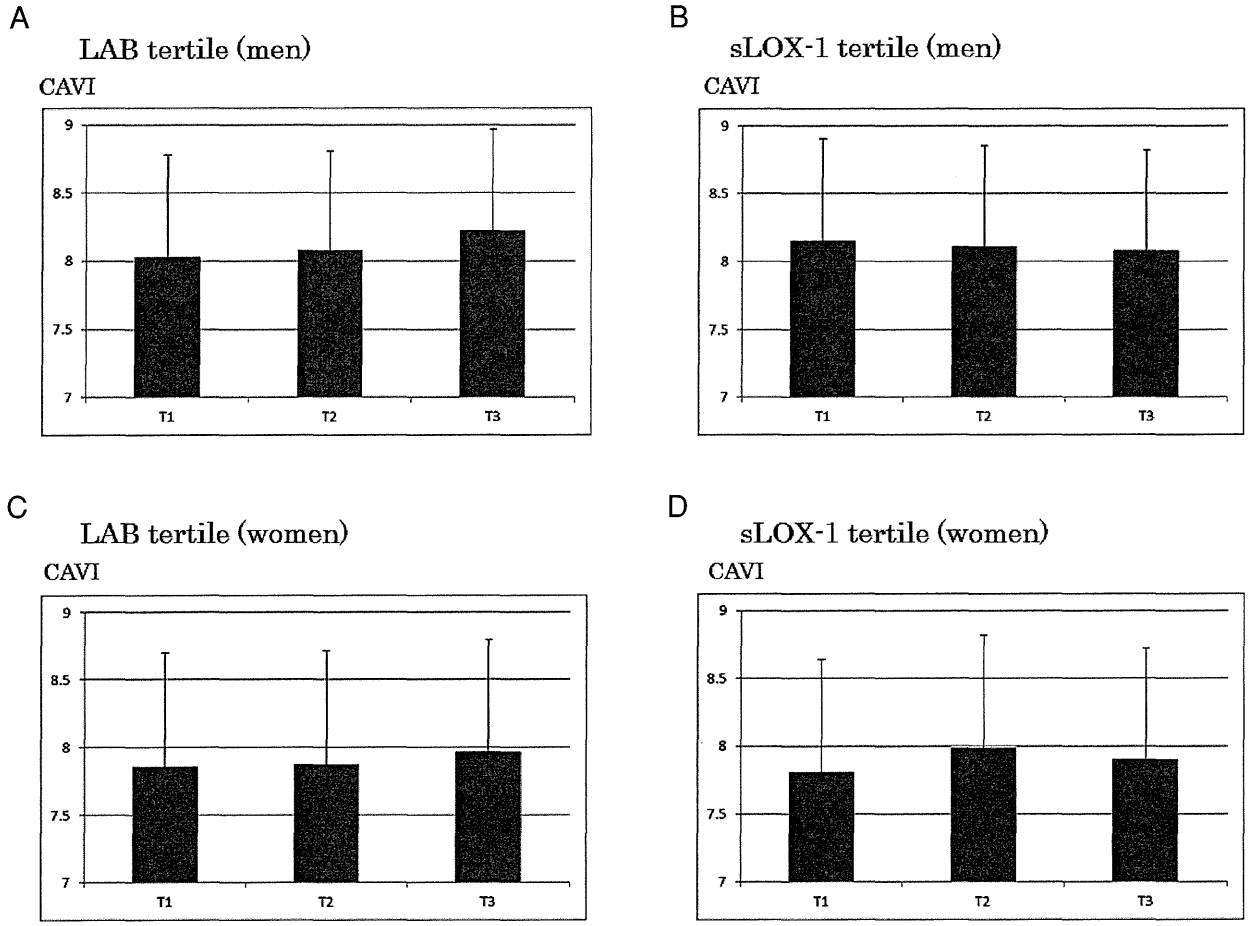

Fig. 1. The multivariable adjusted mean of the CAVI among tertiles of the LAB or sLOX-1.

