GENERAL CARDIOLOGY

Cardiovascular complications of renal disease

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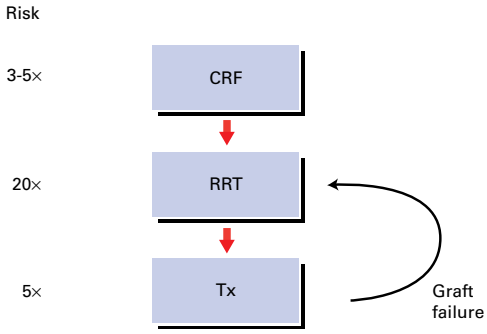

Figure 1. Phases of progressive renal disease with estimates of cardiovascular disease risk compared with the general population. CRF, chronic renal failure; RRT, renal replacement therapy; Tx, transplantation.

Advances in the technology and delivery of renal replacement therapy (dialysis and transplantation) have revolutionised the outcome of patients with progressive renal disease. However, the paradox of this success has been to uncover a greatly increased risk of cardiovascular disease (CVD), up to 20 times that of the normal population, a pattern similar to that seen in diabetes following the discovery of insulin. However, the magnitude of the problem is greater in renal disease and there is less agreement on the mechanisms or evidence on which to base interventional strategies.

The importance of CVD in this population is reflected by recent publications[1–3] and a report from a specific task force of the US National Kidney Foundation. The recognition that large scale outcome studies are required has resulted in the initiation of several studies that will report over the next few years. This review is a personal view in which we will cover the background to CVD at different stages in the natural history of progressive renal disease, current treatments, unresolved problems, and ongoing studies

Why patients with renal disease are different from the general population

To appreciate the problems and management of CVD in progressive renal disease it is necessary to consider the key differences between patients with renal disease and other patient groups. The first is the course of renal disease (fig 1). Patients with progressive renal disease suffer a period of deteriorating renal function, over months to many years (depending on the underlying disease) and leading ultimately to end stage renal disease (ESRD) in a proportion of patients. Most patients with ESRD (around 100 per million population per annum) currently enter renal replacement therapy programmes involving either peritoneal dialysis or haemodialysis. Thereafter, approximately one third will be considered for renal transplantation and, over a period of years, the majority of these will proceed to have a successful cadaveric or living donor transplant. The current predicted half life for renal allograft survival is around 10 years; those patients whose grafts fail are considered for retransplantation. The importance of the natural history of renal disease is that CVD risk and risk factors vary at different stages (fig 1), as does their management and the opportunities for intervention. A unique feature of CVD in patients with primary renal disease is that retarding or preventing progression of progressive renal disease will reduce cardiac risk.

The second feature of specific importance in progressive renal disease is the role of volume dependent mechanisms involved in hypertension and heart failure. The most extreme example of this is seen in anuric patients on haemodialysis, who accumulate on average 2–3 litres of fluid (a proportion of which will be intravascular) between dialysis sessions. Hypertension in such patients is volume dependent, and high weight gains are also associated with the development of pulmonary oedema in susceptible individuals. Fluid retention increases progressively with deteriorating renal function and thus contributes to the development of heart failure and hypertension.

The third unique feature is the nature of vascular disease in this population, which has led to scepticism about the adoption of treatments and treatment strategies proven in the general population. The characteristic feature of the vessels is calcification—to a large extent the result of hyperparathyroidism in renal disease (fig 2)—in peripheral and coronary vessels.[4] The extent to which atherosclerosis in such vessels differs from the general population, and the efficacy of established treatments—such as statins—remains uncertain and unproven.

Finally, the mode of death in advanced renal disease is atypical, classical myocardial infarction being relatively unusual, and sudden death and progressive heart failure being more common. Thus, abnormalities of the myocardium (for example, left ventricular hypertrophy, systolic dysfunction, and ventricular dilatation) that predispose the patient to sudden death, and their determinants, may be of much greater importance than atherosclerotic coronary artery disease in determining the high cardiovascular mortality in this population.

