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慢性心不全におけるメタボリック症候群の

意義に関する研究

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目 次

I. 総合研究報告書	1 ページ
慢性心不全におけるメタボリック症候群の意義に関する研究	
II. 研究成果の刊行に関する一覧表	11 ページ
III. 研究成果の刊行物・別刷	13 ページ

厚生労働科学研究費補助金（循環器疾患等生活習慣病対策総合研究事業）
総合研究報告書

慢性心不全におけるメタボリック症候群の意義に関する研究

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研究要旨

メタボリックシンドロームは、内臓肥満・高血圧・高脂血症・糖尿病の各因子が軽度ではあるものの複合した病態として心血管病の成因に深く関係した病態として注目されている。この背景として、心血管病の成因には、高血圧・高脂血症などの個々の重症度よりも、それらの重複が重要であることが広く認識されるようになった経緯がある。このメタボリックシンドロームの重要性は、虚血性心臓病では広く認識されるようになったが、慢性心不全の発症および進展にどのように関与しているかは、まだ明らかではない。本研究は、慢性心不全におけるメタボリックシンドロームの意義を明らかにし、メタボリックシンドロームの治療が慢性心不全の発症予防や治療標的として有用か否かを、明らかにすることを目的とする。

本研究では多施設共同の中央登録方式による大規模調査研究として実施し、参加施設における慢性心不全患者についてメタボリック症候群の頻度やその臨床的特徴について、全国規模で明らかにする。平成18年度に、我々は全国6施設の全国研究班を組織し、毎年度（平成20年度は6月、9月、12月の計3回に加え、3月に平成20年度第4回目を予定）定例会議を行い、研究遂行における問題点などを議論した。

本研究は、①参加施設とその関連施設の大規模登録データを基に慢性心不全患者におけるメタボリックシンドロームの役割を明らかにし、さらに②メタボリックシンドロームにおける治療介入試験を行う点で独創的である。また、③メタボリックシンドローム患者が将来慢性心不全を発症するか否かを検討する点でも独創的であり、このような臨床研究は、国内外でまだ行われていない。本研究により、慢性心不全に対するより効果的な治療法を確立し、日本人の特性に留意した真にエビデンスに基づく予防・治療体系の確立が期待される。

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A. 研究目的

メタボリックシンドロームの重要性は、虚血性心臓病では広く認識されるようになったが、慢性心不全における意義に関しては、まだ明らかにされていない（図1）。そこで、本研究では、全国各地の第一線の施設の協力を得て、日本人の慢性心不全におけるメタボリックシンドロームの意義に関する多施設共同研究を行うことを目的とする。

メタボリックシンドロームから慢性心不全までの進展

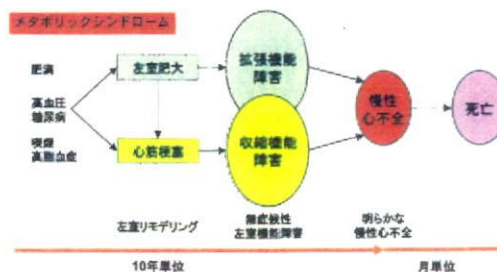


図1. メタボリックシンドロームと慢性心不全の関連

B. 研究方法

本研究では、以下の3つのアプローチをとる（図2）。

1. 慢性心不全におけるメタボリックシンドロームの頻度・臨床的特徴に関する研究
2. メタボリックシンドローム患者における慢性心不全の発症に関する研究
3. メタボリックシンドロームを合併した慢性心不全に対する治療介入の意義に関する研究

目的・心不全におけるメタボリックシンドロームの役割の検討 研究内容

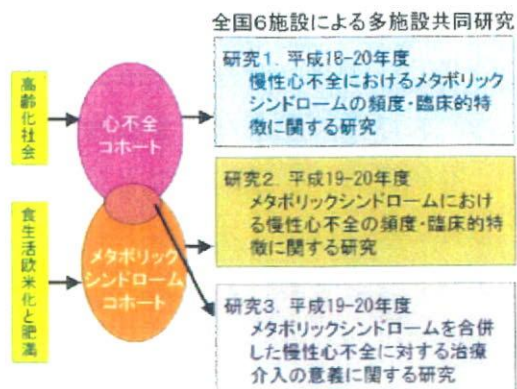


図2. 本研究のフローチャート（目的・方法）

1. 慢性心不全におけるメタボリックシンドロームの頻度・臨床的特徴に関する研究（平成18～20年度）

- 目標症例数：5000例
- 対象患者：慢性心不全患者（アメリカ心臓病学会慢性心不全診断治療ガイドラインにおける Stage C, D）
- 登録時調査：①年齢、性別、身長、体重、腹囲、②基礎疾患（虚血、高血圧、心筋症、弁膜症、不明、その他）、③メタボリックシンドロームの有無（中性脂肪値、HDLコレステロール値、血圧、空腹時血糖値）、④合併疾患（高血圧、糖尿病、高脂血症、脳血管障害、腎不全、慢性心房細動）、⑤症状の重症度、⑥心機能評価、⑦治療内容（薬剤名、手術（弁手術、冠動脈バイパス術など）の有無）、⑧身体活動能力、社会的支援
- 予後調査（1、2、3、4、5年後）：①死亡、入院の有無、心血管イベント、心血管死、②心不全増悪による再入院。③身体活動能力、社会的支援の推移。患者登録システムは5年後の予後調査まで可能である。

解析方法：患者の予後は、種々の臨床的背景因子、基礎疾患、心機能、重症度、合併症、治療内容、社会環境要因などが複雑に関与していると考えられるが、本研究ではメタボリックシンドロームの有無が、生命予後および心血管イベント

に関与しているか否かを検討する。

本研究のために、全国共同研究登録用web-siteを立ち上げ、各施設において倫理委員会の承認を得て研究登録を開始し、研究1においては3,400例以上が登録されている（図3）。

