EXPERT CONSENSUS DOCUMENT

Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates

A Scientific Statement From the American Heart Association and the American College of Cardiology Foundation

*Endorsed by the American Society of Transplant Surgeons,
American Society of Transplantation, and National Kidney Foundation*

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The challenges inherent in conducting accurate, clinically effective, and cost-effective cardiac evaluations among transplantation candidates relate to the large size of the target population, the prevalence of disease, the limited number of donated organs, and the often extended waiting periods between initial evaluation and transplantation surgery. According to Organ Procurement and Transplant Network (OPTN) records, nearly 85,000 candidates were on the waiting list for kidney transplantation in 2010, and ≈17,700 kidney transplantations (including 828 kidney-pancreas transplantations) were performed (1). Also in 2010, 16,000 people were awaiting liver transplantation and 6,000 received liver allografts (1). Marked shifts in the age composition of transplant waitlists toward older adults are also raising the average medical complexity and comorbidity burden among listed candidates. In 2011, 62% of kidney transplantation candidates were ≥50 years of age compared with 28.7% of kidney transplantation candidates in 1991 (1). A similar shift in age distribution has occurred among liver transplantation candidates; now, 77% are ≥50 years of age (1). Cardiovascular disease is a leading cause of morbidity and mortality among patients with end-stage failure of non-cardiac organs before and after transplantation. Estimates of the cumulative incidence of myocardial infarction (MI) based on Medicare billing claims have ranged from 8.7% to 16.7% by 3 years after kidney transplant listing and from 4.7% to 11.1% after kidney transplantation (2,3). Observational data suggest particularly high frequencies of cardiovascular events in the first months after kidney transplantation (2,4,5). Cardiovascular diseases in aggregate make up the most common cause of death in patients with functioning allografts at all times after kidney transplantation, accounting for 30% of mortality overall, with highest rates in the peritransplantation period (6).

Guidelines and position papers by national organizations can serve as useful tools for informing cardiac evaluation practices before noncardiac surgery. However, the discrepancies among existing guidelines and the unique clinical characteristics of patients with end-stage organ failure raise questions about the applicability of available recommendations to transplantation candidates. In 2007, the American College of Cardiology (ACC) and American Heart Association (AHA) issued their most recent version of the "Guidelines on Perioperative Cardiovascular Evaluation and Care

Table 1.   Evidence Grading

Evidence Class: Magnitude of procedure/treatment effect	
I	Conditions for which there is evidence for and/or general agreement that the procedure/therapy is useful and effective
II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of performing the procedure/therapy
IIa	Weight of evidence/opinion is in favor of usefulness/efficacy
IIb	Usefulness/efficacy is less well established by evidence/opinion
III	Conditions for which there is evidence and/or general agreement that the procedure/therapy is not useful/effective and in some cases may be harmful
Evidence Level: Estimate of certainty (precision) of procedure/treatment effect*	
A	Consistent direction and magnitude of effect from multiple randomized controlled clinical trials
B	Consistent retrospective cohort, exploratory cohort, ecological, outcomes research, or case-control studies, or extrapolations from Level A studies
C	Case-series studies or extrapolations from Level B studies

*A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Although randomized trials are not available, there may be a very clear consensus that a particular test or therapy is effective.

for Noncardiac Surgery" (7). The algorithm suggests consideration of further cardiac evaluation in symptomatic patients but does not encourage further testing for patients who have no cardiac symptoms with a functional capacity of ≥4 metabolic equivalent tasks (METS; i.e, ability to climb a flight of stairs), regardless of diabetic status, history of coronary artery disease (CAD), or other traditional cardiac risk factors. Consideration of noninvasive testing was given a Class IIb recommendation in asymptomatic patients with at least 1 to 2 clinical risk markers and poor functional capacity who require intermediate-risk noncardiac surgery if it will change management (Level of Evidence B), with the evidence grade reflecting lack of large randomized trials to support this strategy (Table 1). Similarly, the "2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging" (8) by the American College of Cardiology Foundation (ACCF), along with key specialty and subspecialty societies, deemed that radionuclide imaging is appropriate for perioperative evaluation before intermediate-risk noncardiac surgery in asymptomatic patients only when at least 1 risk marker in present and the patient has poor (<4 METS) or unknown functional capacity (8). The ACC/AHA and ACCF guidelines were not written specifically for patients with end-stage organ failure, and the predictive value of the "absence of cardiac symptoms" may differ in transplantation candidates compared with the general population. These guidelines also take the perspective that noncardiac surgery will be performed shortly after the evaluation and that any management decisions will affect short-term (perioperative) outcomes. In contrast, cardiac evaluation and interventions in transplantation candidates should be considered from both the short- and long-term perspective.

The fundamental basis of the latest ACC/AHA recommendations is grounded in understanding of the role of coronary revascularization before noncardiac surgery. The authors state, "Patients with asymptomatic ischemia. . .do not appear to be candidates for prophylactic preoperative coronary revascularization unless cardiac catheterization reveals high-risk surgical anatomy" (7). This statement is supported by 2 recent randomized trials that did not demonstrate benefit of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) for revascularization of asymptomatic CAD before major vascular surgery (9–11).

In 2005, the National Kidney Foundation published the "Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients" within the Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) (12). The section on CAD suggests more aggressive screening of patients with end-stage renal disease (ESRD) as part of the evaluation to determine candidacy for renal transplantation than would be suggested by ACC/AHA guidelines, although the statements were rated Level of Evidence C, this is, based on either weak evidence or the opinions of the working group. For example, this algorithm recommends that any patient on the kidney transplant waitlist with a history of diabetes mellitus or known CAD undergo noninvasive stress testing at baseline and then subsequently every 12 months until transplantation. There is a similar recommendation for transplantation candidates deemed at high risk per Framingham criteria (≥2 traditional risk factors, left ventricular ejection fraction [LVEF] ≤40%, or peripheral vascular disease) (12).

Other consensus-based recommendations for cardiac risk assessment before kidney transplantation have been offered. These include a 2007 report from an international collaboration of the NKF and the Transplantation Society called the Lisbon Conference (13), the 2001 American Society of Transplantation (AST) guidelines (14), and the 2000 European Renal Association-European Dialysis Transplant Association (ERA-EDTA) "European Best Practice Guidelines" (15). These 2 clinical practice guidelines are now >10 years old, were based on expert consensus panels, and were not the product of systematic review of the evidence. Although all these documents suggest that symptomatic patients should undergo further testing, they offer differing recommendations for asymptomatic patients. A comparison of these 5 clinical documents and their recommendations on testing asymptomatic patients for CAD before renal transplantation is summarized in Table 2.

Several studies document heterogeneity in cardiac evaluation practices before kidney transplantation at the national level (Table 3). In a 1993 survey of directors of OPTN-participating centers, noninvasive stress testing was reported as the most common first approach to cardiac evaluation of asymptomatic patients, prompted by diabetes mellitus at 86% of responding centers, age (mean threshold, 52 years) at 67%, and multiple risk factors at 68% (18). Some centers used routine coronary angiography for patients with diabetes mellitus (15%), older age (7%; mean threshold, 57 years), or multiple risk factors (8%). A subsequent survey of OPTN centers about policies for patients on the deceased donor waiting list found that 8% of programs reported cardiac testing for all candidates, whereas 18% did not routinely

Table 2. Published Recommendations for Testing for CAD in Asymptomatic Kidney Transplantation Candidates

Reference	Recommendations
2012 AHA Scientific Statement	Noninvasive stress testing may be considered in kidney transplantation candidates with no active cardiac conditions on the basis of the presence of multiple CAD risk factors regardless of functional status (Class IIb, Level of Evidence C)
	Relevant risk factors among transplantation candidates include diabetes mellitus, prior cardiovascular disease, >1 y on dialysis, LV hypertrophy, age >60 y, smoking, hypertension, and dyslipidemia; the specific number of risk factors that should be used to prompt testing remains to be determined, but the committee considers ≥3 to be reasonable
2007 ACC/AHA Perioperative Guidelines for Noncardiac Surgery (7)	No testing recommended if functional status ≥4 METS
	If functional status <4 METS or unknown, then consideration of noninvasive stress testing is recommended based on the following clinical risk factors
	Ischemic heart disease
	Compensated or prior heart failure
	Diabetes mellitus
	Renal insufficiency
	Cerebrovascular disease
	Recommendations for testing are stronger if ≥3 clinical risk factors are present but may be considered in those with 1–2 risk factors
2007 Lisbon Conference (13)	Acknowledges that there are no data establishing that screening of asymptomatic patients in itself prevents cardiac events; noninvasive and/or invasive testing should be considered in highest-risk patients with the following conditions
	Diabetes mellitus
	Prior cardiovascular disease
	Multiple cardiac risk factors such as >1 y on dialysis, LV hypertrophy, age >60 y, smoking, hypertension, and dyslipidemia
	Does not specify the number of risk factors to justify testing
2005 NKF/KDOQI Guidelines (12)	Noninvasive stress testing recommended for
	All patients with diabetes; repeat every 12 mo
	All patients with prior CAD
	If not revascularized, repeat every 12 mo
	If prior PCI, repeat every 12 mo
	If prior CABG, repeat after first 3 y and then every 12 mo
	Repeat every 24 mo in "high-risk" nondiabetic patients defined as
	≥2 traditional risk factors
	Known history of CAD
	LVEF ≤40%
	Peripheral vascular disease
2001 AST Guidelines (16)	Noninvasive stress testing recommended for patients at "high risk," defined as renal disease from diabetes, prior history of ischemic heart disease, or ≥2 risk factors
	Coronary angiography for possible revascularization before transplantation recommended for patients with a positive stress test
	Revascularization before transplantation recommended for patients with critical coronary lesions
2000 European Best Practice Guidelines (15)	Thallium scanning recommended for patients with history of myocardial infarction or "high-risk" clinical features
	Coronary angiography recommended if thallium scanning is positive
	Revascularization advised if lesions are suitable

ACC indicates American College of Cardiology; AHA, American Heart Association; AST, American Society of Transplantation; CABG, coronary artery bypass grafting; CAD, coronary artery disease; KDOQI, Kidney Disease Outcomes Quality Initiative; LV, left ventricular; LVEF, left ventricular ejection fraction; METS, metabolic equivalent tasks; and PCI, percutaneous coronary intervention.

order cardiac testing for any asymptomatic patient group; 59% screened patients with diabetes mellitus, 52% screened patients with a history of CAD, and 52% screened patients deemed to be high risk for cardiac events after transplantation given their age or obesity (19). Methods of screening were also variable: 40% pharmacological-nuclear, 33% exercise nuclear, 31% dobutamine stress echocardiography (DSE), and 15% cardiac catheterization. Cardiac surveillance policies among listed candidates also differ across centers. In a survey of 68 centers in 2005, 51% of program representatives indicated reliance on the initial cardiac evaluation and cardiac history, 7% used ACC/AHA criteria for noncardiac surgery in the general population to guide cardiac revaluation, and 32% applied a combination of ACC/AHA criteria, the initial cardiac evaluation, and cardiac history (20).

Survey responses are limited by nonresponse rates, and reported policies may differ from actual practices. A retrospective study of the U.S. Renal Data System (USRDS) registry used billing claims as measures of cardiac evaluation services in Medicare beneficiaries transplanted in 1991 to 2004 (21). Forty-six percent of the sample received noninvasive stress testing or angiography at some time before transplantation (65% of high risk, defined as diabetes mellitus, prior ischemic heart disease, or ≥2 other coronary risk factors, and 20% of lower risk). There was substantial heterogeneity in cardiac evaluation frequency according to patient-level factors even within risk groups. After adjustment for patient traits and consistent within risk profile–stratified samples, transplantation without cardiac evaluation was more likely for black people, women, and patients in

Table 3. Summary of Survey and Registry Data Demonstrating Variation in Cardiac Evaluation Practices Across U.S. Transplantation Centers

Authors, Year	Summary
Ramos et al. (18), 1994	1993 survey of directors of UNOS-participating centers regarding practices for initial candidate evaluations; 81% response rate (147 of 182)
	Noninvasive stress testing was reported as the most common first approach to cardiac evaluation of asymptomatic patients, prompted by diabetes mellitus at 86% of responding centers, age (mean threshold 52 y) at 67%, and multiple risk factors at 68%
	A notable minority of centers espoused first-line angiography for patients with diabetes mellitus (15%), older age (7%; mean threshold, 57 y), or multiple risk factors (8%)
Danovitch et al. (19), 2002	2001 survey of UNOS-participating centers regarding management practices for patients on the deceased donor waiting list 67% final response rate (192 of 287)
	8% of programs reported cardiac testing for all listed candidates, whereas 18% did not order routine cardiac testing for any asymptomatic patient group
Zarifian et al. (20), 2006	2005 survey of U.S. kidney transplantation centers regarding reevaluation practices for patients on the deceased donor waiting list 26% final response rate (68 of 257)
	51% of respondents indicated reliance on the initial cardiac evaluation and cardiac history; 7% of program representatives stated that AHA criteria were used to guide cardiac revaluation; and 32% espoused a combination of AHA criteria, the initial cardiac evaluation, and cardiac history
Lentine et al. (21), 2008	Retrospective study of pretransplantation cardiac evaluation practices among 27,786 Medicare beneficiaries transplanted in 1991–2004
	Pretransplantation cardiac evaluation testing was identified by billing claims for noninvasive stress tests and angiography Clinical traits defining "high" expected IHD risk were defined by AST guidelines (16) as diabetes mellitus, prior IHD, or ≥2 other CAD risk factors
	46.3% (65.4% of high-risk and 20.4% of lower-risk patients) underwent cardiac evaluation testing before transplantation; the adjusted odds of transplantation without cardiac evaluation testing increased sharply with younger age and shorter dialysis duration, and also correlated with black race, female sex, and certain geographic regions
	Overall, 9.5% who received cardiac evaluation testing also received pretransplantation revascularization, but only 0.3% of lower-risk patients undergoing cardiac evaluation testing were revascularized before transplantation

AHA indicates American Heart Association; CAD, coronary artery disease; IHD, ischemic heart disease; and UNOS, United Network for Organ Sharing.

certain geographic regions. Race-related practice variables were notable because in the lower-risk group transplanted without cardiac evaluation, black patients faced higher risks of post-transplantation MI than nonblack patients. Black race has previously been identified as an independent predictor of failure to complete the pretransplantation evaluation (22) and of reduced access to coronary angiography and revascularization in populations without kidney disease (23). Thus, some of the observed practice variation may reflect access barriers rather than appropriate determinations of low clinical risk. An important limitation of studies based on billing data, however, is that claims may not distinguish screening tests from tests performed because of cardiac symptoms.

A recent single-center study examined the approach to the asymptomatic kidney transplantation candidate, which defines the majority of potential candidates at the time of referral (24). In this study, medical charts were reviewed to quantify the hypothetical frequency of recommended testing per practice recommendations and the observed results of cardiac testing (primarily DSE or myocardial perfusion scintigraphy [MPS]) among 204 consecutive patients who were determined to be free of an active cardiac condition by a cardiologist at the time of transplantation evaluation. Active cardiac conditions were defined according to the ACC/AHA definition including significant valvular disease, decompensated heart failure, significant arrhythmias, and unstable coronary syndromes. If followed precisely, the ACC/AHA guidelines recommended testing in only 20% of patients, whereas the KDOQI guidelines would have resulted in 100%

of patients being tested. Among the 178 patients who underwent stress tests, the prevalence of ischemia was similar among those for whom testing was and was not recommended per the ACC/AHA guidelines, 10.3% versus 9.4%, respectively. The relatively low use of coronary revascularization after pretransplantation cardiac evaluation also raises concern for the clinical and cost-effectiveness of pretransplantation cardiac evaluation as applied. Several registry-based and single-center observational studies have found that only 2.9% to 9.5% of patients who receive pretransplantation cardiac stress testing or angiography proceeded to angioplasty or surgical bypass (21,25–28).

Given the variation between practice and prior guidelines in patients being evaluated for solid-organ transplantation, it is important to determine whether evidence can resolve the basis of this difference. The role for stress testing in the absence of symptoms has been called into question among patients undergoing noncardiac surgery because randomized studies of coronary revascularization before vascular surgery have failed to show a consistent benefit (9–11). Outside the perioperative setting, PCI has failed to demonstrate benefit for the risk of major adverse cardiovascular events (MACEs) in a randomized trial among stable patients with CAD (29), including a subgroup with chronic kidney disease (CKD) at trial enrollment (30). Evidence suggests that the only asymptomatic patients in whom coronary revascularization may be helpful are the minority found to have occult high-risk coronary anatomy such as significant left main disease or severe proximal 3-vessel disease, especially in the presence

of reduced left ventricular systolic function (31,31a). However, noninvasive cardiac testing of transplantation candidates might yield findings that call into question the appropriateness of transplantation or identify high-risk coronary lesions associated with long-term benefit from revascularization. This report evaluates the state of evidence regarding cardiac risk evaluation and management in kidney transplantation and liver transplantation candidates, considering data specific to these populations and the appropriateness of extrapolations when data from these populations are lacking. This article focuses on cardiac disease; issues related specifically to the evaluation of carotid or peripheral vascular disease are beyond the scope of this document.

Methodology and Evidence

The AHA Writing Committee on Cardiac Disease Evaluation and Management Among Kidney and Liver Transplantation Candidates conducted a comprehensive review of the literature relevant to perioperative cardiac evaluation of potential kidney or liver transplant recipients, including the prevalence of CAD in these populations; incidence of MACEs before and after transplantation; accuracy of clinical risk markers, symptoms, and noninvasive testing before and after transplant listing for detecting active cardiac conditions and CAD; and clinical outcomes of revascularization and the medical management of atherosclerosis. Each section was assigned to a lead author and coauthor. Literature searches were conducted in the following databases: PubMed, MEDLINE, and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register). Searches were limited to the English language, the years 1990 through March 2010, and human subjects. Related-article searches were conducted in MEDLINE to find additional relevant articles. Finally, committee members recommended applicable articles outside the scope of the formal searches. Interval drafts were discussed during conference calls and 2 face-to-face meetings. Recommendations included an evaluation of the strength of the evidence for or against a particular procedure or treatment in terms of the magnitude of effect (evidence class) and estimate of certainty (evidence level) (Table 1). Recommendations were subjected to formal, anonymous voting. The volume of text devoted to cardiac evaluation and management issues for kidney and liver transplantation candidates, respectively, reflects the relative sizes of the target populations; the number of patients awaiting and receiving kidney transplants is >4 times the number of patients awaiting and receiving liver allografts. Correspondingly, a substantially larger number of publications with liver transplantation candidates.

What Are the Goals of Preoperative Cardiac Risk Evaluation in Transplantation Candidates?

The most compelling goal of preoperative cardiac risk evaluation is to reduce the morbidity and mortality of cardiovascular disease. Any test used to screen a population is associated with false-positive and -negative results that may diminish utility. False-positive results in particular may lead to patient and physician anxiety and the possibility of additional and often unnecessary testing or invasive procedures. Screening asymptomatic patients should be used only if the benefits of screening outweigh the harms. In asymptomatic patients, screening for CAD would be of value if the results of testing lead to management changes that reduce the occurrence of patient-level outcomes. Screening should also be cost-effective. For organ transplantation, cardiac evaluation could also be used to deny transplantation to high-risk patients, provided that it can be shown that patients with severe cardiovascular disease have sufficiently short life expectancy to make transplantation a poor use of scarce donated organs. However, studies have shown that survival is generally improved by transplantation compared with remaining on the transplant waiting list, even among high-risk patients (32–34). Thus, the burden of proof in using screening to determine transplantation candidacy from a patient-centered perspective is to demonstrate that denying transplantation on the basis of test results is in the best interest of the patient. Alternatively, society may decide that cardiovascular evaluation results can help in guiding allocation of organs to recipients who are most likely to benefit in the long term. However, nationally agreed-on allocation priorities of the OPTN use waiting time and a liver failure severity metric (Model for End-Stage Liver Disease score) as the dominant criteria for achieving fairness in kidney and liver allocation, respectively; allocation schemes that seek to maximize net societal benefit from donated allografts have not been adopted. Although prognostic information from noninvasive cardiac testing of asymptomatic patients may be useful for adjusting center performance metrics such as post-transplantation mortality for the "case mix" of each center's recipients, this approach would incur substantial expense compared with the use of information available from the history and physical examination.

Some patients have been shown to undergo renal transplantation safely despite clinical markers of high cardiovascular risk. Jeloka et al. (35) retrospectively classified 429 renal transplant recipients as high cardiovascular risk (n=61) and low cardiovascular risk (n=368). The high-risk group included patients with a history of angina, MI, or significant CAD found on cardiac catheterization. Outcomes of interest were post-transplantation cardiac events (MI, angina, new arrhythmias, heart failure, and/or sudden cardiac death) and overall survival. The distribution of events among the high-risk and low-risk groups was 31.3% versus 6.5%, respectively (p=0.001). Five-year survival in the high-risk group was 82.8% compared with 93.1% in the low-risk group (p=0.004). Among the subgroup who underwent coronary revascularization before transplantation (n=28; 25% PCI, 75% CABG), 43% subsequently experienced a cardiac event. The authors contended that in selected high-risk patients, overall 5-year survival after renal transplantation was actually quite good, superior to the expected 5-year survival with continued dialysis.

With regard to the pathophysiology of perioperative cardiac events, both demand-mediated ischemia and plaque rupture contribute to perioperative cardiac events. The stress

response from surgery can lead to increases in heart rate and blood pressure, which can precipitate episodes of "demand ischemia" in myocardial areas distal to a coronary artery stenosis (36). Long periods of myocardial ischemia (either prolonged individual episodes or cumulative duration of shorter episodes) have been associated with myocardial necrosis and perioperative MI and death (37–39). A major mechanism of MI in the nonoperative setting is plaque rupture of a noncritical coronary stenosis with subsequent coronary thrombosis (40). The perioperative period is characterized by tachycardia, increased sheer stress, and a hypercoagulable state; thus, plaque rupture and thrombosis may also occur in this context (41). Ellis et al. (42) demonstrated that one third of all patients with perioperative MI sustained damage in areas distal to noncritical stenoses. Dawood et al. (43) demonstrated that fatal perioperative MI occurs predominantly in patients with multivessel CAD, especially left main and 3-vessel disease; however, the severity of preexisting underlying stenosis did not predict the resulting infarct territory. Because the nidus for the thrombosis is often a noncritical stenosis, preoperative cardiac evaluation before surgery may fail to identify patients at risk for plaque rupture, although control of heart rate may decrease the propensity of plaque rupture regardless of stenosis severity. The areas distal to a noncritical stenosis typically will not have much collateral coronary flow; therefore, any acute thrombosis may lead to extensive downstream myocardial necrosis. Methods of preoperative cardiovascular testing do not identify patients with mild to moderate but "vulnerable" coronary plaques.

