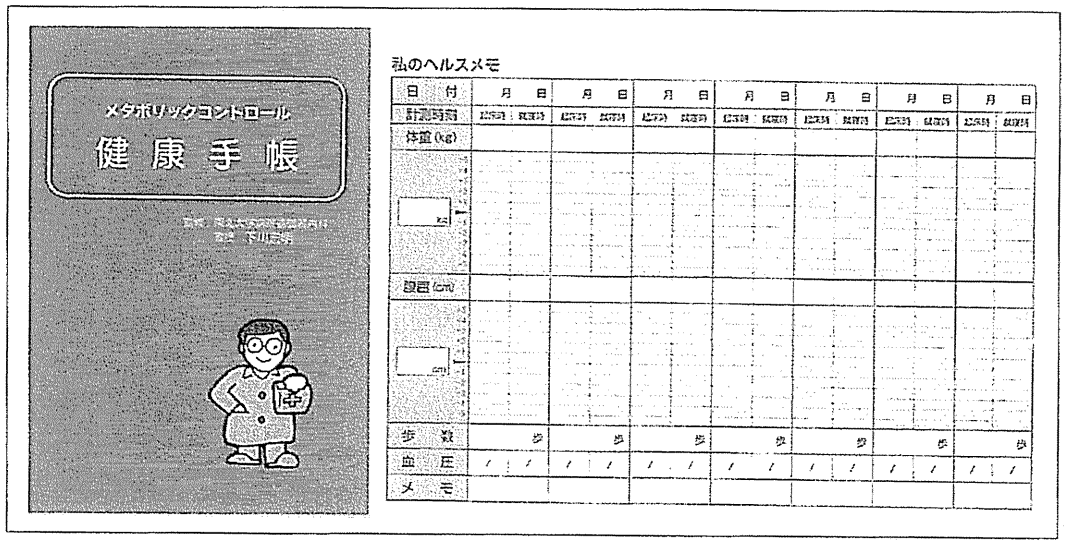

図6　筆者らの使用している健康手帳

ておく必要がある．筆者らは，それぞれの症例において毎日の体重測定・腹囲測定を行い，運動できる患者では万歩計を用いて日常生活における運動量を決定し，健康手帳(図6)をつけることで内臓肥満の是正を図っている．しかしながら，一部の患者では是正されるものの，多くの場合，体重・腹囲のコントロールは不十分であり，近い将来，効果的な治療法の開発が望まれるところである．

内臓脂肪のコントロール以外には，スタチンなどを用いた脂質異常症の改善，降圧薬を用いた至適血圧の維持，抗糖尿病薬を用いた食前・食後血糖のコントロールを行う(図1)．慢性心不全の二次予防には，これらの動脈硬化危険因子のコントロールが非常に重要である．

おわりに

前述のように筆者らは，東北地方における心不全コホートを立ち上げており，1万人規模を登録するCHART-2 studyを開始している．また，全国レベルでも，JCARE-CARD研究，JCARE-GENERAL研究，J-CHF研究などの心不全研究が行われており，それらの結果から，心不全の臨床像と予後との関連，特に治療内容と予後との関連を解析することが可能になり，わが国の慢性心不全患者における予後の規定因子や治療ターゲットの決定，各心不全治療の効果など，きわめて貴重な情報を得ることができると期待される．

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Review

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

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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.

Contents

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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 connection 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.

Table 1 Definition of chronic kidney disease [1].

Criteria
1. Kidney damage for ≥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^2 for ≥3 months, with or without kidney damage

GFR, glomerular filtration rate.

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^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

CKD, chronic kidney disease; GFR, glomerular filtration rate; ↑, increased; ↓, decreased.

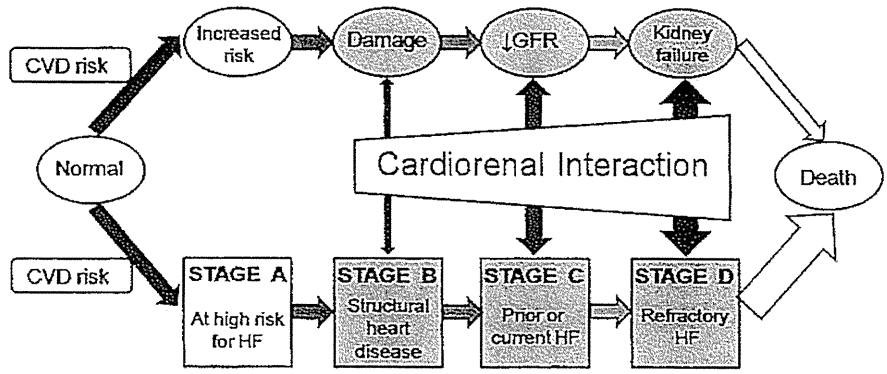

Figure 1 Cardiorenal interaction and stage classification in the initiation and progression of chronic kidney disease and heart failure [1,11]. CVD, cardiovascular disease; HF, heart failure; GFR, glomerular filtration rate.

