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

References

[1] National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39(Suppl. 1):S1–266.

[2] Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS. Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038–47.

[3] Imai E, Horio M, Watanabe T, Iseki K, Yamagata K, Hara S, Ura N, Kiyohara Y, Moriyama T, Ando Y, Fujimoto S, Konta T, Yokoyama H, Makino H, Hishida A, et al. Prevalence of chronic kidney disease in the Japanese general population. Clin Exp Nephrol 2009;13:621–30.

[4] Stevens PE, O'Donoghue DJ, de Lusignan S, Van Vlymen J, Klebe B, Middleton R, Hague N, New J, Farmer CK. Chronic kidney disease management in the United Kingdom: NEOERICA project results. Kidney Int 2007;72:92–9.

[5] Chadban SJ, Briganti EM, Kerr PG, Dunstan DW, Welborn TA, Zimmet PZ, Atkins RC. Prevalence of kidney damage in Australian adults: the AusDiab kidney study. J Am soc Nephrol 2003;14(Suppl. 2):S131–8.

[6] Chronic kidney disease identified in the claims data. 2009 Annual Data Report, United States Renal Data System. Available at http://www.usrds.org/.

[7] Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004;164:659–63.

[8] Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension 2003;42:1050–65.

[9] American Heart Association. Heart Disease and Stroke Statistics – 2005 Update. Dallas, TX: American Heart Association; 2005.

[10] The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008. Eur Heart J 2008;29:2388–442.

[11] Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW. 2009 focused update incorporated into the ACC/AHA 2005 Guidelines for the Diagnosis and Management of Heart Failure in Adults A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines Developed in Collaboration With the International Society for Heart and Lung Transplantation. J Am Coll Cardiol 2009;53:e1–90.

[12] Stewart S, Jenkins A, Buchan S, McGuire A, Capewell S, McMurray JJ. The current cost of heart failure to the National Health Service in the UK. Eur J Heart Fail 2002;4:361–71.

[13] Poole-Wilson PA. History, definition and classification of heart failure. Heart failure 1. New York: Churchill Livingstone; 1997. p. 269–77.

[14] Shulman NB, Ford CE, Hall WD, Blaufox MD, Simon D, Langford HG, Schneider KA. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function: results from the Hypertension Detection And Follow-Up Program Cooperative Group. Hypertension 1989;13(Suppl.):I80–93.

[15] Cheung AK, Sarnak MJ, Yan G, Berkoben M, Heyka R, Kaufman A, Lewis J, Rocco M, Toto R, Windus D, Ornt D, Levey AS. Cardiac diseases in maintenance hemodialysis patients: results of the HEMO Study. Kidney Int 2004;65:2380–9.

[16] Kottgen A, Russell SD, Loehr LR, Crainiceanu CM, Rosamond WD, Chang PP, Chambless LE, Coresh J. Reduced kidney function as a risk factor for incident heart failure: the Atherosclerosis Risk in Communities (ARIC) study. J Am Soc Nephrol 2007;18:1307–15.

[17] Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. J Am Coll Cardiol 2000;35:681–9.

[18] Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000;102:203–10.

[19] Mahon NG, Blackstone EH, Francis GS, Starling III RC, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. J Am Coll Cardiol 2002;40:1106–13.

[20] McClellan WM, Flanders WD, Langston RD, Jurkovitz C, Presley R. Anemia and renal insufficiency are independent risk factors for death among patients with congestive heart failure admitted to community hospital: a population-based study. J Am Soc Nephrol 2002;13:1928–36.

[21] Kearney MT, Fox KA, Lee AJ, Prescott RJ, Shah AM, Batin PD, Baig W, Lindsay S, Callahan TS, Shell WE, Eckberg DL, Zaman AG, Williams S, Neilson JM, Nolan J. Predicting death due to progressive heart failure in patients with mild-to-moderate chronic heart failure. J Am Coll Cardiol 2002;40:1801–8.

[22] Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, Granger CB, Michelson EL, Ostergren J, Cornel JH, de Zeeuw D, Pocock S, van Veldhuisen DJ. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation 2006;113:671–8.

[23] Go AS, Yang J, Ackerson LM, Lepper K, Robbins S, Massie BM, Shlipak MG. Hemoglobin level, chronic kidney disease, and the risks of death and hospitalization in adults with chronic heart failure. The Anemia in Chronic Heart Failure: Outcomes and Resource Utilization (ANCHOR) Study. Circulation 2006;113:2713–23.

[24] Shiba N, Matsuki M, Takahashi J, Tada T, Watanabe J, Shimokawa H. Prognostic importance of chronic kidney disease in Japanese patients with chronic heart failure. Circ J 2008;72:173–8.

[25] Hamaguchi S, Tsuchihashi-Makaya M, Kinugawa S, Yokota T, Ide T, Takeshita A, Tsutsui H, The JCARE-CARD Investigators. Chronic kidney disease as an independent risk for long-term adverse outcomes in patients hospitalized with heart failure in Japan. Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). Circ J 2009;73:1442–7.

[26] Ahmed A, Rich MW, Sanders PW, Perry GJ, Bakris GL, Zile MR, Love TE, Aban IB, Shlipak MG. Chronic kidney disease associated mortality in diastolic versus systolic heart failure: a propensity matched study. Am J Cardiol 2007;99:393–8.

[27] Bhatia RS, Tu JV, Lee DS, Austin PC, Fang J, Haouzi A, Gong Y, Liu PP. Outcome of heart failure with preserved ejection fraction in a population-based study. N Engl J Med 2006;355:260–9.

[28] Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, Yancy CW, Califf RM, Stevenson LW, Hill JA. Cardiorenal interactions-insights from the ESCAPE trial. J Am Coll Cardiol 2008;51:1268–74.

[29] Liang KV, Williams AW, Greene EL, Redfield MM. Acute decompensated heart failure and the cardiorenal syndrome. Crit Care Med 2008;36:S75–88.

[30] Adams Jr KF, Fonarow GC, Emerman CL, LeJemtel TH, Costanzo MR, Abraham WT, Berkowitz RL, Galvao M, Horton DP, ADHERE Scientific Advisory Committee and Investigators. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the acute decompensated heart failure national registry (ADHERE). Am Heart J 2005;149:209–16.

[31] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. OPTIMIZE-HF Investigators and Hospitals. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF registry. J Am Coll Cardiol 2007;50:768–77.

[32] Takagi A, Iwama Y, Yamada A, Aihara K, Daida H. Estimated glomerular filtration rate is an independent predictor for mortality of patients with acute heart failure. J Cardiol 2010;55:317–21.

[33] Tang WHW, Mullens W. Cardiorenal syndrome in decompensated heart failure. Heart 2010;96:255–60.

[34] Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol 2008;52:1527–39.

[35] McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, Tse TF, Wasserman B, Leiserowitz M. The prevalence of anemia in patients with chronic kidney disease. Curr Med Res Opin 2004;20:1501–10.

[36] Anker SD, Negassa A, Coats AJ, Afzal R, Poole-Wilson PA, Cohn JN, Yusuf S. Prognostic importance of weight loss in chronic heart failure and the effect of treatment with angiotensin-converting-enzyme inhibitors: an observational study. Lancet 2003;361:1077–83.

[37] Weiss G. Pathogenesis and treatment of anaemia of chronic disease. Blood Rev 2002;16:87–96.

[38] Maggioni AP, Anand I, Gottlieb SO, Latini R, Tognoni G, Cohn JN, Val-HeFT Investigators (Valsartan Heart Failure Trial). Effects of valsartan on morbidity and mortality in patients with heart failure not receiving angiotensin-converting enzyme inhibitors. J Am Coll Cardiol 2002;40:1414–21.

[39] Silverberg DS, Wexler D, Blum M, Keren G, Sheps D, Leibovitch E, Brosh D, Laniado S, Schwartz D, Yachnin T, Shapira I, Gavish D, Baruch R, Koifman B, Kaplan C, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. J Am Coll Cardiol 2000;35:1737–44.

[40] Kazory A, Ross EA. Anemia: the point of convergence or divergence for kidney disease and heart failure. J Am Coll Cardiol 2009;53:639–47.

[41] Herrlin B, Nyquist O, Sylven C. Induction of a reduction in haemoglobin concentration by enalapril in stable, moderate heart failure: a double blind study. Br Heart J 1991;66:199–205.

[42] Pappas KD, Gouva CD, Katopodis KP, Nikolopoulos PM, Korantzopoulos PG, Michalis LK, Goudevenos JA, Siamopoulos KC. Correction of anemia with erythropoietin in chronic kidney disease (stage 3 and 4): effects on cardiac performance. Cardiovasc Drugs Ther 2008;22:37–44.

[43] Singh AK, Szczech L, Tang KL, Barnhart H, Sapp S, Wolfson M, Reddan D, CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. N Engl J Med 2006;355:2085–98.

[44] Drüeke TB, Locatelli F, Clyne N, Eckardt KU, Macdougall IC, Tsakiris D, Burger HU, Scherhag A, CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. N Engl J Med 2006;355:2071–84.

[45] Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, de Zeeuw D, Eckardt KU, Feyzi JM, Ivanovich P, Kewalramani R, Levey AS, Lewis EF, McGill JB, McMurray JJ, Parfrey P, Parving HH, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009;361:2019–32.

[46] Silverberg DS, Wexler D, Sheps D, Blum M, Keren G, Baruch R, Schwartz D, Yachnin T, Steinbruch S, Shapira I, Laniado S, Iaina A. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol 2001;37:1775–80.

