Should we screen for coronary artery disease in asymptomatic chronic dialysis patients?

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The hemodialysis population is characterized by a high prevalence of 'asymptomatic' coronary artery disease (CAD), which should be interpreted differently from asymptomatic disease in the general population. A hemodynamically significant stenosis may not become clinically apparent owing to impaired exercise tolerance and autonomic neuropathy. The continuous presence of silent ischemia may cause heart failure, arrhythmias, and sudden death. Whether revascularization of an asymptomatic dialysis patient improves outcome remains a moot point, although several observational studies and one small RCT suggest a benefit. It can therefore be defended to screen asymptomatic dialysis patients for CAD. A number of noninvasive screening tests are available, but none has proved equally practical and reliable in the dialysis population as in the general population. Myocardial perfusion scintigraphy (MPS) before and after a pharmacological stress such as dipyridamole can reveal both ischemia and myocardial scarring. When compared with coronary angiography, low sensitivities were reported and attributed to impaired vasodilation to dipyridamole in dialysis patients. A more likely explanation is that not every anatomical stenosis will lead to impaired coronary blood flow on MPS. Numerous studies have shown an incremental prognostic value of dipyridamole-MPS over clinical data for prediction of adverse cardiac events, in some studies even over coronary angiography. Pending the availability of high-quality evidence, in our opinion asymptomatic dialysis patients could undergo dipyridamole-MPS, followed by coronary angiography in case of an abnormal scan. This combined physiological and anatomical evaluation of the coronary circulation allows us to determine which coronary stenosis is clinically relevant and therefore should be revascularized.

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DOES SCREENING MAKE SENSE?

Although the high burden of coronary artery disease (CAD) in the dialysis population is universally recognized, routine screening has not yet been implemented in clinical practice. As for any other disease in any other population, the expected benefits of a screening program should be balanced against the costs and side effects involved. Screening can only be defended when there is a high prevalence of asymptomatic disease in the population that is examined and if intervention during the asymptomatic stage improves outcome.

Prevalence of asymptomatic CAD in hemodialysis patients

In 1984, Rostand *et al.*[1] found that only 10% of asymptomatic dialysis patients had significant CAD (defined as a narrowing of the coronary artery lumen of more than 50%), a prevalence not so different from that reported in the general population at that time. The mean age of the population studied was 48 years and none had diabetes. More than a decade later, Joki *et al.*[2] reported a prevalence of CAD (stenosis of at least 75%) in 54% of asymptomatic patients, examined within 1 month of initiation of hemodialysis. Ohtake *et al.*[3] studied 30 asymptomatic patients, with a mean age of 63 years and a prevalence of diabetes of 40%, and without a history of cardiac disease at the initiation of dialysis. Coronary angiography demonstrated the presence of significant lesions (stenosis of at least 50%) in 53% of the population and in 83% of those with diabetes. The distribution of one-vessel, two-vessel, and three-vessel disease was 62.5%, 25%, and 12.5%, respectively. Charytan *et al.*[4] performed coronary angiography in 67 asymptomatic hemodialysis patients, with a mean age of 57 years, a prevalence of diabetes of 48%, and a dialysis vintage of 3.4 years. Significant CAD (stenosis of at least 50%) was found in 42% of the patients, 75% of whom had multivessel involvement.

Conversely, the majority of dialysis patients with angiographically documented CAD are asymptomatic. Braun *et al.*[5] reported that 75% of diabetic hemodialysis patients with confirmed coronary artery stenoses had no symptoms. In two other studies, 74% and 67% of dialysis patients with CAD were asymptomatic at the time of angiography.[6,7]

In conclusion, the prevalence of asymptomatic CAD in hemodialysis patients appears to rise commensurately with the increasing age and prevalence of diabetes in the hemodialysis population. The absence of symptoms is generally attributed to diabetic and uremic autonomic neuropathy, although it is especially driven by reduced exercise capacity in the dialysis population. Unlike in the general population, the lack of angina does not imply that a hemodynamically significant stenosis is absent. 'Asymptomatic' CAD in dialysis patients should therefore be interpreted very differently from asymptomatic CAD in the population without renal disease.

