The Cardiorenal Syndrome: What the Cardiologist Needs to Know

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Key Words

Cardiorenal syndrome · Chronic kidney disease · Cardiovascular disease · Renal dysfunction · Heart failure

Abstract

Interactions between the heart and the kidneys are increasingly acknowledged among both cardiologists and nephrologists. The term cardiorenal syndrome now applies to the bidirectional nature of how disease in one organ system affects the function of the other organ system. Cardiovascular disease is a major threat to patients with chronic kidney disease, while renal dysfunction is prevalent in patients with cardiac disease and is a significant predictor of prognosis in cardiac patients. Still, renal patients with cardiac disease have largely been excluded from the clinical trials that have been the basis of modern cardiologic treatment. In this review, the current understanding of the pathophysiological mechanisms involved in the cardiorenal syndrome and potential therapeutic implications will be summarized from a nephrologist's point of view. Probably, fragile cardiorenal patients will benefit from an enhanced collaboration between cardiologists and nephrologists to secure the best treatment given under safe conditions.

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Introduction

Interactions between the heart and the kidneys have been known and discussed for decades. Patients with end-stage renal disease (ESRD) treated with dialysis have a more than 10-fold increased risk of cardiovascular death than do age- and gender-matched controls in the general population [1]. Likewise, acquired renal dysfunction in heart failure (HF) patients has been recognized as a poor prognostic factor among cardiologists for many years. However, further progress in the characterization of cardiorenal associations was for a long time limited by the lack of accepted definitions to systematically approach the topic. The introduction of the chronic kidney disease (CKD) classification made it possible to stratify kidney disease more easily and accurately [2]. The classification was based on the MDRD formula for estimation of the glomerular filtration rate (GFR) [3] and has been important for the assessment of the prevalence and prognostic impact of reduced GFR in various clinical conditions. The definition of cardiorenal syndrome (CRS) by Ronco et al. [4] enhanced the awareness of the bidirectional interactions between kidney and heart diseases. The need for multidisciplinary collaboration has become more apparent when dealing with patients with combined kidney

and heart disease. In this review the current knowledge of cardiorenal associations and pathophysiology will be summarized to alert cardiologists of important clinical aspects when treating cardiac patients with accompanying renal disease.

CRS Definition and Epidemiology

The current definition of the CRS includes the bidirectional cross talk between the kidneys and the cardiovascular system. Primary disorders in one organ system often result in secondary dysfunction or injury in the other [4]. The syndrome is defined in an academic manner to understand the pathophysiology of secondary organ dysfunction when primary organ damage occurs. While the definition is less applicable in clinical patient care, it has been important in understanding the interaction between the organs and in guiding further research on mechanisms and treatment principles. The five subtypes of the syndrome will briefly be described with reference to the epidemiology, thereby outlining the magnitude of the problem and why cardiologists should be aware of these patients.

CRS Type 1: Acute CRS

Type 1 CRS is characterized by a rapid worsening of cardiac function leading to acute kidney injury (AKI). Type 1 CRS is a common occurrence as hospitalization for de novo or decompensated HF and other acute cardiovascular events accounts for a substantial proportion of hospitalized patients. AKI occurs in about 25% of hospitalized patients with HF [5, 6], and worsening renal function is identified as a strong independent predictor of in-hospital as well as 1-year mortality, in addition to being a predictor of increased length of hospital stay [5]. AKI is not just a marker of illness severity but also represents a causative factor for accelerated cardiovascular injury through the activation of neurohormonal, immunological, and inflammatory pathways [4, 7, 8].

CRS Type 2: Chronic CRS

Type 2 CRS is characterized by chronic abnormalities in cardiac function (e.g. chronic congestive HF) causing progressive CKD. The prevalence of renal dysfunction in chronic HF is high; close to 50% of patients with chronic HF appear to have $\text{GFR} < 60 \text{ ml/min/1.73 m}^2$ [9–13]. Even

a slight decrease in GFR is a strong independent predictor of all-cause mortality [9–11, 13]. In addition, worsening renal function during follow-up is a strong independent predictor of prognosis [5]. Thus, an effort to preserve renal function seems of utmost importance in patients with chronic HF.

