コードNo.		食品名		重量	重量g（可食部）	備考
	12	100%果汁	1カップ	200	200	
菓子	1	和菓子　甘納豆	1袋	15	15	でん六小袋甘納豆　テトラパック　/　白花いんげん（3粒）
	2	和菓子　今川焼	1個	80	80	
	3	和菓子　ういろう	1個	50	50	青柳ＨＰ　一口サイズ真空パック　　cf　360g/棹
	4	和菓子　カステラ	切（ﾌｰﾄﾞﾓﾃﾞﾙ）	25	25	
	5	和菓子　くし団子（みたらし）	1本	60	60	
	6	和菓子　大福餅	個（ﾌｰﾄﾞﾓﾃﾞﾙ）	70	70	
	7	和菓子　蒸し饅頭	1切	70	70	虎屋栗蒸羊羹1棹　　690ｇ
	8	和菓子　もなか	1個	52	52	白松が最中　　中型　φ6cm
	9	和菓子　羊かん	1切	70	70	虎屋竹皮包羊羹1棹　700ｇ　/　一口サイズ小型羊羹50ｇ
	10	あめ　あめ玉	3個	15	15	のど飴4g　チェルシー4.3g
	11	和菓子　かりんとう	大5個	45	45	
	12	和菓子　そばボーロ	1枚	4	4	
	13	煎餅　ｺﾞﾏ南部煎餅	1枚	15	15	
	14	米菓　あられ	小袋1	35	35	
	15	米菓　揚げ煎餅	1袋	36	36	天乃屋：プチ歌舞伎揚げ（小袋）/　大判1枚10g
	16	米菓　焼き煎餅	1枚	10	10	
		柿ピー　6袋入り(210ｇ)	小袋1	35	35	亀田製菓（せんべい25ｇ　&　ピーナッツ10g）
		ぽたぽた焼き　2枚	小袋1		15	
		ハッピーターン　1枚	小包装		4	
		ソフトサラダ　2枚	小袋1		15	
		まがり煎餅　2枚	小袋1		13	
	17	焼プリン	1個	90	90	モロゾフ
		プリン	1個	75	75	グリコプッチンプリン75g　(3個パック)
	18	ケーキ　カップケーキ	1個	50	50	参考：バターケーキ
	19	ケーキ　シュークリーム	1個	60	60	萩の月　60g
	20	ケーキ　ショートケーキ	1個	100	100	
	21	ゼリー	1個	100	100	マンナンライフ蒟蒻畑　カップ25g

コードNo.		食品名		重量	重量g（可食部）	備考
	22	ドーナツ（ケーキ）	1個	50	50	参考：イーストドーナッツ1個65g(ハニディップ)
	23	ババロア	1個	80	80	
	24	ホットケーキ	1枚	50	50	
	25	クラッカー（オイルスプレー）	5枚	18	18	クラッカー（ナビスコリッツ）　(86kcal)
	26	ｽﾅｯｸ菓子、ポテトチップス	レギュラー	90	90	小袋：24g
	27	ビスケット（ハード）	1枚	8	8	ビスケット（森永マリー） クッキー(カントリマーム)　10.5ｇ/枚 サブレ（ココナッツサブレ）　6ｇ/枚 鳩サブレ　30g/枚
	28	チョコレート（板チョコ）	1枚	20	20	参考 ・明治製菓ミルクチョコレート　55g/枚 ・アーモンドチョコ　5g / 粒　[内訳　チョコ 4g / アーモンド1g) ・ポッキー　20g / 10本　[内訳　ビスケット8ｇ / チョコ12g)
	29	あずきアイス,シャーベット	1本	70	70	井村屋
種実類	1	ピーナッツ、アーモンド、カシューナ	10粒	15	15	
	2	ぎんなん	10粒	20	15	
	3	くり　日本栗(生)	1個	20	16	
	4	くり　甘ぐり（天津）	10個	64	50	甘栗むいちゃいました　1袋100g
	5	クルミ　煎り	5個	10	10	(料理の使用例)　和え物1人前5ｇ　クルミ餅1個10ｇ
	6	ごま　煎り	大さじ1	9	9	
		ごまあえ	大さじ1強	10	10	フードモデル(生100g,ゆで80g)のほうれん草の胡麻和え
	7	だいず　きな粉	大さじ1	6	6	

<参考資料>
※　データは食品メーカーのホームページ
※　「エネルギー早わかり」女子栄養大出版部
※　量は全て可食部です

Ⅱ.研究成果の刊行に関する一覧表

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
河野雄平, 高木洋子	減塩指導の実践：病院での取り組み	土橋卓也, 大屋祐輔, 苅尾七臣	臨床高血圧ワークブック第3巻 生活習慣修正指導のノウハウ	医薬ジャーナル社	大阪	2013	p37-45

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
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Tanaka F, Makita S, Onoda T, Tanno K, Ohsawa M, Itai K, Sakata K, Omama SI, Yoshida Y, Ogasawara K, Ogawa A, Ishibashi Y, Kuribayashi T, Okayama A, Nakamura M; Iwate-Kenco Study Group.	Predictive Value of Lipoprotein Indices for Residual Risk of Acute Myocardial Infarction and Sudden Death in Men With Low-Density Lipoprotein Cholesterol Levels <120 mg/dl.	Am J Cardiol	2013 15;112(8)	1063-1068	2013
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Miura K Ando K Tsuchihashi T Yoshita K Watanabe N Kawarazaki H Matsuura H Kusaka M Kai H Kawano Y	Report of the Salt Reduction Committee of the Japanese Society of Hypertension: (2) Goal and strategies of dietary salt reduction in the management of hypertension	Hypertension Research	36	1020-1025	2013
中谷武嗣、秦　広樹、藤田知之、小林順二郎、村田欣洋、瀬口　理、簗瀬正伸、堀　由美子、和田恭一、植田初江、宮田茂樹、内藤博昭	心臓移植および補助人工心臓の経験。	胸部外科	66(1)	63-67	2013

Ⅲ.研究成果の刊行物・別刷

EUROPEAN SOCIETY OF CARDIOLOGY®

European Journal of Heart Failure (2014) **16**, 309–316
doi:10.1002/ejhf.22

Impact of elevated heart rate on clinical outcomes in patients with heart failure with reduced and preserved ejection fraction: a report from the CHART-2 Study

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Received 4 July 2013; revised 13 October 2013; accepted 18 October 2013; online publish-ahead-of-print 31 December 2013

Aims It is still controversial whether elevated baseline heart rate (HR) is associated with higher mortality in patients with heart failure (HF) with preserved ejection fraction (HFpEF). We compared the impacts of baseline HR on mortality in patients with HFpEF and those with HF with reduced ejection fraction (HFrEF).

Methods and results We enrolled consecutive 2688 patients in Stage C or D HF with sinus rhythm from our Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study ($n = 10\ 219$). The prognostic impact of HR increase was compared between the two groups, defined as left ventricular ejection fraction of $\leq 50\%$ (HFrEF) and $> 50\%$ (HFpEF). Cox regression analysis revealed that elevated baseline HR was associated with increased all-cause mortality in both groups [hazard ratio for the highest tertile (HH) 1.77 in HFrEF, $P = 0.008$; HH1.82 in HFpEF, $P = 0.001$]. However, as for mode of death, elevated HR was associated with cardiovascular (CV) death in HFpEF (HH 2.17, $P = 0.012$), but the association was modest in HFrEF (HH1.49, $P = 0.14$): in particular, impact on HF death was different between HFpEF (HH 3.79, $P = 0.020$) and HFrEF (HH 1.07, $P = 0.864$). In contrast, the prognostic impact of baseline HR on non-CV death was noted only in patients with HFrEF. β-Blocker therapy was associated with reduced HF mortality in HFrEF (hazard ratio 0.49, $P = 0.038$) but not in HFpEF (hazard ratio 0.64, $P = 0.321$).

Conclusions Elevated HR was associated with increased CV death in HFpEF compared with HFrEF, although its impact on all-cause mortality was comparable between the two groups.

