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Letter

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Advances in Cardiorenal Medicine: The Year 2023 in Review

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Introduction

In 2023, there were several new developments in the field of cardionephrology with potential impact on the care of patients with dual burden of heart and kidney disease. With new drugs that have major cardiorenal and metabolic benefits, attempts have been made to revisit the concept of cardiorenal syndrome and improve patients' prognostication. Novel approaches to established pathophysiological principles in cardiorenal medicine have also helped expand the scope of older drug therapies, especially for patients with suboptimal response to conventional decongestive regimens. Sodium-glucose cotransporter 2 inhibitors (SGLT-2i) have remained the focus of much investigation in a variety of patients with heart and kidney disorders and continued to show benefits in more recent studies of diverse patient populations. In this article, we summarize some of the key work that impacted the field of cardionephrology in a meaningful way in 2023, thereby setting the stage for more fertile growth and expansion for the future.

Conceptual Considerations in Cardiorenal Nexus

In late 2023, the American Heart Association (AHA) published a presidential advisory to describe a new multisystem entity called cardiovascular-kidney-metabolic (CKM) syndrome [1]. The authors defined CKM syndrome as a systemic disorder characterized by pathophysiological interactions among metabolic risk factors, chronic kidney disease (CKD), and the cardiovascular system leading to multiorgan dysfunction and a high rate of adverse cardiovascular outcomes. The objective has been to combine chronic cardiorenal syndrome and cardiometabolic disease to highlight the interplay of metabolic risk factors (e.g., obesity and diabetes) with CKD and cardiovascular system. The authors also proposed a staging system starting with no CKM risk factor (stage 0), all the way to clinical cardiovascular disease (stage 4). Following the introduction of this new entity, a risk calculator (Predicting Risk of CVD Events [PREVENT]) was also published that includes several CKM components [2]. These sex-specific models are race-free, integrate heart failure (HF) risk as an outcome that can be calculated separately, and include social determinants of health to enhance their prediction value. Obviously, the widespread use of newer drugs with cardiorenal and metabolic benefits (e.g., SGLT-2i, glucagon-like peptide-1 [GLP-1] receptor agonists, and nonsteroidal mineralocorticoid receptor antagonists) has

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provided the fuel for conceptualization of CKM syndrome by the AHA. Similarly, in late 2023, another group of experts proposed transition from the conventional cardiorenal syndrome to chronic cardiovascular and kidney disorder [3]. This proposal was an attempt to modify the chronology-based definitions of the conventional cardiorenal syndrome (types 2, 4, and 5) and provide a sequence-free approach to patients with both heart and kidney involvement. The authors argued that depending on various combinations of risk factors and precipitating conditions, patients with chronic cardiovascular and kidney disorder may present initially with either cardiovascular disease or hallmarks of CKD.

Cardionephrology as an emerging discipline, subspecialty, or field can be enriched with these discussions and initiatives [4]. While data support concurrent existence of a metabolic component to the cardiorenal interactions in some patients, and there may be a lack of clarity on the chronology of the organ involvement in a subset of patients with cardiorenal syndrome, it remains unknown whether new definitions and proposed nomenclature that are primarily based on already established concepts will have a practical impact on the care of these patients, or the added complexity will hamper their widespread acceptance. Moreover, these new entities focus on chronic conditions and do not address the topics related to acute cardiorenal medicine that have seen substantial advances over the last few years.

Maintaining the Spotlight on Congestion

We started the year 2023 with a long-awaited landmark study, the Torsemide Comparison With Furosemide for Management of Heart Failure (TRANSFORM-HF) [5]. Compared with furosemide, torsemide has higher bioavailability and a longer half-life than furosemide and may portend additional beneficial effects such as reduced aldosterone production. This presumed advantage was supported by a few small studies but was never tested in a robust study. So, the key question has been whether a strategy of torsemide versus furosemide would lead to a lower risk of death in patients with HF. Surprisingly, in this large randomized controlled trial (RCT) that included more than 2,800 patients who were admitted to the hospital for HF, torsemide did not show any advantage over furosemide regarding all-cause mortality during the 1-year follow-up period. Moreover, the sub-studies of TRANSFORM-HF later showed that this lack of advantage was similar for both de novo HF and worsening chronic HF [6], and that there was no difference in improvement of symptoms or quality of life between torsemide and furosemide [7].

The quest for optimal decongestive strategy through sequential nephron blockade in acute HF continued last year with publication of Combination of Loop With Thiazide-type Diuretics in Patients With Decompensated Heart Failure (CLOROTIC) trial [8]. The investigators found that, compared to placebo, addition of oral hydrochlorothiazide to intravenous loop diuretics led to improved decongestion as measured by weight change and urine output. Historically, thiazides have been considered less potent with regard to provoking diuresis and natriuresis in patients with impaired kidney function [9, 10]. However, a post hoc analysis of CLOROTIC revealed that the addition of eGFR-adjusted doses of oral hydrochlorothiazide could improve diuretic response across the eGFR spectrum, albeit with attenuated effect in patients with an eGFR <45 mL/min [11].

