

CLINICAL PRACTICE GUIDELINES

Cardiovascular Disease in CKD

UK Renal Association

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Dr Stephen Holt & Dr David Goldsmith

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Please send feedback for the next edition to

Dr Stephen Holt at & Dr David Goldsmith

steve.holt@bsuh.nhs.uk and or David.Goldsmith@gstt.nhs.uk

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Acknowledgements

Introduction

This clinical practice guideline provides recommendations on the prevention and management of cardiovascular disease in patients with chronic kidney disease (CKD) and serves as an update of the 4th edition module published online in 2007 (www.renal.org). The literature in the English language has been searched and reviewed to take account of studies that have been published between 2006 and February 2010 using a strategy based on the search terms listed below:

Mortality AND (dialysis OR renal failure)
Smoking AND (dialysis OR renal failure)
Diabetic control AND (dialysis OR renal failure)
Cholesterol AND (dialysis OR renal failure)
Lipids AND (dialysis OR renal failure)
Homocysteine AND (dialysis OR renal failure)
(Folic acid OR folate) AND (dialysis OR renal failure)
Cardiovascular disease AND (dialysis OR renal failure)
Coronary artery disease AND (dialysis OR renal failure)
Ischaemic heart disease AND (dialysis OR renal failure)
Cardiovascular risk AND (dialysis OR renal failure)
Exercise AND (dialysis OR renal failure)
(Blood Pressure OR Hypertension) AND (dialysis OR renal failure)
(Blood Pressure OR Hypertension) AND (dialysis OR renal failure)

The recommendations in this update have been graded using the modified GRADE system (1,2) to indicate both the strength of each recommendation (strong or weak) and level of evidence for the recommendation (A-D). Thus, the grading of the recommendations ranges from 1A - 2D.

The authors also reviewed the guidance on cardiovascular disease in CKD from other guideline organisations. The recommendations within this guideline have been harmonised with other national guidance on the management of cardiovascular disease in CKD whenever possible and this guideline supports the recommendations on cardiovascular management of the Joint British Societies (3) and National Collaborating Centre for Chronic Conditions (4).

Guidance on blood pressure measurement and targets in the subgroup of CKD patients on haemodialysis was not included in the last edition given the difficulty in providing recommendations on this topic based on evidence. The recent KDIGO controversies conference on hypertension in dialysis patients re-affirmed this viewpoint (5) and so it is not planned to include recommendations on treatment of hypertension in dialysis patients in the KDIGO guideline on hypertension in CKD due in 2011 (6). However, as clinical staff have requested guidance on the treatment of hypertension in dialysis patients, pre- and post-dialysis blood pressure levels are audited by the UK Renal Registry and a recent meta-analysis broadly supports the lowering of high levels of blood pressure in dialysis patients (7), we have included a section on the management of hypertension in dialysis patients in this edition using the modified GRADE system to qualify its recommendations appropriately with the level of evidence available. The reader is referred to the KDIGO website which is a useful site of reference for comparison of evidence based guidelines internationally (6)

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Summary of clinical practice guidelines for cardiovascular disease in CKD

1. Cardiovascular disease in CKD (CVD) (Guidelines CVD 1.1-1.8)

Guideline 1.1 – CVD: Cardiovascular risk factors

We recommend that a history of and risk factors for cardiovascular disease in patients with CKD Stage 1- 5 and dialysis patients should be recorded in a format that permits audit of the management of such patients. (1B)

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
- Diabetes
- Ethnicity

Guideline 1.2 – CVD: Cardiovascular risk factors

We recommend that a healthy lifestyle should be encouraged in all CKD patients, including dialysis patients. (1C)

Guideline 1.3 - CVD: Cardiovascular risk factors

We suggest that 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. (2B)

Guideline 1.4 - CVD: Cardiovascular risk factors

We suggest that 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. (2C)

Guideline 1.5 - CVD: Cardiovascular risk factors

We suggest that the target glycated haemoglobin (HbA_{1c}) in all CKD, dialysis and kidney transplant patients with diabetes should be between 6% (43 mmol/mol/HbA₀) and 7.5% (58 mmol/mol/HbA₀). (2C)

Guideline 1.6 - CVD: Cardiovascular risk factors

We recommend that statins (or 3 hydroxy-3methylglutaryl-coenzyme A reductase inhibitors) should be considered for primary prevention in all CKD Stages 1-4 and transplant patients with a 10-year risk of cardiovascular disease, calculated as > 20% according to the Joint British Societies' Guidelines (British Hypertension Society British Cardiac Society 2005). (1B)

Guideline 1.7 - CVD: Cardiovascular risk factors

We recommend that a total cholesterol of <4 mmol/l or a 25% reduction from baseline, or a fasting low density lipoprotein (LDL)-cholesterol of <2 mmol/l or a 30% reduction from baseline, should be achieved, whichever is the greatest reduction in all patients. (1B)

Guideline 1.8 - CVD: Cardiovascular risk factors

We suggest that 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. (2C)

