Global Action. Local Change.

KDIGO Controversies Conference on Heart Failure in Chronic Kidney Disease

May 25-28, 2017

Athens, Greece

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 might lead to guidelines in the future.

Background

We are in the midst of concurrent chronic disease epidemics of chronic kidney disease (CKD) and heart failure (HF).[1] Both conditions have increasing incidence and prevalence among older age groups, those with hypertension (HTN), diabetes mellitus (DM), and other cardiovascular and kidney disease risk factors.[2] The presence of one condition appears to accelerate the presentation and progression of the other. These so-called "cardiorenal syndromes" have been associated with increased risks of hospitalization, rehospitalization, need for intensive care unit care, kidney replacement therapy (KRT), and mortality.[3 4 5 6 7 8] Additionally, these patients become difficult to manage with conventional therapies either due to lack of response or their increased toxicity.[9 10]

Relevance of the Conference and Topic

Heart failure is the leading cause of non-traumatic hospitalizations in most developed countries and the costs of care are accelerating due to in-patient costs to a large extent and to a lesser degree, ambulatory resource expenditures including office visits, drugs, and devices. CKD, because of its close relationships with HTN and DM, is expected to rise dramatically in concert with these conditions due to the aging of world population and rise of obesity. It is imperative that we better understand the interface between kidney disease and heart failure to define optimal strategies for their screening/detection, prevention, diagnosis, and management.

Conference Overview

The conference will be led by Dr. Peter McCullough, MD, MPH, cardiologist from Baylor University Medical Center in Dallas, Texas, USA, and Dr. Andrew House, MD, MS, nephrologist from the University of Western Ontario, London, Ontario, Canada. This highly interactive conference will invite key thought leaders from cardiology, nephrology, and other related disciplines who will comprehensively review the literature and current state of understanding in this area. There will be five working groups that will each address: epidemiology, pathogenesis, diagnosis, prognosis, and management for the patient populations outlined below.

	Heart Failure with Preserved Ejection Fraction (HFpEF)	**Heart Failure with Reduced Ejection Fraction (HFrEF)**
Pre-dialysis CKD	*Working Group #1*	*Working Group #2*
Dialysis CKD	*Working Group #3*	*Working Group #4*
Kidney Transplant Patients	*Working Group #5*	

Appendix: Scope of Coverage

Group 1: Heart Failure with Preserved Ejection Fraction (HFpEF) & Pre-Dialysis CKD

In patients with advanced CKD (CKD GFR categories 3b, 4, 5) not on dialysis, and who suffer from heart failure with preserved ejection fraction (HFpEF):[11]

A) In broad terms, what is known about the epidemiology and principle pathophysiologic causes of HFpEF in patients with advanced CKD?

i. How should HFpEF and CKD be defined?
- Does the definition of HFpEF depend on who sees the patient?
- Is CKD the same as reduced GFR?

ii. What proportion of patients require KRT (kidney replacement therapy) and/or die prior to ESKD?

iii. For heart failure, is LVEF or CKD the more important risk marker?

iv. What are the mechanisms of reduced eGFR in HFpEF?
- Intrinsic kidney disease
- Hemodynamics
- Iatrogenic

v. What are the mechanisms (& differential diagnosis) of HFpEF in CKD?
- Hypertension / vascular
- Salt and water
- Myocardial dysfunction (including systolic and diastolic dysfunction) / Infiltration
- CAD
- Atrial fibrillation
- FGF23 and Klotho

vi. What are the key renal and cardiac investigations for HFpEF & CKD?
- Screening
- Diagnosis
- Tailoring therapy
- Monitoring progress

B) Therapeutic Intervention

i. What information from RCTs can inform treatment (for symptoms, morbidity, mortality) of HFpEF with CKD?
   - Do other types of data add further useful information?

ii. Are there studies of interventions for subgroups of patients with CKD that use the development of *de novo* HFpEF as an outcome?
   - Hypertension: SPRINT, ALLHAT, HYVET
   - Diabetes: RENAAL, empagliflozin, bardoxylone
   - Anemia: CHOIR, CREATE, TREAT
   - CKD-mineral and bone disorder: EVOLVE

iii. New interventions for HFpEF & CKD?
   - Sacubitril-Valsartan
   - Potassium-lowering agents
   - Iron (and anemia)
   - CKD-related metabolic disorder
   - Acidosis

iv. How does CKD modify the treatment of HFpEF?

v. How does HFpEF modify the treatment of CKD?

<u>Group 2: Heart Failure with Reduced Ejection Fraction (HFrEF) & Pre-Dialysis CKD</u>

In patients with advanced CKD (G3b, G4, G5) not on dialysis, and who suffer from heart failure with reduced ejection fraction (HFrEF):

1. a) In broad terms, what is known about the epidemiology and principal pathophysiologic causes of HFrEF in patients with advanced CKD?

   b) What is the prognosis of this combination of HFrEF and CKD?

2. What are the key diagnostic or screening tests and when/how should they be applied?

3. a) Are there studies of HFrEF treatment in this population, and if so, what is the nature of these studies and what are the studied outcomes (e.g., symptoms, CV events, mortality)?

In particular, any RCTs in this specific patient population? *A priori* subgroup analysis of broader RCTs? *Post-hoc* analyses? Observational or other quasi-experimental studies?

b) Specifically, how do these questions apply to ACEi/ARBs (alone or in combination), MRAs and beta blockers? CCBs? Nitrates/vasodilators? ARNI (valsartan/sacubitril)?

c) What role does hyperkalemia (and its management) have in the ability to treat this condition? With the new potassium binders, can guideline-directed medical therapy (GDMT) be administered? Are there data that support benefit of implementing GDMT in the context of treating the potassium elevation?