A) The multivariable adjusted mean CAVI among tertiles of the LAB (men)
B) The multivariable adjusted mean of CAVI among tertiles of the sLOX-1 (men)
C) The multivariable adjusted mean of CAVI among tertiles of the LAB (women)
D) The multivariable adjusted mean of CAVI among tertiles of the sLOX-1 (women)
*The tertile of each category [minimum value to max value]
A) T1 [4126 to 19340], T2 [19390 to 27150], T3 [27180 to 61360] (μg/L)
B) T1 [57 to 101], T2 [101 to 125], T3 [126 to 1264] (ng/L)
C) T1 [6324 to 20430], T2 [20630 to 28500], T3 [28670 to 76860] (μg/L)
D) T1 [59 to 103], T2 [104 to 127], T3 [129 to 16460] (ng/L)
CAVI: cardio-ankle vascular index, LAB: LOX-1 ligand containing apolipoprotein B, sLOX-1: soluble form of LOX-1
Adjusted by age, body mass index, systolic blood pressure, heart rate, HbA1c, current smoker or not, current alcohol drinker or not

sex.

The major strength of the present study was that the participants were representative of the healthy population in Japan, without histories of CVD or medication use for risk factors, such as hypertension. Because healthy community dwellers rarely visit hospitals to receive health examinations for atherosclerosis, it is difficult to collect data about the parameters related to early-stage atherosclerosis in healthy individuals compared with unhealthy individuals. While health data obtained from work sites could contribute to investigations of the present study question, it may be impossible to accurately assess the atherosclerotic condition of individuals, because the mean age of patients included in occupational databases is usually lower than that in the general population. There is also a risk of bias due to the healthy worker effect[24].

Both *in vitro* and animal experiments have shown that the LAB is related to endothelial dysfunction, which leads to lipid sedimentation[3,4], inflammation[25], migration and the proliferation of smooth muscle[26], and to the formation of foam cells[27]. All of

these phenomena are thought to enhance the progression of atherosclerosis. In addition, elevation of the serum LAB levels also increased the risk of CVD, including ischemic stroke, in a long-term Japanese cohort study[10]. These experimental and clinical findings were compatible with the results of the present study. LAB may reflect a subclinical state of atherosclerotic findings, so it could predict the risk of future CVD events[10]. In contrast, sLOX1 may be a useful marker for the diagnosis of CVD in the acute phase, because elevated sLOX-1 levels were observed in acute coronary syndrome in previous clinical studies[8, 9].

In a recent report, the serum LAB level was associated with an increased intima-media thickness in Caucasian men in the US after adjusting for other risk factors, but this relationship was not found in Japanese men[11]. The CAVI measures the heart-ankle pulse wave velocity, and is believed to reflect atherosclerosis of the aortic wall. Since previous studies indicated that the progression of atherosclerosis was observed earlier in the aorta than at other sites[12, 13], the CAVI is a useful tool for evaluating early-phase atherosclerosis. In contrast, the result of the intima-media thickness may indicate the progression of advanced atherosclerosis. One of the reasons why the results were different between this study and the previous one[11] may be the difference in the indicators, CAVI vs. intima-media thickness. In addition, there was a difference in the ages of the populations in these studies. The previous study had a younger study population (40-49 years) compared to this study (mean age of men: 61±9 years).

In this study, a positive association between the LAB and the CAVI was observed in men, but not in women. The sex-specific positive association may reflect a potential sex difference in the risk for CVD among Japanese participants. The median levels of LAB and the mean CAVI were not significantly different between men and women, but the proportion of high CAVI levels (CAVI ≥ 9.0) was larger in men than in women (19% and 11%, respectively; $p=0.02$). The mean age in the high CAVI population did not differ by sex. This finding indicates that the early atherosclerotic changes detected by CAVI may tend to progress more in men compared to women of the same age, and this difference may be associated with the relationship between the CAVI and LAB observed in our study. Japanese women tend to have a much lower risk for coronary artery disease (CAD) than Japanese men[28], whose risk for CAD is also lower than that in US populations[21]. Therefore, the determination of risk factors for CAD is difficult to evaluate in Japanese women.

