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Review

# Chronic kidney disease and heart failure—Bidirectional close link and common therapeutic goal

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## KEYWORDS

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Kidney;  
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**Summary** Chronic kidney disease (CKD) is common and the estimated prevalence is about 9–13% in the general adult population. CKD is defined by the presence of kidney damage or decreased glomerular filtration rate. Individuals with CKD have a far greater likelihood of cardiovascular death than progression to end-stage renal disease. Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder and the prevalence is reported to be 2–3% in the general population. The prognosis of HF patients is still poor despite recent advances in HF treatment. Both diseases are major and growing public health problems because aging of the population contributes to the increasing incidence of those diseases. More than 40% of HF patients have CKD and the close relationship between CKD and HF worsens their prognoses. All physicians must evaluate kidney function using estimated glomerular filtration rate calculated by the new Japanese equation in patients with HF. Accurate evaluation of pathophysiology between the two diseases and appropriate intervention are necessary to improve the prognosis of patients with the diseases.

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## Introduction

Chronic kidney disease (CKD) is an extensive public health problem which should be recognized properly by every healthcare provider. The US National Kidney Foundation Kidney Disease Outcome Quality Initiative proposed the concept of CKD and established the definition and classification in 2002 [1].

Studies from the USA, Europe, Australia, and Asia showed that the prevalence of CKD is about 9–13% in the general population [2–5]. The incidence and prevalence of patients with CKD including end-stage renal disease (ESRD) have doubled in the past 10 years in the USA [6]. Many patients with CKD die from cardiovascular disease (CVD) and patients who need renal replacement therapy are fewer, except in those with ESRD [7]. CKD is more prevalent in patients with CVD or with CVD-related risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and metabolic syndrome. Furthermore, CKD is a significant aggravating factor in patients with these conditions and is also an important prognostic risk for them [8].

Heart failure (HF) is also a serious and expanding public health matter and is one of the leading causes of mortality in most developed countries. More than 5 million patients have HF and over 550,000 patients are newly diagnosed with HF every year in the USA [9]. The European Society of Cardiology reports that there are at least 15 million patients with HF in 51 European countries, which have a total population of more than 900 million [10]. The prevalence of HF is approximately 2–3% and rises sharply in elderly populations, and it has been increasing because of the progressive aging of the population and the decreased mortality of patients who survived the first coronary event [11]. The total estimated costs for managing HF were reported to be 27.9 billion dollars in the USA in 2005, and 905 million pounds in the UK in 2000 [11,12]. Approximately 50% of HF patients die at 4 years and 40% of admitted patients with HF are dead or readmitted within 1 year despite the recent improved treatment for HF [10].

Patients with HF usually have much co-morbidity such as arterial hypertension, diabetes mellitus, chronic obstructive pulmonary disease, anemia, cachexia, gout, and renal insufficiency, and such co-morbidity aggravates the condition of HF. Renal dysfunction is especially common in HF patients, and anemia, hyperkalemia, low serum albumin, and uses of renin-angiotensin-system (RAS) inhibitors, aldosterone antagonists, and diuretics are associated with such disorder [10]. The prevalence of renal impairment increases with age, HF severity, a history of hypertension, or diabetes.

Such close interaction between kidney and heart has been called “cardiorenal syndrome (CRS)” and this con-

**Table 1** Definition of chronic kidney disease [1].

Criteria
1. Kidney damage for $\geq 3$ months, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifest by either: Pathological abnormalities; or Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests
2. GFR $< 60$ ml/min/1.73 m <sup>2</sup> for $\geq 3$ months, with or without kidney damage

GFR, glomerular filtration rate.

nection is observed to be the most strong in patients with HF. It seems to be mediated by not only the decreased cardiac output but also by the effects of the activated RAS, the imbalance between nitric oxide and reactive oxygen species, inflammation, anemia, and the increased sympathetic nervous activity.

This brief review describes the close relationship and pathophysiology between CKD and HF, and summarizes treatment strategies in HF patients with CKD.

