

Received for publication: 12.3.10; Accepted in revised form: 13.4.10

doi: 10.1093/ndt/gfq252
Advance Access publication 20 May 2010

ADQI 7: the clinical management of the Cardio-Renal syndromes: work group statements from the 7th ADQI consensus conference


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Keywords: cardio-renal; chronic kidney disease; heart failure; ischaemic heart disease; renal failure

Introduction

Many patients with heart failure have underlying renal dysfunction, and similarly, patients with kidney failure are prone to cardiac failure. This has led to the concept of cardio-renal syndromes, which can be an acute or chronic cardio-renal syndrome, when cardiac failure causes deterioration in renal function, or acute and/or chronic Reno-Cardiatic syndrome, when renal dysfunction leads to cardiac failure. Patients who develop these syndromes have increased risk of hospital admission and mortality. Although there are clinical guidelines for managing both heart failure and chronic kidney disease, there are no agreed guidelines for managing patients with cardio-renal and/or Reno-Cardiatic syndromes, as these patients have typically been excluded from clinical trials. We have therefore reviewed the currently available published literature to outline a consensus of current best clinical practice for these patients.
Cardio-Renal syndromes

The cardiorenal syndromes are a heterogenous group of conditions, comprising both cardiac and renal dysfunction, typically on a background of chronic disease. Cardiac failure has recently been defined by the European Society of Cardiology (ESC) (Table 1) [1]. Heart failure can occur acutely with pulmonary oedema/congestion following acute coronary syndrome (ACS) or sudden rise in blood pressure, or transiently following myocarditis, myocardial infarction or myocardial ischaemia resolved by revascularization. However, in most cases, heart failure is chronic in nature and can be clinically classified as stable, worsening or decompensated. Acute decompensation of chronic heart failure remains the commonest cause of heart failure admissions to hospital.

### Acute Cardio-Renal syndrome (acute impairment in cardiac function causing renal dysfunction)

Acute heart failure is defined as a rapid onset or change in signs and symptoms of heart failure, requiring urgent therapy, and subdivided into five types based on clinical presentation [2]: (i) acute decompensated chronic heart failure [3], typically worsening of already treated chronic heart failure (CHF) usually associated with normal blood pressure and impaired left ventricular ejection fraction (LVEF); (ii) pulmonary oedema and (iii) hypertensive heart failure, characterized by hypertension typically with preserved LVEF; (iv) isolated right ventricular failure; and (v) cardiogenic shock [4].

Underlying causes of acute heart failure include ACS, valvular heart disease, hypertension, arrhythmias, infection and non-compliance with heart failure management [5,6].

### Chronic Cardio-Renal syndrome (chronic cardiac dysfunction causing renal dysfunction)

Coronary artery disease and hypertension are the commonest causes of chronic heart disease, followed by valvular heart disease and cardiomyopathies [1,2] (Table 2). Ascites may complicate severe right-sided heart failure, and the combination of increased intra-abdominal pressure and high right-sided venous pressure may further compromise renal function [7].

### Acute Reno-Cardiac syndrome (acute decline in kidney function causing cardiac dysfunction)

Acute deterioration in kidney function is now classified according to risk, injury, failure, loss and end-stage renal disease criteria (RIFLE) [8] (Table 3) and recently modified to define acute as deterioration ≤48 h time frame [9]. A sud-

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### Table 1. Heart failure is a clinical syndrome based on the combination of symptoms and signs typical of heart failure supported by objective evidence of a structural or functional abnormality of the heart at rest [1]

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breathlessness at rest</td>
<td>Tachycardia</td>
<td>Cardiomegaly</td>
</tr>
<tr>
<td>Breathlessness on exertion</td>
<td>Tachypnoea</td>
<td>Third heart sound</td>
</tr>
<tr>
<td>Fatigue</td>
<td>Pulmonary rales</td>
<td>Cardiac murmurs</td>
</tr>
<tr>
<td>Tiredness</td>
<td>Pleural effusion</td>
<td>Abnormal echocardiogram</td>
</tr>
<tr>
<td>Ankle swelling</td>
<td>Raised jugular venous pressure</td>
<td>Raised natriuretic peptide concentration</td>
</tr>
<tr>
<td></td>
<td>Peripheral oedema</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatomegaly</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Common causes of heart failure (modified from [1])

