



Review

Developing the subspecialty of cardio-nephrology: The time has come. A position paper from the coordinating committee from the Working Group for Cardiorenal Medicine of the Spanish Society of Nephrology

Javier Díez^{a,b,*}, Juan F. Navarro-González^{c,d}, Alberto Ortiz^{d,e}, Rafael Santamaría^{d,f,g}, Patricia de Sequera^h

^a Departments of Nephrology and Cardiology, University of Navarra Clinic, Pamplona, Spain

^b Program of Cardiovascular Diseases, Center of Applied Medical Research, University of Navarra, Pamplona, Spain

^c Division of Nephrology and Research Unit, University Hospital Nuestra Señora de Candelaria, and University Institute of Biomedical Technologies, University of La Laguna, Santa Cruz de Tenerife, Spain

^d Red de Investigación Renal (REDINREN), Madrid, Spain

^e Division of Nephrology IIS-Fundación Jiménez Díaz, University Autónoma of Madrid, Madrid, Spain

^f Division of Nephrology, University Hospital Reina Sofía, Córdoba, Spain

^g Maimonides Biomedical Research Institute of Córdoba (IMIBIC), Spain

^h Nephrology Department, Hospital Universitario Infanta Leonor, University Complutense of Madrid, Madrid, Spain

ARTICLE INFO

Article history:

Received 2 February 2021

Accepted 21 February 2021

Keywords:

Cardio-nephrology

Cardiorenal medicine

Cardiovascular disease

Chronic kidney disease

ABSTRACT

Patients with the dual burden of chronic kidney disease (CKD) and cardiovascular disease (CVD) experience unacceptably high rates of morbidity and mortality, which also entail unfavorable effects on healthcare systems. Currently, concerted efforts to identify, prevent and treat CVD in CKD patients are lacking at the institutional level, with emphasis still being placed on individual specialty views on this topic. The authors of this position paper endorse the need for a dedicated interdisciplinary team of subspecialists in cardio-nephrology that manages appropriate clinical interventions across the inpatient and outpatient settings. There is a critical need for training programs, guidelines and best clinical practice models, and research funding from nephrology, cardiology and other professional societies, to support the development of the subspecialty of cardio-nephrology. This position paper from the coordinating committee from the Working Group for Cardiorenal Medicine of the Spanish Society of Nephrology (S.E.N.) is intended to be the starting point to develop the subspecialty of cardio-nephrology within the S.E.N.. The implementation of the subspecialty in day-to-day nephrological practice will help to diagnose, treat, and prevent CVD in CKD patients in a precise, clinically effective, and health cost-favorable manner.

© 2021 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author.

E-mail address: jadimar@unav.es (J. Díez).

<https://doi.org/10.1016/j.nefro.2021.02.003>

0211-6995/© 2021 Sociedad Española de Nefrología. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Desarrollando la subespecialidad de cardio-nefrología: ha llegado el momento. Un artículo de opinión del Comité Coordinador del Grupo de Trabajo de Medicina Cardiorenal de la Sociedad Española de Nefrología

R E S U M E N

Palabras clave:

Cardio-nefrología
Enfermedad cardiovascular
Enfermedad renal crónica
Medicina cardiorenal

Los pacientes con enfermedad renal crónica (ERC) que presentan enfermedad cardiovascular (ECV) tienen índices de morbilidad y mortalidad inaceptablemente elevados, que impactan desfavorablemente sobre los sistemas de salud. En la actualidad, se requieren actuaciones multidisciplinares para identificar, prevenir y tratar la ECV en los pacientes con ERC, debiendo pues superarse la época de las actuaciones de las especialidades individuales. Los autores de este artículo respaldan la necesidad de un equipo interdisciplinar de subespecialistas en cardionefrología que gestione las intervenciones clínicas adecuadas en el entorno hospitalario y en el ambulatorio. Existe una gran necesidad de programas de formación, de guías y modelos de práctica clínica, y de fondos para la investigación en las sociedades de nefrología, cardiología y otras, para apoyar el desarrollo de la subespecialidad de cardio-nefrología. Este documento de opinión del comité coordinador del Grupo de Trabajo de Medicina Cardiorenal de la Sociedad Española de Nefrología (S.E.N.) pretende ser el inicio del desarrollo de la subespecialidad de Cardionefrología en el marco de la S.E.N. La implementación de la subespecialidad en la práctica nefrológica diaria contribuirá a diagnosticar, tratar y prevenir la ECV en los pacientes con ERC de una manera precisa, clínicamente efectiva y sanitariamente rentable.

© 2021 Sociedad Española de Nefrología. Publicado por Elsevier España, S.L.U. Este es un artículo Open Access bajo la licencia CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

It is well known that cardiovascular disease (CVD) in patients with chronic kidney disease (CKD) develops earlier and is more frequent, more severe, and shows different pathophysiological aspects and clinical manifestations compared with the non-CKD population, thus having a high medical, health and economic burden.^{1,2} Despite this, a group of experts assembled by the International Society of Nephrology identified recently the prevention and management of cardiovascular complications as one among several aspects of CKD that met criteria of unmet medical needs.^{3,4}

It has been suggested that overcoming this situation requires, among other initiatives, uniting knowledge and skills between the fields of cardiology and nephrology for a better prevention and care of CVD in patients with CKD.^{5,6} In this conceptual framework the coordinating committee of the Working Group for Cardiorenal Medicine of the Spanish Society of Nephrology (Grupo de Trabajo de Medicina Cardiorenal de la Sociedad Española de Nefrología [S.E.N.] – CaReSEN) has written this position paper to share with the readers of *Nefrología* their belief that the time has come for nephrologists to incorporate, in a systematic way, cardiovascular knowledge and skills to their expertise in diagnosing and treating patients with CKD. The authors strongly believe that a new generation of nephrologists subspecialized in cardio-nephrology with an avant-garde approach to the screening, detection, diagnosis, prognosis, and management of the cardiovascular complications of patients with CKD is needed.

This article aims to provide arguments that support the notion that CKD is a multisystemic disease with a

dominant cardiovascular component whose proper management exceeds conventional nephrology, as well as to propose the actions to be carried out to develop and integrate the emerging subspecialty of cardio-nephrology into the specialty of nephrology.

CVD in patients with CKD: an unmet medical need

There are multiple interactions between CVD and CKD that increase the disease burden of CKD patients and make CVD a major problem faced by nephrologists, other medical specialists and health systems. Some of the most relevant are briefly reviewed below.

Medical and health burden of CVD in CKD

Current European guidelines on CVD prevention⁷ indicate that CKD should be considered as a high risk condition for CVD. Indeed, established traditional and emerging cardiovascular risk factors are more common in patients with CKD than in subjects without CKD.⁸ In addition, there is a continuously increasing prevalence of CKD with the clustering of multiple cardiovascular risk factors.⁹ CKD is highly prevalent among patients with primarily diagnosed CVD and is associated with increased risk of adverse outcomes, including progression to kidney failure.¹⁰ For instance, an analysis of over 3.4 million patients without heart failure (HF) matched to 156,743 patients with HF indicated that HF patients had a 2.12 higher risk for progression toward CKD.¹¹ Additionally, HF patients are 2.96 times more likely to develop a rapid

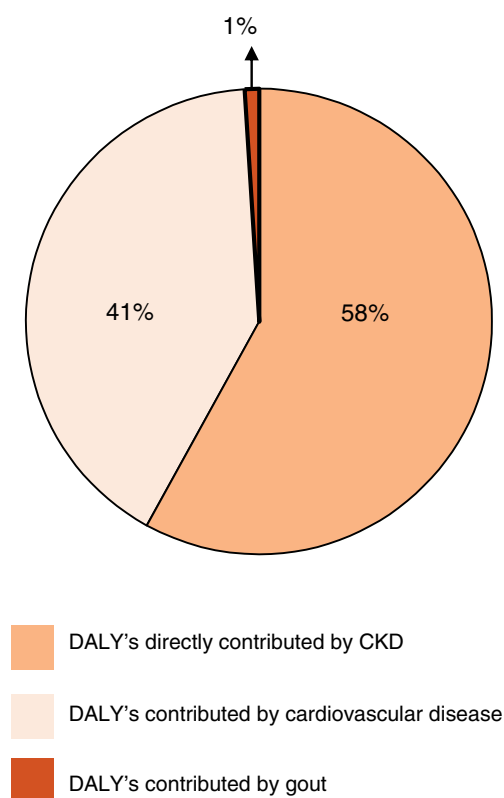


Fig. 1 – Percentages of Age-standardised Disability Adjusted Life Years (DALY's) directly contributed by chronic kidney disease (CKD), cardiovascular disease, and gout in patients with CKD in accordance with the Global Burden of Disease 2017 (adapted from Ref. 13 with permission).

decline in estimated glomerular filtration rate (eGFR) slope (defined as $>5 \text{ mL/min/1.73 m}^2$ per year), which occurs in 22% of HF patients.¹¹ Therefore, there is a bidirectional relationship between CKD and cardiovascular risk.