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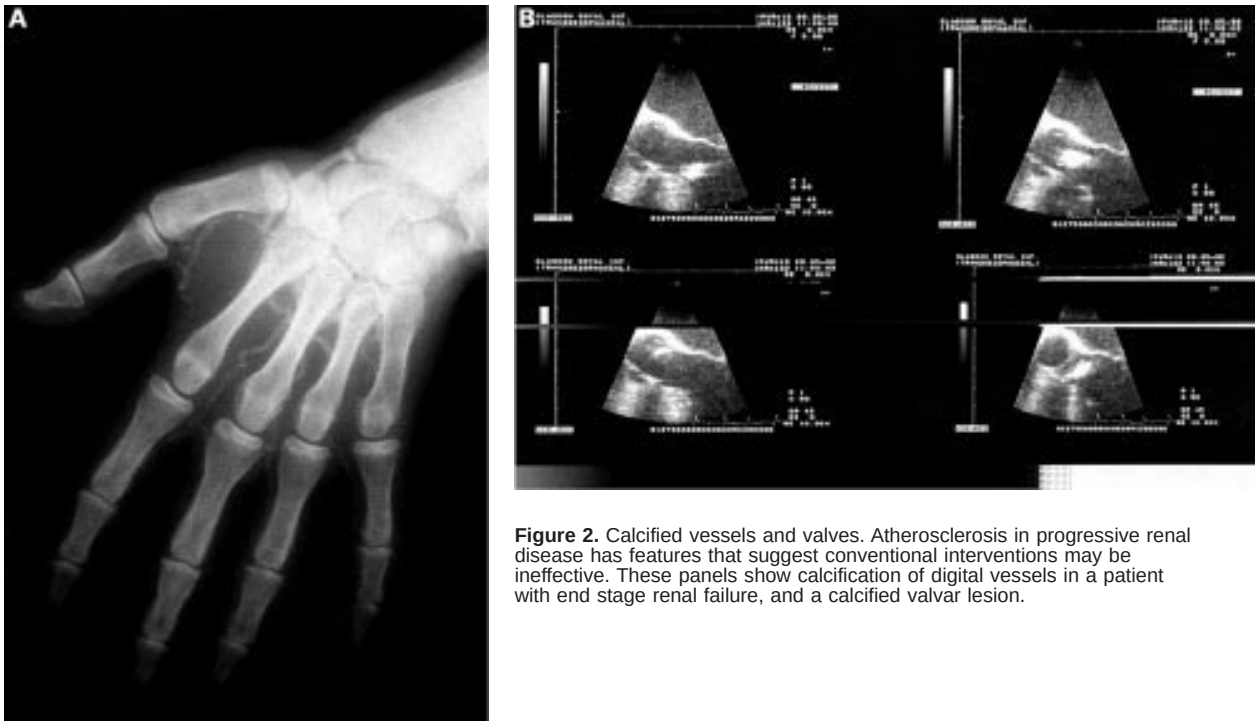

Figure 2. Calcified vessels and valves. Atherosclerosis in progressive renal disease has features that suggest conventional interventions may be ineffective. These panels show calcification of digital vessels in a patient with end stage renal failure, and a calcified valvar lesion.

Cardiovascular disease in uraemia: natural history and epidemiology

The scale of the problem of CVD has been demonstrated in publications from the European and US renal disease registries. In Europe, Raine reported an increase in CVD risk of approximately 20-fold, while a recent study from the US Renal Disease Service provides a more dramatic illustration of the scale of the problem (fig 3).[2 3] This report examined patients on dialysis and shows a major increase in all groups, but with the greatest increase in the youngest patients. Thus, a young adult on dialysis has a similar CVD risk to an elderly patient without renal disease. Moreover, risk increases progressively with deteriorating glomerular filtration rate (GFR) and is increased significantly by the time serum creatinine is elevated.[5] Patients with a functioning transplant have a much smaller increase in relative risk of around fivefold, but this group is highly selected and graft failure is associated with a dramatic increase in risk and mortality.

In the general population, a number of risk factors for CVD are well established, based on large scale epidemiological studies, including cigarette smoking, hyperlipidaemia, hypertension, and past or family history of premature CVD. Relating these factors to the development of CVD, and specifically coronary artery disease, in patients with progressive renal disease has proved difficult for a variety of reasons. The first is that it is likely that CVD evolves at different rates during the different stages of renal disease (fig 1), and the relative importance of risk factors such as hyperlipidaemia and hypertension differs at each stage. Secondly, some potential risk factors, such as hypertension (using standard definitions) are