Our previous study[22] based upon the KOBE study showed that the hs-CRP level was positively associated with the CAVI, and the association between LDL-C and the CAVI was weak. These results indicated that the hs-CRP could be a more useful marker for atherosclerosis than LDL-C to detect early atherosclerosis in a healthy population without traditional risk factors for CVD, such as diabetes. In the present study, the serum hs-CRP level showed a positive association with the CAVI in all models of this study, and the results were concordant with those of the previous study. CRP is a marker for inflammation that is clinically useful in the evaluation of potential atherosclerosis, because inflammation enhances endothelial dysfunction. LAB is also involved in promoting inflammation[25], but it influences various other reactions leading to the progression of atherosclerosis[3, 4, 26, 27]. The positive relationship between the LAB and the CAVI in men in the present study was not influenced by adding the hs-CRP level to regression models; therefore, this result may indicate that the LAB has an influence on the development of atherosclerosis caused not only by inflammation, but also by other pathways. In addition, because the hs-CRP level is affected by infections or inflammatory diseases, the serum LAB levels may be represent another helpful marker that can be used to screen for subclinical atherosclerosis in individuals who have no or few risk factors for CVD.

The present study is associated with several possible limitations. First, this study was a cross-sectional study; thus, causality cannot be determined. The results of this study need to be confirmed in future prospective studies. Second, LOX-1-related modified LDL indicators are new markers for CVD and subclinical atherosclerotic diseases. Much is unknown about their relationship with environmental or lifestyle related factors. Third, the CAVI is also a relatively new method for assessing atherosclerosis; its relationship with future CVD events has not been sufficiently investigated. Fourth, collinearity may exist between the LDL-C and LAB or sLOX-1 in the linear regression models. However, the estimated VIFs for the LDL-C, LAB and sLOX-1 in Models 2, 3 and 4 were small, so there was little evidence for the existence of such collinearity. Finally, the generalizability of our study results is limited, because the KOBE study participants (volunteers) are believed to be more health conscious than the general population. Thus, the results of the present study should be applied to the general population with caution.

Conclusions

In this cross-sectional study of healthy Japanese city dwellers who were considered to be at low risk for atherosclerosis, the LAB was positively associated with the CAVI in men, but not in women, after adjustment for possible confounders. In contrast, no clear association between the sLOX-1 and the CAVI was observed. The LAB may have the potential to be a useful marker for detecting subclinical atherosclerosis, particularly in men, who seem to be at low risk based on the established CVD risk factors. However, the change in the mean CAVI affected by the level of LAB was very small, and there are limited evidences available to evaluate the association between the LAB and the incidence of CVD in epidemiologic studies, so further research will be needed to continue elucidating the relationship and to confirm the present findings.

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Conflicts of Interest

There are no conflicts of interest in the present study.

Declaration

Dr. Sugiyama had full access to all of the data generated in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Prevalence, Clinical Features, and Prognosis of Acute Myocardial Infarction Attributable to Coronary Artery Embolism

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Background—Coronary artery embolism (CE) is recognized as an important nonatherosclerotic cause of acute myocardial infarction. Its prevalence, clinical features, and prognosis remain insufficiently characterized.

Methods and Results—We screened 1776 consecutive patients who presented with de novo acute myocardial infarction between 2001 and 2013. CE was diagnosed based on criteria encompassing histological, angiographic, and other diagnostic imaging findings. The prevalence, clinical characteristics, treatment strategies, in-hospital outcomes, and long-term risk of CE recurrence or major adverse cardiac and cerebrovascular events (cardiac death, fatal arrhythmia, or recurrent thromboembolism) were evaluated. The prevalence of CE was 2.9% (n=52), including 8 (15%) patients with multivessel CE. Atrial fibrillation was the most common cause (n=38, 73%). Only 39% of patients with CE were treated with vitamin K antagonists, and the median international normalized ratio was 1.42 (range, 0.95–1.80). Eighteen of the 30 CE patients with nonvalvular atrial fibrillation had a $CHADS_2$ score of 0 or 1. When those patients were reevaluated using CHA_2DS_2-VASc, 61% were reassigned to a higher risk category. During a median follow-up of 49 months, CE and thromboembolism recurred in 5 atrial fibrillation patients. The 5-year rate of major adverse cardiac and cerebrovascular events was 27.1%. In the propensity score–matched cohorts (n=45 each), Kaplan–Meier analysis showed a significantly higher incidence of cardiac death in the CE group than in the non-CE group (hazard ratio, 9.29; 95% confidence interval, 1.13–76.5; $P<0.001$).

