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Diagnosis and Management of Cardiovascular Disease in Advanced and End-Stage Renal Disease

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Chronic kidney disease (CKD) affects 13% of the US population.[1] Although a significant proportion of these patients progress to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT)[2] or renal transplantation, cardiovascular disease remains the most common cause of mortality and accounts for 53% of all deaths with a known cause in patients on dialysis.[3] Critically, cardiovascular disease also remains the leading cause of death after renal transplantation. Appropriate management of cardiovascular disease in this very high-risk population is of paramount importance.

Pathobiological processes that underpin the progression and severity of cardiovascular disease in CKD include accelerated atherosclerosis and continuous reduction in left ventricular (LV) function as renal function declines.[1] While on hemodialysis, these processes accelerate. Importantly, the risk of developing pulmonary hypertension (PH) also rises proportionately to the duration of hemodialysis.[4] In contrast to dialysis, renal transplantation can help prevent the progression of pathological cardiovascular processes. Renal transplantation can potentially reverse myocardial damage that is thought to result from prolonged exposure to uremic toxins and improve LV systolic function.[5–7]

In this review, we provide a contemporary overview of the pre- and perioperative cardiovascular evaluation of patients with ESRD who are considered suitable candidates for renal transplantation. In addition, we review the evidence-based guidelines on optimal management of cardiovascular disease in patients with advanced CKD with particular focus on coronary artery disease (CAD), congestive heart failure (CHF), valvular disease, and PH. The overall aim is to identify the subset of patients who may maximally benefit from renal transplantation. Finally, we provide evidence-based recommendations for diagnosis, management, and application in clinical practice.

CAD in Patients With ESRD

CAD is highly prevalent in patients with ESRD largely because of the presence of comorbidities such as hypertension, diabetes mellitus, dyslipidemia, obesity, and tobacco use.[8] The incidence of CAD in patients initiating dialysis is up to 38%, with a relative risk of 5- to 20-fold that of the general population.[9] The uremic environment may also contribute to the higher prevalence and accelerated progression of CAD.[1,10] Moreover, atherosclerosis is an inflammatory process.[11,12] Patients with ESRD have high levels of C-reactive protein and proinflammatory cytokines,[1,10,13,14] which predisposes them to plaque formation. Endothelial dysfunction and high oxidative stress further drive atherosclerosis and are exacerbated in the setting of the activated renin–angiotensin–aldosterone system in CKD and ESRD.[1,10,13,14] Moreover, therapies for secondary prevention of CAD such as statins and angiotensin-converting enzyme (ACE) inhibitors may have diminished clinical benefit in ESRD.[12,15]

Coronary plaques in patients with ESRD exhibit extensive heterotopic calcification.[16] On computed tomography coronary angiography in young patients with ESRD, a disproportionate incidence of high calcium scores is detected with the probability of coronary artery calcification increasing with longer durations of dialysis.[16] Calcification occurs in smooth muscle cells in the media or in the neointima of atherosclerotic plaques, contributing to vascular stiffness and death from CAD.[17] In addition to increased plaque complexity, the clinical presentation of CAD is also different. Patients with advanced CKD are more likely to present with acute coronary

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J Am Heart Assoc. 2016;5:e003648 doi: 10.1161/JAHA.116.003648.

syndrome as the first manifestation of CAD, as opposed to angina in patients without renal disease.[18]

Noninvasive Imaging to Assess CAD

Many sets of guidelines aim to guide cardiovascular evaluation in renal transplantation candidates, but there is no universal consensus on an optimal approach. The 2014 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines on perioperative cardiovascular evaluation in the general population undergoing noncardiac surgery do not recommend testing for asymptomatic patients with a functional capacity considered to be moderate (defined as ≥4 metabolic equivalents).[19] Testing in patients with poor functional capacity (<4 metabolic equivalents) or unknown functional status is recommended to be based on combined clinical and surgical risk factors, with noninvasive tests performed for patients at elevated risk[19]. However, it is unclear whether these recommendations should be applied to potential candidates for transplantation.[20] A study of 204 candidates for renal transplantation reported that 80% of patients with no active cardiac conditions had a functional status of ≥4 metabolic equivalents,[20,21] which in part reflects the relatively younger age of transplant candidates. Consequently, a functional status of ≥4 metabolic equivalents is not a reliable predictor of CAD in this population.[20,21] Instead, the 2012 AHA/ACC scientific statement regarding cardiac evaluation in renal transplantation candidates recommends that the decision to proceed with noninvasive stress testing in patients with no active cardiac conditions should be based on the presence of multiple risk factors for CAD most relevant to the transplantation population, regardless of functional status. These risk factors include diabetes mellitus, prior cardiovascular disease, >1 year on dialysis, left ventricular hypertrophy (LVH), age >60 years, smoking, hypertension, and dyslipidemia.[20,22] Although the specific number of risk factors to proceed with stress testing remains to be determined, the AHA/ACC guidelines suggest the presence of ≥3 risk factors as a reasonable threshold for noninvasive testing.[20] Guidelines from the Kidney Disease Outcomes Quality Initiative (KDOQI) recommend annual evaluation for CAD in diabetic patients on the waiting list for transplantation if the initial evaluation for CAD at the start of dialysis is negative. In high-risk patients without diabetes mellitus on the transplantation waitlist (≥2 traditional risk factors, known history of CAD, peripheral vascular disease, and LV ejection fraction [LVEF] ≤40%), evaluation for CAD every 24 months is recommended. Patients on hemodialysis with an LVEF ≤40% or those with new symptoms of concern regarding ischemic heart disease are recommended to be evaluated continuously for CAD.[23,24]

Noninvasive testing with electrocardiogram (ECG), transthoracic echocardiogram, pharmacological stress echocardiography, and nuclear imaging (with single photon emission computed tomography [SPECT] or cardiac positron emission tomography [PET]) are suggested as the first steps in investigating for presence of CAD. Patients should have baseline ECGs to evaluate for Q waves, ST-T changes, T wave inversions, and left bundle branch block, which previously have been shown to be predictive of CAD.[25] Exercise ECG is not recommended, given abnormal baseline ECGs and overall poor exercise tolerance in this patient population. A baseline transthoracic echocardiogram performed at dry weight is also important because it can help identify impaired LVEF and wall motion abnormalities, which may be signs of prognostically significant CAD.[26] A normal cardiac stress test has a high negative predictive value for cardiovascular events[27,28] in the perioperative and follow-up periods, as shown in a study of renal transplant candidates undergoing preoperative SPECT.[29] A hybrid SPECT/computed tomography scan assesses for ischemia and coronary artery calcification, which is highly prevalent in patients with ESRD.[30] Coronary artery calcium score, however, does not independently provide significant incremental prognostic value in predicting mortality or nonfatal myocardial infarction in ESRD.[30] These findings may be explained by the differences in distribution of calcium within the coronary artery in ESRD, as shown by intravascular imaging.[31] Patients with ESRD have a higher prevalence of intimal calcium without greater lipid arc or thin-cap fibroatheroma, which are markers of vulnerable plaque.[31]