Beyond its own kidney disease-related burden, CKD has an indirect impact on global morbidity and mortality by increasing the risks associated with other major non-communicable diseases, including CVD.¹² Indeed, the GBD 2017 study estimated that CKD resulted in 61.3 million Disability Adjusted Life Years (DALYs), of which approximately 58% were directly contributed by CKD, whereas approximately 41% were CVD DALYs and less than 1% were gout DALYs attributable to impaired kidney function (Fig. 1).¹³ Furthermore, the GBD 2013 study estimated that cardiovascular deaths attributed to CKD outnumbered kidney failure deaths throughout the world.¹⁴ Importantly, although age dominates cardiovascular risk factors and the older population has the greatest CVD burden,¹⁵ CKD young adults (25–34 years of age) have at least a 100-fold higher risk of CVD-related mortality than the general population.¹⁶ Furthermore, children with CKD and no traditional cardiovascular risk factors, have increased mortality from CVD.¹⁷

Economic burden of CVD in CKD

CKD is associated with a huge economic burden that has a significant impact on annual health-care budget in many

developed nations.¹⁸ Total costs of care increase substantially with worsening categories of eGFR and with inpatient care. More specifically, CVD-related admissions are responsible for the dominant proportion of costs at all CKD stages.¹⁹ This is not only because CVD is by far the main prevalent primary cause of hospitalization in patients with CKD (31.8% for CVD vs 8.7% for the second cause),²⁰ but also to the costly effect of the combination of both diseases. Indeed, as shown in United Kingdom, the average estimated hospital cost of treating a major adverse cardiovascular event is substantially higher in CKD patients than in non-CKD patients.²¹ On the other hand, the data from the US Renal Data System on expenditures show the enhancer effect of cardiovascular complications on CKD costs.¹⁷ For instance, in the Medicare population aged 65 and older the per-person per-year costs in 2014 increased by 93% in patients with CKD and HF compared to patients with CKD alone.¹⁷ In this regard, data from Spain for the 2008-2010 period show that the direct and indirect health care costs related to HF are 58% higher in patients with eGFR values $<60 \text{ mL/min/1.73 m}^2$ than in patients with values $\geq 60 \text{ mL/min/1.73 m}^2$.²²

Diversity of clinical phenotypes of CVD in CKD

The high cardiovascular death rates associated with all stages of CKD reflect accelerated rates of both atherosclerosis and HF.²³ Indeed, diverse community-based studies showed a robust association between lower renal function and atherosclerosis-related clinical complications, including myocardial infarction, stroke, or peripheral artery disease.²³ These negative outcomes have been observed in any stage of CKD.²⁴ Furthermore, the NEFRONA study (Observatorio Nacional de Atherosclerosis en NEFRología) that prospectively assessed the prevalence and progression of subclinical atherosclerosis confirmed an increased prevalence of this condition in patients with early and intermediate CKD stages and showed that the risk for subclinical atherosclerosis increased with CKD stage.²⁵

Beyond the impact of atherosclerosis on cardiovascular outcomes in CKD patients, it is necessary to recognize also the contribution of non-atherosclerotic cardiac diseases (i.e., primary cardiomyopathies, valvular diseases and arrhythmias) to the bad cardiovascular prognosis associated with CKD.^{1,2} In accordance to the US Renal Data System, the incidence of these cardiac diseases is higher in CKD patients than in non-CKD patients, irrespectively of the influence of non-kidney related potential confounding factors.¹⁷ Either ischemic or non-ischemic cardiac diseases in CKD patients are characterized by progression to chronic congestive HF.²⁶ Combined chronic dysfunction of kidney and heart is referred to as type 4 cardiorenal (or renocardiac) syndrome.²⁷ Interestingly, the prevalence of HF in CKD patients has been reported close to 26%, compared to 6% among patients without CKD.¹⁷ Of note, the presence of HF reduces the probability of survival among patients both with and without CKD, but to a greater extent among those with CKD (p -value for interaction <0.0001).¹⁷ Additionally, cumulative evidence supports that when HF develops in the context of CKD, the ensuing hemodynamic

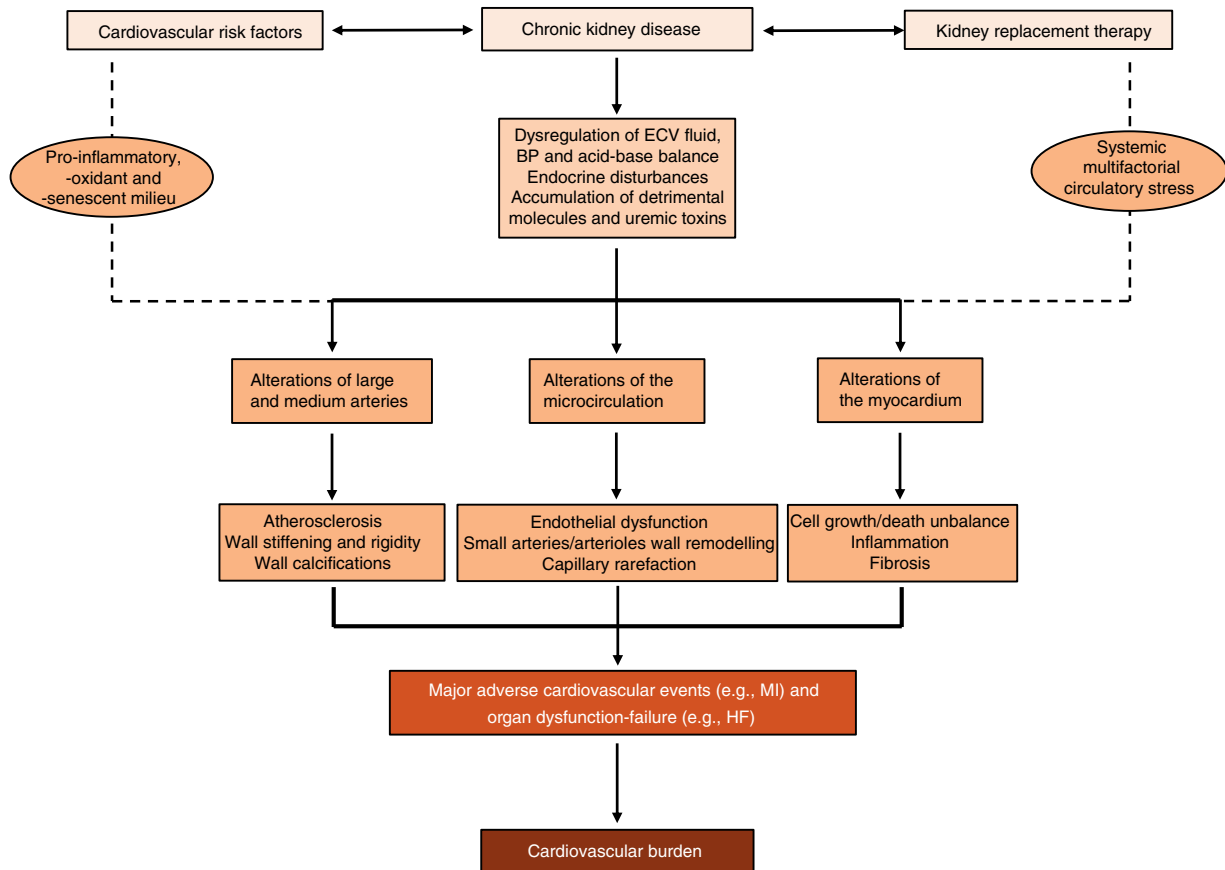


Fig. 2 – Schematic view of the mechanisms involved in the pathogenesis and consequences of cardiovascular disease in chronic kidney disease (ECV, extracellular volume; BP, blood pressure; MI, myocardial infarction; HF, heart failure).

alterations further compromise renal function²⁸ facilitating the progression of CKD.¹¹

Complex pathophysiology of CVD in CKD

As demonstrated in animal models of CKD,^{29,30} the development and progression of CKD involve alterations in the cardiovascular system providing the pathophysiological basis for the phenotypic expression and outcomes of CVD in CKD patients. Indeed, the vascular tree and the heart undergo major structural and functional changes when kidney function declines^{31–33} that are exacerbated by concomitant cardiovascular risk factors³⁴ and when kidney replacement therapy (KRT) is required.³⁵ This facilitates atherosclerotic events (e.g., myocardial infarction)³⁶ and organ dysfunction (e.g. HF)²⁶ causing most of the cardiovascular burden of CKD (Fig. 2).

