CARDIOVASCULAR DISEASE

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GUIDELINES

a. We recommend that all candidates for kidney transplant are screened for cardiovascular risk factors (1B). Indicators of high risk include (1B):
   - Older age;
   - Diabetes mellitus;
   - Abnormal ECG;
   - Previous ischemic heart disease or congestive heart failure;
   - Increased duration of dialysis.
   - Smoker

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 β-blocker therapy. (1B)
   - 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)

UNGRADED SUGGESTIONS FOR CLINICAL CARE

- 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. (ungraded)
- In general, there is no strong evidence to suggest that revascularisation of asymptomatic coronary artery stenosis in patients with renal failure is associated with beneficial outcomes after renal transplantation. (ungraded)
- 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 for carotid plaques. (ungraded)
- Kidney transplant candidates with diabetes mellitus and atrial fibrillation should be identified as having a higher risk of post transplantation cerebrovascular events. (ungraded)

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 has a worse long term prognosis 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 – May 2011) 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:** May 2011 (but including Cochrane Review 1 November 2011).

**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:
4. Elevated CRP [12]  
5. Homocysteinaemia [12]  
6. Angina [13]  
7. Peripheral vascular disease [13]  
9. Evidence of previous myocardial infarction on ECG HR 5.28 [14]  

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 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]. More recently, this has been published as a Cochrane Review [18].

**Systematic review**

Wang et al [17] undertook a systematic review of diagnostic test accuracy studies of any non or minimally invasive 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.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
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<tbody>
<tr>
<td>MPS</td>
<td>0.69 (95% CI 0.48-0.85)</td>
<td>0.77 (95% CI 0.59-0.89)</td>
</tr>
<tr>
<td>DSE</td>
<td>0.80 (95% CI 0.64-0.90)</td>
<td>0.89 (95% CI 0.79-0.94)</td>
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The pooled estimates showed significant heterogeneity. The threshold coronary artery stenosis reference was ≥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.

The more recently published Cochrane Review [18] included a slightly larger number of studies but demonstrated similar sensitivity.

**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, 19].

**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 [20]: 28% patients had reversible defect on preoperative dipyridamole-thallium imaging. 64% of these had at least one coronary artery stenosis of > 50%
- Holley 1991[21]: 43% with positive dipyridamole-thallium imaging had significant coronary artery disease.
- Dahan 1998 [22]: Sensitivity, specificity, positive and negative predictive values for thallium imaging as a predictor of abnormal coronary anatomy were 92%, 89%, 71% and 98% respectively.
- Vanden Berg 1996 [23]: 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 [24]: 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 [25]: 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 [20]: 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 [26]: 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 [27]: 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 [22]: 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 [28]: 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 [29]: 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[30]: 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 [31]: 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 [32]: 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 [33]: 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 [33]: DSE did not predict mortality in patients assessed for renal transplantation.
- Herzog 1999 [32]: 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 [34]: 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 [35]: 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 [36]: 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 [31]: 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% [37] and a specificity of only 48% [38]. 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 and some residual renal function.

Coronary artery stenoses and risk of cardiac events

- De Lima 2003 [39]: 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 [40] 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 [41] 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 = 0.06) when compared with negative tests. In studies evaluating mixed populations of diabetic and non-diabetic 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 [42]: Stress echo and stress radionuclide testing were compared. This paper did not demonstrate any significant difference in the overall accuracy for detecting coronary artery disease (radionuclide testing sensitivity, specificity, PPV, NPV 86%, 94%, 80%, 95% respectively; stress echo sensitivity, specificity, PPV, NPV 83%, 84%, 67%, 93%).
- De Lima [39]: 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 [43]: 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 [44]: 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 [45]: 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 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).

**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 [46]. 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 [47]: 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.[48] 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/ACCA 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 [49]: 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 [50, 51], myocardial infarction [52] and death [53]. 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 ≤ 25%), 41% had concentric left ventricular hypertrophy, 28% had left ventricular dilatation (Volume > 90 mls/m²) 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) [54]

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 [55]

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) [56]

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±5% in the 10 patients who died, but 51±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 [57]

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 [58]

Four patients with an ejection fraction of less than 30% 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 [59] 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 [60]

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) [61].

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. [62]: 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 [63].

