

STATE-OF-THE-ART PAPER

Cardiorenal Syndrome

Claudio Ronco, MD,* Mikko Haapio, MD,† Andrew A. House, MSc, MD,‡ Nagesh Anavekar, MD,§
Rinaldo Bellomo, MD¶

Vicenza, Italy; Helsinki, Finland; London, Ontario, Canada; and Melbourne, Australia

The term cardiorenal syndrome (CRS) increasingly has been used without a consistent or well-accepted definition. To include the vast array of interrelated derangements, and to stress the bidirectional nature of heart-kidney interactions, we present a new classification of the CRS with 5 subtypes that reflect the pathophysiology, the time-frame, and the nature of concomitant cardiac and renal dysfunction. CRS can be generally defined as a pathophysiologic disorder of the heart and kidneys whereby acute or chronic dysfunction of 1 organ may induce acute or chronic dysfunction of the other. Type 1 CRS reflects an abrupt worsening of cardiac function (e.g., acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury. Type 2 CRS comprises chronic abnormalities in cardiac function (e.g., chronic congestive heart failure) causing progressive chronic kidney disease. Type 3 CRS consists of an abrupt worsening of renal function (e.g., acute kidney ischemia or glomerulonephritis) causing acute cardiac dysfunction (e.g., heart failure, arrhythmia, ischemia). Type 4 CRS describes a state of chronic kidney disease (e.g., chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy, and/or increased risk of adverse cardiovascular events. Type 5 CRS reflects a systemic condition (e.g., sepsis) causing both cardiac and renal dysfunction. Biomarkers can contribute to an early diagnosis of CRS and to a timely therapeutic intervention. The use of this classification can help physicians characterize groups of patients, provides the rationale for specific management strategies, and allows the design of future clinical trials with more accurate selection and stratification of the population under investigation. (J Am Coll Cardiol 2008;52:1527-39) © 2008 by the American College of Cardiology Foundation

A large proportion of patients admitted to hospital have various degrees of heart and kidney dysfunction (1). Primary disorders of 1 of these 2 organs often result in secondary dysfunction or injury to the other (2). Such interactions represent the pathophysiological basis for a clinical entity called cardiorenal syndrome (CRS) (3). Although generally defined as a condition characterized by the initiation and/or progression of renal insufficiency secondary to heart failure (4), the term CRS is also used to describe the negative effects of reduced renal function on the heart and circulation (5). The absence of a clear definition and the complexity of this cluster of conditions contribute to lack of clarity with regard to diagnosis and management (6). This is unfortunate, because recent advances in basic and clinical sciences have improved our understanding of organ crosstalk and have demonstrated the efficacy of some therapies in attenuating both cardiac and renal injury (7). Thus, a more articulated definition in terms of clinical presentation, pathophysiology, diagnosis, and management is needed to explore the complex nature of CRS and its different clinical subtypes.

From the *Department of Nephrology, St. Bortolo Hospital, Vicenza, Italy; †Division of Nephrology, Helsinki University Central Hospital, Helsinki, Finland; ‡Division of Nephrology, London Health Sciences Centre, London, Ontario, Canada; §Department of Cardiology, Northern Hospital, Melbourne, Australia; and the ¶Department of Intensive Care, Austin Hospital, Melbourne, Australia.

Manuscript received June 12, 2008; revised manuscript received July 14, 2008, accepted July 28, 2008.

CRS: A Definition

The simplistic view of CRS is that a relatively normal kidney is dysfunctional because of a diseased heart, with the assumption that, in the presence of a healthy heart, the same kidney would perform normally (8). This concept has been recently challenged, and a more articulated definition of the CRS has been advocated (5). The CRS includes a variety of acute or chronic conditions, where the primary failing organ can be either the heart or the kidney (9).

Previous terminology did not allow physicians to identify and fully characterize the chronology of the pathophysiological interactions that characterize a specific type of combined heart/kidney disorder. A diseased heart has numerous negative effects on kidney function but, at the same time, renal insufficiency can significantly impair cardiac function (9). Thus, direct and indirect effects of each organ that is dysfunctional can initiate and perpetuate the combined disorder of the 2 organs through a complex combination of neurohormonal feedback mechanisms. For this reason, a subdivision of CRS into 5 different subtypes seems to provide a more concise and logically correct approach.

CRS type 1 (acute CRS). Type 1 CRS is characterized by a rapid worsening of cardiac function, leading to acute kidney injury (AKI) (Fig. 1). Acute heart failure (HF) may be divided into 4 subtypes: hypertensive pulmonary edema with preserved left ventricular (LV) systolic function,

**Abbreviations
and Acronyms**

ACE	= angiotensin-converting enzyme
AKI	= acute kidney injury
ARB	= angiotensin receptor blocker
BNP	= B-type natriuretic peptide
CKD	= chronic kidney disease
CRS	= cardiorenal syndrome
GFR	= glomerular filtration rate
HF	= heart failure
ICU	= intensive care unit
IL	= interleukin
LV	= left ventricular
NGAL	= neutrophil gelatinase-associated lipocalin
TNF	= tumor necrosis factor

acutely decompensated chronic HF, cardiogenic shock, and predominant right ventricular failure (10). Type 1 CRS is a common occurrence. More than 1 million patients in the U.S. are admitted to the hospital every year with either de novo acute HF or acutely decompensated chronic HF (11). Among these patients, pre-morbid chronic renal dysfunction is a common occurrence and predisposes them to AKI (12,13). The mechanisms by which the onset of acute HF or acutely decompensated chronic HF leads to AKI are multiple and complex (4) (Fig. 1). The clinical importance of each mechanism is likely to vary from patient to patient (e.g., acute cardiogenic shock vs. hypertensive pulmonary edema) and situation to situation (acute HF secondary to perforation of a mitral valve leaflet from endocarditis vs.

worsening right HF secondary to noncompliance with diuretic therapy). In acute HF, AKI appears to be more severe in patients with impaired LV ejection fraction compared with those with preserved LV function, achieving an incidence >70% in patients with cardiogenic shock (14). Furthermore, impaired renal function is consistently found as an independent risk factor for 1-year mortality in acute HF patients, including patients with ST-segment elevation myocardial infarction (15). A plausible reason for this independent effect might be that an acute decline in renal function does not simply act as a marker of illness severity but also carries an associated acceleration in cardiovascular pathobiology through activation of inflammatory pathways (9,16).

In CRS type 1, a salient clinical issue is how the onset of AKI impacts on prognosis and treatment of acute HF. The first clinical principle is that the onset of AKI in this setting implies inadequate renal perfusion until proven otherwise, which should prompt clinicians to consider the diagnosis of a low cardiac output state and/or marked increase in venous pressure leading to kidney congestion through the use of physical examination, ancillary signs, imaging, and laboratory findings.

The second important consequence of type 1 CRS is decreased diuretic responsiveness. In a congestive state, decreased response to diuretics may result from the physiological phenomena of diuretic braking (diminished diuretic effectiveness secondary to postdiuretic sodium retention) (17) and post-diuretic sodium retention (18). In addition, concerns of aggravating AKI by the administration of

diuretics at greater doses or in combination also can act as an additional, iatrogenic mechanism. Diuretics are best provided to HF patients with evidence of systemic fluid overload with the goal of achieving a gradual diuresis. Loop diuretics may be titrated according to renal function, systolic blood pressure, and history of chronic diuretic use. High doses may cause tinnitus, and a continuous low-dose diuretic infusion might be more efficient (19).

Measurement of cardiac output (arterial pressure monitoring combined with pulse contour analysis or by Doppler ultrasound) and venous pressure may help ensure adequate and targeted diuretic therapy (20–22) and allow safer navigation through the precarious situation of combined HF and AKI. If diuretic-resistant fluid overload exists despite an optimized cardiac output, removal of isotonic fluid can be achieved by the use of extracorporeal ultrafiltration (23,24).

The presence of AKI with or without concomitant hyperkalemia may also affect patient outcome by inhibiting the prescription of angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and aldosterone inhibitors (drugs that have been shown in large randomized controlled trials to increase survival in the setting of heart failure and myocardial infarction) (25). However, provided there is close monitoring of renal function and potassium levels, the potential benefits of these interventions often outweigh their risks, even in these patients.

The acute administration of beta-blockers in the setting of type 1 CRS generally is not advised. Such therapy should wait until the patient has stabilized physiologically and until concerns about a low output syndrome have been resolved. In some patients, stroke volume cannot be increased, and relative or absolute tachycardia sustains the adequacy of cardiac output. Blockade of such compensatory tachycardia and sympathetic system-dependent inotropic compensation can precipitate cardiogenic shock with associated high mortality (26). Particular concern applies to beta-blockers excreted by the kidney, such as atenolol or sotalol, alone or in combination with calcium antagonists (27). This should not inhibit the slow, careful, titrated administration of beta-blockers later on, once patients are hemodynamically stable.

