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Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative

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A consensus conference on cardio-renal syndromes (CRS) was held in Venice Italy, in September 2008 under the auspices of the Acute Dialysis Quality Initiative (ADQI). The following topics were matter of discussion after a systematic literature review and the appraisal of the best available evidence: definition/classification system; epidemiology; diagnostic criteria and biomarkers; prevention/protection strategies; management and therapy. The umbrella term CRS was used to identify a disorder of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other organ. Different syndromes were identified and classified into five subtypes. Acute CRS (type 1): acute worsening of heart function (AHF–ACS) leading to kidney injury and/or dysfunction. Chronic cardio-renal syndrome (type 2): chronic abnormalities in heart function (CHF-CHD) leading to kidney injury and/or dysfunction. Acute reno-cardiac syndrome (type 3): acute worsening of kidney function (AKI) leading to heart injury and/or dysfunction. Chronic reno-cardiac syndrome (type 4): chronic kidney disease leading to heart injury, disease, and/or dysfunction. Secondary CRS (type 5): systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney. Consensus statements concerning epidemiology, diagnosis, prevention, and management strategies are discussed in the paper for each of the syndromes.

Keywords Cardio-renal syndromes • Acute heart failure • Acute kidney injury • Chronic kidney disease • Worsening renal function • Chronic heart disease • Chronic heart failure

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Introduction

Cardiac and renal diseases are common and frequently coexist to significantly increase mortality, morbidity, and the complexity and cost of care.[1,2] Syndromes describing the interaction between heart and kidney have been defined and classified[1,3–7] but never as a result of a consensus process. Thus, there is limited appreciation of epidemiology and standardized diagnostic criteria. Moreover, prevention and treatment is fragmented, single organ centred, and not multidisciplinary in approach. As a result, timing and quality of care may suffer. A consensus conference was organized under the auspices of the Acute Dialysis Quality Initiative (ADQI) in Venice, Italy, in September 2008. It involved opinion leaders and experts in nephrology, critical care, cardiac surgery, and cardiology. In this manuscript, we present the findings of this consensus conference.

Methods

The ADQI process was applied.[8] The ADQI methodology comprises a systematic search for evidence, establishment of relevant clinical and physiological outcomes, description of current practice and analysis of areas lacking evidence and setting of a specific research agenda. Before the conference, topics were selected and work groups assembled. Groups identified the key questions and conducted a systematic literature search. During the conference, work groups assembled in breakout sessions, as well as plenary sessions where their findings were presented, debated, and refined. Key questions were identified by the group and subgroups deliberated on these questions, bringing forth recommendations to the group as a whole. Deliberations followed 3 days of discussion among 32 attendees. Summary statements were then developed by the entire group as reported here.

Results

The Steering Committee assembled an expert panel, which was divided into five smaller working groups: (i) definition and classification, (ii) epidemiology, (iii) diagnostic biomarkers, (iv) prevention, and (v) treatment.

Definition and classification

Need for consensus definition

We unanimously agreed that a consensus definition was needed to highlight the coexistence of cardiac and renal disorders and to identify the time course of heart–kidney interaction and the primacy of the organ leading to the syndrome. The goal of this definition would be to facilitate epidemiological studies, identify target populations for intervention, develop diagnostic tools, prevent and manage different syndromes.

Principles of definition and classification

We chose a broad term, using the plural (cardio-renal syndromes, CRS), to indicate the presence of multiple syndromes. We chose subtypes to recognize primary organ dysfunction (cardiac vs. renal) and acute vs. chronic time frame. We considered structural and/or functional abnormalities of both organs necessary. We added an additional subtype to capture systemic conditions affecting both organs simultaneously. We chose definitions to include accepted criteria published by national and international societies.

Consensus definition and classification of cardio-renal syndromes

We considered definitions from the literature and used a specific publication[4] as template. We defined the broad term 'cardio-renal syndromes' as 'disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other'. We identified five subtypes of the syndromes (*Table 1*). Their pathophysiological mechanisms are described in *Figure 1*.

We chose the term CRS to indicate the bidirectional nature of the various syndromes and to recognize that this term was already established in the medical lexicon, despite lack of formal definition.

Acute cardio-renal syndrome (type 1)

Acute worsening of heart function leading to kidney injury and/or dysfunction. This is a syndrome of worsening renal function (WRF) complicating acute heart failure (AHF) and/or acute coronary syndrome (ACS). Between 27 and 40% of patients hospitalized for acute de-compensated heart failure (ADHF) appear to develop acute kidney injury (AKI)[2,9] and fall into this clinical entity. These patients experience higher mortality and morbidity, and increased length of hospitalization.[4]

Chronic cardio-renal syndrome (type 2)

Chronic abnormalities in heart function leading to kidney injury or dysfunction. This subtype refers to a more chronic state of kidney disease complicating chronic heart disease. This syndrome is common and has been reported in 63% of patients hospitalized with congestive heart failure (CHF).[10,11]

Acute reno-cardiac syndrome (type 3)

Acute worsening of kidney function leading to heart injury and/or dysfunction. This subtype refers to abnormalities in cardiac function secondary to AKI. The pathophysiological mechanisms likely go beyond simple volume overload and the recent consensus definition of AKI[12] may help to investigate this syndrome further.