Carotid plaque scoring
Schwaiger: In a cross sectional analyses 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 for carotid plaques 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] [64]
- **International Guidelines**: The American Society of Transplant Physicians has produced evaluation guidelines that include a section on cardiovascular evaluation [65]
- **The European Association of Urology has guidelines that include a section on evaluation for renal transplantation [66]**

**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.
REFERENCES


### Table 1. Clinical Risk Factors

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Outcome Measured</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le et al. 1994 [9]</td>
<td>189</td>
<td>Cardiac death</td>
<td>Positive Predictive Value = 15.7%</td>
<td>Case Series</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Negative Predictive Value = 98.9%</td>
<td></td>
</tr>
<tr>
<td>Lewis et al. 2002 [10]</td>
<td>184</td>
<td>Cardiac death</td>
<td>Positive Predictive Value = 4.5%</td>
<td>Validation of the above</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Negative Predictive Value = 100%</td>
<td>population.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-fatal cardiac events</td>
<td>Positive Predictive Value = 11.6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Negative Predictive Value = 100%</td>
<td></td>
</tr>
<tr>
<td>Chuang et al. 2004 [11]</td>
<td>780</td>
<td>Acute Coronary Syndrome &lt;2 years post-transplant</td>
<td>Diabetes (OR 5.56; P = .0007), smoking (OR 3.56; P = .034), and prior transplant (OR 2.81; P = .047)</td>
<td>Observational case-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Framingham calculator underestimated risk in higher risk. CRP (p=0.009) and homocysteinaemia (p=0.01)</td>
<td>controlled study.</td>
</tr>
<tr>
<td>Ducloux et al. 2004 [12]</td>
<td>344</td>
<td>Acute Coronary Events</td>
<td>Framingham calculator underestimated risk in higher risk. CRP (p=0.009) and homocysteinaemia (p=0.01)</td>
<td>Prospective Cohort Study</td>
</tr>
<tr>
<td>Lentine et al. 2005 [13]</td>
<td>35,847</td>
<td>Post-transplant Myocardial Infarction up to 36 months.</td>
<td>11.5% at 36 months. Predictors included: older age, previous transplants, diabetes, angina, peripheral vascular disease or myocardial infarction.</td>
<td>Retrospective analysis of USRDS</td>
</tr>
<tr>
<td>Ali et al. 2004 [14]</td>
<td>190</td>
<td>Combined cardiac endpoint.</td>
<td>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)</td>
<td>Retrospective case analysis</td>
</tr>
<tr>
<td>Lin et al. 2001 [67]</td>
<td>165</td>
<td>Post-operative myocardial infarction within 1 year.</td>
<td>Negative Predictive Value 98% within one year of test and 97% within one year of transplant.</td>
<td>Retrospective case analysis</td>
</tr>
<tr>
<td>Weinrauch et al. 1992 [56]</td>
<td>47</td>
<td>3 year survival</td>
<td>70% 3 year survival if no infarct, angina or heart failure, 50% if any present.</td>
<td>Case Series</td>
</tr>
<tr>
<td>Manske et al. 1993 [46]</td>
<td>141</td>
<td>Coronary Artery Stenoses (at least 50% in 1 artery)</td>
<td>Sensitivity of 97% Negative Predictive Value of 96%</td>
<td>Case Series</td>
</tr>
<tr>
<td>Koch et al. 1997 [68]</td>
<td>105</td>
<td>Coronary lesions on angiography</td>
<td>No correlation</td>
<td>Case Series</td>
</tr>
</tbody>
</table>
### Table 2. Radionucleotide testing