Keywords Heart failure • Heart rate • Prognosis

Introduction

Elevated baseline heart rate (HR) could be a reflection of activated sympathetic nervous system, a negative force-frequency response of failing myocardium and worsening myocardial ischaemia.[1–3] Furthermore, increased heart rate was associated with increased systemic inflammation and endothelial dysfunction.[4] Thus, it is widely considered to be a predictor of poor prognosis in patients with heart failure (HF). Indeed, unfavourable prognostic impact of elevated baseline HR has been repeatedly noted in patients with HF with reduced ejection fraction (HFrEF).[5–8] For instance, in addition to β-blocker, HR reduction with ivabradine has been reported as effective for patients with HFrEF.[9] In the European Society of Cardiology guidelines, ivabradine is recommended to

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reduce the risk of HF hospitalization in symptomatic (NYHA class II–IV) patients in sinus rhythm with an EF ≤ 35% and a heart rate remaining ≥ 70 bpm despite treatment with an evidence-based dose of β-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB).[10] However, it is still controversial whether elevated baseline HR is associated with poor prognosis in patients with HF with preserved ejection fraction (HFpEF).[11–13] This is possibly because these previous findings regarding the association between baseline HR and prognosis of HFpEF were derived from *post hoc* analysis of randomized control trials[11,13] or from an observational study with a relatively small sample size,[12] and thus likely involved selection bias. Furthermore, even in the positive studies,[11,12] it has not been elucidated which modes of deaths or cardiac events were particularly associated with elevated HR in HFpEF. Thus, it has been awaited to address the prognostic impacts of elevated HR in patients with HFpEF in more detail, using a large-scale prospective observational cohort.

In the present study, we thus examined the prognostic impact of baseline HR in HFpEF in our prospective observational multicentre cohort study, named the Chronic Heart Failure Analysis and Registry in the Tohoku District 2 (CHART-2) Study, where we successfully enrolled consecutive 10 219 patients in Stage B, C, and D HF.[14–16] The aim of the present study was to compare the impact of elevated HR on clinical outcomes between HFpEF and HFrEF, especially on cardiovascular (CV) death and HF death.

Methods

Design of the present study

The CHART-2 Study is a prospective observational multicenter cohort study, as previously reported in detail (NCT00418041).[14] Among 4735 stage C/D patients in the CHART-2 Study ($n = 10\ 219$),[14–16] 2863 in sinus rhythm without history of paroxysmal atrial fibrillation or implantable cardiac device were enrolled in the present study. They were divided into the two groups according to the baseline left ventricular ejection fraction (LVEF) of ≤ 50% (HFrEF) or > 50% (HFpEF) in the present study.[17] The prognostic impact of elevated baseline HR was examined by calculating relative risks in the highest and second highest tertiles of baseline HR compared with the lowest tertile. We also examined whether β-blocker therapy could affect the relationship between HR increase and prognostic endpoints between the HFrEF and the HFpEF groups. Furthermore, we explored optimal cut-off points of HR to split risk of mortality endpoints using the classification and regression tree (CART) method.[18,19]

Statistical analysis

The outcomes of all-cause death, CV death and non-CV death were estimated by Kaplan–Meier curve and log-rank test in both groups. The impact of each tertile defined by baseline HR for the endpoints was examined using the univariate and multivariate Cox proportional hazard model. The covariates for the multivariate analysis included gender, age, body mass index, systolic blood pressure (SBP), LV diastolic diameter (LVDd), LVEF, haemoglobin level, estimated glomerular filtration ratio, malignant diseases, β-blocker, RASI, enrolment location (inpatient or outpatient) and HR categories. The association between β-blockers and outcomes was assessed using univariate and multivariate Cox proportional hazard models with the same covariates except β-blocker use. Statistical analysis was performed using IBM SPSS Statistics 19 software (IBM, Armonk, NY, USA) and R software (version 2.5). To determine the optimal cut-off points of HR to split CV and non-CV mortality for overall, HFrEF and HFpEF patients, respectively, an open-source adaptation of the CART algorithm from R software was used.

Methods are mentioned in more detail in the Supplementary material online, Appendix S1.

Results

Baseline characteristics

Among the 2863 Stage-C/D HF patients in sinus rhythm enrolled in the present study, we finally analysed 2688 (93.9%) patients in whom both HR and LVEF data were available (mean age 67.5 ± 13.0 years, male 70%, and median follow-up period of 3.13 years). *Table 1* shows baseline characteristics of the patients in the HFrEF and HFpEF groups. The number of patients in the HFpEF group was twice that in the HFrEF group. The HFpEF group was characterized by more females, older age, higher SBP, lower HR and NYHA functional class, higher prevalence of hypertension and valvular heart disease, and lower serum brain natriuretic peptide levels. The prevalence of β-blocker use was significantly lower in the HFpEF group than in the HFrEF group (40% vs. 65%, $P < 0.001$). Supplementary material online, Table S1, shows the baseline characteristics of tertiles of baseline HR for both groups. Although almost all backgrounds except β-blocker use were comparable among the tertiles in the HFrEF group, the tertiles in the HFpEF group showed statistically significant trends in LVDd, LVEF value, ischaemic heart disease, prevalence of female sex and loop diuretics use, in addition to β-blocker use.

Impact of HR increase on clinical outcomes

During the follow-up period of median 3.13 years, 133 (15.0%) and 176 (9.8%) all-cause deaths, 79 (8.9%) and 76 (4.2%) CV deaths, 42 (4.7%) and 32 (1.8%) deaths for heart failure, 164 (18.5%) and 122 (6.8%) admission for heart failure, 42 (4.7%) and 86 (4.8%) non-CV deaths were noted in the HFrEF and HFpEF groups, respectively. There were 26 deaths due to unknown origins. The actual number of events and event rate in tertiles are shown in Supplementary material online, Table S2. The Kaplan–Meier curves and multivariate Cox regression analyses revealed that the higher HR tertile had more increased risk of all-cause death in both the HFrEF and HFpEF groups (*Figures 1A,B* and *2*). As for CV and HF death, a significant relationship between HR and mortality was noted in the HFpEF group (hazard ratios of the highest HR tertile 2.17, 95% CI 1.19–3.99, $P = 0.012$ for CV death and 3.79, 95% CI 1.24–11.62, $P = 0.020$ for HF death). In contrast, in the HFrEF group, elevated HR was not significantly associated with increased risk of CV mortality and HF mortality (hazard ratios of the highest HR tertile 1.49, 95% CI 0.87–2.54, $P = 0.143$ for CV death; and 1.07, 95% CI 0.50–2.27, $P = 0.864$ for HF death) (*Figures 1C,D* and *2*). Furthermore, a significant relationship between HR and non-CV

Table 1 Baseline characteristics of two groups defined by baseline LVEF

	Total $n = 2688$ (100%)	HFrEF $n = 885$ (32%)	HFpEF $n = 1803$ (67%)	*P*-value
Patients' characteristics				
Male sex	1874 (70%)	654 (74%)	1220 (68%)	0.001
Age (years)	67.5 ± 13	66.6 ± 13.0	67.9 ± 13.0	0.020
BMI	24.0 ± 3.9	23.5 ± 4.0	24.3 ± 3.8	< 0.001
Systolic BP (mmHg)	127.9 ± 19.0	123.3 ± 19.8	130.2 ± 18.2	< 0.001
Heart rate (bpm)	71.1 ± 13.5	72.9 ± 13.7	70.2 ± 13.3	< 0.001
LVDd (mm)	52.0 ± 9.2	58.6 ± 9.1	48.7 ± 7.3	< 0.001
LVEF (%)	57.2 ± 15.6	38.8 ± 8.8	66.2 ± 8.9	< 0.001
NYHA				< 0.001
I	702 (26%)	154 (17%)	548 (31%)	
II	1701 (64%)	605 (69%)	1096 (61%)	
III	254 (9%)	111 (13%)	143 (8%)	
IV	18 (1%)	11 (1%)	7 (0%)	
Medical history				
Hypertension	2109 (78%)	637 (72%)	1472 (82%)	< 0.001
Diabetes mellitus	758 (28%)	258 (29%)	500 (28%)	0.466
Dyslipidaemia	2079 (77%)	695 (79%)	1384 (77%)	0.327
Stroke	420 (16%)	122 (14%)	298 (17%)	0.070
Malignant disease	280 (10%)	92 (10%)	188 (10%)	1.000
Ischaemic heart disease	1594 (59%)	517 (58%)	1077 (60%)	0.531
Cardiomyopathy	469 (17%)	267 (30%)	202 (11%)	0.000
Valvular heart disease	472 (18%)	89 (10%)	383 (21%)	< 0.001
Laboratory data				
Haemoglobin (g/dL)	13.2 ± 2.0	13.2 ± 2.0	13.2 ± 1.9	0.667
Albumin (mg/dL)	4.1 ± 0.5	4.1 ± 0.5	4.1 ± 0.5	0.005
LDL-C (mg/dL)	105.4 ± 30.7	105.6 ± 31.3	105.3 ± 30.4	0.840
eGFR (mL/min/1.73 m^2)	62.8 ± 25.3	60.7 ± 22.6	63.8 ± 26.5	0.002
BNP [pg/mL, median (IQR)]	71 (29–186)	135 (53–316)	53 (22–131)	< 0.001
Medication				
β-Blockers	1292 (48%)	575 (65%)	717 (40%)	< 0.001
RASI	1966 (73%)	706 (80%)	1260 (70%)	< 0.001
Loop diuretics	1073 (40%)	506 (57%)	567 (31%)	< 0.001
Aldosterone antagonists	548 (20%)	303 (34%)	245 (14%)	< 0.001
Statins	1240 (46%)	407 (46%)	833 (46%)	0.934

BMI, body mass index; BP, blood pressure; LVDd, left ventricular diastolic diameter; LDL-C, low-density lipoprotein-cholesterol; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; RASI, renin–angiotensin system inhibitors.

mortality was noted in the HFrEF group (hazard ratio of the highest HR tertile 2.33, 95% CI 1.09–4.97, $P = 0.029$), but not in the HFpEF group (*Figure 2*). Hazard ratio for HF admission tended to increase according to HR increment in the HFpEF group but not in the HFrEF group (*Figure 2*). The prognostic impact of baseline HR on CV and HF mortality were more evident in the HFpEF than in the HFrEF group, whereas such an impact on non-CV death was noted only in the HFrEF group (*Figure 2*).