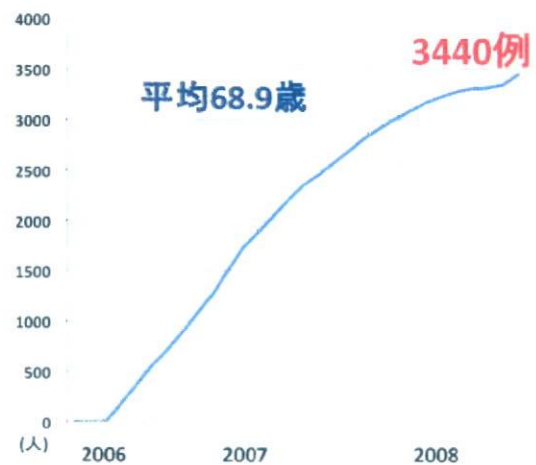


図3. 研究1の登録状況

2. メタボリックシンドローム患者における慢性心不全の発症に関する研究（平成19～20年度）

- 目標症例数：5000例
- 対象患者：慢性心不全リスク患者（アメリカ心臓病学会慢性心不全診断治療ガイドラインにおける Stage A, B）
- 登録時調査：①年齢、性別、身長、体重、腹囲、②メタボリックシンドロームのデータ（中性脂肪値、HDLコレステロール値、血圧、空腹時血糖値）、③合併疾患（高血圧、糖尿病、高脂血症、脳血管障害、腎不全

、慢性心房細動)、④治療内容(薬剤名、手術(弁手術、冠動脈バイパス術など)の有無)、⑤症状の有無、⑥身体活動能力、社会的支援

- 評価項目: 検診後、毎年以下の項目を評価し、最長5年追跡する。①自覚症状の変化(アメリカ心臓病学会慢性心不全診断治療ガイドラインにおける Stage A, Bから Stage C, Dへの移行)、②運動能力、③死亡(全死亡、心血管死)、④心不全による入院、⑤投薬内容、⑥身体活動能力、社会的支援の推移。
- 解析方法: 患者の予後は、種々の臨床的背景因子、基礎疾患、心機能、重症度、合併症、治療内容、社会環境要因などが複雑に関与していると考えられるが、本研究ではメタボリックシンドロームの合併が生命予後および心血管イベントに関与しているか否か検討する。

本研究のために、全国共同研究登録用web-siteを立ち上げ、各施設において倫理委員会の承認を得て研究登録を開始し、研究2においては4,700例以上が登録されている(図4)。

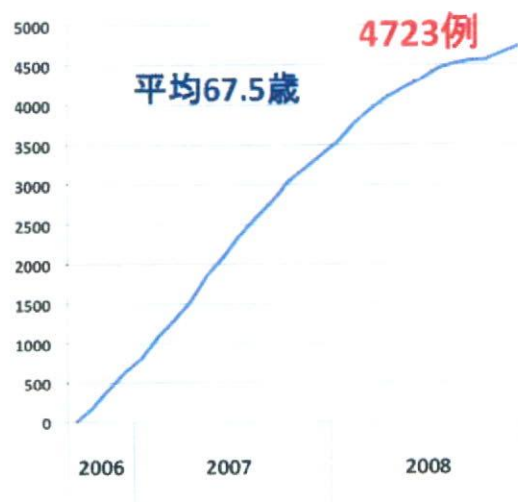


図4. 研究2の登録状況

3. メタボリックシンドロームを合併した慢性心不全に対する治療介入の意義に関する研究(平成19~20年度)

メタボリックシンドロームを合併した慢性心不全患者を2群に分け、1群には積極的な食事療法、運動療法を行い、肥満・高血圧・高脂血症・糖尿病の改善を図る。もう1群には通常の栄養指導および運動療法を行う。その2群間において、症状の重症度・心機能・身体活動能力・心血管イベント・予後などの相関を比較検討する。

- 登録時調査: 観察期、3、6、12、24ヶ月後に以下の項目を評価する。①自覚症状、体重、腹囲、②運動耐容能、③心不全増悪による入院、④採血データ(血清脂質、血糖、BNP、CRP(可能なら高感度CRP))、⑤死亡(全死亡、心血管死)、⑥投薬内容、⑦身体活動能力、社会的支

援

- 予後調査（1、2、3、4、5年後）：①死亡、入院の有無、心血管イベント、心血管死、②心不全増悪による再入院。③身体活動能力、社会的支援の推移。患者登録システムは5年後の予後調査まで可能である。

研究3の介入試験も、現時点で100名以上の患者を登録している。2群に分け、コントロール群には通常の食事療法・運動療法を、介入群には積極的な食事療法・運動療法を行っている。なお研究3では、下記の手帳を作成し、万歩計および腹囲測定用メジャーを用いて、積極的に介入している（図5）。

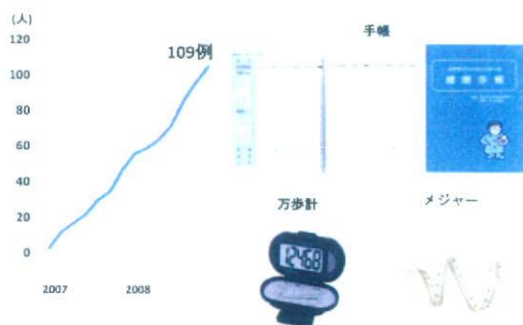


図5. 研究3の登録状況および用いるメタボコントロール手帳など

（倫理面での配慮）

本研究は「疫学研究に関する倫理指針」を遵守して研究を計画・実施するが、特に以下の倫理的配慮を行う。（1）倫理委員会の審査：研究対象患者のプライバシー保護を確実にするために、倫理委員会において倫理面に対する配慮が十

分に行われているか審査を受けた上で承認を得て実施する。倫理委員会が設置されていない施設の参加を可能にするために、各々の参加施設（大学病院など）の倫理委員会に審査を依頼する。（2）対象患者からの同意取得：研究に際しては、あらかじめ研究内容、意義と危険性およびプライバシー侵害の恐れがないこと、同意しなくても不利益は受けないこと、同意は随時撤回できることを患者に説明し、文書で同意を得る。（3）匿名性：症例の登録は、各施設におけるIDで行い、データがどの症例のものかは診療を担当した主治医のみが把握している。研究担当者はIDがどの患者のものか特定できないため患者のプライバシーは保護される。さらに、データベースには別の症例コードを入力するためデータベースから患者個人を特定することは困難である。

C. 研究結果

現時点では登録終了前であるため、中間解析を行った。

まず、現在のメタボリックシンドロームの診断基準が、重症の高血圧、高脂血症、糖尿病を含んでしまうため、軽いメタボリックシンドローム（Early MetS）と重症のメタボリックシンドローム（Advanced MetS）に分けて検討を行った（図6）。

