Editorial

Blood Purification

Blood Purif 2017;44:251–259
DOI: 10.1159/000480318

Published online: October 25, 2017

A Call to Action to Develop Integrated Curricula in Cardiorenal Medicine

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Keywords

Cardiovascular disease · Chronic kidney disease · Acute kidney injury · Heart failure · Acute coronary syndrome · Dialysis · Renal replacement therapy · Education · Training

Abstract

With the adoption of the new definition and classification of cardiorenal syndrome (CRS) and its relevant subtypes, much attention has been placed on elucidating the mechanisms of heart and kidney interactions. Of great interest are the pathophysiological pathways by which acute heart failure may result in acute kidney injury (AKI; type 1), chronic heart failure accelerating the progression of chronic kidney disease (CKD; type 2), AKI provoking cardiac events (type 3), and CKD increasing the risk and severity of cardiovascular disease (type 4). A remarkable interest has also been placed on the acute and chronic systemic conditions, such as sepsis and diabetes, which simultaneously affect heart and kidney function (type 5). Furthermore, the physiology of acute and chronic heart-kidney cross talk is drawing attention to hemodynamics (fluids, pressures, flows, resistances, perfusion), physiochemical (electrolytes, pH, and toxins), and biological (inflammation, immune system activation, neurohormonal signals) processes. Common clinical scenarios call for recognition, knowledge, and skill in managing CRS. There is a clear need for medical and surgical specialists that are well versed in the pathophysiology and the clinical manifestations that arise in the setting of CRS. With this editorial, we are making a call to action to stimulate universities, medical schools, and teaching hospitals to create a core curriculum for cardiorenal medicine to better equip the physicians of the future for these common, serious, and frequently fatal syndromes.

Introduction

For many years increasing efforts have been made to manage patients with simultaneous heart and kidney dysfunction, as evidenced by a rising number of clinical investigations and publications concerning cardiorenal syndromes (CRS) [1, 2]. Nevertheless, very little progress has been made in managing heart or kidney patients with specific attention to preserving the integrity of the cardiorenal axis and the surviving function of both organs [3, 4]. For example, acute heart failure (AHF) patients often have a worsening renal function compared to during the course of intravenous diuretic treatment due to

On October 25, 2017, this Editorial will be published simultaneously in *Blood Purification* (Blood Purif 2017;44:251–259) and *Reviews in Cardiovascular Medicine* (Rev Cardiovasc Med 2017;18:93–100).

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delayed plasma refill and possibly acute kidney injury (AKI) [5]. Whether the setting is AHF or any other hospitalized illness, studies suggest that AKI according to virtually any definition is associated with increased risks for prolonged hospitalization, a need for intensive care unit services, renal replacement therapy, progression of kidney disease, cardiovascular events, rehospitalization, and death [6]. In 2008, a systematic approach to heart and kidney interactions was published in the *Journal of the American College of Cardiology* [7] and immediately followed by a consensus statement of the *European Heart Journal* by the Acute Disease Quality Initiative in order to bring the issue of cardiorenal renal syndromes to a focal point among experts in cardiology, nephrology, and critical care [8].

The first step was to create and drive a consensus on definitions and classifications of CRS in common clinical scenarios with the recognition that the process of organ injury or dysfunction leading to the injury or dysfunction of the other organ could be in some circumstances relatively unidirectional, bidirectional, and interactive [9]. The consequent adoption of the new definition/classification of the CRS led to significant efforts to elucidate pathophysiological mechanisms and to describe the clinical consequences of each subtype [10]. Thus, specific features have been analyzed, such as AKI following AHF (type 1) [11], chronic kidney disease (CKD) induced by chronic heart failure (type 2) [12], acute myocardial dysfunction in the context of AKI (type 3) [13], and finally a high incidence of cardiovascular events in CKD and hemodialysis patients (type 4) [14]. A remarkable interest has also been placed on simultaneous, overwhelming systemic conditions causing the fulminant failure of both organs, for example in the setting of burns, sepsis, and rhabdomyolysis (type 5) [15].