The effect of intervention on outcome in the dialysis population

Whether intervention, either by percutaneous coronary intervention (PCI) or by coronary artery bypass grafting (CAGB), improves outcome in hemodialysis patients with proven CAD, either with or without symptoms, remains at present unresolved. The large randomized controlled trials (RCTs) that have documented the benefits of revascularization in the general population have generally excluded patients with renal disease, particularly those on maintenance dialysis. Conclusions from these trials therefore cannot be extrapolated to the dialysis population, especially as the complication rate of revascularization procedures is significantly increased in these patients. If no benefit is derived, revascularization could even be harmful to dialysis patients.

Observational data suggest that revascularization may provide a survival benefit as compared with conservative treatment alone. Of 640 end-stage renal disease patients experiencing an acute myocardial infarction, only 7% were referred for PCI and 5% underwent CABG.[8] One-year survival rates were 45%, 54%, and 69% in those treated with medical therapy alone, PCI, and CABG, respectively.[8] A large prospective data collection investigated the outcome by treatment (CAGB, PCI, or no revascularization) in patients who fell under three categories of kidney function: dialysis-dependent kidney disease, non-dialysis-dependent kidney disease, and a reference group with a serum creatinine below 2.3 mg/dl.[9] CABG was associated with a survival advantage for all categories of kidney function, and PCI conferred a lower risk of death in dialysis and reference patients, as compared with no revascularization. However, the majority of dialysis and non-dialysis kidney disease patients did not undergo revascularization, even though they were found to have more severe CAD at coronary angiography than did the reference group. These findings reveal the intrinsic problem with all observational studies in the population with renal disease: physicians are reluctant to perform invasive procedures in the most severely ill patients. Although adjustments for clinical risk factors are generally made in observational studies, there is always unmeasured comorbidity that cannot be accounted for. Nonrandomized trials are therefore unavoidably biased at the disadvantage of the conservative approach.

At present, only one RCT has compared invasive and conservative treatment in dialysis patients with CAD. Manske *et al.*[10] randomized 26 asymptomatic dialysis patients with diabetes type 1 and documented CAD either to revascularization with CABG or PCI or to medical treatment with a calcium channel blocker and aspirin. The conservatively managed patients had significantly more nonfatal and fatal myocardial infarctions than did the revascularized group. The results were remarkable, but should be interpreted with caution, as the conservative treatment given at the time differs from what is currently considered to be the 'optimal medical therapy'.

Yasuda *et al.*[11] performed coronary angiography in 259 hemodialysis patients, 122 of whom had no significant lesions. The other patients were informed about the benefits and risks of PCI and made the decision whether to proceed with it (88 patients) or not (49 patients) jointly with the physicians.[11] Both all-cause and cardiac 5-year survival rates were strikingly higher in the PCI group than in the medication-only group. Although this was not an RCT, the survival benefit was so large that it was unlikely the sole consequence of referral bias.

NONINVASIVE SCREENING FOR CAD IN HEMODIALYSIS PATIENTS

Different noninvasive screening techniques are available, but unfortunately all have limitations in the dialysis population (Table 1).

Measurement of cardiac troponins

Cardiac troponin (cTn) T and I are sensitive markers of damage to the myocardium. Serum cTn levels are commonly increased in hemodialysis patients without acute coronary syndrome. This has been attributed to left ventricular

Table 1 | Limitations of the available noninvasive screening techniques in ESRD patients

Noninvasive screening test	Limitations in ESRD patients
Cardiac troponin measurement	Prognostic significance of high-sensitivity assays unknown
Exercise tolerance test	Poor exercise performance High proportion of baseline ECG abnormalities
Myocardial perfusion scintigraphy	Low sensitivity reported
Dobutamine stress echocardiography	Operator dependent Adequate acoustic windows not possible in up to 20%
Quantification of coronary calcium score	No correlation calcification score—stenosis in ESRD
CT coronary angiography	Contrast exposure Low specificity due to high coronary calcium burden
Cardiac PET	No data in patients with ESRD Not widely available
Cardiac MRI	Inability to use gadolinium Technical problems

Abbreviations: CT, computed tomography; ESRD, end-stage renal disease; MRI, magnetic resonance imaging; PET, positron emission tomography.