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 specified 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).

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)

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 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[a]
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[a] 2.1 for eGFR 18–48[a]
20	McClellan	2002	665	–	75.7	40	38.4	66%	44	54	38[b]	–	All-cause mortality	1.24 at 1-year mortality[b]
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[c]	39.2%[c]	19.3[c]	69.1[c]	42.7	3.45 years	All-cause mortality + HF hospitalization	1.31 for eGFR 30–59 1.56 for eGFR <30
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	1.26 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^2); pts, patients; CKD, chronic kidney disease; HF, heart failure; CV, cardiovascular; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

[a] ml/min.

[b] CKD was defined by serum creatinine of ≥1.4 mg/dl for women and ≥1.5 mg/dl for men.

[c] 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^2, 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 subanalyses 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 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.

Table 5 Proposed mechanism in cardiorenal interaction.

Common factors for heart and kidney
Traditional cardiovascular risk factors
Smoking
Obesity
Hypertension
Diabetes
Dyspilidemia
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)

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].

CRS type I (acute CRS)
Abrupt worsening of cardiac function (e.g. acute cardiogenic shock or decompensated congestive heart failure) leading to acute kidney injury
CRS type II (chronic CRS)
Chronic abnormalities in cardiac function (e.g. chronic congestive heart failure) causing progressive and permanent chronic kidney disease
CRS type III (acute renocardiac syndrome)
Abrupt worsening of renal function (e.g. acute kidney ischemia or glomerulonephritis) causing acute cardiac disorder (e.g. heart failure, arrhythmia, ischemia)
CRS type IV (chronic renocardiac syndrome)
Chronic kidney disease (e.g. chronic glomerular disease) contributing to decreased cardiac function, cardiac hypertrophy and/or increased risk of adverse cardiovascular events
CRS type V (secondary CRS)
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^2) 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].

Estimated GFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (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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Validation of Mortality Risk Stratification Models for Cardiovascular Disease

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Risk stratification models are effective tools for the management of cardiovascular diseases. Although several risk scores have been proposed, the relevance and superiority of these predictive models have not been fully validated in an independent and nonclinical trial-based population. We studied 2,472 consecutive patients initially hospitalized in our institution from April 2004 to December 2009. Risk scores were calculated for each patient using 4 risk score models, including the Seattle Heart Failure Model (SHFM), Acute Decompensated Heart Failure National Registry regression model, the American Heart Association Get With The Guidelines-Heart Failure score, and the Association of Health Aging and Body Composition Heart Failure score. The predictive ability for the composite end point, including total death, heart transplantation, and left ventricle assist device implantation, was assessed by calculating the area under the receiver operating characteristic curve for each model. During the follow-up period after admission (median 924.5 days), the combined end point occurred in 295 patients (11.8%), including 27 in-hospital deaths (1.1%). Compared with the other 3 risk score models, the SHFM risk score demonstrated a greater area under the curve for the combined end point at the overall, in-hospital, 30-day, and 1-, 2-, and 3-year follow-up point (0.741 to 0.890). The survival rate predicted by SHFM demonstrated an excellent correlation with the actual survival rate (R^2 = 0.990). In conclusion, these results suggest that the SHFM risk score is the most suitable for the discrimination and calibration of mortality risk stratification in patients with cardiovascular disease. (Am J Cardiol 2011;108: 391–396)

Cardiovascular disease is one of the leading causes of morbidity and mortality, imposing a substantial healthcare cost in most countries. It is, therefore, important to assess the risk status of patients for decision-making process and effective management of patient care. Several predictive risk models have recently been proposed in an attempt to improve risk stratification: the Seattle Heart Failure Model (SHFM)[1]; the Acute Decompensated Heart Failure National Registry (ADHERE)[2]; Get With The Guidelines-Heart Failure (GWTG-HF)[3]; the Association of Health Aging and Body Composition Heart Failure score (ABC).[4] These existing risk models were derived from a limited population mainly from clinical trial studies. Consequently, it remains unclear whether these risk models can provide us with a standardized approach to estimate the risk in all patients with cardiovascular disease in the "real world." The purpose of the present study was to evaluate the prognostic accuracy of these 4 risk models to predict overall, in-hospital, 30-day, and 1-, 2-, and 3-year survival in our large cohort of patients with cardiovascular disease.