Conclusions—Atrial fibrillation is the most frequent cause of CE. Patients with CE represent a high-risk subgroup of patients with acute myocardial infarction and require close follow-up. **(*Circulation*. 2015;132:241-250. DOI: 10.1161/CIRCULATIONAHA.114.015134.)**

Key Words: acute myocardial infarction ■ atrial fibrillation ■ coronary artery ■ embolism

Coronary artery embolism (CE) is recognized as an important nonatherosclerotic cause of acute myocardial infarction (AMI). However, the prevalence of this nonatherosclerotic entity remains unknown because it is difficult to diagnose in the acute setting. In a previous study based on autopsy or coronary angiography findings, 4% to 7% of AMI patients did not have atherosclerotic coronary disease.[1] In another autopsy study, 55 of 419 patients (13%) had coronary artery embolic infarcts.[2] In the era of primary percutaneous coronary intervention (PCI) for AMI, thrombectomy devices are increasingly used and histological examination of the aspirated thrombus provides additional information for diagnosing CE.[3] Because the majority of previous reports describing the clinical characteristics of CE were case reports with a small number of patients,[3–15] with the largest series to date consisting of 55 patients in an autopsy study[2] and 14 patients with probable CE in the clinical setting,[16] a mechanistic study for this important cause of AMI is now warranted.

Editorial see p 223
Clinical Perspective on p 250

Atrial fibrillation (AF) is associated with a high risk of thromboembolic events, and its prevalence is projected to increase because of population aging.[17] Indeed, the thromboembolic complications of AF are an important cause of morbidity and mortality. The $CHADS_2$ and CHA_2DS_2-VASc scores are useful for thromboembolic risk stratification.[18,19]

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The present study was designed to evaluate the prevalence, clinical characteristics, and initial management of CE, and early and late outcomes, as well, in a large consecutive series of patients. We also propose new diagnostic criteria for CE based on histological, angiographic, and other diagnostic imaging findings.

Methods

Study Population and PCI Procedure

We retrospectively analyzed a total of 2135 consecutive patients with AMI from January 2001 to December 2013 in the National Cerebral and Cardiovascular Center AMI database. We excluded 359 patients with a history of previous myocardial infarction (n=241), PCI (n=90), coronary artery bypass grafting (n=18), or both PCI and coronary artery bypass grafting (n=10), resulting in a total of 1776 patients with de novo AMI that were ultimately analyzed in this study (Figure 1). All study patients underwent invasive coronary arteriography and transthoracic echocardiography. The details of imaging modalities used to diagnose CE are presented in Table I in the online-only Data Supplement. This retrospective study was approved by the National Cerebral and Cardiovascular Center institutional review board.

AMI was defined by biomarker evidence of myocardial ischemia with symptoms of ischemia, ECG changes suggestive of new ischemia (new ST-T changes or new left bundle-branch block), or the development of pathological Q waves on ECG.[20] An ST-segment–elevation myocardial infarction (STEMI) was defined as an AMI with new ST elevation at the J point in 2 continuous leads with the following cutoff points: ≥ 0.2 mV in men or ≥ 0.15 mV in women in leads V_2 through V_3 and ≥ 0.1 mV in other leads.[20]

Based on recommendations from the American Heart Association,[21] coronary stenosis was assessed through visual inspection by attending cardiologists in the core laboratory who were blinded to the clinical data. PCI was performed as previously described.[22] In brief, PCI was performed after intravenous administration of 10 000 IU heparin using a 6F or 7F sheath and catheters. Antiplatelet therapy before PCI consisted of aspirin only between January 2001 and November 2007 and aspirin and clopidogrel between October 2007 and December 2013. After crossing the target lesion with the guide wire, coronary thrombus aspiration was performed depending on the operator's judgment. Aspiration was performed using the 6F or 7F Thrombuster (Kaneka, Osaka, Japan), Rescue PT system (Boston Scientific, Maple Grove, MN), TVAC (Nipro, Osaka, Japan), or Eliminate (Terumo, Tokyo, Japan). Some patients with suboptimal results after thrombus aspiration or balloon angioplasty received bare metal or drug-eluting stents.