A critical feature to most analyses has been the status of both intravascular and extravascular volume. A reasonable conclusion that appears to be generalizable in the setting of both acute and chronic CRS as compared to the normal state is that there is a narrowed therapeutic window for volume management. This means that a patient at risk for or with CRS experiences hazards of relative volume depletion, including hypotension and hypoperfusion. On the other end of the spectrum, there appears to be little tolerance for volume overload with consequences ranging from peripheral edema, which is nearly universal in hospitalized patients, to pulmonary edema and respiratory failure, resulting in the need for diuresis, mechanical ventilation, and death [16]. An important recent understanding is that the kidneys are exquisitely sensitive to this volume spectrum. Additionally, the kidneys are the most sensitive organ to hypotension and are more likely to sustain damage with hypotension than any other organ system [17]. While hypotension and volume depletion are well-recognized determinants of prerenal azotemia and AKI, it has been recently appreciated that volume overload can result in renal congestion and a similar manifestation of AKI. In terms of physiochemical stressors, it is becoming increasingly recognized that both the early detection and management of lactic acidosis, electrolyte disturbances, and organ toxicities, including nephrotoxic pharmacologic agents and iodinated contrast, can make meaningful differences in the outcomes of cardiorenal patients [18]. Finally, pathobiological mechanisms involving innate immunity, inflammation, and neurohormonal response have also been highlighted in the bidirectional nature of heart-kidney cross talk [19, 20]. For example, it is well recognized that in the setting of critical illness, even in the absence of hypotension or marked electrolyte disturbances, both the heart and the kidney can manifest evidence of damage with elevations of cardiac troponin and novel markers of AKI [21]. For each mechanism and its resultant clinical syndrome, specific knowledge and skills are required to avoid harmful interventions and to provide the optimal supportive therapy to enable recovery. The need is emerging for a specialist in cardiorenal medicine to offer optimal care to patients at greatest need. This is in order to reduce the burden of serious sequelae, including the need for dialysis, permanent disability due to heart or kidney impairment, and death.

With this editorial, we are making a call to action to stimulate universities, medical schools, and teaching hospitals to create a core curriculum for cardiorenal medicine, as has been done for critical care nephrology, cardiac critical care, and other disciplines that bridge the knowledge and skills between fields of cardiology and nephrology (Fig. 1) [22, 23].

CRS Type 1

This condition occurs across the entire spectrum of hemodynamic subsets of AHF [24]. Commonly, a relatively low cardiac output state or impaired forward perfusion are determinants of the rise in serum creatinine and blood urea nitrogen, and the reduction in urine output after intravenous diuretics [8]. On the other hand, effective perfusion to the kidneys could be impaired due to renal congestion, venous hypertension, and right ventric-

