Module 2: Clinical Practice Guidelines for Complications of Chronic Kidney Disease

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The current version is shown below. Please note that this is a DRAFT.

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Summary of guidelines

SECTION 1: CARDIOVASCULAR DISEASE (CVD)

GUIDELINE C-CVD 1.1: Cardiovascular risk factors

With respect to patients with Chronic Kidney Disease Stage 3 - 5 and Dialysis Patients, a record a history of and risk factors for cardiovascular disease should be recorded in a format that permits audit of the management of such patients. These should include:-

- Angina and myocardial infarction
- Previous coronary angioplasty or coronary artery bypass grafting
- Stroke and transient ischaemic attack
- Previous carotid artery surgery or angioplasty
- Peripheral vascular disease or previous intervention
- Cardiac failure

GUIDELINE C-CVD 1.2: Smoking and exercise

With respect to all Chronic Kidney Disease and Dialysis Patients, healthy lifestyle changes should be encouraged (Good practice). Smoking habits should be recorded and smoking should be actively discouraged in all patients with a reasonable life expectancy and strongly discouraged in those patients on the transplant waiting list (Evidence). Exercise should be encouraged and patients, including dialysis patients, should be enrolled on regular exercise programmes, exercising 3 to 5 times weekly either during dialysis or between dialysis sessions (Evidence).

GUIDELINE C-CVD 1.3: HBA1C

In all Chronic Kidney Disease and Dialysis Patients glycated haemoglobin (HbA1c) should be below 7% in diabetics with all stages of CKD, including CKD stage 5 patients who are on dialysis, and HbA1c should be measured using an assay method which has been harmonized to the Diabetes Control and Complications Trial (DCCT)[1] standard (Evidence in CKD 1 and 2, Good Practice in dialysis patients)

GUIDELINEC-CVD 1.4: Hypercholesterolaemia

All Chronic Kidney Disease and Dialysis Patients
3 hydroxy-3 methylglutaryl-Co-enzyme A reductase inhibitors (statins) should be considered for primary prevention in all CKD patients with a 10-year risk of coronary disease, calculated as 30% according to the Joint British Societies' chart or the coronary risk calculator, ignoring the fact that these calculations may not be accurate in patients with renal disease. A total cholesterol of <5 mmol/l or a 30% reduction from baseline, or a fasting low density lipoprotein (LDL)-cholesterol of <3 mmol/l, should be achieved, whichever is the greatest reduction in all patients (Evidence in CKD 1-3, Good Practice in CKD 4-5 and

dialysis patients). Statins should not be withdrawn from patients in whom they were previously indicated and should continue to be prescribed when such patients start renal replacement therapy (RRT) or change modality. (Good Practice).

GUIDELINE C-CVD 1.5: Hyperhomocysteinaemia and folate supplementation

In all Chronic Kidney Disease and Dialysis Patients,serum or red cell folate should be above the lower limit of the reference range in all CKD patients including those on dialysis. **(Good practice)**

GUIDELINE C-CVD 1.6: Secondary prevention of cardiovascular risk

In all chronic kidney disease and dialysis patients, all CKD patients (including those on dialysis and after transplantation) with a history of myocardial infarction, stroke, peripheral vascular disease, acute coronary syndrome, or who undergo surgical or angiographic coronary revascularisation should be treated with aspirin, an ACE inhibitor, a beta-blocker, and an HMG–CoA reductase inhibitor unless contraindicated. The doses of ACE inhibitors and beta-blockers should be the maximum tolerated (Evidence) In patients in whom lipid-lowering drug treatment is used, total cholesterol should be reduced by 30% or to below 5 mmol/l, or LDL-cholesterol to below 3 mmol/l, whichever reduction is the greatest. (Evidence in CKD 1-3, Good Practice in CKD 4-5 and dialysis patients).

GUIDELINE C-CVD 1.7: Cardiac investigations and coronary revascularization

In all chronic kidney disease and dialysis patients, patients should have unimpeded access to a full range of cardiac investigations including exercise and stress echocardiography, radio-isotopic cardiac scans, and coronary angiography. There should also have unimpeded access to cardiology assessment for coronary angioplasty and stenting and cardiac surgery. **(Good practice).**

GUIDELINE C-CVD 1.8: Hypertension in dialysis patients:

Pre and post-dialysis blood pressure (measured after completion of dialysis, including washback) should be recorded and intra-dialytic blood pressure measured to enable management of the haemodialysis session.
Blood pressure in patients on peritoneal dialysis should be <130/80 mmHg (Good Practice).
Hypertension on dialysis should be managed by ultrafiltration in the first instance(Good practice).

GUIDELINE C-CVD 1.9: Hypertension in renal transplant patients

Target blood pressure for renal transplant patients < 130/80 mm Hg (Good practice).

SECTION 2: MINERAL BONE DISEASE (MBD)

GUIDELINE C-MBD 2.1: Serum calcium in patients with Chronic Kidney Disease

Serum calcium should be kept within the normal reference range for the laboratory used in patients with CKD 1 to 4 (Evidence)

GUIDELINE C-MBD 2.2: Serum calcium i n Dialysis Patients

Serum calcium, adjusted for albumin concentration should be maintained within the normal reference range for the laboratory used (measured before a "short gap" dialysis session in HD patients) (Evidence) and ideally kept below 2.5 mmol/L. (Good Practice)

GUIDELINE C-MBD 2.3: Serum phosphate in patients with CKD stages 3 and 4

Serum phosphate in patients with CKD stages 3 and 4should be maintained between 0.9 and 1.5 mmol/L. (Evidence)

GUIDELINE C-MBD 2.4: Serum phosphate in dialysis patients

Serum phosphate in dialysis patients (measured before a "short gap" dialysis session in HD patients) should be maintained between 1.1 and 1.8 mmol/L. (Evidence)

GUIDELINE C-MBD 2.5: Serum calcium x phosphate product

The serum albumin corrected calcium phosphorus product should be kept below 4.8 $mmol^2/L^2$ and ideally below 4.2 $mmol^2/L^2$ in all CKD patients. **(Evidence)**

GUIDELINE C-MBD 2.6: Measurement of Serum Parathyroid Hormone in CKD

In Chronic Kidney Disease patients PTH needs only to be measured routinely in progressive CKD 3, and stages 4 and 5 CKD. PTH should not be routinely measured in stages 1, 2 nor in non-progressive stage 3 CKD unless there is a clinical indication to do so. (Good Practice).

GUIDELINE C-MBD 2.7: Desired outcome range for Serum Parathyroid Hormone in CKD

The target range should increase from the normal range with CKD stages 1-3, to between the top of the normal range and twice normal for stage 4 CKD and to between 2 to 4 times normal in CKD stage 5 not on dialysis. These targets should also apply to transplant patients. **(Good Practice).**

GUIDELINE C-MBD 2.8: Desired outcome range for Serum Parathyroid Hormone in Dialysis Patients

The target range for parathyroid hormone measured using an intact PTH assay should be between 2 and 4 times the upper limit of normal for the intact PTH assay used (**Good Practice**). The same target range should apply when using the whole molecule PTH assay. **(Good Practice).**

GUIDELINE C-MBD 2.9: VITAMIN D in CKD and Dialysis Patients

Chronic Kidney Disease Patients

Serum 25-hydroxyvitamin D should be measured in all patients with an elevated PTH (**Evidence**). A level of less than 75 nmol/L indicates vitamin D insufficiency **(Opinion)**.

GUIDELINE C-MBD 2.10 Serum aluminum levels in stage 4 and 5 CKD

Aluminum toxicity can occur in stage 4 and 5 CKD and in dialysis patients, if clinically suspected serum aluminum levels should be determined (Good Practice). Care needs to be taken to avoid aluminum contamination of the blood sample (Evidence).

GUIDELINE C-MBD 2.11 Serum aluminum levels in patients on aluminium based phosphate binders

Serum aluminium concentration should be measured every three months in all patients receiving oral aluminium phosphate binders (Good Practice)

GUIDELINE C-MBD 2.12 Aluminium toxicity

Serum levels should be less than 20 ug/L (Good Practice). A desferrioxamine test should be performed to support the diagnosis where random serum levels are indeterminate (20 – 60 ug/L). (Evidence). A bone biopsy provides confirmation of aluminium bone disease (Evidence).

SECTION 3: ANAEMIA (HB)

GUIDELINE C-HB 3.1: Evaluation of anaemia - Haemoglobin level

In the opinion of the working group, anaemia should be evaluated in CKD when Hb<13 g/dl in adult males and post- menopausal females and when Hb <12g/dl for pre-menopausal females **(Good Practice).**

GUIDELINE C-HB 3.2: Evaluation of anaemia - Renal function

CKD should be considered as a possible cause of anaemia when the GFR is <60 ml/min/1.73m^2. It is more likely to be the cause if the GFR is <30mls/min/1.73m^2 (<45 in diabetics) and no other cause, i.e. blood loss, folic acid or B12 deficiency, is identified**. (Evidence)**

GUIDELINE C-HB 3.3: Evaluation of anaemia - Erythropoietin hormone measurement.

In the opinion of the working group measurement of erythropoietin levels for the diagnosis or management of anaemia should not routinely be considered for patients with CKD (Good practice).

GUIDELINE C-HB 3.4: Treatment of Anaemia - Erythropoietic Stimulating Agents

Treatment with ESAs should be offered to patients with anaemia of CKD who are likely to benefit in terms of quality of life and physical function, and to avoid transfusion in patients considered suitable for transplantation (Evidence).

