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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Chronic Kidney Disease and Coronary Artery Disease

JACC State-of-the-Art Review

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ABSTRACT

Chronic kidney disease (CKD) is a major risk factor for coronary artery disease (CAD). As well as their high prevalence of traditional CAD risk factors, such as diabetes and hypertension, persons with CKD are also exposed to other nontraditional, uremia-related cardiovascular disease risk factors, including inflammation, oxidative stress, and abnormal calcium-phosphorus metabolism. CKD and end-stage kidney disease not only increase the risk of CAD, but they also modify its clinical presentation and cardinal symptoms. Management of CAD is complicated in CKD patients, due to their likelihood of comorbid conditions and potential for side effects during interventions. This summary of the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on CAD and CKD (including end-stage kidney disease and transplant recipients) seeks to improve understanding of the epidemiology, pathophysiology, diagnosis, and treatment of CAD in CKD and to identify knowledge gaps, areas of controversy, and priorities for research. (J Am Coll Cardiol 2019;74:1823–38) © 2019 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

AKI = acute kidney injury

AMI = acute myocardial infarction

CABG = coronary artery bypass graft

CAD = coronary artery disease

CKD = chronic kidney disease

CTA = computed tomography angiography

cTn = cardiac troponin

CVD = cardiovascular disease

eGFR = estimated glomerular filtration rate

ESKD = end-stage kidney disease

GFR = glomerular filtration rate

KDIGO = Kidney Disease: Improving Global Outcomes

LVH = left ventricular hypertrophy

PCI = percutaneous coronary intervention

SPECT = single-photon emission tomography

STEMI = ST-segment elevation myocardial infarction

TnI = troponin I

TnT = troponin T

This review summarizes the Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference on coronary artery disease (CAD) and chronic kidney disease (CKD) (including end-stage kidney disease [ESKD] and transplant recipients) and seeks to improve understanding of the epidemiology, pathophysiology, diagnosis, and treatment of CAD in CKD and to identify knowledge gaps, areas of controversy, and priorities for research.

HIGHLIGHTS

- CKD is associated with very high risk of CAD. CAD management is complicated in CKD patients, due to comorbid conditions and potential side effects during interventions.
- There are few trials related to CAD with focus on CKD patients, particularly in those with advanced CKD.
- Additional prospective studies focusing on diagnosis, prevention, and treatment of CAD are needed in CKD.

EPIDEMIOLOGY, PRESENTATION, AND RISK PREDICTION

EPIDEMIOLOGY. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among patients with CKD. Even after adjustment for known CAD risk factors, including diabetes and hypertension, mortality risk progressively increases with worsening CKD (1,2). As glomerular filtration rate (GFR) declines below ~60 to 75 ml/min/1.73 m^2, the probability of developing CAD increases linearly (**Figure 1**) (1,3), and patients with CKD stages G3a to G4 (15-60 ml/min/1.73 m^2) have approximately double and triple the CVD mortality risk, respectively, relative to patients without CKD.

PRESENTATION. CKD and ESKD modify the clinical presentation and cardinal symptoms of CAD. An "oligo-symptomatic" presentation is common; only 44% patients with CKD G3a or higher who present with acute myocardial infarction (AMI) report chest, arm, shoulder, or neck pain compared with 72% of patients with preserved kidney function, but these patients are more likely be dyspneic (4). Similarly, 44% of AMI presentations among dialysis patients are characterized by chest pain, compared with 68% of nondialysis patients (5). Thus, recognition of ischemia in CKD requires an appreciation that coronary syndromes present atypically, and a high index of suspicion is critical for anginal equivalents such as shortness of breath or fatigue. A low functional capacity, common among ESKD patients, may further limit expression of angina. Finally, intradialytic hypotension and myocardial stunning are hemodialysis-specific syndromes associated with mortality and are unique to dialysis patients (6,7).

Patients with CKD are also more likely to have an AMI, rather than stable exertional angina, as their initial clinical manifestation of CAD (8), and it is more likely to be a non-ST-segment elevation myocardial infarction than an ST-segment elevation myocardial infarction (STEMI) (9). These non-STEMI presentations may reflect a supply-demand mismatch, ischemic pre-conditioning, collateralization of blood vessels, and perhaps a higher prevalence of left

Medical; has received honoraria from Fresenius; and has received research grants from Medtronic and the National Institutes of Health (NIH). Dr. Hlatky has served as a Clinical Event Adjudicator for Tricida. Dr. Landmesser has received honoraria from Amgen, Bayer, The Medicines Company, and Sanofi. Dr. Newby has received consulting fees from Biokier and Roche Diagnostics; has served on the Advisory Boards of Metanomics and Ortho Clinical Diagnostics; and has received research grants paid to her institution from Amylin and Boehringer Ingelheim. Dr. Herzog has received consulting fees from AbbVie, Amgen, AstraZeneca, Corvidia, DiaMedica, FibroGen, Janssen, Oxford University, OxThera, Pfizer, and Relypsa; has stock equity in Boston Scientific, General Electric, Johnson & Johnson, and Merck; has received research grants from Amgen, Bristol-Myers Squibb, National Institute of Diabetes and Digestive and Kidney Diseases/NIH, National Heart, Lung, and Blood Institute/NIH, Relypsa, and the University of British Columbia; has received honoraria from the American College of Cardiology; and has received author royalties from UpToDate. Dr. Wheeler has received consulting fees from Amgen, AstraZeneca, Bayer, GlaxoSmithKline, Janssen, Napp/Mundipharma, and Vifor Fresenius Medical Care Renal Pharma; and has received honoraria from Astellas, Boehringer Ingelheim, Janssen, Mitsubishi Tanabe, Ono Pharmaceutical, and Pharmacosmos. Dr. Winkelmayer has received consulting fees and honoraria from Akebia/Otsuka, Amgen, AstraZeneca, Bayer, Daichii-Sankyo, Relypsa, and Vifor Fresenius Medical Care Renal Pharma. Dr. Marwick has received research grants from GE Medical Systems. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Steven Weisbord, MD, MSc, served as Guest Associate Editor for this paper.

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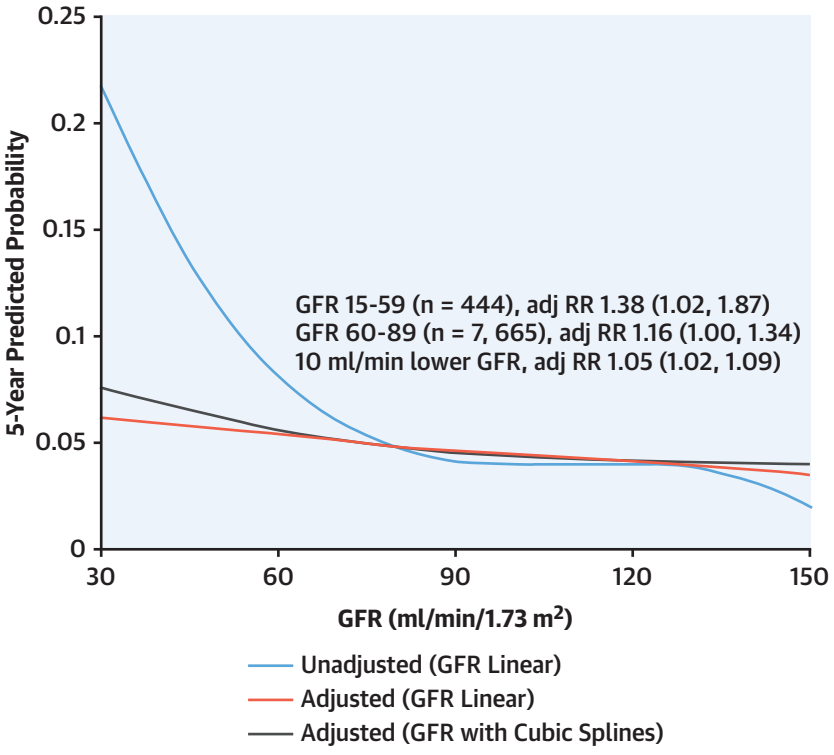
FIGURE 1 Probability of Developing ASCVD in the ARIC Study