<table>
<thead>
<tr>
<th>Major causes of heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Valvular heart disease</td>
</tr>
<tr>
<td>Cardiomyopathies</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Toxins</td>
</tr>
<tr>
<td>Endocrine</td>
</tr>
<tr>
<td>Nutritional</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Circulatory failure</td>
</tr>
</tbody>
</table>

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The cardiorenal syndromes are a heterogenous group of conditions, comprising both cardiac and renal dysfunction, typically on a background of chronic disease. Cardiac failure has recently been defined by the European Society of Cardiology (ESC) (Table 1) [1]. Heart failure can occur acutely with pulmonary oedema/congestion following acute coronary syndrome (ACS) or sudden rise in blood pressure, or transiently following myocarditis, myocardial infarction or myocardial ischaemia resolved by revascularization. However, in most cases, heart failure is chronic in nature and can be clinically classified as stable, worsening or decompensated. Acute decompensation of chronic heart failure remains the commonest cause of heart failure admissions to hospital.
den reduction in kidney function can lead to sodium and water retention. Acute kidney injury (AKI) also causes cardiac changes, due to paracrine effects [10], or the so-called Reno-Cardiac organ cross talk [11,12]. AKI can lead to metabolic acidosis and electrolyte abnormalities, typically hyperkalaemia, which may precipitate cardiac arrhythmias.

Patients with critical renovascular stenosis may present with ‘flash pulmonary oedema’ resulting from acute pulmonary venous congestion in the presence of normal or well-preserved LVEF [13].

### Chronic Reno-Cardiac syndrome (chronic kidney disease causing cardiac dysfunction)

Patients with chronic kidney disease (CKD) are predisposed to cardiac dysfunction [2]. CKD (Table 4) typically leads to progressive sodium retention [14–16] predisposing to arteriosclerosis and hypertension. Increased peripheral pulse wave velocity causes progressive cardiac changes, including left atrial and ventricular remodelling, left ventricular hypertrophy and increased myocardial fibrosis, potentially exacerbated by anaemia [17]. Valvular calcification is increased in dialysis patients. Repeated intradialytic hypotension [18] with myocardial stunning may increase myocardial fibrosis. Carnitine deficiency in long-term haemodialysis patients may reduce LVEF and high flow arterio-venous fistulae may cause high output cardiac failure.

More haemodialysis patients die from sudden cardiac death than myocardial infarction, assumed to be arrhythmic, due to electrolyte disturbances, underlying autonomic neuropathy, increased sympathetic nervous system activity, circulating catecholamines and prolonged QTc interval in a population with increased risk of sleep apnoea [19]. Pericardial effusions may occur in patients with CKD, causing tamponade.

In addition, some diseases and/or toxins can directly affect both organs, either de novo or chronically, as secondary cardio-renal syndromes (Table 5) [2]. Management of these patients may well require additional specialized treatments for the underlying pathology.

### Methods

A multidisciplinary stakeholder committee was convened, and an overall research agenda was developed by the committee as an iterative process using a two-step modified Delphi procedure [20], briefly: a systematic search for evidence with review and evaluation of the available literature pre-conference, with establishment of clinical and physiological outcomes as well as measures to be used for comparison of different treatments, along with the description of current clinical practice and the rationale for the use of current therapies. In addition, analysis was made of areas in which evidence is lacking. Studies were identified via Medline and Web of Science (which also contains abstracts of major conferences) searches and bibliographies of review articles and participants’ files, using Medical Subject Headings of heart failure, cardiac failure, acute coronary syndrome, myocardial infarction and left ventricular failure, refined with kidney disease, renal insufficiency, kidney failure, renal failure and kidney injury. The conference was divided into breakout sessions, with work groups addressing their assigned topic area, and plenary sessions, where their findings were presented, debated and refined. Evidence was classified according to levels per standard evidence-based medicine methodology. A series of summary statements were then developed and refined and research agenda determined by identifying deficiencies in the literature [21].