In patients with kidney dysfunction, undertreatment after myocardial infarction is common (28). Attention should be paid to preserving renal function, perhaps with the same vigor as we attempt to salvage and protect cardiac muscle. Worsening of renal function during admission for ST-segment elevation myocardial infarction is a powerful and independent predictor of in-hospital and 1-year mortality (14,15). In patients who receive percutaneous coronary intervention or cardiac surgery, even a small increase in serum creatinine (>0.3 mg/dl) is associated with increased hospital stay and mortality (29,30). In this context, an increase in creatinine is not simply a marker of illness severity but, rather, it represents the onset of AKI acting as a causative factor for cardiovascular injury acceleration through the activation of neurohormonal, immunological and inflammatory pathways (9,16). No specific kidney-

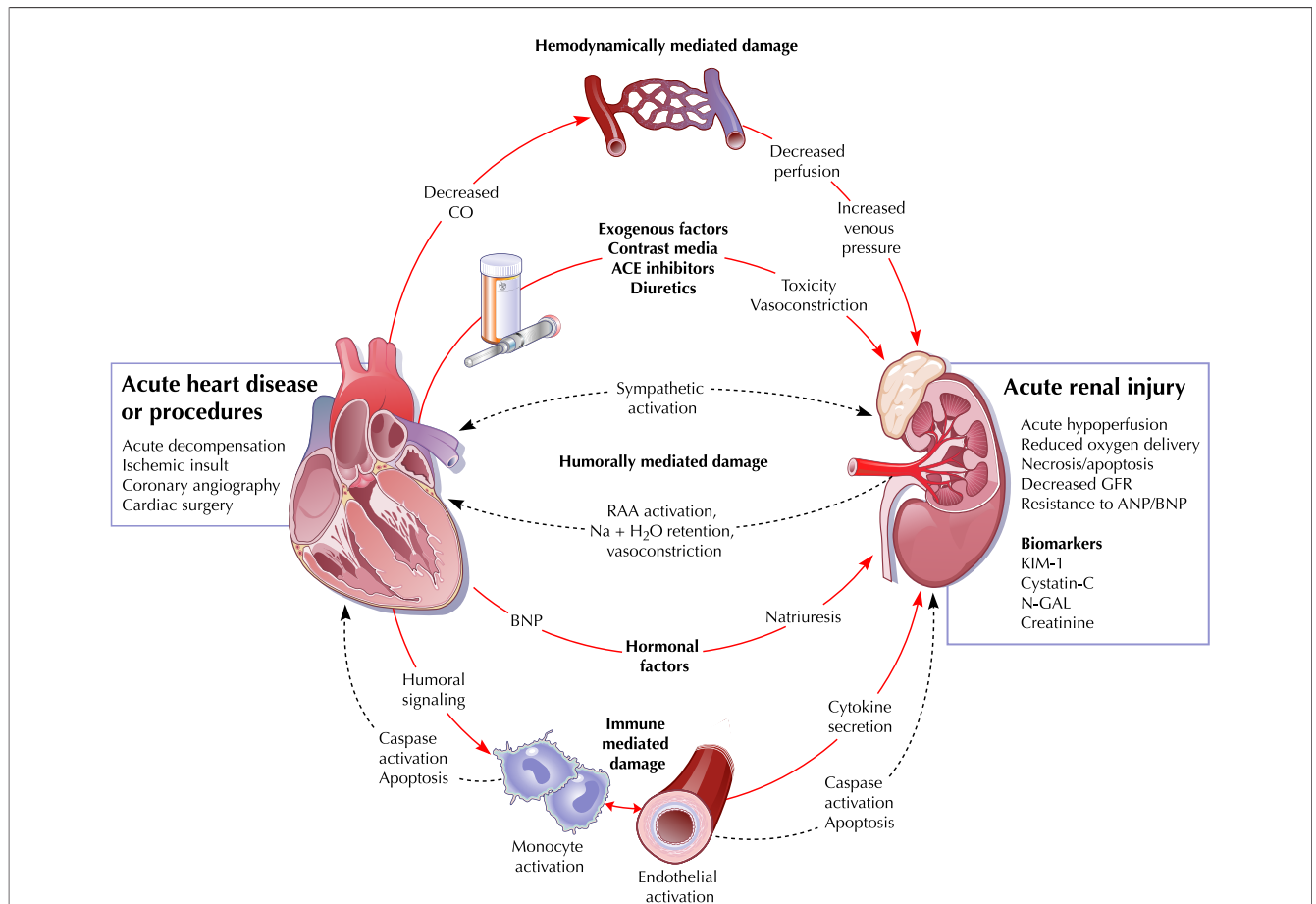


Figure 1 CRS Type 1

Pathophysiological interactions between heart and kidney in type 1 cardiorenal syndrome (CRS) or “acute CRS” (abrupt worsening of cardiac function, e.g., acute cardiogenic shock or acute decompensation of chronic heart failure) leading to kidney injury. ACE = angiotensin-converting enzyme; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CO = cardiac output; GFR = glomerular filtration rate; KIM = kidney injury molecule; N-GAL = neutrophil gelatinase-associated lipocalin; RAA = renin angiotensin aldosterone. Figure illustration by Rob Flewelling.

protective treatments have yet emerged for this condition. Despite some initial promising results, the use of nesiritide remains controversial, and a recent negative randomized controlled trial in these very patients (31) suggests that this agent is unlikely to have significant clinical benefit.

A very specific and common threat to kidney function in the setting of acute cardiac disease relates to the administration of radiocontrast for heart imaging procedures. This topic, recently reviewed in the *Journal* (32), would require separate detailed discussion and is beyond the scope of this article. Suffice it to say that this high-risk group requires appropriate prophylaxis to avoid radiocontrast nephropathy. Given that the presence of type 1 CRS defines a population with high mortality, a prompt, careful, systematic, multidisciplinary approach involving cardiologists, nephrologists, critical care physicians, and cardiac surgeons is both logical and desirable.

In CRS type 1, the early diagnosis of AKI remains a challenge (33). This is also true in CRS type 3, where AKI is believed to be the primary inciting factor leading to

cardiac dysfunction. In both cases, classic markers such as creatinine increase when AKI is already established and very little can be done to prevent it or to protect the kidney. An interesting evolution in the early diagnosis of CRS has been the discovery of novel AKI biomarkers. With the use of a complementary deoxyribonucleic acid microarray as a screening technique, a subset of genes whose expression is up-regulated within the first few hours after renal injury has been discovered (34,35).

Neutrophil gelatinase-associated lipocalin (NGAL) appears to be one of the earliest markers detected in the blood and urine of humans with AKI (36-39). Urine and serum NGAL are early predictors of AKI both in adult and children either in cardiac surgery or patients in the intensive care unit (ICU) (40,41). In these patients, an increase in creatinine is observed only 48 to 72 h later (42). NGAL is also a biomarker of delayed graft function in kidney transplantation (43), AKI caused by contrast-media (44), and AKI in critically ill patients admitted to intensive care (45).

Cystatin C appears to be a better predictor of glomerular function than serum creatinine in patients with chronic kidney disease (CKD) because its blood levels are not affected by age, gender, race, or muscle mass (46). Cystatin C predicts AKI and the requirement for renal replacement therapy earlier than creatinine (47). Serum cystatin C has been compared with NGAL in cardiac surgery-mediated AKI (48). Both biomarkers predicted AKI at 12 h, although NGAL outperformed cystatin C at earlier time points. Considering them together, they may represent a combination of structural and functional damage of the kidney.

Kidney injury molecule 1 is a protein detectable in the urine after ischemic or nephrotoxic insults to proximal tubular cells (49–51) and seems to be highly specific for ischemic AKI. Combined with NGAL which is highly sensitive, it may represent an important marker in the early phases of AKI.

Biomarkers such as *N*-acetyl- β -(D)glucosaminidase (52), interleukin (IL)-18 (53) and others reported in Table 1 have been proposed as an interesting and promising contribution to diagnosis of AKI and progression of CKD. The most likely evolution will be a “panel” of biomarkers that include several molecules both in serum and urine that combine their best characteristics in terms of specificity and sensitivity of each marker molecule.

CRS type 2 (chronic CRS). Type 2 CRS is characterized by chronic abnormalities in cardiac function (e.g., chronic congestive HF) causing progressive CKD (Fig. 2). Worsening renal function in the context of HF is associated with adverse outcomes and prolonged hospitalizations (32). The prevalence of renal dysfunction in chronic HF has been reported to be approximately 25% (54). Even slight decreases in estimated glomerular filtration rate (GFR) significantly increase mortality risk (54) and are considered a marker of severity of vascular disease (55). Independent predictors of worsening function include old age, hypertension, diabetes mellitus, and acute coronary syndromes.

The mechanisms underlying worsening renal function likely differs based on acute versus chronic HF. Chronic HF

is likely to be characterized by a long-term situation of reduced renal perfusion, often predisposed by microvascular and macrovascular disease. Although a greater proportion of patients with low estimated GFR have a worse New York Heart Association functional class, no evidence of association between LV ejection fraction and estimated GFR can be consistently demonstrated. Thus, patients with chronic HF and preserved LV function appear to have similar estimated GFR than patients with impaired LV (ejection fraction <45%) (55).

There is very limited understanding of the pathophysiology of renal dysfunction in the setting of even advanced cardiac failure. In this setting, where one would intuitively consider hemodynamic issues to be dominant, the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Catheterization Effectiveness) trial (56) found no link between any pulmonary artery catheter-measured hemodynamic variables and serum creatinine in 194 patients. The only link was with right atrial pressure, suggesting that renal congestion may be more important than appreciated. Clearly, hypoperfusion alone cannot explain renal dysfunction in this setting. More work needs to be performed to understand the mechanisms at play to develop targeted and physiologically sound approaches to treatment.

Neurohormonal abnormalities are present with excessive production of vasoconstrictive mediators (epinephrine, angiotensin, endothelin) and altered sensitivity and/or release of endogenous vasodilatory factors (natriuretic peptides, nitric oxide). Pharmacotherapies used in the management of HF may worsen renal function. Diuresis-associated hypovolemia, early introduction of renin-angiotensin-aldosterone system blockade, and drug-induced hypotension have all been suggested as contributing factors (4).

More recently, there has been increasing interest in the pathogenic role of relative or absolute erythropoietin deficiency contributing to a more pronounced anemia in these patients than might be expected for renal failure alone (57). Erythropoietin receptor activation in the heart may protect it from apoptosis, fibrosis, and inflammation (58,59). Preliminary clinical studies show that erythropoiesis-stimulating agents in patients with chronic HF, CKD, and anemia lead to improved cardiac function, reduction in LV size, and the lowering of B-type natriuretic peptide (BNP) (60). Patients with type 2 CRS are more likely to receive loop diuretics and vasodilators and also to receive greater doses of such drugs compared with those patients with stable renal function (61). Treatment with these drugs may participate in the development and progression of renal injury. However, such therapies may simply identify patients with severe hemodynamic compromise and, thus, a predisposition to renal dysfunction rather than being responsible for worsening function.

