

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ESA +Parenteral IRON Rx

should be done in consultation with Nephrologists

CKD-MB

apparent in late stage(G3b onwards)

treating earlier stage…prevent &slow progression of CKD

…prevent vascular calcifications

Early CKD (G1-G3a)…measure Ca ,Po4 ,ALPo4 ,PTH at least once as base line value

2017 KDIGO Guideline

Chapter 3.1: Diagnosis of CKD-MBD: biochemical abnormalities

3.1.1: We recommend monitoring serum levels of calcium, phosphate, PTH, and alkaline phosphatase activity beginning in CKD G3a (1C).

Reasonable monitoring intervals would be:

In CKD G3a–G3b: for serum calcium and phosphate, every 6–12 months; and for PTH, based on baseline level and CKD progression.

In CKD G4: for serum calcium and phosphate, every 3–6 months; and for PTH, every 6–12 months.

.

In CKD G5, including G5D: for serum calcium and phosphate, every 1–3 months; and for PTH, every 3–6months.

In CKD G4–G5D: for alkaline phosphatase activity, every 12 months, or more frequently in the presence of elevated PTH

4.1.2: In patients with CKD G3a–G5D,

we suggest lowering elevated phosphate levels toward the normal range (2C).

4.1.3: In adult patients with CKD G3a–G5D,

we suggest avoiding hypercalcemia(2C).

4.1.8: In patients with CKD G3a–G5D, we suggest limiting dietary phosphate intake in the treatment of hyperphosphatemia alone or in combination with other treatments (2D). It is reasonable to consider phosphate source (e.g., animal, vegetable, additives) in making dietary recommendations (NG).

PO4 binders

(1) -Ca based PO4 binder

not used if- hyperCa,

-ABD

-calciphylaxis

-vascular calcifications

(2) -Ca free PO4 binder(Sevelamer,Lanthanum)

-reduce vascular calcifications

- antiinflamation

- improve lipid profile

(3) -Al based PO4 binder

Chapter 4.2: Treatment of abnormal PTH levels in CKD-MBD

4.2.1: In patients with CKD G3a–G5 not on dialysis, the optimal PTH level is not known. However, we suggest that

patients with levels of intact PTH progressively rising or persistently above the upper normal limit for the assay be evaluated for modifiable factors, including hyperphosphatemia, hypocalcemia, high phosphate intake, and vitamin D deficiency (2C).

4.2.2: In adult patients with CKD G3a–G5 not on dialysis, we suggest that calcitriol and vitamin D analogs not be routinely used (2C). It is reasonable to reserve the use of calcitriol and vitamin D analogs for patients with CKDG4–G5 with severe and progressive hyperparathyroidism(NG).

-Treatment of high PTH level

-Active Vit D …calcitriol,alfacalcidol

-New Vit D r/c agonist….paricalcitol,doxercalciferol,

-Calcimimetics….Cinacalcets

-Parathyroidectomy

-PTH dependent hyperCa refractory to med M

Management of CKD-MBD

s/b done in consultation with Nephrologist

FLUID

- A high fluid intake has been postulated to
- lower CKD incidence by increasing solute clearance
- and preventing kidney stones, whereas a lower fluid
- intake may increase metabolic demand in the kidney
- from urinary concentration. Clark et al. (18) had previously
- shown that drinking larger volumes of fluid
- (24-hour urine volumes .3 L/d) was associated with
- a reduced incidence of CKD

- **Fluid intake did not seem to influence GFR in a large Australian cohort.**

VOLUME OVERLOAD

- **Excessive volume overload may be a risk factor for CKD progression independent of hypertension, diabetes, and CVD, because it can lead to vascular remodeling and inflammation.**
- **A Taiwanese cohort study of stages 4 and 5 CKD showed that those with volume overload measured by baseline bioimpedance spectroscopy had an increased risk for RRT and rapid progression.**
- **Tsai et al. felt that fluid overload was more important than diabetes in CKD progression in a separate analysis.**

Tsai *et al*: Is fluid overload more important than diabetes in renal progression in late chronic kidney disease? PLoS One 8: e82566, 2013 PubMed