Presence of inducible ischemia on dobutamine stress echocardiogram (DSE) has been shown to be predictive of future cardiac events and all-cause mortality.[27,32] Although the accuracy of dobutamine stress echocardiogram and SPECT in detecting obstructive CAD (≥70% stenosis) in renal transplantation candidates was not statistically different in a meta-analysis,[33] the presence of concentric and eccentric LVH, common in ESRD, may affect the accuracy of dobutamine stress echocardiogram.[34] PET imaging assesses not only myocardial blood flow but also coronary flow reserve, which can provide additional insights into early stages of atherosclerosis and microvascular dysfunction.[35,36] Recently, coronary flow reserve assessed by cardiac PET has been shown to provide incremental risk stratification for cardiovascular and all-cause mortality in patients on dialysis, even in the absence of overt cardiovascular disease.[36] For the highest risk patients, PET may be advantageous because it has superior sensitivity for detecting CAD.[35,36] In addition, PET exposes patients to far less radiation than SPECT, an important consideration given the potential need for repeated stress testing during the recipient waiting period. Overall, it is important to consider both the local availability of these tests and the expertise in interpreting them when deciding which test is best suited to evaluate for ischemia in this group of patients.

Coronary Angiography and Revascularization

Although coronary angiography is usually reserved for patients with evidence of ischemia on noninvasive imaging to determine their need for preoperative revascularization, it is also reasonable to consider coronary angiography in renal transplantation candidates at high risk of CAD despite normal stress tests. It is important to identify prognostically important CAD that may require revascularization prior to transplantation.[37] Evidence of atherosclerotic vascular disease involving other vascular beds, particularly peripheral arterial disease, may help identify patients with advanced coronary atherosclerosis.[38–41] Since peripheral arterial disease is highly associated with CAD, it may be reasonable to pursue left heart catheterization in patients with peripheral arterial disease despite negative stress tests. Similarly, patients with cardiac autonomic dysfunction, autonomic neuropathy, and retinopathy are at increased risk of CAD.[42–44] The Detection of Ischemia in Asymptomatic Diabetics (DIAD) study found that cardiac autonomic dysfunction was a major predictor of inducible ischemia.[42] Furthermore, some diabetic patients with retinopathy have been found to have reduced coronary flow reserve and cardiovascular disease.[43,44] Taken together, renal transplant candidates with diabetes mellitus as the primary etiology for CKD who have normal stress tests may represent a particularly high-risk group that should be considered for coronary angiography, given their high pretest probability for CAD, as myocardial perfusion imaging has a high false-negative rate in this population.[37]

Revascularization With Coronary Artery Bypass Grafting Versus Percutaneous Coronary Intervention

Observational studies in patients with ESRD who undergo revascularization with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) surgery have shown similar long-term outcomes.[45–49] A recent retrospective analysis of >13 000 patients with CKD treated with CABG or PCI revealed that in the first 3 months after surgery, patients who underwent CABG had a higher risk of progression to ESRD and a higher mortality rate compared with those who underwent PCI.[50] This study used more contemporary interventional approaches such as drug-eluting stents (DESs) as opposed to older generation bare metal stents (BMSs) which helped improve postprocedural cardiovascular outcomes.[50] After the first 6 months, however, CABG portended improved survival. An observational study evaluating >21 000 patients with CKD and multivessel CAD undergoing PCI or CABG revealed improved 5-year survival rates in patients who received CABG[51]; however, these results do not apply to patients with single- or double-vessel CAD. It is important to note that this study did not take into account LV systolic dysfunction, which places patients at a higher risk of sustaining a cardiac event in the perioperative and postoperative periods. It is possible that patients who underwent PCI as opposed to CABG for multivessel disease had a high operative risk that precluded surgical intervention. The KDOQI guidelines recommend CABG for significant left main or 3-vessel CAD.[24]

Although randomized controlled trials to determine the overall mortality benefit of revascularization with PCI in patients with ESRD are lacking, nonrandomized data have suggested that PCI can reduce mortality and lead to greater cardiac event–free survival after transplantation.[52] The ongoing ISCHEMIA-CKD study (ClinicalTrials.gov identifier NCT01985360) will provide critical data for evidence-based management of CAD in patients with CKD. A retrospective analysis of 1460 renal transplant candidates revealed that patients who underwent preoperative coronary revascularization with PCI had significantly improved 5-year survival after renal transplantation compared with patients who were medically managed.[52] Despite similar indications for revascularization in patients with ESRD, this high-risk group of patients was significantly less likely to be revascularized compared with patients with normal renal function,[20,53] in particular those patients with CKD not yet requiring RRT, as contrast-induced nephropathy can precipitate the need for dialysis. To preserve renal function, our group has recently reported the safety and feasibility of cardiac revascularization with PCI guided by intravascular imaging and coronary physiology without utilizing radiocontrast in patients with advanced CKD (stages 4–5).[54] This strategy may be adapted in centers with expertise in intravascular imaging and physiology and may lead to increased provision of PCI while protecting against contrast-induced nephropathy and need for RRT. Unfortunately, even in the setting of acute myocardial infarction, patients with CKD are less likely to be revascularized than patients with normal renal function,[55] despite similar health-related quality of life compared with patients without CKD in the post–myocardial infarction period. In addition, patients with CKD were less likely to be prescribed guideline-recommended therapy including aspirin, statins, and ACE inhibitors at discharge,[55] which may contribute to higher cardiovascular morbidity and mortality. Medical treatment aimed at improving health status after acute myocardial infarction should focus on all patients and be based on current guidelines, regardless of CKD status. The decision to pursue revascularization (CABG or PCI) or to treat medically should be made after a multidisciplinary discussion among interventional cardiologists, nephrologists, and cardiothoracic surgeons and should be individualized to each patient, given the current lack of evidence to guide therapy.[56]