Renal insufficiency is highly prevalent among patients with HF and is an independent negative prognostic factor in both diastolic and systolic ventricular dysfunction and severe HF (62). The logical practical implications of the plethora

Table 1 Protein Biomarkers for the Early Detection of Acute Kidney Injury

Biomarker	Associated Injury
Cystatin C	Proximal tubule injury
KIM-1	Ischemia and nephrotoxins
NGAL (lipocalin)	Ischemia and nephrotoxins
NHE3	Ischemia, pre-renal, post-renal AKI
Cytokines (IL-6, IL-8, IL-18)	Toxic, delayed graft function
Actin-actin depolymerizing F	Ischemia and delayed graft function
α -GST	Proximal T injury, acute rejection
π -GST	Distal tubule injury, acute rejection
L-FABP	Ischemia and nephrotoxins
Netrin-1	Ischemia and nephrotoxins, sepsis
Keratin-derived chemokine	Ischemia and delayed graft function

GST = glutathione S-transferase; IL = interleukin; KIM = kidney injury molecule; L-FABP = L-type fatty acid binding protein; NGAL = neutrophil gelatinase-associated lipocalin; NHE = sodium-hydrogen exchanger.

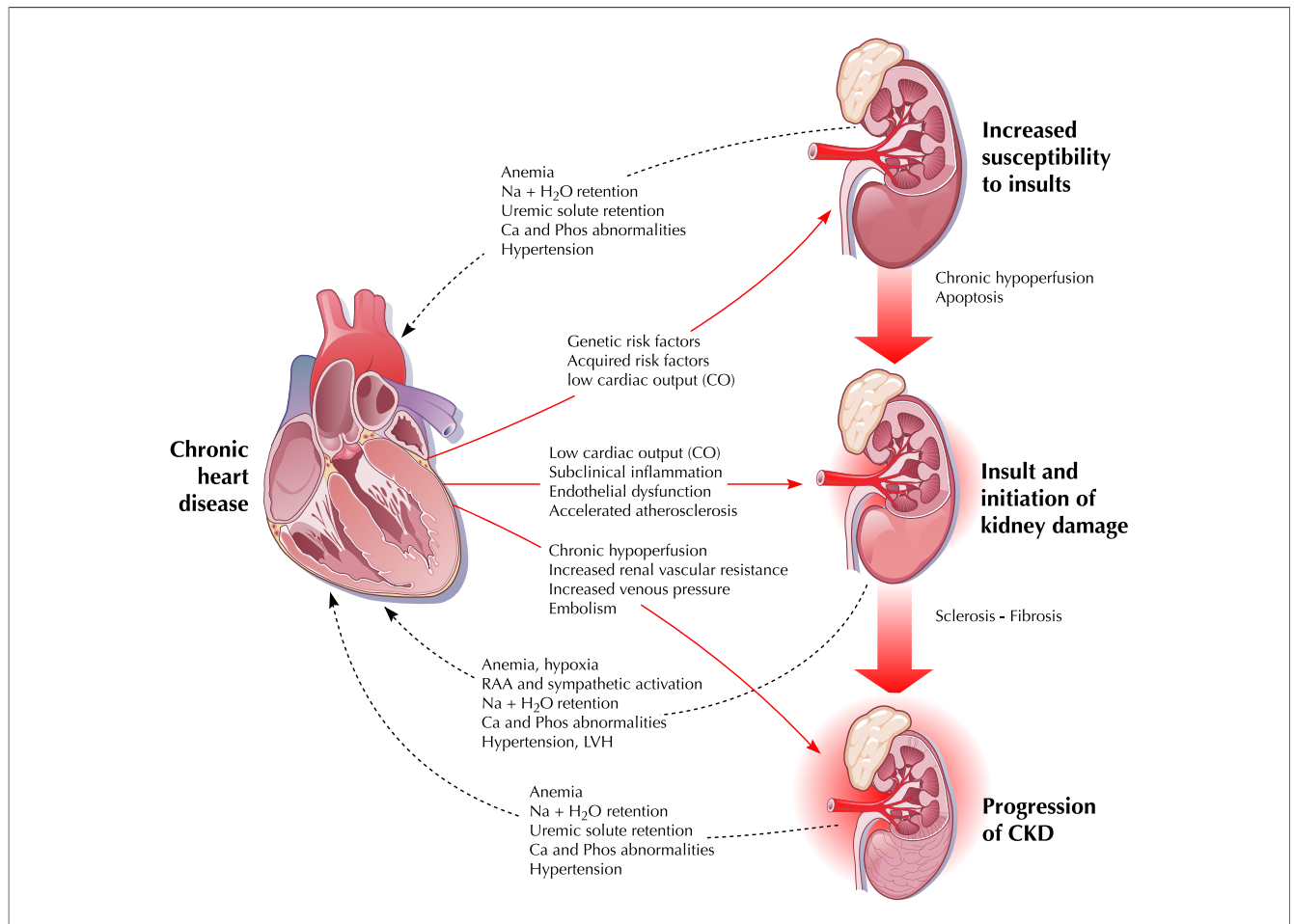


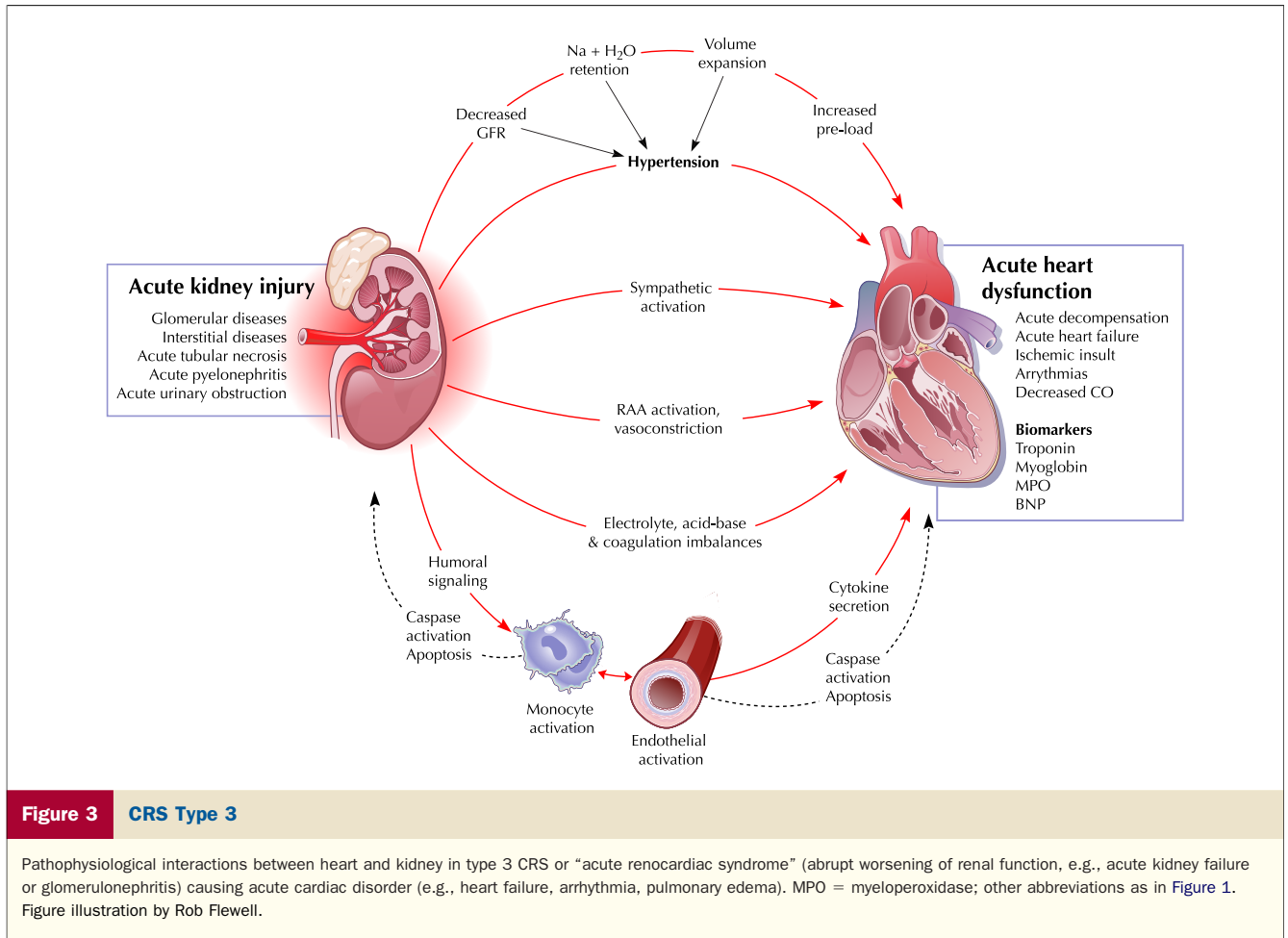
Figure 2 CRS Type 2

Pathophysiological interactions between heart and kidney in type 2 cardiorenal syndrome (CRS) or "chronic CRS" (chronic abnormalities in cardiac function, e.g., chronic heart failure) causing progressive chronic kidney disease (CKD). Figure illustration by Rob Flewell. LVH = left ventricular hypertrophy; RAA = renin angiotensin aldosterone.

of data linking CKD with cardiovascular disease are that more attention needs to be paid to reducing risk factors and optimizing medications in these patients and that undertreatment due to concerns about pharmacodynamics in this setting may have lethal consequences at an individual level and huge potential adverse consequences at a public health level. Nonetheless, it is equally important to acknowledge that clinicians looking after these patients often are faced with competing therapeutic choices and that, with the exception of MERIT-HF (Metoprolol Controlled-Release Randomised Intervention Trial in Heart Failure) (63), large randomized controlled trials that have shaped the treatment of chronic HF in the last 2 decades have consistently excluded patients with significant renal disease. More on the use of specific agents is covered in the sections on type 3 and 4 CRS.