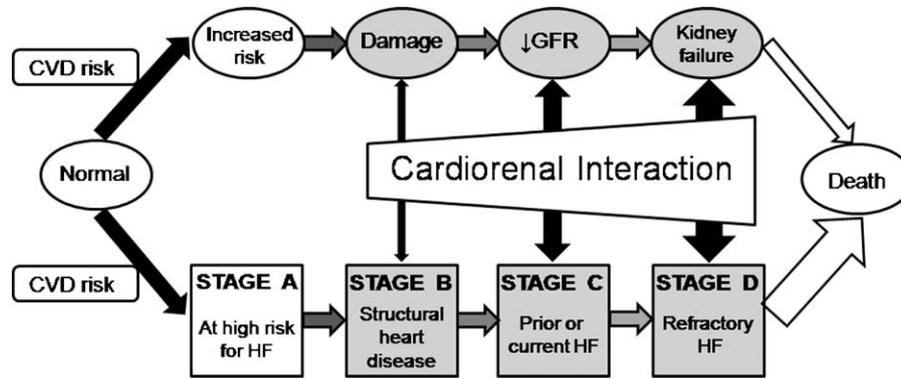
## Definitions of CKD and HF: progressive disorders

The diagnosis of CKD is easily given by the existence of kidney damage or decreased glomerular filtration rate (GFR) for three months or more. GFR is estimated using the formula including serum creatinine level, age, sex, and ethnicity irrespective of cause of the disease. The definition and classification stages of CKD are shown in Tables 1 and 2 [1]. CKD is considered to be a disease that progresses from mild to

**Table 2** CKD classification based on severity [1].

Stage	Description	GFR (ml/min/1.73 m <sup>2</sup> )
1	Kidney damage with normal or $\uparrow$ GFR	$\geq 90$
2	Kidney damage with mild $\downarrow$ GFR	60–89
3	Moderate $\downarrow$ GFR	30–59
4	Severe $\downarrow$ GFR	15–29
5	Kidney failure	$< 15$ (or dialysis)

CKD, chronic kidney disease; GFR, glomerular filtration rate;  $\uparrow$ , increased;  $\downarrow$ , decreased.



**Figure 1** Cardiorenal interaction and stage classification in the initiation and progression of chronic kidney disease and heart failure [1,11]. CVD, cardiovascular disease; HF, heart failure; GFR, glomerular filtration rate.

severe condition as shown in Fig. 1, which is the conceptual model of the course of CKD.

HF is a complex clinical syndrome that can be caused by any structural or functional cardiac disorder that impairs the pump function of the heart [11]. There have been many definitions of HF proposed to date [13]. The common and most important feature of HF syndrome includes symptoms, signs, and objective evidence of a structural or functional abnormality (Table 3). It must be emphasized that HF is not equal to left ventricular dysfunction and HF is characterized by specific symptoms in the past medical course and signs revealed by the physical examination. The Writing Committee of the AHA/ACC Heart Failure Guidelines developed a new stage classification of HF in 2001, which includes 4 stages presenting the development and progression of the HF syndrome (Fig. 1). Stage A denotes patients with CVD risks such as hypertension, diabetes mellitus, metabolic syndrome, etc. and without any geometric or functional disorder in the left ventricle. In contrast, patients who are asymptomatic but show left ventricular hypertrophy and/or left ventricular dysfunction are indicated as Stage B. When patients have symptoms of HF caused by underlying structural heart disease in the current or past medical status, those are considered to reach Stage C. Finally Stage D spec-

ified patients with refractory HF who may need mechanical circulatory support or heart transplantation [11].

Both classifications of CKD and HF have the same characteristics which clearly show the progressive manner of diseases and these classifications can provide a reliable and objective tool to identify patients on the way of developing the diseases (Fig. 1). Furthermore, they can indicate the recommendation for treatments which are considered to be appropriate at each stage of illness and are expected to prevent advancement from one stage to the next.

Patients in the clinical intersection between CKD and HF are at a high risk for poor outcomes. Inter-relationships of CKD and HF include common characteristics, such as common risk factors, bidirectional effects of one disease process on the progression of the other, adverse effects on one disease process when investigating the other, and treatment biases potentially influenced by both diseases. Those clinical and pathophysiological links will be more expanded as the stage progresses and will aggravate the severity of the diseases more seriously (Fig. 1).