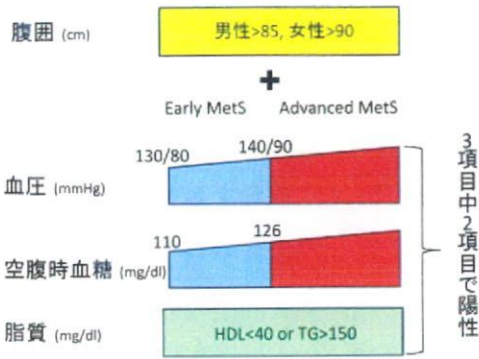


図6. メタボリックシンドローム
診断基準

1. 慢性心不全におけるメタボリックシンドロームの頻度・臨床的特徴に関する研究（平成18～20年度）

研究1は20歳以上の慢性心不全患者を対象とし、メタボリックシンドロームの合併の有無と、基礎心疾患・症状の重症度・心機能・身体活動能力・心血管イベント・予後などの相関を比較検討するものである。この研究1の成果として、慢性心不全患者においてメタボリックシンドロームを有するのは38%であり、軽いメタボリックシンドロームは3%、重症メタボリックシンドロームは35%と、慢性心不全患者におけるメタボリックシンドロームは重症化していることが示唆された（図7）。

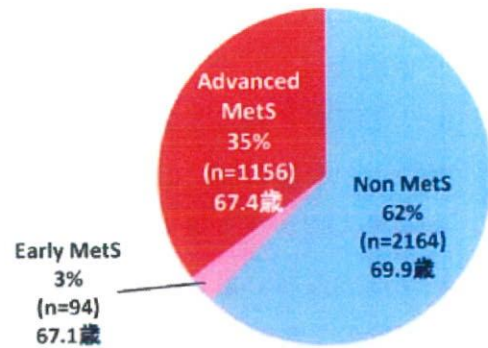


図7. 研究1におけるメタボリックシンドローム合併率

さらに慢性心不全患者の男性患者の内、メタボリックシンドロームを有する割合は47%、女性患者では20%と、これまで一般住民で報告されてきたメタボリックシンドロームの罹患率と比べ、約2倍の合併頻度であった（図8）。

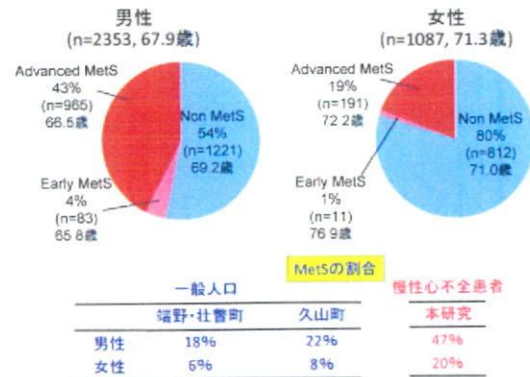


図8. 研究1の男女別メタボリックシンドローム合併率と一般住民との比較

また慢性心不全患者に合併するメタボリックシンドロームの特徴として、治療されているにも関わらず、メタボリックシンドロームが重症化するほど収縮期血圧、空腹時血糖が高値であった（図9）。中性脂肪はまだ治療されていない

軽いメタボリックシンドロームで最も高値を示したが、治療されていても、重症のメタボリックシンドロームでは、非メタボリックシンドロームと比べ、高値を示した（図9）。

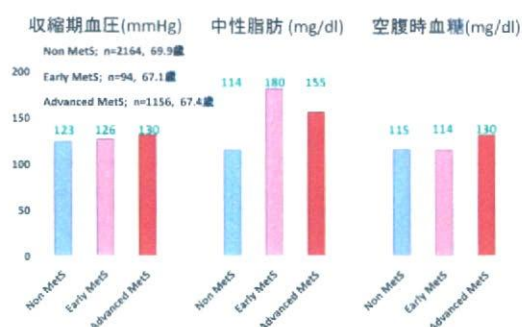


図9. 研究1の収縮期血圧、中性脂肪、空腹時血糖値

さらに、慢性心不全患者に合併するメタボリックシンドロームの特徴として虚血性心疾患の合併頻度を検討したところ、重症化したメタボリックシンドロームで多く合併していた（図10）。

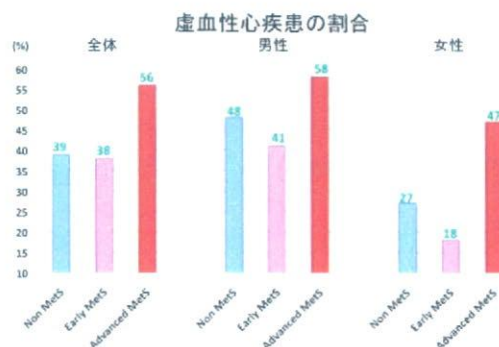


図10. 研究1における虚血性心疾患の割合

2. メタボリックシンドローム患者における慢性心不全の発症に関する研究（平成19～20年度）

この研究2は、20歳以上のメタボリックシンドローム患者を対象とし、心不全発症の有無と、心機能・身体活動能力・心血管イベント・予後などとの相関を検討するものである。

研究2は心不全症状のない心疾患患者（心不全予備群）を登録し、メタボリックシンドロームの有無で2群に分け、追跡調査を行い、メタボリックシンドロームの有無が慢性心不全の発症に影響するか否かを検討するものである。研究2におけるベースラインの特徴は、心不全予備群においてメタボリックシンドロームを有するのは41%と、心不全予備群においてもメタボリックシンドロームを有する割合が高かったことが明らかとなった（図11）。

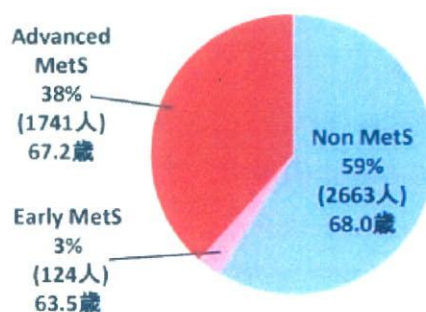


図11. 研究2におけるメタボリックシンドローム合併率

この研究2はメタボリックシンドロームの有無が将来慢性心不全を発症する頻度・特徴を検討するものであり、今後5年間経過を追跡し、その結果が得られる予定である。

3. メタボリックシンドロームを合併した慢性心不全に対する治療介入の意義に関する研究(平成19～20年度)

研究3はメタボリックシンドロームを合併した慢性心不全患者を2群に分け、1群には積極的な食事療法、運動療法を行い、肥満・高血圧・高脂血症・糖尿病の改善を図る。もう1群には通常の栄養指導および運動療法を行う。その2群間において、症状の重症度・心機能・身体活動能力・心血管イベント・予後などの相関を比較検討する。