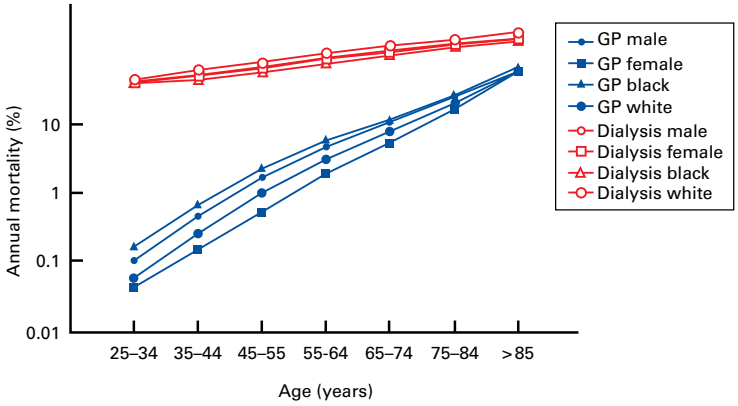

Figure 3. Data from the US Renal Disease Service (USRDS) showing CVD mortality rates in patients on renal replacement therapy compared with normal background population. The most dramatic relative increase is seen in the youngest patients on dialysis programmes.[3]

so common as to have no discriminatory potential. Finally, there are unique CVD risk factors in this population including progression between stages in the natural history and the effect of graft failure (and its determinants—for example, acute rejection, chronic rejection, and graft function at specific time points following transplantation (fig 4)[6]). An additional consideration is the increasing age of patients entering renal replacement therapy programmes and the associated increase in pre-existing disease.

These issues have been intensively studied by Kasiske whose longitudinal follow up studies in transplant recipients have greatly increased understanding of CVD risk in, at least, this subset of patients on renal replacement therapy. Although his early studies identified age, diabetes, male sex, and pre-existing vascular disease as the main determinants of outcome, together with a history of acute rejection (a marker for early graft failure), more

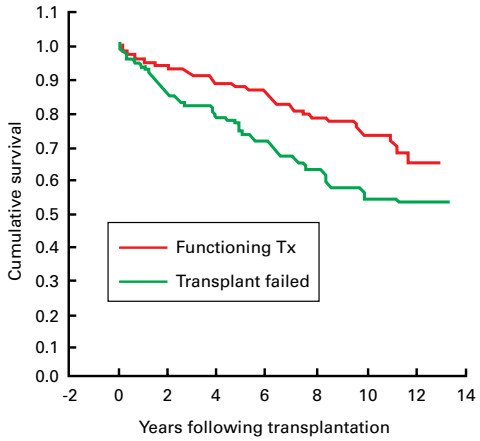

Figure 4. Kaplan–Meier survival curves from patients receiving cadaveric transplants at the Western Infirmary, Glasgow. Comparison of patients with continuing graft function and all transplants including graft failures.[6]

Table 1 Estimated relative risk of cardiovascular disease event in renal transplants recipients. Impact of individual risk factors.[7]

Risk factor	*Increase relative risk*
• Age	3% per annum
• Diabetes	2-fold
• Male	2-fold
• Pre-existing IHD, PVD or CVD	5–10-fold
• Smoking	2-fold
• Graft failure	5-fold
• BP (> 160/100 *v* < 130/80 mm Hg)	1.5-fold
• Total cholesterol (> 7.4 *v* < 4.2 mmol/l)	2-fold
Other risk factors (unknown relative risk)	
• Homocysteine	
• Lp (a)	
• Parathyroid hormone	
• Anaemia	
• C-reactive protein	
• Acute rejection episodes	

BP, blood pressure; CVD, cardiovascular disease; IHD, ischaemic heart disease; PVD, peripheral vascular disease.

recent work (using the Framingham equation) confirms the importance of conventional risk factors such as smoking, high cholesterol, and high blood pressure (when absolute lipid and blood pressure readings are used rather than diagnostic labels[7] (table 1)).

Conventional CVD risk factors and patterns of CVD disease

Hypertension

Hypertension is a common presenting feature in all forms of primary renal disease, even in patients with near normal GFR. In the initial phases of progressive renal disease, increased or inappropriately high activity of the renin angiotensin and other vasoconstrictor systems plays a major role. However, with progressive fall in GFR, salt and water retention predominate. Thus, it is possible to control high blood pressure in some dialysis patients by careful attention to fluid balance, either by limiting intake, or effective fluid removal by dialysis and ultrafiltration. Following transplantation, "hypertension" is almost universal; in addition, the influence of longstanding hypertension is a consequence of allograft dysfunction, and of the direct and indirect effects of immunosuppressive agents—specifically the calcineurin inhibitors (cyclosporin A and tacrolimus) and corticosteroid treatment.

