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.

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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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3．日本人における心電図脚ブロックの心血管死予測能力について—
—NIPPON DATA80 24年追跡結果

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目的

完全左脚ブロックは正常に比べ一般に予後不良と考えられている。しかし一部にこのことを否定する研究報告がある。今回NIPPON DATA80 24年追跡データセットを用いて検討した。

方法

NIPPON DATA80 24年追跡データセットを用いて種々の心電図脚ブロックが心血管死および総死亡に及ぼす影響について検討した。追跡開始時の1980年に30歳以上の無作為抽出住民に生活習慣調査、既往歴聴取、診察、血液・心電図他の検査等を実施した。9,090人（男性44%、平均年齢51歳）を対象に追跡を行った。

結果

24年の追跡期間中に886人の心血管死、2,597人の総死亡があった。研究参加者のうち0.2%に完全左脚ブロックが、1.3%に完全右脚ブロックがあり、4.3%にその他の心室内伝導障害があった。生化学検査結果、他の心電図所見などを調整因子とした多変量Cox解析によると完全左脚ブロックは心室内伝導障害を有しない参加者に比べ有意に高い心血管死亡率と総死亡率を示した（男女合計結果－心血管死亡：ハザード比[HR]=2.71, 95%信頼区間[CI]:1.35-5.45, P=0.005; 総死亡：HR=2.07, 95%CI:1.26-3.39, P=0.004)。しかし完全右

脚ブロックと他の心室内伝導障害は心血管死、総死亡に対して有意な影響を示さなかった。

結論

完全左脚ブロックは背景因子および他の心電図所見とは独立して血管死、総死亡に対して有意な影響を示した。

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Prognostic values of bundle branch blocks for cardiovascular mortality in Japanese (24 year follow-up of NIPPON DATA80)☆

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Abstract

Aims: Left bundle branch block (LBBB) is generally considered to be associated with a poorer prognosis in comparison with normal controls. However, there are some studies that showed no difference in prognosis of LBBB in comparison with normal controls.

Methods and Results: We studied prognostic values of BBBs on cardiovascular disease (CVD) and total mortality using the NIPPON DATA80 database with a 24-year follow-up. At the baseline in 1980, data were collected on study participants, ages 30 years and over, from randomly selected areas in Japan. We followed 9,090 participants (44% men, mean age 51). During the 24 year follow-up, there were 886 CVD, and 2,597 total mortality cases. Among participants, 0.2% of them were in LBBB, 1.3% in RBBB, 4.3% in other ventricular conduction defect (VCD) groups. The multivariate-adjusted hazard ratio (HR) using the Cox model including biochemical and other ECG variables revealed that LBBB was significantly positively associated with CVD (HR = 2.71, 95% confidence intervals [CI]: 1.35–5.45, P = 0.005), and total (HR = 2.07, 95%CI: 1.26-3.39, P = 0.004) mortality in men and women combined compared to participants without VCD. RBBB and other VCDs did not carry any significant risk for CVD or total mortality.

Conclusions: We found significant positive associations of LBBB with CVD and total mortality independent of confounding factors including other ECG changes.

Keywords: Electrocardiography; Bundle branch blocks; Total mortality; Cardiovascular mortality

Introduction

Among ventricular conduction defects (VCD), complete left (LBBB) and right bundle branch (RBBB) are distinct findings of ECG.[1] RBBB is generally considered to be benign in the absence of any underlying cardiac abnormality such as congenital heart disease.[2–5] LBBB, on the other hand, is generally considered to be associated with a poorer

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prognosis in comparison with normal controls.[5,6] However, there are some studies that showed no difference in prognosis of LBBB in comparison with normal controls.[2,7–9] There are not many epidemiological studies evaluating the prognostic significance of LBBB and RBBB in general populations, and studies that incorporate lifestyle related and blood chemical risk factors into analyses are quite rare. The aim of the present study was to assess the independent prognostic values of LBBB, RBBB and other VCDs for CVD and total mortality in a large cohort of participants obtained from randomly selected health districts in Japan.[10,11]

Methods

Participants

Cohort studies of the National Survey on Circulatory Disorders, Japan, are known as NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged). The present study analyzed data from NIPPON DATA80, in which baseline surveys were performed in 1980. Details of this cohort have been reported elsewhere.[10,11]

Three hundred health districts throughout Japan were randomly selected. The overall population, ages 30 years and over, in the participating health districts was 13,771. All of them were invited to participate in the study. Among them, a total of 10,546 community-based participants agreed to participate in the study. The participation rate was 76.6 % (10,546 of 13,771) before exclusion for reasons mentioned below. The survey consisted of history-taking, physical examinations, blood tests, a standard 12-lead ECG recording in the supine position, and a self-administered questionnaire on lifestyle. For the present study, participants were followed up to 2004 (NIPPON DATA 80, 1980–2004).

Participants were excluded from follow-up because of missing baseline data (N = 139), a past history of coronary heart disease (CHD) or stroke at the baseline (N = 153), or loss to follow-up (N = 1,104). The latter group was excluded because of the absence of a permanent address that was needed to link to vital statistical records. We also excluded participants with baseline ECG abnormalities including moderate or major Q wave abnormalities (Minnesota Code (MC), 1-1- or 1-2-), third-degree atrio-ventricular block (MC 6–1), and Wolf-Parkinson-White syndrome (MC 6-4-) (N = 60).[12,13] There were no participants with Mobitz type II AV block or with artificial ventricular pacemaker. The final sample comprised 9,090 participants (3,970 men and 5,120 women). There were no significant differences between participants who were lost to follow-up and those who were included in the current study in terms of several risk factors.

Biochemical and baseline examinations

The baseline surveys were conducted at public health centers according to a standardized manual. Blood pressure was measured by trained research nurses using a standard mercury sphygmomanometer on the right arm of seated participants after at least 5 min of rest. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, use of antihypertensive agents or any combination of these. Height and weight were measured in stocking feet and light clothing. BMI was calculated as weight (kg) divided by the square of height (m^2).

A lifestyle survey was also carried out using a self-administered questionnaire. Participants were asked about their alcohol drinking habit (never, past, occasional, and daily drinkers). Reported information was confirmed by public health nurses through interviews with the study participants regarding smoking, drinking habit, and present and past medical histories.