β-Blocker use and prognostic impact of HR

When the baseline characteristics were examined according to LVEF and use of β-blockers, the patients treated with β-blockers were younger and had lower HR compared with those treated without β-blockers in both the HFrEF and the HFpEF groups (Supplementary material online, Table S3). SBP was lower in the patients with β-blockers compared with those without β-blockers in the HFrEF group (121.4 ± 19.6 vs. 126.8 ± 19.7 mmHg), but not in the HFpEF group (130.3 ± 18.4 vs. 130.1 ± 18.1 mmHg). Importantly, both univariate and multivariate Cox regression analyses revealed that use of β-blockers was significantly associated with a reduction in HF death in the HFrEF but not in the HFpEF group (*Table 2*). Risk reduction by β-blockers for all-cause death, CV death and HF death were observed in the HFrEF patients but not in the HFpEF patients (*Table 2*). In contrast, use of β-blockers was not associated with reduced risk of admission for HF in either group. The association of mortality with HR categories was notable for all-cause death and CV death only in patients with HFpEF and treated without β-blockers.

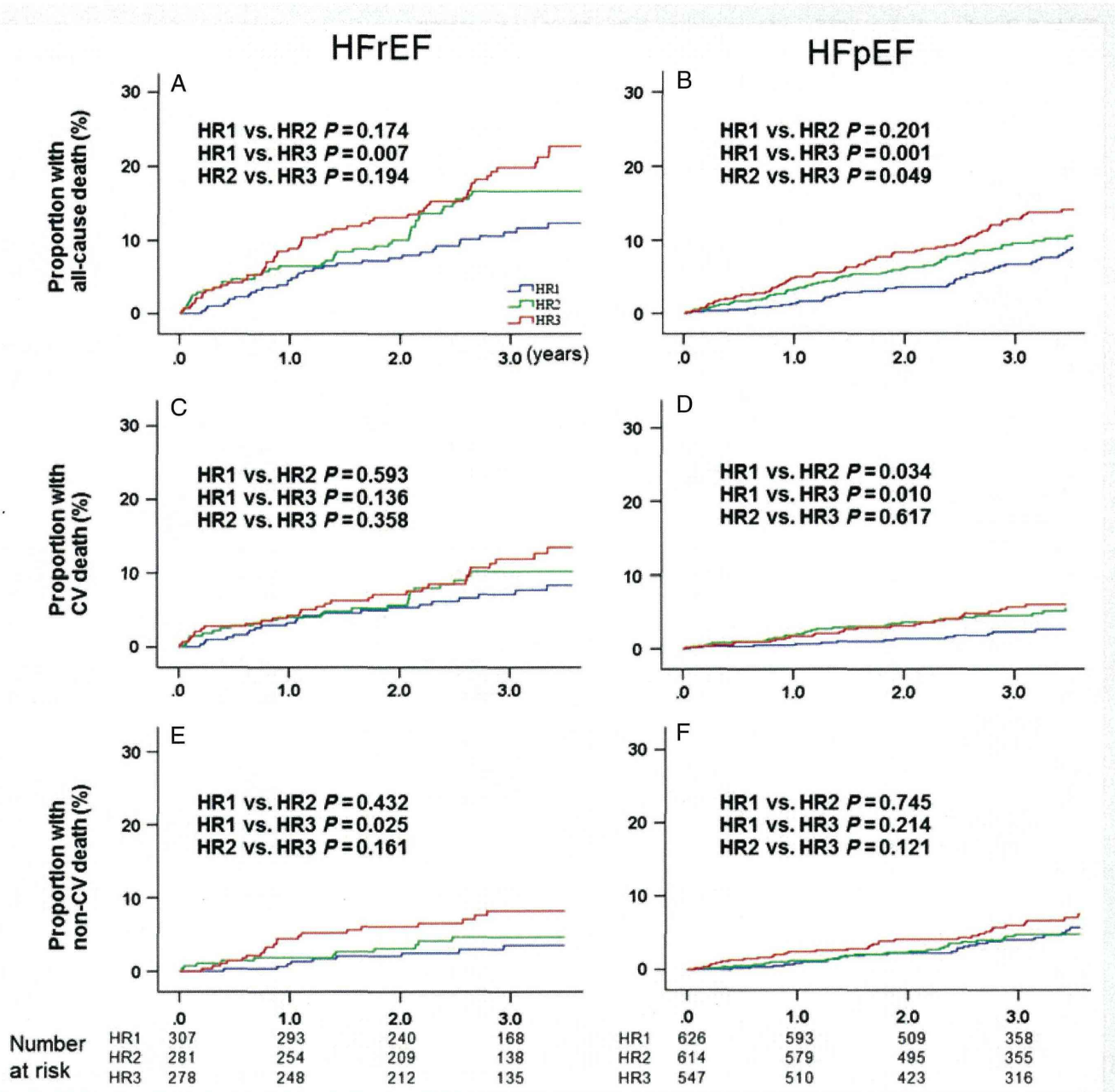

Figure 1 Kaplan–Meier curves for outcomes in HFrEF and HFpEF. Kaplan–Meier curves for all-cause death of HFrEF (*A*) and HFpEF (*B*), CV death of HFrEF (*C*) and HFpEF (*D*), and non-CV death of HFrEF (*E*) and HFpEF (*F*).

Cut-off value of HR for CV death

We attempted to search cut-off values of HR to split both HFrEF and HFpEF patients for CV death based on CART analysis (*Table 3*). CART analysis suggested that the primary cut-off value in baseline HR to discern a high-risk population for CV death were 63.5, 69.5, and 63.5 bpm in the overall, HFrEF, and HFpEF patients, respectively, and that those for non-CV death were all 71.5 bpm (*Table 3*). A total of 1683 (62.6%), 511 (57.7%), and 1172 (65.0%) patients had HR equal to or more than the cut-off values with hazard ratios of 1.85 (95% CI 1.26–2.73, $P=0.002$), 1.60 (1.00–2.55, $P=0.051$), and 2.04 (1.17–3.53, $P=0.012$) for CV death in the overall, HFrEF, and HFpEF patients, respectively (*Table 3*).

Discussion

In the present study, we examined the difference in the prognostic impact of HR status between the HFpEF and HFrEF groups in the CHART-2 study, the largest-scale prospective observational study for patients in Stage B, C, and D HF in Japan.[14–16] The present study is the first to report an association in detail between elevated HR and modes of death in HFpEF in comparison with those

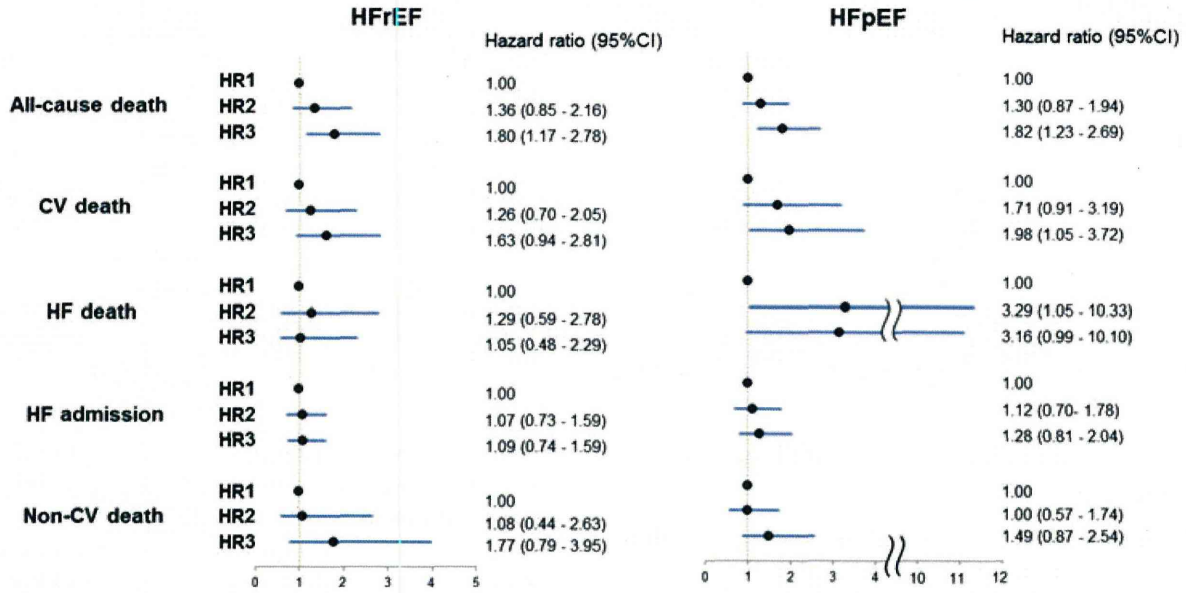

Figure 2 Association between baseline HR and outcomes in HFrEF and HFpEF. Adjusted hazard ratio for all-cause death, CV death, HF death, HF admission, and non-CV death in HFrEF and HFpEF.