Determining Whether the Transplantation Candidate Has an Active Cardiac Condition

A primary goal of the preoperative evaluation is to establish whether an active cardiac condition is present. Clinical assessment should occur during the initial evaluation and again immediately before anticipated transplantation to determine whether there has been an interval change in cardiovascular conditions. "Active" conditions include unstable coronary syndromes (e.g., unstable angina, severe angina, or recent MI), decompensated heart failure, significant arrhythmias, and severe valvular disease. The presence of one or more of these conditions is associated with high rates of perioperative cardiovascular morbidity and mortality and may require delay or cancellation of surgery.

Recommendation

1. **A thorough history and physical examination are recommended to identify active cardiac conditions before solid-organ transplantation** *(Class I; Level of Evidence C).*

A number of chronic cardiac conditions also merit consideration and at times may require further assessment before surgery. These include chronic limiting angina, an MI that is <30 days old but without symptoms of unstable angina, a prior history of CABG or PCI, decompensated heart failure, moderate valvular disease or prior valve surgery, or stable arrhythmias.

Perioperative Risk Assessment Based on Symptoms and Exercise Tolerance

The presentation of acute and chronic ischemia may differ in patients with ESRD compared with people without kidney failure. Among patients hospitalized with acute MI and recorded in the third National Registry of Myocardial Infarction, chest pain at presentation was reported less commonly among patients on dialysis compared with non–dialysis-dependent patients (44.4% versus 68.3%) (44). In the community-based study of patients hospitalized with acute MI in Worcester, MA, patients with kidney disease were less likely to report chest pain (adjusted odds ratio [OR], 0.57) and more likely to report shortness of breath (OR, 1.35) compared with patients without kidney disease in the setting of acute MI (45). In a preliminary report of symptoms during PCI among 111 patients who had undergone 256 interventions, silent myocardial ischemia, defined as the absence of chest pain in response to balloon dilatation of the affected vessel, was present in 59.1% of the sample with CKD (defined as estimated glomerular filtration rate [eGFR] <60 mL/min/1.3 m^2) compared with 29.1% without CKD (46). However, the value of screening to identify asymptomatic patients likely to benefit from revascularization is unclear. In the randomized DIAD (Detection of Ischemia in Asymptomatic Diabetics) trial of MPS versus medical follow-up among asymptomatic patients with type 2 diabetes mellitus, use of MPS screening had no discernable effect on subsequent cardiac events over 5 years of follow-up (47).

Exercise tolerance is 1 correlate of perioperative risk and is a cornerstone of the testing algorithm reported in the "ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery" (7). In 1 study of outpatients referred for evaluation before major noncardiac procedures, patients were asked to estimate the number of blocks they could walk and flights of stairs they could climb without experiencing cardiac symptoms (48). Patients who could not walk 4 blocks and climb 2 flights of stairs were considered to have poor exercise tolerance and were found to have twice as many perioperative cardiovascular complications as those with better functional status. The likelihood of serious complications was inversely related to the number of blocks that could be walked or flights of stairs that could be climbed. Further work is needed to determine the ability of functional status to discriminate the likelihood of prognostically significant CAD among transplantation candidates.

Imperfect Correlations of Angiographic CAD and Clinical Outcomes in ESRD

Angiographic studies from the 1970s to early 1990s reported detection of coronary stenoses in high proportions of patients on long-term dialysis (49–52). More recently, angiographi-

cally significant CAD was found in 53% of a sample of 30 patients with incident ESRD without known cardiac history who consented to screening angiography, including 10 of the 12 participants (83%) with diabetes mellitus, although notably angiographic significance was liberally defined as lesions >50% (54). Recent reports of angiography in patients undergoing transplantation evaluation have documented CAD in 42% to 90% of participants, with a higher prevalence in samples defined as high risk by clinical criteria and with use of more liberal angiographic definitions of CAD (26,59–61) (Table 4).

Studies describing associations of angiographic coronary stenoses with subsequent clinical events in patients with ESRD, including those undergoing transplantation evaluations, have reported variable results (Table 4). In 1 prospective study of 106 renal transplantation candidates clinically classified as moderate (age ≥50 years) or high (diabetes mellitus, extracardiac vascular disease, or known CAD) coronary risk, participants underwent MPS, DSE, and coronary angiography (56). Clinical risk stratification and coronary angiography predicted MACEs after a median follow-up of 46 months, but results of MPS and DSE did not. Several observational studies reported an increased unadjusted risk of all-cause mortality and MACEs in patients with angiographic CAD (55,58), whereas other investigations identified excess risk in only certain patient subgroups such as those with proximal CAD (57) or with nondiabetic renal failure (59). Several recent studies have found no associations of CAD with subsequent patient survival (28,60,61).

Accuracy of Noninvasive Testing for CAD in Kidney Transplantation Candidates

Noninvasive testing for CAD has imperfect sensitivity and specificity in patients with renal failure. Table 5 summarizes the association between cardiac stress testing results and occlusive coronary artery lesions on angiography in cohorts with CKD stage 5 (GFR <15 mL/min/1.73 m² or dialysis dependent). Studies were included if stress was induced by exercise or pharmacological means and if CAD was detected by electrocardiography, echocardiography, or radionuclide imaging. Studies were excluded if not all subjects selected for stress testing underwent angiography. Across this collection of studies, DSE and MPS had sensitivities varying from 0.44 to 0.89 and 0.29 to 0.92 and specificities ranging from 0.71 to 0.94 and 0.67 to 0.89, respectively, for identifying 1 or more coronary stenoses >70% (55,56,63–69). The type of stress imaging may have different operational characteristics in ESRD patients. In 1 study of coronary flow reserve in 64 patients with normal epicardial arteries, 57% (12 of 21) of those with diabetic nephropathy had high resting coronary basal flow with no incremental response to adenosine compared with 18% of patients (2 of 11) with diabetes mellitus without renal failure and 9% (3 of 32) of patients without diabetes mellitus (70), suggesting impaired vasodilator reserve in patients with ESRD with diabetes mellitus. Overall, the accuracy of inotropic stress echocardiography for the purpose of screening to identify

high-risk anatomy may be somewhat superior to that of vasodilator stress nuclear perfusion imaging.

Nonetheless, abnormal MPS and DSE test results have been associated with prognostic value for cardiac events and mortality in the ESRD population (27,55,67,69,71–76). In a meta-analysis of 12 studies involving either thallium-201 scintigraphy or DSE, patients with ESRD with inducible ischemia had ≈6 times the risk of MI and 4 times the risk of cardiac death as patients without inducible defects (77). Moreover, patients with fixed defects had nearly 5 times the risk of cardiac death. Among 485 patients with advanced kidney disease, the percentage of ischemic segments by DSE was an independent predictor of mortality and offered prognostic information beyond clinical characteristics alone (78). In a study of 126 patients with ESRD who underwent technetium-99m MPS as part of their pretransplantation assessment, the presence of a reversible defect was associated with 3 times the risk of post-transplantation cardiac events and nearly twice the risk of death compared with normal test results (79).

Considerations for Kidney Transplantation Candidates With Diabetes Mellitus

One of the main discrepancies between guideline recommendations from the ACC/AHA and the renal/transplant organizations (NKF/KDOQI, AST) is that the latter advise routine cardiac screening with noninvasive cardiac imaging in patients with diabetes mellitus on the basis of concerns for "silent" (asymptomatic) ischemia (12,14). NKF/KDOQI also advocates repeat screening annually while a patient with diabetes mellitus is on the waitlist (12). In consideration of cardiac evaluation practices in patients with diabetes mellitus with ESRD, it is useful to review strategies that have been applied to reduce cardiac risk in the broader diabetic population.

In 1998, the American Diabetes Association recommended routine stress testing in asymptomatic patients with diabetes mellitus with ≥2 traditional cardiovascular risk factors in addition to diabetes mellitus (80). More recent data call these recommendations into question. In the prospective DIAD study (47), 1,123 asymptomatic patients with type 2 diabetes mellitus 50 to 75 years of age were randomized to adenosine technetium-99m sestamibi-MPS or medical follow-up. The primary endpoint was cardiac death or nonfatal MI over 5 years. Coronary revascularization within 120 days of randomization occurred in 1.6% of the screened group and 0.4% of the nonscreened group. There was no difference in the frequency of the primary endpoint according to screening assignment: 7 nonfatal MIs and 8 cardiac deaths (2.7%) occurred in the screened group compared with 10 nonfatal MIs and 7 cardiac deaths (3.0%) in nonscreened group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.44 to 1.88; p=0.73). There was also no difference in the incidence of unstable angina, chronic heart failure, or stroke between the groups. Of those screened, 409 patients had normal MPS; 33 patients with large or moderate defects had an annual event rate of 2.4% compared with the 50 patients with small perfusion defects and an annual event rate of 0.4%.

Table 4. Recent Descriptions of the Outcome Implications of Angiographic CAD in Patients With ESRD, Including Transplantation Candidates

Authors, Year	Participants and Design	Selection Criteria for Angiography	Angiographic Definition of CAD	Estimated CAD Prevalence	Associations of CAD With Clinical Events
De Lima et al. (56), 2003	106 patients presenting for KT evaluation at 1 center and deemed at moderate or high coronary risk (1998–2002) Prospective	Moderate risk: age ≥50 y High risk: history of diabetes, MI, angina, stroke, LV dysfunction, peripheral vascular disease Willing to consent	≥70% stenosis in ≥1 epicardial arteries by visual estimation Evaluation by 2 observers	CAD present in 42% (44 of 106) 1-, 2-, and 3-vessel CAD in 19%, 16%, and 7%, respectively	MACEs, defined as sudden death, MI, arrhythmia, heart failure, unstable angina, or revascularization Unadjusted probability of reaching endpoint at 1, 2, and 4 y was higher with angiographic CAD (p<0.001): 13%, 39%, and 46% versus 2%, 6%, and 6% in the absence of CAD
Sharma et al. (55), 2005	125 consecutive patients referred for KT evaluation	Age >18 y Free of severe aortic stenosis or unstable angina Willing to consent	Severity by degree of luminal narrowing: mild, <50%; moderate, 50%–70%; severe, >70% Evaluation by 2 observers	CAD present in 64% (80 of 125) Severe, moderate, and mild CAD in 29%, 14%, and 21%	Unadjusted survival at 2 years was significantly lower among those with versus without CAD (85% versus 100%; p=0.005)
Charytan et al. (57), 2007	67 prevalent hemodialysis patients (1998); subset of a larger study (N=224) Prospective	Free of ischemic symptoms at enrollment Free of coronary events within 4 wk No coronary angiography within previous 2 y Willing to consent	>50% narrowing compared with adjacent normal segment by digital calipers Evaluation by 2 observers	CAD in 42% (28 of 67), including involvement of proximal third of an epicardial vessel in 28.5% Of 28 subjects with CAD, 75% had multivessel and 68% had proximal lesions	Over a median 2.7 y of observation, the presence of any CAD was associated with increased risk of death Only proximal CAD was associated with mortality in adjusted analyses (aHR, 3.14; 95% CI, 1.34 to 7.33)
Gowdak et al. (58), 2007	301 patients referred for KT evaluation and deemed at high coronary risk	Inclusion criteria: history of diabetes mellitus, prior cardiovascular disease (MI, unstable angina, stroke, LV dysfunction, or extracardiac atherosclerosis), or age >50 y Willing to consent	≥70% luminal reduction in ≥1 epicardial arteries Evaluation by 2 observers	Significant CAD in 45% (136 of 301)	MACEs, defined as MI, unstable angina, sudden death, unplanned coronary or peripheral arterial revascularization, stroke, or heart failure Over a median 1.8-y observation, crude incidence of MACEs was higher in those with CAD (45% versus 18%; p<0.001)
Gowdak et al. (59), 2007	288 patients referred for KT evaluation; portion of the cohort in the previous study (58)	High clinical risk, as defined previously (58)	≥70% luminal reduction in ≥1 epicardial arteries Evaluation by 2 observers	Significant CAD in 43% (124 of 288)	MACE as defined previously (58) CAD was associated with significantly higher crude relative risk of MACEs among nondiabetic patients (HR, 4.3; 95% CI, 2.4 to 7.9; p<0.001) No significant association of CAD with MACEs in diabetic patients

(Continued)

Table 4. Continued

Authors, Year	Participants and Design	Selection Criteria for Angiography	Angiographic Definition of CAD	Estimated CAD Prevalence	Associations of CAD With Clinical Events
Hage et al. (60), 2007	260 patients studied by angiography from a cohort of 3,698 referred for KT evaluation at 1 center (2001–2004) Retrospective	Positive stress MPS, known CAD, or discretion of cardiologist	>50% lumen diameter narrowing in any of 3 major coronary arteries or major branches; left main considered equivalent to 2-vessel CAD Results obtained from clinical reports	CAD in 62% (162 of 260) 1-, 2-, and 3-vessel CAD in 16%, 13%, and 33%, respectively, of the sample submitted to angiography 36% (94 of 260) of the angiography group underwent revascularization	Presence and severity of CAD were not associated with crude survival among those who underwent angiography; 2-y survival: 80%, 88%, 86%, and 78% for 0-, 1-, 2-, and 3-vessel disease (p=0.6)
Patel et al. (28), 2008	99 patients studied by angiography from a cohort of 300 referred for KT evaluation at 1 center (2002–2005) Retrospective	Angiography suggested if age >50 y, ESRD caused by diabetes mellitus, symptomatic IHD or positive noninvasive testing Final selection based on clinical judgment and patient preference	Obstructive, >75% Nonobstructive, stenosis present but ≤75%	CAD in 57.6% (57 of 99) Obstructive CAD in 34.3% (34 of 99), including 1-, 2-, 3-vessel CAD in 13%, 15%, and 6%, respectively, of the angiography sample Nonobstructive CAD in 23% 17% (17 of 99) of the angiography group underwent revascularization	No difference in crude 4-y survival in patients found to have CAD and revascularized compared with those who underwent angiography without revascularization or those not studied by angiography (p=0.7)
Hickson et al. (61), 2008	132 patients studied by angiography from a cohort of 644 referred for KT evaluation at 1 center (2004–2006) Retrospective	Angiography performed if DSE was positive, cardiologist recommended	Severity by highest degree of stenosis of single major epicardial arteries: mild, <50%; moderate, 50%–70%; severe, >70%	CAD present in 90% (119 of 132) of those studied by angiography Severe, moderate, and mild in 56%, 10%, and 25% of the angiography sample 40 of 644 of the full cohort underwent revascularization before listing	Over a median 6-mo observation, severity of CAD by angiography was not significantly associated with mortality in the full cohort (p=0.2)

aHR indicates adjusted hazards ratio; CAD, coronary artery disease; CI, confidence interval; DSE, dobutamine stress echocardiography; ESRD, end-stage renal disease; HR, hazards ratio; IHD, ischemic heart disease; KT, kidney transplantation; LV, left ventricular; MACEs, major adverse cardiovascular events; MI, myocardial infarction; and MPS, myocardial perfusion scintigraphy.

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In DIAD and another prospective study of asymptomatic patients with diabetes mellitus, the proportion of patients with an abnormal MPS was identical in those who did and did not meet American Diabetes Association criteria for recommended screening (47,81). In 1 study, the only difference was related to the extent of CAD, with more severe CAD identified in the group recommended for screening (81).

Is screening necessary in asymptomatic patients with diabetes mellitus without known CAD to justify more aggressive medical therapy or to identify patients who should be considered for coronary revascularization? Regarding the option of optimal medical therapy, patients with diabetes mellitus without prior MI appear to have cardiac event rates comparable to those of patients without diabetes mellitus with a history of prior MI (82). Thus, results of screening will not generally mitigate the need for optimal medical management. Using the specific example of statin therapy in this subgroup, Diamond and colleagues (83) argue that the strategy of "test no one and treat everyone" is more cost-effective than "screen everyone with a test and treat only those with an abnormal test," thereby obviating the need for routine screening.

The value of screening to identify asymptomatic patients likely to benefit from coronary revascularization procedures is even less clear. As previously mentioned, certain small subgroups with high-risk coronary artery anatomy probably achieve survival benefit from CABG surgery (31,31a). In patients with stable CAD and lesser extents of coronary disease, coronary revascularization has not been demonstrated to provide benefit over optimal medical therapy when studied in a randomized fashion before elective vascular surgery (9–11). In the DIAD study (47), coronary revascularization was infrequent (<2% within 120 days of randomization in both arms), and the treatment after MPS screening did not significantly reduce the risk of cardiac events. The authors concluded that MPS screening of asymptomatic patients with type 2 diabetes mellitus to identify revascularization candidates did not reduce cardiac event rates. This study did not address patients with renal failure.

In summary, on the basis of available data, routine noninvasive screening of patients with diabetes mellitus either for peritransplantation cardiac evaluation or for long-term care is not justified by existing evidence.

Table 5.   Accuracy of Noninvasive Testing for Detection of Coronary Artery Stenosis in End-Stage Renal Disease Patients

Authors, Year	Study Population	n	Stress Test	Endpoint	Endpoint Prevalence	Sensitivity	Specificity	PPV	NPV
Marwick et al. (63)	100% KT candidates	45	Dipyridamolethallium SPECT	CAS ≥50%	0.42	0.37	0.73	0.50	0.61
	Mean age 49±11 y			CAS ≥70%					
	56% had diabetic nephropathy				0.31	0.29	0.68	0.29	0.68
Boudreau et al. (64)	100% KT candidates	80	Dipyridamole thallium	QCAS ≥70%	0.53	0.86	0.79	0.82	0.83
	100% had diabetes mellitus								
Vandenberg et al. (65)	100% KT candidates	41	Dipyridamole/adenosinethallium	CAS ≥50%	0.46	0.53	0.73	0.63	0.36
	Mean age 37±9 y			CAS ≥75%					
	100% had diabetes mellitus				0.39	0.63	0.76	0.63	0.24
		35	Exercise thallium	CAS ≥50%	0.46	0.44	0.63	0.50	0.57
				CAS ≥75%	0.40	0.50	0.67	0.50	0.67
Dahan et al. (66)	HD for 6 mo, no overt CAD	60	Dipyridamole/exercise thallium SPECT	CAS ≥70%	0.22	0.92	0.89	0.71	0.98
	Mean age 54±11 y								
	23% had diabetes mellitus								
Herzog et al. (67)	100% KT candidates	50	DSE	QCAS ≥50%	0.54	0.52	0.74	0.70	0.57
	Mean age 51±11 y			QCAS ≥70%	0.24	0.75	0.71	0.45	0.90
	78% had diabetic nephropathy			CAS ≥75%	0.32	0.75	0.76	0.60	0.87
Worthley et al. (68)	100% KT candidates	40	Exercise/pacingtetrofosmin nuclide imaging	CAS >70%	0.38	0.87	0.88	0.81	0.92
	Mean age 50±9 y								
	78% had diabetes mellitus								
de Lima et al. (56)	100% KT candidates	89	DSE	CAS ≥70%	0.38	0.44	0.87	0.53	0.60
		102	Dipyridamole SPECT	CAS ≥70%	0.23	0.35	0.76	0.72	0.68
Sharma et al. (55)	100% KT candidates	125	DSE	CAS >70%	0.29	0.89	0.94	0.86	0.95
	Mean age 52±12 y								
	39% had diabetes mellitus								
	55% were on dialysis								
Ferreira et al. (69)	100% KT candidates	148	Dobutamine/atropine echocardiography	CAS >50%		0.530.71	0.870.85		
	Mean age 52±9 y			CAS >70%					
	27% had diabetic nephropathy								

CAD indicates coronary artery disease; CAS, visual coronary angiographic stenosis; DSE, dobutamine stress echocardiography; HD, hemodialysis; KT, kidney transplantation; NPV, negative predictive value; PPV, positive predictive value; QCAS, quantitative coronary angiographic stenosis; and SPECT, single photon emission computed tomography.

Summary and Recommendations Regarding Noninvasive Stress Testing in Kidney Transplantation Candidates Without Active Cardiac Conditions

Noninvasive cardiac stress testing by DSE or MPS has some prognostic value for cardiac events and mortality but imperfect sensitivity and specificity for detecting angiographically defined CAD in patients with ESRD. Associations of CAD by angiography with subsequent survival in ESRD are also inconsistent, likely because plaque instability is more important for risk of MACEs than angiographic stenosis and many plaque ruptures producing MI are not localized to sites of angiographic stenosis (40). Furthermore, coronary revascularization in asymptomatic patients without end-stage organ failure has failed to show benefit except in a small subset of high-risk anatomic lesions. Evidence does not support sufficient prevalence of such high-risk anatomy among asymptomatic patients to warrant routine coronary angiography in all potential transplantation candidates. In the randomized DIAD trial of MPS versus medical follow-up among asymptomatic patients with type 2 diabetes mellitus for the purpose of identifying revascularization candidates who may not otherwise come to clinical attention, coronary revascularization was infrequent (47).

The Writing Committee acknowledges that there are no definitive data at this time for or against screening for myocardial ischemia among kidney transplantation candidates who are free of active cardiac conditions. However, until more data are available, it may be useful to use aggregate CAD risk factors to target screening of patients with the highest pretest likelihood of prognostically significant CAD.

The "ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery" highlight 4 "active cardiac conditions" that indicate major clinical risk (7). These include unstable coronary syndromes (unstable angina or recent MI), decompensated heart failure, significant arrhythmia, and severe valvular heart disease. If none of the active cardiac conditions is present, the patient is then risk stratified on the basis of functional capacity. If the functional status is estimated as ≥4 METS in a patient without an active cardiac condition, then that patient is deemed low risk and no further testing is advocated. If functional capacity is <4 METS, it is difficult to know whether the low level of exertion is preventing manifestation of an active cardiac condition or whether cardiac conditions are truly absent. Therefore, such patients with low functional capacity are considered to be of indeterminate cardiac risk. The ACC/AHA approach then further risk stratifies asymptomatic patients with low functional capacity according to the presence or absence of risk markers: ischemic heart disease, compensated or prior heart failure, diabetes mellitus, renal insufficiency, and cerebrovascular disease. Because the presence of any of these risk markers is associated with increased likelihood of CAD among patients with poor functional status, the diagnostic yield of noninvasive stress testing theoretically improves as one acquires more risk factors. Thus, to avoid testing everyone with a poor functional status

but to consider "pretest probability" in the strategy for noninvasive stress testing, the ACC/AHA guideline recommends preoperative stress testing on the basis of the presence of a certain number of risk factors depending on the surgery-specific risk. However, this scheme was designed for a wide age range of patients (including the elderly) with a wide range of chronic medical conditions.