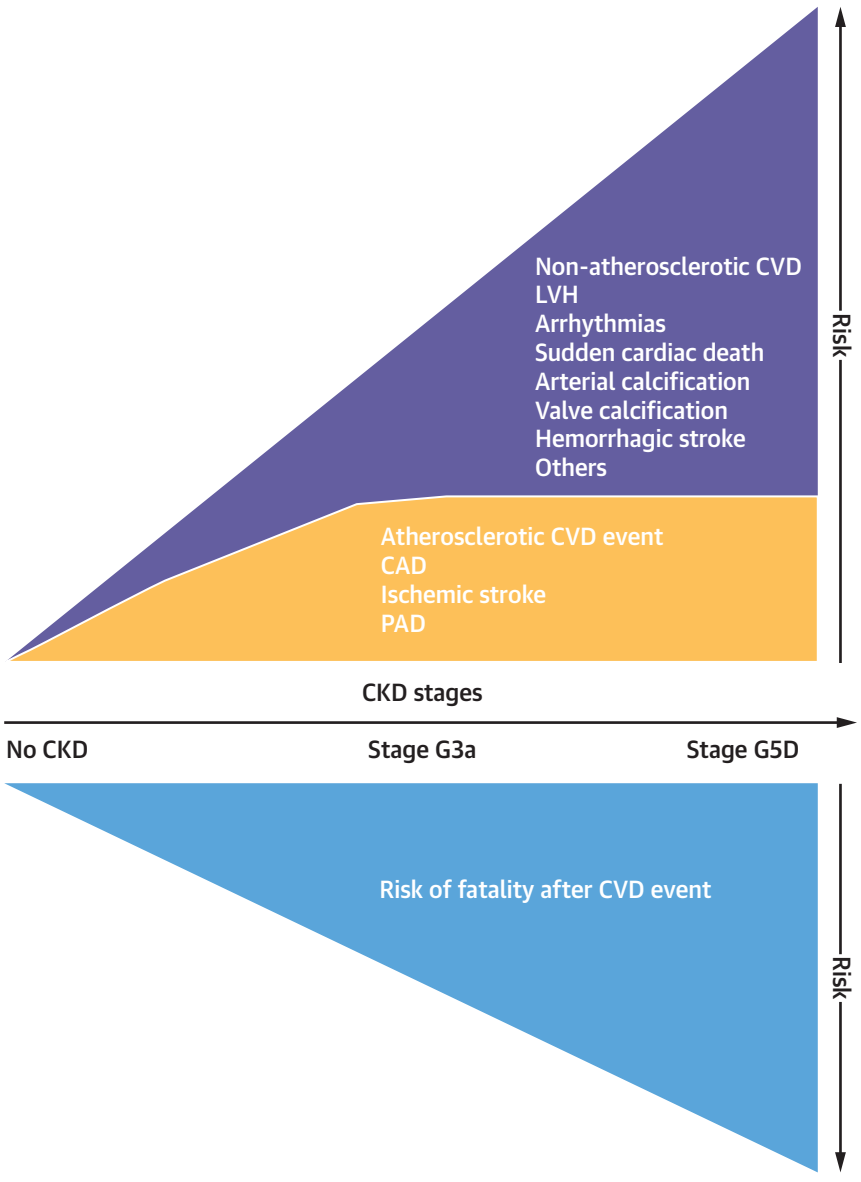
Probability of developing atherosclerotic cardiovascular disease (ASCVD) in the ARIC (Atherosclerosis Risk In Communities) study. Reproduced with permission from Manjunath et al. (3). adj = adjusted; GFR = glomerular filtration rate; RR = risk ratio.

ventricular hypertrophy (LVH) altering the electrocardiographic findings. In addition, it is possible there is less plaque rupture with superimposed occlusive thrombus. Sudden death is particularly common in ESKD, perhaps because the shifts in volume, electrolytes, and drug concentrations may trigger arrhythmias in patients with a myocardial disease (LVH and heart failure). As GFR declines, nonatherosclerotic events assume a higher proportion of the CVD events (**Central Illustration**) (10). The risks of sudden death and heart failure are attenuated after kidney transplantation, with attendant improvements in metabolic status, reversal of uremia, and restoration of normal fluid balance.

PREDICTION OF CAD. Risk assessments (e.g., from the pooled cohorts equation) that inform decisions about CAD prevention rest on population studies (11). However, patients with CKD exemplify the shortcomings of risk assessment from population data, as their predicted risks are well below their observed risk, and model discrimination is poor. Unfortunately, this underestimation is nonuniform, so recalibration of the pooled cohort equations is not sufficient to resolve inaccuracies in risk stratification in CKD (**Figure 2**) (12). However, the calibration and discrimination of risk prediction can be improved by adding kidney-specific variables of estimated glomerular filtration rate (eGFR) and albuminuria (13). Whereas standard clinical guidelines recognize CKD as a "modifying factor" to be considered in using the standard risk equations (14), they do not formally incorporate kidney-specific variables, even though eGFR is readily available.

Additional risk markers may help to refine atherosclerotic CVD risk estimates when benefits and risks of treatment are uncertain (14). Coronary artery calcification can facilitate primary prevention decisions in the general population (14). Coronary calcification is prevalent among patients with CKD, and although the prognostic value is likely similar to that in the general population, the progression of coronary calcification is faster with worsening CKD (15). Similarly, the prognostic significance of various circulating biomarkers, such as C-reactive protein, cardiac troponin, and natriuretic peptides (16), may be similar to that of the general population. However, it remains to be

CENTRAL ILLUSTRATION Changes in Cardiovascular Disease Risk During Chronic Kidney Disease Progression



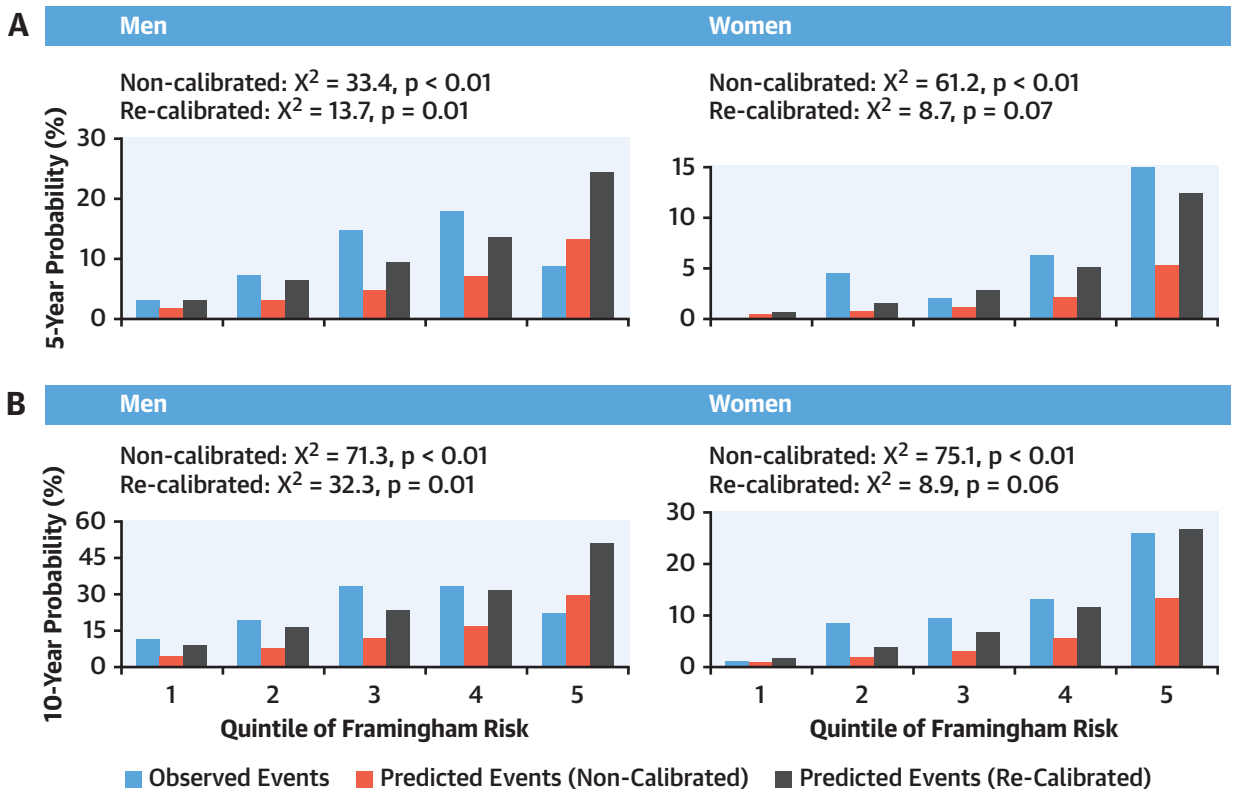
Sarnak, M.J. et al. J Am Coll Cardiol. 2019;74(14):1823-38.