この研究3のメタボリック症候群を有する慢性心不全患者における積極的食事療法・運動療法の介入研究に関しても、今後5年間経過を追い、結果が得られる予定である。

D. 考察

本研究の特色として、第一に、慢性心不全患者を全国規模の多施設で登録したデータベースを用いて解析する点である。第二に、全国多施設で登録した心不全予備群患者をメタボリックシンドロームの有無に分けて長期観察し、心不全の発症を検討する点で特色がある。第三に、メタボリックシンドロームの治療介入、すなわち内臓肥満の改善が心不全の治療となり得るか否かを検討する点で特色がある。

本研究により、メタボリックシンドロームが心不全増悪因子であることが示され、その治療の重要性が明らかになれ

ば、現在、我が国で増加している心不全患者に対する効率的治療法が確立され、大幅な医療費抑制効果が期待される(図12)。

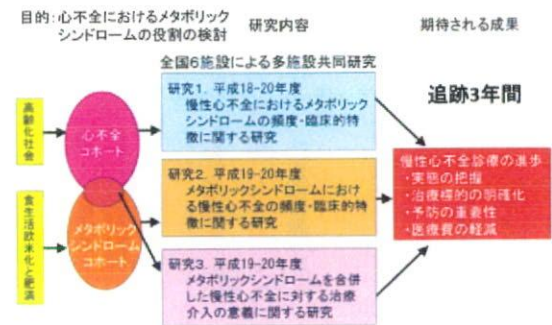


図12. 本研究のフローチャート(目的・方法・期待される効果)

E. 結論

研究1は現在心不全症状のある患者におけるメタボリックシンドロームの頻度および特徴を検討するもので、平成20年度末まで登録するため、最終結果が得られるのは、平成21年度に入ってからとなる。また研究2・3の最終結果が得られるのは5年間の観察以降の予定であるが、本研究で得られた患者登録データに基づいて、メタボリックシンドロームが心不全増悪因子であることが示されれば、慢性心不全治療におけるメタボリックシンドロームの治療の重要性が明らかになる。また、慢性心不全の重症度や予後が、メタボリックシンドロームの有無で違いがあればその治療目的がより明確になる。その結果、早期より効果的に慢性心不全を予防すること

が可能になり、臨床応用できる極めて有用なエビデンスが得られることが期待される。

F. 健康危険情報

特になし

G. 研究発表

1. 論文発表

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2. 学会発表

第72回日本循環器学会総会・学術集会
福岡 平成20年3月28日

Nobuyuki Shiba, Mika Matsuki, Jun Takahashi, Yoshihiro Fukumoto, Yutaka Kagaya, Hiroaki Shimokawa (Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine)

Large Cohort Studies for the Establishment of Guidelines of Chronic Heart Failure in Japan.

第105回日本内科学会総会・講演会プレナリーセッション 東京 平成20年4月13日

多田智洋、柴信行、下川宏明（東北大学循環器病態学）

日本人におけるメタボリックシンドローム診断の至適ウエスト周囲径とは？

第3回宮城循環器談話会 仙台 平成20

年5月31日

福本義弘（東北大学病院 循環器内科）
慢性心不全におけるメタボリックシンドロームの役割

第31回日本高血圧学会 札幌 平成20年10月11日

後岡広太郎、柴信行、下川宏明（東北大学 循環器病態学）

メタボリックシンドロームにおける高血圧症の意義-第二次東北慢性心不全登録の中間報告から-

性差医学・医療学会 第2回学術集会 東京 平成21年2月7日

後岡広太郎、柴信行、下川宏明（東北大学 循環器病態学）

日本人女性の慢性心不全は将来増加する

日本循環器学会 第147回東北地方会 仙台 平成21年2月14日

後岡広太郎、柴信行、下川宏明（東北大学 循環器病態学）

CKDを合併する慢性心不全例でのレニン-アンジオテンシン系阻害薬の予後に対するインパクト

日本内科学会 第187回東北地方会 仙台 平成21年2月21日

後岡広太郎、柴信行、下川宏明（東北大学 循環器病態学）

慢性心不全における使用薬剤の評価

CHART-2中間解析より

第73回日本循環器学会総会・学術集会 大阪 平成21年3月20日

Nobuyuki Shiba, Hiroaki Shimokawa

(Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine)

Central obesity is a significant risk independent of insulin resistance in the development of cardiovascular disease.

第73回日本循環器学会総会・学術集会 大阪 平成21年3月21日

Koutaro Nochioka, Nobuyuki Shiba, Hiroaki Shimokawa (Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine)

Penetration rate of standard treatment in Japanese patients with chronic heart failure: Interim analysis of the CHART-2 Study.

H. 知的所有権の出願・取得状況（予定を含む）

なし

研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の 編集者名	書 籍 名	出版社名	出版地	出版年	ページ
福本義弘、 下川宏明	虚血性不全心とは ？		新・心臓病診療 プラクティス 冠動脈疾患の 病態に迫る	文光堂	東京	2008	p232-239

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
福本義弘、 下川宏明	脂質異常症治療の進歩	臨床と研究	85	1124-1128	2008

Emerging Problems of Heart Failure Practice in Japanese Women

— Lessons From the CHART Study —

Nobuyuki Shiba, MD*;**; Kotaro Nochioka, MD**; Haruka Kohno, RN**;
Mika Matsuki, RN*;**; Jun Takahashi, MD**; Tomohiro Tada, MD**;
Yutaka Kagaya, MD**; Hiroaki Shimokawa, MD*;**

Background The prognosis of patients with chronic heart failure (CHF) is poor in both men and women. However, the characteristics of, and effective treatment strategy for, female CHF patients still remain unclear. This study was designed to evaluate the prognosis and characteristics of female patients in a CHF cohort termed the Chronic Heart Failure Analysis and Registry in the Tohoku District.

Methods and Results Of 1,278 patients registered in the cohort, the study population comprised 1,166 symptomatic CHF patients with sufficient data. As compared with male patients, female patients were more likely to be older, have preserved systolic function and non-ischemic etiology of CHF, and underuse standard CHF medications. Although a previous study showed that sex-difference was not a significant prognostic factor in CHF patients, the unadjusted survival analysis revealed an increased event rate in female patients in the present study. Multivariate analysis revealed that older age, diabetes, ventricular tachycardia and anemia were significant prognostic risks in both men and women with CHF.