Table 2 Unadjusted and adjusted hazard ratios of β-blocker for all-cause death, CV death, HF death, and HF admission in HFrEF and HFpEF

	Unadjusted				Adjusted[a]			
	HFrEF		HFpEF		HFrEF		HFpEF	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
All-cause death	0.70 (0.50–0.99)	0.042	0.81 (0.59–1.10)	0.174	0.71 (0.49–1.03)	0.075	1.11 (0.79–1.54)	0.553
CV death	0.68 (0.43–1.06)	0.088	0.79 (0.49–1.27)	0.326	0.68 (0.42–1.11)	0.123	0.96 (0.58–1.59)	0.874
HF death	0.51 (0.28–0.94)	0.030	0.51 (0.23–1.13)	0.096	0.49 (0.25–0.96)	0.038	0.64 (0.26–1.55)	0.321
HF admission	1.16 (0.84–1.63)	0.351	0.98 (0.68–1.41)	0.926	1.05 (0.74–1.49)	0.797	0.97 (0.66–1.43)	0.887

[a]Adjusted by age, sex, BMI, systolic blood pressure, LVEF, LVDd, Hb, eGFR, RASI, and HR catgories.
CV, cardiovascular; HF, heart failure.

in HFrEF. The results demonstrated that the impact of elevated baseline HR on CV mortality was notable in the HFpEF group compared with the HFrEF group, particularly on HF mortality.

Elevated baseline HR and all-cause mortality in HF

The present study demonstrated the impacts of HR status on all-cause mortality in both HFrEF and HFpEF patients, where the increased risk of all-cause deaths in patients with higher HR was noted even after adjustment for patient background, medication, and possible other confounders for mortality and morbidity. This relationship between elevated baseline HR and increased mortality appears to be reasonable in the clinical setting, because elevated HR could be a reflection of neurohumoral activation of the sympathetic nervous system, an excessive compensation for reduced cardiac output and myocardial ischaemia. However, it is still controversial whether elevated baseline HR is associated with increased all-cause mortality in HFpEF as in HFrEF. For example, in the subanalysis of the CHARM programmes, the correlation of baseline HR and risks for all-cause death was noted in both the HFrEF and HFpEF groups,[11] whereas the subanalysis of the DIG study revealed that elevated HR was associated with all-cause death in HFrEF but not in HFpEF patients.[13] Thus, our results regarding prognostic impacts of elevated HR on all-cause mortality are consistent with those of the CHARM programmes, but not with those of the DIG study, providing additional evidence for the relationship between baseline HR and clinical outcomes in a large cohort of patients receiving contemporary management for Stage C/D HF in the real-world setting.

Table 3 Split point of HR for outcomes in overall patients, HFrEF and HFpEF

		First split point of HR	Hazard ratio of higher HR group[a]	95% CI	*P*-value
CV death	All	63.5 bpm	1.85 (≥ 64 bpm)	1.26–2.73	0.002
	HFrEF	69.5 bpm	1.60 (≥ 67 bpm)	1.00–2.55	0.051
	HFpEF	63.5 bpm	2.04 (≥ 64 bpm)	1.17–3.53	0.012
Non-CV death	All	71.5 bpm	1.68 (≥ 72 bpm)	1.19–2.38	0.004
	HFrEF	71.5 bpm	1.34 (≥ 72 bpm)	1.22–4.50	0.011
	HFpEF	71.5 bpm	1.45 (≥ 72 bpm)	0.95–2.22	0.082

[a]Unadjusted hazard ratios of patients with HR more than optimal split point indicated by CART analysis (higher HR group) over those with HR not more than indicated (lower HR group). The minimum HRs of the higher HR group are shown in parentheses next to the hazard ratios.

Different impact of baseline HR between HFrEF and HFpEF

Bui *et al.* demonstrated that HFpEF was associated with a higher risk of in-hospital mortality with increasing admission HR compared with HFrEF among patients hospitalized for HF, suggesting that higher HR might have imparted increased in-hospital mortality in HFpEF patients.[20] As for the impacts of elevated baseline HR on long-term CV mortality, the present study may provide the first evidence that such impacts on CV death, particularly on HF death, are rather significant in HFpEF compared with HFrEF (*Figure 2*). The relationship between elevated HR and increased CV mortality in HFpEF appears reasonable, since HFpEF is generally complicated by diastolic dysfunction and thus could be further worsened by shortening of the diastolic period according to an increase in HR.[21] In the present study, there was no association between HR and hospitalization for HF in HFrEF or HFpEF (*Figure 2*). In addition, the present study may provide the first evidence for the association between baseline HR and non-CV death in HFrEF patients, following an association between HR and non-CV mortality being observed in the general population.[22–24] Although the precise mechanisms remain to be elucidated, low physical activity, elevated adrenergic activity and smoking might be possible explanations for the association between elevated HR and increased non-CV mortality.[22–24]

Cut-off value of HR for CV death in HFrEF and HFpEF

In order to determine the cut-off point for HR to partition Stage C/D patients according to the mortality rates, we performed CART analysis, demonstrating that 63.5, 69.5, and 63.5 bpm could be the primary splitting points for CV death among the overall, HFrEF, and HFpEF patients, respectively (*Table 3*). The univariate Cox regression analysis revealed that HFpEF patients with HR ≥ 63.5 bpm had an increased risk for CV death with a statistical significance (hazard ratio 2.04, $P = 0.012$ for patients with HR ≥ 64 bpm), and HFrEF patients with HR ≥ 69.5 bpm with a tendency (hazard ratio 1.60, $P = 0.051$ for patients with HR ≥67 bpm). These results may suggest that the therapeutic range of HR to reduce CV mortality could be lower in HFpEF compared with HFrEF patients (63.5 vs. 69.5 bpm). This was likely because a longer duration of the diastolic period is necessary to reduce CV mortality in patients with diastolic dysfunction compared with systolic dysfunction. In this context, HR reduction therapy could be an option to reduce CV mortality in HFpEF patients. Indeed, it has been reported that selective HR reduction by ivabradin improves vascular stiffness and left ventricular systolic and diastolic function in mice.[25] A subanalysis of the SHIFT trial, which enrolled patients with HF and EF < 35%, revealed that the prognostic impact of HR reduction by ivabradine was greater in patients who had baseline HR ≥ 75 and had achieved < 60 bpm or heart rate reductions > 10 bpm.[26] Although the cut-off point of HR to discern CV mortality may vary according to the baseline ejection fraction, further reduction of HR with ivabradine could be effective in patients with HFpEF. However, further investigations are required to elucidate whether HR reduction is effective in the management of HFpEF patients in real-world practice.

β-Blocker therapy in HFpEF

It is widely accepted that β-blocker therapy improves LVEF and reduces mortality in HFrEF patients through inhibition of sympathetic nervous activity and reduction in HR and oxygen consumption.[27,28] The present study suggested different prognostic impacts of β-blockers between HFrEF and HFpEF, as β-blocker therapy was associated with decreased HF mortality in patients with HFrEF but not in those with HFpEF. β-Blockers could theoretically be beneficial in patients with HFpEF because shortening of the diastolic period could exacerbate diastolic dysfunction, a common feature of the disorder.[21] However, it was previously reported that β-blockers may not be so useful in HFpEF patients,[29] a consistent finding of the present study. However, there remains a possibility that standard doses of β-blockers (for Japanese patients) in the present study was not sufficient to reduce CV mortality for HFpEF patients. In fact, Yamamoto *et al.* recently reported that a higher dose of carvedilol was associated with lower incidence of a composite of cardiovascular death and unplanned hospitalization for any cardiovascular cause in patients with HFpEF in the Japanese population.[30] Thus, further studies are warranted to examine whether higher doses of β-blockers could improve the mortality of HFpEF patients.