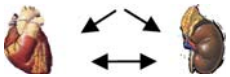
Chronic reno-cardiac syndrome (type 4)

Chronic kidney disease (CKD) leading to heart injury, disease, and/or dysfunction. This subtype refers to disease or dysfunction of the heart occurring secondary to CKD. There is a graded and independent association between the severity of CKD and adverse cardiac outcomes. In a recent meta-analysis,[13] an exponential relation between the severity of renal dysfunction and the risk for all-cause mortality was described with excess cardiovascular deaths constituting over 50% of overall mortality.

Secondary cardio-renal syndromes (type 5)

Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney. Although this subtype does not have primary and/or secondary organ dysfunction, it refers to situations where both organs are simultaneously affected by systemic illnesses, either acute or chronic. Examples include sepsis, systemic

Table 1 Cardio-renal syndromes: classification, definitions, and work group statements

Syndromes	Acute cardio-renal (type 1)	Chronic cardio-renal (type 2)	Acute reno-cardiac (type 3)	Chronic reno-cardiac (type 4)	Secondary CRS (type 5)
Organ failure sequence					
Definition	Acute worsening of heart function (AHF–ACS) leading to kidney injury and/or dysfunction	Chronic abnormalities in heart function (CHF-CHD) leading to kidney injury or dysfunction	Acute worsening of kidney function (AKI) leading to heart injury and/or dysfunction	Chronic kidney disease (CKD) leading to heart injury, disease and/or dysfunction	Systemic conditions leading to simultaneous injury and/or dysfunction of heart and kidney
Primary events	Acute heart failure (AHF) or acute coronary syndrome (ACS) or cardiogenic shock	Chronic heart disease (LV remodelling and dysfunction, diastolic dysfunction, chronic abnormalities in cardiac function, cardiomyopathy)	AKI	CKD	Systemic disease (sepsis, amyloidosis, etc.)
Criteria for primary events	ESC, AHA/ACC	ESC, AHA/ACC	RIFLE–AKIN	KDOQI	Disease-specific criteria
Secondary events	AKI	CKD	AHF, ACS, arrythmias, shock	CHD (LV remodelling and dysfunction, diastolic dysfunction, abnormalities in cardiac function), AHF, ACS	AHF, ACS, AKI, CHD, CKD
Criteria for secondary events	RIFLE–AKIN	KDOQI	ESC, AHA/ACC	ESC, AHA/ACC	ESC, AHA/ACC, RIFLE/AKIN ESC, AHA/ACC KDOQI
Cardiac biomarkers	Troponin, CK-MB, BNP, NT-proBNP, MPO, IMA	BNP, NT-proBNP, C-reactive protein	BNP, NT-proBNP	BNP, NT-proBNP, C-reactive protein	C-reactive protein, procalcitonin, BNP
Renal biomarkers	Serum cystatine C, creatinine, NGAL. Urinary KIM-1, IL-18, NGAL, NAG	Serum creatinine, cystatin C, urea, uric acid, C-reactive protein, decreased GFR	Serum creatinine, cystatin C, NGAL. Urinary KIM-1, IL-18, NGAL, NAG	Serum creatinine, cystatin C, urea, uric acid, decreased GFR	Creatinine, NGAL, IL-18, KIM-1, NAG
Prevention strategies	Acutely decompensated heart failure and acute coronary syndromes are most common scenarios Inciting event may be acute coronary ischaemia, poorly controlled blood pressure, and noncompliance with medication and dietary sodium intake Randomized trials improving compliance with heart failure care management have reduced rates of hospitalization and mortality, and a reduction in the rates of acute cardio-renal syndrome (type 1) can be inferred	A common pathophysiology (neurohumoral, inflammatory, oxidative injury) could be at work to create organ dysfunction Drugs that block the renin–angiotensin system reduce the progression of both heart failure and CKD It is unknown whether other classes of drugs can prevent chronic cardio-renal syndrome (type 2)	Acute sodium and volume overload are part of the pathogenesis It is unknown whether sodium and volume overload is prevented with different forms of renal replacement therapy and if this will result in lower rates of cardiac decompensation	The chronic processes of cardiac and renal fibrosis, left ventricular hypertrophy, vascular stiffness, chronic Na and volume overload, and other factors (neurohumoral, inflammatory, oxidative injury) could be at work to create organ dysfunction A reduction in the decline of renal function and albuminuria has been associated with a reduction in cardiovascular events The role of chronic uraemia, anaemia, and changes in CKD-mineral and bone disorder on the cardiovascular system is known in chronic reno-cardiac syndrome	Potential systemic factors negatively impact function of both organs acutely It is uncertain if reduction/elimination of the key factors (immune, inflammatory, oxidative stress, thrombosis) will prevent both cardiac and renal decline.