2. Cardiovascular disease in CKD (CVD) (Guidelines CVD 2.1-2.3)

Guideline 2.1 - CVD: Hyperhomocysteinaemia and folate supplementation

We suggest that folic acid supplements should be offered to all renal patients considered nutritionally at risk from deficiency of folic acid. Serum and red cell folate should be above the lower limit of the reference range in all CKD patients including patients on dialysis and after transplantation. (2C)

Guideline 2.2 - CVD: Hyperhomocysteinaemia and folate supplementation

We suggest that red cell folate levels should be checked if MCV remains high despite normal or high serum folate. (2C)

Guideline 2.3 - CVD: Hyperhomocysteinaemia and folate supplementation

We suggest that serum folate levels and B12 should be checked 6 monthly in CKD stage 4/5 patients and 3 monthly in dialysis patients or more frequently if patients remain anaemic or deficient on initial sampling. (2D)

3. Cardiovascular disease in CKD (CVD) (Guideline CVD 3.1-3.6)

Guideline 3.1 - CVD: Secondary prevention of cardiovascular risk

We recommend that CKD stage 1-3 patients with a history of chronic stable angina, acute coronary syndrome, myocardial infarction, stroke, peripheral vascular disease, or who undergo surgical or angiographic coronary revascularisation, should be prescribed aspirin, an ACE inhibitor, a beta-blocker, and an HMG–CoA reductase inhibitor unless contraindicated as per NICE Guidance. (1B)

Guideline 3.2 - CVD: Secondary prevention of cardiovascular risk

We suggest that CKD stage 4/5 patients (including those on dialysis and after transplantation) with a history of chronic stable angina, acute coronary syndrome, myocardial infarction, stroke, peripheral vascular disease, or who undergo surgical or angiographic coronary revascularisation, should be prescribed aspirin, an ACE inhibitor, a beta-blocker, and an HMG–CoA reductase inhibitor unless contraindicated as per NICE Guidance. (2C)

Guideline 3.3 - CVD: Secondary prevention of cardiovascular risk

We suggest that aspirin and clopidogrel is indicated for up to 12 months post angioplasty and stenting and in non-ST elevation MI but may have an excess in bleeding complications. (2C)

Guideline 3.4 - CVD: Secondary prevention of cardiovascular risk

We suggest that aspirin is indicated for secondary prevention but not primary prevention of vascular disease in renal failure. (2C)

Guideline 3.5 - CVD: Secondary prevention of cardiovascular risk

We suggest that the doses of ACE inhibitors and beta-blockers should be the maximum tolerated. (2C)

Guideline 3.6 - CVD: Secondary prevention of cardiovascular risk

We suggest that patients on lipid-lowering drug treatment should have total cholesterol reduced by 25% or to below 4 mmol/l, or LDL-cholesterol to below 2 mmol/l, or reduced by 30%, whichever reductions are the greatest. (2B)

4. Cardiovascular disease in CKD (CVD) (Guideline CVD 4.1-4.3)

Guideline 4.1 - CVD: Cardiac investigations and coronary revascularization

We suggest that CKD and dialysis patients should have unimpeded access to a full range of cardiac investigations including exercise and stress echocardiography, radio-isotopic cardiac scans and coronary angiography. They should also have unimpeded access to cardiology assessment for coronary angioplasty, coronary stenting and cardiac surgery. (2D)

Guideline 4.2 - CVD: Cardiac investigations and coronary revascularization

We suggest that there should be no clinically important delay for pre-dialysis and dialysis patients in receiving assessment by cardiology colleagues for their suitability for transplantation. These issues are often best addressed by regular/joint working with other disciplines. (2D)

Guideline 4.3 - CVD: Cardiac investigations and coronary revascularization

We suggest that the patient's view of the risk and benefit in deciding whether to undergo complex procedures, including renal transplantation, should always carry significant weight in the eventual decisions reached. (2D)

5. Cardiovascular disease in CKD (CVD) (Guideline CVD 5.1-5.7)

Guideline 5.1 - CVD: Hypertension in non-dialysis patients

We suggest that BP in CKD stage 1-4 patients should be managed according to NICE guidance: <140/90 in patients without significant proteinuria and <130/80 in those with proteinuria or diabetics. (2C)

Guideline 5.2 - CVD: Hypertension in dialysis patients

We suggest that pre- and post-dialysis blood pressure (measured after completion of dialysis, including washback) should be recorded and intra-dialytic blood pressure measurements should be made to facilitate good management of the HD session. (2D)

Guideline 5.3 - CVD: Hypertension in dialysis patients

We suggest that home or ambulatory blood pressure recordings should be performed if pre- and post- HD blood pressures are consistently elevated. (2C)

Guideline 5.4 - CVD: Hypertension in dialysis patients

Blood pressure targets for dialysis patients are difficult to recommend in the absence of RCTs showing survival benefit, and even more difficult to achieve in practice. However we suggest that it would be sensible to avoid sustained BP extremes and, in order to try to provide some guidance we suggest that systolic blood pressure during the inter-dialytic period on HD and for PD patients should not regularly exceed >160mmHg (2C)

Guideline 5.5 - CVD: Hypotension / Hypertension in dialysis patients

We suggest that systolic blood pressure should not routinely be treated with pharmacological agents with antihypertensive properties if SBP is regularly <110mmHg pre dialysis. Discussion with cardiological colleagues may be prudent if ACEI, ARB or betablockers are being used for LV systolic or diastolic dysfunction in the context of low BP (2D).

