

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

#### **Breakout Questions**

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

For all topics, please compile the evidence according to HF type (HFrEF [HF with reduced ejection fraction], HFmrEF [HF with mildly-reduced EF], or HFpEF [HF with preserved EF]) and consider whether a distinction is clinically important (especially between HFrEF and HFpEF).

#### Bidirectionality of HF and kidney disease

- 1. How do risk factors contribute to the parallel development of HF (HFpEF, HFrEF, and HFmrEF) and kidney disease?
  - a) What mechanisms, such as inflammation/endothelial dysfunction, are activated by comorbidities, and how do these contribute to the development of kidney disease and HF?
  - b) 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) Are there specific differences in pathophysiology for HFpEF and HFrEF?
  - c) What is the role of elevated central venous and intra-abdominal pressure and decreased cardiac output, and are these of equal importance?
  - d) What are the roles of neurohormones, inflammation, endothelial dysfunction, kidney capsule, gut translocation, pulmonary hypertension, fibrosis, liver function, and ventricular interdependence?

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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 (cystatin C and creatinine-based estimates of glomerular filtration rate [GFR]) versus tubular function in HF and kidney dysfunction?
  - a) What are tubular adaptations in HF? And what is the role of tubular injury biomarkers?
  - b) How can we assess tubular function in HF?
  - c) Does tubular function add prognostic information to glomerular function in HF?
- 5. What are the differences in mechanisms and prognostic implications of hemodynamic decline versus injury-associated decline of kidney function?



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

For all topics, please compile the evidence according to HF type (HFrEF, HFmrEF, or HFpEF) and consider whether a distinction is clinically important (especially between HFrEF and HFpEF).

- 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–HF, and what are the barriers?
  - c) How do estimated GFR (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?

For all topics, please compile the evidence according to HF type (HFrEF, HFmrEF, or HFpEF) and consider whether a distinction is clinically important (especially between HFrEF and HFpEF).

- 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 (for example, hyperkalemia), 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 an exemption to the definition of AKI 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 and oral iron (with and without iron deficiency anemia) in patients with both kidney disease and HF?
  - 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 serum and urine electrolytes in personalizing diuretic strategies (i.e., sodium and chloride)?

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- 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 HF or tricuspid valve disease?
  - f) When and how should we consider ultrafiltration in the treatment of HF?
- 6) What are specific considerations for durable and non-durable mechanical circulatory support in patients with HF 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 kidney failure 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 (e.g., ejection fraction [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, ejection fraction) differ in decompensation settings such as AKI or acute HF? 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)?