

# Cardiovascular Disease

Date written: August 2011

Final submission:

Author: Helen Pilmore

## Guidelines

- a. We recommend that all candidates for kidney transplant are screened for cardiovascular risk factors (1A). Indicators of high risk include (1A):
  - Older age;
  - Diabetes mellitus;
  - Abnormal ECG;
  - Previous ischemic heart disease or congestive heart failure;
  - Increased duration of dialysis.
- b. We suggest that kidney transplant candidates with a low clinical risk of cardiovascular disease do not require stress testing for coronary artery disease. (2B).
- c. We suggest that kidney transplant candidates with a moderate or high clinical risk of cardiovascular disease undergo cardiac stress testing prior to transplantation (2B). The following should be noted in relation to cardiac stress testing in dialysis patients:
  - Exercise ECG has a poor predictive value in patients on dialysis. (2B)
  - The use of a cardiac stress test such as dipyridamole thallium testing or stress echocardiography is predictive of significant coronary artery disease and major cardiac events in patients with higher clinical risk. Where possible this testing should be performed without concurrent  $\beta$ -blocker therapy. (2B)
  - As the prognostic accuracy of cardiac stress testing in dialysis patients is of limited duration, it is suggested that testing be repeated in high risk patients. The interval at which testing should take place has not been well defined, however, the predictive value of a positive test diminishes after 24 months. (2C)
- d. We recommend that coronary angiography be considered for kidney transplant candidates with abnormalities on screening procedures. (1B)
- e. We suggest that the benefit of revascularisation prior to transplantation be reviewed on an individual basis. (2C)

## SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

- Reduced left ventricular systolic function is predictive of reduced survival for patients with end-stage renal failure. A reduced fractional shortening, or an increased end-systolic diameter, are the best validated echocardiographic indices for predicting this.
- In general, there is no evidence to suggest that revascularisation of asymptomatic coronary artery stenoses in patients with renal failure is associated with beneficial outcomes after renal transplantation.
- Dialysis patients with carotid plaque are likely to be at higher risk of mortality than those without carotid plaque, however there is no evidence to suggest which patients should be screened.
- Kidney transplant candidates with diabetes mellitus and atrial fibrillation should be identified as having a higher risk of post transplantation cerebrovascular events.

## **IMPLEMENTATION AND AUDIT**

There are no guidelines as defined by the CARI process, and hence no proposal for Implementation and Audit.

## **BACKGROUND**

Cardiovascular disease is one of the most common causes of morbidity, and the most frequent cause of mortality in patients on dialysis as well as those with kidney transplants. Therefore assessing patients for the presence of cardiac disease is an important aspect of assessment for renal transplantation.

These suggestions do not determine which patients are, and therefore by inference, which patients are not, suitable for transplantation. There is no good evidence that any group of patients referred for renal transplantation does worse by having a transplant, than by staying on dialysis [1-8]. However, as there are more patients requiring renal replacement therapy than potential donors, most units routinely screen for patients at high risk of cardiovascular events after renal transplantation.

In this guideline, we review the current data regarding cardiovascular risk factors and cardiac screening and the relationship of screening to cardiovascular events and mortality. Additionally we review the evidence for revascularisation prior to transplantation in patients with coronary artery disease.

The assessment of patients to receive a renal transplant on the basis of their cardiovascular disease does not lend itself to randomised-controlled trials. Where possible, Cohort studies that look at the impact of cardiovascular disease on the outcomes of renal transplantation have been reviewed here. Where such studies are lacking, the data from less direct studies (e.g. survival of dialysis patients or of the general population) have been considered. Studies of patients without renal failure have not generally been included. Where they are included it will be clearly stated.

## **SEARCH STRATEGY**

**Databases searched:** Medline (1966 – March 2010) was searched. Initially a more specific search was used, namely: ("cohort studies"[MESH] OR "case-control studies"[MESH] OR (odds[tw] AND ratio[tw]) OR prognosis[tw] OR mortality[tw] OR (relative[tw] AND risk[tw])) AND "heart diseases"[MESH] AND "kidney transplantation"[MESH] NOT "non-heart-beating"[TW] NOT asystolic[tw]. From that search, relevant papers were identified manually, and searching for "related articles" was undertaken. A further, more general search was undertaken, that yielded many more papers, but many fewer of relevance, namely: ("cohort studies"[MESH] OR "case-control studies"[MESH] OR (odds[tw] AND ratio[tw]) OR prognosis[tw] OR mortality[tw] OR (relative[tw] AND risk[tw])) AND "heart diseases"[MESH] AND ("kidney failure, chronic"[MESH] OR "dialysis"[MESH] OR dialysis[TW]) NOT "kidney transplantation"[MESH] NOT "non-heart-beating"[TW] NOT asystolic[tw]. The Cochrane Clinical Trials Register was also searched, but given the lack of suitability of randomized controlled trials in addressing this issue, it did not reveal any studies that warranted inclusion in this "Guideline."

**Date of search/es:** March 2010.

## **WHAT IS THE EVIDENCE?**

## **Note on assessment of evidence quality**

The evidence supporting the guideline topic as identified by the search strategy has been reviewed following the “Grading of Recommendations Assessment, Development and Evaluation” (GRADE) approach (refer to <http://www.gradeworkinggroup.org/>). An assessment of the overall quality of the evidence has been made to enable a strength of recommendation to be assigned. Studies relevant to the topic have been described in the text. In addition evidence summary tables and/or evidence profiles for the relevant studies have been included in the Appendix.

## **Risk factors for CVS disease**

There have been a large number of studies examining clinical risk factors predictive of cardiac events after renal transplantation. All data is observational and many studies are comprised of only small numbers of patients.

Patients at lower risk for cardiovascular disease are [9, 10]:

1. Less than 50 years of age
2. No history of Angina
3. No history of Diabetes
4. No history of congestive heart failure
5. Normal ECG

Patients in this category had only a 1% risk of cardiac mortality compared to a risk of 17% for patients with at least one of these risk factors.

Risk factors for cardiovascular disease are:

1. Diabetes OR 5.56 [11]
2. Smoking OR 3.56 [11]
3. Previous renal transplant OR 2.81 [11]
4. Elevated CRP [12]
5. Homocysteinaemia [12]
6. Angina [13]
7. Peripheral vascular disease [13]
8. History of myocardial infarction [13]
9. Evidence of previous myocardial infarction on ECG HR 5.28 [14]
10. Carotid artery plaque [15]

The largest observational data comes from the PORT registry (Patient outcomes in renal transplant). This large registry examined data on 23 575 patients from 14 centres from the US, Europe, New Zealand, Japan and Canada. Factors predictive of coronary heart disease events at the time of transplantation were: [16]

1. Increasing age > 35 years OR 2.07 – 4.99
2. Male gender OR 1.22
3. History of diabetes OR 2.00
4. History of cancer OR 1.38
5. One previous cardiovascular event OR 3.76
6. Two previous cardiovascular events OR 5.89
7. Deceased donor renal transplant OR 1.24
8. Obesity (BMI > 35) OR 1.55
9. Increased duration of dialysis > 2 years OR 1.41

## **Cardiac stress testing**

There have been a large number of cohort studies examining the efficacy of provocative stress testing and coronary angiography. These are discussed below. Recently a systematic review (a companion publication to a Cochrane Review that had not published at the time of writing)

examining cardiac stress tests and the ability to predict coronary stenosis compared to coronary angiography in potential kidney transplant recipients has been published by Wang et al [17].

