Cardiorenal Syndrome

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Invited Editorial

Henry J. Dargie, MB, ChB, FRCP, FESC, FRSE
Department of Cardiology - Western Infirmary - Glasgow - Scotland - UK

THE CARDIORENA L SYNDROME AS
THE CARDIOLOGIST SEES IT

A eons before modern treatments, worsening kidney function in heart failure was commonplace. It was not called “cardiorenal syndrome.” It signaled the end stage of heart failure. Although angiotensin-converting enzyme (ACE) inhibitors, β-blockers, aldosterone antagonists, and angiotensin receptor blockers have greatly improved symptoms and outcomes, the fickle kidneys still plague the lives of both patient and doctor. The kidneys have always been at the heart of heart failure treatment. William Withering, in his “An Account of the Foxglove and Some of its Medical Uses” published in 1785, describes many cases of “dropsy,” which responded well to digitalis. “The patient took five draughts which made her very sick and acted very powerfully upon the kidney, for within the first twenty-four hours she made upwards of eight quarters of water.” This fluid loss of nearly 7 liters was associated with dramatic symptomatic relief in a patient who lived for many more years sustained by intermittent less toxic doses of digitalis. Withering recounts that those who responded best to digitalis had a “weak, often intermittent pulse” suggestive of atrial fibrillation and a cardiac cause for the widespread edema.1

Richard Bright was one of three great “guys” of Guy’s Hospital in 19th-century London, his compatriots being Thomas Addison and Thomas Hodgkin. Bright described the clinical features of nephritis, which in many patients also included dropsy, thus demonstrating that “dropsy” was not universally attributable to heart failure. In some of these patients there was cardiac hypertrophy often, but not always, associated with hypertension.

Withering, therefore, in his description of what the heart could do to the kidney, and Bright, on what the kidney could do to the heart, were early commentators on the “cardiorenal syndrome.”

See page 248 for the companion Invited Editorial by David Goldsmith:
THE CARDIORENA L SYNDROME AS THE NEPHROLOGIST SEES IT

Professor Henry J. Dargie, MB, ChB, Department of Cardiology, Western Infirmary, Dumbarton Road, Glasgow G11 6NT, UK
(e-mail: henry.dargie@glasgow.ac.uk)
The increasing awareness of the bidirectional influences of heart and kidney was the stimulus to the broadening of the term “cardiorenal syndrome.” In their review of the topic in the *Journal of the American College of Cardiology* in 2008, Ronco and his colleagues recognized no fewer than five varieties of the cardiorenal syndrome. It has also been argued that anemia is such a common and important aspect of the coexistence of heart and kidney disease that “cardio-renal-anemia syndrome” (CRAS) is a legitimate subtype of cardiorenal syndrome, and, since iron deficiency is a major cause of the anemia that the term “cardio-renal-anemia-ID syndrome” (CRAIDS) is also valid and useful.

At this point the reader may be excused for being daunted by the apparent considerable complexity of the cardiorenal syndrome and related subsyndromes. In this issue of *Dialogues*, however, four excellent articles combine to demonstrate the present scope and scale of malevolent heart and kidney interactions. They also seek to clarify their various presentations.

Firstly, the brothers Paul R. Kalra and Philip A. Kalra, of whom one is a cardiologist and the other a nephrologist, succinctly summarize the cardiorenal syndrome. Essentially, Types 1 and 3 are acute heart failure as a cause or effect of acute kidney injury. In Types 2 and 4, chronic heart failure is either a cause or effect of chronic kidney disease (CKD). In Type 4, however, when severe CKD appears to have caused cardiac dysfunction, clinical heart failure need not be present for the case to be considered a cardiorenal syndrome. In Type 5 cardiorenal syndrome, both heart and kidney may be affected simultaneously by the same pathology. Acutely, this may result from severe systemic infections and chronically by diseases that can affect either organ, especially atherosclerosis, diabetes, and hypertension, and, more rarely, amyloidosis.

For cardiologists, the most common clinical scenario of the cardiorenal syndrome is the patient with, primarily, heart failure, in whom renal dysfunction supervenes. There are several candidate causes. The common clinical assumption is a presumed fall in renal blood flow, though this is rarely confirmed due to lack of suitable clinical methods of measurement. Renal perfusion is preserved over a wide range of blood pressures, but either due to heart failure itself and a poor cardiac output all specific treatments for heart failure lower the blood pressure and risk compromising renal blood flow and function.

More recently, as discussed by Paul R. Kalra and Philip A. Kalra in their Lead Article, tubular dysfunction may supervene especially in acute heart failure. The development of novel markers for this, such as NGal (neutrophil gelatinase-associated lipocalin), opens a new door of therapeutics since earlier objective recognition of renal damage may lead to a more urgent, possibly better targeted approach to its treatment.
An important aspect of this is the extent to which such damage is reversible and whether this might mitigate or prevent the resultant renal dysfunction. In acute coronary syndromes (ACS), there is a sense of urgency in addressing the underlying pathophysiology with antithrombotic or fibrinolytic treatments being applied immediately and appropriately on diagnosis. Aspects of quality of care in ACS are time to application of treatment as it is recognized that time delays mean loss of myocytes. By analogy, time delay could also be regarded as loss of nephrons. Thus, simple time to the institution of appropriate diuretic, vasodilator, or even inotropic therapy in order to reduce renal congestion and improve renal blood flow could become a quality marker.

Secondly, Robert N. Foley and Charles A. Herzog focus on severe or end-stage kidney disease (ESKD) causing ventricular dysfunction leading not only to heart failure, but also to sudden cardiac death from presumed ventricular arrhythmia. Indeed, this is a major unsolved problem for such patients. In recent years, the impact of primary renal disease on the heart, apart from, or in addition to, the secondary effects of associated hypertension has attracted much interest.

It was the development of renal replacement therapy with chronic dialysis that has allowed large numbers of patients with ESKD to survive long enough for the effects of sustained renal failure on the heart to become apparent. And, although the major success of renal transplantation is greatly appreciated, it has brought another set of issues related to long survival times for patients with hearts previously affected by uremia and chronic hypervolemia only partially corrected by hemodialysis. The notion of a specific uremic cardiomyopathy receives support from recent studies in which cardiac magnetic resonance imaging has demonstrated patchy late enhancement consistent with fibrosis occurring in a noninfarction distribution.

Robert N. Foley and Charles A. Herzog raise the issue of the severe lack of adequately powered clinical trials of prevention of sudden death in these patients. Encouraging, but not conclusive, evidence of benefit comes from small studies of β-blockers in ESKD especially with carvedilol. Foley also raises the issue of large randomized studies of intracardiac defibrillators (ICDs) in this population for many of whom the first clinical manifestation of heart disease may be sudden cardiac death due to presumed lethal ventricular arrhythmia. Interesting in itself, that research also would contribute greatly to establishing the cause of sudden cardiac death as any arrhythmia would be captured by the device.

Thirdly, Ewa A. Jankowska and Piotr Ponikovski discuss the multiple causes and consequences of anemia in patients with heart failure. Deficiency of, or resistance to, the normal physiological effects of hemopoietic factors, especially erythropoietin and
iron, are the major causes of anemia, similar to the anemia of other chronic illnesses.\(^8\)

They recommend that patients with CKD be screened for anemia and iron deficiency and that full hematological testing is appropriate for the adequate management of anemia. Large clinical trials are under way to investigate the impact of iron therapy, especially intravenously, on quality of life and outcomes in patients with heart failure.

Finally, **Luis M. Ruilope** argues that the cardiorenal syndrome is an intrinsic component of the “cardiovascular continuum” from risk factors to target organ damage and hence to overt atherosclerotic cardiovascular disease.\(^9\) Diabetes and hypertension remain the major population-attributable causes of kidney disease in the community contributing substantially to both covert and overt renal dysfunction.\(^4\) Early kidney disease has not convincingly been shown to cause cardiovascular disease (CVD) and if CVD is present in early CKD it seems most likely that hypertension and or diabetes will have been responsible for both the CVD and renal impairment.\(^10\)

The strong clinical message here, as stressed by **Luis M. Ruilope**, is the utmost importance of the primary and secondary prevention of target organ damage from hypertension, atherosclerosis, and diabetes. This review also reminds us that when patients with heart failure develop problems with kidney function there may well be covert permanent structural damage, which their worsening heart failure has rendered overt. This is a common clinical conundrum that is of vital importance to all patients with heart failure and especially to those who otherwise would be good candidates for heart transplantation. At present, our ability, clinically, to assess early intrinsic kidney disease, is limited.

It is beyond doubt that the “cardiorenal syndrome” is no single entity. The sheer variety of causes, consequences, and mechanisms, together with their multiple implications for treatment, demand that it should surely always be referred to in the plural. The obvious clinical comparison is with acute coronary syndromes (ACS), a term that emphasizes differences among its components according to clinical presentation with distinct management pathways based on the underlying pathophysiology. Current classifications of cardiorenal interactions have been helpful in categorizing the different clinical scenarios, but they are essentially descriptive and should stimulate more targeted research into mechanisms and treatment.
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1. Withering W. An Account of the Foxglove and Some of its Medical Uses. 1735.


Invited Editorial

David Goldsmith, MA, MB, BChir, FRCP(UK), FRCP(Edin), FASN, FERA
Reader in Renal Medicine - King’s College London - UK

THE CARDIORENAL SYNDROME AS THE NEPHROLOGIST SEES IT

The need for a deepening and more solid basis for collaboration and cooperation between cardiologists and nephrologists has never been more important than it is now. So many of the patients seen by cardiologists have chronic kidney disease (CKD) (made easier to spot now using estimated glomerular filtration rate [eGFR measurements])—manifest by reduced kidney function, and, when tested for, by albuminuria-proteinuria. Patients with reduced GFR and albuminuria-proteinuria are at an especially high cardiovascular risk. Luis M. Ruilope in this journal edition makes that point forcefully. Moreover, so many of the pharmacological interventions used by cardiologists—diuretics, renin-angiotensin-aldosterone system (RAAS) blockers to name but two—have an impact on kidney function (and often plasma potassium, too).

Looking at the situation the other way around, from the nephrological perspective, so many of our CKD stage 3a and 3b patients (GFR 45-60 and 30-44 mL/min/1.73 m² respectively) have co-incident cardiovascular disease burdens, usually, but not exclusively, in the form of abnormal endothelial function, macrovascular atherosclerosis, arterial stiffness, and left ventricular hypertrophy. The major cause of death in CKD stage 3a and 3b is cardiovascular, and it is a much rarer outcome to progress to CKD stage 4 and beyond.

How to reduce the toll of cardiovascular disease in this numerically quite large cohort—perhaps 4% to 6% of the population, so numerous as say diabetes—is still a challenge, though strict blood pressure control and lipid-lowering therapy seem sensible, rational, and safe interventions for either or both of the kidney and the cardiovascular system.

See page 243 for the companion Invited Editorial by Henry J. Dargie:
THE CARDIORENAL SYNDROME AS THE THE CARDIOLOGIST SEES IT

Dr David Goldsmith, MB, BChir, Renal and Transplantation Department, 6th Floor, Borough Wing, Guy’s Hospital, Great Maze Pond, London SE1 9RT, UK (goldsmith@london.com)
In this exciting and well-written journal issue, guest-edited by the Brothers Kalra, there is much to savor. The excellent critical analysis by Paul R. Kalra and Philip A. Kalra of the oversimplistic and nonbiologically plausible Ronco classification of the “cardiorenal syndrome” is long overdue. Although simplification can be, and often is, a boon and a blessing, where the simplification leads to confusion or conflation of ideas, it stands in the way of a deeper understanding. There is a major opportunity, likely to be taken by many, to examine these complex, shifting, and often subtle cardiorenal interrelationships using large cohorts, with nested detailed investigational and interventional substudies, testing out novel biomarkers to help predict patients more or less likely to reach a cardiovascular rather than a renal end point.

The pressing need for common research and investigational goals and studies is clear for all to see now. This can be done by colocalizing good quality clinical care with cutting-edge research projects, so that all can benefit from the latest thoughts, ideas, and therapies, and more rapid progress can be made. In the UK, the establishment of national research networks has driven a major increase in recruitment of subjects to clinical trials, and in time, this will be a rich harvest.

The exciting issue of anemia and iron deficiency in heart failure is well tackled by Ewa A. Jankowska and Piotr Ponikovski. In nephrology, we have long used iron, oral or intravenous, as a means to augment or stimulate hemopoiesis as anemia is so commonly associated with our chronically comorbidly challenged CKD patients. The short-term safety and effects of iron on the bone marrow are well known, but the long-term safety of this approach is much less robustly understood, as iron could theoretically help, by improving mitochondrial function, or hinder, by stoking oxidative stress (a major player in more advanced CKD). The use of IV iron in heart failure is now a major new theme, and many heart failure specialists are taking this up enthusiastically. I would strongly advocate doing as many trials as possible until it is abundantly clear this is both safe and a good health-economic intervention. In nephrology, over 25 years or more, we have learnt now a bitter lesson about accepting the “good” that an expensive intervention can bring—erythropoietin—but not seeing the harm (thrombosis, hypertension, possible acceleration of cancer) that can also dictate patient outcomes.

Blood pressure control, and RAAS blockade, of course, remain central to the nephrologists’ interventional strategy to try to stem the tide of patients suffering cardiac or renal diseases, which often progress remorselessly without treatment. Luis M. Ruilope expertly chronicles this complex area, and its links with sympathetic nervous system overactivity, highlighting important observations and trials to guide therapy with more logic and precision.
Sudden cardiac death is of course not confined to CKD patients, but the death rates from this are higher in dialysis patients than in any other patient cohort except those with congenital/genetic reasons for arrhythmia. Not only is this a common problem, but it is also currently seriously deficient in good quality research—we don’t even know the balance between asystole and ventricular fibrillation, and the predisposing factors and early-warning signs for either. The article by Robert N. Foley and Charles A. Herzog elegantly lays bare the worrying lack of key information and knowledge, while sensibly marshaling the evidence for intervention (small though it is). This is an area where electrophysiologists and nephrologists could really potentially make a big difference.

Let us hope that on reading this stimulating series of articles, both nephrologists and cardiologists will feel more collaborative, more cooperative, and more ready to compromise and share the management of a complex and challenging patient group. We in nephrology need commitment and help from the cardiology specialty as never before, as we cannot pretend any longer to be able to do the job alone. We in nephrology would venture to suggest back that we have quite a lot to offer the other way around!
Cardiorenal syndrome: epidemiology, pathogenesis, and outcomes

Paul R. Kalra*, MD, FRCP; Philip A. Kalra†, MD, FRCP

*Department of Cardiology - Portsmouth Hospitals NHS Trust - Portsmouth - UK
†Department of Nephrology - Salford Royal Foundation NHS Trust - Salford - UK

The cardiorenal syndrome is a broad term used to describe the association of heart failure and renal impairment. A recent classification has sought to separate different clinical presentations, but the underlying pathophysiological causes are not readily differentiated in this way. Patients developing the cardiorenal syndrome are at major risk of mortality and morbidity due to multiple and complex interactions. There is now growing interest in the role of anemia in worsening outcome. Standard medical therapy, such as β-blockers and renin-angiotensin blocking agents, are effective, but underused in patients with heart failure and renal impairment, and other standard therapies such as high-dose diuretics potentially have nephrotoxic effects; the response to diuretic therapy is also blunted in the presence of renal dysfunction. Emerging therapies such as peritoneal dialysis and hemofiltration have potential to improve the outcome of hemodynamically unstable patients with severe cardiorenal disease. As is the case in all areas of medicine, preventative strategies are of paramount importance, and therapies that help prevent development of cardiovascular complications in patients with chronic kidney disease and, conversely, strategies that allow successful treatment of acute or chronic heart failure without exacerbation of renal dysfunction, are awaited.

Keywords: anemia; cardiorenal syndrome; chronic kidney disease; heart failure; neurohormonal activation

Address for correspondence: Dr Paul R. Kalra, Department of Cardiology, Portsmouth Hospitals NHS Trust, Queen Alexandra Hospital, Southwick Hill Road, Cosham, Portsmouth PO6 3LY, UK (e-mail paul.kalra@porthosp.nhs.uk); Professor Philip A. Kalra, Department of Nephrology, Salford Royal Foundation NHS Trust, Stott Lane, Salford M6 8HD, UK (e-mail: philip.kalra@salfh.nhs.uk)


SELECTED ABBREVIATIONS AND ACRONYMS

AKI acute kidney injury
ARVD atherosclerotic renovascular disease
CAD coronary artery disease
CHF chronic heart failure
CKD chronic kidney disease
CRS cardiorenal syndrome
eGFR estimated glomerular filtration rate
ESA erythropoietin-stimulating agent
ESCAPE Effect of Strict blood pressure Control and ACE-inhibition on ProgReSsion of chronic renal failure in pediatric patients
ESRD end-stage renal disease
GFR glomerular filtration rate
HOPE Heart Outcomes Prevention Evaluation
LVH left ventricular hypertrophy
LVMI left ventricular mass index
POSH Prospective Outcomes Study in Heart failure
RAAS renin-angiotensin-aldosterone system
SCD sudden cardiac death
WRF worsening renal function
ment has a major adverse effect upon outcome. This is now well established in the two preeminent cardiac conditions that cause disease in the Western world. Patients with coronary artery disease (CAD) fare worse when impaired glomerular filtration rate (GFR) is evident, and the latter has a significant negative effect upon outcomes in those undergoing coronary revascularization procedures. Likewise, those patients with heart failure, whether acutely decompensated or chronic, have particularly bad outcomes if renal impairment is either already present or if it supervenes during the course of treatment.

In this article we will be concentrating on the relationship between heart failure and renal dysfunction, a commonly occurring association described under the umbrella heading of “cardiorenal syndrome” (CRS). We will consider the definition/classification, epidemiology, pathogenesis, and outcomes of the condition, and also the currently available treatments to improve the prognosis of these high-risk patients. Specific and topical aspects of the CRS, namely anemia, sudden cardiac death, and optimal pharmacotherapeutic management, will then be considered in more detail by our internationally renowned contributors.

DEFINITION AND CLASSIFICATION OF THE CARDIORENAL SYNDROME

A number of terms to address the coexistence of heart failure and renal dysfunction have been proposed. CRS is now generally favored. Historically, this term has typically been used to describe declining renal function in the setting of advanced or decompensated heart failure. It has also been used to describe the more specific development of acute kidney injury (AKI) in response to heart failure treatment that then leads to diuretic resistance, fluid overload, and worsening heart failure.