GUIDELINE C-HB 3.5: Treatment of Anaemia - Choice of ESA

Choice of ESA will depend on local availability of ESAs and consideration of the patients clinical status. **(Good practice)**

GUIDELINE C-HB 3.6: Treatment of Anaemia – Route of administration

The prescriber should consider that when using short acting ESAs, subcutaneous administration allows the use of lower doses of drugs than intravenous administration**. (Evidence)**

GUIDELINE C-HB 3.7: Target haemoglobin

Patients with CKD should achieve an outcome distribution of haemoglobin of 10.5-12.5 g/dl. **(Evidence).**

GUIDELINE C-HB 3.8: ESA Dose adjustments

Adjustments to ESA doses should be considered when Hb is <11 or >12g.dl.in order that the population distribution has the maximum proportion of patients in the range 10.5-12.5 as is possible **(Evidence).**

GUIDELINE C-HB 3.9: Iron status

Patients should be iron replete to achieve and maintain target Hb whether receiving ESAs or not **(Evidence).**

GUIDELINE C-HB 3.10: Initiation of ESA and iron status

ESA therapy should not be initiated in the presence of absolute iron deficiency (ferritin <100ng/ml) without also managing the iron deficiency[1]. In patients with functional iron deficiency, iron supplements should be given concurrently with initiating ESA therapy **(Evidence).**

GUIDELINE C-HB 3.11: Iron status – Oral vs. Intravenous iron

Oral iron will, in general, be sufficient to attain and maintain the Hb above targets in CKD patients not yet requiring dialysis and in those on peritoneal dialysis (PD); in contrast, most HD patients will require intravenous iron**.** (Evidence)

GUIDELINE C-HB 3.12: Upper limit for iron therapy

For patients treated with iron, ferritin should not exceed 800ng/ml and to achieve this iron management should be reviewed when the ferritin > 500ng/ml **(Evidence).**

GUIDELINE C-HB 3.13: Monitoring during ESA therapy.

In the opinion of the working group Hb concentration should be monitored every 2-4 weeks in the correction phase and every 1-3 months for stable hospital patients[1-3]. More frequent monitoring will depend on clinical circumstances **(Good practice).**

GUIDELINE C-HB 3.14: Monitoring during iron therapy.

In the opinion of the working group regular monitoring of iron status (1-3 monthly) is recommended during treatment to avoid toxicity (Good practice): a serum ferritin consistently greater than 800 µg/l is suggestive of iron overload[1-3]. (Good practice)

GUIDELINE C-HB 3.15: Resistance to ESA therapy.

Failure to reach the target Hb level despite sc epoetin dose >300 IU/kg/week (450 IU/kg/week iv epoetin), or darbepoetin dose >1.5mcg/kg/week defines inadequate response (‘resistance’). Hyporesponsive patients who are iron replete should be screened clinically and by investigations for other common causes. (Evidence)

GUIDELINE C-HB 3.16: Hypertension during ESA therapy.

Blood pressure should be monitored in all patients receiving ESAs and, if present, hypertension treated by volume removal and/or hypotensive drugs. (Evidence)

GUIDELINE C-HB 3.17: Transfusion

In circumstances where transfusion is required in CKD patients, haematology transfusion guidelines[1] should be adhered to and target Hb recommendations above do not apply to transfusion **(Evidence).**

SECTION 4: NUTRITION (NUTR)

GUIDELINE C-NUTR 4.1: Nutritional Screening

All patients with stage 4-5 CKD should undergo regular nutritional screening (Good practice).

Summary of Audit Measures

Audit parameters are suggested for each of the guidelines where appropriate. Subsequent analyses of the variables audited may be performed by the UK Renal Registry.

Audit measures

Section 1:

- A record of cardiovascular co-morbidity at the time of referral to a renal unit, when starting renal replacement therapy and annually thereafter.
- Number of patients smoking and proportion referred for active help regarding cessation
- Record of glycated haemoglobin concentrations.
- Record of prescribed statins
- Plasma cholesterol.
- Serum or red cell folate
- Systems in place for drug monitoring against cardiovascular comorbidity and cholesterol levels.
- Systems in place to monitor referral practices and care pathways to cardiology
- Pre and post dialysis blood pressure in haemodialysis patients
- Blood pressure in peritoneal dialysis patients
- Home and /or ambulatory blood pressure recordings
- Blood pressure in renal transplant patients

Section 2:

- Predialysis Serum unadjusted calcium
- Predialysis Serum Albumin
- Predialysis Serum phosphate
- Predialysis Calcium phosphate product
- Predialysis Serum parathyroid hormone level
- Vitamin D levels
- Proportion of patients prescribed aluminium phosphate binders.

Section 3: Anaemia

- eGFR by 4 variable MDRD method
- Haemoglobin
- The proportion of patients on an ESA
- Record of type of ESA
- The proportion of patients with an Hb 10.5-12.5g/dl
- Monitoring ESA dose adjustments
- Serum ferritin
- % Hypochromic red cells
- %Transferrin saturation
- ESA dose
- Blood pressure

- Ferritin levels at start of treatment with ESA.
- Proportion of haemodialysis patients receiving intravenous iron
- Number of patients transfused
- Number of units of packed cells transfused

Section 4: Nutritional assessment:

- Record of body weight prior to onset of ill health (well weight),
- Current body weight
- Ideal body weight;
- Body mass index (weight/height^2);
- Subjective global assessment, based on either a 3- or 7-point scale

General introduction

Module 2 contains four sections relating to complications of CKD including patients on renal replacement therapy (RRT). These areas are;

1. Cardiovascular disease
2. Mineral bone disorder
3. Anaemia of CKD
4. Nutrition in CKD

Hypertension in CKD patients not yet on RRT is covered in the CKD module (module 1).

The Renal Association and Royal College of Physicians endorse the NICE guidelines for Anaemia Management in Chronic Kidney Disease (CKD) 2006[1]. The reader is referred to these guidelines as well as to the European Best Practice Guidelines for Anaemia in CKD[2] and the DOQI[3] guidelines for management of anemia in CKD. The KDIGO website (www.kdigo.org)[4] is a useful site of reference for evidence based reviewed guidelines internationally.

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3) NKF-K/DOQI Clinical Practice Guidelines for Anemia of Chronic Kidney Disease: update 2000. Am.J.Kidney Dis. 2001; 37: S182-S238
4) www.kdigo.org

Section 1: MANAGEMENT OF CARDIOVASCULAR DISEASE: C-CVD

Primary and secondary prevention of atherosclerotic cardiovascular disease

GUIDELINE C-CVD 1.1: Cardiovascular risk factors

With respect to patients with Chronic Kidney Disease Stage 3 - 5 and Dialysis Patients, a record a history of and risk factors for cardiovascular disease should be recorded in a format that permits audit of the management of such patients. These should include:-

- Angina and myocardial infarction
- Previous coronary angioplasty or coronary artery bypass grafting
- Stroke and transient ischaemic attack
- Previous carotid artery surgery or angioplasty
- Peripheral vascular disease or previous intervention
- Cardiac failure

(Good Practice)

AUDIT MEASURE

A record of cardiovascular co-morbidity at the time of referral to a renal unit, when starting renal replacement therapy and annually thereafter.

RATIONALE

Cardiovascular disease is the main cause of death in patients with CKD. The increased risk compared with the general population is more prominent in younger patients, a 35-year old haemodialysis patient for example has the same risk of death from cardiovascular disease as an 80-year old in the general population [1]. In addition to traditional risk factors associated with increased risk of cardiovascular disease such as hypertension, hypercholesterolaemia, other complications in patients with CKD notably anaemia[2] and disordered mineral metabolism[3] may contribute to this. Both anaemia and disorders of bone and mineral metabolism develop early in the course of CKD and may be detected when eGFR is below 60 ml/min (CKD stage 3) and both are nearly universal in patients with CKD stage 5.

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Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2006 ; 69 (11): 1945-1953,

GUIDELINE C-CVD 1.2: Smoking and exercise

With respect to all Chronic Kidney Disease and Dialysis Patients, healthy lifestyle changes should be encouraged (Good practice). Smoking habits should be recorded and smoking should be actively discouraged in all patients with a reasonable life expectancy and strongly discouraged in those patients on the transplant waiting list (Evidence). Exercise should be encouraged and patients, including dialysis patients, should be enrolled on regular exercise programmes, exercising 3 to 5 times weekly either during dialysis or between dialysis sessions (Evidence).

AUDIT MEASURE

Number of patients smoking and proportion referred for active help regarding cessation.

RATIONALE

Cigarette smoking is associated with an increased cardiovascular risk in the general population, with more rapid progression of CKD[1] and with cardiovascular mortality following transplantation.[2]

Exercise is of proven benefit in reducing cardiovascular risk in the general population. Reduced exercise capacity and muscle strength is detectable in stage 3 CKD and decreases with declining kidney function. Exercise training improves maximal exercise capacity, muscle strength and endurance in predialysis patients in all age groups[3]. Morphological and metabolic benefits in skeletal muscle have been well-documented in HD patients following exercise training programs. Such beneficial adaptations increase endurance and muscle strength and contribute to improved work capacity. Regular exercise may also contribute to reduced mortality. In a study of 2,507 new dialysis patients mortality risk was highest in those patients with severe limitations to moderate or vigorous physical activity and lowest in patients exercising up to 4 to 5 times weekly [4]. There was no association with increased survival with daily exercise and this warrants further study. Exercise training can result in a beneficial effect within a few weeks in HD patients. Exercise programs also have been shown to improve blood pressure control and reduce arterial stiffness though the beneficial effects taper off after 1 month of stopping training. In a randomised clinical trial over 12 weeks intradialytic cycling and pre-dialysis strength training resulted in beneficial effects on behavioural change, physical fitness and quality of life[5] Improvement is sustained up to 4 years but dropout rates from the exercise program are more likely to occur when the exercise program is between dialysis sessions rather than intra-dialytic.[6]. This should be taken into consideration when designing an exercise program. Less data is available to illustrate the benefits for patients receiving peritoneal dialysis.

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6) Kouidi E, Grekas D, Deligiannia A, Tourkantonis A. Outcomes of long-term training in dialysis patients: comparison of two training programs. *Clin Nephrol*, 2004; 61 Suppl 1: S31-8.

GUIDELINE C-CVD 1.3: HBA1C

In all Chronic Kidney Disease and Dialysis Patients glycated haemoglobin (HbA1c) should be below 7% in diabetics with all stages of CKD, including CKD stage 5 patients who are on dialysis, and HbA1c should be measured using an assay method which has been harmonized to the Diabetes Control and Complications Trial (DCCT)[1] standard (Evidence in CKD 1 and 2, Good Practice in dialysis patients)

AUDIT MEASURE

Record of glycated haemoglobin concentrations.

