Evaluation and treatment of coronary artery disease in patients with end-stage renal disease

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Evaluation and treatment of coronary artery disease in patients with end-stage renal disease. Patients with end-stage renal disease (ESRD) are at increased risk of death from coronary artery disease (CAD). The metabolic milieu that results from renal dysfunction appears to accelerate the atherosclerotic process by decades in patients with ESRD. The extremely high prevalence of atherosclerosis in patients with ESRD mandates risk factor identification and treatment. Traditionally, CAD in this patient population has been treated conservatively. Analysis of large databases has highlighted the scope and complexity of this problem; nonetheless, there is a paucity of randomized, controlled trials of CAD in patients with ESRD. In this paper the following issues related to evaluation and treatment of patients with chronic kidney disease are addressed: (*1*) optimal CAD risk management; (*2*) evaluation for CAD in patients with ESRD, including the identification of coronary calcification; (*3*) treatment of CAD with medical therapy and revascularization; (*4*) relative merits of percutaneous coronary intervention versus bypass surgery. In general, an aggressive approach to medical management of CAD is warranted, even in the setting of subclinical CAD. A low threshold for diagnostic testing should be employed in patients with ESRD. When significant CAD is identified, ESRD patients appear to benefit more from revascularization compared to conservative medical management. Thus, if clinically reasonable, patients with ESRD and CAD should be managed aggressively to improve survival and reduce the incidence of future cardiac events.

Patients with end-stage renal disease (ESRD) are at increased risk of death from cardiac causes [1]. The prevalence of angiographically significant coronary artery disease (CAD) ranges from 25% in young, non-diabetic hemodialysis patients [2] to 85% in older ESRD patients with longstanding diabetes [3]. It has been estimated that the risk of cardiac death in dialysis patients younger than age 45 is 100 times greater than that the general population [4]. Even more striking is that, while only 0.1% of the population requires dialysis in the United States, more than 2.5% have some degree of renal insufficiency, and these individuals with chronic kidney disease are also at increased risk of cardiovascular disease and its complications [5]. Chronic kidney disease

(CKD) can be defined in 5 stages [6]. Detectable risk for procedural complications typically occurs below an estimated glomerular filtration rate of 60 mL/min/1.73m^2. This article will focus on stage 5 CKD, which is mainly composed of those patients with ESRD on maintenance dialysis.

The prevalence and severity of CAD among patients with ESRD is daunting in terms of both occurrence and extent of poor outcomes. Medicare beneficiaries with kidney disease who are not yet on dialysis are 60% more likely to have a billing claim submitted for the diagnosis of cardiovascular disease (CVD), and 70% more likely to have a claim submitted for "atherosclerotic heart disease" [7]. At the time of initiation of dialysis, a substantial proportion, perhaps the majority, had established CAD [8, 9]. In diabetic renal transplant candidates, 30% will have one or more lesion with greater than 75% stenosis [10]. When compared to patients without CKD who undergo evaluation for CAD, those with ESRD have substantially more numerous and severe coronary artery lesions, as well as more severe left ventricular dysfunction [11, 12].

Moreover, patients with ESRD have poor outcomes from CAD. In 3106 patients with acute myocardial infarction (AMI), in-hospital mortality rates were 2% in patients with normal renal function, 6% in those with mild renal dysfunction, 14% in those with moderate renal dysfunction, 21% in those with severe renal dysfunction, and 30% in those with ESRD [13]. A comparable directional trend was observed for increasing risk of postdischarge death with advancing degrees of CKD [7]. Similarly, in a group of 34,189 patients on long-term dialysis who were hospitalized for a first myocardial infarct, the mortality rate from cardiac causes was 40.8% at 1 year, 51.8% at 2 years, and 70.2% at 5 years [14]. Overall, CVD accounts for approximately 50% of ESRD deaths [7]. Despite this high mortality rate after AMI, and although rates of mortality for all cardiovascular diseases have increased 14.5% since 1991, mortality rates due to atherosclerotic heart disease and AMI have fallen 13% to 15% among patients with CKD [7].