[47] Palazzuoli A, Silverberg D, Iovine F, Capobianco S, Giannotti G, Calabrò A, Campagna SM, Nuti R. Erythropoietin improves anemia exercise tolerance and renal function and reduces B-type natriuretic peptide and hospitalization in patients with heart failure and anemia. Am Heart J 2006;152, 1096.e9–1096.15.

[48] Ghali JK, Anand IS, Abraham WT, Fonarow GC, Greenberg B, Krum H, Massie BM, Wasserman SM, Trotman ML, Sun Y, Knusel B, Armstrong P, Study of Anemia in Heart Failure Trial (STAMINA-HeFT) Group. Randomized double-blind trial of darbopoetin alfa in patients with symptomatic heart failure and anemia. Circulation 2008;117:526–35.

[49] McMurray JJ, Anand IS, Diaz R, Maggioni AP, O'Connor C, Pfeffer MA, Polu KR, Solomon SD, Sun Y, Swedberg K, Tendera M, van Veldhuisen DJ, Wasserman SM, Young JB, RED-HF Committees and Investigators. Design of the Reduction of Events with Darbepoetin alfa in Heart Failure (RED-HF): a Phase III, anaemia correction, morbidity-mortality trial. Eur J Heart Fail 2009;11:795–801.

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.

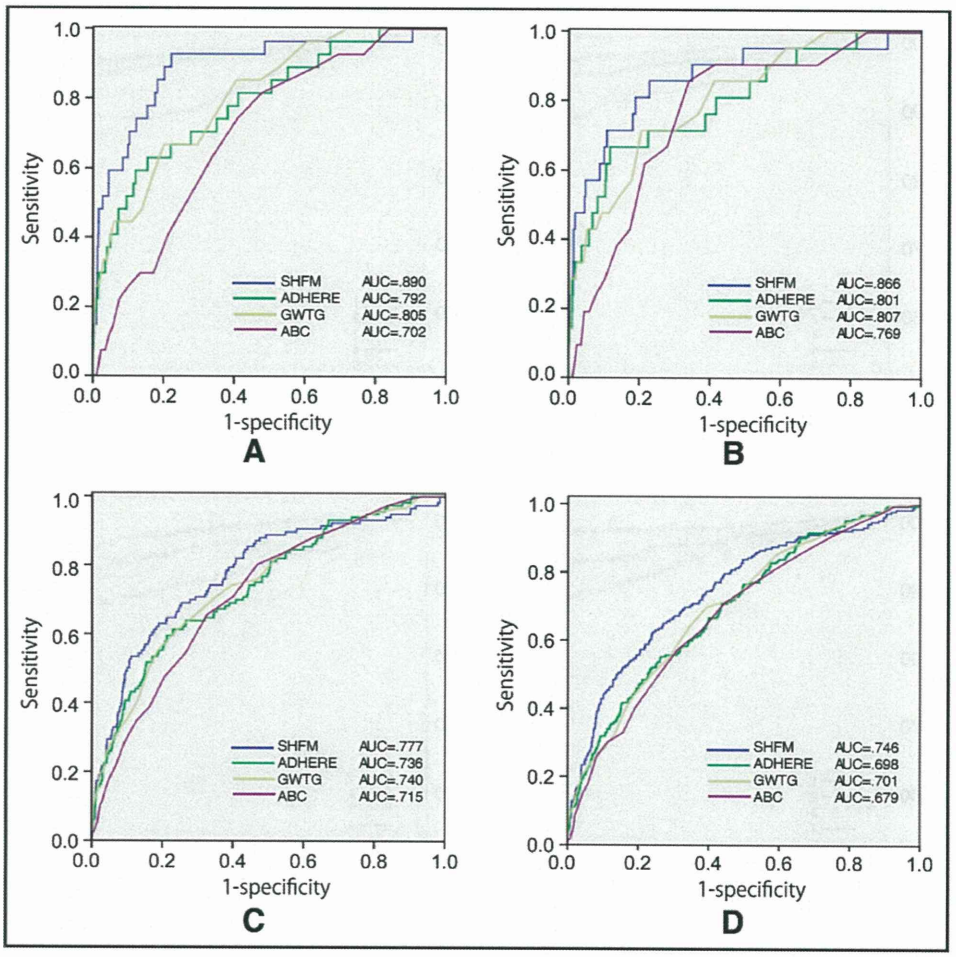

Figure 1. AUCs for combined end point of death, heart transplantation, or left ventricular assist device (LVAD) implantation for SHFM, ADHERE, GWTG-HF, and ABC, for *(A)* in-hospital death, and combined end points at *(B)* 30 days and *(C)* 1- and *(D)* 2 years of follow-up.

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

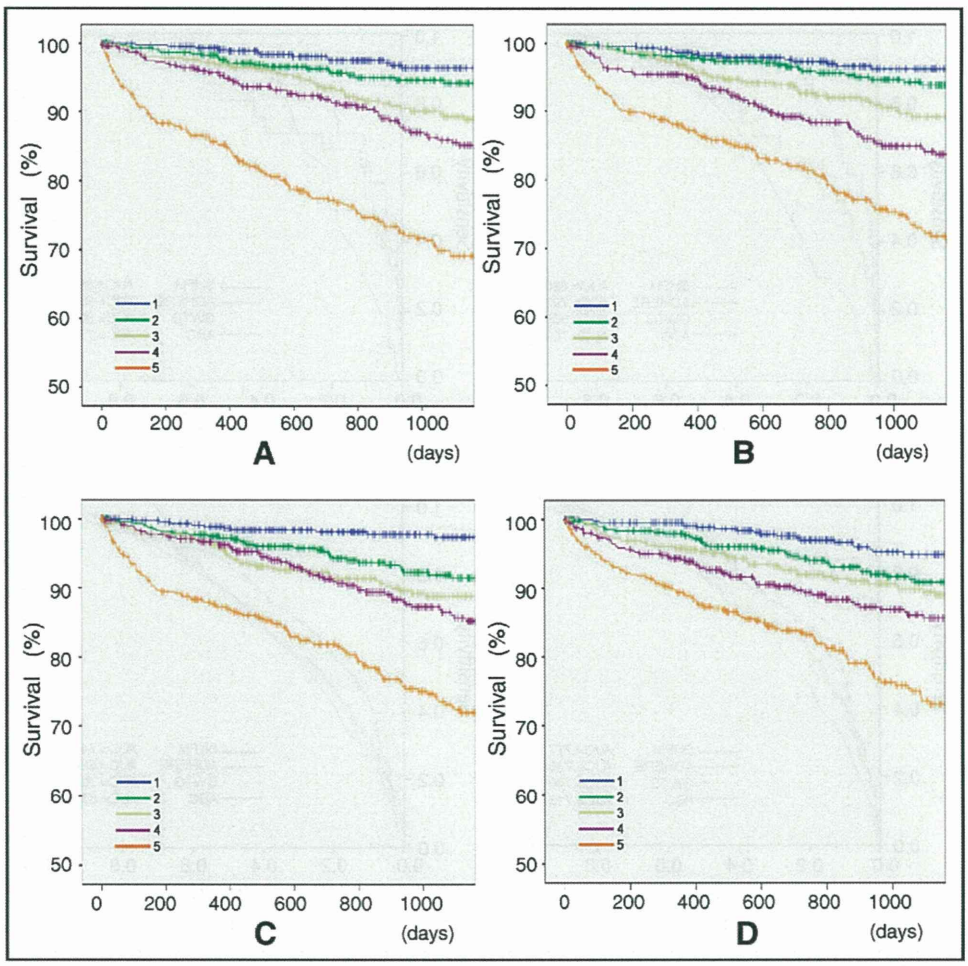

Figure 2. Kaplan-Meier curves for quintiles of risk score models during 2-year period in *(A)* SHFM, *(B)* GWTG-HF, *(C)* ADHERE, and *(D)* ABC.