Continued

Table 1 *Continued*

Syndromes	Acute cardio-renal (type 1)	Chronic cardio-renal (type 2)	Acute reno-cardiac (type 3)	Chronic reno-cardiac (type 4)	Secondary CRS (type 5)
Management strategies	Specific—depends on precipitating factors General supportive—oxygenate, relieve pain & pulmonary congestion, treat arrhythmias appropriately, differentiate left from right heart failure, treat low cardiac output or congestion according to ESC guidelines[6], avoid nephrotoxins, closely monitor kidney function.	Treat CHF according to ESC guidelines[a], exclude precipitating pre-renal AKI factors (hypovolaemia and/or hypotension), adjust therapy accordingly and avoid nephrotoxins, while monitoring renal function and electrolytes Extracorporeal ultrafiltration	Follow ESC guidelines for acute CHF[a] specific management may depend on underlying aetiology, may need to exclude renovascular disease and consider early renal support, if diuretic resistant	Follow KDOQI guidelines for CKD management, exclude precipitating causes (cardiac tamponade). Treat heart failure according to ESC guidelines[a], consider early renal replacement support	Specific—according to etiology. General—see CRS management as advised by ESC guidelines* 2008

AKI, acute kidney injury; CKD, chronic kidney disease; NGAL, neutrophil gelatinase-associated lipocalin; NAG, *N*-acetyl-*β*-(D)glucosaminidase.
[a]As advised by ESC guidelines 2008.

lupus erythematosus, diabetes mellitus, amyloidosis, or other chronic inflammatory conditions.

The ADQI working group recognized that many patients may populate or move between subtypes during the course of their disease. This classification is not meant to fix patients into one immovable category (*Figure 2*). The group discussed and considered further sub-classification, to include situations of transient or reversible dysfunction, slowly or acutely progressive vs. stable disease, however it chose a more parsimonious classification system.

Epidemiology of cardio-renal syndromes

Cardio-renal syndromes are characterized by significant heart–kidney interactions that share similarities in pathophysiology. However, they are also likely to have important discriminating features, in terms of predisposing or precipitating events, natural history, and outcomes. A description of the epidemiology of heart–kidney interaction, stratified by the CRS subtypes, is a critical initial step towards understanding the overall burden of disease for each CRS subtype and vital in determining the presence of gaps in knowledge and helping design future trials.

Acute cardio-renal syndrome (type 1)

A large body of literature has examined AKI due to worsening heart function. Most studies are retrospective, secondary, and/or *post hoc* analyses from large databases[2,9,14–18] or clinical trials of drug therapy.[19,20] The term 'WRF' has been used to describe the acute and/or sub-acute changes in kidney function in patients ADHF or ACS. Its incidence estimates range between 19 and 45%. This broad range is largely attributable to variations in the definitions of WRF, the observed time-at-risk and the population under study. Most studies have found that WRF/AKI in ADHF/ACS occurs early after presentation to hospital. In both ADHF and ACS, the development of WRF/AKI has been associated with greater short- and long-term all-cause and cardiovascular mortality, prolonged duration of hospitalization,[9,15,21–23] increased readmission rates,[24,25] accelerated progression to CKD stages 4–5,[17] and higher healthcare costs.[15] In addition, there seems to be a biological gradient between severity of AKI and risk of death.[24] Two studies have also shown the risk of poor outcome persists regardless of whether WRF/AKI was transient or sustained[22,25] and that even small acute changes in SCr (0.3 mg/dL) can modify the risk of death.[19] Venous congestion may be an important haemodynamic factor driving WRF in patient with ADHF.[26] In ICU patients admitted with ADHF, WRF was associated with greater central venous pressure (CVP) on admission and after intensive medical therapy. This finding was apparent across the spectrum of systemic blood pressure, pulmonary capillary wedge pressure, cardiac index, and estimated glomerular filtration rates.[26]

Chronic cardio-renal syndrome (type 2)

Chronic heart disease and CKD frequently co-exist, and often the clinical scenario does not permit to distinguish which disease came first. Large database studies do not distinguish between type 2 and type 4 CRS. Nevertheless, between 45 and 63.6% of patients with CHF have evidence of CKD.[11,27] In these studies, CKD was associated with higher all-cause and cardiac-specific mortality.