Table 1. Therapeutic opportunities to improve cardiovascular care in patients with end-stage renal disease

Therapeutic opportunity	Rationale
Weight loss/weight maintenance at BMI ≤25 kg/m^2	Improvement of the dysmetabolic syndrome and diabetes
Low sodium intake	Reduce blood pressure
	Make blood pressure more responsive to medications
	Reduce volume retention between dialysis sessions
Aspirin 81 mg p.o. qd or clopidogrel 75 mg p.o. qd if aspirin intolerant	Primary prevention of AMI and stroke
Lipid control (diet, statin, fibrates, niacin, others)	Primary prevention of AMI, stroke, and CVD death
LDL-C <100 mg/dL	Possible reduction in progression of CKD
TG <150 mg/dL	
HDL-C >50 mg/dL	
Blood pressure control to target of SBP <130 mm Hg	Primary prevention of AMI, stroke, heart failure, and CVD death
RAAS blocking agents	Preserve residual urine volume in peritoneal dialysis patients
Beta-blocking agents	Reduce left ventricular hypertrophy
Other add-on agents	Treatment of subclinical cardiac ischemia
Blood glucose control in diabetes	Reduction in risk of AMI, stroke, and CVD death
	Reduction in worsened nephropathy/retinopathy
Reduce homocysteine	Possible reduction in risk of AMI, stroke, and CVD death
–Folic acid	
–Vitamin B$_6$ and B$_{12}$	

Abbreviations are: BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; RAAS, renin angiotensin aldosterone system; AMI, acute myocardial infarction; CVD, cardiovascular disease; ESRD, end-stage renal disease. Adapted from reference [55].

OPTIMAL MEDICAL THERAPY

The patient with incipient ESRD on maintenance dialysis should be considered to be the highest cardiovascular risk patient in medicine, with an expected rate of coronary heart disease (CHD) death that is many-fold the rate expected for a non-ESRD patient in whom every conventional cardiovascular risk factor is present [15]. Thus, ESRD is more than a cardiovascular risk equivalent. Hence, in ESRD patients, therapeutic strategies should be undertaken that are even more aggressive than those recommended in conventional guidelines (Table 1).

Blood pressure control

Despite the use of multiple medications, most published series of ESRD patients from either clinical trials or registries indicate that the mean systolic blood pressure is approximately 155 mm Hg. This reflects the fact that 80% of ESRD patients have hypertension (HTN), and that it is adequately controlled in only 30% [16]. Long-term cardiorenal protection involves 2 important concepts: blood pressure control to a much lower target of a systolic blood pressure (SBP) <130 mm Hg [17], and use of an agent that blocks the renin-angiotensin aldoserterone system (RAAS), such as an angiotensin-converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB) as the base of therapy. How can an ACEI/ARB be effective in a patient with ESRD—particularly one who is anephric? The RAAS angiotensin system appears to have considerable redundancy, and is able to maintain systemic function, if not increase its overall level of activity without participation by the kidneys [18]. Hence, this hyperactivation of the RAAS is a target for therapy in ESRD. In this regard, ACEI and

ARB treatment has been shown to reduce LVH and improve myocardial function in ESRD. Clinical outcomes evidence for the benefit of ACEI/ARB in the general population also extends to ESRD patients [19]. Very importantly, a recent trial has demonstrated that ramipril was related to preservation of residual urine output in those receiving peritoneal dialysis, which is a consistently favorable management issue in ESRD [20]. One study has demonstrated that although only approximately 20% of patients with ESRD and CAD receive ACEI, those who were given these agents after CAD events had improved all-cause mortality over the next 5 years [21]. Unfortunately, treatment with ACEI/ARB may result in worsening hyperkalemia in patients with ESRD. As tolerated, the clinician should consider adjusting the dialytic regimen to optimize potassium balance and continue treatment with ACEI/ARB. To date, available evidence indicates that patients with ESRD appear to benefit from ACEI/ARB therapy provided the serum potassium and blood pressure can be adequately controlled.

With an ACEI/ARB as a base of therapy, the antihypertensive regimen can be further modified according to blood pressure lowering efficacy and CAD event reduction. Beta-blockers can be used as both an antihypertensive and an anti-ischemic agent [22]. In patients with heart failure, beta-blockers improve left ventricular ejection fraction, reduce rates of hospitalization, sudden death, and all-cause mortality [23, 24]. Studies have demonstrated large relative risk reductions in all-cause mortality for patients with ESRD who receive beta-blockers therapy after CAD events [24].