(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

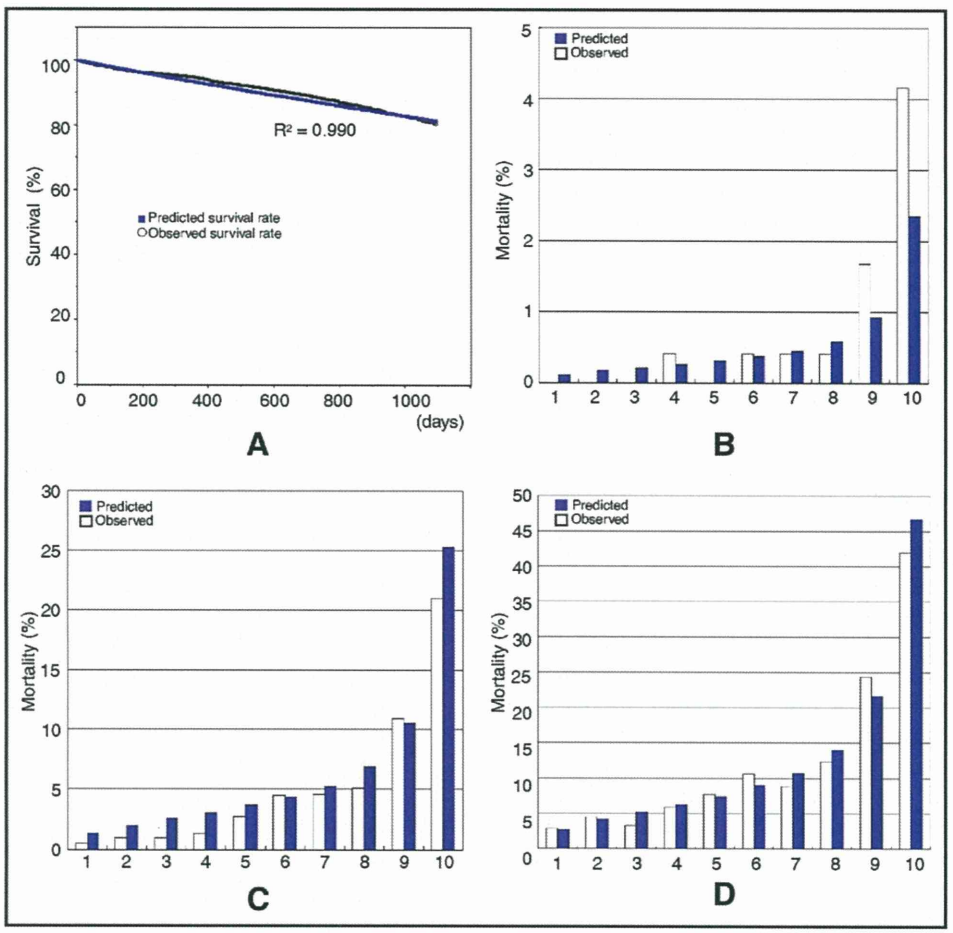

Figure 3. *(A)* Comparison of predicted and observed survival for SHFM. Predicted *(blue)* versus observed *(white)* survival rate at each day plotted during follow-up period of ≤3 years. Calibration plots for composite outcome at *(B)* 30 days and *(C)* 1 and *(D)* 2 years for SHFM. Predicted *(blue)* 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.

1. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, Anand I, Maggioni A, Burton P, Sullivan MD, Pitt B, Poole-Wilson PA, Mann DL, Packer M. The Seattle Heart Failure Model: prediction of survival in heart failure. *Circulation* 2006;113:1424–1433.
2. Fonarow GC, Adams KF, Jr., Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. *JAMA* 2005;293:572–580.
3. Peterson PN, Rumsfeld JS, Liang L, Albert NM, Hernandez AF, Peterson ED, Fonarow GC, Masoudi FA. A validated risk score for in-hospital mortality in patients with heart failure from the American Heart Association Get With The Guidelines program. *Circ Cardiovasc Qual Outcomes* 2010;3:25–32.
4. Butler J, Kalogeropoulos A, Georgiopoulou V, Belue R, Rodondi N, Garcia M, Bauer DC, Satterfield S, Smith AL, Vaccarino V, Newman AB, Harris TB, Wilson PW, Kritchevsky SB. Incident heart failure prediction in the elderly: the health ABC heart failure score. *Circ Heart Fail* 2008;1:125–133.
5. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology* 1983;148:839–843.
6. Scheltens T, Verschuren WM, Boshuizen HC, Hoes AW, Zuithoff NP, Bots ML, Grobbee DE. Estimation of cardiovascular risk: a comparison between the Framingham and the SCORE model in people under 60 years of age. *Eur J Cardiovasc Prev Rehabil* 2008;15:562–566.
7. Nutter AL, Tanawuttiwat T, Silver MA. Evaluation of 6 prognostic models used to calculate mortality rates in elderly heart failure patients with a fatal heart failure admission. *Congest Heart Fail* 2010;16:196–201.
8. Pilotto A, Addante F, Franceschi M, Leandro G, Rengo G, D'Ambrosio P, Longo MG, Rengo F, Pellegrini F, Dallapiccola B, Ferrucci L. Multidimensional Prognostic Index based on a comprehensive geriatric assessment predicts short-term mortality in older patients with heart failure. *Circ Heart Fail* 2010;3:14–20.
9. May HT, Horne BD, Levy WC, Kfoury AG, Rasmusson KD, Linker DT, Mozaffarian D, Anderson JL, Renlund DG. Validation of the Seattle Heart Failure Model in a community-based heart failure population and enhancement by adding B-type natriuretic peptide. *Am J Cardiol* 2007;100:697–700.
10. Packer M, O'Connor CM, Ghali JK, Pressler ML, Carson PE, Belkin RN, Miller AB, Neuberg GW, Frid D, Wertheimer JH, Cropp AB, DeMets DL. Effect of amlodipine on morbidity and mortality in severe chronic heart failure. Prospective Randomized Amlodipine Survival Evaluation Study Group. *N Engl J Med* 1996;335:1107–1114.
11. Kalogeropoulos AP, Georgiopoulou VV, Giamouzis G, Smith AL, Agha SA, Waheed S, Laskar S, Puskas J, Dunbar S, Vega D, Levy WC, Butler J. Utility of the Seattle Heart Failure Model in patients with advanced heart failure. *J Am Coll Cardiol* 2009;53:334–342.
12. Levy WC, Mozaffarian D, Linker DT, Farrar DJ, Miller LW. Can the Seattle Heart Failure Model be used to risk-stratify heart failure patients for potential left ventricular assist device therapy? *J Heart Lung Transplant* 2009;28:231–236.
13. Schaffer JM, Allen JG, Weiss ES, Patel ND, Russell SD, Shah AS, Conte JV. Evaluation of risk indices in continuous-flow left ventricular assist device patients. *Ann Thorac Surg* 2009;88:1889–1896.
14. Ketchum ES, Moorman AJ, Fishbein DP, Mokadam NA, Verrier ED, Aldea GS, Andrus S, Kenyon KW, Levy WC. Predictive value of the Seattle Heart Failure Model in patients undergoing left ventricular assist device placement. *J Heart Lung Transplant* 2010;29:1021–1025.
15. Vasan RS, Larson MG, Leip EP, Evans JC, O'Donnell CJ, Kannel WB, Levy D. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001;345:1291–1297.
16. Kannel WB, Wolf PA. Framingham Study insights on the hazards of elevated blood pressure. *JAMA* 2008:300:2545–2547.
17. Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole-Wilson PA, Sutton GC. Survival of patients with a new diagnosis of heart failure: a population based study. *Heart* 2000;83:505–510.
18. Gheorghiade M, Abraham WT, Albert NM, Greenberg BH, O'Connor CM, She L, Stough WG, Yancy CW, Young JB, Fonarow GC. Systolic blood pressure at admission, clinical characteristics, and outcomes in patients hospitalized with acute heart failure. *JAMA* 2006;296:2217–2226.
19. Zugck C, Kruger C, Kell R, Korber S, Schellberg D, Kubler W, Haass M. Risk stratification in middle-aged patients with congestive heart failure: prospective comparison of the Heart Failure Survival Score (HFSS) and a simplified two-variable model. *Eur J Heart Fail* 2001;3:577–585.
20. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. *JAMA* 2003;290:2581–2587.

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

– Comparison Between Preserved and Reduced Ejection Fraction Heart Failure –

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ORIGINAL ARTICLE
Heart Failure

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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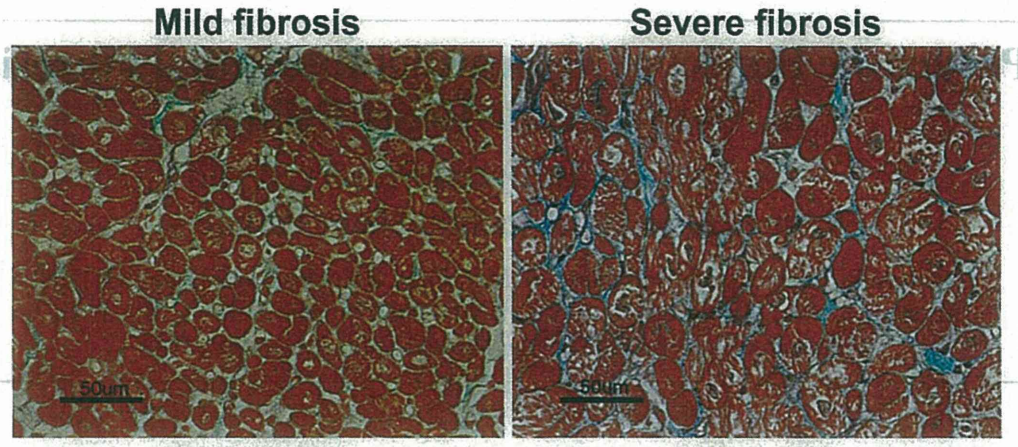

Figure 1. Representative histology of the (**Left**) mild and (**Right**) severe fibrosis groups. Myocardial fibrosis, stained in blue by Elastica–Masson staining. CVF, collagen volume fraction. Scale bar, 50 μm.

Methods

The ethics committees of Tohoku University Hospital approved the study protocol and all patients provided written informed consent.

Subjects

We examined 172 consecutive patients with chronic HF enrolled in the Tohoku University Hospital database, and who underwent cardiac catheterization and endomyocardial biopsy to determine the etiology of HF between January 2001 and September 2008. We performed endomyocardial biopsy in all HF patients with suspected cardiomyopathy but we did not perform the procedure in those who had apparent ischemic or valvular heart disease documented on echocardiography and/or cardiac catheterization.

For each patient, we collected clinical, hemodynamic, biochemistry and prognostic data and analyzed endomyocardial biopsy samples.

Definition of HF

In the present study, we included patients in stage B, C and D, according to the chronic HF ACC/AHA 2005 guidelines. According to the ESC 2007 HF guideline, we also divided them into 2 groups: HF with preserved ejection fraction (HFPEF; LVEF ≥50%, n=81) and HF with reduced LVEF (HFREF; LVEF <50%, n=91).

