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KDIGO Controversies Conference on Central & Peripheral Arterial Diseases in CKD

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Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of kidney disease patients worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences on topics of importance to patients with kidney disease. These conferences are designed to review the state of the art on a focused subject and to ask conference participants to determine what needs to be done in this area to improve patient care and outcomes. Sometimes the recommendations from these conferences lead to KDIGO guideline efforts and other times they highlight areas for which additional research is needed to produce evidence that may lead to guidelines in the future. This current Controversies Conference sponsored by KDIGO is the fourth in our cardiovascular series and relates to Central and Peripheral Arterial Diseases in Chronic Kidney Disease (CKD). The preceding conferences addressed arrhythmias, heart failure, and coronary and valvular heart disease in the setting of CKD.

BACKGROUND

The burden and challenges in the management and treatment of cardiovascular diseases (CVD) in patients with CKD and those on dialysis are well documented as summarized in the recent 3 Controversies Conferences covering arrhythmias, chronic heart failure, and coronary and valvular heart diseases in the setting of kidney disease.[1-4] Not surprisingly, the risks for other CVD subtypes such as cerebrovascular diseases, central aortic disease, renovascular disease and peripheral arterial diseases are also elevated in persons with CKD.

Cerebrovascular Disease. The risk for stroke is approximately doubled for patients with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2,[5] and the incident risk of stroke is 43% higher compared with those with preserved kidney function.[6] The risk is even higher among dialysis patients who have 2-7 times the risk of stroke compared with those without CKD.[9] Risk of recurrent stroke is also increased in patients with reduced eGFR.[7] Another facet of CKD, proteinuria, was also found to convey a 71% higher risk of stroke compared with those without proteinuria. Although much is known about management of traditional risk factors such as hypertension, dyslipidemia, and atrial fibrillation, the relative contribution of CKD-specific etiologies (e.g., CKD-Mineral Bone Disorder), dialysis-related factors, erythropoiesis-stimulating agents for treatment of anemia) vs. these traditional risk factors is still unclear. Although atrial fibrillation is a major source of stroke in CKD, knowledge about the contribution of cerebrovascular disease on the high rates of stroke remains scarce. As such there are still numerous uncertainties and controversies related to its treatment such as optimal use of antiplatelet, anticoagulation, thrombolysis, endovascular, and surgical revascularization therapies for this patient population. However, recent studies have since emerged that could shed additional light on these issues.[10-12]

Central Aortic Disease. A recent prospective study first demonstrated that low eGFR and albuminuria are independent risk factors for incident abdominal aortic aneurysm (AAA).[13] In addition, the degree of CKD severity is an important predictor of perioperative and long-term survival after AAA repair, with highest risk reported in those with advanced CKD (G4-G5)[14] and on dialysis;[15] high mortality rates were observed in patients with kidney failure (formerly known as end-stage kidney disease, ESKD) for both open surgical and endovascular interventions.[16] Conversely, acute kidney injury is common after vascular and endovascular procedures,[17] especially with open repair surgery,[18] although long-term decline in kidney function has also been reported with endovascular repair.[19-21] Uncertainties still surround the timing and the selection of optimal treatment based on individual demographics and risk factors, appropriate renoprotection during aortic surgery, and proper follow-up care in high-risk patient groups.

Renovascular Disease. Although hypertension and diabetes are the most frequent causes for CKD, atherosclerotic vascular lesions in the renal arteries are also common. They account for many cases of renovascular disease and are often associated with other vascular disease such as coronary, aortic and peripheral vascular disease. In one small series, rates of renovascular disease have been reported to be as high as 20-40% among newly started dialysis patients, and US Medicare claims data revealed that up to 9.7% of new kidney failure patients have identified atherosclerotic renovascular disease (but considered it as the primary cause of the kidney disease less than half the cases).[22] The pathophysiology of underlying atherosclerotic renovascular disease is not well understood, but recent research indicates that renal oxygenation is preserved despite reduced perfusion of up to 30-45%, and tissue hypoxia triggers inflammatory processes only when renal blood flow is more severely affected.[23] A recent systematic review that included the ASTRAL and CORAL trials favored the use of medical therapy over revascularization,[24] which was also echoed in the 2017 European Society of Cardiology guideline.[25] However, open questions remain about the appropriate indication and treatment approach in cases of rapidly declining kidney function with bilateral atherosclerotic renal artery stenosis, uncontrolled hypertension, flash pulmonary edema and the proper identification of patients who would benefit from revascularization.[26, 27]