CRS Type 3: Acute Renocardiac Syndrome

Type 3 CRS is characterized by a primary worsening of renal function (e.g. ischemia, hypoperfusion, glomerulonephritis) leading to acute cardiac dysfunction (e.g. HF, arrhythmia, ischemia). AKI defined by RIFLE criteria [14] appears to affect close to 20% of hospitalized patients [15], and in intensive care units more than 35% of patients have been observed to have AKI [16]. AKI is identified as a strong predictor of hospital mortality. Fluid overload, electrolyte disturbances, accumulation of myocardial depressant factors, neurohormonal activation, and systemic inflammation may affect cardiac function [4].

CRS Type 4: Chronic Renocardiac Syndrome

Type 4 CRS is characterized by primary CKD contributing to decreased cardiac function and an increased risk of cardiovascular events. CKD is prevalent in the general population, affecting more than 10% of the adult population in Western countries [17]. Individuals with ESRD have a manifold increased risk of cardiac death compared to age-/gender-matched controls without CKD, meaning patients in dialysis aged 30 years have the same risk of cardiovascular death as patients aged 80 years in the general population [1]. Even in less severe stages of CKD the increased risk of cardiovascular events is tremendous, and both albuminuria and GFR are strong independent risk factors for cardiovascular disease [18–21]. CKD is considered a greater predictor of cardiovascular disease than diabetes mellitus [22]. Furthermore, the risk of cardiovascular death is higher than the risk of reaching ESRD in all stages of CKD, making cardiovascular prevention a major issue in nephrology practice.

CRS Type 5: Secondary CRS

Type 5 CRS is characterized by the presence of comorbid cardiac and renal dysfunction due to either acute or chronic systemic disorders. Diabetes mellitus, sepsis, and

amyloidosis are examples of such diseases affecting both renal and cardiac function. Further description of these systemic disorders is beyond the scope of this review.

How Does Cardiac Disease Contribute to Renal Disease?

In understanding how cardiac disease may affect renal function, it is essential to have knowledge of renal hemodynamics. The GFR may be understood as a product of the renal blood flow and the proportion of the plasma filtrated (filtration fraction) in the glomeruli. The filtration fraction is determined by Starling forces, i.e. the differences in hydrostatic and oncotic pressure between the glomeruli capillaries and Bowman’s space. Potent regulatory mechanisms act to control both the renal blood flow and the glomerular filtration pressure through the regulation of vasoconstriction and vasodilatation of the afferent and/or the efferent arteriole. Thus, the kidneys are able to maintain the GFR and renal blood flow through various physiological conditions (fig. 1).

As a response to cardiac disease, when the heart is not able to pump enough blood to meet the body’s needs, pressor systems like the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone-system (RAAS) are activated. Both systems act as potent vasoconstrictors mainly of the afferent and the efferent arteriole, respectively. Ljungman et al. [23] demonstrated that, while the renal blood flow decreases by up to 50% when the cardiac output is reduced by 25%, the GFR is relatively preserved. Increased glomerular filtration pressure, achieved by efferent vasoconstriction, contributes to maintenance of the GFR in low-output states, but the increased vascular resistance will decrease renal perfusion. The reduced renal blood flow may cause tubular hypoxic injury which with time will lead to a loss of nephrons and progressive renal dysfunction [24].

Activation of the SNS and RAAS also induces sodium and water retention, thus elevating the central venous pressure and causing organ congestion. Increased renal venous pressure is associated with reduced GFR when renal perfusion is low [25] and could be the most important hemodynamic factor for worsening renal function in acute decompensated HF [26]. Increased renal venous pressure will lower the glomerular filtration pressure as the pressure in Bowman’s space increases. Furthermore, renal congestion activates both the RAAS and the SNS and induces tubulointerstitial inflammation which may contribute to progressive GFR loss [27].