### Table 3. RIFLE staging of acute kidney injury [10]

<table>
<thead>
<tr>
<th>RIFLE stage</th>
<th>GFR criteria</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>↑ SCreat × 1.5 or ↓ GFR &gt;25%</td>
<td>&lt;0.5 mL/kg/h for 6 h</td>
</tr>
<tr>
<td>Injury</td>
<td>↑ SCreat × 2.0 or ↓ GFR &gt;50%</td>
<td>&lt;0.5 mL/kg/h for 12 h</td>
</tr>
<tr>
<td>Failure</td>
<td>↑ SCreat × 3.0 or ↓ GFR &gt;75% or SCreat ≥4 mg/dL or absolute ↑ SCreat ≥0.5 mg/dL</td>
<td>&lt;0.3 mL/kg/h for 24 h or anuria × 12 h</td>
</tr>
<tr>
<td>Loss</td>
<td>Dialysis dependence &gt;4 weeks</td>
<td>–</td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>Dialysis dependence &gt;3 months</td>
<td>–</td>
</tr>
</tbody>
</table>

GFR, glomerular filtration rate; SCreat, serum creatinine (mg/dL; to convert to μmol/l multiply by 0.88). This was modified by the Acute Kidney Injury Network to define the acute nature of acute kidney injury as a rise in creatinine or fall in urine output within a 48-h time frame [9].

### Table 4. Staging of chronic kidney disease according to estimated glomerular filtration rate (eGFR)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>eGFR mL/min/1.73 m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ eGFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ eGFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3a</td>
<td>Moderate ↓ eGFR</td>
<td>45–59</td>
</tr>
<tr>
<td>3b</td>
<td>Moderate ↓ eGFR</td>
<td>30–45</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ eGFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

CCB, calcium channel blocker; SLE, systemic lupus erythematosus; HUS, haemolytic uraemic syndrome.
<table>
<thead>
<tr>
<th>Drug classes</th>
<th>Indication</th>
<th>Intended action and effects</th>
<th>Side effects and problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors and ARBS</td>
<td>Acute CRS</td>
<td>No consensus on the ideal timing for initiation. Treatment should be continued whenever possible in those already treated. Treatment should be initiated before hospital discharge</td>
<td>Deterioration of kidney function if already on board Hypotension</td>
</tr>
<tr>
<td></td>
<td>Chronic CRS</td>
<td>Life saving, reduce morbidity Prevent cardiac remodelling ARBs as an alternative only in patients intolerant to ACEI</td>
<td>Monitor kidney function and electrolytes Hypotension</td>
</tr>
<tr>
<td></td>
<td>Acute RCS</td>
<td>–</td>
<td>Contraindicated in renal artery stenosis</td>
</tr>
<tr>
<td></td>
<td>Chronic RCS</td>
<td>Nephroprotection RAAS antagonism Decrease proteinuria</td>
<td>Mild transient deterioration of kidney function Careful monitoring in dialysis patients (hypotension)</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>Acute CRS</td>
<td>In those already treated, dose may need to be reduced temporarily; in general should not be withdrawn unless signs of low output Treatment should be initiated before hospital discharge</td>
<td>Bradykinin reactions, bradyarrhythmias</td>
</tr>
<tr>
<td></td>
<td>Chronic CRS</td>
<td>Life saving Reduce morbidity Prevent remodelling</td>
<td>Hypotension, bradyarrhythmias Deterioration in heart failure symptoms (transient) Asthma As above</td>
</tr>
<tr>
<td></td>
<td>Chronic RCS</td>
<td>Cardioprotection and prevention of tachyarrhythmias</td>
<td></td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>Chronic CRS</td>
<td>Life saving in moderate-severely symptomatic CHF, reduce morbidity Prevent myocardial and vascular fibrosis</td>
<td>Hyperkalaemia in patients treated with ACEIs, ARBs, and decreased eGFR</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Acute CRS</td>
<td>Natriuresis, reduction of fluid overload, Na and H₂O elimination Symptomatic benefit Loops diuretics preferred</td>
<td>Potential hypovolemia, hypotension and worsening of renal failure</td>
</tr>
<tr>
<td></td>
<td>Chronic CRS</td>
<td>Control of diuresis and extracellular fluid volume Symptoms relief</td>
<td>Volume depletion, hypotension, worsening renal failure, hyperuricemia, K imbalance, Diuretic resistance</td>
</tr>
<tr>
<td></td>
<td>Acute RCS</td>
<td>Maintenance of non oliguric AKI Frusemide preferred</td>
<td>No evidence for renal protection nor reduction of need for RRT</td>
</tr>
<tr>
<td></td>
<td>Chronic RCS</td>
<td>Maintenance of diuresis in CKD 4 and 5. Control of hypertension and fluid balance</td>
<td>Potential toxic effects</td>
</tr>
<tr>
<td></td>
<td>Secondary CRS</td>
<td>Maintenance of diuresis and fluid balance</td>
<td>Direct and cumulative toxicity with other drugs (antibiotics, anti-inflammatory)</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Chronic CRS and chronic RCS</td>
<td>Reduce HF hospitalizations Improve symptoms Mortality unchanged</td>
<td>Toxicity if reduced GFR Monitor plasma levels and adjust dosage (when &gt;1 pg/mL increased risk arrhythmias) As above</td>
</tr>
<tr>
<td></td>
<td>Acute CRS</td>
<td>To reduce ventricular rate in patients with fast atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Hydralazine and nitrates</td>
<td>Chronic CRS</td>
<td>May improve survival and symptoms when ACEIs and ARBs cannot be given In African-American patients reduce mortality and morbidity and improve quality of life</td>
<td>Headache, dizziness, hypotension</td>
</tr>
</tbody>
</table>