Casual blood samples were drawn and centrifuged within 60 min of collection and stored at −70 °C until analyses as described previously.[10,11,14,15] Serum concentrations of glucose were measured by the cupric-neocuproline method, and the value was converted so as to better correspond with the more widely used hexokinase method.[16]

The ECG findings were independently evaluated by 2 trained researchers independent of the NIPPON DATA research group in each of 12 institutions according to the MC as previously described.[17] Codes in agreement were accepted, whereas inconsistent codes were decided by a panel of study epidemiologists and cardiologists.[17] Major ECG findings for the present study were LBBB (MC7-1-1, -2), RBBB (MC7-2-1, -2), and other VCDs (MC7-3 to 7–7). There were no participants with code 7.4 plus codable Q wave. Additional ECG findings (www.sph.umn.edu/epi/ecg/mncode.pdf[13]) that we examined were minor Q wave abnormality (MC1-3-) (yes/no), first- or second-degree atrio-ventricular block (1° or 2° AV block) (MC6-2-2, 6-2-3 or 6–3) (yes/no), atrial or ventricular premature beats (APC or VPC) (MC8-1-) (yes/no), atrial fibrillation or flutter (AF or AFL) (MC8-3-) (yes/no). The following ECG codes were suppressed in the presence of LBBB according to MC: MC ([1-2-3, 1-2-7, 1-2-8: these three were in the exclusion criteria in the present study], 1-3-2, 1-3-6, all 2-, 3-, 4-, and 5-codes, 7–7, 9–2, 9–4, 9–5).[18] Most of these MCs were also suppressed in the presence of RBBB Thus, these codes were not entered in the analyses.

Endpoint determination

To determine the cause of death after 24 years follow-up, we used the National Vital statistics database of Japan with permission from the Management and Coordination Agency, Government of Japan. The underlying causes of death were coded according to the 9th International Classification of Disease (ICD-9) through the end of 1994 and ICD-10 from the beginning of 1995. The details of classification in the present study are described elsewhere.[19–21] CVD (ICD-9: 393 to 459 and ICD-10: I00 to I99) was identified. Approval for the study was obtained from the Institutional review Board of Shiga University of Medical Science (No. 12–18, 2000).

Statistical analysis

SAS version 9.2 for Windows (SAS Institute, Cary, NC) was used throughout the analyses. Variables were compared among the four groups according to ECG findings of VCDs (normal, LBBB, RBBB and other VCDs). The chi-square test was used to compare dichotomous variables, followed

Table 1
Baseline characteristics and mortality according to ventricular conduction defect categories NIPPON DATA80, 1980-2004.

Type	Normal	LBBB	RBBB	Other VCDs	P
N (% of total N)	8558 (94.1%)	20 (0.2%)	117 (1.3%)	395 (4.3%)	
Age (y)	50.3 ± 13.0	65.0 ± 10.3†	64.2 ± 12.4†	54.1 ± 14.1†	<0.001
Men (%)	42.8	50.0	65.0†	55.7†	<0.001
BMI (kg/m^2)	23.0 ± 15.3	22.0 ± 3.5	22.0 ± 3.2	21.6 ± 3.2	0.301
Hypertension (%)	44.8	65.0	63.3†	49.4	<0.001
Smoker (%)	32.0	45.0	40.2	40.8†	<0.001
Alcohol drinker (%)	43.6	35.0	42.7	48.9	0.182
Total Cholesterol (mg/dl)	188.7 ± 33.6	187.4 ± 30.4	184.0 ± 32.8	188.3 ± 31.9	0.514
BS (mg/dl)	101.3 ± 30.3	104.2 ± 30.8	105.0 ± 30.8	101.9 ± 29.9	0.549
Creatinine (mg/dl)	0.92 ± 0.23	1.03 ± 0.34	1.03 ± 0.23†	0.96 ± 0.17*	<0.001
CVD death (%)	9.5	40.0†	18.8†	11.9	<0.001
Total death (%)	27.5	80.0†	64.1†	38.0†	<0.001

Values are shown as the mean ± SD, or in %. P values are from the chi-square test, or from a one-way analysis of variance. * P < 0.05, † P < 0.01 compared to the normal group. Baseline characteristics, CVD and total mortality were compared among the four groups according to VCD type (normal, LBBB, RBBB, and others). The chi-square test was used to compare dichotomous variables, followed by a post hoc application of Bonferroni's method when P < 0.05. A one-way analysis of variance was used to compare means among the groups, followed by a post hoc application of Dunnett's test when the F value showed a significant difference at P < 0.05. VCD = ventricular conduction defect, BMI = body mass index, Alcohol drinker = those participants who admitted to drinking alcohol daily, Smoker = those participants who admitted to smoking currently, Total Cholesterol = serum total cholesterol concentration, BS = blood glucose concentration, CVD = cardiovascular diseases.

by a post hoc application of Bonferroni's method when P < 0.05. A one-way analysis of variance was used to compare means among the groups, followed by a post hoc application of Dunnett's test when the F value showed a significant difference at p < 0.05.

To examine the factors associated with CVD, and total mortality, multivariate-adjusted hazard ratios (HR) and P values were calculated using a Cox proportional hazards model. Men and women were combined. Covariates in model 1 were sex, age, and VCD categories (normal, LBBB, RBBB, and other VCDs). Model 2: model 1 covariates + BMI (5 categories divided at 18.5, 23, 25, and 30 kg/m^2; 18.5-23: a reference), hypertension, cigarette smoking (never and past smokers, 3 current smokers categories divided at 20, and 40 cigarettes/day; never smokers: a reference), alcohol drinking (ex-drinker or current drinker, never-drinker; never drinkers: a reference), serum total cholesterol, and blood glucose concentrations (standardized to have the mean = 0 and standard deviation = 1), serum creatinine (divided at 75 percentile,1.0 mg/dl), and interaction terms (age x hypertension, age x smoking, and age x standardized blood glucose). These interaction terms were entered because they contributed significantly. Model 3: model 2 covariates + other ECG findings separately (minor Q wave, 1° or 2° atrio-ventricular block [except for Mobitz type II], atrial or ventricular premature contractions, atrial fibrillation or atrial flutter), and interaction terms. Model 3 analysis stratified by sex was also performed.

Results

Descriptive statistics

During follow-up for 24 years (191,942 person-years), 886 CVD deaths (429 in men, 457 in women), and 2,597 total deaths (1,374 in men, 1,223 in women) were confirmed.