Cardiovascular disease (CVD) event **(upper triangle)**; contributions of atherosclerotic CVD **(yellow)**; nonatherosclerotic CVD **(purple)**, and risk of fatality after CVD event **(blue)**. Reproduced with permission from Wanner et al. (10). CAD = coronary artery disease; LVH = left ventricular hypertrophy.

determined whether incorporation of these biomarkers into clinical care will affect outcomes.

Whereas some adjustment may improve the performance of standard cardiac risk assessment methods in early stage CKD, standard risk prediction methods function poorly in patients with ESKD (17). ESKD appears to modify the effects of standard risk factors (hypercholesterolemia, blood pressure, and high glucose), and the increased rates of sudden death and heart failure are not captured by standard risk methods. Entirely new CV risk models may be needed in ESKD.

FIGURE 2 Framingham Predictive Instrument in CKD: Predicted and Actual 5- and 10-Year Risk of Cardiac Events



Graphical presentation of actual 5-year **(A)** and 10-year **(B)** risk of cardiac outcomes in men and women with chronic kidney disease (CKD) along with predicted risk, with and without recalibration for higher event rates in CKD stratified by quintile of predicted Framingham risk. Reproduced with permission from Weiner et al. (12).

The Framingham risk equation underestimates risk in kidney transplant recipients and modified equations have not been sufficiently validated in this population (18). **Table 1** outlines additional research that is required in the areas of epidemiology, presentation, and risk prediction.

SCREENING. Regular assessment for atherosclerotic CVD risk should be distinguished from screening for asymptomatic CAD. In the absence of evidence that pre-emptive coronary revascularization is effective in reducing death or MI risk in asymptomatic patients, screening for underlying anatomic CAD lacks either a rationale or evidence—even in at-risk asymptomatic patients (19). However, as noted herein, there is a rationale for screening in transplant candidates.

PATHOLOGY AND PATHOPHYSIOLOGY

PREVALENCE OF PATHOLOGICAL ABNORMALITIES AS GFR DECLINES. As GFR declines, the prevalence of clinical manifestations of CAD increases, in parallel with the prevalence of large-vessel coronary disease, arteriosclerosis, microvascular disease, LVH, and myocardial fibrosis. Cardiovascular abnormalities in CKD are associated with traditional (e.g., diabetes and hypertension) and nontraditional CKD-related CVD risk factors (e.g., mineral and bone disease abnormalities, anemia, inflammation, and oxidative stress), as well as dialysis-related factors (type and frequency of dialysis and dialysate composition). Vascular calcification also increases as GFR declines and is associated with mortality in ESKD; calcification of the subintima and media of large vessels are both associated with all-cause and cardiovascular mortality (20).

PATHOLOGY. Autopsy studies (21–23) have demonstrated more advanced atherosclerotic plaques and a higher prevalence of calcified atherosclerotic lesions in CKD versus non-CKD; however, there appears to be only limited medial calcification in the coronary arteries of those with CKD (24). Other studies have demonstrated more inflammation in the coronary plaques in CKD compared with non-renal control cases (25).