Continued
Results

The following questions were considered:

Q 1: What are the key management goals in the treatment of patients with cardio-renal syndromes?

Q 2: What is the best clinical management for heart failure patients who develop acute cardio-renal syndrome?

Q 3: What is the best clinical management for heart failure patients who develop chronic cardio-renal syndrome?
Q 4: What is the best clinical management for renal failure patients who develop acute Reno-Cardiac syndrome?
Q 5: What is the best clinical management for renal failure patients who develop chronic Reno-Cardiac syndrome?
Q 6: What clinical research agenda is required to evaluate these management strategies?

A literature search was made concentrating on core management areas, both from the patient’s perspective in terms of relief of symptoms, morbidity, quality of life and survival (clinical effectiveness) and for the clinician treating the patient to improve cardiac output and renal function.

**Discussion**

Although there are data concerning the minimum mean systemic arterial blood pressure to maintain renal auto-regulation for dogs and rats (75 and 85 mmHg, respectively) [22], there are no human data. Low blood pressure is associated with increased mortality, and during cardiac bypass surgery neurological damage increased with mean perfusion pressures ≤60 mmHg [23,24]. Cardiac perfusion relies upon the diastolic pressure, but there is no apparent critical threshold beyond which irreversible cardiac damage occurs. Thus, there are no simple clinical targets in terms of cardiac output and blood pressure for goal-directed therapy.

Similarly, there are no evidence-based clinical targets for managing patients with both cardiac and renal disease, whereas there are standard treatment protocols for patients with both heart failure [25] and kidney disease. The question arises as to whether management of patients with heart failure requires modification for those patients with kidney failure and vice versa. Thus, the ADQI group reviewed the currently available literature to synthesize an expert opinion consensus treatment strategy for these patient groups.

**Acute Cardio-Renal syndrome**

Impaired baseline renal function in acute heart failure and deterioration in renal function early in the course of treatment are strong adverse prognostic factors for patient survival and morbidity. Thus, renal protection is an important pathophysiological target, and any treatment for acute heart failure should at least have a neutral effect or preferably improve renal function [1].

Whereas there are many clinical trials on CHF, the management of acute heart failure remains essentially empiric (level C evidence). Patients should be oxygenated to achieve a peripheral oxygen saturation >90% (unless the patient has severe obstructive pulmonary disease) and may require non-invasive positive pressure ventilation and morphine to relieve distress, anxiety or pain. Clinical assessment should establish whether acute heart failure is associated with signs of congestion (common) or of low cardiac output (rare) or both. In all cases, an underlying cause needs to be identified and treated. This is particularly important in the case of acute arrhythmias, myocardial infarction, hypertension crisis, cardiac tamponade, aortic dissection and pulmonary embolus, where specific therapies are required.