## HF in patients with CKD

The overlap between CKD and other chronic diseases, most notably diabetes, hypertension, chronic obstructive pulmonary disease, and CVD is common. The annual data report of the United States Renal Data System (USRDS) in 2009 reported that the prevalence of CVD reached 63% in CKD patients compared to 5.8% of those without CKD, and it graded the association with both CKD severity and age [6]. While CKD is a risk multiplier for the development of CVD, the largest hazard occurs for HF. Compared with patients without CKD, the relative risk for the development of HF was 1.45 and 1.68 in patients with CKD of stage 1–2 and 3–5, respectively, when evaluating Medicare patients age 66 and older [6]. The event rate of HF diagnosis in those patients was the highest among all CVD and it was 56 events per 1000 patient years for patients without CKD and 176 for those with CKD of stage 3–5. Age-adjusted survival of CKD patients with HF was poor; one-year mortality of patients with CKD of stage 3–5 was nearly 25% although that of those without CKD was 17% [6].

**Table 3** Definition of heart failure [10].

*Heart failure is a clinical syndrome in which patients have the following features:*

**Symptoms typical of heart failure**

(breathlessness at rest or on exercise, fatigue, tiredness, ankle swelling)

and

**Signs typical of heart failure**

(tachycardia, tachypnoea, pulmonary rales, pleural effusion, raised jugular venous pressure, peripheral edema, hepatomegaly)

and

**Objective evidence of a structural or functional abnormality of the heart at rest**

(cardiomegaly, third heart sound, cardiac murmurs, abnormality on the echocardiogram, raised natriuretic peptide concentration)

**Table 4** Prevalence and hazard of chronic kidney disease in patients with chronic heart failure.

Ref. no.	Study	Year	No. of pts	NYHA	Age, years	Male, %	EF, %	BP or HTN	DM, %	RASi, %	eGFR < 60, %	Follow-up	Outcome	Adjusted hazard comparing with pts without CKD for the outcome
17	SOLVD-T	2000	2,161	I–IV	60.7	81.5	24.7	40.4%	24.9	50.3	35.7	–	All-cause mortality	1.41 for eGFR <60 <sup>a</sup>
18	PRIME-II	2000	1,906	III–IV	64.7	80.4	26.2	121.6/ 75.1 mmHg	20.7	91.6	49 (eGFR ≤ 58)	277 days (median)	All-cause mortality	1.91 for eGFR 44–58 2.85 for eGFR <44
19	DIG	2002	585	II/III: 85%	65	73.9	35	128.3/ 75.3 mmHg	40.3	88	50 (eGFR ≤ 63.8)	2.6 years (median)	All-cause mortality	1.6 for eGFR 47–64 <sup>a</sup> 2.1 for eGFR 18–48 <sup>a</sup>
20	McClellan	2002	665	–	75.7	40	38.4	66%	44	54	38 <sup>b</sup>	–	All-cause mortality	1.24 at 1-year mortality <sup>b</sup>
21	UK-HEART	2002	553	II/III: 98%	62.7	76	42	–	0	82	–	–	All-cause mortality	1.09 in each 10 μmol/l increase of creatinine
22	CHARM	2006	2,680	II–IV	65.3	66.6	38.5	128.2/ 73.6 mmHg	37.2	45.5	36	34.4 months	CV death + HF hospitalization	1.54 for eGFR 45–59.9 1.86 for eGFR <45
23	ANCHOR	2006	59,772	–	71.8	54.2	NA	61%	32.4	24	39.2	2.07 years (median)	All-cause mortality + HF hospitalization	1.39 for eGFR 30–44 2.28 for eGFR 15–29
24	CHART	2008	920	II–IV	68.3	65.1	49.3 <sup>c</sup>	39.2% <sup>c</sup>	19.3 <sup>c</sup>	69.1 <sup>c</sup>	42.7	3.45 years	All-cause mortality + HF hospitalization	1.31 for eGFR 30–59
25	JCARE-CARD	2009	2,013	1.8 (mean)	71.5	58.7	44.8	54.5%	30.7	ACEi: 36.7 ARB: 46.1	70.3	2.4 years	All-cause mortality	1.56 for eGFR <30 1.26 for eGFR 30–59 2.48 for eGFR <30

EF, ejection fraction; BP, mean blood pressure; HTN, hypertension; DM, diabetes mellitus; RASi, renin–angiotensin-system inhibitor; eGFR, estimated glomerular filtration rate (ml/min/1.73 m<sup>2</sup>); pts, patients; CKD, chronic kidney disease; HF, heart failure; CV, cardiovascular; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

<sup>a</sup> ml/min.