RATIONALE

Measurement of HbA1c blood levels is an established tool to monitor glycaemic control in diabetic patients. Differences in methodology and a lack of standardization between laboratories however have made comparisons between sites difficult. Despite harmonisation between laboratories with the use of lyophilized calibrators standardized to the method used in the DCCT the mean difference in HbA1C may be as great as 1.7. In patients with CKD 4 and 5 measurements may be further unreliable because of the presence of anaemia, assay interference from uraemia, and decreased red blood cell

survival. Measuring HbA1c using a turbidimetric immunoassay avoids these potential errors.

In type 1 diabetes the DCCT demonstrated that strict glycaemic control can both delay the onset and slow the progression of microvascular complications over a nine year period. The mean HbA1C values during the nine-year study were 7.2 percent with intensive therapy and 9.1 percent with conventional therapy. Subsequent studies have confirmed these findings. In type 2 diabetes improved glycaemic control appears to provide a similar benefit in delaying microvascular complications. Strict glycaemic control slows the increase in urinary albumin excretion in CKD 1 and 2 patients[2]. The UKPDS also demonstrated that improved glycemic control in newly diagnosed type 2 diabetic patients reduced the incidence of diabetic microvascular complications[3].

Though intensive glycaemic control can delay the onset and slow progression of retinopathy, nephropathy and neuropathy no intensive glycemic control trial to date has resulted in a significant reduction in cardiovascular end points. However in a meta-analysis of 13 prospective cohort studies, 10 of which were in type 2 diabetics, the relative risk of any cardiovascular event was 1.18 (95% CI 1.10-1.26) for every one-percentage point increase in glycated haemoglobin[4]. Further information will be available from the Veterans Affairs Diabetes Trial in type 2 diabetes which started in December 2000 with follow up of 5-7 years. Initial results however show no effect on health status with intensive glucose control over 2 years [5].

In dialysis patients with diabetes optimal glycaemic control goals are not established and it is important to individualise management. The effect of reaching an HbA1C of less than 7% in many elderly type 2 diabetics on dialysis is likely to have at best a modest effect on outcome and needs to be weighed against the risk of hypoglycaemic events. Haemodialysis per se has no significant long-term effect on glycaemic control in insulin-treated type 2 diabetic patients as opposed to peritoneal dialysis where the glucose load necessitates increased requirements for insulin or oral hypoglycaemic agents.

In renal transplant patient's recurrent diabetic nephropathy can be prevented by pancreas transplant and both the characteristic glomerular and arteriolar lesions can be prevented with intensive glycaemic control. New-onset diabetes after renal transplantation occurs in between 2% and 54% of patients and in the absence of contrary evidence it would seem sensible to aim for the same HbA1C target in this group of patients.

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GUIDELINEC-CVD 1.4: Hypercholesterolaemia

3 hydroxy-3 methylglutaryl-Co-enzyme A reductase inhibitors (statins) should be considered for primary prevention in all CKD patients with a 10-year risk of coronary disease, calculated as 30% according to the Joint British Societies' chart or the coronary risk calculator, ignoring the fact that these calculations may not be accurate in patients with renal disease. A total cholesterol of <5 mmol/l or a 30% reduction from baseline, or a fasting low density lipoprotein (LDL)-cholesterol of <3 mmol/l, should be achieved, whichever is the greatest reduction in all patients (Evidence in CKD 1-3, Good Practice in CKD 4-5 and dialysis patients). Statins should not be withdrawn from patients in whom they were previously indicated and should continue to be prescribed when such patients start renal replacement therapy (RRT) or change modality. (Good Practice).

AUDIT MEASURES

Record of prescribed statins
Plasma cholesterol.

RATIONALE

Treatment designed to lower cardiovascular risk is only cost-effective if targeted at patients who are at high risk of atherosclerotic events. This is the principle behind the Joint British Societies' Guidelines, in which a risk table or coronary risk calculator (available at http://www.hyp.ac.uk/bhs/risk.xls) is used to estimate risk. Estimation of cardiovascular risk will require accurate recording of data for each dialysis patient regarding smoking, family history of premature vascular disease, blood pressure, total and HDL-cholesterol, and the presence or absence of diabetes, in addition to age and sex.

Hyperlipidaemia is common in dialysis patients; the usual pattern is an elevated triglyceride value, low level of high density lipoprotein (HDL)-cholesterol and variable changes in LDL and total cholesterol. All are dependent on nutrition, co-morbidity and dialysis modality. Large-scale epidemiological studies in HD patients have shown an inverse or U-shaped relationship between serum cholesterol and subsequent mortality[1]. This inverse association is probably a good example of reverse causation: chronic disease, chronic inflammation, and malnutrition all cause hypocholesterolaemia and are independent risk factors for death. Though hypercholesterolaemia may have the same role in atherogenesis this may have a smaller impact in dialysis patients as these patients die from cardiovascular deaths other than due to coronary artery disease. This may in part explain the negative results in a randomised study of atorvastatin in non-insulin dependent diabetics patients on dialysis[2]. Two studies in continuous ambulatory peritoneal dialysis (CAPD) patients have shown a direct correlation between total cholesterol or total:HDL-cholesterol ratio and survival.[3,4]. At present there are no data suggesting that statins are of benefit in patients receiving dialysis although several ongoing studies, including SHARP and AURORA will inform this debate. Until further evidence is available that confirms the results of the 4D study in larger numbers of dialysis patients including those without type 2 diabetes the advice is to continue to treat these patients with statins to achieve the above targets.

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GUIDELINE C-CVD 1.5: Hyperhomocysteinaemia and folate supplementation

In all Chronic Kidney Disease and Dialysis Patients,serum or red cell folate should be above the lower limit of the reference range in all CKD patients including those on dialysis. **(Good practice)**

AUDIT MEASURE

Serum or red cell folate.

RATIONALE

In case-control studies, plasma homocysteine levels are frequently higher in patients with clinical evidence of vascular disease than in those without, both in the general population and in renal disease. Hyperhomocysteinaemia is common even in minor renal impairment[1]. Correction of folic acid deficiency, if present, reduces plasma homocysteine levels in patients with renal impairment but even very high doses (eg 60 mg daily) of folic acid or methylated derivates do not completely normalise homocysteine levels. The evidence that hyperhomocysteinaemia is causally related to atherogenesis from longitudinal studies is less persuasive than that from cross-sectional studies[2]. A recent secondary analysis of the Irbesartan Diabetic Nephropathy Trial (IDNT) study, which enrolled 1575 patients followed for 2.6 years, demonstrated no association between plasma homocysteine and arteriosclerotic outcomes in a univariate model or after adjustment for study randomization and established cardiovascular risk factors[3]. The authors suggest that previous positive findings could be explained by the role of homocysteine as a sensitive surrogate marker for kidney disease which itself is a cardiovascular risk factor. There is as yet very little evidence that intervention to lower homocysteine levels affects the risk of cardiovascular disease either in the general population or patients with renal disease. There is also evidence to suggest that defects in folate absorption or impairment in folate metabolism is not the cause of hyperhomocysteinemia in haemodialysis dialysis patients[4]. In stable renal transplant recipients an elevated fasting homocysteine blood level is an independent risk factor for cardiovascular disease[5]. The ongoing FAVORIT study should provide the answer to whether standard multivitamin therapy with folic acid and vitamins B6 and B12 will affect cardiovascular outcomes in renal transplant recipients. However, correction of folate deficiency is good clinical practice irrespective of any possible effect on homocysteine levels or vascular disease risk.

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GUIDELINE C-CVD 1.6: Secondary prevention of cardiovascular risk

In all chronic kidney disease and dialysis patients, all CKD patients (including those on dialysis and after transplantation) with a history of myocardial infarction, stroke, peripheral vascular disease, acute coronary syndrome, or who undergo surgical or angiographic coronary revascularisation should be treated with aspirin, an ACE inhibitor, a beta-blocker, and an HMG–CoA reductase inhibitor unless contraindicated. The doses of ACE inhibitors and beta-blockers should be the maximum tolerated (Evidence) In patients in whom lipid-lowering drug treatment is used, total cholesterol should be reduced by 30% or to below 5 mmol/l, or LDL-cholesterol to below 3 mmol/l, whichever reduction is the greatest. (Evidence in CKD 1-3, Good Practice in CKD 4-5 and dialysis patients).

AUDIT MEASURE

Systems in place for drug monitoring against cardiovascular comorbidity and cholesterol levels.

RATIONALE

Survival after myocardial infarction in CKD patients is poor and correlates with the degree of renal impairment[1]. There is no reason, however, to expect that the important survival advantages conferred by treatment with ACE inhibitors, beta-adrenergic blockers, aspirin and HMG–CoA reductase inhibitors would not apply to patients with renal disease with ischaemic heart disease. Guidelines for the management of non-renal patients with proven ischaemic heart disease should be followed[2]. The rationale for the use of HMG–CoA reductase inhibitors in CKD is discussed in recommendation 3.

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GUIDELINE C-CVD 1.7: Cardiac investigations and coronary revascularization

In all chronic kidney disease and dialysis patients, patients should have unimpeded access to a full range of cardiac investigations including exercise and stress echocardiography, radio-isotopic cardiac scans, and coronary angiography. There should also have unimpeded access to cardiology

assessment for coronary angioplasty and stenting and cardiac surgery. **(Good practice).**

AUDIT MEASURE

Systems in place to monitor referral practices and care pathways to cardiology

RATIONALE

Diagnosis of coronary disease in dialysis patients may be problematic. Angina with normal coronary arteries is not uncommon[1], but is matched by an equally high prevalence of clinically silent coronary disease[2]. Standard exercise electrocardiography is unreliable as a result of poor exercise tolerance and a high prevalence of pre-existing electrocardiographic abnormalities. Minimising premature deaths by revascularisation in patients with prognostically important coronary disease requires accurate identification of such patients; many will only be identified by coronary angiography. It is particularly important to identify patients on the waiting list for transplantation who might have coronary disease, to minimise the risk of intra- or post-operative death from myocardial infarction either by removing such patients from the list or by revascularisation. Risk markers for the presence of coronary artery disease in dialysis patients include:

- symptomatic angina
- unexplained arrythmias
- recurrent dialysis-related hypotension
- heart failure, ECG abnormalities, and
- wall motion abnormalities on echocardiography.