Baseline characteristics, CVD and total mortality according to VCD groups are shown in Table 1. Among participants, 0.2% of them were in LBBB, 1.3% in RBBB, 4.3% in other VCD groups. Mean age in the three VCD groups was higher than in the normal group, and mean creatinine in RBBB and other VCD groups were higher than in that in normal groups. Prevalence of men, hypertension, and smokers were different among the groups. Mean BMI, total cholesterol, blood sugar and prevalence of alcohol drinkers were not different among the groups. CVD mortality in LBBB and RBBB were higher than in the normal group. Total mortality in the three VCD groups were higher than in the normal group.

Baseline ECG characteristics according to VCD groups are shown in Table 2. Prevalence of 1° or 2° AV block (except for Mobitz type II) in other VCD group was higher than in the normal group. Other ECG findings were not different among the groups.

Associations of VCD types with CVD, and total mortality

Results of Cox analyses on the associations of VCD types with CVD and total mortality are shown in Table 3. With

Table 2
Baseline ECG characteristics (%) according to ventricular conduction defect type – NIPPON DATA80, 1980-2004.

Type	Normal	LBBB	RBBB	Other VCDs	P
Minor Q wave (MC1-3-) (%)	1.43	0	1.71	1.52	0.945
1° or 2° AV block (%)	2.15	5.00	4.27	4.05*	0.033
APC or VPC (%)	1.11	5.00	0.85	2.03	0.141
AF or AFL (%)	0.61	0	1.71	1.01	0.355

Values are shown as in %. Baseline ECG characteristics were compared among the four groups according to the VCD type (normal, LBBB, RBBB, and others; normal: as a reference). The chi-square test was used, followed by a post hoc application of Bonferroni's method. * P < 0.05, † P < 0.01 compared to normal controls. BBB = bundle branch block, VCD = ventricular conduction defect, AV = atrioventricular, APC = atrial premature contractions, VPC = ventricular premature contractions, AF = atrial fibrillation, AFL = atrial flutter.

Table 3
Ventricular conduction defect categories and mortality – NIPPON DATA80, 1980-2004.

	LBBB			RBBB			Other VCDs		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
CVD									
Model 1	2.65	1.32–5.32	0.006	0.78	0.51–1.19	0.775	0.86	0.64–1.15	0.301
Model 2	2.62	1.30–5.26	0.007	0.73	0.48–1.12	0.731	0.88	0.65–1.18	0.879
Model 3	2.71	1.35–5.45	0.005	0.75	0.49–1.15	0.190	0.85	0.63–1.14	0.264
Total									
Model 1	2.11	1.29–3.45	0.003	1.04	0.83–1.32	0.726	0.99	0.84–1.17	0.939
Model 2	2.03	1.24–3.33	0.005	1.01	0.80–1.28	0.916	0.99	0.84–1.17	0.991
Model 3	2.07	1.26–3.39	0.004	1.03	0.81–1.30	0.833	0.97	0.82–1.14	0.709

Covariates in model 1 were sex, age, and VCD categories. Model 2: model 1 + BMI, hypertension, cigarette smoking, alcohol drinking, serum total cholesterol, and blood glucose concentrations, serum creatinine, and interaction terms. Model 3: model 2+ other ECG findings (minor Q wave, 1° or 2° atrioventricular block [except for Mobitz type II], atrial or ventricular premature contractions, atrial fibrillation or atrial flutter), and interaction terms. BBB = bundle branch block, VCD = ventricular conduction defect.

adjustment for age and sex, statistical significances were noted for CVD and total mortality in LBBB. Statistical significance of CVD and total mortality in LBBB remained in the fully adjusted model (Model 3). In comparison with the normal group, HR and 95% confidence intervals (CI) for CVD mortality in LBBB were 2.71 (95%CI: 1.35-5.45, P = 0.005), and were 2.07 (95%CI: 1.26-3.39, P = 0.004) for total mortality. In model 3 analyses stratified by sex, statistical significances of LBBB in men remained (CVD: HR = 5.60 [95%CI: 2.44-12.82], P < 0.001; total: HR = 2.42 [95%CI: 1.24-4.70], P = 0.009), but statistical significances disappeared in women (CVD: HR = 1.09 [95%CI: 0.27-4.39], P = 0.904; total: HR = 1.69 [95%CI: 0.80-3.55], P = 0.171).

Kaplan-Meier survival curves for CVD and total mortality of LBBB and normal groups are shown in Figs. 1 and 2. For the both mortality curves, lines diverge obviously after 5 years of follow-up.

Discussion

We found a significant positive association of LBBB with CVD and total mortality. We also found that RBBB and other VCDs did not carry any significant risk for CVD or total mortality.

The results of previous studies on the prognostic significance of LBBB have been conflicting. Rotman et al. performed a follow-up study of 394 participants with RBBB and 125 participants with LBBB out of over 237,000 individuals at the United States Air Force (USAF) School of Aerospace Medicine.[2] They observed no differences in follow-up morbidity of CVD or mortality with LBBB or RBBB compared to normal controls with a mean follow-up period of 10.8 years. In a cohort study in Iceland, Hardarson et al. found that mortality from coronary artery disease or hypertension was not increased in those with LBBB.[8] Kreger et al. reported the results of the Framingham study with over 18 years of follow-up. They found that age-adjusted incidence of myocardial infarction, angina pectoris, and coronary death were unrelated to baseline QRS prolongation, and that participants with LBBB fared no worse than those with RBBB.[9] However, in more recent cohort studies with a larger number of participants and with a longer duration of follow-up, it has been shown that LBBB is associated with a poorer prognosis. Imanishi et al. studied 17,361 participants over a 40-year period in Hiroshima and Nagasaki in the follow-up program of atomic bomb survivors, and they found