Vasodilators nitroglycerine, isosorbide dinitrate and nitroprusside [26,27] and loop diuretics are widely recommended for decompensated heart failure (recommendation class 1 level B) (Table 6). Nesiritide, a recombinant B-type natriuretic peptide, is a potent vasodilator with modest natriuretic effects (Figure 1). Initial studies reported deterioration in renal function when nesiritide was administered with diuretics [28–31]. Typically, CHF patients have underlying CKD and previously prescribed diuretics, so larger doses of loop diuretics are often required, and infusions are more potent than simple boluses (recommendation class 1, level A) [32,33].

Loop diuretics may potentially predispose to hypokalaemia, hyponatraemia and hyperuricaemia but, importantly, hyponatraemia with increased neurohumoral activation, worsening renal function [34,35]. Vasodilators, including nesiritide [28], and to a lesser extentularitide [31], by precipitating hypotension [36], can exacerbate renal injury [30].

Both endothelin and adenosine cause renal vasoconstriction [37], so endothelin (A and also both A and B) [38] and adenosine A1 receptor blockers have been evaluated in clinical trials with decompensated CHF patients [39]. Currently, endothelin receptor blockers have not proved successful in acute heart failure, and trials of adenosine A1 receptor blockers are ongoing.

Severe heart failure causes hyponatraemia, and vasopressin receptor 2 antagonists can increase renal free-water clearance. Short-term studies reported improvement in hyponatraemia and weight loss, without survival benefit [40–43].

Some patients fail to respond to non-invasive ventilation, vasodilators and diuretics, and selected patients may require ultrafiltration to reduce volume overload [44]. However, ultrafiltration does not improve renal function. If congestion coincides with hypotension, inotropic agents should be considered [45].

Low cardiac output syndromes, such as cardiogenic shock [6], often lead to AKI, and treatments are designed to increase cardiac output and restore renal blood flow. A fluid challenge, with saline, may be clinically indicated if blood pressure and organ perfusion do not respond to inotropes (Figure 1). Although inotropes, typically dobutamine, with inotropic and chronotropic actions (stimulation of beta1-adrenergic receptors), and dopamine (dopaminergic, alpha1 and beta-adrenergic receptor agonist), may tide patients over acutely, these often may result in potential midterm poorer outcome [6]. Phosphodiesterase inhibitors, milrinone [46] and enoximone, should be used cautiously in patients with ischaemic heart disease. Levosimendam, a lusitropic agent that increases cardiac contractility without affecting intracellular calcium, also reduces peripheral vascular resistance [47,48].

If the systemic blood pressure remains low, cautious introduction of norepinephrine may be considered (recommendation class IIb, level C). Elective ventilation and/or insertion of an intra-aortic balloon pump (ABP) may be required, as ABP or external counter-pulsation may improve renal and other organ perfusion [49]. Depending up-
on pre-existing co-morbidity and underlying aetiology, left ventricular assist devices [50,51] as a bridge to transplantation or cardiac surgery may be appropriate [52,53]. Patients with acute right heart failure often do not respond to fluid challenges, typically become severely hypotensive when intubated and may potentially benefit from lusitropic agents [54].

**Chronic Cardio-Renal syndrome**

Therapeutic approaches to patients with CHF are complex and comprise elimination and treatment of the underlying cause or disease causing damage to the cardiovascular system and CHF progression. Increased survival remains the major goal and key end point in clinical trials, coupled with therapies directed towards improvement in quality of life, provided they do not adversely affect the natural history of CHF.

Non-pharmacological management or ‘self-care management’ is an integral part of successful CHF treatment. It contains ‘self-care management’, defined as actions aimed to maintain physical stability, avoid behaviour that can worsen the disease and detect early symptoms of deterioration. The following behaviours may be considered: adherence to treatment [55], proper symptom recognition (recommendation class 1 evidence level C), weight control, lifestyle changes including diet and nutrition, smoking cessation, exercise training and education (recommendation class 2a level C) [56–58]. These need to be clearly explained with patients and relatives. The optimal model of outpatient review remains to be determined [59].