Hypertension is associated with increased rate of progression of primary renal disease; blood pressure reduction (specifically with angiotensin converting enzyme (ACE) inhibitors[8]) retards progression. Whether ACE inhibitors have independent beneficial effects, over and above their effects on blood pressure, remains unresolved. The issue of patient survival and hypertension in progressive renal disease has not been formally addressed in adequately powered studies, although the increasing CVD risk associated with progression to end stage renal failure (ESRF) will be delayed by effective antihypertensive treatment. Target blood pressure levels are also poorly defined. In cohort studies (such as the modification of diet in renal disease (MDRD) study) and in diabetic nephropathy[9] blood pressures below 125–130/75–80 mm Hg are associated with significant benefits. However, whether these targets are achievable in clinical practice remains to be established.

The situation is even more complex in patients receiving dialysis. When fluid balance is tightly regulated,[2 3 10] CVD risk increases with increasing levels of blood pressure, regardless of whether the patient is "hypertensive". However, the opposite has also been reported most recently from the US Renal Disease Service (that is, those with the lowest blood pressure being at highest risk[2 3]). This may be a reflection of pre-existing cardiac disease in patients with low blood pressure, specifically symptomatic heart failure—itself an independent risk factor for poor outcome.[3] However, an alternative explanation is that ventricular hypertrophy places critical importance on diastolic coronary perfusion. Thus, blood pressure control in this group is achieved by judicious fluid balance, with the addition—if necessary—of antihypertensive agents.

Finally, in transplant recipients there is strong evidence linking absolute blood pressure levels with graft failure.[11] Recent studies demonstrate increased CVD risk associated with higher levels of blood pressure and suggest that targets below 130/80 mm Hg are likely to be associated with reduced risk; whether such targets are readily achievable need to be established by interventional trials.

The choice of antihypertensive agent is also unclear. Thiazide diuretics are ineffective in the presence of even modest renal impairment, whereas loop diuretics are effective antihypertensive agents in patients with volume dependent hypertension. ACE inhibitors are proven agents of choice in patients with chronic renal failure, diabetic nephropathy, and glomerulonephritis because of their ability to retard progression and reduce proteinuria. However, they may have catastrophic effects in patients with renovascular disease and their use may be limited by hyperkalaemia in patients with renal impairment. ACE inhibitors should be used with caution and it is worthwhile excluding

transplant artery stenosis by Doppler ultrasound before initiating treatment.

Smoking

Until recently there was little evidence linking smoking to CVD in patients with progressive renal disease and a reluctance to restrict the lifestyle of patients (particularly those on haemodialysis) who are already on restrictive fluid and dietary regimens. However, it is now clear that smoking has a similar impact on CVD risk to the general population[7] and may also promote progression of primary renal disease. Although the newer anti-smoking treatments have not been formally assessed in this population, they are likely to be safe and will add to non-pharmacological approaches to smoking cessation.

Lipids and renal disease

Hyperlipidaemia is a feature of progressive renal disease; the pattern and severity of which varies with the stage of renal disease.[2] For example, the nephrotic syndrome may occur in patients with well maintained renal excretory function, and is associated with severe mixed hyperlipidaemia. Patients with non-nephrotic primary renal disease also have raised total cholesterol and low density lipoprotein (LDL) cholesterol, concentrations of which tend to rise with rising serum creatinine and urinary protein excretion. In patients with ESRF the pattern of lipid abnormalities depends on the mode of renal replacement therapy. Haemodialysis may result in low total and LDL cholesterol, while peritoneal dialysis is associated with raised total and LDL cholesterol and triglycerides. Overall the pattern of lipoprotein abnormalities in patients with advanced chronic renal failure or ESRF is a shift towards triglyceride rich and atherogenic (for example, small dense LDL) particles, regardless of concentrations of total or LDL cholesterol. Following transplantation, restoration of renal function, appetite, and the effects of steroids and cyclosporin A contribute to the observed increase in triglycerides, LDL, and total cholesterol, particularly in the early post-transplant period. One problem of the shifting patterns of lipid abnormalities that accompany progressive renal disease is that it is difficult to integrate lipid concentrations in individual patients and their absolute importance on CVD risk over time. As a consequence there have been surprisingly few studies that associate lipids and risk or outcome.