In an attempt to differentiate between acute and chronic interactions and identify the “primary” driving pathophysiological abnormality, Ronco and colleagues have proposed a classification based around five types of the CRS (Table I). Worsening or decompensated heart failure as a cause or effect of AKI constitutes types 1 and 3, respectively. Chronic heart failure (CHF) as a cause and effect of CKD is suggested as types 2 and 4, respectively. Type 5 is classed as cardiovascular and renal damage from a common underlying pathology; acutely, this might be sepsis, whereas chronically, diabetes mellitus, atherosclerosis, and/or hypertension are more likely. There are limitations to this classification, particularly since the precise pathophysiological relationships in the different clinical scenarios are not fully (and often poorly) understood (see below). Furthermore, each type of CRS is more likely to occur in the presence of another. For example, AKI is more likely in a patient with decompensated heart failure if the patient has underlying diabetes (underlying systemic condition) with associated CKD and CAD. In addition, it is plausible that a patient with CHF, for example, will exhibit pathophysiological changes typical of distinct subgroups at different stages of their heart failure syndrome. While the precise mechanisms are not fully understood, it is apparent that dysfunction of one organ system may cause or exacerbate dysfunction of the other, and a spiral of decline can occur, with resultant adverse prognosis.

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<table>
<thead>
<tr>
<th>CRS Type</th>
<th>Title</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Type I</td>
<td>Acute cardiorenal syndrome</td>
<td>Rapid worsening of cardiac function leading to acute kidney injury</td>
</tr>
<tr>
<td>Type II</td>
<td>Chronic cardiorenal syndrome</td>
<td>Chronic abnormalities of cardiac function leading to progressive CKD</td>
</tr>
<tr>
<td>Type III</td>
<td>Acute renocardiac syndrome</td>
<td>Acute and primary worsening of kidney function leading to cardiac dysfunction</td>
</tr>
<tr>
<td>Type IV</td>
<td>Chronic renocardiac syndrome</td>
<td>Chronic and primary renal disease (CKD) leading to CHF</td>
</tr>
<tr>
<td>Type V</td>
<td>Secondary cardiorenal syndrome</td>
<td>Systemic conditions causing simultaneous cardiac and renal dysfunction, eg, sepsis</td>
</tr>
</tbody>
</table>

Table I. The 5 proposed subtypes of the cardiorenal syndrome (CRS).

Abbreviations: CHF, chronic heart failure; CKD, chronic kidney disease; CRS, cardiorenal syndrome.

populations have used the “AKIN” (Acute Kidney Injury Network) definition. In this report, AKI was suggested as reflecting an abrupt (within 48 hours) reduction in kidney function manifest by:

- An increase in serum creatinine ≥26.4 μmol/L (0.3 mg/dL), or
- An increase in serum creatinine of ≥50% (1.5-fold from baseline), or
- Oliguria (< 0.5 mL/kg per hour for more than 6 hours).

**Formula for conversion of serum creatinine units**

Serum creatinine: 1 mg/dL = 88.4 μmol/L

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**EPIDEMIOLOGY OF CARDIORENAAL SYNDROME**

Although the previously described classification of the CRS may be an oversimplification of what is often a more complex pathophysiological interaction between these two important and interdependent organ systems, it does help in defining the clinical situations in which patients are at risk and enables a logical separation which aids further discussion. Acute decompen sed heart failure complicated by AKI has a very poor outcome, but even minor rises of creatinine (eg, <10 μmol/L) have been shown to prolong hospitalization and increase mortality in these patients. In a study of over 1000 patients hospitalized for decompen sed heart failure, 25% had a rise in serum creatinine of >26.5 μmol/L (which fulfills the definition for AKI), with increased risk of this in those with diabetes, hypertension, or prior CKD. This finding is consistent across a number of studies, with the development of AKI being associated with worse outcomes not only in hospital, but over the next 6 to 12 months as well. A recent meta-analysis of studies in patients with heart failure (n=18,634) showed that around 25% patients exhibited an increase in serum creatinine >0.2 mg/dL (>18 μmol/L) or a decrease in estimated glomerular filtration rate (eGFR) ≥5 mL/min/1.73 m²; when present, this was associated with a higher risk for mortality (odds ratio [OR], 1.62; 95% confidence interval [CI], 1.45-1.82; \( P < 0.001 \)) and hospitalization [OR, 1.30; 95% CI, 1.04-1.62; \( P = 0.022 \)]. Additional associations of AKI in this situation are anemia, age, and the use of renin-angiotensin blocking agents and diuretics, these latter drugs presumably further reducing renal perfusion in patients with low cardiac output states.

Insight into the prevalence of CKD in patients with acute cardiac decompensation is provided by the Acute Decompensated Heart Failure National Registry (ADHERE), a database which includes over 100,000 patients—one analysis showed that 64% of patients had at least moderate CKD (<60 mL/min/1.73 m²) and only 9% had normal eGFR. The epidemiology of renal impairment in patients with CHF is less clear because much of the available data are derived from clinical trials or studies that have tended to exclude patients with more advanced CKD. Age is strongly associated with both CHF and CKD and so it is no surprise that the majority of elderly patients with heart failure will have some degree of CKD. A prospective cohort study of all-comers to one heart failure clinic found that about 80% had an abnormal creatinine clearance (previously used as a surrogate for eGFR, but having even greater limitations). Overall, over 50% of patients with CHF have evidence of stages 3 to 5 CKD (GFR <60 mL/min), and increasing mortality is seen with reducing GFR when the latter is analyzed as a covariate. The degree of renal impairment as estimated by serum creatinine is also associated with adverse prognosis (Figure 1). Indeed, advanced CKD is as prognostically important as left ventricular systolic dysfunction in this population.
So what about the reverse association, cardiac dysfunction complicating acute or chronic kidney disease? The incidence of severe AKI varies between 50 and 1000 cases/million/year, depending upon age grouping. 9% of all hospital admissions have AKI, and the latter is found in 35% of all intensive care unit admissions. Fluid overload, which can be life-threatening if left untreated, frequently complicates AKI. Its mechanism is multifactorial and includes oliguria, cardiac dysfunction due to neurohormonal abnormalities, capillary leak syndrome due to multisystem illness (especially sepsis), and hypoalbuminemia. Surprisingly, there is a paucity of data regarding the true incidence of this “acute renocardiac failure,” and even less relating to systematic study of structural and functional cardiac changes occurring both during the episode and in the recovery period.

In patients with CKD, a plethora of interrelated cardiovascular risk factors exist, and some of these undoubtedly contribute to the development of CHF. These will be considered more extensively in the section on pathophysiology, but nonetheless some are worthy of mention here. Structural myocardial disease, termed by some as “uremic cardiomyopathy,” is important and the prevalence of left ventricular hypertrophy (LVH) increases with declining GFR, and its cause is both multifactorial and complex. LVH is associated with hypertension (present in >70% of patients with stage 4 CKD and >90% of dialysis patients), vitamin D deficiency, volume status, anemia, and increased arterial stiffness, and the latter in turn is related to endothelial dysfunction and medial vascular calcification, which are now the subject of much research. When patients reach end-stage renal disease (ESRD), defined as eGFR <15 mL/min, up to three quarters of those starting renal replacement therapy (RRT) will have echocardiographic evidence of LVH; 36% already have left ventricular dilatation, and 15% severe left ventricular (LV) dysfunction. In a Canadian cohort of 259 patients followed from dialysis inception, serial echocardiography showed that 70% had an increase in LV mass index (LVMI) and 50% an increase in LV cavity volume compared with baseline, after the patients had been followed for a mean of 41 months. A new diagnosis of heart failure was more likely in those with greatest LVMI. 33% of patients had CHF at the end of the study, and new onset CHF accounted for half of the cases. The importance of hypertension was emphasized as each 10 mm Hg rise in mean arterial pressure predicted a 44% increased risk of de novo heart failure. The incidence of new-onset heart failure in patients with earlier stage (ie, before dialysis) CKD has not been well evaluated. Although the risk of this association is accentuated by the pathophysiological factors described above, which may progressively worsen as eGFR falls, it is also likely that many affected patients will have concomitant coronary artery disease and/or diabetes. However, it is well known that LVH develops early in CKD, in a study of 175 consecutive patients attending a predialysis clinic, LVMI increased as creatinine clearance fell and LVH was independently associated with age and systolic hypertension.

Underpinning all of the cardiorenal associations described above is the fact that many common conditions can lead to both cardiovascular and renal complications in parallel. Classic examples are diabetes and hypertension; diabetes is the primary disease in at least 20% of UK patients with ESRD, and over 30% of patients receiving dialysis are diabetic. The figures are considerably greater in the US, with around 60% of the dialysis population having diabetes. These patients have a very high prevalence (70%) of cardiac abnormalities, including coronary artery disease and heart failure. The association of hypertension with LVH and heart failure in ESRD has already been mentioned above.

**PATHOPHYSIOLOGY OF THE CARDIORENAL SYNDROME**

CHF is characterized by the inability of the heart to preserve cardiac output. The net result is a reduction in perfusion to key peripheral organs. Typical symptoms of dyspnea, peripheral edema, and weight gain together with the classic physical signs such as jugular venous distension, rales, and edema relate in part to the inability of the body to excrete sodium and secondary water. While this excessive salt and water retention is related to decreased GFR, it is vital to understand why GFR is reduced in CHF.

Cardiovascular and renal disease may both occur as a consequence of the same underlying disease. In addition, the presence of CKD is an independent risk factor for developing cardiovascular disease, particularly CAD and LVH. Epidemiological studies suggest that CAD is responsible for more than half of incident cases of heart failure. Furthermore, arterial disease is a major cause of renal disease. As such, teasing out the precise pathophysiology of the CRS is complex and fraught with difficulty. We will now briefly discuss some of the putative pathways and mechanisms involved (Figure 2).
Hemodynamic abnormalities

Historically, the reduction in GFR in CHF was thought to be mainly attributable to a decrease in renal blood flow. \(^22\) Circulatory integrity (preservation of mean arterial pressure) is the main determinant of renal sodium and water excretion. \(^28,29\) A reduction in cardiac output results in a series of systemic and intrarenal responses that aim to retain fluid and restore cardiac output at an increased circulatory volume. With a further drop in cardiac output, renal blood flow becomes impaired, which activates a number of complex responses that further decrease renal function, but fail to normalize cardiac output. \(^30\) A recent cross-sectional study that determined GFR and renal blood flow by radiolabeled tracer techniques in patients with CHF receiving blockers of the renin-angiotensin-aldosterone system (RAAS) has consolidated this belief. \(^31\) Blockade of the RAAS is the cornerstone of evidence-based heart failure management. However, drug-induced reduction in renal perfusion may have a deleterious effect upon renal function under certain circumstances as a consequence of actions on glomerular hemodynamics (these are beneficial when perfusion is preserved).

Yet, hypotension is not present in all patients who develop AKI. There is increasing interest in the relationship between renal venous congestion and associated renal dysfunction and AKI. \(^14\) Damman et al \(^32\) have shown in a large cohort of patients with cardiovascular disease that elevated central venous pressure was associated with lower eGFR independent of cardiac output. Furthermore, a substudy of the ESCAPE trial (Effect of Strict blood pressure Control and ACE-inhibition on Progression of chronic renal failure in pediatric patients) demonstrated that the single (invasively determined) parameter associated with reduced renal function was right atrial pressure. \(^33\)

Common underlying disease

Hypertension and LVH

Elevated blood pressure is extremely common in patients with CKD and is associated with a high rate of de novo cardiac failure and CAD. Even modest elevations in blood pressure are associated with LVH and cardiomyopathy. Optimal control of hypertension appears to be fundamental to patients with either CKD or cardiovascular disease. However, in ESRD, mortality is strongly associated with low blood pressure. \(^32\)

Advanced heart failure will often lead to a low blood pressure irrespective of renal function. As such, the use of antihypertensive therapy will need to be reevaluated in patients who develop heart failure.

Atherosclerosis

Atherosclerosis is a multisystem disease. Underlying CAD is the most common cause of heart failure. \(^35\) and around 40% of patients with CKD have evidence of CAD. \(^34\) The presence of CKD appears to be a proa-

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**Figure 2. Basic schematic overview of the pathophysiological abnormalities contributing to the cardiorenal syndrome (CRS).**

Shared etiological risk factors, eg.

- Hypertension
- Atherosclerosis
- Smoking
- Diabetes
- High cholesterol

Substrate for sudden cardiac death

Impaired cardiac function (LVSD, LVH)

Chronic activation of RAAS

Arterial hypoperfusion

Venous congestion

Anemia

CKD and/or AKI

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; RAAS, renin-angiotensin-aldosterone system.

erosclerotic condition and atherosclerosis itself can lead to and/or exacerbate CKD as a consequence of microvascular damage. Traditional risk factors for atherosclerosis such as smoking are associated with the development and progression of cardiovascular disease and CKD. When present, it is thought that pathophysiological abnormalities associated with CKD can exacerbate the atherosclerotic process (see below).

**Diabetes mellitus and the metabolic syndrome**

Diabetes is a common comorbidity in patients with CHF and CKD. It is often encountered in conjunction with other established vascular risk factors in the metabolic syndrome (coexistent obesity, hypertension, high triglycerides, and low-density lipoprotein (LDL) cholesterol, and high circulating levels of prothrombotic/proinflammatory markers); this in part explains why the presence of diabetes is associated with such a high cardioareal morbidity and mortality.

Diabetic nephropathy accounts for around 20% of new dialysis cases in the UK and 40% in the US. Endothelial dysfunction secondary to insulin resistance and chronic hyperglycemia leads onto the development of microvascular disease (CAD and CKD). Microvascular disease and early endothelial disruption in the kidneys results in albuminuria. The presence of even microalbuminuria (urine albumin-to-creatinine ratio of 30-299 mg/g), an early marker of endothelial dysfunction, is associated with a marked increased risk of progression to established diabetic nephropathy. A large meta-analysis has confirmed that microalbuminuria is an independent predictor of all-cause mortality and adverse cardiovascular outcomes. There appears to be an amplified risk when considering the presence of increasing degrees of microalbuminuria and deteriorating renal function. The HOPE (Heart Outcomes Prevention Evaluation) trial showed that the presence of microalbuminuria was associated with an adjusted threefold relative risk of hospitalization for heart failure, which was similar for patients with and without diabetes.

**Neurohormonal activation**

Activation of the RAAS is a protective physiological mechanism that attempts to prevent underperfusion of vital organs such as the kidney. While acutely this may help preserve central aortic pressure, continued activation (as seen in CHF) leads to excess sodium and water retention and vasoconstriction with resultant adverse hemodynamic effects such as left ventricular dilatation and increased afterload. Angiotensin II and aldosterone also exert direct unfavorable effects on the kidney (intraglomerular hypertension and intrarenal fibrosis) and heart (myocardial cellular hypertrophy, progressive loss of myocardial function with myocyte hypertrophy and interstitial fibrosis) (Figure 3).

The neurohumoral hallmark of both patients with CKD or CHF is chronic overactivation of the RAAS, and this system appears to play a prominent pathophysiological role in worsening renal and cardiac disease. Activation of the RAAS is a protective physiological mechanism that attempts to prevent underperfusion of vital organs such as the kidney. While acutely this may help preserve central aortic pressure, continued activation (as seen in CHF) leads to excess sodium and water retention and vasoconstriction with resultant adverse hemodynamic effects such as left ventricular dilatation and increased afterload. Angiotensin II and aldosterone also exert direct unfavorable effects on the kidney (intraglomerular hypertension and intrarenal fibrosis) and heart (myocardial cellular hypertrophy, progressive loss of myocardial function with myocyte hypertrophy and interstitial fibrosis) (Figure 3).

**Inflammation**

Inflammatory immune activation is found in patients with CKD and/or CHF, and it is believed this contributes to disease progression. In CHF, inflammatory cytokines such as tumor necrosis factor and interleukin 6 are independent predictors of adverse outcome. This is particularly apparent in advanced or decompensated heart failure, disordered gut wall function (eg, second-
ary to edema from elevated right atrial pressure) may facilitate translocation of bacterial endotoxin (lipopolysaccharide), which in turn is a potent stimulus for inflammatory cytokine activation.

Renal disease as a cause of cardiovascular disease

Not only do patients with CKD exhibit an excess of traditional vascular disease risk factors, but vascular calcification and associated arterial stiffness are common and associated with excess mortality. The pathophysiology of calcification is complex and is linked to hyperphosphatemia, hypercalcemia, hyperparathyroidism, and a reduction in endogenous inhibitors of calcification (eg, fetuin A). The net result is an increase in vascular stiffness, which is associated with LVH and may predispose to heart failure. Endothelial dysfunction, with an associated loss of endothelium-mediated vasodilatory response to nitric oxide (NO), is common in patients with CHF and linked to cardiovascular mortality. Activation of RAAS further exacerbates endothelial dysfunction. CKD is a major contributor to endothelial dysfunction, which in part relates to circulating proinflammatory cytokines.

Anemia

Patients with CHF commonly have low hemoglobin as a comorbid finding, when present it is an important determinant of impaired exercise capacity and mortality. Silverberg et al highlighted its pathophysiological importance in patients with both CHF and CKD, introducing the term “cardio-renal-anemia syndrome.” The etiology of anemia in CHF is complex and not fully understood. However, absolute and functional iron deficiency appears to be extremely common. Blunted erythropoietin production has also been demonstrated. As such, there is much interest in the potential use of iron and erythropoietin-stimulating agents (ESA) in this area.

The use of intravenous iron and ESA has become an integral part of the management of patients with ESRD. The need for large-scale studies assessing both efficacy and safety prior to routine clinical use in patients with CHF has been exemplified by a number of recent studies of ESA in patients with CKD. Understanding who might benefit, which therapy to use, and appropriate targets (hemoglobin and iron parameters) is fundamental. (See in this issue the paper by Ewa A. Jankowska and Piotr Ponikowski: “Should anemia be actively treated in cardiorenal syndrome?”—page 284).

Atherosclerotic renovascular disease

Atherosclerotic renovascular disease (ARVD) is common, and it is frequently seen in association with cardiovascular diseases. ARVD (here defined as renal artery stenosis >50%) is present in around one third of elderly patients presenting to hospital with heart failure and just over 50% of outpatient cohorts with CHF. Heart failure is present in around two fifths of elderly patients with ARVD and is associated with excess mortality when present (almost threefold). Renal revascularization therapy may provide substantial clinical benefit, but this needs to be evaluated further.

The above description of the interactions between the heart, kidneys, neurohormonal, immune, and other systems represents a simplification; numerous interactions between systems occur via intricate feedback loops. As such, a number of interrelating factors may contribute to CRS and it is highly likely that for any one patient a number of mechanisms may be at play.