While enhanced distal tubular sodium absorption has conventionally been the main focus of investigation in acute HF and cardiorenal syndrome, agents with mechanisms of action that are primarily related to proximal tubules (SGLT-2i and carbonic anhydrase inhibitors) have gained momentum in the last 2 years. In 2022, the landmark Acetazolamide in Decompensated Heart Failure with Volume Overload (ADVOR) trial showed that addition of acetazolamide to intravenous loop diuretics can lead to more efficient decongestion in patients with acute HF [12]. A series of prespecified post hoc analyses of ADVOR were published throughout 2023 further exploring the details of the original findings. Increased serum bicarbonate levels, once considered simple contraction alkalosis, may indeed be a marker of neurohormonal activation in HF [13–15]. Since acetazolamide decreases serum bicarbonate level (in parallel with an increase in serum chloride concentration), a substudy of ADVOR evaluated the impact of serum bicarbonate on the efficacy of acetazolamide [15]. It was found that the drug has the ability to improve congestion over the entire range of bicarbonate levels, with the treatment effect enhanced in those patients with higher serum bicarbonate concentrations. Similarly, in another analysis, the investigators reported that the salutary effects of acetazolamide in acute HF are not impacted by the left ventricular ejection fraction [16]. However, there was a signal that the moderate rise in serum creatinine that is seen with acetazolamide use during decongestion may be more pronounced in the setting of HF with reduced ejection fraction. Two additional sub-studies found that the benefits of acetazolamide (natriuresis and diuresis) are consistent across the entire range of renal function,

and that this medication does not lead to clinically important hypokalemia or hyponatremia [17, 18].

While the accumulating data imply that acetazolamide can be an excellent candidate when combination of diuretic therapy is considered in those patients with acute HF and suboptimal response to loop diuretics, its natriuretic properties are somewhat hampered by hyperactivity of the distal segments of the nephron. Since congestion has been recognized as the primary driver of adverse outcomes in this patient population, the quest for optimization of our decongestive strategies using available diuretic agents has continued [19–21].

Gliflozins, the Miracle Drugs That Continue to Conquer

The impressive success of SGLT-2i continued in 2023 with publication of a multitude of studies. In January, the landmark Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY) trial was published [22]. In this multinational RCT that included more than 6,600 patients with CKD (eGFR of 20–90 mL/min), empagliflozin led to a 28% lower risk of progression of kidney disease or cardiovascular mortality. The trial was stopped early after 2 years due to the efficacy of the intervention arm. The benefits of empagliflozin were seen among both patients with or without diabetes, although to a lesser degree in those without diabetes. EMPA-KIDNEY further expanded the evidence base for the use of gliflozins in the treatment of CKD. Of note, however, the subgroup analysis suggested that in patients who were not receiving renin-angiotensin-aldosterone system (RAAS) blockade, the beneficial effects of empagliflozin were not as evident.

Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER) trial previously showed that dapagliflozin could reduce the risk of worsening HF or cardiovascular death among more than 6,200 patients with HF and a mildly reduced or preserved ejection fraction (median ejection fraction of 54%) [23]. The observed rise in serum creatinine was initially considered a potential safety concern due to the natriuretic and osmotic diuretic effects of SGLT-2i. A secondary analysis of DELIVER examined the implications of the initial decline in eGFR and concluded that it was a frequent observation with dapagliflozin (40% of patients experiencing an initial drop of greater than 10%), but was not associated with subsequent risk of cardiovascular or kidney events [24]. Of note, lack of an adverse impact on the outcomes by the initial dip in eGFR had previously been reported in HF with reduced ejection fraction [25].

In addition to conventional cardiorenal endpoints, the impact of gliflozins on volume status was also investigated in 2023. In a sub-study of EMPA-KIDNEY, using bioimpedance measurements, the investigators evaluated the impact of empagliflozin on fluid overload (an estimate of excess extracellular water) in 660 patients with CKD. They found that empagliflozin was associated with a sustained reduction in fluid overload [26]. Moreover, a multicenter, open-label, RCT compared the diuretic effect of dapagliflozin with metolazone in the setting of acute HF and diuretic resistance [27]. The investigators reported that while there was no statistically significant difference in weight loss between the two arms, the patients assigned to dapagliflozin received a larger cumulative dose of furosemide and experienced less decline in serum sodium levels. Emerging data suggest that gliflozins may portend other beneficial effects on fluid and electrolytes beyond what has so far been explored in CKD and HF. In that regard, a small pilot RCT suggested that empagliflozin may be a promising new treatment option for hyponatremia associated with chronic syndrome of inappropriate antidiuresis and possibly lead to improved neurocognitive function in these patients [28]. The success with SGLT-2i continues, and while these agents are now an established component of the therapy of CKD, HF, and diabetes, newer studies are likely to expand their application to other areas such as acute HF and hyponatremia.

Hypertension, Vascular Calcification, and More

In addition to the abovementioned themes that were addressed in 2023, there were several important articles that tried to answer a number of clinical questions related to cardionephrology. Here is a selected summary.