Fig. 1. Renal hemodynamics. The GFR is a product of the renal blood flow (RBF) and filtration fraction (FF) in the glomeruli. Different stimuli affect the vasomotor tone in the afferent (aff) and efferent (eff) arteriole and thereby affect the renal blood flow and filtration fraction and, as a consequence, the GFR. NSAIDs = Non-steroidal anti-inflammatory drugs; Ca blockade = calcium-blocking drugs; α₁ blockade = α-1 sympathetic blocking drugs; RAAS blockade = ACEi and ARB drugs.

Thus, renal hemodynamics is regarded as the main contributor to kidney disease in both acute and chronic cardiac patients and is closely associated with neurohormonal activation (fig. 2). Especially the role of RAAS in CKD progression is well documented [28].

Comorbidities like hypertension, atherosclerosis, and diabetes mellitus contribute to the high prevalence of renal dysfunction in cardiac patients as they are prevalent risk factors in both renal and cardiac patients. Furthermore, diagnostic and therapeutic procedures, like coronary angiography, might also hinder renal function due to nephrotoxicity or ischemia caused by the radiological contrast agents. In addition, medical treatment may affect renal hemodynamics and alter renal function; this will be further discussed in a later section.

The identification of tubular biomarkers of kidney injury has contributed to the knowledge of tubular injury as a major mechanism of kidney disease in cardiac patients. Albuminuria in patients with HF is thought to reflect tubular damage as reabsorption of albumin in the proximal tubule is altered due to tubular damage [29]. More recently, neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1), among other bio-

Fig. 2. Schema showing how cardiac disease causes progressive renal dysfunction. Renal hemodynamics and neurohormonal activation counteract to cause the pathological findings of kidney injury in cardiac patients. Tubular injury causes loss of nephrons and progressive renal dysfunction. Comorbidities and therapeutic interventions may augment the tubular and glomerular changes and add to the progressive renal dysfunction.

markers, are identified as sensitive indicators of injury to renal tubular cells in both acute and chronic cardiorenal patients [30, 31]. They may be measured in serum (NGAL) or urine (NGAL and KIM1). Biomarker levels increase prior to declining GFR, and they predict the prognosis independently of GFR [32]. Possibly, in the future more sensitive biomarkers of tubular injury will help the clinician to identify patients at risk of AKI and a progressive GFR loss and may guide medical treatment via early identification of unfavorable renal effects.

How Does Renal Disease Contribute to Cardiovascular Disease?

CKD patients have a considerable increased risk of cardiovascular disease and mortality. Even in CKD stages 3 and 4, the risk of dying because of cardiovascular disease is higher than the risk of reaching ESRD and the need for renal replacement therapy. As a consequence, preventing cardiovascular disease is a major issue for nephrologists.

Cardiovascular disease and CKD share many risk factors. Diabetes mellitus, hypertension, smoking, and overweight are among the classical risk factors for cardiovascular disease and are all associated with the development of CKD. Some of the burden of cardiovascular events in CKD patients is therefore attributed to the shared risk profile. However, in kidney disease the GFR and albuminuria are both strong independent risk factors of car-

diovascular disease even after correction for traditional risk factors [18, 33]. Classical risk factors seem to be less important than in the general population [34], and uremic toxins, i.e. the retention of solutes with biological activity, may be of great importance [35]. The kidneys are important in many physiological processes like regulation of the body composition of electrolytes and water, regulation of blood pressure, removal of uremic toxins, and endocrine functions like activation of the RAAS, SNS, and vitamin D and production of erythropoietin. Hence, alterations in kidney function may lead to metabolic and functional disturbances in many organs, including the heart and vasculature.

As a consequence, it appears that the spectrum of cardiovascular disease in CKD patients is different from that in the non-CKD population [36]. While coronary heart disease is the major cardiovascular cause of death in the general population, primary cardiac arrhythmias account for about 50% of cardiovascular deaths in the ESRD population treated with dialysis [37]. Thus, as renal dysfunction becomes more advanced, pathological processes other than atherosclerosis appear to be increasingly important.

Vascular Changes in CKD

Arteriosclerosis is a general term used to describe the pathological processes involved in arterial stiffening. Atherosclerosis, arteriolosclerosis, and media calcifica-

tion of the arteries are all included in the term arteriosclerosis and pose as major concern in CKD patients.