Data Collection

Baseline demographic data, hemodynamic data obtained via catheterization, stage of HF, medications and comorbidities (hypertension, diabetes mellitus, hyperlipidemia, and atrial fibrillation) were obtained based on medical records. The hemodynamic parameters measured via cardiac catheterization included LVEF, LV end-diastolic volume index (LVEDVI), mean aortic pressure, LV end-diastolic pressure (LVEDP), mean pulmonary artery pressure, pulmonary capillary wedge pressure (PCWP) and cardiac index. Before cardiac catheterization, we measured serum levels of hemoglobin, brain natriuretic peptide (BNP), creatinine and high-sensitivity C-reactive protein and estimated creatinine clearance using the Cockroft-Gault formula.

The primary endpoints included all-cause death, and the secondary combined endpoints included cardiovascular death, sudden death and admission for worsening of HF. Follow-up data were obtained from the database.

Quantitative Morphometry of Biopsy Samples

Trans-venous endomyocardial biopsy samples were obtained from the interventricular septum using 6-Fr Biotom (Cordis, Bridgewater, NJ, USA). There were no major complications related to the procedures during the study period. The tissues were immediately fixed in 10% buffered formalin and embedded in paraffin. Tissue sections were stained with hematoxylin–eosin and Elastica–Masson. Images of these sections were acquired with a projection microscope (×400; **Figure 1**). Subsequent image analysis was performed using Macscope 2.5 (Mitani, Fukui, Japan) to determine cardiomyocyte diameter and extent of myocardial interstitial fibrosis, which was expressed as CVF (%). CVF was calculated as the sum of all connective tissue areas divided by the sum of all connective tissue and muscle areas averaged over 2–5 representative fields of the section (mean, 3.6±0.9 fields), where there was no endocardium or blood vessel.[16,17] Myocardial diameter was determined at the nucleus level in 8–15 representative cardiomyocytes (mean, 12.0±2.5 fields) per section, where we also counted the number of inflammatory mononuclear cells in the same fields (mean, 6.0±1.8). This histological evaluation was performed by a well-trained cardiologist without knowledge of which patient provided the tissue sections.

We divided both the HFPEF and HFREF groups into 2 groups using median CVF (HFPEF and HFREF, 1.36% and 1.34%, respectively). We defined mild and severe fibrosis as CVF smaller and greater than the median, respectively (**Figure 1**).

Statistical Analysis

Continuous variables are expressed as mean±SD. Comparisons between 2 groups were conducted using unpaired t-test for continuous variables and chi-squared test for categorical

Table 1. Baseline Subject Characteristics

	HFPEF (n=81)	HFREF (n=91)	P value
Age (years)	54.3±14.1	55.9±12.8	0.429
BMI (kg/m²)	23.4±4.5	23.9±4.2	0.408
Male	54 (67)	66 (73)	0.404
Hypertension	34 (42)	39 (43)	0.962
Diabetes mellitus	9 (11)	13 (14)	0.533
Dyslipidemia	21 (26)	21 (23)	0.631
Sinus rhythm	69 (85)	65 (71)	0.028*
Medication			
ACEI	36 (44)	57 (63)	0.017*
ARB	15 (19)	35 (38)	0.004*
β-blocker	39 (48)	66 (73)	0.001*
Diuretics	13 (16)	41 (45)	<0.001*
Spironolactone	10 (12)	31 (34)	0.001*
Warfarin	12 (15)	46 (51)	<0.001*
Digitalis	7 (9)	28 (31)	<0.001*
CCB	26 (32)	11 (12)	0.001*
Antiplatelet	13 (16)	27 (30)	0.033*
Statin	7 (9)	17 (19)	0.054
Amiodarone	5 (6)	8 (9)	0.514
Stage of heart failure			<0.001*
B	40 (49)	15 (16)	
C	39 (48)	68 (75)	
D	2 (2)	8 (9)	
Laboratory data			
Hemoglobin (g/dl)	13.8±2.0	14.1±1.8	0.277
hsCRP (mg/dl)	0.21±0.46	0.33±0.93	0.294
BNP (pg/ml)	248±342	367±491	0.089
LDL (mg/dl)	110±41	121±39	0.103
HDL (mg/dl)	54.9±24.0	45.1±12.8	0.001*
TG (mg/dl)	131±98	137±75	0.669
Glucose (mg/dl)	106±37	106±21	0.934
CCr (ml/min)	90.1±25.1	88.2±35.4	0.694
Hemodynamic data			
LVEDVI (ml/m²)	75.7±20.4	114.5±35.1	<0.001*
EF (%)	67.8±11.3	35.6±11.0	<0.001*
mAoP (mmHg)	96±15	90±17	0.023*
LVEDP (mmHg)	14±6	13±7	0.420
mPAP (mmHg)	16.7±4.8	19.9±7.7	0.002*
PCWP (mmHg)	9.5±4.2	11.2±6.5	0.050
Cardiac index ($L \cdot min^{-1} \cdot m^{-2}$)	2.9±0.7	2.6±0.7	0.021*
Morphometric data			
CVF (%)	1.83±1.54	2.07±2.35	0.440
MyD (μm)	19.2±3.2	19.7±2.8	0.362
Inflammatory cell (/field)	4.9±4.9	7.0±6.0	0.015*
All-cause death	0 (0)	9 (10)	0.004*
Cardiac events	4 (5)	15 (16)	0.016*
Cardiac or sudden death	0 (0)	4 (4)	
Admission for HF	4 (5)	11 (12)	

Data given as mean±SD or n (%). *P<0.05, HFPEF vs. HFREF.
HFPEF, heart failure patients with preserved left ventricular ejection fraction; HFREF, heart failure patients with reduced left ventricular ejection fraction; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium cannel blocker; hsCRP, high-sensitivity C-reactive protein; BNP, brain natriuretic peptide; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CCr, creatinine clearance; LVEDVI, left ventricular end-diastolic volume index; EF, ejection fraction; mAoP, mean aortic pressure; LVEDP, left ventricular end-diastolic pressure; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CVF, collagen volume fraction; MyD, cardiomyocyte diameter; HF, heart failure.

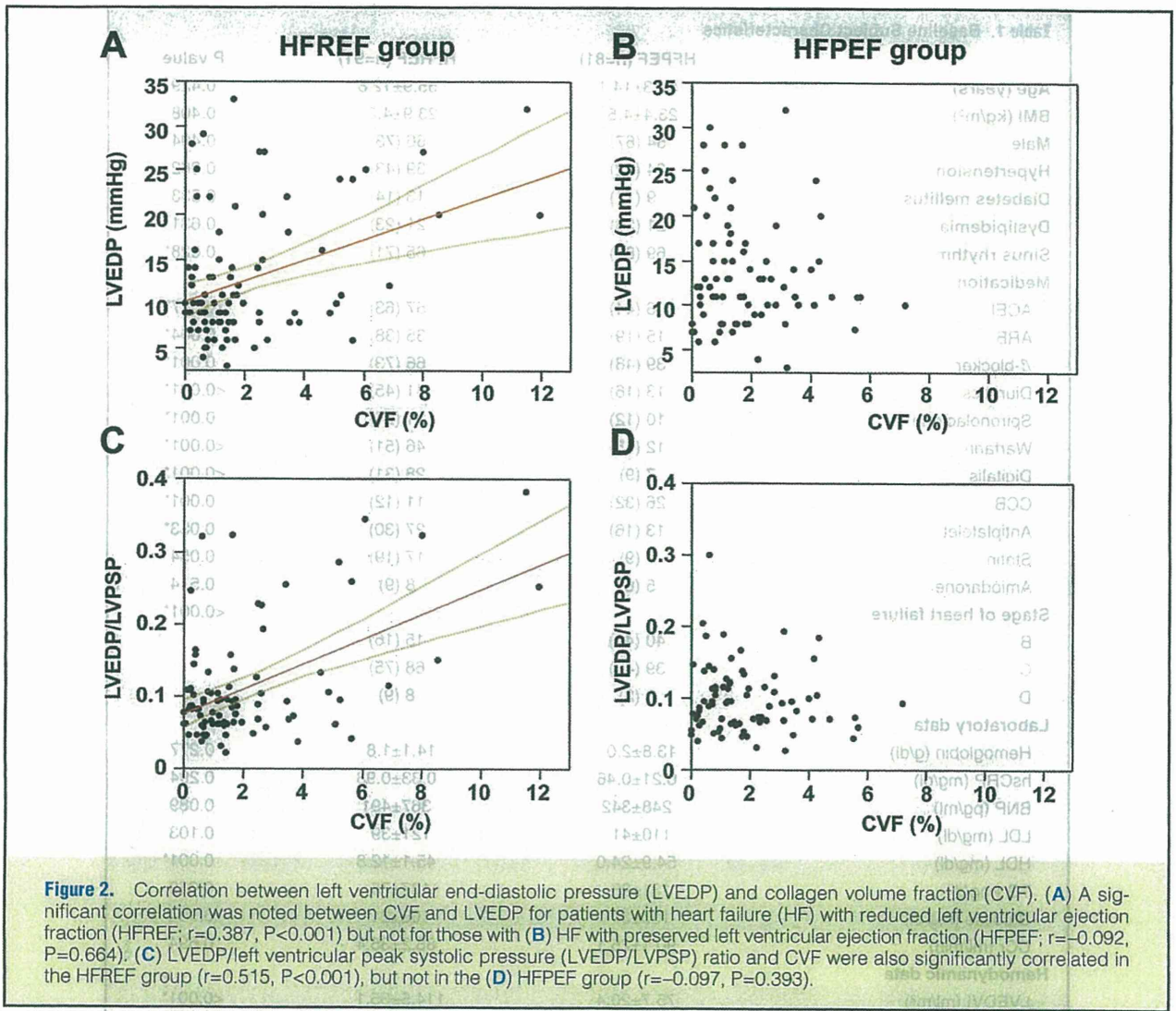

Figure 2. Correlation between left ventricular end-diastolic pressure (LVEDP) and collagen volume fraction (CVF). (**A**) A significant correlation was noted between CVF and LVEDP for patients with heart failure (HF) with reduced left ventricular ejection fraction (HFREF; r=0.387, P<0.001) but not for those with (**B**) HF with preserved left ventricular ejection fraction (HFPEF; r=–0.092, P=0.664). (**C**) LVEDP/left ventricular peak systolic pressure (LVEDP/LVPSP) ratio and CVF were also significantly correlated in the HFREF group (r=0.515, P<0.001), but not in the (**D**) HFPEF group (r=–0.097, P=0.393).