Methods

We studied 3,026 consecutive patients initially admitted to our institution from April 2004 to December 2009. The data prospectively collected from the medical records included the clinical characteristics, medical history, therapy, laboratory tests, and follow-up information. In addition, deaths were determined by conducting a telephone survey of family members and local hospitals. We calculated the risk scores for each patient using the published models: (1) SHFM, (2) ADHERE, (3) GWTG-HF, and (4) ABC. The variables required for SHFM scoring were age, gender, New York Heart Association class, body weight, left ventricular ejection fraction, systolic blood pressure (SBP), etiology of cardiomyopathy, medication (angiotensin-converting enzyme inhibitors, β blockers, angiotensin II receptor blocker, statin, allopurinol, or K-sparing diuretics), diuretic dosage, laboratory values, and implanted device status.[1] Specifically, the SHFM score was determined as follows; SHFM score = age/10 × ln(1.09) + (if male) ln(1.089) + New York Heart Association class × ln(1.60) + 100/ejection fraction × ln(1.03) + (if ischemic heart disease) ln(1.354) + (if SBP <160 mm Hg) SBP/10 × ln(0.877) + (if SBP ≥160 mm Hg) 160/10 × ln(0.877) + 100/cholesterol × ln(2.206) + (if angiotensin-converting enzyme inhibitor treated) ln(0.77) + (if angiotensin II receptor blocker treated) ln(0.85) + (if β blocker treated) ln(0.66) + (if K-sparing diuretics treated) ln(0.74) + (if statin treated) ln(0.63) + diuretic/kg × ln(1.178) + (if sodium <138) (138 − sodium) × ln(1.05) + (if hemoglobin <16) (16 − hemoglobin) × ln(1.124) + (if hemoglobin >16) (hemoglobin − 16) × ln(1.336) + percentage of lymphocytes/5 ×

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Table 1
Patient characteristics (n = 2,472)

Characteristic	Value
Age (years)	61.6 ± 15.8
Men	63.8%
New York Heart Association class	
I	60%
II	21%
III	11%
IV	8%
Hypertension	51.2%
Ejection fraction	60.2 ± 17.3%
Myocardial ischemia	37.5%
Angina pectoris	14.9%
Old myocardial infarction	7.8%
Acute myocardial infarction	5.4%
Other	9.5%
Arrhythmia	25.4%
Atrial fibrillation/flutter	8.0%
Sick sinus syndrome/atrioventricular block	5.0%
Ventricular tachycardia/fibrillation	4.0%
Paroxysmal supraventricular tachycardia	3.7%
Other	4.7%
Cardiomyopathy	15.5%
Dilated cardiomyopathy	7.3%
Hypertrophic cardiomyopathy	3.3%
Hypertensive heart disease	3.2%
Other	1.7%
Valvular disease	6.8%
Mitral regurgitation	2.4%
Aortic stenosis	1.9%
Aortic regurgitation	1.6%
Other	0.9%
Pulmonary artery disease	5.7%
Idiopathic pulmonary hypertension	2.1%
Pulmonary embolism	1.9%
Other	2.7%
Diabetes mellitus	24.6%
Chronic obstructive pulmonary disease	8.4%
Atrial fibrillation	23.4%
Smoking	30.1%
Systolic blood pressure at admission (mm Hg)	124.7 ± 22.5
Diastolic blood pressure at admission (mm Hg)	73.0 ± 14.1
Heart rate (beats/min)	77 ± 20
Creatinine (mg/dl)	1.1 ± 1.1
Sodium (mEq/L)	141.1 ± 3.5
Blood urea nitrogen (mg/dl)	18.6 ± 11.2
Uric acid (mg/dl)	6.0 ± 1.9
Total cholesterol (mg/dl)	181.9 ± 40.2
High-density lipoprotein (mg/dl)	48.0 ± 14.4
Albumin (g/dl)	3.9 ± 0.6
Hemoglobin (g/dl)	13.1 ± 2.1
Fasting blood glucose (mg/dl)	118.2 ± 46.0
Lymphocytes (%)	25.4 ± 10.3
Cardiac device	15.2%
Defibrillator	4.0%
Biventricular	0.6%
Combined	1.0%
Pacemaker	9.6%
Angiotensin-converting enzyme inhibitor	36.7%
Angiotensin-receptor blocker	29.4%
β Blockers	36.4%
Aldosterone antagonist	18.1%
Statins	31.0%
Amiodarone	4.4%
Warfarin	27.7%
Loop diuretics	29.0%
Daily diuretic use (mg/kg) (if used, furosemide equivalent)	29.3 ± 16.8

ln(0.897) + uric acid × ln(1.064) + (if cardiac resynchronization therapy implanted) ln(1.00) + (if implantable cardioverter-defibrillator implanted) ln(0.73) + (if cardiac resynchronization therapy-defibrillator implanted) ln(0.79), with ln representing natural log. Survival at time (t) for score (s) was calculated by the following equation: Survival (t) = $e^{(-0.0405\times t)\times e^{(s)}}$.