hypertrophy, silent myocardial ischemia, or heart failure.[12] A large body of evidence supports the prognostic value of elevated cTn in asymptomatic dialysis patients.[12] A meta-analysis of 28 studies covering 3931 patients revealed that cTnT measured at a single time point correlated with all-cause and cardiac mortality, whereas the data for cTnI were less straightforward, mainly because of the lack of assay standardization.[13] The presence of elevated levels of cTnT may thus identify a subgroup of patients who deserve further cardiac evaluation and more aggressive treatment. Serial measurement of cTnT may improve the predictive value of the test.[14] The newest generation of cTn assays has reduced the limit of detection by 10- to 100-fold and is being adopted by a growing number of medical institutions. Using these high-sensitivity assays, elevated cTnI has been reported in 41% of asymptomatic hemodialysis patients,[15] whereas cTnT was increased in 100% of patients.[16] The prognostic significance of these findings is at present unstudied.

Exercise tolerance test

In the general population, the sensitivity and specificity of exercise testing for obstructive CAD are 68% and 77%, respectively,[17] assuming that an adequate exercise level (85% of age-adjusted predicted maximal heart rate) is attained. Dialysis patients are, however, notorious for their reduced exercise capacity, owing to deconditioning and to vascular, neurological, or musculoskeletal comorbidities. Moreover, many of these patients have a blunted chronotropic response as a result of autonomic dysfunction. Several studies have documented that only 7–53% of dialysis patients achieve the target heart rate.[18–22] The increasing age and comorbidity of the dialysis population can only reduce the likelihood of obtaining a diagnostic test. In addition, the high prevalence of baseline electrocardigram abnormalities in dialysis patients hampers the interpretation of an exercise test. Exercise tolerance testing is therefore not generally recommended as a screening tool in the dialysis population.

Myocardial perfusion scintigraphy (MPS)

Myocardial blood flow can be measured by injecting a radioactive tracer that distributes through the myocardium in proportion with blood flow. The tracers used are ^{99m}Technetium-methoxyisobutylisonitrile, ^{99m}Technetium-tetrofosmin, and ^{201}Thallium. The distribution of these tracers is measured with single-photon emission computed tomography. The test is always conducted both at rest and after a cardiac stress, the latter to reveal flow heterogeneity induced by a hemodynamically significant coronary stenosis. A perfusion defect that is only present during stress and not at rest is indicative of ischemia (= reversible defect). Areas of myocardial infarction with scarring will show as perfusion defects both at stress and at rest studies (= irreversible defect).

Currently used cardiac stressors are exercise, dipyridamole (Persantine, Boehringer Ingelheim, Brussels, Belgium), adenosine, and dobutamine. In the dialysis population, exercise-MPS has the same limitations as exercise-electrocardiogram, related to the inadequate exercise performance and chronotropic incompetence of the patients. The most frequently used cardiac stressor is dipyridamole. It increases levels of adenosine, which induces regional hyperemia commensurate with the flow reserve of each coronary artery. Dobutamine is a β1-adrenergic receptor agonist that increases myocardial oxygen consumption through its combined inotropic and chronotropic effect, and thus mainly indirectly causes coronary vasodilation. A prospective head-to-head comparison of dipyridamole and dobutamine as cardiac stressors in 121 hemodialysis patients revealed that dobutamine stress induced more, larger and more intense reversible perfusion defects than did dipyridamole stress, especially in the anteroseptal segments.[23] However, a perfusion defect during dipyridamole was more specific in demonstrating a coronary stenosis and was a better predictor of a future cardiac event than was a perfusion defect during dobutamine.[23] The chronotropic action of dobutamine may induce alterations of wall motion leading to spurious perfusion defects, similar to the artifacts seen with left bundle branch block. These data were confirmed by a head-to-head comparison of dobutamine stress echocardiography, dobutamine MPS, and adenosine MPS, showing that dobutamine stress echocardiography (DSE) and dobutamine MPS did not provide incremental prognostic information when added to clinical data and ejection fraction, in contrast to adenosine MPS.[24] Therefore, dipyridamole is the cardiac stressor of choice in the hemodialysis population.

