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TREATMENT UPDATE

Key updates in Cardio-Nephrology from 2018: springboard to a bright future

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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 patho-physiological principles in cardiorenal syndrome, new drug therapies with major cardio-reno-metabolic benefits, increasing momentum for the call for the need for a "cardio-nephrology" sub-specialty as well as deserved prominence for cardio-renal 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.

1. Decongestion in Acute Heart Failure: 'Drier' is Better in Type 1 Cardiorenal Syndrome

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. Amongst more than 50,000 patients enrolled in the ADHERE (Acute Decompensated Heart Failure National Registry) study, only 33% lost ≥ 2.27 kg (5 lbs.), and 16% of subjects gained weight during hospitalization (Gheorghiade, 2005). 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 cardiorenal syndrome (CRS), less than 10% of subjects in the trial achieved complete clinical decongestion through either strategy (Bart et al., 2012). 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 subjects at discharge. Imposing temporal limits to AHF hospitalizations (McCullough et al., 2015), gaps in the effective transition of the patient with AHF into a stable and compensated state as 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 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 (Ahmad et al., 2018). In this analysis, subjects that 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 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 (Fudim et al., 2018). 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 hazard ratio for WRF on 30-day death or heart failure hospitalization was 1.49 (95% CI, 1.06-2.09) in significantly congested patients than those without congestion (Metra et al., 2008). Between these three 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 regards to the management of AHF hospitalizations for cardiologists as well as nephrologists. Changing the emphasis to achieving effective decongestion in the inpatient setting albeit the colloquial "bumps in serum creatinine" in the process, will help reduce the burden of HF related re-admissions, related economic consequences and poor clinical outcomes. Better methods to rapidly and accurately quantify plasma volume at the bedside, novel routes of administration of diuretics in HF "bridge" clinics (Rangaswami and McCullough, 2018) and establishing "decongestion stewardship" teams for AHF hospitalizations akin to the team approach used routinely for surveillance of inpatient antibiotic use and sepsis recognition, may help eliminate some of the additional barriers encountered with achieving decongestion and GDMT optimization in AHF.

2. Goal Directed Medical Therapies in Acute Heart Failure: 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 highlighting the benefits of initiating and maintaining RAASi in the setting of AHF (Bhagat et al., 2019). 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 in subjects with an eGFR < 30 cc/min), with non-use of RAASi and beta blockers being one of major determinants of the risk of hypokalemia (Savarese et al., 2019). 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 initiating therapy (ratio of change, 0.76; 95% CI, 0.69 to 0.85), as well as lower rates of rehospitalization for HF with sacubitril-valsartan in an analysis of exploratory clinical outcomes (Velazquez et al., 2018). Reassuringly, the recently published position paper on diuretic strategies in heart failure with congestion by Mullens et al on behalf of the Heart Failure Association of the European Society of Cardiology concurred with maintenance of appropriate GDMT during diuresis in AHF (Mullens et al., 2019). 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 for precipitating hyperkalemia which is also a predictor of worse outcomes across HF phenotypes (Savarese et al., 2019), the availability of two novel oral anti-hyperkalemic agents: patiromer acetate and sodium zirconium sulfate offer new potential to test the feasibility of initiating and maintaining GDMT in AHF while avoiding deleterious effects on potassium balance (Weir et al., 2015; Packham et al., 2015; McCullough et al., 2016).

3. Updates from Cardiovascular and Renal Outcomes Trials in 2018

Clinical trials of sodium glucose co-transporter 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 (Butler et al., 2017). 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 vs. placebo for adults with type 2 diabetes and chronic kidney disease (CKD) (Jardine et al., 2017), 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 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 pre-existing CKD and is anticipated to report results in 2022. The Dapagliflozin and Cardiovascular Outcomes in Diabetes (DECLARE -TIMI 58) trial also reported in 2018 which evaluated 17,160 patients (including 10,186 without atherosclerotic cardiovascular disease) who were followed for a median of 4.2 years (Wiviott et al., 2018). 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 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 (hazard ratio, 0.73; 95% CI, 0.61 to 0.88). Notably, baseline renal function in DECLARE -TIMI 58 varied significantly from EMPA-REG OUTCOME and CANVAS: dapagliflozin is recommended for patients with eGFR ≥ 60 mL/min/1.73 m^2 body-surface area and 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 this 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 real world setting and achieve comparable risk/benefit profiles.

The glucagon like receptor 1 receptor agonists (GLP 1- RAs)

are another class of novel oral anti-diabetic 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 to 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 to 0.91) (Mann et al., 2017). 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 m^2, 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 m^2 (HR, 0.94; 95% CI, 0.83-1.07) (Mann et al., 2018). 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 non- steroidal mineralocorticoid receptor blockers (finerenone) also offer hope towards an overhaul of the landscape of treating diabetic kidney disease in the future, along with the remarkable progress made with the novel oral anti-diabetic agents (Muskiet et al., 2018). 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 (ESKD) development in diabetic kidney disease in this trial are awaited at this time.

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 intra-glomerular hemodynamics and single nephron GFR. Whether an increase in eGFR will translate into 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 (Pergola et al., 2011) and the Bardoxolone Methyl Evaluation in Patients with CKD and Type 2 Diabetes Mellitus: The Occurrence of Renal Events (BEACON) trial (de Zeeuw et al., 2013), to minimize risk.

4. 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 (LVAD) implantation and ESKD 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 ESRD that underwent placement of LVADS. After adjustment for several relevant confounders, the adjusted risk of death was markedly increased (hazard ratio, 36.3; 95% CI, 15.6-84.5), with most subjects surviving for less than 3 weeks (Bansal et al., 2018). In contrast, Walther et al 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 risk of death to differences in the cohorts and patient selection (Walther et al., 2018). Despite these differences, the increasing economic burden in the patients with advanced CRS and 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 ESKD (McCullough et al., 2016; Rangaswami and McCullough, 2018). 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 in those who are not candidates for definitive advanced therapies including dual organ transplantation (Iadarola et al., 2013). 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 quality and quantity of life.

5. 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 (Bright, 2018). 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), American Society of Nephrology and the Cardiorenal 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 (Maini et al., 2018), 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 Candidates 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 (Ronco et al., 2017; Kazory et al., 2018). To that end, the growth of the field witnessed in 2018 is very encouraging. We look forward to participating in the continuation of growth of cardio-nephrology in 2019 and beyond, to provide the best evidence- based multidisciplinary care for this vulnerable group of patients.

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Conflict of Interest

The authors have no competing conflicts of interest to disclose.

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