The following pharmacological therapies have been proven to reduce mortality and morbidity and potentially reduce disease progression (recommendation class 1, grade A) angiotension converting enzyme inhibitors (ACEIs) [1,60–62], beta-blockers [1,63–65], angiotensin II receptor blockers (ARBs) [1,66] and aldosterone antagonists [1,67,68] (Table 6). They all target neuroendocrine activation differently, and so combinations are desirable. The optimal approach is to use ACEIs and beta-blockade in incremental doses to which either ARBs or aldosterone antagonists are subsequently added depending on individual responses [66]. ARBs have been shown to be non-inferior to ACEIs [69–74]. The addition of an ARB to an ACEI has been shown to improve outcomes (recommendation grade 1, level A); however, the ONTARGET trial did not observe any additional benefit of adding an ARB in a high-risk population compared to an ACEI alone [74,75]. Additionally, a combination of all four neuroendocrine blockers (ACEI, ARB, \(\beta\)-blocker and aldosterone antagonist) is not recommended. In symptomatic patients unable to tolerate ACEIs/ARBs, a combination of hydralazine and nitrates may be an alternative [76]. Digoxin and diuretics which improve symptoms in CHF have no effect on mortality [77].

Implantation devices may become an alternative effective treatment for selected CHF patients. Cardiac resynchronization therapy is recommended for patients who remain symptomatic New York Heart Association (NYHA III–IV) despite optimal pharmacological treatment with poor LVEF and QRS prolongation (recommendation grade 1 level A) (Figure 2) [1,78–80], and implantable cardiac defibrillators are recommended not only for survivors of cardiac arrest or sustained ventricular arrhythmias but also for symptomatic CHF patients with impaired LVEF (recommendation class 1 level A) [1].

Recent studies have showed no advantages for statins in patients with symptomatic CHF [81,82], although n-3 polyunsaturated fatty acids may be of modest benefit [83].

![Algorithm for the management of acute heart failure. ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; nitrate, nitroglycerin or nitroprusside; phosphodiesterase inhibitor: milrinone, enoximone.](image)
In selected patients who do not respond to treatment, mechanical assist devices and/or cardiac transplantation may be appropriate [51,83–88] depending upon other co-morbidities.

Whereas there have been many clinical trials in the management of patients with CHF, there are very few studies involving patients with right-sided heart failure due to pulmonary hypertension (Table 7) [89]. Treatment depends upon whether the right ventricle is under- or over-filled but should also be directed towards the underlying cause [6,90]. Paracentesis should be considered for those with ascites.

Management of CHF patients with renal disease (based on the current ESC guidelines)

Renal dysfunction, even mild, constitutes a risk factor for CHF and is a strong independent predictor of increased morbidity and mortality [1,91,92]. The prevalence of renal dysfunction increases with CHF severity, age and other co-morbidities (such as hypertension and diabetes mellitus). Potentially reversible causes, including hypotension, dehydration, drug effects and renovascular disease should always be excluded [13]. Therapy of CHF patients with concomitant renal impairment is not evidence-based, as these patients were underrepresented in CHF trials [93,94].

CHF patients with renal dysfunction often have excessive salt and water retention [14] and require more intensive diuretic treatment [95]. In patients with creatinine clearance <30 mL/min/1.73 m², standard thiazide diuretics may be ineffective and loop diuretics preferred, with infusions more potent than intermittent boluses (recommendation class 1 level A). [96,97]. As increasing doses of loop diuretics are associated with worse outcome [34,98], combinations with epithelial sodium channel blockers, aldosterone antagonists or metolazone should be considered [33,99].

Therapy with ACEIs and ARBs is usually associated with a mild deterioration in renal function, frequently transient and reversible. Patients with CKD and renal artery stenosis are at a higher risk. In all cases, careful monitoring is recommended. If renal function declines, other secondary causes such as excessive diuresis, persistent hypotension and concurrent nephrotoxic therapies should be excluded. ACEIs and ARBs cause potassium retention,
which is exacerbated by type IV renal tubular acidosis and aldosterone antagonists [69]; thus, CKD patients are advised to restrict dietary potassium and sodium [100].