CRS type 3 (acute renocardiac syndrome). Type 3 CRS is characterized by an abrupt and primary worsening of kidney function (e.g., AKI, ischemia, or glomerulonephritis), leading to acute cardiac dysfunction (e.g., HF, arrhythmia,

ischemia). Type 3 CRS appears less common than type 1 CRS, but this may only be due to the fact that, unlike type 1 CRS, it has not been systematically studied. AKI is a growing disorder in hospital and ICU patients. When the RIFLE (risk, injury, and failure; loss; and end-stage kidney disease) consensus definition is used, AKI has been identified in close to 9% of hospital patients (64). In a large ICU database, AKI was observed in more than 35% of patients (65). Acute kidney injury can affect the heart through several pathways (Fig. 3), whose hierarchy is not yet established. Fluid overload can contribute to the development of pulmonary edema. Hyperkalemia can contribute to arrhythmias and may cause cardiac arrest. Untreated uremia affects myocardial contractility through the accumulation of myocardial depressant factors (66) and pericarditis (67). Acidemia produces pulmonary vasoconstriction (68), which can significantly contribute to right-sided HF. Acidemia appears to have a negative inotropic effect (69) and might, together with electrolyte imbalances, contribute to an increased risk of arrhythmias (70). Finally, renal ischemia



itself may precipitate activation of inflammation and apoptosis at cardiac level (9).

A unique situation leading to type 3 CRS is bilateral renal artery stenosis (or unilateral stenosis in a solitary kidney). Patients with this condition may be prone to acute or decompensated HF because of diastolic dysfunction related to chronic increase of blood pressure from excessive activation of the renin-angiotensin-aldosterone axis, renal dysfunction with sodium and water retention, and acute myocardial ischemia from an increase in myocardial oxygen demand related to intense peripheral vasoconstriction (71,72). In these patients, angiotensin blockade is generally required to manage the hypertension and HF. However, the GFR is highly dependent upon angiotensin and significant decompensation of kidney function may ensue. Although the management of these unusual patients has not been subject to scrutiny in large randomized trials, those exhibiting renal decompensation with ACE inhibition or ARB are likely candidates for renal revascularization (72).

Sensitive and specific biomarkers of cardiac injury may help physicians to diagnose and treat type 3 CRS earlier and perhaps more effectively (73). Cardiac troponins are biomarkers for ischemic myocardial injury (74,75), and they

correlate with outcomes in the general population and specifically in renal patients (76–78). A marker of myocyte stress is BNP and allows the diagnosis of acute and acutely decompensated chronic HF (79). It also is an independent predictor of cardiovascular events and overall mortality in the general population (80,81) and also in patients with renal insufficiency (82–84). In HF, despite high levels of serum BNP, its physiological effects (vasodilatory, diuretic, and natriuretic) do not appear sufficient to prevent the disease progression and CRS. Recent findings suggest a resistance to BNP (85) and/or a relative preponderance of the biologically inactive precursor of BNP (86). In CRS type 4 (discussed in the following text), an association between increased levels of BNP and the accelerated progression of nondiabetic CKD to end-stage kidney disease has been observed (87).

Myeloperoxidase is a marker of altered myocyte metabolism, oxidative stress, and inflammation, especially in acute coronary syndrome (88). Oxidative stress may cause myocyte apoptosis and necrosis, and it is associated with arrhythmias and endothelial dysfunction with a potential role in the pathogenesis of CRS (89). Cytokines such as tumor necrosis factor (TNF), IL-1, and IL-6 may have a diagnostic role as early biomarkers of CRS, but also a pathogenic role causing myocardial cell

injury and apoptosis (90,91) and mediating myocardial damage in ischemic AKI (92).

The development of AKI can affect the use of medications normally prescribed in patients with chronic HF. For example, an increase in serum creatinine from 1.5 mg/dl (130 μ mol/l) to 2 mg/dl (177 μ mol/l), with diuretic therapy and ACE inhibitors, may provoke some clinicians to decrease or even stop diuretic prescription; they may also decrease or even temporarily stop ACE inhibitors. This may, in some cases, lead to acute decompensation of HF. It should be remembered that ACE inhibitors do not damage the kidney but rather modify intrarenal hemodynamics and reduce filtration fraction. They protect the kidney by reducing pathological hyperfiltration. Unless renal function fails to stabilize, or other dangerous situations arise (i.e., hypotension, hyperkalemia) continued treatment with ACE inhibitors and ARBs may be feasible.

Finally, if AKI is severe and renal replacement therapy is necessary, cardiovascular instability generated by rapid fluid and electrolyte shifts secondary to conventional dialysis can induce hypotension, arrhythmias, and myocardial ischemia (93). Continuous techniques of renal replacement, which minimize such cardiovascular instability, appear physiologically safer and more logical in this setting (94).

CRS type 4 (chronic renocardiac syndrome). Type 4 CRS is characterized by a condition of primary CKD (e.g., chronic glomerular disease) contributing to decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events (Fig. 4). Today, CKD is divided into 5 stages based on a combination of severity of kidney damage and GFR (95). When these criteria are used, current estimates of CKD account for at least 11% of the U.S. adult population (96), thus becoming a major public health problem. In fact CKD today includes individuals with serum creatinine levels previously dismissed as not representative of significant renal dysfunction.

Individuals with CKD are at extremely high cardiovascular risk (97). More than 50% of deaths in CKD stage 5 cohorts are attributed to cardiovascular disease. The 2-year mortality rate after myocardial infarction in patients with CKD stage 5 is estimated to be 50% (98). In comparison, the 10-year mortality rate post-infarct for the general population is 25%. Patients with CKD have between a 10- and 20-fold increased risk of cardiac death compared with age-/gender-matched control subjects without CKD (98–100). Part of this problem may be related to the fact that such individuals are also less likely to receive risk-modifying interventions compared to their non-CKD counterparts (101).

Less severe forms of CKD also may be associated with significant cardiovascular risk. Evidence for increasing cardiovascular disease morbidity and mortality tracking with mild-to-moderate renal dysfunction (stages 1 to 3) has mainly stemmed from community-based studies (102–105). These studies documented an inverse relationship between renal

function and adverse cardiovascular outcomes (consistently occurring at estimated GFR levels <60 ml/min/1.73 m²).

Among high-risk cohorts, baseline creatinine clearance is a significant and independent predictor of short-term outcomes, namely death and myocardial infarction (99). Similar findings also were noted among patients presenting with ST-segment elevation myocardial infarction (106), an effect independent of the Thrombolysis In Myocardial Infarction risk score (107).

In large-scale studies (e.g., SOLVD [Studies Of Left Ventricular Dysfunction], TRACE [Trandolapril Cardiac Evaluation], SAVE [Survival And Ventricular Enlargement], and VALIANT [Valsartan in Acute Myocardial Infarction]) in which the authors excluded individuals with baseline serum creatinine of ≥ 2.5 mg/dl, reduced renal function was associated with significantly greater mortality and adverse cardiovascular event rates (108–111).

Adverse cardiovascular outcomes in renal patients are associated with plasma levels of specific biomarkers (112–114). Troponins, asymmetric dimethylarginine, plasminogen-activator inhibitor type 1, homocysteine, natriuretic peptides, C-reactive protein, serum amyloid A protein, hemoglobin, and ischemia-modified albumin are biomarkers whose levels correlate with cardiovascular outcomes in patients with CKD (115–117). These observations provide a mechanistic link between chronic inflammation (118), subclinical infections (119), accelerated atherosclerosis, heart–kidney interactions, and negative cardiovascular and renal outcomes.

The proportion of individuals with CKD receiving appropriate cardiovascular risk modification treatment is lower than in the general population. This “therapeutic nihilism” (120) is based on the concern of worsening kidney function (121,122) and leads to treating $<50\%$ of patients with CKD with the combination of aspirin, beta-blockers, ACE inhibitors, and statins (123). In a cohort involving $>140,000$ patients, 1,025 with documented CKD were less likely to receive aspirin, beta-blockade, or ACE inhibition after infarction than patients without CKD. Yet CKD patients had 30-day mortality risk reductions similar to non-CKD patients when receiving the drug combination (123).

Potential reasons for this subtherapeutic performance include concerns about further worsening of renal function, and/or therapy-related toxic effects due to low clearance rates (124,125). Many medications necessary for management of complications of advanced CKD generally are considered safe with concomitant cardiac disease. These include regimens for calcium-phosphate balance and hyperparathyroidism, vitamins, and erythropoiesis-stimulating agents (126–129). The same appears to hold true for novel regimens, for instance, endothelin system antagonists, adenosine and vasopressin receptor antagonists, and inflammation suppressors (130–133). For immunosuppressive drugs, controversy exists regarding the effects of certain agents on the heart, indicating a need for more research in the area (134).