## **Systematic review**

Wang et al [17] undertook a systematic review of diagnostic test accuracy studies of any non or minimally test used to diagnose coronary artery disease in potential kidney transplant recipients with coronary angiography as the reference test. In summary the review identified the following:

- Dobutamine stress echocardiography (DSE) 11 studies (690 participants).
- Myocardial perfusion scintigraphy (MPS) – 7 studies (317 participants).
- Exercise stress electrography – 2 studies (129 participants).
- Digital subtraction fluorography – 1 study (86 participants).
- Exercise ventriculography – 1 study (35 participants).

The pooled sensitivity and specificity for the DSE and MPS studies are summarised below.

MPS	Sensitivity	0.69 (95% CI 0.48-0.85)
	Specificity	0.77 (95% CI 0.59-0.89)
DSE	Sensitivity	0.80 (95% CI 0.64-0.90)
	Specificity	0.89 (95% CI 0.79-0.94)

The pooled estimates showed significant heterogeneity. The threshold coronary artery stenosis reference was  $\geq 70\%$  in the majority of the study and excluding those few trials with lower threshold values had minimal effect on both the pooled estimates and the heterogeneity. Further assessment of the source of heterogeneity was not possible due to the limited number and small size of the studies. The analysis of the pooled data showed no significant difference between the accuracy of MPS and DSE tests. The following key conclusions were made on the basis of the pooled estimates of test accuracy:

- Both MPS and DSE are useful in ruling out coronary artery disease in patients considered at low risk.
- The true discriminating value of the tests is in detecting coronary artery disease in patients considered to be of intermediate risk and help to reclassify these patients into either high or low risk.
- A positive result of the tests in high risk patients confirms the high risk of severe coronary artery disease, however it is not ruled out by a negative result.

## **Individual studies**

### ***Exercise ECG stress testing***

Relatively few formal studies of exercise stress testing exist in the dialysis population. The value of such testing has been limited by the inability of a number of patients to achieve the workload required to maximally stress the heart. Thus the predictive value of this test is often low [14, 18].

### ***Radionucleotide imaging***

A large number of studies have looked at radionucleotide cardiac scanning as a screening tool prior to renal transplantation. Studies have looked at both the ability of radionucleotide imaging to

predict coronary artery stenoses and to predict events. Studies using this mode of non-invasive testing are referenced below.

### **Prediction of coronary artery stenoses**

There are a large number of studies indicating that radionucleotide cardiac testing predicts coronary artery stenoses although, as with all stress tests, there are both false negatives and positives when patients are followed up with angiography.

#### **Summary of studies**

- Mistry 1998 [19]: 28% patients had reversible defect on preoperative dipyridamole-thallium imaging. 64% of these had at least one coronary artery stenosis of > 50%
- Holley 1991[20]: 43% with positive dipyridamole-thallium imaging had significant coronary artery disease.
- Dahan 1998 [21]: Sensitivity, specificity, positive and negative predictive values for thallium imaging as a predictor of abnormal coronary anatomy were 92%, 89%, 71% and 98% respectively.
- Vandenberg 1996 [22]: Sensitivity and specificity for detecting coronary artery stenosis of at least 75% were 62% and 76% respectively. For detecting at least 50% stenosis the sensitivity was 53% and the specificity was 73%
- Worthley 2003 [23]: Sensitivity, specificity, positive and negative predictive values for tachycardic stress as a predictor of abnormal coronary anatomy were 87%, 88%, 81% and 92% respectively.
- Marwick 1990 [24]: Sensitivity 36%; Specificity 73%

### **Prediction of cardiac events**

Reversible defects on stress thallium scans using dipyridamole or exercise are predictive of cardiac events in dialysis and transplant patients both with and without diabetes. There is however, a false negative rate and some patients with abnormal scans will not have cardiac events.

#### **Summary of studies**

- Mistry 1998 [19]: 1 of 111 (0.9%) diabetic recipients of a kidney or kidney-pancreas transplant, who had a normal pre-operative dipyridamole-thallium scan, had a myocardial infarction or acute cardiac death in the first 6 weeks post-operatively. Three of the 27 (11.1%) patients with reversible defects and at least one coronary artery stenosis of over 50% had a major cardiac event in the first 6 weeks, despite 12 of the patients having been revascularised pre-transplant.
- Le 1994 [9]: During a mean follow-up period of 46 months, patients with reversible thallium defects had a higher cardiac mortality than patients with no reversible defects (23% vs 5%;  $p < 0.05$ ). Patients with fixed thallium defects also had a higher rate of cardiac mortality (29%;  $p < 0.05$ ), but deaths among those patients with fixed defects tended to occur later than among those with reversible defects.
- Patel 2003 [25]: Prospective outcome data were collected on 600 consecutive renal transplant recipients for an average of 42 months after surgery. Stress single-photon emission computed tomographic (SPECT) myocardial perfusion imaging was performed in 174 patients before surgery, 136 (78%) of whom had diabetes mellitus. There were 17 cardiac deaths, 14 nonfatal myocardial infarctions, and 28 non-cardiac deaths in total. There were 12 cardiac events and 11 non-cardiac deaths among those who had SPECT myocardial perfusion imaging. In a multivariate analysis, age ( $p = 0.003$ ) and diabetes ( $p = 0.005$ ) were the predictors of cardiac events in patients who did not undergo stress SPECT perfusion imaging. In the subgroup who had stress perfusion imaging, an abnormal perfusion SPECT study was the only predictor of cardiac events ( $p = 0.006$ ). The 42-month cardiac event-free survival rate was 97% in patients

with normal SPECT images and 85% in patients with abnormal SPECT images (RR 5.04, 95% confidence interval 1.4 to 17.6,  $p = 0.006$ ).

- Brown 1993 [26]: Exercise-thallium imaging had a test sensitivity for predicting a cardiovascular event was 88% and specificity 70%, with a positive predictive value of 73%.
- Dahan 1998 [21]: Abnormal thallium uptake in a dipyridamole thallium scan had a positive predictive value of 47% and its negative predictive value was 91% in asymptomatic haemodialysis patients.
- Brown 1989 [27]: Dipyridamole-thallium imaging was performed in 65 candidates for renal transplant surgery (36 with diabetes). Logistic regression analysis was used to compare the predictive value of clinical data and radionuclide data, but only the presence of reversible thallium defects or a depressed ejection fraction predicted future cardiac events ( $p < 0.01$ ).
- Morrow 1983 [28]: Positive thallium stress testing in diabetic renal transplant candidates was associated with an increased incidence of myocardial infarction, although a history of cardiac symptoms or an abnormal baseline ECG had similar predictive value.
- Derfler 1991 [29]: A positive dipyridamole thallium scan was associated with an increased incidence of fatal or non-fatal cardiac events in dialysis and renal transplant patients (78% versus 7%;  $p < 0.0001$ ).

### **Stress echocardiography**

Similarly, dobutamine or exercise stress echo predicts major adverse cardiac events however, as with radionuclide scans, sensitivity and specificity are variable.

### **Prediction of coronary artery stenoses**

#### **Summary of studies**

- Reis 1995 [30]: DSE had a sensitivity of 95% (92% for one vessel disease and 100% for disease in 2 or more vessels), a specificity of 86% and accuracy of 90% for the detection of coronary artery disease (at least a 50% stenosis).
- Herzog 1999 [31]: DSE diagnosed a quantitatively measured coronary stenosis of at least 50% with a sensitivity and specificity of 52% and 74% respectively. The sensitivity was 75% and specificity 76% for diagnosing a visually estimated coronary stenosis of greater than 75%.
- Sharma 2005 [32]: The sensitivity, specificity, positive and negative predictive values for DSE in detecting significant coronary artery disease were 88%, 94%, 86% and 95%.