Decisions on whether a patient is 'fit' for renal transplantation, therefore, have to be made on an individual basis. These decisions will also be influenced by local policy governing access to the transplant waiting list (see Renal Transplantation module). Both percutaneous angioplasty with or without stenting[3] and surgical revascularisation[4] are associated with worse survival, a higher complication rate and higher re-stenosis rates in CKD patients. However similar survival rates are found when comparing coronary revascularisation in dialysis patients with CKD patients stages 3-5 not on dialysis. The first trial (ARTS) to compare coronary artery stenting and bypass surgery for multivessel coronary disease in patients with CKD stages 3-5 has recently been published[3]. One hundred and forty-two patients with multivessel coronary disease were randomly assigned to stent implantation (*n*=69) or CABG (*n*=73). At 5 years, there was no significant difference between the two groups in terms of cardiovascular or all cause mortality. In those patients who survived without a cardiovascular event 18.8% in the stent group underwent a second revascularization procedure compared to 8.2% in the surgery group (*P*=0.08). The event-free survival at 5 years was 50.7% in the stent group and 68.5% in the surgery group (*P*=0.04).

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C-CVD 8 Hypertension: Chronic Kidney Disease on renal replacement therapy

GUIDELINE C-CVD 1.8: Hypertension in dialysis patients:

Pre and post-dialysis blood pressure (measured after completion of dialysis, including washback) should be recorded and intra-dialytic blood pressure measured to enable management of the haemodialysis session.
Blood pressure in patients on peritoneal dialysis should be <130/80 mmHg (Good Practice).

Hypertension on dialysis should be managed by ultrafiltration in the first instance(Good practice).

Audit Measure

Pre and post dialysis blood pressure in haemodialysis patients
Blood pressure in peritoneal dialysis patients
Home and /or ambulatory blood pressure recordings

RATIONALE

No properly designed randomised controlled studies of hypertension control in dialysis patients are available to provide class 'A' advice. Hypertension guidelines for dialysis and transplant patients are therefore extrapolated from the evidence base in CKD patients not yet on dialysis and epidemiological studies showing the U shaped curve between mortality and blood pressure. However studies on incident dialysis patient cohorts demonstrate improved survival in normotensive dialysis patients[1]. Ambulatory blood pressure measurement studies have demonstrated that pre and post dialysis blood pressure measurements are of no value in predicting the presence of left ventricular hypertrophy on echocardiogram[2]. Home blood pressure recordings with a mean systolic BP > 150mmHg has a sensitivity of 80% and specificity of 84% for diagnosing hypertension defined by ambulatory BP>135/85 between dialysis sessions[3].

Several large studies have shown a U-shaped relationship between blood pressure and mortality, with both low and high blood pressure being associated with an increased relative risk of death. The most likely explanation for the findings is that in study cohorts, cardiac failure, whether due to hypertensive heart disease or to ischaemic heart disease, carries a high risk of early mortality and is associated with low blood pressure. Hypertension on the other hand is associated with increased late mortality. However, there have been no controlled trials examining the effect of blood pressure reduction on outcome in HD patients. Such trials would be complicated because blood pressure control can be achieved by both fluid removal and drug therapy in dialysis patients.

Pulse pressure is increasingly recognised as a more powerful predictor of mortality than diastolic or systolic pressure alone[5, 6]. Increased vascular and

ventricular stiffness may mean that in dialysis patients, coronary perfusion (dependent on diastolic pressure) may need to be maintained by higher pressures. These questions need investigation by properly organised randomised controlled trials and until then caution should be exercised in interpreting blood pressure guidelines.

In the management of essential hypertension, the need for care in the interpretation of blood pressure measurements, and the unreliability of casual measurements, taken while the patient is stressed or anxious, are well recognised. Current recommendations[7] suggest that blood pressure should be taken after five minutes rest in a chair, after at least 30 minutes of abstention from caffeine or nicotine, with the patient seated comfortably, and with the arm supported at heart level. At least two measurements should be taken, several minutes apart, to allow for the alerting response to blood pressure measurement. If the second measurement is significantly lower than the first, a third measurement should be taken, with further repeats if there is a further fall in measured blood pressure. The blood pressure recorded should be the mean of the later measurements. These recommendations are not easily met in haemodialysis patients arriving for therapy.

Hypertension may be difficult to control in dialysis patients despite multiple medications. Hypertension that is refractory to combination anti-hypertensive medication is frequently due to sub-clinical salt and water overload, even in the absence of peripheral or pulmonary oedema. Adequate control of extracellular volume by dietary salt restriction and ultra-filtration is, therefore, the 'first line' treatment for hypertension in HD patients[4]. Individualising dialysate sodium prescription is associated with reduced inter-dialytic weight gain and reduction in blood pressure in hypertensive dialysis patients[8]. Long hours and / or nocturnal has long been associated with better blood pressure control[9]. Long hours haemodialysis improves blood pressure and left ventricular hypertrophy compared to conventional dialysis[10]. Similarly daily dialysis improves blood pressure control and left ventricular hypertrophy compared to conventional dialysis[11]. After adequate control of extracellular volume by dietary salt restriction and ultra-filtration any ongoing hypertension suggested by pre and post dialysis blood pressure recordings should be investigated using home or ambulatory blood pressure recordings.

Possibly of greatest contention are whether current national and international guidelines for management of blood pressure in dialysis patients are attainable. Further research is urgently needed on blood pressure control strategies in dialysis patients. Audit by the UK Renal Registry[12] shows that only 42% of HD patients achieve the pre-dialysis standards and 48% achieve the post-dialysis standard. 37% of PD patients and 31% of transplant patients achieve the standards. The S.D. for systolic and diastolic blood pressure post dialysis in 2005 in the UK Renal Registry report was 26 and 14 respectively. If blood pressure is normally distributed then with mean systolic and diastolic blood pressures of 130 and 80 respectively then given that 15% of patients will have values that lie below the 'mean – 1 S.D.' then 15% of patients already have blood pressures below 104mmHg (130-26) systolic and 66mmHg (80-14) diastolic. The ability to narrow the distribution of blood

pressure in the dialysis population will be required to achieve better compliance with the standard if a significant proportion of patients are not to be rendered hypotensive. Alternatively, recognition that not all patients can be managed to these levels is required. Systolic hypertension and wide pulse pressures resulting from many years at risk from hypertension, CKD and arterial calcification may be the horse that has already bolted. Our greatest need is for large randomised controlled studies to investigate whether or not attempts to achieve these blood pressure outcomes actually reduce overall cardiovascular risk and mortality.

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GUIDELINE C-CVD 1.9: Hypertension in renal transplant patients

Target blood pressure for renal transplant patients < 130/80 mm Hg (Good practice).

AUDIT MEASURE

Blood pressure

RATIONALE

Patients with CKD in the kidney transplant should be treated with anti-hypertensive therapy using preferred agents first when indicated[1].

Although there is a wealth of evidence demonstrating better long-term outcome with lower blood pressure in renal transplant recipients there are no comparative studies of target blood pressure outcomes in renal transplantation. The evidence is therefore mostly extrapolated from the management of CKD and aims to reduce progression of renal impairment and reduce cardiovascular risk.

There is a high prevalence of hypertension in kidney transplant recipients in the UK[2] and worldwide (>90% of patients) most of which have at least CKD stage 2 (or higher) by definition. Hypertension is also poorly controlled in the transplant population despite being under regular nephrology follow up. The UK Renal Registry reports that 55% of UK transplant patients have a diastolic BP>80mmHg. 69% have a systolic>130mmHg. High blood pressure in kidney transplant recipients is a risk factor for faster progression of CKD and development of CVD. Type of immunosuppressive regime affects the prevalence of hypertension. Calcineurin inhibitor use increases the prevalence of hypertension post transplantation, though tacrolimus slightly less so than ciclosporin[3, 4]. Hypertension is associated with increased risk of rejection[5], chronic allograft nephropathy[6] and long-term graft survival with or without rejection[7]. A large registry study showed that recipients with well-controlled blood pressure have improved long-term survival[8].

Although there appears to be a strong relationship between hypertension and long-term kidney transplant outcome, there are no clinical trials that assess the level of blood pressure control and long-term outcomes. Current AST guidelines define hypertension as >140/90 and the K-DOQI guidelines[9] recommend target blood pressures of <135/85 without proteinuria and <125/75 with proteinuria. These recommendations have no randomised controlled trials to back them up.

All classes of anti-hypertensive agents are effective in controlling blood pressure post transplantation. Of the calcium channel blockers, verapamil and diltiazem are negatively inotropic and chronotropic and inhibit hepatic p-450 enzymes. The dihydropyridines cause peripheral dilatation but have minimal effects of the hepatic p-450 enzymes. Most transplant centres avoid ACEIs in the early post-transplant period until the creatinine is stable. There is a risk of delay of recovery from preservation injury and interaction with calcineurin inhibitors risking renal vasoconstriction. Calcium channel blockers antagonise the vasoconstrictive effect of ciclosporin and may improve transplant function over a 2-year period compared to ACEI for control of hypertension[10]. When

ARB use was compared to calcium channel blockers, in the immediate post-transplant period, a higher incidence of hyperkalaemia but lower incidence of peripheral oedema was noted[11]. Both ARBs[12] ACEIs and B-blockers[13] are *associated* with reduction in left ventricular mass index over a two-year period. Retrospective studies in patients on ACEI and ARBs with biopsy proven chronic allograft nephropathy show an association with longer graft and patient survival compared to patients not on these agents, despite a higher prevalence of hypertension[14]. There is a need for randomised controlled trials to establish the ideal outcome blood pressure and also to establish the preferred anti-hypertensive agents post-transplantation.