Although the pathophysiology of CVD in CKD has been extensively studied, there are some emerging issues that are worth considering. Most research in CKD-related vascular disease has been devoted to macrovascular complications. However, a recent review of all publications evaluating structure and function of the microcirculation in humans and animals with CKD found that capillary rarefaction resulting in a significant decrease in microvascular density, is a quintessential finding.³⁷ For instance, the median capillary density was reduced by 24% in the heart in animal

models of CKD³⁸ and by 12% and 16% in necropsy studies in CKD patients and patients on dialysis, respectively.³⁹ As shown experimentally, CKD results in the loss of coherent vessel systems distal to smaller arterioles, generating a typical heterogeneous pattern with avascular patches, resulting in a dysfunctional endothelium with diminished perfusion, shunting and tissue hypoxia.⁴⁰ Therefore, microvascular disease is a principal pathogenic factor in the progression of CKD and the development of widespread severe organ dysfunction and multimorbidity in CKD patients.

Beyond the classically recognized macroscopic left ventricular hypertrophy (LVH) in patients with CKD, myocardial interstitial fibrosis (MIF) is a frequent finding in endomyocardial biopsies and necropsy studies in these patients.⁴¹ Indeed, clinical and population-based pathological post-mortem studies have shown that patients with CKD have significantly more interstitial fibrotic tissue in the heart compared with subjects without CKD, and that the stage of CKD directly correlates with the extent of MIF, thus being the more severe fibrosis found in patients with kidney failure and patients on KRT.^{39,42} Interestingly, coronary microvascular rarefaction and MIF are closely correlated in CKD patients.³⁹ Recent scientific work has identified causal connections between CKD and MIF.⁴³ Furthermore, it has been proposed that MIF may play a key role in the development of HF in CKD patients.⁴⁴ In this framework, limited data and a large potential for impact make it necessary to

develop optimal strategies for the diagnosis of MIF in CKD patients, as well as strategies aimed at individualized prevention and management of MIF in patients with kidney failure and on KRT.⁴⁵

Finally, patients with CKD are at high risk for acute kidney injury (AKI) and accumulating evidence supports the notion that cardiovascular damage due to AKI leads to poor long-term cardiovascular outcomes,⁴⁶ independent of or intertwined with the cardiovascular risks associated with CKD itself. Indeed, a 2017 meta-analysis of 25 studies involving a total of 254,408 patients, including 55,150 with AKI,⁴⁷ showed that AKI was associated with an 86% increase in the risk of death from cardiovascular causes during a median follow-up of 1.4 years, a 58% increase in the risk of chronic HF during 2.9 years of follow-up, a 40% increase in the risk of acute myocardial infarction during 2.3 years of follow-up, and a 15% increase in the risk of stroke over a period of 2.7 years.⁴⁷ Beyond AKI-associated hydroelectrolytic disturbances that promote acute cardiac dysfunction, defined as type 3 cardiorenal syndrome, AKI induces structural myocardial damage, with low-grade inflammation and cellular apoptosis and necrosis developing within days or weeks after an event and MIF developing months or years later.⁴⁸ Thus the cardiovascular impact of CKD is further reinforced in conditions of abrupt decline of kidney function whatever its cause.

Underdiagnosis and undertreatment of CVD in CKD

CVD is systematically underdiagnosed in CKD patients as the diagnostic sensitivities and specificities of clinical manifestations and non-invasive tests are questionable in this population. Two examples (e.g. coronary artery disease and HF) may illustrate this issue. The classic triad of ischemic symptoms, elevated cardiac biomarkers, and electrocardiographic changes is frequently absent in CKD patients suffering from acute coronary syndrome, who are more likely to present with systolic or diastolic dysfunction causing HF symptoms, or with syncope.⁴⁹ Exercise electrocardiography is limited by lack of specificity of the ST-segment response and by inability of many CKD patients to exercise to a diagnostic workload.⁵⁰ The accuracy of exercise and of pharmacological myocardial perfusion imaging is reduced in CKD patients compared with the general population, and sensitivities and specificities <80% have been reported.⁵¹ Conversely, creatine kinase MB isoform and cardiac troponins may be elevated in the absence of true myocardial necrosis, possibly because of myocardial apoptosis or small coronary vessel disease that develops in CKD.⁵²

As regards to HF, its diagnosis as defined by the European Society of Cardiology (ESC)⁵³ has limitations when applied to CKD patients. First, almost all patients with kidney failure develop signs and symptoms consistent with fluid overload due to inability of the severely diseased kidneys to excrete sodium and water independently of the presence or absence of cardiac dysfunction.²⁶ Second, structural heart disease, for instance LVH, is highly prevalent in patients with CKD, the prevalence increasing progressively with the loss of renal function and thus being present in more than 80% of patients with kidney failure.⁵⁴ Finally, CKD is one of the numerous causes of elevated natriuretic peptides that may weaken their diagnostic utility in HF.⁵⁵

Patients with advanced CKD or kidney failure and patients on long-term dialysis are usually excluded from cardiovascular clinical trials conducted in the general population or in at-risk populations.⁵⁶ This excluding behavior also extends into kidney transplant patients.⁵⁷ It is noteworthy that regardless of the exclusion criteria (either serum creatinine levels above a threshold or eGFR values below a threshold) the percentage of trials that exclude patients with CKD has increased in recent years.⁵⁸ This is particularly relevant for the use of HF modifying therapies in patients with any stage of CKD or on KRT and concomitant HF either with reduced or with preserved ejection fraction (Fig. 3).⁵⁹ In addition, there are no universally agreed selection criteria and cardiovascular outcomes for trials conducted specifically in these populations.^{60,61} As a consequence, the treatment of CVD in patients with advanced CKD stages and patients on KRT is not based on evidence, but rather empirical with variable screening protocols and lack of consensus on optimal management which collectively gives rise to undertreatment that, in turn, facilitates the high cardiovascular burden in CKD patients, namely in those with HF.⁶²

Added cardiovascular burden of KRT

An additional factor that further reinforces the relationship between CKD and CVD is the high cardiovascular morbidity and mortality of patients on KRT. The prevalence of any CVD in people on prevalent dialysis exceeds 60%, being well above that of patients with stage 5 CKD,¹⁷ with no global clear-cut differences between patients on hemodialysis and patients on peritoneal dialysis, although this aspect may depend of the type of CVD to be considered.^{17,63,64} Data from a systematic review and meta-analysis indicate that the incidence of *de novo* CVD is also similar in the two dialytic therapies.⁶⁵ On the other hand, CVD accounts for >50% of deaths in people on either modality of dialysis,^{16,17,64} and CVD mortality remains up to 30 times higher in dialysis than in the general population.¹⁶ Analysis of available studies comparing cardiovascular mortality between the two dialysis modalities show discrepant results with either similar mortality for either modality⁶⁵ or significantly lower mortality for hemodialysis compared to peritoneal dialysis.⁶⁶ Given the inability to perform randomized studies, the existence of confounders cannot be ruled out.