### **Prediction of cardiac events and mortality:**

#### **Summary of studies**

- Sharma 2005 [32]: DSE did not predict mortality in patients assessed for renal transplantation.
- Herzog 1999 [31]: After a mean of 22.5 months, 6 of 30 (20%) patients with a negative DSE and 11 of 20 patients (55%) with a positive DSE had a cardiac death, myocardial infarction or coronary revascularization ( $p = 0.01$ ). Four out of 20 patients (20%) with a positive test and 2 out of 30 (6.7%) with a negative test suffered a cardiac death or myocardial infarction ( $p = 0.20$ , NS).
- Brennan 1997 [33]: A negative DSE in patients assessed for renal transplantation had a negative predictive value for predicting early post-operative cardiac complications of 95%.
- Marwick 1998 [34]: In patients with CKD, DSE demonstrated ischemia in 19% and scarring in 19%. Normal studies were obtained from 121 patients. 69 patients (36%) had a suboptimal heart-rate response. The event-free survival in patients with ischaemia was 66% compared to 84% in those without ( $p = 0.006$ ). The event rate increased from 8% to 16% between 24 and 40 months. Ischaemia was an independent predictor of outcome over 24 months. It was not predictive at 40 months, suggesting that these tests have a limited period of validity in these patients.

- Bates 1996 [35]: In patients evaluated with DSE prior to kidney or kidney-pancreas transplantation, cardiac events occurred in 45% of those with an abnormal DSE and 6% of those with a normal DSE ( $p=0.002$ ). In a multivariate analysis the result of the DSE was an independent predictor of outcome with an odds ratio of 12.7 ( $p=0.003$ ).
- Reis 1995 [30]: Sixty-eight of 97 patients with end-stage renal failure awaiting renal transplantation had a normal DSE. This group had a good prognosis with 97% of them being free of cardiac complications or death during a mean follow-up of 12 months.

## **Electron beam CT**

This modality examines for coronary stenoses using measures of coronary artery calcification. There is variation in the measurement of sensitivity and specificity of this test differing between 85.7% and 82.6% [36] and a specificity of only 48% [37]. Hence, the validity of electron beam CT has not been proven in the renal population.

## **Coronary angiography**

Coronary angiography is still seen as the gold standard for detection of coronary stenoses. Angiography however is invasive, costly and is associated with a risk of contrast nephropathy in patients with renal failure.

## **Coronary artery stenoses and risk of cardiac events:**

- De Lima 2003 [38]: Coronary angiography was studied in high risk patients with renal failure resulting in the probability of event-free survival at 6, 12, 24, 36, and 48 months of 98%, 98%, 94%, 94%, and 94% in patients with less than 70% stenosis on angiography and 97%, 87%, 61%, 56%, and 54% in patients with greater than 70% stenosis. Multivariate analysis showed that the sole predictor of cardiac events was critical coronary lesions ( $P=0.003$ ).
- Jones 2009 [39] Coronary angiography was performed on 253 patients on dialysis. Of these, only half had no evidence of significant coronary artery disease (defined as any coronary artery stenosis of more than 50%). There was a significant increase in cardiovascular and all cause mortality in those with coronary artery disease compared to those without and this was most marked in those with stenoses in 2 or more vessels.

## **Multiple modalities**

- Rabbat et. al [40] published a meta-analysis of 12 studies, all of which reported cardiac death data, and 9 of which reported myocardial infarction. Four of the studies used thallium scintigraphy with pharmacological stress, another 4 used thallium scintigraphy with exercise stress, and 4 used dobutamine stress echocardiography. Positive tests indicated a significantly increased relative risk (RR) of myocardial infarction (2.73 [95% CI, 1.25 to 5.97];  $P = 0.01$ ) and of cardiac death (2.92 [95% CI, 1.66 to 5.12];  $P < 0.001$ ). In studies of diabetic patients, positive tests showed a RR of myocardial infarction of 2.68 (95% CI, 0.95 to 7.57;  $P = 0.06$ ), and a RR of cardiac death of 3.95 (95% CI, 1.48 to 10.5;  $P = 0.006$ ) when compared with negative tests. In studies evaluating mixed populations of diabetic and nondiabetic patients, positive tests were associated with a RR of myocardial infarction of 2.79 (95% CI, 0.85 to 9.21;  $P = 0.09$ ) and a RR of cardiac death of 2.52 (95% CI, 1.25 to 5.08;  $P = 0.01$ ). The presence of reversible defects was associated with an increased risk of myocardial infarction in diabetic patients and of cardiac death in both subgroups; fixed defects were associated with an increased risk of cardiac death but not myocardial infarction.
- Dahan 2002 [41]: Stress echo and stress radionucleotide testing were compared. This paper did not demonstrate any significant difference in the overall accuracy for detecting coronary artery disease (radionucleotide testing sensitivity, specificity, PPV, NPV 86%, 94%, 80%, 95% respectively; stress echo sensitivity, specificity, PPV, NPV 83%, 84%, 67%, 93%).

- De Lima [38]: 126 moderate to high risk subjects were studied with both coronary angiography and non-invasive tests. The prevalence of coronary artery disease by angiography was 42%. Both dobutamine stress echocardiography and SPECT scanning gave both sensitivity and negative predictive value of less than 75%.
- Dussol 2004 [42]: examined patients with exercise-thallium SPECT and most also had a dobutamine stress echocardiogram. Major adverse cardiac events were predicted by both diabetes and by inducible ischaemia. Among those patients with inducible ischaemia, the risk of cardiac death over four years was 25% (3/12). Only one of the 85 patients without inducible ischaemia had a cardiac death in the same time period.
- Schmidt 2001 [43]: performed coronary angiography in 42 renal transplant recipients and 42 chronic haemodialysis patients. The patients also underwent clinical history for angina, exercise ECG and nucleotide scanning. Forty-three of the patients had significant coronary disease on angiography (at least one stenosis of over 70%). Angina pectoris had a sensitivity of 65% and a specificity of 66% for predicting significant stenoses. Exercise ECG could not be performed on a majority of patients. Resting ECG had a sensitivity of 67% and specificity of 52%. Nucleotide scanning had a sensitivity of 80% and specificity of 37%.
- De Vriese [44]: 121 patients on haemodialysis underwent myocardial perfusion scintigraphy with both dipyridamole and dobutamine. This study showed reversibility with dipyridamole but not dobutamine, was independently associated with mortality due to coronary artery disease (CAD), and with fatal and non-fatal CAD.

### **Coronary revascularisation**

There are very few studies examining outcomes of coronary revascularisation in patients specifically prior to renal transplantation. The risks of revascularisation in patients with renal disease are significantly greater than those of the general population. Patients on dialysis have a significantly increased risk of both early and late mortality, infectious complications, bleeding and adverse cardiac events than occurs in the general population. The risks have been clearly described in the updated CARI guideline on cardiovascular disease (updated 2009). [NEED TO INCLUDE LINK]

### **Studies in renal population**

- Manske: There is only one RCT comparing revascularisation or medical therapy in patients with diabetes who were candidates for renal transplantation [45]. Only 26 patients were randomised, with 13 in each group. Ten of the 13 medically managed and 2 of the 13 revascularised patients had a cardiovascular endpoint within a median of 8.4 months ( $p < 0.01$ ). Four medically managed patients died. Although the results suggested that revascularisation was beneficial, this study was underpowered and optimal medical management was not undertaken in those treated conservatively and hence revascularisation cannot be uniformly recommended from the results of this study.
- Patel [46] In a more recent study, patients being assessed for renal transplantation with coronary angiography were examined. Of ninety-nine patients who underwent coronary angiography; 65 had normal or low-grade CAD and 34 obstructive CAD. There was no apparent survival difference between patients who underwent PCI or coronary artery bypass graft compared to those who underwent angiography without intervention or no angiography ( $p = 0.67$ ).
- There is one recent paper in which 519 patients underwent coronary angiography.[47] Of these 230 had coronary artery stenoses of more than 70%. Patients who fulfilled the AHA/ACC criteria for revascularisation were offered revascularisation while the remainder underwent medical therapy consisting of beta blockade, aspirin, statin and ACE/ARB treatment. Of the 46 who met the AHA/ACCA criteria for revascularisation, 16 refused to have the intervention.