If the blood pressure cannot be adequately controlled with ACEI/ARB and beta-blockers therapy, additional antihypertensive agents can be added to the regimen

based on ease of management, compliance, and lack of adverse effects. The goal is to create a blood pressure environment for the cardiovascular system where the mean systolic blood pressure, on 24-hour monitoring, for example, is at or below 130 mm Hg. Guidelines for non-ESRD patients state the optimal systolic blood pressure should be <120 mm Hg [17]. This goal is often difficult to achieve in patients with ESRD while avoiding intradialytic hypotension. Given the high rates of severe CAD in ESRD, hypotension during dialysis almost certainly is related to clinical and subclinical myocardial ischemia, which should be suspected in the presence of chest discomfort, shortness of breath, ST-segment depression on electrocardiography, or elevations of cardiac troponins on blood testing [25].

The key lifestyle changes with ESRD that can assist with blood pressure control include dietary sodium restriction (2–4 g/day), weight reduction to a target body mass index <25 kg/m^2, and exercise for 60 minutes per day most days of the week. Limiting alcohol intake to 1 drink or less (14 g of alcohol) per day is also a valuable tool in the nonpharmacologic management of hypertension [17].

Treatment of dyslipidemia

Data are, in general, supportive of low-density lipoprotein cholesterol (LDL-C) reduction, in most cases with HMG CoA reductase inhibitors (statins), in patients with ESRD with an expected relative risk reduction in CVD events [26, 27]. The most common dyslipidemia profile consists of an elevated triglyceride (TG) level, depressed high-density lipoprotein cholesterol (HDL-C), and modestly elevated LDL-C. Agents that reduce TG and raise HDL-C, including nicotinic acid and fibrates, can be used according to the National Cholesterol Education Project Adult Treatment Panel III (NCEP-ATP-III) Guidelines [28].

Blood glucose control in diabetics with end-stage renal disease

In ESRD with diabetes, blood glucose control to a target glycohemoglobin <7 mg/dL can be expected to reduce rates of microvascular disease (retinopathy) and, to a lesser extent, clinically important atherosclerotic disease elsewhere (AMI, stroke, CVD death) [29].

Smoking cessation

Although reported rates of smoking are lower in ESRD patients than the general population, it is worth mentioning this important risk factor since it has been clearly shown to raise CVD death rates in ESRD to very high levels [30]. The nicotine in cigarette smoke becomes addictive to the human body at a daily dose above 5 cigarettes per day [31]. The many components of "tar" in cigarette smoke have been linked to the up-regulation of adhesion molecules and other factors that promote oxidation and entry of LDL-C into the vascular subendothelium [32]. This process can occur at any dose of cigarette smoke, including sidestream smoke. Hence, there is a strong rationale for encouraging patients to wean down to below 5 cigarettes per day, and then create a cessation plan with nicotine replacement if needed. In patients with established CAD, those who have successfully stopped smoking have enjoyed approximately 50% risk reduction in all-cause mortality [33].

Antiplatelet agents

Primary prevention measures for CVD event reduction in the general population apply to the patient with early nephropathy. Low-dose aspirin (81 mg daily) has been associated with a 20% to 30% reduction in the risk of stroke, AMI, and CVD death across many populations [34]. The effect of aspirin on renal end points is unknown; however, given its CVD protective effect, it is recommended for adult patients with ESRD [35]. For those who are aspirin intolerant, general cardiology guidelines recommend the use of clopidogrel, although there are no published studies of clopidogrel on cardiovascular outcomes in the setting of ESRD.

Novel risk factors

Patients with ESRD are known to have markedly elevated levels of homocysteine and other thiols [36]. Given the reported association of gradations of homocysteine elevation to increased ESRD mortality, it is reasonable to provide some attempt at homocysteine reduction in ESRD patients until we have results from clinical trials [37]. Homocysteine reduction is largely accomplished with supplemental folic acid, which can be used up to 25 g orally per day. Vitamins B$_6$ (pyridoxine) and B$_{12}$ are also needed, but in more conventional quantities (25 mg and 1 mg, respectively). The usual doses required to bring a predialysis homocysteine level near the 14 μmol/L target is 1 to 5 g per day. However, studies have shown it is difficult if not impossible to "normalize" homocysteine in patients with ESRD [38].