Increased vessel thickness and calcification of both media and intima are vascular changes which occur early in CKD patients [38]. These changes contribute to arterial stiffness and augmented pulse pressures [39]. Increased arterial stiffness measured by pulse wave velocity predicts mortality in patients with ESRD [40, 41].

Endothelial dysfunction is recognized as one of the initial mechanisms that lead to atherosclerosis and is present in renal disease [42, 43]. Endothelial dysfunction may contribute to cardiovascular mortality even in mild renal dysfunction [44] as well as progression of renal disease [45]. Asymmetric dimethylarginine (ADMA) is a potent vasoconstrictor and an endogenous inhibitor of nitric oxide (NO) availability. ADMA is associated with intima-media thickening, left ventricular hypertrophy (LVH), progression of renal disease, and cardiovascular mortality [46]. ADMA levels are increased in renal disease and, together with other uremic toxins that accumulate in renal disease, may be important in the endothelial dysfunction and vascular changes found in CKD patients.

CKD causes a complex disorder in the mineral metabolism, especially when the GFR falls below 45 ml/min/1.73 m² [47, 48]. The result is demineralization of bone and excessive calcification of soft tissue including vascular structures and heart valves, which leads to arterial stiffening, high pulse pressures, and LVH. Diminished vitamin D activation, hyperphosphatemia, hyperparathyroidism, and high calcium-phosphate product and fibroblast growth factor 23 (FGF23) have all been identified as independent predictors of vascular calcification and cardiovascular disease in CKD patients. However, the primary defect and the ideal therapeutic target to correct the mineral bone disorders in CKD has not yet been identified [49].

CKD is an inflammatory disorder with increased levels of proinflammatory cytokines affecting endothelial function and the lipid profile. CKD is also related to oxidative stress [50, 51]. Renal dysfunction causes changes in plasma components and endothelial structure and function that favor vascular injury and trigger the inflammatory response. Protein-energy wasting is a consequence of severe renal dysfunction [52]. The typical lipid profile of CKD patients includes elevated triglycerides and low HDL cholesterol. The serum level of lipoprotein(a) is increased in patients with reduced GFR, as it is normally cleared by the kidneys. LDL cholesterol levels are often lower than in the general population, but the circulating LDL particles are vulnerable to oxidation and glycosylation, possibly making them more atherogenic [53].

Cardiac Changes in CKD

LVH is highly prevalent in patients starting renal replacement therapy, as 75% have echocardiographic evidence of LVH [54]. Hypertension is a major predictor of LVH and is often present early in CKD patients. However, the hypertrophy in CKD patients also involves the right ventricle, indicating that simple hemodynamic factors are not the only explanation. Cardiac remodeling is demonstrated even in the early stages of CKD [55], and pathological studies have identified not only muscular hypertrophy, but also excessive interstitial fibrotic tissue in uremic patients [56]. Vascular changes, neurohormonal activation, anemia, and underperfusion of myocardial tissue all tend to contribute to the LVH and interstitial fibrosis. Kidney disease induces adverse cardiac remodeling independently of known risk factors [36, 57], making CKD patients prone to arrhythmias and development of HF.

As a consequence of the progressive cardiac and vascular changes, CKD patients may experience myocardial ischemia and symptoms of angina pectoris without evidence of occluding coronary disease [58]. Myocardial ischemia further promotes the myocardial fibrosis and disposition for cardiac arrhythmia.

Neurohormonal activation including the RAAS and SNS has multiple effects on the cardiovascular system as well as the kidneys. Both pressor systems interact to induce systemic vasoconstriction and salt and water retention. RAAS-blocking drugs are proven to reduce LVH and fibrosis independently of a blood pressure effect in CKD patients [59]. As renoprotective effects have also been established, these drugs are considered the cornerstone of cardiorenal protection in CKD patients.