Dietary intervention is of limited use in patients whose diet is already restricted. Fibrates and statins have similar relative efficacy to other patient populations but are associated with an increase risk of side effects. The association of renal failure with fibrates has limited their use and statins are now the agents of choice for patients at any stage of progressive renal disease. The only caveat is that there is a higher incidence of myositis and rhabdomyolisis (albeit small), and a significant interaction with calcineurin inhibitors (that inhibit the microsomal enzyme CyP-3A4) and simvastatin, lovastatin, and atorvastatin (but not fluvastatin or pravastatin), resulting in increased plasma concentrations of these agents. Thus, statins should be initiated at low doses in transplant patients.[2 12]

Table 2 Influence of immunosuppressive agents on cardiovascular disease risk factors, including rejection rate, blood pressure, lipids, and post-transplant diabetes. Nearly all immunosuppressive agents impact on risk factors, thus the use of combinations allows maximisation of immunosuppressive effects while minimising side effects

	Rejection	*High BP*	*Lipids*	*Diabetes mellitus*
Steroid	+	++	++	++
Cyclosporin	++	+++	++	+
Tacrolimus	++	+++	++	++
Rapamycin	+++	–	+++	–
MMF	+/++	–	–	–
Azathioprine	+	–	–	–

BP, blood pressure; MMF, mycophenolate mofetil

Diabetes

Diabetic nephropathy is the leading cause of ESRF (accounting for approximately one third of all patients starting renal replacement therapy and about 10% of all transplant recipients). Most patients have type I diabetes as patients with nephropathy caused by type II diabetes rarely survive to require dialysis or transplantation. The 2–3 fold increase in CVD risk (attributable to diabetes) multiplied by the risk associated with ESRF results in an increased CVD risk of around 50-fold in patients with ESRF caused by diabetic nephropathy.

A second issue is that of diabetes following transplantation which affects around 10% of all transplant recipients[13] and is associated with an increase in risk similar to diabetes in the general population, with a lag time of about 8–10 years from the development of disease to onset of complications. Post-transplant diabetes is a complication of immunosuppressive therapy (table 2) and is discussed below.

Other risk factors

Much less is known about other risk factors and their influence on treatment. Thus, although patients with progressive renal disease have increased concentrations of homocysteine, acute phase proteins, and lipoprotein Lp(a), and reduced antioxidant concentrations, the associated risks are not known. There has been considerable interest in the role of parathyroid hormone that contributes to extra-articular calcification. However, although vascular calcification is a major problem, the role of parathyroid hormone remains unresolved.

Following transplantation, the use of immunosuppressant drugs alters a number of CVD risk factors. Thus, the immunosuppressant agents themselves become risk factors, and modifying immunosuppressive treatment becomes an aspect of CVD risk factor management. The impact of these effects is offset by benefits on acute rejection rates and graft survival, that also have an impact on patient survival and CVD risk (fig 4). However, it is a measure of the increasing importance of CVD in this population that these effects are now considered when prescribing and licensing immunosuppressive agents.

Uraemic cardiomyopathy

Echocardiographic abnormalities are more strongly associated with outcome than conventional risk factors. There is a high prevalence of echocardiographic abnormalities in patients starting renal replacement therapy.[2 3 14] Parfrey has characterised uraemic cardiomyopathy into three groups: systolic dysfunction, hypertrophic cardiomyopathy, and dilated cardiomyopathy. On initiation of dialysis they found the prevalence of these abnormalities to be 16%, 41%, and 28%, respectively, with 16% of patients having a normal echocardiogram.[15] Median survival was 38 months in patients with systolic dysfunction, 48 months in concentric hypertrophy, 56 months in left ventricular dilatation, and 66 months in the normal group.[15] The echocardiographic abnormalities may co-exist and overlap for methodological reasons that may limit comparison with other populations; however, each is strongly associated with reduced patient survival. A similar pattern has been reported in patients undergoing renal transplantation (approximately 75% of whom have hypertrophic cardiomyopathy, and over 50% systolic dysfunction or dilated cardiomyopathy) with a similar adverse effect on patient outcome. The characteristic pathophysiological feature of uraemic cardiomyopathy is fibrosis, which is well established by the time patients reach ESRF, raising questions about the reversibility that have not been systematically investigated.