Conclusions Female sex had a significant link with elderly CHF patients. Given the explosive increase in elderly patients in Westernized countries, further studies are needed to elucidate the evidence for treatment of female CHF patients. (Circ J 2008; 72: 2009–2014)

Key Words: Elderly; Non-ischemic cardiac disease; Preserved systolic function; Sex difference

Chronic heart failure (CHF) is a leading cause of mortality in most developed countries! The prognosis of CHF patients is still poor despite the recent progress in treatment from both the pharmacological and non-pharmacological aspect. Furthermore, ongoing rapid aging of populations in westernized countries will increase the number of CHF patients. The Japanese population has also been aging rapidly over the past few decades. The percentage of the population aged 65 years or older was 19.9% in 2005 and is expected to reach almost 30% by 2030? Japanese physicians urgently need an effective treatment strategy to improve the prognosis of elderly CHF patients and effective measures to prevent the development of congestive heart failure in these patients. Other developed countries, including the United States, will experience the same problem of aging in the near future.

Guidelines for CHF treatment have been developed based on accumulating scientific evidence obtained in randomized controlled trials with thousands of patients, but the entry

criteria usually exclude minorities such as females or elderly patients.³ Most female CHF patients are elderly and many of those are categorized as CHF with preserved systolic function, for which there is currently no ideal treatment. These patients have many comorbidities and unsolved treatment problems, and CHF in female patients is an emerging serious problem that we have to manage urgently. In our previous reports we have already noted that the sex difference was not significantly associated with the mortality of patients with CHF^{4,5} but there is still insufficient investigation of female CHF patients in Japan. Thus, the present study was designed to evaluate the current characteristics and prognosis of Japanese female patients with CHF in a CHF cohort, termed the Chronic Heart Failure Registry and Analysis in the Tohoku District (CHART) Study^{4,5}

Methods

The CHART Study and the Study Population

The CHART Study is a prospective cohort of CHF patients that was started in February 2000 in cooperation with 26 affiliated hospitals in the Tohoku region, located in the northeastern area in Japan^{4,5} Patients were registered in the cohort when at least 1 of the following 3 criteria was fulfilled: (1) certain organic heart diseases in which the echocardiographic left ventricular ejection fraction (LVEF) was 50% or less, (2) organic heart disease in which the echocardiographic left ventricular (LV) end-diastolic dimension was 55 mm or more, or (3) organic heart disease and a documented history of clinical congestive heart failure defined by the Framingham criteria⁶ We performed annual follow-

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Table 1 Baseline Characteristics of Patients

	Male	Female	p value
n	749	417	
Age (years)	66.3±13.7	72.2±12.0	<0.001
≥75 years (%)	28.1	46.6	<0.001
Follow-up period (years)	3.3±1.6	3.1±1.7	NS
NYHA class	2.0±0.6	2.1±0.6	<0.05
BMI (kg/m ²)	23.3±3.9	22.3±3.9	<0.05
BMI <18.5 kg/m ² (%)	6.6	15.1	<0.01
Blood pressure (mmHg)			
Systolic	126.1±19.2	126.9±18.8	NS
Diastolic	72.3±10.8	70.2±11.2	<0.05
Heart rate (beats/min)	74.5±14.1	75.4±14.9	NS
LV end-diastolic dimension (mm)	58.1±9.2	52.8±10.0	<0.01
LVEF (%)	47.2±14.9	52.2±17.0	<0.001
≥50% (%)	39.3	53.1	<0.05
Etiology of CHF (%)			<0.001
Ischemic cardiomyopathy	28.0	17.0	
Valvular heart disease	22.0	34.1	
LV hypertrophy	13.4	16.5	
Nonischemic cardiomyopathy	31.5	25.4	
Medical treatment (%)			
ACEI/ARB	74.7	61.7	<0.001
β-blocker	32.1	20.2	<0.001
Diuretics	78.7	82.5	NS
Digitalis	47.3	50.1	NS
Calcium antagonist	30.4	29.8	NS
Nitrate	17.0	15.3	NS
Antiarrhythmic	18.3	17.3	NS
Medical history			
Hypertension (%)	38.9	41.0	NS
Diabetes (%)	18.7	19.4	NS
Dyslipidemia (%)	16.3	14.9	NS
Atrial fibrillation (%)	40.3	37.2	NS
Ventricular tachycardia (%)	18.6	13.9	0.05
Admission for congestive heart failure (%)	74.8	80.3	<0.05
Hemoglobin (g/dl)	13.6±2.2	12.0±1.9	<0.001
Anemia (%)	35.5	48.1	<0.01
Serum creatinine (mg/dl)	1.1±0.8	1.0±0.8	<0.05
GFR (ml·min ⁻¹ ·1.73 m ⁻²)	60.0±35.2	60.4±33.4	NS
B-type natriuretic peptide (pg/ml)	244±332	313±360	<0.05

NYHA, New York Heart Association; BMI, body mass index; LV, left ventricular; LVEF, LV ejection fraction; CHF, chronic heart failure; ACEI, angiotensin-converting-enzyme inhibitor; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate calculated by the Cockcroft-Gault equation.

up surveys. Most patients usually visited the outpatient clinic of the 26 hospitals. We also conducted a telephone survey to minimize the drop out rate in cases of patients who changed their addresses. The 1-, 2-, and 3-year follow-up rates were 97.4%, 93.0%, and 87.4%, respectively.⁴ The endpoint of this study was the all-cause mortality and hospital admission for a cardiovascular cause was also recorded. The major outcome and other details of the CHART Study have previously been reported.^{4,5} Of 1,278 CHF patients who were registered in the CHART Study, the study population consisted of 1,166 symptomatic CHF patients with sufficient data.

Data Analysis

Comparisons of the baseline characteristics of male and female patients were performed using unpaired t-test or chi-square test. Numerical data are presented as the mean value±standard deviation (SD). Cumulative survival curves were constructed by the Kaplan-Meier method and the difference between the curves was evaluated for significance using the log-rank test. Multivariate Cox regression analysis was used to estimate the factors that were significantly associated with the prognosis of the study population. The

endpoint of the analysis was a composite event of admission because of congestive heart failure and all-cause mortality. The selection of covariates was performed using the backward stepwise method. The covariates evaluated in the model were age ≥75 years, anemia as defined by the WHO criteria, atrial fibrillation, diabetes, dyslipidemia, LVEF <50%, history of congestive heart failure, hypertension, ischemic etiology of CHF, serum creatinine level, the use of angiotensin-converting-enzyme inhibitors (ACEI) or angiotensin II receptor blockers (ARB), the use of β-blockers, and ventricular tachycardia. The association between disuse of CHF medication and patients' background factors was evaluated using multivariate logistic regression analysis. The covariates included in the model were age, anemia, atrial fibrillation, body mass index, diabetes, diastolic blood pressure, dyslipidemia, ejection fraction (EF), female sex, history of admission because of congestive heart failure, hypertension, ischemic etiology of CHF, New York Heart Association functional class, serum creatinine level, systolic blood pressure, and ventricular tachycardia. The selection of covariates was performed using the backward stepwise method.