The question arises as to whether the overall ACC/AHA scheme could be customized to the transplantation population. Of note, the transplantation population is on average younger than the general population. Therefore, the functional status of 4 METS may not be as discriminating. One study of 204 consecutive transplantation candidates with no active cardiac conditions reported that 80% had a functional status ≥4 METS and that functional status was not a useful discriminator for the presence of CAD (24). Importantly, patients scheduled for renal transplantation have at least 1 clinical risk marker (azotemia), and diabetes mellitus is a common additional risk marker in this population, rendering the provided list less useful for risk stratification. Furthermore, the ACC/AHA guideline is also designed for short-term risk assessment, whereas both short-term management and long-term management of CAD are important considerations among transplantation candidates.

Kidney transplantation is typically considered an "intermediate-risk" surgery. However, few studies have evaluated the utility of clinical risk markers for the risk of MACEs during the transplantation hospitalization or within 30 days of transplantation surgery (the usual approach in nontransplantation, noncardiac surgery). This distinction is important because perioperative risk stratification has traditionally focused on identifying patients with undiagnosed or unstable CAD as a way to reduce the risk of MACEs after surgery. In a retrospective study of 2,187 transplant recipients, Aalten et al. (84) reported independent associations of recipient age, diabetic nephropathy, claudication, and prior cardiac events with an increased risk of cardiac events (defined as MI, coronary revascularization, stroke, or cardiac death) within the first 3 months after kidney transplantation.

With respect to longer-term prognostication, the Framingham Heart Study (FHS) score, a composite index designed to predict coronary heart disease in the general population based on traditional risk markers of age, sex, cholesterol levels, hypertension, and diabetes mellitus status, has modest to moderate ability to predict long-term coronary events among kidney transplantation patients. Although individual Framingham risk factors are significantly associated with coronary risk among kidney transplant recipients, effect sizes are altered so that FHS risk predictions are generally lower than observed risk in this population. Features of this miscalculation include largest errors among patients at highest risk, driven in part by underestimation of diabetes mellitus–related risk. For example, in a retrospective study of 1,124 kidney transplant recipients with stable graft function at the first transplantation anniversary, the FHS score underestimated the risk of coronary events as a result of increased observed risk conferred by diabetes mellitus (HR in men, 2.8 versus 1.5 in FHS; HR in women, 5.4 versus 1.8 in FHS) and, to a lesser extent, age and smoking in the transplanted sample (85). In

another historical cohort study of transplant recipients with functional allografts at 1 year after transplantation, the FHS predicted 59% of observed coronary events (86). A prospective cohort evaluation of 540 prevalent transplant recipients enrolled at average of 6.6 years after transplantation and followed up for an average of 4.7 years found that the ratio of observed to predicted cardiac events based on the FHS was 1.64 for the cohort overall (87). Observed cardiac events rates exceeded FHS predictions in patients with pretransplantation diabetes mellitus and those with prior cardiac disease, being 2.74 times the predicted risk in patients 45 to 60 years of age with prior cardiac disease or diabetes mellitus (87). However, observed risk did not exceed predictions in older patients considered without regard to comorbidity or in younger patients free of prior diabetes mellitus or cardiac history.

One alternative to use of the ACC/AHA-defined CAD risk factors for the general population is to consider risk factors more specific to the transplantation population, as suggested in the 2007 Lisbon Conference report (13). Compared with the ACC/AHA approach, this strategy appeared to improve sensitivity and specificity for the identification of CAD (sensitivity, 94% versus 77%; specificity, 33% versus 24%) and to reduce the overall frequency of testing in 1 single center (24). The risk factors for CAD deemed relevant to transplantation candidates in the Lisbon Conference report include diabetes mellitus, prior cardiovascular disease, >1 year on dialysis, left ventricular hypertrophy, age >60 years, smoking, hypertension, and dyslipidemia.

Recommendation

1. **Noninvasive stress testing may be considered in kidney transplantation candidates with no active cardiac conditions based on the presence of multiple CAD risk factors regardless of functional status. Relevant risk factors among transplantation candidates include diabetes mellitus, prior cardiovascular disease, more than 1 year on dialysis, left ventricular hypertrophy, age greater than 60 years, smoking, hypertension, and dyslipidemia. The specific number of risk factors that should be used to prompt testing remains to be determined, but the committee considers 3 or more as reasonable (*Class IIb; Level of Evidence C*).**

Cardiac Surveillance After Listing for Transplantation

Just as there is uncertainty about which patients to screen, the optimal frequency for repeat noninvasive stress testing for patients awaiting renal transplantation is not known. The NKF/KDOQI guidelines recommended repeat stress testing with imaging once a year among subgroups on the transplant list including patients with diabetes mellitus regardless of symptoms (12). These guidelines mirror recommendations from the AST's 2002 conference on management of the transplant waitlist (88). However, the cardiac event rate (cardiac death or nonfatal MI) was only 0.6% over 2 to 3 years in 7,376 patients with a normal MPS, suggesting that the "warranty" on a normal stress perfusion scintigram is at

least 2 years in a general population (90); however, only 10% of participants in this study were diabetic. There are few data defining the long-term prognosis conferred by a normal study in individuals with diabetes mellitus. A large cohort study found low and similar cardiac event rates between individuals with and without diabetes mellitus up to 2 years after normal stress MPS beyond that, the cohort with diabetes mellitus experienced a greater event rate (90). Prognosis after a normal MPS also varies with renal function. In an observational cohort study of the Veterans Affairs database with an average of 2 years of follow-up that considered outcomes according to CKD status (defined as eGFR <60 mL/min/1.73 m^2), the annualized rate of cardiac death after a normal MPS (defined as no scar or ischemia) rose in a graded manner with declining renal function: eGFR ≥90 mL/min/1.73 m^2 to 0.4%; eGFR 60 to 89 mL/min/1.73 m^2 to 0.9%; eGFR 30 to 59 mL/min/1.73 m^2 to 2.2%; and eGFR <30 mL/min/1.73 m^2 to 4.7% (91).

In a cohort study from Brisbane, Australia, including 107 patients with CKD with baseline and repeat DSE tests after a mean follow-up of 1.8 years, 19% of the 73 patients with normal DSE results at baseline developed inducible ischemia or new scar on repeat testing (92). Despite this potential for conversion of normal noninvasive tests to abnormal at a rate of ≈10%/y, an argument that "periodic cardiac surveillance testing after waitlist may be unnecessary" is supported by a prospective, observational study of patients on the kidney transplant waitlist in British Columbia in 1998 to 2001 (93). Among kidney transplantation candidates with normal cardiac stress testing at listing, the reference cardiac surveillance guideline included recommendation for annual testing in those with diabetes mellitus, testing every 2 years in those with ischemic heart disease or peripheral vascular disease, and testing every 3 years in others. Surveillance based on ongoing clinical assessment resulted in fewer investigations than suggested by guidelines over a mean follow-up period of 3.7 years. There was no difference in total cardiovascular event rates after listing among subsets who received the recommended frequency of investigations compared with those in whom testing was guided by symptoms.

Recommendation

1. **The usefulness of periodically screening asymptomatic kidney transplantation candidates for myocardial ischemia while on the transplant waiting list to reduce the risk of MACEs is uncertain (*Class IIb; Level of Evidence C*).**

Supplemental Testing

Evidence for Resting Echocardiography in Kidney Transplantation Candidates

The NKF/KDOQI "Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients" recommend that a resting echocardiogram "should be performed in all patients at the initiation of dialysis, once the patient has achieved dry weight (ideally within 1–3 months of dialysis initiation)" (12). This is considered by the working group as a Level of Evidence A recommendation, which implies the strongest

recommendation. A number of studies have demonstrated the predictive value of resting echocardiographic findings for adverse events in dialysis patients.

Foley et al. (94) collected clinical and echocardiographic data at the time of hemodialysis initiation in 433 patients and followed the cohort prospectively for survival over 41 months. Cardiovascular disease was common at baseline, and at least 1 cardiovascular condition was noted in 43%. Baseline echocardiographic abnormalities included left ventricular hypertrophy in 74%, dilated left ventricle in 36%, and systolic dysfunction in 15%. Predictors of mortality included advanced age, chronic heart failure, diabetes mellitus, and echocardiographic parameters of left ventricular enlargement or systolic dysfunction, whereas a history of CAD alone was not associated with survival.

Sharma et al. (55) examined 125 potential renal transplantation candidates by resting electrocardiogram (ECG), exercise ECG, DSE, and coronary angiography (Table 4). Correlates of coronary stenosis of ≥70% included abnormal resting ECG, increased left ventricular size, decreased LVEF, resting wall motion abnormalities, and ischemia identified by echocardiographic imaging, whereas cardiac symptoms and exercise ECG findings were not significantly associated with angiographic CAD.

Among 485 patients with advanced kidney disease, independent predictors of mortality over 2.3±1.8 years included resting LVEF and ischemia on stress echocardiogram; once again, stress ECG findings were not associated with mortality (78). Three-year survival was superior in patients with a normal stress echocardiogram (70%) compared with patients with fixed defects or ischemia in ≤25% left ventricular segments (57%), and survival was poorest (48%) in patients with ischemia in >25% of left ventricular segments.

Two reports from 1 large center using stress MPS in potential candidates meeting AST criteria for pretransplantation CAD evaluation found left ventricular systolic dysfunction, defined as LVEF <40% to 45%, in 16% to 18% of patients (95,96). The majority (61%–63%) of these patients did not have evidence of ischemia by perfusion imaging. Median survival in patients with LVEF <40% was 49 months compared with 72 months in patients with higher LVEF; after adjustment for ischemia and other risk factors, the relative risk of mortality increased by 2.5% for each percent decline in LVEF (96).

In one of the largest series reported to date, Yamada et al. (97) examined 1,254 consecutive incident hemodialysis patients in Japan with echocardiography within 1 month after dialysis initiation. LVEF levels ≥60%, 50% to 60%, 40% to 50%, 30% to 40%, and <30% were observed in 67.1%, 19.7%, 8.5%, 3.3%, and 1.4% of patients, respectively. On Kaplan-Meier analysis, 7-year event-free rates from cardiovascular death were 84.2%, 83.7%, 73.6%, 59.4%, and 30.9%, respectively, according to each 10% decrease in LVEF. In multivariate models, LVEF bore graded associations with the risk of subsequent cardiovascular and all-cause mortality, with more than 9 times the relative risk of cardiovascular death (adjusted HR, 9.42; 95% CI, 3.82 to 23.3) among those with LVEF <30% compared with LVEF ≥60%.

In summary, collective evidence supports the concept that echocardiographic findings at rest and after stress provide prognostic information for long-term mortality in patients with CKD. The strong relationship between LVEF and outcomes supports the need for vigorous efforts to identify any reversible cause of poor LVEF and, where possible, and to correct these causes before proceeding to transplantation. Carvedilol treatment reduced the risk of cardiovascular mortality (relative risk [RR], 0.32), all-cause death (RR, 0.51), and hospitalizations (RR, 0.44) compared with placebo in a small randomized trial of 114 dialysis patients with dilated cardiomyopathy (98), supporting the use of echocardiography for guiding therapy and for prognostication. Notably, improvement in abnormal LVEF and heart failure symptoms in some patients with ESRD, probably those with uremic cardiomyopathy, has been reported after transplantation (16,99–101).

Recommendation

1. **It is reasonable to perform preoperative assessment of left ventricular function by echocardiography in potential kidney transplantation candidates (*Class IIa; Level of Evidence B*). There is no evidence for or against surveillance by repeated left ventricular function tests after listing for kidney transplantation.**

Other findings on a baseline echocardiogram beyond wall motion assessment may have prognostic significance for the renal transplantation candidate.

Valve Disease

Overall, the management of valvular heart disease in renal transplantation candidates is similar to that in the general population, and the reader is directed to the "2008 Focused Update Incorporated into the ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease" for details (102). However, a few issues specific to renal transplantation candidates are highlighted below.

First, a large retrospective study of 35,215 patients on the kidney transplant waitlist in 1994 to 1997 suggested that uncorrected valve disease is a barrier to transplantation (103). Specifically, patients with value disease who did not undergo surgical correction had lower rates of transplantation compared with patients without valve disease, whereas transplantation rates were not reduced among patients with valve disease who underwent pretransplantation valve surgery. In addition, transplantation was associated with a reduction in the risk for hospitalization for valvular heart disease.

Second, observational studies in the ESRD population have demonstrated an increased incidence of aortic and mitral valve calcification, thought to be related to abnormalities of calcium and phosphate metabolism (104). The increased rate of aortic stenosis progression is roughly twice normal, estimated at 0.23 cm^2/y compared with 0.05 to 0.1 cm^2/y for the general population (12). This potentially classifies ESRD patients with aortic stenosis in the subgroup with a high likelihood of rapid progression, a subgroup that may be considered for aortic valve replacement even in the absence of symptoms, according to the "2008 Focused Update of the

ACC/AHA 2006 Guidelines for the Management of Patients With Valvular Heart Disease" (102). These guidelines include a Class IIb recommendation stating that aortic valve replacement "may be considered for adults with severe asymptomatic aortic stenosis if there is a high likelihood of rapid progression (age, calcification, and CAD) or if surgery might be delayed at the time of symptom onset." Emerging research in the dialysis population has suggested that other factors such as neopterin (a marker of cellular immune system activation) may play a role in the rapid progression of aortic stenosis (105). Although it remains to be determined whether phosphate binders or anti-inflammatory medications can reduce the rate of progression of aortic stenosis in ESRD patients, it seems reasonable to monitor patients with ESRD with moderate or more severe aortic stenosis with an echocardiogram at least once per year and to assess clinically for symptoms.

Third, the increased prevalence of calcification in ESRD patients mentioned in the last section may also affect mitral valve function. The process of valvular calcification may begin as mitral annular calcification with encroachment into both mitral leaflets, leading to mitral regurgitation, mitral stenosis, or both. Assessing the clinical significance of this scenario may present a dilemma to the clinician because the severity of mitral regurgitation may range from mild to severe on the basis of preload (volume status) and afterload (blood pressure). Thus, it is recommended that patients be evaluated when they are at their dry weight (immediately after dialysis or the intradialytic day) and with optimal hemodynamics (heart rate and blood pressure control) (12). Because this is a form of "functional" mitral regurgitation, some patients will experience an improvement in severity with renal transplantation (and concomitant improved volume management) even in the absence of mitral valve surgery (106).

Finally, if valve replacement is deemed necessary, the preferred type of prosthetic valve (bioprosthetic versus mechanical) is probably more dependent on traditional risk factors than the presence of ESRD. It is mostly of historical interest that the 1998 "ACC/AHA Guidelines for the Management of Patients With Valvular Heart Disease" gave a Class III recommendation ("conditions for which there is evidence and/or general agreement that the procedure is not useful and in some cases may be harmful") to placement of a bioprosthetic heart valve in patients with renal failure, hemodialysis, or hypercalcemia because of the risk of accelerated structural degeneration (107). Since that time, this warning has been challenged and removed from the updated ACC/AHA valvular guidelines on the basis of multiple studies. One study of 5,858 dialysis patients who underwent valve replacement (aortic, mitral, or both) in 1978 to 1998 reported no difference in survival regardless of whether the patient received a bioprosthetic or mechanical valve (108). A follow-up study by the same group of 1,335 kidney transplantation patients hospitalized in 1991 to 2004 for cardiac valve replacement also reported no significant difference in survival regardless of bioprosthetic versus mechanical valve, with a trend favoring a bioprosthetic valve (2-year survival rates: 61.5% for bioprosthesis, 59.5% for mechanical; p=0.30) (109). Design and production advances from the

first-generation bioprosthetic valves may make them more resistant to rapid calcification in ESRD as was once feared, and more recent studies have not demonstrated a survival advantage for mechanical valves in these patient populations. Although some bioprosthetic valves claim a durability of 15 to 20 years, the true long-term durability of these valves in ESRD patients remains poorly defined. It is also unknown how renal transplantation changes the natural history of prosthetic valves in patients with ESRD. In conclusion, data suggest that bioprosthetic and mechanical valves appear to be associated with similar survival rates, and it is probably reasonable to choose the optimal prosthetic valve on the basis of other factors in accordance with the standard 2008 ACC/AHA valvular guidelines such as age, bleeding risk, and indications/contraindications for warfarin.

Recommendation

1. **It may be reasonable to consider ESRD patients with moderate aortic stenosis to be equivalent to demonstrated "rapid progressors" who warrant a yearly echocardiogram and monitoring for early symptoms (*Class IIb; Level of Evidence C*).**

Pulmonary Hypertension

The importance of pulmonary hypertension in patients considered for liver transplantation is well known; however, the significance for patients considered for renal transplantation is less clear. Several studies suggest that elevated pulmonary pressures are associated with adverse outcomes after renal transplantation. Among 255 kidney transplant recipients at 1 center with reports from a preoperative echocardiogram that included adequate evaluation of the pulmonary artery systolic pressure (PASP), Zlotnick et al. (110) reported PASP >35 mm Hg in 38%. Specificities of PASP levels >35 mm Hg and >45 mm Hg for prediction of a combined outcome of delayed or slow graft function were 56% and 80%, respectively. The presence of an arteriovenous fistula and the amount of time on dialysis correlated with the likelihood of elevated pulmonary pressures. In another study with data on estimated PASP by echocardiography in 215 potential renal transplantation candidates, estimated PASP ≥50 mm Hg was associated with an increased risk of post-transplantation death (HR, 3.75; p=0.016), and time on dialysis was the strongest correlate of an elevated PASP (111). Although further study is needed to confirm these findings, recent advances in the pharmacological management of pulmonary hypertension (112) make this another possible area for risk reduction before renal transplantation.

From these observations, we suggest consideration of further evaluation of pulmonary hypertension among kidney transplantation candidates with echocardiographic evidence of right ventricular systolic pressure >45 mm Hg, the threshold associated with post-transplantation outcomes in observational studies to date (110,111), or with ancillary evidence of right ventricular pressure overload according to the 2010 American Society of Echocardiography "Guidelines for the Echocardiographic Assessment of the Right Heart in Adults" (113) such as right ventricular hypertrophy or a right ventricular pressure overload pattern of interventricular septal motion. Furthermore, because volume status may affect the echocardiographic assessment of the right heart, the 2005 NKF/KDOQI "Clinical Practice Guidelines for Cardiovascular Disease in Dialysis Patients" recommend that echocardiograms be performed in all patients at the initiation of dialysis, once patients have achieved a dry weight (ideally within 1 to 3 months of dialysis initiation), and at the time of evaluation for kidney transplantation (12).

Recommendations

1. **It is reasonable to evaluate kidney transplantation candidates with echocardiographic evidence of significant pulmonary hypertension for underlying causes (e.g., obstructive sleep apnea, left heart disease) (*Class IIa; Level of Evidence C*).**
2. **It may be reasonable to confirm echocardiographic evidence of elevated pulmonary arterial pressures in kidney transplantation candidates by right heart catheterization (*Class IIb; Level of Evidence C*). Echocardiographic evidence of significant pulmonary hypertension in this population is defined by right ventricular systolic pressure more than 45 mm Hg or ancillary evidence of right ventricular pressure overload.**
3. **If right heart catheterization confirms the presence of significant pulmonary arterial hypertension (as defined by mean pulmonary artery pressure ≥25 mm Hg, pulmonary capillary wedge ≤15 mm Hg, and pulmonary vascular resistance of >3 Wood units) in the absence of an identified secondary cause (e.g., obstructive sleep apnea, left heart disease), referral to a consultant with expertise in pulmonary arterial hypertension management and advanced vasodilator therapies is reasonable (*Class IIa; Level of Evidence C*).**

Subclinical Myocardial Disease

The prognostic value of newer echocardiographic markers such as tissue Doppler and strain parameters was examined in 129 kidney transplantation candidates free of ischemia on DSE (114). Beyond traditional clinical predictors, abnormal tissue Doppler findings improved the prediction of cardiovascular events and mortality. Among the subgroup of patients who underwent renal transplantation, a significant improvement in left ventricular wall thickness, left ventricular volume, tissue Doppler velocity, and strain was noted after transplantation. In contrast, the same parameters worsened over the same time period in patients who remained on dialysis. This suggests that untoward left ventricular structural changes occur on dialysis even when normal left ventricular function is maintained and ischemia is absent on traditional echocardiographic imaging.

Evidence for Preoperative 12-Lead ECG in Kidney Transplantation Candidates

Based on expert consensus, the ACC/AHA "Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery" (7) suggest that supplemental preoperative cardiac evaluation includes an ECG and that the optimal timing of this test is within 30 days of the planned surgery (7). These recommendations are based on several reports that

have studied the utility of the preoperative 12-lead ECG as a predictor of adverse outcomes in both the general population and in the renal transplantation population.

Although there is a paucity of data on the value of preoperative ECG in the renal transplantation population, data are available on the natural history of baseline ECG abnormalities in patients on dialysis, the relationship between abnormal ECG findings at baseline and high-risk MPS results in patients with diabetes mellitus, and the value of exercise ECG in transplantation patients. Abe et al. (115) evaluated routine 12-lead ECG findings in a consecutive series of 221 patients on long-term hemodialysis compared with patients with CKD not on dialysis and patients without kidney disease. The prevalence of abnormal ECG findings was 65%, 41%, and 5% for these 3 groups, respectively. Significant differences between the patients on dialysis and the normal control subjects included left ventricular hypertrophy (19% versus 0.7%), evidence of ischemia (7.2% versus 0.6%), premature ventricular contractions (6.8% versus 0.3%), non-specific ST-T changes (6% versus 0.3%), atrial fibrillation (5.4% versus 0%), left atrial enlargement (2.7% versus 0%), and old MI (1.4% versus 0%). In addition, 87 hemodialysis patients were followed for a mean of 7.5 years with serial ECGs. With respect to ECG findings, 39% remained normal throughout the monitored period, 31% were considered abnormal but stable, 25% had worsening of their ECG findings, and 5% had apparent improvement.

Rajagopalan et al. (116) studied the correlation of ECG findings with MPS results in 1738 asymptomatic patients with diabetes mellitus who were free of known CAD. The presence of Q waves on ECG was the strongest independent correlate of abnormal high-risk MPS results (OR, 3.92). Sixty-one percent of patients with high-risk MPS results were found to have angiographic evidence of left main CAD, 3-vessel CAD, or 1- or 2-vessel CAD with proximal left anterior descending artery disease.

In summary, it seems reasonable to obtain a baseline ECG in all renal transplantation candidates given the low cost and the predictive value of abnormal ECG findings for overall risk stratification. It is worth noting, however, that the prevalence of abnormal ECG findings is higher among patients with advanced kidney failure than in the general population. The high prevalence of some abnormalities (i.e., left ventricular hypertrophy) may decrease the utility of standard ECG treadmill testing in patients with kidney failure. Serial changes on ECG in hemodialysis patients can be expected over time, and periodic monitoring of ECGs (e.g., annually) while on a transplant waitlist may be appropriate, although there are no data to support a firm recommendation on an optimal time interval between ECG tests.