variables. For echocardiographic comparison before and after medical treatment, paired t-test was used. Five-year survival free from all-cause death and that from cardiac events was estimated using the Kaplan-Meier method. We used Cox proportional hazards model to adjust covariates. After comparison of covariates between the mild and severe fibrosis groups, the covariates with P<0.05 were used in the final multivariate models. Furthermore, we evaluated the prognostic value of CVF as a continuous variable. We used the variables with P<0.05 on univariate analysis in the final multivariate models, in which age, cardiac index, LV filling pressure, and stage of HF were controlled for, and we chose the parameters for final models using the step-up method. In these analyses, we used PCWP as a parameter of LV filling pressure, because LVEDP data were lacking in 3 cases. Furthermore, as previously reported,[18] we tested the proportionality assumptions of each parameter of the final models, with P<0.05 indicating non-proportionality. All statistical analysis was performed using JMP 7.0.2 (SAS Institute, Cary, NC, USA) and R 2.8.1(www.r-project.org/). All P-values were 2-sided, and P<0.05 was considered to be statistically significant.

Results

HFPEF Group vs. HFREF Group

All patients were successfully followed up in the present study. Mean follow-up period in the HFPEF and the HFREF groups was 41±33 months and 41±26 months, respectively. The HFREF group was characterized by more advanced stage of HF (**Table 1**). There were more all-cause deaths and cardiac events in the HFREF group than in the HFPEF group (**Table 1**). Five-year prognosis was significantly lower in the HFREF group than in the HFPEF group, in terms of survival from all-cause death (P=0.006) and survival from cardiac events (P=0.034). After the adjustment of HF stage of HF, however, there was no significant difference in cardiac events between the 2 groups.

The prevalence of the use of medications for HF at cardiac catheterization, including angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), β-blockers, diuretics, spironolactone and digitalis, was significantly higher in the HFREF than in the HFPEF group (**Table 1**). In contrast, the use of calcium cannel blockers (CCB) was more common in the HFPEF group (**Table 1**). The HFREF group had significantly larger LV volume, lower LVEF and lower cardiac index compared with the HFPEF group

Table 2. Subject Characteristics vs. Level of Fibrosis

	HFPEF			HFREF		
	Mild fibrosis (n=40)	Severe fibrosis (n=41)	P value	Mild fibrosis (n=46)	Severe fibrosis (n=45)	P value
Age (years)	57±11	52±16	0.082	58±12	54±14	0.21
BMI (kg/m²)	23±5	23±4	0.96	24±4	24±4	0.372
Male	29 (73)	25 (63)	0.238	34 (74)	32 (70)	0.949
Hypertension	13 (33)	21 (53)	0.164	21 (46)	18 (39)	0.739
Diabetes mellitus	5 (13)	4 (10)	0.906	5 (11)	8 (17)	0.521
Dyslipidemia	10 (25)	11 (28)	0.894	12 (26)	9 (20)	0.66
Sinus rhythm	31 (78)	38 (93)	0.281	31 (67)	34 (76)	0.389
Medication						
ACEI	17 (43)	19 (48)	0.941	28 (61)	29 (63)	0.892
ARB	7 (18)	8 (20)	0.874	18 (39)	17 (37)	0.934
β-blocker	19 (48)	20 (50)	0.902	32 (70)	34 (74)	0.685
Diuretics	7 (18)	6 (15)	0.884	17 (37)	24 (52)	0.174
Spironolactone	7 (18)	3 (8)	0.255	16 (35)	15 (33)	0.94
Warfarin	5 (13)	7 (18)	0.862	20 (43)	26 (57)	0.248
Digitalis	5 (13)	2 (5)	0.371	17 (37)	11 (24)	0.287
CCB	14 (35)	12 (30)	0.64	6 (13)	5 (11)	0.969
Antiplatelet	6 (15)	7 (18)	0.884	14 (30)	13 (28)	0.946
Statin	2 (5)	5 (13)	0.491	8 (17)	9 (20)	0.96
Amiodarone	5 (13)	0 (0)	0.053	3 (7)	5 (11)	0.687
Stage of heart failure			0.236			0.577
B	23 (58)	17 (43)		9 (20)	6 (13)	
C	16 (40)	23 (58)		34 (74)	34 (74)	
D	1 (3)	1 (3)		3 (7)	5 (11)	
Laboratory data						
Hemoglobin (g/dl)	14±2	14±2	0.357	14±2	14±2	0.674
hsCRP (mg/dl)	0.16±0.29	0.26±0.58	0.317	0.35±1.12	0.32±0.69	0.888
BNP (pg/ml)	255±377	243±314	0.892	245±347	494±584	0.019*
LDL (mg/dl)	108±38	113±44	0.635	116±38	125±40	0.239
HDL (mg/dl)	52±21	58±26	0.269	45±14	45±11	0.952
TG (mg/dl)	125±75	137±116	0.603	145±86	129±62	0.305
Glucose mg/dl)	112±43	100±29	0.134	104±19	109±23	0.315
CCr (ml/min)	90±25	90±26	0.898	89±30	87±40	0.804
Hemodynamic data						
LVEDVI (ml/m²)	76±18	75±22	0.874	107±28	122±40	0.040*
EF (%)	66±11	69±11	0.275	38±11	33±11	0.053
mAoP (mmHg)	97±16	96±15	0.775	92±15	88±19	0.189
LVEDP (mmHg)	14±7	13±6	0.236	11±6	14±8	0.06
mPAP (mmHg)	17±4	17±5	0.736	19±7	21±9	0.136
PCWP (mmHg)	10±4	9±4	0.926	10±5	12±8	0.161
Cardiac index (L·min⁻¹·m⁻²)	2.9±0.7	2.9±0.7	0.932	2.7±0.7	2.6±0.6	0.367
Morphometric data						
CVF (%)	0.64±0.41	2.93±1.38	<0.001*	0.61±0.4	3.56±2.58	<0.001*
MyD (μm)	19±1.9	20±4.1	0.287	19±2	20±3	0.055
Inflammatory cell (/field)	4.7±4.6	5.1±5.2	0.696	8±6	6±6	0.116
All-cause death	0 (0)	0 (0)	–	1 (2)	8 (18)	0.013*
Cardiac events	3 (8)	1 (2)	0.293	3 (7)	12 (27)	0.001*
Cardiac or sudden death	0 (0)	0 (0)		1 (2)	3 (7)	
Admission for HF	3 (8)	1 (2)		2 (4)	9 (20)	

Data given as mean±SD or n (%). *P<0.05, mild fibrosis vs. severe fibrosis.
Abbreviations see in Table 1.

(Table 1). Although LVEDP and CVF were comparable between the 2 groups (Table 1), CVF was significantly correlated with LVEDP, and also with LV peak systolic pressure (LVPSP) after adjustment in the HFREF group (Figures 2A,C), but not in the HFPEF group (Figures 2B,C).

Morphometric Variables as Prognostic Indicators

When comparing the mild and the severe fibrosis groups, a statistically significant difference was noted in terms of LVEDVI and BNP in the HFREF group (Table 2), but not in the HFPEF group (Table 2).