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Outcome Measured</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mistry et al. 1998 [20]</td>
<td>176</td>
<td>Coronary Anatomy</td>
<td>64% (of 42) with reversible defects had at least one stenosis &gt;50%</td>
<td>Retrospective Case Analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major Cardiac Event</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Holley et al. 1991 [21]</td>
<td>189</td>
<td>Coronary Anatomy</td>
<td>Beta-blockers predict inadequacy. 43% (of 77) with abnormal or inadequate test had disease.</td>
<td>Case Series</td>
</tr>
<tr>
<td>Dahan et al. 1998 [22]</td>
<td>60</td>
<td>Coronary Anatomy</td>
<td>Sensitivity 92% Specificity 89% Positive Predictive Value 71% Negative Predictive Value 98%</td>
<td>Case Series</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major Coronary Event</td>
<td>Positive Predictive Value 47% Negative Predictive Value 91%</td>
<td></td>
</tr>
<tr>
<td>Vandenberg et al. 1996 [23]</td>
<td>41 (all diabetic)</td>
<td>Coronary Anatomy</td>
<td>For lesions &gt;75% - Sensitivity 62%, Specificity 76%. For lesions &gt;50% - Sensitivity 53%, Specificity 73%.</td>
<td>Case Series</td>
</tr>
<tr>
<td>Worthley et al. 2003 [24]</td>
<td>40</td>
<td>Coronary Anatomy</td>
<td>Sensitivity 87% Specificity 88% Positive Predictive Value 81% Negative Predictive Value 92%</td>
<td>Case Series</td>
</tr>
<tr>
<td>Iqbal et al. 1991 [69]</td>
<td>36 (all diabetic)</td>
<td>Coronary Anatomy</td>
<td>7 of 10 with abnormal scans and angiography had abnormal arteries</td>
<td>Case Series</td>
</tr>
<tr>
<td>Marwick et al. 1990 [25]</td>
<td>45</td>
<td>Coronary Anatomy</td>
<td>Sensitivity 36% Specificity 73%</td>
<td>Case Series</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiac Death</td>
<td>5 of 6 patients suffering cardiac death had normal thallium scan.</td>
<td></td>
</tr>
<tr>
<td>Le et al. 1994 [9]</td>
<td>189</td>
<td>Cardiac Mortality</td>
<td>High risk patients. Reversible defects predict death compared to normals (23% v 5%; p&lt;0.05). Fixed defects (29% v 5%); p&lt;0.05</td>
<td>Case Series</td>
</tr>
<tr>
<td>Patel et al. 2003 [26]</td>
<td>174</td>
<td>Cardiac Events</td>
<td>42 month event free survival 97% with normal scan or 85% with abnormal scan. RR = 5.04 p=0.006</td>
<td>Case Series</td>
</tr>
<tr>
<td>Lewis et al. 2002 [10]</td>
<td>112</td>
<td>Fatal and non-fatal cardiac events</td>
<td>All events occurred in high risk patients with abnormal scans.</td>
<td>Case Series</td>
</tr>
<tr>
<td>Brown et al. 1993 [27]</td>
<td>103</td>
<td>Cardiovascular Event</td>
<td>Sensitivity 88% Specificity 70% Positive Predictive Value 73%</td>
<td>Case Series</td>
</tr>
<tr>
<td>Feola et al. 2002 [70]</td>
<td>82</td>
<td>Cardiac event</td>
<td>Nil among 61 patients with normal scans or fixed defects only.</td>
<td>Case Series</td>
</tr>
<tr>
<td>Camp et al 1990 [71]</td>
<td>40 (all diabetic)</td>
<td>Cardiac Event</td>
<td>All 6 occurred in the 9 patients who had reversible defects.</td>
<td>Case Series</td>
</tr>
<tr>
<td>Brown et al. 1989 [28]</td>
<td>65</td>
<td>Cardiac Event</td>
<td>3 of 3 patients with reversible defects (100%) v 3 of 62 (5%) without: p=0.0001</td>
<td>Case Series</td>
</tr>
<tr>
<td>Morrow et al. 1983 [29]</td>
<td>85 (all diabetic)</td>
<td>Fatal Myocardial Infarct</td>
<td>4 of 18 with a positive test (22%) v 3 of 67 (4%) with a negative test; p&lt;0.05</td>
<td>Case Series</td>
</tr>
</tbody>
</table>
### Table 3. Stress echocardiography testing