Survival was significantly reduced in patients with coronary artery stenoses compared to those without significant coronary artery disease. There was no difference in survival or cardiac events between the revascularisation group and those who were treated medically however those who

fulfilled the AHA/ACC criteria for revascularisation but refused this treatment had a significantly greater mortality and more cardiovascular events. However the number of patients in this group was small.

### **Studies in non-renal population**

McFalls [48] : The coronary artery revascularization prophylaxis (CARP) trial examined the impact of prophylactic coronary revascularization in patients requiring major vascular surgery. In this study, patients were randomized to either revascularization using either CABG or angioplasty, or medical management. Revascularization was not associated with a benefit in patient survival with a 22% incidence of mortality in the revascularization group and 23% in the group who were medically managed. In addition, there was no difference in survival in any high-risk group examined. The results of this study concur with the guidelines from the American College of Physicians which do not recommend revascularization prophylactically in patients undergoing non-cardiac surgery, stating that there are clear potential risks and no evidence of either a short- or long-term benefit from revascularization.

### **Retesting after coronary revascularisation**

There are no studies in patients with renal failure, evaluating retesting for myocardial ischaemia after coronary artery revascularisation. Some studies have however been performed in patients without renal impairment. These suggest that demonstration of inducible ischaemia in patients following revascularisation was associated with an increased risk of major cardiac events [49, 50], myocardial infarction [51] and death [52]. The optimal interval at which screening should take place after revascularisation has not been determined.

### **Left ventricular function**

Left ventricular dysfunction predicts reduced survival for patients with end-stage renal failure. At the commencement of dialysis in 432 patients, 16% had systolic dysfunction (fractional shortening  $\leq 25\%$ ), 41% had concentric left ventricular hypertrophy, 28% had left ventricular dilatation (Volume  $> 90 \text{ mls/m}^2$ ) and only 16% had normal echocardiograms. Median survival was 38 months for systolic dysfunction ( $p < 0.001$  compared to normals), 48 months for concentric hypertrophy (NS compared to normals), 56 months in LV dilatation and more than 66 months in the normal group (NS compared to normals) [53]

The prognostic significance of left ventricular dysfunction prior to renal transplantation is less clear. Echocardiography was performed in 141 patients on the eve of renal transplantation. 34 patients subsequently died. Apart from age, only systolic function (fractional shortening 27 vs 33%;  $p < 0.01$ ) and end systolic diameter (4.3 vs 3.4 cm;  $p < 0.01$ ) were predictive of death. Ejection fraction was not predictive [54]

Pre-operative echocardiography was performed in 47 renal transplant recipients with diabetes mellitus. Radiological evidence of cardiomegaly or congestive cardiac failure, and echocardiographic measurements of ejection fraction, left ventricular end-diastolic diameter or posterior wall thickness were not predictive of survival. Increased end-systolic diameter was predictive. Patients with this finding ( $n=10$ ) had a 30% 3 year survival vs 69% for those without ( $p < 0.05$ ) [55]

Of 56 patients aged over 50 years old, who underwent cadaveric renal transplantation, 10 died within 2 years. The mean, pre-transplant left ventricular ejection fraction was  $38 \pm 5\%$  in the 10 patients who died, but  $51 \pm 7\%$  in the 46 survivors ( $p < 0.001$ ). A preoperative ejection fraction of  $< 40\%$  was much more common (60% v 4%;  $p < 0.001$ ) among those who died, compared to the survivors [56]

Part of the difficulty in interpreting left ventricular failure in the pre-transplantation period, arises because the cardiac function of some patients will improve post-transplantation. Wali et al reviewed 103 patients who underwent renal transplantation with left ventricular ejection fraction of less than 40%. The mean left ventricular ejection fraction increased from 31.6% (95% confidence interval [CI] 30.3% to 32.9%) pre-operatively, to 52.2 (95% CI 49.9 to 54.6,  $p = 0.002$ ) at 12 months after transplantation. There were no perioperative deaths. After transplantation, 69.9% of patients achieved an ejection fraction of 50% or more. A longer duration of dialysis was the strongest predictor of a failure to improve the ejection fraction to more than 50%. During a mean of 36.8 months follow-up, there were 25 deaths (24%) overall. The risk of death was approximately 8-fold higher in patients whose ejection fraction did not normalize after transplantation [57]

Four patients with an ejection fraction of less than 30%, each received a renal transplant from a living donor. Their mean ejection fraction increased from 25.9% to 69% after 6 months ( $p < 0.001$ ), although 2 patients experienced “cardiac arrest” requiring resuscitation [58] Twelve patients with systolic dysfunction before renal transplantation normalized their fractional shortening after transplantation (from a mean of 21.5% to 33.5%). The patients had a mean age of just 37 years, only 2 had coronary artery disease and patients who lost graft function (or presumably who died) within 12 months of transplantation were removed from analysis [59]

It is clear however, that an improvement in LV parameters does not occur in all patients and in a more recent study [46] there was no significant change in LVMI between patients who underwent renal transplantation and those who remained on dialysis.

### **Valvular disease**

Abbott et al looked at valvular heart disease in 35,215 patients from USRDS who were enrolled on the transplant waiting list. Patients with valvular disease were significantly less likely to be transplanted (adjusted rate for RT 0.38, 95% CI: 0.20 - 0.45), but patients who received valve replacement surgery were not affected (adjusted rate for RT 1.10, 95% CI: 0.52 - 2.32, not significant) [60].

### **Carotid artery stenoses**

There are few studies examining risk factors for cerebrovascular events and no papers specifically examining screening for carotid artery stenosis in patients after renal transplantation.

### **Risk factors for cerebrovascular events**

There is one study examining the incidence of stroke in a RCT after renal transplantation. [61]: This study examines the incidence of cerebrovascular events in patients in the ALERT study where patients were randomised to either fluvastatin or placebo. This post hoc analysis of 1652 patients demonstrated an incidence of cerebrovascular events of 8.8% with no benefit demonstrated in the fluvastatin arm. There was no difference in non-fatal or fatal stroke, or haemorrhagic or ischaemic stroke when comparing the treatment arms. Patients who had a haemorrhagic stroke however, had a high incidence of mortality (48%) compared to those with an ischaemic stroke (6%).

Risk factors for cerebrovascular events in a multivariate analysis were:

- Ischaemic Stroke
  - Diabetes mellitus (HR 3.54; 95% CI 2.42 – 5.18)
  - Previous cerebrovascular event (HR 3.53; 95% CI 2.23 – 5.59)
  - Increasing age (HR 1.06; 95% CI 1.04 – 1.08)
  - Serum Creatinine (HR 1.01; 95% CI 1.00 – 1.01)
- Haemorrhagic Stroke
  - Diabetes mellitus (HR 4.91; 95% CI 2.08 – 11.59)
  - Left ventricular hypertrophy (HR 2.95; 95% CI 1.21 – 7.18)

- Polycystic kidney disease (HR 4.15; 95% CI 1.43 – 11.95)
- Systolic BP (HR 1.02; 95% CI 1.00 – 1.04)

Aull-Watschinger: in 1617 patients examined for pre-transplant risk factors for TIA and Stroke after transplant, the risk for stroke in a multivariate analysis were significantly increased in patients with diabetes mellitus and atrial fibrillation [62].