Guideline 5.6 - CVD: Hypertension in dialysis patients

We suggest that dialysis patients should be on a restricted sodium (<5g/day) diet. (2C)

Guideline 5.7 - CVD: Hypertension in dialysis patients

We suggest that hypertension on dialysis should be managed by ultrafiltration in the first instance. (2D)

Summary of audit measures for Cardiovascular Disease in CKD

1. Compliance with recording of cardiovascular co-morbidity at the time of referral to a renal unit and when starting renal replacement therapy.

2. Proportion of patients smoking and proportion referred for active help regarding cessation.
3. Proportion of patients performing regular exercise on haemodialysis
4. Record of glycated haemoglobin concentrations in IFCC (mmol/mmol) and HBA1C%.
5. Record of prescribed statins allied to indications and co-morbidities of patients
6. Cholesterol concentrations in patients prescribed HMG CoA reductase inhibitors
7. Delay between referral to cardiology for an assessment for renal transplantation and the final cardiological sign-off indicating fitness to proceed should be less than 3 months.
8. Pre, post and intra-dialytic blood pressure in HD patients
9. Blood pressure in peritoneal dialysis patients
10. Home and /or ambulatory blood pressure recordings

Rationale of clinical practice guidelines for Cardiovascular Disease in CKD

1. Cardiovascular disease in CKD (CVD) (Guidelines CVD 1.1-1.8)

Guideline 1.1 – CVD: Cardiovascular risk factors

We recommend that a history of and risk factors for cardiovascular disease in patients with CKD Stage 1- 5 and dialysis patients should be recorded in a format that permits audit of the management of such patients. (1B)

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
- Diabetes
- Ethnicity

Guideline 1.2 – CVD: Cardiovascular risk factors

We recommend that a healthy lifestyle should be encouraged in all CKD patients, including dialysis patients. (1C)

Audit measure

Record of cardiovascular co-morbidity at the time of referral to a renal unit and when starting renal replacement therapy

Rationale for 1.1 and 1.2

Patients with renal impairment have a higher burden of vascular disease than age matched controls at all levels of renal dysfunction (1) and cardiovascular disease is the main cause of death in these patients. This risk is more apparent in younger patients where for example a 35 year old man on dialysis has the same risk of a cardiovascular death as an 80 year old not on dialysis (2). Accurate recording of traditional cardiovascular risk factors and co-morbid cardiovascular disease will enable adjustment for case-mix in analysis of patient outcomes.

Obesity is a risk factor in developing renal disease (3) and weight loss programmes can help obese pre dialysis patients in by reducing proteinuria, BP and rate of renal decline (4). Exercise in addition to Orlistat and dietary intervention has also been used to help improve suitability for transplantation (5). Less data is available for patients treated by PD.

In addition to traditional risk factors associated with increased risk of cardiovascular disease such as hypertension and hypercholesterolaemia, other factors complicate and may accelerate vascular disease in patients with CKD, notably disordered mineral metabolism (2). While plentiful epidemiological evidence continues to accumulate relating plasma phosphate concentrations in particular to adverse outcomes, there are no RCTs of phosphate reduction to show any cardiovascular benefit from that intervention. Ethnicity also affects cardiovascular risk (6). Anaemia was thought to play a role in the early development of cardiovascular disease and may still be important (7). However the publication of several RCTs including CREATE (8), CHOIR (9), and in particular the placebo-controlled TREAT (10) have challenged the “cardiovascular” rationale behind anaemia correction. This remains controversial; partial correction may be important and different targets may apply to different subgroups (11). However it is now recognised that complete anaemia correction may not be advisable in pre-dialysis or dialysis patients (12).

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, especially stage 5D (dialysis) patients. Readers are referred to the Renal Association guidelines on anaemia and mineral and bone disorders in CKD @ www.renal.org and the KDIGO guideline on mineral and bone disorders (13).

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Guideline 1.3 - CVD: Cardiovascular risk factors

We suggest that 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. (2B)

Audit measure

Proportion 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 (1). In CKD, smoking is associated with more rapid progression of renal disease (2), higher levels of established renal failure (3) and higher cardiovascular mortality following transplantation (4,5).

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Guideline 1.4 - CVD: Cardiovascular risk factors

We suggest that 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. (2C)

Audit measure

Proportion of patients performing regular exercise on haemodialysis

Rationale

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 is poor in dialysis patients compared to age matched controls (1). Exercise training improves maximal exercise capacity, muscle strength and endurance in pre dialysis patients in all age groups (2).

Morphological and metabolic benefits in skeletal muscle have been well documented in HD patients following exercise training programs and there may be other benefits e.g. in reducing restless leg syndrome. However the benefit of exercise in dialysis patients is based on small numbers of studies with few patients. In these studies, exercise is claimed to improve quality of life, increase haematocrit, enhance exercise capacity and VO₂ max, and increase endurance and muscle strength (3-5) 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 (6). There was no association between increased survival and daily exercise so 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 after 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 (7). Improvement is sustained for 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 during dialysis (8).