All statistical analyses were performed using SPSS 15.0J

for Windows (SPSS, Chicago, IL, USA) and statistical significance was defined as a p-value less than 0.05.

Results

Baseline Characteristics and Characteristics of Female CHF Patients

Mean follow-up period was 3.2 ± 1.6 years and female patients accounted for 35.8% of the study population. Baseline characteristics of the CHF patients are shown in Table 1. The mean age of the female patients at the entry was significantly older than that of the male patients (72.2 ± 12.0 vs 66.3 ± 13.7 years). The prevalence of patients aged 75 years or older was 46.6% in the females and 28.1% in the males ($p < 0.001$). Fig 1 shows the frequency of CHF patients by age and sex. Patients aged 79 years or younger were more frequently male; however, patients aged 80 years or older were relatively more often female. Female patients had significantly more different etiologies of CHF compared with male patients (Table 1). Valvular heart disease and LV hypertrophy were more frequently observed in female patients, whereas ischemic cardiomyopathy was a significantly less common etiology of CHF. More than half of the female patients had LVEF $\geq 50\%$ and the mean LVEF was significantly higher in female patients than in male patients (Table 1: 52.2 ± 17.0 vs $47.2 \pm 14.9\%$, $p < 0.001$). Medication for CHF in the study population is shown in Table 1. The overall usage rates of ACEI, ARB, and β -blockers were surprisingly low at the entry of patients. Furthermore, sex-related differences in the prescribed CHF medications were noted for ACEI/ARB, and β -blockers.

Prognosis of Female CHF Patients

Unadjusted survival analyses using the Kaplan-Meier method were performed to evaluate the prognosis of female CHF patients using 2 endpoints: (1) composite event of all-cause mortality plus admission because of congestive heart failure and (2) composite event of cardiac-cause mortality plus admission because of congestive heart failure. These analyses clearly showed significantly increased crude event rates in female CHF patients during the follow-up period (Fig 2).

Prognostic Risks in Female and Male CHF Patients

Separate multivariate Cox regression analyses were also performed for the female (Table 2) and male (Table 3) patients to seek the factors associated with the composite event of admission because of congestive heart failure and all-cause mortality. Older age, diabetes, ventricular tachycardia, and anemia were significantly associated with the composite endpoint in both male and female patients. Reduced LVEF was a significant prognostic predictor in male patients; however, the significant association between LVEF and the composite endpoint was lost in female patients (Table 2).

Factors Associated With Disuse of the Authorized CHF Treatment

We constructed multivariate logistic regression analyses to examine which factors were related to disuse of standard CHF medical treatments such as ACEI/ARB and β -blockers. Initial analysis was performed using the overall study population and then we also separately analyzed the relationship between such disuse of medication and background characteristics in female and male patients. When using the overall

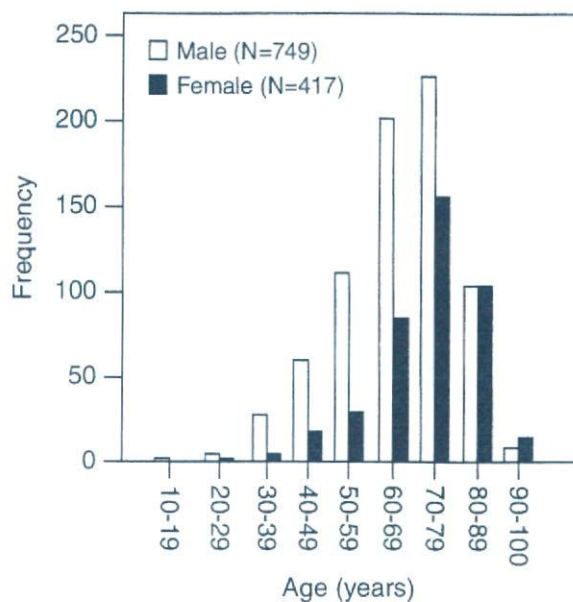


Fig 1. Number of patients with chronic heart failure by age and sex.

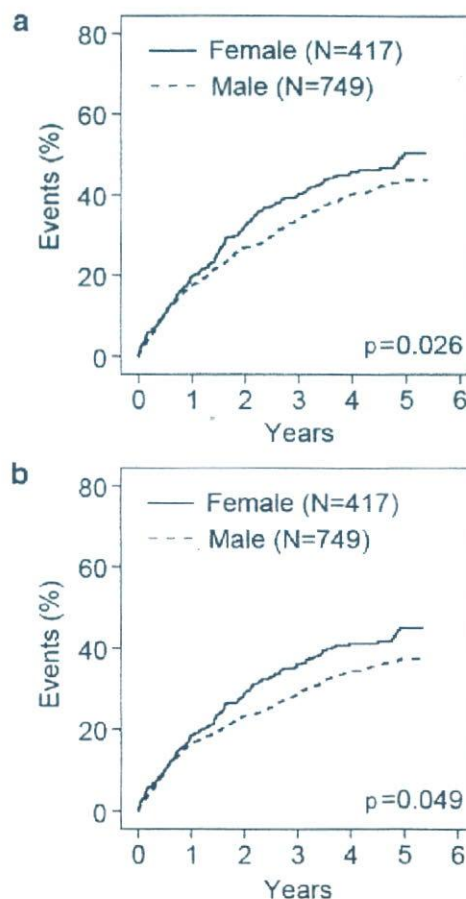


Fig 2. Unadjusted survival analyses of patients with chronic heart failure by sex. Endpoint: (a) composite event of all-cause mortality plus admission because of congestive heart failure, and (b) composite event of cardiac-cause mortality plus admission because of congestive heart failure.

Table 2 Results of Multivariate Cox Regression Analysis: Factors Associated With Composite Endpoint of Admission for Congestive Heart Failure and All-Cause Mortality in 379 Female Patients

Covariate	Hazard ratio (95%CI)	p value
Age ≥ 75 years	2.012 (1.461–2.771)	<0.001
Diabetes	1.638 (1.141–2.352)	0.007
Ventricular tachycardia	1.522 (1.017–2.276)	0.041
Anemia	1.399 (1.019–1.921)	0.038

CI, confidence interval.