Several studies have evaluated the diagnostic ability of dipyridamole MPS by using coronary angiography as 'the gold standard'.[16,23,25–29] Widely varying sensitivities and specificities have been reported (Table 2). A factor that may account for low sensitivity is the presence of balanced ischemia when flow is equally diminished in all myocardial areas. Balanced ischemia does not show on MPS, as the technique measures relative, as opposed to absolute, perfusion. The low sensitivities have also been attributed to an impaired vasodilatory response to adenosine in the dialysis population. It has been contended that dialysis patients have abnormally high resting levels of adenosine, although the only evidence to support this is the notion of decreased lymphocyte adenosine deaminase activity in patients with renal failure.[30] However, a blunted vasodilation to adenosine has been reported in diabetes and left ventricular hypertrophy, both of which are common in dialysis patients.

Another potential explanation for the apparently low diagnostic ability of MPS is that coronary angiography may not be the best standard to assess the performance of MPS. MPS is a functional test that measures coronary blood flow, whereas coronary angiography provides only anatomical information. Multiple factors may intervene between a stenosis of a coronary artery and diminished blood flow, including the functional severity of the stenosis, the presence of collateral circulation, and the status of the distal vascular bed and the microcirculation. If extensive collateral

Table 2 | Studies examining the diagnostic ability of dipyridamole myocardial perfusion scintigraphy, using coronary angiography as the gold standard

Author	*n*	Stress	Criterium %	Sensitivity	Specificity	Accuracy
Orie *et al.*[25]	20	Dipyridamole	50	73	100	85
Boudreau *et al.*[26]	80	Dipyridamole	70	86	79	83
Marwick *et al.*[27]	45	Dipyridamole	50	37	73	58
			70	29	68	56
Vandenberg *et al.*[28]	47	Dipyridamole/adenosine	50	53	73	63
			70	62	76	71
Dahan *et al.*[29]	76	Dipyridamole+exercise	70	92	89	90
Schmidt *et al.*[21]	55	Dipyridamole	70	80	37	59
De Vriese *et al.*[23]	62	Dipyridamole	70	62	54	58

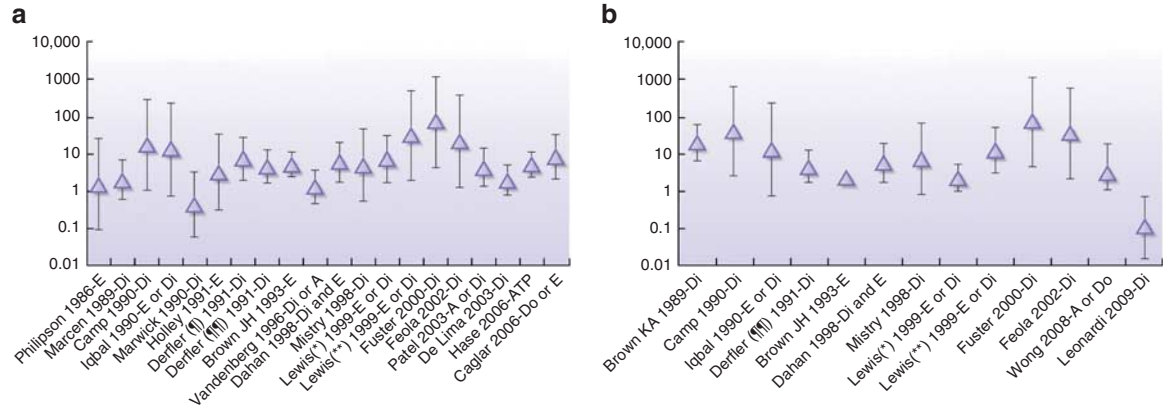

Figure 1 | Hazard ratios for composite cardiac end points in patients with end-stage kidney disease reported in studies on myocardial perfusion scintigraphy (MPS). End points variably included cardiac death, unstable angina, myocardial infarction, congestive heart failure or pulmonary edema, arrhythmia, and need for revascularization. The stressors are: E = exercise, Di = dipyridamole, Do = dobutamine, A = adenosine, ATP = adenosine triphosphate; some studies have used different stressors in different patients; Dahan *et al.*[29] have used a combination of E and Di in every patient. Studies that reported different data sets may appear twice (¶hemodialysis patients; ¶¶renal transplant patients; *patients followed up for cardiac death; **patients followed up for cardiac death or nonfatal cardiac events). Hazard ratios are given for results demonstrating ischemia versus those without evidence for ischemia (**a**) and for results demonstrating either ischemia or scar vs. those without evidence for ischemia or scar (**b**). The 95% confidence intervals of the hazard ratio are presented on a semilogarithmic scale.

circulation has developed, a coronary stenosis may not result in decreased myocardial blood flow. Conversely, extensive microvascular disease may cause decreased myocardial blood flow in the absence of a flow-limiting stenosis of the epicardial coronary arteries. The ability to predict CAD-related events may therefore be a more relevant criterion to judge MPS rather than the comparison with coronary angiography.