Outcomes of patients with the cardiorenal syndrome

The presence or subsequent development of renal impairment in patients with acute or chronic cardiac failure confers an increased risk of adverse outcome. In acute decompensated heart failure, the degree of increase in creatinine appears to be of greater prognostic significance than the baseline value. In POSH (Prospective Outcomes Study in Heart failure), AKI was termed “worsening renal function” (WRF—as with other studies a 26.5 μmol/L or greater rise in creatinine). WRF was more likely to occur with a higher serum creatinine value on admission (OR, 3.02) and in those with pulmonary edema (OR, 3.35). The presence of WRF increased average length of hospital stay by 2 days, but in this study it did not influence readmission rates and mortality. Interestingly, analysis of the ESCAPE trial has shown that even an improvement in renal function is as poor an adverse prognostic marker as WRF in patients with decompensated heart failure. A suggested explanation for this counterintuitive finding is that patients who manifest altered renal function have more advanced disease than those who remain stable during the decompensation. The heterogeneous pathophysiology of acute heart failure must be of importance here, and its influence can be seen by the variable response of patients to diuretic therapy. It is well known that some patients manifest a deterioration in renal function, presumed secondary to poor
renal perfusion, following diuretic-induced decrease in cardiac filling pressure and cardiac output. However, some patients respond to diuretics with an increase in GFR, possibly achieved by an off-loading of intra-abdominal and renal venous pressure. Other patients have no change in renal function, and these patients may have cardiac physiology that manifests the flat part of the Starling curve, where changes in LV end-diastolic pressure have little effect upon cardiac output. An alteration in hemodynamics must play a central role in the above changes in renal function in acute heart failure and is emphasized by the improvements in GFR seen in patients treated with ventricular assist devices or cardiac resynchronization therapy.

In CHF, the presence of renal impairment has a major detrimental impact upon survival, and this has been extensively studied. In a meta-analysis of 16 studies that included >80 000 patients with CHF, the annual mortality was 24% in patients with normal renal function, 38% in those with mild renal impairment (GFR = 53-89 mL/min) and 51% in the presence of moderate impairment (defined here as GFR <53 mL/min). The increased risk of mortality was quantified as 15% for every 10 mL/min decline in GFR. In the CHARM program (Candesartan in Heart failure–Assessment of mortality and Morbidity), 80% of patients with CHF and renal impairment (GFR <53 mL/min) had mortality risk >2.92 times greater for patients with GFR <45 mL/min compared with those with GFR >75 mL/min, and this was independent of LV ejection fraction.

Conversely, cardiovascular disease accounts for over 50% of deaths in patients with CKD. Studies from the US Medicare system highlight the accentuation of risk brought about by various combinations of CKD (not at ESRD), heart failure, and anemia according to claims data. In a 5% annual random cohort from the Medicare database that included over 1.3 million subjects aged >65 years, the annual mortality for patients with no history of anemia, CKD, or heart failure was 4%. The baseline annual mortality for patients with CKD was independent of LV ejection fraction and was 2.92 times greater for patients with GFR <45 mL/min compared with those with GFR >75 mL/min, and this was independent of LV ejection fraction.

The baseline annual mortality for patients with no history of anemia, CKD or heart failure was 4%.

Abbreviations: CHF, congestive heart failure; CKD, chronic kidney disease.


### Table II. Relative annual mortality figures for patients who have had inpatient hospital visits relating to anemia, CKD, and heart failure.

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<td>Anemia, CHF, and CKD</td>
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This is now an area of increasing research in dialysis patients, as up to 25% of all deaths are attributed to SCD. Although SCD will be covered in one of the three reviews that follow this article, it is worth emphasizing the comparative epidemiology—SCD in the dialysis population occurs at 70 times the rate of that in the general population. Predisposing factors include the cardiac structural factors already discussed, myocardial changes (e.g., myocardial stunning) that occur during the dialysis procedure, as well as fluxes in electrolytes and water balance that are prone to develop around the time of a hemodialysis session.

### THE CLINICAL MANAGEMENT OF CARDIORENAL SYNDROME: HOW CAN WE OPTIMIZE OUTCOMES?

When considering the clinical management of the CRS, we find limitations when trying to separate disease states according to the classification. As there is a complex interrelationship between the organ systems, some therapies are applicable to most or all clinical presentations. Hence, hypertension control is a generic requirement and blockade of the RAAS would be considered routine in all patients with acute and chronic heart failure. It is also applicable to the majority of patients with CKD with the aim of controlling hypertension, ameliorating proteinuria, slowing progressive loss of renal function, and reducing cardiovascular risk. The treatment of anemia with intravenous iron and/or erythropoiesis-stimulating agents (ESA) has been embedded as a core part of CKD management for many patients with CKD and heart failure.
years, despite a rather limited evidence base, and it is now gaining a lot of attention in cardiology, particularly in heart failure treatment. Further discussion of this topic is merited and is covered in the already cited review by Ewa A. Jankowska and Piotr Ponikowski in this issue.

Class 3 CRS, when acute pulmonary edema complicates AKI, is seen very frequently in oliguric AKI from any cause and its management usually involves acute hemofiltration during dialytic therapy, which is outside the scope of this account. However, there are less common, but specific, related clinical scenarios that are worthy of mention, one being flash pulmonary edema. This accounts for around 5% of renovascular presentations and refers to acute heart failure occurring in the absence of significant myocardial ischemic injury, despite the absence of randomized trial evidence, there is a definite consensus that this presentation should be treated with renal revascularization therapy, which is now via percutaneous intervention in 99% of cases.

Limiting the development of cardiovascular complications in patients with CKD is a fundamental tenet of management in renal clinics, with hypertension control, renin-angiotensin blockade, lipid management, anemia correction, and reduction of vascular calcification risk being central. This is a huge topic and detailed discussion falls outside the scope of this review. The remainder of this section will provide a brief overview of therapies available for patients primarily presenting with heart failure, and having class 1 or 2 CRS.

Medical therapy

Blockade of the RAAS axis in the cardiorenal syndrome is covered by Luis M. Ruilope in this issue (cited above) and will not be discussed here. Blockade improves survival in patients with stage 3 CKD, CAD and heart failure (OR 0.75), whereas dialysis patients with heart failure also benefit, one study showing a 2-year all-cause mortality of 52% with carvedilol compared with 73% for placebo. Preemptive treatment with a β-blocker can also reduce the likelihood of developing de novo heart failure. However, as is the case with most medical therapies in heart failure, there is underutilization in patients with CKD compared with those without renal impairment, despite absence of any adverse evidence.

The historic core of medical therapy for heart failure involves diuretics, but nephrotoxicity and decline in renal function accompanying their use can cause a therapeutic dilemma. Those patients with decompensated heart failure and either associated AKI or underlying CKD are more prone to suffer further AKI due to diuretic drugs. Consequently, renin-angiotensin blockers are often discontinued during an acute admission because of AKI or hyperkalemia, but they should be reintroduced when the acute risk has passed. Patients with AKI or CKD are less responsive to diuretics than patients with preserved renal function. Higher-dose diuretic therapy correlates with poor outcome in heart failure, presumably because diuretic resistance reflects more severe CRS and more fragile hemodynamic status. Nesiritide, a B-type natriuretic peptide analog, does not reduce the need for diuretic or increase urine output in acute heart failure. Nitrates and hydralazine are useful alternatives to blockade of the RAAS when heart failure exacerbations are complicated by AKI, although hypotension may preclude their use. If nitrates are unable to stabilize a patient with severe heart failure who has AKI and diuretic resistance, the treatment options are then rather limited, at which point mechanical ultrafiltration may need to be considered.

Inotropic agents were once often used for treating severe decompensated heart failure, but this practice has now fallen from favor. For decades, low-dose dopamine has been used to encourage a diuresis in AKI based upon the knowledge that a response of specific intra-renal receptors resulted in an increase in renal blood flow (without significant inotropic effect), but in normal physiological conditions. Some physicians still use dopamine with the belief that it improves diuretic responsiveness and reduces the incidence and progression of AKI, but sound evidence of benefit is lacking.

Dialysis and hemofiltration for cardiorenal syndrome

Off-loading the heart in type 1 CRS by rapid removal of fluid with either dialysis or hemofiltration is an interesting development that has been used sporadically in the past, but which is now undergoing more robust scientific evaluation. Hemofiltration is the ultrafiltration of fluid via an extracorporeal machine, and has advantages over diuretic therapy in that rapid fluid and sodium removal can be achieved in the early phase of an admission with decompensated heart failure, minimizing the chance of deteriorating renal function or hypotension that frequently accompanies high-dose diuretic therapy. The hemofiltration process can be controlled and can thus be beneficial for very unstable patients who have labile blood pressure responses during treatment. Acute hemodialysis would be far more
risky in these unstable patients. Studies have shown short-term benefits with hemofiltration compared with intravenous diuretics in acute admissions with heart failure, but evidence regarding longer term outcome is needed. The logistics and safety of inserting a peritoneal dialysis catheter in an acutely unwell patient limit the applicability of peritoneal dialysis for the management of acute heart failure. However, the possibility of using peritoneal dialysis for refractory chronic heart failure in patients with and without advanced CKD is now gaining support. One small study of 17 patients started on peritoneal dialysis for refractory heart failure showed that it improved 1-year survival and resulted in fewer hospital admissions. Trials are now being developed to assess the efficacy of the therapy in a more robust manner.

When considering chronic dialytic therapies for ESRD, there has been a trend toward offering peritoneal dialysis rather than hemodialysis to patients with coexistent heart failure. This has been based on an assumption that patients with markedly impaired ventricular function will benefit from gradual fluid removal and so be less likely to suffer hypotensive collapse and/or serious arrhythmias that might result from hemodialysis. The evidence to support this practice is conflicting.

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Cardiorenal Syndrome

Expert Answers to Three Key Questions

1. How can we reduce sudden cardiac death in cardiorenal syndrome?
   
   R. N. Foley, C. A. Herzog

2. What is the optimal pharmacotherapeutic approach to cardiorenal syndrome?
   
   L. M. Ruilope

3. Should anemia be actively treated in cardiorenal syndrome?
   
   E. A. Jankowska, P. Ponikowski
How can we reduce sudden cardiac death in cardiorenal syndrome?

Robert N. Foley, MB, FRCP; Charles A. Herzog, MD
Chronic Disease Research Group - and Department of Medicine - University of Minnesota - Minneapolis - Minn - USA

While sudden cardiac death rates are inordinately high in advanced chronic kidney disease, evidence-based prevention algorithms are lacking. This article examines the difficulties of case definition in observational studies of intrinsically unhealthy populations, associations between event rates and declining kidney function, potentially modifiable risk markers, and the lack of evidence-based therapies. On the basis of high event rates, trials in the general population, and temporal patterns of event rates in dialysis patients, we argue that definitive trials of implanted cardioverter defibrillators, β-blockers, and more frequent hemodialysis need urgent consideration.

Keywords: β-blocker; cardiovascular event; chronic kidney disease; hemodialysis; dysrhythmia; implanted cardiac defibrillator; prevention; risk factor/marker; sudden cardiac death

Address for correspondence:
Robert N. Foley, MB, Chronic Disease Research Group, 914 South 8th Street, Suite S-406, Minneapolis, MN 55404, USA (e-mail: rfoley@cdrg.org)


SELECTED STUDY ACRONYMS

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Howomatous coronary artery disease is a very common condition in latter-day dialysis populations. In the early days of maintenance dialysis, when clinically overt coronary artery disease was a strict exclusion criterion for an extremely scarce therapy, it soon became clear that cardiovascular event rates were orders of magnitude beyond expectations. A pivotal paper was published in 1974 describing the clinical experience of 39 patients who received long-term hemodialysis in Seattle since 1960, with over 6.5 years of treatment per patient. 

Mortality rates were unexpectedly high for a population starting dialysis therapy with an average age of 37 years: 23 deaths were observed and “14 of 23 deaths could be attributed to arteriosclerotic complications, myocardial infarction being responsible for 8, strokes for 3, and refractory congestive heart failure for 3 deaths.” By today’s standards, autopsies were performed in a highly impressive 91% of cases. However, as the study was retrospective, pathological criteria for assigning cause of death were not systematically applied, and it was telling that the terms “arteriosclerosis” and “atherosclerosis” appear to have been used interchangeably in the study report. Ultimately, the title of this study “Accelerated Atherosclerosis in Prolonged Maintenance Hemodialysis” became an accepted pathogenetic concept in the end-stage renal disease community, one that resonates to this day.

Laying aside the still unsubstantiated hypothesis of accelerated atherosclerosis, there is something different about the uremic heart. For example, there is convincing experimental evidence that uremia leads to pathological cardiac hypertrophy, fibrosis, diastolic dysfunction, vascular and valvular calcification, and arterial stiffening. Even hemodialysis patients with pristine coronary arteries are continuously exposed to varying conditions of cardiac preload, afterload, ion fluxes, as well as repetitive myocardial ischemia and localized ventricular stunning from hemodialysis. In dialysis patients, while the relative proportions of atherosclerotic and nonatherosclerotic arteriosclerosis

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are usually unknown, there seems little doubt that patients enter into states of end-stage renal disease with disproportionately high burdens of clinically meaningful atherosclerotic vascular disease. Finally, while autonomic neuropathy is a classic feature of the untreated state, treated end-stage renal disease has been more recently characterized as a state of sympathetic nervous system overdrive.9

EPIDEMIOLOGY OF SUDDEN CARDIAC DEATH IN END-STAGE RENAL DISEASE

Event rates in dialysis patients

Some basic epidemiological observations suggest that cardiovascular disease event profiles are “different” in dialysis patients. For example, when reimbursement claims were examined in US dialysis patients, claims for cardiac failure, peripheral vascular disease, and sudden cardiac death far outstripped those for typical coronary heart disease.10

Sudden cardiac death is often defined as unexpected death within one hour of the onset of symptoms, or an unobserved, unexpected death without obvious noncardiac cause in a patient who was known to be well within the past 24 hours.11 If one assumes that all individuals don’t usually reside in hospital, this definition requires nonhospitalization for functionality in observational studies. This proviso poses challenges in dialysis patients, given that they typically have high burdens of comorbidity, spend a substantial amount of time in medical institutions, their deaths are usually unobserved, and precise timing of death may be impossible to determine. In addition, multiple cardiac and multiple noncardiac causes of death may be applicable in a given situation. Fashion and usage issues may also be important; for example, in situations where death is unobserved, sudden cardiac death may be a label of convenience in situations of indeterminate timing and causation.

Regarding attribution of cause of death, this is believed to be highly inaccurate in dialysis populations, especially in the current era where autopsy is rare. For example, in the well-known Hemodialysis (HEMO) Study, cause of death on the standard (in US patients) Death Notification Form (Form 2746) and death classified by the HEMO Study adjudication committee were in poor agreement. Using the HEMO Study designation as gold standard, sensitivity values for cause of death from the Death Notification Form were 9% for congestive heart failure, 38% for ischemic heart disease, and 39% for dysrhythmias and conduction disorders.12 To date, few if any studies have attempted to quantify the ability of predictor variables to discriminate sudden cardiac death from other deaths. If, as seems likely, one cannot reliably discriminate cardiac from noncardiac death, the epidemiological foundations of sudden cardiac death may be unsound. If these arguments turn out to be valid, it is a truism that the associations of sudden cardiac death are the same as for all-cause mortality, and vice versa.

Another neglected issue concerns the requirement for not being in hospital for case definition. With usual case definitions, admitting all patients to hospital indefinitely would completely eradicate the “disease,” at least in observational studies. In classic epidemiology, disease events can only be counted when they occur during a period when subjects are considered to be at risk. If one accepts this argument, it seems reasonable to propose that calculation of sudden cardiac death rates should account for periods of time in hospital in the calculation of the total time at risk. To date, these niceties have often been ignored and interim hospitalizations have usually been ignored in the calculation of exposure time. Some of these important theoretical issues are illustrated in Figure 1. As a preambule, two basic types of analysis are considered. With typical survival analysis (such as Cox regression), all follow-up ends at the first instant subjects are not at risk, whether or not they become at risk again in the future; returning to our scenario, if sudden cardiac death is predicated on occurrence outside of a hospitalization, follow-up ends at the first hospitalization. In a scenario of a period outside hospital, followed by a period in hospital, followed by a period outside hospital, only the information from the first of these time periods is used. With typical rate-based analysis (such as Poisson regression), the first and third periods would also contribute outcome information. In Figure 1, cases A and B are never hospitalized, and contribute identical event rates and follow-up time per person, and the issue of ignoring follow-up time is moot; there is one sudden cardiac death (as the event occurred outside hospital). Case C terminates with a cardiac death and D exits alive, as the cardiac death occurred in hospital neither case is classified as a sudden cardiac death; the follow-up time, however, depends on whether interim hospitalization time is considered (in which case the denominator for calculation of rates is 1 unit of time) or ignored (in which case the denominator is 3 units of time). In case E, depending on the analytic technique the rate of sudden cardiac death is 1/3, 0/1 or 1/2, in case F, three answers...
are also possible, 0/3, 0/1, or 0/2. Ultimately, if one totals all the sudden cardiac deaths and exposure times, the sudden cardiac death rate can be 2/18 (= 1/9), 1/10, or 2/12 = (1/6), depending only on the statistical technique used and the approach used to handle interim hospitalizations. Clearly, then, in populations where hospitalization is a common occurrence, working definitions dependent on nonhospitalization need close scrutiny.

Problems with case definition notwithstanding, sudden cardiac death appears to be common in dialysis patients. Bearing in mind that cardiovascular mortality rates are approximately 500 and 10 times higher than in the general population at ages 15 to 25 and 75 to 85, respectively, it is notable that sudden cardiac death is believed to underlie a quarter of the approximately 20% annual mortality seen in the US dialysis population. While registry data rarely undergo formal validation, it is of interest that cause of death breakdowns from larger randomized clinical trials and prospective studies of dialysis cohorts are very similar.\(^\text{14-17}\) Though, admittedly, cardiac arrest (whether fatal or not) is not well studied, there is general agreement among studies about high mortality rates after cardiac arrest, with reported 6-month survival spanning 3% to 11%.\(^\text{18-21}\)

**Figure 1. Definition of sudden cardiac death: methodological considerations.**

Dark green lines represent time out of hospital, light green lines, time in hospital. Dark green circles represent exit from follow-up because of sudden cardiac death, open green circles, other causes.