DES Versus BMS

The choice of the types of stents used for PCI in patients with CKD and ESRD presents a clinical dilemma. Compared with patients with normal renal function, restenosis rates in patients with CKD and ESRD are significantly higher.[51,53,57–59] Several studies have shown that the implantation of a DES is associated with lower rates of target vessel revascularization compared with patients who receive a BMS. Nevertheless, the risk of restenosis with a DES in patients with ESRD compared with patients with normal renal function is still higher.[51,53,57–59] A randomized multicenter study evaluating the efficacy of everolimus-eluting stents versus BMSs of identical size and implanted in the same patient showed a reduction in ischemia-driven target vessel revascularization in patients with CKD who received DESs.[60] Nevertheless, it is important to note that a BMS may be preferred in patients in whom renal transplantation is planned within 6 to 12 months, such as those planned to receive living donor transplants, to limit the duration of dual antiplatelet therapy (DAPT). More novel stents that are polymer- and carrier-free but are drug-coated have been shown to be superior to BMSs with respect to requiring target vessel revascularization on only 1 month of DAPT.[61] This type of stent confers the benefit of a DES with an improved safety profile over a BMS, with the additional advantage of a short course of DAPT, which may be ideal for patients with ESRD.[61] Aggressive medical therapy is also an option, given the high restenosis rates in patients with CKD and ESRD.[62–64] These risks must be weighed against the observed improved survival rate after PCI versus medical therapy alone in patients with ESRD.[65]

Duration of DAPT

The 2014 ACC/AHA guidelines recommend that in patients undergoing urgent noncardiac surgery performed <4 to 6 months after BMS or DES implantation, DAPT should be continued unless the relative risk of bleeding outweighs the benefit of prevention of stent thrombosis.[19] Moreover, DAPT should be continued for at least 6 months in patients with DESs if the risk of surgical delay is greater than the risk of DES thrombosis. Importantly, the ACC/AHA guidelines also recommend that perioperative management of DAPT should be discussed by a multidisciplinary team including the operating surgeon, cardiologist, anesthesiologist, and patient to weigh the risks of bleeding and stent thrombosis in an individualized fashion. Important factors to consider in perioperative DAPT management are the type, number, and size of stents versus the risk of delaying renal transplantation in favor of prolonging DAPT to prevent stent thrombosis. A newer generation of DESs with enhanced biocompatibility and reduced thrombogenicity may require only 1 to 6 months of DAPT depending on the type of stent, but more evidence is needed.[61,66,67] These considerations highlight the fact that DAPT should be tailored to the individual patient. For example, patients requiring multivessel PCI with the use of a DES for lesions involving coronary ostia, long lesions, bifurcation lesions, chronic total occlusions, or for cases in which the minimal stent area achieved is small, may benefit from a prolonged course of DAPT. In contrast, patients with high bleeding risk or single-vessel disease who undergo PCI with a DES for simpler coronary lesions (AHA type A/B1) with a large minimal stent area achieved by imaging guidance may require shorter duration of DAPT.[68,69] Moreover, it is important to note that patients with CKD have less platelet inhibition by clopidogrel.[70] Prasugrel and ticagrelor have not been well studied in CKD, and ticagrelor has a relative contraindication in patients with CKD. Data from a few recent clinical series show similar outcomes of renal transplantation performed on DAPT soon after DES implantation. Patients on DAPT or aspirin alone compared with patients not receiving antiplatelet therapy did not have a statistically significant increase in bleeding risk, requirement for blood transfusion, or reoperation.[71,72] These studies should be interpreted with caution because the long-term effects of increased periprocedural bleeding and the need for transfusion on graft survival are lacking.

Effects of Renal Transplantation on Incidence of Acute Coronary Syndrome

Renal transplantation decreases the incidence of acute coronary syndrome compared with maintenance dialysis.[73–75] Renal transplantation is also independently associated with a lower risk of acute coronary syndrome in patients with ESRD secondary to diabetes mellitus compared with patients maintained on hemodialysis.[74] Furthermore, transplantation is associated with a 17% lower adjusted risk of acute coronary syndrome compared with patients remaining on the waiting list for transplantation regardless of the etiology of ESRD.[74] In the posttransplantation period, the risk of ischemic heart disease persists, albeit attenuated, compared with maintenance dialysis; acute graft failure, LVH, and traditional cardiovascular risk factors are the major predictors of ischemic events.[23] Furthermore, immunosuppressive therapy with calcineurin inhibitors and steroids required in transplanted patients can induce diabetes mellitus and worsen glycemic control, hypertension, and dyslipidemia.[1] Consequently, it is important to continue with aggressive risk modification to maintain the cardiovascular benefit of the normalized renal function after renal transplantation.

Recommendations for Management of CAD

The following recommendations take an institutional approach to the management of cardiovascular disease in patients with

advanced CKD based on a comprehensive review of the literature and the currently available guidelines.

Given the importance of preexistent CAD for outcomes after renal transplantation, transplantation candidates should have a thorough evaluation for CAD prior to inclusion on the waiting list, as outlined in Figure 1. Careful clinical history and baseline ECG should be performed in all patients. We perform echocardiography to assess ventricular dimensions and function, recognizing that no studies have specifically addressed appropriateness and cost-effectiveness of this universal approach in transplant candidates. Moreover, given the presence of multiple risk factors for CAD in this patient population, noninvasive testing with dobutamine stress echocardiogram or, preferably, nuclear stress imaging with SPECT or PET are the initial tests that we use to screen for the presence of CAD. Negative results should be interpreted in the context of the pretest probability in individual patients, especially in patients with diabetes mellitus with autonomic dysfunction and microvascular complications.[37,42–44] Patients with multiple risk factors for CAD (≥3 risk factors: diabetes mellitus, prior cardiovascular disease, >1 year on dialysis, LVH, peripheral arterial disease, age >60 years, smoking, hypertension, dyslipidemia) should be considered for further imaging or cardiac catheterization despite a negative stress test in some instances. In such patients, noninvasive imaging with PET is a prudent second-line investigation if coronary angiography is to be avoided because of advanced CKD and risk of progression to RRT. A normal PET stress test with abnormal multivessel coronary flow reserve is also a consideration for coronary angiography.[36] Repeated evaluation is recommended on an annual basis in patients at high risk, with reevaluation every 3 years for low-risk patients.