The ADHERE regression model requires information on blood urea nitrogen levels, SBP, heart rate, and age.[2] The GWTG-HF risk score also uses age, blood urea nitrogen, SBP, heart rate, sodium concentration, and the presence of chronic obstructive pulmonary disease.[3] The ABC includes age, SBP, heart rate, creatinine, albumin, fasting glucose, history of coronary artery disease, smoking status, and the presence of left ventricular hypertrophy.[4] The left ventricular ejection fraction was determined by echocardiography or left ventriculography. The Minnesota code criteria were applied for the diagnosis of left ventricular hypertrophy from the electrocardiograms. From the data obtained, the ejection fraction was missing in 7.7%, the heart rate at admission was missing in 6.7%, an electrocardiogram was missing for 4.1%, the serum high-density lipoprotein cholesterol level was missing for 4.1%, smoking habits were missing for 2.8%, and other variables were missing for <2%. The diuretic dose was converted to the furosemide equivalent dose as follows: furosemide 40 mg = torasemide 20 mg = azosemide 60 mg = indapamide 2 mg = trichlormethiazide 2 mg. To evaluate the risk score precisely, we did not replace the missing covariates with imputed values, such as the cohort mean. Therefore, 92% of the patients had all variables for the SHFM (n = 2,793), 93% for ADHERE (n = 2,823), 93% for GWTG (n = 2,810), and 87% for ABC (n = 2,633). Finally, 81% of the patients (n = 2,472) had all the variables for these 4 models and were analyzed for the present study.

The discrimination of the risk score was assessed by calculating the area under the receiver operating characteristic curve (AUC) for each of the risk models at different points of follow-up using a statistical test and the Hanley and McNeil approach.[5] The calibration of model performance was assessed using the Hosmer-Lemeshow statistic. We also compared the predicted mortality with the observed composite end point, including death, heart transplantation, or implantation of left ventricular assist device. All analyses were performed using the Statistical Package for Social Sciences, version 17.0, for Windows (SPSS, Chicago, Illinois). A p value of <0.05 (2 tailed) was considered statistically significant.

The patients' identifying information was removed before analysis. We had access to all the data, take complete responsibility for its integrity, and have read and agreed to the report as written.

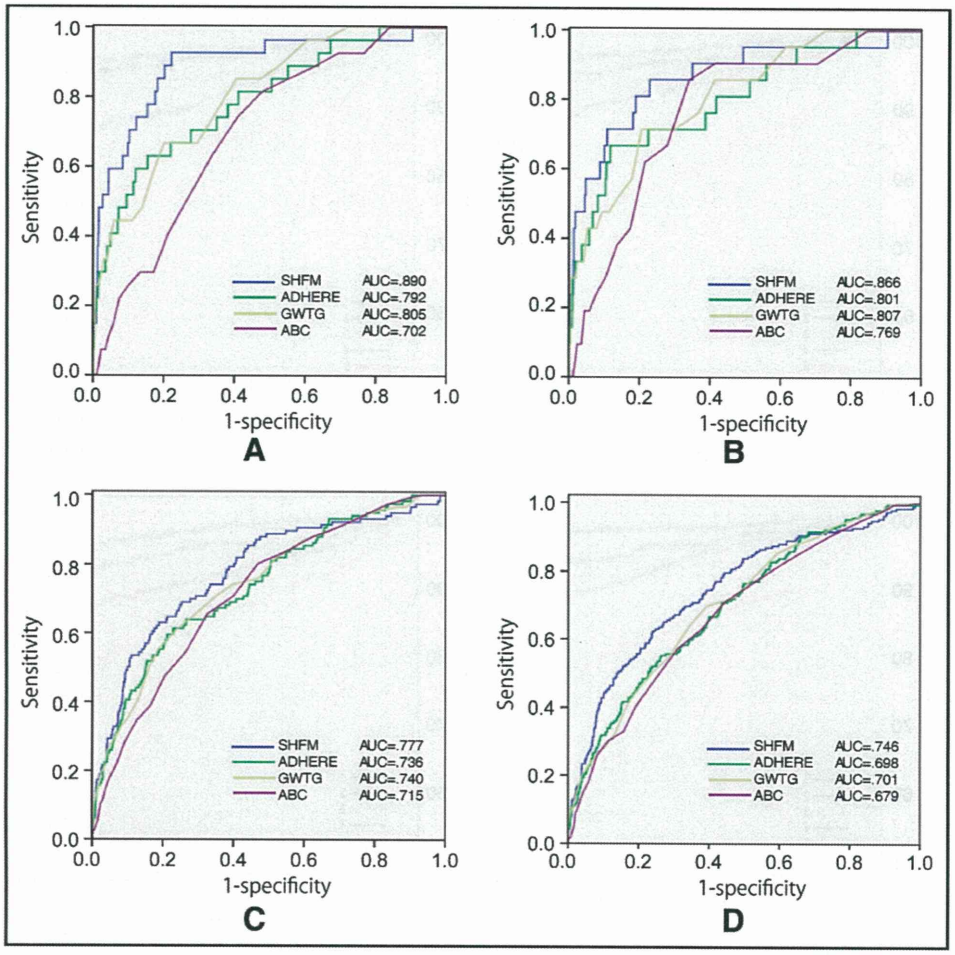

Figure 1. AUCs for combined end point of death, heart transplantation, or left ventricular assist device (LVAD) implantation for SHFM, ADHERE, GWTG-HF, and ABC, for *(A)* in-hospital death, and combined end points at *(B)* 30 days and *(C)* 1- and *(D)* 2 years of follow-up.