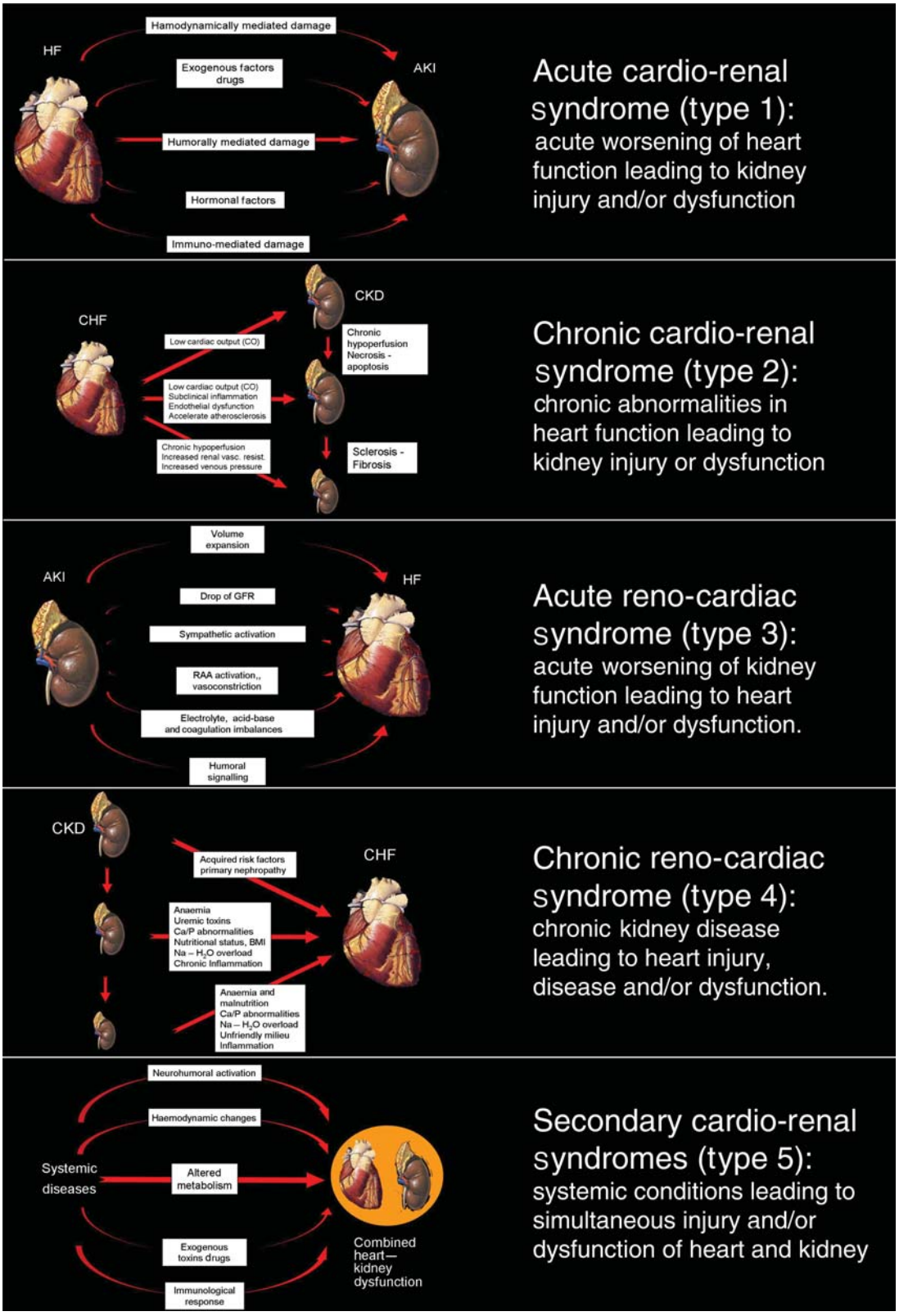


Figure 1 Pathophysiology and definitions of the five subtypes of cardio-renal syndrome (modified by Ronco *et al.*[105]).