Recommendations

1. **A preoperative resting 12-lead ECG is recommended for potential kidney transplantation candidates with known coronary heart disease, known peripheral arterial disease, or any cardiovascular symptoms (*Class I; Level of Evidence C*).**

2. **A preoperative resting 12-lead ECG is reasonable in potential kidney transplantation candidates without known cardiovascular disease (*Class IIa; Level of Evidence C*).**

3. **Annual performance of 12-lead ECG after listing for kidney transplantation may be reasonable (*Class IIb; Level of Evidence C*).**

Biomarkers as Tools for Cardiac Evaluation in Kidney Transplantation Candidates

Putative applications of biomarkers such as cardiac troponins (cTns) in kidney transplantation candidates include risk stratification within protocols for initial disease screening, surveillance after listing, and as a reference against which to compare levels if symptoms of an acute coronary syndrome arise. Risk stratification of asymptomatic patients with biomarkers is distinct from the diagnosis of acute coronary syndromes. Although cTns are excreted by the kidney, the source of elevations in the bloodstream even in patients with ESRD appears to be the myocardium. A dynamic rise and fall in cTn with appropriate clinical signs or symptoms suggests an acute coronary syndrome, but persistent elevations in cTn may result from other sources of prognostically important cardiac stress such as volume overload, uncontrolled hypertension, or left ventricular hypertrophy (117). Persistent elevations of cTnT isoform levels correlate with all-cause and cardiac mortality in asymptomatic patients on dialysis. A meta-analysis of 28 studies found that cTnT >0.10 ng/mL in patients with ESRD predicts more than twice the mortality risk of patients with ESRD with lower cTnT levels (118). The prognostic value of cTnI isoform levels has been less consistent, perhaps because of a lack of assay standardization and/or use of a broader range of threshold values in studies to date. Based on such data, the Food and Drug Administration approved the use of cTnT levels for mortality prognostication in patients with chronic renal failure in 2004. However, routine use has not yet been supported by the NKF/KDOQI guidelines (12).

Associations of cTnT with mortality before and after kidney transplantation (Table 6) have also been studied. Concomitant elevations of cTnT >0.06 ng/mL and ischemia-modified albumin >95 kU/L measured in a cohort of 144 potential transplantation candidates were associated with 7 times the odds of mortality after an average of 2.3 years, with adjustment for factors including severe coronary disease and results from positive DSE (119). Hickson et al. (61) studied 644 potential transplantation candidates and found that each increment in cTnT level (<0.01, 0.01–0.03, 0.04–0.09, and ≥0.10 ng/mL) was associated with 64% higher adjusted relative risk of transplantation-censored mortality. cTnT measured before transplantation also predicted post-transplantation cardiac events and death (121). Over a mean follow-up of 28 months, each increment in cTnT was associated with 58% higher relative risk of MACEs after transplantation. Another study reported that mortality at 3.8 years of follow-up was nearly 3 times higher in patients with cTnT ≥0.03 versus <0.01 ng/mL (120). Although this finding is intriguing, it remains uncertain how data from biomarker assessment should be

Table 6.   Summary of Recent Studies of Associations of Cardiac Biomarkers With Clinical Outcomes in Kidney Transplantation Candidates and Recipients

Authors, Year	Design and Data Source	Participants and Selection	Study Measures and Distributions	Clinical Outcomes	Associations/Effect Sizes
Sharma et al. (119), 2006	Prospective cohort Medical records and phone calls for follow-up	114 evaluated for KT candidacy at 1 center in the United Kingdom (2002–2003) Free of unstable angina or severe aortic stenosis	Single cTnT level; distribution ≥0.06 ng/mL, 45% Single IMA level; distribution >95 KU/L, 40% cTnT and IMA were both elevated in 33%	Death over observation (multivariate modeling by logistic regression and thus not time dependent) After mean 2.3 y of follow-up, 15.8% died (55.6% of deaths were cardiovascular)	Combined cTnT and IMA elevations significantly associated with 7 times the odds of death (aOR, 7.12; 95% CI, 4.14 to 10.12; p=0.005) compared with normal levels of both markers after adjustment, including severe CAD and positive DSE cTnT and IMA individually associated with mortality in bivariate but not multivariate models
Connolly et al. (120), 2008	Prospective cohort Registry mortality data and phone calls for follow-up	Convenience sample of 379 with functioning KT at 2 Irish hospitals >3 mo after KT and well at enrollment (2000–2002)	Single cTnT level Distribution: <0.01 ng/mL, 91.7%; 0.02 ng/mL, 2.7%; ≥0.03 ng/mL, 5.6%	Death over observation After median 3.8 y of follow-up, 16.4% died (39% of deaths were cardiovascular)	cTnT ≥0.03 versus <0.01 significantly associated with 2.7 times the risk of death (aHR, 2.70; 95% CI, 1.20 to 6.06; p=0.02) after adjustment, including eGFR and C-reactive protein levels
Hickson et al. (61), 2008	Retrospective cohort Clinical records of 1 center	644 evaluated for KT candidacy at 1 Midwestern center (2004–2006)	Single cTnT level analyzed, most recent from initial evaluation or annual follow-up if waitlisted Distribution across 4 levels: <0.01 ng/mL, 39%; 0.01–0.03 ng/mL, 29%; 0.04–0.09 ng/mL, 20%; ≥0.10 ng/mL, 13%	Death, censored at KT or December 2007 After median 6.2 mo of follow-up, 5.4% died (33% of known causes were cardiovascular), and 58.5% received KT	Each increment in cTnT level (as defined) significantly associated with 64% increase in death risk (aHR, 1.64; 95% CI, 1.07 to 2.51; p=0.02)
Hickson et al. (121), 2009	Retrospective cohort Clinical records of 1 center	603 evaluated for KT candidacy at 1 Midwestern center (2004–2007)	Single cTnT level analyzed, most recent from initial evaluation or annual follow-up if waitlisted Distribution across 4 levels:<0.01 ng/mL, 43.8%; 0.01–0.03 ng/mL, 26.5%; 0.04–0.09 ng/mL, 19.1%; ≥0.10 ng/mL, 10.6%	All-cause death or MACEs (AMI, CABG or PCI) after KT, censored at graft loss After a mean 28 mo of follow-up, 5.6% reached the endpoint (including death in 4%)	Each increment in cTnT level (as defined) significantly associated with 58% increase in the composite end point (aHR, 1.58; 95% CI, 1.13 to 2.23; p=0.008)

aHR indicates adjusted hazards ratio; AMI, acute myocardial infarction; aOR, adjusted odds ratio; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; cTnT, cardiac troponin T; DSE, dobutamine stress echocardiography; eGFR, estimated glomerular filtration rate; IMA, ischemia-modified albumin; KT, kidney transplantation; MACEs, major adverse cardiovascular events; and PCI, percutaneous coronary intervention.

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used to treat patients and/or to select recipients for organ transplantation.

Recommendation

1. **Measurement of cTnT level at the time of evaluation for kidney transplantation may be considered an additional prognostic marker** *(Class IIb; Level of Evidence B).*

Evidence for Cardiac Computed Tomography in Kidney Transplantation Candidates

Noncontrast computed tomography (CT) for the detection and quantification of coronary artery calcification has been shown to improve cardiovascular risk prediction compared with the FHS score in asymptomatic patients without kidney disease (122). Raggi et al. (123) found evidence of elevated CT calcium scores in >83% of a sample of 205 adult maintenance hemodialysis patients, and other studies have reported significantly greater intracoronary calcification in patients with ESRD compared with patients without ESRD, with the greatest disparities in young cohorts (124–126). Although 1 study reported CT calcium scores to be an independent predictor of death in patients on long-term hemodialysis (127), the role of CT calcium scoring as a prognostic marker in the ESRD population is uncertain (128). Other studies report poor correlation between coronary artery calcium scores and the likelihood of angiographic CAD in patients with advanced kidney disease (129–131), a finding that may reflect the high burden of medial vascular calcification in ESRD compared with the intimal calcification seen

in the non-ESRD population (132). Cardiac CT angiography (64–320 slice and dual source) is a highly sensitive tool for evaluating symptomatic patients with low to intermediate pretest probability of obstructive CAD (133,134). However, this modality has not been studied in patients with significant kidney disease, and its accuracy may be limited in this population because of a high burden of calcified coronary atherosclerosis. Furthermore, safety may be limited in patients with kidney disease by the attendant exposure to iodinated contrast. The "ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 Appropriate Use Criteria for Cardiac Computed Tomography" consider CT angiography a potential option among patients undergoing heart surgery for noncoronary indications (e.g., valve replacement surgery or atrial septal defect closure) when the pretest CAD risk is either intermediate (appropriate) or low (uncertain) but deem that there are no appropriate indications for coronary CT angiography as part of the preoperative evaluation for noncardiac surgery (135). The usefulness of noncontrast CT calcium scoring and cardiac CT angiography is uncertain for the assessment of pretransplantation cardiovascular risk.

Recommendation

1. **The usefulness of noncontrast CT calcium scoring and cardiac CT angiography is uncertain for the assessment of pretransplantation cardiovascular risk (*Class IIb; Level of Evidence B*).**

Evidence on Prophylactic Coronary Revascularization to Reduce Perioperative Cardiac Complications

There is a significant gap in the literature in terms of the outcomes of prophylactic coronary revascularization in the renal transplantation candidate population. Only 1 small randomized trial and a few observational studies have focused on this patient population. In 1992, Manske et al. (136) randomly assigned 31 transplantation candidates with insulin-dependent diabetes mellitus with CAD (>75% stenosis) to revascularization or medical therapy with a calcium channel blocker and aspirin. Ultimately, 10 of 13 medically managed and 2 of 13 revascularized patients reached the endpoint comprising unstable angina, MI, or cardiac death. Contemporary relevance of these findings is limited by the small sample size, high event rate among the medically managed group, and advances that have occurred in "standard" medical management of CAD, including the use of angiotensin-converting enzyme inhibitors and statins.

Several observational studies have reported outcomes after coronary revascularization in selected cohorts of potential kidney transplantation candidates. In a study of 300 patients who underwent multimodality testing as part of the candidate evaluation at 1 center, crude survival was not different in patients who underwent revascularization compared with those who underwent angiography without revascularization or no angiography, although there was a suggestion of a benefit with revascularization in the subset of 34 patients found to have obstructive CAD (15% versus 52% mortality)

(28). In the description of 3698 patients evaluated for kidney transplantation at a single center by Hage et al. (60), MPS was performed in 60%, and 7% of the patients subsequently underwent coronary angiography. The presence and severity of CAD on angiography were not predictive of survival (Table 4), and coronary revascularization was associated with survival only in patients with 3-vessel CAD.

A recent study described the experience at 1 center under a protocol in which all potential kidney transplantation candidates were evaluated by angiography for any of the following criteria: age >50 years, diabetes mellitus, any cardiac symptoms, or ECG evidence of ischemia or prior infarction (137). Among the 657 patients who underwent angiography in 2006 to 2009, significant CAD (defined as >75% stenosis of 1 or more coronary arteries, >50% left main stem lesion, or an equivocal lesion with flow limitation) was found in 28%, of whom 55% were free of symptoms and prior CAD history. Those with significant CAD who underwent revascularization followed by transplantation (n=51; 1-year survival, 100%; 3-year survival, 97%) or by continued waiting (n=177; 1-year survival, 95%; 3-year survival, 81%) had survival superior to that of the 16 patients who declined revascularization (1-year survival, 75%; 3-year survival, 37%). Although this study demonstrates excellent survival in transplant recipients who received preemptive revascularization, the lack of a comparator group of similar patients who did not undergo angiography before transplantation prevents conclusions on the impact of the authors' approach compared with a less aggressive strategy. Further data on the potential benefits of prophylactic revascularization are based on extrapolation of a prophylactic revascularization strategy in other high-risk groups such as patients undergoing vascular surgery and patients with diabetes mellitus as discussed below.

Coronary Artery Revascularization Prophylaxis (CARP) Trial

The potential benefits of coronary revascularization before noncardiac surgery were evaluated in the CARP (Coronary Artery Revascularization Prophylaxis) trial. Patients awaiting vascular surgery (n=510) with concomitant CAD on coronary angiography (excluding those with left main disease or severely depressed LVEF [<20%]) were randomized to CABG (59%) or PCI (41%) versus optimal medical therapy before vascular surgery (10). At 2.7 years after randomization, mortality in the coronary revascularization group was not significantly different (22%) from that in the no-revascularization group (23%). Within 30 days after the vascular operation, a postoperative MI, defined by elevated cTn levels, occurred in 12% of the revascularization group and 14% of the no-revascularization group (p=0.37). The authors concluded that preoperative coronary revascularization is not indicated in patients with stable CAD who are on optimal medical therapy. Although patients with unprotected left main CAD were excluded from randomization, retrospective analysis of this subset (who made up 4.6% of the 1,048 patients assessed by preoperative coronary angiography) suggested improved survival with versus without revascularization of left main disease CAD before vascular surgery (138).

Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography V (DECREASE-V)

The potential benefits of screening and coronary revascularization before noncardiac surgery have also been evaluated in the DECREASE-V (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography V) pilot study (9). Among 1,880 patients scheduled for major elective vascular surgery, those (n=430) with 3 risk markers (age >70 years, angina pectoris, MI, heart failure, stroke, diabetes mellitus, renal failure) underwent stress imaging with DSE or MPS. Patients (n=101) with extensive stress-induced ischemia were randomly assigned to additional coronary revascularization or medical therapy only. Prophylactic coronary revascularization in vascular surgery patients with extensive ischemia was not associated with an improved immediate postoperative outcome (9) or with survival over 2.8 years (11).

Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)

COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) was a randomized trial of 2287 people in the United States and Canada that evaluated whether PCI plus optimal medical therapy (beta-blockers, calcium channel blockers, and nitrates) reduces the risk of all-cause mortality or nonfatal MI in patients with stable CAD (>70% stenosis in at least 1 proximal epicardial coronary artery and objective evidence of myocardial ischemia) compared with optimal medical therapy alone (29). CKD was not an exclusion for enrollment. The primary analysis revealed no differences among the PCI group and the medical therapy alone group in the composite endpoint (death, MI, or stroke) or in MI alone over a median 4.6 years of follow-up. Secondary analysis of 320 participants with CKD defined as eGFR <60 mL/min/1.73 m^2 demonstrated that, although CKD was associated with an increased risk of death or nonfatal MI over 36 months (adjusted HR, 1.48; 95% CI, 1.15 to 1.90), the incidence of death or MI was similar in patients with CKD treated with PCI and medical therapy compared with those treated with medical therapy alone (30). Additional subgroup analyses also did not support benefit of PCI compared with optimal medical management on the primary endpoint in subgroups of individuals with diabetes mellitus, patients with multivessel CAD or those with prior MI (29). From the results of the COURAGE trial, PCI is indicated for mitigating medically refractory symptoms but not for preventing MI or cardiac death in stable patients.

The role of preoperative PCI in reducing untoward perioperative cardiac complications appears limited to patients with unstable active CAD who would be appropriate for emergent or urgent revascularization under the published ACC/AHA/SCAI PCI guidelines (139,140,141a). Patients with ST-segment elevation MI or those with unstable angina and non–ST-segment elevation MI benefit from early invasive management, as outlined in the "2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction" (140) and the "2011 ACC/

AHA/SCAI Guideline for Percutaneous Coronary Intervention" (141a). PCI has been shown to reduce the incidence of angina, not to improve survival in stable patients; PCI may increase the short-term risk of MI and does not lower the long-term risk of MI.

Patients with asymptomatic ischemia or stable angina (stable ischemic heart disease) do not appear to benefit from prophylactic preoperative coronary revascularization unless cardiac catheterization reveals high-risk anatomy in which revascularization would result in a survival advantage. The anatomic subsets and revascularization strategies that confer a survival advantage are discussed in detail in the "2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery" and "2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention" developed in conjunction with the Stable Ischemic Heart Disease and the Percutaneous Coronary Intervention Guideline Writing Committees (31a,141a). These recommendations are summarized in Table 7.

High-risk unprotected left main CAD in a noncardiac surgical candidate is a special case. The issues involved in case selection and risk stratification for revascularization of left main CAD are discussed in detail in the "2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery" (31a). The utility of a PCI left main revascularization strategy in the context of impending transplantation is unknown. In terms of durability of result and the need for prolonged dual antiplatelet therapy, CABG remains the revascularization procedure of choice, if appropriate, for prospective transplantation patients with left main or left main–equivalent CAD.

In conclusion, in patients with stable CAD, the indications for CABG and PCI in the preoperative setting should be identical to those developed by the harmonized ACCF/AHA CABG and ACCF/AHA/SCAI PCI revascularization guidelines (31a,141a). There is no evidence to support prophylactic preoperative percutaneous revascularization in patients with asymptomatic ischemia or stable angina.

PCI Versus CABG in Patients With ESRD

The best method of coronary revascularization in patients with ESRD is controversial. Szczech et al. (142) examined New York State Health Department data for patients who received CABG surgery or PCI in 1993 to 1995 to study survival after revascularization procedures in patients with CKD (serum creatinine >2.5 mg/dL) or ESRD. Among patients with ESRD, CABG was associated with a 61% relative mortality reduction compared with PCI (RR, 0.39; 95% CI, 0.22 to 0.67) after adjustment for severity of CAD left ventricular dysfunction, and other comorbid conditions. A survival benefit of CABG over PCI was seen in all CAD anatomic subgroups. An analysis of the Duke cardiac revascularization database found a graded relationship between renal insufficiency and increased mortality compared with patients with normal renal function (143). Among patients with estimated creatinine clearance <15 mL/min/1.73 m^2 or on dialysis, CABG was associated with a survival benefit compared with medical management (adjusted HR, 0.45;

Table 7. Revascularization to Improve Survival Compared With Medical Therapy

Anatomic Setting	Class of Recommendation	Level of Evidence
UPLM or complex CAD		
CABG and PCI	I: Heart team approach recommended	C
CABG and PCI	IIa: Calculation of the STS and SYNTAX scores	B
UPLM*†		
CABG	I	B
PCI	IIa: For SIHD when both of the following are present	B
	Anatomic conditions associated with a low risk of PCI procedural complications and high likelihood of good long-term outcome (e.g., a low SYNTAX score of ≤22, ostial or trunk left main CAD)	
	Clinical characteristics that predict a significantly increased risk of adverse surgical outcomes (e.g., STS-predicted operative mortality ≥5%)	
	IIa: For UA/NSTEMI if not CABG candidate	B
	IIa: For STEMI when distal coronary flow is less than TIMI 3 and PCI can be performed more rapidly and safely than CABG	C
	IIb: For SIHD when both of the following are present	B
	Anatomic conditions associated with a low to intermediate risk of PCI procedural complications and intermediate to high likelihood of good long-term outcome (e.g., low to intermediate SYNTAX score of <33, bifurcation left main CAD)	
	Clinical characteristics that predict an increased risk of adverse surgical outcomes (e.g., moderate to severe COPD, disability from prior stroke, or prior cardiac surgery; STS-predicted operative mortality >2%)	
	III, harm: For SIHD in patients (versus performing CABG) with unfavorable anatomy for PCI and who are good candidates for CABG	B
3-Vessel disease with or without proximal LAD disease*†		
CABG	I	B
	IIa: It is reasonable to choose CABG over PCI in patients with complex 3-vessel CAD (e.g., SYNTAX >22) who are good candidates for CABG	B
PCI	IIb: Of uncertain benefit	C
2-Vessel disease with proximal LAD disease*†		
CABG	I	B
PCI	IIb: Of uncertain benefit	C
2-Vessel disease without proximal LAD disease*†		
CABG	IIa: With extensive ischemia	B
	IIb: Of uncertain benefit without extensive ischemia	C
PCI	IIb: Of uncertain benefit	C
Single-vessel proximal LAD disease†		
CABG	IIa: With LIMA for long-term benefit	B
PCI	IIb: Of uncertain benefit	C
Single-vessel disease without proximal LAD involvement†		
CABG	III, harm	B
PCI	III, harm	B
LV dysfunction		
CABG	IIa: EF 35%–50%	B
CABG	IIb: EF <35% without significant left main CAD	B
PCI	Insufficient data	
Sudden cardiac death survivors with presumed ischemia-mediated VT caused by ischemia		
CABG	I	B
PCI	I	C

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; LAD, left anterior descending; LIMA, left internal mammary artery; LV, left ventricular; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SIHD, stable ischemic heart disease; STEMI, ST-elevation myocardial infarction; STS, Society of Thoracic Surgeons; SYNTAX, Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina; UPLM, unprotected left main disease; and VT, ventricular tachycardia.

*In patients with multivessel disease who also have diabetes mellitus, it is reasonable to choose CABG (with LIMA) over PCI (Class IIa, Level of Evidence B).

†Revascularization (CABG or PCI) might be reasonable to improve survival in patients with chronic kidney disease (creatine clearance <60 mL/min), with CABG associated with a greater benefit than PCI among patients with more advanced renal dysfunction (Class IIb, Level of Evidence B).

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95% CI, 0.27 to 0.74), whereas PCI was not. Other observational studies have demonstrated improved survival with CABG (compared with medical therapy) in patients with CKD and multivessel CAD (144).

A retrospective study of dialysis patients captured in the USRDS before the widespread use of drug-eluting stents (DES) suggested a slight long-term benefit of CABG over PCI. However, these data are limited by the retrospective design and the inherent risk of procedure-related referral bias based on coronary anatomy and patient characteristics (145). An updated analysis of USRDS data from 2003 to 2005 by the same authors, including patients treated with DES, found superior 12-month unadjusted postprocedural survival in patients on dialysis who received DES (69.7%) compared with CABG (66.6%) or non-DES PCI (63.6%) (146). However, unadjusted 36-month survival favored CABG over DES (42.0% versus 38.1%), especially among patients who received an internal mammary artery bypass conduit. In multivariable regression, there was no significant difference in overall adjusted mortality with DES versus bypass, although non-DES PCI was associated with a higher adjusted risk compared with surgery. These data also demonstrate the poor prognosis faced by patients on hemodialysis who undergo CABG compared with the 5-year survival after CABG in the general population of 85% to 90% (31). Other studies have reported increased frequencies of surgical complications, including mediastinitis, stroke, and prolonged mechanical ventilation, after CABG in patients with ESRD compared with patients without ESRD (147).

PCI Versus CABG in Patients With Diabetes Mellitus

Large randomized studies of revascularization in renal transplantation candidates with diabetes mellitus are lacking, but some insight can be gained from the extensive study of the management of CAD in patients with diabetes mellitus without advanced renal failure. Several trials have addressed the question of the relative benefit of CABG versus PCI in patients with diabetes mellitus with CAD.