TABLE 1 Research Needs Regarding CKD and CAD

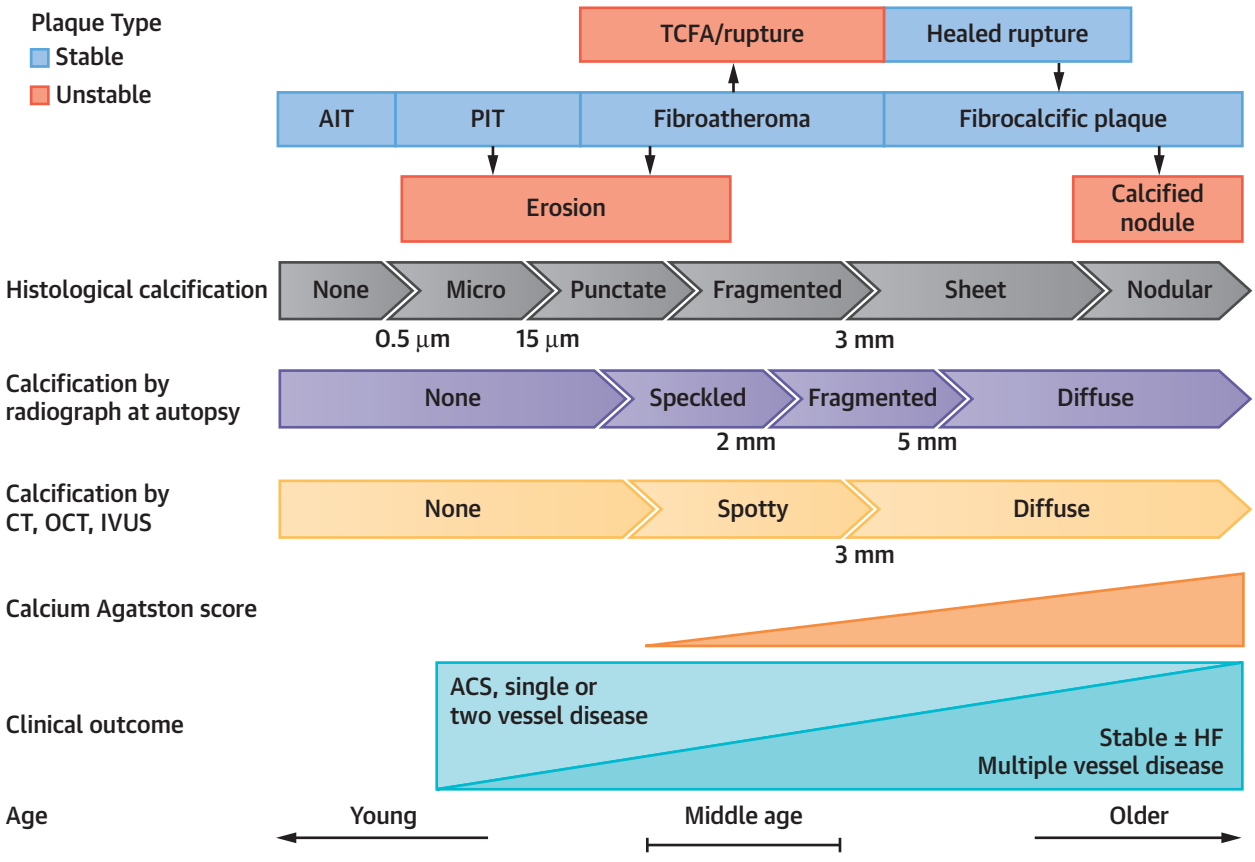
Epidemiology
Population-based cohorts of individuals with kidney disease at late stages (e.g., CRIC) and early stages (e.g., Kaiser, other general populations) to study longitudinal cardiovascular outcomes.
Standardization of clinical endpoints (particularly in relation to composite endpoints) and differentiation among endpoints that may be due to different mechanisms (e.g., atherosclerotic vs. arrhythmic vs. heart failure) in future clinical cohorts and clinical trials.
Frequency of sudden death as the initial presentation of CAD in CKD and mechanisms in CKD patients (primary arrhythmic vs. ischemic vs. other). Prevalence of CAD in incident dialysis patients either through angiography or CTA.
Presentation
Studies evaluating the pathophysiology underlying the differential electrocardiographic signs and clinical symptomatology of ischemia in CKD.
Studies evaluating the diagnostic accuracy of standard ECG metrics of ischemia in the setting of CKD.
Investigation of the etiology of intradialytic hypotension and whether this should be a considered an angina equivalent.
Additional mechanistic studies of myocardial stunning and its relationship to CAD.
Prediction
Studies to adapt widely accepted ASCVD risk predictors to the CKD population.
Addition of CKD-specific terms such as eGFR and ACR, based on individual patient data in large generalizable cohorts.
Assessment of need for refitting models based on altered relations of conventional risk factors with ASCVD risk in CKD.
Assessment of the utility of novel risk markers to improve prediction (e.g., coronary calcification, cTnT, BNP, troponins, and markers of Ca/P metabolism).
Development and validation of ESKD-specific CVD risk prediction scores, including potentially specific scores for major endpoint categories such as HF, sudden cardiac death, and MI.
Development and validation of risk equations in the post-kidney transplant patient population.
Pathology/Pathophysiology
Additional autopsy studies evaluating pathology of CAD in CKD and/or ESKD.
Frequency of plaque erosion or rupture across the CKD spectrum.
Studies evaluating association of calcification and its subtypes with risk of plaque erosion versus plaque rupture.
Mechanisms of sudden death in ESKD patients (primary arrhythmic vs. ischemic vs. other).
Role of dialysis associated factors such as dialysis modality (HD vs. PD) and different forms of HD (frequent, IHD, nocturnal) on CAD pathology.
Trials targeting inflammation (and senescence) in CKD to prevent calcification.
Trials to reduce calcification and association with outcomes.
Observational studies evaluating the effect of kidney transplantation on CAD pathology.
Kidney Transplant Recipients
Observational studies and trials evaluating whether transplant recipients should be screened for CAD. If so, in which patients and at what frequency?
Observational studies and trials evaluating whether screening strategies should be different in deceased donor transplantation versus living donors.
Development of strategies to mitigate the risk of CAD events post-operatively from a kidney transplant.
Evaluation of risk factors and development of risk equations for post-operative MI after kidney transplantation.
Observational studies evaluating risk factors for development of CAD post-transplant.
Prediction equations for development of CAD post-transplant.
Trials of accepted (e.g., blood pressure targets and agents, lipid-lowering therapies, beta-blockers) and novel therapies to prevent and treat CAD in kidney transplant recipients.

ACR = albumin-to-creatinine ratio; ASCVD = atherosclerotic cardiovascular disease; BNP = B-type natriuretic peptide; CAD = coronary artery disease; CKD = chronic kidney disease; CRIC = Chronic Renal Insufficiency Cohort; CTA = computed tomographic angiography; cTnT = cardiac troponin T; CVD = cardiovascular disease; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ESKD = end-stage kidney disease; HD = hemodialysis; HF = heart failure; IHD = intermittent hemodialysis; MI = myocardial infarction; PD = peritoneal dialysis.

Pathological and radiological studies in the general population have suggested that calcification in the coronaries may be either “micro” or “macro” (**Figure 3**) (26). Microcalcification occurs primarily in younger patients and is particularly associated with inflammation and plaque instability leading to acute coronary syndromes (ACS). In contrast, macrocalcifications tend to occur in older patients with more stable CAD and multivessel CAD. It is not exactly clear how CKD modifies this paradigm, although as mentioned calcified and more advanced plaques are highly prevalent in CKD. Whereas atherosclerosis in early CKD is driven by traditional CAD risk factors, nontraditional risk factors play a predominant role as GFR declines, leading to fibrocalcific lesions. Modification of lipoproteins (e.g., low-density lipoprotein carbamylation, high-density lipoprotein dysfunction) in CKD likely contributes to accelerated progression of CAD, and risk factors for calcification include inflammation, senescence, mechanical factors (e.g., shear stress, elastin fatigue), and potentially accumulation of microbiome-dependent metabolites such as trimethylamine N-oxide.

ACS. Both plaque rupture and superficial erosion lead to ACS (**Figure 4**) (27), but it is unclear how the presence of CKD influences each of these abnormalities, and the causes and treatments are likely different.

FIGURE 3 CAC by Plaque Type, Histology, and Radiographic Noninvasive and Invasive Assessments



Coronary artery calcification (CAC) by plaque type (stable and unstable), histology, radiographic noninvasive (computed tomography [CT], Agatston score) and invasive (optical coherence tomography [OCT], intravascular ultrasound [IVUS]) assessment. Reproduced with permission from Mori et al. (26). ACS = acute coronary syndrome; AIT = adaptive intimal thickening; HF = heart failure; PIT = pathologic intimal thickeing; TCFA = thin-cap fibroatheroma.