**Table I (page 270)**

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**Relationships between kidney function and sudden cardiac death**

Associations between sudden cardiac death and declining glomerular filtration rate appear to be routinely present when searched for, whether within subjects in controlled trials of automatic defibrillators or a heterogeneous group of cohort study settings.\(^\text{22-26}\) Thus, sudden cardiac death seems to parallel other cardiovascular events with respect to relationships with declining glomerular filtration rate. Importantly, risk is usually evident with apparently trivial declines in kidney function. While the overlap between declining kidney function and classic cardiovascular risk factors is usually substantial in public health settings, only a small proportion of the risk associated with declining kidney function is explained by overrepresentation of classic risk factors in typical epidemiological studies.\(^\text{27}\) With virtually every study showing similar broad findings, it is tempting to assume that the loss of kidney function causes cardiovascular disease. As a counterargument, it is interesting that uninephrectomy among kidney donors appears to add little if anything to cardiovascular risk, suggesting that shared (but unmeasured) risk factors account for the association between declining kidney function and cardiovascular outcomes.\(^\text{28}\)

**Potentially modifiable risk factors for sudden cardiac death in chronic kidney disease**

Possibly by virtue of being a nascent field, few planned, prospective studies have evaluated risk factors for sudden cardiac death in populations with clinically relevant kidney disease. For example, a PubMed search performed in October, 2011 with the search terms “(sudden cardiac death) and ([chronic kidney disease]) or [kidney function] or [renal function] or [end-stage renal disease] or [renal replacement therapy] or [dialysis]” yielded 503 citations and the vast majority of these were noninformative with regard to potentially modifiable risk factors. Table I shows associations of sudden cardiac death in dialysis populations, beyond expected entities like older age, diabetes, myocardial infarction, poor systolic function and left ventricular hypertrophy, and dilatation. One other study of a nondialedyzed population was relevant, a post-hoc analysis of MADIT-II (Multicenter Automatic Defibrillator Implantation Trial-II) among subjects with estimated glomerular filtration rates be-
Factors relating to delivery of dialysis are prominent in Table I. Hemodialysis is usually delivered three times weekly, with two 1-day intervals and one 2-day interval between dialysis sessions. As end-stage renal disease severely limits the capacity to tolerate volume and potassium-related deviations from normality, the 2-day interdialytic interval has long been a source of concern. Two clinical trials of daily hemodialysis—demonstrating beneficial effects on intermediate outcome like left ventricular mass and quality of life—have reignited interest in the issues of timing and frequency of hemodialysis session delivery.

Table I. Associations of sudden death in dialysis populations. *Numbers are citation references.

<table>
<thead>
<tr>
<th>Related to HD Procedure</th>
<th>Comments</th>
<th>Design*</th>
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<tbody>
<tr>
<td><strong>Comments</strong></td>
<td>Prospective</td>
<td>Retrospective</td>
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<tr>
<td><strong>Related to HD Procedure</strong></td>
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<td>Interval between HD</td>
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<td>Low potassium dialysate</td>
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<td>Low calcium dialysate</td>
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<td>High HD ultrafiltration</td>
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<td>Catheter for HD</td>
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<tr>
<td><strong>Electrocardiographic</strong></td>
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<td>Absence of sinus rhythm</td>
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<td>Increased heart rate</td>
<td>Holter monitoring</td>
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<td>QT interval</td>
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<tr>
<td>Impaired baroreflex sensitivity</td>
<td>Electrocardiogram and beat-to-beat BP recorded continuously</td>
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<td>QT dispersion</td>
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<tr>
<td>Sympathetic hyperactivity</td>
<td>Holter-based beat-to-beat variability</td>
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<td><strong>Blood levels</strong></td>
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<td>Predialysis K</td>
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<tr>
<td>Glycosylated hemoglobin</td>
<td>HD with diabetes, RCT of atorvastatin</td>
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<tr>
<td>Vitamin D deficiency</td>
<td>HD with diabetes, RCT of atorvastatin</td>
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<tr>
<td>Copeptin</td>
<td>Hypothesized as a surrogate for arginine-vasopressin. HD with diabetes, RCT of atorvastatin</td>
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<td>Ca-P product</td>
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<td>C-reactive protein</td>
<td>HD with diabetes, RCT of atorvastatin</td>
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<td>Low serum albumin</td>
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<td>Interleukin-6</td>
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<td>Predialysis creatinine</td>
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<td>P-selectin</td>
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<td>Low urinary output</td>
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<td>High systolic BP</td>
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<td>Low diastolic BP</td>
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<td>N-terminal pro-BNP</td>
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Abbreviations: BNP, brain natriuretic peptide; BP, blood pressure; Ca, calcium; HD, hemodialysis; K, potassium; P, phosphorus; RCT, randomized controlled trial.
To date, the observational studies examining the associations of the long interdialytic interval have concentrated on sudden cardiac death and cardiac arrest. The landmark study of Bleyer et al examined 7-day patterns of sudden death and cardiac death in US hemodialysis patients between 1977 and 1997. Sudden death and cardiac death were approximately 40% more likely than expected on Mondays and Tuesdays. The same group examined the timing of sudden death in hemodialysis patients in a retrospective study including 228 patient deaths. 35% of which were considered to be “sudden.” The risk of death increased by a factor of 1.7 during the 12-hour period starting with the dialysis procedure and by a factor of 3 in the 12-hour period at the end of the long interdialytic interval. Another group examined 400 cardiac arrests occurring in dialysis units affiliated with a large dialysis chain, between 1998 and 1999. The observed cardiac arrest rate was equivalent to 1.1 per 100 person-years and cardiac arrest was much more likely on Mondays; case fatality rates were 60% within 48 hours following cardiac arrest.

We have recently reexamined the close-to-universal paradigm of three times weekly schedules in a nationally representative sample of US patients receiving hemodialysis at the end of calendar years 2004 through 2007, followed for 2.2 years. Adverse event rates were noticeably higher on the day after the 2-day interdialytic interval than on other days: all-cause mortality, 23% (higher); mortality from cardiac causes, 36%; mortality from cardiac arrest, 30%; admissions for any cardiovascular event, 124% higher and admissions for dysrhythmia, 90% higher than at other times during the dialysis week. When examined by days of the dialysis week, adverse events followed a downward-tilted sawtooth pattern with the following characteristics: highest rates on the dialysis day following the long interdialytic interval, higher rates on dialysis days than on ensuing nondialysis days; higher rates early in the week than later (Figure 2).

Finally, when examined by subgroup, the finding of heightened risk after the long interval appeared to be a close-to-universal phenomenon. With most observational studies, one looks at a single outcome in different segments of the population. When differences are found, it is impossible to refute the argument that unmeasured differences in the population segments are responsible for differences in study outcomes. A different argument needs to be invoked when examining outcomes on different days of the week: thus, identical populations are being considered when outcomes on

![Figure 2. Annualized mortality (A) and cardiovascular disease admission rates (B) on different days of the hemodialysis (HD) week.](image-url)
How can we reduce sudden cardiac death in cardiorenal syndrome? - Foley and Herzog

Mondays, for example, are being compared with outcomes on other days. Accordingly, if one finds disparities in outcome rates related to days of the hemodialysis week, the corresponding irrefutable explanatory hypothesis is that an unmeasured temporal factor links the excess mortality on certain days to the scheduling of dialysis sessions.

RISK STRATIFICATION: GENERAL POPULATION FACTORS THAT MAY BE APPLICABLE IN CHRONIC KIDNEY DISEASE

It is generally believed that most sudden cardiac death cases in the general population exhibit coronary artery disease on autopsy. Though likely to be very common, the true burden of coronary artery disease is usually unclear in dialysis patients, as definitive diagnostic studies are rarely applied systematically. To date, there is little evidence to prove that coronary artery disease is the dominant underlying factor, at least on a proportionate basis, a hypothesis that appears to be supported by the failure of statins to confer benefit in dialysis populations in well-designed clinical trials. Lack of autopsy data has clearly retarded pathophysiological insights, as, to date, only one study has reported autopsy findings in dialysis patients who died suddenly. In the latter study, causes of sudden death were investigated in 113 Japanese patients who died between 1979 and 1989. Autopsy was performed in 93 of the cases, and 35 of these were considered to be sudden deaths.

Dissecting aortic aneurysm was the most common cause of sudden death (5), followed by cerebral hemorrhage (3), acute subdural hematoma (3), acute myocardial infarction (2), cerebral infarction (2), and subarachnoid hemorrhage (1). While the applicability of these findings to latter-day populations is clearly uncertain, and cerebrovascular events are much more common in Japanese than Western populations, these findings are still noteworthy.

Though likely to be very common, left ventricular hypertrophy, which is strongly associated with sudden death in the general population, is typically present in about 4/5 of maintenance dialysis patients. Possibly because the issue of sudden cardiac death has only recently come to prominence, associations between left ventricular hypertrophy and sudden cardiac death have yet to be clearly defined.

INTERVENTIONS TO PREVENT SUDDEN CARDIAC DEATH

Sadly, there are no definitive randomized trials to guide preventive therapy for sudden cardiac death in patients with advanced chronic kidney disease. When “trial” was added to the PubMed search terms described above, only yielded 3 relevant citations (Table II) were found (for implanted cardiac defibrillators, nicorandil, and candesartan); none of these trials was both specific to a population with clinically meaningful chronic kidney disease and designed with sudden cardiac death as primary outcome.

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Secondary outcome</th>
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<tr>
<td>CKD only</td>
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<tr>
<td>Nicorandil</td>
<td>D59</td>
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<td>ICD</td>
<td>ND52</td>
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<td>Candesartan</td>
<td>D57</td>
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Table II. Interventions to reduce sudden cardiac death in CKD: evidence base.
Numbers are citation references.
Abbreviations: CKD, chronic kidney disease; D, dialysis; ICD, implanted cardiac defibrillator; ND, nondialysis.

Left ventricular hypertrophy, which is strongly associated with sudden death in the general population, is typically present in about 4/5 of maintenance dialysis patients. Possibly because the issue of sudden cardiac death has only recently come to prominence, associations between left ventricular hypertrophy and sudden cardiac death have yet to be clearly defined.
How can we reduce sudden cardiac death in cardiorenal syndrome? - Foley and Herzog

Cardiac death in dialysis patients, combined with the inability to define phenotypic characteristics that could reliably discriminate low- and high-risk subgroups, support the argument that a trial of implanted cardiac defibrillators should be applied to all dialysis patients where a primary indication does not already exist. In a less ideal world, one could argue that patients with at least moderate systolic dysfunction or left ventricular hypertrophy, overt coronary artery disease, and diabetic nephropathy might be candidates for this hypothetical trial.

A number of interesting observational studies of dialysis patients have been reported. Among them was a retrospective cohort study whose objectives were to examine implanted cardiac defibrillator use and survival associations. A subset of approximately 6000 US dialysis patients who survived to discharge following hospitalization for ventricular fibrillation or cardiac arrest was identified. Mortality associations of implanted cardiac defibrillators placed within 30 days of admission were examined with both a comorbidity-adjusted Cox model and a propensity model approach. Of these patients, 7.6% had an implanted cardiac defibrillator and associated 1-, 2-, 3-, 4-, and 5-year survivals were 71%, 53%, 36%, 25%, and 22%, respectively. Corresponding values were lower in the group without an implanted cardiac defibrillator, at 49%, 33%, 23%, 16%, and 12%. Survival disparities persisted with standard comorbidity adjustment and with the propensity-adjusted approach. Similar issues were examined in a more recent cohort of US dialysis patients over a longer time frame, 1994 to 2006, wherein mortality in implanted cardiac defibrillator recipients and otherwise similar nonimplanted cardiac defibrillator patients were compared with high-dimensional propensity score matching. More than 88% of implanted cardiac defibrillators were placed after 2000, with implanted cardiac defibrillators in the 1990s exclusively used for secondary prevention, in contrast to the situation in 2006, when half the implanted cardiac defibrillators were used for primary prevention. All-cause and cardiovascular mortality rates remained high in dialysis patients even after implantation, and device infections were not uncommon. Although implanted cardiac defibrillator use in US dialysis patients accelerated from 2000 to 2005, data for subsequent years suggest a plateau after 2005, possibly reflecting concerns about long-term efficacy.

Considering their up-front cost, it seems clear that randomized controlled trials are needed to streamline appropriate use of these devices. In this regard, the ICD2 (Second Implantable Cardioverter Defibrillators in Dialysis Patients) trial is of great relevance. This trial plans to evaluate the effect of preventive implanted cardiac defibrillator therapy on sudden cardiac death rates in dialysis patients aged 55 to 80 years. The study plans to enroll a total of 200 patients, with 4 years of follow-up. While the sample size of this study is likely to be beset by Type II power issues, it should provide invaluable information about the feasibility of doing a larger more definitive study.

Among pharmacological therapies, β-blockers are an attractive option for a future randomized trial in advanced chronic kidney disease. In this regard, the findings of a study by Cic et al were noteworthy. In a placebo-controlled trial of 114 dialysis patients with dilated cardiomyopathy, carvedilol led to a favorable left ventricular phenotype, lower mortality, lower cardiovascular mortality, fewer all-cause and heart-failure related admissions to hospital and fewer fatal myocardial infarctions and strokes. Another group assessed whether the subgroup of systolic heart failure patients with chronic kidney disease benefited from carvedilol therapy by performing a post-hoc analysis of pooled individual patient data from the CAPRICORN (Carvedilol Post infarction survival CoNtrolled) and COPER-NICUS (CarvedilolOIl ProspEctive RaNdomized, CUMulative Survival) studies. Among the 60.8% of study subjects with estimated glomerular filtration rates below 60 mL/min/1.73 m², treatment with carvedilol decreased the risks of death, first heart failure hospitalization, and the composite of cardiovascular mortality or heart failure hospitalization. Interestingly, a clear effect on sudden cardiac death was not discernible. Finally, based on observational evidence linking 2-day intervals to adverse outcomes in typical hemodialysis populations, trials of strategies that avoid these intervals need serious consideration.

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Prevention of sudden cardiac death: rationale and design of the Implantable Cardioverter Defibrillators in Dialysis patients (ICD2) Trial—a prospective pilot study.

Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: a prospective, placebo-controlled trial.
What is the optimal pharmacotherapeutic approach to cardiorenal syndrome?

Luis M. Ruilope, MD, PhD
Chief Hypertension Unit - Hospital 12 October - and Professor of Public Health and Preventive Medicine
Autonomous University of Madrid - Madrid - SPAIN

“Cardiorenal syndrome” refers to the different combinations of simultaneous impairment in cardiac and renal function. The presence of albuminuria and/or diminished estimated glomerular filtration rate (eGFR) results in increased risk of cardiovascular (CV) events and of developing end-stage renal disease. The high prevalence of chronic kidney disease along the CV continuum is explained by the fact that they share common pathophysiological mechanisms. This also explains the similarities in pharmacological treatment aimed at protecting the CV and renal systems. Decreased eGFR can contraindicate dual blockade of the renin-angiotensin-aldosterone system with an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker, in combination with an aldosterone blocker.

Keywords: albuminuria; aldosterone blocker; angiotensin-converting enzyme inhibitor; angiotensin receptor blocker; cardiorenal continuum; chronic kidney disease; glomerular filtration rate; hyperkalemia; renin-angiotensin-aldosterone system

Address for correspondence: Professor Luis M. Ruilope, MD, PhD, Unidad de Hipertensión, Hospital 12 de Octubre, Avda Córdoba s/n, 28041 Madrid, Spain (e-mail: ruilope@ad-hocbox.com)


Figure 1. Representation of cardiorenal continuum.

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease.
carotid plaques) to predict CV mortality independently of SCORE (Systemic Coronary Risk Evaluation from the European Society of Cardiology [ESC] stratification).9 is an argument in favor of preventing TOD. It is also important to take into account other preventable types of TOD, such as, for example, alterations in microvascular function: thus, hyperemic velocity has recently been recognized as an important parameter for improving risk stratification in apparently low-risk healthy men.10 Also, this is the stage where it is important to look for early markers of renal damage in an attempt to define a pre-CKD stage, in a similar way as we define prehypertension or prediabetes today.

• Stage 2 is characterized by the presence of one or several types of subclinical TOD, such as the presence of CKD. Adequate control of BP and other risk factors can facilitate the regression of TOD. Preliminary data indicate that regression of albuminuria11,12 and LVH13,14 is associated with a significant decrease in number of CV events. In contrast, increase in urinary albumin excretion predicts the development of CV events or death.12 These findings suggest the usefulness of monitoring TOD in patients at this stage of the cardiorenal continuum and of including prevention of TOD as an end point in future trials, in particular in hypertensive patients.

• Stage 3 is characterized by the presence of clinically overt CV disease and/or advanced renal failure due to the progression of TOD and atherosclerosis. Both conditions ultimately result in CV mortality or end-stage renal disease (ESRD), which in the absence of dialysis is also fatal. Active intervention on BP and associated cardiovascular risk factors together with therapies specifically directed at overt CV and renal disease in many cases unfortunately only delays the appearance of new CV or renal events. Identification of patients at high risk of developing CV and renal events in the first two stages described above is therefore of enormous importance because the great majority of CV and renal events take place in patients belonging to those two stages. Age, clustering of CV and renal risk factors, and presence of diverse forms of TOD together with the emerging role of genetics and newer techniques such as proteomics will greatly facilitate this task.

In summary, adequate management of modifiable CV risk factors as soon as they are detected will greatly contribute to slowing the progression of atherosclerosis and CKD, thereby ensuring long-term benefits.

The term cardiorenal syndrome describes five situations in which the heart and the kidney interact: acute situations where failure of the one affects the other (= 2), situations in which a chronic condition of one affects the other (= 2), and finally systemic alterations that can affect heart and kidney simultaneously (= 1).15 In this paper I will exclusively refer to the cross-talk between heart and kidney in situations of chronic kidney disease and how the latter influences our therapeutic attitude in patients with heart disease.

DETECTION OF CHRONIC KIDNEY DISEASE

The two relevant measures to detect the presence of CKD are the calculation of glomerular filtration rate (usually estimated using a formula = eGFR) and the finding of albumin in the urine. The CKD-EPI16 formula is the most widely used one because it corrects for much of the overestimation of CKD, especially among eGFR values between 60 and 89 mL/min/1.73 m². Formulas to estimate GFR rely on the accuracy of serum creatinine measurement, avoiding the presence of chromogens, which can increase its value by up to 20%.

Albuminuria can be determined over the 24 h (mg/24 h) or overnight (μg/min), but the presence of albuminuria is most frequently assessed by obtaining three early morning spot urine samples at different times over 1 or 2 months. Two out of the three with values above 30 mg/g of

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**SELECTED ABBREVIATIONS AND ACRONYMS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ARB</td>
<td>angiotensin receptor blocker</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>CKD</td>
<td>chronic kidney disease</td>
</tr>
<tr>
<td>CV</td>
<td>cardiovascular</td>
</tr>
<tr>
<td>DRI</td>
<td>direct renin inhibitor</td>
</tr>
<tr>
<td>eGFR</td>
<td>estimated glomerular filtration rate</td>
</tr>
<tr>
<td>ESRD</td>
<td>end-stage renal disease</td>
</tr>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
</tr>
<tr>
<td>LVH</td>
<td>left ventricular hypertrophy</td>
</tr>
<tr>
<td>RAAS</td>
<td>renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>SCORE</td>
<td>Systemic Coronary Risk Evaluation</td>
</tr>
<tr>
<td>TOD</td>
<td>target-organ damage</td>
</tr>
</tbody>
</table>
Creatinine is enough to declare the presence of microalbuminuria. Values above 300 mg/dL define the presence of macroalbuminuria or proteinuria.

The definition and classification of CKD is contained in Table 1, where five stages can be seen, according to eGFR values. In the first two, CKD is only defined by the presence of albuminuria while in the other three it is the level of eGFR that defines the presence of CKD, rather than albuminuria.