Table 2
Comparison of area under receiver operating characteristic curve (AUC) for Seattle Heart Failure Model (SHFM), Acute Decompensated Heart Failure National Registry (ADHERE), Get With The Guidelines-Heart Failure (GWTG-HF), and Association of Health Aging and Body Composition Heart Failure Score (ABC)

Variable	SHFM	ADHERE	GWTG-HF	ABC
In-hospital death	0.890* (0.819–0.961)	0.792 (0.701–0.882)	0.805 (0.728–0.883)	0.702 (0.617–0.787)
Combined end point				
Overall	0.747* (0.717–0.777)	0.714† (0.683–0.745)	0.711† (0.681–0.742)	0.642 (0.609–0.676)
30 Days	0.866 (0.774–0.958)	0.801 (0.696–0.905)	0.807 (0.716–0.898)	0.769 (0.680–0.858)
1 Year	0.777 (0.729–0.824)	0.736 (0.688–0.784)	0.740 (0.693–0.788)	0.715 (0.670–0.760)
2 Years	0.746* (0.707–0.785)	0.698 (0.659–0.737)	0.701 (0.663–0.740)	0.679 (0.640–0.718)
3 Years	0.744‡ (0.709–0.778)	0.709 (0.673–0.744)	0.712 (0.677–0.747)	0.694 (0.658–0.730)

Data are presented as AUC (95% CI).
* $p < 0.05$, SHFM vs ADHERE, GWTG-HF, or ABC; † $p < 0.05$ ADHERE or GWTG-HF vs ABC; ‡ $p < 0.05$, SHFM vs ABC.

Results

The baseline patient characteristics are listed in Table 1. The average length of hospital stay was 23.0 ± 1.3 days. During 6,687.3 patient years of follow-up (median 924.5 days), 291 (11.8%) of 2,472 patients died (annual mortality rate 5.7% 95% confidence interval 4.5% to 7.0%). In addition, 4 patients underwent heart transplantation and/or left ventricular assist device support. Therefore, the combined end point occurred in 295 patients (11.9%). In-hospital death occurred in 27 patients (1.1%). The total number of patients experiencing the combined end point after the 30-day and 1-, 2-, and 3-year follow-up visit was 18 (0.8%), 113 (5.2%), 189 (11.2%), and 247 (19.3%), respectively.

The AUC for the combined end point in the models is shown in Figure 1. The values of AUC with the 95% confidence interval and p values are summarized in Table 2. Compared to the other models, the SHFM risk score demonstrated a significantly greater AUC for overall outcomes