A pooled analysis of coronary revascularization trials in patients with diabetes mellitus published in 2005 (148) included 6 randomized clinical trials comparing CABG with PCI among 950 patients with diabetes mellitus. A mortality benefit of CABG over balloon-only PCI at 3 to 5 years was consistently noted. Use of stents narrowed the mortality advantage of CABG, but higher rates of repeat revascularization were seen with stent PCI compared with CABG, even with DES. Another recent meta-analysis summarized data comparing CABG and PCI among 7,812 patients from 10 clinical trials demonstrated similar findings (149).

Registry data also support a survival advantage of CABG over PCI in patients with diabetes mellitus with severe multivessel CAD. A report from the Northern New England Cardiovascular Study Group identified 10,198 CABG patients and 4,293 PCI patients with multivessel CAD in a BARI (Bypass Angioplasty Revascularization Investigation)–like cohort (150). Adjusted long-term survival for patients with 3-vessel CAD was better after CABG than PCI (HR,

0.60; p<0.01) but not for patients with 2-vessel CAD (HR, 0.98; p=0.77). Survival advantage with CABG for patients with 3-vessel disease was present in all subgroups, including women, the elderly, and individuals with diabetes mellitus.

Recommendations for Referral to a Cardiologist

Although a relationship of the organizational structure of the consulting cardiology service with clinical outcomes has not been formally evaluated, it is reasonable that each program attempt to identify a primary cardiology consultant for questions related to potential transplantation candidates.

Recommendations

1. **Referral criteria: Kidney transplantation candidates who have an LVEF less than 50%, evidence of ischemic left ventricular dilation, exercise-induced hypotension, angina, or demonstrable ischemia in the distribution of multiple coronary arteries should be referred to a cardiologist for evaluation and long-term management according to ACC/AHA guidelines for the general population (*Class I; Level of Evidence B*).**
2. **Coordination of care: It may be reasonable for each program to identify a primary cardiology consultant for questions related to potential kidney transplantation candidates (*Class IIb; Level of Evidence C*).**

Among the issues that should be managed by a cardiologist experienced in pretransplant evaluations is minimization of the risk of contrast-induced acute injury, if coronary angiography or PCI are indicated. The risk of contrast-induced acute kidney injury is inversely related to a patient's eGFR (150a) and is of particular concern in patients with stages 4 and 5 CKD because of the potential for accelerating the need for dialysis. Other clinical and periprocedural risk factors for contrast-induced nephropathy include diabetes mellitus, intravascular volume depletion, hemodynamic instability, concomitant use of nephrotoxic drugs, and high contrast loads (150a,150b). Recent small, retrospective studies have suggested that minimization of the risk of contrast-induced acute kidney injury from coronary angiography among kidney transplantation candidates may be possible with careful patient selection and careful management before, during, and after the procedure (150c,150d). However, the risk contrast-induced acute kidney injury after pretransplant coronary angiography has not been evaluated in prospective studies with large numbers of patients and control groups.

Recommendations for Coronary Revascularization and Related Care Before Kidney Transplantation

Evidence-based indications for coronary revascularization in the general population are based on improving survival or symptoms. The "2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery" (31a) (Table 7) recommends

that decisions on coronary revascularization be based on a knowledge of symptoms, ischemic burden, coronary anatomy, complexity of CAD and cardiac function, and the relative risks and benefits of guideline-directed medical therapy, CABG, and PCI. These criteria define patients in whom revascularization is indicated for either symptom relief or survival advantage, regardless of the need for noncardiac surgery.

When PCI is considered for any patient who is a candidate for transplantation, the durability of the result should be a primary consideration, and avoiding repeat procedures involving radiographic contrast administration is desirable. In transplantation candidates with diabetes mellitus in particular, it appears that elective revascularization with CABG offers superior outcomes compared with PCI. CABG is the preferred method of revascularization in patients with diabetes mellitus with left main, 3-vessel CAD, and 2-vessel CAD involving the proximal left anterior descending artery and should be strongly considered in terms of durability and the reduced incidence of recurrent revascularization procedures in all transplantation candidates needing coronary revascularization.

Recommendations

1. **Coronary revascularization before transplantation surgery should be considered in patients who meet the criteria outlined in the "2011 ACCF/AHA Guidelines for Coronary Artery Bypass Graft Surgery"** (*Class I; Level of Evidence B*). **It is recognized that in some asymptomatic transplantation candidates, the risk of coronary revascularization may outweigh the risk of transplantation and these risks must be weighed by the multidisciplinary transplantation team on a case-by-case basis until further studies are performed in this population.**
2. **CABG is probably recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes mellitus** (*Class IIa; Level of Evidence B*).
3. **CABG to improve survival and/or to relieve angina despite optimal medical therapy may be reasonable for patients with ESRD with significant (>50%) left main stenosis or significant (≥70%) stenoses in 3 major vessels or in the proximal left anterior descending artery plus 1 other major vessel, regardless of left ventricular systolic function** (*Class IIb; Level of Evidence B*).
4. **It is not recommended that routine prophylactic coronary revascularization be performed in patients with stable CAD, absent symptomatic or survival indications, before transplantation surgery** (*Class III; Level of Evidence B*).

Interval Between PCI and Subsequent Surgery

The need for noncardiac surgery in patients who have undergone recent PCI is a common dilemma. After balloon angioplasty, delaying noncardiac surgery for very long increases the chance that restenosis at the angioplasty site will have occurred and theoretically increases the chances of perioperative ischemia or MI. However, performing the surgical procedure too soon after the PCI procedure is also hazardous. Arterial recoil and/or acute thrombosis at the site of balloon angioplasty are most likely to occur within hours to days after balloon coronary angioplasty. Delaying surgery for at least 4 to 6 weeks after balloon angioplasty to allow healing of the vessel injury at the balloon treatment site is supported by observational data (151). Daily antiplatelet therapy should be continued perioperatively. The risk of stopping the aspirin must be weighed against the benefit of lowering the risk of bleeding complications from the planned surgery.

If a coronary stent was used in the revascularization procedure, as in the majority of percutaneous revascularization procedures, further delay of noncardiac surgery may be beneficial. Bare-metal stent (BMS) thrombosis is most common in the first 2 weeks after stent placement and is exceedingly rare (<0.1% of most case series) >4 weeks after stent placement (152,153). Given that stent thrombosis will often result in Q-wave MI or death when it occurs and given that the risk of BMS thrombosis diminishes after endothelialization of the stent has occurred, it appears reasonable to delay elective noncardiac surgery for 3 months, to allow at least partial endothelialization of the BMS, but not for >6 months, when restenosis may occur.

Timing surgery after DES placement presents a greater challenge. There appears to be a compelling need for prolonged dual antiplatelet medication to prevent stent thrombosis, usually aspirin 81 to 162 mg daily and a thienopyridine (clopidogrel 75 mg daily, ticlopidine 250 mg twice daily, or prasugrel 10 mg daily).

Two retrospective studies from the Mayo Clinic analyzed the risk of cardiac complications after noncardiac surgery in the 2 years after BMS and DES implantation (154,155). There was a temporal relationship between the frequency of MACEs (death, MI, stent thrombosis, repeat revascularization) and the time since BMS implantation (<30 days, 10.5%; 30 to 90 days, 3.8%; and >90 days, 2.8%) (154). The authors concluded that noncardiac surgery should be delayed for 90 days after BMS placement. In a companion study of 520 patients undergoing noncardiac surgery after DES implantation, the authors found that the rate of MACEs was lowest beyond 1 year after DES implantation (155).

A retrospective single-center observational study from The Netherlands identified 550 patients (376 DES, 174 BMS) who underwent noncardiac surgery after coronary stent placement (156). The authors found an inverse relation between the interval from PCI to noncardiac surgery and perioperative MACEs. In the PCI BMS group, the rate of MACEs during the intervals of <30 days, 30 days to 3 months, and >3 months was 50%, 14%, and 4%, respectively (overall p<0.001). In the PCI DES group, the rate of MACEs changed significantly with the interval after PCI over a longer time frame: 35%, 13%, 15%, 6%, and 9% for patients undergoing noncardiac surgery within <30 days, 30 days to 3 months, 3 to 6 months, 6 to 12 months, and >12 months, respectively (overall p<0.001).

An additional retrospective observational study from the Cleveland Clinic addressed the risk of surgery, including cardiac surgery, after DES placement (157). The primary

outcome was Academic Research Consortium definite and probable stent thrombosis (158). Among 606 surgeries in 481 patients, the mean interval from stent placement to noncardiac surgery was 1.07 ± 0.89 years. Stent thrombosis occurred after 2.0% of surgeries and a combined endpoint of death, MI, or stent thrombosis after 9% of surgeries. The risk of either endpoint declined significantly in the first 1 to 6 months after stent placement; however, the risk did not disappear even after 12 months. Independent correlates of the combined endpoint were emergency surgery, prior MI, preoperative heparin, and stent length. Antiplatelet therapy was not an independent correlate of risk. The authors concluded that there is a significant risk of stent thrombosis and MACEs within 30 days of DES placement, with 1% to 2% risk extending to 2 to 3 years.

Antiplatelet Therapy in the Context of Recent PCI

In general, treatment with dual antiplatelet agents is recommended for a minimum of 1 month after BMS implantation and for ≥12 months after DES implantation. Premature discontinuation of antiplatelet agents is one of the strongest predictors of subacute stent thrombosis. Thus, gauging the risk of stent thrombosis in patients who require noncardiac surgery and are taking dual antiplatelet agents after PCI is important.

The optimal duration of clopidogrel therapy beyond 1 year has not been established and should depend on the physician's judgment of the risk-to-benefit ratio for the individual patient. Expert opinion suggests that continuation of thienopyridine (clopidogrel) therapy beyond 1 year may be considered in higher-risk patients undergoing DES placement.

The 2007 AHA/ACC/SCAI/ACS/ADA Science Advisory on the "Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents" concluded that premature discontinuation of dual antiplatelet therapy markedly increases the risk of catastrophic stent thrombosis and death and/or MI (159) (Table 8). Consideration should be given to continuing dual antiplatelet therapy in the perioperative period for any patient needing noncardiac surgery that falls within the time frame of recommended therapy, particularly those who have received DES. In addition, consideration should be given to continuing dual antiplatelet therapy perioperatively beyond the recommended time frame in any patient thought to be at high risk for the consequences of stent thrombosis, such as patients in whom previous stent thrombosis has occurred and in those after left main stenting, multivessel stenting, or stent placement in the only remaining coronary artery or graft conduit. Even after thienopyridines have been discontinued, serious consideration should be given to continuation of aspirin therapy perioperatively in any patient with previous placement of a DES. The risk of stopping antiplatelet therapy should be weighed against the benefit of lowering the risk of bleeding complications from the planned surgery. If thienopyridines must be discontinued before major surgery, aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible. There is no evidence that warfarin, antithrombotics, or glycoprotein IIb/IIIa agents reduce the risk of

Table 8.   Recommendations from the 2007 AHA/ACC/SCAI/ ACS/ADA Science Advisory on the "Prevention of Premature Discontinuation of Dual Antiplatelet Therapy in Patients With Coronary Artery Stents" (159)

1. Before implantation of a stent, the physician should discuss the need for dual antiplatelet therapy. In patients not expected to comply with 12 mo of thienopyridine therapy, whether for economic or other reasons, strong consideration should be given to avoiding a DES.

2. In patients who are undergoing preparation for PCI and are likely to require invasive or surgical procedures within the next 12 mo, consideration should be given to implantation of a BMS or performance of balloon angioplasty with provisional stent implantation instead of the routine use of a DES.

3. A greater effort by healthcare professionals must be made before patient discharge to ensure patients are properly and thoroughly educated about the reasons they are prescribed thienopyridines and the significant risks associated with prematurely discontinuing such therapy.

4. Patients should be specifically instructed before hospital discharge to contact their treating cardiologist before stopping any antiplatelet therapy, even if instructed to stop such therapy by another healthcare provider.

5. Healthcare providers who perform invasive or surgical procedures and are concerned about periprocedural and postprocedural bleeding must be made aware of the potentially catastrophic risks of premature discontinuation of thienopyridine therapy. Such professionals who perform these procedures should contact the patient's cardiologist if issues regarding the patient's antiplatelet therapy are unclear to discuss optimal patient management strategy.

6. Elective procedures for which there is significant risk of perioperative or postoperative bleeding should be deferred until patients have completed an appropriate course of thienopyridine therapy (12 mo after DES implantation if they are not at high risk of bleeding and a minimum of 1 mo for BMS implantation).

7. For patients treated with DES who are to undergo subsequent procedures that mandate discontinuation of thienopyridine therapy, aspirin should be continued if at all possible and the thienopyridine restarted as soon as possible after the procedure because of concerns about late stent thrombosis.

BMS indicates bare-metal stent; DES, drug-eluting stent; and PCI, percutaneous coronary intervention.

stent thrombosis after discontinuation of oral antiplatelet agents (159).

A recent publication studied the safety of short-term discontinuation of antiplatelet therapy in patients with DES (160). A total of 161 cases of late (30 days to 1 year) or very late (>1 year) stent thromboses were identified from the literature; 19 cases occurred in patients who were taking dual antiplatelet agents (aspirin and thienopyridine). Median time to stent thrombosis was 7 days in patients who stopped both agents or had previously stopped the thienopyridine and subsequently stopped aspirin. Median time to stent thrombosis was 122 days in patients who stopped thienopyridine but were maintained on aspirin. The authors concluded that if aspirin therapy is maintained, short-term discontinuation of thienopyridine may be relatively safe. The authors present a potential management strategy for patients who must undergo noncardiac surgery but also have an elevated bleeding risk. According to this strategy, elective noncardiac surgery should ideally be delayed until 1 year after DES placement. If a procedure cannot be delayed, it is optimal to continue both

antiplatelet agents throughout the perioperative period if at all possible. If continuation of both antiplatelet agents is not possible, the authors suggest holding the thienopyridine for 5 days, performing the procedure, and then restarting the thienopyridine on day 6 with maintenance of low-dose aspirin throughout the perioperative period. If the patient is deemed to be at such a high risk of bleeding that both aspirin and thienopyridine need to be stopped, the antiplatelet agents should be stopped no sooner than 5 days before the surgery and should be restarted as soon as possible after the surgery, certainly within 5 days of the procedure. The latter strategy should be used only in cases when bleeding risk outweighs the risk of stent thrombosis.

Recommendations for PCI and Duration of Thienopyridine Therapy Before Kidney Transplantation

The following recommendations regarding PCI, type of stent, and timing of surgery are consistent with the "ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery" (7). These recommendations assume that the transplantation surgeon will not perform an elective kidney transplantation while the patient is on dual antiplatelet therapy (aspirin plus thienopyridine), in which case the decision making is similar to that for any other noncardiac surgery that has excessive bleeding risk (see recommendation below for details). Because some centers consider the bleeding risk of kidney transplantation to be low and thus will operate while patients continue taking dual antiplatelet therapy, it seems reasonable (until further data become available) for these centers to have the optimal stent selection determined by the cardiologist in accordance with standard PCI guidelines (140,141b). In these cases, timing transplantation surgery can then be determined less by the presence of a stent/dual antiplatelet therapy and more by the clinical context of stent placement (i.e., after MI) and other issues typically addressed by the transplantation team.

Recommendations

1. **In patients in whom coronary revascularization with PCI is appropriate for mitigation of cardiac symptoms and who need transplantation surgery in the subsequent 12 months, a strategy of balloon angioplasty or BMS placement followed by 4 to 12 weeks of dual antiplatelet therapy is probably indicated (*Class IIa; Level of Evidence B*).**

2. **In patients who have received DES and who must undergo urgent surgical procedures that mandate the discontinuation of thienopyridine therapy, it is reasonable to continue aspirin if at all possible and to restart the thienopyridine as soon as possible (*Class IIa; Level of Evidence C*).**

3. **In cases when urgent surgery must be performed in patients taking aspirin and thienopyridines after coronary stent placement and who are at high risk for bleeding complications, a strategy of stopping the thienopyridine 5 days before surgery and continuing aspirin perioperatively may be reasonable. The thien-**

opyridine should be restarted as soon as possible postoperatively (*Class IIb; Level of Evidence B*).

4. **It may be reasonable to perform kidney transplantation surgery without interruption of clopidogrel therapy if the risk of bleeding is low (*Class IIb; Level of Evidence C*).**

5. **Transplantation surgery within 3 months of BMS placement and within 12 months of DES placement is not recommended, particularly if the anticipated time of poststent dual antiplatelet therapy will be shortened (*Class III; Level of Evidence B*).**

6. **Transplantation surgery is not recommended within 4 weeks of coronary revascularization with balloon angioplasty (*Class III; Level of Evidence B*).**

Preoperative Cardiovascular Risk Factor Modification in Renal Transplantation Candidates

Blood Pressure Management in Kidney Transplantation Candidates

The optimal management of blood pressure for dialysis patients remains an enigma. The NKF/KDOQI "Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease" recommend predialysis and postdialysis blood pressure goals of <140/90 and <130/80 mm Hg, respectively, in large part on the basis of clinical trials in patients with CKD and 1 prospective observational trial in a dialysis population in whom blood pressure <140/90 mm Hg minimized the occurrence of cardiovascular complications and death (161).

Diagnosing and treating hypertension in patients on hemodialysis remains controversial despite the NKF/KDOQI and Kidney Disease: Improving Global Outcomes (KDIGO) opinion-based guidelines (161,162). There is no evidence from randomized controlled trials that lowering blood pressure in dialysis patients reduces subsequent MACEs. Some cohort studies suggest that when the NKF/KDOQI targets are achieved, patients on hemodialysis have more frequent episodes of intradialytic hypotension (163). In addition, there is only a weak correlation between predialysis and postdialysis blood pressure measurements and interdialytic 44-hour ambulatory blood pressure (164,165). More recently, clinical studies have demonstrated that interdialytic home blood pressure measurements are more reflective of interdialytic 44-hour ambulatory blood pressure monitoring (166). Moreover, home and 44-hour ambulatory blood pressure monitoring are better determinants of all-cause mortality in patients on hemodialysis compared with predialysis or postdialysis recordings (167,168). These data in dialysis patients are consistent with observations in nondialyzed patients with CKD. In patients with CKD, home blood pressure recordings are a better predictor of risk for ESRD and all-cause mortality compared with office-based readings (169). Although several observational cohort studies indicate that hypertension in dialysis patients is associated with increased mortality risk, other studies have reported associations between low systolic and diastolic blood pressures and increased mortality (170).

Although this paradoxical observation may reflect a greater prevalence of systolic and diastolic dysfunction in patients on dialysis, it raises important questions about optimal blood pressure goals. A recent meta-analysis of randomized controlled trials of blood pressure–lowering treatment in dialysis patients who achieved average systolic and diastolic reductions of 4.5 and 2.3 mm Hg, respectively, found that therapy was associated with lower risks of cardiovascular events (RR, 0.71; 95% CI, 0.55 to 0.92), all-cause mortality (RR, 0.80; 95% CI, 0.66 to 0.96), and cardiovascular mortality (RR, 0.71; 95% CI, 0.50 to 0.99) compared with control regimens (171). Home blood pressure recordings during the interdialytic period may be the optimal measure of blood pressure in dialysis patients. Whether a blood pressure goal <130/80 mm Hg is optimal in this regard requires examination in future clinical trials.

There is also limited information on optimal approaches for lowering blood pressure in patients on hemodialysis. Recent clinical studies have demonstrated probing of dry weight by a progressive reduction in volume of patients on hemodialysis as a simple and efficacious strategy to improve blood pressure control (172). The study reported ultrafiltration-attributable changes in systolic and diastolic blood pressure of −6.9 and −3.1 mm Hg, respectively, at 8 weeks (172). In addition, many patients still require antihypertensive medications even if appropriate dry weight is attained. Often, drugs that block the renin-angiotensin system are recommended as first-line agents in patients on hemodialysis for lowering blood pressure. This recommendation is based in part on their tolerability and extrapolation of evidence indicating benefit for reducing MACEs in patients with earlier stages of CKD (173,174). Only 1 prospective randomized controlled trial compared an angiotensin-converting enzyme inhibitor, fosinopril, with placebo in patients on hemodialysis (175). In the Fosinopril and Dialysis Trial, 400 patients on hemodialysis >50 years of age were randomized to fosinopril 20 mg/d versus placebo. After 4 years of follow-up, there was no overall difference in the incidence of cardiovascular death or fatal and nonfatal cardiovascular events between the treatment and control groups. However, it is quite likely that this trial was underpowered and thus unable to answer the study question. Another small randomized trial of an angiotensin receptor blocker (candesartan) demonstrated a nearly 3-fold reduction in cardiovascular events compared with placebo (176). However, this small study needs to be replicated, preferably with a much larger sample.

None of the available studies have evaluated blood pressure medications in dialysis patients on the basis of the presence or absence of diabetes mellitus. Consequently, there is insufficient information to suggest that hypertension in dialysis patients with diabetes mellitus needs to be treated any differently than hypertension in dialysis patients without diabetes mellitus. In addition, no studies of antihypertensive medications have been performed selectively in patients on peritoneal dialysis. However, epidemiological data indicate that the rate of cardiac arrest is ≈50% higher for patients on hemodialysis compared with patients on peritoneal dialysis within 3 months after dialysis initiation, whereas the rates are similar ≈2 years after initiation and somewhat higher in patients on peritoneal dialysis beyond 3 years after initiation (177). There is also intriguing information that long-duration quotidian dialysis is more effective for blood pressure control and reducing left ventricular mass compared with traditional thrice-weekly hemodialysis (178).

More information is available on the treatment of blood pressure in predialysis patients with CKD. The NKF/KDOQI "Clinical Practice Guidelines on Hypertension and Antihypertensive Agents in Chronic Kidney Disease" suggest that a blood pressure goal below 130/80 mm Hg is appropriate in all types of CKD (161). They also recommend the use of drugs that block the renin-angiotensin system in patients with CKD, with or without diabetes mellitus, who have a spot urine total protein-to-creatinine ratio >200 mg/g regardless of blood pressure. The guidelines recommend moderate to high doses of these drugs because large clinical trials indicate that optimal blood pressure control and renin-angiotensin system blockade with moderate to high doses of either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers may slow the progression of proteinuric kidney disease. The NKF/KDOQI guidelines also suggest the use of other medications to reduce cardiovascular disease risk and to achieve blood pressure goals, in concert with the "Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure" recommendations (180). Thus, most patients with CKD will require a diuretic, preferably a thiazide-type diuretic for patients with CKD stages 1 to 3. Loop diuretics are generally necessary in patients with CKD stages 4 and 5. Other medications such as beta-blockers and calcium channel blockers can be added as necessary to achieve the target blood pressure.

There is evidence that beta-blockers may be an effective therapeutic strategy in patients on hemodialysis with LVEF <35%. Cice et al. (98) randomized 114 patients with dilated cardiomyopathy who were on dialysis to carvedilol 25 mg twice daily or placebo for a period of 2 years. The investigators reported that carvedilol treatment reduced the risk of cardiovascular mortality (RR, 0.32), all-cause death (RR, 0.51), and hospitalizations (RR, 0.44) (98).