Both an eGFR < 60 mL/min/1.73 m² and the presence of microalbuminuria are independent and additive predictors of future CV morbidity and mortality. CKD is a common process whose prevalence is over 10% in the general population, with 6% to 7% having only microalbuminuria and 3% to 5% having a diminished eGFR. Most of the perceived prevalence of CKD is accounted for by individuals older than 60 years, and according to El Nahas such a high prevalence of CKD in people with advanced age represents a situation of diffuse and age-related cardiorenal damage that requires careful evaluation and treatment.

Why is CKD so prevalent in CVD and vice versa?

The Framingham study showed that established CV risk factors (age, body mass index, diabetes, smoking, hypertension, high-density lipoprotein (HDL)-cholesterol, and the level of eGFR) are associated with the development of new-onset kidney disease. In many cases, the same risk factors contribute to the simultaneous development of CV and renal disease. Patients with eGFR < 90 mL/min/1.73 m² and established CV risk factors should be monitored for the progression of kidney disease. Their common origin explains why CV and renal disease are so frequently seen together and why the presence of CKD worsens the prognosis of established CV disease.

PHARMACOTHERAPY IN CARDIORENAL DISEASE

Figure 2 (page 280) depicts the pathophysiological mechanisms underlying the cross-talk between CV and renal disease. The main factors involved in injury to the CV system and the kidney include activation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems (SNS) and alteration in renal sodium excretion (DNaU). Their action combines to promote the clinical manifestations of CV disease (coronary artery disease, heart failure, stroke, and peripheral artery disease) as well as the progression of CKD and the onset of albuminuria. Once renal function is altered, new risk factors appear that hasten the progression of CV and renal disease, such as anemia, calcium-phosphate disorders, and vitamin D deficiency, while the deleterious effect of the three main factors—RAAS, SNS, and DNaU—further increases.

As can be seen in Figure 2, the optimal therapy is similar for both CV and renal protection and includes appropriate lifestyle measures such as physical activity and quitting smoking, and achieving adequate control of BP, blood lipids, HbA1c, and body weight. Pharmacotherapy consists of an ACE inhibitor or an ARB at the highest tolerated dose, usually in conjunction with other antihypertensive drugs, in particular calcium channel blockers and diuretics when BP is elevated, and anti-diabetic therapy in diabetics. The use of a statin is mandatory as is diabetic therapy in diabetics. The use of aspirin when CKD is present. New forms of therapy have to be added when impairment in renal function progresses, such as phosphate binders, vitamin D supplements (including vitamin D receptor agonists), and erythropoietin. These new treatments also contribute to counteract the progression of CV and renal damage.

RAAS AND SNS AS PRIMARY THERAPEUTIC OBJECTIVE IN CARDIORENAL DISEASE: ADVANTAGES AND RISKS

Chronic activation of the RAAS and SNS is implicated in a wide range of chronic diseases, including hypertension, diabetes, and heart failure. RAAS inhibition has been shown to improve renal function and reduce proteinuria in patients with diabetic nephropathy.

Table 1. The five stages of chronic kidney disease (CKD).

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>At increased risk</td>
<td>Risk factors for kidney disease (diabetes, high blood pressure familial history, older age, ethnic group)</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Stage 1</td>
<td>Kidney damage (albuminuria) and normal renal function</td>
<td>&gt; 90</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Kidney damage and mild decrease in GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Moderate decrease in GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Severe decrease in GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>Stage 5</td>
<td>Kidney failure (dialysis needed soon)</td>
<td>&lt; 1</td>
</tr>
</tbody>
</table>

of CV diseases, as described in Figure 3. As can be seen, these two systems promote the development and progression of TOD in the brain, vessels, kidney, and heart, leading to the development of CV events and CKD, resulting in death. Thus, a series of mechanisms starting with endothelial dysfunction lead to the development and progression of atherosclerosis, arteriosclerosis, hypertrophy and increased stiffness of the vessels, decrease in eGFR and albuminuria, resulting in progressive glomerulosclerosis, cardiac hypertrophy, fibrosis and remodeling, and ultimately coronary artery disease and heart failure.

Blocking the adverse effects of the RAAS has been a main goal in the treatment of CV and renal disease for the past 30 years. Use of ACE inhibitors, ARBs, and more recently direct renin inhibitors (DRIs) should be started in clinical practice from the very first stages of the cardiorenal continuum to prevent the development of TOD or regress its manifestations.1-4 Early RAAS suppression also prevents the development of established hypertension.5-7

Early RAAS suppression started to be used following initial positive results obtained in heart failure, post myocardial infarction, and patients with increased global CV risk or advanced renal failure. Initially, the benefits of these drugs were mostly attributed to the suppression of the effects of angiotensin II, while the role of aldosterone and of the mineralocorticoid receptor received less attention because it was initially assumed that treatment with an ACE inhibitor would also suppress aldosterone. The mechanisms of angiotensin II binding to the AT1 and AT2 receptors is depicted in Figure 4. The clinical interest in blocking aldosterone in patients already treated with an ACE inhibitor or ARB has been stimulated by recent trials in heart failure9 and resistant hypertension.10 In both cases, spironolactone and eplerenone were found to be very effective.

However, RAAS suppression may give rise to unwanted and deleterious side effects. Hypotension, decrease in eGFR, and hyperkalemia are the main complications associated with RAAS suppressors. Pre-existing sodium depletion and reduced eGFR are the most important factors contributing to these complications. Aldosterone blockers, in
particular when added to an ACE inhibitor or an ARB should be used with caution when eGFR values are below 30 mL/min/1.73 m². However, each case should be considered on an individual basis and the risk/benefit ratio carefully assessed. This means that in patients with established CV disease in whom the enhancement of CV risk due to the presence of CKD is the highest, the possibility of using RAAS blockade obtained with an ACE inhibitor, ARB, or DRI in combination with an aldosterone blocker may be limited by the potential development of hyperkalemia, particularly in patients with serum potassium levels above 5 mmol/dL before introducing the aldosterone blocker.

Combination therapy with β-blockers also contributes to increasing the risk of hyperkalemia as does a high potassium intake or the use of nonsteroidal anti-inflammatory drugs. Administration of higher doses of loop diuretics can increase urinary potassium excretion. Finally, the usefulness of chronic treatment with potassium binders is currently being evaluated.

Evidence has accumulated over the past three decades that SNS activation is crucial in the development of CV disorders, most notably heart failure and arterial hypertension, and that its activity is significantly increased in CKD, as reflected by high cardiac norepinephrine spill-over and reduced myocardial norepinephrine stores. These pathophysiological findings have translated into better treatment for heart failure patients thanks to the introduction of β-adrenergic blockers. However, evidence of efficacy has been established only for some β-adrenergic blockers (bisoprolol, metoprolol succinate, carvedilol, and nebivolol), and, therefore, patients receiving therapy for a comorbid condition have to be switched to one of the above β-adrenergic blockers. In the case of arterial hypertension, it is now well established that renal sympathetic innervation plays a pivotal role in the pathogenesis of essential hypertension by influencing renin release, GFR, and

Figure 3. Implications of the RAAS and SNS in cardiovascular and renal diseases.
Abbreviations:
CKD, chronic kidney disease;
RAAS, renin-angiotensin-aldosterone system;
SNS, sympathetic nervous system.

Figure 4. Cardiorenal consequences of the binding of angiotensin II to AT₁ and AT₂ receptors.

AT₁ receptor
- Aldosterone Secretion
- Sodium retention
- Vasoconstriction
- Inflammation
- Cell growth
- Hypertrophy
- Angiogenesis

AT₂ receptor
- Vasodilation
- Antigrowth
- Antihypertrophic effect (?)
- Apoptosis
- Angiogenesis (?)

Modulation of cardiovascular and renal damage
renal tubular sodium reabsorption. Antiadrenergic therapies include aerobic exercise training, and caloric restriction, in addition to the use of centrally acting sympathetic suppressants, imidazoline-binding agents such as moxonidine and rilmenidine. However, these drugs are underused in the treatment of arterial hypertension.

Very recently, a new technique using renal artery catheter-based renal denervation has been shown to control the blood pressure in resistant hypertension, opening a new way to improve the influence of sympathetic nervous activity in other situations such as milder forms of hypertension and heart failure.

**SUMMARY**

The presence of CKD is very frequent throughout the CV continuum. The term cardiorenal syndrome refers to the various combinations of simultaneous impairment in cardiac and renal function. The presence of albuminuria and/or diminished eGFR contribute to increasing the risk of CV events, mortality and progression to end-stage renal disease. The high prevalence of CKD in the CV continuum is explained by the fact that they share similar pathophysiological mechanisms; this also explains the similarity between pharmacological treatments to protect the CV and renal systems. Advanced forms of renal failure require addition of specific therapy to achieve dual protection of the CV system and kidney. Diminished eGFR may contraindicate dual RAAS blockade with an ACE inhibitor or an ARB together with an aldosterone blocker.

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Should anemia be actively treated in cardiorenal syndrome?

Ewa A. Jankowska, MD, PhD, FESC; Piotr Ponikowski, MD, PhD, FESC
Department of Heart Diseases - Wroclaw Medical University - and Center for Heart Diseases - Military Hospital - Wroclaw - POLAND

Anemia and/or iron deficiency (ID) is a frequent comorbidity in patients with cardiorenal syndrome, and together with heart failure (HF) and chronic kidney disease (CKD) constitutes the cardio-renal-anemia syndrome. There are substantial differences in the pathogenesis of anemia as well as in the effect of treatment with erythropoietin (EPO) or its analogs (with or without iron), depending on whether anemic patients have primary HF or primary CKD. Studies with EPO or its analogs in anemic patients with HF are still inconclusive, and show evidence of EPO resistance, in most cases associated with inflammation and/or ID. IV iron improves functional status, quality of life, and exercise capacity in ID patients with HF and may potentially become a novel therapeutic approach in anemic HF patients in the near future.

Althouigh in recent years there has been an enormous progress in the management of patients with heart failure (HF), both quality of life and prognosis remain poor in this clinical syndrome, and HF still constitutes a serious economic burden in modern societies. Therefore, there is an urgent need for the implementation of novel therapies.

There is no doubt that myocardial damage is the very first event in the complex pathophysiology of HF, and that this precipitates the subsequent changes occurring in most body organs and tissues, including renal and hematopoietic systems. Importantly, there is increasing evidence that these triggered peripheral pathophysiological mechanisms and comorbidities (such as renal failure and/or anemia), which are directly related to augmented symptoms and poor outcomes, are potential therapeutic targets in patients with HF.

Impairment of renal function is a relatively common and ominous disorder occurring in the course of HF, and the combination of these two entities forms the so-called cardio-renal syndrome. The combination of chronic kidney disease (CKD) and HF is of particular importance, because each disorder can accelerate the progression of the other and negatively affect outcomes. It has recently been recognized that due to common pathophysiological mechanisms and etiological and risk factors, these disorders frequently coexist with anemia and/or iron deficiency (ID), prompting the following designations, cardiorenal-anemia syndrome [CRAS] and cardiorenal-anemia-ID syndrome [CRAIDS], respectively, to be proposed.

It was more than 50 years ago that anemia and ID were first reported to further worsen the compromised hemodynamics in HF, but surprisingly these intriguing observations remained neglected. Recently, anemia and ID have been receiving growing interest among both scientists and clinicians as potential novel therapeutic targets in patients with HF.

**PATHOPHYSIOLOGICAL MECHANISMS LEADING TO ANEMIA AND IRON DEFICIENCY IN HEART FAILURE**

The pathophysiology of anemia and/or ID in patients with HF is complex, multifactorial, and still unclear. Several pathophysiological mechanisms are presumed to contribute to the development of anemia in the course of HF (Table I). Angiotensin II diminishes renal perfusion and as a consequence increases erythropoietin (EPO) secretion by the kidneys, hence inhibition of angiotensin-converting enzyme (ACE) inhibitors or signal-
Inflammation (due to treatment with angiotensin receptor blockers [ARBs]) may reduce circulating EPO in patients with HF. ACE inhibition also blocks the disintegration of N-acetyl-seryl-aspartyl-lysyl-proline (a suppressor of hematopoietic stem cell proliferation) and inhibits bradykinin degradation (which induces migration and homing of endothelial progenitor cells and endothelial repair).

Augmented generalized inflammation with high circulating proinflammatory mediators and their increased expression in myocardium and peripheral tissues constitutes a crucial element of the complex pathophysiology of HF. In most cases, anemia occurring in patients with HF is an anemia of chronic disease (ACD), of immunologic origin, or/and anemia due to ID, where the involvement of immune mechanisms has also been postulated, but not been definitively proven.

In the study of Opasich et al, 20% of anemic patients with systolic HF had microcytic anemia (accompanied by absolute ID), and 57% of them had ACD (accompanied mainly by functional ID). It is suggested that in patients with HF, proinflammatory mediators (such as interleukin 6 [IL-6]) also impair the functioning of the hematopoietic system. Namely, they contribute to the reduced EPO production by the kidneys, decrease bone marrow responsiveness to EPO, induce EPO resistance within extrahematopoietic tissues, and restrict iron availability for hematopoiesis and other metabolic needs.

Patients with HF have high circulating EPO levels, which increase proportionally to the severity of heart disease. Among patients with HF (but not in healthy subjects), there is only a weak negative correlation between circulating EPO and hemoglobin levels, which may reflect the impaired response of bone marrow to EPO stimulus (resistance to EPO). In addition to augmented generalized inflammation, there are other potential causes of EPO resistance in HF, such as: ID, infections, malignancy, secondary hyperparathyroidism, vitamin B\textsubscript{12} or folic acid deficiencies, intrinsic bone marrow dysfunction, hemolysis, and drug interactions.

Table 1. Major potential pathophysiological mechanisms favoring the development of anemia in heart failure.

<table>
<thead>
<tr>
<th>Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; EPO, erythropoietin; ID, iron deficiency.</th>
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<tr>
<td>(hs)CRP</td>
</tr>
<tr>
<td>ACD</td>
</tr>
<tr>
<td>CHOIR</td>
</tr>
<tr>
<td>CKD</td>
</tr>
<tr>
<td>CREATE</td>
</tr>
<tr>
<td>EPO</td>
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<td>ESA</td>
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<td>FAIR-HF</td>
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<tr>
<td>HF</td>
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<tr>
<td>ID</td>
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<tr>
<td>MCV</td>
</tr>
<tr>
<td>NT-proBNP</td>
</tr>
<tr>
<td>RDW</td>
</tr>
<tr>
<td>RED-HF</td>
</tr>
<tr>
<td>STAMINA–HeFT</td>
</tr>
<tr>
<td>TIBC</td>
</tr>
<tr>
<td>TREAT</td>
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<td>TSAT</td>
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iron stores in the organism, whereas functional ID is diagnosed when there is an inadequate iron supply to meet actual metabolic demand despite normal or even abundant body iron stores, and presence of iron within the reticuloendothelial cells. In case of both absolute and functional ID, iron remains unavailable to cellular metabolism. The potential causes of absolute ID seen in HF are: poor nutrition lacking sufficient iron supply, reduced gastrointestinal absorption (due to, eg, mucosal edema), drug interactions, and gastrointestinal blood loss (also occult), excessive menstrual bleeding, medications favoring bleeding.

Functional ID is thought to be driven mainly by inflammatory stimuli (eg, IL-6), which induce the liver synthesis of hepcidin. Hepcidin is the major regulator of iron metabolism, and when released into the circulation, blocks intestinal iron absorption, traps iron in the reticuloendothelial cells, and as a consequence results in a blockade of iron influx to iron metabolizing cells. Importantly, this pathophysiological mechanism, although seen in CKD patients and cancer, has not been evidenced to date in the clinical setting of HF.

It should be emphasized that although there are many similarities in the pathophysiological mechanisms leading to anemia in patients with HF and CKD, there are also some differences. Most importantly, patients with CKD usually exhibit absolute EPO deficiency, although circulating EPO levels are also increased, but are inappropriately low in relation to hemoglobin levels. In contrast, patients with HF have very high circulating EPO, and EPO resistance is the prominent feature of anemia associated with HF. These pathophysiological differences may at least partially explain the discrepancies observed in the effects of erythropoiesis stimulating agents (ESA) in patients with HF and those with CKD (see comment below).

DEFINITION AND PREVALENCE OF ANEMIA AND IRON DEFICIENCY IN HEART FAILURE

According to the World Health Organization, anemia is diagnosed when hemoglobin is <13 g/dL in men and <12 g/dL in postmenopausal women. According to the National Kidney Foundation, anemia is diagnosed when hemoglobin is <12 g/dL in both men and postmenopausal women.

Anemia occurs relatively frequently in HF, with a prevalence varying from approximately 10% to 55%, due to differences in the severity of heart disease in studied HF populations and in definitions of anemia. Anemia is more prevalent in patients at advanced stages of HF, in older and female subjects, in those with multiple comorbidities (eg, renal failure), and in patients with cardiac cachexia.

Whereas the diagnosis of anemia, based only on hemoglobin level, is straightforward, on the contrary, the diagnosis of ID is more complex, particularly in patients with chronic inflammatory diseases. Direct assessment of iron stores in bone marrow biopsy is the gold standard for the diagnosis of ID, but in the majority of cases this procedure is replaced by parameters measured in peripheral blood, such as: serum ferritin, transferrin saturation (TSAT), the ratio of serum iron and total iron binding capacity (TIBC) by transferrin, multiplied by 100 (TIR), serum soluble transferrin receptor (sTfR), or indices of iron-restricted erythropoiesis, such as: mean corpuscular volume (MCV); red cell distribution width (RDW); percentage of hypochromic red cells (PHRC); or content of hemoglobin in reticulocytes (CHR).

The diagnosis of absolute ID, defined as insufficient iron stores, is based on circulating ferritin, which is secreted from iron-storing cells. In the general population, absolute ID is diagnosed when serum ferritin is <30 µg/L but in patients with inflammatory chronic diseases (such as HF) higher cutoffs of serum ferritin (<100 µg/L) are used, because inflammatory stimuli, regardless of iron status, can induce ferritin secretion. Reduced TSAT (<20%) is a commonly accepted surrogate of insufficient iron available for metabolizing cells. When serum ferritin is between 100-300 µg/L (ie, when iron stores are normal/slightly increased), TSAT <20% allows diagnosis of functional ID. Therefore, a definition of ID combining absolute and functional ID, could be applied in patients with HF, as it was done in few clinical trials, eg, FERRIC-HF (FERRic Iron Sucrose in Heart Failure) and FAIR-HF (Ferinject® Assessment in patients with IRon deficiency and chronic Heart Failure).