Patients with evidence of ischemia on stress test should be referred for left heart catheterization to identify prognostically significant CAD. Revascularization by PCI or CABG for 3-vessel disease should be pursued if indicated. The choice to place a BMS or a DES should be individualized to each patient. BMSs or polymer- and carrier-free DESs may be used in patients

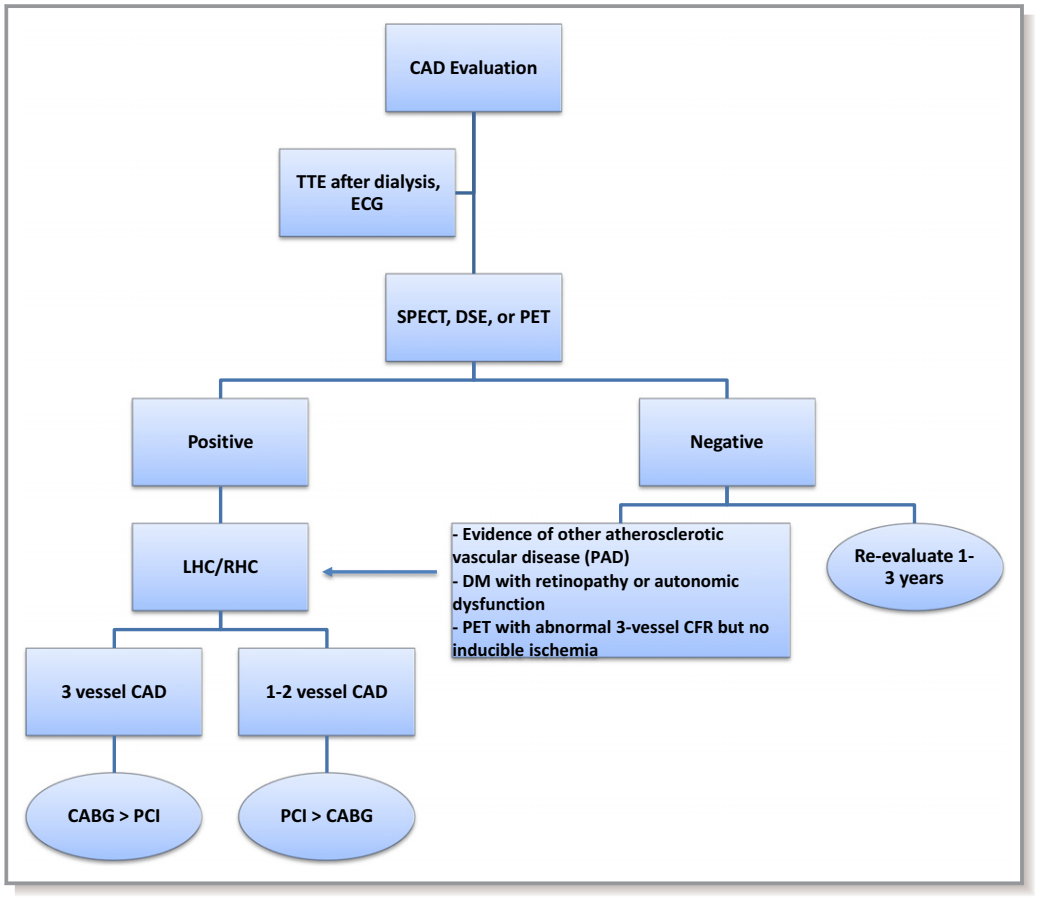

Figure 1. Algorithm for evaluation and treatment of CAD. CABG indicates coronary artery bypass grafting; CAD, coronary artery disease; CFR, coronary flow reserve; DM, diabetes mellitus; DSE, dobutamine stress echocardiography; ECG, electrocardiogram; LHC, left heart catheterization; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PET, positron emission tomography; RHC, right heart catheterization; SPECT, single photon emission computed tomography; TTE, transthoracic echocardiogram.

who require more urgent renal transplantation and a shorter course of DAPT.[61] Stent placement with intravascular imaging guidance is recommended to optimize the intervention as imaging guidance has been shown to result in a larger final minimal stent area, minimizing the risk of restenosis and stent thrombosis.[69]

CHF in Patients With ESRD

It is estimated that up to 36% of all patients with ESRD have CHF at the initiation of dialysis[76]—12 to 36 times higher than the rate in the general population.[9] Another 25% of patients on dialysis develop de novo CHF with an incidence of 7% per year.[77] The underlying causes of CHF in patients with ESRD at the initiation of dialysis are similar to those in the general population including advancing age, diabetes mellitus, and ischemic heart disease.[9,77] More specific to CKD, toxins from the uremic milieu may affect myocardial contractility and function,[7] and anemia secondary to CKD is associated with a higher incidence of CHF in this population.[76] Chronic volume overload and poorly controlled hypertension are also major risk factors for CHF in patients with CKD and ESRD. Therefore, it is important to control hypertension and volume status through diuresis and dialysis to reduce the risk of incident CHF.

Management of CHF in Patients With CKD

Medical treatment of CHF in patients with advanced CKD is similar to patients without renal disease. A meta-analysis of 8 studies conducted in patients with CKD (stages 3–5) and CHF showed that beta blocker therapy lowered all-cause and cardiovascular mortality with an increased risk of bradycardia and hypotension.[78] Nevertheless, there is a paucity of data regarding beta blocker therapy in patients with ESRD on dialysis. The clinical use of ACE inhibitors in this population is also variable, perhaps due to the potential adverse effects on renal function in patients with advanced CKD who are not yet on RRT. ACE inhibition, however, has been shown to be effective at preventing progression of CKD in patients with an estimated glomerular filtration rate of ≥20 mL/min.[79] A drop in estimated glomerular filtration rate of >25% or development of hyperkalemia (>5.5 mmol/L) is an indication for discontinuing therapy.[79]

LVH is present in 75% of patients with ESRD[12] and often is accompanied by cardiac fibrosis, increasing the risk of developing LV dysfunction and ventricular arrhythmias, which are significant causes of morbidity and mortality in this patient population.[80,81] Although many pathological processes drive the development of LVH in patients with ESRD, adequate volume and afterload reduction remain the primary practical targets for preventing and alleviating LVH. Strategies such as salt restriction, ACE inhibition, and use of loop diuretics should be adopted early in the onset of CKD to prevent LVH. Moreover, the usual thrice-weekly hemo- or peritoneal dialysis sessions are inadequate for managing hypervolemia and increased afterload. The Frequent Hemodialysis Network has found that longer, more frequent sessions of RRT are required to decrease LV mass.[82] In patients with ESRD, small studies investigating the effect of ACE inhibition on LVH have shown variable results.[12,76] The Fosinopril in Dialysis study (FOSIDIAL), a randomized controlled trial conducted to evaluate the efficacy of fosinopril in helping prevent major adverse cardiac events in patients on dialysis, found no statistically significant difference between the 2 arms in reducing the risk of major adverse cardiac events.[83] However, this study was underpowered because of a small sample size, and fewer than expected major adverse cardiac events occurred in the study groups. In the absence of specific data from sufficiently powered randomized controlled trials for treatment of CHF with ACE inhibitors in patients on dialysis, this group of drugs is currently recommended based on the extrapolation of data from patients without ESRD.[76] Larger scale studies are needed to investigate the effect of ACE inhibition on LV dimension and function and on clinical outcomes of CHF in patients with ESRD. Renal transplantation has been shown to consistently reduce LVH in dialysis patients after transplant.[80,81,84,85] This suggests that the most effective method of treating LVH and the associated impaired LV dysfunction is restoring renal function.[80,81]