Several studies have evaluated the value of MPS to predict cardiac events in patients with end-stage renal disease.[14,27–29,31–46] The large majority found that abnormal MPS predicted cardiac events in univariate analysis (Figure 1a and b). Several studies have corroborated that the predictive power of MPS remains after correction for clinical variables in multivariate analysis.[29,40,42,43] In a meta-analysis of 12 studies using dobutamine stress echocardiography or MPS with either pharmacological or exercise stress, the presence of a reversible defect was associated with a significantly increased risk of myocardial infarction and cardiac death.[47]

In a prospective study of 150 patients being evaluated for renal transplantation, the prognostic ability of MPS and coronary angiography was compared.[48] In a multivariate model, only an abnormal MPS result and diabetes were independent predictors of death, whereas the number of narrowed coronary arteries was not. Thus, MPS had better prognostic power than coronary angiography in this study. Similarly, in a study of 47 patients being assessed for kidney transplantation, the accuracy for predicting all-cause death was higher for MPS than for coronary angiography.[49] In contrast, the presence of a coronary stenosis better predicted future cardiac events than did an abnormal MPS or dobutamine stress echocardiography in another prospective study of 126 renal transplant candidates.[41] Angiographic evidence of CAD was the only independent predictor of major cardiac events in a cohort of 280 diabetic transplant candidates who had also undergone MPS.[50] Observational trials in this matter are inevitably confounded by the revascularization procedures that may follow coronary angiography, making it difficult to dissociate the effect of the therapeutic act from the impact of either the absence or presence of CAD.

Dobutamine stress echocardiography

Dobutamine stress echocardiography is often recommended as a valid screening test in the end-stage renal disease

population.[51] Besides demonstrating CAD, it may reveal the location and extent of the ischemia and scar. In addition, DSE can provide information on valvular disease, left ventricular hypertrophy, and volume status.

The technique is based on the recognition of wall motion disturbances: if present at rest, they signify scar; if appearing or worsening at stress, they signify ischemia. As with MPS, stressors may be vasodilatory agents[29,52] or, far more frequently, dobutamine. Many dialysis patients do not achieve target heart rate,[51,53–56] thereby decreasing the sensitivity of the test, although failure to attain maximal stress may itself be a risk factor for subsequent cardiac events.[57] In addition, a substantial number of patients show hypertensive responses to the infusion of dobutamine,[41] which may be predicted by the presence of hypertension at baseline.[52] Other studies have found no higher incidence of dose-limiting side effects in chronic renal failure patients compared with the general population.[54] Finally, the interpretation of the test is operator dependent and requires extensive experience. From a technical point of view, adequate acoustic windows may not be obtained in up to 20% of the tests. As many dialysis patients have left ventricular hypertrophy, the small intracavitary volume at peak dobutamine stress may obscure the detection of wall motion abnormalities.[51]

The diagnostic accuracy of DSE for the detection of significant epicardial coronary stenoses is variable. Much of what has been said of MPS, being a functional test as opposed to the anatomical evaluation of the coronary arteries by coronary angiography, holds for DSE as well. It is noteworthy that the only study that directly compared DSE and dipyridamole MPS in a cohort of high-risk transplant candidates concluded that both were similarly associated with inadequate sensitivities, although the negative predictive values were fair.[41]

Several studies examined the prognostic power of DSE in the end-stage renal disease population.[17,41,51,52,54,55,58,59] The ability of DSE to predict cardiac events in a univariate analysis has generally been reported as excellent (Figure 2a and b). Similar to MPS, most studies have documented that the predictive powers of DSE remain after correction for clinical variables in multivariate analysis.[17,52,54,55,58]