The amount of exercise that patients should take is not known but studies usually describe graded exercise individualised to patients with both low cardiovascular exercises (<3 times a week for <20 minutes) or cardiovascular exercise that exceeds this. Benefits have been described with both approaches (9).

However, exercise is generally considered an important part of staying well and this should be taken into consideration when designing an exercise programs for patients with CKD.

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Guideline 1.5 - CVD: Cardiovascular risk factors

We suggest that the target glycated haemoglobin (HbA_{1c}) in all CKD, dialysis and kidney transplant patients with diabetes should be between 6% (43 mmol/mol/HbA₀) and 7.5% (58 mmol/mol/HbA₀). (2C)

Audit measure

Record of glycated haemoglobin concentrations in IFCC (mmol/mol) and HbA_{1c}%

Rationale

Previously HbA_{1c} was measured using an assay method harmonized to the Diabetes Control and Complications Trial (DCCT) standard (1). Recent international discussion of HbA_{1c} methodology coordinated by the international federation of clinical chemistry (IFCC) has meant that all laboratories should move to new units of HbA_{1c} expressed as a fraction of HbA₀ with respect to HgA₀ (mmol/mol). Thus the agreed calculation to convert the DCCT% value to the IFCC value is: IFCC (mmol/mol HbA₀) = (DCCT% - 2.15) x 10.929 (2).

Measurement of HbA_{1c} 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. 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 HbA_{1c} values during the nine-year study were 7.2% (55 mmol/mol) with intensive therapy and 9.1% (76 mmol/mol) 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 type 1 and type 2 patients (3). The UKPDS also demonstrated that improved glycaemic control in newly diagnosed type 2 diabetic patients reduced the incidence of diabetic microvascular complications (4).

Though intensive glycaemic control can delay the onset and slow progression of retinopathy, nephropathy and neuropathy no intensive glycaemic control trial to date has resulted in a significant reduction in cardiovascular end points.

Observational studies suggest that HbA_{1c} influences cardiovascular event rates (5) and survival (6). 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 glycosylated haemoglobin (7). The Veterans Affairs Diabetes Trial (VADT) in type 2 diabetes showed that intensive treatment improves cardiovascular events but only in those with less extensively calcified coronary disease (8). This may mean that for many dialysis patients there is less protective effect of intensive glucose control. Thus the effect of reaching an HbA_{1c} of less than 7.5% in many elderly type 2 diabetics on dialysis may have a modest effect on outcome and needs to be weighed against the risk of hypoglycaemic events. Three recent studies in the non-CKD setting (VADT(8), ACCORD (9) and ADVANCE (10)) remind us that more intensive blood glucose control in the frailer older type 2 diabetic patient might be detrimental not beneficial (11). HD *per se* has no significant long-term effect on glycaemic control in insulin-treated type 2 diabetic patients. In PD patients the glucose load may require an increase in insulin or oral hypoglycaemic drugs.

New-onset diabetes after renal transplantation (NODAT) occurs in between 2% and 54% of patients, depending on a large number of factors from age, gender and race to immunosuppressive protocols employed. It is associated with worse graft and patient survival. In the absence of contrary evidence it would seem sensible to aim for a similar HbA_{1c} target in transplanted patients with diabetes, but again no data exists specifically in this cohort.

Recommendations from other guidelines:

- JBS 2 recommend a HbA_{1c}% target of < 6.5%, with an audit standard of < 7.5% (12).
- NICE recommend for each individual the target HbA_{1c} should be set between 6.5% and 7.5% (13)
- KDOQI recommend a target of < 7.0% for people with diabetes irrespective of the

presence or absence of CKD (14)

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Guideline 1.6 - CVD: Cardiovascular risk factors

We recommend that statins (or 3 hydroxy-3methylglutaryl-coenzyme A reductase inhibitors) should be considered for primary prevention in all CKD Stages 1-4 and transplant patients with a 10-year risk of cardiovascular disease, calculated as > 20% according to the Joint British Societies' Guidelines (1). (1B)

Guideline 1.7 - CVD: Cardiovascular risk factors

We recommend that a total cholesterol of <4 mmol/l or a 25% reduction from baseline, or a fasting low density lipoprotein (LDL)-cholesterol of <2 mmol/l or a 30% reduction from baseline, should be achieved, whichever is the greatest reduction in all patients. (1B)

Guideline 1.8 - CVD: Cardiovascular risk factors

We suggest that 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. (2C)

Audit measures

Record of prescribed statins allied to indications and comorbidities of patients

Cholesterol concentrations in patients prescribed HMG CoA reductase inhibitors

Rationale for guidelines 1.6-1.8

Management should seek to lower cardiovascular risk through a multidisciplinary approach to risk factors, targeting patients with and those who are at high risk of atherosclerotic events. This is the principle behind the Joint British Societies' Guidelines, in defining cardiovascular risk (1). Estimation of cardiovascular risk will require accurate recording of data for each patient

regarding smoking, family history of premature vascular disease, blood pressure, total and HDL-cholesterol and presence of diabetes in addition to age and gender .