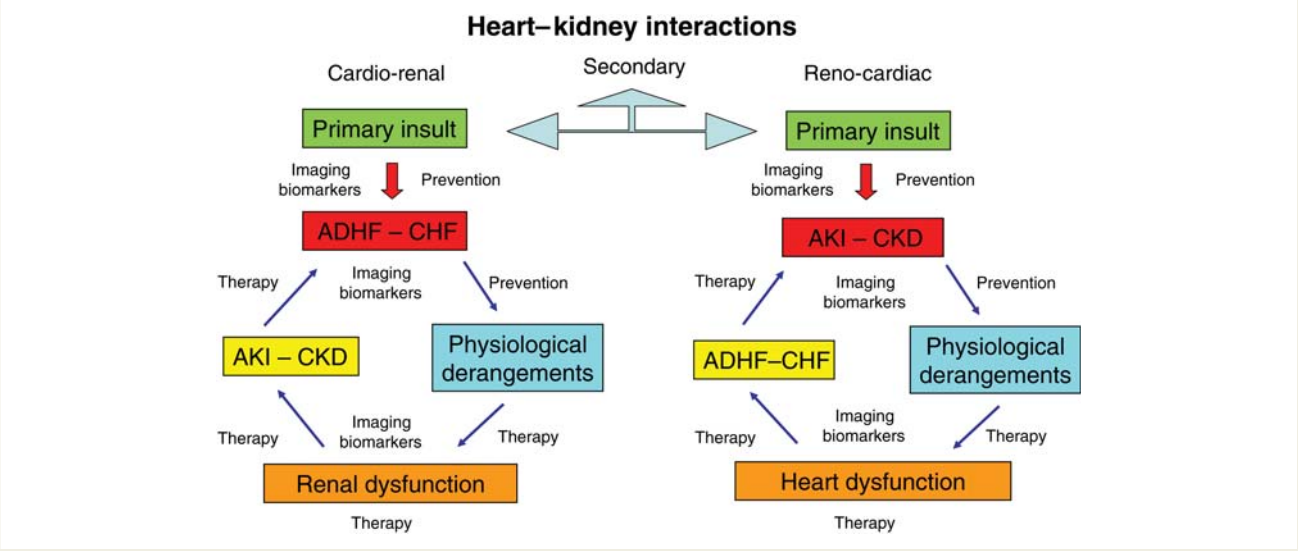


Figure 2 In cardio-renal syndromes, there are two important aspects: the first is the sequence of organ involvement and the second is the bi-directionality of signalling leading to a vicious cycle. Another important aspect is the time frame in which the derangements occur (chronic or acute). In all cases, there are moments in which prevention is possible, in others mitigation of the insult is potentially feasible, in others, therapeutic strategies must be implemented. At different times, a crucial role is played by imaging techniques and biomarkers enabling the clinician to make an early diagnosis, establish illness severity, and to potentially predict outcomes. This flowchart describes a series of conditions indicating that patients may move from one type to another of cardio-renal syndromes.

A 'dose–response' or graded association between decline in kidney function and worse clinical outcome was generally noted. An example of Type 2 CRS could be congenital heart disease (CHD). In selected circumstances, long-standing CHD results in adaptive alterations in kidney perfusion and neurohormonal activation. In a study of 1102 adult patients with CHD, over 50% had evidence of kidney dysfunction, and 9% had eGFR < 60 mL/min/1.73 m^2.[28] This latter group had a three-fold increase in mortality. Kidney dysfunction was observed even among CHD patients with simple anatomical cardiac defects. A further challenge in describing the epidemiology of type 2 CRS is that patients may also transition between type 1 and type 2 CRS at various time points.

Acute reno-cardiac syndrome (type 3)

Defining the epidemiology of acute reno-cardiac syndrome (type 3) is challenging for several reasons: (i) considerable heterogeneity in predisposing conditions, (ii) different methods for defining AKI, (iii) variable baseline risk for the development of acute cardiac dysfunction (i.e. increased susceptibility in individuals with sub-clinical cardiovascular disease), and (iv) failure of many clinical studies of AKI to report the occurrence of acute cardiac dysfunction as outcomes. Accordingly, incidence estimates and clinical outcomes of acute cardiac dysfunction secondary to AKI are largely context and disease-specific. The group deliberated that RIFLE/AKIN criteria should be used to define AKI in the epidemiological studies.[12]

An example of type 3 CRS could be the development of an ACS, arrhythmia, or AHF after the onset of AKI or after acute glomerulonephritis or acute cortical necrosis. Toxaemia, fluid and sodium retention, humoral mediators, and electrolyte derangements may all contribute to acute dysfunction of the heart. Another case could be cardiac surgery-associated AKI (CSA-AKI), where AKI contributes to fluid overload and to the development of latent cardiac dysfunction. We also recognize that CSA-AKI may also represent type 1 CRS. This discrimination may have relevance as these two presentations may be characterized by important differences in epidemiology, risk factors, associated outcomes, and need for differing therapeutic interventions. The incidence of CSA-AKI has been reported between 0.3 and 29.7%.[29–34] This large range in incidence is attributed to the different definitions used.[35] However, the challenge in understanding the epidemiology of type 3 CRS is that its incidence and associated risk factors fail to consider the inciting event for CSA-AKI as either primarily AKI-related or heart-related.

Chronic reno-cardiac syndrome (type 4)

Several observational studies have evaluated the cardiovascular event rates and outcomes in selected CKD populations.[36–48] Cardiac disease in CKD patients is common and cardiac-specific mortality rates are 10- to 20-fold higher compared with age and sex-matched non-CKD populations.[36,42,49,50] In non-renal replacement therapy (RRT) dependent CKD patients, the prevalence of CVD correlates with severity of CKD. Several observational studies have found graded increases in the prevalence of CVD and heart failure (HF), along with higher risk of subsequent cardiac events associated with degree of decline in kidney function.[40,45–48] This dose–response trend also translated into similar trends for the risk of cardiac-specific and all-cause mortality.[36,40,43–45,48] Thus CKD likely accelerates the risk for and development of CVD.[39,46,47]

Secondary cardio-renal syndromes (type 5)

There are limited data on the epidemiology of secondary CRS (type 5) due to the large number of potential contributing acute and chronic systemic conditions. Accordingly, estimates of

incidence, risk identification, and associated outcomes for type 5 CRS are considered largely disease and/or context-specific and may be time varying. We recognize that several chronic systemic illnesses (i.e. diabetes mellitus, hypertension, amyloidosis) could potentially fulfil the definition for CRS type 5, however, they may also at particular times in their natural history, fulfil criteria for other CRS subtypes. Importantly, in this context, there is currently an incomplete understanding of the pathophysiological mechanisms of secondary heart–kidney interactions.