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Outcome Measured</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reiss et al. 1995</td>
<td>97</td>
<td>Coronary stenosis &gt;50%</td>
<td>Sensitivity 95% Specificity 86% Accuracy 90% 97% of those with a normal DSE were free of cardiac complications over 12 months</td>
<td>Case Series</td>
</tr>
<tr>
<td>Herzog et al. 1999</td>
<td>50</td>
<td>Coronary stenosis &gt;50%</td>
<td>Sensitivity 52% Specificity 74%</td>
<td>Case Series</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coronary stenosis &gt;75%</td>
<td>Sensitivity 75% Specificity 76%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Death, infarct or revascularisation</td>
<td>6/30 (21%) with neg test v 11/20 (55%) with pos test (p=0.01)</td>
<td></td>
</tr>
<tr>
<td>Brennan et al. 1997</td>
<td>47</td>
<td>Early post-op cardiac complications</td>
<td>Negative predictive value 95%</td>
<td>Case Series</td>
</tr>
<tr>
<td>Beleslin et al. 1999</td>
<td>Non-renal patients</td>
<td>Coronary stenosis &gt;50%</td>
<td>Sensitivity &amp; specificity for: Exercise 88% and 82% Dobutamine 82% and 77% Dipyridamole 74% and 94%</td>
<td>Case Series</td>
</tr>
<tr>
<td>Marwick et al. 1992</td>
<td>114 (non-renal)</td>
<td>Coronary stenosis &gt;50%</td>
<td>Sensitivity 84% False negatives with submaximal exercise and moderate stenoses (50-70%)</td>
<td>Case Series</td>
</tr>
<tr>
<td>Marwick et al. 1998</td>
<td>193</td>
<td>Cardiac event free survival</td>
<td>66% if ischaemia v 84% without (p=0.006). Not predictive after 40 months.</td>
<td>Case Series</td>
</tr>
<tr>
<td>Bates et al. 1996</td>
<td>53 (diabetic)</td>
<td>Death, infarct, angina or revascularisation</td>
<td>Odds ratio 12.7 (p=0.003)</td>
<td>Case Series</td>
</tr>
<tr>
<td>West et al. 2000</td>
<td>33</td>
<td>Cardiac complications or death</td>
<td>Negative predictive value 92%</td>
<td>Case Series</td>
</tr>
</tbody>
</table>

### Table 4. Coronary angiography

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Outcome Measured</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramanathan et al. 2005</td>
<td>97 (all diabetic)</td>
<td>&gt; 70% stenosis</td>
<td>33% of type 1 and 48% of type 2</td>
<td>Case Series</td>
</tr>
<tr>
<td>De Lima et al. 2003</td>
<td>126</td>
<td>Cardiac Event free survival at 6, 12, 24, 36 and 48 months. &lt; 70% stenosis v &gt;70%</td>
<td>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%</td>
<td>Case Series</td>
</tr>
<tr>
<td>Herzog et al. 1999</td>
<td>50</td>
<td>Cardiac death or myocardial infarction</td>
<td>Coronary angiography was predictive if the nuclear scan was abnormal, but not if the nuclear scan was normal.</td>
<td>Case Series</td>
</tr>
</tbody>
</table>
Table 5. Coronary revascularisation outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Percentage survival for all patients at various time points after surgery.</th>
<th>Percentage survival for out of hospital survivors at various time points after surgery.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molina et al. 2004 [76]</td>
<td>77 (all IDDM)</td>
<td>100 1 Year 2 Years 3 Years 5 Years</td>
<td>100 1 Year 2 Years 3 Years 5 Years</td>
</tr>
<tr>
<td>Ferguson et al. 1999 [77]</td>
<td>83</td>
<td>89 2 Years 77 3 Years 65</td>
<td></td>
</tr>
<tr>
<td>Labrousse et al. 1999 [78]</td>
<td>82</td>
<td>71 2 Years 56 3 Years 39</td>
<td>83 2 Years 66 3 Years 46</td>
</tr>
<tr>
<td>Nakayama et al. 1999 [79]</td>
<td>47</td>
<td></td>
<td>89 2 Years 84 3 Years 71</td>
</tr>
<tr>
<td>Frenken et al. 1999 [80]</td>
<td>30</td>
<td>90 2 Years 73 3 Years 67</td>
<td>67 2 Years 67 3 Years 67</td>
</tr>
<tr>
<td>Manske et al. 1998 [81]</td>
<td>30 (all IDDM)</td>
<td>80 2 Years 73 3 Years 66 (4 years)</td>
<td></td>
</tr>
<tr>
<td>Rinehart et al. 1995 [82]</td>
<td>60</td>
<td></td>
<td>66 2 Years 66</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Outcome Measured</th>
<th>Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cottin et al. 2001 [50]</td>
<td>152</td>
<td>Death, infarct or revascularisation</td>
<td>24/47 (51%) of ischaemic patients v 11/105 (10%) – p&lt;0.001</td>
<td>Case Series</td>
</tr>
<tr>
<td>Alazraki et al. 1999 [52]</td>
<td>336</td>
<td>Myocardial Infarction or death</td>
<td>11.7% at 3 years in those with reversible defects v 4.5% in those without</td>
<td>Case Series</td>
</tr>
<tr>
<td>Lauer et al. 1998 [53]</td>
<td>873</td>
<td>Death</td>
<td>Any defect 9% v 3% (p=0.0004)</td>
<td>Case Series</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major Cardiac Event</td>
<td>Any defect 11% v 4% (p=0.0002)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Death</td>
<td>Reversible defect 12% v 5% (p=0.002)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Major Cardiac Event</td>
<td>Reversible defect 13% v 7% (p=0.004)</td>
<td></td>
</tr>
<tr>
<td>Miller et al. 1998 [51]</td>
<td>411</td>
<td>Overall mortality Cardiac death Cardiac event</td>
<td>P=0.007 P=0.004 P=0.005</td>
<td>Case Series</td>
</tr>
</tbody>
</table>
Table 7. Evidence Profile diagnostic test accuracy – cardiac stress testing for in potential kidney transplant recipients (MPS and DSE).