There is scarce evidence on the prevalence of ID in anemic and non-anemic patients with HF. In the study by Ezekowitz et al, who analyzed the data from national and health care insurance systems, anemia was found in 17% of patients hospitalized for HF, and ID was confirmed in 21% of anemia cases. In the observational study of Opa-sich et al, the presence of ID was demonstrated in 36% of all anemic patients with systolic HF and in 64% of subjects with ACD. Nanas et al confirmed the presence of ID based on depleted iron stores in bone marrow in 73% of anemic patients.
with decompensated advanced HF in New York Heart Association (NYHA) class IV. Adlibrecht et al showed the presence of ID (serum ferritin <30 µg/L or TSAT <15%) in 26%, 16%, and 54% of all patients with systolic HF, nonanemics, and anemics, respectively. We have shown that ID (serum ferritin <100 µg/L or serum ferritin 100-300 µg/L with TSAT <20%) was present in 37%, 32%, and 57% of all patients with systolic HF, nonanemics, and anemics, respectively. In our study, ID was more prevalent in patients in advanced NYHA class, women, those with high plasma N-terminal prohormone of brain natriuretic peptide (NT-proBNP) and high serum high-sensitivity C-reactive protein (hsCRP) (Figure 1). 

In the study by Okonko et al, ID (serum ferritin <100 µg/L or serum ferritin 100-300 µg/L, with TSAT <20%) was more prevalent, being present in 69%, 78%, and 65% of all, anemic, and nonanemic patients with HF, respectively.

**CLINICAL AND PROGNOSTIC CONSEQUENCES OF ANEMIA AND IRON DEFICIENCY IN HEART FAILURE**

In patients with HF, reduced hemoglobin is associated with impaired exercise capacity (expressed as reduced 6-minute walking distance and diminished peak oxygen consumption), poor quality of life, and more advanced depressive symptoms. The presence of ID is accompanied by reduced peak oxygen consumption and increased ventilatory response to exercise, as well as by more severe depressive symptoms, irrespective of the severity of HF. These associations between iron status and exercise capacity and depressive symptoms are present in both nonanemic and anemic patients with systolic HF (Figure 2).

Anemia is a strong and independent predictor of high hospitalization rates and increased cardiovascular and all-cause mortality in patients with HF. Anemia also predicts poor outcome in patients with decompensated HF. Moreover, the reduction in hemoglobin levels in HF is related to the increased morbidity and mortality in this group of patients. Finally, high circulating EPO (an indirect measure of EPO resistance), irrespective of hemoglobin and other clinical prognosticators, is also related to poor outcome in patients with HF and anemic patients with HF with circulating EPO higher than expected (which may suggest the presence of EPO resistance) have increased mortality compared with those with serum EPO equal to or lower than expected, even after adjustment for clinical prognosticators.
So far only three observational studies have evidenced a link between iron status and prognosis in patients with systolic dysfunction and systolic HF. In the study of Varma et al in patients with systolic dysfunction, ID-associated anemia was related to high cardiac mortality, whereas malignancy-related anemia predicted increased noncardiac mortality. In our study, the presence of ID in patients with systolic HF, irrespective of hemoglobin and other clinical prognosticators, was a strong and independent predictor of death and heart transplantation during the 3-year follow-up. In the study by Okonko et al, ID defined as TSAT <20% was associated with increased mortality in patients with HF.

**EFFECTS OF ERYTHROPOIETIN THERAPY IN PATIENTS WITH HEART FAILURE**

The relatively high prevalence of anemia in patients with HF—particularly those with advanced stages of heart disease—and the unfavorable clinical and prognostic consequences of this comorbidity, provided a strong rationale to study whether this group of patients would benefit from the correction of hemoglobin levels using EPO or its analogs.

Several studies (mainly small, uncontrolled studies) evidenced the following advantageous effects of EPO or its analogs in patients with HF: (i) reduction in HF symptoms and improvement in exercise capacity (reduced NYHA class, increased peak oxygen consumption); (ii) improvement in quality of life; (iii) reduction in circulating natriuretic peptides; (iv) reduction in daily diuretic dose; (v) improvement in systolic and diastolic left ventricular function ventricle, assessed using echocardiography; (vi) attenuation of certain peripheral pathophysiological mechanisms (reduction in circulating markers of apoptosis and inflammation) (reviewed in 45,46).

However, the results of available small randomized clinical trials with EPO analogs in anemic patients with HF appeared to be inconclusive and partially disappointing regarding both the nonsatisfactory improvement in exercise capacity and prognosis. For example, in STAMINA-HeFT (Study of Anemia in Heart Failure Trial), Ghali et al found only a trend toward reduced rates of death or HF hospitalization after 1 year in patients treated with darbepoetin vs those receiving placebo. Interesting information was provided by the meta-analysis by Kotecha et al, which included 11 randomized controlled trials (nine studies were placebo controlled and five studies were double blind; a total 794 anemic patients with symptomatic systolic HF were included) comparing patients treated with erythropoiesis-stimulating agents (ESA) with controls during up to 12 months of follow-up. In this meta-analysis, ESA therapy significantly prolonged 6-minute walking distance, increased peak oxygen consumption, reduced NYHA class, increased left ventricular ejection fraction, reduced plasma BNP, improved quality of life, and, importantly, reduced HF hospitalization rate. There was only a marginally significant reduction in all-cause mortality in one group receiving ESA, but in the subgroups with different lengths of follow-up the statistical significance of this effect was lost. Importantly, ESA therapy did not increase the risk of potential adverse events, such as hypertension, stroke, and myocardial infarction or other thromboembolic events. Similar results were provided by another meta-analysis by Lawler et al. However, the reader should be aware that evidence on the safety of ESA in patients with HF with various degrees of renal function impairment comes only from small studies and these meta-analyses, which is fraught with obvious weaknesses and limitations.

Findings from studies on ESA in patients with CKD and accompanying cardiovascular disease are rather discouraging. Therapy with ESAs in patients with CKD (and in cancer patients as well) is associated with adverse effects, especially when high doses are used, such as impaired blood viscosity, deranged nitric oxide metabolism, uncontrolled hypertension, thromboembolic events, and, as a consequence, increased mortality rates.

The results of the CHOIR trial (Correction of Hemoglobin and Outcomes In Renal insufficiency) showed that patients with CKD who achieved higher target hemoglobin levels (13.5 g/L) on ESA therapy had increased rates of cardiovascular events (eg, myocardial infarction, stroke, HF hospitalization, and death) as compared with those who achieved lower hemoglobin levels (11.3 g/dL). Similar unfavorable effects of ESA therapy aiming to achieve normal hemoglobin/hematocrit values in patients with CKD and accompanying cardiovascular disease are rather discouraging. Therapy with ESAs in patients with CKD (and in cancer patients as well) is associated with adverse effects, especially when high doses are used, such as impaired blood viscosity, deranged nitric oxide metabolism, uncontrolled hypertension, thromboembolic events, and, as a consequence, increased mortality rates.
hemoglobin levels or the high EPO doses that had to be used in order to achieve these hemoglobin levels. Indeed, additional analyses from the CHOIR trial revealed that the worse outcome in CKD patients treated with ESA was associated with an ineffective response in terms of hemoglobin levels during increasing ESA doses. In the TREAT trial, anemic patients with CKD and diabetes with a poor response to darbepoetin α (defined as the lowest quartile of percent change in hemoglobin level (<2%) after the first two standardized doses of the drug) compared with those with a better hemoglobin response, received higher doses of darbepoetin α, and had increased rates of cardiovascular events and death. Moreover, ESA treatment consumes iron stores, hence when not substantial the induced negative iron balance may also negatively affect the myocardium and erythron, and induce EPO resistance. Finally, due to the slightly different pathophysiological background of anemia in patients with HF and CKD, it is doubtful whether the results of trials with ESA in CKD populations could also be implemented in HF cohorts.

Meta-analyses of small randomized controlled trials (RCTs) suggest that ESA treatment may be safe, well-tolerated, and can improve exercise tolerance, reduce symptoms, and have beneficial effects on some clinical outcomes in at least some anemic patients with HF. However, the evidence of at least partial futility of EPO therapy cannot be ignored. The insufficient effectiveness of ESA therapy in patients with CKD and/or HF may be a consequence of EPO resistance, which in most cases results from inflammation itself and/or associated ID (absolute or functional), the latter not being properly recognized and, consequently, corrected.

Indeed, in patients with CKD requiring dialysis, TSAT and ferritin levels identified patients with CKD with poor response to EPO therapy, and in this group of patients, IV iron therapy allowed reduction in the EPO doses needed to achieve target hemoglobin levels. There is much current debate on the dosage of EPO, the need for concomitant iron therapy (oral versus intravenous), and which hemoglobin level should be achieved. It is hoped that the ongoing RED-HF (Reduction of Events with Darbepoetin alfa in Heart Failure) trial, a multicenter placebo-controlled double-blind study of darbepoetin α in 3400 anemic patients with HF, will be able to confirm the results of these meta-analyses. This trial was designed to evaluate the effect of darbepoetin α (dosed to achieve a hemoglobin level between 13 and 14.5 g/dL) on mortality, morbidity (primary end point: time to death from any cause or first hospital admission for worsening HF, whichever occurs first), and quality of life in patients with symptomatic systolic HF and anemia (baseline hemoglobin level between 9 to 12 g/dL).
clearance; trend toward reduction in circulating cystatin C and CRP (reviewed in reference 6).

To date, the FAIR-HF trial is the largest randomized double-blind placebo-controlled multicenter trial, in which 24-week IV iron therapy (or placebo) was administered to 459 iron-deficient anemic and non-anemic patients with systolic HF. Intravenous iron supplementation reduced NYHA class and improved patient global assessment, and these beneficial effects were evidenced in several clinical subgroups (eg, regardless of baseline hemoglobin and serum ferritin or presence of renal dysfunction and anemia), without any increased risk of side effects. There was also a trend toward a reduced rate of first cardiovascular hospitalization in patients receiving IV iron. As excess of iron generates oxidative stress and can be toxic, safety issues need to be addressed and optimal serum ferritin and TSAT determined before IV iron can be recommended in iron-deficient patients with HF. Further large and longer-running trials are therefore needed to assess the safety effects of IV iron therapy on morbidity and mortality in ID patients with HF, both with and without accompanying anemia.

CONCLUSIONS

Anemia is a frequent comorbidity in patients with HF, and together with renal failure forms the cardio-renal-anemia syndrome. Its pathophysiology is complex and not fully elucidated. The anemia is usually of the ACD type and/or is associated with ID. Both anemia and ID remain under-recognized in the cardiovascular setting. Patients with HF, particularly those with concomitant CKD, should be screened for the presence of anemia and ID. Basic hematological findings, including low hemoglobin levels with reduced MCV and increased RDW, suggest the existence of iron-restricted compromised erythropoiesis. Standard laboratory screening for iron status should include serum ferritin and TSAT, calculated as the ratio of serum iron to TIBC or the ratio of serum iron to serum transferrin. Although not yet
Should anemia be actively treated in cardiorenal syndrome? - Jankowska and Ponikowski

tested in HF patients, soluble transferrin receptor has been found to be useful in the diagnosis of iron status in patients with hematological disorders or with chronic diseases.

Although the rationale for anemia (with/without ID) correction in patients with HF and accompanying CKD is strong, at the moment there is huge uncertainty about the optimal hemoglobin level and how this level should be achieved. The guidelines of the European Society of Cardiology for the management of patients with HF acknowledge anemia as a relatively common and alarming comorbidity, but its correction is still not considered as part of standard therapy.

Reduced EPO signaling and depleted tissue iron are serious negative effects for both hematopoietic and extrahematopoietic tissues, while EPO and/or iron activate cardioprotective pathways. Studies with EPO or its analogs in anemic patients with HF are still inconclusive. The partial futility of EPO therapy is explained by EPO resistance, which in most cases is the consequence of inflammation and/or ID. Clinical evidence suggests that IV iron improves functional status, quality of life, and exercise capacity in ID patients with HF. Treatment with EPO and/or iron is a novel and promising therapeutic approach in anemic HF patients, but reliable evidence from multicenter trials on the effects of ESA or iron therapy on morbidity and mortality end points is needed before it can be recommended in anemic and/or ID patients with HF as well as for determining the optimal effective and safe levels of hemoglobin, ferritin, and TSAT that should be achieved in this particular group of patients.

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In this “Lexicon of the Heart” Fascinoma article, we look at letter “H” for the heart and “K” for the kidney. And first, as with any proper lexicon or dictionary, a few words about etymology. Of course, there are no Latin or Greek roots in Chinese, one must go all the way back to the late Shang Dynasty (1200-1050 BCE) and the earliest characters found on ritual bronze vessels and the so-called “oracle bones” (often ox shoulder blades) used for divination purposes. Actually, the character for heart (xin, 心) has hardly evolved at all since its first appearance. Figure 1 shows the ancient form of the character (left), and the form as painted with a brush (right), which is quasi identical to the printed form (心).

According to Léon Wieger’s “Chinese Characters” published in 1915,1 which is based on ancient Chinese etymological treatises and is to this day one of the best sources for etymology in a European language, the early form “represents the heart with, on top, the pericardium opened; in the middle, the organ; at the bottom, a summary delineation of the aorta.”

The character for kidney (shen, 肾) is in three parts, the bottom part is the “classifier” or “radical” for “flesh,” “meat” (rou, 肉, 月), which represents pieces of smoke-dried meat (the two inverted “Vs”) gathered in a bundle (the round “envelope” around them). 肉 is the character occurring independently, 肥 is the form used in compound characters, as in “kidney,” considered as belonging in the general category of “meaty” objects (see Figure 2 below, left panel: left, the ancient characters, right the brush scripts). The middle panel represents “chen” (臣), a “minister, attendant on a prince; the character, which is straightened in modern writing (top), represents the minister prostrate before his master (left, bottom). To this character is added a hand (shown in the right panel in the ancient form with three fingers [top], and as 鼎 in brush script [bottom]): hence the meaning becomes: to have a hold (the hand) on one’s ministers/vasals/men. This meaning then evolved to signify “firm, solid” (right panel). In total, if we now look at the complete character composed of the three parts described above, the meaning is “a fleshy organ that is very firm”—I’m sure you will admit that it’s quite an adequate description of a kidney!

The following is just a brief foray into how the ancient Chinese understood the function of the heart and kidneys, by means of three examples from three different medical works from the 17th-18th centuries, although “real dates” of first authorship are very difficult to ascertain, as is often the case in China, since successive generations of authors kept building upon earlier editions.

THE HEART

Sancai Tuhui (三才圖會) or Collected Illustrations of the Three Realms, by Ming dynasty (1368-1644) author Wang Siyi (王思義), was an encyclopedia published in 1609. “Sancai” refers to the three realms of heaven (天), earth (地), and man (人), in other words “everything,” and “Tuhui” (圖會) means “collection of illustrations.”

Figure 3 (page 296) shows the form and position of the heart, and the accompanying text states that it is situated beside the 5th vertebra, below the lung, above the diaphragm. The heart (xin, 心) is fed by the aorta, (the large vertical conduit), and from the heart issue four other smaller arteries to the lung (fei, 肺), spleen (pi, 胃), kidneys (shen, 肾), and liver (gan, 肝).

A Lexicon of the Heart
Heart and kidney in early Chinese medicine
Frederick Scheffler, MD
Ramsey County Lane - St Paul - Minnesota - USA

Address for correspondence:
Frederick Scheffler, MD, Ramsey County Lane, St Paul, Minnesota, USA
(e-mail: dma_cb@me.com)


Figure 1.

Figure 2.

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These five organs constitute the “viscera,” (zang, 脏), over which the heart “rules,” thus being so to speak a “primus inter pares.” Traditional Chinese Medicine (TCM) divides the body’s organs into two categories, the five “zang,” as listed above, which are “yin” (陰) in nature, and whose main function is to store “energy” or “Qi” (氣) and blood (xie, 血).

The other category is that of the six “entrails,” receptacles,” or “bowels” (fu, 腹), which are considered to be “yang” (陽) in nature, and which are the small intestine (xiaochang, 小腸), large intestine (dachang, 大腸), gall-bladder (dan, 胆), urinary bladder ( pangguang, 膀胱), stomach (wei, 胃), and “triple warmer,” “sanjiao” (三焦), thought by some to refer to the parasympathetic nervous system.

THE KIDNEY

“Problem 36” (Figure 4, from Tu Zhu Ba Shi Yi Nan Jing Bian Zhen (圖註八十一難經辨真) or Corrected Edition of the Canon of 81 Problems, Illustrated and Annotated, published in the Wan Li reign period of the Ming Dynasty (1573-1620) by Zhang Shixian (張世賢) illustrates the distinct physiological functions of the left and right kidneys in Chinese medical theory. The left kidney (shen, 腎), partakes of the nature of water (shui, 水), while the right kidney, (mingmen, 命門), i.e., Portal of Life) partakes of the nature of fire (huo, 火). The “mingmen” is crucial to life, it is the place where innate Qi (氣) is stored, the origin of life processes, the very root of existence. The fire in “mingmen” is expressed in the yang (陽) functions of the kidneys (in modern times, taken to include the function of the adrenal gland). There were two views of the “mingmen” in ancient Chinese medicine. According to one theory, it corresponded to the right kidney, according to the other, it...
corresponded to both kidneys, as embodied in the dynamic interchange of Qi between them. The first theory is represented in this diagram.

“CARDIORENAL”?

The *Shang Han Lun* (傷寒論) or *Shang Han Za Bing Lun* (傷寒雜病論), known in English as the *Treatise on Cold Damage Disorders* or the *Treatise on Cold Injury*, is a Chinese medical treatise that was compiled by Zhang Zhongjing (張仲景) sometime before the year 220 BC, at the end of the Han dynasty. It is the oldest complete clinical textbook in the world. Composed of 12 volumes, the book has 397 sections with 112 herbal prescriptions. It organizes all the diseases into the six divisions called “six channels,” based on the ways treatment can be applied accordingly.

Of all of China’s early medical classics, the *Shang Han Lun* is undoubtedly the one with the greatest relevance to the modern practice of Chinese medicine, and the one most deserving of Western attention. It was the first book to attempt to incorporate medicinal therapy into the medicine of systematic correspondences and channels and network vessels. Far ahead of its time in both theory and practice, it is not surprising that the prescriptions it contains comprise an important part of today's medicinal formulary.

**CONCLUSION**

To talk about a pathophysiological entity such as “cardiorenal syndrome” in early Chinese medicine—the term in modern Chinese is “xinshenzonghe-bing” (心腎綜合病), where you now recognize the first two characters as “heart” and “kidney”—would be promising more than one can deliver.