A prototypical condition that may lead to CRS type 5 is sepsis. Sepsis is common and its incidence is increasing,[51,52] with a mortality estimated between 20 and 60%.[51–53] Approximately 11–64% of septic patients develop AKI that is associated with a higher morbidity and mortality.[54–60] Abnormalities in cardiac function are also common in sepsis.[61–63] Observational data have found ~30–80% of septic patients have elevated cardiac-specific troponins,[64–70] that often correlate with reduced left ventricular function.[62,64,69,70] Acute kidney injury and myocardial injury/dysfunction in severe sepsis/septic shock are exceedingly common, yet there is a lack of integrative and epidemiological studies that have specifically examined for insight on its pathophysiology, incidence, risk identification, and associated outcomes.

Diagnosis and biomarkers of cardio-renal syndromes

The consensus group deliberated on the role of biomarkers in the diagnosis of the different types of the syndrome. The intention was to integrate biomarkers into the diagnosis of the various CRS, especially those that deal with AKI on top of acute cardiac disease. If biomarkers are to be clinically useful in these settings, physicians must be able to answer the following questions: (i) can biomarkers be used to (early) identify and classify CRS? (ii) Can biomarkers be used to risk-stratify patients with regard to reversibility? (iii) Can biomarkers be used as targets for treatment? (iv) Can biomarkers be used to monitor the effects of treatment?[6,63–69] (v) Can imaging of the heart and kidneys be combined effectively with biomarkers across the spectrum of diagnosis and treatment of CRS?

Natriuretic peptides and heart failure

B-type natriuretic peptides (BNP and NT-proBNP) are established diagnostic tools in ADHF[71] and represent independent predictors of cardiovascular events and overall mortality in critical illness,[72] ACS,[73] and stable HF.[74] Natriuretic peptides (NPs) are elevated in patients with CRS (type 1) in which AKI occurs as a consequence of ADHF. Moreover, they have shown prognostic utility in patients with various stages of renal insufficiency,[75,76] demonstrating potential applications in CRS types 2 and 4. Although many previous studies support the usefulness of BNP in the diagnosis and management of HF patients,[77,78] the relationship between BNP, renal function, and the severity of HF is less clear. Patients with CKD have higher levels of BNP and NT-proBNP than age- and gender-matched subjects without reduced renal function, even in the absence of clinical CHF.[79] Although these higher levels of NPs have been attributed to reduced renal clearance, there is likely some contribution from other mechanisms.[80,81]

Biomarkers of renal injury

Neutrophil gelatinase-associated lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) seems to be one of the earliest kidney markers of ischaemic or nephrotoxic injury in animal models and is detected in the blood and urine of humans soon after AKI.[82–88] In a recent study, a single measurement of urinary NGAL was able to differentiate those with subsequent AKI, with a sensitivity and specificity of 90 and 99%, respectively. Neutrophil gelatinase-associated lipocalin could be used as an earlier marker of impending WRF during the treatment of ADHF.

Cystatin C

Cystatin C appears to be a better predictor of glomerular function than serum creatinine in patients with CKD. In AKI, urinary excretion of cystatin C has been shown to predict the requirement for RRT earlier than creatinine.[89,90]

Kidney injury molecule-1

Kidney injury molecule-1 (KIM-1) is a protein detectable in the urine after ischaemic or nephrotoxic insults to proximal tubular cells.[91–93] Urinary KIM-1 seems to be highly specific for ischaemic AKI and not for pre-renal azotemia, CKD, or contrast induced nephropathy.[94]

N-*acetyl-β-(D)glucosaminidase*

N-acetyl-*β*-(D)glucosaminidase is a lysosomal brush border enzyme found in proximal tubular cells.[94–96] *N*-acetyl-*β*-(D)glucosaminidase has been shown to function as a marker of kidney injury, reflecting particularly the degree of tubular damage.[94] It is not only found in elevated urinary concentrations in AKI and CKD, but also in diabetic patients, patients with essential hypertension, and HF.[97–99]

Interleukin-18

Interleukin-18 (IL-18) is a pro-inflammatory cytokine detected in the urine after acute ischaemic proximal tubular damage.[100] It displays good sensitivity and specificity for ischaemic AKI with an AUC $> 90\%$[101] with increased levels 48 h prior to increases in serum creatinine.[102] Urinary NGAL and IL-18 have been studied as joint biomarkers for delayed graft function following kidney transplantation.[103]

Of the biomarkers presented above, NGAL (urine and plasma) and Cystatin C are most likely to be integrated into clinical practice in the near future. Clinical trials will be needed to see if earlier identification of AKI and the use of specific treatment algorithms based on these markers will improve prognosis.

Bioimpedance vector analysis

There is a general agreement that bioimpedance vector analysis (BIVA) may contribute to a better definition of the patient's hydration status. This may be used in combination with NGAL and BNP to guide fluid management strategies. In this way, patients will be kept within the narrow window of adequate hydration preventing worsening of both kidney and heart function.