Dyslipidaemia is very prevalent in CKD and is influenced by renal function and by degree of proteinuria. There is a reduction of total, HDL and LDL cholesterol concentrations as GFR declines; it is clearly known that significant hypoalbuminaemia secondary to heavy proteinuria, as seen in nephrotic syndrome, is accompanied by a secondary dyslipidaemia (2,3). The use of statins in patients with CKD stages 1-4 has been extensively studied and found to be safe and effective at reducing cardiovascular mortality (4). There are also some data suggesting that their use may retard progression of renal disease via a non lipid mechanism (5). This remains controversial and may only be answered (in 2011) by UK-HARP-2. A Cochrane review, incorporating the ALERT study (6), of the use of statins in the post transplantation setting concludes that these agents provide protection against cardiovascular events but there is as yet no evidence of a mortality benefit (4).

Studies in HD patients have shown a U-shaped relationship between serum cholesterol and subsequent mortality (7). This counterintuitive association is probably an example of reverse causation: chronic disease, chronic inflammation, and malnutrition all lead to a reduction in cholesterol levels and are strong independent risk factors for death.

Two large observational studies have suggested benefit from statins in the dialysis population (8,9). However, much more powerful information has come from more recent large randomised controlled trials and the data from these studies do not support this position (10,11). Other trials, most notably UK-HARP-2, are ongoing to determine whether cholesterol lowering has a role in primary prevention of cardiovascular disease in dialysis patients (12).

Although hypercholesterolaemia may have the same role in atherogenesis this may have a smaller impact in dialysis patients as these patients may die from cardiovascular causes other than those directly related to coronary artery atheromatous disease. Sudden cardiac death is a good example. A recent Cochrane report on statins in dialysis patients, looked at studies of statin versus placebo and failed to identify all cause mortality (10 studies) or cardiovascular mortality (9 studies) benefits from statin therapy (4). However these studies do not suggest that there is any harm from such statin-based therapy, with side effect profiles being similar to those seen in the general population. Until further evidence is available the advice is to continue to treat these patients with statins to achieve the above targets.

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2. Cardiovascular disease in CKD (CVD) (Guidelines CVD 2.1-2.3)

Guideline 2.1 - CVD: Hyperhomocysteinaemia and folate supplementation

We suggest that folic acid supplements should be offered to all renal patients considered nutritionally at risk from deficiency of folic acid. Serum and red cell folate should be above the lower limit of the reference range in all CKD patients including patients on dialysis and after transplantation. (2C)

Guideline 2.2 - CVD: Hyperhomocysteinaemia and folate supplementation

We suggest that red cell folate levels should be checked if MCV remains high despite normal or high serum folate. (2C)

Guideline 2.3 - CVD: Hyperhomocysteinaemia and folate supplementation

We suggest that serum folate levels and B12 should be checked 6 monthly in CKD stage 4/5 patients and 3 monthly in dialysis patients or more frequently if patients remain anaemic or deficient on initial sampling. (2D)

Rationale for Guidelines 2.1-2.3

Homocysteine levels are associated with vascular disease in the general population and can be reduced by supplementation with folic acid by ~25%, and vitamin B12 by ~7% (1), while vitamin B6 may have a minor role. There are of course sound haematopoietic rationales for the use of these supplements if there is anaemia or macrocytosis which can be attributed to deficiency of folate (2). Folate deficiency occurs within 3-6 months if no intake is given.

Homocysteine levels are higher in patients with all levels of renal impairment (3), and are ~3 times higher in patients with established renal failure (4). The elevation of homocysteine levels seen in CKD mirrors closely the degree of loss of renal function; indeed this is a major potential confounder when considering epidemiological associations between plasma homocysteine concentrations and adverse events. While there does seem to be a graded relationship between adverse outcomes and plasma homocysteine concentrations in CKD in most series and meta-analyses (5), some would argue that there is significant reverse causality in operation with inflammation and malnutrition being more prevalent with lower levels (6).

Intriguingly, acute administration of IV folate may have some vascular protective effects in HD patients (7) but this needs confirming, and, there is no evidence yet that these vascular changes will impact favourably on outcomes. This area is further complicated by the possibility that folate/folinic acid may have biological effects which are not related to any alteration in plasma homocysteine concentrations.

The homocysteine response to these vitamins varies in established renal failure, but there is no problem with absorption of these vitamins in HD patients (8). However there may be differences in response to these vitamins on homocysteine levels between HD and PD patients (9). Mutations in the gene regulating methylenetetrahydrofolate reductase, which increase homocysteine levels in patients with renal failure, are associated with enhanced cardiovascular mortality (10). RCTs of vitamin treatment in the general population with normal kidney function have been largely negative (11). Trials of vitamins in renal failure have been equally disappointing (3). Specifically, there was no overall benefit on mortality (12), or on cognitive function (13) as a result of folate supplementation. Folate deficiency is rare in countries that supplement foods routinely with this vitamin. Nevertheless correction of folate deficiency is good clinical practice irrespective of putative effects on homocysteine levels or vascular disease risk.