### **Carotid plaque scoring**

Schwaiger: In a cross sectional analysis of 167 haemodialysis patients, carotid plaques were present by Doppler ultrasound in 65%. The mean plaque score was significantly higher in those who had a cardiovascular end point and those who died due to any cause. There is however, no data to suggest which patients should be screened and what outcomes can be improved upon with screening [15]

## **SUMMARY OF THE EVIDENCE**

The screening of renal transplant candidates for cardiovascular disease is an important consideration, and many, often small studies have been undertaken. There are virtually no randomised controlled trials, and the issue does not lend itself to that type of investigation.

The initial screening would usually be clinical, and there is evidence that the absence of clinical risk factors such as age under 50, no diabetes, no angina and a normal ECG helps to define a population at a low risk of post-operative cardiac problems.

Further risk stratification can be achieved with non-invasive testing, including echocardiography, with or without stress and with nucleotide imaging. The role of exercise ECG testing is limited by the reduced exercise capacity of patients with end-stage renal failure. There is little head to head testing of these modalities, and neither is clearly better than the other. The preferred modality will typically depend upon local availability and expertise. In general these investigations should be performed without concurrent beta-blocker therapy, and it should be noted that the validity of testing is markedly reduced after 24 months.

Coronary angiography is clearly the gold-standard for anatomy, although less clearly for survival information. Exactly which patients require it is not clear from the evidence, but patients with severe abnormalities on screening procedures are at increased risk of cardiac events. Despite this, there is no current evidence that revascularisation is beneficial in most instances and current data demonstrates a survival benefit with transplantation in patients even with substantial coronary artery disease (Jones).

## **WHAT DO THE OTHER GUIDELINES SAY?**

**Kidney Disease Outcomes Quality Initiative:** No recommendation.

**UK Renal Association:** No recommendation.

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** ERA-EDTA and ESOT. As cardiac disease is the main cause of mortality after transplantation, careful evaluation is mandatory to detect and treat symptomatic coronary artery disease, congestive heart failure due to valvular failure or cardiomyopathy and pericardial constriction [Evidence level B] [63]

**International Guidelines:** The American Society of Transplant Physicians has produced evaluation guidelines that include a section on cardiovascular evaluation [64]

The European Association of Urology has guidelines that include a section on evaluation for renal transplantation [65]

## **SUGGESTIONS FOR FUTURE RESEARCH**

1. The prospective gathering of data to allow better prediction of outcomes after renal transplantation. This should include more specific data than currently collected, including symptoms, history of infarction and imaging results as far as is known at the time of transplantation.
2. Ideally RCTs in the areas of screening and revascularisation would assist with decision making in this area.

## **CONFLICT OF INTEREST**

Helen Pilmore has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by CARI.

**DRAFT**

## REFERENCES

1. Johnson DW, Herzig K, Purdie D et al. A comparison of the effects of dialysis and renal transplantation on the survival of older uremic patients. *Transplantation*. 2000; **69**: 794-9.
2. Khauli RB, Steinmuller DR, Novick AC et al. A critical look at survival of diabetics with end-stage renal disease. Transplantation versus dialysis therapy. *Transplantation*. 1986; **41**: 598-602.
3. McDonald SP and Russ GR. Survival of recipients of cadaveric kidney transplants compared with those receiving dialysis treatment in Australia and New Zealand, 1991-2001. *Nephrol Dial Transplant*. 2002; **17**: 2212-9.
4. Medin C, Elinder CG, Hylander B et al. Survival of patients who have been on a waiting list for renal transplantation. *Nephrol Dial Transplant*. 2000; **15**: 701-4.
5. Meier-Kriesche HU, Ojo AO, Port FK et al. Survival improvement among patients with end-stage renal disease: trends over time for transplant recipients and wait-listed patients. *J Am Soc Nephrol*. 2001; **12**: 1293-6.
6. Ojo AO, Port FK, Wolfe RA et al. Comparative mortality risks of chronic dialysis and cadaveric transplantation in black end-stage renal disease patients. *Am J Kidney Dis*. 1994; **24**: 59-64.
7. Rabbat CG, Thorpe KE, Russell JD et al. Comparison of mortality risk for dialysis patients and cadaveric first renal transplant recipients in Ontario, Canada. *J Am Soc Nephrol*. 2000; **11**: 917-22.
8. Wolfe RA, Ashby VB, Milford EL et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med*. 1999; **341**: 1725-30.
9. Le A, Wilson R, Douek K et al. Prospective risk stratification in renal transplant candidates for cardiac death. *Am J Kidney Dis*. 1994; **24**: 65-71.
10. Lewis MS, Wilson RA, Walker KW et al. Validation of an algorithm for predicting cardiac events in renal transplant candidates. *Am J Cardiol*. 2002; **89**: 847-50.
11. Chuang P, Gibney EM, Chan L et al. Predictors of cardiovascular events and associated mortality within two years of kidney transplantation. *Transplant Proc*. 2004; **36**: 1387-91.
12. Ducloux D, Kazory A, and Chalopin J-M. Predicting coronary heart disease in renal transplant recipients: a prospective study. *Kidney Int*. 2004; **66**: 441-7.
13. Lentine KL, Brennan DC, and Schnitzler MA. Incidence and predictors of myocardial infarction after kidney transplantation. *J Am Soc Nephrol*. 2005; **16**: 496-506.
14. Ali M, Giblin L, Farhad K et al. Pretransplant cardiac investigations in the Irish renal transplant population--the effectiveness of our current screening techniques in predicting cardiac events. *Renal Failure*. 2004; **26**: 375-80.
15. Schwaiger JP, Lamina C, Neyer U et al. Carotid plaques and their predictive value for cardiovascular disease and all-cause mortality in hemodialysis patients considering renal transplantation: a decade follow-up. *Am J Kidney Dis*. 2006; **47**: 888-97.
16. Israni AK, Snyder JJ, Skeans MA et al. Predicting coronary heart disease after kidney transplantation: Patient Outcomes in Renal Transplantation (PORT) Study. *Am J Transplant*. 2010; **10**: 338-53.
17. Wang LW, Fahim MA, Hayen A et al. Cardiac Testing for Coronary Artery Disease in Potential Kidney Transplant Recipients: A Systematic Review of Test Accuracy Studies. *Am J Kidney Dis*. 2011; **57**: 476-487.