Measurement of coronary calcium score

Electron-beam computed tomography and multislice computed tomography are both sensitive tools to detect and quantify deposits of calcium in soft tissues, in general, and in coronary arteries, in particular.[60] Although these two technologies provide the same type of information, they operate on the basis of different imaging platforms. Electron-beam computed tomography uses a rotating fan of X-rays produced by the impact of a beam of electrons against a tungsten ring and obtains 3 mm contiguous slices. Multislice computed tomography uses a paired X-ray source detector revolving around the patient and obtains 2–64 simultaneous sections with a thickness varying from 1.5 to 0.6 mm, thus providing a higher spatial resolution than does electron-beam computed tomography. Electron-beam computed tomography requires specific equipment that is not available outside research settings, which is a major obstacle to its routine application.

Computed tomography imaging allows the precise quantification of coronary calcifications by means of the two-dimensional Agatston score or the three-dimensional volume score.[60] Coronary calcium scores predict mortality in dialysis patients.[61,62] However, unlike in the general population, coronary calcium scores in dialysis patients do not appear to correlate well with angiographic findings.[63] A low or negative calcium score had a high negative predictive value, but once substantial calcifications were present they did not predict luminal narrowing.[63] Measurement of coronary calcifications is therefore not the best tool to identify a coronary stenosis and predict the future need for a coronary intervention in dialysis patients.

Computed tomography coronary angiography

Computed tomography coronary angiography is used in the general population to evaluate patients with a

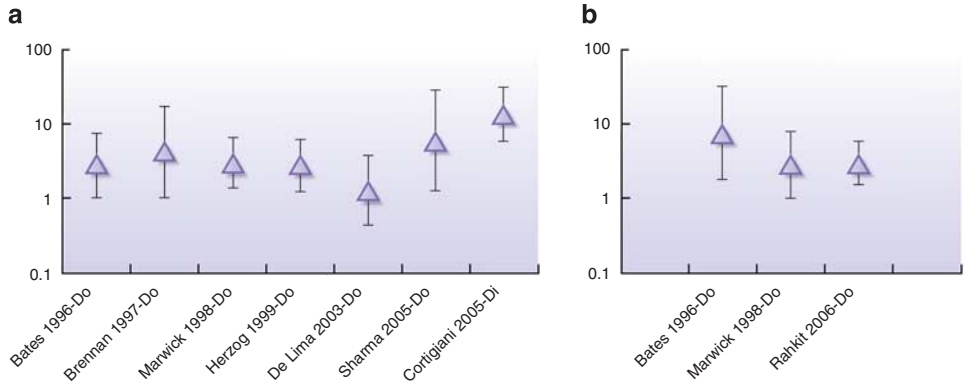

Figure 2 | Hazard ratios for composite cardiac end points in patients with end-stage kidney disease reported in studies on echocardiography. The stressors used in the studies are specified (Di = dipyridamole, Do = dobutamine). Hazard ratios are given for results demonstrating ischemia versus those without evidence for ischemia (**a**) and for results demonstrating either ischemia or scar versus those without evidence for ischemia or scar (**b**). The 95% confidence intervals of the hazard ratio are presented on a semilogarithmic scale.

low-to-intermediate pretest probability of CAD in order to avoid an invasive procedure. The technique has not been studied extensively in the dialysis population.[64] Exposure to iodinated contrast has been reduced to 70–80 ml with newer equipment and shorter acquisition times, but may still affect residual renal function. In addition, advanced coronary calcifications may hamper the interpretation, because they generate an intense signal that may be difficult to distinguish from the contrast-enhanced vessel lumen.

Cardiac positron emission tomography

This modality of nuclear imaging uses a positron emission tomography camera and short-lived positron emitters such as ^{82}Rubidium and ^{13}N-ammonia as flow tracers. Similar to the flow tracers used with traditional MPS, these positron-emitting tracers can be injected intravenously during stress. Unlike traditional MPS, positron emission tomography allows for absolute quantification of myocardial blood flow.[65] Cardiac positron emission tomography detects angiographic stenoses with considerable accuracy and adds risk prediction to clinical risk models. However, the technique is not widely available and has not been validated in patients on renal replacement therapy.