Imaging

Imaging techniques have an additional role with respect to the laboratory biomarkers in CRS. They may enhance, extend, and refine

our ability to quantify renal damage and function. In patients affected by suspected CRS, it is prudent to avoid the use of iodinated contrast media if not strictly necessary. The presence of coronary disease should be excluded by stress echo or stress myocardial perfusion (SPECT/PET) in types III, IV, and V CRS and in types I and II CRS when the primary cardiac disease is valvular, congenital, or myopathic. In the future, research should be directed toward experimental studies that apply molecular imaging techniques (MRI and MRS, PET, etc.) to the search for *in vivo* specific markers for diagnosis and severity evaluation of the different types of CRS. Also in the future, non-invasive imaging techniques should be refined to quantify renal blood flow. Such data can then be correlated with cardiac and renal biomarkers and most importantly guide ongoing therapy designed to optimize renal blood flow and ultimately preserve kidney function. As for type 1 CRS, venous congestion and high CVP seem to be associated with impaired renal function and independently related to all-cause mortality in a broad spectrum of patients with cardiovascular disease.[104]

Prevention of cardio-renal syndromes

The rationale for the prevention of CRS is based on the concept that once the syndrome begins it is difficult to interrupt, not completely reversible in all cases, and associated with serious adverse outcomes. We approached prevention using a proposed classification system.[4,105,106]

Acute cardio-renal syndrome (type 1)

The most important preventive approach in patients with *de novo* HF consists of the basic preventive strategies of the American Heart Association/American College of Cardiology for Stage A and B HF. These call for blood pressure control, use of drugs that block the renin–angiotensin–aldosterone system, beta-adrenergic blockers (BB), coronary artery disease risk factor modification, and compliance with dietary and drug treatments. As venous congestion seems to be an important haemodynamic factor driving WRF[26] in ADHF, future studies should evaluate whether a CVP-tailored therapy might prevent WRF in those patients.

Chronic cardio-renal syndrome (type 2)

In this setting, therapies that improve the natural history of chronic HF include angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), BB, aldosterone receptor blockers, combination of nitrates and hydralazine, and cardiac re-synchronization therapy.[106,107]

Acute reno-cardiac syndrome (type 3)

The clinical problem in many cases is sodium and water retention. Avoidance of hypervolaemia should help prevent cardiac decompensation. In addition, uremic changes, hyperkalaemia, and mediators of inflammation can have adverse cardiac consequences.[106,108] As mentioned previously, prototypical scenarios for type 3 CRS include forms of AKI (e.g. rapidly progressive glomerulonephritis) that secondarily lead to LV dysfunction. Contrast-induced AKI in most cases is asymptomatic[106,109] and unlikely to cause cardiac dysfunction. However, some patients with contrast-induced AKI develop progressive renal failure, volume overload, and ADHF requiring intensive care treatment and/or transient and sometimes permanent dialysis.[110]

Chronic reno-cardiac syndrome (type 4)

Type 4 CRS is a common syndrome since it involves the progression of CKD, often due to diabetes mellitus and hypertension, with accelerated calcific atherosclerosis, progressive LVH, and the development of diastolic and systolic dysfunction.[111] The core prevention concept beyond attention to usual risk factor modification is that the reduction in the rate of progression of CKD may lead to reduced rates of type 4 CRS.

Secondary cardio-renal syndrome (type 5)

A core concept is that treatment of the primary illness (diabetes mellitus, amyloidosis, sepsis, rhabdomyolysis, haemorrhagic shock, etc.) in general improves both heart and kidney function.

Management strategies of cardio-renal syndromes

Although there are clinical guidelines for managing both HF and CKD,[10,112,113] there are no agreed guidelines for managing patients with cardio-renal and/or reno-cardiac syndromes.[114]

Acute cardio-renal syndrome (type 1)

Both abnormal renal function and also a deterioration early in the course of treatment of ADHF increase mortality. Thus, any treatment for HF should have a neutral effect or preferably improve renal function.[112]

The management of ADHF is described in the recent ESC/ESICM guidelines.[112] Vasodilators[115] and loop diuretics are widely recommended in cases of ADHF and in CRS type 1. However, loop diuretics predispose to electrolyte imbalances, and hypovolaemia leading to neurohumoral activation, reduced renal glomerular flow with further rises in serum urea and creatinine.[116] Vasodilators (e.g. nesiritide) may also affect renal function[117] and in some cases exacerbate renal injury. Vasopressin receptor 2 antagonists can improve hyponatraemia, but without any clear survival benefit.[118] If congestion coincides with low blood pressure, inotropic agents should be considered.

In cardiogenic shock, treatments are designed to increase cardiac output and restore renal blood flow. Although inotropic drugs, typically dobutamine or dopamine, may tide patients over, they are often associated with increased mid-term mortality.[119] Other agents include phosphodiesterase inhibitors, milrinone, and levosimendan.[112] Extracorporeal ultrafiltration may be useful in ADHF associated with diuretic resistance. If systemic hypotension persists, then norepineprine may be considered, along with elective ventilation and/or intra-aortic balloon pumping. Depending upon pre-existing co-morbidity and the underlying aetiology, left ventricular assist devices as a bridge to transplantation or cardiac surgery may be appropriate.[120] It should be mentioned that over-treatment with loop diuretics, ACE-I, and/or spironolactone may induce AKI.