Another area of interest is the role of inflammatory factors and cytokines as novel risk markers in ESRD. The most commonly reported nonspecific measure of systemic inflammation in ESRD is high-sensitivity C-reactive protein (hs-CRP) [34]. Studies have consistently shown that ESRD is an inflammatory state with levels of hs-CRP typically higher that the fourth quartile of most asymptomatic, disease-free populations [39]. Unfortunately, data regarding the utility of hs-CRP measurements are heavily confounded by a multitude of other CVD-modifying features, such as smoking, dyslipidemia,
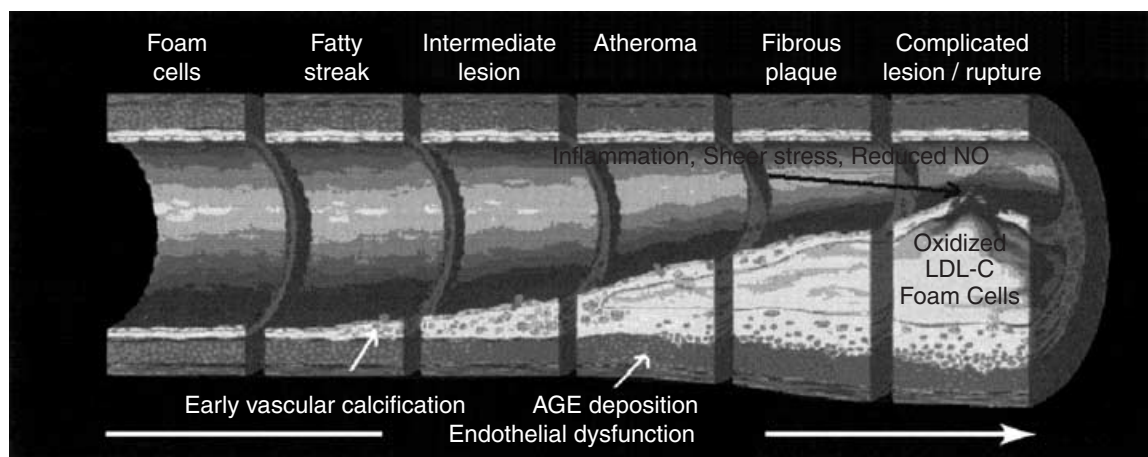
Fig. 1. The processes related to the acceleration of coronary disease and plaque rupture in patients with renal disease. NO, nitric oxide; LDL-C, low-density lipoprotein cholesterol; AGE, advanced glycation end products. Reproduced with permission from reference [41].

physical inactivity, obesity, and diabetes. However, medications including statins and some diabetes medications lower hs-CRP. It should be noted that therapeutic intervention specifically aimed at reduction of hs-CRP is not a proven strategy, but to the extent that hs-CRP is lowered by weight reduction, glucose control, and lipid control, it can be viewed as a favorable sign. Lastly, hs-CRP can serve as a reminder that those with the highest levels of this factor will benefit from a markedly reduced relative risk for future CAD events provided they take aspirin 81 to 325 mg daily [40].

Finally, deposition of advanced glycation end products and reduced nitric oxide availability have both been implicated in acceleration of anatomic CAD disease, and with increase risk of acute rupture of coronary plaques (Fig. 1). Since patients with ESRD and coronary artery disease are at high risk for cardiovascular events, they represent a unique and instructive population for researchers interested in the pathogenesis of atherosclerosis.