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Section 2: MANAGEMENT OF METABOLIC BONE DISEASE: C-MBD

GUIDELINE C-MBD 2.1: Serum calcium in patients with Chronic Kidney Disease

Serum calcium should be kept within the normal reference range for the laboratory used in patients with CKD 1 to 4 (Evidence)

GUIDELINE C-MBD 2.2: Serum calcium i n Dialysis Patients

Serum calcium, adjusted for albumin concentration should be maintained within the normal reference range for the laboratory used (measured before a "short gap" dialysis session in HD patients) (Evidence) and ideally kept below 2.5 mmol/L. (Good Practice)

AUDIT MEASURE

Serum calcium.
Serum albumin

RATIONALE

Estimation of serum calcium, corrected for albumin, is susceptible to all the problems of inter-assay variation (see section on albumin). In addition, there are several formulae in use for "correction" of serum calcium for albumin concentration. Comparison of standards of care between units, with regard to control of serum calcium will, therefore, remain difficult until these problems have been resolved. Reasons for controlling serum calcium include the need to prevent stimulation of parathyroid gland activity by hypocalcaemia and the need to prevent symptomatic hypocalcaemia. Mortality also relates to calcium levels. In a large retrospective analysis of over 40,000 haemodialysis patients all cause mortality was higher the higher the corrected serum calcium level was, with no lower limit to the linear relationship in dialysis patients[1]. To address the concern that this may just reflect the reciprocal relationship between calcium and phosphate the risk of death was also measured within subsets of narrow ranges of serum phosphate and within each range of phosphate a higher serum calcium was associated with a significantly increased mortality risk. Recent data has been published from the Dialysis Outcomes and Practice Patterns Study (DOPPS) in the United States, Europe, and Japan from 1996 to 2001[2]. In 17,236 haemodialysis patients from 307 participating centres all-cause mortality was significantly and independently associated with calcium (RR 1.10 per 0.25 mmol/l, $P < 0.0001$). As mortality falls with lower calcium it may be preferable to maintain corrected calcium towards the lower end of the target range[3], however, this is likely to make control of hyperparathyroidism more difficult.

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Serum phosphate

GUIDELINE C-MBD 2.3: Serum phosphate in patients with CKD stages 3 and 4

Serum phosphate in patients with CKD stages 3 and 4should be maintained between 0.9 and 1.5 mmol/L. (Evidence)

GUIDELINE C-MBD 2.4: Serum phosphate in dialysis patients

Serum phosphate in dialysis patients (measured before a “short gap” dialysis session in HD patients) should be maintained between 1.1 and 1.8 mmol/L. (Evidence)

AUDIT MEASURE

Serum phosphate

RATIONALE

Hyperphosphataemia is one of the commonest biochemical abnormalities developing in CKD and often one of the most difficult to control. Elevated phosphorus levels in CKD and dialysis patients contribute to the development of hyperparathyroidism. Serum phosphate is also the main factor determining the calcium x phosphate product and the prevalence of metastatic calcification including vascular (and coronary artery) calcification and heart valve calcification[1].

Hyperphosphataemia is also associated with increased morbidity and mortality in CKD patients. In a large cross-sectional and retrospective analysis of a database of over 40,000 haemodialysis patients the lowest relative risk of death was seen in patients with serum phosphate concentrations between 0.97 to 1.6 mmol/L.[2] Serum phosphorus concentrations >1.6 were associated

with an increased relative risk of death as follows 1.07, 1.25, 1.43, 1.67, and 2.02 for serum phosphorus 1.6 to 1.9, 1.9 to 2.3, 2.3 to 2.6, 2.6 to 2.9, >2.9 mmol/L respectively. Renal registry data shows a similar pattern with the lowest risk of death with serum phosphate concentrations of between 1.1 and 1.8 mmol/L.[3] The risk of death associated with increasing phosphate levels is the same for PD and HD patients. Data from DOPPS also confirms that there is a bimodal relationship of serum phosphate to mortality risk and there was a significantly increased risk of death with serum phosphate levels less than 1.13 mmol/L and above 2.1 mmol/L.[4]

All units should have adequate access to dedicated renal dieticians as recommended by the Renal Workforce plan. Patients with chronic renal failure should be educated by a renal dietician about dietary means of reducing phosphate intake at an early stage and dietary phosphorus should be restricted to between 800 and 1000 mg/day. Dietary restriction of phosphate intake to below 800 mg/day is not recommended since this will have a negative effect on protein intake. Intensive dietetic support is required to optimise compliance and the effectiveness of dietetic input is being assessed in a randomised controlled trial. Dietary phosphate restriction alone is unlikely to control serum phosphate in advanced renal failure (CKD 4 and 5) and phosphate binders are required. Phosphate binders available include calcium carbonate, calcium acetate, aluminium hydroxide, lanthanum carbonate and sevelemar. The choice of agents should be individualised, as all currently available agents carry different cost:benefit ratios. Total elemental calcium intake should not exceed 2 grams per day and this may limit use of calcium containing binders as will targets of calcium and calcium x phosphate product. Aluminium binders should only be used in the short term (< 3 months) to control severe hyperphosphataemia to reduce the risk of aluminium toxicity. The effects of standard HD on serum phosphate are limited, due to the high volume of distribution, which leads to rapid rebound of serum phosphate after dialysis. However daily HD results in normalisation of serum phosphate concentrations and may lead to the development of hypophosphataemia.

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Serum calcium x phosphate product

All Chronic Kidney Disease and Dialysis Patients

GUIDELINE C-MBD 2.5: Serum calcium x phosphate product

The serum albumin corrected calcium phosphorus product should be kept below 4.8 $mmol^2/L^2$ and ideally below 4.2 $mmol^2/L^2$ in all CKD patients. **(Evidence)**

AUDIT MEASURE

Calcium x phosphate product

RATIONALE

Numerous studies have shown a high serum calcium x phosphate product is associated with metastatic calcification in visceral and non-visceral tissues and in particular in heart valves and blood vessels[1]. Cross sectional studies have shown an increasing risk of relative mortality with increasing calcium x phosphate product. In a random sample (controlled for age, sex, race, diabetes, smoking, AIDS and malignancy) of 2669 patients on haemodialysis for > 1 year taken from the US Renal Data System Dialysis morbidity and mortality study wave 1 there was an increasing relative mortality risk above a calcium (corrected to serum albumin 40g/L) x phosphate product measured in mg/dL of 52 (equivalent to 4.16 $mmol^2/L^2$) [2]. The relative mortality risk was 1.08 for calcium x phosphate products ($mmol^2/L^2$) between 4.23 and 4.8, 1.13 for products of 4.9 to 5.76 and 1.34 for products of 5.8 to 10.6.

Though calcification occurs in vessels and is associated with a raised serum calcium x phosphate product more evidence is needed to confirm that this is directly related to increased cardiovascular mortality. Arterial calcification occurs both in the intima and the media of the vessel wall and the latter results in increased stiffness of the vessel and a wider pulse pressure that is likely to be associated with poor cardiovascular outcome. In a recent study of 202 patients on haemodialysis for over 1 year intimal calcification occurred more commonly in older patients with atherosclerosis whereas medial calcification occurred in younger patients without conventional risk factors for atherosclerosis [3]. Both types of calcification were associated with a higher serum calcium x phosphate product. The serum calcium x phosphate product was 3.96 ± 0.98 in those without calcification (n=73), 4.76 ± 1.01 in those with medial calcification (n=54) and 4.60 ± 1.04 in those with intimal calcification (n=75). Survival was worst in the group with intimal calcification, but all cause and cardiovascular mortality was also worse in those with medial calcification compared to those without calcification. The serum calcium x phosphate product in chronic kidney disease patients is determined mainly by the serum phosphate and the level of the product is only one factor of many that may promote metastatic calcification and should not be looked at in isolation.

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SERUM PARATHYROID HORMONE

GUIDELINE C-MBD 2.6: Measurement of Serum Parathyroid Hormone in CKD

In Chronic Kidney Disease patients PTH needs only to be measured routinely in progressive CKD 3, and stages 4 and 5 CKD. PTH should not be routinely measured in stages 1, 2 nor in non-progressive stage 3 CKD unless there is a clinical indication to do so. (Good Practice).

GUIDELINE C-MBD 2.7: Desired outcome range for Serum Parathyroid Hormone in CKD

The target range should increase from the normal range with CKD stages 1-3, to between the top of the normal range and twice normal for stage 4 CKD and to between 2 to 4 times normal in CKD stage 5 not on dialysis. These targets should also apply to transplant patients. **(Good Practice).**

GUIDELINE C-MBD 2.8: Desired outcome range for Serum Parathyroid Hormone in Dialysis Patients

The target range for parathyroid hormone measured using an intact PTH assay should be between 2 and 4 times the upper limit of normal for the intact PTH assay used (**Good Practice**). The same target range should apply when using the whole molecule PTH assay. **(Good Practice).**

AUDIT MEASURE

Serum parathyroid hormone

RATIONALE

Blood levels of PTH start to increase in stage 3 CKD[1]. As renal function declines secondary hyperparathyroidism progresses driven by

hyperphosphataemia, hypocalcaemia and lower calcitriol production. Normal bone turnover requires higher than normal PTH levels in CKD to overcome skeletal resistance to the hormone. Skeletal resistance to PTH probably increases with increasing uraemia. There is also evidence that the current most commonly used "intact" PTH assays in addition to detecting the 1-84 aminoacid peptide also measure a 7-84 fragment of PTH (cyclase inactive PTH or CIP) which accumulates in CKD[2]. The identification of this inhibitory fragment has led to new assays being developed utilizing an antibody to the 1-7 region of the molecule combined with an antibody to the 39-84 region thus eliminating cross-reactivity from 7-84 fragments. The 1-84 molecule has been termed cyclase activating PTH (CAP) or "whole molecule" PTH. The reference range for these new assays is 7 – 36 ng/L about half that for intact PTH. It is not known whether the recommended target range should be lowered when using this assay; it is likely that the target ranges will require revision when further evidence is available using these newer assays. Until this evidence is available it is recommended that the intact PTH assay (measured in laboratories participating in the NEQAS (National External Quality Assessment Service) PTH scheme) is used for comparative audit purposes. Serum PTH should be measured in dialysis patients at least every 3 months[3].