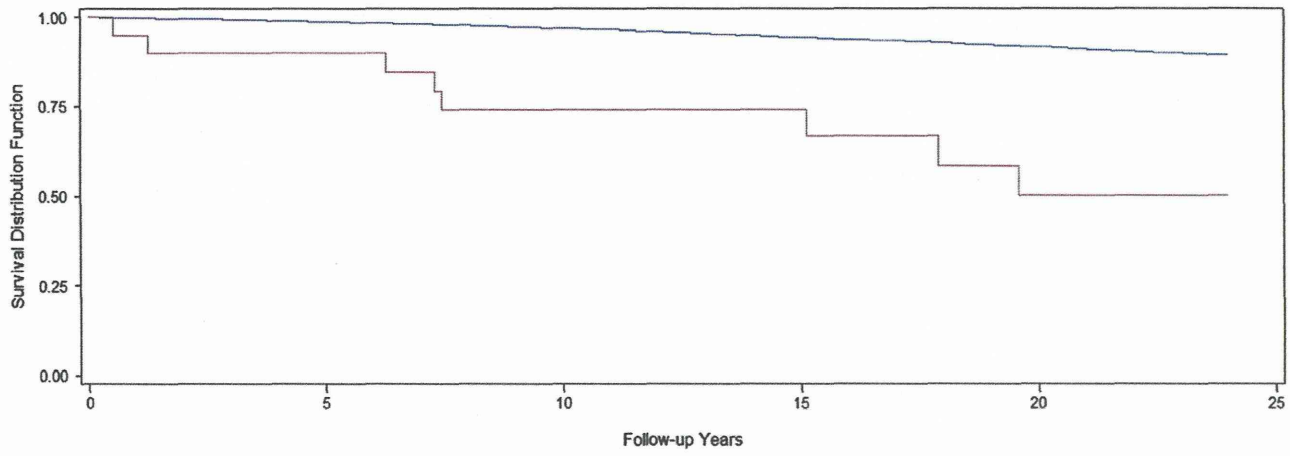

Fig. 1. Kaplan-Meier Survival Curve for CVD Mortality of LBBB and the For the Normal Groups. Upper line indicates survival for the participants with no ventricular conduction defects, and lower line with LBBB.

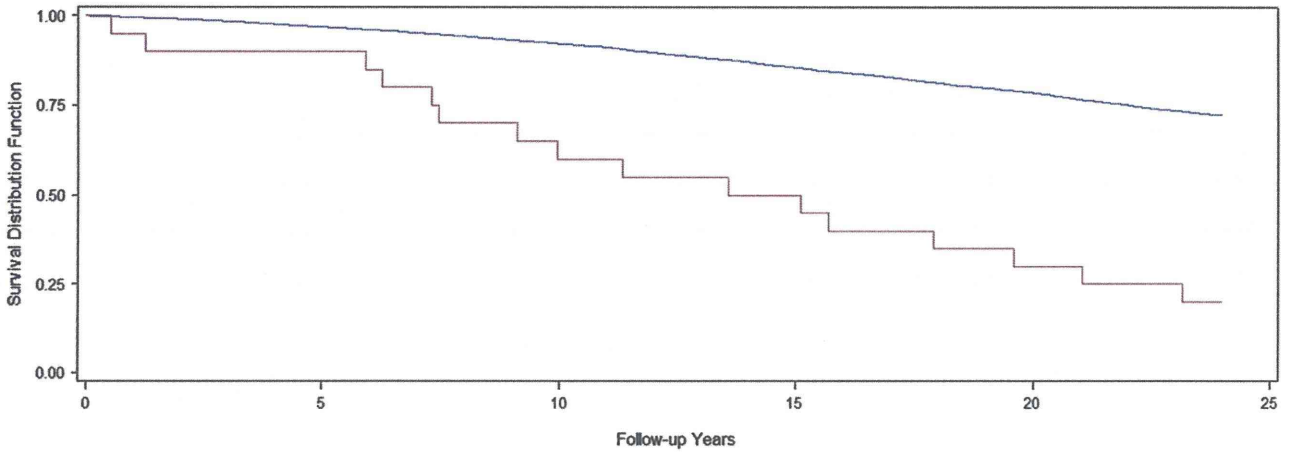

Fig. 2. Kaplan-Meier Survival Curve for Total Mortality of LBBB and the Normal Groups. Upper line indicates survival for the participants with no ventricular conduction defects, and lower line for LBBB.

that LBBB predicted mortality from heart failure, but not for all-cause mortality.[6] Zhang et al. evaluated mortality risk associated with BBBs during 14 years of follow-up in 66,450 participants from the Women's Health Initiative study, and found that prevalent LBBB in CVD-free women was a significant predictor of coronary heart disease mortality.[5] Differences in the results of previous studies on the prognostic significance of LBBB may be related to differences in the number of cases and the durations of follow-up. In a USAF study, the majority of participants were flyers in exceptionally good health.[2,22] The chance of unnoticed inclusion of participants with subclinical underlying heart disease must be minimal in such a study.

Several underlying mechanisms involved in apparently healthy participants with LBBB from general populations have been postulated. These include subclinical myocarditis,[23] a degenerative fibrotic process involving the conduction system,[24–27] and silent coronary artery disease.[2] Furthermore, without evident heart disease, LBBB may induce abnormalities in left ventricular performance due to abnormal asynchronous contraction patterns.[28–30] Asynchronous electrical activation of the ventricles causes regional differences in workload which may lead to asymmetric hypertrophy, left ventricular dilatation, and increased wall mass in late-activated regions.[31] These may aggravate preexisting left ventricular pumping performance or even induce it. Some reports showed that patients with LBBB and normal left ventricular dimensions and the normal ejection fraction at rest, but presented with an abnormal increase in pulmonary artery pressure during exercise, production of lactate during high-rate pacing, and abnormal ultrastructural findings on myocardial biopsy.[30,32,33]

Horibe et al. studied the NIPPON DATA80 dataset with 19 years of follow-up, and reported that total mortality in those with RBBB was significantly higher without any adjustment.[17] In the present study, RBBB was not associated with any mortality risk when adjusted for age and sex. Lack of prognostic significance of RBBB and other VCDs in our study is consistent with previous studies.[2–5]

We had a large cohort of participants obtained from randomly selected health districts in Japan. The participants in our study were observed for 24 years, which is along follow-up period and this increases the value of our study.

Study limitations

There are some limitations to the current study. Firstly, we had a relatively large number of lost to follow-up: 1,104 participants (about 10%). However, there were no significant differences between participants who were lost to follow-up and those who were included in the current study in terms of several risk factors. Therefore, the potential bias regarding the participants lost to follow-up may be negligible. However, unobserved information related to outcomes may have led participants to drop out of our study early. We cannot exclude the fact that this may lead to a bias. Secondly, we used a single ECG at the baseline. It is well recognized that single biologic measurements are subject to variability and ECG abnormalities could have changed over time. However, this possible variability generally tends to result in underestimate of the risk. Third, MC was coded by visual reading in our study. Computerized ECG analysis is reportedly superior to visual reading in terms reliability[34]; however, computerized ECG analysis was not available in the 1980s, and ECG readings in the study were performed under the best standardized quality control by well trained physicians. Fourth, we have no data on PQ prolongation. Fifth, the number of participants with LBBB was small, and thus we could not perform subclass CVD analysis. However, the statistical significance of HR remained with several statistical adjustments. This supports lack of confounding, and supports also that LBBB are independent predictors of CVD and total mortality.