***Peripheral Arterial Diseases*.** The National Health and Nutrition Examination survey (NHANES) estimated that at least one million individuals over the age of 40 years with mild to moderate CKD suffer from peripheral arterial disease (PAD), and another study reported that as many as 20-30% patients with kidney failure have coexistent PAD.[28] Although US national registry data reveal that rates of lower extremity amputations in patients on dialysis have decreased by 51% during a recent 15-year period,[29] nearly one in ten patients with kidney failure nevertheless underwent amputation in their last year of life.[30] In addition, one-year mortality was extremely high after amputation at 46%.[29] The CKD-Prognosis Consortium also demonstrated that both decreased eGFR and presence of albuminuria are independent risk factors for incident PAD,[31, 32] and non-traditional risk factors such as inflammation, pro-thrombotic state, oxidative stress, etc. may also play a role.[33] Increasing severity of CKD was also associated with stepwise elevated risk of amputation, higher in-hospital mortality, higher costs and longer length of hospital stay.[34] High rates of vein graft failure, post-operative myocardial infarction

and mortality have also been reported in patients with severe CKD and on dialysis.[35] Despite the increased use of endovascular procedures over open procedures,[36] controversies still persist on the optimal treatment for patients with kidney failure and critical limb threatening ischemia; as such, risk models such as Society of Vascular Surgery's Wound, Ischemia and Foot Infection (WIFI) and others may allow a more individualized approach to inform clinician and patient decision-making.[37, 38]

CONFERENCE OVERVIEW

Given the importance of integrated coordinated care for patients with these cardiovascular comorbid conditions, this KDIGO conference will gather a global panel of multidisciplinary clinical and scientific expertise (i.e., nephrology, cardiology, neurology, surgery, radiology, pathology, pharmacology, health economics, and other allied health professionals, etc.) to identify key issues relevant to the optimal detection, management and treatment of cerebrovascular diseases, central aortic disease, renovascular disease and peripheral arterial diseases in the setting of CKD. The goal of this KDIGO conference is to determine best practice and summarize areas of uncertainty; review key relevant literature; address ongoing controversial issues; and propose a research agenda to address any gaps in knowledge.

Drs. Kirsten Johansen (Hennepin Healthcare, Chronic Disease Research Group, and University of Minnesota, Minneapolis, USA) and Holger Reinecke (University Hospital Muenster, Germany) will co-chair this conference. The format of the conference will involve topical plenary session presentations followed by focused discussion groups that will report back to the full group for consensus building. Invited participants and speakers will include worldwide leading experts who will address key clinical issues as outlined in the **Appendix: Scope of Coverage**. The conference output will include publication of a position statement that will help guide KDIGO and others on the effective diagnosis, management and treatment of central and peripheral arterial diseases in CKD.

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APPENDIX: SCOPE OF COVERAGE

Group 1: Cerebrovascular Disease (atherosclerotic disease as primary focus)

1. What is the epidemiology in the context of CKD/dialysis?
   a) What is the incident risk of stroke with CKD, proteinuria, kidney failure (i.e., ESKD), and in kidney transplant recipients?
   b) Are eGFR, proteinuria, dialysis type independent risk factors for stroke?
   c) What are the most frequently occurring stroke subtypes by eGFR, proteinuria, dialysis modality and in kidney transplant recipients?
   d) Do patients with CKD get more severe strokes? Is stroke mortality higher with CKD/dialysis? Are there predictors of severity or mortality in this setting?