Although the severity of CVD is reduced after kidney transplantation, it still remains the leading cause of premature patient and allograft loss, as well as a source of significant morbidity.^{67,68} Whereas all major phenotypes of CKD-associated CVD are represented in the kidney transplant recipient population, pre-existing risk factors for cardiovascular disease are amplified by superimposed cardio-metabolic derangements after transplantation such as the metabolic effects of immunosuppressive regimens, as well as the detrimental impact of allograft dysfunction.⁶⁹

Developing the subspecialty of cardio-nephrology

It is undeniable that the high burden and complexity of CVD in CKD patients requires dedicated and highly committed car-

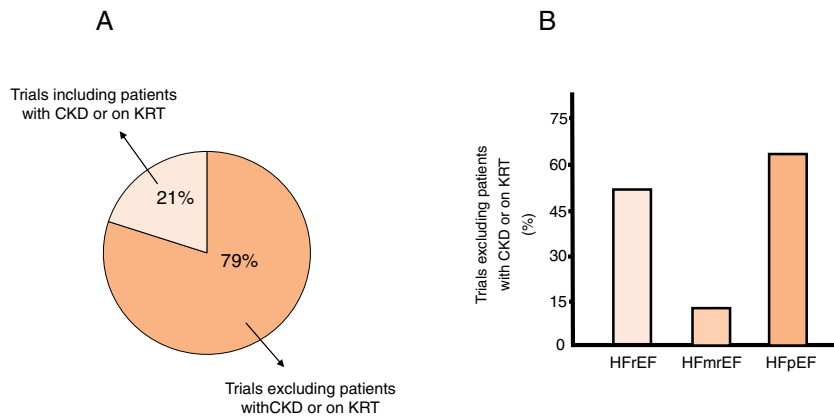


Fig. 3 – Summary of data from published systematic reviews reporting the percent of cardiovascular trials that excluded patients with heart failure (HF) and chronic kidney disease (CKD) (i.e., any stage of CKD or on kidney replacement therapy [KRT]) from HF clinical trials. Panel A. Presents the data in HF patients not separated according to ejection fraction (EF) values. Panel B. Presents the data of trials in which HF patients were stratified according to EF values in patients with HF with reduced EF (HFrEF), mid-range EF (HFmrEF) and preserved EF (HFpEF) (adapted with permission from Ref. 59).

cardiovascular care which, in turn, requires both a demanding training plan and an adequate clinical environment.

The need of the subspecialty

Nephrology is facing a period of remarkable and unprecedented change. Despite the successful scientific, clinical and health policy developments produced during the last years, significant barriers exist to ensure a robust pipeline of well-qualified nephrologists. There is widespread agreement, however, that any initiative to reassert the ‘appeal’ of nephrology must include significant focus on reinvigorating the trainee experience before and during fellowship.⁷⁰ Indeed, current nephrology fellows perceive several gaps in training. Innovation in education and training is needed to better prepare future nephrologists for the growing challenges of kidney care.⁷¹ As the clinical complexity of nephrology is well recognized⁷² the interface between nephrology and other fields of medicine continues to expand, thus providing opportunities for subspecialization.⁷³

In this conceptual framework, the members of the Western Europe Regional Board, International Society of Nephrology have recently proposed a training program in the subspecialty of cardio-nephrology as one of the potential goals for European nephrology in the future.⁶ The proposal is based in the notion that CVD in CKD patients represents a challenge and opportunity to develop strategies to enhance the skills and capabilities of current and, namely, future nephrologists.

In parallel with this proposal, the American Heart Association Council on the Kidney in Cardiovascular Disease and Council on Clinical Cardiology have endorsed the need for a dedicated cardiorenal interdisciplinary team that spearheads early identification of patients with the dual burden of heart and kidney disease and jointly manages appropriate clinical interventions across the inpatient and outpatient settings.⁵ This collaborative would also oversee cross-training among nephrology and cardiology fellows and nursing and allied

healthcare providers in both specialties to foster a deeper understanding of the intricacies of cardiorenal cross-talk.

S.E.N. commitment to cardio-nephrology

In October 2019 the CaReSEN created the cardiorenal medicine working group (CaReSEN) taking into account four major arguments: (i) there is a critical need for guidelines and best clinical practice models from the S.E.N. geared specifically toward cardiorenal medicine outcomes and for research funding to focus on the needs of future cardiovascular therapies in CKD patients; (ii) implementation of national task forces that emphasize quality improvement measures in cardiorenal disease and the introduction of national quality benchmarks for cardiorenal outcomes will help reduce the morbidity, mortality, and economic burden of CVD in CKD patients; (iii) implementing cross-specialty educational programs across all levels in cardiovascular medicine and nephrology will help train future nephrologists who have the ability to diagnose, treat, and prevent the disease burden associated with CVD and CKD in a precise, clinically effective, and cost-favorable manner; and (iv) as it is a reality that for years the specialty of nephrology faces major fellowship recruitment challenges in our country and worldwide, the potentiation of subspecialties as cardio-nephrology can help instill new interest and enthusiasm in choosing nephrology as a career amongst trainee physicians.^{73–75}

In accordance with these arguments, the main objective of the CaReSEN is to develop the subspecialty of cardio-nephrology within the specialty of nephrology. To achieve this objective, the CaReSEN has proposed a series of initiatives (Table 1). It is crucial to identify the pending priorities of nephrology in the following cardiorenal fields: (i) care (e.g. creation of multidisciplinary teams between nephrologists and cardiologists with shared clinical protocols); (ii) education (e.g. modification of the undergraduate and postgraduate Medicine study plans, modification of the training program ‘médicos internos y residentes’ [MIR] in nephrology, and modification of

Table 1 – Main initiatives proposed by CaReSEN to launch the subspecialty of cardio-nephrology.

Identify the pending priorities of nephrology in the fields of cardiorenal care, cardiorenal education and cardiorenal research
Cooperate with national and international medical associations related to cardiorenal medicine
Promote collaborations between public institutions for the development of the aforementioned priorities
Collaborate with private institutions in medical training, translational research and health dissemination related to cardiorenal medicine
Cooperate with kidney patient organizations in initiatives aimed at education in cardiovascular issues

the continuous training of nephrologists to stimulate the cardiorenal vision of nephrological diseases); and (iii) research (e.g. facilitation of the development of cardiorenal translational research, and of clinical trials that include or focus on patients with advanced stages of CKD, patients with kidney failure, and patients on KRT).

It is also mandatory to promote collaborations at two different levels: (i) public institutions (e.g. clinical centers, academic institutions, research centers, and health, scientific and educational administrations); and (ii) scientific societies (e.g. national and international medical societies with background in the implementation of cardiorenal medicine). In this regard, the CaReSEN is planning to share its actions with the European RENal and Cardiovascular Medicine (EURECA-m) Working Group of the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) that was created in 2010 with the mission to promote collaborations among European centers and medical specialties pursuing education and research in the overlapping area of cardiovascular and renal medicine.⁷⁶

Finally, it also seems convenient to interact with private institutions involved in the dissemination of the nature and actions of the subspecialty to facilitate its integration into real world healthcare. In this regard, one specific objective would be to explore with kidney patients associations the creation of a 'Cardiorenal School' aimed at educating them in the prevention and management of the cardiovascular aspects of their disease. The role of national nonprofit global organizations fostering these initiatives, as it is the case of the Cardio Renal Society of America,⁷⁷ deserves to be considered.

Integrating cardio-nephrology training into nephrology training

Current general nephrology training, while helpful for providing the core knowledge and skills needed for managing patients with CKD and AKI, does not seem to be sufficient for covering the rapidly evolving field of cardiorenal medicine. Therefore, a proposal was made some years ago for an innovative program to enhance the education of both cardiology and nephrology training.⁷⁸ This program is meant to shape the foundation for a more comprehensive view of cardiorenal medicine than the conventional nephrology fellowship training.

Depending on the scope of practice of the teaching facility, the 6-month educational cardiorenal program can be offered

as a cumulative block of elective time of the nephrology training, preferably during the second half of the 4-year period of fellowship. Alternatively, it can be offered as a "specialty track" such as those currently offered by a number of centers in other areas of nephrology.

A variety of topics related to cardiorenal medicine can be considered for inclusion in the program, relating to both acute and chronic processes as well as the inpatient or outpatient setting (Table 2).⁷⁴ While the core knowledge would remain the same to ensure consistency, the interest of the trainee as well as the expertise and clinical focus area of the attending physicians would supplement and guide the specific subject materials covered. Obviously, the patient population as well as any related local disciplines and programs (e.g. the presence of an active cardiovascular surgery service or an extracorporeal membrane oxygenation program) will affect the educational content and value of the program.

The long-range view is for the nephrologist to develop and utilize competence in electrocardiography, echocardiography, vascular and lung ultrasound, and also physiologic studies such as body composition and impedance. While the classically referred studies would still be best performed by experienced specialists in the respective fields, advanced cardiorenal-trained nephrologists would gain competence in performing and interpreting some studies (e.g., point-of-care ultrasound)⁷⁹ and generate real-time data relevant to patient care.

Table 2 – Some illustrative examples of topics to cover in the cardiorenal program by the nephrologist trainee.