Both high and low bone turnover states are associated with reduced bone mineral density, increased fracture risk and metastatic calcification including vascular calcification (common), heart valve calcification (common) and calciphlaxis (rare).

Numerous studies have shown that measuring serum iPTH is useful in predicting both high and low turnover bone disease. Levels in dialysis patients greater than 4 times normal are associated with a greater frequency of high bone turnover disease and levels less than twice normal are associated with a higher frequency of low bone turnover disease or adynamic bone disease. The optimal level of serum iPTH in an individual patient however is difficult to determine. Though a useful predictor of high and low bone turnover when compared to bone biopsy data there is insufficient sensitivity and specificity to reliably diagnose high bone turnover with levels < 500 ng/L and adynamic bone disease with levels >100 ng/L [3]. In patients with CKD not yet on dialysis the optimal target for PTH levels is opinion based only and the individual clinician should decide on the degree to which hyperparathyroidism should be corrected and on how it should be achieved. There is no doubt, however, that an iPTH concentration of over four times the upper limit of normal is associated with an increased risk of significant bone disease, and then this should therefore be avoided by medical (or if necessary surgical) treatment of hyperparathyroidism. Alfacalcidol and calcimimetics may be used in the medical treatment of hyperparathyroidism. Similarly measures should be taken to allow a serum iPTH level below twice normal in dialysis patients to rise[4]. A small proportion of patients will have such significant co-morbidity and limited life expectancy that their physicians may choose not to treat asymptomatic hyperparathyroidism.

Whether and how frequently iPTH should be measured in stage 3 CKD is debatable. Our opinion is that it should be measured routinely in those patients who are considered to have progressive CKD and in the majority of patients with non-progressive stage 3 CKD measured only in those patients in which there is an abnormality of calcium and phosphate or another clinical indication for example bone pain or a reduction in bone mineral density.

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VITAMIN D

GUIDELINE C-MBD 2.9: VITAMIN D in CKD and Dialysis Patients

Chronic Kidney Disease Patients

Serum 25-hydroxyvitamin D should be measured in all patients with an elevated PTH (**Evidence**). A level of less than 75 nmol/L indicates vitamin D insufficiency **(Opinion)**.

Dialysis Patients

The routine measurement of` serum 25-hyrdoxyvitamin D in dialysis patients is not included in these guidelines due to the current lack of evidence regarding value and interpretation of the levels (**Opinion).**

AUDIT MEASURE
Vitamin D levels

RATIONALE

Vitamin D deficiency is a well recognized cause of secondary hyperparathyroidism. The bodv stores of vitamin D are best determined by

measuring serum 25-dihydroxyvitamin D[1] . Though there is debate over what the "normal range" is generally levels lower than 70 - 80 nmol/L are considered to indicate vitamin D insufficiency[2] and levels lower than 12 nmol/L indicate severe deficiency. It is clear that vitamin D insufficiency is common in the general population[3] and CKD may be a further risk factor for this [4]. Secondary hyperparathyroidism due to vitamin D insufficiency or deficiency is associated with bone loss in the general population[5,]. It should be measured in CKD patients as correction of vitamin D insufficiency can improve bone health. In a recent meta-analysis oral vitamin D supplementation in a dose of between 700 and 800 IU/day reduced the risk of hip and non-vertebral fractures by about 25%[6] in ambulatory or institutionalized elderly persons. The role of calcium supplementation is less clear though a dietary intake of > 700mg/day is necessary to reduce fracture risk.

In patients requiring dialysis supplementation with ergocalciferol will not raise 1,25 dihydroxyvitamin D levels. Therefore unless there is a clinical indication for severe vitamin D deficiency (eg suspicion of osteomalacia) there does not appear to be a rationale for the routine measurement of vitamin D in these patients.

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GUIDELINE C-MBD 2.10 Serum aluminum levels in stage 4 and 5 CKD

Aluminum toxicity can occur in stage 4 and 5 CKD and in dialysis patients, if clinically suspected serum aluminum levels should be determined (Good

Practice). Care needs to be taken to avoid aluminum contamination of the blood sample (Evidence).

GUIDELINE C-MBD 2.11 Serum aluminum levels in patients on aluminium based phosphate binders

Serum aluminium concentration should be measured every three months in all patients receiving oral aluminium phosphate binders (Good Practice)

GUIDELINE C-MBD 2.12 Aluminium toxicity

Serum levels should be less than 20 ug/L (Good Practice). A desferrioxamine test should be performed to support the diagnosis where random serum levels are indeterminate (20 – 60 ug/L). (Evidence). A bone biopsy provides confirmation of aluminium bone disease (Evidence).

AUDIT MEASURE

Proportion of patients prescribed aluminium phosphate binders.

RATIONALE

There is some debate whether aluminium levels need to be measured routinely in haemodialysis patients as recommended in the K-DOQI guidelines[1]. Certainly the current guideline of measuring aluminium 3 monthly in all HD patients is not being followed[2] Aluminium toxicity is now rarely encountered in dialysis patients since the major cause of toxicity, dialysate water contamination, has been eliminated, we therefore have not included this in our recommendations. Toxicity is still occasionally seen usually associated with intensive use of aluminium containing phosphate binding gels. Aluminium absorption from the gut can be enhanced by the concomitant use of citrate containing salts and the combination must be avoided. Iit is important clinicians be aware of the symptoms and signs [3-5] as well as the biochemical characteristics [6] of aluminium toxicity and if the clinical suspicion is there levels should be measured. Aluminium is a ubiquitous substance and great care is required in obtaining the sample to avoid contamination. Plasma levels should be less than 20 ug/L. Aluminium bone disease diagnosed by bone biopsy was determined with a sensitivity of 82% and specificity of 86% when blood levels were 60 ug/L or greater in one study [7]. The desferrioxamine test[8] is an effective predictor of aluminium toxicity and can be used when blood levels are indeterminant of the clinical suspicion of toxicity is high. Low dose desferrioxamine (5mg/kg BW) reduces the risk of desferrioxamine toxicity. A rise of greater than 50 ug/L after desferrioxamine is considered a positive test. Bone biopsy is considered to be the gold standard for diagnosing aluminium bone disease by which other tests are compared [9]. In clinical practice this is rarely required.

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Section 3: C-HB:MANAGEMENT OF RENAL ANAEMIA GUIDELINES

Summary of Guidelines for Anaemia

The Renal Association and Royal College of Physicians endorse the NICE guidelines for Anaemia Management in Chronic Kidney Disease (CKD) 2006[1]. The reader is referred to these guidelines as well as to the European Best Practice Guidelines for Anaemia in CKD[2] and the DOQI[3] guidelines for management of anemia in CKD. The KDIGO website (www.kdigo.org)[4] is a useful site of reference for evidence based reviewed guidelines internationally.

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GUIDELINES

GUIDELINE C-HB 3.1: Evaluation of anaemia - Haemoglobin level

In the opinion of the working group, anaemia should be evaluated in CKD when Hb<13 g/dl in adult males and post- menopausal females and when Hb <12g/dl for pre-menopausal females **(Good Practice).**

RATIONALE

Anaemia is defined as having a haemoglobin value below the established cut off defined by the World Health Organisation[1]. Different defined groups have different cut offs.
For adults:

Pregnant women	<11.0g/dl.
Non-pregnant premenopausal women	<12.0g/dl
Postmenopausal women and men	<13.0g/dl

In addition to gender, age and pregnancy, other factors influence haemoglobin level including smoking, race and genetic disorders (thalassaemia and sickle cell). In CKD patients anaemia should be defined using these same criteria. Degree of renal impairment affects the likelihood of any patient developing anaemia.

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GUIDELINE C-HB 3.2: Evaluation of anaemia - Renal function

CKD should be considered as a possible cause of anaemia when the GFR is <60 ml/min/1.73m^2. It is more likely to be the cause if the GFR is

<30mls/min/1.73m^2 (<45 in diabetics) and no other cause, i.e. blood loss, folic acid or B12 deficiency, is identified**. (Evidence)**

AUDIT MEASURES

1). eGFR by 4 variable MDRD method[3]
2. Haemoglobin

RATIONALE

The prevalence of anaemia in patients with CKD increases as the GFR progressively falls. NHANES III data demonstrate a prevalence of anaemia in CKD of 1%, 9% and 33% for an eGFR of 60, 30 and 15 respectively[1]. UK data of > 112,000 unselected patients in the general population showed a population prevalence of CKD 3-5 of 4.9%[2]. In these patients the prevalence of gender specific anaemia (<12 men: < 11 women) was 12%. The prevalence of Hb< 11.0g/dl was 3.8%.

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GUIDELINE C-HB 3.3: Evaluation of anaemia - Erythropoietin hormone measurement.

In the opinion of the working group measurement of erythropoietin levels for the diagnosis or management of anaemia should not routinely be considered for patients with CKD (Good practice).

RATIONALE

In renal anaemia, serum erythropoietin levels can be in high, normal or low, but lower than required considering the degree of anaemia.

GUIDELINE C-HB 3.4: Treatment of Anaemia - Erythropoietic Stimulating Agents

Treatment with ESAs should be offered to patients with anaemia of CKD who are likely to benefit in terms of quality of life and physical function, and to avoid transfusion in patients considered suitable for transplantation (Evidence).

AUDIT MEASURE

The proportion of patients on an ESA

RATIONALE

Treatment of anaemia in CKD[1] can be expensive, takes time to work and carries a small but significant risk to the patient. It is therefore reasonable, as with any therapy, to treat only those who are expected to benefit in the time frame that therapy is being considered. For example, patients with severe sepsis/ inflammation/acute bleeding are unlikely to respond. Patients with a very short life expectancy (days or weeks) are not likely to survive long enough for therapy to provide benefit in terms of an increase in Hb. The clinician and patients should agree on a therapeutic plan and review, at an appropriate time, whether therapy is providing benefit enough to continue treatment.