National Cerebral and Cardiovascular Center Criteria for the Clinical Diagnosis of CE

The case definition of CE used in this study consisted of 3 major and 3 minor criteria (Table 1). Scores based on these criteria were used to distinguish between definite and probable cases of CE in patients with AMI. The 3 major criteria included (1) angiographic evidence of coronary artery embolism and thrombosis without atherosclerotic components, (2) concomitant multisite CE, and (3) concomitant systemic embolization excluding left ventricular thrombus attributable to AMI. The 3 minor criteria included (1) coronary angiography shows <25% stenosis, except for the culprit lesion; (2) evidence of an embolic source detected by any imaging modality; and (3) coexistence of a potential for thromboembolic disease, that is, AF, cardiomyopathy, rheumatic valvular disease, infective myocarditis, prosthetic valve implantation, recent cardiac surgery, hypercoagulable state, patent foramen ovale, or atrial septal defect. We propose that the diagnosis of definite CE be based on the presence of ≥2 major criteria, 1 major criterion plus ≥2 minor criteria, or 3 minor criteria. Patients were categorized as probable CE if they fulfilled 1 major criterion plus 1 minor criterion or 2 minor criteria. We excluded patients with the following findings: (1) pathological evidence of atherosclerotic thrombus, (2) coronary artery ectasia,[23] (3) plaque disruption or coronary erosion detected by intravascular ultrasound or optic coherence tomography on the proximal site of the culprit lesion, and (4) history of coronary revascularization defined as a history of myocardial infarction, PCI for angina pectoris with proven ischemia, or silent myocardial ischemia diagnosed with stress myocardial scintigraphy, or coronary artery bypass grafting. Patients with ≥25% coronary artery stenosis outside of the culprit lesion on coronary angiography after the onset of CE were excluded.

Figure 2 shows a representative case of definite CE. This patient met 3 major criteria (concomitant multiple coronary vessel embolization, evidence of fresh thrombus without atherosclerotic components, and concomitant systemic embolization) and 3 minor criteria (evidence of an embolic source detected by transesophageal echocardiography), no significant coronary stenosis except after thrombus aspiration, and chronic AF).

Analysis of Embolic Risk Using the $CHADS_2$ and CHA_2DS_2-VASc Scores

We assessed the embolic risk of CE patients with nonvalvular AF (NVAF) using the $CHADS_2$ and the CHA_2DS_2-VASc scores.[24] The $CHADS_2$ scoring system assigns 1 point for heart failure, hypertension (HT), age ≥ 75 years, and diabetes mellitus (DM), and 2 points for previous stroke or transient ischemic attack. The CHA_2DS_2-VASc score extends the $CHADS_2$ scoring system with more detailed

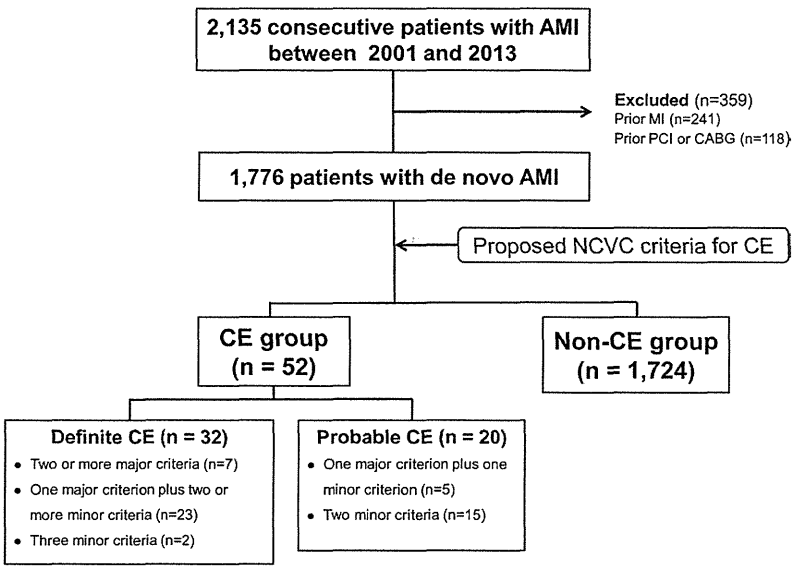

Figure 1. Flow chart of the study patients. We initially screened 2135 patients with AMI hospitalized between 2001 and 2013. We excluded 359 patients with previous MI, PCI, or CABG. A total of 1776 patients with AMI were ultimately analyzed in this study. According to the NCVC criteria for CE (see Table 1), 52 patients (2.9%) were diagnosed with CE; there were 32 patients diagnosed with definite CE and 20 patients diagnosed with probable CE. AMI indicates acute myocardial infarction; CABG, coronary artery bypass grafting; CE, coronary artery embolism; MI, myocardial infarction; NCVC, National Cerebral and Cardiovascular Center; and PCI, percutaneous coronary intervention.