Coronary artery calcification in patients with end-stage renal disease

An attractive hypothesis accounting for the high rates of CAD events in ESRD is the abnormal and accelerated vascular calcification that occurs in these patients [41–43]. The calcification in ESRD is thought to occur at 2 sites in the vessel wall, including the media, where it is known as Mönckeberg's sclerosis, and in the intima, where it is invariably associated with atherosclerosis. Cell biology studies suggest that coronary artery calcification is an active process analogous to bone formation, given that several genes characteristic of the osteoblast phenotype are also expressed by calcifying vascular smooth muscle cells (VSMC) [44]. Bone matrix proteins, including osteocalcin, matrix Gla protein, and osteopontin have been found in calcified arterial vessels. In vitro data de-
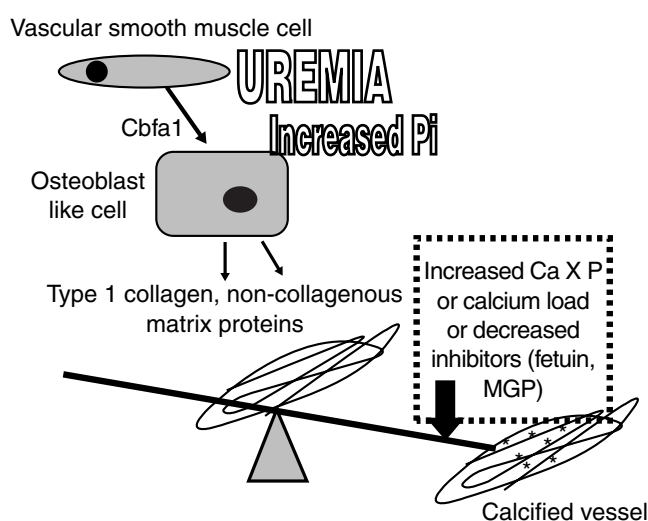
Fig. 2. Postulated three-step mechanism in the induction of uremic vascular calcification: (1) vascular smooth muscle cells dedifferentiate to become osteoblast-like; (2) osteoblast-like cells lay down a matrix of collagen and noncollagen proteins that serve as a nidus for subsequent mineralization; (3) promineralizing forces (increased calcium-phosphorus product, hyperphosphatemia, or increased calcium load) outweigh the antimineralizing forces of inhibitors (fetuin and matrix Gla protein). Cbfa1, a transcription factor for osteoblast differentiation and the expression of the bone matrix proteins; MGP, matrix gla protein; Pi, phosphorus. Reproduced with permission from reference [45].

rived from work with modified VSMCs (which arise from the same pluripotent cell as does the osteoblast) suggest that elevated phosphorus concentration in the culture medium can lead to calcification, and induce Cbfa1 (a transcription factor critical for osteoblast differentiation and the expression of the bone matrix proteins osteopontin, osteocalcin, and type I collagen) and the expression of bone matrix proteins. Hyperphosphatemia, a laboratory abnormality common in ESRD patients, therefore, could represent an important stimulus by which uremia
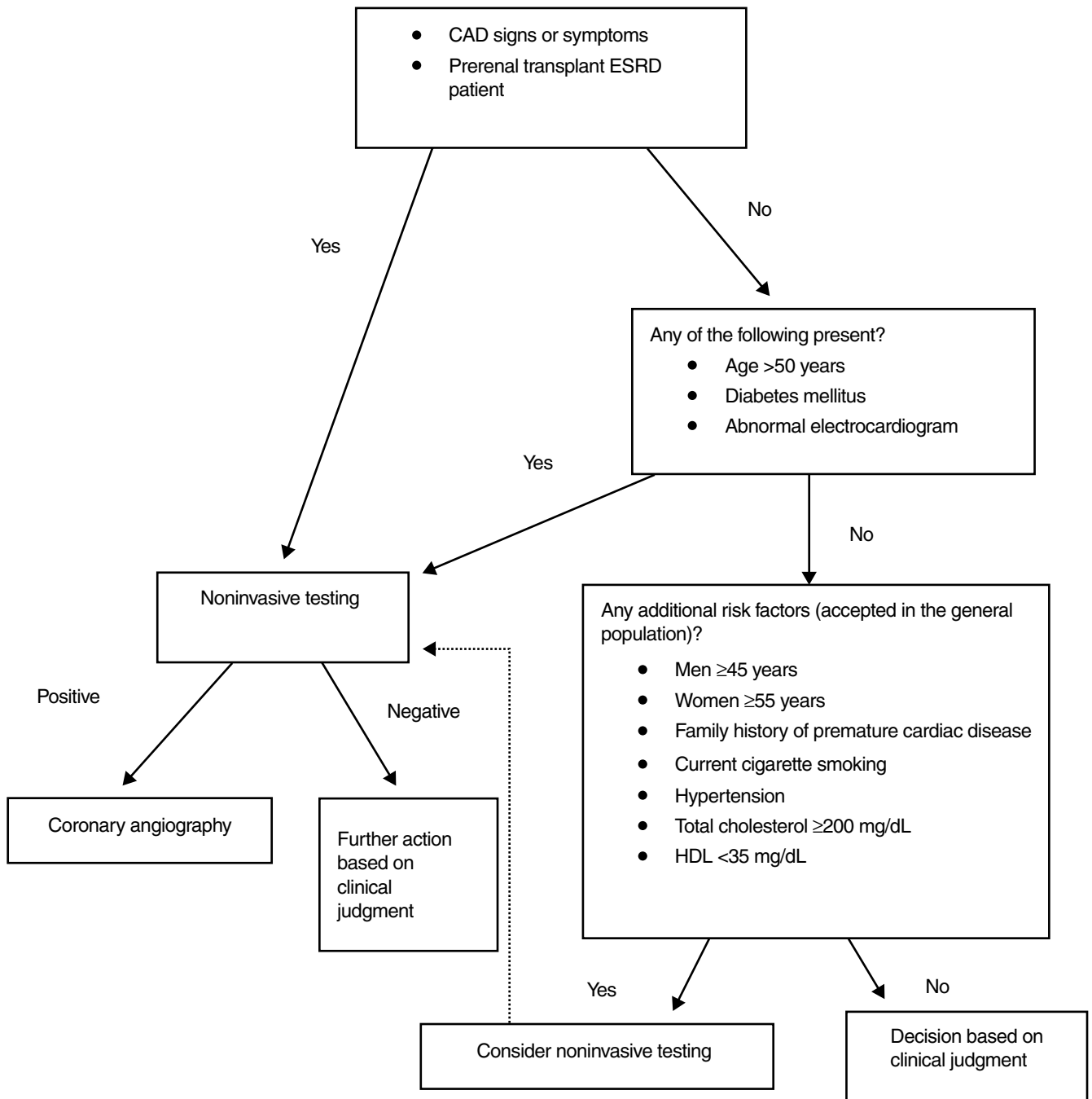
Fig. 3. Algorithm for evaluation of patients with ESRD for suspected coronary artery disease (adapted from reference [41]).