Device Therapy for Primary Prevention of Sudden Cardiac Death

Severe LV systolic dysfunction (LVEF <35%) in patients with ESRD raises a question about primary prevention of fatal cardiac arrhythmias with device therapy. The utility of implantable cardioverter-defibrillators (ICDs) has not been well studied in patients with CKD and ESRD, who historically have been excluded from clinical trials investigating ICD use in patients with CHF. Patients who meet the criteria for ICD placement for primary prevention often are not offered these devices because of lower life expectancy, higher rates of device complications, and other comorbidities.[86] Patients with advanced CKD and ESRD tend to have higher rates of acute and chronic complications from device placement and higher mortality unrelated to cardiac arrhythmias.[86] A study of a cohort of >9500 patients on chronic dialysis implanted with ICDs revealed that 11% of patients died of an infection at 1.4 years of follow-up, with most infections occurring 1 year after device implantation.[87] The incidence of device infection in patients with ESRD is 2 to 5 times greater than in patients without ESRD,[88,89] and this may be the result of frequent bloodstream access for hemodialysis.[88,89] Device extraction is usually recommended as part of the treatment for device

infection, but patients with ESRD are often treated medically, perhaps because they are too ill to safely sustain a procedure.[88] A decision analysis model analyzing the benefits of ICD therapy found that in patients with mild to moderate CKD (stages 1 and 2), ICD implantation reduces mortality, with patients with more advanced CKD having a higher procedural risk and decreased life expectancy. In contrast, ICD implantation in patients aged <65 years with stage 5 CKD deemed favorable results.[86]

Subcutaneous ICDs (S-ICDs) present a novel alternative to ICDs, with potential wide clinical application in patients with ESRD. S-ICDs are approved by the US Food and Drug Administration, do not require transvenous leads, and were recently studied in patients with ESRD on dialysis for both primary and secondary prevention. A retrospective study found that patients on chronic dialysis who received an S-ICD had no device-related infections over a mean follow-up of 7 months.[87] Moreover, a reduced risk of central venous stenosis and hematogenous and endocardial bacterial infections was noted in a recent case series.[89] This result was later confirmed in other studies.[90] The incidence of appropriate shocks delivered by S-ICD was significantly higher in the dialysis cohort compared with the nondialysis group, with a low risk of inappropriate shocks.[87] Given the high prevalence of CHF in the dialysis population, S-ICD appears to be an appropriate alternative to transvenous ICD for primary and secondary prevention. Evaluation by an electrophysiologist experienced in S-ICD implantation should be pursued for renal transplant candidates in whom LVEF remains <35% despite optimization of medical therapy.

Effects of Renal Transplantation on LV Systolic Function

Patients on dialysis with systolic heart failure often are not referred for renal transplantation because of concern about perioperative mortality and the increased risk of cardiovascular events after transplantation. Recent studies, however, have indicated that not only is the risk of perioperative death low, but improvement in LV systolic function is also frequently observed.[7,87,91] In a study of >100 patients with ESRD and mean LVEF values of 31.6±6.7 undergoing renal transplantation, LV function improved in 86% of the patients, increasing to a mean of 47.2±10.7 at 6 months, with continued improvement to 52.2±12.0 at 12 months after transplantation.[7] New York Heart Association (NYHA) functional class also improved. Prior to transplant, 0% of patients reported a functional class of NYHA class 1. This number increased from 0% to 73% in the post–renal transplantation period, with only 24% of patients reporting a functional class of NYHA class 4.[7] Time spent on dialysis was the only significant predictor of improvement in LVEF. Patients with longer durations of dialysis therapy were less likely to have normalization of LVEF (defined as ≥40%) after transplantation.

The 3-year survival rate of patients on dialysis after diagnosis of CHF is reported as only 17%.[77,92] Moreover, the median survival of patients with systolic dysfunction is 38 months compared with 66 months in patients with normal systolic function.[92] In a study of nearly 3700 patients with ESRD, LVEF was the best predictor of mortality, with a 2.7% morality increase for each 1% decrease in LVEF for patients awaiting renal transplantation.[93] Similarly, a study of >60 000 patients with renal transplantation found that although there was a modest risk of cardiovascular mortality early in the postoperative period, the cardiac death rate dropped significantly 3 months after transplantation compared with patients who remained on the waiting list.[73] In patients with diabetes mellitus, LV end-systolic diameter and indexes of fiber shortening on echocardiography were predictors of survival, with LV end-systolic diameter >4.0 cm associated with 30% survival at 3 years versus 69% in those with normal LV end-systolic diameter. Furthermore, no significant impact on survival with renal transplantation was observed in patients with LV end-systolic diameter ≥6 cm, LV posterior wall thickness ≥1.6 cm, or LVEF ≤43%.[94] In a more recent prospective study of >200 renal transplant recipients, age, LV end-systolic diameter ≥3.5 cm, maximal wall thickness ≥1.4 cm, and mitral annular calcification were shown to be independent predictors of mortality.[95] Thus, it is recommended that renal transplantation be considered early for patients with CHF or for those at risk of developing CHF because the beneficial effects of transplantation diminish with a prolonged course of dialysis.[7] KDOQI guidelines recommend that patients should be evaluated with an echocardiogram at the initiation of dialysis once dry weight is achieved, ideally 1 to 3 months after the initiation of dialysis, and at 3-year intervals thereafter[24] to assess LVEF, structural abnormalities, and valvular disease.[20] Although many studies have demonstrated that patients with low LVEF can safely undergo renal transplantation[7,92,96]—most notably, a report of 11 patients with LVEF ≤20%[7]—there is currently no consensus regarding the minimum LVEF required to safely undergo renal transplantation.

