Editorial

Key Updates in Cardio-Nephrology from 2018: Springboard to a Bright Future

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Introduction

The year of 2018 marked an exciting phase in the field of cardio-nephrology, with several new developments impacting the care of patients with the dual burden of heart and kidney disease. Novel approaches to older pathophysiological principles in cardiorenal syndrome (CRS), new drug therapies with major cardio-reno-metabolic benefits, and increasing momentum for the call for the need for a “cardio-nephrology” subspecialty, as well as deserved prominence for cardiorenal research in major cardiology and nephrology publications and conferences, represent some of these exciting changes. In this editorial, we summarize some of the key work that impacted the field of cardio-nephrology in a meaningful way in 2018, thereby setting the stage for more fertile growth and expansion for the future.

Decongestion in Acute Heart Failure: “Drier” Is Better in Type 1 CRS

Appropriate decongestion as quantified by weight loss, resolution of clinical signs of congestion, and symptomatic relief is rarely achieved in hospitalizations for acute heart failure (AHF), including in tightly controlled settings such as randomized controlled trials. Among the more than 50,000 patients enrolled in the ADHERE (Acute Decompensated Heart Failure National

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Registry) study, only 33% lost ≥ 2.27 kg (5 lb), and 16% of the subjects gained weight during hospitalization [1]. In the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARESS-HF) trial, which compared high-dose loop diuretics to ultrafiltration as modalities for decongestion in subjects with type 1 CRS, less than 10% of the subjects achieved complete clinical decongestion through either strategy [2]. Similarly, in a post hoc analysis of the Diuretic Optimization Strategy Evaluation in Acute Decompensated Heart Failure (DOSE-AHF) and CARESS-HF trials, persistent orthopnea and/or peripheral edema (as quantified by a composite orthodema congestion score) were present in 48% of the subjects at discharge. Imposing temporal limits on AHF hospitalizations [3], gaps in the effective transition of the patient with AHF into a stable and compensated state as an outpatient, and the reluctance to push decongestive therapies and appropriate goal-directed medical therapies (GDMT) during the AHF hospitalization due to fluctuations in renal function have all been contributory to the phenomenon of ineffective decongestion in AHF. In this context, Ahmad et al. [4] in early 2018 demonstrated that worsening renal function (WRF), as detected by fluctuations in serum creatinine and serum cystatin in patients undergoing aggressive diuresis for AHF, was not associated with renal tubular injury as quantified with urine tubular injury biomarkers. In this analysis, subjects who achieved maximal decongestion (even with elevations in serum creatinine/cystatin C) experienced the highest cumulative survival at 1 year, thereby showing that clinical decongestion triumphed maintaining serum creatinine values at “baseline ranges” in patients with HF. Small fluctuations in serum creatinine levels in the setting of aggressive diuresis and/or institution of goal-directed therapies for HF likely represented benign hemodynamic changes rather than actual tubular injury or necrosis. Along the same lines, Fudim et al. [5] showed that WRF did not carry the same negative prognostic value when effective decongestion at discharge was achieved, as compared to persistent congestion with WRF in a post hoc analysis of the Evaluation Study of congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial across several methods of assessing congestion. Similar findings were also confirmed in a post hoc analysis of the Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial, wherein the HR for WRF on 30-day death or heart failure hospitalization was 1.49 (95% CI 1.06–2.09) in significantly congested patients compared to those without congestion [6]. Among these 3 analyses, the cumulative data in favor of effective decongestion as a primary outcome of interest as opposed to “stabilization” of glomerular filtration markers in AHF send a strong signal towards a radical change in clinical practice with regard to the management of AHF hospitalizations for cardiologists as well as nephrologists. Changing the emphasis to achieving effective decongestion in the inpatient setting despite the colloquial “bumps in serum creatinine” in the process, will help to reduce the burden of HF-related readmissions, related economic consequences, and poor clinical outcomes. Better methods to rapidly and accurately quantify the plasma volume at the bedside, novel routes of administration of diuretics in HF, “bridge” clinics [7], and the establishment of “decongestion stewardship” teams for AHF hospitalizations akin to the team approach used routinely for surveillance of inpatient antibiotic use and sepsis recognition, may help to eliminate some of the additional barriers encountered with achieving decongestion and GDMT optimization in AHF.

