Changing the Trajectory of Heart Failure and Kidney Disease
A Call for Action

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Introduction

In 1836, Sir Richard Bright, widely regarded as the founder of the field of nephrology, described the structural cardiac changes on autopsy seen in patients with “shrunk kidneys” who were secretors of albuminous urine (1). This report is perhaps the earliest description of the cardiorenal connection in contemporary literature of what is known today as CKD-associated cardiomyopathy. This connection is driven by shared risk factors, such as diabetes, hypertension, and obesity, as well as maladaptive cardiorenal cross-talk pathways resulting in bidirectional organ failure.

The Cardiorenal Link: A Historic Perspective

Notwithstanding major advances in the fields of cardiology and nephrology, clinical outcomes remain poor for patients with heart failure and CKD. With diabetes in particular, despite achieving guideline-directed treatment targets, there is a substantial unmet need for reducing the risks of heart failure and CKD. In fact, some earlier glucose-lowering therapies for diabetes, such as thiazolidinediones and sulfonylureas, are associated with higher cardiovascular disease risks (2). This prompted the Food and Drug Administration mandate in 2008 for the demonstration of cardiovascular safety before and after market approval for newer glucose-lowering agents (3). In this backdrop, sodium-glucose cotransporter-2 inhibitor (SGLT2i) serendipitously became a landmark cardiorenal-protective therapy when tested for cardiovascular safety as a monitor of patients with CKD from cardiovascular trials – related disability and death through clinical, translational, and basic science research; communication; advocacy; and education relevant to the role of the kidneys in all phenotypes of cardiovascular disease. We hereby summarize some of the key conclusions generated from our cross-specialty collaboration, which offer perspective on current challenges and potential solutions for optimizing outcomes in patients with heart failure and CKD.

Structural Inequities

In 2004, Chertow et al. (4) described the phenomenon of “renalism,” referring to the systematic exclusion of patients with CKD from cardiovascular trials of medical therapies and procedures due to a misconception of futility and/or harm. For example, in a systematic review of 706 RCTs for therapies in heart failure with reduced ejection fraction between 2010 and 2020, over a third of the trials had no information reported on kidney function (5). The number of trials that included patients with CKD was inversely related to eGFR, and patients on maintenance dialysis and kidney transplant recipients were included in <60 trials. Ironically, renalism was propagated in clinical practice despite the recognition of CKD as an independent risk factor for all major phenotypes of cardiovascular diseases (6). It is gratifying to note that recent major trials with SGLT2i, such as EMPEROR, have included patients with eGFR as low as 20 ml/min per 1.73 m² (7). Patients with moderate to advanced CKD are also well represented in recent kidney outcome trials such as CRESCENDO and DAPA-CKD.
Therapeutic Inertia: Old Habits Die Hard

Much concern has been expressed about therapeutic inertia, with slower than expected uptake of newer therapies for heart failure and CKD, especially SGLT2i, reminiscent of several previous high-impact therapies, including statins. We must reverse this phenomenon given the mismatch between available effective therapies and the population at risk. Inertia results from barriers, including inadequate insurance coverage and high out-of-pocket costs; fragmented workflows between different specialties; and prioritizing “volume” over “value”-based care in the United States. Additionally, the inappropriate use of terms, such as “AKI,” to describe the functional decrease in eGFR due to therapeutic hemodynamic changes creates fear of harm, especially with the concomitant use of therapies such as renin-angiotensin system inhibitors, SGLT2i, and MRAs. To this end, improving affordability and access to SGLT2i with joint lobbying across specialty organizations and guidance from specialty societies on specific terminology to differentiate true kidney injury from benign fluctuations in kidney biomarkers, such as serum creatinine or cystatin C, would go far in effectively implementing these agents. Finally, educating patients and their caregivers about the benefits of SGLT2i that are incurred even within weeks of initiation is key to promoting adherence while actively engaging in strategies to reduce polypharmacy and deprescribing less effective agents.