<table>
<thead>
<tr>
<th>No. of studies and design</th>
<th>Study Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Number of patients</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Effect per 1000</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome: True Positives</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>MPS 7 Obs. (a)</td>
<td>Serious (b)</td>
<td>Serious (c)</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>None identified</td>
<td>317</td>
<td>0.69 (0.48-0.85) (a)</td>
<td>0.77 (0.59-0.89) (a)</td>
<td>Prevalence 80% - 552</td>
<td>Low</td>
<td>Critical</td>
</tr>
<tr>
<td>DSE 11 Obs. (a)</td>
<td>Serious (b)</td>
<td>Serious (c)</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>None identified</td>
<td>680</td>
<td>0.80 (0.64-0.90) (a)</td>
<td>0.89 (0.79-0.94) (a)</td>
<td>Prevalence 80% - 640</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome: True Negatives</strong></td>
<td></td>
<td></td>
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<tr>
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<td>Serious (c)</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>None identified</td>
<td>317</td>
<td>0.69 (0.48-0.85) (a)</td>
<td>0.77 (0.59-0.89) (a)</td>
<td>Prevalence 80% - 154</td>
<td>Low</td>
<td>Critical</td>
</tr>
<tr>
<td>DSE 11 Obs. (a)</td>
<td>Serious (b)</td>
<td>Serious (c)</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>None identified</td>
<td>680</td>
<td>0.80 (0.64-0.90) (a)</td>
<td>0.89 (0.79-0.94) (a)</td>
<td>Prevalence 80% - 178</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome: False Positives</strong></td>
<td></td>
<td></td>
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<tr>
<td>MPS 7 Obs. (a)</td>
<td>Serious (b)</td>
<td>Serious (c)</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>None identified</td>
<td>317</td>
<td>0.69 (0.48-0.85) (a)</td>
<td>0.77 (0.59-0.89) (a)</td>
<td>Prevalence 80% - 138</td>
<td>Low</td>
<td>Critical</td>
</tr>
<tr>
<td>DSE 11 Obs. (a)</td>
<td>Serious (b)</td>
<td>Serious (c)</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>None identified</td>
<td>680</td>
<td>0.69 (0.48-0.85) (a)</td>
<td>0.77 (0.59-0.89) (a)</td>
<td>Prevalence 80% - 22</td>
<td>Low</td>
<td></td>
</tr>
<tr>
<td><strong>Outcome: False Negatives</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>MPS 7 Obs. (a)</td>
<td>Serious (b)</td>
<td>Serious (c)</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>None identified</td>
<td>317</td>
<td>0.69 (0.48-0.85) (a)</td>
<td>0.77 (0.59-0.89) (a)</td>
<td>Prevalence 80% - 248</td>
<td>Low</td>
<td>Critical</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>No. of studies and design</th>
<th>Study Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other Considerations</th>
<th>Number of patients</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>Effect per 1000</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSE 11 Obs. (a)</td>
<td>Serious (b)</td>
<td>Serious (c)</td>
<td>No serious limitations</td>
<td>No serious limitations</td>
<td>None identified</td>
<td>680</td>
<td>0.80 (0.64-0.90) (a)</td>
<td>0.89 (0.79-0.94) (a)</td>
<td>Prevalence 80% - 160 40% - 80 10% - 20</td>
<td>Low</td>
</tr>
</tbody>
</table>

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.