Metabolic Acidosis

common in CKD stage 4 -5

Associated with

(a) muscle wasting &malnutrition

(b)hyperK as body shifts H intracellularly in exchange with K

(c)Renal bone d/s as body utilize the bone as a source of buffer

(d)Breathlessness d/t compensatory respiratory alkalosis

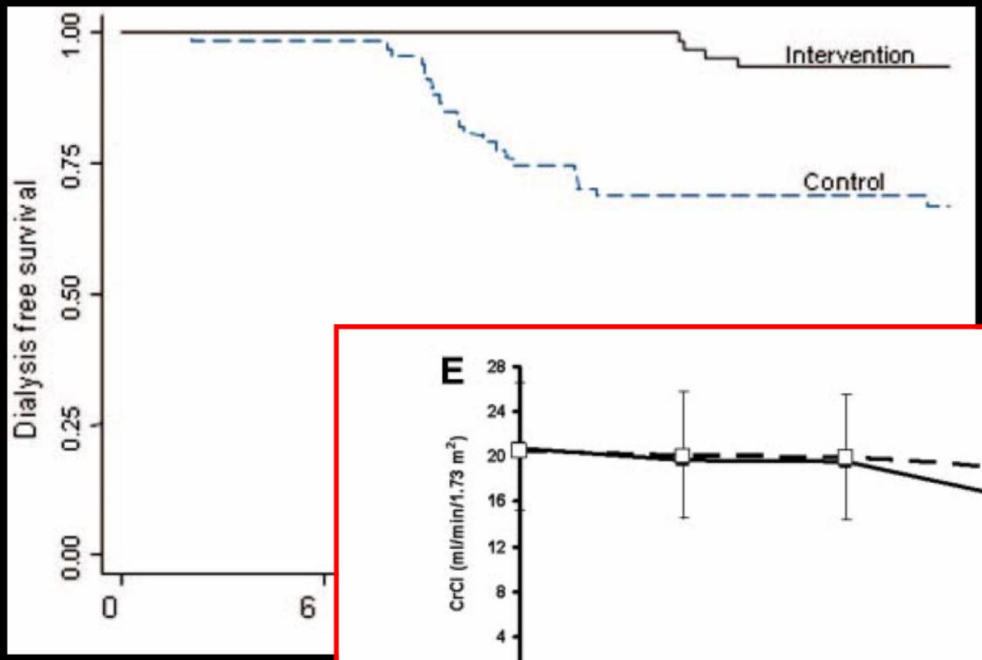
(e)Impair LV function

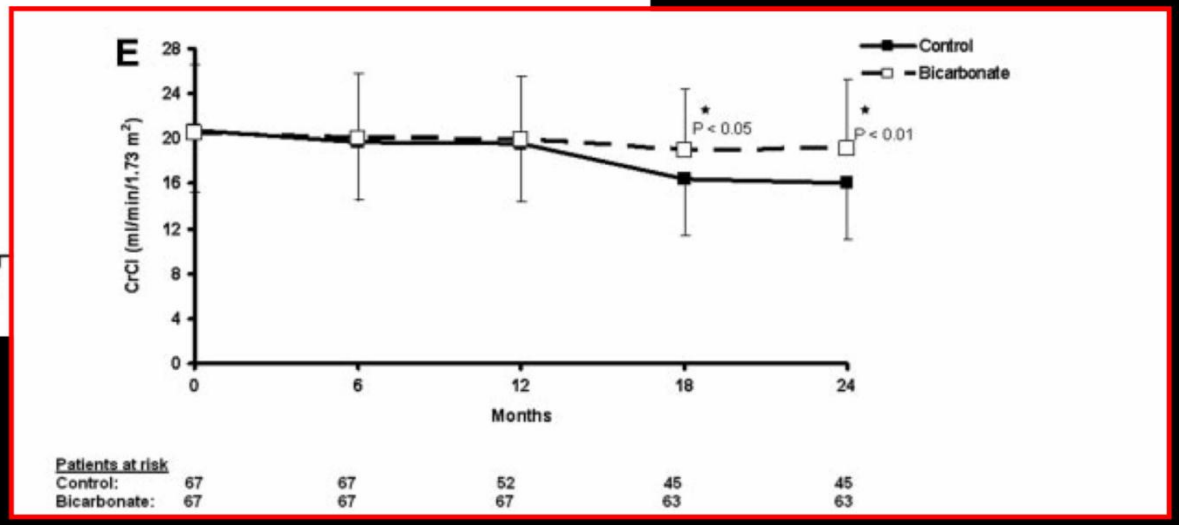
KDIGO Guideline

3.4.1:suggest that people with CKD and serum HCO_3 concentration<22 mmol/l treatment with oral HCO_3 supplementation be given to maintain serum HCO_3 within the normal range ,unless contraindicated(2B)

BICARBONATE

Bicarbonate Supplementation Slows Progression of CKD





Ione de Brito-Ashurst, JASN 2009

PROTEIN

-Higher protein intake increase glomerular hyperfiltration & may eventually lead to incident CKD.

-A pilot study using a low protein diet supplemented with a keto analog of EAA showed some initial promise in slowing eGFR loss in those with rapidly progress stage 3,stage 4 or non dialysis stage 5 CKD & those with refractory proteinuria.

Indications for Referral of Patients with CKD to a Nephrologist

-Patients with CKD of uncertain cause/etiology (e.g., need for renal biopsy)
-Persistent or severe albuminuria (e.g., category A3)
-Persistent hematuria (i.e. RBC > 20 per HPF or urinary red cell casts)
-Rapid decline in GFR or new AKI
-Refer all patients with stage G4 or G5 CKD to initiate discussion of potential renal replacement therapy
-Consider referral at earlier stages to assist with management of CKD complications:

- Refractory hypertension (e.g., 4 or more antihypertensive medications)
- Persistent hyperkalemia
- Anemia
- Mineral bone disease
- Fluid overload and/or malnutrition

THANK YOU