4. Are there studies of interventions (e.g., diabetes, hypertension, anemia/iron deficiency, CKD-MBD, etc.) that examine the development of *de novo* HFrEF as an outcome in this population?

5. What are the roles of left ventricular assist devices (LVAD or other devices) in this population? What level of decreased kidney function should encourage kidney transplant and heart transplant in a patient with an LVAD?

6. Is there a creatinine or GFR level at which the RAAS inhibitors should be stopped or not started? If the serum creatinine rises, how can one distinguish "kidney injury" from simply a physiologic response?

7. What is the role of diuretics in the natural history of patients with HFrEF and CKD?

8. How does treatment of diabetes in patients with HFrEF and CKD influence the natural history of both conditions?

Group 3: Heart Failure with Preserved Ejection Fraction (HFpEF) & Dialysis CKD

In patients who are on dialysis, and who suffer from heart failure with preserved ejection fraction (HFpEF):

1. a) In broad terms, what is known about the epidemiology and principle pathophysiologic causes of HFpEF in patients on dialysis (CKD G5D)?

   b) What is the prognosis of this combination of HFpEF and CKD G5D?

2. What are the key diagnostic or screening tests and when/how should they be applied?

3. a) Are there studies of HFpEF treatment in this population, and if so, what is the nature of these studies and what are the studied outcomes (e.g., symptoms, CV events, mortality)? In particular, any RCTs in this specific patient population? *A priori* subgroup analysis of broader RCTs? *Post-hoc* analyses? Observational or other quasi-experimental studies?

   b) Specifically, how do these questions apply to ACEi/ARBs (alone or in combination), MRAs and beta blockers? CCBs? Nitrates/vasodilators? ARNI (valsartan/sacubitril)? What is the role of diuretics as an adjunctive therapy to dialysis-based fluid removal?

   c) What role do different dialysis modalities have in the prevention or treatment of HFpEF (e.g., conventional intermittent hemodialysis, quotidian (frequent) hemodialysis including short daily or nocturnal dialysis, peritoneal dialysis)?

4. Are there studies of interventions (e.g., treatment of diabetes, hypertension, anemia/iron deficiency, CKD-MBD, etc.) that examine the development of *de novo* HFpEF as an outcome in this population?

Group 4: Heart Failure with Reduced Ejection Fraction (HFrEF) & Dialysis CKD

In patients who are on dialysis, and who suffer from heart failure with reduced ejection fraction (HFrEF):

1. a) In broad terms, what is known about the epidemiology and principle pathophysiologic causes of HFrEF in patients on dialysis (CKD G5D)?

   b) What is the prognosis of this combination of HFrEF and CKD G5D?

2. What are the key diagnostic or screening tests and when/how should they be applied?

3. a) Are there studies of HFrEF treatment in this population, and if so, what is the nature of these studies and what are the studied outcomes (e.g., symptoms, CV events, mortality)? In particular, any RCTs in this specific patient population? *A priori* subgroup analysis of broader RCTs? *Post-hoc* analyses? Observational or other quasi-experimental studies?

   b) Specifically, how do these questions apply to ACEi/ARBs (alone or in combination), MRAs and beta blockers? CCBs? Nitrates/vasodilators? ARNI (valsartan/sacubitril)? What is the role of diuretics as an adjunctive therapy to dialysis-based fluid removal?

c) What role do different dialysis modalities have in the prevention or treatment of HFrEF (e.g., conventional intermittent hemodialysis, quotidian (frequent) hemodialysis including short daily or nocturnal dialysis, peritoneal dialysis)?

4. Are there studies of interventions (e.g., diabetes, hypertension, anemia/iron deficiency, CKD-MBD, etc.) that use the development of *de novo* HFrEF as an outcome in this population?
5. What are the roles of LVAD (or other devices) in this population?

Group 5: Kidney Transplant Patients

Regarding kidney transplantation in patients with heart failure (HFpEF or HFrEF):

1. a) In terms of epidemiology what is known about the prevalence of pre-existing heart failure at the time of transplant and how it impacts on perioperative outcomes and longer term patient and graft survival?

   b) What is known about the development of heart failure following kidney transplantation, including its epidemiology, pathophysiology, risk factors (including obesity, immunosuppression) and prognosis?

2. What are the key diagnostic or screening tests for heart failure in patients with end stage kidney disease being evaluated for kidney transplant and in kidney transplant recipients; when / how should they be applied?

3. a) Are there studies of HF treatment in kidney transplant recipients, and if so, what is the nature of these studies and what are the studied outcomes (e.g., symptoms, CV events, mortality)? In particular, any RCTs in this specific patient population? *A priori* subgroup analysis of broader RCTs? *Post-hoc* analyses? Observational or other quasi-experimental studies?

   b) Specifically, how do these questions apply to ACEi/ARBs (alone or in combination), MRAs and beta blockers? CCBs? Nitrates/vasodilators? ARNI (valsartan/sacubitril)?

   c) What role does hyperkalemia (and its management) have in the ability to treat this

condition in transplant patients?

4. Are there studies of interventions (for CVD, graft rejection, hyperhomocysteinemia, proteinuria, etc.) that examine the development of *de novo* heart failure as an outcome in this population?

5. What are the effects of arteriovenous fistulas (AVFs) on cardiac structure and function, and pulmonary hypertension?

6. What are the effects of kidney transplant on cardiac structure and function?

7. Are heart transplant outcomes improved by simultaneous heart and kidney transplant?

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