predisposes to excessive vascular calcification (Fig. 2) [45–47]. The effect of calcium loading with or without changes in the serum calcium on the basic processes leading to vascular calcification is unknown. A recent systematic review concluded that clinical studies in ESRD suggest the process is driven much more by the patient's age, length of time on dialysis, and lipid status [48]. While it may appear that phosphorus level and mortality are related, the causal pathway is poorly understood, though some recently postulated mechanisms are listed below.

Moreover, it is also not clear whether or not the increased mortality risk associated with hyperphosphatemia is secondary to coronary artery calcification [48].

A recent study in patients with ESRD on dialysis demonstrated that there is no significant positive correlation between the severity of coronary artery calcification measured by EBCT and the degree of occlusive coronary artery disease [49]. However, the total absence of any CAC strongly correlated with the absence of significant atherosclerotic disease. Although the numbers of patients

examined were small, the study was powered to detect a significant correlation (if it was present) between individual CAC score and plaque burden (power = 0.93, N = 52 vessels) [49]. Does attenuation of the progression of CAC in ESRD patients, when the score is already at high levels, reduce the chances of a CAD event attributed to a calcified lesion? This critically important question will be difficult to answer since the therapies (statins and sevelamer) that attenuate progression do so primarily by reducing LDL-C, and likely stabilizing less severe plaques elsewhere in the coronary bed [44]. Currently, routine testing for CAC or specific treatment based on the finding of CAC in ESRD patients is not recommended. Treatment strategies for use of dietary phosphate binders and other drugs that influence calcium-phosphorus balance should be based on the need to achieve K/DOQI guidelines for control of serum calcium and phosphorus, Ca × P product, and PTH rather than on the basis of a the coronary artery calcification score, per se.

Diagnostic testing for coronary disease

With regard to noninvasive screening tests for CAD, the utility and predictive ability of decision statistics (sensitivity, specificity, positive predictive value, negative predictive value, and accuracy) varies for different studies depending on the population tested and the gold standard utilized for the diagnosis of CAD. Details regarding each possible test, potential difficulties in their utilization among patients with ESRD, and their decision statistics have been summarized previously [50]. In general, any ESRD patient with cardiovascular symptoms, signs of ischemia during dialysis (chest pain, ST-segment changes, or elevation of cardiac troponin levels), and those awaiting renal transplantation should undergo diagnostic testing for CAD (Fig. 3) [50]. Standard testing with a nuclear stress test or stress echocardiography should be undertaken. Deconditioning, amputations, obesity, arthritis, and other factors often make exercise impossible; hence, dipyridamole or adenosine nuclear or dobutamine echocardiographic should be performed [50]. Currently, given the ubiquitous nature of coronary artery calcium in ESRD, use of electron beam or ultrafast computed tomography is not recommended [51]. Once significant CAD has been found, there is considerable controversy over the optimal approach to revascularization [52].

