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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. 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-MBD, 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 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 ESKD 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 ESKD 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 ESKD 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 ESKD 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: Atherosclerotic Cerebrovascular Disease (excluding intracerebral disease)

1. What is the epidemiology in the context of CKD/dialysis? (e.g., types of strokes, risk factors, outcomes of interest)

2. What are the pathophysiology and potential differences compared with non-CKD patients? (e.g., management of atrial fibrillation in CKD/dialysis)

3. What are the means for its diagnosis and optimal evaluation in CKD? Role of imaging and biomarkers?

4. What are the factors governing conservative management; endovascular vs surgical treatment; pharmacotherapies?

5. How may ethnic differences differ for all of the above? Are there management differences in different populations? (e.g., women)

Group 2: Central Aortic Disease

1. What is the epidemiology in the context of CKD/dialysis? Bidirectional nature: CKD as a risk factor for AAA vs AKI/CKD as a consequence of AAA (e.g., CKD after EVAR)?

2. What are the pathophysiology and potential differences compared with non-CKD patients?

3. What are the means for diagnosis and optimal evaluation in CKD, including the value of duplex ultrasound, CT, MRI and angiography?

4. What is the optimal management (e.g., open surgery vs endovascular) indication for treatment of aortic disease including prevention of periprocedural kidney failure?

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

Group 3: Renovascular Disease

1. What is the epidemiology in the context of CKD/dialysis?

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

3. What are the means for diagnosis and optimal evaluation, including value of duplex ultrasound, CT, MRI and angiography?

4. What are the management and indications for treatment? (e.g., surgical revascularization, medical, vs stenting)

5. How may management differ in special populations? (e.g., non-dialysis patients; stenoses in kidney transplants)

Group 4: Peripheral Arterial Diseases

1. What is the epidemiology in the context of CKD/dialysis? (e.g., types of PAD)

2. What are the pathophysiology and potential differences compared with non-CKD patients? Role of inflammation, oxidative stress, uremic toxins?

3. What are the means for its diagnosis and optimal evaluation in CKD?

4. What are the means for its management and treatment in CKD?

5. How may management differ in special populations? (e.g., chronic limb threatening ischemia; patients with polyvascular disease; PAD as predictor for allograft failure)