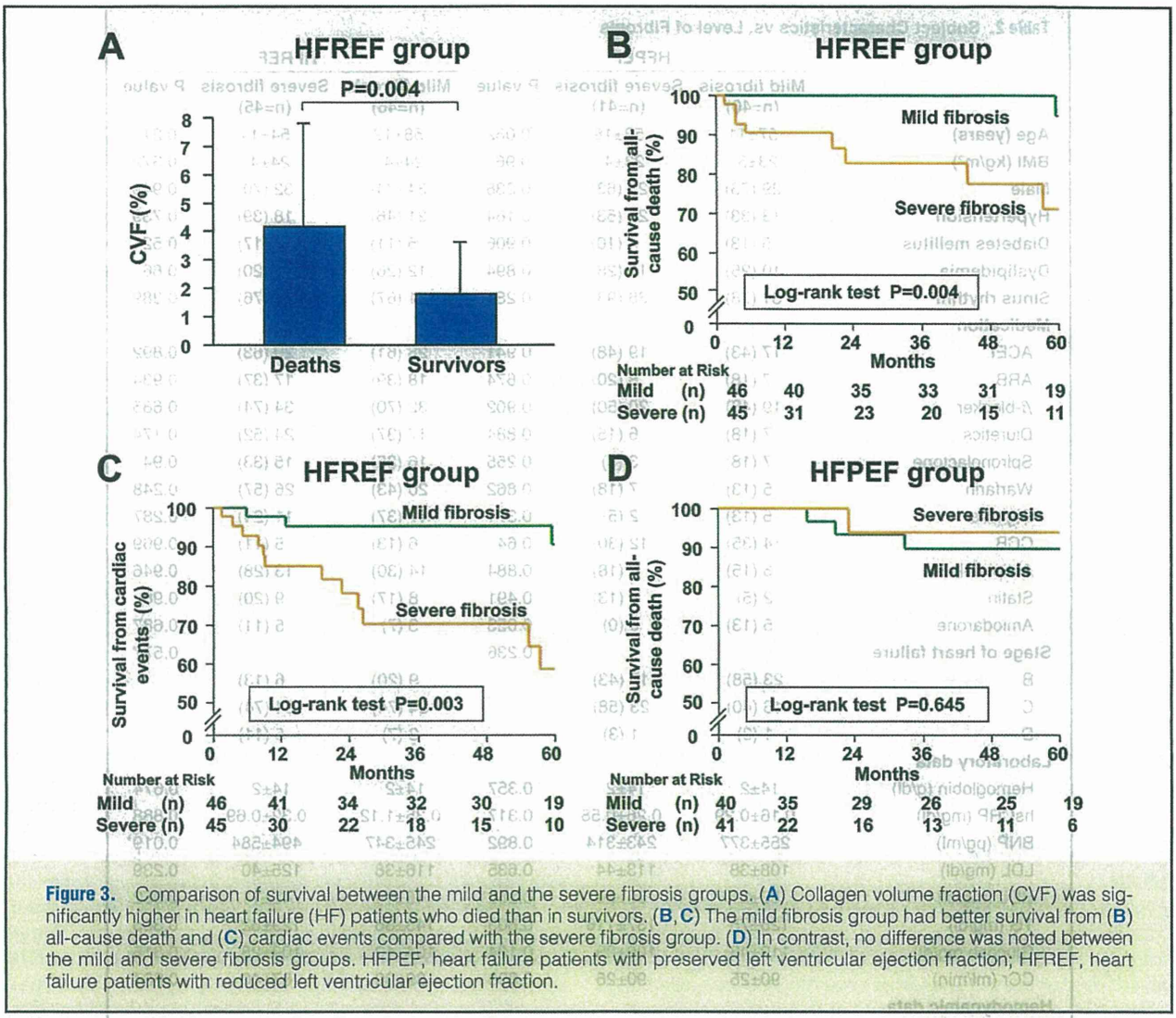

Figure 3. Comparison of survival between the mild and the severe fibrosis groups. (**A**) Collagen volume fraction (CVF) was significantly higher in heart failure (HF) patients who died than in survivors. (**B**,**C**) The mild fibrosis group had better survival from (**B**) all-cause death and (**C**) cardiac events compared with the severe fibrosis group. (**D**) In contrast, no difference was noted between the mild and severe fibrosis groups. HFPEF, heart failure patients with preserved left ventricular ejection fraction; HFREF, heart failure patients with reduced left ventricular ejection fraction.

In the HFREF group, CVF was significantly higher in HF patients who died than in survivors (**Figure 3A**). Indeed, there were more all-cause deaths and cardiac events in the severe fibrosis group than in the mild fibrosis group (**Table 2**). Five-year survival from all-cause death was significantly lower in the severe fibrosis group than in the mild fibrosis group (P=0.004; **Figure 3B**), and was so even after adjustment with the covariate (severe fibrosis vs. mild fibrosis; hazard ratio [HR], 13.5; 95% confidence interval [CI]: 2.01–307, P=0.006). Similarly, survival after cardiac events was significantly lower in the severe fibrosis group than in the mild fibrosis group in the HFREF subjects (P=0.003; **Figure 3C**), and was so even after adjustment with the covariate (severe fibrosis vs. mild fibrosis; HR, 6.20; 95%CI: 1.52–25.4, P=0.011). In contrast, in the HFPEF group, there was no significant difference in the cardiac events (**Table 1**) or survival rate (**Figure 3D**) between the mild and severe fibrosis groups. In the HFREF group, multivariate analysis showed that a 1% elevation of CVF increased the risk of all-cause death and that of cardiac events by 1.50-fold (95%CI: 1.18–1.95, P=0.002) and 1.28-fold (95%CI: 1.07–1.50, P=0.008), respectively (**Figure 4**). Furthermore, other histological parameters (eg, cardiomyocyte hypertrophy) were not significant predictors in the present study.

Discussion

The novel findings of the present study are as follows: (1) CVF was similar between the HFPEF and HFREF groups; (2) CVF was an independent predictor of all-cause death and cardiac events in the HFREF group but not in the HFPEF group; and (3) CVF was significantly correlated with LVEDP in the HFREF group but not in the HFPEF group. To the best of our knowledge, this is the first report to demonstrate the prognostic impact of CVF in non-ischemic HF patients with systolic dysfunction.

HFPEF Group vs. HFREF Group

Several studies have shown that the prognosis is comparable between patients with HFPEF and those with HFREF.[19–21] In the present study, the patients with HFPEF had a significantly better prognosis than those with HFREF, but after adjustment for stage of HF, the survival became similar between the 2 groups. In the present study, the 5-year survival rate from all-cause death was better than in the previous study,[22] probably because we followed up the patients monthly to control sodium intake and blood pressure. It has been reported that intensive medical treatment for HF patients with close fol-

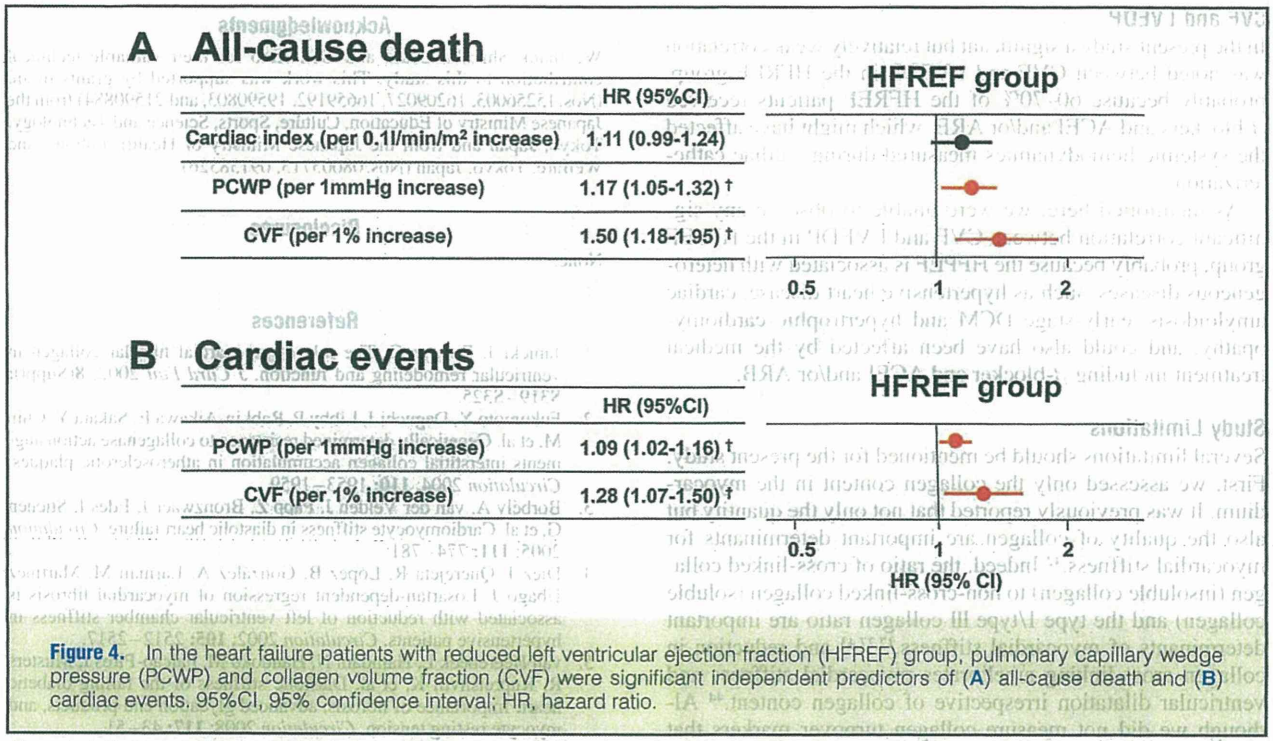

Figure 4. In the heart failure patients with reduced left ventricular ejection fraction (HFREF) group, pulmonary capillary wedge pressure (PCWP) and collagen volume fraction (CVF) were significant independent predictors of (A) all-cause death and (B) cardiac events. 95%CI, 95% confidence interval; HR, hazard ratio.

low-up can reduce re-admission for HF and cardiac deaths,[23] suggesting that the regular follow-up in the present study was effective to improve the prognosis of the HF patients.

Morphometric Variables and Cardiac Function as Prognostic Indicators

Myocardial fibrillar collagen, the main component of ECM, is a major contributor to myocardial stiffness.[3] In the present study, CVF in the HFPEF and the HFREF groups was 1.83% and 2.07%, respectively, consistent with the previous report.[24]

Recently, degradation of interstitial collagen has been reported in patients with mild to moderate dilated cardiomyopathy (DCM).[25,26] In contrast, marked accumulation of myocardial interstitial fibrosis has also been reported in patients with end-stage HFREF (eg, explanted heart).[27] The present study also demonstrated that CVF was significantly higher in HF patients who died than in survivors and that CVF and LVEDP were significantly correlated in HFREF patients. Taken together, these results suggest that reduction of myocardial interstitial collagen causes LV dilatation complicated with systolic dysfunction in the early stage of HFREF and that the increased myocardial interstitial collagen causes diastolic dysfunction in the advanced stage of HFREF with the resultant poor prognosis.