Coronary revascularization in ESRD

Three analyses suggest that patients with ESRD and coronary artery disease who receive conservative medical management tend to fare the worst among all treatment groups [53–55]. Therefore, in the absence of life-threatening comorbid conditions, most ESRD patients are candidates for angiographic evaluation and pos-

**Table 2.** Risks associated with coronary revascularization in patients with ESRD (Adapted from reference 43)

Complication	Risk
PCI	
Short-term mortality	0–14%
AMI (with or without ST elevation)	2.0–23%
Stroke	0.6–2.5%
Major bleeding	0–43.1%
Acute renal failure	<1–37%
Vascular complications	1.6–20%
Clinical restenosis	13–81%
Recurrent angina	44–71%
Need for emergent CABG	0–5%
CABG	
Short-term mortality	0–31%
AMI (with or without ST elevation)	4.2–18%
Stroke	0–20%
Major bleeding	3–11%
Worsened renal failure	1.1–26%
Mediastinitis	3.6–8%
Vascular complications	8.6%
Recurrent angina	6.0%

ESRD = end-stage renal disease; AMI = acute myocardial infarction; PCI = percutaneous coronary intervention; CABG = coronary artery bypass surgery.

sible revascularization. At angiography, multivessel CAD is the most frequent finding, and so the next question is what is the optimal approach—multivessel percutaneous coronary intervention (PCI) or coronary artery bypass grafting? It is widely accepted that patients with ESRD undergoing mechanical coronary revascularization procedures are at increased risk for adverse events including death (Table 2). Dialysis-dependent patients undergoing CABG face a 4.4 times greater risk of in-hospital death, a 3.1 times greater risk of mediastinitis, and a 2.6 times greater risk of stroke compared to those patients undergoing CABG who were not on dialysis [54]. While newer surgical techniques have been successful in high-risk patients with renal failure, the long-term results compared to traditional surgical and percutaneous techniques are not yet known. In general, despite this significant "upfront" risk of surgery, the literature suggests that in patients with ESRD, outcomes for CABG are superior to those achieved with percutaneous interventions [51]. In single-vessel CAD and multivessel CAD without good bypass targets, recent trends suggest that PCI with stenting is a favorable approach for patients with ESRD (Fig. 4) [51]. It is possible that increased utilization of drug-eluting stents in patients with ESRD will favorably impact the high restenosis rates typically seen in this population, and may tip the risk-benefit scale in favor of percutaneous intervention.

CONCLUSION

Patients with ESRD have more than coronary artery disease risk equivalent status in their baseline CAD risk assessment. An aggressive approach to medical
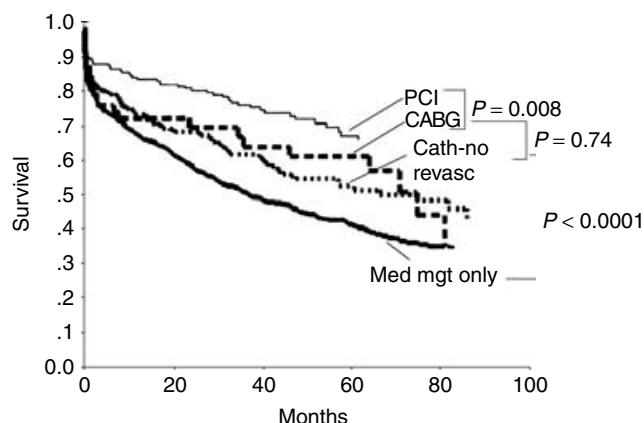
Fig. 4. Long-term survival according to CAD management strategy in patients with CrCl <60 ml/min or with ESRD on dialysis (Reproduced with permission from reference 45).

management for coronary artery disease is warranted, even in the setting of subclinical disease [55]. A low threshold for diagnostic testing should be employed in ESRD patients. When significant CAD is found, ESRD patients appear to benefit from revascularization compared to conservative medical management, and if clinically reasonable, should be given that opportunity for improved survival and reduction in future cardiac events.

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