<sup>b</sup> CKD was defined by serum creatinine of ≥1.4 mg/dl for women and ≥1.5 mg/dl for men.

<sup>c</sup> Data were retrieved from the previous study that included 1154 patients.

Unadjusted all-cause mortality evaluating Medicare patients age 66 and older showed the declining trend in patients with CKD during the past 10 years. However, relative risk of mortality was almost 3 times higher when CVD accompanied CKD [6]. Approximately 50% of CKD patients died of complications of CVD before they reached ESRD [14]. Keith et al. revealed that death was more common than progression to ESRD by evaluating more than 28,000 patients with CKD from a health maintenance organization [7]. Only about 20% of patients with stage 4 CKD had progressed to dialysis, whereas 46% had died of cardiovascular complications.

CVD accounted for 43.7% of the all-causes of death in dialysis patients in the USRDS database in 2005–2007 [6]. The percentage of HF as a cause of mortality was 5.3%, however event rates for congestive HF in dialysis patients reached 270 per 1000 patient years [6]. A report from the HEMO study indicated that HF prevalence in ESRD patients is about 40% [15].

The prevalence and incidence of HF, and the percentage of mortality due to HF in patients with mild to moderate CKD is not well described, because such patients have a broad spectrum of characteristics including CKD stage, age, and cardiovascular risks. Kottgen et al. studied the role of impaired kidney function as a risk factor for incident HF evaluating 14,857 middle-aged individuals without HF who were enrolled in The Atherosclerosis Risk in Communities Study [16]. Crude HF incidences were 5.7, 5.9, and 17.7 per 1000 person-years in those with estimated GFR  $\geq$  90, 60–89, and  $<$ 60 ml/min/1.73 m<sup>2</sup>, respectively, and a greater decline in kidney function during the follow-up period occurred in individuals concomitant with HF hospitalization/death compared to those who did not develop HF.

## CKD in patients with HF

CKD is common in patients with HF. Table 4 shows the major publications including our report describing the prognosis and characteristics of chronic HF patients with CKD that were published after 2000 [17–25]. CKD was present in 35–70% of HF patients evaluated in cohort studies or sub-analyses of randomized controlled trials. Furthermore, the comorbidity of CKD was associated with increased hospitalization due to worsening HF and all-cause/cardiovascular deaths. The hazard ratio for all-cause mortality in HF patients with moderate to severe CKD was about 1.3–2.9 compared to those without CKD (Table 4). The prognostic impact of CKD was observed in a broad spectrum of HF patients [22], however Ahmed et al. reported accompanying CKD was more strongly associated with mortality in patients with preserved ejection fraction than in those with reduced ejection fraction [26].

One of the major mechanisms of worsening renal function in patients with HF is considered to be long-term reduced renal perfusion. However, estimated GFR in HF patients with preserved ejection fraction was similar compared with that in those with reduced ejection fraction [27] and the ESCAPE trial revealed that renal congestion might be a more important factor for renal impairment compared to increased pulmonary artery pressure [28]. Other contributing factors of hypoperfusion