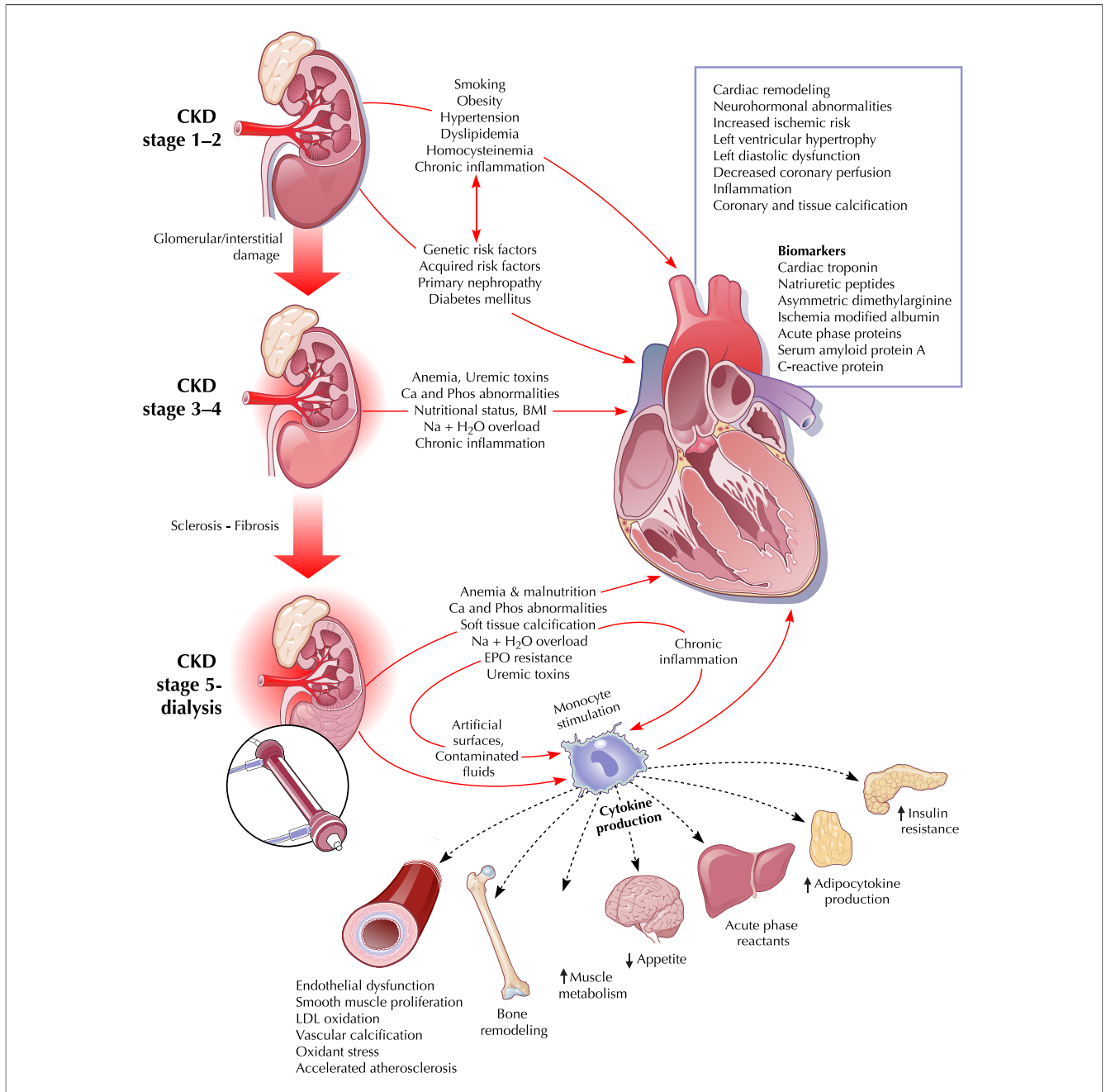


Figure 4 CRS Type 4

Pathophysiological interactions between heart and kidney in type 4 cardiorenal syndrome (CRS) or “chronic renocardiac syndrome” (chronic kidney disease [CKD], e.g., chronic glomerular disease, contributing to decreased cardiac function, cardiac hypertrophy, or increased risk of adverse cardiovascular events). BMI = body mass index; EPO = erythropoietin; LDL = low-density lipoprotein. Figure illustration by Rob Flewell.

Bleeding concerns contribute to the decreased likelihood of patients with severe CKD receiving aspirin and/or clopidogrel despite the minor bleeding risk and benefits that are sustained in these patients (135). Other medications requiring thorough considerations of pros and cons include diuretics, digitalis, calcium-channel blockers, and nesiritide (136–141). Nevertheless, when appropriately titrated and monitored, cardiovascular medications can be safely admin-

istered to CKD patients with benefits similar to the general population (142).

Lack of CKD population-specific treatment effect data makes therapeutic choices particularly challenging. In particular, in patients with advanced CKD, the initiation or increased dosage of ACE inhibitors or ARBs can precipitate clinically significant worsening of renal function or marked hyperkalemia. The latter may be dangerously exacerbated by the use of

aldosterone antagonists. Such patients, if aggressively treated, become exposed to a significant risk of developing dialysis dependence or life-threatening hyperkalemic arrhythmias. Yet, if too cautiously treated, they may develop equally life-threatening cardiovascular complications.

It is comforting to note that up to a 30% increase in creatinine that stabilizes within 2 months was actually associated with long-term nephroprotection in a systematic review of 12 randomized controlled studies (143). This result leads to the practical advice that ACE inhibitors and ARBs can be cautiously used in patients with CKD, provided the serum creatinine does not increase beyond this amount and potassium remains consistently <5.6 mmol/l. Regarding patients with end-stage renal disease, and in particular those with anuria and a tendency to hyperkalemia interdialytically, the administration of ACE inhibitors or ARBs may be problematic; however, even the combination of these medications has been used safely in select populations (144). At present, most end-stage kidney disease patients with LV dysfunction seem to be undertreated with ACE inhibitors or ARBs (145).

With respect to aldosterone blockade, drugs such as spironolactone have been widely used for severe HF patients with evidence of beneficial effects on morbidity and mortality (146). Concerns have been raised, however, about the use of aldosterone blockade, particularly in conjunction with angiotensin blockade, since after publication of RALES (Randomized Aldactone Evaluation Study) (146), prescriptions for spironolactone and rates of hospitalizations and mortality related to hyperkalemia increased sharply (147). Proper patient selection, including patients with diminished LV ejection fraction and excluding ones with moderate CKD (creatinine level ≥ 2.5 mg/dl) or hyperkalemia >5 mmol/l, would help minimize potential life-threatening hyperkalemia (140).

CRS type 5 (secondary CRS). Type 5 CRS is characterized by the presence of combined cardiac and renal dysfunction due to acute or chronic systemic disorders (Fig. 5). There is limited systematic information on type 5 CRS, although there is an appreciation that as more organs fail in this setting, mortality increases. There is limited insight into how combined renal and cardiovascular failure may differentially affect such an outcome com-

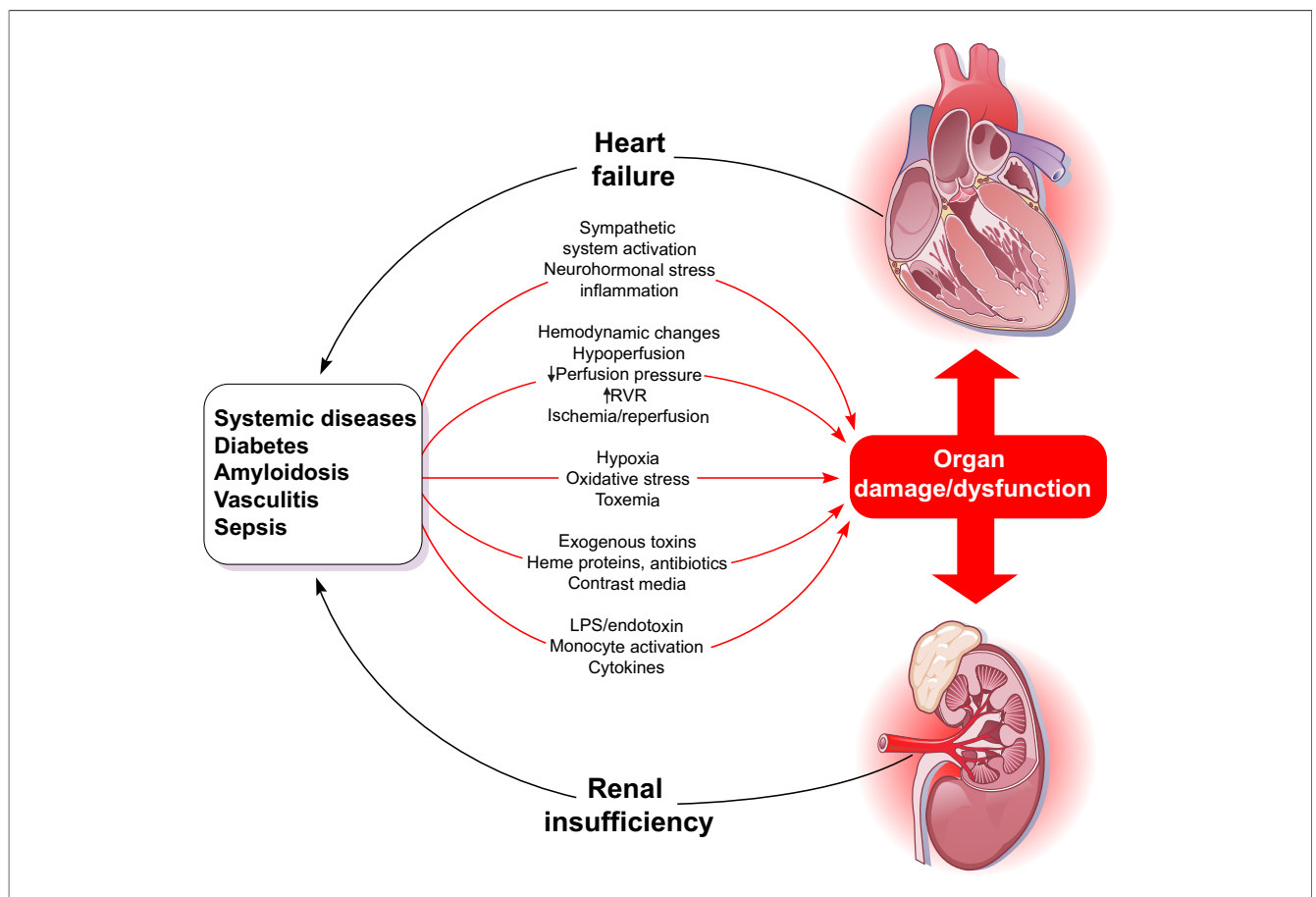


Figure 5 CRS Type 5

Pathophysiological interactions between heart and kidney in type 5 cardiorenal syndrome (CRS) or "secondary CRS" (systemic condition, e.g., diabetes mellitus, sepsis, causing both cardiac and renal dysfunction). LPS = lipopolysaccharide (endotoxin); RVR = renal vascular resistance. Figure illustration by Rob Flewell.

pared to, for example, combined pulmonary and renal failure. Nonetheless, it is clear that several acute and chronic diseases can affect both organs simultaneously and that the disease induced in one can affect the other and vice versa. Examples include sepsis, diabetes, amyloidosis, systemic lupus erythematosus, and sarcoidosis. Several chronic conditions such as diabetes and hypertension may contribute to type 2 and 4 CRS.