Table 3 Results of Multivariate Cox Regression Analysis: Factors Associated With Composite Endpoint of Admission for Congestive Heart Failure and All-Cause Mortality in 668 Male Patients

Covariate	Hazard ratio (95%CI)	p value
Age ≥ 75 years	2.264 (1.761–2.911)	<0.001
Anemia	1.855 (1.454–2.366)	<0.001
Ventricular tachycardia	1.536 (1.173–2.011)	0.002
LVEF <50%	1.391 (1.077–1.798)	0.012
Diabetes	1.357 (1.003–1.837)	0.048

Abbreviations see in Tables 1, 2.

Table 4 Results of Multivariate Logistic Regression Analysis: Factors Associated With Disuse of CHF Medication

Medication	Covariate	Overall		Female		Male	
		OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
ACEI/ARB	Serum creatinine (mg/dl)	1.336 (1.046–1.707)	0.02	2.009 (1.071–3.769)	0.03		
	Age (years)	1.030 (1.013–1.047)	<0.001			1.036 (1.014–1.058)	0.001
	Hypertension	0.496 (0.326–0.754)	0.01	0.289 (0.135–0.618)	0.001		
	LVEF (%)			1.026 (1.005–1.048)	0.02		
β -blocker	Age (years)	1.041 (1.025–1.057)	<0.001	1.081 (1.046–1.116)	<0.001	1.030 (1.012–1.049)	0.001
	Ischemic etiology			0.312 (0.121–0.805)	0.02		

OR, odds ratio. Other abbreviations see in Tables 1, 2.

patient group, there was a significant association between the disuse of ACEI/ARB and renal insufficiency, elderly patients, and absence of hypertension (Table 4). Similarly, the disuse of β -blockers was significantly associated with elderly patients. Importantly, these analyses in the overall study population did not show a significant relationship between sex and disuse of standard CHF treatment. When only female patients were included in the analysis, renal insufficiency, absence of hypertension, and higher LVEF were associated with disuse of ACEI/ARB, and elderly patients and non-ischemic etiology were associated with disuse of β -blockers. When only male patients were included, the significant association between disuse of standard CHF medications and elderly patients was also observed, but such an association was lost in female patients regarding the use of ACEI/ARB (Table 4).

Discussion

We clarified the characteristics of female CHF patients in our CHART cohort study. The major findings of the present study are as follows: (a) elderly patients, CHF with preserved systolic function, and non-ischemic etiology of CHF were frequently observed among the female patients, (b) the penetration rate of standard CHF treatment, such as ACEI/ARB and β -blockers, was relatively low in female patients, (c) although the sex difference was not a significant prognostic factor as presented in our previous study^{4,5} the crude incidence rates of cardiovascular events were apparently higher in female patients after study entry, and (d) most of the characteristics exclusively observed in female patients may originate in the dominance of female patients in the elderly. These findings suggest an emerging problem of female CHF patients because the population in most developed countries is rapidly aging, with a resultant increase in the number of CHF patients.

Sex Difference and the Prognosis of CHF Patients

Cardiovascular disease is the second leading cause of death in Japan. Many retrospective studies suggest that there

are some clinically relevant differences between female and male patients in terms of prevalence, appearance, management and prognosis of the disease. For instance, women with atrial fibrillation have a greater risk of stroke than men with atrial fibrillation and women with diabetes have a significantly higher mortality from cardiovascular disease than men with diabetes.^{7,8} However, little is known of the reasons why cardiovascular disease affects female and male individuals differently.

The impact of sex differences on the prognosis of CHF patients is still controversial. Several observational studies and subanalyses of randomized controlled trials have reported that female patients have a better prognosis than male patients.^{9–16} The most recent report using the population of the CHARM Program showed that fewer women (30.4%) than men (33.3%) experienced cardiovascular death or heart failure hospitalization during the study period and that this prognostic advantage in females was maintained after adjustment for other background variables including age.¹⁷ In contrast to those findings, there are several reports that describe a comparable prognosis between male and female CHF patients.^{18–20} Furthermore, the SOLVD study revealed that male patients have a significantly better prognosis than female patients.²¹ Although our previous study failed to show that the sex-difference was a significant predictor of all-cause mortality^{4,5} in the present study the unadjusted survival analyses constructed by Kaplan-Meier method showed that the crude event rates of the combined outcomes in female patients were apparently higher compared with male patients in a real clinical setting (Fig 2). The reason for these inconsistent results remains unknown; however, different background factors of the study populations may have influenced the results, because the sex is not a factor that can be randomized and the adjustment by multivariate analysis may not be perfect to eliminate the influence of confounding factors such as the etiology of heart failure and the age of patients. We speculate that the high proportion of elderly population in female patients in the present study is the main reason for the apparently poor prognosis in female CHF patients.

Prognostic Risks in CHF Patients

There have been many investigations of the prognostic predictors in patients with CHF, including our previous reports.^{4,5} The present study results suggest that reduced LVEF may not be associated with the prognosis of female CHF patients. The real mechanism of such sex-specific difference is unknown; however, the higher incidence of patients with preserved LVEF among females may be a reason. Bhatia et al have reported that CHF patients with preserved EF are more likely to be older and female, and the adjusted 1-year mortality was similar between patients with LVEF <50% and those with LVEF ≥50%.²² Owan et al also reported that survival did not improve over time for CHF patients with preserved EF, despite recent progress in CHF treatment.²³

Characteristics of Female CHF Patients

Previous studies have demonstrated that female CHF patients are characterized by the following: (1) many of them are elderly, (2) LV systolic function is preserved in many patients, and (3) non-ischemic etiology of CHF is frequent.¹⁻²¹ The present findings are consistent with those results. We also found that cachexia was frequent among the female patients, and the usage rates of standard CHF medications were lower. Most of the profiles observed in the female CHF patients were considered to be characteristics commonly found in elderly CHF patients.