Recommendations for Management of CHF

All patients under evaluation should have baseline echocardiography at dry weight. For patients with an LVEF <35% not yet on RRT, right and left heart catheterization should be performed to assess for ischemic heart disease and targets for revascularization, with PCI or CABG performed if indicated. In patients with CKD who are not yet on RRT, ultra–low-contrast angiography followed by staged low- or no-contrast PCI[97] should be considered if feasible. Treatments such as beta blockers and ACE inhibitors or angiotensin receptor

blockers should be initiated to prevent cardiac remodeling and to improve LVEF (Figure 2). Side effects such as hypotension, electrolyte abnormalities, and bradycardia should be monitored closely once therapy has begun. Importantly, many angiotensin receptor blockers are not dialyzed and are preferred over ACE inhibitors, which are dialyzable. If no improvement in cardiac contractility is achieved and LVEF remains <35% despite optimal medical therapy, the benefits and risks of ICD and S-ICD for primary prevention should be discussed with the patient. Patients with normal LVEF should be reevaluated by echocardiography within 3 years. Cardiac evaluation should be performed annually for patients with LV systolic dysfunction and more frequently for patients with LVEF <35% for titration of medical therapy based on guidelines for management of patients with severe LV dysfunction.[98]

Valvular Disease in Patients With ESRD

Valvular abnormalities are very prevalent in patients with ESRD and often pose barriers to renal transplantation. Degenerative valvular calcification is more prevalent and progresses faster in ESRD than in the general population, likely because of abnormal calcium and phosphate metabolism, secondary hyperparathyroidism, and vitamin D and calcium supplementation.[99–101] These metabolic abnormalities lead to increased calcium deposition in the mitral annulus and aortic valve. Consequently, the incidence of aortic valve calcification (AVC) is nearly twice that in the general population and has a direct relationship with time spent on dialysis.[99–101] In patients on dialysis, AVC is often severe and can lead to rapidly progressing aortic stenosis (AS)[20]. Notably, the rate of AS progression in ESRD is twice the rate in the general population (0.23-cm^2 reduction in valve area per year compared with 0.05–0.1 cm^2/year).[20] Severe AVC leads to the development of premature AS. One study demonstrated severe AVC at a mean age of 52 years in up to 28% of patients with ESRD on dialysis who had trileaflet aortic valves.[20] The premature development of AVC and AS was associated with longer time spent on dialysis, higher serum calcium and phosphate, and high calcium phosphate product.[101]

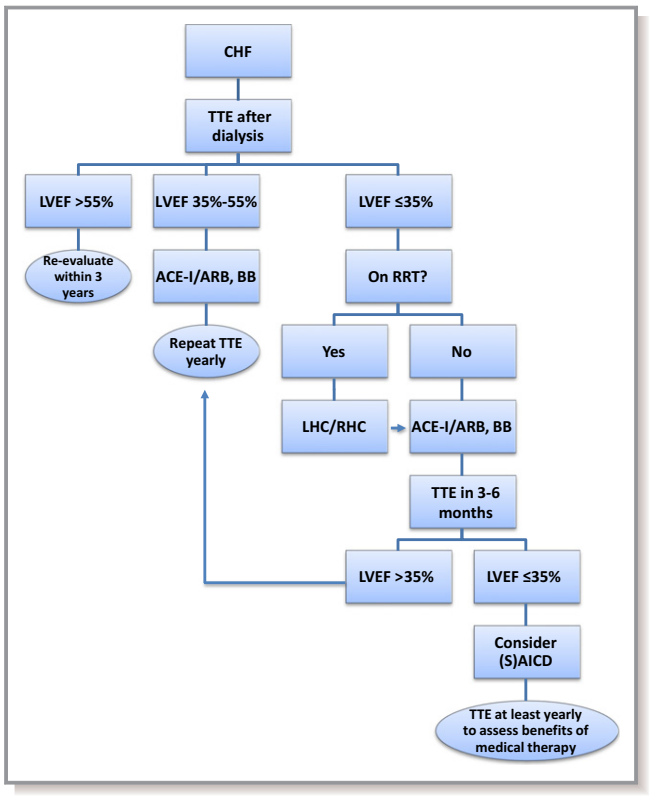

Figure 2. Algorithm for evaluation and treatment of CHF. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, beta blocker; CHF, congestive heart failure; LVEF, left ventricular ejection fraction; RRT, renal replacement therapy; (S)AICD indicates (subcutaneous) automated implantable cardioverter-defibrillator; TTE, transthoracic echocardiogram.

Similar to accelerated AVC, 36% of patients had mitral annular calcification that was associated with age, age at initiation of dialysis, calcium phosphate product, and time spent on dialysis.[101] Progressive mitral annular calcification can cause functional impairment by encroachment to the mitral leaflets, leading to mitral regurgitation and/or mitral stenosis. To assess mitral valve function, echocardiography should be performed at dry weight because functional mitral regurgitation will improve with improved hemodynamics[24] and often resolves after renal transplantation without further intervention.[102] It is also important to differentiate primary and secondary mitral regurgitation to determine appropriate treatment strategies. Primary mitral regurgitation may benefit from mitral valve repair or replacement, as per the AHA/ACC 2014 guidelines, whereas secondary mitral regurgitation should be treated by addressing the underlying cause, as identified by transthoracic echocardiogram.[103]

Transcatheter Versus Surgical Therapy of Valvular Disease

The overall management of valvular disease in candidates for renal transplantation is similar to that for patients without CKD.[20] In a retrospective analysis of >35 000 patients with ESRD, patients with valvular heart disease were less likely to undergo renal transplantation[104]. Patients that received corrective valvular surgery were successfully transplanted at rates similar to patients without valvular disease. Transplantation was associated with the halting of valvular disease progression, particularly AS.[104] Although surgical replacement with either a bioprosthetic or mechanical valve has been shown to confer a reduction in mortality in patients who survive the perioperative period, perioperative mortality with

cardiac surgery in patients with ESRD remains extremely high and limits the surgical options in this patient population.[105–108] According to the Society of Thoracic Surgeons risk model, aortic valve replacement (AVR) in patients with ESRD is associated with significantly high perioperative mortality, with an odds ratio of 2.8 for operative mortality defined as death within the same hospitalization as surgery and within 30 days after discharge.[109] Similarly, mitral valve repair is associated with an odds ratio of 4.59 for operative mortality.[109] These high rates of perioperative mortality should be considered against the high mortality from uncorrected valvular disease. Symptomatic AS without definitive treatment is associated with 75% mortality in "all comers" within 3 years, and the risk is likely even higher in patients with ESRD.[110]

Transcatheter AVR (TAVR) may be an attractive alternative for patients with ESRD and severe AS. In a study of 8 renal transplant recipients who underwent TAVR prior to transplantation, mortality at 12 months was 0%, with 1 reported cardiovascular event (stroke), compared with 30-day mortality of 11.2% and 1-year mortality of 16.7% in patients who underwent surgical AVR (SAVR).[111] Although patients with ESRD were not included in the initial clinical trials evaluating TAVR, case reports have not found any absolute contraindication to TAVR, especially in those who may otherwise be denied renal transplantation.[111,112] In the new 2014 AHA/ACC guidelines for the management of patients with valvular heart disease, TAVR has a class 1 indication for patients who have prohibitive risk for SAVR and post-TAVR survival >12 months.[103] TAVR is a reasonable alternative to SAVR in renal transplantation candidates.