Chronic cardio-renal syndrome (type 2)

Therapeutic approaches to patients with CHF are complex and involve the elimination and treatment of the underlying cause

and/or disease leading to damage of the cardiovascular system and CHF progression. Self-care management is an important strategy in CHF, encompassing adherence to treatment, symptom recognition, and lifestyle changes (diet and nutrition, smoking cessation, exercise training).[112]

Angiotensin converting enzyme inhibitors,[121] beta-blockers,[122] ARBs,[123] and aldosterone antagonists[124] significantly reduce mortality and morbidity in CHF. The optimal approach is to combine ACE-I and beta-blocker, titrate dosages, to which either an ARB or aldosterone antagonist is subsequently added depending on clinical condition and patient characteristics. In patients unable to tolerate these agents, hydralazine and nitrates may be an option.[112] Digoxin and diuretics improve symptoms in CHF but have no effect on mortality.[119]

Cardiac re-synchronization therapy is now recommended for symptomatic CHF patients (NYHA III–IV) with poor left ventricular ejection fraction (LVEF) and QRS prolongation,[112] as are implantable cardiac defibrillators for both survivors of cardiac arrest and/or sustained ventricular arrhythmias and also for symptomatic CHF patients with impaired LVEF. In selected patients who do not respond to treatment, mechanical assist devices and/or cardiac transplantation may be appropriate.[120]

Therapy of CHF with concomitant renal impairment is still not evidence-based, as these patients are generally excluded from CHF trials.[121–124] Typically, these patients are hypervolemic, and more intensive diuretic treatment is needed.[113] Thiazide diuretics may be less effective, and loop diuretics are preferred.[113] To improve natriuresis, loop diuretic infusions are more potent, and combinations with amiloride, aldosterone antagonists, or metolazone may be considered,[124] as increasing doses of loop diuretics are associated with worse outcomes.[125] In refractory cases, RRT may be required.

Angiotensin converting enzyme inhibitor and ARB initiation may cause deterioration in renal function, which is frequently transient and reversible. Patients with CKD or renal artery stenosis are at a higher risk, and careful monitoring is recommended. If renal function declines, then other secondary causes such as excessive diuresis, persistent hypotension, prescription of nephrotoxic agents or underlying renovascular disease should be excluded. Hyperkalaemia occurs with these agents and dietary restriction may be required.[121,123,124]

Anaemia is often present in patients with type 2 CRS, and correction of anaemia may improve symptoms without increasing survival.[112] Renal dysfunction is associated with altered drug clearances, and some drugs, e.g. digoxin and allopurinol, require dose adjustment, and the risk of spontaneous haemorrhage with warfarin is increased.

Acute reno-cardiac syndrome (type 3)

As previously discussed, type 3 CRS has only recently been recognized as a clinical entity, hence there is little known about the treatment of this complication. Since a typical clinical scenario would include AKI following contrast exposure, or following cardiovascular surgery (CSA-AKI), prevention likely affords a better chance to improve outcome than treating established disease. To prevent contrast nephropathy, many potential preventive strategies have been studied, and available evidence indicates that isotonic fluids have been the most successful intervention to date, with conflicting data surrounding *N*-acetylcysteine.[126,127] Recently, Solomon *et al.*,[128] using a more sensitive definition of AKI, identified a possible role for the low-osmolar, non-ionic monomer iopamidol. Germane to the discussion of CRS, they identified that patients suffering AKI secondary to contrast were almost twice as likely to suffer downstream adverse events, including cardiovascular events, in the year following the contrast exposure, indicative of the serious consequences of type 3 CRS.

In terms of prevention of CSA-AKI, in a recent prospective, double-blind study of patients with left ventricular dysfunction undergoing cardiac surgery, nesiritide was associated with improved post-operative renal function compared with patients without nesiritide, thus suggesting a renoprotective property.[129]

Chronic reno-cardiac syndrome (type 4)

The aetiology of HF in CKD is multifactorial. Despite cardioprotective strategies such as ACE-Is and/or beta-blockers only a minority of dialysis patients are prescribed these drugs.[130] Antihypertensives have been thought to increase intradialytic hypotension, but this has not been proven.[131]

Progressive CKD often leads to sodium retention due to reduced renal excretion,[113] and similarly during haemodialysis due to dietary noncompliance, inappropriately high dialysate sodium and inability to achieve target or 'dry' weight.[132] Besides preventing hypervolaemia and a positive sodium balance, the other key management strategies include correcting anaemia and minimizing vascular calcification.[113,114]

Conclusions

The aim of the ADQI consensus conference on CRS was to facilitate better understanding of their epidemiology, opportunities for early diagnosis through biomarkers, development of preventive strategies, and application of evidence-based management strategies (where available). A further aim was to allow identification of gaps in the literature and provide direction for future research including clinical trials. We have defined five syndromes that can now be the target of future studies, described series of biomarkers which may facilitate the identification and treatment of such syndromes and have outlined general strategies for prevention and management. We hope this document will serve as starting point for focused research into the care of these conditions which affect so many people worldwide.

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