Although cardiac MRI is well established as a method for evaluating cardiac fibrosis, it cannot detect all cases of severe fibrosis, especially in HFREF patients with non-ischemic etiology.[28] It has also been reported that diffuse cardiac fibrosis is not able to be detected on cardiac MRI.[29] Furthermore, a recent study has shown that late gadolinium enhancement does not always indicate the change in myocardial interstitium.[30] Our preliminary data showed that there was no significant difference in CVF between the patients with and those without delayed enhancement on cardiac MRI (unpublished observation). Thus, we consider that the extent of myocardial fibrosis should be evaluated in multiple ways, including on endomyocardial biopsy, MRI and via serum markers of collagen turnover.

It has been reported that HFREF patients with diastolic dysfunction had a worse prognosis than those without it.[31,32] In the present study, elevated LVEDP was significantly related to increased CVF. Therefore, accumulation of myocardial interstitial fibrillar collagen may have caused ventricular diastolic dysfunction in the HFREF group with a resultant poor prognosis. The Randomized Aldactone Evaluation Study (RALES) showed that spironolactone improves prognosis in HF patients.[33] Interestingly, the RALES subanalysis showed that this benefit of spironolactone is noted only in patients with a high level of collagen synthesis marker (PIIINP) but not in those with low PIIINP.[11,33] It has also been shown that spironolactone reduced LV diastolic dysfunction only in DCM patients with increased myocardial fibrosis.[34]

In contrast, HFPEF seems to be a very different condition from HFREF in terms of response to medical treatment. Although ARB and ACEI could decrease myocardial fibrosis in HFPEF,[4,35,36] large clinical trials failed to demonstrate any beneficial effects of ARB or ACEI (eg, irbesartan, candesartan, enalapril, and valsartan) in patients with HFPEF.[37–40] This is consistent with the present finding that no significant correlation was noted between myocardial fibrosis and cardiac events in the HFPEF group, suggesting that the prognostic impact of myocardial fibrosis might be small in HFPEF. It has been previously reported, however, that in approximately 20% of patients with HFPEF, LVEF was significantly decreased during the 3-month follow-up period,[41] which is consistent with the present study, in which LVEF was significantly decreased in 11% of patients with HFPEF during follow-up. Thus, patients with severe myocardial fibrosis should be closely followed up because HFPEF patients with large CVF are at higher risk for disease progression and poor prognosis.

CVF and LVEDP

In the present study a significant but relatively weak correlation was noted between CVF and LVEDP in the HFREF group, probably because 60–70% of the HFREF patients received β-blockers and ACEI and/or ARB, which might have affected the systemic hemodynamics measured during cardiac catheterization.

As mentioned here, we were unable to observe any significant correlation between CVF and LVEDP in the HFPEF group, probably because the HFPEF is associated with heterogeneous diseases, such as hypertensive heart disease, cardiac amyloidosis, early-stage DCM and hypertrophic cardiomyopathy, and could also have been affected by the medical treatment including β-blocker and ACEI and/or ARB.

Study Limitations

Several limitations should be mentioned for the present study. First, we assessed only the collagen content in the myocardium. It was previously reported that not only the quantity but also the quality of collagen are important determinants for myocardial stiffness.[42] Indeed, the ratio of cross-linked collagen (insoluble collagen) to non-cross-linked collagen (soluble collagen) and the type I/type III collagen ratio are important determinants of myocardial stiffness,[17,27,43] and reduction in collagen cross-linking ameliorates myocardial stiffness and ventricular dilatation irrespective of collagen content.[44] Although we did not measure collagen turnover markers that have been established as prognostic in HF patients, it has been reported that there is a significant correlation between CVF and procollagen I carboxy-terminal peptide (PICP), a collagen synthesis marker.[45] Thus, the quality of ventricular fibrosis should be evaluated in biopsy specimens in future studies.

Second, because myocardial fibrosis may exist in a patchy fashion, we obtained at least 3 endomyocardial biopsy samples in each patient and evaluated CVF in as many fields as possible (mean, 3.6±0.9 fields) in order to minimize errors from patchy distribution of myocardial fibrosis in the present study. We still consider that we should evaluate the extent of myocardial fibrosis in multiple ways, including on endomyocardial biopsy, MRI and via serum markers of collagen turnover.

Third, in the present study, the HF subject group might be biased because we included patients who underwent endomyocardial biopsy alone and excluded those with other major causes of HF, such as ischemic heart disease and valvular heart disease. But because we did not include HF patients with valvular or ischemic etiology, we were able to minimize the overestimation of LVEF due to those factors in the present study.

Fourth, the present study was an observational study with a relatively small number of patients, and for reasons of ethics we were unable to perform repetitive myocardial biopsy to evaluate the time-course of HF. Thus, a future study with a large number of patients with a longer follow-up is required to address this issue.

Finally, the relatively small number of events limits the generalization of the present findings. Although we analyzed the present results with several statistical models, we found that the Cox proportional hazard model was the best. Thus, after univariate analysis, we used the Cox proportional hazard model with as small covariates as possible.

In conclusion, we have demonstrated that myocardial CVF evaluated with biopsy samples is a useful predictor for long-term survival in patients with HFREF (but not in those with HFPEF), and may be an important therapeutic target as well.

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Disclosures

None.

References

1. Janicki J, Brower G. The role of myocardial fibrillar collagen in ventricular remodeling and function. *J Card Fail* 2002; **8**(Suppl): S319–S325.
2. Fukumoto Y, Deguchi J, Libby P, Rabkin-Aikawa E, Sakata Y, Chin M, et al. Genetically determined resistance to collagenase action augments interstitial collagen accumulation in atherosclerotic plaques. *Circulation* 2004; **110:** 1953–1959.
3. Borbély A, van der Velden J, Papp Z, Bronzwaer J, Edes I, Stienen G, et al. Cardiomyocyte stiffness in diastolic heart failure. *Circulation* 2005; **111:** 774–781.
4. Díez J, Querejeta R, López B, González A, Larman M, Martínez Ubago J. Losartan-dependent regression of myocardial fibrosis is associated with reduction of left ventricular chamber stiffness in hypertensive patients. *Circulation* 2002; **105:** 2512–2517.
5. van Heerebeek L, Hamdani N, Handoko M, Falcao-Pires I, Musters R, Kupreishvili K, et al. Diastolic stiffness of the failing diabetic heart: Importance of fibrosis, advanced glycation end products, and myocyte resting tension. *Circulation* 2008; **117:** 43–51.
6. Hein S, Arnon E, Kostin S, Schönburg M, Elsässer A, Polyakova V, et al. Progression from compensated hypertrophy to failure in the pressure-overloaded human heart: Structural deterioration and compensatory mechanisms. *Circulation* 2003; **107:** 984–991.
7. Graham H, Trafford A. Spatial disruption and enhanced degradation of collagen with the transition from compensated ventricular hypertrophy to symptomatic congestive heart failure. *Am J Physiol Heart* 2007; **292:** H1364–H1372.
8. Bello D, Fieno D, Kim R, Pereles F, Passman R, Song G, et al. Infarct morphology identifies patients with substrate for sustained ventricular tachycardia. *J Am Coll Cardiol* 2005; **45:** 1104–1108.
9. Assomull R, Prasad S, Lyne J, Smith G, Burman E, Khan M, et al. Cardiovascular magnetic resonance, fibrosis, and prognosis in dilated cardiomyopathy. *J Am Coll Cardiol* 2006; **48:** 1977–1985.
10. Jellis C, Martin J, Narula J, Marwick T. Assessment of nonischemic myocardial fibrosis. *J Am Coll Cardiol* 2010; **56:** 89–97.
11. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: Insights from the Randomized Aldactone Evaluation Study (RALES): RALES Investigators. *Circulation* 2000; **102:** 2700–2706.
12. Cicoira M, Rossi A, Bonapace S, Zanolla L, Golia G, Franceschini L, et al. Independent and additional prognostic value of aminoterminal propeptide of type III procollagen circulating levels in patients with chronic heart failure. *J Card Fail* 2004; **10:** 403–411.
13. Braunwald E. Biomarkers in heart failure. *N Engl J Med* 2008; **358:** 2148–2159.
14. Soylemezoglu O, Wild G, Dalley AJ, MacNeil S, Milford-Ward A, Brown CB, et al. Urinary and serum type III collagen: Markers of renal fibrosis. *Nephrol Dial Transplant* 1997; **12:** 1883–1889.
15. Leroy V. Other non-invasive markers of liver fibrosis. *Gastroenterol Clin Biol* 2008; **32**(Suppl 1): 52–57.
16. van Heerebeek L, Borbély A, Niessen H, Bronzwaer J, van der Velden J, Stienen G, et al. Myocardial structure and function differ in systolic and diastolic heart failure. *Circulation* 2006; **113:** 1966–1973.
17. Fukui S, Fukumoto Y, Suzuki J, Saji K, Nawata J, Tawara S, et al. Long-term inhibition of Rho-kinase ameliorates diastolic heart failure in hypertensive rats. *J Cardiovasc Pharmacol* 2008; **51:** 317–326.
18. Tribouilloy C, Rusinaru D, Mahjoub H, Soulière V, Lévy F, Peltier M, et al. Prognosis of heart failure with preserved ejection fraction: A 5 year prospective population-based study. *Eur Heart J* 2008; **29:** 339–347.
19. Senni M, Redfield M. Heart failure with preserved systolic function: A different natural history? *J Am Coll Cardiol* 2001; **38:** 1277–1282.