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GUIDELINE C-HB 3.5: Treatment of Anaemia - Choice of ESA

Choice of ESA will depend on local availability of ESAs and consideration of the patients clinical status. **(Good practice)**

AUDIT MEASURE

Record of type of ESA

RATIONALE

Many studies have been published comparing different ESA products against each other when used at different dosing intervals, by different routes of administration and in different patient groups. All the available products are efficacious when administered according to the manufacturers recommendations. The choice of ESA will be dependent upon the clinician and patient agreeing a management plan in the light of locally agreed cost variables and dependent on a secured supply of ESA[1].

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GUIDELINE C-HB 3.6: Treatment of Anaemia – Route of administration

The prescriber should consider that when using short acting ESAs, subcutaneous administration allows the use of lower doses of drugs than intravenous administration**. (Evidence)**

AUDIT MEASURES

1 – Route of ESA administration
2 – Frequency of ESA administration

RATIONALE

Subcutaneous administration of short acting ESAs are associated with approximately 33% reduction in dose requirements compared to intravenous administration[1].

Other factors such as nature of treated population (ie iv ESA impractical in patients not on haemodialysis), pain of injection, frequency of administration, preferences of the patient, efficacy and cost of drug supply should all be taken into consideration when deciding upon the route of administration[2].

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GUIDELINE C-HB 3.7: Target haemoglobin

Patients with CKD should achieve an outcome distribution of haemoglobin of 10.5-12.5 g/dl. **(Evidence).**

AUDIT MEASURE

The proportion of patients with an Hb 10.5-12.5g/dl

RATIONALE

The health economics of anaemia therapy using ESAs has been subject to a NICE review[1]. The report concludes that treating to a target Hb 11-12g/dl is cost effective in haemodialysis patients. In a US study the incremental cost per QALY of target Hb 12.0-12.5 g/dl vs 11.0-12.0g/dl was $613,015. An additional $828,215 per additional QALY gained was required to achieve a target Hb of 14g/dl versus 12.0-12.5g/dl[1].

To put this guideline Hb distribution into current context, the Eighth UK Renal Registry Report Dec 2005[2] reports the outcome for participating renal units in E&W. The mean Hb was 11.7g/dl (S.D. 1.6g/dl) with 85% compliance with Hb>10g/dl. The IQR was 10.6-12.8g/dl. The compliance with %>11.0g/dl was 68%.

Besarab et al[3] reported a study of normalisation of haemoglobin in patients with high cardiovascular risk on haemodialysis. Normalisation of haemoglobin showed no benefit in risk reduction but did show an improvement in quality of life. The trial was associated with a trend to increased risk thou the trial was stopped on the grounds that the study was highly unlikely to show benefit from normalisation.

For patients not yet on dialysis two recent studies require discussion. The outcome of the CHOIR[4] study showed no benefit of higher haemoglobin outcome in CKD patients (11.3g/dl vs. 13.5g/dl). Higher outcome target Hb demonstrated increased risk (using composite end-points of death, myocardial infarction, or hospitalisation for congestive cardiac failure) and no incremental improvement in quality of life. The CREATE[5] study in CKD patients showed that early correction of anaemia to normalised Hb outcome (13-15g/dl vs. 10.5-11.5g/dl) did not reduce risk of cardiovascular events. Indeed the hazards ratio for primary endpoints of death from any cause or death from cardiovascular disease consistently (but not significantly) favoured the lower haemoglobin target group. The trend to increase in events appeared to occur after initiation of dialysis with no difference seen in endpoints after censoring of data on patients receiving dialysis. Quality of life was significantly better in the higher Hb outcome group. Although GFR was not significantly different between the two groups more patients started renal replacement therapy earlier in the higher Hb outcome group (p=0.03) with the difference apparent from 18 months.

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GUIDELINE C-HB 3.8: ESA Dose adjustments

Adjustments to ESA doses should be considered when Hb is <11 or >12g.dl.in order that the population distribution has the maximum proportion of patients in the range 10.5-12.5 as is possible **(Evidence).**

AUDIT MEASURE

Monitoring ESA dose adjustments

RATIONALE

It is acknowledged that a dialysis population Hb distribution has a S.D. that prevents the majority of values lying between 11-12g/dl[1-3]. The NICE guidelines for anaemia management in chronic kidney disease[3] recommend an outcome Hb 10.5-12.5. If a population Hb outcome distribution is centred on this outcome with a mean of 11.5g/dl then the previous RA minimum standard for Hb of 85%>10.0g/dl is met. The NICE guidelines contain suggested treatment algorithms.

The NICE algorithms require validation in clinical practice. Achievement of the outcome distribution complying with a mean of ~11.5g/dl produces 85% Hb values >10.0g/dl, with 40-50% of values lying between 10.5-12.5g/dl. The use of these particular intervention values of 11.0g/dl and 12.0g/dl for changes to ESA doses has been validated using computerised decision support systems[1,4].

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GUIDELINE C-HB 3.9: Iron status

Patients should be iron replete to achieve and maintain target Hb whether receiving ESAs or not **(Evidence).**

AUDIT MEASURES

Serum ferritin
%Hypochromic red cells

%Transferrin saturation

RATIONALE

A definition of adequate iron status[1] is a serum ferritin

	200-500µg/l in haemodialysis patients,
	100-500ng/ml in non-haemodialysis patients
and either	<6% hypochromic red cells (HRC)
or	transferrin saturation >20%(TSAT) .

Several studies have reported that the dose of ESA required to achieve and maintain a given Hb outcome is inversely correlated to iron status[2-7]. Iron deficiency (absolute or functional) has historically been the main cause of ESA resistance in the UK although that may now have changed in the dialysis population in the modern era with adequate iron replacement strategies[8].
In haemodialysis patient populations the inverse relationship between ESA dose and iron status continues to maintain a linear relationship up to a mean ferritin of 500ng/ml. Compliance with ferritin >200 predicts compliance of the RA minimum standard for Hb of >85% Hb values >10.0g.dl[9]. Randomised studies of oral versus intravenous iron in haemodialysis patients have shown iv iron to be superior[10, 11].

In peritoneal dialysis patients and patients not on dialysis the evidence is not as strong. Hence for this patient population the lower ferritin of 100ng/ml is quoted by NICE[1].

One randomised study of intravenous iron versus oral iron in pre-dialysis patients demonstrated a greater improvement in Hb outcome in those on intravenous iron but no difference in the proportion of patients who had to commence ESA after the start of the study[12]. Two before and after studies in predialysis patients not on ESA demonstrated improvements in Hb outcome[13, 14]. Oral iron is easy and cheap to prescribe. It seems reasonable to treat patients who have not responded to, or been intolerant of, oral iron with intravenous iron.

Two randomised controlled studies of oral versus intravenous iron supplementation in pre-dialysis patients receiving concomitant ESAs are in agreement. In the first study over a mean 5.2 months follow-up there was no difference in Hb or ESA dose between the oral and iv group receiving EPO[15]. Iron stores were greater in the iv than oral group. Similar findings appeared in a later study comparing 5 weeks of iv iron or 29 days of thrice daily oral iron. There was no difference in Hb or ESA dose but greater increase in ferritin in the iv group[16].

In peritoneal dialysis patients a cross over study of oral and intravenous iron demonstrated higher Hb and lower ESA doses after 4 months oral iron followed by a washout period and a single total dose of intravenous iron[17].

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GUIDELINE C-HB 3.10: Initiation of ESA and iron status

ESA therapy should not be initiated in the presence of absolute iron deficiency (ferritin <100ng/ml) without also managing the iron deficiency[1]. In patients with functional iron deficiency, iron supplements should be given concurrently with initiating ESA therapy **(Evidence).**

AUDIT MEASURES

Ferritin levels at start of treatment with ESA.

RATIONALE

Iron is a required for production of new red cells. Iron must be supplied to the erythropoietic tissue at an adequate rate, particularly if stimulated by ESA therapy. If iron stores are low ESAs can still be used if renal anaemia is a likely contributor to the anaemia, as long as iron is made directly available to the erythropoietic tissues coincident with the initiation of ESA therapy.

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GUIDELINE C-HB 3.11: Iron status – Oral vs. Intravenous iron

Oral iron will, in general, be sufficient to attain and maintain the Hb above targets in CKD patients not yet requiring dialysis and in those on peritoneal dialysis (PD); in contrast, most HD patients will require intravenous iron**.** (Evidence)

AUDIT MEASURE

Proportion of haemodialysis patients receiving intravenous iron

RATIONALE

The evidence base for intravenous iron in CKD patients not yet on dialysis or on peritoneal dialysis is limited.

The evidence base for intravenous iron over oral iron in predialysis patients and peritoneal dialysis patients is severely limited. Oral iron, if tolerated, appears to be adequate in most patients particularly in combination with ESA therapy. In patients who appear resistant to ESA therapy on oral iron, or are intolerant of oral iron, a therapeutic trial of intravenous iron trial seems reasonable. A study in predialysis patients and peritoneal dialysis patients with functional iron deficiency despite oral iron therapy is needed. At present oral iron should remain first line and intravenous iron used when either patients are intolerant of oral iron or remain absolute or functionally iron deficient despite oral iron. From the evidence to date intravenous iron is at least equivalent to oral iron therapy in efficacy so can be administered to patients unable to take oral iron[1, 2].

Haemodialysis patients have additional iron losses in terms of GI bleeding, blood tests and losses to the dialysis lines that result in iron supplementation requirements that outstrip the capacity of the gut to absorb iron. Maintenance intravenous iron in haemodialysis patients greatly reduces ESA costs[1-4]. Increasing the haemoglobin in anaemic patients places the greatest demand for iron in the erythropoietic tissues. During ESA induction therapy iron requirements will depend on the rate of eryrthropoiesis, the Hb deficit, and ongoing iron loses. Once the target Hb has been reached and Hb stabilised the iron requirements will be dependent of ongoing iron losses. When adequate iron status is achieved, CKD patients on ESA therapy should be given maintenance iron.