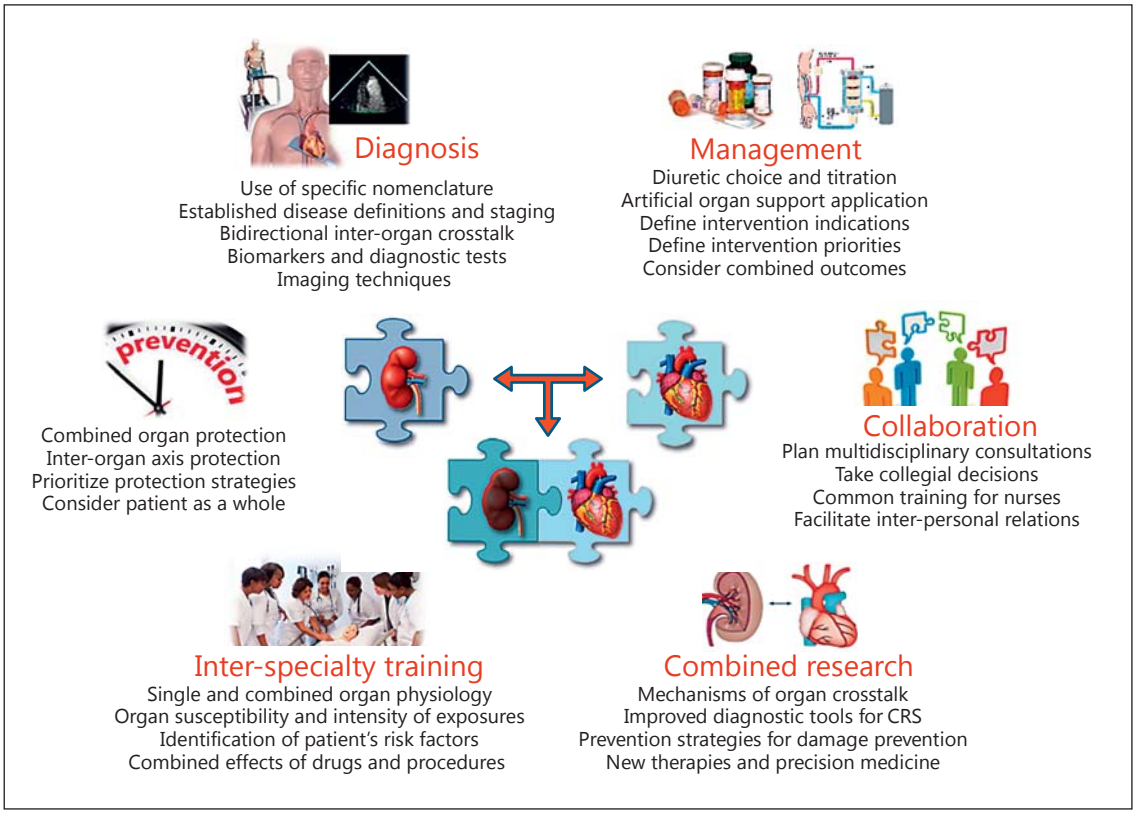

Fig. 1. Conditions and opportunities for common intervention and collaboration between cardiologists and nephrologists in patients with combined disorders of the heart and kidneys. The pieces of the puzzle may come together thanks to a combined effort of interdisciplinary training, common research, and strong commitment for collaboration. Multiple areas from pathophysiology to diagnosis, prevention, and treatment represent the ideal arena for this future exercise, hopefully leading to a true cardiorenal medicine.

ular dysfunction. Diastolic dysfunction and acute heart decompensation may represent additional risk factors and precipitating events leading to decreased kidney perfusion. The underlying pathophysiology is complex and involves oxidative stress and dysfunctional cell signaling; hence, there is hope for future therapies [25, 26]. In this syndrome, there is a need for coordinating the balance between optimizing hemodynamics and decongesting the kidneys within an appropriate timeline [27]. The development of novel therapies has been hampered by "short termism" among pharmaceutical sponsors and investigators, with the uniform failure of agents given for just 48 h [28]. The acute and extended use of drugs and strategies should be considered as a way forward. A combined strategy should be undertaken to achieve organ function recovery and symptom relief with maintenance or improvement in renal filtration function. Concerted efforts by cardiologists, nephrologists, and critical care specialists are needed to identify specific phenotypes of CRS type 1, and then design management strategies for that phenotype to maximize both cardiac and renal outcomes [29].

CRS Type 2

Chronic heart failure is one of the most common cardiovascular conditions, with ischemic heart disease contributing to two-thirds of those with reduced LV function and to about half with preserved LV function [30]. The vast majority of patients have longstanding antecedent hypertension with ostensibly normal renal filtration function but subclinical kidney disease and an impaired renal functional reserve. This means that, in the setting of stress or load of any type, the kidneys have a reduced ability to adapt to and manage a filtered load of solute and are

at risk of creating volume overload and azotemia [9]. Small episodes of acute decompensation or superimposed ischemic events may unveil a latent CKD and cause further damage in a highly susceptible kidney, leading to a rise in serum creatinine, proteinuria, and CKD progression [31]. In these patients, it is quintessential to coordinate a treatment that combines the clinical demand for neurohormonal modulation, maintenance of diuresis, control of blood pressure, management of potassium and the acid base, and maintenance of adequate body hydration. In particular, the use of diuretics and disease-modifying drugs for heart failure should be carefully titrated with a multidisciplinary approach based on the criteria of precision and personalized medicine.

CRS Type 3

For many years, AKI was considered an isolated entity to be managed with the intent of replacing renal function and maintaining the fluid and solute balance in patients at risk for severe pathophysiological derangements [32]. Today, AKI is perceived as a syndrome with evident consequences on distant organ function [10]. Among these, the renocardiac effects mediated though physical, chemical, and immunological signals may result in severe myocardial dysfunction [33]. Not only should the acid base and electrolyte be carefully managed, but also the fluid balance and blood pressure must be controlled in patients with AKI. In patients undergoing renal replacement therapy for severe oliguria and uremia, these tasks should be accomplished by different extracorporeal techniques whose prescription and delivery must be accurate and carefully executed using an accepted nomenclature [34]. The experience of the nephrologist is paramount in establishing the scope and goals of diuretic and extracorporeal therapy. The prescription and delivery of renal treatments should aim towards physiological targets covering the magnitude and timing of the desired changes in volume in relation to the response in right and left ventricular function. In this endeavor, the combined effort of the nephrologist with a cardiologist in the care of the critically ill patient will be the winning strategy.