Conclusions

We found a significant positive association of LBBB with CVD and total mortality independent of confounding factors including other ECG changes.

Acknowledgments

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4．　＊日本語解説については「NIPPON DATA80/90/2010における心電図の解析について」“2）上室性期外収縮と循環器疾患死亡”をご参照ください。

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PLOS ONE

Long-Term Outcome of Healthy Participants with Atrial Premature Complex: A 15-Year Follow-Up of the NIPPON DATA 90 Cohort

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Abstract

Background: Atrial premature complexes (APC) are among the most frequently encountered electrocardiographic abnormalities. However, their prognostic value among healthy individuals is unclear. This study aimed to clarify the role of APC in predicting cardiovascular events in a large Japanese community cohort using long-term follow-up data.

Methods: National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1990-2005, (NIPPON DATA 90) was a large cohort study of cardiovascular disease (CVD) in Japan. A total of 7692 otherwise healthy participants with no history of myocardial infarction, stroke, atrial fibrillation, or atrial flutter were enrolled (men, 41.5%; mean age, 52.5 ± 13.7 years).

Results: A total of 64 (0.8%) participants had at least one beat of APC on screening 12-lead electrocardiogram. During the follow-up of 14.0 ± 2.9 years (total, 107,474 patient-years), 338 deaths occurred due to CVD. The association between APC and CVD outcome was assessed using Cox proportional hazard models. Cox regression analysis revealed that the presence of APC was an independent predictor for CVD deaths (HR: 2.03, 95% CI: 1.12–3.66, $P = 0.019$). The association of APC on CVD death was more evident in participants with hypertension (P-value for interaction, 0.03).

Conclusions: APC recorded during the screening electrocardiogram are significantly associated with an increased risk of CVD deaths in a Japanese community-dwelling population and are a strong prognostic factor for hypertensive participants.

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Introduction

Cardiovascular disease (CVD) is the largest single cause of death, accounting for approximately 30% of all deaths worldwide[1]. Electrocardiographic (ECG) screening has been performed in various situations to identify the early signs of CVD, and atrial premature complexes (APC) are among the most frequently recorded abnormal findings[2,3]. Nevertheless, APC detected in participants with apparently normal hearts

have been regarded as a relatively benign phenomenon and do not contribute to prognostic risk stratification.

However, with the elaboration of cohort studies and large-scale registries in recent years, the potential hazards of premature complexes associated with various cardiac conditions have gradually been recognized. Frequent APC have been shown to be associated with a risk of atrial fibrillation, which subsequently leads to an increased risk of cerebral infarction[4-6]. Previous studies were limited in terms of being mostly derived from studies that used a 24-hour ambulatory ECG to evaluate relatively high-risk populations such as the elderly or those with certain risk factors, including hypertension. Furthermore, although atrial fibrillation leading to cerebral infarction is a major clinical event, the association of APC and actual mortality remains unclear.

In this study, we sought to investigate the prognostic value of APC recorded during the screening ECG in a large community cohort study that enabled analyses of long-term CVD outcomes in Japan.

Methods

Participants

The cohort studies of the National Survey on Circulatory Disorders, Japan, are referred to as NIPPON DATA (National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged), including a total of 2 cohort studies. The details of this cohort have been reported previously[7-19]. The baseline surveys were performed in 1980 and 1990 (NIPPON DATA 80 and NIPPON DATA 90). In the present study, we analyzed the data from NIPPON DATA 90, because the baseline survey of NIPPON DATA 80 recorded VPC and APC as a single category that was not further discriminated.

A total of 8383 healthy participants (3504 men and 4879 women, ≥30 years of age) from 300 randomly selected districts throughout Japan were followed from 1990 until 2005. The total population aged ≥30 years in these selected districts was 10,956; therefore, the participation rate was 76.5% before exclusion for the reasons given below. The survey consisted of history taking, physical examinations, blood tests, standard 12-lead ECG recordings, and self-administered questionnaires on lifestyle.

A total of 691 participants were excluded for the following reasons: history of a known vascular condition, such as myocardial infarction or stroke (n = 248); presence of atrial fibrillation or flutter (n = 54); some missing information at the baseline survey (n = 120); and absence of a permanent address that was needed to link to these vital statistical records (n = 269). The remaining 7692 otherwise healthy participants were included in our study (Figure 1).

Baseline Examination

A standard 12-lead ECG was recorded in the resting supine position. Each ECG was reviewed independently by 2 trained coders according to the Minnesota Code (MC), as described previously[7-9,12,17]. Codes in agreement were accepted, whereas discordant results were adjudicated by a panel of

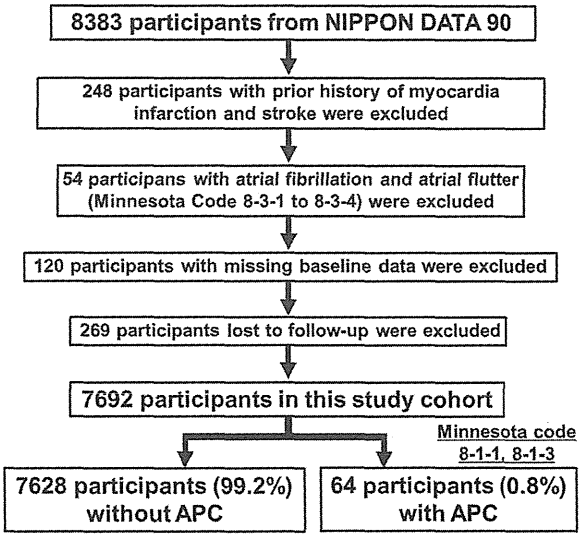

Figure 1. Study cohort creation. APC, atrial premature complexes.

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study epidemiologists and cardiologists. Participants with at least one beat of APC (more than 10% of recorded QRS complexes) were determined as having APC; they were further classified according to the presence of APC (MC 8-1-1 or MC 8-1-3). Additional ECG findings examined included Q-wave abnormality (MC 1-1, 1-2, 1-3), QRS axis deviation (MC 2-1, 2-2, 2-3), high R wave (MC 3-1 to 3-4), ST depression (MC 4-1 to 4-4), T-wave abnormality (MC 5-1 to 5-5), intraventricular conduction block (MC 7-1-1 to 7-8), P-wave abnormality (MC 9-3-1 or 9-3-2), clockwise or counterclockwise rotation (MC 9-4-1 or 9-4-2), and ventricular premature complexes (MC 8-1-2 or MC 8-1-3).

