



KDIGO Controversies Conference on Kidney Disease and Heart Failure: Recent Advances and Current Challenges

March 21 – 24, 2024

Vancouver, Canada

Scope of Work

Kidney Disease: Improving Global Outcomes (KDIGO) is an international organization whose mission is to improve the care and outcomes of people with kidney disease worldwide by promoting coordination, collaboration, and integration of initiatives to develop and implement clinical practice guidelines. Periodically, KDIGO hosts conferences to review the state of the art on a focused subject pertaining to kidney disease and set priorities for improving patient care and outcomes. In addition to highlighting areas for which additional research is needed, sometimes the conferences lead to KDIGO guideline development efforts.

CONFERENCE BACKGROUND AND RELEVANCE

Heart failure and kidney disease commonly co-exist, share similar risk factors, and present with overlapping symptoms, with one condition heralding the onset of the other¹ and increasing the risk of adverse patient outcomes.^{2,3} Indeed, heart failure is a leading form of cardiovascular disease in patients with kidney disease,⁴ and kidney disease is present in up to 70% of patients with heart failure.⁵ This population of patients with concurrent heart failure and kidney disease continues to grow, and they are at very high risk of poor clinical outcomes, such as death, loss of kidney function, or frequent hospitalizations,⁶ as well as poor quality of life.

In 2017, KDIGO held a Controversies Conference on Heart Failure in CKD,⁷ and since then there have been significant advances in understanding heart failure pathophysiology and diagnosis. However, much remains unknown regarding the pathophysiology, diagnosis, and treatment of patients with both heart failure and kidney disease, leading to critical treatment gaps.⁸ In particular, heart failure with

preserved ejection fraction (HFpEF), the most prevalent heart failure subtype, remains incompletely understood in patients with kidney disease.⁹ The pathophysiology is complex and may reflect bidirectional organ injury or shared risk factors. Despite the availability of many diagnostic tests for heart failure, identification of persons with kidney disease at risk for heart failure remains challenging. Heart failure is a clinical syndrome characterized by specific symptoms, including dyspnea and fatigue, and signs, including edema and rales. Although this constellation of symptoms and signs may be consistent with heart failure, these symptoms also occur in many individuals with kidney disease even in the absence of heart failure. Furthermore, there is a need for better classification of short- and long-term kidney function to inform prognosis in patients with heart failure, particularly in response to guideline-directed medical therapy.

New therapies, such as sodium-glucose cotransporter-2 inhibitors (SGLT2i), are now widely available to improve both heart failure and kidney outcomes.¹⁰ Yet there are unique challenges in their implementation in patients with kidney disease. There is also a need to better understand whether other novel heart failure treatment approaches can be applied to patients with kidney disease and whether more individualized approaches with kidney replacement therapy are needed for this population. Finally, this is an opportune time to plan the conduct and design of future clinical trials of patients with kidney disease and heart failure, with special attention to studying diverse populations to ensure equitable health care advancement.

CONFERENCE OVERVIEW

Drs. Nisha Bansal (University of Washington, USA) and Carolyn Lam (National Heart Centre Singapore and Duke-National University of Singapore, Singapore) 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. This highly interactive conference will invite key thought leaders and relevant stakeholders, including patients, in nephrology, cardiology, and other related disciplines who will comprehensively review the literature and current state of understanding in this area and address clinical issues as outlined in the **Appendix: Scope of Coverage**. Four breakout groups will address pathophysiology, diagnosis, treatment, and clinical trials for patients with heart failure and kidney disease. Each breakout group will comprehensively cover all types of heart failure (with



reduced, mildly reduced, and preserved ejection fraction) as well as all stages of kidney disease. The conference output will include publication of a position statement that will help guide KDIGO and others on therapeutic management and future research.

APPENDIX: SCOPE OF COVERAGE

Breakout Group 1: Pathophysiology of Heart Failure (HF) and Kidney Disease

Bidirectionality of HF and kidney disease

1. How do risk factors contribute to the parallel development of HF (HFpEF, HF with reduced EF [HFrEF], and HF with mid-range EF [HFmEF]) and kidney disease?
 - a) Are there specific differences in pathophysiology for HFpEF, HFrEF, and HFmEF?
 - b) What mechanisms, such as inflammation/endothelial dysfunction, are activated by comorbidities, and how do these contribute to the development of kidney disease and HF?
 - c) Is there a specific phenotype of kidney disease and HF driven by comorbidities, such as obesity, diabetes, or hypertension?
2. How does HF contribute to the development of kidney dysfunction?
 - a) What is the natural history of decline in kidney function in HF and does this differ by HF subtype? What is the association of this decline with severity and comorbidities in HF?
 - b) What is the role of elevated central venous pressure and decreased cardiac output, and are these of equal importance?
 - c) What are the roles of neurohormones, inflammation, endothelial dysfunction, kidney capsule, gut translocation, pulmonary hypertension, and ventricular interdependence?
3. What are the mechanisms by which kidney disease contributes to the development of HF? Do the mechanisms differ by severity/stage of kidney disease (including dialysis)?