20. Miyagishima K, Hiramitsu S, Kimura H, Mori K, Ueda T, Kato S, et al. Long term prognosis of chronic heart failure: Reduced vs preserved left ventricular ejection fraction. *Circ J* 2009; **73:** 92–99.
21. Tsuchihashi-Makaya M, Hamaguchi S, Kinugawa S, Yokota T, Goto D, Yokoshiki H, et al. Characteristics and outcomes of hospitalized patients with heart failure and reduced vs preserved ejection fraction: Report from the Japanese Cardiac Registry of Heart Failure in Cardiology (JCARE-CARD). *Circ J* 2009; **73:** 1893–1900.
22. Owan T, Hodge D, Herges R, Jacobsen S, Roger V, Redfield M. Trends in prevalence and outcome of heart failure with preserved ejection fraction. *N Engl J Med* 2006; **355:** 251–259.
23. Capomolla S, Febo O, Ceresa M, Caporotondi A, Guazzotti G, La Rovere M, et al. Cost/utility ratio in chronic heart failure: Comparison between heart failure management program delivered by day-hospital and usual care. *J Am Coll Cardiol* 2002; **40:** 1259–1266.
24. López B, González A, Querejeta R, Larman M, Díez J. Alterations in the pattern of collagen deposition may contribute to the deterioration of systolic function in hypertensive patients with heart failure. *J Am Coll Cardiol* 2006; **48:** 89–96.
25. Schwartzkopff B, Fassbach M, Pelzer B, Brehm M, Strauer B. Elevated serum markers of collagen degradation in patients with mild to moderate dilated cardiomyopathy. *Eur J Heart Fail* 2002; **4:** 439–444.
26. Timonen P, Magga J, Risteli J, Punnonen K, Vanninen E, Turpeinen A, et al. Cytokines, interstitial collagen and ventricular remodelling in dilated cardiomyopathy. *Int J Cardiol* 2008; **124:** 293–300.
27. Marijianowski M, Teeling P, Mann J, Becker A. Dilated cardiomyopathy is associated with an increase in the type I/type III collagen ratio: A quantitative assessment. *J Am Coll Cardiol* 1995; **25:** 1263–1272.
28. Bello D, Shah D, Farah G, Di Luzio S, Parker M, Johnson M, et al. Gadolinium cardiovascular magnetic resonance predicts reversible myocardial dysfunction and remodeling in patients with heart failure undergoing beta-blocker therapy. *Circulation* 2003; **108:** 1945–1953.
29. Iles L, Pfluger H, Phrommintikul A, Cherayath J, Aksit P, Gupta SN, et al. Evaluation of diffuse myocardial fibrosis in heart failure with cardiac magnetic resonance contrast-enhanced T1 mapping. *J Am Coll Cardiol* 2008; **52:** 1574–1580.
30. Yilmaz A, Kindermann I, Kindermann M, Mahfoud F, Ukena C, Athanasiadis A, et al. Comparative evaluation of left and right ventricular endomyocardial biopsy: Differences in complication rate and diagnostic performance. *Circulation* 2010; **122:** 900–909.
31. Bruch C, Gotzmann M, Stypmann J, Wenzelburger F, Rothenburger M, Grude M, et al. Electrocardiography and Doppler echocardiography for risk stratification in patients with chronic heart failure: Incremental prognostic value of QRS duration and a restrictive mitral filling pattern. *J Am Coll Cardiol* 2005; **45:** 1072–1075.
32. Whalley G, Doughty R, Gamble G, Wright S, Walsh H, Muncaster S, et al. Pseudonormal mitral filling pattern predicts hospital re-admission in patients with congestive heart failure. *J Am Coll Cardiol* 2002; **39:** 1787–1795.
33. Pitt B, Zannad F, Remme W, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure: Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; **341:** 709–717.
34. Izawa H, Murohara T, Nagata K, Isobe S, Asano H, Amano T, et al. Mineralocorticoid receptor antagonism ameliorates left ventricular diastolic dysfunction and myocardial fibrosis in mildly symptomatic patients with idiopathic dilated cardiomyopathy: A pilot study. *Circulation* 2005; **112:** 2940–2945.
35. Brilla C, Funck R, Rupp H. Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease. *Circulation* 2000; **102:** 1388–1393.
36. Brilla C, Rupp H, Maisch B. Effects of ACE inhibition versus non-ACE inhibitor antihypertensive treatment on myocardial fibrosis in patients with arterial hypertension: Retrospective analysis of 120 patients with left ventricular endomyocardial biopsies. *Herz* 2003; **28:** 744–753.
37. Zile M, Gaasch W, Anand I, Haass M, Little W, Miller A, et al. Mode of death in patients with heart failure and a preserved ejection fraction: Results from the Irbesartan in Heart Failure With Preserved Ejection Fraction Study (I-Preserve) trial. *Circulation* 2010; **121:** 1393–1405.
38. Yusuf S, Pfeffer M, Swedberg K, Granger C, Held P, McMurray J, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: The CHARM-Preserved Trial. *Lancet* 2003; **362:** 777–781.
39. Kitzman D, Hundley W, Brubaker P, Morgan T, Moore J, Stewart K, et al. A randomized, double-blinded trial of enalapril in older patients with heart failure and preserved ejection fraction: Effects on exercise tolerance and arterial distensibility. *Circ Heart Fail* 2010; **3:** 477–485.
40. Parthasarathy H, Pieske B, Weisskopf M, Andrews C, Brunel P, Struthers A, et al. A randomized, double-blind, placebo-controlled study to determine the effects of valsartan on exercise time in patients with symptomatic heart failure with preserved ejection fraction. *Eur J Heart Fail* 2009; **11:** 980–989.
41. Cahill J, Ryan E, Travers B, Ryder M, Ledwidge M, McDonald K. Progression of preserved systolic function heart failure to systolic dysfunction: A natural history study. *Int J Cardiol* 2006; **106:** 95–102.
42. Kass D, Bronzwaer J, Paulus W. What mechanisms underlie diastolic dysfunction in heart failure? *Circ Res* 2004; **94:** 1533–1542.
43. Badenhorst D, Maseko M, Tsotetsi O, Naidoo A, Brooksbank R, Norton G, et al. Cross-linking influences the impact of quantitative changes in myocardial collagen on cardiac stiffness and remodelling in hypertension in rats. *Cardiovasc Res* 2003; **57:** 632–641.
44. Woodiwiss A, Tsotetsi O, Sprott S, Lancaster E, Mela T, Chung E, et al. Reduction in myocardial collagen cross-linking parallels left ventricular dilatation in rat models of systolic chamber dysfunction. *Circulation* 2001; **103:** 155–160.
45. López B, González A, Varo N, Laviades C, Querejeta R, Díez J. Biochemical assessment of myocardial fibrosis in hypertensive heart disease. *Hypertension* 2001; **38:** 1222–1226.

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Trend of Westernization of Etiology and Clinical Characteristics of Heart Failure Patients in Japan

– First Report From the CHART-2 Study –

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Background: Hospitalization due to acute heart failure syndrome (AHFS) is an indicator of worsened prognosis for patients with cardiovascular disease (CVD). The Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study was designed to elucidate characteristics and prognosis of patients at high risk for CVD progression due to AHFS.

Methods and Results: The CHART-2 Study is a prospective observational multicenter cohort study. Patients with overt HF, structural cardiac disorder but without HF, or with coronary artery disease (CAD) have been consecutively enrolled from October 2006. As of March 2010, a total of 10,219 patients have been recruited, making the Study the largest multicenter prospective cohort of HF patients in Japan. The mean patient age was 68.2± 12.3 years and male patients accounted for 69.8%. Overt HF was observed in 46.3% of patients; and 53.7% did not have HF but were at high risk for AHFS. As HF stage progressed, the prognostic risks (eg, chronic kidney disease, reduced ejection fraction, and increased B-type natriuretic peptide level) became more prominent. Compared with the previous CHART-1 study, the prevalence of ischemic etiology and risk factors (hypertension, diabetes) have increased, as in Western studies.

Conclusions: This first report demonstrates the trend of westernization of ischemic etiology and clinical characteristics of HF patients in Japan, indicating the importance of appropriate management and prevention of CAD to prevent AHFS. (*Circ J* 2011; **75:** 823–833)

Key Words: Coronary artery disease; Heart failure; Prognosis; Risk factors

Cardiovascular disease (CVD) is the leading cause of death in most developed countries.[1] Furthermore, many developing countries are now catching up with regard to this trend.[1] Heart failure (HF) is the end-stage of CVD and is becoming more common all over the world because of the westernization of lifestyle, the rapid aging of the population, and the increased number of survivors of serious cardiovascular illness due to recent advances in medical and surgical treatment.[2,3] We previously performed a multicenter prospective cohort study of HF patients (Chronic Heart Failure Analysis and Registry in the Tohoku District 1 Study: CHART-1) from February 2000 to December 2005 (n=1,278). The CHART-1 Study found that HF patients were also prevalent in Japan and that the prognosis was similarly poor compared with that in Western countries.[4,5] The most prevalent etiology of HF in the CHART-1 Study was non-ischemic cardiomyopathy (28.6%), and coronary artery disease (CAD) accounted for only 25.4% of the total HF patients, which was considerably low compared with a Western HF study.[3] Hospitalization due to the onset of acute heart failure syndrome (AHFS) is a key event in the disease progression of HF and CVD. Thus, it is important to avoid the decompensation of chronic HF and prevent de novo development of congestive HF in CVD patients in order to improve their long-term quality of life.[6,7] Western studies reported that the most frequent etiology of AHFS was ischemic in origin,[8,9] but the characteristics of such patients at high risk in Japan and the type of pathophysiologic derangement that causes decompensation from stable HF remain uncertain. Furthermore, although a large number of studies have shown that most

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