In the acute setting, severe sepsis represents the most common and serious condition which can affect both organs. It can induce AKI while leading to profound myocardial depression. The mechanisms responsible for such changes are poorly understood but may involve the effect of TNF and other mediators on both organs (148,149). The onset of myocardial functional depression and a state of inadequate cardiac output can further decrease renal function as discussed in type 1 CRS, and the development of AKI can affect cardiac function as described in type 3 CRS. Renal ischemia may then induce further myocardial injury (9) in a vicious cycle, which is injurious to both organs. Treatment is directed at the prompt identification, eradication, and treatment of the source of infection while supporting organ function with invasively guided fluid resuscitation in addition to inotropic and vasopressor drug support.

In this setting, all the principles discussed for type 1 and 3 CRS apply. In these septic patients, preliminary data derived from the use of more intensive renal replacement technology suggest that blood purification may have a role in improving myocardial performance while providing optimal small solute clearance (150). Despite the emergence of consensus definitions (151) and many studies (152,153), no therapies have yet emerged to prevent or attenuate AKI in critically ill patients. However, evidence of the injurious effects of pentastarch fluid resuscitation in septic AKI recently has emerged (154). Such therapy should, therefore, be avoided in septic patients.

Conclusions

In both chronic and acute situations, an appreciation of the interaction between heart and kidney during dysfunction of each or both organs has practical clinical implications. The depth of knowledge and complexity of care necessary to offer best therapy to these patients demands a multidisciplinary approach, combining the expertise of cardiology, nephrology, and critical care. In addition, achievement of a consensus definition for each type of cardiorenal syndrome will allow physicians to describe treatments and interventions that are focused and pathophysiologically sound. It will also help to conduct and compare epidemiological studies in different countries and more easily identify aspects of each syndrome. This is a priority for improvement and further research. Randomized controlled trials can then be designed to target interventions aimed at decreasing morbidity and mortality in these increasingly common conditions. Developing awareness, the ability to identify and define, and physiological understanding will help improve the outcome of these complex patients.

Acknowledgments

The authors thank Drs. Alan Maisel, Alexandre Mebazaa, Alan Cass, and Martin Gallagher for their useful advice in the development of the manuscript.

Reprint requests and correspondence: Dr. Claudio Ronco, Department of Nephrology, St. Bortolo Hospital, Viale Rodolfi 37, 36100 Vicenza, Italy. E-mail: cronco@goldnet.it.

REFERENCES

1. Dar O, Cowie MR. Acute heart failure in the intensive care unit: epidemiology. *Crit Care Med* 2008;36:S3–8.
2. Schrier RW. Cardiorenal versus renocardiac syndrome: is there a difference? *Nat Clin Pract Nephrol* 2007;3:637.
3. Ronco C. Cardiorenal and renocardiac syndromes: clinical disorders in search of a systematic definition. *Int J Artif Organs* 2008;31:1–2.
4. Liang KV, Williams AW, Greene EL, Redfield MM. Acute decompensated heart failure and the cardiorenal syndrome. *Crit Care Med* 2008;36:S75–88.
5. Ronco C, House AA, Haapio M. Cardiorenal syndrome: refining the definition of a complex symbiosis gone wrong. *Intensive Care Med* 2008;34:957–62.
6. Patel J, Heywood JT. Management of the cardiorenal syndrome in heart failure. *Curr Cardiol Rep* 2006;8:211–6.
7. Silverberg DS, Wexler D, Iaina A, Steinbruch S, Wollman Y, Schwartz D. Anemia, chronic renal disease and congestive heart failure—the cardio renal anemia syndrome: the need for cooperation between cardiologists and nephrologists. *Int Urol Nephrol* 2006;38:295–310.
8. Bongartz LG, Cramer MJ, Doevendans PA, Joles JA, Braam B. The severe cardiorenal syndrome: ‘guyton revisited.’ *Eur Heart J* 2005;26:11–7.
9. Berl T, Henrich W. Kidney-heart interactions: epidemiology, pathogenesis, and treatment. *Clin J Am Soc Nephrol* 2006;1:8–18.
10. Mebazaa A, Gheorghide M, Pina IL, et al. Practical recommendations for prehospital and early in-hospital management of patients presenting with acute heart failure syndromes. *Crit Care Med* 2008;36:S129–39.
11. Haldeman GA, Croft JB, Giles WH, Rashidee A. Hospitalization of patients with heart failure: national hospital discharge survey, 1985 to 1995. *Am Heart J* 1999;137:352–60.
12. Adams KF, Jr, Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the acute decompensated heart failure national registry (ADHERE). *Am Heart J* 2005;149:209–16.
13. Fonarow GC, Stough WG, Abraham WT, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry. *J Am Coll Cardiol* 2007;50:768–77.
14. Jose P, Skali H, Anavekar N, et al. Increase in creatinine and cardiovascular risk in patients with systolic dysfunction after myocardial infarction. *J Am Soc Nephrol* 2006;17:2886–91.
15. Goldberg A, Hammerman H, Petcherski S, et al. Inhospital and 1-year mortality of patients who develop worsening renal function following acute ST-elevation myocardial infarction. *Am Heart J* 2005;150:330–7.
16. Tokuyama H, Kelly DJ, Zhang Y, Gow RM, Gilbert RE. Macrophage infiltration and cellular proliferation in the non-ischemic kidney and heart following prolonged unilateral renal ischemia. *Nephron Physiol* 2007;106:54–62.
17. Ellison DH. Diuretic resistance: physiology and therapeutics. *Semin Nephrol* 1999;19:581–97.
18. Almeshari K, Ahlstrom NG, Capraro FE, Wilcox CS. A volume-independent component to postdiuretic sodium retention in humans. *J Am Soc Nephrol* 1993;3:1878–83.
19. Howard PA, Dunn MI. Aggressive diuresis for severe heart failure in the elderly. *Chest* 2001;119:807–10.