There is no absolute serum creatinine level that is a contraindication to the use of ACEIs/ARBs. However, specialist supervision is recommended by the European Society of Cardiology [1] when the serum creatinine is ≥2.75 mg/dL (250 μmol/L). Whereas the combination of ACEIs and ARBs is advantageous in the general population, a recent report observed that the combination failed to reduce the rate of deterioration of renal function compared to ACEI alone [101] and that ARB alone was not different to placebo alone in a high-risk group [102].

If CHF patients become refractory to diuretics, then ultrafiltration may be considered [103–105] (recommendation class IIa, level B), although initial trials did not show improvement in renal function [106–109].

Patients with CHF are often recommended to take aspirin combined with clopidogrel post coated coronary artery stenting, which may increase bleeding at fistula needling sites and gastrointestinal haemorrhage in patients with CKD [110]. Warfarin anticoagulation is standard management for CHF patients with atrial fibrillation to reduce the risk of stroke (recommendation class I level A) [111], which increases the risk of spontaneous haemorrhage from 2% to around 10%/year for dialysis patients [112–114].

As renal dysfunction is associated with impaired clearance of many drugs used in CHF, for example digoxin and allopurinol, dose adjustments and careful monitoring of plasma levels may be required.

Anaemia is often present in CHF patients with CKD. Such coexistence may further impair exercise tolerance and quality of life and adversely affect mortality and morbidity [115]. Although correction of anaemia has not been established as routine therapy in CHF, the use of erythropoetin stimulating agents and/or intravenous iron currently represent an unproven option, even though some reports have suggested improvements in exercise tolerance and reduction in NYHA classification of heart failure but without survival benefit [116–120].

Management of heart failure in patients with chronic kidney disease

Correction of anaemia, aiming for a Hb >10 g/dL has been shown to reduce left ventricular hypertrophy in CKD patients [121]. Hypertension is common in CKD [122–124], but surprisingly there is no proven association with cardiovascular outcomes for haemodialysis patients [124,125]. However, this may be due to reliance on pre- and post-haemodialysis measurements [126], as more recent studies have shown survival benefit with lower home blood pressure recordings [127]. Interdialytic weight gains should be minimized to prevent volume overload and heart failure [128]. Dietary sodium restriction [100] and lower sodium dialysates [129] reduce interdialytic weight gains, lowering ultrafiltration requirements and reducing intradialytic hypotension [130] and repetitive ischaemic stunning to the heart [131] and brain [132].

Repeated studies have shown that only a small proportion of CKD patients are prescribed cardioprotective ACEIs and beta-blockers, despite these drugs having been shown to reduce cardiovascular morbidity and mortality [25,133,134]. Although many patients with CKD were excluded from the major trials, smaller prospective studies reported a benefit for carvedilol [135]. The prescription of cardioprotective medications has not been shown to increase the incidence of intradialytic hypotension [128]. However, hypotension can occur following bradykinin generation, which may be exacerbated by ACEIs [18].

Additional management strategies include correcting anaemia, controlling calcium and phosphate product and parathyroid hormone to minimize vascular calcification [136,137] and providing adequate dialysis [138].

Conflict of interest statement. None declared.

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Post-transplant lymphoproliferative disorder in view of the new WHO classification: a more rational approach to a protean disease?

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Abstract
Post-transplant lymphoproliferative disorders (PTLDs) are serious, life-threatening complications of solid-organ transplantation (SOT) and bone marrow transplantation leading to a high mortality (30–60%). PTLD represents a heterogeneous group of lymphoproliferative diseases. They become clinically relevant because of the expansion of transplantation medicine together with the development of potent immunosuppressive drugs. Although the diagnostic morphological criteria of different forms of PTLD are commonly known, rapid and correct diagnosis is not always easy. Because of the limited number of clinical trials, a consensus is lacking on the optimal treatment of PTLD. This review focuses on incidence, risk factors, clinical picture of the disease and diagnostic tools including histopathology relating to the new classification introduced in 2008 by the World Health Organisation (WHO) and treatment of PTLD.

Keywords: EBV; histopathology; PTLD; SOT; transplantation

Introduction
The term ‘post-transplant lymphoproliferative disorder’ or disease (PTLD) was first introduced in 1984 by Starzl [1]. Today, it represents a heterogeneous group of lymphoprolif-