Table 1. Proposed NCVC Criteria for the Clinical Diagnosis of Coronary Artery Embolism

Major criteria
▪ Angiographic evidence of coronary artery embolism and thrombosis without atherosclerotic components
▪ Concomitant coronary artery embolization at multiple sites*
▪ Concomitant systemic embolization without left ventricular thrombus attributable to acute myocardial infarction
Minor criteria
▪ <25% stenosis on coronary angiography, except for the culprit lesion
▪ Evidence of an embolic source based on transthoracic echocardiography, transesophageal echocardiography, computed tomography, or MRI
▪ Presence of embolic risk factors: atrial fibrillation, cardiomyopathy, rheumatic valve disease, prosthetic heart valve, patent foramen ovale, atrial septal defect, history of cardiac surgery, infective endocarditis, or hypercoagulable state
Definite CE
Two or more major criteria, or
One major criterion plus ≥2 minor criteria, or
Three minor criteria
Probable CE
One major criterion plus 1 minor criterion, or
Two minor criteria
A diagnosis of CE should not be made if there is
Pathological evidence of atherosclerotic thrombus
History of coronary revascularization
Coronary artery ectasia
Plaque disruption or erosion detected by intravascular ultrasound or optic coherence tomography in the proximal part of the culprit lesion

The present proposed diagnostic criteria for CE include 3 major and 3 minor criteria. Weighted scoring of the criteria is used to differentiate between definite and probable CE in patients with acute myocardial infarction. CE indicates coronary artery embolism; and NCVC, National Cerebral and Cardiovascular Center.

*Indicates multiple vessels within 1 coronary artery territory or multiple vessels in the coronary tree.

embolic risk assessment. This scoring system assigns 2 points for age ≥ 75 years and previous stroke or transient ischemic attack, and 1 point each for age 65 to 74 years, HT, DM, heart failure, vascular disease, and female sex. We also assessed the risk of bleeding using the HAS-BLED score.[25] The HAS-BLED scoring system assigns 1 point each for HT, renal dysfunction, liver dysfunction, stroke, bleeding history, labile international normalized ratio, age > 65 years, drug concomitantly, and alcohol abuse. A score of ≥3 indicates high bleeding risk.

End Points and Statistical Analysis

The major objective of this study was to estimate the prevalence of CE among patients with de novo AMI. We calculated the prevalence of CE among patients in our AMI database. We adopted the Bayesian-derived Jeffreys 95% confidence intervals (CIs) for proportions after comparing various CIs,[26] which were calculated by using the STATA CI command.[27]

End points included recurrent CE and major adverse cardiac and cerebrovascular events (MACCE), which consisted of cardiac death, myocardial infarction, ventricular tachycardia/ventricular fibrillation, stroke, or recurrent thromboembolism including CE >30 days after the onset of the initial CE event. Thromboembolic events include cardiogenic stroke, acute limb thromboembolism, and thromboembolic events in other organs. In-hospital and long-term outcomes were determined through medical record review, and, when necessary, through a questionnaire by mail and telephone follow-up. Because our AMI database (ie, non-CE group) had been followed only for cardiac and all-cause mortality but not MACCE, we presented the incidence of MACCE only in the CE group and compared the incidence of cardiac and all-cause mortality between the CE and non-CE groups.

Non-CE and CE subjects with AMI were matched based on a propensity score that included age; sex; history of DM, HT, and dyslipidemia; current smoking; and left ventricular ejection fraction. The propensity score was estimated using probit regression models,[28,29] with de novo AMI as the outcome and baseline clinical history and presentation characteristics as predictors (covariates are listed in Table 2, models 1 and 2). A propensity score–matched cohort was constructed with CE and non-CE patients on a 1:1 basis by using the nearest-neighbor matching method within a caliper of 0.01 of the propensity score with the psmatch2 procedure in the STATA program.[30] Details on how propensity score matching was performed are described in Materials in the online-only Data Supplement and Tables II through V in the online-only Data Supplement.

To compare the prognostic effects of CE between matched pairs, we used shared frailty models, which are used to model within-group correlations.[31,32] We used the matched pair as the random intercept in the Cox model with the STATA "shared" option for Cox regression.