CHF Treatment in Female Patients

Female CHF patients in the present study showed the lower usage rates of standard CHF treatments such as ACEI/ARB or β -blocker (Table 1). Previous reports showed that the association between sex and reduced prescription rates of evidence-based cardiovascular medications was inconsistent, as with heart failure; however, there was a strong decline in ACEI and β -blocker prescription with increasing age in most studies.²⁴⁻²⁷ Masoudi et al reported that underuse of ACEI was commonly observed in elderly patients with CHF and they also revealed that patient, physician, and hospital factors were not strongly associated with underuse of ACEI/ARB, except for serum creatinine level.²⁸

Several investigators have reported possible reasons for the underuse of standard treatment in CHF patients. Komajda et al showed that the low prescription rates of ACEI and β -blockers could be explained by the several factors: (1) underestimation of the poor prognosis of CHF patients, (2) underestimation of the benefit of such CHF treatment, (3) concerns about the potential adverse reactions, (4) elderly population, who are commonly CHF patients, tend to have many comorbidities such as asthma, pulmonary disease, diabetes, and stroke, (5) the etiology of the CHF might influence the prescription rate, (6) the medical specialty, such as cardiology or general practice, may influence the prescription rate, and (7) the high proportion of CHF patients with preserved LVEF, often because of hypertension, may be treated by calcium-channel blockers rather than the recommended CHF drugs.²⁹ The underuse of such CHF treatment was significantly associated with age in our analysis using the overall population (Table 4). The analysis using only female patients revealed that disuse of ACEI/ARB was significantly associated with renal dysfunction and preserved LVEF, but was not associated with elderly patients. The reason of this inconsistency remains unknown, but we speculated the following: (1) physicians were reluctant to prescribe ACEI/ARB in female CHF patients with renal dysfunction or preserved LVEF regardless of whether they

were elderly or not, (2) because both renal dysfunction and preserved LVEF were frequently observed in elderly patients, these factors might have acted as confounding variables in our multivariate model.

Aging Society and Female CHF Patients

For the past 3 decades, Japanese people have been enjoying the longest life expectancy, 79.0 years in males and 85.8 years in females.³⁰ The most important contributory factor in the longevity of Japanese people is the reduced death rate in the elderly population,³¹ which suggests an explosive increase in the number of elderly CHF patients in the near future in Japan. The most evident characteristic of the female CHF patients in the present study was older age, which might cause many of the other characteristics of female CHF patients. Female and elderly would be the common profile of future CHF patients, in whom we still need scientific evidence for the effective treatment of CHF and the prevention of congestive heart failure.

Study Limitations

In the multivariate Cox regression model used in the present study, 38 female patients and 81 male patients were excluded because of missing baseline data, which might have influenced the correct analysis of the difference between female and male CHF patients. The percentage of female patients who had coronary angiography before the entry might be different from that of male patients. Because our CHF cohort has no baseline data regarding coronary angiography, our diagnosis of ischemic heart disease may be not perfect in a small number of patients. This possible misdiagnosis of ischemic heart disease might influence the findings. Our CHF cohort did not include data regarding exercise tolerance in patients with CHF, which is considered to be an important prognostic predictor in these patients. Furthermore, the results cannot be extrapolated to the general population or patients with noncardiovascular diseases because the study population was a subpopulation of a cohort of CHF patients.

Conclusion

Most developed countries are currently rapidly aging with a resultant explosive increase in the number of CHF patients, many of whom are elderly and female, which is a group that has not been enrolled in randomized controlled trials. We urgently need scientific evidence in order to improve the prognosis and quality of life for these patients.

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Prognostic Importance of Chronic Kidney Disease in Japanese Patients With Chronic Heart Failure

— Implications of the CHART Study —

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Background Renal insufficiency is common in patients with chronic heart failure (CHF), so to improve the prognosis of patients with cardiovascular risks clinical guidelines recommend estimating the glomerular filtration rate (GFR), which detects chronic kidney disease more accurately than does the serum creatinine level alone. However, the clinical usefulness of the estimated GFR (eGFR) in Japanese CHF patients is still unclear.

Methods and Results Of 1,278 patients registered in a Japanese CHF registry, termed the Chronic Heart Failure Analysis and Registry in the Tohoku District study, the study population included 920 symptomatic patients with sufficient data. Baseline eGFR ($\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$) was calculated using the Cockcroft-Gault equation. Patients were divided into three groups based on eGFR: ≥ 60 , 30–59, and $< 30 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$. Kaplan-Meier analysis revealed that the incidence of the combined event of all-cause death and admission because of CHF was significantly higher in patients with reduced eGFR and such patients were older and more frequently had an ischemic etiology of CHF, a higher prevalence of diabetes, lower hemoglobin level, and higher B-type natriuretic peptide level. Multivariate Cox regression analysis showed that reduced eGFR was significantly associated with the combined endpoint.

Conclusions GFR should be evaluated in all Japanese patients with CHF to improve risk stratification and treatment. (Circ J 2008; 72: 173–178)

Key Words: Estimated glomerular filtration rate; Heart failure; Prognosis; Renal insufficiency; Risk stratification

Chronic heart failure (CHF) is the most frequent cause of mortality in many developed countries and the prevalence of patients with CHF will explosively increase in Japan, because of the rapid aging of the Japanese population.¹ Investigation of the risk factors for mortality and risk stratification of CHF patients is the first-line strategy to improve the prognosis and quality of life (QOL) of these patients.^{2,3} Many Western investigators have reported that renal insufficiency is common in CHF patients and severe chronic kidney disease (CKD) is associated with mortality.^{4,5} The serum creatinine level has been the commonly used marker for evaluating renal function in the clinical setting; however, this examination may not be sufficient for accurate diagnosis of CKD. The guidelines from the United States National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) recommend estimating the glomerular filtration rate (GFR) in all patients with risk factors for cardiovascular diseases to identify CKD earlier in order to slow disease progression. The estimated GFR (eGFR), calculated from the serum creatinine level using a prediction equation, detects CKD more accurately than does the serum creatinine level alone⁶ and it is also used in dis-

ease staging. The purpose of the present study was to elucidate the prognostic importance of CKD evaluated by eGFR in Japanese patients with CHF using a heart failure cohort from the Chronic Heart Failure Analysis and Registry in the Tohoku District (CHART) study.

Methods

Study Population

The rationale and details of the CHART study have been described previously.² Eligible subjects were stable patients with at least one of the following clinical findings: (1) certain organic heart disease and a documented history of clinical CHF defined by the Framingham criteria;⁷ (2) organic heart disease and an echocardiographic ejection fraction (EF) $\leq 50\%$; or (3) organic heart disease and an echocardiographic left ventricular end-diastolic dimension ≥ 55 mm. We started the entry of patients on February 2000 and follow-up surveillance was performed annually. Of 1,278 patients who were included in the CHART registry, the present study population comprised 920 patients with sufficient data who had at least New York Heart Association (NYHA) class II symptoms. Patients on chronic hemodialysis at study entry were excluded.

Renal Function

We calculated the baseline eGFR using the Cockcroft-Gault (CG) equation (ml/min)⁸ and the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation ($\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$)⁹ (Table 1). We adjusted the eGFR for body surface area (BSA: m^2) by multiplying by $1.73/\text{BSA}$

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