2. Can we predict stroke in CKD/dialysis?
   a) Are there valid risk prediction tools that can be applied to CKD, dialysis populations?
   b) Are novel population-specific prediction tools required?
   c) What is the utility of the addition of kidney function to CHA_2DS_2–VASc scores (e.g., CHA_2DS_2–VASc-R and CHA_2DS_2–VAK scores)?
   d) Should we routinely screen patients with CKD for AF?
   e) Is there a timepoint in the course of their disease (or dialysis) that patients are most vulnerable to cerebrovascular events e.g., starting dialysis for the first time, with long interdialytic gaps?

3. What are the key pathophysiology and CKD/dialysis-related risk factors compared with non-CKD patients? (e.g., mineral metabolism/vascular calcification, dialysis procedure, etc.)
   a) Do the mechanisms differ between those with and without proteinuria, and between those who are and aren't dialysis-dependent?
   b) What is the role of hypertension?
   c) How important are 'non-traditional' risk factors?
   d) Are there hemodialysis-specific factors in related to cerebral hypoperfusion/altered vasoregulation?

4. How best to diagnose and evaluate stroke in CKD/dialysis?
   a) Role of imaging and biomarkers? Is there a tendency to suboptimally investigate these patients, particularly with regard to vascular or MR imaging because of concerns regarding contrast/gadolinium, or because of limiting co-morbidities/frailty (e.g., preventing the patient from lying flat for MRI etc.)?
   b) Challenges in ascertainment of outcomes, especially in dialysis patients
   c) How should we manage silent/incidental infarcts? What are their implications in terms of predictive ability for future symptomatic stroke risk (ischemic/hemorrhage/both), association with cognitive complaints/dementia, gait and balance abnormalities, and falls?

5. Therapies and prevention:
   a) Is there equity in stroke care delivery in CKD?
   b) Pharmacotherapies in acute stroke: BP management; role of thrombolysis, access to acute stroke unit
   c) What is the safety and efficacy of endovascular and surgical interventions for ischemic and hemorrhage strokes respectively?
   d) How should dialysis prescription be altered in the acute phase?
   e) What are the key tenets of primary and secondary prevention?
   f) What progress has been made since the 2016 KDIGO Arrhythmias Conference in terms of anticoagulation challenges and what is the role of a left atrial appendage occlusion device in CKD patients with AF? Are reversal agents safe in CKD and should they influence the choice of anticoagulant?
   g) Are the outcomes of carotid interventions in advanced CKD/kidney failure (i.e., ESKD) improving?

6. What are the functional/neuropsychiatric outcomes after stroke?
   a) Physical and functional recovery, return to independence
   b) Neurocognitive changes
   c) Psychiatric concerns

7. What are the short and long-term medical complications after stroke and how to mitigate
   a) short and long-term (e.g., pneumonia, ACS)
   b) dialysis considerations

Group 2: Central Aortic Disease

1. What is the epidemiology of AAA in the context of CKD/dialysis?
   a) What is the evidence for CKD as a risk factor for AAA development?
   b) Is there any effect of pre-surgery GFR on post-surgery outcomes?
   c) What is the association of AAA and AAA treatment with various techniques for CKD development/ eGFR loss or cardiovascular outcomes/mortality?

2. Association of central aortic disease and renovascular disease: What is the evidence of prevalence of renal artery stenosis in patients with AAA?

3. Acute kidney injury and AAA
   a) What is the incidence of AKI after AAA? Is there a difference according to different management (open vs endovascular types? Are there other pre-disposing factors?)
   b) What is the impact of AKI post-treatment of AAA on kidney and cardiovascular outcomes?

4. What are the potential differences in pathophysiology, natural history and risk of rupture of AAA between patients with and without CKD and between CKD stages?

5. a) What are the means for diagnosis and optimal initial evaluation in CKD, including the value of duplex ultrasound, CT, MRI and angiography?
   b) What is the optimal follow-up algorithm for post-procedure evaluation in patients with CKD?