**Table 5** Proposed mechanism in cardiorenal interaction.

Common factors for heart and kidney	
Traditional cardiovascular risk factors	
	Smoking
	Obesity
	Hypertension
	Diabetes
	Dyslipidemia
Other risk factors	
	Malnutrition
	Genetic risk factors
Humorally mediated factors	
	Elevated sympathetic nervous system
	Elevated renin-angiotensin system
Other common factors	
	Inflammation
	Endothelial dysfunction
	Immune mediated damage
	Oxidative stress
	Coagulation imbalance
Treatment related factors	
	Undertreatment
	Toxic agents
Organ-specific factors	
Hemodynamics mediated factors	
	Decreased cardiac output (heart)
	Renal hypoperfusion (heart)
	Elevated venous pressure (heart)
	Sodium and water retention (kidney)
	Hypertension (kidney)
Other specific factors	
	Brain natriuretic peptide (heart)
	Anemia (kidney)
	Uremic solute retention (kidney)
	Calcium and phosphate abnormality (kidney)
	Electrolyte, acid-base imbalances (kidney)

are the increased vasoconstrictive mediators (epinephrine, angiotensin, endothelin) and pharmacotherapy-related effects including diuresis-associated hypovolemia, RAS inhibitors, and drug-induced hypotension [29]. Other possible mechanisms of kidney–heart interaction are shown in Table 5.

## Acute kidney injury in patients with acute heart failure

Acute heart failure (AHF) is defined as a rapid onset or change in the signs and symptoms of HF, which may be either new HF or worsening of pre-existing chronic HF. Although AHF is usually characterized by pulmonary congestion, acutely reduced cardiac output and tissue hypoperfusion are also important hemodynamic aspects, which sometimes cause multiorgan failure. A rapid worsening of cardiac function also leads to acute kidney injury

**Table 6** Proposed definitions of cardiorenal syndrome [34].

<b>CRS type I (acute CRS)</b>
Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury
<b>CRS type II (chronic CRS)</b>
Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease
<b>CRS type III (acute renocardiac syndrome)</b>
Abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)
<b>CRS type IV (chronic renocardiac syndrome)</b>
Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
<b>CRS type V (secondary CRS)</b>
Systemic condition (e.g. diabetes mellitus, sepsis) causing both cardiac and renal dysfunction

CRS, cardiorenal syndrome.

(AKI) and pre-morbid chronic renal dysfunction has been reported as a common precursor for AKI in HF patients [30,31]. Worsening renal function, defined as a rise in serum creatinine level  $>0.3$  mg/dl, during hospitalization for HF is observed in 20–30% of HF patients [29]. Any change in serum creatinine has been reported to be associated with longer hospital stay, increased costs, and increased short-term/long-term mortality [29]. Lower estimated GFR on HF admission was also an independent predictor for long-term mortality in AHF patients [32]. The mechanisms of the relationship are multiple and complex including persistent vasoconstriction, high renal venous pressure, elevated intra-abdominal pressure, adenosine and tubuloglomerular feedback, and medicine perturbing intrarenal hemodynamics (Table 5) [29,33].

## Classification of cardiorenal syndrome

The bidirectional natures of heart and kidney interaction represent the pathophysiological basis for a clinical entity that has been called cardiorenal syndrome (CRS) (Fig. 1). Ronco et al. proposed the new classification of CRS to help physicians characterize groups of patients, to provide the rationale for specific management strategies, and to allow the design of future clinical trials [34]. They defined CRS 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, and divided CRS into 5 different subtypes (Table 6). The proposed mechanism of kidney–heart interaction is also shown in Table 5. The benefit and validity of using this classification should be confirmed in future studies.

## Anemia in patients with CKD and/or HF

Anemia develops relatively early in the disease course of CKD and worsens with CKD severity. McClellan et al. reported that anemia was present in 47.7% in 5222 enrolled patients with CKD [35] and the prevalence of anemia was strongly associated with decreased GFR. The major mechanisms of the development of anemia are decreased erythropoietin production and increased erythropoietin resistance, and other causes include decreased red blood cell life span due to uremic toxins, chronic blood loss caused by platelet dysfunction, nutritional deficiencies [36], iron deficiency, and elevated inflammatory cytokines [37] that may cause bone marrow suppression.

Anemia also frequently occurred in HF patients, with reports ranging widely from 9.0% to 79.1% [38,39], but the majority of studies described more than 20% [40]. Previous reports suggested that decreased hemoglobin level was associated with increased rates of death and HF-related admission [23]. Anemia observed in HF patients mainly is attributed to kidney-related factors described above, and is also related with bone marrow suppression by frequent angiotensin-converting enzyme (ACE) inhibitor use in HF patients [41]. Because CKD and anemia frequently co-exist and worsen the prognosis in patients with HF, CRS is also named as “cardio-renal-anemia syndrome” [40].