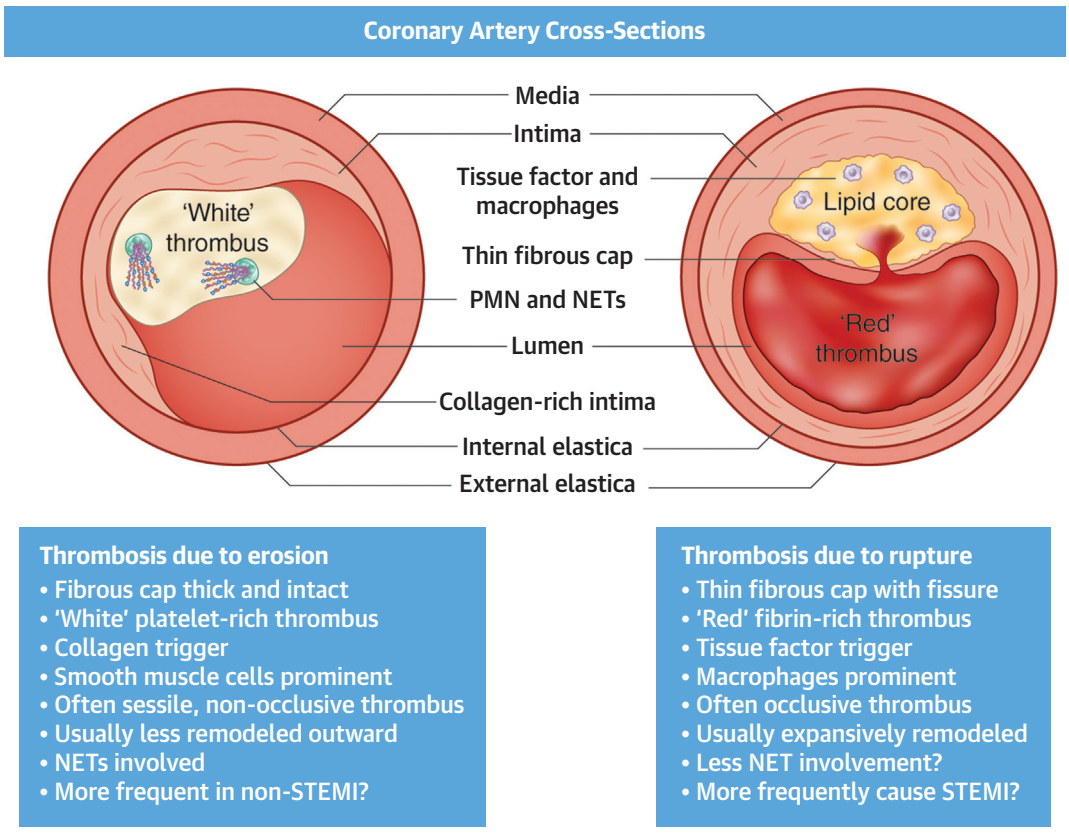
DIAGNOSIS

STRESS TESTING. In the symptomatic patient or asymptomatic potential transplant recipient, functional stress testing and noninvasive coronary imaging are used to quantify the burden of atherosclerosis, evaluate prognosis, and risk stratify individuals for coronary revascularization or medical optimization. These tests are more widely used in individuals with advanced CKD than in those with preserved kidney function (28). However, there are potentially important distinctions regarding use of these modalities in the setting of CKD versus those with preserved kidney function.

Prediction of anatomic CAD. Exercise testing and pharmacologic perfusion imaging have reduced accuracy for detecting CAD in CKD, with a higher rate of both false-negative and false-positive tests (29,30). Among kidney transplant candidates, both myocardial perfusion scintigraphy and dobutamine stress echocardiography have only moderate accuracy for detecting obstructive atherosclerosis (**Figure 5**) (30).

There are several provisos to the use of functional testing in CKD. Exercise testing is frequently limited by an inability of CKD patients to reach diagnostic workloads (31). Second, exercise testing in the CKD population is often limited by baseline electrocardiographic abnormalities (e.g., LVH) that could limit ability to detect ST-segment changes during exercise. Third, most existing data were derived from studies of transplant candidates—the extent to which these data are generalizable to dialysis patients or non-transplant candidates who are likely to have more comorbidities, a lower functional capacity, and a higher burden of atherosclerosis is uncertain. Finally, the prevalence of obstructive atherosclerotic lesions increases as eGFR declines (23). Given the high

FIGURE 4 ACS: Plaque Rupture Versus Superficial Erosion



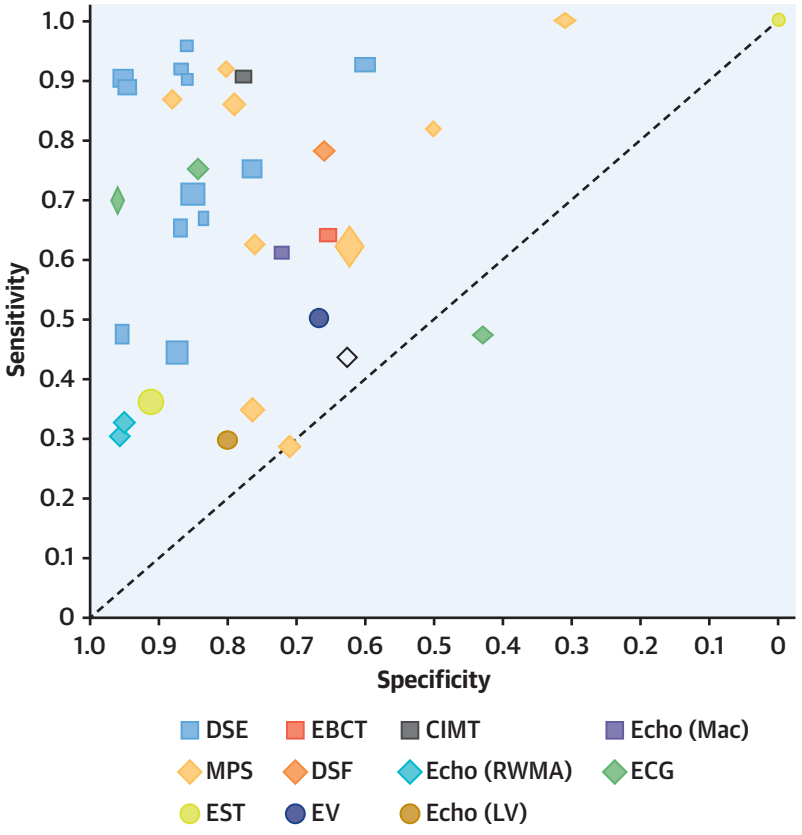
The coronary artery cross section showing thrombosis due to erosion **(left)** and rupture **(right)**. Reproduced with permission from Libby et al. (27). ACS = acute coronary syndrome; NET = neutrophil extracellular trap; PMN = polymorphonuclear leukocytes; STEMI = ST-segment elevation myocardial infarction.

probability of atherosclerosis and the moderate sensitivity of noninvasive tests, noninvasive tests may have a low negative predictive value and may not exclude the presence of functionally significant or anatomically high-risk disease. Thus, maintaining a high index of suspicion is critical in evaluating noninvasive cardiac testing in CKD and ESKD patients.

Coronary artery calcium score or computed tomography angiography (CTA) may offer significant advantages over functional imaging modalities in the setting of CKD. In a comparison of coronary artery calcium score, CTA, exercise, or pharmacologic stress single-photon emission tomography (SPECT) in which stenosis >50% was detected by quantitative coronary angiography in 138 transplant candidates, coronary artery calcium score and SPECT had only modest specificity (67% and 53%) and sensitivity (77% and 82%), and CTA had a high sensitivity (93%) but poor specificity (63%) (29). However, risks of acute kidney injury (AKI) need to be considered with CTA, particularly in late-stage CKD. In pre-dialysis kidney transplant candidates with mean eGFR of 12.7 ml/min/1.73 m^2, CTA was associated with a 12% incidence of AKI and with a higher incidence among those with diabetes or contrast doses >0.8 ml/kg, but creatinine returned to baseline within 1 month in all patients and none required dialysis (32).

Prognosis. Despite the questionable accuracy of noninvasive testing for detecting CAD in CKD, these tests appear to be useful for risk stratification. The risk of death is nearly doubled among CKD patients with abnormal SPECT, with a significant interaction between worsening kidney function and ischemia (33). However, SPECT-myocardial perfusion imaging was not useful for identifying CKD patients at lower risk, as annual mortality with normal imaging was still >10%. The poor negative predictive value may partially relate to nonatherosclerotic mechanisms of death (**Central Illustration**), which are not targeted by

FIGURE 5 Coronary Artery Disease in Chronic Kidney Disease: Stress Tests Versus Coronary Angiography in Potential Kidney Transplant Recipients



Plot of sensitivity versus specificity for different stress tests compared with a gold standard of coronary angiography in potential kidney transplant recipients. Height and width of symbols are proportional to the inverse standard error of the sensitivity and specificity, respectively. Each symbol represents results of a single report. Adapted with permission from Wang et al. (30). CAD = coronary artery disease; CIMT = carotid intimal medial thickness; CKD = chronic kidney disease; DSE = dobutamine stress echocardiography; DSF = digital subtraction fluorography; EBCT = electron beam computed tomography; ECG = resting electrocardiography; Echo (LV) = echocardiography (left ventricular dysfunction or cardiomegaly); Echo (MAC) = echocardiography (mitral annular calcification); Echo (RWMA) = echocardiography (resting wall motion abnormality); EST = exercise stress electrocardiography; EV = exercise ventriculography; MPS = myocardial perfusion scintigraphy.