Baseline blood pressures were measured by trained observers using a standard mercury sphygmomanometer on the right arm with the subject in a seated position. Hypertension was defined as systolic blood pressure of 140 mmHg or higher, diastolic blood pressure of 90 mmHg or higher, use of antihypertensive agents, or any combination of these. Non-fasting blood samples were centrifuged within 60 minutes of collection and were stored at -70°C until analysis. The blood samples were analyzed at the central laboratory (SRL, Tokyo, Japan) using established methods, as described previously[10,14-16]. Hypercholesterolemia was defined as serum total cholesterol ≥240 mg/dL, the use of medications for hypercholesterolemia, or both. Plasma glucose was also measured enzymatically. Diabetes mellitus was defined as plasma glucose ≥200 mg/dL, the use of medications for diabetes mellitus, or both. Body mass index was calculated as weight (kg) divided by the square of height (m). Public health nurses obtained information on smoking, drinking, and medical histories[13].

Follow-up Survey

To determine the cause of death after the 15-year follow-up, we used the National Vital Statistics Database of Japan with permission from the Management and Coordination Agency, Government of Japan. The underlying causes of death were coded according to the International Classification of Diseases, Ninth Revision (ICD-9) until the end of 1994, and according to the International Classification of Diseases, Tenth Revision (ICD-10) from the beginning of 1995. The details of the follow-up survey and the classification of causes of death in the present study are described elsewhere[7-19]. Permission to use the National Vital Statistics was obtained from the Management and Coordination Agency, of the national government of Japan. Because of the voluntary participation of community dwellers to the national survey, of which data was matched to the National Vital Statistics, and anonymous nature of the data for the analysis, informed consent was waived. Approval for the study was obtained from the institutional review board of Shiga University of Medical Science (No. 12-18, 2000).

Statistical Analysis

All data were expressed as mean ± standard deviation. Differences in each variable between participants with and those without APC were evaluated using the chi-square test or Fisher's exact test for categorical variables and Student's unpaired *t*-test for continuous variables. Event-free survival in patients with and those without APC was estimated by the Kaplan–Meier method, and statistical differences were evaluated by means of the log-rank test. Cox proportional hazard models were used to evaluate risk factor-adjusted associations of APC with each endpoint.

In Cox models with endpoints including all-cause deaths and CVD deaths, adjustment was made in Models 1, 2, and 3. Covariates in Model 1 were age and gender. Model 2 consisted of Model 1 plus the conventional risk factors of body mass index, current smoking, drinking habit (never, past, and current drinker categories, with "never drinker" as a reference), hypercholesterolemia, diabetes mellitus, systolic blood pressure, and serum creatinine. Model 3 consisted of Model 2 plus other ECG findings (high R-wave, ST depression, T-wave abnormality, ventricular premature complexes). Covariates included in these models were clinically associated with CVD, significantly related to CVD deaths by univariate analysis, and also included the factors that were associated with APC at a level of significance $P < 0.05$ at baseline.

Analyses of data were performed using SPSS, version 20 (SPSS Inc., Chicago, IL). All *P*-values were two-sided, and significance was defined as $P < 0.05$ for all analyses.

Results

Sixty-four participants (0.8%) had APC, as determined by the screening ECG. The associated variables at baseline and the participants' clinical outcomes are summarized in Table 1. Age, systolic blood pressure, and certain ECG findings (ST depression and T-wave abnormality) were significantly different between participants with and those without APC.

Table 1. Baseline characteristics of the study group.

	APC		
	No	Yes	
	(n = 7628)	(n = 64)	*p*
Male, n (%)	3159 (41.4%)	32 (50.0%)	0.165
Age, years	52.4	67.3	<0.001
BMI, kgm^{-2}	22.9	22.0	0.022
Systolic blood pressure (mmHg)	135	148	<0.001
Diastolic blood pressure (mmHg)	81	83	0.111
Hypertension, n (%)	1606 (21.1%)	21 (32.8%)	0.022
Hypercholesterolemia, n (%)	517 (6.8%)	6 (9.4%)	0.411
Diabetes mellitus, n (%)	362 (4.8%)	4 (6.3%)	0.59
Current smoking, n (%)	2185 (28.6%)	16 (25.0%)	0.521
Drinking			
Ex-drinker	237 (3.1%)	2 (3.1%)	0.993
Current drinker	2156 (28.3%)	16 (25%)	0.564
Laboratory tests			
Total Cholesterol (mg/dL)	204	203	0.892
HDL Cholesterol (mg/dL)	54	53	0.741
Fasting blood glucose (mg/dL)	103	106	0.218
Creatinine (mg/dL)	0.81	0.85	0.119
Other ECG findings			
QRS axis deviation, n (%)	251 (3.3%)	2 (3.1%)	1
High R, n (%)	802 (10.5%)	12 (18.8%)	0.033
ST depression, n (%)	184 (2.4%)	6 (9.4%)	0.005
T-wave abnormality, n (%)	605 (7.9%)	15 (23.4%)	<0.001
Bundle branch block, n (%)	559 (7.3%)	4 (6.3%)	1
Rotation, n (%)	3810 (50%)	35 (54.7%)	0.45

Abbreviations: APC, atrial premature complex; BMI, body mass index; HDL, high density lipoprotein; ECG, electrocardiogram. All values are expressed as the mean ± SD or as a number with the percentage of participants in parentheses.

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The total follow-up time for the 7692 participants (men, 41.5%; mean age, 52.5 ± 13.7 years) in this study was 107,474 person-years (mean, 14.0 ± 2.9 years). During the follow-up, there were 1211 all-cause deaths and 338 CVD deaths, including 68 due to coronary artery disease, 73 due to heart failure, and 138 due to stroke. Table 2 represents the cumulative mortality, which indicated that participants with APC tended to have higher all-cause, CVD, heart failure or stroke mortality. Figure 2 shows Kaplan-Meier survival curves for CVD deaths in participants with and without APC. These curves indicate that participants with APC at baseline had a significantly lower survival rate during the follow-up period ($P < 0.001$ by log-rank test).

Cox regression analysis (Table 3) revealed that the presence of APC was an independent predictor for all-cause death (HR: 1.55, 95% CI: 1.07–2.24, $P = 0.020$) and CVD death (HR: 2.03, 95% CI: 1.12–3.66, $P = 0.019$).