CRS Type 4

The effects of CKD on the "4 corners of cardiovascular disease," including atherosclerosis, myocardial disease, arrhythmias, and valvular disease, are well known [35]. Every CKD and end-stage renal disease (ESRD) patient is almost inevitably a cardiac patient with several issues to be considered [36]. From the point of view of the kidneys, the main task is the reduction of CKD progression through the control of intraglomerular hemodynamics and hyperfiltration, the limitation of protein and salt intake, neurohormonal modulation, and control of blood pressure [37]. Recent evidence has pointed out that chronic inflammation, anemia, and metabolic alterations typical of uremia (e.g., hyperuricemia) [38, 39] even at its early stages may influence the rate of vascular calcification, myocardial fibrosis, aortic and mitral calcification, and the propensity for atrial and ventricular arrhythmias [40, 41]. In this syndrome, there appears to be opportunities to improve the micronutrient status of patients with the goal of reducing frailty and complications over time [42, 43]. We suggest that every CKD patient should be regularly followed up by both a nephrologist and cardiologist with mutual interests in cardiorenal medicine [44]. Particular attention should be paid to the detection and management of asymptomatic left ventricular dysfunction, atrial fibrillation, and valvular disease with an eye on the risk for bacterial endocarditis [45, 46]. Assessment of the functional classification is important for nephrologists working with ESRD patients in order to speak the same language as heart failure specialists [47]. The message is clear: CKD and ESRD are signals for cardiovascular care just as much as congenital heart disease, severe dyslipidemia, or a family history of premature cardiovascular disease are [48]. Additionally, there are considerable opportunities to collaborate on the mode of dialysis in order to optimize cardiovascular outcomes [49]. For example, patients appropriate selected for short daily home hemodialysis have been found to have significantly lower rates of heart failure hospitalizations, but this is balanced against higher risks of infection [50].

CRS Type 5

Simultaneous dysfunction of the heart and kidneys may result from systemic disorders such as sepsis from burns, or other fulminant syndromes [12]. These conditions may affect each organ through common mechanisms (e.g., endotoxin) but also through disease-associated or pathogen-associated molecular patterns [51, 52]. Specialists in the field of cardiology and nephrology may fruitfully collaborate to identify simultaneous cardiac and renal dysfunction in the setting of multiorgan system failure. Specialty-driven decisions may help to modify the