Given the paucity of data on hard cardiovascular endpoints, there is insufficient evidence to support recommendations for 1 class of antihypertensive agents over another in dialysis patients.

Individualized decisions on how to reach a desirable blood pressure for an individual patient need to be based on volume assessment and the presence or absence of autonomic insufficiency. Volume assessment is important not only in patients on dialysis, so that an appropriate dry weight can be chosen, but also in patients with CKD, so that diuretics can be used judiciously. Autonomic insufficiency may limit the ability to adjust dry weight and to use medications that clinicians may believe are necessary for cardioprotection such as beta-blockers or renin-angiotensin system blockers. No studies have been done to test the hypothesis that dialysis patients may have less cardiovascular risk if their dry weight is raised to allow the use of a beta-blocker or renin-angiotensin system blocker. Consequently, therapy should be individualized.

Lipid Management in Kidney Transplantation Candidates

The optimal use of lipid-lowering therapy in patients on dialysis is also controversial. Understanding the role of hypolipemic therapy in patients on dialysis has been complicated by conflicting data on the overall relationship of dyslipidemia with clinical outcomes in this population. Several observational studies reported associations of lower total serum cholesterol levels in patients on dialysis with increased risk of cardiovascular and all-cause mortality (181–183), although others found mortality relationships parallel to that of the general population (184). A recent prospective cohort study of 823 patients receiving incident dialysis clarified the role of confounding in the apparent "reverse epidemiology" of lipid levels and ESRD mortality (185). Higher total cholesterol levels were associated with reduced risk of all-cause death overall and in the subgroup with malnutrition and/or inflammation (defined as serum albumin levels <3.6 mg/dL, C-reactive protein ≥10 mg/L, or elevated interleukin-6). In contrast, each 40-mg/dL increment in baseline cholesterol was associated with increased risk of both all-cause (HR, 1.32; 95% CI, 1.07 to 1.63) and cardiovascular (HR, 1.41; 95% CI, 1.04 to 1.89) death among the participants without inflammation/malnutrition. These findings support mediation of the apparent survival advantage of hypercholesterolemia in ESRD by cholesterol-lowering effects of malnutrition and/or inflammation rather than by true protective effects of high cholesterol levels.

Data on the impact of statin therapy on cardiovascular outcomes and mortality in large cohorts of dialysis patients began with observational studies. A large observational study of prospective outcomes among patients receiving incident peritoneal dialysis and hemodialysis enrolled in the USRDS DMMS (Dialysis Morbidity and Mortality Study) Wave 2 cohort suggested significant, >30% relative reductions in cardiovascular and total mortality among statin users compared with nonusers (186). Similar effect sizes were reported with more extended follow-up of the subcohort receiving peritoneal dialysis (187). In an analysis of prospectively collected data for prevalent hemodialysis patients in the United States, Europe, and Japan participating in DOPPS (Dialysis Outcomes and Practice Patterns Study), statin prescription was associated with a 31% lower relative risk of death and 23% lower relative risk of cardiac death compared with no statin prescriptions (188). Notably, only 11.8% of this cohort received statin prescriptions. Importantly, none of these observational studies analyzed the duration of statin treatment before enrollment. Moreover, observational findings are limited by the potential for selection bias and residual confounding. Beginning in the late 1990s, a number of studies enrolled small samples of dialysis patients in clinical trials comparing statin therapy and placebo, but most were of short duration and examined lipid levels or other surrogate measures as primary outcomes (Table 9) (189–196). These studies documented effective lipid lowering by statins at low to moderate doses without significantly increased risks of adverse side effects. On the basis of the available body of evidence in patients on dialysis and extrapolation from general population trials, the 2003 NKF/KDOQI "Clinical

Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease" recommended treatment to reduce low-density lipoprotein (LDL) cholesterol to <100 mg/dL in adults with stage 5 (end-stage) CKD (197). These guidelines paralleled recommendations of the Adult Treatment Panel (ATP) for higher-risk members of the general population without established coronary heart disease (198).

Three randomized trials of statin therapy in dialysis patients using clinical endpoints have since been published (Table 9). Stegmayr et al. (199) randomly assigned 143 patients with CKD, including 110 on dialysis, to atorvastatin 10 mg daily or placebo. After a mean observation time of 33 months in the dialyzed subgroup, there was no significant difference in the risk of the primary outcome of all-cause death, MI, or coronary revascularization according to treatment assignment (OR, 1.01; 95% CI, 0.65 to 1.55). The 4D Study (Deutsche Diabetes Dialyze Studie), randomized 1,255 patients on hemodialysis with type 2 diabetes mellitus to atorvastatin 20 mg daily or placebo (199a). Participants had been dialysis dependent for an average of 8 months at enrollment. Median LDL cholesterol levels declined by 42% to 72 mg/dL after 4 weeks in the statin group compared with a 1.3% reduction with placebo. Despite effective lipid lowering, atorvastatin did not significantly affect the composite primary endpoint of cardiac death, MI, or stroke (RR, 0.92; 95% CI, 0.77 to 1.10) after a median follow-up of 4 years. Secondary endpoint analysis demonstrated nominally significant associations of atorvastatin with a higher frequency of fatal stroke (27 versus 13 events; RR, 2.03; 95% CI, 1.05 to 3.93; p=0.04) but protection against any cardiac event (RR, 0.82; 95% CI, 0.68 to 0.99; p=0.03). AURORA (Assessment of Survival and Cardiovascular Outcomes), which did not restrict enrollment according to ESRD pathogenesis, randomized 2,776 patients 50 to 80 years of age on chronic hemodialysis for at least 3 months to rosuvastatin 10 mg daily or placebo (200). Mean LDL cholesterol levels declined by 43% after 12 weeks in the statin group to <60 mg/dL compared with a 1.9% reduction with placebo. There was no difference in the incidence of the primary endpoint of cardiovascular death, nonfatal MI, or stroke (RR, 0.96; 95% CI, 0.84 to 1.11) in the statin compared with placebo arms, nor were there any differences in the risk of individual components of the primary endpoint. The lack of an effect of rosuvastatin therapy on the primary endpoint was consistent in prespecified subgroups, including patients with diabetes mellitus and preexisting cardiovascular disease.

The findings of the 4D Study and AURORA contrast with treatment-related benefits found in CARDS (Collaborative Atorvastatin Diabetes Study), a trial conducted in 2,838 patients with type 2 with diabetes mellitus without significant renal impairment at enrollment (serum creatinine levels <1.7 mg/dL) (201). After a median follow-up of 3.9 years in CARDS, atorvastatin 10 mg produced a 37% relative reduction in MACEs and a 27% reduction in all-cause mortality compared with placebo (201). Cardiac death in patients on dialysis is often sudden, resulting from arrhythmia or heart failure, and these competing risks have presented challenges for powering trials to detect benefits on atherosclerotic events in this population. One possibility for these discrepancies is that the increased risk for sudden death in

Table 9.   Summary of Published Randomized Clinical Trials of Statin Therapy in Dialysis Patients

Trial Authors, Year	Sample Size, Dialysis Modality	Statin, mg/d, and Comparison	Enrollment in Relation to ESRD Onset, mo	Trial Duration, mo	Primary Outcome	Results
Robson et al. (189), 1997	107 HD or PD	SIMV 10 versus placebo (factorial with enalapril versus placebo)		6	Lipid levels at 6 mo	Significantly lower TCHOL (13%) and LDL (17%) at 6 mo with SIMV versus placebo
Chang et al. (190), 2002	62 HD	SIMV 20 versus no drug	21 (median)	2	Longitudinal change in lipid and inflammatory marker levels	Significant longitudinal reductions in TCHOL (29%), LDL (41%), TG (17%) and hs-CRP only with SIMV
Harris et al. (191), 2002	177 PD	ATORV 10–40 versus placebo	>3	4	Longitudinal change in lipid levels	Significantly larger longitudinal reductions in TCHOL (29% versus 6%), LDL (40% versus 9%) and TG (14% versus 11%) and larger HDL increase (7% versus 4%) with ATORV versus placebo
Saltissi et al. (192), 2002	22 HD, 16 PD	SIMV 5–20 versus placebo	>3	6	Longitudinal change in lipid levels	Significantly larger longitudinal reductions in TCHOL and LDL with SIMV versus placebo in both HD and PD groups
Lins et al. (193), 2004	42 HD	ATORV 10–40 versus placebo		3	Lipid levels at 3 mo	Significantly lower TCHOL (33%) and LDL (43%) at 3 mo with ATORV versus placebo
Diepeveen et al. (194), 2005	23 HD, 21 PD	ATORV 40 versus placebo (factorial with vitamin E versus placebo)	Unspecified	3	Longitudinal change in nonfasting lipid levels	Significant longitudinal reductions in TCHOL (34%), LDL (43%), and TG (34%) only with SIMV
Baigent et al. (195), 2005	34 HD, 39 PD (subset of 448 CKD)	SIMV 20 versus placebo (factorial with aspirin versus placebo)	Unspecified	12	Nonfasting lipid levels at 12 mo	Significantly lower TCHOL (16%), LDL (20%), and TG (38%) at 12 mo with SIMV versus placebo
Ichihara et al. (196), 2002	22 HD	FLUV 20 versus placebo	>6	6	Longitudinal change in arterial stiffness	Significant longitudinal decrease in arterial pulse wave velocity only with FLUV
Stegmayr et al. (199), 2005	97 HD, 13 PD (subset of 143 CKD)	ATORV 10 versus placebo	Unspecified	33 (mean)	All-cause death, MI, CABG or PCI	No outcome difference: OR, 1.01; 95% CI, 0.65 to 1.55
Wanner et al. (199a), 2005	1,255 HD	ATORV 20 versus placebo	<24 (mean 8)	48 (median)	Cardiac death, nonfatal MI, or stroke	No significant outcome difference: RR, 0.92; 95% CI, 0.77 to 1.10
Fellstrom et al. (200), 2009	2,776 HD	ROSUV 10 versus placebo	42±46 (mean)	46 (median)	Cardiovascular death, nonfatal MI, or stroke	No significant outcome difference: RR, 0.96; 95% CI, 0.84 to 1.11
Baigent et al. (202), 2011	2,527 HD, 496 PD (subset of 9,720 CKD)	SIMV 20 plus ezetimibe 10 versus placebo	Unspecified	59 (median)	Nonfatal MI or coronary death, non–hemorrhagic stroke, or arterial revascularization	Significant reduction in composite event rate with SIMV plus ezetimibe in the full cohort (RR 0.83; 95% CI, 0.74 to 0.94; p=0.002). No evidence of heterogeneity of effects among dialysis versus non-dialysis patients

ATORV indicates atorvastatin; CABG, coronary artery bypass grafting; CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; FLUV, fluvastatin; HD, hemodialysis; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; PD, peritoneal dialysis; ROSUV, rosuvastatin; RR, relative risk; SIMV, simvastatin; TCHOL, total cholesterol; and TG, triglycerides.

patients on dialysis may not be mitigated by cholesterol-lowering therapy, which may be much more important for ischemic, atherosclerotic events. Thus, the 4D Study may not have been able to show a modest benefit on atherosclerotic endpoints given the large numbers of patients who had arrhythmic death or congestive failure. Furthermore, decisions on target LDL cholesterol goals may be limited by the fact that many patients on dialysis have low LDL cholesterol related to malnutrition or concomitant inflammation.

Importantly, results from the SHARP (Study of Renal and Heart Protection) clinical trial were published in 2011 (202). The study included 9,270 patients with CKD (defined as serum creatinine level ≥1.7 mg/dL in men or serum creatinine level ≥1.5 mg/dL in women, on hemodialysis, or on peritoneal dialysis), ≥40 years of age, and no prior history of MI or coronary revascularization who were randomly assigned to receive simvastatin 20 mg plus ezetimibe 10 mg or placebo. The primary endpoint of MACEs was defined as a composite of nonfatal MI or coronary death, non–hemorrhagic stroke, or arterial revascularization (excluding dialysis access procedures) but, in contrast to 4D and AURORA, did not include sudden cardiac death. After a median 4.9 years of treatment and follow-up, average LDL cholesterol was 42 mg/dL lower in the simvastatin plus ezetimibe group compared with placebo group by intention-to-treat analysis. The simvastatin plus ezetimibe group experienced a 17% reduction in the relative risk of MACEs (RR 0.83; 95% CI, 0.74 to 0.94; p=0.002). Non-significantly fewer patients allocated to simvastatin plus ezetimibe had a non-fatal MI or died from coronary heart disease (RR 0.92, 95% CI 0.76 to 1.11; p=0.37), and there were significant reductions in non–hemorrhagic stroke (RR 0.75, 95% CI 0.60 to 0.94; p=0.01) and arterial revascularization procedures (RR 0.79, 95% CI 0.68 to 0.93; p=0.0036). After weighting for subgroup-specific reductions in LDL cholesterol in a planned comparison, there was no heterogeneity of effects among dialysis-dependent patients (one third of the total) compared with patients not on dialysis, but the study was not powered to assess outcomes among the dialysis group alone. Further, because approximately one third of the patients who were not on dialysis at baseline began dialysis during the trial, the effects of simvastatin plus ezetimibe in the dialysis subgroup are reinforced by the consistent results in the non-dialysis subgroup. The excess risk of myopathy was 2 per 10,000 patients per year of treatment with simvastatin plus ezetimibe compared with placebo. There was no evidence of excess risks of hepatitis, gallstones, or cancer, and there was no significant excess of death from any non-vascular cause.

A meta-analysis and meta-regression of randomized controlled trials of statins in CKD patients (broadly defined as predialysis, dialysis, and transplantation populations) included the 4D Study but not AURORA or SHARP (204). In pooling effects across 43 trials, the authors detected a 19% relative reduction in fatal cardiovascular events with statin use (RR, 0.81; 95% CI, 0.73 to 0.90), an effect that approximates the benefits of statin treatment in the general population. Statistical assessment for heterogeneity supported consistency of the cardiovascular benefit across the predialysis, dialysis, and transplantation samples, although power for detecting heterogeneity

was limited. Statins were associated with a trend toward lower overall mortality, but this effect was not significant (RR, 0.92; 95% CI, 0.82 to 1.03; p=0.13). The authors concluded that the findings "provide support for the widespread use of statins for the prevention of cardiovascular disease in people with chronic kidney disease who are at high cardiovascular risk . . ., but that the effects of treatment in people at lower absolute risk and the effects on total mortality remain to be defined." Meta-analysis of the dialysis populations in SHARP, 4D, and AURORA examining the combined effects of treatment on the "atherosclerotic" endpoint as it was defined in SHARP will further refine the evidence of the impact of statins on vascular risk in dialysis-dependent patients.

The reported trials using low- to moderate-dose statins in patients on dialysis support safety and tolerability at this dose range in the dialyzed population. Frequencies of liver function test abnormalities, creatinine phosphokinase elevations, and participant withdrawals were similar with statins compared with placebo or control (191–193,195,199,199a,200). The AURORA study observed 3 cases of rhabdomyolysis (0.2%) in patients randomized to rosuvastatin and 2 cases in the placebo group (0.1%) (200). Although there were more fatal stroke events in the atorvastatin group in the 4D Study (199a), this nominally significant finding is not consistent with major trials such as CARDS and the Heart Protection Study, which demonstrated 25% to 48% relative reductions in stroke risk with statins in high-risk general population samples (201,205). There was no significant difference in nonfatal stroke with rosuvastatin compared with placebo in AURORA (p=0.42) (200). Simvastatin plus ezetimibe was associated with a significant 25% relative reduction in non–hemorrhagic stroke (p=0.01) in the full SHARP cohort (202).

Recommendation

1. **It may be reasonable to administer statins to kidney transplantation candidates to reduce the risk of vascular disease events (*Class IIb; Level of Evidence B*).**

Perioperative Medical Management of Cardiovascular Risk Before Kidney Transplantation

There are several important perioperative management strategies to consider for reducing the risk for cardiovascular events in patients with CKD and ESRD without known CAD. The most important include management considerations for blood pressure, glycemic control, and antiplatelet therapy. Important questions include whether patients should take some or all of their antihypertensive medication the day of surgery. Often, especially with deceased donor transplantation, the timing of the surgery precludes advanced planning for medications. In addition, one has to consider interactions with other medications during surgery, especially analgesics. Data indicate that beta-blockers improve cardiovascular outcomes in CKD patients having noncardiac surgery. In a retrospective study of 2,000 vascular surgery patients, half of whom had abdominal aortic aneurysm repairs, Welten et al (206) reported that the benefit of judiciously titrated beta-

blockers in reducing cardiovascular events increased with declining creatinine clearance. The overall benefit was first noted when estimated creatinine clearance by the Cockcroft and Gault formula was <60 mL/min and most evident when estimated creatinine clearance was <30 mL/min, suggesting that CKD patients may benefit from perioperative use of beta-blockers. Whether CKD patients require long-term beta-blocker treatment in the absence of clinically evident cardiovascular disease is unknown. Certainly, patients receiving beta-blockers as long-term therapy before surgery should be continued on beta-blockers perioperatively and postoperatively because the risk for rebound blood pressure elevations can be substantial and may precipitate coronary ischemia. In addition, medications such as clonidine, if given before transplantation, should be continued perioperatively and postoperatively to avoid rebound blood pressure elevations. Beta-blockers can be given intravenously and clonidine transcutaneously in cases of postoperative ileus.

Perioperative medical therapy can be useful for reducing perioperative cardiovascular complications in patients with established CAD. Mangano et al. (207) administered atenolol or placebo beginning the morning of surgery and continuing for 7 days postoperatively to a cohort of 200 patients with known coronary disease or CAD risk factors undergoing high-risk noncardiac surgery. There was a marked reduction in the incidence of perioperative myocardial ischemia and an improvement in survival at 6 months in the atenolol group, with benefit persisting for at least 2 years. The authors speculated that the lower incidence of myocardial ischemia was the result of beta-blockers protecting against plaque destabilization, with a resultant reduction in subsequent MI or death. Poldermans et al. (208) studied the perioperative use of bisoprolol versus routine care in elective major vascular surgery in the DECREASE trial. Bisoprolol was started at least 7 days preoperatively, titrated to achieve a resting heart rate ≤60 bpm, and continued postoperatively for 30 days. Of note, the study was confined to patients with at least 1 clinical marker of cardiac risk (prior MI, diabetes mellitus, angina pectoris, heart failure, age >70 years, or poor functional status) and evidence of inducible myocardial ischemia on a preoperative DSE. Patients with extensive regional wall abnormalities (large zones of myocardial ischemia) were excluded. Bisoprolol, when titrated carefully, reduced perioperative MI or cardiac death by nearly 80% in this high-risk population.

In contrast, several recent studies have demonstrated that beta-blockers may not be effective if heart rate is not well controlled or when given unselectively to lower-risk patients (209–211). The POISE (Perioperative Ischemic Evaluation) trial reported on 8,351 high-risk, beta-blocker–naïve patients randomized to high-dose continuous-release metoprolol the night before and the morning of surgery versus placebo (212). Treatment was associated with a significant reduction of the primary outcome of cardiovascular events and with a 30% reduction in MI risk, but was also associated with significantly increased risk of 30-day all-cause mortality and stroke. POISE has been criticized because the use of high-dose beta-blocker therapy the night before and morning of surgery probably led to higher rates of hypotension, stroke, and death.

The DECREASE-IV trial enrolled patients who were ≥40 years of age, were scheduled for elective noncardiac surgery, and had an estimated risk of MI or cardiovascular death of >1% (212a). Participants were randomized according to an open-label, factorial design to 1) beta-blocker therapy (bisoprolol), 2) statin (fluvastatin), 3) a combination of beta-blockers and statins (bisoprolol and fluvastatin 80 XL), or 4) neither beta-blockers nor statins (control group). The starting dose of bisoprolol was 2.5 mg orally per day if resting heart rate was >50 bpm and increased incrementally to a maximum dose of 10 mg. Patients randomized to bisoprolol (n=533) had a lower incidence of perioperative cardiac death and nonfatal MI than those randomized to control (2.1% versus 6.0% events; HR, 0.34; 95% CI, 0.17 to 0.67). Ischemic stroke occurred in 0.7% of patients (n=7), of whom 4 (0.8%) were randomized to bisoprolol and 3 (0.6%) to bisoprolol-control (p=0.68).

The "ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery" (7) and the "2009 ACCF/AHA Focused Update on Perioperative Beta Blockade" (213) have advocated that perioperative beta-blockade is a Class I indication (should be provided) for patients previously on beta-blockers for indications such as angina, symptomatic arrhythmias, and hypertension. Beta-blockers are recommended for those with a positive stress test undergoing major vascular surgery, although short-term administration without titration may be associated with harm. The short-term administration of these agents in the perioperative period is being rereviewed in light of the POISE results. The "2009 ACCF/AHA Focused Update on Perioperative Beta Blockade Incorporated into the ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery" focused predominantly on the prophylactic use of beta-blockers perioperatively to minimize cardiac risk (213). The DECREASE-IV trial demonstrated a safe and effective manner of providing these agents (212a). The cardiovascular evaluation process in patients undergoing solid-organ transplantation presents an opportunity to initiate this therapy in patients with Class I recommendations for beta-blockers independently of surgery and to perform appropriate titration before the perioperative period. The potential benefits of continuing perioperative beta-blockers could then be realized with a low risk of detrimental side effects.

Recommendations

1. **Among patients already taking beta-adrenergic blockers before renal transplantation, continuing the medication perioperatively and postoperatively is recommended to prevent rebound hypertension and tachycardia (*Class I; Level of Evidence A*).**

2. **Among patients being considered for renal transplantation with clinical markers of cardiac risk (diabetes mellitus, prior known coronary heart disease, prior heart failure, extracardiac atherosclerosis) and those with unequivocal myocardial ischemia on preoperative stress testing, it is reasonable to initiate beta-blockers preoperatively and to continue them postoperatively provided that dose titration is done carefully to avoid bradycardia and hypotension (*Class IIa; Level of Evidence C*).**

3. **Perioperative initiation of beta-blockers in beta-blocker–naïve patients may be considered in kidney transplantation candidates with established coronary heart disease or 2 or more cardiovascular risk markers to protect against perioperative cardiovascular events if dosing is titrated and monitored** (*Class IIb; Level of Evidence C*).

4. **Initiating beta-blocker therapy in beta-blocker–naïve patients the night before and/or the morning of noncardiac surgery is not recommended** (*Class III; Level of Evidence A*).