It is recommended that echocardiographic studies be performed on the post-dialysis day with patients close to their "ideal weight" and, by inference, at a normal intravascular volume. This reflects theoretical and observed difficulties in the interpretation of echocardiographic measurements, particularly in patients receiving dialysis treatment. Because of the changes in intravascular volume during haemodialysis (and in the interdialytic period), and the dependence of standard algorithms for the estimation of left ventricular mass index (LVMI) on chamber diameters, calculated LVMI may differ by up to 50 g in the same individual. Echocardiographic measurements of chamber volume will also vary with time in the dialysis cycle, resulting in variable classification of dilated cardiomyopathy, and systolic function. Thus, although echocardiographic abnormalities have prognostic importance in population studies, it is difficult to identify targets for intervention in individuals or an estimate of risk to an individual at a given time point (for example, pre-transplant assessment).

An important development in this area is the use of cardiac magnetic resonance imaging (MRI), which permits the direct estimation of left ventricular mass, independent of chamber diameters.[16] In a comparison with echocardiographic measurements of LVMI we found (fig 5) that as left ventricular mass and chamber diameter increase, echocardiographic measurements progressively overestimate mass. The more widespread availability of MRI may result in revision of the definition of uraemic cardiomyopathy and its management.

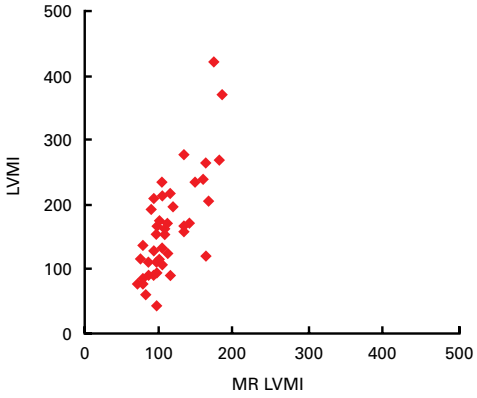

Figure 5. Comparison of magnetic resonance (MR) (x axis) and echocardiographic (y axis) estimates of left ventricular mass index (LVMI) in haemodialysis patients. Because of the dependence of echocardiographic estimates of left ventricular mass on chamber diameter, echocardiography progressively overestimates left ventricular mass with increasing mass.

There are other issues regarding cardiac abnormalities: when do they develop, what happens following transplantation, can they be reversed, and how are they linked to death? There are no longitudinal studies on the natural history of uraemic cardiomyopathy. However, left ventricular hypertrophy is present in patients from the earliest stages of progressive renal disease, in many cases before there is a significant reduction in renal function,[17] a consequence of hypertension, although other contributing factors have not been fully investigated.

Several small studies have examined the change in LVMI following transplantation but without consistent findings, reflecting inconsistencies in methodology, and specifically the reduction in intravascular volume that follows successful transplantation. The reported regression of left ventricular hypertrophy associated with erythropoietin use may also be, at least partly, methodological. The link between echocardiographic findings and mode of death (specifically progressive heart failure and sudden death) is more intuitive. Left ventricular hypertrophy is associated with increased QT dispersion which is increased in patients on all forms of renal replacement therapy. Moreover, QT dispersion is increased by dialysis and may contribute to an increased risk of sudden death in the hours following a haemodialysis treatment.[18]

Coronary artery disease

Prevalence

The cumulative incidence of coronary artery disease, in surviving patients with functioning transplants, is reported to be around 23% in the first 15 years following transplantation. The rates for peripheral and cerebrovascular disease are similar, at 15% over 15 years. However, the cumulative incidence is likely to be much

Cardiac assessment of patients with end stage renal failure

- Echocardiography: good prognostic indicator but varies during dialysis cycle
- Standard exercise test: little use because of poor exercise capacity and resting ECG abnormalities
- Isotope scanning: useful when combined with dipyridamole or dobutamine stress
- Coronary angiography: required for most patients

higher in those patients who return to maintenance dialysis after graft failure[6] and in patients starting renal replacement therapy, reflecting the increasing age of patients entering renal replacement therapy programmes with pre-existing disease.