Continuous variables are presented as means±standard deviation (SD) for normally distributed variables; they were compared using the *t* test. Nonnormally distributed variables are presented as medians (interquartile range). They were compared using the Mann-Whitney *U* test. Categorical baseline variables were compared using the Fisher exact test or the χ^2 test as appropriate. Kaplan–Meier methods were used to estimate survival curves for follow-up events. All *P* values <0.05 were considered statistically significant. All analyses were performed with SPSS (SPSS Japan, Tokyo, Japan) or STATA 13 (StataCorp, College Station, TX).

Results

Prevalence of CE in AMI and Comparison of Baseline Characteristics Between CE and Non-CE Patients

According to the proposed National Cerebral and Cardiovascular Center diagnostic criteria for CE, 52 (2.9%) of the 1776 patients with de novo AMI had CE (Figure 1), including 32 patients (62%) who fulfilled the criteria for definite CE and 20 patients (38%) categorized as having probable CE. The prevalence of CE was 2.9% (95% CI, 2.22–3.79). Table 2 compares the baseline clinical characteristics of the CE and non-CE groups. Of the 52 CE patients, 31 (60%) were male, with a mean age of 66±14 years. In comparison with the non-CE group, the CE group had a lower prevalence of HT (*P*=0.007), DM (*P*<0.001), dyslipidemia (*P*=0.001), and smoking (*P*=0.005). The CE group had a lower total number of coronary risk factors than the non-CE group (1.5±1.0 versus 2.6±1.2; *P*<0.001). The prevalence of AF was significantly higher in the CE group than in the non-CE group (73% versus 7%, *P*<0.001); there were 30 patients (58%) with NVAF in the CE group and 104 patients (6%) with NVAF in the non-CE group. The presenting diagnosis was STEMI in 65% of the CE group and 80% of the non-CE group (*P*=0.023). Peak creatine kinase was significantly higher in the non-CE group than in the CE group (3158±4013 versus 2210±2379 U/L, *P*=0.013), whereas no significant differences in left ventricular ejection fraction were seen between the two groups. Interestingly, although 30-day mortality in

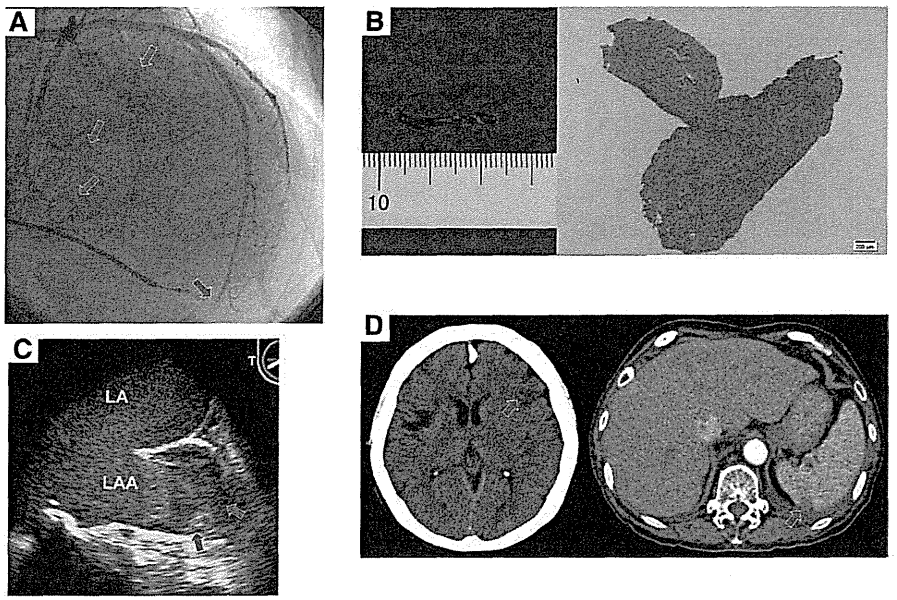

Figure 2. Representative case of definite CE. A 64-year-old woman presented with ST-segment–elevation myocardial infarction. **A**, Coronary angiography demonstrated total occlusion (red arrows) of the distal portion of the left anterior descending and circumflex arteries. **B**, Histological examination of the aspirated samples showed fresh red thrombus without evidence of an atherosclerotic component. **C**, Transesophageal echocardiography showed thrombus (red arrows) in the left atrial appendage (LAA). **D**, Computed tomography showed cerebral infarction (red arrow) and splenic infarction (red arrow). Based on these findings and a history of chronic atrial fibrillation, this patient was diagnosed with AMI attributable to definite CE (3 major criteria and 3 minor criteria for CE). AMI indicates acute myocardial infarction; CE, coronary artery embolism; and LA, left atrium.

the 2 groups was comparable (3 patients [6%] versus 55 patients [3%], P=0.240), all 3 CE patients died of noncardiac causes (lung cancer, n=2; stomach cancer, n=1). On the other hand, the 30-day cardiovascular death rate was significantly higher in the non-CE group than in the CE group (3% versus 0%, P<0.001).