SPECT-myocardial perfusion imaging. Similarly, whereas coronary angiography is slightly better than noninvasive tests at predicting all-cause mortality, noninvasive tests are as good at predicting CV mortality and major adverse cardiovascular events (34).

Absolute myocardial blood flow provided by positron emission tomography may further refine risk prediction. Coronary flow reserve provides information on both coronary atherosclerosis and small vessel function and may be a particularly powerful prognostic tool. In moderate-to-severe CKD, reduced flow reserve was associated with a 2.1-fold increase in the risk of CV death and provided incremental information to traditional risk factors and flow defects (35).

Additional ancillary markers have been proposed and studied to improve stress test accuracy (36). However, the majority of studies have been done in a pre-transplant population, and additional investigations that include other CKD patients are needed to determine performance in other settings.

TROPONINS. Cardiac troponins (cTn) are frequently elevated in advanced CKD in the absence of ACS, but the mechanism of this remains unclear. Severe atherosclerotic CAD is more common among ESKD patients with elevated troponin T (TnT) (37), and elevations in TnT and troponin I (TnI) may indicate subclinical myocardial damage, such as the transient myocardial stunning that occurs during hemodialysis (38). Elevation may also indicate the presence of

cardiac hypertrophy (39). Regardless of cause, TnT and TnI elevations (both in the presence and absence of ischemia) are associated with increased all-cause and CV mortality in CKD, with this more consistently demonstrated for cTnT than cTnI (40,41). Although the sensitivity of high-sensitivity TnI for the diagnosis of MI was not modified by kidney function, specificity decreases from 93% to 95% with preserved GFR to 40% to 41% in patients on dialysis (41). Thus, a normal Tn assay may be sufficient to rule out infarction, but elevated values are less definitive. However, contextualization of previous testing may be helpful. There is minimal variability in high-sensitivity TnT of stable dialysis patients (42), so routine outpatient testing to establish a baseline "healthy" TnT value in stable CKD could improve diagnosis of ACS. It is also unknown whether elevations in baseline measurements should trigger additional investigation to assess cardiac structure or atherosclerosis. More data are needed to better understand whether a CKD-specific high-sensitivity cTn threshold for absolute cTn values or dynamic change could improve sensitivity and specificity of MI diagnosis.

TREATMENT

MEDICAL THERAPY. Although medical therapy is the cornerstone of CAD treatment, challenges exist in CKD for a number of reasons: 1) the proportional contribution of atherosclerosis to events in those with advanced CKD and especially ESKD is low (**Central Illustration**); and 2) patients with CKD (especially advanced CKD and/or ESKD) are under-represented in clinical trials and as such the evidence to support recommendations is limited (43).

Lipid-lowering therapy. Controversy surrounds the use of lipid-lowering therapy (especially statins) in patients with CKD (**Table 2**). The benefit (reduction in major vascular events) with statin-based treatment becomes smaller as eGFR declines, with no evidence of benefit among patients on dialysis. The KDIGO guideline proposing the use of statins in CKD patients >50 years of age but not in dialysis patients was based on null results in the 4D (Deutsche Diabetes Dialyse Studie) and AURORA (A study to evaluate the Use of Rosuvastatin in subjects On Regular haemodialysis: an Assessment of survival and cardiovascular events) trials, and lack of benefit in the dialysis subgroup of SHARP (Study of Heart and Renal Protection) (44). However, in the SHARP trial, simvastatin and ezetimibe reduced major atherosclerotic events compared with placebo, without significant heterogeneity between nondialysis and dialysis patients ($p = 0.25$) (45). As the statin trials in dialysis patients enrolled only a small proportion of patients with known CAD, it remains to be determined whether statins are indicated in dialysis patients with prevalent CAD. A recent study has shown that the benefits of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors extend to those with CKD stages G2 (60-90 ml/min/1.73 m^2) and G3a-G3b (30-60 ml/min/1.73 m^2) (46).

REVASCULARIZATION. The choice of medical therapy alone or revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) in symptomatic patients with CKD and/or ESKD is controversial (**Table 2**). In the absence of dedicated clinical trials, CKD patients presenting with a STEMI undergo the same invasive approach as those with normal kidney function. Although observational studies seem to support an early invasive over a conservative approach (47), there was no survival benefit from early intervention among patients with CKD stages G3a to G5 (<60 ml/min/1.73 m^2) in non-ST-segment elevation-ACS randomized controlled trials (48).

Patients with CKD (especially advanced CKD and/or ESKD) are under-represented in recent clinical trials of patients with stable CAD—including COURAGE ([Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation], which included revascularization plus intensive medical therapy versus intensive medical therapy alone in Class I to III angina) (49) and BARI-2D ([Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes], which included revascularization versus medical therapy in asymptomatic or mildly symptomatic angina in diabetic patients with objective evidence of ischemia) (50)—showing no outcome benefit of routine intervention versus medical therapy. The ongoing ISCHEMIA-CKD (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches—Chronic Kidney Diseases) trial has randomized CKD patients with moderate ischemia on a clinically indicated stress test to medical therapy with or without revascularization to clarify the value of revascularization in the setting of stress-induced ischemia (51).

Trials of revascularization in asymptomatic patients without CKD and/or ESKD undergoing preoperative evaluation have also not shown benefit from revascularization. Among patients with clinically stable CAD scheduled for major vascular surgery, long-term mortality after prophylactic coronary artery revascularization was similar to optimal medical therapy (23% vs. 22%, $p = 0.92$) (52).