Morphology of atheroma in patients with progressive renal disease

Although the distribution of atherosclerotic lesions appears similar to the general population, the morphology in coronary artery disease is unique[19] with striking medial calcification in addition to intimal hyperplasia. A recent study compared the postmortem morphology of atheromatous lesions in 27 patients with progressive renal disease (average age 69.5 years) and appropriate controls.[20] The major differences in renal patients were that coronary vessels had significantly increased media thickness with atheroma consisting of calcified plaques in contrast to the fibroatheromatous plaques of control patients. However, coronary artery calcification is not exclusive to elderly patients with progressive renal disease, and a recent study of dialysis patients aged 20–30 years had evidence of coronary artery calcification[21] detected by electron beam computed tomography. Coronary calcification was 17.5 times that of the general population and was associated with length of time on dialysis, average serum calcium × phosphate product (a determinant of calcium phosphate deposition), and intake of calcium containing phosphate binders. Moreover, the chemical composition of calcified plaques in dialysis patients is primarily hydroxyl apatite and calcium phosphate, and the calcium × phosphate product has previously been identified as an independent predictor of mortality in this population.[22] The morphology of coronary lesions in patients with progressive renal disease (that is, calcified versus fibroatheromatous plaques) is an important factor when considering the likely response to either medical or invasive treatments and the adoption of strategies proven in the general population.

Assessment and diagnosis

Screening for coronary artery disease in patients with progressive renal disease has been performed principally in the assessment of patients for renal transplantation. The incidence of asymptomatic coronary artery disease is perhaps 10 times higher in this group than in the general population. A small study in patients with diabetic ESRF demonstrated benefits of routine angiography (followed by surgery if required) in asymptomatic patients. This has been generally adopted in patients with diabetic nephropathy awaiting transplantation and also, to a variable extent, in patients with other forms of progressive renal disease despite the absence of specific evidence. The American Society of Transplantation recently published guidelines to address this issue (table 3). These recommendations are based on a prospective study evaluating five risk factors: history of coronary artery disease; history of heart failure; abnormal resting ECG; diabetes; and age > 50 years. The absence of all five risk factors was associated with a negative predictive value of 0.99 at 46 months, the recommendation being that such individuals do not require screening tests. For patients with multiple risk factors screening is recommended. For symptomatic patients screening should include coronary angiography. However, the investigation of asymptomatic patients with multiple risk factors should initially involve non-invasive investigations.

The choice of non-invasive testing for coronary artery disease is plagued by similar problems to that of interpretation of echocardiography. Few patients with ESRF, have adequate exercise capacity for conventional electrocardiographic exercise tests, and almost invariably have abnormal resting ECGs. Thallium imaging and non-exercise based stress tests involving dobutamine or dipyridamole are preferable. For patients with advanced chronic renal failure or ESRF in our experience, difficulties in interpreting non-invasive tests often lead to coronary angiography being performed. In patients with modest renal impairment or good renal function following transplantation, conventional investigational strategies should be used.

Management

The management of coronary artery disease in patients with early renal failure is the same as

Table 3 American Society of Transplantation cardiac screening recommendations

	Risk category		
	Low risk	*High risk*	
Risk history	No history of CAD or CHF	History of CAD or CHF	Symptomatic CAD
Risk factors	Non-diabetic, age < 50 years	Diabetic, age < 50 years; non-diabetic, age > 50 years	Diabetic, age > 50 years
Stress testing?	No	Yes	No, proceed to angiography

CAD, coronary artery disease; CHF, congestive heart failure.

for the normal population. In patients with ESRD, the decision of whether or not to intervene is usually based on data from the general population. There is no consensus on the management of lesions identified during screening of asymptomatic, potential transplant recipients. In patients with advanced renal failure or ESRF, the success of non-surgical intervention is poor. Primary angioplasty in patients with advanced renal failure is associated with an increased primary failure rate, and a restenosis rate at six months in excess of 40%.[23] Reasons for the high restenosis rate include calcified plaques, more severe artery narrowing, more extensive disease, and a relatively thrombophilic state seen in dialysis patients with increased platelet and fibrin deposition. Although a recent report by Le Feuvre suggests that angioplasty associated with a "stent-like" success (stenosis < 30%) is as achievable in dialysis patients as it is in control patients,[24] overall the chance of similar success in patients with advanced chronic renal failure before dialysis and on various forms of renal replacement therapy is reduced. Many centres consider primary angioplasty inappropriate in this population.

Stenting offers a more effective treatment and may be as successful (technically) in patients with progressive renal disease as it is in the general population. Further studies are needed to assess the efficacy in comparison to coronary artery bypass grafting. For many patients with advanced progressive renal disease coronary artery bypass grafting remains the only viable option. However, there is a significant increase in morbidity and mortality following bypass grafting in patients receiving dialysis and a significant risk of precipitating renal failure in patients with advanced chronic renal failure or poor graft function.[25 26] Thus, these risks must be offset by the potential benefits of successful revascularisation to the patient and in many cases it may be appropriate to opt for stenting as the primary procedure. Whether or not conventional thresholds for intervention are appropriate in patients with ESRF is also uncertain, particularly in view of the difficulties in assessing left ventricular function non-invasively. While most physicians would recommend revascularisation for left main stem lesions and severe triple vessel disease, other strategies including correction of anaemia and regression of left ventricular hypertrophy may have benefits in patients with symptomatic angina and less extensive disease.