As shown in Figure 3, the impact of APC on CVD death was more evident in participants with hypertension. The probability value for an interaction between APC and hypertension on CVD death was 0.03. Indeed, the adjusted hazard ratios of APC for all-cause death (HR: 3.19, 95% CI: 1.87–5.45, $P <$ 0.001) and CVD death (HR: 4.66, 95% CI: 2.09–10.4, $P <$

Table 2. Baseline ECG abnormalities and outcomes for the study group.

	APC		
	No	Yes	
	(n = 7628)	(n = 64)	*p*
Total death, n (%)	1181 (15.5%)	30 (46.9%)	<0.001
CVD death, n (%)	326 (4.3%)	12 (18.8%)	<0.001
CHD death, n (%)	67 (0.9%)	1 (1.6%)	0.388
HF death, n (%)	69 (0.9%)	4 (6.3%)	<0.001
Stroke death, n (%)	133 (1.7%)	5 (7.8%)	<0.001

Abbreviations: ECG, electrocardiogram; APC, atrial premature complex; CVD, cardiovascular disease; CHD, coronary heart disease; HF, heart failure. All values are expressed as a number with the percentage of participants in parentheses. The statistical differences were evaluated using a log-rank test.

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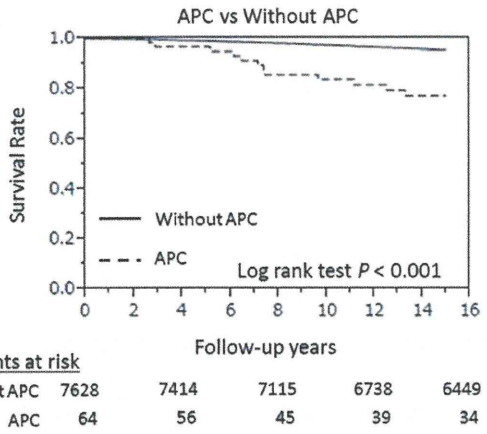

Figure 2. Kaplan–Meier estimates of cumulative hazard for cardiovascular disease for participants with and those without APC. APC, atrial premature complexes.

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0.001) were statistically significant in the hypertensive participants. Further adjustment of anti-hypertensive medication did not alter the results (data not shown). Independent analysis of other major subgroups such as the elderly (≥65 years of age), women, obese individuals (body mass index ≥ 24 kg/m^2) and current drinkers did not yield significant results (Figure 3).

Discussion

The major finding of this prospective cohort study of a large sample of healthy Japanese individuals was that at least one beat of APC, recorded through the screening ECG, was associated with an increased risk of CVD mortality in healthy Japanese participants. Although APC was not frequently observed in our study (less than 1%), this long-term follow-up study clarified its potential hazards. Of note, this adverse effect of APC was particularly prominent in hypertensive participants.

Table 3. Hazard ratios for each outcome by ECG abnormality status at baseline.

	APC	*p* value
	HR (95% CI)	
All causes mortality		
Unadjusted	3.98 (2.77-5.71)	<0.001
Model 1	1.50 (1.04-2.16)	0.03
Model 2	1.60 (1.11-2.31)	0.012
Model 3	1.55 (1.07-2.24)	0.020
Cardiovascular death		
Unadjusted	5.79 (3.25-10.3)	<0.001
Model 1	2.06 (1.15-3.68)	0.015
Model 2	2.11 (1.17-3.81)	0.013
Model 3	2.03 (1.12-3.66)	0.019

Abbreviation: ECG, electrocardiogram; APC, atrial premature complex; HR, hazard ratio; CI, Confidence Interval.

Multivariate-Adjusted for Model 1 (age and gender), Model 2 (age, gender, body mass index, smoking habit, drinking habit, hypercholesterolemia, diabetes mellitus, systolic blood pressure, serum creatinine) and Model 3 (Model 2 + other ECG findings).

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The clinical significance of APC has been investigated for decades. Recent studies of the 24-hour ambulatory ECG have demonstrated that excessive APC are associated with a higher risk for the development of atrial fibrillation and CVD mortality[4,6,20]. Our findings extend the prognostic significance of APC to healthy participants who have premature complexes recorded on a routine 12-lead ECG. In this cohort, with a follow-up of more than 100,000 person-years (mean, 14.0 ± 2.9 years), the finding of APC on routine ECG was associated with an increase in CVD mortality, particularly due to heart failure and stroke.

The mechanisms by which APC may increase the risk of heart failure are not clear, but several possibilities exist. First, APC may be an early manifestation of underlying heart disease that elevates left ventricular (LV) filling pressure. Early diastolic dysfunction may lead to elevated LV filling without clinical manifestations, with the exception of subtle left atrial remodeling that may be the cause of frequent APC[21]. A previous study conducted in the general community using Doppler echocardiography reported that although only approximately 5% of the population had systolic dysfunction, as many as approximately 30% had diastolic dysfunction, regardless of its severity, without any apparent heart failure[22]. In addition, some reports demonstrated that excessive APC were observed in participants with higher levels of N-terminal prohormone B-type natriuretic peptide[2,4]. These previous reports suggest that many general participants may have subclinical heart failure status, and APC are likely to become apparent with increased filling pressure. The adverse impact of APC on long-term outcome was apparent in participants with hypertension, which is associated with an increased LV filling pressure and diastolic dysfunction[23].