18. Bennett WM, Kloster F, Rosch J et al. Natural history of asymptomatic coronary arteriographic lesions in diabetic patients with end-stage renal disease. *Am J Med.*1978; **65**: 779-84.
19. Mistry BM, Bastani B, Solomon H et al. Prognostic value of dipyridamole thallium-201 screening to minimize perioperative cardiac complications in diabetics undergoing kidney or kidney-pancreas transplantation. *Clin Transplant.* 1998; **12**: 130-5.
20. Holley JL, Fenton RA, and Arthur RS. Thallium stress testing does not predict cardiovascular risk in diabetic patients with end-stage renal disease undergoing cadaveric renal transplantation. *Am J Med.*1991; **90**: 563-70.
21. Dahan M, Viron BM, Faraggi M et al. Diagnostic accuracy and prognostic value of combined dipyridamole-exercise thallium imaging in hemodialysis patients. *Kidney Int.* 1998; **54**: 255-62.
22. Vandenberg BF, Rossen JD, Grover-McKay M et al. Evaluation of diabetic patients for renal and pancreas transplantation: noninvasive screening for coronary artery disease using radionuclide methods. *Transplantation.* 1996; **62**: 1230-5.
23. Worthley MI, Unger SA, Mathew TH et al. Usefulness of tachycardic-stress perfusion imaging to predict coronary artery disease in high-risk patients with chronic renal failure. *Am J Cardiol.* 2003; **92**: 1318-20.
24. Marwick TH, Steinmuller DR, Underwood DA et al. Ineffectiveness of dipyridamole SPECT thallium imaging as a screening technique for coronary artery disease in patients with end-stage renal failure. *Transplantation.* 1990; **49**: 100-3.
25. Patel AD, Abo-Auda WS, Davis JM et al. Prognostic value of myocardial perfusion imaging in predicting outcome after renal transplantation.[Erratum appears in *Am J Cardiol.* 2004 Jan 1;93(1):129-30]. *Am J Cardiol.* 2003; **92**: 146-51.
26. Brown JH, Vites NP, Testa HJ et al. Value of thallium myocardial imaging in the prediction of future cardiovascular events in patients with end-stage renal failure. *Nephrol Dial Transplant.* 1993; **8**: 433-7.
27. Brown KA, Rimmer J, and Haisch C. Noninvasive cardiac risk stratification of diabetic and nondiabetic uremic renal allograft candidates using dipyridamole-thallium-201 imaging and radionuclide ventriculography. *Am J Cardiol.* 1989; **64**: 1017-21.
28. Morrow CE, Schwartz JS, Sutherland DE et al. Predictive value of thallium stress testing for coronary and cardiovascular events in uremic diabetic patients before renal transplantation. *Am J Surg.* 1983; **146**: 331-5.
29. Derfler K, Kletter K, Balcke P et al. Predictive value of thallium-201-dipyridamole myocardial stress scintigraphy in chronic hemodialysis patients and transplant recipients. *Clin Nephrol.* 1991; **36**: 192-202.
30. Reis G, Marcovitz PA, Leichtman AB et al. Usefulness of dobutamine stress echocardiography in detecting coronary artery disease in end-stage renal disease. *Am J Cardiol.* 1995; **75**: 707-10.
31. Herzog CA, Marwick TH, Pheley AM et al. Dobutamine stress echocardiography for the detection of significant coronary artery disease in renal transplant candidates. *Am J Kidney Dis.* 1999; **33**: 1080-90.
32. Sharma R, Pellerin D, Gaze DC et al. Dobutamine stress echocardiography and the resting but not exercise electrocardiograph predict severe coronary artery disease in renal transplant candidates. *Nephrol Dial Transplant.* 2005; **20**: 2207-14.
33. Brennan DC, Vedala G, Miller SB et al. Pretransplant dobutamine stress echocardiography is useful and cost-effective in renal transplant candidates. *Transplant Proc.* 1997; **29**: 233-4.

34. Marwick TH, Lauer MS, Lobo A et al. Use of dobutamine echocardiography for cardiac risk stratification of patients with chronic renal failure. *J Intern Med.* 1998; **244**: 155-61.
35. Bates JR, Sawada SG, Segar DS et al. Evaluation using dobutamine stress echocardiography in patients with insulin-dependent diabetes mellitus before kidney and/or pancreas transplantation. *Am J Cardiol.* 1996; **77**: 175-9.
36. Haydar AA, Hujairi NMA, Covic AA et al. Coronary artery calcification is related to coronary atherosclerosis in chronic renal disease patients: a study comparing EBCT-generated coronary artery calcium scores and coronary angiography. *Nephrol Dial Transplant.* 2004; **19**: 2307-12.
37. Sharples EJ, Pereira D, Summers S et al. Coronary artery calcification measured with electron-beam computerized tomography correlates poorly with coronary artery angiography in dialysis patients. *Am J Kidney Dis.* 2004; **43**: 313-9.
38. De Lima JJG, Sabbaga E, Vieira MLC et al. Coronary angiography is the best predictor of events in renal transplant candidates compared with noninvasive testing. *Hypertension.* 2003; **42**: 263-8.
39. Jones DG, Taylor AM, Enkiri SA et al. Extent and severity of coronary disease and mortality in patients with end-stage renal failure evaluated for renal transplantation. *Am J Transplant.* 2009; **9**: 1846-52.
40. Rabbat CG, Treleaven DJ, Russell JD et al. Prognostic value of myocardial perfusion studies in patients with end-stage renal disease assessed for kidney or kidney-pancreas transplantation: a meta-analysis. *J Am Soc Nephrol.* 2003; **14**: 431-9.
41. Dahan M, Viron BM, Poiseau E et al. Combined dipyridamole-exercise stress echocardiography for detection of myocardial ischemia in hemodialysis patients: an alternative to stress nuclear imaging. *Am J Kidney Dis.* 2002; **40**: 737-44.
42. Dussol B, Bonnet J-L, Sampol J et al. Prognostic value of inducible myocardial ischemia in predicting cardiovascular events after renal transplantation. *Kidney Int.* 2004; **66**: 1633-9.
43. Schmidt A, Stefenelli T, Schuster E et al. Informational contribution of noninvasive screening tests for coronary artery disease in patients on chronic renal replacement therapy. *Am J Kidney Dis.* 2001; **37**: 56-63.
44. De Vriese AS, De Bacquer DA, Verbeke FH et al. Comparison of the prognostic value of dipyridamole and dobutamine myocardial perfusion scintigraphy in hemodialysis patients. *Kidney Int.* 2009; **76**: 428-36.
45. Manske CL, Thomas W, Wang Y et al. Screening diabetic transplant candidates for coronary artery disease: identification of a low risk subgroup. *Kidney Int.* 1993; **44**: 617-21.
46. Patel RK, Mark PB, Johnston N et al. Prognostic value of cardiovascular screening in potential renal transplant recipients: a single-center prospective observational study. *Am J Transplant.* 2008; **8**: 1673-83.
47. De Lima JJG, Gowdak LHW, de Paula FJ et al. Treatment of coronary artery disease in hemodialysis patients evaluated for transplant—a registry study. *Transplantation.* 2010; **89**: 845-50.
48. McFalls EO, Ward HB, Moritz TE et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med.* 2004; **351**: 2795-804.
49. Cottin Y, Rezaizadeh K, Touzery C et al. Long-term prognostic value of 201Tl single-photon emission computed tomographic myocardial perfusion imaging after coronary stenting. *Am Heart J.* 2001; **141**: 999-1006.
50. Miller TD, Christian TF, Hodge DO et al. Prognostic value of exercise thallium-201 imaging performed within 2 years of coronary artery bypass graft surgery. *J Am Coll Cardiol.* 1998; **31**: 848-54.