The management of asymptomatic severe AS remains uncertain and controversial because no randomized control trials have compared AVR, either SAVR or TAVR, with conservative medical therapy. A recent meta-analysis of 2486 patients with severe asymptomatic AS found a 3.5-fold higher mortality rate in patients who were treated with a watchful waiting strategy compared with early AVR.[113] These results, however, had many potential confounders. Patients with asymptomatic severe AS may be referred for stress testing to determine whether symptoms are unmasked by strenuous exercise.[103,113] Current guidelines recommend AVR in patients with asymptomatic severe AS and an LVEF <50% who have a decreased systolic opening of a calcified aortic valve with an aortic valve velocity ≥4.0 m/s or mean pressure gradient ≥40 mm Hg.[103] Nevertheless, patients with advanced CKD and ESRD represent a population that is at high risk for rapid progression of AS.[20,99–101] LVH, reduced LVEF, and PH are all linked to a higher risk of adverse events in patients with AS and are highly prevalent in patients with advanced CKD and ESRD.[113–116] With these considerations in mind, it may be reasonable to correct severe asymptomatic AS prior to renal transplantation with SAVR or TAVR.

Recommendations for Management of Valvular Disease

Patients with clinically significant valvular abnormalities should be considered for definitive management prior to transplantation. TAVR should be used as an alternative to SAVR in patients at high or intermediate risk for surgery.[117,118] The decision to proceed with TAVR or SAVR should be made in consultation with a cardiac surgeon and an interventional cardiologist (Figure 3). Mitral valve surgery should be performed only after documentation of severe valve dysfunction on echocardiography following right heart catheterization showing normal filling pressures.

PH in Patients With ESRD

PH is common in patients with ESRD, and multiple studies have estimated the prevalence to be 26% to 48% depending on the mean age of the population studied and the time spent on dialysis.[4,119] The majority of PH observed in patients receiving RRT occurs in patients with arteriovenous fistulae (AVF) for hemodialysis. Patients on peritoneal dialysis also have a higher incidence of PH compared with the general population.[4,119] Several factors place patients with ESRD at risk for the development of PH: placement of AVF, chronic hypervolemia, and anemia. These risk factors can lead to a state of high cardiac output, which can further contribute to the development of PH. It is essential to dialyze patients to their dry weights to prevent chronic volume overload and reduce the risk of development of PH, which is frequently observed in this patient population.[120,121] Compression of AVF for 1 minute has been shown to decrease cardiac output and pulmonary arterial pressure and may be a useful diagnostic maneuver to determine the reversibility of PH.[122] Given the massive capacitance of the pulmonary vasculature, increased cardiac output alone might not be the only driving force for the development of PH in patients on dialysis.[120] Endothelial dysfunction caused by decreased nitric oxide production may also play a role[122]. It has been shown that patients with PH on dialysis have reduced serum levels of nitric oxide both before and after hemodialysis compared with patients on dialysis without PH.[122] This suggests that the uremic environment may reduce the capacitance of the pulmonary vasculature, predisposing patients on dialysis with high cardiac outputs to the development of PH.[119,122]

Treatment of PH

Development of PH is associated with significant morbidity and mortality.[121–125] Patients on dialysis with PH have significantly lower survival rates than their counterparts without PH, with respective survival rates of 78.6% versus

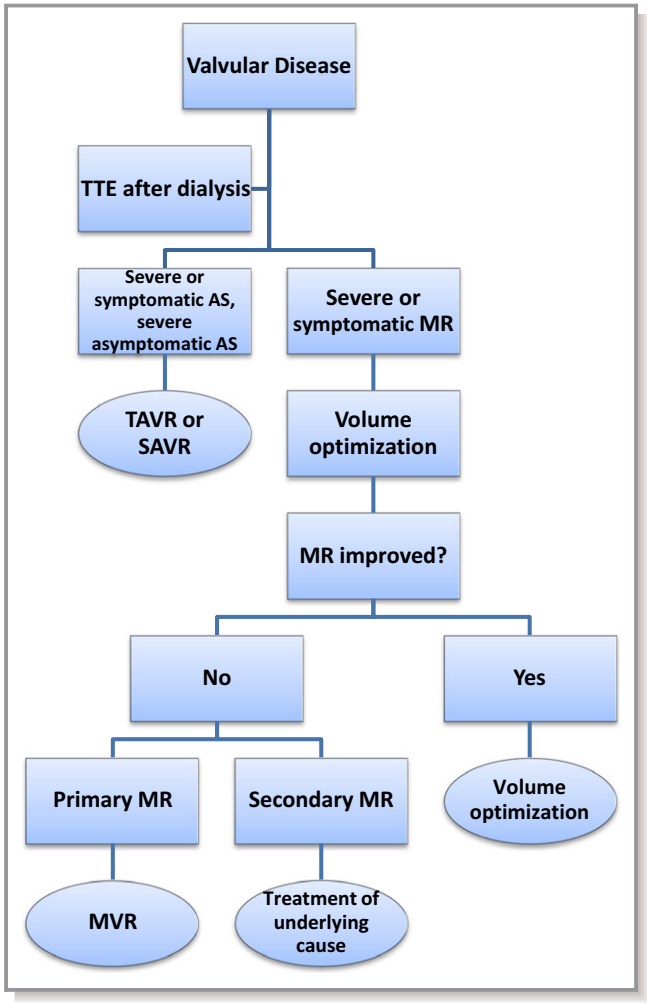

Figure 3. Algorithm for evaluation and treatment of valvular disease. AS indicates aortic stenosis; MR, mitral regurgitation; MVR, mitral valve repair/replacement; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; TTE, transthoracic echocardiogram.