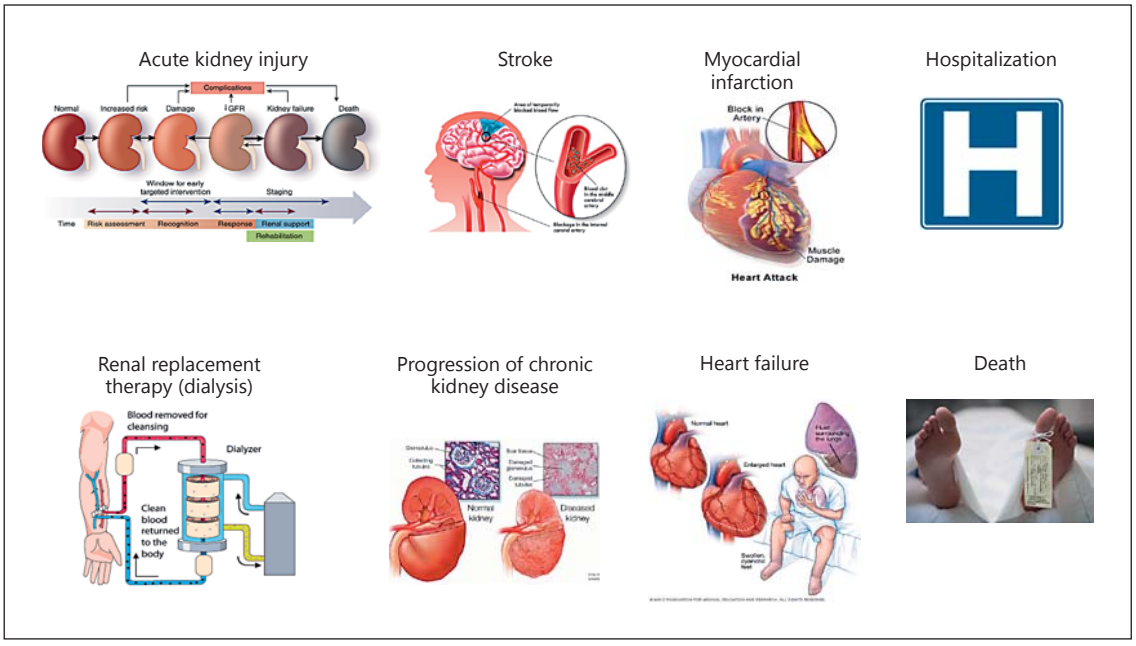

Fig. 2. Major adverse renal and cardiac events (MARCE) are strongly associated with AKI and raise the possibility of strategies that reduce AKI, translating into improved clinical outcomes as measured by the time to first MARCE event in clinical trials.

course or mitigate the effects of the main disease on the single organ, including inotropic support, renal replacement therapy, and extracorporeal oxygenation. The interpretation of laboratory testing and decisions to perform diagnostic procedures or specific therapies require the coordinated evaluation of each single case [53]. Optimal strategies defined for type 5 CRS will be paramount to improving the outcomes of these dire cases.

Unmet Clinical Needs

Heart and kidney interactions are bidirectional and time dependent [10]. It becomes evident from what has been described above that it is misleading and even dangerous to manage a single organ dysfunction without considering the secondary organ in the cardiorenal axis. It is worthless to consider the primary organ involvement and the origin of the syndrome without considering the vicious circle that may engage once both organs are affected.

Today, the cardiologist mainly manages cardiorenal syndromes type 1 and 2, while the nephrologist mainly treats types 3 and 4. There are no concerted efforts for the prevention of CRS at the individual or institutional level [54]. Very little interaction is institutionally defined. Occasional interdisciplinary activity may take place on the basis of a consultation, but often comes too late in patient care [55]. There is no uniform utilization of novel biomarkers to phenotypically classify and manage patients [53, 56, 57]. A multidisciplinary combined approach to CRS is lacking and patients are suffering from partial or restricted care due to a narrow medical perspective of the primary specialty [58]. We are making a call to action for specialists of different disciplines, namely cardiology and nephrology, to collaborate and to share information and knowledge concerning the critically ill patient both at the bedside and in the classroom, in order to provide a platform for this increasingly ill and expanding population of patients [59].

Educational Proposal

We are making a special call for specialists from either field to work side by side to achieve optimal care for every given cardiorenal patient. The last 20 years have seen major changes in the practice of medicine. The perception and understanding of AKI and CKD as multipliers for cardiovascular risk has evolved significantly in recent

years. At the same time, the understanding of the importance of preserving renal function and protecting the kidney during cardiac operations and acute cardiac events has also increased significantly (Fig. 2). A particularly striking development is the increase in common literature between cardiology and nephrology, with papers and books on CRS and heart/kidney-associated disorders. Initially sustained by passionate specialists interested in the cross-fertilization between the 2 fields, cardiorenal medicine is now a discipline whose time has come.