Other than beta-blocker treatment and clonidine, there is no evidence to support the continued use of any specific antihypertensive therapy. Calcium channel blockers may be restarted as the blood pressure rises postoperatively. Drugs that block the renin-angiotensin system such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are usually withheld within the first few days to weeks after transplantation to avoid functional changes in GFR, which could delay recovery from ischemia and reperfusion injury and thus possibly confuse clinical management. An ideal postoperative blood pressure goal should be individualized on the basis of the patient's presurgical blood pressure goals. Often in the perioperative period, blood pressure is low because of the effects of anesthesia and concomitant use of analgesic medications. Consequently, an individualized decision to progressively add medications should be done on a case-by-case and day-by-day basis. Hypotension should be avoided because it may worsen ischemic injury to the kidney and possibly precipitate graft thrombosis. Patients with presurgical tolerance to opiate analgesics may experience postoperative rebound in blood pressure if inadequate opiates are provided to relieve wound discomfort. In such patients, adjusting opiate doses for postoperative hypertension rather than adding blood pressure medications may be the best strategy.

There is no evidence to indicate that dopamine improves renal perfusion or diminishes the risk of delayed graft function after transplantation when administered to the recipient (214), although data indicate some benefit for kidney function if given to the deceased donor (215). In some recipients, dopamine may increase heart rate, blood pressure, and myocardial workload, effects that may increase the risk for an ischemic event. Because no data indicate benefit from the use of dopamine perioperatively, it should not be routinely used. Likewise, there is no evidence that perioperative use of calcium channel blockers reduces the risk of delayed graft function. Again, the use of these drugs perioperatively and postoperatively needs to be individualized on the basis of the need for control of blood pressure, not unproven hypothetical opportunities for improving postimplantation graft function.

Recommendation

1. **Administration of dopamine to the kidney transplant recipient is not beneficial for renal allograft function, and administration may be harmful** (*Class III; Level of Evidence C*).

Decisions on antiplatelet therapy perioperatively cannot be generalized. No randomized controlled trials have evaluated the efficacy of aspirin for the primary prevention of cardiovascular disease in patients on dialysis, although 1 controlled trial found a reduced risk of MI with aspirin therapy in CKD patients (216). A recent secondary analysis of the HOT (Hypertension Optimal Treatment) trial, which randomly assigned patients with diastolic hypertension to aspirin 75 mg or placebo, detected a 66% reduction (95% CI, 33 to 83) in MACEs and a 49% reduction (95% CI, 6 to 73) in mortality, respectively, among the subgroup with baseline eGFR <45 mL/min/1.73 m^2 (217). This potential benefit must be offset by the risk of gastrointestinal bleeding, albeit minor in the majority of cases. On the other hand, observational studies demonstrate that aspirin therapy is associated with reduced mortality in patients with CKD who have had a previous MI (218,219). Decisions on continuing antiplatelet therapy during surgery and perioperatively need to be individualized based on indication and bleeding risk because there are insufficient data to guide management in this regard. Although some programs routinely continue low-dose aspirin therapy in patients with CKD and ESRD perioperatively, many surgeons prefer not to continue clopidogrel given concern about increased risk of bleeding. Please see "Antiplatelet Therapy in the Context of Recent PCI" section above for a discussion of antiplatelet therapy in the context of recent PCI.

Recommendation

1. **It is reasonable to continue aspirin indefinitely after renal transplantation in patients with known CAD, following the ACC/AHA guidelines for secondary prevention for patients with coronary artery disease** (*Class IIa; Level of Evidence B*).

With respect to perioperative use of statins, Durazzo et al. (220) performed a randomized trial among 200 patients receiving vascular surgery (without ESRD) in whom statins were started an average of 30 days before surgery. A significant reduction in perioperative cardiovascular complications was demonstrated with this protocol. Schouten et al. (221) performed a randomized trial of fluvastatin started an average of 30 days before noncardiac surgery compared with placebo in 497 statin-naïve, high-risk patients and found a significant reduction in perioperative MI and cardiac death. Le Manach et al. (222) demonstrated that statin withdrawal for >4 days before vascular surgery was associated with 2.9 times the odds of cardiac morbidity. Therefore, the recent guidelines advocate continuing statin therapy in patients taking statins as a Class I recommendation.

Recommendations

1. **For patients undergoing renal transplantation who are taking statin therapy, it is recommended that statin treatment be continued perioperatively and postoperatively** (*Class I; Level of Evidence B*).

2. **For patients undergoing renal transplantation in whom preoperative evaluation established unequivocal evidence of atherosclerosis, it is reasonable to initiate**

low- to moderate-dose statin therapy preoperatively
and to continue treatment postoperatively (*Class IIa;
Level of Evidence B*).

Glycemic control holds promise for reducing cardiovascular mortality in the perioperative period for patients with diabetes mellitus receiving kidney transplantation. A meta-analysis of 35 randomized controlled trials with mortality data on critically ill hospitalized adult patients treated with insulin reported a 15% reduction in the relative risk of short-term mortality (RR, 0.85; 95% CI, 0.75 to 0.97) with insulin versus control therapy, including benefit among the subgroup in the surgical intensive care unit (RR, 0.58; 95% CI, 0.22 to 0.62) (223). Similarly, a more recent systematic review and meta-analysis suggested that perioperative insulin infusion versus control therapy may reduce perioperative mortality in patients undergoing any surgery, including a nearly significant benefit in patients with acute MI who did not receive reperfusion therapy, but at the "expense" of an increased risk of hypoglycemia (224). Meta-analysis of 5 studies (3 randomized trials and 2 cohort) comparing intensive and conventional insulin in critically ill patients reported a reduction in the incidence of acute kidney injury by 38% with intensive therapy (RR, 0.62; 95% CI, 0.47 to 0.83) (225). These observations suggest potential benefit for intensive insulin in reducing delayed graft function after transplantation. However, the recently published NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation) study, a large randomized trial of intensive versus conventional insulin therapy among 6104 adults in medical or surgical intensive care units who were expected to require insulin on at least 3 consecutive days, found higher 90-day mortality (RR, 1.14; 95% CI, 1.02 to 1.28) with a more intensive glucose management target of 81 to 108 mg/dL compared with a target of <180 mg/dL (226). Thus, although glycemic control may offer a benefit in the perioperative setting, caution with intensive therapy is warranted.

Many transplantation centers routinely admit incident transplantation patients to monitored beds for the first few days postoperatively. Often, this is part of the management strategy for routine assessment of fluid management in the perioperative period. However, no data suggest that routine monitoring for a prespecified period of time affects the risk for cardiovascular events.

In summary, there are limited published data on optimal perioperative medical management of cardiovascular risks in patients with CKD and ESRD undergoing renal transplantation. Perhaps most important is an individualized approach to managing blood pressure to minimize fluctuations, to avoid hypotension, and to progressively reinstitute safe and effective therapies that will not interact with other medications or alter GFR. Cautious reintroduction of medications as anesthesia and analgesia are tapered can be individualized on a case-by-case basis.

Recommendation

1. **The usefulness of strict control of blood glucose concentration during the perioperative period is uncertain**

in patients with diabetes mellitus undergoing kidney transplantation (*Class IIb; Level of Evidence B*).

Postoperative Medical Management of Cardiovascular Risk After Kidney Transplantation

Treatment of Elevated LDL Cholesterol Levels in Kidney Transplant Recipients

To date, there are no definitive data indicating that treatment of hyperlipidemia in kidney transplant recipients improves clinical outcomes such as patient survival, allograft survival, or risk of cardiovascular events. However, there is indirect evidence of benefits with statin therapy. The Assessment of Lescol in Renal Transplantation (ALERT) is the only randomized controlled trial of dyslipidemia management in this population that used cardiovascular disease events as the outcome measure (227). The ALERT trial randomized 2,102 renal transplant recipients with mean total cholesterol levels of 250 mg/dL to fluvastatin or placebo. After a mean follow-up of 5.1 years, LDL levels were 32% lower in the statin-treated compared with the placebo group (average difference of 38 mg/dL). Statin therapy was associated with a trend toward lower incidence of the primary composite outcome of cardiac death, nonfatal MI, or coronary interventions, although the risk reduction did not reach statistical significance (RR, 0.83; 95% CI, 0.64 to 1.06). In contrast, an extension of the ALERT study in which patients were offered fluvastatin for an additional 2 years found significant long-term reduction in the primary composite outcome among the original statin arm (228). At a mean follow-up of 7 years after enrollment, the fluvastatin-treated patients had a lower risk of the primary cardiac composite outcome compared with the original placebo group (HR, 0.79; 95% CI, 0.63 to 0.99), but there was no significant difference in overall mortality.

Posthoc analysis of the ALERT trial suggested significantly lower risk of cardiac death or nonfatal MI with fluvastatin compared with placebo (RR, 0.65; 95% CI, 0.48 to 0.88) (229). Patients who started statin therapy earlier after transplantation appeared to benefit more than those who began treatment later (230). Compared with those who initiated statin therapy >6 years after transplantation, those who began therapy between years 0 to 2 after transplantation experienced 59% lower risk of cardiac death and nonfatal MI.

A number of smaller randomized clinical trials have evaluated associations of statin therapy with surrogate measures of atherosclerotic vascular disease risk in renal allograft recipients such as lipid profiles and measures of endothelial function (Table 10). Findings of these trials include average reductions in total cholesterol of 18% to 33%, LDL cholesterol reductions of 20% to 42%, triglyceride reductions of 0% to 32%; and average high-density lipoprotein (HDL) levels increases of 0% to 13% (195,231–235). Improvements in statin-treated groups have been reported in ultrasonographic measures of endothelial and vessel wall function (242,244), carotid intimal-medial thickness (243), and renal allograft vasculopathy (241).

A large, observational cohort study of 2041 consecutive, first-time kidney transplant recipients at 1 center in Austria in 1990 to 2003 used pharmaceutical and death records to examine survival in relation to statin use in a time-dependent regression analysis (246). The study estimated a 36% relative reduction in adjusted mortality over up to 12 years of follow-up in statin-treated patients (adjusted HR, 0.64; 95% CI, 0.48 to 0.86).

Notably, the ATP III and NKF/KDOQI guidelines were published before more recent data suggesting benefit with more aggressive lipid-lowering in high-risk general population samples, albeit with increased frequency of adverse events (247–250), and evidence that statin therapy may reduce MACEs in apparently healthy individuals without hyperlipidemia but with elevated serum inflammatory markers (251). However, recommendations for more aggressive lipid lowering have not been adopted by the recent KDIGO guidelines. Data on the safety and efficacy of the cholesterol-uptake inhibitor ezetimibe in transplant recipients are limited to small observational studies (252–255). The 2004 NKF/KDOQI "Clinical Practice Guidelines for Managing Dyslipidemias in Kidney Transplant Patients" advised that ezetimibe should probably not be used in the transplantation population until its safety is established (256).

Observational studies have identified HDL cholesterol <40 mg/dL as an independent risk factor for coronary heart disease even after adjustment for LDL cholesterol levels. The first line of treatment for this pattern of dyslipidemia is therapeutic lifestyle change. There are no reported studies of treatment of isolated low HDL cholesterol levels in kidney transplant recipients.

With respect to side effects of antidyslipidemic drug in kidney transplant recipients, the randomized controlled trials of statin use among renal allograft recipients have reported some adverse event data, but ascertainment methods varied across studies (195,227,231–243,245). The ALERT trial captured the largest sample for the longest follow-up (>10,000 patient-years) and found no difference in the frequencies of total or types of adverse events among patients treated with fluvastatin compared with placebo, including no differences in infections, malignancies, substantial creatinine kinase elevations, or rhabdomyolysis (227). Importantly, these studies do not suggest harm attributable to statin therapy started before or perioperatively in patients undergoing kidney transplantation. Limited data are available on the safety of combining fibrates with statins in patients with kidney disease, and NKF/KDOQI guidelines advise avoiding this combination unless further data establish the safety and efficacy in patients with reduced GFR (256).

Lipid-Lowering Therapy and Risks of Acute Rejection Risk and Graft Loss After Transplantation

Several clinical trials have reached conflicting conclusions about the effects of statin therapy on acute rejection after kidney transplantation. The earliest randomized trials of statins for prevention of acute rejection in renal allograft recipients reported absolute risk reductions of 30% to 40% in the statin arms (236,247). Notably, these studies were small

and characterized by unusually high acute rejection rates in the control groups. Three subsequent larger trials found no association of statin therapy with rejection risk (238–240).

There are limited data on the relationship of dyslipidemia therapy with preservation of allograft function after kidney transplantation. In the ALERT trial, there was no difference in the predefined, secondary composite endpoint of graft loss, doubling of serum creatinine concentration, and decline in GFR in patients receiving fluvastatin compared with placebo (227,257). A large observational cohort study of first-time renal allograft recipients in 1993 to 2000 found that statin use was associated with improved patient survival but no significant difference in allograft survival (adjusted HR, 0.86; 95% CI, 0.55 to 1.04) (246).

Recommendation

1. **Consistent with the recommendations of the NKF/KDOQI Clinical Practice Guidelines for Managing Dyslipidemias in Kidney Transplant Patients, it is reasonable to pursue an LDL cholesterol goal of less than 100 mg/dL in kidney transplant recipients without known CAD (*Class IIa; Level of Evidence B*).**

These guidelines parallel recommendations of the ATP III for higher-risk members of the general population without established coronary heart disease (198) and have been incorporated in the 2009 "KDIGO Clinical Practice Guideline for the Care of Kidney Transplant Recipients" (258).

Recommendations

1. **When therapeutic lifestyle change alone is insufficient to achieve LDL goals, it is reasonable to initiate statin therapy in transplanted patients with LDL cholesterol levels above 100 mg/dL (*Class IIa; Level of Evidence B*).**
2. **Extrapolating from the ATP III and NKF/KDOQI guidelines, it is reasonable to initiate therapy to reduce non-HDL cholesterol to less than 130 mg/dL among kidney transplant recipients with LDL less than 100 mg/dL, triglyceride levels above 200 mg/dL, and non-HDL cholesterol above 130 mg/dL (*Class IIa; Level of Evidence B*).**

This pattern of dyslipidemia is managed with therapeutic lifestyle changes, including moderation of alcohol intake, regular exercise, smoking cessation, and control of body mass and glycemia, ideally under the guidance of a dietician experienced in the care of kidney transplant recipients. If further intervention is needed, a statin is recommended for patients not already receiving a statin for treatment of elevated LDL cholesterol.

Recommendations

1. **Consistent with the NKF/KDOQI guidelines, for patients who do not achieve goals with statins, it is reasonable to discontinue the statin and replace it with a fibrate. As noted, the 2004 KDOQI guidelines stated that ezetimibe should probably not be used in the transplantation setting until its safety has been established (*Class IIa; Level of Evidence C*).**

Table 10. Summary of Published Randomized Clinical Trials of Statin Therapy in Kidney Transplantation Recipients

Trial Authors, Year	Sample Size, Donor Types	Immunosuppression	Statin, mg/d, and Comparison	Enrollment in Relation to KT	Trial Duration, mo	Primary Outcome	Results
Martinez-Hernandez et al. (231), 1993	26, DD or LD	AZA, steroids, plus CSA in 50%	SIMV 5 versus placebo	PTD ≥182	2	Longitudinal change in fasting lipid levels	Significant TCHOL (18%) and LDL reductions (20%) at 2 mo in SIMV group only (p<0.001)
Arnadottir et al. (232), 1994	40, unspecified	CSA, AZA, steroids	SIMV 10–20 versus placebo	PTD ≥182	4	Longitudinal change in fasting lipid levels	Significant longitudinal TCHOL (20%) and LDL reductions (29%) and HDL increase (9%) only with SIMV (p<0.01)
Lepre et al. (233), 1999	51, unspecified	CSA based	SIMV 5 versus placebo	PTD ≥365	3	Longitudinal change in lipid levels	Significant longitudinal TCHOL (22%) and LDL reductions (32%) and HDL increase (13%) only with SIMV (p<0.01)
Renders et al. (234), 2001	30, unspecified	CSA based	ATORV 10 versus CERIV 0.2 versus no drug	PTD ≥182	3	Longitudinal change in fasting lipid levels	Significant TCHOL (30%, 33%), LDL (42%, 38%), and TG reductions (23%, 23%) at 3 mo only with ATORV and CERIV (p<0.05)
Santos et al. (235), 2001	67, DD or LD	AZA, steroids, plus CSA in 71%–85%	SIMV 10 versus placebo	PTD >182	6	Lipid levels at 1, 3, and 6 mo	Significantly lower TCHOL (22%) and LDL (35%) at 6 mo with SIMV versus placebo
Baigent et al. (195), 2005	133, unspecified (subset of 448 CKD)	Unspecified	SIMV 20 versus placebo (factorial with aspirin versus placebo)	Unspecified	12	Nonfasting lipid levels at 12 mo	Significantly lower TCHOL (18%), LDL (22%), and TG (11%) at 12 mo with SIMV versus placebo
Katznelson et al. (236), 1996	44 DD	CSA, steroids	PRAV 20 versus no drug	PTD <7	4	BCAR	Significantly lower BCAR at 4 mo with PRAV versus no drug (25% versus 58%; p<0.01)
Tuncer et al. (237), 2000	57, DD or LD	CSA, AZA, steroids, plus ATG in DD	SIMV 10 versus PRAV 20 (TCHOL ≥240 mg/dL) or versus no drug (TCHOL <240 mg/dL)	PTD 7–14	12	BCAR	Significantly lower BCAR at 12 mo with SIMV (31%) and PRAV (25%) versus no drug (64%; p=0.04 and p=0.01)
Kaisiske et al. (238), 2001	141, DD or LD	CSA, plus MMF in 85%	SIMV 10 versus placebo versus gemfibrozil	PTD ≤3	3	BCAR	No significant difference in BCAR at 3 mo with SIMV (28%), gemfibrozil (28%), or placebo (23%)
Holdaas et al. (239), 2001	363, DD or LD	CSA, steroids, ±AZA	FLUV 40 versus placebo	After transplantation	3	Steroid-treated rejection	No difference in rejection at 3 mo (47.3% versus 47.8%; p=0.92)
Sahu et al. (240), 2001	65 LD	CSA, AZA, steroids	LOV 20 versus placebo	PTD 5	3	BCAR	No significant difference in BCAR at 3 mo (15% versus 19%)
Seron et al. (241), 2008	57 (of 89 randomized), unspecified	CSA, MMF, steroids	FLUV 80 versus placebo	At transplantation	6	Progression of allograft mean intimal arterial volume fraction, from pre-implant to 6-mo biopsies	No difference in primary outcome; significantly lower transplantation vasculopathy with FLUV in secondary analysis (7% versus 33%; p=0.02)
Hausberg et al. (242), 2001	40 DD	CSA, steroids	FLUV 40 versus placebo	PTD ≥182	6	Longitudinal change in ultrasonographic measures of vasodilation	Significant increase in brachial artery flow-mediated vasodilation at 6 mo only with FLUV
Cofan et al. (243), 2002	47, unspecified	CSA, steroids	PRAV 20 versus low-fat diet	PTD >365	12	Longitudinal change in ultrasonographic measures of carotid atherosclerosis	Significant reductions in intima-medial thickness and plaque number at 12 mo with PRAV (48% and 54%, versus unspecified control proportions)

(Continued)

Table 10. Continued

Trial Authors, Year	Sample Size, Donor Types	Immunosuppression	Statin, mg/d, and Comparison	Enrollment in Relation to KT	Trial Duration, mo	Primary Outcome	Results
Kosch et al. (244), 2003	26, DD	CSA, steroids	FLUV 40 versus placebo	PTD >182	36	Longitudinal change in ultrasonographic measures of arterial distensibility and vasodilation	Significant increase in brachial flow-mediated vasodilation at 36 mo only with FLUV; no change in other outcomes in either group over time
Asberg et al. (245), 2003	75, unspecified	CSA, AZA, steroids	FLUV 40 versus placebo	PTD ≤2	3	Laser Doppler flowmetric measures of endothelial function	No between-group differences
Holdaas et al. (227), 2003	2,102, DD or LD	CSA based	FLUV 40 versus placebo	PTD ≥182	61 (mean)	Composite of cardiac death, nonfatal MI, or coronary intervention	Nonsignificant reduction in composite event rate with FLUV (RR, 0.83; 95% CI, 0.64 to 1.06)

ATG indicates antithymocyte globulin; ATORV, atorvastatin; AZA, azathioprine; BCAR, biopsy-confirmed acute rejection; CERIV, cerivastatin; CI, confidence interval; CKD, chronic kidney disease; CSA, cyclosporine; DD, deceased donor; FLUV, fluvastatin; HDL, high-density lipoprotein; KT, kidney transplantation; LD, living donor; LDL, low-density lipoprotein; LOV, lovastatin; MI, myocardial infarction; MMF, mycophenolate mofetil; PRAV, pravastatin; PTD, post-transplantation day; RR, relative risk; SIMV, simvastatin; TCHOL, total cholesterol; and TG, triglycerides.

2. **Consistent with NKF/KDOQI guidelines, given the risks of pharmacological therapy to raise HDL (in the absence of high LDL or high triglycerides), it is not recommended to initiate such therapy in patients with kidney disease (*Class III; Level of Evidence B*).**

3. **Lipid-lowering therapy specifically for the goals of preventing acute rejection or preserving allograft function is not recommended (*Class III; Level of Evidence B*).**

Liver Transplantation Candidates

The goals of cardiovascular assessment in liver transplantation candidates are to 1) determine whether a patient can be expected to survive the operation and immediate postoperative period and 2) to determine whether a patient has such severe cardiopulmonary disease that transplantation would be futile and an inappropriate use of a scarce donor organ.

There are fundamental differences between renal and liver transplantation candidates that have a major impact on the preoperative cardiovascular risk assessment. Diabetes mellitus with diffuse cardiovascular disease is far less common in liver transplantation candidates than in renal transplantation candidates. Most patients with cirrhosis have glucose intolerance and are often labeled as "diabetic"; however, very few have retinopathy, nephropathy, vascular disease, or a family history of diabetes mellitus. Thus, the overall risk of CAD and diffuse vascular disease is far lower in candidates for liver transplantation than among patients who are candidates for renal transplantation. When present in liver transplantation candidates, diabetes mellitus is often accompanied by various degrees of obesity.

Hypertension also is far less common in patients with end-stage liver disease (ESLD) compared with patients with ESRD. Patients with cirrhosis and portal hypertension often develop a hyperdynamic circulation with extremely low peripheral vascular resistance and a compensatory increase in cardiac output (259). Blood pressure in most patients is normal or low. Thus, the need for pretransplantation treatment of hypertension is unusual.

Several cardiopulmonary problems are distinctly common among or unique to liver transplantation candidates. These include pulmonary hypertension and the hepatopulmonary syndrome, defined as hypoxia from intrapulmonary shunts in patients with cirrhosis and portal hypertension.