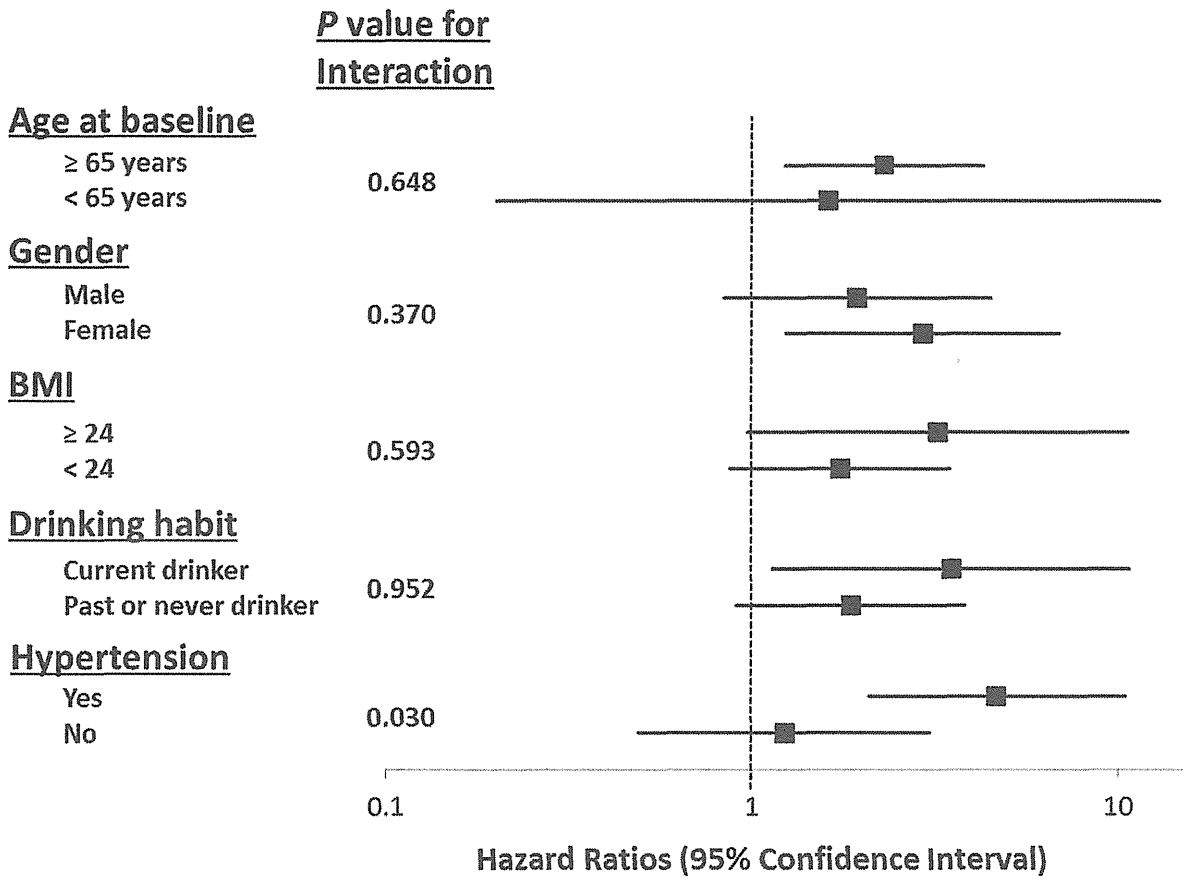

Figure 3. Adjusted hazard ratios of atrial premature complexes for cardiovascular disease deaths in various subgroups. Multivariate-adjusted Model 3 (age, gender, body mass index, smoking habit, drinking habit, hypercholesterolemia, diabetes mellitus, systolic blood pressure, serum creatinine, and other ECG findings).
BMI, body mass index.
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The other likely explanation is that APC triggers atrial fibrillation (AF) or is a forerunner of AF, resulting in the exacerbation of heart failure. Recent studies using 24-hour ECG monitoring demonstrated that frequent APC were correlated with a new occurrence of AF[4,6], while studies conducted in patients with acute stroke revealed that frequent APC predicted paroxysmal AF[20,24]. These findings suggest that APC could be a surrogate marker or a prodromal stage of AF, which is one of the independent prognostic factors in participants with heart failure. Furthermore, current concepts support the view that this paroxysmal or subclinical AF is also associated with an increased risk of acute stroke[25]. In our study, the presence of APC was associated with an increased risk of CVD mortality, particularly due to heart failure and stroke, reinforcing the possibility of an association between the presence of APC and the occurrence of AF, eventually leading to cardioembolic strokes[26].

Although in the present study, we have shown that CVD deaths occur twice as frequently in participants with APC than in those without APC, a previous large-scale study from the atherosclerosis risk in communities (ARIC) study reported conflicting results[3]. The latter study, however, focused only on sudden cardiac death or coronary heart disease, whereas the incidence of all CVD deaths, including heart failure or stroke—which are considered to be the most important outcomes related to APC—was not evaluated. These differences regarding endpoints might have reduced the prognostic impact of APC in that study.

It remains controversial whether an ECG examination should be performed in asymptomatic individuals. Our findings regarding APC are in concordance with western guidelines, which recommend the use of ECG screening in participants who have a high risk for CVD, such as patients with hypertension[27,28]. Screening for APC and other electrocardiographic abnormalities may be of assistance in

performing further risk stratification in these patients; patients in a higher risk category may benefit from aggressive lifestyle modification or cardiovascular investigation. On the other hand, our results also demonstrated few associations of APC and CVD mortality in participants with lower risk for underlying heart diseases, especially in participants without hypertension, which may justify not performing ECG screening for apparently healthy population.

Limitations

Our study has several limitations. First, although the participants in our cohort were limited to Japanese populations only, previous studies have demonstrated that the prognostic values of other ECG findings, proven in the United States or Europe, were also applicable to Japanese populations[8,12,17,29]. Asians reportedly have a different risk profile from western populations, with a significantly better overall cardiovascular prognosis[30,31], but a higher incidence of stroke than of coronary artery disease[32]. As shown in this study, the importance of APC as an independent predictor of stroke is beginning to be understood, and it is meaningful to evaluate the association of APC and adverse CVD outcomes, including stroke, in such a Japanese population. Second, sub-classifications of stroke events were not available. Although the etiology of stroke associated with premature complexes is likely to include the increased risk of cardioembolism, further studies are needed to confirm this. Last, we used a single ECG at baseline. Single biological measurements are known to be subject to variability. Therefore, the sensitivity of a single 12-lead ECG for the detection of premature complexes should be lower than that for more sensitive strategies, including 2-minute rhythm strips or a 24-hour ambulatory ECG. However, the presence of premature complexes on a single 12-lead ECG recorded in only 6 seconds might indicate that participants with such APC were likely to have frequent ectopic beats as a whole.

Conclusions

APC recorded during the screening ECG serve as an independent predictor of CVD deaths in a Japanese community-dwelling population. This tendency seemed to be most apparent in hypertensive participants, in whom the presence of APC was a predictor of CVD death, particularly due to heart failure and stroke.

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Author Contributions

Conceived and designed the experiments: TI SK. Performed the experiments: TI SK TO MW YN AH AK NO TO KM AO HU. Analyzed the data: TI SK TO MW YN AH AK NO TO KM AO HU. Contributed reagents/materials/analysis tools: TO MW YN AH AK NO TO KM AO. Wrote the manuscript: TI SK TO. Revising the macuscript critically, TI SK TO MW YN AH AK NO TO KM AO HU Final approval of the version to be published, TI SK TO MW YN AH AK NO TO KM AO HU.