In stable renal transplant recipients an elevated fasting homocysteine blood level is an independent risk factor for cardiovascular disease (14). The ongoing FAVORIT study may provide evidence as to whether standard multivitamin therapy including folic acid and vitamins B12 will affect cardiovascular outcomes in renal transplant recipients (15).

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3. Cardiovascular disease in CKD (CVD) (Guideline CVD 3.1-3.6)

Guideline 3.1 - CVD: Secondary prevention of cardiovascular risk

We recommend that CKD stage 1-3 patients with a history of chronic stable angina, acute coronary syndrome, myocardial infarction, stroke, peripheral vascular disease, or who undergo surgical or angiographic coronary revascularisation, should be prescribed aspirin, an ACE inhibitor, a beta-blocker, and an HMG–CoA reductase inhibitor unless contraindicated as per NICE Guidance. (1B)

Guideline 3.2 - CVD: Secondary prevention of cardiovascular risk

We suggest that CKD stage 4/5 patients (including those on dialysis and after transplantation) with a history of chronic stable angina, acute coronary syndrome, myocardial infarction, stroke, peripheral vascular disease, or who undergo surgical or angiographic coronary revascularisation, should be prescribed aspirin, an ACE inhibitor, a beta-blocker, and an HMG–CoA reductase inhibitor unless contraindicated as per NICE Guidance. (2C)

Guideline 3.3 - CVD: Secondary prevention of cardiovascular risk

We suggest that aspirin and clopidogrel is indicated for up to 12 months post angioplasty and stenting and in non-ST elevation MI but may have an excess in bleeding complications. (2C)

Guideline 3.4 - CVD: Secondary prevention of cardiovascular risk

We suggest that aspirin is indicated for secondary prevention but not primary prevention of vascular disease in renal failure. (2C)

Guideline 3.5 - CVD: Secondary prevention of cardiovascular risk

We suggest that the doses of ACE inhibitors and beta-blockers should be the maximum tolerated. (2C)

Guideline 3.6 - CVD: Secondary prevention of cardiovascular risk

We suggest that patients on lipid-lowering drug treatment should have total cholesterol reduced by 25% or to below 4 mmol/l, or LDL-cholesterol to below 2 mmol/l, or reduced by 30%, whichever reductions are the greatest. (2B)

Audit measures

Cholesterol concentrations in patients prescribed HMG CoA reductase inhibitors

Rationale

Survival after myocardial infarction in CKD patients is poor and correlates with the degree of renal impairment (1). There is evidence for underuse of guideline based therapies in this group but this does not account for all the excess risk conferred by renal impairment (2).

Guidelines for the management of non-renal patients with proven cardiovascular disease should be followed (3). This includes both non-pharmacological therapies (Guidelines 1.2-1.4) and pharmacological treatments with ACE inhibitors, beta-adrenergic blockers, aspirin and HMG-CoA reductase inhibitors.

Recent data have cast doubt on the role of aspirin for primary prevention of vascular disease in all but the very high risk individual with normal renal function because of the risk of haemorrhagic stroke and the relatively low (compared with secondary prevention patients) risk of a vascular event (4). There are no data that allow us to know this information in patients with renal impairment, although the benefits appear to outweigh the risks in secondary prevention in both the normal and the CKD patient. There are conflicting data, and observational studies have raised some concerns, that aspirin may not be as safe in established renal failure. Analysis of DOPPS data (5) suggests that it reduces stroke but failed to demonstrate benefit in cardiovascular disease – indeed, there was an excess incidence of MI in aspirin users, but there are confounding factors that make these data difficult to interpret. The safety study that preceded UK-HARP-2, known as UK-HARP-1 (6) which included aspirin use, did not suggest any special safety concerns. There are no randomised controlled studies of the use of aspirin in CKD patients, and current advice is that aspirin for secondary prevention probably should be prescribed at “low dose” (75-150) mg in patients with CKD stage 5 (7).

Clopidogrel similarly has a lack of RCT data but some studies, although not looking at this outcome, suggest that it is safe (8) and thus it could be used for secondary prevention in those intolerant of aspirin. The combination of aspirin and clopidogrel is suggested as secondary prevention up to 12 months after angioplasty and in non STEMI. This combination was beneficial overall in a retrospective analysis of Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) data in patients with renal impairment with a moderate increase in the risk of haemorrhage (9).

The rationale for the use of HMG–CoA reductase inhibitors in CKD is discussed in the rationale after Guidelines 1.6-1.8.

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4. Cardiovascular disease in CKD (CVD) (Guideline CVD 4.1-4.3)

Guideline 4.1 - CVD: Cardiac investigations and coronary revascularization

We suggest that CKD and dialysis patients should have unimpeded access to a full range of cardiac investigations including exercise and stress echocardiography, radio-isotopic cardiac scans, and coronary angiography. They should also have unimpeded access to cardiology assessment for coronary angioplasty, coronary stenting and cardiac surgery. (2D)

Guideline 4.2 - CVD: Cardiac investigations and coronary revascularization

We suggest that there should be no clinically important delay for pre-dialysis and dialysis patients in receiving assessment by cardiology colleagues for their suitability for transplantation. These issues are often best addressed by regular/joint working with other disciplines. (2D)

Guideline 4.3 - CVD: Cardiac investigations and coronary revascularization

We suggest that the patient's view of the risk and benefit in deciding whether to undergo complex procedures, including renal transplantation, should always carry significant weight in the eventual decisions reached. (2D)

Audit measure

Delay between referral to cardiology for an assessment for renal transplantation and the final cardiological sign-off indicating fitness to proceed should be less than 3 months.