In the setting of diagnosis
<i>Assessment of volume status</i>
Use of bioimpedance and point-of-care ultrasound
<i>Focused diagnosis of heart failure</i>
Knowledge of specific echocardiographic and blood biomarker criteria in CKD patients
In the setting of treatment
<i>Therapy of fluid overload</i>
Handling of diuretic resistance and use of ultrafiltration with dialysis techniques
<i>Personalization of cardiovascular therapy</i>
Knowing the impact of kidney failure and KRT on cardiovascular drug pharmacology
In the setting of prevention
<i>Prevention of cardio-renal disease onset and progression</i>
Management of common risk factors
<i>Prevention of AKI in the setting of cardiovascular diagnostic procedures</i>
Application of protocols to minimize contrast-associated risk
<i>Prevention of WRF in the setting of cardiovascular surgical procedures</i>
Application of protocols to minimize hemodynamic instability-associated risk
In the setting of decision making
<i>Decisions on procedures and interventions</i>
Delivering effective clinical care while ensuring adequate use of resources (e.g., indication of cardioprotective instead of conventional HD)
<i>End-of-life decisions</i>
Recognition of cardiac terminal cases (e.g., indications of comprehensive conservative treatment instead of KRT)

CKD, chronic kidney disease; KRT, kidney replacement therapy; AKI, acute kidney injury; WRF, worsening renal function; HD, hemodialysis.

Knowledge of the relevant consensus guidelines of medical professional societies and initiatives (e.g. the ESC guidelines for the diagnosis and treatment of acute and chronic HF,⁵³ and the Acute Dialysis Quality Initiative XI Workgroup functional classification system of HF in patients with kidney failure⁸⁰) should be part of this educational program. A better understanding of the role of cardiorenal interactions in CKD and HF in symptom development, disease progression and prognosis (e.g., evaluation of kidney function throughout the HF trajectory,⁸¹ and impact of HF pathophysiology⁸² and treatment²⁶ on the continuum of cardiac dysfunction in CKD) needs also be considered.

To enhance academic skills, the trainees will be required to develop a clinical research project in cardiorenal medicine. The research could focus on three fundamental thematic axes: (i) the search for new mechanisms involved in the crosstalk between the diseased kidney and the cardiovascular system^{83,84}; (ii) the development of clinical studies aimed at increasing evidence based-practice in the diagnosis and treatment of CVD in patients with kidney failure and patients with KRT⁸⁵; and (iii) the investigation of the impact of different cardiorenal multidisciplinary models on care outcomes and utilization of health care resources.⁸⁶

As difficulties to providing any new educational cardiorenal program usually include a lack of external funding and faculty time constraints, integrating cardio-nephrology training into nephrology training should be done, at least in its beginning, with the use of already existing resources and with a minimal time commitment from faculty members. This said, it is important to remark that program-specific mentors should exist to ensure curriculum development and ensures trainees have an adequate experience.

Collaboration with the Spanish Society of Cardiology (SEC)

It is undeniable that patients with combined CKD and CVD are complex and difficult to manage, and it is clear that CKD is the most important predictor of cardiovascular outcomes in all areas of cardiology and that CVD is the leading cause of death in kidney patients. Although these are the most important and obvious clinical reasons for collaborative care between nephrologists and cardiologists, there have been obstacles to collaboration. For instance, the customary training in cardiology never really focused on areas outside of CVD. The same is true for nephrology and CKD, although a more comprehensive education has always been part of this specialty because of the impact of systemic disease on the kidneys.⁸⁷ 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.⁸⁸ A second obstacle to an interdisciplinary collaboration may reside in the desire to maintain control of acute patients while chronic and hopeless patients are “left to the others”. Although it might be true that one specialist has advanced knowledge and skills concerning certain acute disorders (e.g. acute coronary syndrome or AKI) while the other is an expert in a given therapy for advanced patients (e.g. LV assist support or hemodialysis),⁸⁹ 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. Two examples support the advantages of a multidisciplinary approach when treating cardiorenal patients. On the one hand, fluid overload resulting in intravascular and tissue congestion is a prominent finding in both decompensated HF⁹⁰ and late stages of CKD,⁹¹ namely when the two conditions coexist, that should be treated with a novel vision not limited simply to forcing diuresis, but to normalize the extracellular volume and its distribution between tissues and blood vessels, without worsening heart or kidney function. On the other hand, accumulating evidence suggest that thanks to sodium-glucose cotransporter 2 (SGLT2) inhibitors the heart and the kidney work better together, thus offering a unique opportunity for clinicians to treat cardiac and renal disease in concert rather than in discord.^{92,93}

Therefore, the time has come for the collaboration between nephrologists and cardiologists in two major areas: (i) the development of a common educational cardiorenal program to enhance the curriculums and the clinical training in both cardiology and nephrology, thus facilitating the creation of subspecialists in cardio-nephrology⁷⁸; and (ii) the development of cardiorenal clinical units in which teams of cardiologists and nephrologists participate in paired consultation and co-management of cardiorenal patients based on common protocols and goals collected in clinical practice guidelines to maximize all chances for organ and patient recovery.⁹⁴ Some specific aims to be accomplished in this collaborative educational and clinical initiative are presented in Table 3. In this sense, the S.E.N. and the SEC have initiated an institutional collaboration through a team of nephrologists and cardiologists to develop these two areas. Of note, this collaboration is open to the involvement of other medical specialties also dealing with patients eventually presenting with cardiorenal problems (e.g., internists and intensivists).

Table 3 – Specific objectives to achieve in the cardiorenal collaboration of the S.E.N. and the SEC.

To develop fully combined educational programs resulting in board certification in cardio-nephrology
To provide that nephrology fellows spend at least 6 months in a cardiology department learning the diagnostic approach to and the therapeutic management of cardiac patients and the point of view of the cardiologist on patients in the cardiorenal interface
To provide that cardiology fellows spend at least 6 months in a nephrology department learning the diagnostic approach to and the therapeutic management of kidney patients and the point of view of the nephrologist on patients in the cardiorenal interface
To develop multidisciplinary clinical units of cardiorenal medicine allocated to the combined management of cardiorenal patients with special emphasis on the diagnosis and management of heart failure in kidney failure and <i>viceversa</i> , and the indication, prescription, and modality of delivery of extracorporeal support therapies
To create a joint platform to perform basic, translational, preclinical, and clinical studies in cardiorenal areas allowing cardiology and nephrology faculties to develop careers in cardio-nephrology

S.E.N., Sociedad Española de Nefrología; SEC, Sociedad Española de Cardiología.

Conclusions

Almost two centuries have passed since Sir Richard Bright identified alterations in cardiac structure in patients with advanced stages of CKD,⁹⁵ thus the interdependence between CKD and CVD has been part of the history of nephrology. Due to its large clinical consequences and its impact on public health and society, the time has come to professionalize the management of this interdependence, enabling the training of subspecialists in cardio-nephrology within the specialty of nephrology. The S.E.N. is committed to this and through the CaReSEN is developing a training plan for subspecialists in cardio-nephrology to which it welcomes its members as well as other medical specialists also related to the CKD–CVD binomial.