51. Alazraki NP, Krawczynska EG, Kosinski AS et al. Prognostic value of thallium-201 single-photon emission computed tomography for patients with multivessel coronary artery disease after revascularization (the Emory Angioplasty versus Surgery Trial [EAST]). *Am J Cardiol.* 1999; **84**: 1369-74.
52. Lauer MS, Lytle B, Pashkow F et al. Prediction of death and myocardial infarction by screening with exercise-thallium testing after coronary-artery-bypass grafting. *Lancet.* 1998; **351**: 615-22.
53. Parfrey PS, Foley RN, Harnett JD et al. Outcome and risk factors for left ventricular disorders in chronic uraemia. *Nephrol Dial Transplant.* 1996; **11**: 1277-85.
54. McGregor E, Jardine AG, Murray LS et al. Pre-operative echocardiographic abnormalities and adverse outcome following renal transplantation. *Nephrol Dial Transplant.* 1998; **13**: 1499-505.
55. Weinrauch LA, D'Elia JA, Monaco AP et al. Preoperative evaluation for diabetic renal transplantation: impact of clinical, laboratory, and echocardiographic parameters on patient and allograft survival. *Am J Med.* 1992; **93**: 19-28.
56. Biesenbach G, Eichbauer-Sturm G, Janko O et al. Left ventricular ejection fraction less than 40% is a useful predictor for poor patient survival in kidney transplant recipients over age 50 years. *Transplant Proc.* 2002; **34**: 3079-81.
57. Wali RK, Wang GS, Gottlieb SS et al. Effect of kidney transplantation on left ventricular systolic dysfunction and congestive heart failure in patients with end-stage renal disease. *J Am Coll Cardiol.* 2005; **45**: 1051-60.
58. Cho WH, Kim HT, Park CH et al. Renal transplantation in advanced cardiac failure patients. *Transplant Proc.* 1997; **29**: 236-8.
59. Parfrey PS, Harnett JD, Foley RN et al. Impact of renal transplantation on uremic cardiomyopathy. *Transplantation.* 1995; **60**: 908-14.
60. Abbott KC, Hshieh P, Cruess D et al. Hospitalized valvular heart disease in patients on renal transplant waiting list: incidence, clinical correlates and outcomes. *Clin Nephrol.* 2003; **59**: 79-87.
61. Abedini S, Holme I, Fellstrom B et al. Cerebrovascular events in renal transplant recipients. *Transplantation.* 2009; **87**: 112-7.
62. Aull-Watschinger S, Konstantin H, Demetriou D et al. Pre-transplant predictors of cerebrovascular events after kidney transplantation. *Nephrol Dial Transplant.* 2008; **23**: 1429-35.
63. European Renal Association. European Best Practice Guidelines for Renal Transplantation (part 1). *Nephrol Dial Transplant.* 2000; **15 Suppl 7**: 1-85.
64. Kasiske BL, Cangro CB, Hariharan S et al. The evaluation of renal transplantation candidates: clinical practice guidelines. *Am J Transplant.* 2001; **1 Suppl 2**: 3-95.
65. Kalble T, Lucan M, Nicita G et al. EAU guidelines on renal transplantation. *European Urology.* 2005; **47**: 156-66.

## APPENDICES

Table 1. Clinical Risk Factors

Study	No. of Patients	Outcome Measured	Result	Level Of Evidence	Comment
Le et al. 1994 [9]	189	Cardiac death	Positive Predictive Value = 15.7% Negative Predictive Value = 98.9%	IV	Case Series
Lewis et al. 2002 [10]	184	Cardiac death  Non-fatal cardiac events	Positive Predictive Value = 4.5% Negative Predictive Value = 100%  Positive Predictive Value = 11.6% Negative Predictive Value = 100%	IV	Validation of the above population.
Chuang et al. 2004 [11]	780	Acute Coronary Syndrome <2 years post-transplant	Diabetes (OR 5.56; P = .0007), smoking (OR 3.56; P = .034), and prior transplant (OR 2.81; P = .047)	III	Observational case-controlled study.
Ducloux et al. 2004 [12]	344	Acute Coronary Events	Framingham calculator underestimated risk in higher risk. CRP (p=0.009) and homocysteinemia (p=0.01)	III	Prospective Cohort Study
Lentine et al. 2005 [13]	35,847	Post-transplant Myocardial Infarction up to 36 months.	11.5% at 36 months. Predictors included: older age, previous transplants, diabetes, angina, peripheral vascular disease or myocardial infarction.	IV	Retrospective analysis of USRDS
Ali et al. 2004 [14]	190	Combined cardiac endpoint.	The strongest predictors were: Age (HR 1.7, CI 1.24-2.31), past CVA (HR 3.62, CI 1.19-10.99) or anterior Q-wave on ECG (HR 5.28, CI 2.14-13.05)	IV	Retrospective case analysis
Lin et al. 2001 [66]	165	Post-operative myocardial infarction within 1 year.	Negative Predictive Value 98% within one year of test and 97% within one year of transplant.	IV	Retrospective case analysis
Weinrauch et al. 1992 [55]	47	3 year survival	70% 3 year survival if no infarct, angina or heart failure. 50% if any present.	IV	Case Series
Manske et al. 1993 [45]	141	Coronary Artery Stenoses (at least 50% in 1 artery)	Sensitivity of 97% Negative Predictive Value of 96%	IV	Case Series
Koch et al. 1997 [67]	105	Coronary lesions on angiography	No correlation	IV	Case Series

**Table 2. Radionucleotide testing**

Study	No. of Patients	Outcome Measured	Result	Level Of Evidence	Comment
Mistry et al. 1998 [19]	176	Coronary Anatomy  Major Cardiac Event	64% (of 42) with reversible defects had at least one stenosis >50%  1 of 141 with normal scan, fixed defect, or reversible defect and normal angiogram had events. 3 of 27 (11%) with reversible scans and abnormal angiograms did.	IV	Retrospective Case Analysis
Holley et al. 1991 [20]	189	Coronary Anatomy	Beta-blockers predict inadequacy. 43% (of 77) with abnormal or inadequate test had disease	IV	Case Series
Dahan et al. 1998 [21]	60	Coronary Anatomy  Major Coronary Event	Sensitivity 92% Specificity 89% Positive Predictive Value 71% Negative Predictive Value 98%  Positive Predictive Value 47% Negative Predictive Value 91%	IV	Case Series
Vandenberg et al. 1996 [22]	41 (all diabetic)	Coronary Anatomy	For lesions >75% - Sensitivity 62%, Specificity 76%. For lesions >50% - Sensitivity 53%, Specificity 73%.	IV	Case Series
Worthley et al. 2003 [23]	40	Coronary Anatomy	Sensitivity 87% Specificity 88% Positive Predictive Value 81% Negative Predictive Value 92%	IV	Case Series
Iqbal et al. 1991 [68]	36 (all diabetic)	Coronary Anatomy	7 of 10 with abnormal scans and angiography had abnormal arteries	IV	Case Series
Marwick et al. 1990 [24]	45	Coronary Anatomy  Cardiac Death	Sensitivity 36% Specificity 73%  5 of 6 patients suffering cardiac death had normal thallium scan.	IV	Case Series
Le et al. 1994 [9]	189	Cardiac Mortality	High risk patients. Reversible defects predict death compared to normals (23% v 5%; p<0.05).	IV	Case Series

**The CARI Guidelines – Caring for Australians with Renal Impairment**

			Fixed defects (29% v 5%); p<0.05)		
Patel et al. 2003 [25]	174	Cardiac Events	42 month event free survival 97% with normal scan or 85% with abnormal scan. RR = 5.04 p=0.006)	IV	Case Series
Lewis et al. 2002 [10]	112	Fatal and non-fatal cardiac events	All events occurred in high risk patients with abnormal scans.	IV	Case Series
Brown et al. 1993 [26]	103	Cardiovascular Event	Sensitivity 88% Specificity 70% Positive Predictive Value 73%	IV	Case Series
Feola et al. 2002 [69]	82	Cardiac event	Nil among 61 patients with normal scans or fixed defects only.	IV	Case Series
Camp et al 1990 [70]	40 (all diabetic)	Cardiac Event	All 6 occurred in the 9 patients who had reversible defects.	IV	Case Series
Brown et al. 1989 [27]	65	Cardiac Event	3 of 3 patients with reversible defects (100%) v 3 of 62 (5%) without; p<0.0001	IV	Case Series
Morrow et al. 1983 [28]	85 (all diabetic)	Fatal Myocardial Infarct	4 of 18 with a positive test ((22%) v 3 of 67 (4%) with a negative test; p<0.05	IV	Case Series