Study limitations

Several limitations should be mentioned for the present study. First, the number of HFrEF patients was smaller than that of HFpEF patients, and therefore the power might not be enough to detect a statistical significance in HFrEF patients; thus, interpretation should be made with caution. Second, the CHART-2 Study is a prospective, observational study that reflects the real-world practice of HF, as consecutive HF patients were enrolled with a minimal selection bias; however, we have to consider influences on the results by unknown confounders. Third, in the present study, we only used the data at the entry and did not take into consideration the possible changes in LVEF, HR, episodes of arrhythmia, particularly those of atrial fibrillation, medication, and other covariates during the follow-up period. In addition, no data were available for β-blocker therapy, such as timing of initiation, daily doses, adherence, discontinuation, and reasons for the presence or absence of prescription. Thus, it was difficult to elucidate the prognostic impact of β-blocker therapy in the present study. Fourth, in the present study, according to European Society of Cardiology guidelines,[15] we chose the cut-off value of LVEF 50% to define HFpEF. However, caution is needed in interpreting the present results when comparing other cohorts with different cut-off values to discriminate between HFrEF and HFpEF, such as 35% or 40%.[8,10] Finally, all subjects in the CHART-2 Study were Japanese people, which may limit generalization of the present results to patients in other countries.

Conclusions

We demonstrated the different impacts of elevated baseline HR on CV and non-CV mortality between HFrEF and HFpEF in the CHART-2 Study. Although the influence of elevated baseline HR on all-cause mortality was comparable, elevated HR was significantly associated with CV death in HFpEF, but insignificantly in HFrEF, particularly for HF death. Further studies are needed to elucidate the relationship between elevated baseline HR and mortality in order to improve the survival of HF patients.

Acknowledgements

We thank all the members of the Tohoku Heart Failure Society and the staff of the Department of Evidence-based Cardiovascular Medicine for their valuable contributions.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics of tertiles defined by baseline heart rate of the two groups

Table S2. Actual number of event for tertiles in HFrEF and HFpEF

Table S3. Baseline characteristics across four groups defined by LVEF and β-blocker

Appendix S1. Impact of elevated heart rate on clinical outcomes in patients with heart failure with reduced and preserved ejection fraction: a report from the CHART-2 study

Funding

The Ministry of Health, Labour, and Welfare, Tokyo, Japan (#18190401, #21170901, #24120301, #24140601); and the Ministry of Education, Culture, Sports, Science, and Technology, Tokyo, Japan (#24790605, #25330032).

Conflict of interest: The Department of Evidence-based Cardiovascular Medicine, Tohoku University Graduate School of Medicine, is supported in part by the unrestricted research grants from Daiichi Sankyo Co., Ltd. (Tokyo, Japan), Bayer Yakuhin, Ltd. (Osaka, Japan), Kyowa Hakko Kirin Co., Ltd. (Tokyo, Japan), Kowa Pharmaceutical Co., Ltd. (Tokyo, Japan), Novartis Pharma K.K. (Tokyo, Japan), Dainippon Sumitomo Pharma, Co., Ltd. (Osaka, Japan), and Nippon Boehringer Ingelheim Co., Ltd. (Tokyo, Japan). H.S. has received lecture fees from Bayer Yakuhin, Ltd, (Osaka, Japan), Daiichi Sankyo Co., Ltd. (Tokyo, Japan) and Novartis Pharma K.K., (Tokyo, Japan).

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HbA_{1c} and the Risks for All-Cause and Cardiovascular Mortality in the General Japanese Population

NIPPON DATA90

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OBJECTIVE—Associations between HbA_{1c} and cardiovascular diseases (CVD) have been reported mainly in Western countries. It is not clear whether HbA_{1c} measurements are useful for assessing CVD mortality risk in East Asian populations.

RESEARCH DESIGN AND METHODS—The risk for cardiovascular death was evaluated in a large cohort of participants selected randomly from the overall Japanese population. A total of 7,120 participants (2,962 men and 4,158 women; mean age 52.3 years) free of previous CVD were followed for 15 years. Adjusted hazard ratios (HRs) and 95% CIs among categories of HbA_{1c} (<5.0%, 5.0–5.4%, 5.5–5.9%, 6.0–6.4%, and ≥6.5%) for participants without treatment for diabetes and HRs for participants with diabetes were calculated using a Cox proportional hazards model.

RESULTS—During the study, there were 1,104 deaths, including 304 from CVD, 61 from coronary heart disease, and 127 from stroke (78 from cerebral infarction, 25 from cerebral hemorrhage, and 24 from unclassified stroke). Relations to HbA_{1c} with all-cause mortality and CVD death were graded and continuous, and multivariate-adjusted HRs for CVD death in participants with HbA_{1c} 6.0–6.4% and ≥6.5% were 2.18 (95% CI 1.22–3.87) and 2.75 (1.43–5.28), respectively, compared with participants with HbA_{1c} <5.0%. Similar associations were observed between HbA_{1c} and death from coronary heart disease and death from cerebral infarction.

CONCLUSIONS—High HbA_{1c} levels were associated with increased risk for all-cause mortality and death from CVD, coronary heart disease, and cerebral infarction in general East Asian populations, as in Western populations.

Diabetes Care 36:3759–3765, 2013

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Received 19 November 2012 and accepted 17 May 2013.
DOI: 10.2337/dc12-2412
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-2412/-/DC1.
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Since the association between HbA_{1c} and microangiopathy was established in patients with diabetes, HbA_{1c} has been used for not only the determination of glucose control among patients with diabetes but also the diagnosis of diabetes (1). Measurement of HbA_{1c} is also recommended for cardiovascular risk assessment in asymptomatic adults without a diagnosis of diabetes (2) because the association between HbA_{1c} and the risk for cardiovascular disease (CVD) in general populations has been reported, mainly from Western countries (3–10).

There have been only a few studies regarding the associations between HbA_{1c} and CVD in Asian populations (11–13). Furthermore, these studies were from Japan, and HbA_{1c} measurements were expressed mainly using Japan Diabetes Society (JDS) values rather than National Glycohemoglobin Standardization Program (NGSP) values; thus, we cannot compare these results with those from Western countries. Recently, the JDS provided an equation for the conversion from HbA_{1c} (JDS) to HbA_{1c} (NGSP) units (14), which allows a comparison of the results from Japanese studies and previous studies from Western countries.

CVD in East Asian people is characterized by a higher rate of stroke and lower rate of coronary heart disease compared with CVD in Western populations (15). In one previous study evaluating the association between HbA_{1c} and incidence of stroke in Japan, ischemic stroke, but not hemorrhagic stroke, was associated with HbA_{1c} in Asian populations (12). Other studies from Japan (11,13) showed a significant association between HbA_{1c} and CVD; however, the number of participants and CVD events were too small to calculate the risk by subtype of CVD, such as coronary heart disease, stroke, cerebral infarction, and cerebral hemorrhage.

The current study was performed to examine the association between HbA_{1c} using NGSP values and the risks for death from all causes and from CVD (coronary

heart disease, cerebral infarction, and cerebral hemorrhage) in a 15-year cohort study of representative Japanese men and women randomly selected from the overall Japanese population.

RESEARCH DESIGN AND METHODS—NIPPON DATA (National Integrated Project for Prospective Observation of Noncommunicable Disease And its Trends in the Aged) is a cohort study of participants in the National Survey on Circulatory Disorders of Japan, which has been conducted by the Ministry of Health, Labor and Welfare of Japan. NIPPON DATA includes two cohort studies in which the baseline data were surveyed in 1980 (NIPPON DATA80) and in 1990 (NIPPON DATA90); the details of the studies have previously been described (16–21). Here, we investigated the data from NIPPON DATA90 because HbA_{1c} was not measured in the NIPPON DATA80 baseline survey.

A total of 8,383 residents (3,503 men and 4,880 women, aged ≥30 years) from 300 randomly selected districts from all over Japan participated in the baseline survey and were followed until November 2005. The participation rate in this survey was 76.5%. Of the 8,383 participants, 1,263 were excluded because of a history of coronary heart disease or stroke (n = 358), missing information in the baseline survey (n = 649), or incomplete residential access information (n = 256). The remaining 7,120 participants (2,962 men and 4,158 women) were analyzed in the current study. The institutional review board of Shiga University of Medical Science (no. 12-18, 2000) approved this study.