Evaluation for CAD in Liver Transplantation Candidates

The reduced patient survival among orthotopic liver transplant recipients >60 years of age has been associated with nonhepatic causes of infection, neurological events, and cardiac events (278). The prevalence of CAD in patients with ESLD is equal to or greater than the incidence in the normal population, particularly in patients with diabetes mellitus with cirrhosis, ranging from 2.5% to 27% (279–283).

Older reports suggested a high risk of postoperative mortality and morbidity in patients with CAD who undergo liver transplantation. For example, 1 small retrospective study reported a 50% postoperative mortality in patients with CAD who underwent liver transplantation (284). As a result, many transplantation centers perform myocardial stress testing in liver transplantation candidates with traditional CAD risk factors. Most centers use pharmacological stress with dipyridamole, dobutamine, or adenosine because many liver transplantation candidates are too debilitated to complete adequate exercise testing. Fewer than 10% of these tests are positive for provocable ischemia (282). Furthermore, there is a poor correlation between the abnormalities noted, angiographic findings, and postoperative complications resulting from CAD (282,285,286). In a series of 772 consecutive liver transplantation candidates who underwent MPS at 1 center, 710 were thought to be at low risk, 36 at intermediate risk, 17 at high risk, and 9 had incomplete studies (287). All patients considered to be at high risk on the basis of stress imaging

underwent coronary angiography. A total of 26 patients with positive MPS and angiographic evidence of CAD were denied transplantation; however, CAD was the sole reason for denial in only 7 patients. A total of 291 patients subsequently underwent transplantation. In this group, 18 (6.2%) had an intermediate- or high-risk MPS, only one of whom had a history of CAD. After a median follow-up of 25 months, 10 patients had a total of 13 postoperative or subsequent coronary events: 5 within 30 days and 8 within the first postoperative year. All 5 patients with coronary events within the first 30 postoperative days had low-risk preoperative MPS. Thus, more recent studies suggest a lower incidence of CAD among liver transplantation candidates and a far lower risk of postoperative complications than was found in prior studies.

With respect to the accuracy of noninvasive testing modalities for CAD among liver transplantation candidates, single-photon emission computed tomography perfusion imaging demonstrated a poor sensitivity and specificity for detecting CAD in liver transplantation candidates in 1 study (285). DSE may be used to screen low-risk liver transplantation candidates for CAD (281). The prevalence of CAD among 80 liver transplantation candidates evaluated by DSE was 5% and was associated with diabetes mellitus. DSE was positive in 7.5% of patients and had a high sensitivity and specificity for CAD in this cohort, but the number of patients studied was small. A study of coronary artery calcium scores in 101 liver transplantation candidates found an elevated coronary artery calcium score in 74% of asymptomatic patients (288), with 37.6% having scores in the moderate-risk range (>100, or ≈2% predicted annual risk of cardiac events) and 19.8% having scores in the high-risk range (>400, or ≈3% to 5% predicted annual risk of cardiac events) (289).

There is considerable concern about the efficacy and cost-effectiveness of the screening strategy used for CAD identification before liver transplantation. One particular concern is that the vasodilated state of many liver transplantation candidates lends poorly to the characteristics of some pharmacological agents used for MPS (285) such as adenosine or dipyridamole stress-perfusion studies.

The 2005 "AASLD Practice Guidelines: Evaluation of the Patient for Liver Transplantation" (260), include an opinion-based recommendation that "chronic smokers, patients over the age of 50, and those with a clinical or family history of heart disease or diabetes should undergo evaluation for CAD." Based on cohort or case-control analytic studies, the guidelines also state that "DSE appears to be an effective screening test in this setting; however, positive test results should be confirmed with cardiac catheterization." Information on the extent of CAD may help risk stratify the patient and better define the patient's candidacy for liver transplantation (283).

Cardiac catheterization may be performed despite coagulopathy in patients with ESLD, although at increased risk of bleeding complications. Sharma et al. (290) reported that 88 patients with ESLD undergoing cardiac catheterization had lower baseline hemoglobin and higher international normalized ratio and serum creatinine levels than matched control subjects. Patients with ESLD had a higher rate of vascular complications (5.7% pseudoaneurysms) than control subjects (0%) and higher rates of requirements for red cell transfusion

(16% versus 4%; p=0.008), fresh-frozen plasma (51.7% versus 1.2%; p<0.001), and platelet transfusions (48.3% versus 1.2%; p<0.001). Major bleeding with angiography occurred in 14.8% of the ESLD group versus 3.7% of matched control subjects.

Recommendations

1. **Noninvasive stress testing may be considered in liver transplantation candidates with no active cardiac conditions on the basis of the presence of multiple CAD risk factors regardless of functional status. Relevant risk factors among transplantation candidates include diabetes mellitus, prior cardiovascular disease, left ventricular hypertrophy, age greater than 60 years, smoking, hypertension, and dyslipidemia. The specific number of risk factors that should be used to prompt testing remains to be determined, but the committee considers 3 or more to be reasonable (*Class IIb; Level of Evidence C*).**

2. **It may be reasonable for each program to identify a primary cardiology consultant for questions related to potential liver transplantation candidates (*Class IIb; Level of Evidence C*).**

Management of Flow-Limiting CAD in Liver Transplantation Candidates

Early reports suggested an unacceptably high mortality and morbidity associated with liver transplantation in patients with concomitant CAD. Plotkin (284) reported 32 patients with CAD who underwent liver transplantation. Overall 1- to 3-year mortality was 50%. Twenty patients with prior CABG had 50% mortality and 80% morbidity. The 9 patients with medically treated CAD and had 56% mortality after transplantation.

CABG surgery is associated with high morbidity and mortality in patients with ESLD. In early reports, CABG in ESLD patients was associated with 30% to 40% mortality and significant morbidity in 70% to 100% (291,292). A more recent report of 18 patients with Child class A (n=13), B (n=4), and C (n=1) cirrhosis undergoing CABG suggested better in-hospital survival of 94% and a major complication frequency of 39% in patients with Child class A and 80% in patients with Child class B/C cirrhosis. A case series of 27 CABG surgeries in patients with cirrhosis reported 26% operative mortality (Child class A, 11%; B, 18%; C, 67%) (293). One-year survival including the in-hospital period was 80% in Child class A, 45% in class B, and 16% in class C patients. The authors concluded that, when necessary, CABG can be performed in patients with cirrhosis and that the Child classification predicted in-hospital and 1-year mortality.

There are also several reports of combined CABG and liver transplantation. Axelrod et al. (294) reported combined CABG and orthotopic liver transplantation in 5 patients with severe 3-vessel CAD. There were no interoperative deaths, and combined graft and patient survival at 35 months was 80% (4 of 5; 1 patient died of recurrent hepatitis C and liver failure).

Thus, the available studies show that significant CAD may alter suitability for liver transplantation. Patients with Child class

A liver failure can probably undergo CABG if indicated but with higher risks of mortality and morbidity than in patients without liver failure. There is no information in the literature about the outcomes of PCI in patients with CAD and ESLD. However, it has been suggested that symptomatic, medically refractory angina in liver transplantation candidates should be treated with PCI (preferably BMS and limited dual antiplatelet therapy). There are no clinical data to support this recommendation, but it is not unreasonable given the lack of studies.

Acute coronary syndromes in liver transplantation candidates should probably be treated with PCI per the "2011 ACCF/AHA Focused Update Incorporated Into the ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction" (140), taking into account the increased bleeding risk from antiplatelet agents. Cardiac surgery can be performed after liver transplantation with acceptable morbidity and mortality, as reported in a series of 15 patents from Baylor (295). This series reported no early deaths, 20% minor complications, and no rejection episodes. At a mean of 26.5 months of follow-up, 13.3% had died and 25% had recurrent angina.

Recommendation

1. **Liver transplantation candidates who have an LVEF less than 50%, evidence of ischemic left ventricular dilation, exercise-induced hypotension, angina, or demonstrable ischemia in the distribution of multiple coronary arteries should be referred to a cardiologist for evaluation and long-term management according to ACC/AHA guidelines for the general population (*Class I; Level of Evidence B*).**

Evaluation for Pulmonary Hypertension in Liver Transplantation Candidates

Pulmonary arterial hypertension has been increasingly recognized as a cardiovascular complication among patients with ESLD. An earlier study that linked the 2 disease states based on a consecutive series of 17,901 autopsies found a prevalence of biopsy-proven pathological changes consistent with pulmonary arterial hypertension in 0.13% of all patients but a 5-fold higher prevalence (0.73%) among patients with hepatic cirrhosis (261). More recent studies have used echocardiographic Doppler techniques to identify the presence of elevated PASP. One consecutive series of 83 patients with hepatic cirrhosis reported a 20% prevalence of pulmonary hypertension (defined as PASP >30 mm Hg) compared with 0% in healthy volunteers (262). Confirmation by right heart catheterization was available in this study.

The presence of severe pulmonary hypertension is associated with a marked decrease in survival among liver transplantation candidates and transplant recipients (263–266). For example, in a retrospective study of 1,205 liver transplant recipients, 3-year mortality rose in a graded manner among those with absent (PASP <30 mm Hg), mild (31 to 44 mm Hg), moderate (45 to 59 mm Hg), and severe (>60 mm Hg) pulmonary hypertension (263). Two-dimensional and Doppler echocardiography has been shown in most studies to be an effective screening tool for pulmonary hypertension in liver transplantation candidates (267–270). Because of the high prevalence of pulmonary hypertension in liver transplantation candidates and adverse prognostic implications of severe disease, it is prudent to perform echocardiography in every potential liver transplantation candidate. Although it has been shown to be a sensitive screening tool, potential technical pitfalls may lead to an underestimation or overestimation of the severity of disease (271,272). In addition, common echocardiographic techniques are used to estimate the PASP, whereas the severity and treatment of pulmonary hypertension are generally based on the mean pulmonary artery pressure, pulmonary capillary wedge pressure, and pulmonary vascular resistance. Although these parameters can be derived with echocardiography (273), the proposed methods are less well validated and adopted in clinical practice. Thus, moderate and severe pulmonary hypertension detected on echocardiography should be confirmed by right heart catheterization (267,268).

Echocardiography with agitated saline contrast can also be used to detect intrapulmonary arteriovenous shunt, which is a common finding in patients with ESLD, with an estimated prevalence of 17% and 47% (274). This finding is an important component of hepatopulmonary syndrome, defined by the presence of chronic liver disease, significant hypoxemia, and intrapulmonary shunt. Liver transplantation is considered to be the only effective treatment for this condition in most patients (274). Microbubbles that appear late (after a time delay of 4 to 8 cardiac cycles) in the left side of the heart after agitated saline injection into the venous system are consistent with the diagnosis. Immediate or early shunting is more consistent with an atrial septal defect or patent foramen ovale. If diagnostic questions remain after performance of a transthoracic study, a transesophageal echocardiogram can provide increased sensitivity (51% versus 32%; p<0.001) and direct visualization of bubbles entering the left atrium from the pulmonary veins rather than crossing the interatrial septum (275).

Recommendation

1. **It is reasonable to perform resting echocardiography in patients who are potential liver transplant recipients for the purpose of identifying pulmonary hypertension and/or intrapulmonary arteriovenous shunt (*Class IIa; Level of Evidence B*).**

There is no consensus or guideline on the threshold value of PASP measured by Doppler echocardiography that should be used to trigger further invasive testing with right heart catheterization. The presence of severe pulmonary hypertension (PASP >60 mm Hg) on noninvasive testing has most clearly been associated with adverse outcomes in the liver transplantation population. Because of the margin of error of the measurement, a cutoff value of >45 mm Hg may be reasonable until more data are available.

Recommendation

1. **If right heart catheterization confirms the presence of significant pulmonary arterial hypertension (as defined by mean pulmonary artery pressure ≥25 mm Hg,**

Table 11.   Proposed Randomized Controlled Trials in Kidney and Liver Transplantation Candidates

1. Screening for obstructive CAD among potential transplantation candidates

   Target population: potential candidates for deceased and living donor kidney and/or liver transplantation

   Intervention: randomized comparison of 4 approaches to the preoperative cardiovascular evaluation: 1) cardiac catheterization for all candidates, including fractional flow reserve measurement in indeterminate lesions, 2) noninvasive stress testing for all patients, 3) noninvasive stress test based on presence of 3 or more cardiac risk factors,* 4) ACC/AHA cardiac evaluation and care algorithm for noncardiac surgery (7)

   Primary outcome

      MACEs

        Timing: pretransplant, peritransplant, and 1, 5, and 10 y post-transplant

   Secondary outcomes

      Access to transplantation

      Cost-effectiveness

2. Optimal preoperative treatment strategy for 1- or 2-vessel CAD (excluding left main or proximal LAD)

   Target population: asymptomatic potential kidney and/or liver transplantation candidates (without active cardiac conditions) referred for cardiac catheterization because of the presence of ischemia on noninvasive testing in whom 1- or 2-vessel CAD is identified at cardiac catheterization, with fractional flow reserve in indeterminate lesions

   Intervention: randomized comparison of PCI versus optimal medical therapy

   Primary outcome

      MACEs

        Timing: pretransplant, peritransplant, and 1, 5, and 10 y post-transplant

   Secondary outcomes

      Access to transplantation

      Waitlist mortality

      Cost-effectiveness

3. Optimal surveillance strategy for obstructive CAD on the waitlist

   Target population: kidney and/or liver transplantation candidates with multiple CAD risk factors* actively listed for deceased donor transplantation

   Intervention: randomized comparison of 4 strategies for repeat noninvasive stress testing: 1) annual, 2) every 2 years, 3) every 3 years, or 4) only based on a change in symptoms

   Primary outcome

      MACEs

        Timing: pretransplant, peritransplant, and 1, 5, and 10 y post-transplant

   Secondary outcomes

      Access to transplantation

      Waitlist mortality

      Cost-effectiveness

4. Other cardiac conditions

   4a. Valvular heart disease

      Target population: potential kidney and/or liver transplantation candidates with asymptomatic severe aortic stenosis (aortic valve area $\leq$1.0 cm^2)

      Intervention: randomized comparison of standard care (per the ACC/AHA guidelines for the management of valvular heart disease [102]) versus pretransplantation valve replacement.

      Primary outcome

        MACEs

          Timing: pretransplant, peritransplant, and 1, 5, and 10 y post-transplant

   4b. Pulmonary hypertension

      Target population: potential kidney and/or liver transplantation candidates with pulmonary arterial hypertension confirmed on right heart catheterization (mean pulmonary artery pressure $\geq$25 mm Hg, pulmonary capillary wedge pressure $\leq$15 mm Hg, pulmonary vascular resistance >3 Wood units)

      Intervention: randomized comparison of vasodilator strategies: endothelin receptor blockers versus phosphodiesterase inhibitors

      Primary outcome

        MACEs

          Timing: pretransplant, peritransplant, and 1, 5, and 10 y post-transplant

      Secondary outcomes

        Access to transplantation

        Waitlist mortality

        Change in functional capacity, defined by the 6-min walk test

(Continued)

Table 11. Continued

5. Medical management of cardiovascular risk
   Target population: kidney and/or liver transplantation candidates
   Intervention: aspirin versus placebo for primary prevention of MACEs
     Primary outcome
       MACEs
         Timing: pretransplant, peritransplant, and 1, 5, and 10 y post-transplant

ACC/AHA indicates American College of Cardiology/American Heart Association; CAD, coronary artery disease; LAD, left anterior descending; MACEs, major adverse cardiac events; and PCI, percutaneous coronary intervention.

*CAD risk factors are as defined under "Summary and Recommendations Regarding Noninvasive Stress Testing in Kidney Transplantation Candidates Without Active Cardiac Conditions."

pulmonary capillary wedge ≤15 mm Hg, and pulmonary vascular resistance of >3 Wood units) in the absence of an identified secondary cause (e.g., obstructive sleep apnea, left heart disease), referral to a consultant with expertise in pulmonary arterial hypertension management and advanced vasodilator therapies is reasonable (*Class IIb; Level of Evidence C*).

Despite the adverse prognostic implications of pulmonary hypertension, successful presurgical treatment of pulmonary hypertension is associated with excellent survival after liver transplantation (265,266). It has been shown that many patients can discontinue vasodilator therapy within months after liver transplantation. Every patient with severe pulmonary hypertension who is otherwise a good candidate for liver transplantation should be considered for treatment with vasodilator therapy. Patients who have an excellent response to treatment have outcomes after liver transplantation comparable to those of other transplantation candidates (276,277).

Medical Management of Cardiovascular Risk in Liver Transplantation Candidates

Preoperative medical management of hypertension, lipid disturbances, and atherosclerotic risk in liver transplantation candidates differs considerably from that of renal transplantation candidates. Because of the hyperdynamic circulation that develops in most patients with ESLD with portal hypertension, preoperative or postoperative hypertension is an unusual complication in most liver transplantation candidates. Most liver transplantation candidates with hypertension have intrinsic renal disease as a comorbid condition. All of the modern antihypertensives appear to be safe in ESLD; thus, those few patients who are hypertensive can be managed in a fashion similar to that used for renal transplantation candidates. Patients with large esophageal varices benefit particularly from nonselective beta-blockers (propranolol or nadolol) to reduce the risk of variceal hemorrhage (296). A retrospective study of 413 liver transplant recipients at 1 center found that the 27% of the sample receiving propranolol or metoprolol in the perioperative period experienced a marked reduction in the adjusted odds of nonfatal MI or death within 30 days (adjusted OR, 0.20; 95% CI, 0.07 to 0.59) compared with no beta-blocker use (297). However, additional study, ideally in a randomized trial, is needed before conclusions can be made specifically about the use of beta-blockers for cardioprotection before liver transplantation.

Recommendation

1. **It is reasonable to initiate nonselective beta-blockers in liver transplantation candidates with large esophageal varices (*Class IIa; Level of Evidence B*).**

Because of the generally short duration of the waiting time before liver transplantation, control of lipid abnormalities and medical management of atherosclerotic risk factors are not high priorities in the pretransplantation management of most liver transplantation candidates. Furthermore, the lipid abnormalities that develop in patients with severe cholestatic liver diseases have not been shown to be associated with an increased risk of coronary events (298). In addition, because many liver transplantation candidates have a coagulopathy with prolonged prothrombin times, thrombocytopenia from hypersplenism, and esophageal and gastric varices, any form of anticoagulation is generally avoided unless or until the patient has well-documented CAD. Furthermore, any nonsteroidal medication (including aspirin) is generally avoided because of the risks of gastric irritation, bleeding, and exacerbation of renal dysfunction in patients with ESLD.

Prospective studies on optimal screening strategies for the presence of CAD and the indications, timing, and outcomes of interventional therapy in patients with ESLD are lacking and much needed.

Conclusions

Patients with ESRD or ESLD are at increased risk for cardiac events compared with the general population. Cardiovascular disease remains the most common cause of death in solid-organ transplant recipients, with the highest rates occurring immediately after transplantation. This increased cardiovascular risk may be related to traditional and nontraditional risk factors and is associated with a somewhat different pathophysiology compared with the pathophysiology in patients without end-stage organ disease. The presence of symptoms of cardiovascular disease is an important prognostic marker that warrants cardiac evaluation. Noninvasive methods for screening for CAD have prognostic value for mortality but imperfect sensitivity and specificity for detecting angiographically defined CAD in patients with kidney or liver failure. Associations of CAD by angiography with subsequent survival are also inconsistent, likely because many plaque ruptures producing MI are not localized to sites of angiographic stenosis. The efficacy and best methods of myocardial revascularization

have not been examined in large, contemporary clinical trials among patients with CKD or chronic liver disease. At this time, there is no strong evidence for or against routine cardiac screening of asymptomatic transplantation candidates. More evidence is required, ideally from randomized clinical trials, to guide strategies for pretransplantation cardiac risk assessment in potential kidney or liver transplantation candidates and to optimize risk factor management before, during, and after transplantation. Clinical trials proposed by the work group are provided in Table 11.

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Appendix 1. Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speaker's Bureau/ Honoraria	Ownership Interest	Consultant/ Advisory Board	Other
Kim Eagle, Chair	University of Michigan	None	None	None	None	None	None
Krista L. Lentine, Co-Chair	Saint Louis University	None	None	None	None	None	None
Salvatore P. Costa, Co-Chair	Dartmouth Hitchcock Medical Center	None	None	None	None	None	None
Andrew D. Auerbach	University of California, San Francisco	None	None	None	None	None	None
Kline Bolton	University of Virginia	None	None	None	None	None	None
Robert L. Carithers	University of Washington	None	None	None	None	None	None
Lee A. Fleisher	University of Pennsylvania	Pfizer*	None	None	None	None	None
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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all writing group members are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10,000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10,000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Appendix 2. Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Kevin Abbott	Walter Reed Army Medical Center	K08 DK073036 with Dr Lentine*	None	None	None	Johnson & Johnson*	None	Have been coauthor with Dr Lentine before*
Eric R. Bates	None	None	None	None	None	None	AstraZeneca*; BMS*; Daiichi Sankyo*; Eli Lilly*; Ikaria*; Merck*; Sanofi Aventis*	MAQUET*; Takeda*
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Christopher Defilippi	University of Maryland	Roche Diagnostics†	None	Roche Diagnostics†	None	None	Roche Diagnostics*	None
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Michael S. Lauer	NHLBI	None	None	None	None	None	None	None
Glenn N. Levine	U.S. government (VA)	None	None	None	None	None	None	None
David J. Moliterno	None	None	None	None	None	None	Merck-Schering Plough*; Boston Scientific*	None
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Peter K. Smith	None	None	None	None	None	None	Baxter*; Bayer*; Eli Lily*	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10,000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10,000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant"under the preceding definition.

*Modest.

†Significant.

Appendix 3.   Abbreviations

ACC	American College of Cardiology
ACCF	American College of Cardiology Foundation
ADA	American Diabetes Association
AST	American Society of Transplantation
BMS	Bare-metal stent
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CI	Confidence interval
CKD	Chronic kidney disease
cTn	Cardiac troponin
cTnT	Cardiac troponin T
DES	Drug-eluting stent
DSE	Dobutamine stress echocardiography
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ESLD	End-stage liver disease
ESRD	End-stage renal disease
FHS	Framingham Heart Study
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
HR	Hazard ratio
IHD	Ischemic heart disease
KDIGO	Kidney Disease: Improving Global Outcomes
LAD	Left anterior descending
LDL	Low-density lipoprotein
LVEF	Left ventricular ejection fraction
MACEs	Major adverse cardiovascular events
METS	Metabolic equivalent tasks
MI	Myocardial Infarction
MPS	Myocardial perfusion scintigraphy
NKF/KDOQI	National Kidney Foundation/Kidney Disease Outcomes Quality Initiative
OPTN	Organ Procurement and Transplantation Network
OR	Odds ratio
PASP	Pulmonary artery systolic pressure
PCI	Percutaneous coronary intervention
RR	Relative risk
RVSP	Right ventricular systolic pressure
USRDS	U.S. Renal Data System