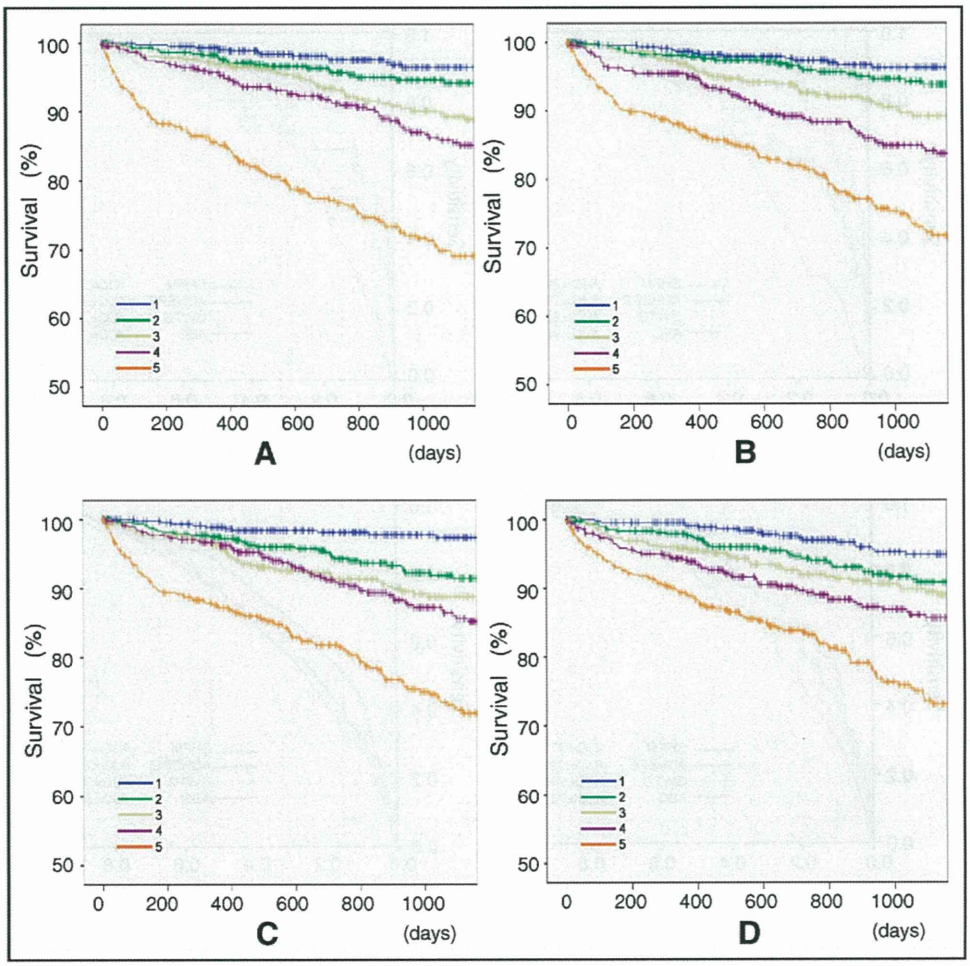

Figure 2. Kaplan-Meier curves for quintiles of risk score models during 2-year period in *(A)* SHFM, *(B)* GWTG-HF, *(C)* ADHERE, and *(D)* ABC.

(p = 0.028 vs ADHERE, p = 0.018 vs GWTG-HF, and p < 0.001 vs ABC), in-hospital death (p = 0.039 vs ADHERE, p = 0.045 vs GWTG-HF, and p < 0.001 vs ABC), and mortality at 2 years (p = 0.040 vs ADHERE, p = 0.042 vs GWTG-HF, and p = 0.018 vs ABC). We noted a significant difference in AUC between the SHFM and ABC for combined mortality at 3 years (p = 0.034 vs ABC). The SHFM also showed a nonsignificant tendency toward greater AUCs for the 30-day and 1-year mortality compared to the other models. Both the ADHERE and GWTG-HF risk scores demonstrated significantly greater AUCs for overall combined end points compared to ABC (ADHERE vs ABC, p <0.001; and GWTG-HF vs ABC, p <0.001). Kaplan-Meier curves for the risk score models categorized by quintiles are shown in Figure 2. All models demonstrated excellent risk stratification.

The predicted survival and observed survival during follow-up are compared in Figure 3. With the SHFM risk score, the predicted survival rate at 30 days and 1 and 2 years was 99.2%, 93.2%, and 87.1%, and the observed survival rate was 99.4%, 94.7%, and 88.7%, respectively. A good correlation between the predicted and observed survival was noted (R^2 = 0.990). Figure 3 shows good calibration of the predicted and observed end point probabilities across deciles of predicted risk using the Hosmer-Lemeshow test at 30 days and 1 and 2 years of follow-up.

Discussion

In the present study, we compared the 4 risk score models for the prediction of mortality in our large cohort of patients with cardiovascular disease. All models were validated using the same data set to ensure a proper comparison. Our results showed that the SHFM was superior to other models in predicting, not only the short-term outcome (e.g., in-hospital mortality), but also the long-term (2-year) and overall follow-up (AUCs of 0.744 to 0.890) outcomes. Thus, the SHFM is an adequate application tool for risk stratification in the general population of patients with cardiovascular disease.

Risk score models are important tools, not only for guiding the treatment plan for the physician, but also for evaluating the cost-effectiveness in public health. Although several models have been developed for this purpose, few studies have compared such models in the ability to predict patient outcomes.[6–8] In addition, these models were mainly derived from clinical trial data, in which a patient population might have been limited because of strict enrollment criteria, resulting in the exclusion of patients with severe conditions, such as liver