Baseline examination

BMI was calculated as weight in kilograms divided by the square of height in meters. Trained observers measured baseline blood pressure using a standard mercury sphygmomanometer on the right arm of seated participants. Nonfasting blood samples were obtained at the baseline survey. Serum was separated by centrifugation soon after blood coagulation. Plasma samples were collected into siliconized tubes containing sodium fluoride and shipped to a central laboratory (SRL, Tokyo, Japan) for blood measurements. HbA_{1c} was measured using the high-performance liquid chromatography method. The range of coefficient of variance of HbA_{1c} measurement in this laboratory was 1.19–1.79% intra-assay and 0.24–0.45% interassay in the 1990s. HbA_{1c} (JDS) values were converted to HbA_{1c} (NGSP) values using the conversion formula provided by JDS: HbA_{1c} NGSP value (%) = 1.02 × JDS value (%) + 0.25 (14). All present analyses adopted the HbA_{1c} values of the NGSP method. Serum total cholesterol (milligrams per deciliter) was measured using an enzymatic method, and HDL cholesterol was measured after heparin-calcium precipitation (22). Public health nurses collected the information about smoking, alcohol consumption, habitual exercise, and medical history. Treatment for diabetes was self-reported, which included diet, exercise, and medication with regular visits to hospitals.

End points

We reported previously that participants who had died in each area were confirmed by computer matching with data from the National Vital Statistics database, using area, sex, date of birth, and death as key codes (16,23). The underlying causes of death in the National Vital Statistics were coded according to the ICD-9 until 1994 and according to the ICD-10 from 1995. Details of these classifications have previously been described (16,17,20,23). Deaths coded were defined as follows: CVD, from 393 to 459 (ICD-9) and from I00 to I99 (ICD-10); coronary heart disease, from 410 to 414 (ICD-9) and from I20 to I25 (ICD-10); stroke, from 430 to 438 (ICD-9) and from I60 to I69 (ICD-10); cerebral infarction, 433, 434, 437.8a, and 437.8b (ICD-9) and I63 and I69–3 (ICD-10); cerebral hemorrhage, from 431 to 432 (ICD-9) and I61 and I69.1 (ICD-10).

Statistical analysis

Participants were divided into six groups; five groups of participants without treatment for diabetes according to HbA_{1c} level, <5.0% (31 mmol/mol), 5.0–5.4% (31–36 mmol/mol), 5.5–5.9% (37–41 mmol/mol), 6.0–6.4% (42–47 mmol/mol), and ≥6.5% (48 mmol/mol), and one group for participants with treatment for diabetes. One-way ANOVA or the χ^2 test was used to compare characteristics of participants at baseline according to HbA_{1c} categories. We calculated crude mortality and hazard ratios (HRs) for death due to all causes, CVD, coronary heart disease, stroke, cerebral infarction, and cerebral hemorrhage according to the six categories. The Cox proportional hazards model was used to calculate adjusted HRs. Adjustment for possible confounders was performed sequentially: for age and sex (age- and sex-adjusted model), then plus BMI, smoking habit (non-, ex-, or current smoker), drinking habit (non-, ex-, or daily drinker), habitual exercise (yes or no), systolic blood pressure, total cholesterol, HDL cholesterol, and medical treatment for hypertension and dyslipidemia (multivariate-adjusted model). HRs for death associated with a 1% increment in HbA_{1c} were calculated for participants without treatment for diabetes. HRs were also calculated separately for each sex, and the interaction between sex and HbA_{1c} on the mortality from each cause of death was calculated. As HbA_{1c} was affected by anemia (24), we evaluated the HRs for participants without anemia (n = 5,978) for sensitivity analyses. Anemia was defined as hemoglobin concentration <13.5 g/dL for men and <12.0 g/dL for women. The statistical analysis package SPSS 17.0 for Windows (SPSS, Chicago, IL) was used for all statistical analyses. All probability values were two tailed, and the significance level was set at $P < 0.05$.

RESULTS—The baseline characteristics of study participants are shown in Table 1. The mean age at baseline was 52.3 years, and the mean BMI was 22.9 kg/m^2. The mean HbA_{1c} level was 5.3% (34 mmol/mol). Participants with higher HbA_{1c} levels were older and had higher values for BMI, systolic and diastolic blood pressure, and serum total cholesterol; lower HDL cholesterol levels; and higher smoking rates.

There were 99,605 person-years of follow-up for the 7,120 participants. Among all of the participants, there were 1,104 deaths, including 304 deaths from CVD, 61 from coronary heart disease, and 127 from stroke (78 from cerebral infarction, 25 from cerebral hemorrhage, and 24 from unclassified stroke).

Mortality and adjusted HRs according to HbA_{1c} categories are shown in Table 2. The multivariate-adjusted HR for CVD death associated with a 1% increment in HbA_{1c} was 1.32. Relations to HbA_{1c} with CVD death were graded and continuous, and the multivariate-adjusted HR for CVD death in participants with HbA_{1c} 6.0–6.4% (42–47 mmol/mol) was 2.18 (95% CI 1.22–3.87), and that in participants with HbA_{1c} ≥6.5% (48 mmol/mol) was 2.75 (1.43–5.28); both HRs were significantly higher than that in participants with HbA_{1c} <5.0% (31 mmol/mol). Similarly, HR for CVD death in participants with treatment for diabetes was 2.04 (1.19–3.50) and was significantly higher than that in participants with HbA_{1c} <5.0% (31 mmol/mol). Similar associations were

observed between HbA_{1c} and death from coronary heart disease and death from cerebral infarction. On the other hand, cerebral hemorrhage was not significantly associated with HbA_{1c}.

When the association was evaluated separately by sex (Table 3), the results were similar between men and women, and no interaction was observed between sex and HbA_{1c} with regard to the association with all-cause death or death from any CVD (*P* for interactions: 0.283 for all-cause death, 0.405 for CVD death, 0.119 for death from coronary heart disease, 0.709 for death from stroke, 0.880 for death from cerebral infarction, and 0.390 for death from cerebral hemorrhage). The results were similar when the associations were evaluated after excluding those with anemia (Table 3).

CONCLUSIONS—In the present prospective, community-based study in Japan, the HbA_{1c} level in individuals without treatment for diabetes was significantly and positively associated with an increased risk for all-cause mortality and death from CVD. Among CVDs, coronary heart disease and cerebral infarction were associated with HbA_{1c} levels. The multivariate-adjusted HR for death from CVD was significantly higher for the participants with HbA_{1c} >6.0% (42 mmol/mol) compared with HbA_{1c} <5.0% (31 mmol/mol), even though they were not diagnosed as having diabetes based on HbA_{1c} levels.

Since the association between HbA_{1c} and microangiopathy in patients with diabetes was established, HbA_{1c} has been used for not only the determination of glucose control among patients with diabetes but also the diagnosis of diabetes (1). Macrovascular complications are not specific to diabetes, and the association between HbA_{1c} and the risk for CVD has been reported in the general population (3–13) as well as patients with diabetes (25–28). Recent American College of Cardiology Foundation and American Heart Association guidelines indicate that measurement of HbA_{1c} may be reasonable for cardiovascular risk assessment in asymptomatic adults without a diagnosis of diabetes (2). However, the association between HbA_{1c} and the risk for CVD has been reported mainly from Western countries. A recent study in Japan found a significant association between HbA_{1c} and the incidence of CVD (13), although the number of participants was small (n = 1,607) and no association between HbA_{1c} and the incidence of myocardial infarction

Table 1—*Baseline characteristics of study participants according to HbA_{1c} levels at baseline: NIPPON DATA90*