REFERENCES

- Herzog CA, Asinger RW, Berger AK, Charytan DM, Díez J, Hart RG, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2011;80:572–86, <http://dx.doi.org/10.1038/ki.2011.223>.
- Wang V, Vilme H, Maciejewski ML, Boulware LE. The economic burden of chronic kidney disease and end-stage renal disease. *Semin Nephrol.* 2016;36:319–30, <http://dx.doi.org/10.1016/j.semnephrol.2016.05.008>.
- Bello AK, Alrukhaimi M, Ashuntantang GE, Basnet S, Rotter RC, Douthat WG, et al. Complications of chronic kidney disease: current state, knowledge gaps, and strategy for action. *Kidney Int Suppl.* 2017;7:122–9, <http://dx.doi.org/10.1016/j.kisu.2017.07.007>.
- Levin A, Tonelli M, Bonventre J, Coresh J, Donner JA, Fogo AB, et al. Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet.* 2017;390:1888–917, [http://dx.doi.org/10.1016/S0140-6736\(17\)30788-2](http://dx.doi.org/10.1016/S0140-6736(17)30788-2).
- Rangaswami J, Bhalla V, Blair JEA, Chang TI, Costa S, Lentine KL, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation.* 2019;139:e840–78, <http://dx.doi.org/10.1161/CIR.0000000000000664>.
- Rondeau E, Luyckx VA, Anders HJ, Eckardt KU, Florquin S, Marti HP, et al. Challenges and opportunities for nephrology in Western Europe. *Kidney Int.* 2019;95:1037–40, <http://dx.doi.org/10.1016/j.kint.2018.09.028>.
- Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts). Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J.* 2016;37:2315–81, <http://dx.doi.org/10.1093/eurheartj/ehw106>. Epub 2016 May 23.
- Major RW, Cheng MRI, Grant RA, Shantikumar S, Xu G, Oozeerally I, et al. Cardiovascular disease risk factors in chronic kidney disease: a systematic review and meta-analysis. *PLoS ONE.* 2018;13:e0192895, <http://dx.doi.org/10.1371/journal.pone.0192895>, eCollection 2018.
- Gorostidi M, Sánchez-Martínez M, Ruilope LM, Graciani A, de la Cruz JJ, Santamaría R, et al. Chronic kidney disease in Spain: prevalence and impact of accumulation of cardiovascular risk factors. *Nefrología.* 2018;38:606–15, <http://dx.doi.org/10.1016/j.nefro.2018.04.004>.
- McClellan WM, Langston RD, Presley R. Medicare patients with cardiovascular disease have a high prevalence of chronic kidney disease and a high rate of progression to end-stage renal disease. *J Am Soc Nephrol.* 2004;15:1912–9, <http://dx.doi.org/10.1097/O1.asn.0000129982.10611.4c>.
- George LK, Koshy SKG, Molnar MZ, Thomas F, Lu JL, Kalantar-Zadeh K, et al. Heart failure increases the risk of adverse renal outcomes in patients with normal kidney function. *Circ Heart Fail.* 2017;10:e003825, <http://dx.doi.org/10.1161/CIRCHEARTFAILURE.116.003825>.
- Couser WG, Remuzzi G, Mendis S, Tonelli M. The contribution of chronic kidney disease to the global burden of major noncommunicable diseases. *Kidney Int.* 2011;80:1258–70, <http://dx.doi.org/10.1038/ki.2011.368>. PMID: 21993585.
- GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet.* 2020;395:709–33, [http://dx.doi.org/10.1016/S0140-6736\(20\)30045-3](http://dx.doi.org/10.1016/S0140-6736(20)30045-3).
- Global Burden of Disease 2013 GFR Collaborators, CKD Prognosis Consortium, and Global Burden of Disease Genitourinary Expert Group. Global cardiovascular and renal outcomes of reduced GFR. *J Am Soc Nephrol.* 2017;28:2167–79, <http://dx.doi.org/10.1681/ASN.2016050562>.
- Paneni F, Diaz Cañestro C, Libby P, Lüscher TF, Camici GG. The aging cardiovascular system: understanding it at the cellular and clinical levels. *J Am Coll Cardiol.* 2017;69:1952–67, <http://dx.doi.org/10.1016/j.jacc.2017.01.064>.
- Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis.* 1998;32 Suppl. 3:S112–9, <http://dx.doi.org/10.1053/ajkd.1998.v32.pm9820470>.
- Saran R, Robinson B, Abbott KC, Agodoa LY, Albertus P, Ayanian J, et al. US renal data system 2016 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2017;69 Suppl. 1:A7–8, <http://dx.doi.org/10.1053/j.ajkd.2016.12.004>.
- Levey AS, Atkins R, Coresh J, Cohen EP, Collins AJ, Eckardt KU, et al. Chronic kidney disease as a global public health problem: approaches and initiatives—a position statement from Kidney Disease Improving Global Outcomes. *Kidney Int.* 2007;72:247–59, <http://dx.doi.org/10.1038/sj.ki.5002343>.
- Nichols GA, Ustyugova A, Déruaz-Luyet A, O’Keeffe-Rosetti M, Brodovicz KG. Health care costs by type of expenditure across eGFR stages among patients with and without diabetes, cardiovascular disease, and heart failure. *J Am Soc Nephrol.* 2020;31:1594–601, <http://dx.doi.org/10.1681/ASN.2019121308>.
- Schrauben SJ, Chen H-Y, Lin E, Jepson C, Yang W, Scialla JJ, et al. Hospitalizations among adults with chronic kidney disease in the United States: a cohort study. *PLoS Med.* 2020;17:e1003470, <http://dx.doi.org/10.1371/journal.pmed.1003470>.
- Kent S, Schlackow I, Lozano-Kühne J, Reith C, Emberson J, Haynes R, et al. What is the impact of chronic kidney disease stage and cardiovascular disease on the annual cost of hospital care in moderate-to-severe kidney disease? *BMC Nephrol.* 2015;16:65, <http://dx.doi.org/10.1186/s12882-015-0054-0>.
- Sicras Mainar A, Navarro Artieda R, Ibáñez Nolla J. Economic impact of heart failure according to the effects of kidney failure. *Rev Esp Cardiol.* 2016;68:39–46, <http://dx.doi.org/10.1016/j.rec.2014.02.021>.
- Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population