And yet, one of the central tenets of Chinese medicine since its inception—as described in one of the earliest treatises, the *Huangdi Neijing* (黃帝內經) or the “Yellow Emperor's Classic of Medicine”, dated between 475 BCE and 221 CE—was the belief that all the body's organs were physiologically and pathophysiologically interrelated. For them, the organs were ruled by the cyclic concepts of “yin” (陰) (= female, dark, wet, cold, moon) and “yang” (陽) (= male, bright, dry, warm, sun), influenced each other’s functions, and produced and received “energy” (Qi, 氣) from one another, which circulated in “canals,” the “meridians” familiar to those who know a thing or two about acupuncture. “Qi” and the concepts of “yin” and “yang” constituted a far more sophisticated and realistic theory than that of the “four humors” of ancient Greece, championed by Hippocrates (ca 460 BC to ca 370 BC), and which remained the prevailing view of the (patho)physiology of the human body in Western medicine, only to finally die out in the 19th century. In fact, traditional Chinese physiology anticipated by more than two millennia the discovery of the “milieu intérieur” by Claude Bernard (1813-1878), renamed “homeostasis” by American physiologist Walter Cannon (1871-1945).
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Heart and kidney in early Chinese medicine - Scheffler
Cardiorenal Syndrome

Summaries of Ten Seminal Papers

Paul R. Kalra, MD, FRCP; Philip A. Kalra, MD, FRCP

Department of Cardiology - Portsmouth Hospitals NHS Trust - Portsmouth - UK (paul.kalra@porthosp.nhs.uk)
Department of Nephrology - Salford Royal Foundation NHS Trust - Salford - UK (philip.kalra@srf.t.nhs.uk)

Dialogues Cardiovasc Med. 2011;16:299-310

1. The clinical epidemiology of cardiac disease in chronic renal failure

2. Hormones and hemodynamics in heart failure

3. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia...

4. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals
   H. C. Gerstein. JAMA. 2001

5. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality

6. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization

7. The severe cardiorenal syndrome: “Guyton revisited”
   L. G. Bongartz et al. Eur Heart J. 2005

8. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure

9. Cardiorenal syndrome

10. Ferric carboxymaltose in patients with heart failure and iron deficiency
The clinical epidemiology of cardiac disease in chronic renal failure

P. S. Parfrey, R. N. Foley


In the 1990s, these two authors forged a strong research partnership in St John's, Newfoundland, Canada, one which focused on the nature and epidemiology of cardiovascular disease that occurs in patients with advanced chronic renal disease. They had been involved in several important original studies including a seminal investigation of the evolution of echocardiographic changes in over 250 patients commencing dialysis, and then followed for over 2 years. They are currently both heralded as leading experts in this field; Dr Foley now works in Minneapolis, Minn, USA. Although this particular article was a review and not an original study, it was very important in comprehensively summarizing the latest evidence of the time relating to the heterogeneous cardiovascular diseases suffered by patients receiving dialysis. Prior to this period, the majority of nephrologists would more often direct their clinical attention to dialysis-related complications, dialysis membranes and process, and acute renal failure (now known as acute kidney injury) or their research interests to the pathophysiology of the relatively rare, but intellectually stimulating, glomerular diseases, rather than to the cardiovascular disease, which was by far the biggest killer of their patients.

The review stressed the high relative mortality of dialysis patients—stark data from the United States Renal Data System (USRDS), which showed young dialysis patients (eg, 25-30 years old), male or female, having a 100-200-fold increased death risk compared with similar aged normal individuals, a mortality risk close to that experienced by 85-year-old individuals in the general population, which is an incredible statistic. Of these deaths, 50% are thought to be due to cardiac causes, and the authors described the pathophysiological changes contributing to cardiovascular disease in advanced kidney disease. The review emphasized the importance of ‘nontraditional’ risk factors—ie, not the usual diabetes, smoking, coronary artery atheroma and family history—with abnormalities such as left ventricular hypertrophy and dilatation, arterial stiffness and vascular calcification, inflammation, and especially heart failure being cited as risk factors of major importance in dialysis patients. Comparative epidemiology of cardiac changes in hemodialysis and peritoneal dialysis patients showed that the former was more likely to lead to progressive increases in left ventricular muscle mass and ventricular volume, forerunners of cardiac failure, which itself was appearing as one of the major risk factors for death in dialysis populations. On the other hand, evidence from certain studies that renal transplantation could improve these cardiac changes was cited, and was welcome relief from the rather depressing data summarized throughout the review. At the time, topics such as vascular calcification, hypovitaminosis D, and sudden cardiac death (now thought to account for a quarter of all dialysis deaths) were only just emerging in the renal literature, and hence were given little mention in the article. Now it would be difficult to attend a conference without finding at least one session devoted to each of these topics. Another limitation was that interventional strategies to ameliorate the cardiovascular changes were only given minimal consideration in the paper, but this more reflected that randomized clinical trials and other studies of therapeutic interventions for patients with advanced renal failure had been overlooked by the renal community, especially in comparison with the trial portfolio that was appearing in cardiology and diabetology. Nevertheless, the manuscript provided the nephrologist with a comprehensive summary of the epidemiology and pathogenesis of the cardiovascular disease burden suffered by dialysis patients, bringing this to the fore as a subject for future research and of great importance in patient management. Subsequently, there has been a major proliferation of interest in this area, which is ever increasing.

Philip Kalra

John F. Kennedy Jr and his wife are killed when their plane crashes off the coast of Martha’s Vineyard; Lance Armstrong wins his first Tour de France; and Moroccan middle distance runner Hicham El Guerrouj breaks the world mile record in a time of 3:43:13 minutes
Hormones and hemodynamics in heart failure

R. W. Schrier, W. T. Abraham


So why does a review article make into the top 10, when there are so many excellent scientific papers around the cardiorenal syndrome? Well this is an absolute belter, an all-time favorite of mine! Schrier and Abraham present a clear and succinct overview of what was understood at the time regarding the pathophysiology of chronic heart failure, with a focus on abnormal hemodynamics and neurohormonal activation. From a personal perspective it has been highly influential; as a callow youth I remember reading this at the time of publication (1999) and suddenly becoming excited about heart failure, which until then I had thought of (quite incorrectly) as a "Cinderella specialty." Furthermore, large amounts of the original scientific data referenced in this review are the work of the two authors and this article highlights the crucial role they have played in understanding the pathophysiology of heart failure, and the subsequent contribution to improved patient outcomes. Although this article is now over a decade old, if you have any input into the clinical management of patients with chronic heart failure (or chronic kidney disease) it is still most worthy of a bedtime read. All of this is achieved in just 7 pages of text and figures—for this in itself the authors should be wholeheartedly congratulated.

The review focuses on fluid and electrolyte metabolism in heart failure and therefore inevitably brings the heart and the kidney together. The article is accompanied by a number of relatively simple, but extremely useful, figures, which add to the clarity of explanation. The hemodynamic focus is on arterial underfilling and includes discussion around the afferent sensing mechanisms and the subsequent neurohormonal activation. A key innate response to any threat or disease process is to maintain arterial integrity. The same afferent and efferent systems come into play irrespective of the threat to the circulation and thereby this forms a unifying hypothesis of the regulation of body fluid status in edematous states (ie, this is applicable to disorders other than heart failure, for example, cirrhosis).

Subsequent sections detailing activation of the sympathetic nervous system, renin-angiotensin-aldosterone system, and other hormones (eg, nonosmotic release of vasopressin) capture the crucial link between an abnormality in cardiac function and the subsequent impact on the function of the kidney and its various responses. Schrier and Abraham highlight the adverse impact of neurohormonal activation on sodium and water retention (performed by the kidney) and hemodynamics (such as arterial vasoconstriction and increased afterload). In addition, they introduce the concept that angiotensin II and aldosterone in particular have further direct detrimental effects on heart and kidney structure and function. Understanding these abnormalities is fundamental to understanding the mainstay of the contemporary management of chronic heart failure (that is, how angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, β-blockers, and aldosterone antagonists exert their benefits). Ever since this publication we have more data supporting the beneficial use of these agents for nearly all stages of chronic heart failure secondary to left ventricular systolic dysfunction. In many respects it is remarkable to see just how far we have come in improving the outcomes for patients with chronic heart failure over the last 2 to 3 decades. This is one of the major success stories in modern medicine, although of course there is much more to discover and hopefully this will lead onto novel treatments that will further advance care. However, I don’t believe this would have been achieved without a clear understanding of the basic pathophysiological principles of hormones and hemodynamics in heart failure!

Paul Kalra

A total solar eclipse occurs in Europe and Asia; more than 17 000 are killed and 44 000 injured when a 7.4-magnitude earthquake strikes Istanbul and northwestern Turkey; and a brief war is triggered when Chechen guerrillas invade the Russian republic of Dagestan
The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations


*J Am Coll Cardiol. 2000;35(7):1737-1744*

This paper was instrumental in igniting the current interest in the area of anemia and heart failure. Despite the obvious limitations of a retrospective cohort study and a small unblinded intervention study (n=26) that was not placebo controlled, the results captured the enthusiasm of the heart failure community worldwide. The rest as they say is history! A second study by the same group published several months later in the same journal reinforced these findings (Silverberg et al. *J Am Coll Cardiol* 2001;37(7):1775-1780). Up until this stage it had been recognized that low hemoglobin was seen in patients with chronic heart failure, but there had been scant attention paid to the possible impact on outcomes and potential correction. Indeed, by the very fact that mild anemia was so common it appeared to have become accepted as the “norm” in clinical practice.

The authors evaluated patients attending a specialized heart failure clinic (n=142) and detailed that 56% were anemic (hemoglobin <12 g/dL). Low hemoglobin was more prevalent in highly symptomatic individuals (New York Heart Association [NYHA] Class II 19%; Class III 53%; and Class IV 79%). Twenty-six highly symptomatic patients (NYHA Class of III or more) despite maximal tolerated standard therapy with hemoglobin <12 g/dL entered the intervention study (essentially a proof of concept or feasibility study). They were truly sick and were receiving high doses of oral or intravenous loop diuretics and had required frequent recent hospitalizations. Treatment consisted of intravenous iron sucrose in a dose of 200 mg every week until serum ferritin reached 400 μg/L or iron saturation reached 40%. Erythropoietin was given subcutaneously on a weekly basis at a dose that attempted to maintain a target hemoglobin of 12 g/dL. During the study, drugs used for treatment of heart failure were unaltered, except diuretics, which were adjusted according to clinical status.

Treatment was feasible and tolerated, resulting in an increase in hemoglobin from 10.16±0.95 g/dL at baseline to 12.20±1.21 g/dL at the end of the study (P<0.001). This was associated with a remarkable reduction in diuretic requirement and hospitalizations (91% reduction as compared with a similar time period prior to the study). Left ventricular ejection fraction and NYHA class were both seen to significantly improve. The authors concluded that mild anemia was extremely common and its correction may be an important addition to the treatment in chronic heart failure.

Despite the limitations in design, as already mentioned, this landmark study paved the way for a number of small randomized studies evaluating the use of erythropoietin-stimulating agents (ESA) and/or intravenous iron. Larger-scale studies have subsequently been initiated: see FAIR-HF (Ferinject Assessment in patients with IRon deficiency and chronic Heart Failure) evaluating intravenous iron therapy, which is discussed by Ewa A. Jankowska and Piotr Ponikowski in this issue. The result of RED-HF (Reduction of Events with Darbepoetin alfa in Heart Failure), which is evaluating the impact of ESA in patients with chronic heart failure is eagerly awaited.

Don Silverberg and colleagues from the departments of nephrology and cardiology at the Tel Aviv Medical Center were instrumental in highlighting the importance of anemia and iron deficiency in chronic heart failure. They identified potential benefits of this therapeutic approach and also noted the relation between heart failure, anemia, and chronic kidney disease, introducing the concept of “cardio-renal-anemia syndrome” or CRAS. The investigators have also highlighted the achievements that can be made when cardiologists and nephrologists actually develop a symbiotic relationship!

Paul Kalra

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**2000**

A preliminary draft of the Human Genome is published; South Korean President Kim Dae Jung visits North Korea; and Tiger Woods wins the US Open by a record 15 shots.
Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals


*JAMA*. 2001;286(4):421-426

S tatisticians and methodologists usually scoff at the importance and results of post-hoc analyses, for protein reasons including lack of power for the analysis, ascertainment bias, and because the analyses were not preconsidered in the study design. Having had some experience in the design of large trials, observing the flimsy initial data upon which the primary outcome measure might sometimes be based, the guesswork that can be involved in arriving at the effect size of one treatment versus another, and the way in which secondary outcome measures can be selected, I would take an opposing view. All studies are expensive to run, especially randomized control trials (RCT) whose costs can run into tens of millions, but most importantly, patients willingly give their consent and time to participate and without them there would be no clinical research. For the latter two reasons I believe that the output from RCT should be maximized. Most of all, we owe it to the patients to find out all we can from a study to help guide their appropriate treatment in the future.

To move away from this particular soapbox it then naturally follows that this paper, a post-hoc analysis of HOPE (Heart Outcomes Prevention Evaluation), provides significant clinical insights that have changed our thinking with regard to the importance of microalbuminuria in relation to hard clinical outcomes in both high-risk nondiabetics and diabetics. The HOPE study randomized 9000 individuals without diabetes, but with cardiovascular disease, or with higher-risk diabetes (cardiovascular disease, high cholesterol, smoking, or other risk factors) to treatment with either ramipril or placebo, to examine the effects upon all-cause mortality, myocardial infarction or stroke, and heart failure hospitalization. The main trial result showed that all patients were benefited by ramipril. Subsequent analyses showed that the diabetic subgroup (MICRO-HOPE) had reduced cardiovascular events and progression to nephropathy when treated with the active agent, whereas an analysis of baseline albuminuria (only in or below the microalbuminuric range, as patients with dipstick-positive proteinuria, ie, likely macroproteinuria, were excluded) demonstrated the negative effects of microalbuminuria upon outcomes in all patients, including nondiabetics. More specifically, this post-hoc analysis showed that all endpoints were more likely to occur in both nondiabetics and diabetics, and there was a clear relationship between risk and increasing quantity of microalbuminuria. The hazard ratios relating albuminuria to risk were greatest for hospitalization for heart failure. Most strikingly, when patients were divided into quartiles dependent upon their baseline level of microalbuminuria, it was clear that there was a continuum of increasing risk related to increasing albuminuria even when this was well below the cutoff value used for diagnosis of early diabetic nephropathy (a urinary albumin creatinine ratio (uACR) of >2 mg/mmol)—ie, below the conventional microalbuminuric range. Hence, diabetics and nondiabetics with a uACR of >0.5 mg/mmol (crudely equating to only 5 mg/L) had a significantly increased risk of death or cardiovascular events compared with those with negligible albuminuria. There were major limitations within the paper, the authors acknowledged that there had been only one baseline uACR available for study, and the hypothesis linking microalbuminuria to increased risk was rather weakly stated, suggesting this was likely to represent generalized vascular permeability and “endothelial dysfunction.” Nevertheless, the study really did change our mind-set regarding the importance of albuminuria as an independent adverse risk factor in the higher-risk general and diabetic populations, and the fact that it confers a continuum of risk even below the microalbuminuric range.

Philip Kalra

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Simeon Saxe-Coburg-Gotha, the last Tsar of Bulgaria, is sworn in as Prime Minister following the election; novelist Jeffrey Archer is sentenced to four years in prison for perjury; and the London Stock Exchange goes public
With the dawn of the new millennium it was becoming increasingly recognized that arterial and valvular calcifications were frequently present in dialysis patients, and possibly related to the quantity of calcium imbibed by patients in phosphate binders. French renal research groups were leaders in this field, and Gerard London, together with his former colleagues Blacher and Safar, had previously demonstrated the relationship between the extent of vascular calcification and mortality in end-stage renal disease. They had been pioneers in changing our thinking about the importance of the state of the arterial wall in renal patients, and had helped introduce noninvasive measurement of arterial stiffness as a parameter that could quantitate the "hardening" of the vessel wall. Hence, their studies had found a close relationship between pulse wave velocity and mortality in dialysis patients, which provided a plausible mechanism by which vascular calcification could lead to cardiac damage and then mortality.

The study reported in this article was led by London at a dialysis center in Fleury-Merogis, France, and it focused on the precise location of the calcification within vessel walls. Two hundred and two hemodialysis patients were included in what was a simple investigative and analytical study design. All patients had undergone a plain radiograph of the pelvis and/or thigh, and the type of calcification was qualitatively classed as being intimal (arterial intimal calcification, AIC) or medial (arterial medial calcification, AMC) by two observers. The presence or absence of vascular calcification, and particularly the differing type of vessel calcification, was then considered in relation to a range of basic clinical parameters and to long-term mortality. However, it was not clear within the paper whether patients had undergone baseline (at dialysis commencement) radiographs in protocolled fashion, or more likely, if patients who had previously undergone x-ray study were simply a "convenience sample," ripe for study. The key findings of the study were that any calcification was associated with a higher risk of mortality than no calcification, and that any calcification was associated with increased dose of oral calcium-containing phosphate binder and duration of time receiving dialysis.

A crucial observation was that there were major differences between the two patterns of calcification. AIC was associated with older age, prior cardiovascular disease at time of commencing dialysis, and with diabetes or atherosclerotic etiologies of the renal disease. In contrast, AMC was associated with younger patients, who typically had no conventional cardiovascular risk factors, longer duration of dialysis, and greater calcium dosage in terms of calcium carbonate. The mortality was high with both calcification patterns, although patients with AMC lived longer than AIC, which was partly explained by age. The authors concluded that AIC tended to develop in patients prone to atheroma, the calcification being present on the surface of intimal plaques. In contrast, all dialysis patients would be at risk of developing AMC due to perturbations of calcium-phosphate balance, calcium dose in binders, and other factors. Although this study used basic techniques to assess calcification, now superseded by quantitative techniques such as CT calcification score, it was fundamental in changing our thinking with regard to the epidemiology of vascular disease in dialysis patients.

Philip Kalra

The foreign minister of Sweden, Anna Lindh, is fatally stabbed while shopping; Sweden rejects adopting the euro in a referendum; and American singer-songwriter Johnny Cash dies at the age of 71.
Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization

A. S. Go, G. M. Chertow, D. Fan, C. E. McCulloch, C. Y. Hsu


Certainly, the sheer scale of the numbers of subjects in this study gets it into the top 10! The message is also crucial and this paper has helped highlight the adverse and independent impact of chronic kidney disease (CKD)—even when mild—on adverse cardiovascular outcomes. The data are derived from a registry of a large integrated health care system (insured) within the San Francisco Bay Area. The authors acknowledge that the data therefore may not be representative of other cohorts/regions (do Californians see themselves as anything other than normal?). While there are always limitations in such data sets, this had huge advantages not just in terms of numbers, but also the extent of other data related to cardiovascular risk and lifestyle that were available.

120,295 adults with an estimated glomerular filtration rate (eGFR) were included in the analysis. Previous data had documented that patients with end-stage renal failure experienced extraordinarily high cardiovascular event rates. However, until this megastudy was published there were relatively limited data suggesting that mild impairment of renal function might be associated with adverse cardiovascular outcomes, and it was uncertain as to whether any relation was independent of conventional cardiovascular risk factors.