GDMT in AHF: A Call for Action

Along the lines of reducing decongestive therapies in AHF with the goal of preventing fluctuations in clinically used markers of glomerular filtration, the culture of withholding GDMT in AHF, particularly inhibitors of the renin-angiotensin-aldosterone axis (RAASi), also remains a

major unsolved problem. This problem was called to attention in a recent summary by Bhagat et al. [8], highlighting the benefits of initiating and maintaining RAASi in the setting of AHF. Another recent analysis of dyskalemias across a range of ejection fraction values in heart failure (outpatient and inpatient settings) highlighted the increased risk of mortality and adverse cardiovascular disease outcomes with hypokalemia (including subjects with an eGFR <30 cm³/min), with non-use of RAASi and β -blockers being one of the major determinants of the risk of hypokalemia [9]. The Angiotensin-Neprilysin Inhibition in Acute Decompensated Heart failure (PIONEER-HR) trial from 2018 demonstrated comparable safety profiles with the initiation of sacubitril-valsartan in the setting of AHF and greater reductions in pro-BNP, in as little as a week after the initiation of therapy (ratio of change = 0.76; 95% CI 0.69–0.85), as well as lower rates of rehospitalization for HF with sacubitril-valsartan in an analysis of exploratory clinical outcomes [10]. Reassuringly, the recently published position paper on diuretic strategies in heart failure with congestion by Mullens et al. [11] on behalf of the Heart Failure Association of the European Society of Cardiology concurred with maintenance of appropriate GDMT during diuresis in AHF. Further studies are needed in this area wherein the benefits of well-tested therapies in chronic HF need to be redefined in the context of AHF preferably in a randomized controlled setting, thereby bridging the gap between AHF hospitalizations and maintenance therapies in the outpatient setting. In the context of concerns regarding precipitation of hyperkalemia, which is also a predictor of worse outcomes across HF phenotypes [9], the availability of 2 novel oral antihyperkalemic agents, i.e., patiromer acetate and sodium zirconium sulfate, offers new potential to test the feasibility of initiating and maintaining GDMT in AHF while avoiding deleterious effects on potassium balance [12–14].

Updates from Cardiovascular and Renal Outcomes Trials in 2018

Clinical trials of sodium glucose cotransporter 2 inhibitors (SGLT2i) in patients with diabetes mellitus with cardiovascular and/or kidney disease have demonstrated significant cardiorenal benefits for the class as a whole, with major implications in future trials for heart failure risk reduction, including in patients without diabetes [15]. Perhaps the most notable update from 2018 was the announcement of the early termination of phase 3 of the Canagliflozin and Renal Endpoints in Diabetics with Established Nephropathy Clinical Evaluation (CREDENCE) trial, evaluating the efficacy and safety of the SGLT2i canagliflozin versus placebo for adults with type 2 diabetes and chronic kidney disease (CKD) [16], based on the achievement of pre-specified efficacy criteria. The full results of this trial are awaited at this time and will lay the foundation for a new phase in the reduction of diabetic kidney disease progression, along with its known cardiovascular benefits. Similar trials across the drugs in the SGLT2i class will help to shed light on any drug-specific differences with cardio-renal protection. The proposed EMPA-KIDNEY trial (NCT03594110) is designed to investigate the effect of empagliflozin on kidney disease progression or cardiovascular death on top of standard of care in patients with preexisting CKD and it is anticipated to report results in 2022. The Dapagliflozin and Cardiovascular Outcomes in Diabetes (DECLARE-TIMI 58) trial, also reported in 2018, evaluated 17,160 patients (including 10,186 without atherosclerotic cardiovascular disease) who were followed for a median of 4.2 years [17]. In patients with type 2 diabetes who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but it did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure (HR = 0.73; 95% CI 0.61–0.88). Notably, the baseline renal function in DECLARE-TIMI 58 varied significantly from those in EMPA-REG OUTCOME and CANVAS. Dapagliflozin is recommended for patients with eGFR ≥ 60 mL/min/1.73 m² body-surface area and it is contraindicated for patients with eGFR <30 ; study patients were

required to have creatinine clearance ≥ 60 mL/min, but no minimum eGFR was specified. Thus, the overall baseline GFR in the study population of DECLARE-TIMI 58 had more preserved renal function at baseline and may partly explain the lower number of CV events seen in that study. Further head-to-head comparisons in more homogeneous study populations across the various drugs in the SGLT2i class are necessary to be able to extrapolate information from these trial settings into the real-world setting and achieve comparable risk/benefit profiles.

The glucagon-like receptor 1 receptor agonists (GLP 1-RA) are another class of novel oral antidiabetic agents that have cardio-renal protective effects. The Liraglutide and Renal Outcomes in Diabetes trial reported on the composite renal outcome occurring in fewer participants in the liraglutide group than in the placebo group (HR = 0.78; 95% CI 0.67–0.92). This result was driven primarily by the new onset of persistent macroalbuminuria, which occurred in fewer participants in the liraglutide group than in the placebo group (161 vs. 215 patients; HR = 0.74; 95% CI 0.60–0.91) [18]. A recent post hoc analysis of the Liraglutide Effect and Action in Diabetes (LEADER) trial reported that in patients with eGFR < 60 mL/min/1.73 m² the risk reduction for the primary composite cardiovascular outcome with liraglutide was greater (HR = 0.69; 95% CI 0.57–0.85) versus those with eGFR ≥ 60 mL/min/1.73 m² (HR = 0.94; 95% CI 0.83–1.07) [19]. These results appear to apply across the CKD spectrum enrolled, which is another encouraging development in cardio-renal risk reduction in diabetic kidney disease for the future. Other reno-protective agents in diabetic kidney disease such as atrasentan (selective endothelin A receptor agonist) and nonsteroidal mineralocorticoid receptor blockers (finerenone) also offer hope towards an overhaul of the landscape of treatment of diabetic kidney disease in the future, along with the remarkable progress made with the novel oral antidiabetic agents [20]. The Study of diabetic Nephropathy with AtRasentan (SONAR) trial completed enrollment in 2018, and data on the effects on serum creatinine doubling or end-stage kidney disease development in diabetic kidney disease in this trial are awaited at this time.