Myocardial Biomarkers in CKD

Cardiac biomarkers have become increasingly available in recent years for the diagnosis of cardiac disease and prediction of the prognosis. The troponin T (TnT) and brain natriuretic peptides (BNP)/proBNP are established biomarkers in the non-CKD population, reflecting myocardial cell damage and myocardial wall stress, respectively, thereby being sensitive diagnostic markers of acute coronary syndromes and HF. Both markers are also sensitive predictive markers of cardiovascular events and all-cause mortality and are thought to detect subclinical pathologic changes in cardiac structure and function [60–63]. The interpretation in CKD patients is

more difficult as both peptides are considered dependent of renal clearance, and increased levels in patients with renal dysfunction may be explained by accumulation [64]. However, increasing evidence suggests that the increased levels of TnT and BNP/ProBNP reflect cardiac and cardiovascular abnormalities such as LVH, myocardial dysfunction, and increased afterload even in the CKD population [65–71]. Therefore, these biomarkers provide important diagnostic and prognostic information also in patients with renal disease and should be evaluated carefully. Future trials are warranted to establish the exact role of cardiac biomarkers in cardiorenal patients [72].

How to Deal with Cardiorenal Patients

A substantial number of CKD patients are treated by cardiologists, but unfortunately there is not enough evidence to describe the optimal treatment of cardiac disease in these patients. Modern treatments of acute coronary syndromes and congestive HF are founded in large clinical trials that generally have excluded patients with renal dysfunction. As a consequence, knowledge of the best treatment for cardiorenal patients is, to a large degree, based on substudies of large randomized trials as well as observational studies. Despite these studies showing that renal patients benefit at least as much from the recommended treatment as do non-CKD patients, they are generally less likely to receive treatment recommended by the guidelines [73]. Some investigators state that this treatment nihilism accounts for a considerable part of the worsened prognosis in renal patients [74].

It is important to regard renal patients as fragile patients, meaning that every procedure, change in medication, intercurrent illness, and change in fluid status may be a threat to the equilibrium and thus may cause decompensated cardiac function and/or worsening renal function. This does not mean that the treatments are contraindicated and that patients should not receive the usual care, but close monitoring is necessary when treating renal patients. In the care of CKD patients, beyond treatment of hypertension and RAAS-blocking drugs, few randomized trials have shown a clear effect of a single intervention aimed to reduce cardiovascular end points. Early referral to a nephrologist is shown to delay the progression of CKD; conversely, late referral is associated with higher mortality and worse secondary outcomes [75]. This may reflect the multifactorial association between CKD and cardiovascular disease as

many variables have to be considered in concert to achieve the goal of improved outcomes. Cardiorenal patients at cardiology departments would likely benefit from a closer collaboration between cardiologists and nephrologists when decide on treatment modalities and care.

Pharmacokinetics

Many drugs used by cardiologists are dependent on renal excretion and should undergo dosage reduction when the patient has renal dysfunction. Recommended dosage adjustment is most often based on the remaining renal function expressed as the GFR. As an example, angiotensin-converting enzyme (ACE) is mainly eliminated through the kidneys, and the initial dosage is recommended to be lower in patients with reduced GFR. However, angiotensin II receptor blockers (ARB) are mainly metabolized in the liver, and adjustment of the initial dosage is not necessary. Nonetheless, the hemodynamics effects of these two drug regimens are similar in kidney patients.

Renal clearance of drugs is, however, dependent not only on the GFR but also on tubular reabsorption, and the secretion of drugs may be affected due to disturbances in kidney function. Renal dysfunction may also affect the volume of distribution and binding to proteins through alterations in the body composition of water and acid/base balance. Furthermore, the activity of several drug-metabolizing enzymes and drug transporters may be impaired in CKD and even drug absorption may be affected [76]. When patients are treated with dialysis the pharmacokinetics may be even harder to predict.

Even when recommended dosage adjustments are carefully followed, adverse drug reactions remain common in patients with CKD. Nephrologists prefer to ‘start low and go slow’ and thereby titrate the patients to the optimal combination of drugs tolerated, assuming that small doses are better than no treatment [77]. This strategy presupposes a close follow-up of the patients but may ensure that the patients are provided essential treatment.