The median follow-up was 2.84 years giving over 3.1 million subject-years of follow-up! During follow-up, 3171 subjects began dialysis. In contrast, there were 51,424 deaths and 138,291 cardiovascular events. Subjects were grouped according to their eGFR. A value of ≥60 mL/min/1.73m² formed the reference (and lowest-risk) group. The key finding was that a consistent independent progressive worsening of risk was seen as renal function deteriorated. While an excess risk was present in those subjects with even a mild reduction in eGFR (45-59 mL/min/1.73m²), a particular step-up in risk was seen for those subjects in CKD stage 3B or worse. For example, when considering cardiovascular events a doubling of risk was seen for subjects in stage 3B (eGFR 30-44 mL/min/1.73m²) as compared with the reference group. This study firmly established impaired renal function (ie, CKD) as a risk factor for all-cause death and the development of adverse cardiovascular events. Enhanced risk was seen in subjects with even mild renal impairment, with values of serum creatinine or eGFR that perhaps would have previously been clinically overlooked. While this study has been unable to distinguish whether CKD is merely a marker of advanced risk or a modifiable risk factor, it has I believe stimulated a major sea change in clinical practice. Much greater attention is applied to assessment of renal function and its implications. Subsequent studies have replicated the results across a range of subjects with various underlying conditions.

Another key finding from this study is that it is only a minority of subjects with CKD who progress on to end-stage renal failure; in contrast they are far more likely to die prematurely or suffer an adverse cardiovascular event. Reducing the risk in this massive cohort of patients remains a major health care challenge. While not always the case in life, this study certainly showed that bigger is better!

*Paul Kalra*

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Terrorists seize a school in North Ossetia, killing 335 hostages, including 156 children; the first direct image of a planetary system outside our solar system is captured at the Yepun telescope in Chile; and Greek Orthodox Patriarch of Alexandria Peter VII is killed in a helicopter crash.
The severe cardiorenal syndrome: “Guyton revisited”


Eur Heart J. 2005;26(1):11-17

As discussed elsewhere in this issue of Dialogues in Cardiovascular Medicine, the cardiorenal syndrome is frequently encountered in clinical practice, yet there has been scant attention given to the potential pathophysiological mechanisms that underlie it. In this manuscript the authors concentrate on “severe cardiorenal syndrome” and return to the basic renal and cardiac physiological mechanisms as extolled by the famous American physiologist Arthur Clifton Guyton (1919-2003), in trying to explain why patients with heart and kidney failure often develop a rapidly downhill clinical course.

Their basic hypothesis involves four interrelated physiological responses, which, when activated, interact to trigger worsening fluid retention, sympathetic overactivity, declining cardiac and renal function, and increased inflammation. They term this pathophysiological reaction the “cardiorenal connection.” The main components of the proposed cardiorenal connection can be considered in turn (activation of the renin-angiotensin system [RAS]), imbalance in endothelial function, inflammation, and activation of the sympathetic nervous system [SNS]), although it does not follow that the sequence of events is stepwise, but more likely they occur in parallel with progressive perturbation and ever-worsening consequences.

Low renal perfusion leads to activation of the RAS, which not only increases salt and water retention, so worsening cardiac failure, but reactive oxygen species (ROS) are also generated. Angiotensin II is also known to stimulate vascular inflammation via nuclear factor-κB–mediated inflammation.

Persistent inflammation has been found in both renal and heart failure. By altering ROS functioning, and promoting ROS and norepinephrine (NE) formation, inflammation contributes to the positive feedback loops in the cardiorenal connection.

Sympathetic nervous activity is increased in both renal and heart failure. By affecting the other cardiorenal connectors it can play a significant role in the severe cardiorenal syndrome. It stimulates renin release from the kidneys, generates ROS, and induces inflammation.

**Abbreviations:** NADPH, reduced nicotinamide adenine dinucleotide phosphate; NE, norepinephrine; NF-κB, nuclear factor-κB; NO, nitric oxide; NPY, neuropeptide Y; ROS, reactive oxygen species; SNS, sympathetic nervous system.

**Figure.** (A) Angiotensin II affects the other cardiorenal connectors: SNS activation in kidney failure, generation of ROS, and NF-κB-mediated proinflammatory gene expression. (B) Imbalance between NO and ROS is a central event in cardiovascular diseases. In the cardiorenal connection, this balance may influence sympathetic nervous activity, release of renin and angiotensin, and promote inflammation by oxidative modification of substances. (C) Persistent inflammation has been found in both renal and heart failure. By altering ROS functioning, and promoting ROS and norepinephrine (NE) formation, inflammation contributes to the positive feedback loops in the cardiorenal connection. (D) Sympathetic nervous activity is increased in both renal and heart failure. By affecting the other cardiorenal connectors it can play a significant role in the severe cardiorenal syndrome. It stimulates renin release from the kidneys, generates ROS, and induces inflammation.

Abbreviations: NADPH, reduced nicotinamide adenine dinucleotide phosphate; NE, norepinephrine; NF-κB, nuclear factor-κB; NO, nitric oxide; NPY, neuropeptide Y; ROS, reactive oxygen species; SNS, sympathetic nervous system.

ator kappa B (NF-κB) pathway, and to lead to activation of the SNS, leading to vasoconstriction and further organ ischemia. The balance between nitric oxide and ROS is thought to be important in the control of blood pressure and extracellular fluid volume by regulation of vasodilatation, natriuresis, and desensitization of tubuloglomerular feedback. In the severe cardiorenal syndrome, there is imbalance in this system due to excess production of ROS, diminished levels of native ROS scavengers, and lower levels of nitric oxide (due to reaction with ROS and the inhibitory effects of asymmetric dimethylarginine [ADMA]). Vasoconstriction results, with further renin release as a consequence. ROS also lead to tissue damage, with production of oxidatively altered lipids, carbohydrates, and proteins, which then induce further inflammation; there are stimuli that also trigger SNS activation.

By now the suggested complex interplay should be getting clearer! It so happens that there is evidence that both inflammation and SNS activation can have stimulatory effects upon each other, and also mutual interactions with RAS activation and nitric oxide/ROS imbalance. Hence, inflammation stimulates renin release as part of the systemic stress response, ROS are produced by activated macrophages, and cytokines released by inflammatory cells trigger SNS activation. As you now would anticipate, the latter can itself upregulate the RAS by renin release from renal sympathetic neurons, and prolonged stimulation can result in cardiomyocyte hypertrophy, apoptosis, and focal necrosis, in part caused by ROS induction. Norepinephrine can stimulate cytokine release, again exacerbating inflammation. For good measure, SNS activation results in release of the neurohormone neuropeptide Y, which is thought to trigger inflammation, RAS activity by vasoconstriction, and neointimal hyperplasia, an important step in accelerated atherosclerosis.

To summarize: the authors suggest that disturbances of the underlying physiological systems in the kidney, heart, and blood vessels lead to parallel, interrelated, and mutual activation of four important hormonal and mediator pathways, resulting in a progressively deleterious “cardiorenal connection” that would explain the serious outcome of the severe cardiorenal syndrome. Although there is plausibility in their suggestion, as ever, it is likely that the interactions will turn out to be even more complex, with subtleties in the purported interdependencies.

I had hoped to be able to summarize the manuscript succinctly and without a diagram, but having re-read my critique, I now feel that the latter is necessary. Figure 2 from the review should suffice!

Philip Kalra

2005

Italy introduces a ban on smoking in public places; Zhao Ziyang, former Premier of the People’s Republic of China and General Secretary of the Communist Party of China, dies aged 85; and Bill Gates donates $750 million to the Global Alliance for Vaccines and Immunization to provide vaccines to children in poor countries.
Renal function as a predictor of outcome in a broad spectrum of patients with heart failure


Circulation. 2006;113(5):671-678

While it had been previously recognized that impaired renal function was an independent predictor of adverse prognosis in patients with heart failure, data from the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) studies permitted analysis in patients with impaired and preserved systolic function, and in those intolerant of angiotensin-converting enzyme (ACE) inhibition. A number of the authors originate from the University of Groningen, Netherlands, where researchers have been instrumental in highlighting the close and important association between the heart and kidneys.

The CHARM program consisted of three separate, but concurrent, studies of candesartan versus placebo: (i) CHARM-Preserved, in patients with left ventricular ejection fraction (LVEF) greater than 40%; (ii) CHARM-Added, in patients with LVEF of 40% or less already receiving an ACE inhibitor; (iii) CHARM-Alternative, in patients with LVEF of 40% or less already with a documented intolerance of an ACE inhibitor. The data in this analysis are derived from 2680 patients from these studies in whom there were sufficient data, including renal function (estimated glomerular filtration rate, eGFR).

eGFR was calculated by the Modified Diet in Renal Disease equation. Major outcomes assessed included cardiovascular death and hospitalization for heart failure and all-cause mortality. Chronic kidney disease (CKD) was common: 36% of subjects had eGFR ≤60 mL/min/1.73 m². In comparison to “real life” practice this is likely to underestimate the true burden of CKD, since clinical studies in general exclude the very elderly and patients with major comorbidity. Indeed, the mean age in this analysis was around 65 years, which is over a decade lower than the median age of presentation with heart failure in the United Kingdom.

During a median follow-up of just under 3 years, cardiovascular death or hospitalization for heart failure occurred in 950 subjects. A number of parameters, including eGFR and LVEF, were entered into multivariable analysis. Both reduced renal function (eGFR) and left ventricular function (LVEF) remained independent predictors of adverse outcome. This was consistently seen across the three different study populations, irrespective of whether the patients were receiving blockers of the angiotensin system.

A stepwise reduction in prognosis was seen with reducing renal function (or worse categories of CKD). As compared to subjects with an eGFR of > 60 mL/min/1.73 m², those with eGFR of 45 to 60 mL/min per 1.73 m² (CKD stage 3A) had an adjusted hazard ratio of 1.54 for the primary end point (P<0.001) and 1.50 for all-cause mortality (P=0.006). For patients with eGFR <45 mL/min per 1.73 m² (CKD stage 3B or worse), the respective adjusted hazard ratios were 1.86 (P<0.001) and 1.91 (P=0.001).

So what are the key take home clinical messages from this analysis? Firstly, impaired renal function is common in patients with chronic heart failure. Secondly, when present, even a modest reduction in renal function is a marker of higher absolute risk of an adverse event (including death). Thirdly, there is no evidence that the beneficial effect of candesartan (ie, inhibition of the angiotensin system) was modified by baseline eGFR. Drugs such as angiotensin-converting enzyme inhibitors and aldosterone blockers are generally underutilized in patients with impaired renal function. Yet, these data would suggest that such patients are at high risk of an event and therefore have potentially much to gain. When these drugs are used, careful monitoring of clinical and biochemical status is required.

Paul Kalra

The 2006 Winter Olympics open in Turin, Italy; Facebook makes its debut and goes viral; and an intact pharaonic tomb is discovered the Valley of the Kings, the first since the discovery of the tomb of Tutankhamen in 1922
Cardiorenal syndrome

C. Ronco, M. Haapio, A. A. House, N. Anavekar, R. Bellomo

*J Am Coll Cardiol.* 2008;52(19):1527-1539

This paper is the "marmite" of articles—you either love it or hate it! The authors' justification of this "state of the art" paper is to provide a definition of the cardiorenal syndrome (CRS) that in turn helps the identification and full characterization of the chronology of the pathophysiological interactions that typify a specific type of combined heart/kidney disorder. This paper, together with its subsequent citations, associated editorials, and reviews has certainly helped raise awareness of this important clinical relationship and has inspired constructive debate. Prior to this paper a number of proposed definitions and hypotheses for CRS were in circulation. The authors highlight many of the limitations seen with these, including the fact that many were too simplistic. Although they do also acknowledge that "a more articulated definition of the CRS has been advocated"—interestingly this is a publication by 3 of the 4 authors of this manuscript!

Ronco and colleagues propose a classification based around five types of the CRS. This results from the need to differentiate between acute and chronic interactions and identify the "primary" driving pathophysiological abnormality in each clinical scenario. Each subtype is described in turn and supported by very detailed figures with multiple arrows showing the pathophysiological abnormalities that characterize the differing scenarios. The reader would be mistaken if they were to assume that we have clear understanding of what the arrows really mean (one respected nephrologist described the arrows as representing potential causal relations with liberal sprinkling of magic pixie dust).

The 5 subtypes of CRS can be summarized as worsening or decompensated heart failure as a cause or effect of acute kidney injury (AKI, constituting types 1 and 3, respectively), chronic heart failure (CHF) as a cause and effect of chronic kidney disease (CKD, types 2 and 4, respectively), and cardiovascular and renal damage from a common underlying pathology (type 5, e.g., acute sepsis, or chronic conditions such as diabetes mellitus, atherosclerosis, and/or hypertension). The classification is logical in separating different clinical presentations of heart/kidney disease.

Previously there was no or little distinction between, e.g., acute heart failure resulting in acute kidney injury, as opposed to CHF leading onto CKD. Moreover, it has certainly helped the clinician to realize the high risk associated with particular clinical situations.

There are, however, major limitations to this classification particularly since as already mentioned the precise pathophysiological relationships in the different clinical scenarios are not fully understood. Each type of CRS may occur in the presence of another. For example, AKI is more likely in a patient with decompensated heart failure if the patient has diabetes (underlying systemic condition) with associated CKD and coronary artery disease (CAD). In addition, it is plausible that a patient with CHF will exhibit pathophysiological changes typical of distinct subgroups at different stages of their heart failure syndrome. While the precise pathophysiological mechanisms are not fully understood, it is apparent that dysfunction of one organ system may cause or exacerbate dysfunction of the other and a spiral of decline can occur, with resultant adverse prognosis. In many respects, the major attribute of this paper, in my opinion, is how it highlights just how poorly we understand CRS. It emphasizes that we cannot sit on our laurels and expect an improvement in clinical outcomes without coordinating top quality research into this area. However, it probably adds little to the understanding of the pathophysiology. Cardiologists and nephrologists must work on CRS, which is currently seen through a glass, darkly.

Paul Kalra

2008

Lewis Hamilton becomes the youngest and first black Formula One World Champion; Democrat Barack Obama defeats Republican John McCain to win the 2008 US presidential election; and India sends 10 satellites into orbit in a single launch.
Ferric carboxymaltose in patients with heart failure and iron deficiency


The FAIR-HF study (Ferinject Assessment in patients with Iron deficiency and chronic Heart Failure) is the largest published trial of IV iron treatment in patients with chronic heart failure (CHF). It produced notable results, and the only criticism regarding its value and impact on clinical care is as a consequence of relatively short duration and slightly weak end points. The study design highlighted a number of difficulties within this area, such as how to truly double-blind a study in which the IV preparation (ie, iron) looks like Coca-Cola (!) and how to define iron deficiency in CHF. Patients received the drug into a cannula placed with their arm through a makeshift curtain and study personnel included a blinded and unblinded group. In light of the fact that ferritin levels are influenced by coexistent inflammation, a normal value does not exclude iron deficiency in CHF and hence arbitrary (but sensible) cutoffs were chosen.

A total of 459 patients with left ventricular (LV) systolic dysfunction and New York Heart Association (NYHA) class II or III and ejection fraction (LVEF) ≤45% were recruited. It is important to note that patients did not need to be anemic to enter the study, merely iron deficient. Iron deficiency was defined as serum ferritin of <100 μg/L or between 100-299 μg/L and a transferring saturation (TSAT) of <20%. Patients were randomized 2:1 to IV 200 mg ferric carboxymaltose or placebo. A correction (therapy every 2 weeks) and then maintenance phase (therapy every 4 weeks) were incorporated into the protocol. The primary end points were the self-reported Patient Global Assessment (PGA) and NYHA Class at 24 weeks. Safety of IV iron therapy was assessed at 26 weeks.

Treatment was associated with significant improvements in the primary end point: 50% of patients receiving IV iron reported being much or moderately improved according to the PGA as compared with 28% patients receiving placebo. An odds ratio for improving one or more NYHA classes of 2.40 (95% CI, 1.55-3.71) was seen with active treatment versus placebo. Secondary end points such as 6-minute walk distance were similarly improved. Findings were consistent irrespective of whether patients were anemic or not, ie, iron deficiency is the key. Benefits appeared as early as 4 weeks from starting treatment, suggesting that beneficial mechanisms extend beyond impact on hemoglobin.

Treatment with IV iron was safe, with no severe allergic reactions reported. It is of note that during the maintenance phase treatment interruption only occurred if hemoglobin exceeded 16.0 g/dL or serum ferritin >800 μg/L or serum ferritin >500 μg/L, if TSAT >50%. These ferritin values might seem extremely high to “non-nephrologists.” However, their incorporation into the protocol has provided further reassurance of the safety of treating iron deficiency.

How is FAIR-HF likely to impact on clinical practice? The data suggest that correcting iron deficiency in patients with CHF is safe in the short term and associated with improved functioning and quality of life. However, heart failure specialists are used to megastudies with hard clinical end points such as mortality and hospitalization. To impact whole scale changes in clinical practice, a larger study with long-term follow-up and such end points is required.

*Paul Kalra*

2009

The body of billionaire Friedrich Karl Flick, stolen from the family mausoleum in 2008 and held for ransom, is returned to his family; the 25th anniversary of the industrial disaster in Bhopal in which 3787 were killed is marked in India; and the discovery of a new Triassic theropod dinosaur genus, *Tawa*, is announced.
# Bibliography of One Hundred Key Papers

selected by **Paul R. Kalra**, MD, FRCP  
Department of Cardiology - Portsmouth Hospitals NHS Trust - Portsmouth - UK  (e-mail: paul.kalra@porthosp.nhs.uk)  
and  
**Philip A. Kalra**, MD, FRCP  
Department of Nephrology - Salford Royal Foundation NHS Trust - Salford - UK  (e-mail: philip.kalra@srf.nhs.uk)

## Cardiorenal Syndrome

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Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure.


Cardiac calcification in renal patients: what we do and don’t know.


The regulation and measurement of plasma volume in heart failure.


Water and sodium regulation in chronic heart failure: the role of natriuretic peptides and vasopressin.


Hemoglobin concentration does not predict prognosis in incident (new) cases of heart failure.


Sympathetic activation and malignant ventricular arrhythmias: a molecular link?


Renal artery revascularization improves heart failure control in patients with atherosclerotic renal artery stenosis.


Severe coronary stenosis is an important factor for induction and lengthy persistence of ventricular arrhythmias during and after hemodialysis.


Serum and dialysate potassium concentrations and survival in hemodialysis patients.


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Natriuretic peptides.

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Instructions for authors

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Respondent articles should not exceed 15 standard typed pages (3000 to 4000 words), including an abstract of no more than 125 words, no more than 10 references, and a minimum of 3 - maximum of 5 illustrations (figures and tables). A maximum of 5-10 keywords should be included.

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Fascinoma Cardiologica articles (A Lexicon of the Heart; Icons of Cardiology; Plants and the Heart; Trails of Discovery, etc) should not exceed 2000 words (8 standard typed pages), should include 3 to 5 illustrations (figures and tables), and cite no more than 15 references. A maximum of 5-10 keywords should be included. No abstract.