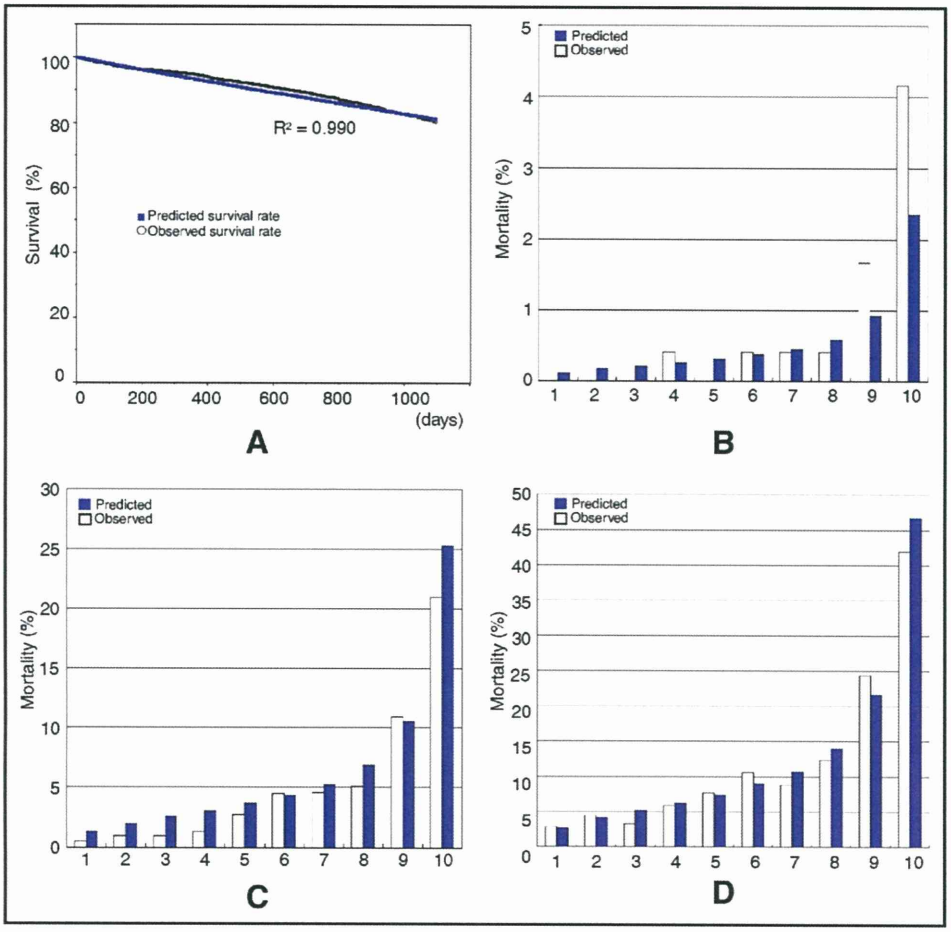

Figure 3. *(A)* Comparison of predicted and observed survival for SHFM. Predicted *(blue)* versus observed *(white)* survival rate at each day plotted during follow-up period of ≤3 years. Calibration plots for composite outcome at *(B)* 30 days and *(C)* 1 and *(D)* 2 years for SHFM. Predicted *(blue)* versus observed *(white)* mortality according to decile of risk shown. Hosmer-Lemeshow chi-square was 7.21 (p = 0.51), 11.15 (p = 0.19), and 5.04 (p = 0.74) at 30 days and 1 and 2 years, respectively.

dysfunction and severe renal insufficiency. The outcome from these models would be different in clinical settings. For application in the "real world," risk models should be validated using a broader patient population. Furthermore, because risk score models require a number of covariates from clinical information, many validation studies usually have a great deal of data missing and have imputed the cohort means for missing values. For example, in the study by May et al,[9] many values were missing for several variables (New York Heart Association 72.1%; lymphocytes 34.7%; uric acid 66.2%; ejection fraction 25.0%; total cholesterol 19.8%), which were estimated using multiple imputations. This could have resulted in an underestimation of the dispersion and led to incorrect inferences. Thus, we included all data to perform a complete case analysis. The present study should be considered as entirely representative of a general patient population with cardiovascular disease.

Several explanations for the superiority of the SHFM can be provided. First, the SHFM has been validated in several databases. The model was originally derived from the Prospective Randomized Amlodipine Survival Evaluation database[10] and validated in 5 other study populations, including patients with a wide age range (14 to 100 years), ejection fraction (1% to 75%), and heart failure severity (New York Heart Association class I to IV).[1] This could explain why the SHFM was the most applicable to the present study population, a broad sample of patients hospitalized for cardiovascular disease. Previous studies of the SHFM have reported that it is a good risk prediction model for patients with severe heart failure,[9,11] including patients who are potential candidates for, or recipients of, a left ventricular assist device.[12–14] Our results indicate that the SHFM is also an adequate risk prediction model in those with milder heart failure or no heart failure. Second, the SHFM risk model requires information about medications and clinical devices. The inclusion of this information could contribute to the better prediction of mortality than clinical characteristics alone, because medications and devices are critically altered by physicians to improve the chances of survival of their patients. Other risk prediction models do not use information pertaining to medications and clinical devices. Third, blood pressure data have a different effect on the SHFM risk score than on the score for the GWTG and ADHERE. In the SHFM, the inclusion of data regarding blood pressure elevation increases the risk score, because hypertension is known to be a common and powerful contributor to all the major cardiovascular diseases.[15,16] In contrast, a lower systolic blood pressure actually increases the risk score in the GWTG and ADHERE, consistent with the finding that lower systolic blood pressure at admission correlated significantly with greater mortality from acute congestive heart failure.[17,18] Both models were devel-

oped to predict the short-term outcome in patients with acute heart failure and greater in-hospital mortality (ADHERE, 4.0%; GWTG, 2.9%; the present study, 1.1%) and provided adequate risk stratification for in-hospital mortality.[2,3] Nevertheless, the SHFM was significantly better in predicting in-hospital mortality than the GWTG, despite the greater AUC of the GWTG score for in-hospital mortality in our study than in the original study (0.81 vs 0.75, respectively).[3] The AUC of the ADHERE was not reported in the original study.[2] In contrast, the ABC score model did not provide accurate predictions in the present study, although the elevation of blood pressure increases the risk scores for both the ABC and the SHFM. The different patient populations, including the older age range (73.6 ± 3 years) and female predominance (53.1%) in the ABC population, might explain the apparent discrepancies.