20. Opdam HI, Wan L, Bellomo R. A pilot assessment of the FloTrac cardiac output monitoring system. *Intensive Care Med* 2007;33:344-9.
21. Wan L, Naka T, Uchino S, Bellomo R. A pilot study of pulse contour cardiac output monitoring in patients with septic shock. *Crit Care Resusc* 2005;7:165.
22. Nguyen HB, Losey T, Rasmussen J, et al. Interrater reliability of cardiac output measurements by transcutaneous Doppler ultrasound: Implications for noninvasive hemodynamic monitoring in the ED. *Am J Emerg Med* 2006;24:828-35.
23. Ronco C, Ricci Z, Brendolan A, Bellomo R, Bedogni F. Ultrafiltration in patients with hypervolemia and congestive heart failure. *Blood Purif* 2004;22:150-63.
24. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2007;49:675-83.
25. Verma A, Solomon SD. Optimizing care of heart failure after acute MI with an aldosterone receptor antagonist. *Curr Heart Fail Rep* 2007;4:183-9.
26. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. *Lancet* 2005;366:1622-32.
27. Yorgun H, Deniz A, Aytemir K. Cardiogenic shock secondary to combination of diltiazem and sotolol. *Intern Med J* 2008;38:221-2.
28. Tessone A, Gottlieb S, Barbash IM, et al. Underuse of standard care and outcome of patients with acute myocardial infarction and chronic renal insufficiency. *Cardiology* 2007;108:193-9.
29. Roghi A, Savonitto S, Cavallini C, et al. Impact of acute renal failure following percutaneous coronary intervention on long-term mortality. *J Cardiovasc Med* 2008;9:375-81.
30. Lassnigg A, Schmid ER, Hiesmayr M, et al. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? *Crit Care Med* 2008;36:1129-37.
31. Witteles RM, Kao D, Christopherson D, et al. Impact of nesiritide on renal function in patients with acute decompensated heart failure and pre-existing renal dysfunction: a randomized, double-blind, placebo-controlled clinical trial. *J Am Coll Cardiol* 2007;50:1835-40.
32. McCullough PA. Contrast induced nephropathy. *J Am Coll Cardiol* 2008;51:1419-28.
33. Han WK, Bonventre JV. Biologic markers for the early detection of acute kidney injury. *Curr Opin Crit Care* 2004;10:476-82.
34. Devarajan P, Mishra J, Supavekin S, Patterson LT, Steven Potter S. Gene expression in early ischemic renal injury: clues towards pathogenesis, biomarker discovery, and novel therapeutics. *Mol Genet Metab* 2003;80:365-76.
35. Nguyen MT, Ross GF, Dent CL, Devarajan P. Early prediction of acute renal injury using urinary proteomics. *Am J Nephrol* 2005;25:318-26.
36. Ronco C. NGAL: an emerging biomarker of acute kidney injury. *Int J Artif Organs* 2008;31:199-200.
37. Xu S, Venge P. Lipocalins as biochemical markers of disease. *Biochim Biophys Acta* 2000;1482:298-307.
38. Mishra J, Ma Q, Prada A, et al. Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury. *J Am Soc Nephrol* 2003;14:2534-43.
39. Supavekin S, Zhang W, Kuchelapati R, Kaskel FJ, Moore LC, Devarajan P. Differential gene expression following early renal ischemia/reperfusion. *Kidney Int* 2003;63:1714-24.
40. Mori K, Nakao K. Neutrophil gelatinase-associated lipocalin as the real-time indicator of active kidney damage. *Kidney Int* 2007;71:967-70.
41. Mishra J, Dent C, Tarabishi R, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. *Lancet* 2005;365:1231-8.
42. Wagener G, Jan M, Kim M, et al. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. *Anesthesiology* 2006;105:485-91.
43. Parikh CR, Jani A, Mishra J, et al. Urine NGAL and IL-18 are predictive biomarkers for delayed graft function following kidney transplantation. *Am J Transplant* 2006;6:1639-45.
44. Bachorzewska-Gajewska H, Malyszko J, Sitniewska E, Malyszko JS, Dobrzycki S. Neutrophil-gelatinase-associated lipocalin and renal function after percutaneous coronary interventions. *Am J Nephrol* 2006;26:287-92.
45. Zappitelli M, Washburn KK, Arikian AA, et al. Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study. *Crit Care* 2007;11:R84.
46. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis* 2002;40:221-6.
47. Herget-Rosenthal S, Marggraf G, Husing J, et al. Early detection of acute renal failure by serum cystatin C. *Kidney Int* 2004;66:1115-22.
48. VandeVoerde RG, Katlman TI, Ma Q, et al. Serum NGAL and cystatin C as predictive biomarkers for acute kidney injury. *J Am Soc Nephrol* 2006;17:404A.
49. Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney injury molecule-1 (KIM-1): A novel biomarker for human renal proximal tubule injury. *Kidney Int* 2002;62:237-44.
50. Ichimura T, Hung CC, Yang SA, Stevens JL, Bonventre JV. Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury. *Am J Physiol Renal Physiol* 2004;286:F552-63.
51. Vaidya VS, Ramirez V, Ichimura T, Bobadilla NA, Bonventre JV. Urinary kidney injury molecule-1: a sensitive quantitative biomarker for early detection of kidney tubular injury. *Am J Physiol Renal Physiol* 2006;290:F517-29.
52. Liangos O, Perianayagam MC, Vaidya VS, et al. Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. *J Am Soc Nephrol* 2007;18:904-12.
53. Parikh CR, Abraham E, Ancukiewicz M, Edelstein CL. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. *J Am Soc Nephrol* 2005;16:3046-52.
54. Hillege HL, Nitsch D, Pfeffer MA, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. *Circulation* 2006;113:671-8.
55. Bhatia RS, Tu JV, Lee DS, et al. Outcome of heart failure with preserved ejection fraction in a population-based study. *N Engl J Med* 2006;355:260-9.
56. Nohria A, Hasselblad V, Stebbins A, et al. Cardiorenal interactions—insights from the ESCAPE trial. *J Am Coll Cardiol* 2007;51:1268-74.
57. Jie KE, Verhaar MC, Cramer MJ, et al. Erythropoietin and the cardiorenal syndrome: Cellular mechanisms on the cardiorenal connectors. *Am J Physiol Renal Physiol* 2006;291:F932-44.
58. Fu P, Arcasoy MO. Erythropoietin protects cardiac myocytes against anthracycline-induced apoptosis. *Biochem Biophys Res Commun* 2007;354:372-8.
59. Riksen NP, Hausenloy DJ, Yellon DM. Erythropoietin: ready for prime-time cardioprotection. *Trends Pharmacol Sci* 2008;29:258-67.
60. Palazzuoli A, Silverberg DS, Iovine F, et al. Effects of beta-erythropoietin treatment on left ventricular remodeling, systolic function, and B-type natriuretic peptide levels in patients with the cardiorenal anemia syndrome. *Am Heart J* 2007;154:645.e9-15.
61. Butler J, Forman DE, Abraham WT, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J* 2004;147:331-8.
62. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: Prognostic and therapeutic implications from a prospective cohort study. *Circulation* 2004;109:1004-9.
63. Hjalmarson A, Goldstein S, Fagerberg B, et al. MERIT-HF Study Group. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). *JAMA* 2000;283:1295-302.
64. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med* 2006;34:1913-7.
65. Bagshaw SM, George C, Dinu I, Bellomo R. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008;23:1203-10.

66. Blake P, Hasegawa Y, Khosla MC, Fouad-Tarazi F, Sakura N, Paganini EP. Isolation of "myocardial depressant factor(s)" from the ultrafiltrate of heart failure patients with acute renal failure. *ASAIO J* 1996;42:M911-5.
67. Meyer TW, Hostetter TH. Uremia. *N Engl J Med* 2007;357:1316-25.
68. Figueras J, Stein L, Diez V, Weil MH, Shubin H. Relationship between pulmonary hemodynamics and arterial pH and carbon dioxide tension in critically ill patients. *Chest* 1976;70:466-72.
69. Brady JP, Hasbargen JA. A review of the effects of correction of acidosis on nutrition in dialysis patients. *Semin Dial* 2000;13:252-5.
70. McCullough PA, Sandberg KR. Chronic kidney disease and sudden death: strategies for prevention. *Blood Purif* 2004;22:136-42.
71. Gandhi SK, Powers JC, Nomeir AM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. *N Engl J Med* 2001;344:17-22.
72. Hirsch AT, Haskal ZJ, Hertzner NR, et al. ACC/AHA guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine and Biology, and the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). *J Am Coll Cardiol* 2006;47:e1-192.
73. Parikh SV, de Lemos JA. Biomarkers in cardiovascular disease: integrating pathophysiology into clinical practice. *Am J Med Sci* 2006;332:186-97.
74. Cameron SJ, Sokoll LJ, Laterza OF, Shah S, Green GB. A multi-marker approach for the prediction of adverse events in patients with acute coronary syndromes. *Clin Chim Acta* 2007;376:168-73.
75. Howie-Esquivel J, White M. Biomarkers in acute cardiovascular disease. *J Cardiovasc Nurs* 2008;23:124-31.
76. Ooi DS, Veinot JP, Wells GA, House AA. Increased mortality in hemodialyzed patients with elevated serum troponin T: a one-year outcome study. *Clin Biochem* 1999;32:647-52.
77. Needham DM, Shufelt KA, Tomlinson G, Scholey JW, Newton GE. Troponin I and T levels in renal failure patients without acute coronary syndrome: a systematic review of the literature. *Can J Cardiol* 2004;20:1212-8.
78. Sommerer C, Beimler J, Schwenger V, et al. Cardiac biomarkers and survival in haemodialysis patients. *Eur J Clin Invest* 2007;37:350-6.
79. Maisel A, Hollander JE, Guss D, et al. Primary results of the rapid emergency department heart failure outpatient trial (REDHOT). A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. *J Am Coll Cardiol* 2004;44:1328-33.
80. Meyer B, Huelsmann M, Wexberg P, et al. N-terminal pro-B-type natriuretic peptide is an independent predictor of outcome in an unselected cohort of critically ill patients. *Crit Care Med* 2007;35:2268-73.
81. Latini R, Masson S, Anand I, et al. The comparative prognostic value of plasma neurohormones at baseline in patients with heart failure enrolled in Val-HeFT. *Eur Heart J* 2004;25:292-9.
82. Carr SJ, Bavanandan S, Fentum B, Ng L. Prognostic potential of brain natriuretic peptide (BNP) in predialysis chronic kidney disease patients. *Clin Sci (Lond)* 2005;109:75-82.
83. Austin WJ, Bhalla V, Hernandez-Arce I, et al. Correlation and prognostic utility of B-type natriuretic peptide and its amino-terminal fragment in patients with chronic kidney disease. *Am J Clin Pathol* 2006;126:506-12.
84. Suresh M, Farrington K. Natriuretic peptides and the dialysis patient. *Semin Dial* 2005;18:409-19.
85. Forfia PR, Lee M, Tunin RS, Mahmud M, Champion HC, Kass DA. Acute phosphodiesterase 5 inhibition mimics hemodynamic effects of B-type natriuretic peptide and potentiates B-type natriuretic peptide effects in failing but not normal canine heart. *J Am Coll Cardiol* 2007;49:1079-88.
86. Liang F, O'Rear J, Schellenberger U, et al. Evidence for functional heterogeneity of circulating B-type natriuretic peptide. *J Am Coll Cardiol* 2007;49:1071-8.
87. Spanaus KS, Kronenberg F, Ritz E, et al. B-type natriuretic peptide concentrations predict the progression of nondiabetic chronic kidney disease: the mild-to-moderate kidney disease study. *Clin Chem* 2007;53:1264-72.
88. Loria V, Dato I, Graziani F, Biasucci LM. Myeloperoxidase: a new biomarker of inflammation in ischemic heart disease and acute coronary syndromes. *Mediators Inflamm* 2008;2008:135625.
89. Braunwald E. Biomarkers in heart failure. *N Engl J Med* 2008;358:2148-59.
90. Krishnagopalan S, Kumar A, Parrillo JE, Kumar A. Myocardial dysfunction in the patient with sepsis. *Curr Opin Crit Care* 2002;8:376-88.
91. Chen D, Assad-Kottner C, Orrego C, Torre-Amione G. Cytokines and acute heart failure. *Crit Care Med* 2008;36:S9-16.
92. Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol* 2003;14:1549-58.
93. Selby NM, McIntyre CW. The acute cardiac effects of dialysis. *Semin Dial* 2007;20:220-8.
94. Ronco C, Bellomo R, Ricci Z. Continuous renal replacement therapy in critically ill patients. *Nephrol Dial Transplant* 2001;16 Suppl 5:67-72.
95. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Am J Kidney Dis* 2002;39:S1-266.
96. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 2003;41:1-12.
97. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;32:S112-9.
98. Herzog CA. Dismal long-term survival of dialysis patients after acute myocardial infarction: can we alter the outcome? *Nephrol Dial Transplant* 2002;17:7-10.
99. Johnson DW, Craven AM, Isbel NM. Modification of cardiovascular risk in hemodialysis patients: an evidence-based review. *Hemodial Int* 2007;11:1-14.
100. Logar CM, Herzog CA, Beddhu S. Diagnosis and therapy of coronary artery disease in renal failure, end-stage renal disease, and renal transplant populations. *Am J Med Sci* 2003;325:214-27.
101. Collins AJ, Li S, Gilbertson DT, Liu J, Chen SC, Herzog CA. Chronic kidney disease and cardiovascular disease in the Medicare population. *Kidney Int Suppl* 2003;87:S24-31.
102. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-305.
103. Garg AX, Clark WF, Haynes RB, House AA. Moderate renal insufficiency and the risk of cardiovascular mortality: Results from the NHANES I. *Kidney Int* 2002;61:1486-94.
104. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. *Arch Intern Med* 2004;164:659-63.
105. Sarnak MJ, Coronado BE, Greene T, et al. Cardiovascular disease risk factors in chronic renal insufficiency. *Clin Nephrol* 2002;57:327-35.
106. Al Suwaidi J, Reddan DN, Williams K, et al. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. *Circulation* 2002;106:974-80.
107. Gibson CM, Pinto DS, Murphy SA, et al. Association of creatinine and creatinine clearance on presentation in acute myocardial infarction with subsequent mortality. *J Am Coll Cardiol* 2003;42:1535-43.
108. Al-Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001;38:955-62.
109. Sorensen CR, Brendorp B, Rask-Madsen C, Kober L, Kjoller E, Torp-Pedersen C. The prognostic importance of creatinine clearance after acute myocardial infarction. *Eur Heart J* 2002;23:948-52.
110. Tokmakova MP, Skali H, Kenchaiah S, et al. Chronic kidney disease, cardiovascular risk, and response to angiotensin-converting enzyme inhibition after myocardial infarction: the survival and ventricular enlargement (SAVE) study. *Circulation* 2004;110:3667-73.

111. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004;351:1285-95.
112. Rattazzi M, Puato M, Faggini E, Bertipaglia B, Grego F, Pualetto P. New markers of accelerated atherosclerosis in end-stage renal disease. *J Nephrol* 2003;16:11-20.
113. Liuzzo G, Biasucci LM, Gallimore JR, et al. The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med* 1994;331:417-24.
114. Panichi V, Maggiore U, Taccola D, et al. Interleukin-6 is a stronger predictor of total and cardiovascular mortality than C-reactive protein in haemodialysis patients. *Nephrol Dial Transplant* 2004 May;19:1154-60.
115. Tonelli M, Wiebe N, Culleton B, et al. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol* 2006;17:2034-47.
116. Urquhart BL, House AA. Assessing plasma total homocysteine in patients with end-stage renal disease. *Perit Dial Int* 2007;27:476-88.
117. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: Impact of decline in hemoglobin. *Am J Kidney Dis* 1999;34:125-34.
118. Schindler R, Beck W, Deppisch R, et al. Short bacterial DNA fragments: Detection in dialysate and induction of cytokines. *J Am Soc Nephrol* 2004;15:3207-14.
119. Cazzavillan S, Ratanarot R, Segala C, et al. Inflammation and subclinical infection in chronic kidney disease: a molecular approach. *Blood Purif* 2007;25:69-76.
120. McCullough PA. Cardiorenal risk: an important clinical intersection. *Rev Cardiovasc Med* 2002;3:71-6.
121. Wright RS, Reeder GS, Herzog CA, et al. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med* 2002;137:563-70.
122. Beattie JN, Soman SS, Sandberg KR, et al. Determinants of mortality after myocardial infarction in patients with advanced renal dysfunction. *Am J Kidney Dis* 2001 37:1191-200.
123. Berger AK, Duval S, Krumholz HM. Aspirin, beta-blocker, and angiotensin-converting enzyme inhibitor therapy in patients with end-stage renal disease and an acute myocardial infarction. *J Am Coll Cardiol* 2003;42:201-8.
124. French WJ, Wright RS. Renal insufficiency and worsened prognosis with STEMI: a call for action. *J Am Coll Cardiol* 2003;42:1544-6.
125. Levin A, Foley RN. Cardiovascular disease in chronic renal insufficiency. *Am J Kidney Dis* 2000;36:S24-30.
126. Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 2007;72:1130-7.
127. Garside R, Pitt M, Anderson R, et al. The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: A systematic review and economic evaluation. *Health Technol Assess* 2007;11:iii, xi, xiii, 1-167.
128. Silverberg DS, Wexler D, Blum M, et al. 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;35:1737-44.
129. Ghali JK, Anand IS, Abraham WT, et al. Randomized double-blind trial of darbepoetin alfa in patients with symptomatic heart failure and anemia. *Circulation* 2008;117:526-35.
130. Neuhofer W, Pittrow D. Role of endothelin and endothelin receptor antagonists in renal disease. *Eur J Clin Invest* 2006;36 Suppl 3:78-88.
131. Gottlieb SS, Brater DC, Thomas I, et al. BG9719 (CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. *Circulation* 2002;105:1348-53.
132. Gheorghade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: A randomized controlled trial. *JAMA* 2004;291:1963-71.
133. Duffield JS, Hong S, Vaidya VS, et al. Resolvin D series and protectin D1 mitigate acute kidney injury. *J Immunol* 2006;177:5902-11.
134. Sakata Y, Masuyama T, Yamamoto K, et al. Calcineurin inhibitor attenuates left ventricular hypertrophy, leading to prevention of heart failure in hypertensive rats. *Circulation* 2000;102:2269-75.
135. Keltai M, Tonelli M, Mann JF, et al. Renal function and outcomes in acute coronary syndrome: Impact of clopidogrel. *Eur J Cardiovasc Prev Rehabil* 2007;14:312-8.
136. Sun WY, Reiser IW, Chou SY. Risk factors for acute renal insufficiency induced by diuretics in patients with congestive heart failure. *Am J Kidney Dis* 2006;47:798-808.
137. Knight EL, Glynn RJ, McIntyre KM, Mogun H, Avorn J. Predictors of decreased renal function in patients with heart failure during angiotensin-converting enzyme inhibitor therapy: results from the Studies Of Left Ventricular Dysfunction (SOLVD). *Am Heart J* 1999;138:849-55.
138. Ramadan FH, Masoodi N, El-Solh AA. Clinical factors associated with hyperkalemia in patients with congestive heart failure. *J Clin Pharm Ther* 2005;30:233-9.
139. Pitt B, Zannad F, Remme WJ, et al., Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.
140. Ko DT, Juurlink DN, Mamdani MM, et al. Appropriateness of spironolactone prescribing in heart failure patients: a population-based study. *J Card Fail* 2006;12:205-10.
141. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005;111:1487-91.
142. Ruggenti P, Perna A, Remuzzi G, Gruppo Italiano di Studi Epidemiologici in Nefrologia. ACE inhibitors to prevent end-stage renal disease: when to start and why possibly never to stop: a post hoc analysis of the REIN trial results. *Ramipril Efficacy In Nephropathy*. *J Am Soc Nephrol* 2001;12:2832-7.
143. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor-associated elevations in serum creatinine: is this a cause for concern? *Arch Intern Med* 2000;160:685-93.
144. Han SW, Won YW, Yi JH, Kim HJ. No impact of hyperkalemia with renin-angiotensin system blockades in maintenance haemodialysis patients. *Nephrol Dial Transplant* 2007;22:1150-5.
145. Roy P, Bouchard J, Amyot R, Madore F. Prescription patterns of pharmacological agents for left ventricular systolic dysfunction among hemodialysis patients. *Am J Kidney Dis* 2006;48:645-51.
146. Jessup M. Aldosterone blockade and heart failure. *N Engl J Med* 2003;348:1380-2.
147. Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the randomized aldactone evaluation study. *N Engl J Med* 2004;351:543-51.
148. Cunningham PN, Dyanov HM, Park P, Wang J, Newell KA, Quigg RJ. Acute renal failure in endotoxemia is caused by TNF acting directly on TNF receptor-1 in kidney. *J Immunol* 2002;168:5817-23.
149. Kumar A, Paladugu B, Mensing J, Kumar A, Parrillo JE. Nitric oxide-dependent and -independent mechanisms are involved in TNF-alpha-induced depression of cardiac myocyte contractility. *Am J Physiol Regul Integr Comp Physiol* 2007;292:R1900-6.
150. Honore PM, Jamez J, Wauthier M, et al. Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. *Crit Care Med* 2000;28:3581-7.
151. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, Acute Dialysis Quality Initiative Workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the second international consensus conference of the Acute Dialysis Quality Initiative (ADQI) group. *Crit Care* 2004;8:R204-12.
152. Bagshaw SM, Delaney A, Haase M, Ghali WA, Bellomo R. Loop diuretics in the management of acute renal failure: a systematic review and meta-analysis. *Crit Care Resusc* 2007;9:60-8.
153. Duke GJ. Renal protective agents: a review. *Crit Care Resusc* 1999;1:265-75.
154. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med* 2008;358:125-39.

Key Words: chronic kidney disease ■ heart failure ■ cardiorenal syndrome ■ renocardiac syndrome ■ heart-kidney interaction ■ biomarkers ■ cardiovascular risk.