Sodium-Glucose Cotransporter-2 Inhibitor in the Basic Translational Space

No single mechanism can fully explain the early separation of survival curves seen reproducibly across SGLT2i trials from low- to very high-risk populations, those with and without diabetes, across ejection fraction, and eGFR strata. Several unanswered questions remain from a mechanistic perspective. (1) Do changes in energy kinetics in the myocardium and proximal tubules contribute to the consistent benefits for heart failure and CKD? (2) Will SGLT2is

Table 1. Key questions for future research in the cardiorenal space

<table>
<thead>
<tr>
<th>Key Questions for Future Research</th>
<th>Research Domain(s)</th>
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<tbody>
<tr>
<td>Can cardiac and kidney biomarkers guide a precision medicine-based approach to use guideline-directed medical therapies in patients with heart failure and kidney disease?</td>
<td>Basic science/risk assessment/disease progression</td>
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<tr>
<td>Can artificial intelligence complement precision medicine-based approaches to identifying patients for appropriate use of guideline-directed medical therapies in heart failure and kidney disease?</td>
<td>Population health/risk assessment/health care delivery</td>
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<td>How can delivery of optimal guideline-directed medical therapies be achieved in the context of structural disparities in health care?</td>
<td>Social determinants of health care</td>
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<td>How can an increasingly complex medication regimen with the advent of newer heart-kidney therapies be implemented in a patient-centric fashion with emphasis on quality of life, costs, pill burden, and side effects?</td>
<td>Patient-centered care/lifestyle</td>
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<td>How can the cardiology and nephrology communities leverage the support of key stakeholders to implement policy changes to ensure equitable access to lifesaving therapies in patients with heart failure and kidney disease?</td>
<td>Health care policy/structural inequities</td>
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<td>Is there an opportunity to provide a unifying care platform spanning across primordial prevention, primary prevention, comprehensive lifestyle modification, and state-of-the-art therapies for patients with heart failure and kidney disease?</td>
<td>Lifestyle/prevention/social determinants of care</td>
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<td>Can a cardiorenal care model for clinician practice and trainee education help with the seamless integration of evidence-based care pathways in patients with/at risk of heart failure and kidney disease?</td>
<td>Quality of care/health care economics/medical education</td>
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have the potential to be deployed for primary prevention of heart failure and CKD if maladaptive neurohormonal and hemodynamic pathways can be attenuated before organ damage has occurred? (3) Although the clinical benefits with SGLT2i may partly be explained by metabolic and BP control, weight loss, uric acid excretion, and improvement in anemia, are there other mechanisms that are operative, akin to the pleiotropic effects with statins? (4) Do proximal tubular effects of SGLT2i complement pathways in the distal nephron to attenuate the hyperkalemia that often occurs with MRAs? There are many more translational questions that exist. However, the incomplete understanding of the precise mechanistic pathways for SGLT2i must not preclude rapid uptake of these agents in clinical practice. Additional deeper dives into these mechanisms will advance understanding of how far these agents can be extended therapeutically, including into primary prevention. The benefits noted with SGLT2i for heart failure and CKD draw parallels to the benefits that statins have shown for atherosclerotic cardiovascular disease and will go down in history as one of the most effective cardiorenal therapies of the twenty-first century.

Future Directions

The cardiology and nephrology communities are faced with a veritable embarrassment of riches with the advent of SGLT2i, nonsteroidal MRAs, glucagon-like peptide-1 receptor agonists, and more promising therapies in development. We have a moral and ethical obligation to ensure rapid, safe, and equitable implementation of these life- and organ-protecting therapies, as appropriately indicated. Although rapid uptake of these newer therapies is key, it is equally important to ensure that existing cardioprotective therapies in patients with CKD are effectively implemented. Disruptive models of care with emphasis on implementing high-quality and evidence-based therapies must be deployed to overcome barriers posed by current health care systems. Mirroring the RCTs where both major cardiovascular and kidney end points are prespecified in heart and kidney disease trials, we must share accountability for reducing cardiovascular and kidney disease burdens between cardiology and nephrology in clinical practice. A multidisciplinary approach in key areas for future research is critical toward advancing knowledge across several domains (Table 1). Finally, high-level engagement of patients, caregivers, industry stakeholders, and legislators is critical for ensuring that these remarkable innovations are delivered to patients effectively and equitably. By accomplishing these objectives, we will have come full circle from the early nineteenth century, using old wisdom on heart-kidney crosstalk to save lives and organs and improve quality of life.