TABLE 2 CKD and CAD

What Is Known	What Is Not Known	Future Directions
Lipid-lowering therapy in CKD		
Statins are beneficial in early CKD Less clear benefit of statins in advanced CKD and/or ESKD Statins (including high intensity statins) are safe in CKD Benefits of PCSK9 inhibitors extend to CKD stage G3b	Whether statins are beneficial for secondary prevention in advanced CKD and/or ESKD Role of statins for kidney outcomes Role of PCSK9 inhibitors and/or fibrates in advanced CKD	PCSK9 inhibitors and CV outcomes trial in advanced CKD Fibrates and CVD outcomes in advanced CKD
Indications for revascularization		
CKD and/or ESKD patients under-represented in clinical trials ACC/AHA 2014 guidelines indications for revascularization—stable CAD Persistent angina despite OMT Possible survival benefit (LM disease, 3v CAD, 2v CAD involving proximal LAD) ACC/AHA 2014 guidelines indications for revascularization—NSTE-ACS Early invasive strategy if refractory angina, hemodynamic instability without comorbidities such as CKD (Level of Evidence: A) Early invasive strategy not recommended if kidney failure, because risks likely outweigh benefits (Class IIIC recommendation) Invasive strategy reasonable in patients with CKD stages G2 to G3b (Class IIA recommendation) Early invasive strategy for STEMI	Stable CAD What is OMT in CKD and/or ESKD? What is the benefit of revascularization to improve prognosis? High upfront risk (death and/or AKI) High competing risks In NSTE-ACS-CKD/ESKD Value of early invasive strategy? How to individualize therapy based on risk and/or benefit and patient preference?	Patient-centric approaches for management strategies* Understand CKD patients' preferences for CAD management Evaluate the most important attributes of treatment choices for patients with CKD Develop models and decision aids to provide individualized estimates of patient-centered outcomes Implementation and testing of shared decision models in the area of CAD and CKD CKD-specific trials of OMT CKD-specific trials of revascularization in ACS
PCI vs. CABG for multivessel disease in patients with CKD		
Data from mainly nonrandomized studies Nondialysis CKD patients Short term: higher risk of death, stroke, AKI with CABG vs. PCI Long term: similar risk of death but higher MI and repeat revascularization with PCI when compared with CABG Dialysis patients Short term: higher risk of death and stroke with CABG vs. PCI Long term: higher risk of death, MI, and repeat revascularization with PCI when compared with CABG Selection bias?	Outcomes with PCI vs. CABG in CKD/ESKD patients from RCT Progression to ESKD Mortality and CV outcomes Outcomes with multiarterial grafts with CABG Implications of using radial artery for multiarterial grafts	RCT of PCI vs. CABG in CKD/ESKD Multiarterial graft in CKD Studies of hybrid PCI (robotic LIMA to LAD) Patient-centric decision making ESKD-related prognosis/risk of AKI and/or CKD progression
Prevention of AKI in PCI vs. CABG		
No benefit of bicarbonate and/or NAC on reduction of AKI over normal saline Risk of dialysis-dependent AKI low with ultra-low volume contrast strategies and hydration Risk of AKI considerably higher with CABG than PCI Preservation of residual kidney function by prevention of AKI critical for PD and perhaps for HD patients Recommended strategies to reduce risk include stopping offending drugs (e.g., NSAID, diuretics), hydration, titrating BP to maintain perfusion during surgery, low contrast volumes and/or zero contrast PCI Rates of CI-AKI are low in high-risk patients—should rarely be a reason to withhold needed PCI in CKD patients	Rates of AKI in contemporary practice Contrast-associated vs. contrast-induced Optimal prevention strategies for residual kidney function protection in PD and/or HD patients Strategies to reduce AKI incidence post-cardiac surgery	Trials to determine optimal strategies for AKI prevention in cardiac surgery Novel therapeutics but also surgical strategies and/or care pathways
Use of femoral vs. TRA for PCI		
CKD patients are categorized as high bleeding risk TRA reduces the risk of bleeding Potential reduction in mortality in patients with high risk of bleeding (e.g., STEMI) Potential reduction in AKI Increased risk of radial artery occlusion Histopathological changes in the radial artery after TRA AVF generally in the nondominant arm whereas right arm preferred for TRA	Incidence of radial artery occlusion in late stage CKD (smaller arteries with calcification) Incidence of radial artery stenosis after instrumentation	Evaluate radial artery stenosis and occlusion in CKD cohorts after TRA
DAPT consideration in CKD patients		
Advanced CKD patients have both increased risks of bleeding and thrombosis Newer-generation DES have lower rates of stent thrombosis compared with older generation DES Minimum DAPT duration for stable CAD now reduced to 6 months for stable CAD (3 months for HBR patients) Minimum duration for ACS still 12 months Limited data to support new $P2Y_{12}$ over clopidogrel in those with CKD Reduced dose DOAC + $P2Y_{12}$ vs. triple therapy reduces bleeding in AF patients needing PCI	Optimal duration in CKD Optimal choice of DAPT agent in ESKD Optimal treatment choice for ACS + AF in CKD and ESKD	Trials of 1–3 months of DAPT ongoing Trials of SAPT (ticagrelor) ongoing Trials to define optimal treatment in CKD and/or ESKD with AF + PCI Role of platelet function testing and genetic testing to guide optimal antiplatelet therapy

*Although we have focused and provided examples of patient-centric approaches for management strategies in the "indications for revascularization" section, this concept could be more broadly incorporated into all areas of future research in the field of CAD and CKD.

2v = 2-vessel; 3v = 3-vessel; ACC = American College of Cardiology; ACS = acute coronary syndrome; AF = atrial fibrillation; AHA = American Heart Association; AKI = acute kidney injury; AVF = arteriovenous fistula; BP = blood pressure; CABG = coronary artery bypass graft; CI-AKI = contrast-induced acute kidney injury; DAPT = dual antiplatelet therapy; DES = drug-eluting stents; DOAC = direct oral anticoagulant; HBR = high-bleeding risk; HD = hemodialysis; LAD = left anterior descending coronary artery; LIMA = left internal mammary artery; LM = left main; NAC = n-acetylcysteine; NSAID = nonsteroidal anti-inflammatory drugs; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; PCSK9 = proprotein convertase subtilisin/kexin type 9; PD = peritoneal dialysis; RCT = randomized controlled trial; SAPT = singe antiplatelet therapy; STEMI = ST-segment elevation myocardial infarction; TRA = transradial access; other abbreviations as in Table 1.

PCI versus CABG. Short-term procedural risks (of both PCI and CABG) are higher among patients with CKD compared with those without CKD. The data to support PCI or CABG in patients with CKD (especially in those with advanced CKD and/or ESKD) are sparse and mainly from nonrandomized studies (Table 2). A meta-analysis of randomized trials suggested some benefits to CABG over PCI in moderate CKD; however, the analysis included few patients with advanced CKD (53). Among dialysis patients, observational studies suggest a short-term higher risk of mortality and stroke with CABG versus PCI, but a long-term higher risk of death, MI, and repeat vascularization with PCI versus CABG. The frailty and comorbidity burden of patients with CKD makes it critical to use patient-centric decision making that takes into consideration the relative short- and long-term risks and/or benefits of intervention, overall CKD related-prognosis, and patient preference (54).

Special considerations for revascularization in patients with CKD. These include AKI, access site for cardiac catheterization, and duration of dual antiplatelet therapy (Table 2).

Both PCI and CABG are associated with higher risk of AKI among patients with CKD and with higher risk for CABG versus PCI (55). Many strategies have been proposed to reduce the risk of AKI during PCI or CABG, although none are based on large randomized trials.

Recent guidelines, driven by data from randomized controlled trials, endorse transradial over transfemoral access to reduce bleeding risk. However, the association of transradial access with small risk of radial artery occlusion or potentially stenosis has led to a controversy over the use of transradial access in those with advanced CKD who may need radial access for an arteriovenous fistula (Table 2). Radial artery grafts may also result in better outcomes than saphenous vein grafts after CABG. Decisions about access site for catheterization and use of radial artery grafts for CABG should be made using a "heart-kidney" team approach.

Limited data exist to guide the duration of dual antiplatelet therapy in CKD patients undergoing PCI. This is an important consideration because of the risk of ischemic and bleeding complications in patients with CKD (Table 2) and warrants dedicated studies. Available data suggest that in the setting of advanced CKD, extended duration may be associated with excessive bleeding risks and unclear benefits (56–58). There are also no prospective or randomized controlled trial data available to guide the management of antiplatelet and anticoagulation for CKD and/or ESKD patients with atrial fibrillation undergoing PCI.

PRE-TRANSPLANT SCREENING FOR CAD

OBJECTIVES OF SCREENING FOR CAD PRIOR TO TRANSPLANTATION.

Deceased donor kidney transplantation is an elective surgery performed under emergent conditions. Accordingly, the objectives of screening candidates for CAD in deceased donor transplantation are more numerous than those for other elective surgical procedures and include the following.

Selection of appropriate candidates for activation to deceased donor waiting list. It is futile to activate patients to the wait list whose life expectancy is less than the anticipated waiting time for transplantation.

Informing patient transplant options. CAD screening tests are used by transplant physicians to advise patients about their individual transplant options. Patients with a high burden of CAD may be advised that they are only candidates for living donor transplantation (59) or to accept a kidney from a donor with an increased risk of infectious disease transmission or one with lower estimated longevity in exchange for reduced waiting time on dialysis.

Maintaining patient eligibility for transplantation during wait listing. Monitoring and maintaining the medical fitness of wait-listed transplant candidates is challenging for transplant programs: the unpredictability of deceased organ donation requires patients to be maintained in state of readiness for surgery over several years. CAD testing may be the only means to delist patients who develop new or progressive CAD that poses an unacceptable risk for transplantation.

Avoiding peritransplant CAD events. The consequences of perioperative events in kidney transplant recipients exceed those of other surgical procedures because of the potential impact on transplant kidney function. Transplant physicians are also acutely aware of their societal responsibility to ensure judicious use of scarcely available deceased donor organs. Transplant centers are closely monitored for their short-term outcomes.