**Table 3. Stress echocardiography testing**

Study	No. of Patients	Outcome Measured	Result	Level Of Evidence	Comment
Reiss et al. 1995 [30]	97	Coronary stenosis >50%	Sensitivity 95% Specificity 86% Accuracy 90% 97% of those with a normal DSE were free of cardiac complications over 12 months	IV	Case Series
Herzog et al. 1999 [31]	50	Coronary stenosis >50%	Sensitivity 52% Specificity 74%	IV	Case Series
		Coronary stenosis >75%	Sensitivity 75% Specificity 76%		
		Death, infarct or revascularisation	6/30 (21%) with neg test v 11/20 (55%) with pos test (p=0.01)		
Brennan et al. 1997 [33]	47	Early post-op cardiac complications	Negative predictive value 95%	IV	Case Series
Beleslin et al.	Non-renal	Coronary stenosis >50%	Sensitivity & specificity for:	IV	Case Series

**The CARI Guidelines – Caring for Australians with Renal Impairment**

1999 [71]	patients		Exercise 88% and 82% Dobutamine 82% and 77% Dipyridamole 74% and 94%		
Marwick et al. 1992 [72]	114 (non-renal)	Coronary stenosis >50%	Sensitivity 84% False negatives with submaximal exercise and moderate stenoses (50-70%)	IV	Case Series
Marwick et al. 1998 [34]	193	Cardiac event free survival	66% if ischaemia v 84% without (p=0.006). Not predictive after 40 months.	IV	Case Series
Bates et al. 1996 [35]	53 (diabetic)	Death, infarct, angina or revascularisation	Odds ratio 12.7 (p=0.003)	IV	Case Series
West et al. 2000 [73]	33	Cardiac complications or death	Negative predictive value 92%	IV	Case Series

**Table 4. Coronary angiography**

<b>Study</b>	<b>No. of Patients</b>	<b>Outcome Measured</b>	<b>Result</b>	<b>Level Of Evidence</b>	<b>Comment</b>
Ramanathan et al. 2005 [74]	97 (all diabetic)	> 70% stenosis	33% of type 1 and 48% of type 2	IV	Case Series
De Lima et al. 2003 [38]	126	Cardiac Event free survival at 6,12, 24, 36 and 48 months. < 70% stenosis v >70%	6 months 98% v 97% 12 months 98% v 87% 24 months 94% v 61% 36 months 94% v 56% 48 months 94% v 54%	IV	Case Series
Herzog et al. 1999 [31]	50	Cardiac death or myocardial infarction	Coronary angiography was predictive if the nuclear scan was abnormal, but not if the nuclear scan was normal.	IV	Case Series

**Table 5. Coronary revascularisation outcomes.**

Study	No. of Patients	Percentage survival for all patients at various timepoints after Surgery.				Percentage survival for out of hospital survivors at various timepoints after Surgery.			
		1 Year	2 Years	3 Years	5 Years	1 Year	2 Years	3 Years	5 Years
Molina et al. 2004 [75]	77 (all IDDM)	100				100			
Ferguson et al. 1999 [76]	83	89		77	65				
Labrousse et al. 1999 [77]	82	71		56	39	83		66	46
Nakayama et al. 1999 [78]	47					89		84	71
Frenken et al. 1999 [79]	30	90	73	67	67				
Manske et al. 1998 [80]	30 (all IDDM)	80	73	66 (4 yrs)					
Rinehart et al. 1995 [81]	60		66						

**Table 6. Retesting after coronary revascularisation. (NOT performed in renal patients)**

Study	No. of Patients	Outcome Measured	Result	Level Of Evidence	Comment
Cottin et al. 2001 [49]	152	Death, infarct or revascularisation	24/47 (51%) of ischaemic patients v 11/105 (10%) – p<0.001	IV	Case Series
Alazraki et al. 1999 [51]	336	Myocardial Infarction or death	11.7% at 3 years in those with reversible defects v 4.5% in those without	IV	Case Series

**The CARI Guidelines – Caring for Australians with Renal Impairment**

Lauer et al. 1998 [52]	873	Death Major Cardiac Event	Any defect 9% v 3% (p=0.0004) Any defect 11% v 4% (p=0.0002)	IV	Case Series
		Death Major Cardiac Event	Reversible defect 12% v 5% (p=0.002) Reversible defect 13% v 7% (p=0.004)		
Miller et al. 1998 [50]	411	Overall mortality Cardiac death Cardiac event	P=0.007 P=0.004 P=0.005	IV	Case Series

DRAFT

**Table 7. Evidence Profile diagnostic test accuracy – cardiac stress testing for in potential kidney transplant recipients (MPS and DSE).**

Quality Assessment						Summary of findings					Importance
No. of studies and design	Study Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Number of patients	Sensitivity (95% CI)	Specificity (95% CI)	Effect per 1000	Quality	
<b>Outcome: True Positives</b>											
MPS 7 Obs. (a)	Serious (b)	Serious (c)	No serious limitations	No serious limitations	None identified	317	0.69 (0.48-0.85) (a)	0.77 (0.59-0.89) (a)	Prevalence 80% - 552 40% - 276 10% - 69	Low	Critical
DSE 11 Obs. (a)	Serious (b)	Serious (c)	No serious limitations	No serious limitations	None identified	680	0.80 (0.64-0.90) (a)	0.89 (0.79-0.94) (a)	Prevalence 80% - 640 40% - 320 10% - 80	Low	
<b>Outcome: True Negatives</b>											
MPS 7 Obs. (a)	Serious (b)	Serious (c)	No serious limitations	No serious limitations	None identified	317	0.69 (0.48-0.85) (a)	0.77 (0.59-0.89) (a)	Prevalence 80% - 154 40% - 462 10% - 693	Low	Critical
DSE 11 Obs. (a)	Serious (b)	Serious (c)	No serious limitations	No serious limitations	None identified	680	0.80 (0.64-0.90) (a)	0.89 (0.79-0.94) (a)	Prevalence 80% - 178 40% - 534 10% - 801	Low	
<b>Outcome: False Positives</b>											
MPS 7 Obs. (a)	Serious (b)	Serious (c)	No serious limitations	No serious limitations	None identified	317	0.69 (0.48-0.85) (a)	0.77 (0.59-0.89) (a)	Prevalence 80% - 46 40% - 138 10% - 207	Low	Critical
DSE 11 Obs. (a)	Serious (b)	Serious (c)	No serious limitations	No serious limitations	None identified	680	0.69 (0.48-0.85) (a)	0.77 (0.59-0.89) (a)	Prevalence 80% - 22 40% - 66 10% - 99	Low	
<b>Outcome: False Negatives</b>											

**The CARI Guidelines – Caring for Australians with Renal Impairment**

Quality Assessment						Summary of findings					Importance
No. of studies and design	Study Limitations	Inconsistency	Indirectness	Imprecision	Other Considerations	Number of patients	Sensitivity (95% CI)	Specificity (95% CI)	Effect per 1000	Quality	
MPS 7 Obs. (a)	Serious (b)	Serious (c)	No serious limitations	No serious limitations	None identified	317	0.69 (0.48-0.85) (a)	0.77 (0.59-0.89) (a)	Prevalence 80% -248 40% - 124 10% -31	Low	Critical
DSE 11 Obs. (a)	Serious (b)	Serious (c)	No serious limitations	No serious limitations	None identified	680	0.80 (0.64-0.90) (a)	0.89 (0.79-0.94) (a)	Prevalence 80% - 160 40% - 80 10% - 20	Low	

Footnotes:

(a) Systematic review – Wang et al 2011 [17]

(b) Based on QADAS tool. Of the studies only 50% provided sufficient information to allow scoring hence there is a high degree of uncertainty as to overall limitations. Unclear as to blinding of reference and index tests in a number of studies and partial verification used in 2 studies.

(c) Significant heterogeneity.