Cardiac magnetic resonance imaging

Because of the association of gadolinium-based contrast with nephrogenic systemic fibrosis, the use of these agents for screening purposes is no longer an option in the hemodialysis population. Flow-related enhancement without the use of gadolinium can also be used for the visualization of coronary arteries. However, accurate three-dimensional data acquisition requires respiratory gating and cardiac triggering and takes a long time (12–15 min in some patients), often resulting in movement of artifacts. Further technical adjustments will therefore be required before the technique can be validated as a screening tool for CAD.

CORONARY ANGIOGRAPHY

Coronary angiography remains 'the gold standard' for the diagnosis of CAD. Coronary angiography has been criticized as a screening tool because of its high costs, invasive nature, and the presumed untoward effects on residual renal function. Roughly one-third of patients with glomerular filtration rate <30 ml/min develop contrast-induced nephropathy after PCI, even when prehydration prophylaxis is adequately applied.[66] Patients who develop acute kidney injury following coronary angiography are at increased risk for progressive long-term loss of kidney function.[67] In spite of this, the direct consequence of coronary angiography on residual renal function in dialysis patients has been evaluated in only a few studies, none of which were randomized.[68,69] Rather contraintuitively, no acceleration of the decline in residual renal function was reported.

The rational use of coronary angiography as a screening test implies that the finding of 'significant' stenosis is followed by an intervention. In the general population, however, coronary intervention does not improve survival in asymptomatic patients.[70,71] In non-renal patients, most myocardial infarctions result from erosion or rupture of unstable atherosclerotic plaques in coronary arteries that were not necessarily significantly narrowed (referred as Type 1 myocardial infarction).[72] In dialysis patients, however, sudden death and congestive heart failure are more common causes of cardiovascular death than is Type 1 acute myocardial infarction. A sizeable number of cardiac deaths in the dialysis population may be caused by Type 2 (ischemia due to either increased oxygen demand or decreased supply) and Type 3 (sudden cardiac death with signs or symptoms suggestive of myocardial ischemia, but occurring before cardiac biomarkers can be obtained) myocardial infarctions.

In addition, it may well be that the asymptomatic stenoses in dialysis patients are more severe and hemodynamically significant than those in the general population, as autonomic neuropathy and the sedentary lifestyle of these patients may prevent these stenoses from becoming clinically apparent. A severe stenosis has a greater probability of progressing to occlusion and to cause either a myocardial infarction or ischemic ventricular dysfunction. Taken together, 'asymptomatic' CAD may have very different pathophysiological causes and consequences in the dialysis than in the general population, and therefore should be addressed differently.

The importance of combined physiological and anatomical rather than solely anatomical assessment of the coronary circulation was demonstrated recently in 1005 patients with multivessel involvement.[73] The FAME (Fractional Flow Reserve versus Angiography for Guiding PCI in Patients with Multivessel Coronary Artery Disease) trial studied the additive value of a fractional flow reserve (FFR) measurement in the decision whether or not to revascularize a coronary stenosis. FFR is calculated as the ratio of the pressure distal to the coronary stenosis and the aortic pressure at maximal hyperemia induced by adenosine, and it is an index of the physiological significance of the stenosis. FFR-guided PCI was associated with a better outcome, a lower complication rate, and lower costs compared with PCI directed by angiographical criteria alone. Although the FAME trial was conducted in the general population,[73] it may help to resolve the dilemma of how to approach a coronary stenosis in an asymptomatic dialysis patient. Ischemia-producing lesions, which can be identified by an abnormal FFR or by a reversible perfusion defect in the relevant area, should undergo revascularization. Lesions that do not induce ischemia can probably be safely managed conservatively. A potential but yet unstudied limitation of FFR measurements in the dialysis population is a possible impaired vasodilatory response to adenosine.

WHO DESERVES TO BE SCREENED?