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 often difficult because 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 should not depend on whether a patient has CKD or is on dialysis and so dialysis patients should benefit from this intervention (3). Many such patients 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. However, sensible though this sounds, it has not been demonstrated to be beneficial clinically. Moreover, if there is significant delay in receiving all of the appropriate investigations, there is a risk of a patient succumbing to a dialysis-related adverse event before having the chance to be transplanted. This is especially important in the pre-dialysis, pre-emptive transplantation setting, and also for patients with identified living renal transplant donors.

Risk markers for the presence of coronary artery disease in dialysis patients include:

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

Decisions on whether a patient is 'fit' for renal transplantation, therefore, have to be made on an individual basis, taking into account the patient's views and knowledge of their likely survival on dialysis. These decisions will also be influenced by local policy governing access to the transplant waiting list (see Renal Transplantation module). Prophylactic coronary intervention is controversial and is not currently advocated (4)

Percutaneous angioplasty with or without stenting (5) and surgical revascularisation (6) are associated with worse survival, a higher complication rate and higher re-stenosis rates in CKD patients compared to subjects without significant CKD. However similar survival rates are found when comparing coronary revascularisation in dialysis patients with CKD patients stages 3-5 not on dialysis. The ARTS trial was designed to compare coronary artery stenting with bypass surgery for multivessel coronary disease in patients with CKD stages 3-5. 142 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 (5). 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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5. Cardiovascular disease in CKD (CVD) (Guideline CVD 5.1-5.6)

Guideline 5.1 - CVD: Hypertension in non-dialysis patients

We suggest that BP in CKD stage 1-4 patients should be managed according to NICE guidance: <140/90 in patients without significant proteinuria and <130/80 in those with proteinuria or diabetics (2C).

Guideline 5.2 - CVD: Hypertension in dialysis patients

We suggest that pre- and post-dialysis blood pressure (measured after completion of dialysis, including washback) should be recorded and intra-dialytic blood pressure measurements should be made to facilitate good management of the HD session. (2D)

Guideline 5.3 - CVD: Hypertension in dialysis patients

We suggest that home or ambulatory blood pressure recordings should be performed if pre- and post- HD blood pressures are consistently elevated. (2C)

Guideline 5.4 - CVD: Hypertension in dialysis patients

Blood pressure targets for dialysis patients are difficult to recommend in the absence of RCTs showing survival benefit, and even more difficult to achieve in practice. However we suggest that it would be sensible to avoid sustained BP extremes and, in order to try to provide some guidance we suggest that systolic blood pressure during the inter-dialytic period on HD and for PD patients should not regularly exceed >160mmHg (2C)

Guideline 5.5 - CVD: Hypotension / Hypertension in dialysis patients

We suggest that systolic blood pressure should not routinely be treated with

pharmacological agents with antihypertensive properties if SBP is regularly <110mmHg pre dialysis. Discussion with cardiological colleagues may be prudent if ACEI, ARB or betablockers are being used for LV systolic or diastolic dysfunction in the context of low BP (2D).

Guideline 5.6 - CVD: Hypertension in dialysis patients

We suggest that dialysis patients should be on a restricted sodium (<5g/day) diet. (2C)

Guideline 5.7 - CVD: Hypertension in dialysis patients

We suggest that hypertension on dialysis should be managed by ultrafiltration in the first instance. (2D)

Audit measures

Pre, post and inter-dialytic blood pressure in HD patients
Blood pressure in peritoneal dialysis patients
Home and /or ambulatory blood pressure recordings

Rationale

Blood pressure (BP) has been confirmed as a major risk factor for renal (1) and cardiovascular mortality (2). BP reduction in the general population has proven cardiovascular benefit (3) and similar benefit has advocated for patients with CKD stages 1-4 and these patients should be treated with antihypertensive agents as per NICE Guidance (4) which recommends BP targets for CKD 1-4 patients as follows:

In people with CKD aim to keep the systolic blood pressure below 140 mmHg (target range 120–139 mmHg) and the diastolic blood pressure below 90 mmHg.

In people with diabetes and CKD or when the ACR is ≥ 70 mg/mmol or PCR ≥ 100 mg/mmol (approximately equivalent to PCR ≥ 100 mg/mmol, or urinary protein excretion ≥ 1.0 g/24 h) aim to keep the systolic blood pressure below 130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg.