RAAS-Blocking Drugs

ACE inhibitors (ACEi) and ARB are beneficial in cardiovascular and renal diseases [78–80]. Patients with renal dysfunction are less likely to receive RAAS-blocking

Fig. 3. Potential effects of ACEi and ARB on the progression of CKD. Normally the GFR of CKD patients decreases at a yearly steady rate. The renoprotective effect of ACEi and ARB is to flatten the progression of GFR loss; to achieve this, an initial increase in creatinine of 30% should be tolerated. If renal perfusion is low, the patient will be at risk of severe renal dysfunction if ACEi and ARB are initiated, and an effort to increase renal perfusion should be made so that patients can tolerate the medication.

drugs for fear of a further reduction of renal function [73]. Increasing evidence, though, claims that the benefit of RAAS-blocking drugs in patients with CKD is comparable to that in the non-CKD population [9, 10, 81, 82]. As the absolute risk is higher in CKD patients, proper use of RAAS-blocking drugs might be of great importance in these patients.

The initial hemodynamic effect of ACEi and ARB in the kidneys is a reduction of the glomerular filtration pressure as the efferent arteriole dilates. In many renal patients this effect is wanted, as increased filtration pressure promotes proteinuria and glomerular damage. However, reduction of the filtration pressure may lead to an initial decrease in GFR, and in patients with severely reduced renal perfusion it may even cause severe kidney failure. Thus, kidney function has to be carefully monitored in patients in need of RAAS-blocking drugs.

The combination of reduced glomerular filtration pressure and increased renal perfusion is the hemodynamic explanation for the renoprotective nature of RAAS-blocking drugs in CKD patients [28, 79, 83]. Improved renal blood flow reduces the tubular injury caused by tubular hypoxia and ischemia also in cardiorenal patients. An increase of up to 30% in the creatinine level, which stabilizes within 2 months, is associated with improved long-term preservation of kidney function in

CKD patients [84] (fig. 3). The same recommendation seems to be valid for cardiorenal patients. If creatinine levels increase by more than 30%, one should suspect low renal perfusion due to dehydration, hypotension, or renal vascular disease, and an effort should be made to optimize the renal blood flow prior to a new attempt to introduce RAAS-blocking drugs.

However, when treating renal patients with RAAS-blocking drugs, one must be aware that interfering with the patients' autoregulatory mechanisms makes them vulnerable to acute worsening renal function. Renal blood flow is affected by dehydration, hypotension, and neurohormonal activation. Patients have to be informed to reduce or stop treatment when they experience dehydration or intercurrent disease. Patients should consult their doctor, and the treatment should be restarted when they reach their habitual state after kidney function has been controlled. To achieve safe treatment with RAAS-blocking drugs, cardiorenal patients should be monitored closely.

The effects of dual blockade of the RAS system have been investigated both in renal patients and in cardiovascular patients. No definite benefit has been found; rather, an increased risk of adverse events, i.e. hyperkalemia and reduced renal function, has been noted [85]. Dual blockade should therefore not be used.

Mineralocorticoid Receptor Antagonists

The RALES study was the first to find a beneficial effect on all-cause mortality with low-dose spironolactone in patients with advanced HF [86]. As a consequence, the prescription of spironolactone increased and the hospital admissions for hyperkalemia increased dramatically in the years following the publication of the study [87]. Later, eplerenone was found to increase survival after myocardial infarction complicated by HF [88]. Concern about the safety of mineralocorticoid receptor antagonists (MRA) is highly relevant, as hyperkalemia and worsening renal dysfunction related to the treatment is more common than reported in clinical trials [13, 89, 90]. Patients with renal dysfunction have been largely excluded from the randomized trials, and CKD patients are especially at risk of experiencing adverse effects of the treatment [89]. Still, MRA have potential for renal protection, as hyperaldosteronism seems to contribute to inflammation and fibrosis not only in the heart but also in the kidneys [91]. If CKD patients tolerate the treatment, the absolute benefit of spironolactone may be greatest in patients with re-

duced GFR [92]. It may be that the initial worsening renal function should be tolerated to some extent in advanced HF patients treated with spironolactone [92], as the beneficial effect may counter the effect of worsened renal dysfunction. However, further research is warranted to determine the place of MRA in CKD patients, and clinicians should be aware of the potential adverse effects, especially hyperkalemia, and use this treatment with caution in CKD patients.