- with chronic kidney disease in a large managed care organization. *Arch Intern Med.* 2004;164:659–63, <http://dx.doi.org/10.1001/archinte.164.6.659>.
24. Valdivielso JM, Rodríguez-Puyol D, Pascual J, Barrios C, Bermúdez-López M, Sánchez-Niño MD, et al. Atherosclerosis in chronic kidney disease: more, less, or just different? *Arterioscler Thromb Vasc Biol.* 2019;39:1938–66, <http://dx.doi.org/10.1161/ATVBAHA.119.312705>.
 25. Betriú A, Martínez-Alonso M, Arcidiacono MV, Cannata-Andía J, Pascual J, Valdivielso JM, et al. Investigators from the NEFRONA Study Prevalence of subclinical atheromatosis and associated risk factors in chronic kidney disease: the NEFRONA study. *Nephrol Dial Transplant.* 2014;29:1415–22, <http://dx.doi.org/10.1093/ndt/gfu038>.
 26. House AA, Wanner C, Sarnak MJ, Pina IL, McIntyre CW, Komenda P, et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2019;95:1304–17, <http://dx.doi.org/10.1016/j.kint.2019.02.022>.
 27. House AA. Cardio-renal syndrome type 4: epidemiology, pathophysiology and treatment. *Semin Nephrol.* 2012;32:40–8, <http://dx.doi.org/10.1016/j.semnephrol.2011.11.006>.
 28. Takahama H, Kitakaze M. Pathophysiology of cardiorenal syndrome in patients with heart failure: potential therapeutic targets. *Am J Physiol Heart Circ Physiol.* 2017;313:H715–21, <http://dx.doi.org/10.1152/ajpheart.00215.2017>.
 29. Liu S. Heart-kidney interactions: mechanistic insights from animal models. *Am J Physiol Renal Physiol.* 2019:F974–85, <http://dx.doi.org/10.1152/ajprenal.00624.2017>.
 30. Getz GS, Reardon CA. Animal models of atherosclerosis. *Arterioscler Thromb Vasc Biol.* 2012;32:1104–15, <http://dx.doi.org/10.1161/ATVBAHA.111.237693>.
 31. Wang X, Shapiro JJ. Evolving concepts in the pathogenesis of uraemic cardiomyopathy. *Nat Rev Nephrol.* 2019;15:159–75, <http://dx.doi.org/10.1038/s41581-018-0101-8>.
 32. Briet M, Burns KD. Chronic kidney disease and vascular remodelling: molecular mechanisms and clinical implications. *Clin Sci (Lond).* 2012;123:399–416, <http://dx.doi.org/10.1042/CS20120074>.
 33. Savira F, Magaye R, Liew D, Reid C, Kelly DJ, Kompa AR, et al. Cardiorenal syndrome: multi-organ dysfunction involving the heart, kidney and vasculature. *Br J Pharmacol.* 2020;177:2906–22, <http://dx.doi.org/10.1111/bph.15065>.
 34. Menon V, Gul A, Sarnak MJ. Cardiovascular risk factors in chronic kidney disease. *Kidney Int.* 2005;68:1413–8, <http://dx.doi.org/10.1111/j.1523-1755.2005.00551.x>.
 35. Wanner C, Amann K, Shoji T. The heart and vascular system in dialysis. *Lancet.* 2016;388:276–84, [http://dx.doi.org/10.1016/S0140-6736\(16\)30508-6](http://dx.doi.org/10.1016/S0140-6736(16)30508-6).
 36. Sarnak MJ, Amann K, Bangalore S, Cavalcante JL, Charytan DM, Craig JC, et al. Chronic kidney disease and coronary artery disease: JACC state-of-the-art review. *J Am Coll Cardiol.* 2019;74:1823–38, <http://dx.doi.org/10.1016/j.jacc.2019.08.1017>.
 37. Querfeld U, Mak RH, Pries AR. Microvascular disease in chronic kidney disease: the base of the iceberg in cardiovascular comorbidity. *Clin Sci (Lond).* 2020;134:1333–56, <http://dx.doi.org/10.1042/CS20200279>.
 38. Amann K, Törnig J, Buzello M, Kuhlmann A, Gross ML, Adamczak M, et al. Effect of antioxidant therapy with dl-alpha-tocopherol on cardiovascular structure in experimental renal failure. *Kidney Int.* 2002;62:877–84, <http://dx.doi.org/10.1046/j.1523-1755.2002.00518.x>.
 39. Charytan DM, Padera R, Helfand AM, Zeisberg M, Xu X, Liu X, et al. Increased concentration of circulating angiogenesis and nitric oxide inhibitors induces endothelial to mesenchymal transition and myocardial fibrosis in patients with chronic kidney disease. *Int J Cardiol.* 2014;176:99–109, <http://dx.doi.org/10.1016/j.ijcard.2014.06.062>.
 40. Prommer HU, Maurer J, von Websky K, Freise C, Sommer K, Nasser H, et al. Chronic kidney disease induces a systemic microangiopathy, tissue hypoxia and dysfunctional angiogenesis. *Sci Rep.* 2018;8:5317, <http://dx.doi.org/10.1038/s41598-018-23663-1>.
 41. Kaesler N, Babler A, Floege J, Kramann R. Cardiac remodeling in chronic kidney disease. *Toxins (Basel).* 2020;12:161, <http://dx.doi.org/10.3390/toxins12030161>.
 42. Izumaru K, Hata J, Nakano T, Nakashima Y, Nagata M, Fukuhara M, et al. Reduced estimated GFR and cardiac remodeling: a population-based autopsy study. *Am J Kidney Dis.* 2019;74:373–81, <http://dx.doi.org/10.1053/j.ajkd.2019.02.013>.
 43. Hulshoff MS, Rath S, Xu X, Zeisberg M, Zeisberg EM. Causal connections from chronic kidney disease to cardiac fibrosis. *Semin Nephrol.* 2018;38:629–36, <http://dx.doi.org/10.1016/j.semnephrol.2018.08.007>.
 44. Zannad P, Rossignol P. Cardiorenal syndrome revisited. *Circulation.* 2018;138:929–44, <http://dx.doi.org/10.1161/CIRCULATIONAHA.117.028814>.
 45. Romero-González G, González A, López B, Ravassa S, Díez J. Heart failure in chronic kidney disease: the emerging role of myocardial fibrosis. *Nephrol Dial Transplant.* 2020;gfaa284(December), <http://dx.doi.org/10.1093/ndt/gfaa284>.
 46. Bagshaw SM, Hoste EA, Braam B, Briguori C, Kellum JA, McCullough PA, et al. Cardiorenal syndrome type 3: pathophysiologic and epidemiologic considerations. *Contrib Nephrol.* 2013;182:137–57, <http://dx.doi.org/10.1159/000349971>.
 47. Odutayo A, Wong CX, Farkouh M, Altman DG, Hopewell S, Emdin CA, et al. AKI and long-term risk for cardiovascular events and mortality. *J Am Soc Nephrol.* 2017;28:377–87, <http://dx.doi.org/10.1681/ASN.2016010105>.
 48. Legrand N, Rossignol P. Cardiovascular consequences of acute kidney injury. *N Engl J Med.* 2020;382:2238–47, <http://dx.doi.org/10.1056/NEJMra1916393>.
 49. Sosnov J, Lessard D, Goldberg RJ, Yarzebski J, Gore JM. Differential symptoms of acute myocardial infarction in patients with kidney disease: a community-wide perspective. *Am J Kidney Dis.* 2006;47:378–84, <http://dx.doi.org/10.1053/j.ajkd.2005.11.017>.
 50. Karthikeyan V, Ananthasubramaniam K. Coronary risk assessment and management options in chronic kidney disease patients prior to kidney transplantation. *Curr Cardiol Rev.* 2009;5:177–86, <http://dx.doi.org/10.2174/157340309788970342>.
 51. Schmidt A, Stefenelli T, Schuster E, Mayer G. Informational contribution of noninvasive screening tests for coronary artery disease in patients on chronic renal replacement therapy. *Am J Kidney Dis.* 2001;37:56–63, <http://dx.doi.org/10.1053/ajkd.2001.20584>.
 52. Freda BJ, Tang WH, Van Lente F, Peacock WF, Francis GS. Cardiac troponins in renal insufficiency: review and clinical implications. *J Am Coll Cardiol.* 2002;40:2065–71, [http://dx.doi.org/10.1016/s0735-1097\(02\)02608-6](http://dx.doi.org/10.1016/s0735-1097(02)02608-6).
 53. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2016;37:2129–200, <http://dx.doi.org/10.1093/eurheartj/ehw128>.
 54. Di Lullo L, Gorini A, Russo D, Santoboni A, Ronco C. Left ventricular hypertrophy in chronic kidney disease patients: from pathophysiology to treatment. *Cardiorenal Med.* 2015;5:254–66, <http://dx.doi.org/10.1159/000435838>.