The problem of interpreting BP values in CKD stage 5D patients is very challenging indeed. In any individual there is a complex interplay between volume overload with salt (and water) which may be appropriately addressed by diuretics or dialysis, and/or vasoconstriction caused by neurohumoral mechanisms and this may be treated with antihypertensive drugs. These mechanisms lead to vascular and cardiac dysfunction and may be important in the observation of the “U-shaped” mortality curve seen when considering blood pressure in dialysis patients (5). The most likely explanation of this counterintuitive relationship between blood pressure and mortality, 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 (6). The NICE CKD stages 1-4 guidance suggests that low blood pressures (<120/60) are associated with adverse outcomes (4) but no full recommendations were made about this.

Nevertheless, there were strong implications in these guidelines that lower pressures were suboptimal, perhaps by causing underperfusion of the coronary circuit. There are accumulating data in HD patients that suggest low blood pressure and other factors contribute to myocardial dysfunction during dialysis and this contributes to vascular morbidity and mortality (7). How to best respond to this particular challenge awaits planned RCTs.

The correct measurement of BP in the setting of regular HD is especially challenging. Preparation and travel for dialysis, the practice of dialysis, and other factors such as the use of, or abandonment of, anti-hypertensive medication (and the effect of dialysis on the bioactivity of anti-hypertensives) all conspire to mean that the convenient (but often poorly standardised) practice of obtained BP levels just before and just after dialysis sessions is profoundly misleading. In the management of essential hypertension, care in the interpretation of blood pressure measurements is just as important – these should be taken while the patient is free from anxiety or stress. Current recommendations (8) 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. It is recognised that the practicalities of such recommendations mean that these are usually aspirational procedures and are sadly highly unlikely to be achieved in any UK renal unit outside of a clinical trial setting. Indeed many automated BP measurements taken in dialysis units were found to be $>14/7$ mmHg higher than standard human recordings (9). Thus if pre and post HD blood pressures are consistently elevated, home or ambulatory blood pressure recordings (ABPM) should be considered in trying to confirm or refute the presence of inappropriately raised or lowered BP levels (10) in order to decide if treatment is required.

Ambulatory blood pressure measurement studies have demonstrated that pre and post dialysis blood pressure measurements are of little value in predicting the presence of left ventricular hypertrophy at echocardiography (11). However, some data suggest that pre dialysis SBP's $>150-160$ are associated with excess mortality in haemodialysis patients (12-14). Certainly very high pre dialysis SBP (>200) seems to confer an adverse prognosis (15). Home blood pressure recordings with a mean systolic BP > 150 mmHg has a sensitivity of 80% and specificity of 84% for diagnosing hypertension, defined by ambulatory BP $> 135/85$ between dialysis sessions (11). Another recent study suggests that mortality is lowest when home systolic blood pressure was 120 - 130 and ABPM SBP was 110 - 120 (16). There are also data suggesting that HD patients lose their normal diurnal BP variation and this loss is independently associated with left ventricular mass (17). On ABPM the blood pressure will also increase during the interdialytic period, so timing of the test will influence outcomes (18). Moreover the size of the variability of pre dialysis BP measurements is associated with mortality (19). There have been a few controlled trials suggesting that blood pressure treatment, but not necessarily achieved BP, may be associated with improved outcome in HD patients (20,21).

However, there is a worry that lowering BP too aggressively may lead to intradialytic hypotension (22), which is an independent predictor of mortality (23,24). Further data from some

studies suggests excess mortality was associated with pre dialysis SBP <120 mmHg (25) (5). Patients with SBP < 111 mmHg on PD are similarly at increased risk (26). Thus patients who have persistently low pre dialysis BP or recurrent intradialytic hypotension should be investigated further, with a view to changing target weight, reducing antihypertensive agents or investigating cardiac dysfunction. Preventing intradialytic hypotension may also retard the decline in residual renal function

Pulse pressure is increasingly recognised as a more powerful predictor of mortality than diastolic or systolic pressure alone (27,28) and fall in pulse pressure on dialysis may be beneficial (29). 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.

There is therefore considerable debate about how and when to measure blood pressure and the targets for dialysis patients. These questions need investigation by properly organised randomised controlled trials and until then significant caution should be exercised in interpreting blood pressure guidelines. However, we feel that guideline writing committees have a duty to make some recommendations on this no matter how difficult (30), based on what evidence does exist. Thus while, there are not enough data to make robust recommendations, we have attempted to make some sensible suggestions, to avoid excessively high SBP (aim <160mmHg). As a separate recommendation (albeit with weaker evidence) we feel we that there is enough evidence accumulating evidence that that low pressure may be counterproductive, and that SBP should not be lowered with drugs to <110mmHg. These targets may therefore serve as a realistic target which may be practically auditable and achievable in a large proportion of the dialysis population.

We make no recommendation about how this can be achieved, but the KDIGO controversies conference report makes some suggestions with respect to treatment of hypertension in dialysis (31). Longer term studies in patients without major co-morbidities and studies on incident dialysis patient cohorts demonstrate improved survival when BP is corrected by whatever means (14,32). Two recent meta-analyses broadly support the concept of blood pressure lowering in patients on dialysis (27,33). Nevertheless, it is not at all clear whether the cardiovascular protection afforded by antihypertensive agents is due to blood pressure lowering or if these agents work through other protective mechanisms.

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