Renal Denervation and Hypertension

Inconsistent results have been reported from studies on endovascular catheter-based renal denervation for treatment of hypertension. A Study of the ReCor Medical Paradise System in Clinical Hypertension (RADIANCE II) is the latest component of the RADIANCE trials that are multicenter randomized sham-controlled studies investigating the role of endovascular ultrasound renal denervation to treat hypertension. In 224 patients with hypertension that were included in RADIANCE II, the procedure could reduce systolic blood pressure by 7.9 mm Hg at 2 months in the absence of antihypertensive

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medications that had previously been identified as a potentially confounding factor. Later, a patient-level pooled analysis of all RADIANCE trials, including 506 patients, revealed the maintenance of the salutary effect of this procedure at 6 months, with fewer added antihypertensive medications [29].

Magnesium Supplementation and Vascular Calcification

In patients with CKD, coronary artery calcification increases with progression of the disease and is associated with an increase in the risk of cardiovascular events. Magnesium has been shown to prevent vascular calcification in animal models and may lower cardiovascular events in patients with CKD. Bressendorf and colleagues used magnesium hydroxide supplementation for 12 months in an RCT (Effects of Magnesium Supplementation on Vascular Calcification in Chronic Kidney Disease [MAGiCAL-CKD]) on 148 patients with CKD to explore its impact on vascular calcification [30]. In this study, magnesium hydroxide supplementation (15 mmol twice daily) did not slow progression of coronary artery calcification score despite a significant increase in serum levels.

Sodium Bicarbonate and Blood Pressure

Since acidosis is associated with the risk of CKD progression and elevated systolic blood pressure, bicarbonate supplementation may be helpful in this setting, though it also runs the risk of increasing blood pressure due to its sodium content. In a systematic review and meta-analysis, the investigators included 14 RCTs with more than 2,000 participants to explore this point [31]. They found that sodium bicarbonate supplementation does not increase systolic blood pressure or the requirement for antihypertensive medication or diuretics in patients with CKD.

Spironolactone in Hemodialysis

Spironolactone has been shown to reduce the risk of cardiovascular events and sudden death in patients with HF. Previously, Safety and Cardiovascular Efficacy of Spironolactone in Dialysis-Dependent ESRD (SPin-D) trial had shown the safety of spironolactone in maintenance hemodialysis patients. In a post hoc analysis, the investigators used extended electrocardiographic monitoring with a wearable device to investigate its impact on arrhythmia events over a 36-week period in 57 patients receiving maintenance hemodialysis [32]. They reported a higher frequency of bradycardia and conduction blocks among those patients treated with spironolactone treatment compared with placebo. The risk was most pronounced at the highest evaluated dose of 50 mg/day.

Aldosterone Synthase Inhibition and Kidney

The deleterious effects of aldosterone in the setting of CKD and HF are well known. Conventional blockers of RAAS do not fully block the effects of aldosterone. BI 690517 is a highly selective aldosterone synthase inhibitor that directly lowers aldosterone production, potentially enhancing the effectiveness of current therapies. In a phase-2 multinational RCT, the safety and efficacy of BI 690517 were explored in 586 patients with CKD and urine albumin-to-creatinine ratio of 200–5,000 mg/g who were receiving RAAS blockers [33]. BI 690517 was found to reduce albuminuria, with or without empagliflozin, suggesting an additive efficacy for patients with CKD. This new family of medicines is certainly a promising new therapy that may prove helpful as an add-on agent along with conventional therapies such as RAAS inhibitors and SGLT-2i in patients with kidney or heart disease. We need to wait for phase-3 outcome trials to explore this possibility.

GLP-1 Receptor Agonists in Non-Diabetics

GLP-1 receptor agonists are among the key therapeutic options for type 2 diabetes that have been shown to reduce the risk of cardiovascular events in those patients with diabetes and obesity. Whether these beneficial effects would extend to non-diabetics was examined in a multinational RCT that included more than 17,000 patients [34]. In this study, semaglutide was used for patients with preexisting cardiovascular disease and a body mass index of 27 or greater who did not have diabetes. Of note, patients with class IV HF or end-stage kidney disease were excluded from the study. Over a period of 2 years, semaglutide could reduce cardiovascular events by 20% compared to placebo, albeit with a higher rate of adverse events that led to discontinuation of the medication (e.g., gastrointestinal disorder). Weight loss was also more pronounced in the semaglutide arm. It seems that similar to SGLT-2i, the clinical benefits of GLP-1 receptor agonists continue to expand beyond management of diabetes.

Conclusion

In 2023, the field of cardionephrology made significant strides that are very promising. There were attempts to reconstruct and redefine the heart-kidney

interactions and expand the field by inclusion of metabolic parameters. To that end, newer terminology and risk assessment tools were proposed and novel decongestive approaches using older medicines were tested with success. Several high-impact trials were published with the potential to advance evidence-based multidisciplinary care of this vulnerable group of patients. Given the ever-accumulating data and the widening scope of the field of cardiorenal medicine, it seems crucial that we provide educational resources for nephrologists and cardiologists to spearhead excellence in clinical care.

Conflict of Interest Statement

None of the authors has any relevant conflict of interest.

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Author Contributions

Amir Kazory has crafted the initial draft. Claudio Ronco has provided critical revisions and additions.

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