Several limitations should be mentioned for the present study. First, the risk score we calculated used the data obtained on the initial admission to our hospital. During a long follow-up period, the risk score should be recalculated after changes in clinical status or medications and devices. Nonetheless, our results indicate that a SHFM score calculated at the initial hospitalization was accurate in predicting the mortality in patients with cardiovascular disease. Second, the present study shares the limitations of all observational nonrandomized studies; however, it was a wide-ranging study and diligent in patient ascertainment. Third, it is possible that our findings might not be applicable to other settings, because the SHFM risk score was created using a United States population. Even in the original study of the SHFM, the question was raised about the need to recalibrate for different ethnic populations. However, the present study has demonstrated the SHFM is an excellent predictive model in the Japanese population, as well as in the United States. Fourth, we did not study all risk score models. For example, the Heart Failure Survival Score is a clinical prognostic model derived and validated in 2 cohorts of patients with a mean age of >75 years.[19] However, the Heart Failure Survival Score requires a peak oxygen consumption value, which, although a good index for predicting the prognosis, is not applicable to all patients with cardiovascular disease, particularly for patients for whom heart failure is not a factor. In fact, oxygen consumption data were available for <5% of the patients in our study. Therefore, because of the lack of easily obtainable oxygen consumption information, we did not evaluate the Heart Failure Survival Score risk model. Likewise, in the present study, we did not include the Enhanced Feedback for Effective Cardiac Treatment model,[20] because of the large amount of missing data for the respiratory rate. This was the case, not only for low-risk patients, but also for high-risk patients, at our institution. Although we could impute a respiratory rate of <20 for almost all low-risk patients, the calculated risk score might not be accurate if we had imputed a speculative respiratory rate for the high-risk patients. This point needs to be examined in a future study.

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Prognostic Impact of Myocardial Interstitial Fibrosis in Non-Ischemic Heart Failure

– Comparison Between Preserved and Reduced Ejection Fraction Heart Failure –

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Prognostic Impact of Myocardial Interstitial Fibrosis in Non-Ischemic Heart Failure

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Background: Although myocardial fibrosis plays an important role in the progression of heart failure (HF), its prognostic impact still remains to be clarified.

Methods and Results: A total of 172 consecutive patients with chronic HF, who underwent cardiac catheterization and endomyocardial biopsy between January 2001 and September 2008, were examined. They were divided into 2 groups: HF with preserved ejection fraction (HFPEF; left ventricular ejection fraction [LVEF] ≥50%, n=81); and HF with reduced LVEF (HFREF; LVEF <50%, n=91). The collagen volume fraction (CVF) in biopsy samples was calculated and its prognostic impact examined. Mean follow-up in the HFPEF and the HFREF groups was 41±33 months and 41±26 months, respectively. Although CVF was similar between the 2 groups (1.83±1.54% vs. 2.07±2.35%), CVF was significantly correlated with LV end-diastolic pressure in the HFREF group but not in the HFPEF group. When HF stage was adjusted, the long-term prognosis was comparable between the 2 groups. When the patients were divided into 2 groups according to median CVF, however, severe fibrosis was a significant predictor for all-cause death (P=0.014) and cardiac events (P=0.02) in the HFREF, but not in the HFPEF group.

Conclusions: Myocardial fibrosis evaluated on biopsy samples is a useful indicator for long-term survival, suggesting that it may be an important therapeutic target as well. (*Circ J* 2011; **75**: 2605–2613)

Key Words: Collagen volume fraction; Ejection fraction; Fibrosis; Heart failure; Prognosis

Myocardial extracellular matrix (ECM) plays an important role in maintaining the structure of myocytes and blood vessels to strengthen myocardial tissue.[1,2] Myocardial collagen is the major constituent of ECM, and myocardial collagen volume is an important determinant of ventricular remodeling that affects ventricular functions.[3] It has previously been demonstrated that myocardial collagen content is correlated with left ventricular (LV) stiffness in patients with heart failure (HF),[4,5] and that the extent of myocardial collagen is correlated with a reduction in LV ejection fraction (LVEF) and is involved in the process of LV dilatation and progression of HF.[6,7] Furthermore, the presence of excessive collagen fibers may induce fatal ventricular arrhythmia.[8] Thus, it is important to estimate the extent of myocardial interstitial fibrosis in order to determine prognosis in HF patients.

Cardiovascular magnetic resonance imaging (MRI) is a useful tool to evaluate myocardial fibrosis that can be used to estimate the prognosis of HF patients by evaluation of LV midwall fibrosis using late gadolinium enhancement.[9] Indeed, MRI can detect and quantify regional myocardial fibrosis in a ventricle but not diffuse myocardial fibrosis.[10] Although serum levels of collagen synthesis markers (eg, procollagen type III amino-terminal peptide, PIIINP) may be useful to estimate the prognosis of HF patients,[11–13] those markers may reflect systemic fibrosis.[14,15] Indeed, little is known about the relationship between the prognosis of HF patients and the extent of myocardial fibrosis calculated directly from biopsy specimens in HF patients. In the present study, we thus examined whether collagen volume fraction (CVF) obtained from LV endomyocardial biopsy samples has a prognostic impact in HF patients with or without systolic dysfunction.

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