



EDITORIAL COMMENT

The need for a cardioneurology subspecialty

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ABSTRACT

Chronic kidney disease (CKD) has structural and functional repercussions for the cardiovascular system that facilitate the development of cardiovascular disease (CVD). In fact, cardiovascular complications are frequent in the CKD population and thus cause a great clinical, public health and economic burden. Despite this challenge, the prevention and management of cardiovascular complications is one among several aspects of CKD that meets the criteria of an unmet medical need. This probably has to do with the misperception by the nephrologist of the global relevance of CVD in the CKD patient which, in turn, may be due to insufficient cardiovascular training during nephrology specialization. Therefore a change in approach is necessary to understand CKD as a disease in which the manifestations and complications related to CVD become so frequent and important that they require dedicated multidisciplinary clinical management. From this perspective, it makes sense to consider training in the subspecialty of cardioneurology to provide adequate cardiovascular care for CKD patients by the nephrologist. In addition, the cardioneurology subspecialist would be better able to interact with other specialists in multidisciplinary care settings created to achieve a deeper understanding and more effective clinical handling of the interactions between CKD and CVD.

Keywords: cardioneurology, cardiovascular disease, chronic kidney disease

As recommended 20 years ago by the American Heart Association (AHA) [1] and recognized in the current European guidelines on cardiovascular disease (CVD) prevention [2], people with chronic kidney disease (CKD) should be considered in the highest-risk group for the prevention, detection and treatment of CVD. However, management of CVD in CKD patients is still an unmet medical need [3, 4]. Among the various reasons that may explain this inconsistency is the lack of global perception of CVD in the CKD patient by the nephrologist. In fact, although CKD is now viewed as a systemic and multiorgan disease [5, 6], its cardiovascular aspects do not receive the attention that corresponds to their burden of disease and the

nephrologist's intervention is limited to cardiovascular risk reduction (e.g. blood lipids and blood pressure management). Therefore a new approach towards CKD as an initially renal disease that evolves to become predominantly a CVD is required. And, as a consequence of this, it is also necessary to rethink the training of specialists in nephrology to give more relevance to specific knowledge and practice in cardiovascular medicine [7, 8].

The aim of this editorial is to emphasize the most relevant epidemiological, pathophysiological and clinical evidence that supports the view of CVD in CKD patients as a challenge with implications for the nephrologist, in the sense that its proper

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management should be the subject of the subspecialty of cardioneurology integrated in multidisciplinary cardiorenal teams.

THE CHALLENGE OF CVD IN CKD PATIENTS

CVD enhances the medical, health and economic burden of CKD

As glomerular filtration rate (GFR) declines and/or the urinary loss of albumin increases and CKD progresses, so does the incidence and prevalence of CVD and its complications [9, 10] (Figure 1). Systematic analyses of the world burden of CKD reveal that it has a major effect on global health, both as a direct cause of global morbidity and mortality and as an important risk factor for CVD-mediated morbidity and mortality [11, 12]. In this regard, it is increasingly apparent that individuals with CKD are more likely to die of CVD than to develop kidney failure [11] or to die from kidney failure [11]. In addition, CVD is less well tolerated in patients with CKD than in patients without CKD. For instance, heart failure (HF) hospitalizations and cardiovascular mortality are higher in HF patients with CKD than in patients without CKD [13]. On the other hand, patients with CKD are at high risk for acute kidney injury (AKI) and accumulating evidence supports the notion that cardiovascular damage due to AKI increases both short-term and long-term cardiovascular risk in CKD [14].

Data from the US Renal Data System show the enhancer effect of cardiovascular complications on the economic burden of CKD, thus aggravating the tremendous impact of CKD on healthcare budgets [15]. In particular, the high rates of hospitalization due to cardiovascular complications increase the direct costs, thus increasing the economic burden of CKD from its early stages [16].

CVD is facilitated by the impact of CKD on blood vessels and the heart

CKD facilitates the development of systemic macro- and microvascular damage, as well as cardiac remodelling, through multiple pathways. Indeed, several studies have shown associations between CKD and atherosclerosis-related clinical complications [17] and subclinical atherosclerosis prevalence and progression

[18]. The prevalence of calcifications in the intima and media of the arterial wall is increased in CKD patients, likely as a result of complex interactions between atherosclerotic changes in the vascular bed, mineral metabolites and other uremic factors [19], and is associated with adverse cardiovascular outcomes. For instance, coronary calcification is associated with myocardial infarction, HF and all-cause mortality in CKD patients [20]. Finally, studies evaluating the structure and function of the microcirculation in humans [21] and animals [22] with CKD reported that capillary rarefaction resulting in decreased microvascular density is a constant finding in different organs, including the heart.

In accordance with the US Renal Data System, the incidence and prevalence of non-cardiac diseases different from atherosclerotic ischaemic heart disease (e.g., cardiomyopathies and valvular diseases) is higher in CKD patients than in non-CKD patients, irrespective of the influence of non-kidney-related potential confounding factors [15]. Of note, cardiac diseases in CKD patients are characterized by progression to HF [23]. Recent experimental and clinical evidence suggests that fibrosis of the myocardium may facilitate the development of HF in CKD patients, as several mechanisms are operative along the different stages of CKD that may converge to alter fibroblasts and collagen turnover in the heart, thus resulting in myocardial remodelling that alters both diastolic and systolic function [24].