		HbA_{1c} in participants without treatment for diabetes						
Characteristics	Any	<5.0% (<31 mmol/mol)	5.0–5.4% (31–36 mmol/mol)	5.5–5.9% (37–41 mmol/mol)	6.0–6.4% (42–47 mmol/mol)	≥6.5% (≥48 mmol/mol)	Participants with treatment for diabetes	*P**
N	7,120	2,143	3,505	964	191	126	191	
Age (years)	52.3 ± 13.6	46.7 ± 12.6	52.9 ± 13.3	58.4 ± 12.7	60.4 ± 12.2	56.0 ± 11.7	62.7 ± 10.5	<0.001
Women	58.4	65.7	58.0	49.8	42.9	46.0	51.3	<0.001
BMI (kg/m^2)	22.9 ± 3.2	22.3 ± 2.8	22.9 ± 3.2	23.6 ± 3.5	23.8 ± 3.6	25.0 ± 4.4	23.5 ± 3.2	<0.001
Systolic blood pressure (mmHg)	135.1 ± 20.6	129.3 ± 19.9	135.4 ± 20.0	140.7 ± 20.4	145.3 ± 19.2	146.7 ± 22.5	146.9 ± 19.2	<0.001
Diastolic blood pressure (mmHg)	81.2 ± 11.9	79.0 ± 11.8	81.7 ± 11.6	83.0 ± 12.3	84.0 ± 12.4	86.7 ± 12.9	82.7 ± 11.2	<0.001
Total cholesterol (mg/dL)	203.0 ± 37.8	191.7 ± 33.4	204.8 ± 36.8	214.9 ± 39.2	218. 5 ± 41.0	223.6 ± 47.8	207. 4 ± 46.7	<0.001
HDL cholesterol (mg/dL)	54.2 ± 15.3	56.4 ± 15.3	54.3 ± 15.3	51.6 ± 14.8	49.1 ± 15.4	47.1 ± 15.1	48.7 ± 12.9	<0.001
Hemoglobin (g/dL)	13.7 ± 1.6	13.6 ± 1.5	13.6 ± 1.6	13.7 ± 1.7	13.8 ± 1.9	14.2 ± 1.9	13.9 ± 1.6	<0.001
Smoking status								<0.001
Never smoker	60.3	67.7	60.1	50.9	46.1	48.4	51.3	
Ex-smoker	11.0	10.4	10.2	12.7	16.8	12.7	18.3	
Current smoker	28.7	21.9	29.7	36.4	37.2	38.9	30.4	
Alcohol consumption								<0.001
Never drinker	68.5	70.8	70.1	62.8	55.0	58.7	62.8	
Ex-drinker	3.0	2.8	2.7	2.6	5.2	4.8	9.4	
Current drinker	28.5	26.4	27.2	34.6	39.8	36.5	27.7	
Regular exercise	19.9	17.5	19.5	23.7	25.7	15.9	32.5	<0.001
Medical treatment for								
hypertension	12.9	8.3	11.6	18.3	29.8	24.6	38.2	<0.001
Medical treatment for dyslipidemia	2.7	1.4	2.3	3.8	8.9	5.6	12.6	<0.001

Data are means ± SD or percentages. *One-way ANOVA for continuous variables and χ^2 test for categorical variables.

Table 2—*Risk of death according to the baseline HbA_{1c} levels in 7,120 participants: NIPPON DATA90, 1990–2005*

	HbA_{1c} in participants without treatment for diabetes						
	<5.0% (<31 mmol/mol)	5.0–5.4% (31–36 mmol/mol)	5.5–5.9% (37–41 mmol/mol)	6.0–6.4% (42–47 mmol/mol)	≥6.5% (≥48 mmol/mol)	Participants with treatment for diabetes	HbA_{1c} 1% increment †
Person-years of follow-up	30,864	49,192	13,123	2,372	1,727	2,327	
All-cause death							
Cases	199	529	211	63	31	71	
Mortality (per 1,000 person-years)	6.4	10.8	16.1	26.6	17.9	30.5	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	1.04 (0.89–1.23)	1.01 (0.83–1.23)	1.75 (1.32–2.33)	1.61 (1.11–2.36)	1.66 (1.26–2.19)	1.16 (1.05–1.27)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	1.08 (0.92–1.28)	1.07 (0.88–1.31)	1.95 (1.46–2.61)	1.72 (1.17–2.52)	1.80 (1.37–2.38)	1.20 (1.09–1.32)
Death from CVD							
Cases	44	147	64	17	12	20	
Mortality (per 1,000 person-years)	1.4	3.0	4.9	7.2	6.9	8.6	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	1.28 (0.91–1.79)	1.32 (0.89–1.94)	2.11 (1.21–3.70)	2.83 (1.50–5.37)	2.02 (1.19–3.43)	1.29 (1.10–1.52)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	1.31 (0.93–1.84)	1.38 (0.93–2.04)	2.18 (1.22–3.87)	2.75 (1.43–5.28)	2.04 (1.19–3.50)	1.32 (1.12–1.56)
Death from coronary heart disease							
Cases	9	27	14	2	3	6	
Mortality (per 1,000 person-years)	0.3	0.5	1.1	0.8	1.7	2.6	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	1.20 (0.57–2.56)	1.55 (0.67–3.59)	1.23 (0.27–5.69)	3.45 (0.93–12.7)	3.10 (1.10–8.77)	1.38 (1.01–1.87)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	1.15 (0.53–2.48)	1.46 (0.62–3.47)	1.11 (0.23–5.31)	3.19 (0.83–12.3)	2.77 (0.95–8.06)	1.40 (1.02–1.92)
Death from stroke							
Cases	20	60	29	9	3	6	
Mortality (per 1,000 person-years)	0.6	1.2	2.2	3.8	1.7	2.6	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	1.14 (0.69–1.89)	1.30 (0.73–2.30)	2.48 (1.13–5.45)	1.58 (0.47–5.31)	1.32 (0.53–3.29)	1.19 (0.90–1.58)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	1.19 (0.71–1.99)	1.38 (0.76–2.48)	2.74 (1.21–6.18)	1.57 (0.46–5.38)	1.40 (0.55–3.55)	1.20 (0.89–1.60)
Death from cerebral infarction							
Cases	8	42	15	5	2	6	
Mortality (per 1,000 person-years)	0.3	0.9	1.1	2.1	1.2	2.6	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	1.98 (0.93–4.22)	1.58 (0.67–3.74)	3.72 (1.21–11.4)	2.78 (0.59–13.1)	3.26 (1.13–9.41)	1.31 (0.93–1.85)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	2.13 (0.99–4.59)	1.84 (0.76–4.43)	5.28 (1.66–16.8)	3.30 (0.68–15.9)	4.09 (1.38–12.1)	1.38 (0.98–1.92)
Death from cerebral hemorrhage							
Cases	8	8	4	4	1	0	
Mortality (per 1,000 person-years)	0.3	0.2	0.3	1.7	0.6	—	
Age- and sex-adjusted HR (95% CI)	1.00 (ref.)	0.41 (0.15–1.09)	0.52 (0.16–1.75)	2.82 (0.84–9.42)	1.31 (0.16–10.5)	—	1.01 (0.49–2.04)
Multivariate-adjusted HR (95% CI)*	1.00 (ref.)	0.44 (0.16–1.18)	0.50 (0.15–1.74)	2.46 (0.69–8.78)	1.29 (0.16–10.7)	—	0.96 (0.45–2.04)

*Adjusted for age, sex, BMI, smoking status, alcohol consumption, habitual exercise, systolic blood pressure, total cholesterol, HDL cholesterol, and medical treatment for hypertension and dyslipidemia. †Participants with treatment for diabetes were excluded from the analyses.

Table 3—*Multivariate-adjusted HR* of death according to the baseline HbA_{1c} levels in men, women, and participants without anemia: sensitivity analyses, NIPPON DATA90, 1990–2005*

	HbA_{1c} in participants without treatment for diabetes					Participants with treatment for diabetes
	<5.0% (<31 mmol/mol)	5.0–5.4% (31–36 mmol/mol)	5.5–5.9% (37–41 mmol/mol)	6.0–6.4% (42–47 mmol/mol)	≥6.5% (≥48 mmol/mol)	
All-cause death						
Men (*n* = 2,962)	1.00 (ref.)	1.09 (0.86–1.37)	1.19 (0.90–1.56)	1.96 (1.33–2.88)	1.96 (1.19–3.21)	1.85 (1.28–2.67)
Women (*n* = 4,158)	1.00 (ref.)	1.03 (0.81–1.31)	0.92 (0.68–1.24)	1.94 (1.24–3.05)	1.28 (0.68–2.40)	1.73 (1.14–2.65)
Participants without anemia (*n* = 5,978)	1.00 (ref.)	1.07 (0.88–1.30)	0.93 (0.73–1.18)	1.67 (1.18–2.39)	1.59 (1.01–2.51)	1.72 (1.24–2.39)
Death from CVD						
Men (*n* = 2,962)	1.00 (ref.)	1.12 (0.69–1.80)	1.17 (0.67–2.05)	1.71 (0.75–3.87)	3.98 (1.81–8.74)	1.86 (0.90–3.88)
Women (*n* = 4,158)	1.00 (ref.)	1.46 (0.89–2.39)	1.51 (0.86–2.67)	2.78 (1.22–6.32)	1.16 (0.27–5.02)	2.21 (0.98–4.96)
Participants without anemia (*n* = 5,978)	1.00 (ref.)	1.31 (0.88–1.95)	1.10 (0.68–1.77)	1.63 (0.80–3.32)	2.16 (0.97–4.82)	2.03 (1.10–3.75)
Death from coronary heart disease						
Men (*n* = 2,962)	1.00 (ref.)	1.46 (0.48–4.47)	2.71 (0.85–8.65)	1.16 (0.13–10.6)	4.83 (0.83–28.3)	4.37 (1.11–17.2)
Women (*n* = 4,158)	1.00 (ref.)	0.83 (0.29–2.40)	0.32 (0.06–1.73)	0.99 (0.10–9.26)	2.57 (0.29–22.9)	1.00 (0.11–9.11)
Participants without anemia (*n* = 5,978)	1.00 (ref.)	0.99 (0.43–2.28)	1.01 (0.37–2.73)	1.13 (0.23–5.59)	3.16 (0.79–12.7)	2.25 (0.69–7.28)
Death from stroke						
Men (*n* = 2,962)	1.00 (ref.)	0.91 (0.46–1.83)	0.86 (0.37–2.02)	1.75 (0.55–5.64)	2.37 (0.63–8.94)	1.47 (0.46–4.71)
Women (*n* = 4,158)	1.00 (ref.)	1.48 (0.68–3.22)	2.02 (0.85–4.80)	4.39 (1.36–14.2)	—	1.20 (0.25–5.86)
Participants without anemia (*n* = 5,978)	1.00 (ref.)	1.24 (0.67–2.28)	1.10 (0.53–2.28)	1.40 (0.44–4.42)	1.30 (0.29–5.91)	1.18 (0.38–3.68)
Death from cerebral infarction						
Men (*n* = 2,962)	1.00 (ref.)	1.38 (0.54–3.54)	0.44 (0.11–1.85)	2.05 (0.39–10.7)	3.23 (0.55–19.0)	2.88 (0.77–10.8)
Women (*n* = 4,158)	1.00 (ref.)	3.98 (1.21–25.6)	5.57 (1.21–25.6)	16.5 (2.61–104.1)	—	7.54 (1.02–55.8)
Participants without anemia (*n* = 5,978)	1.00 (ref.)	3.30 (1.15–9.49)	2.20 (0.67–7.26)	3.53 (0.62–20.2)	3.34 (0.36–31.3)	4.83 (1.16–20.1)
Death from cerebral hemorrhage						
Men (*n* = 2,962)	1.00 (ref.)	0.45 (0.11–1.83)	1.11 (0.26–4.72)	1.70 (0.28–10.2)	1.44 (0.14–14.6)	—
Women (*n* = 4,158)	1.00 (ref.)	0.27 (0.06–1.15)	—	2.73 (0.38–19.5)	—	—
Participants without anemia (*n* = 5,978)	1.00 (ref.)	0.22 (0.06–0.77)	0.36 (0.09–1.51)	0.92 (0.17–5.05)	1.00 (0.11–8.78)	—