Maintaining iron stores / maintaining a population ferritin outcome at steady state in a haemodialysis population requires 50-60mg/week of intravenous iron[4]

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GUIDELINE C-HB 3.12: Upper limit for iron therapy

For patients treated with iron, ferritin should not exceed 800ng/ml and to achieve this iron management should be reviewed when the ferritin > 500ng/ml **(Evidence).**

AUDIT MEASURE

Serum ferritin

RATIONALE

The UK Renal Registry Report 2005[1] demonstrates that the proportion of individuals in a haemodialysis population with values >100ng/ml, or >200ng/ml or indeed ferritin >800ng/ml is dependent on the median ferritin. As the distribution increases the compliance with values above minimum standards improves but the risk of breaching 800ng/ml (and therefore risk of toxicity) also increases. At a median ferritin of 500ng/ml 5-25% of individual patients may have a ferritin>800ng/ml. The lower the S.D. for ferritin, the lower the risk of a significant proportion of patients breaching 800ng/ml.

Discontinuation of adequate maintenance intravenous iron when an individual's ferritin > 500ng/ml produces a population mean that straddles the 500ng/ml ceiling[2]. On going iron therapy in patients with ferritin >500ng/ml results in higher median ferritin outcome[3].

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GUIDELINE C-HB 3.13: Monitoring during ESA therapy.

In the opinion of the working group Hb concentration should be monitored every 2-4 weeks in the correction phase and every 1-3 months for stable hospital patients[1-3]. More frequent monitoring will depend on clinical circumstances **(Good practice).**

RATIONALE

The response to ESA therapy varies widely between different patient groups and individuals within those groups. In addition an individuals response can vary greatly dependent on other clinical variables. During ESA initiation therapy, after drug dose adjustments or changes in an individual's clinical condition, more frequent monitoring is advised in order that under-treatment (ongoing anaemia) and over-treatment (rapidly rising Hb / hypertension or polycythaemia) be avoided.

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GUIDELINE C-HB 3.14: Monitoring during iron therapy.

In the opinion of the working group regular monitoring of iron status (1-3 monthly) is recommended during treatment to avoid toxicity (Good practice): a serum ferritin consistently greater than 800 µg/l is suggestive of iron overload[1-3]. (Good practice)

AUDIT MEASURE

Serum ferritin

RATIONALE

Intravenous iron therapy in particular has potential risks as well as benefits. Toxicity associated with high ferritin outcomes was originally reported in the

context of multiple transfusions in the pre-ESA era. The risk persists that intravenous iron may reproduce similar toxicity and thus regular monitoring during therapy is required. Similarly with ongoing iron losses on haemodialysis, regular monitoring to avoid worsening iron deficiency is required.

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GUIDELINE C-HB 3.15: Resistance to ESA therapy.

Failure to reach the target Hb level despite sc epoetin dose >300 IU/kg/week (450 IU/kg/week iv epoetin), or darbepoetin dose >1.5mcg/kg/week defines inadequate response ('resistance'). Hyporesponsive patients who are iron replete should be screened clinically and by investigations for other common causes. (Evidence)

AUDIT MEASURE

ESA dose

RATIONALE

The Revised European Best Practice Guidelines define ESA resistance as above. Failure to respond at an earlier stage in therapy should however raise the suspicion of resistance earlier. Comparison of the individual Hb outcome achieved and the dose of ESA used can provide a useful way of highlighting individuals that are resistant during local unit audit[1, 2]. ESA therapy is efficacious in most patients. However many conditions and treatment variables can cause resistance to ESA therapy. Adequate investigation and management of these underlying conditions is crucial in achieving satisfactory outcome haemoglobin values as well as requiring therapy in their own right. Extensive publications are available on the topic of resistance including the Revised European Best Practice Guidelines[3]. Anti EPO antibody associated PRCA is a very rare cause of resistance characterised by transfusion dependency, low reticulocyte count, lack of pro-erythroid progenitor cells in the bone marrow and neutralising anti-EPO antibodies[4].

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GUIDELINE C-HB 3.16: Hypertension during ESA therapy.

Blood pressure should be monitored in all patients receiving ESAs and, if present, hypertension treated by volume removal and/or hypotensive drugs. (Evidence)

AUDIT MEASURE

Blood pressure

RATIONALE

Hypertension is the most common complication in CKD. Hypertension is a recognised complication of ESA therapy[1] that can exacerbate the tendency to high blood pressure that already exists. Early studies demonstrated higher incidence rates of hypertension though ESA doses used were higher in these trials. It is now more common to start at reduced doses and increase doses incrementally according to response. The commonest cause of hypertension in CKD is not ESA therapy. Exacerbation of hypertension in ESA therapy patients may be associated with polycythaemia or rapidly rising haemoglobin levels. These complications should be looked for in hypertensive patients but in the absence of these complicating factors and in the absence of severe hypertension, ESA therapy can usually continue. Hypertension should be adequately controlled prior to initiating ESA therapy to reduce the incidence of confusion that may arise as to its cause.

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GUIDELINE C-HB 3.17: Transfusion

In circumstances where transfusion is required in CKD patients, haematology transfusion guidelines[1] should be adhered to and target Hb recommendations above do not apply to transfusion **(Evidence).**

AUDIT MEASURE

Number of patients transfused
Number of units transfused

RATIONALE

Treatment by ESA therapy is preferred to transfusion in order that the associated risks of transfusion are avoided and in order that scarce blood product resources are used most appropriately. Transfusion practice should be based on transfusion thresholds and targets that are set by local guidelines rather than similar targets for ESA therapy. When ESA therapy fails and the patient is stable and without cardiovascular disease transfusion is likely to be appropriate to maintain haemoglobin levels in the range 70-90 g/l. Transfusion is unlikely to be appropriate at haemoglobin levels >90 g/l. Indeed, particularly for younger patients and those patients who are on the transplant list (or may be on the transplant list in the future) then transfusion at or even below the lower end of this range may be deemed clinically appropriate.

For patients known to have or likely to have cardiovascular disease transfusion is likely to be appropriate to maintain haemoglobin in the range 90-100g/l.

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Section 4: C-NUTR – MANAGEMENT OF NUTRITION IN CKD

GUIDELINE C-NUTR 4.1: Nutritional Screening

All patients with stage 4-5 CKD should undergo regular nutritional screening (Good practice).

AUDIT MEASURE

Nutritional assessment should include a minimum of a record of body weight prior to onset of ill health (well weight), current body weight and ideal body weight; body mass index (weight/height^2); subjective global assessment, based on either a 3- or 7-point scale **(Good practice)**.

A diagnosis of undernutrition should be considered if any of the following criteria are met:

- unintentional fall in oedema free weight (>10% in last 6 months)
- unintentional fall in BMI or a BMI <18.5 kg/m^2
- SGA score of B/C (3-point scale) or of 1-2 (severe malnutrition) or 3-5 (mild to moderate malnutrition) (7-point scale).

A diagnosis of obesity should be considered if:

- BMI > 35 kg/m^2
- BMI > 30 kg/m^2 and considering renal transplantation

RATIONALE

Malnutrition is a frequent finding in ESRF, affecting 30-40% of patients (1). Undernurition worsens with falling GFR and increasing age. Extensive US (2) and European (3) guidelines on the assessment of nutrition in renal patients are available.

A number of potential measures of nutritional state, including serum creatinine (4) (creatinine is dependent on both renal function and muscle mass), serum cholesterol (4), serum albumin (4, 5), subjective global assessment (6), body mass index (7), lean body mass (6), and handgrip strength (8) predict worsened patient survival. This decrease in survival has been attributed to poor nutrition. However there is also a strong correlation between inflammation, atherosclerosis and poor nutrition, referred to as the MIA complex (9). The association between a low serum albumin and poor survival of dialysis patients predominantly reflects the association between serum albumin and inflammation (10), co-morbidity (11) and fluid overload (12).

There is no single ‘gold standard’ measure of nutritional state. Therefore a panel of measurements should be used, reflecting the various aspects of protein-calorie nutrition.

Assessment of nutrition in undernourished patients

If undernutrition is suspected then a full nutritional assessment should be undertaken by a clinician and/or renal dietitian. This should include a medical history, assessment of dietary intake (3-day food diary and measurement of protein equivalent of nitrogen appearance), anthropometric measures (mid-arm muscle circumference, triceps skinfold thickness and calculated mid-arm muscle circumference), and estimation of dialysis adequacy and of residual renal function. (Good practice).

Subjective global assessment includes gastrointestinal symptoms (appetite, anorexia, nausea, vomiting, diarrhoea), weight change in the preceding 6 months and last 2 weeks, evidence of functional impairment and a subjective visual assessment of subcutaneous tissue and muscle mass.

Serum albumin has been considered a marker of visceral protein and often used as a measure of nutritional state. Serum albumin is strongly predictive of mortality in pre-dialysis, dialysis and transplant populations. However the

relationship between serum albumin and nutritional state is weak and in general causes other than malnutrition should be excluded (13). Assessment might include C-reactive protein, evidence of atherosclerosis, 24-hour urinary protein loss, 24-hour peritoneal protein loss and determination of circulatory volume status by either clinical examination or supplementary technique (such as bio-electric impedance). (Good practice).

Many factors predispose to the development of undernutrition in patients with CRF. Some, such as changes in appetite, dental problems, vomiting and diarrhoea, may be identified through the patient's medical history. A decrease in appetite secondary to either uraemia or underdialysis should be confirmed with an assessment of dietary intake, residual renal function and dialysis dose. Protein intake can be obtained indirectly through the normalised equivalent of total protein nitrogen appearance (PNA) although this may give a spuriously high estimate in the presence of weight loss or active catabolism (14). A variety of techniques are available for recording dietary intake; food intake records and dietary recall are the commonest. The dietary protein intake in pre-dialysis patients who are not being prescribed a low protein intake should be at least 0.75 g/kg/day; in HD and PD patients 1.2 g/kg/day has been recommended. The recommended dietary energy intake in all three groups is at least 35 kcal/kg/day, although 30 kcal/kg/day may be sufficient in those over the age of 60. However many patients do not achieve these intakes and the consequences of this are not clear.

Acidosis is an established catabolic factor and to minimise this the bicarbonate concentration of CAPD and HD patients should be maintained within target range. **(Good practice).**

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