Whether the correction of anemia using erythropoiesis-stimulating agents is beneficial or not in patients with CKD or HF is still controversial. Previous trials have reported that the complete normalization of hemoglobin levels in CKD patients did increase adverse outcomes, although it might improve cardiac function [42]. The CHOIR study revealed the surprisingly higher rates of adverse events in CKD patients targeted for the high hemoglobin level (13.5 g/dl) compared with those in the low hemoglobin group (11.3 g/dl) [43]. The CREATE and the TREAT studies also showed that the complete correction of hemoglobin level did not demonstrate any improvement in cardiovascular events [44,45]. Meanwhile, some previous studies evaluating patients with HF showed a beneficial impact of anemia correction on HF symptoms, left ventricular ejection fraction, and quality of life [46,47]. However, in a recent trial in HF patients (STAMINA-HeFT), darbepoetin alfa treatment did not significantly improve exercise duration, NYHA functional class, or even health-related quality of life [48]. A large-scale, double-blind, randomized morbidity and mortality trial (RED-HF) is currently ongoing and it may demonstrate the impact of anemia correction on mortality in those patients [49].

## Treatments of CKD patients with HF and of HF patients with CKD

A complete description or details of treatment in patients with CKD or HF are beyond the scope of this article, which may appear in the authoritative clinical practice guidelines for the treatment of CKD or HF [1,10,11]. The following part highlights the issue regarding the treatment using RAS inhibitors, which is the most commonly recommended therapy in patients with HF or CKD.

Reduction of proteinuria or albuminuria by treatment is associated with the slowing of the progression of CKD and is associated with reducing the cardiovascular events [50–52]. Major clinical practice guidelines recommended RAS inhibitors as the first-line therapy for patients with proteinuric nephropathy [53–55]. However, several researchers indicated that RAS blockade was not effective in patients with early-stage CKD [56,57]. Furthermore, O'Hare et al. estimated that 40.6% of the US population older than 70 years had stage 3 or 4 CKD, most of whom were diagnosed only by the decreased estimated GFR with lower urinary protein excretion. They noted that such a population was poorly represented in randomized controlled trials of CKD progression [58] and thus, whether there is a benefit of RAS inhibitors in such elderly CKD patients is still unknown.

Many studies have shown that the use of ACE inhibitors increased survival in HF patients with reduced left ventricular function [59–61]. Angiotensin II receptor blockers (ARB) provide comparable beneficial effect on cardiovascular outcomes in those patients [62,63]. Several researchers have shown that the beneficial effect of RAS inhibition on HF and CKD seems to be independent to lowering blood pressure (BP) [64,65].

Whether the interventions aimed at lowering BP by way of RAS inhibition and lowering protein excretion are beneficial simultaneously to both cardiovascular and renal outcome is still controversial. The IDNT trial revealed that the relative risk for reaching a renal end point progressively decreased with the lowering in achieved systolic BP using irbesartan, and the group below 120 mmHg did not show the increased risk [64]. However, the risk for both all-cause mortality and cardiovascular mortality rose in patients who achieved less than 120 mmHg of systolic BP by a relative risk of 3.05 and 4.06, respectively, and the decrements of diastolic BP were significantly associated with the increased rate of myocardial infarction [65]. Meanwhile, the RENAAL trial showed that patients with more than 30% reduction in urine protein excretion were associated with a significantly reduced risk for renal outcome compared with those without such a reduction. Furthermore, the reduction in proteinuria was also associated with reduced cardiovascular event rates [51].

## Medical recommendations in treating HF patients with renal impairment

Because HF patients with CKD have been not adequately represented in randomized controlled trials of HF, most treatments in such patients are not usually prescribed in an evidence-based manner. The following recommendations must be validated in future studies [10,11].

### 1. General principles

- (1) Evaluate the CKD stage using estimated GFR and urine albumin:creatinine ratio.
- (2) Check etiology of CKD.
- (3) Control BP appropriately using anti-hypertensive medicines including RAS-inhibitors and/or beta-blockers (<130/80 mmHg).