Optimizing post-transplant survival. CAD events after transplantation may compromise long-term patient survival and allograft function. It is hoped (but not proven) that treatment invoked by screening may prevent early post-transplant CAD events and improve long-term outcomes.

EVALUATING PRE-TRANSPLANT PATIENTS FOR CAD.

Patients with signs or symptoms suggestive of CAD should be evaluated. Among asymptomatic patients, some form of screening for occult CAD is entrenched in clinical transplant practice, despite limited evidence that screening reduces the risk

of CAD events (60) and in contrast to recommendations for management of nontransplant surgical candidates.

Transplant guidelines recommend screening based on the presence of CAD risk factors, using noninvasive screening tests both at the time of activation to the wait list and periodically during wait-listing with the objective of identifying patients with occult disease who are candidates for revascularization or medical therapy. Whether screening improves patient survival or transplant outcomes is uncertain, and it is possible that screening may paradoxically cause harm by unnecessarily subjecting patients to invasive procedures and delaying or excluding patients from transplantation (**Table 1**) (31,61).

The current screening paradigm is challenged by several factors. First, CV mortality in CKD may be related to arrhythmia due to uremic cardiomyopathy rather than to AMI. Second, noninvasive screening tests lack sensitivity and specificity to identify asymptomatic patients with clinically significant coronary artery stenoses that would warrant revascularization (30). Finally, even if a clinically significant stenosis were identified, the evidence that revascularization would improve outcomes is lacking (30). A scientific statement for transplant candidates (60) recommended that initial screening prior to wait-list activation "may be considered" in transplant candidates with no active disease but with multiple CAD risk factors (Class IIB, Level of Evidence: C). The statement acknowledged the lack of strong evidence for or against routine cardiac screening of asymptomatic transplant candidates.

TEST SELECTION. As described, noninvasive testing for CAD has imperfect sensitivity and specificity in ESKD patients. Current guidelines recommend testing be done with an exercise or pharmacological stress echocardiogram or nuclear scintigraphy. The choice of exercise or pharmacological stress is determined by the presence of physical limitations (e.g., osteoarthritis). There are limited data on the role of coronary CTA in dialysis patients undergoing prerenal transplantation cardiac risk stratification (62).

SCREENING CANDIDATES IN DECEASED VERSUS LIVING DONOR TRANSPLANTATION. The risk of perioperative delayed graft function and death are significantly lower among living compared with deceased donor transplantation. However, the consequences of a perioperative event in a living donor recipient are potentially greater than in the deceased donor setting: losing a living donor kidney may have substantial emotional impact. A single transplant failure may lead to increased regulatory scrutiny and penalties for transplant programs, because of the expected excellent outcomes with living donor transplantation. Consequently, there may be an even lower threshold to screen and intervene in asymptomatic living donor candidates despite the relative absence of evidence that this practice is beneficial. Given these differences from deceased donor transplantation, development of a distinct evidence-based screening strategy for living donor candidates should be evaluated (**Table 1**).

FREQUENCY OF EVALUATION FOR CAD. In addition to screening prior to acceptance onto the transplant waiting list, the current standard of care involves screening asymptomatic patients at variable intervals after wait-listing until transplantation. The American College of Cardiology/American Heart Association scientific statement reflects uncertainty about periodic screening after wait-listing (Class IIB, Level of Evidence: C) (60). Some transplant programs have adopted a strategy of deferred screening in which only patients who have accrued significant waiting time and are expected to receive a deceased donor offer in the near future are screened. Until new evidence becomes available, the utility of periodically screening asymptomatic patients during wait-listing remains uncertain. The CARSK (Canadian-Australasian Randomised Trial of Screening Kidney Transplant Recipients for Coronary Artery Disease) trial (NCT03674307) will test the hypothesis that a conservative strategy of cardiac evaluation (only after a clinical event) is noninferior to an aggressive strategy of mandated (and repeated) screening among asymptomatic patients wait-listed for kidney transplantation (**Table 1**).

PERITRANSPLANT CV MANAGEMENT

PREDICTION OF PERIOPERATIVE ATHEROSCLEROTIC PLAQUE RUPTURE. The propensity of plaques in noncritically stenosed beds to rupture challenges the current screening paradigm (63). One-third of patients with perioperative MI sustain damage in areas distal to noncritical stenosis (64). Available screening tests do not identify vulnerable plaques, but the development of new imaging modalities and biomarkers may allow identification and stratification of this risk.

MANAGEMENT TO MITIGATE PERIOPERATIVE CV RISK. Acceptable candidates for transplantation with high-risk coronary anatomy (left main disease, proximal stenosis of the left anterior descending artery, and multivessel disease) should be considered for revascularization (65). In the absence of high-risk coronary anatomy, a model of shared decision

making that incorporates the patient's perspective and informed by combined transplant and cardiology team expertise is preferred.

Trials to inform the optimal method of revascularization in CKD patients are not available, and most transplant programs follow recommendations informed by evidence from non-CKD populations. However, all types of revascularization are associated with a higher risk of morbidity and mortality in CKD compared with non-CKD patients. The approach to revascularization should include consideration of higher rates of restenosis, stent thrombosis, and bleeding among CKD patients. The risk that revascularization may permanently exclude or delay patients from transplantation should also be considered.

NONSURGICAL THERAPIES FOR REDUCING PERIOPERATIVE CAD EVENTS. Trials in transplant candidates are not available. Extrapolation from studies in nontransplant surgical patients supports continuation but not initiation of beta-adrenergic-blocking drugs in the perioperative period (66) and continuation of acetylsalicylic acid if the risk of ischemia exceeds the risk of bleeding, although evidence to initiate acetylsalicylic acid perioperatively to prevent ischemic events is lacking (67). Statins should be also continued perioperatively with appropriate dose adjustments or medication substitutions in patients taking cyclosporine (65).

POST-OPERATIVE RISK. Delayed graft function, typically defined by the use of dialysis in the first week after kidney transplantation, occurs in approximately 30% of all deceased donor transplants and is associated with increased risk of early allograft failure, acute rejection, and death (68). An association between AMI and delayed graft function has also been reported (69). Because the risk of delayed graft function is predictable prior to transplantation, strategies to mitigate the risk of CAD events in this setting are potential areas of future research.

RISK STRATIFICATION. Risk stratification of patients after transplantation may be based on traditional and nontraditional risk factors and composite risk scores, use of structural or functional parameters (e.g., LVH), clinical evaluation (e.g., blood pressure), and biomarkers (e.g., TnT, B-type natriuretic peptide). Restoration of kidney function with transplantation profoundly reduces the risk of MI and death (70), and decreased GFR is a strong predictor of CV outcomes after transplantation (71). The Framingham risk score underestimates the risk of ischemic events after transplantation, and the degree of underestimation is greatest among patients with diabetes (18). A number of other composite risk scores have been developed, but few have been externally validated (72,73).

CONCLUSIONS

The association of CKD with CAD is driven by a high prevalence of traditional as well as uremia-related CAD risk factors. The management of CAD in these patients must be informed by the modification of its clinical presentation in CKD, as well as comorbidity and risks of treatment side effects. The extent to which clinical outcomes may be improved with development of better estimators of risk as opposed to increased emphasis on treatment of established risk factors is uncertain. Several studies suggest that there are significant opportunities to improve treatment of established risk factors, and KDIGO guidelines for the care of kidney transplant recipients (74) and for lipid management in CKD (44) provide specific treatment recommendations. Nonetheless, there are several reasons why treatment of established cardiac risk factors is lacking, including weak evidence for efficacy or extrapolation of evidence from the non-CKD setting. Ongoing work is needed to better understand the epidemiology, pathophysiology, diagnosis, and treatment of CAD in CKD.

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APPENDIX For a list of other conference participants, please see the online version of this paper.