Glomerular versus tubular function

4. Is there a distinction between the importance of glomerular versus tubular function in HF and kidney dysfunction?
 - a) What are tubular adaptations in HF?
 - b) How can we assess tubular function in HF?
 - c) Does tubular function add prognostic information to glomerular function in HF?
5. What are differences in hemodynamic decline versus injury-associated decline of kidney function, and what are the underlying mechanisms?

Breakout Group 2: Diagnostic Dilemmas in Heart Failure and Kidney Disease

- 1) For diagnostics of HF in patients with kidney disease (e.g. imaging, biomarkers), what is available now, and what is on the horizon?
 - a) What is the role of brain natriuretic peptide (BNP) measures in patients with HF and CKD for differential diagnosis? Does the accuracy of BNP change as CKD progresses? How are BNP measures affected by other comorbidities in patients with kidney disease (atrial fibrillation, obesity, etc)
 - b) Does the use of echocardiography help with diagnosis and management of fluid overload?
 - c) How can symptom assessment help in assessment of HF?
 - d) How do we attribute fluid overload to HF versus kidney disease (especially in HFpEF)?

- 2) What is the role of kidney measures (e.g., albuminuria) in diagnosis, risk stratification, management, or prognostication of HF?
 - a) Synergistic prognosis implications of concurrent HF and CKD
 - b) For the cardiologist, what is the role for urine albumin-creatinine ratio (UACR) in the diagnosis and management of cardiorenal disease, pre-heart failure, and what are barriers?
 - c) How do estimated glomerular filtration rate (eGFR) and UACR measures guide treatment selection and monitoring of renin-angiotensin system inhibitors (RASi), SGLT2i, glucagon-like peptide-1 receptor agonists (GLP1RA), and non-steroidal mineralocorticoid receptor antagonists (nsMRA)?

- 3) Do we need to clarify/revisit nomenclature for classification of acute and chronic kidney disease in patients with HF to better reflect pathophysiology? For example, HF publications used terms such as “worsening renal function” for mild or transient increases in serum creatinine during decongestion therapy or after RASi or SGLT2i, but this might lead to inappropriate diagnosis of acute kidney injury (AKI), which may result in withholding of HF or decongestion therapies.
 - a) What is an expected acute change in eGFR after drug initiation, and what can/should be done when chronic changes in eGFR occur with drug therapies?

- 4) What are the implications of new definitions of HF stages (including AHA CKM, ACC/AHA/HFS HF staging system) for patients with comorbid kidney disease? Do we need a new HF staging system for patients with kidney disease?
 - a) How should eGFR and UACR be used in HF staging, including subclinical HF?



b) How should HF be defined in patients with CKD?

Breakout Group 3: Treatment of Heart Failure and Kidney Disease – Overlapping Pillars of Guideline-Directed Medical Therapy?

- 1) Is GDMT for acute and chronic HF appropriate in kidney disease? Consider acute versus chronic HF, AKI versus CKD (including kidney failure), and gaps in implementation of GDMT for patients with kidney disease.
 - a) What are the unique considerations of GDMT in patients with kidney disease, including adverse effects, or monitoring? Are some therapies to be avoided in kidney disease?
 - b) Do the pillars need to be implemented in a stepwise manner for those with kidney disease?

- 2) How best do we address sudden dips in GFR or increases in creatinine and other adverse effects during the HF trajectory or treatment course? Describe prognosis and management of GFR variations (ie, worsening renal function with and without hemoconcentration) and considerations for stopping/adjusting therapies.
 - a) Should there be exemption to acute kidney injury definition for rise in creatinine following successful decongestion or initiation of RASi, SGLT2i, or MRA?

- 3) Other HF therapies
 - a) What is the role of intravenous iron (with and without iron deficiency anemia) in patients with both kidney disease and heart failure?
 - b) What is the role of non-medical interventions (e.g., lifestyle, nutrition)? Discuss sodium restriction and rehabilitation programs.