Disclosures

V. Bhalla reports consultancy agreements with Bayer Pharmaceuticals, CareDx, Guidepoint LLC, LEK Consulting, Maxim Integrated, and Reata; reports ownership stock in Pyramis Health and Viscira LLC; reports honoraria from Bayer Pharmaceuticals; reports other interests or relationships as the immediate past-chair of the Kidney and Cardiovascular Disease Council of the American Heart Association (AHA) and as a member of the Hypertension Council of AHA and the American Medical Association Validated Device Listing—Blood Pressure Measurement Devices; and is a co-site investigator for the Controlling and Lowering Blood Pressure with MobiusHD 2 (CALM-2) trial sponsored by Vascular Dynamics, Inc. V. Bhalla reports serving in an advisory or leadership role for American Journal of Physiology Renal Physiology (editorial board: July 2007 to present), European Journal of Clinical Investigation (scientific advisory board: February 2013 to present), Physiologic Reports (associate editor: April 2018 to present), the Pyramis Scientific Advisory Board, and the Relypsa Scientific Advisory Board. V. Bhalla’s spouse reports research funding from CareDx, honoraria from CareDx, serving on the CareDx Scientific Advisory Board, and serving on speakers bureau for CareDx. E. Braunwald reports consultancy agreements with Amgen, Boehringer-Ingelheim/Lilly, Bristol Myers Squibb (MyoKardia), Cardu- rion, Novo Nordisk, and Verve; research funding from AstraZeneca, Daiichi Sankyo, Merck, and Novartis (all through the author’s institution, Brigham and Women’s Hospital); and serving in an advisory or leadership role for Broadview Ventures (not for profit) and the Heart Failure Network (National Heart, Lung, and Blood Institute [NHLBI]: no compensation). G.M. Chertow reports consultancy agreements with Akebia, Amgen, Ardelyx, Astra Zeneca, Baxter, Cricket, DiaMedica, Gilead, Miromatrix, Reata, Sanifit, Unicymc, and Vertex; reports ownership interest in Arde- lyx, CloudCath, Durect, DnNow, Eliax Therapeutics, Outset, Physiowave, and PuraCath; reports research funding from Amgen, the National Institute of Allergy and Infectious Diseases, and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK); has received fees from AstraZeneca for the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAFPA-CKD) trial steering committee; has received fees for advisory boards for Cricket, DiaMedica, and Reata; has received fees from Akebia, Sanifit, and Vertex for trial steering committees; reports serving in an advisory or leadership role as coeditor of Bremner & Rector’s The Kidney (Elsevier) and on the board of directors for Satellite Healthcare; and has received fees for DSMB service from Angion, Bayer, NIDDK, and ReCor. R.A. Harrington reports consultancy agreements with Atropos, Bitterroot, BMS, BridgeBio, Element Science, and WebMD; research funding from the Baim Institute (Data and Safety Monitoring Board [DSMB]), Commonwealth Serum Laboratories (Randomized Controlled Trial [RCT] executive committee), Janssen (RCT chair), NHLBI (RCT executive committee; DSMB chair), and Patient-Centered Out- comes Research Institute (RCT chair); and serving on the board of directors for AHA. J. Rangaswami reports consultancy agreements with AstraZeneca, Boehringer-Lily, and Edwards Lifesciences; serves on the medical advisory board of Procyrion Inc. (Aor- tix); and is chair-elect of KCVD of the AHA. A. Staruschenko reports research funding from the Department of Veteran Affairs and the National Institutes of Health (NIH); serving as chair of the Kidney in Cardiovascular Disease of the AHA Council; serving as deputy editor of American Journal of Physiology Renal Physiology and associate editor for Frontiers in Physiology Renal and Epithelial Physiol- ogy; and serving on the editorial boards of American Journal of Physiology Cell Physiology, BMC Nephrology, Kidney360, and Scientific Reports. K. Tuttle reports consultancy agreements with AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly and Company, Gilead, Goldfinch Bio, Janssen, Novo Nordisk, and Travere; reports research funding from Bayer, Goldfinch Bio, and Travere; is sup- ported by a Centers for Disease Control and Prevention contract and six NIH grants; and reports honoraria from Bayer, Boehringer Ingelheim, Gilead, and Novo Nordisk.
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V. Bhalla, J. Rangaswami, and A. Staruschenko conceptualized the study; K. Tuttle was responsible for visualization; J. Rangaswami wrote the original draft; and V. Bhalla, E. Braunwald, G.M. Chertow, R.A. Harrington, A. Staruschenko, and K. Tuttle reviewed and edited the manuscript.

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