6. What is the optimal management, indication for treatment of AAA including prevention of periprocedural acute kidney injury?
   a) Is there a difference between modes of treatment (e.g., open surgery vs endovascular vs supra- or infrarenal graft fixation)
   b) What is the evidence on optimal peri-procedural management (including isotonic fluid administration) for AKI prevention?

7. How may management differ in special populations? (e.g., in cases of acute ruptures; care of the older adults >75 yrs)

8. What is the evidence on aortic dissection epidemiology and natural course in patients with CKD? Are there differences in optimal treatment of aortic dissection between patients with or without CKD?

Group 3: Renovascular Disease

1. What is the epidemiology in the context of CKD/dialysis? What are the determinants of good and bad outcomes (e.g., proteinuria; kidney size)

2. What is the pathophysiology? (e.g., role of hypoxia, inflammation, etc.; novel biomarkers?)

3. What are the clinical signs associated with atherosclerotic renovascular disease (ARVD)?

4. What are the means for diagnosis and optimal evaluation, including value of duplex ultrasound, CT, MRI (non-contrast and contrast studies) and angiography?

5. Which patients should be investigated for ARVD?

6. What standard medical therapy should be given to all patients with ARVD? Is there evidence on optimal treatment in patients with both AAA and critical RAS?

7. In particular, what are the risks and benefits of renin angiotensin blockade (ACE-I or ARB) in ARVD?

8. Which cases should be selected for surgical revascularization (e.g., unilateral vs. bilateral disease, progressive CKD, etc)?

a) What are the indications for renal revascularization treatment with angioplasty/stenting?

b) What are the indications for surgical revascularization?

9. How may management differ in special populations? (e.g., dialysis patients; stenoses in kidney transplants, renovascular fibromuscular dysplasia in patients

with atherosclerotic disease)

Group 4: Peripheral Arterial Diseases

1. What are key gaps in the epidemiology of PAD in CKD/dialysis/transplant?
a) How to define and measure PAD in CKD for reliable epidemiological estimates? Potential of underestimating the burden of PAD in CKD.
b) Lacking data on PAD epidemiology in transplant?
c) Lacking data on patient-reported outcomes?
d) What are important outcomes for patients with PAD and CKD to be explored in future epidemiological studies
e) Sparse data on cost-effectiveness
f) Limited data on acute limb ischemia (ALI)?

2. What are the key pathophysiological mechanisms behind disproportionally high burden of PAD in CKD with implications on PAD diagnosis and management?
a) Vascular calcification
b) Uremic toxins
c) Others like inflammation, oxidative stress

3. What are the optimal approaches to diagnose PAD in CKD?
a) Ankle-brachial index (ABI), toe-brachial index (TBI), waveforms
b) Imaging
    - Modalities
    - Contrast (e.g., angiography, CT, MRI, etc.)
c) Who should get screened? All CKD or subpopulations (e.g., diabetes)
d) Should approaches differ by CKD types (e.g., dialysis or transplant)?
e) What is the role of biomarkers/prediction models?

4. What are key challenges in the management and treatment of PAD in CKD?
a) Level of evidence base for treatment of PAD in CKD/dialysis/transplant
    - Statin
    - Antiplatelet
    - Revascularization
    - PCSK9 inhibitors
    - Diabetic therapy (regular foot care, a concern of SGLT2 inhibitors)
    - Lifestyle (smoking cessation)

- Supervised exercise therapy

b) Compliance of evidence-based treatments of PAD in CKD

c) Amputation-related issues
   - Eligibility
   - Post-amputation care
   - Role of palliative care
     Any new treatments?
   - Podiatrists/multidisciplinary team care

d) Any specific treatments to specific populations?
   - Specific discussion about diabetes
   - Diagnostic approach
   - Regular footcare
   - SGLT2 inhibitors
   - Amputation

e) Impact of PAD on CKD management
   - Prognosis
   - Transplantability
   - Vascular access
   - Upper-extremity PAD (probably most relevant to dialysis)
     Impact of CKD on PAD management
   - Contrast for revascularization