Although no studies have unequivocally demonstrated that candidates for renal transplantation benefit from screening for CAD,[74] it remains a pillar of the pretransplant evaluation

process and is reiterated in all relevant guidelines.[75–78] It should be noted that these guidelines are at odds with those of the American College of Cardiology/American Heart Association, which do not recommend screening asymptomatic patients before surgery provided that their functional status allows them to perform four or more metabolic equivalent tasks.[79]

In addition to the patients being evaluated for renal transplantation, the K-DOQI (Kidney Disease Outcomes Quality Initiative) guidelines advocate screening for CAD in patients with a history of revascularization, a significant reduction in left ventricular function, and a change in clinical status suggestive of a cardiac problem. Finally, they recommend screening in selected high-risk patients at the discretion of the treating physician. In view of the large proportion of asymptomatic disease in dialysis patients, which is only partially predicted by clinical risk factors, it appears nonsequitur to recommend screening in these selected categories and not in the dialysis population as a whole.

There are only few data on the optimal time to repeat screening in patients who have tested negatively at the initial evaluation. Out of 191, 51 chronic renal failure patients with a normal DSE had a subsequent cardiac event rate of 4% within 2 years, but this increased to 10% at 40 months.[54] Similarly, in a study on 485 patients with chronic kidney disease, 12% of 203 patients with a normal DSE died in the first year after the test, whereas the mortality rate increased to 30% at 3 years.[56] Of 100 hemodialysis patients with a normal coronary angiography and/or MPS, 5 developed a major adverse cardiac event during the second year following the test.[80] A normal MPS (normal global perfusion and left ventricular ejection fraction $>45\%$) was associated with a 2-year cardiac event rate of 15%.[23] These data should be compared with cardiac event rates below 1% per year following a normal MPS in the general population.[81] Retesting of patients with normal studies every 2 years thus seems reasonable.

CONCLUSION

Asymptomatic CAD is very common in the dialysis population on account of the increasing age and prevalence of diabetes. However, the absence of symptoms cannot be considered reassuring, because it is the consequence of autonomic neuropathy and low exercise tolerance, rather than of hemodynamically nonsignificant disease. The continuous presence of silent ischemia may be responsible for the development of heart failure, arrhythmias, and sudden death in dialysis patients. The approach to asymptomatic CAD in dialysis patients thus cannot be extrapolated from studies conducted in the general population.

No high-quality studies examined whether revascularization improves the outcome of dialysis patients with CAD. However, the available observational data, prospective studies, and one small RCT documented a survival advantage for patients treated with PCI or CABG compared with those managed with medication only.

Patients on dialysis may not tolerate aggressive medical therapy for CAD because of the hemodynamic effects of beta-blockers, nitrates, and calcium channel blockers during dialysis, hampering the achievement of target dry weight and thus abrogating the potential benefit of the drug. What constitutes an optimal medical therapy for CAD in the general population may therefore not be applicable to dialysis patients.[82,83]

Historically, revascularization procedures have been associated with high complication rates in the dialysis population. As a consequence, dialysis patients often have been denied invasive therapies. However, recent sophistications may have decreased the adverse effects of these techniques and may be tipping the balance in favor of invasive treatment.

Taken together, all these issues reinforce the need for a large RCT that examines the incremental benefit of revascularization in addition to medical therapy in asymptomatic dialysis patients with CAD. Such a trial should be conducted under the aegis of National and/or International Societies and independently of the industry. For CAD screening in the context of the pretransplant evaluation process, power calculations have been made on the basis of preliminary studies.[74,84] Assuming a 25% reduction in cardiac events with revascularization and taking into account a recruitment and follow-up period of 2.5 years, one needs to randomize more than 700 patients with potentially remediable CAD in order to obtain a sufficiently powered trial.[74] To include this number of patients, more than 8000 potential renal transplant recipients would need to be evaluated.[74] Taking a somewhat different approach, standard screening with prophylactic revascularization was compared with screening of only high-risk patients.[84] To detect a 20% decrease in major adverse cardiovascular events, about 4000 transplant candidates would need to be enrolled.[84]

Pending the results of a large RCT, in our opinion all incident dialysis patients could be screened with MPS, followed by a coronary angiography in patients with a positive test and revascularization of only those stenoses that cause ischemia. In patients with a negative test, MPS may be repeated every 2 years because of the potentially rapid progression of CAD. As absence of evidence does not indicate evidence of absence, we should not be discouraged to act consistently with clinical intuition while awaiting the results of conclusive studies, and refer the conservative approach to the realm of therapeutic nihilism.

DISCLOSURE

All the authors declared no competing interests.

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