Clinical management of CVD is suboptimal in patients with later stages of CKD

The high incidence of cardiovascular events in patients with kidney failure and patients on kidney replacement therapy (KRT) (Figure 1) could also be related to the fact that these populations are less likely to be diagnosed with CVD and to receive appropriate cardiovascular protective treatments. Indeed, CVD is usually underdiagnosed in these patients, as cardiovascular protocols are underrepresented in the general screening and diagnostic procedures for CKD [25]. In addition, the sensitivities and specificities of both the clinical manifestations and imaging and biochemical cardiovascular tests are questionable in patients with later stages of CKD, as it is the case for the diagnosis of HF [26]. On the other hand, patients with kidney failure, and particularly patients on KRT, are usually excluded from cardiovascular clinical trials conducted in the general population

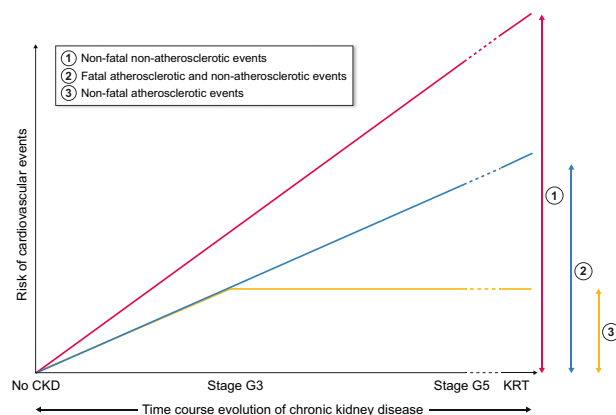


FIGURE 1: Conceptual arbitrary representation of the risk of cardiovascular events along the progression of CKD (independent of the time that a patient spends in each stage of the Kidney Disease: Improving Global Outcomes classification) and during KRT (independent of the modality of therapy). Partially adapted from Wanner C, Amman K, Shoji T. *Lancet* 2016; 388: 276–284.

or in at-risk populations [27, 28]. Thus, as evidence-based management of CVD is lacking, the efficacy and safety of cardiovascular therapies in these patients are uncertain [29]. The underuse of diverse therapeutic alternatives with cardiovascular impact (within a wider attitude of therapeutic nihilism) has repeatedly been associated with adverse outcomes in patients with kidney failure [30]. However, this is also observed earlier in the course of CKD, especially for older individuals [31].

An additional aspect to consider in the challenging management of CVD in patients on KRT is the detrimental cardiovascular effect of dialysis, specially haemodialysis [15], and to a lesser extent of kidney transplantation [32], which would explain the high cardiovascular risk of patients on KRT (Figure 1). Systemic circulatory 'stress' resulting from haemodialysis and acting as a CVD amplifier [33] and the cardiometabolic effects of immunosuppressive therapies in kidney transplanted patients [34] may account for additional cardiovascular risk in these populations. In this regard, the European Society of Cardiology Systemic Coronary Risk Evaluation (ESC-SCORE), Framingham Heart Study SCORE (Framingham-SCORE), Prospective Cardiovascular Munster Study SCORE (PROCAM-SCORE) or Assessing cardiovascular risk using Scottish Intercollegiate Guidelines Network SCORE (ASSIGN-SCORE) algorithms can predict cardiovascular risk after kidney transplantation at the time of entering the waiting list and may be used to guide therapy [35].

IMPLICATIONS OF THE CHALLENGE FOR THE NEPHROLOGIST

The relevance of CVD in patients with CKD is a real challenge for the nephrologist that can only be faced through a demanding training plan and an appropriate clinical environment. The first must be the objective of the subspecialty of cardioneurology and the second must be the result of collaboration with other specialists in cardiorenal care teams.

Current general nephrology training does not seem to be sufficient for covering the broad and rapidly evolving field of cardiovascular medicine and thus a specific training programme to enhance the knowledge and clinical capability of the nephrologist in CVD is needed [7]. A variety of topics related to acute and chronic clinical cardiac and vascular problems present in CKD patients must be considered for inclusion in the programme [8]. The cardioneurology training programme may be offered both as a cumulative period during the nephrology specialization time and as a subspecialty track to allow senior nephrologists the opportunity to train and develop proficiency in cardiovascular medicine [36].

The subspecialty of cardioneurology offers the nephrologist the opportunity to integrate into dedicated cardiorenal interdisciplinary teams jointly involved in early identification and appropriate management of patients with the dual burden of CKD and CVD across the inpatient and outpatient settings [37]. These cardiorenal multidisciplinary teams represent an optimal setting for 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 on KRT [38].

Finally, the implementation of the subspecialty of cardioneurology in daily clinical practice can be an opportunity contributing to broadening the academic and scientific horizons of nephrology in collaboration with other specialties, as well as stimulating clinical trials research, an area where nephrology has fallen greatly behind other specialties [39]. In

addition, the subspecialty of cardioneurology may facilitate the recruitment of the new generations of nephrologists [40, 41], thus helping to attract trainee physicians [42].

In summary, it is necessary to recognize that the development of CVD in patients with CKD has such important clinical and health consequences that it challenges the capacities of current nephrologists to deal with them. Therefore, the time has come to encourage and support the training of subspecialists in cardioneurology with the clear objective of minimizing the burden that CVD places on CKD. In this framework, the authors of this article call on the members of the Union of European Medical Specialties Renal Section and the European Renal Association-European Dialysis and Transplant Association responsible for the European Certificate in Nephrology (ECN) [43] to consider knowledge and handling of cardiorenal issues among the most demanding requirements of the ECN.

CONFLICT OF INTEREST STATEMENT

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