There have been barriers to collaboration. Historically, the customary training in cardiology never really focused on areas outside of heart disease. In fact, some institutions have branched their departments of cardiology out from internal medicine, further increasing the distance both clinically and intellectually between cardiologists and the other specialties. The same is true for nephrology, although a more comprehensive education has always been part of this specialty as a branch of internal medicine because of the impact of systemic disease on the kidneys [60]. Thus, physicians in post-graduate medical education were oriented to a specialty rather than to actual patient problems [60]. This sectorial education often resulted in a sort of adversarial "them and us" mentality. Thus, specialists are often consulted for a procedure (e.g., cardiac catheterization or initiation of dialysis) with little collaboration on addressing the cardiorenal health of the patient [61]. In addition, complex syndromes encompassing heart and kidney disorders require the application of complex knowledge and familiarity with hemodynamic assessment, the skilled use of the clinical laboratory, pharmacology, and the use of invasive procedures [62]. This "package" is seldom present in a single physician or practice. The result is that such specialists often clash and provide only a partial consultation and therapeutic strategies of limited vision, fueling the fire of antagonism rather than cooperation. A second cause for a delayed interdisciplinary collaboration may reside in the desire to maintain control of acute patients while chronic and hopeless patients are "left to the others." This may be different in a full-coverage social security system versus a private practice and insurance-based for-profit environment. The truth is that a combined path of diagnosis and care can only come from a multidisciplinary approach in which cardiologists and nephrologists cooperate mutually and respectfully. It might be true that one specialist has advanced knowledge and skills concerning certain pathophysiological disorders (e.g., acute coronary syndrome) while the other is an expert in a given therapy (e.g., hemodialysis). However, neither specialist is fully competent to manage a patient in which organ cross talk is continuous and even amplified by an ever-changing clinical profile. Control of patient care defines power within the medical structure for the individual physician and his or her practice or department. In the pursuit of higher standing in the medical community, specialists clash instead of cooperating. There are important and obvious clinical reasons for collaborative care. Patients with combined heart and renal failure are complex and difficult to manage, and the secondary dysfunction of one organ may affect the outcomes and results of treatments of the primary organ. This is the case in patients undergoing interventional procedures or cardiac surgery. In fact, the occurrence of AKI strongly influences the clinical course and often dominates outcomes (intensive care unit length of stay, general care, need of dialysis, rehospitalization, and death). An additional consideration is the need to allocate resources appropriately with recognition of terminal cases, where both the cardiologist and nephrologist can jointly convey a terminal prognosis to the patient and family members. A combined-care model of specialists might redefine the use of drugs such as inotropic agents, vasopressors, diuretics and renin angiotensin system inhibitors, anticoagulants, lipid-lowering therapy, and agents to modify electrolytes (bicarbonate, phosphate binders, calcium, etc.). New perspectives might be developed to help revise criteria for extracorporeal therapy and mechanical ultrafiltration in patients with CRS.

Common goals should be established for both organ protection and the prevention of CRS, while maximum attention and a combined effort should be given to maximize all chances for organ and patient recovery. There should be no financial penalties for those physicians who participate in paired consultation and comanagement [63].

This area undoubtedly needs an injection of focused attention, and effort should be incorporated in the structure of training and research, clinical application, and creativity [64]. We propose an innovative educational program to enhance the curriculums in both cardiology and nephrology training:

1. Nephrology fellows should spend at least 6 months in a cardiology department learning the approach to the cardiac patient and the point of view of the paired specialty, providing answers to problems that currently seem insoluble, including the management of heart failure, hemodynamic assessment, electrocardiography, and noninvasive imaging. Particular emphasis should be placed on the detection and management of

arrhythmias as well as noninvasive imaging of the hemodialysis patient who is often remote from cardiovascular care.

2. Cardiology fellows who intend to take an active role in the management of patients with acute and chronic heart failure at high risk of developing CRS should spend at least 6 months in a nephrology department learning the indication, prescription, and modality of delivery of extracorporeal support therapies. The cardiology fellow should acquire competency on the indications, initiation, and delivery of continuous renal replacement therapy for the cardiac patient with kidney problems. For this purpose, a special training program should be identified and enforced [65].
3. It is desirable, in large institutions, to develop fully combined programs resulting in board certification in both cardiology and nephrology. Fellowship status in aligned organizations, such as the Cardiorenal Society of America, is encouraged [66].
4. All tertiary institutions should have a "task force" allocated to the combined management of CRS and seek quality improvement and research opportunities in cardiorenal medicine.
5. Large institutions should encourage cardiology and nephrology faculties to develop career focus areas in cardiorenal medicine, with research platforms in basic, translational, preclinical, and clinical studies. Participation and leadership in multidisciplinary courses, such as the annual Vicenza Critical Care Nephrology course, the Cardiorenal Society of America Annual Meeting, and the Acute Dialysis Quality Initiative series of meetings, should be strongly encouraged in cardiorenal faculties with support from department chairs [48, 67, 68].

In conclusion, cardiologists and nephrologists should form a new union of cardiorenal medicine, as was the case many decades ago. This pivotal branch of internal medicine should deal with the most critically ill patients in our hospitals and clinics today. The only way to make this happen is with formal collaboration.

Our views may be criticized as being overly ambitious and out of proportion with the significance of renal disease in the cardiology world and vice versa. However, it is clear that renal disease is the most important predictor of cardiovascular outcomes in all areas of cardiology and that cardiovascular disease is the leading cause of death in kidney patients, therefore barriers to collaboration must be overcome. We need a new generation of cardiorenal physicians with an avant-garde approach to the screening, detection, diagnosis, prognosis, and management of CRS. With these enthusiastic words, we pledge our professional efforts in realizing these aspirations and call on each and every one of you to play a role in the evolution of this specialty.

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