96.5% at 1 year, 42.9% versus 78.8% at 3 years, and 25.5% versus 66.4% at 5 years.[126] Thus, patients with ESRD and severe PH should be referred to a PH specialist for PH-specific therapies. Unfortunately, therapeutic options for patients with ESRD and PH are limited. Treatments such as phosphodiesterase type 5 inhibitors or endothelin receptor antagonists have not been studied specifically in patients with ESRD and PH. Surgical reduction of AVF should be considered in patients with very high cardiac output in whom improvements in cardiac output and PH by temporary AVF closure has been shown.[121,122,126,127] An AVF flow rate ≥2 L/min and cardiac output of ≥8 L/min place patients at high risk of high-output cardiac failure.[128,129] The definitive treatment for PH in this population is renal transplantation if the etiology is secondary to high cardiac output from AVF. These patients should be considered for renal transplantation as soon as possible.[123,124,126]

Evidence-based guidelines for the perioperative management of patients with PH are lacking because the AHA/ACC practice guidelines for noncardiac surgery do not list PH as an independent risk factor for postoperative complications.[125] Several small studies, however, have suggested that PH is a risk factor for increased peri- and postoperative morbidity and mortality. According to the AHA/ACC recommendations specifically addressing cardiac disease evaluation among kidney transplantation candidates, right heart catheterization is reasonable to pursue to confirm echocardiographic evidence of elevated pulmonary arterial pressures.[20] Right heart catheterization is also warranted to assess the severity of PH before transplantation to determine whether there is an association with a state of high cardiac output.[20,125] Consultation with a PH specialist should also be considered early because therapy with phosphodiesterase type 5 inhibitors or endothelin receptor antagonists may be needed to facilitate renal transplantation in patients with refractory PH not secondary to AVF-dependent high cardiac output.[121] During surgery, systemic hypotension or abrupt increases in pulmonary artery pressures can cause right ventricular overload and lead to right ventricular systolic dysfunction and decreased cardiac output. Therefore, intraoperative invasive hemodynamic monitoring of pulmonary circulation should be considered.[125] Nevertheless, renal transplantation has been shown to be curative for PH under certain circumstances. If the pulmonary pressures do not preclude a surgical procedure, renal transplantation should be pursued aggressively to improve morbidity and mortality in this group of patients.

Recommendations for Management of PH

Evidence of PH on echocardiogram (≥40 mm Hg) should be confirmed with repeat echocardiography following hemodialysis to ensure that PH is not simply caused by volume overload (Figure 4). If pulmonary artery pressures remain elevated despite optimization of volume status by dialysis, right heart catheterization to assess severity and potential etiology of PH should be performed. Severe PH (mean pulmonary artery pressure ≥40 mm Hg) in the setting of elevated pulmonary capillary wedge pressure (≥18 mm Hg) should be treated with more aggressive diuresis to optimize volume status, at times requiring inpatient admission to perform daily dialysis. When PH is present in the absence of elevated pulmonary capillary wedge pressure but with high cardiac output (>8 L/min), attention should be paid to the AVF. Evidence of decreased cardiac output and improved pulmonary pressures acutely during AVF occlusion in the catheterization laboratory are suggestive of AVF as the etiology of PH, and surgical revision should be considered. Patients with PH with normal left atrial pressures and normal cardiac output should undergo reversibility testing with

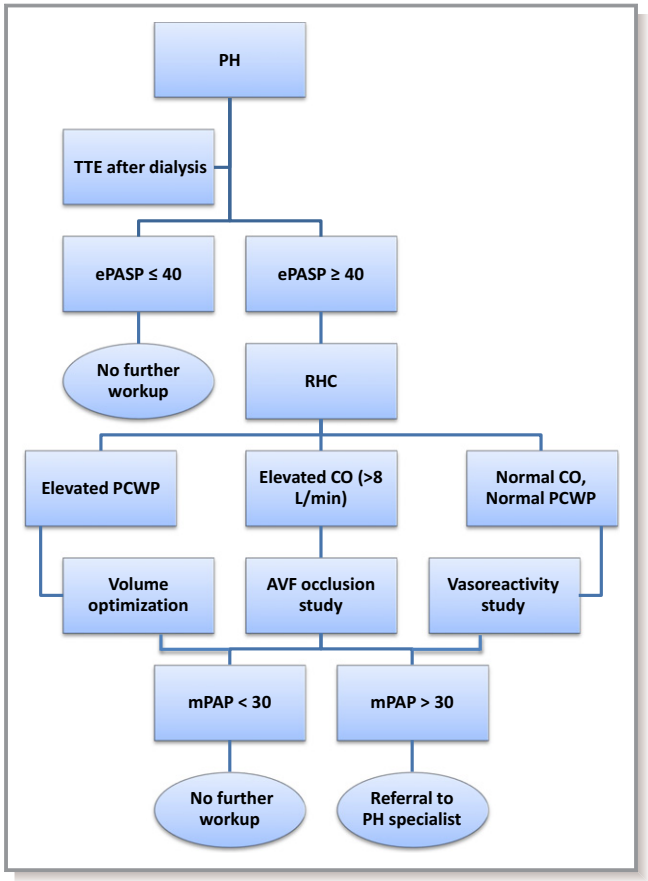

Figure 4. Algorithm for evaluation and treatment of PH. AVF indicates arteriovenous fistula; CO, cardiac output; ePASP, estimated pulmonary artery systolic pressure (echocardiography); mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; RHC, right heart catheterization; TTE, transthoracic echocardiogram.

intravenous and with or without inhaled vasodilators to determine the potential response to medical therapy. Patients with severe PH should be referred to a PH specialist for help with perioperative management. A multidisciplinary approach for perioperative management should be considered, including consultation with anesthesiology to help determine the optimal intraoperative plan of care.[125]

Conclusions

Cardiovascular disease processes are highly prevalent and have major negative impacts on clinical outcomes in patients with advanced CKD. Nevertheless, optimal cardiovascular management in this population remains challenging due to the absence of data from randomized clinical trials, from which this high-risk group continues to be excluded. Encouraging data on improvement of cardiovascular outcomes after successful renal transplantation with appropriate cardiovascular workup and management highlights the urgent need for clinical trials to investigate a wide array of unresolved clinical issues related to cardiovascular pathologies in advanced CKD.

Disclosures

None.

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Key Words: cardiovascular disease • chronic kidney disease • renal transplant