55. Maisel A, Mueller C, Adams K Jr, Anker SD, Aspromonte N, Cleland JG, et al. State of the art: using natriuretic peptide levels in clinical practice. *Eur J Heart Fail.* 2008;10:824–39, <http://dx.doi.org/10.1016/j.ejheart.2008.07.014>.
56. Maini R, Wong DB, Addison D, Chiang E, Weisbord SD, Jneid H. Persistent underrepresentation of kidney disease in randomized, controlled trials of cardiovascular disease in the contemporary era. *J Am Soc Nephrol.* 2018;29:2782–6, <http://dx.doi.org/10.1681/ASN.2018070674>.
57. Carpenter MA, Weir MR, Adey DB, House AA, Bostom AG, Kusek JW. Inadequacy of cardiovascular risk factor management in chronic kidney transplantation – evidence from the FAVORIT study. *Clin Transplant.* 2012;26:E438–46, <http://dx.doi.org/10.1111/j.1399-0012.2012.01676.x>.
58. Zannad F, Rossignol P. Cardiovascular outcome trials in patients with advanced kidney disease: time for action. *Circulation.* 2017;135:1769–71, <http://dx.doi.org/10.1161/CIRCULATIONAHA.117.027338>.
59. Konstantinidis I, Nadkarni GN, Yacoub R, Saha A, Simoes P, Parikh CR, et al. Representation of patients with kidney disease in trials of cardiovascular interventions: an updated systematic review. *JAMA Intern Med.* 2016;176:121–4, <http://dx.doi.org/10.1001/jamainternmed.2015.6102>.
60. Rossignol P, Agarwal R, Canaud B, Charney A, Chatellier G, Craig CG, et al. Cardiovascular outcome trials in patients with chronic kidney disease: challenges associated with selection of patients and endpoints. *Eur Heart J.* 2019;40:880–6, <http://dx.doi.org/10.1093/eurheartj/ehx209>.
61. O'Lone E, Viecelli AK, Craig JC, Tong A, Sautenet B, Roy D, et al. Cardiovascular outcomes reported in hemodialysis trials. *J Am Coll Cardiol.* 2018;71:2802–10, <http://dx.doi.org/10.1016/j.jacc.2018.04.012>.
62. Romero-González G, Ravassa S, González O, Lorenzo I, Rojas MA, García-Trigo I, et al. Burden and challenges of heart failure in patients with chronic kidney disease. A call to action. *Nefrologia.* 2020;40:223–36, <http://dx.doi.org/10.1016/j.nefro.2019.10.005>.
63. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int.* 1995;47:186–92, <http://dx.doi.org/10.1038/ki.1995.22>.
64. Cheung AK, Sarnak MJ, Yan G, Berkoben M, Heyka R, Kaufman A, et al. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO study. *Kidney Int.* 2004;65:2380–9, <http://dx.doi.org/10.1111/j.1523-1755.2004.00657.x>.
65. Lozier MR, Sanchez AM, Lee JJ, Tamariz LJ, Valle GA. Comparison of cardiovascular outcomes by dialysis modality: a systematic review and meta-analysis. *Perit Dial Int.* 2019;39:306–14, <http://dx.doi.org/10.3747/pdi.2018.00227>.
66. Ng CH, Ong ZH, Sran HK, Wee TB. Comparison of cardiovascular mortality in hemodialysis versus peritoneal dialysis. *Int Urol Nephrol.* 2020;(October), <http://dx.doi.org/10.1007/s11255-020-02683-9>.
67. Arend SM, Mallat MJ, Westendorp RJ, van der Woude FJ, van Es LA. Patient survival after renal transplantation; more than 25 years follow-up. *Nephrol Dial Transplant.* 1997;12:1672–9, <http://dx.doi.org/10.1093/ndt/12.8.1672>.
68. Ojo AO, Hanson JA, Wolfe RA, Leichtman AB, Agodoa LY, Port FK. Long-term survival in renal transplant recipients with graft function. *Kidney Int.* 2000;57:307–13, <http://dx.doi.org/10.1046/j.1523-1755.2000.00816.x>.
69. Rangaswami J, Mathew RO, Parasuraman R, Tantisattamo E, Lubetzky M, Rao S, et al. Cardiovascular disease in the kidney transplant recipient: epidemiology, diagnosis and management strategies. *Nephrol Dial Transplant.* 2019;34:760–73, <http://dx.doi.org/10.1093/ndt/gfz053>.
70. Shaikh A, Patel N, Nair D, Campbell KN. Current paradigms and emerging opportunities in nephrology training. *Adv Chronic Kidney Dis.* 2020;27:291–6, <http://dx.doi.org/10.1053/j.ackd.2020.05.011>.
71. Rope RW, Pivert KA, Parker MG, Sozio SM, Merell SB. Education in nephrology fellowship: a survey-based needs assessment. *J Am Soc Nephrol.* 2017;28:1983–90, <http://dx.doi.org/10.1681/ASN.2016101061>.
72. Tonelli M, Wiebe N, Manns RJ, Klarenbach SW, James MT, Ravani P, et al. Comparison of the complexity of patients seen by different medical subspecialists in a universal health care system. *JAMA Netw Open.* 2018;1:e184852, <http://dx.doi.org/10.1001/jamanetworkopen.2018.4852>.
73. Sachdeva M, Shah AD, Singh HK, Malieckal DA, Rangaswami J, Jhaveri KD. Opportunities for subspecialization in nephrology. *Adv Chronic Kidney Dis.* 2020;27:320–7, <http://dx.doi.org/10.1053/j.ackd.2020.05.002>.
74. Kazory A, McCullough PA, Rangaswami J, Ronco C. Cardioneurology: proposal for a futuristic educational approach to a contemporary need. *Cardiorenal Med.* 2018;8:296–301, <http://dx.doi.org/10.1159/000490744>.
75. Rangaswami J, Mathew RO, McCullough PA. Resuscitation for the specialty of nephrology: is cardioneurology the answer? *Kidney Int.* 2018;93:25–6, <http://dx.doi.org/10.1016/j.kint.2017.10.002>.
76. Covic A, Fliser D, Goldsmith D, Lindholm B, London G, Martinez A, et al., Promoting scientific collaboration and education in cardiovascular–renal medicine: EURECAM: An ERA-EDTA-based working group. *NDT Plus.* 2009;2:522–5, <http://dx.doi.org/10.1093/ndtplus/sfp121>.
77. Cardio Renal Society of America. 2010. <https://www.cardiorenalsociety.org>.
78. Ronco C, Ronco F, McCullough PA. A call to action to develop integrated curricula in cardiorenal medicine. *Blood Purif.* 2017;44:251–9, <http://dx.doi.org/10.1159/000480318>.
79. Koratala A, Segal MS, Kazory A. Integrating point-of-care ultrasonography into nephrology fellowship training: a model curriculum. *Am J Kidney Dis.* 2019;74:1–5, <http://dx.doi.org/10.1053/j.ajkd.2019.02.002>.
80. Chawla LS, Herzog CA, Costanzo MR, Tumlin J, Kellum JA, McCullough PA, et al. Proposal for a functional classification system of heart failure in patients with end-stage renal disease: proceedings of the acute dialysis quality initiative (ADQI) XI workgroup. *J Am Coll Cardiol.* 2014;63:1246–52, <http://dx.doi.org/10.1016/j.jacc.2014.01.020>.
81. Mullens W, Damman K, Testani JM, Martens P, Mueller C, Lassus J, et al. Evaluation of kidney function throughout the heart failure trajectory – a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail.* 2020;22:584–603, <http://dx.doi.org/10.1002/ejhf.1697>.
82. Verbrugge FH, Guazzi M, Testani JM, Borlaug BA. Altered hemodynamics and end-organ damage in heart failure: impact on the lung and kidney. *Circulation.* 2020;142:998–1012, <http://dx.doi.org/10.1161/CIRCULATIONAHA.119.045409>.
83. Virzi GM, Clementi A, Battaglia GG, Ronco C. Multi-omics approach: new potential key mechanisms implicated in cardiorenal syndromes. *Cardiorenal Med.* 2019;9:201–11, <http://dx.doi.org/10.1159/000497748>.
84. Kanbay M, Yerlikaya A, Sag AA, Ortiz A, Kuwabara M, Covic A, et al. A journey from microenvironment to macroenvironment: the role of metaflammation and epigenetic changes in cardiorenal disease. *Clin Kidney J.* 2019;12:861–70, <http://dx.doi.org/10.1093/ckj/sfz106>.
85. Baigent C, Herrington WG, Coresh J, Landray MJ, Levin A, Perkovic V, et al. Challenges in conducting clinical trials in

- nephrology: conclusions from a Kidney Disease-Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2017;92:297–305, <http://dx.doi.org/10.1016/j.kint.2017.04.019>.
86. Rangaswami J, Tuttle K, Vaduganathan M. Cardio-renal-metabolic care models toward achieving effective interdisciplinary care. *Circ Cardiovasc Qual Outcomes.* 2020;13:e007264, <http://dx.doi.org/10.1161/CIRCOUTCOMES.120.007264>.
87. Agrawal V, Agarwal M, Ghosh AK, Barnes MA, McCullough PA. Identification and management of chronic kidney disease complications by internal medicine residents: a national survey. *Am J Ther.* 2011;18:e40–7, <http://dx.doi.org/10.1097/MJT.0b013e3181bbf6fc>.
88. Agarwal V, Ghosh AK, Barnes MA, McCullough PA. Perception of indications for nephrology referral among internal medicine residents: a national online survey. *Clin J Am Soc Nephrol.* 2009;4:323–8, <http://dx.doi.org/10.2215/CJN.03510708>.
89. Agarwal V, Ghosh AK, Barnes MA, McCullough PA. Awareness and knowledge of clinical practice guidelines for CKD among internal medicine residents: a national online survey. *Am J Kidney Dis.* 2008;52:1061–9, <http://dx.doi.org/10.1053/j.ajkd.2008.06.022>.
90. Boorsma EM, Ter Maaten JM, Damman K, Dinh W, Gustafsson F, Goldsmith S, et al. Congestion in heart failure: a contemporary look at physiology, diagnosis and treatment. *Nat Rev Cardiol.* 2020;17:641–55, <http://dx.doi.org/10.1038/s41569-020-0379-7>.
91. de Ruiter A, Bello A, Braam B. Fluid management in chronic kidney disease: what is too much, what is the distribution, and how to manage fluid overload in patients with chronic kidney disease? *Curr Opin Nephrol Hypertens.* 2020;29:572–80, <http://dx.doi.org/10.1097/MNH.0000000000000640>.
92. Zelniker TA, Braunwald E. Mechanisms of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;75:422–34, <http://dx.doi.org/10.1016/j.jacc.2019.11.031>.
93. Zelniker TA, Braunwald E. Clinical benefit of cardiorenal effects of sodium-glucose cotransporter 2 inhibitors: JACC state-of-the-art review. *J Am Coll Cardiol.* 2020;75:435–47, <http://dx.doi.org/10.1016/j.jacc.2019.11.036>.
94. Sankaranarayanan R, Douglas H, Wong C. Cardio-nephrology MDT meetings play an important role in the management of cardiorenal syndrome. *Br J Cardiol.* 2020;27:80–2, <http://dx.doi.org/10.5837/bjc.2020026>.
95. Bright R. Cases and observations illustrative of renal disease accompanied by the secretion of albuminous urine. *Guys Hospital Rep.* 1836:338.