*Adjusted for age, sex, BMI, smoking status, alcohol consumption, habitual exercise, systolic blood pressure, total cholesterol, HDL cholesterol, and medical treatment for hypertension and dyslipidemia.

was shown owing to the small number of cases. Our results demonstrate that HbA_{1c} was significantly associated with not only all-cause mortality and death from CVD but also death from coronary heart disease in a Japanese population. The Atherosclerosis Risk in Communities Study showed that multivariate-adjusted HRs in participants with HbA_{1c} 6.0–6.4% and ≥6.5% were 1.88 (95% CI 1.55–2.28) and 2.46 (1.84–3.28) for the incidence of coronary heart disease and 2.19 (1.58–3.05) and 2.96 (1.87–4.67) for ischemic stroke, respectively, compared with participants with HbA_{1c} 5.0–5.5% (10). The European Prospective Investigation into Cancer (EPIC)-Norfolk study also evaluated the HbA_{1c} categories and CVD death, and relative risk of the participants with HbA_{1c} 5.5–6.9% was ~2.5 compared with the participants with HbA_{1c} <5.0% (3). Thus, the relative strength of the association of HbA_{1c} with CVD risk in Japanese people was similar to that in Western individuals.

Previous studies in Western countries indicated increased cardiovascular risk with an increase in HbA_{1c} within the nondiabetic range (3–8,10,29). In the current study, participants with HbA_{1c} 6.0–6.4% (42–47 mmol/mol) had a significantly increased risk of death from CVD and cerebral infarction. HbA_{1c} values were more closely related to postprandial hyperglycemia than to fasting glucose levels (30). High-normal HbA_{1c} levels, even within the nondiabetic range, may reflect the presence of impaired glucose tolerance and postprandial hyperglycemia, which are important risk factors for CVD (31). Individuals with an HbA_{1c} level of 6.0–6.4% (42–47 mmol/mol) are at high risk for progression to diabetes (1) as well as high risk for CVD. Future public health campaigns targeting CVD and type 2 diabetes should focus on lifestyle and other risk factors in these high-risk individuals.

Significant linear associations between HbA_{1c} and all-cause death and death from CVD were observed in our study. Recently, a J-shape relationship between HbA_{1c} and all-cause mortality was reported in a study of the New Zealand general population (8). Participants with

HbA_{1c} <4.0% (20 mmol/mol) had the highest mortality rates of those without diabetes, and the HR was 2.90 compared with participants with an HbA_{1c} of 4.0–4.9% (20–30 mmol/mol). As discussed by the authors, it was difficult to determine whether the increased risk of mortality for participants with very low HbA_{1c} levels was causal or merely a result of reserve causation due to preexisting disease. In our study, the number of participants with HbA_{1c} <4.0% (20 mmol/mol) was too small (n = 15) to evaluate the risk of death.

The association between the incidence of hemorrhagic stroke and diabetes is controversial. Studies have indicated an increased risk for hemorrhagic stroke in individuals with diabetes diagnosed by fasting glucose levels (32); a decreased risk in individuals with overt diabetes (33); or no association in individuals with overt diabetes (34) or with diabetes defined by fasting (35), 1-h (36), or 2-h post–glucose load measurements (35). Similar to our results, those of one previous study showed no association between hemorrhagic stroke and HbA_{1c} level (12). The etiology and pathophysiology of ischemic and hemorrhagic stroke are different (37), which may also indicate different risk factors for the two stroke subtypes.

The strength of the current study was that these data were from a large, nationally representative cohort, and thus our findings can be generalized to the whole Japanese population. Another strength lies in the large sample size and long-term follow-up period compared with those in other Asian studies. Therefore, we could evaluate the associations separately for subtypes of CVD. Third, most previous studies in Asian countries were from Japan and used JDS values for HbA_{1c}, whereas our analyses used NGSP values for HbA_{1c}, allowing our data to be compared with those from Western countries. The main limitation of this study was that because fasting glucose was not measured in all participants, analyses on fasting glucose could not performed. It is difficult to obtain fasting blood samples at a mass health check-up. However, fasting is not necessary for assessment of HbA_{1c}, and our data suggested that HbA_{1c} would facilitate assessment of CVD risk associated with glucose metabolism at mass health check-ups, even if a fasting blood sample is not obtained. Another limitation was that deaths from stroke, especially hemorrhagic stroke, were too few to detect any significant relationship. Similarly, the number of participants with very low HbA_{1c} levels was too few to allow evaluation of the mortality risk in these individuals. Another limitation was that we did not have data for some CVD risk factors associated with glucose metabolism, such as waist circumference and fasting triglycerides levels. A further limitation was that we used a single measurement of HbA_{1c} at baseline, which might have underestimated the relationship owing to regression dilution bias (38), and changes in HbA_{1c} during the 15-year follow-up period were not taken into account.

In conclusion, HbA_{1c} was significantly and positively associated with an increased risk for all-cause mortality and mortality from CVD and coronary heart disease in this long-term cohort from a representative Japanese population. A higher risk of CVD was observed even in participants with HbA_{1c} levels of 6.0–6.4% (42–47 mmol/mol), which are below the threshold for diabetes. HbA_{1c} is a useful marker of glucose metabolism for mass screening because fasting is not required for its assessment. Our results showed that HbA_{1c} was associated with CVD death in general East Asian populations, as in Western populations. Further study is needed to establish whether the measurement of HbA_{1c} is useful for cardiovascular risk assessment in general East Asian populations.

Acknowledgments—This study was supported by a grant-in-aid from the Ministry of Health, Labor and Welfare under the auspices of the Japanese Association for Cerebrocardiovascular Disease Control; a Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labor and Welfare; and a Health and Labor Sciences Research Grant, Japan (Comprehensive Research on Aging and Health [H11-Chouju-046, H14-Chouju-003, H17-Chouju-012, and H19-Chouju-Ippan-014], and Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus [H22-Jyunkankitou-Seisyu-Sitei-017]).

No potential conflicts of interest relevant to this article were reported.

M.S. performed the analysis, wrote the manuscript, and approved the final version of the manuscript. S.S. collected data, performed the analysis, wrote the manuscript, and approved the final version of the manuscript. K.M. and H.N. collected data, contributed to discussion, reviewed and edited the manuscript, and approved the final version of the manuscript. H.O. and H.A. contributed to discussion, reviewed and edited the manuscript, and approved the final version of the manuscript. A.K., Y.K., T.H., T.Ohk., A.O., T.Oka., and H.U. collected data, contributed to the discussion, reviewed and edited the manuscript, and approved the final version of the manuscript. K.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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