- 4) What is the best approach to diuretics?
 - a) Urine sodium versus urine volume and weight for guided diuretic therapy.
 - b) Is there a role for aquaretics (e.g., tolvaptan)?
 - c) Is there a role for other urine electrolytes in personalizing diuretic strategies (ie, chloride)?
 - d) What is the next step after loop diuretics (thiazides versus acetazolamide; SGLT2i) and could sequential nephron blockade with low doses of multiple classes of diuretics be more effective than step-by-step addition of therapies (polypill vs. individual therapies)? Does choice of thiazides or loop diuretics matter?
 - e) What is the role of hypertonic saline and albumin in diuresis?

- 5) Ultrafiltration and hemodynamic monitoring to guide therapies

- a) What is the role of pulmonary artery catheter-based monitoring of pulmonary capillary wedge pressure (PCWP) in specific patients?
 - b) What is the role of echocardiography monitoring for velocity time integral, venous excess, lung ultrasound score, bioimpedance, microcirculation, capillary refill, lactate-guided therapy?
 - c) Is intrabdominal pressure helpful in HF management?
 - d) What is the role of implantable pulmonary artery pressure sensors for monitoring?
 - e) How do you interpret hemodynamic measures in right heart failure or tricuspid valve disease?
- 6) What are specific considerations for durable and non-durable mechanical circulatory support in patients with heart failure and kidney disease?
- a) Describe major indications for continuous renal replacement therapy (CRRT) in non-durable mechanical circulatory support (MCS) and extracorporeal membrane oxygenation (ECMO), advantages and disadvantages of shared circuit versus independent CRRT access, anticoagulation, timing, and indications to initiate continuous.
 - b) Assessment of reversibility of AKI in patients being considered for left ventricular assist devices (LVADs)? Should LVADs be considered in ESRD patients?
 - c) Peritoneal dialysis for chronic management of HF in diuretic resistant patients

Breakout Group 4: Clinical Trials in Heart Failure and Kidney Disease – A Move Toward Cardiorenal Trials

Concepts and Frameworks

- 1) What trials would be helpful for assessing cardiac and kidney questions (population, endpoints, primary/secondary prevention, etc)?
 - a) What are some potential design challenges and solutions?
 - b) What statistical methods can aid interpretation of the separate effects on cardiac and kidney disease endpoints?
 - c) How can eTrials and other technology be used to improve the efficiency and success of trials in this population?

- 2) What are the strategies to match risk or clusters of risk to targeted benefit (e.g. how to identify individuals with higher risk for HF to treat with drugs that prevent HF in the era of multiple agents demonstrating benefit in prevention of HF)?

- 3) Should there be a core set of data that should be used for inclusion and outcomes in trials in both the acute (AKI and acute HF) and chronic (HF and CKD/kidney failure) settings (eg, EF [HFpEF/HFrEF], eGFR, albuminuria, etc)?
 - a) What is the role of cardiac and/or kidney markers of risk (EF, NT-proBNP, eGFR, albuminuria) in trials (stratification, descriptors, inclusion)?
 - b) How would the inclusion criteria differ in these settings?
 - c) How would the collection and interpretation of continuous variables (eg, eGFR, UACR, EF) differ in decompensation settings such as acute kidney injury or acute heart failure? What are the implications for assessment of baseline function for characterization and assessment of endpoints?
 - d) How would the evaluation of longitudinal change of heart and kidney function differ in decompensation settings (collection and interpretation of acute and chronic eGFR change)?

Endpoints and role of PROMs and role of hierarchical endpoints (including Win ratio) in HF & kidney disease trials

- 4) Which cardiac and kidney endpoints should be considered?
 - a) What is the role of composite, co-primary, and ordered endpoints?
 - b) Are there appropriate surrogate or intermediate endpoints ready for use?
 - c) What is the role of different endpoint analytic methods (composite endpoints, Win ratios, Bayesian frameworks, recurrent event analyses, etc)?



- d) Which endpoints should be considered for pragmatic versus explanatory trials, and should they be different?
- 5) What patient-reported outcome measures (PROMs) should be considered for cardiorenal trials?
- a) Are there important components of the patient experience that are not adequately captured by existing PROMs?
 - b) What further testing/validation (if any) is required of existing PROMs for utilization as trial endpoints?
 - c) Should PROMs be selected to reflect the patient experience of beneficial outcomes only, or should the experience of safety or adverse events be similarly evaluated?
 - d) Are there adequate PROMs to capture safety?
- 6) How to account for social determinants of health and execute inclusive trials (within countries, globally)?

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