- (4) Appropriate management of other traditional cardiovascular risks including diabetes, dyslipidemia, smoking, etc. is necessary.
  - (5) Check all CKD-related risks including anemia, serum electrolyte abnormality, serum albumin level, renotoxic agents, etc.
  - (6) When using ACE inhibitors/ARB, contraindications in patients must be checked thoroughly and consider reducing dose in patients with moderate-severe CKD.
  - (7) Aldosterone antagonists should be used with caution as they may cause significant hyperkalemia.
  - (8) Renal dysfunction is usually associated with impaired clearance of HF medicines. The start or maintenance doses should be reduced and plasma levels must be monitored frequently to avoid toxicity, if possible.
  - (9) HF patients with CKD often have excessive salt and water retention, which needs more intensive diuretic treatment. In patients with severe CKD, loop diuretics are more effective than thiazide diuretics.
2. AHF Patients with AKI (CRS Type 1)
- (1) Evaluate status of cardiac output and renal congestion.
  - (2) A gradual diuresis is recommended and extracorporeal ultrafiltration may be considered in case of severely decreased diuretic responsiveness [66].
  - (3) Close monitoring of renal function and hyperkalemia is necessary especially when RAS inhibitors are used [67].
  - (4) The administration of beta-blockers is not recommended until the patient has stabilized physiologically [68].
  - (5) The radiocontrast agent should be used in the careful consideration for nephropathy and needs appropriate prophylaxis [69].
3. Chronic HF Patients with CKD (CRS Type 2)
- (1) Attention needs to be paid to reducing risk factors and optimizing medication.
  - (2) Diuresis-associated hypovolemia, RAS inhibitors, and drug-induced hypotension are contributing factors for renal impairment [29].
  - (3) In patients with diabetic nephropathy and overt proteinuria, the risk for congestive HF may increase when systolic BP is decreased to less than 120 mmHg [65].
  - (4) Peritoneal dialysis may be a therapeutic option for refractory HF patients with severe CKD [70].

## Current status of CKD in Japan

Iseki et al. reported that the prevalence of CKD was higher in Japan than in other Asian countries and the USA and that individuals with a low GFR (<60 ml/min/1.73 m<sup>2</sup>) were estimated to be 20% of the adult population [71]. According to the Japanese Society for Dialysis Therapy, the prevalence of patients with ESRD was greater than 2000 per million population since 2005. CKD is also a major public health problem in Japan and the Japanese Society of Nephrology published a CKD Practice Guideline in September 2007 [72].

Most patients with CKD are diagnosed by decreased GFR, which is usually estimated from serum creatinine level, age, sex, and ethnicity by using the Modification of Diet

**Table 7** The equation for estimated GFR in Japan [72,74].

$$\text{Estimated GFR (ml/min/1.73 m}^2\text{)} = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739 \text{ (if female)}$$

GFR, glomerular filtration rate.

in Renal Disease (MDRD) Study equation. Several studies have revealed that the equation for estimated GFR must be modified properly in non-white individuals, because of the variation in serum creatinine caused by the difference in muscle mass, the calibration difference in serum creatinine assay, or the different method to measure true GFR [73]. Matsuo et al. reported the revised GFR-equation in 2009 to enable more accurate estimation of GFR in the Japanese population (Table 7) [74]. Imai et al. re-evaluated the prevalence of CKD patients using this new equation in 74,024 members of the adult population who participated in a large-scale annual health check-up program in 2005. They concluded that about 13% of Japanese adult population, approximately 13.3 million people, were predicted to have CKD in 2005 [3].

## Conclusions

CKD is frequently observed in HF patients and GFR had an inverse graded association with HF severity. CKD is one of the major predictors for admission for worsening HF and cardiovascular/all-cause mortality in such patients. Although a major focus of HF treatment has been on the heart, treatment strategies also should be targeted on the kidney. Evaluation of GFR should be performed in all patients with HF and patients with CKD must be treated carefully considering common pathophysiologic nature between two organs. Given the increased incidence of both diseases which pose significant impact on public health, patients with CKD should be appropriately included in future trials of HF to develop clinical evidence, which will improve the prognosis and quality of life in patients with HF.

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