Diuretics

Thiazide diuretics are important antihypertensive drugs, but they have little effect alone when the GFR is reduced, and loop diuretics are therefore often necessary antihypertensive drugs in CKD patients [93]. In addition, loop diuretics are essential in HF patients as they are efficacious in relieving clinical symptoms of shortness of breath and organ congestion. Patient outcomes with loop diuretics in HF have not been fully evaluated in large clinical trials. In some observational studies, diuretics have been associated with increased mortality [94–96]. However, proper decongestion with diuretics has also been found to be associated with a better prognosis [97, 98].

Loop diuretics may convey diverging outcomes with regard to renal endpoints. They may increase the GFR and delay the progression of CKD through reducing renal congestion [99]. However, high doses may also alter renal perfusion and thereby decrease the GFR and promote the progression of CKD [100].

Worsening renal function and electrolyte disturbances may explain some of the increased risk observed with higher doses of diuretics. Furthermore, diuretics are potent activators of neurohormonal systems like the RAAS and SNS [101, 102]. Recently, the risk associated with high-dose loop diuretics was found to be closely associated with markers of neurohormonal activation [103].

The combination of thiazide diuretics (often used in fixed combination with ARB or ACEi) and loop diuretics may have synergistic action and induce increased diuresis that may cause severe volume depletion, hypokalemia, hyponatremia, hypotension, and worsening renal function and should be avoided in the usual care of HF patients unless closely the patients are monitored in a hospital setting [104].

The definitive role of diuretics remains undecided. Pending obvious alternatives to achieve decongestion

without neurohormonal activation, diuretics are essential in the treatment of both hypertension and HF. However, one should be aware of the potential negative effects of diuretics and continuously aim for the lowest effective dose to prevent neurohormonal activation and reduced renal perfusion.

Statins

Coronary heart disease accounts for the majority of cardiovascular events and cardiovascular death in the general population. Statin treatment has been found to reduce coronary events and improve life expectancy in a wide range of high-risk populations and is recommended in primary and secondary prevention for a wide variety of indications [105]. Therefore, the expectations for a substantial effect in the ESRD population were high. However, trials could not prove any effect on cardiovascular events and all-cause mortality in the dialysis population [106, 107]. Later the Study of Heart and Renal Protection (SHARP) provided evidence for a beneficial effect of cholesterol lowering via the combination of simvastatin and ezetimibe in the CKD population with a reduction of the incidence of major cardiovascular events [108]. The effect was mainly driven by a decrease in events in the non-ESRD CKD population and no significant effect was found on all-cause mortality.

These observations support the epidemiological data stating that the increased cardiovascular risk in CKD patients, and especially in ESRD patients, is not only related to accelerated atherosclerosis. Cardiovascular disease in CKD patients involves other pathological processes in the heart and vasculature that make the patients prone to HF, ischemic myocardium, and arrhythmias unrelated to atherosclerosis. Thus, statins are recommended in the CKD population, but it is important to acknowledge that they do not deal with all aspects of arteriosclerosis seen in renal patients.

Conclusion

Cardiorenal associations are highly prevalent in patients treated by cardiologists, and renal function is an important predictor of the prognosis. Moreover, renal disease affects the cardiovascular system via specific mechanisms not seen in the general population. Thus, identification and proper handling of cardiorenal patients should be essential in the cardiologist's practice.

Even though cardiorenal patients have been excluded from studies founding modern cardiology treatment, it appears that most treatments, if tolerated, are equally effective in cardiorenal patients.

Cardiorenal patients are fragile and they are at an increased risk for decompensated heart and kidney function. As a consequence, they are in need of close follow-up and dynamic treatment to sustain renal perfusion and

volume status. Increased collaboration between nephrologists and cardiologists is warranted to best manage the increasing load of cardiorenal patients.

Conflict of Interest

None.

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