The year 2018 witnessed an interesting debate over the merits of a GFR-increasing strategy with bardoxolone (previously studied in trials of diabetic kidney disease) in the yet-to-report CARDINAL trial (NCT 03019185) for patients with Alport's syndrome. Traditionally, established reno-protective strategies in CKD result in modest declines in eGFR as a result of changes in intraglomerular hemodynamics and single-nephron GFR. Whether an increase in the eGFR will translate into a long-term renal benefit such as with bardoxolone remains to be seen. This also raises the possibility of exploring different angles to the old problem of reduction in CKD progression, especially with available safety data from previous studies with bardoxolone, such as the Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM) trial [21] and the Bardoxolone Methyl Evaluation in Patients with CKD and Type 2 Diabetes Mellitus: the Occurrence of Renal Events (BEACON) trial [22], to minimize risk.

Advanced Heart Failure Therapies and Kidney Disease Outcomes

The patient with advanced HF and CKD represents the biggest challenge in the cardio-renal realm in terms of achieving optimal perfusion, decongestion, time free of HF-related hospitalizations and quality of life. This fraction of patients with cardiorenal disease also represents one of the biggest financial resource utilizers in the health care system. Two studies on outcomes in patients with destination left ventricular assist device implantation and end-stage kidney disease in 2018 drew different pictures of the magnitude of adverse clinical outcomes in this population. Bansal et al reported on a United States Renal Data System dataset on patients with end stage kidney disease that underwent placement of left ventricular assist devices. After adjustment for several relevant confounders, the adjusted risk of death was markedly increased (HR = 36.3; 95% CI 15.6–84.5), with most subjects surviving for less than 3 weeks [23]. In

contrast, Walther et al. [24] reported an HR of 2.3 (95% CI 1.4–3.8) in their analysis of the National Inpatient Sample for the same question. The authors attributed the difference in the magnitude of the risk of death to differences in the cohorts and patient selection. Despite these differences, the increasing economic burden in patients with advanced CRS and the relatively dismal outcomes despite expensive treatments raises the question of how to identify best clinical practices in these patients with advanced heart and kidney failure, to provide appropriate therapies in a cost-effective manner. As more devices and pharmacotherapies evolve in the field of cardio-nephrology, this will become a central issue for key opinion leaders and stakeholders in the field. In this context, a strong emphasis on frequent and home dialytic therapies to provide tight volume control and improved quality of life is imperative to be able to successfully balance the coexistence of HF and end-stage kidney disease [25, 26]. The role of peritoneal dialysis in patients with refractory and advanced CRS has also been described and is an attractive maintenance option for patients, especially those who are not candidates for definitive advanced therapies including dual organ transplantation [27]. This also underscores the importance of utilizing early palliative care involvement in advanced CRS to be able to integrate patient priorities and preferences into clinical plans that tend to be difficult to tolerate, with relatively less improvement in the quality and quantity of life.

Conclusions and Future Extensions

Overall, the field of cardio-nephrology made significant strides in 2018 with novel approaches to the dilemma of pathological heart-kidney interactions, a problem well described and rooted in history [28]. The increasing relevance of this interface was recognized appropriately in publications as well as national conferences in cardiology and nephrology. Notably, collaborative efforts between key organizations such as the American Heart Association (Kidney Council), the American Society of Nephrology, and the Cardio-renal Society of America have been successful in highlighting the importance of this niche field. In a welcome trend deviating from the well-documented exclusion of patients with kidney disease from cardiovascular trials [29], key trials in cardio-renal medicine such as the International Study of Comparative Health Effectiveness of Medical and Invasive Approaches-CKD (NCT01985360), the Coronary Artery Disease Screening in Kidney Transplant Candidate trial (CARSK) (NCT02082483), the RENAL-AF trial (NCT02942407), and the STOP ACEi trial (SRCTN62869767) will report in the near future, allowing important questions to be answered with randomized controlled data in cardiorenal medicine. Obtaining high-quality data unique to this subset of patients is the biggest service that can ultimately be provided by cardiologists and nephrologists caring for patients with cardiorenal disease. Given the widening scope of the field of cardio-nephrology, efforts to create center-specific cardio-renal teams to accelerate and spearhead clinical care and research in this field are necessary to be able to train physician-scientists of the future to integrate the care of these patients in the best possible way [30, 31]. To that end, the growth of the field witnessed in 2018 is very encouraging. We look forward to participating in the continuation of the growth of cardio-nephrology in 2019 and beyond, to provide the best evidence-based multidisciplinary care for this vulnerable group of patients.

Disclosure Statement

None.

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