The medical management of coronary artery disease in this population is essentially the same as for the general population. However, it is important to reinforce the need to assess factors such as anaemia and its correction by the use of erythropoietin and parenteral iron.

Myocardial infarction

The diagnosis of myocardial infarction in patients with advanced chronic renal failure and ESRF (regardless of the form of renal replacement therapy) is complicated by the high prevalence of ECG abnormalities. Moreover, the ECG may change across a dialysis session[18] reflecting changes in intravascular volume and electrolytes. Serum creatinine kinase concentrations also tend to be slightly higher than normal, even in the absence of myocardial infarction. The management of myocardial infarction is generally the same as for the general population, despite the absence of specific studies in patients with advanced renal disease. Furthermore the outcome of patients with ESRF following myocardial infarction is much worse than patients without renal disease.[27]

Intervention for coronary artery disease

- High risk in patients with end stage renal failure
- Angioplasty has unacceptably high failure rate
- Coronary stenting unproven
- Coronary bypass graft surgery remains treatment of choice for most patients

Secondary prevention

Similar considerations apply to secondary prevention. Although renal patients have been excluded from large outcome studies of CVD, there is a general consensus that patients with ESRF should not be denied proven secondary prevention measures (for example, statin treatment following myocardial infarction or ACE inhibitors for chronic heart failure).

Valve disease

Another feature of extra-articular calcification in renal disease is accelerated valve calcification and an increased prevalence of aortic valve disease. The decision to intervene is generally based on conventional criteria but, like coronary bypass surgery, preoperative complications are more common and mortality and morbidity substantially increased (fig 2).

Ongoing trials

Although long overdue there are now several ongoing trials with cardiovascular end points in patients with primary renal disease. The ALERT (a study of Lescol and renal transplantation) has recruited 2100 stable renal transplant recipients, in northern Europe and Canada, to a five year study with death and major adverse cardiac events as the primary end points. The patients were randomised to 40 mg (increasing to 80 mg) per day of fluvastatin or placebo. The study is based on the 4S (Scandinavian simvastatin survival study) trial, with the assumption that the event rate in this population will be approximately twice that of 4S. Recruitment closed in the autumn of 1997

and the trial should report in 2002. The UK-HARP (heart and renal protection) study is a 2 × 2 study of aspirin and simvastatin versus placebo in patients with chronic renal failure, patients on dialysis programmes, and renal transplant recipients. After an extensive pilot phase to ensure safety and the logistics of the study design in this population, a full scale study is planned. In dialysis patients the CHORUS (cerivastatin heart outcomes in renal disease: understanding survival) study will examine the effects of cerivastatin (400 µg/day) or placebo in a two year study of 690 dialysis patients. The small size of this study reflects the annual CVD event rate in this population, although the absence of similar interventional studies, and thus information on recruitment profiles and event rates, makes it difficult to provide accurate targets for power calculations. One recent study merits comment. The SPACE study examined the effects of vitamin E supplementation in patients on haemodialysis with a reported benefit in CVD end points.

Conclusions

Accelerated CVD is now the leading cause of death in patients with progressive renal disease. Risk increases progressively from the earliest stages of renal disease, when serum creatinine is close to normal values. Appropriate management is unclear because of the absence of specific studies and the issue of whether or not strategies established in the general population can be applied in a population with atypical CVD. However, we believe that prevention should begin in the earliest phases of progressive renal disease, when serum creatinine rises outwith the normal range with the use of statins and antihypertensive treatment—with the aim of achieving lower targets for blood pressure control that limit the development of left ventricular hypertrophy. In patients with advanced disease strategies should aim to limit, or regress, ventricular abnormalities, rather than simply "control" blood pressure, and should involve antihypertensive agents and meticulous control of fluid balance. Finally, there should be a low threshold for the investigation of patients with advanced renal disease (even in the absence of symptoms).

Overall, the message is clear. Improved understanding and management of CVD in this population will have more immediate benefits that the foreseeable advances in dialysis, transplantation or the treatment of primary renal disease.

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