Clinical Presentation, Causes, and Angiographic Findings of CE

Table 3 shows the clinical characteristics of CE. The most common underlying disease was AF (n=38; 73%). Cardiomyopathy was the next most common cause (n=13; 25%), followed by valvular heart disease (n=8, 15%). Of all 38 AF patients, 13

Table 2. Baseline Characteristics of Unmatched and Propensity Score–Matched Groups

	Unmatched Groups			Propensity Score-Matched Groups Model 1		Propensity Score-Matched Groups Model 2	
	CE (n=52)	non-CE (n=1724)	*P* Value	CE (n = 45)	non-CE (n=45)	CE (n=30)	non-CE (n=30)
Age, y	66±14	68±12	0.338	65±13	62±14	66±12	70±13
Male sex	31 (60)	1,229 (71)	0.087	27 (60)	31 (69)	19 (63)	15 (50)
Hypertension	25 (48)	1,155 (67)	0.007	22 (49)	21 (47)	15 (50)	19 (63)
Diabetes mellitus	4 (8)	692 (40)	<0.001	4 (9)	2 (4)	3 (10)	1 (3)
Dyslipidemia	16 (31)	936 (54)	0.001	14 (31)	19 (42)	10 (33)	12 (40)
Smoking	27 (52)	1226 (71)	0.005	24 (53)	23 (51)	18 (60)	11 (37)
Obesity (BMI ≥25 kg/m^2)	8 (15)	484 (28)	0.058				
Number of major coronary risk factors	1.5±1.0	2.6±1.2	<0.001				
Atrial fibrillation	38 (73)	116 (7)	<0.001				
Nonvalvular atrial fibrillation	30 (58)	104 (6)	<0.001				
STEMI	34 (65)	1371 (80)	0.023			21 (70)	19 (63)
Peak CK, units/L	2210±2379	3158±4013	0.013			1899±1502	2124±1569
Left ventricular EF, %	46±14	45±10	0.920	46±14	45±8	46±13	49±9
Chronic renal insufficiency							
30-day mortality	3 (6)	55 (3)	0.240				
Cardiovascular death	0 (0)	52 (3)	<0.001				
Noncardiovascular death	3 (6)	3 (0.2)	<0.001				

Categorical variables are expressed as n (%); continuous variables as mean±SD. Major coronary risk factors include hypertension, diabetes mellitus, dyslipidemia, smoking, and obesity. BMI indicates body mass index; CE, coronary artery embolism; CK, creatine kinase; EF, ejection fraction; SD, standard deviation; and STEMI, ST-segment–elevation myocardial infarction.

Table 3. Clinical Characteristics of CE

	CE (n=52)
Underlying cause of CE	
AF	38 (73)
Paroxysmal AF	13 (34)
Chronic AF	25 (66)
Nonvalvular AF	30 (58)
Cardiomyopathy	13 (25)
Idiopathic dilated cardiomyopathy	6 (46)
Hypertrophic cardiomyopathy	5 (38)
Hypertensive cardiomyopathy	1 (8)
Alcoholic cardiomyopathy	1 (8)
Valvular heart disease	8 (15)
Mitral valve stenosis	4 (50)
Aortic valve stenosis	4 (50)
Prosthetic valve	4 (50)
Malignancy	5 (10)
Lung	2 (40)
Stomach	1 (20)
Prostate	1 (20)
Breast (with tamoxifen therapy)	1 (20)
Septic emboli from IE	2 (4)
Embolism from a deep vein thrombus through a ASD	2 (4)
Involved vessel	
LMT	1 (2)
LAD	18 (35)
RCA	17 (33)
LCx	18 (35)
Multivessel embolization	8 (15)
Simultaneous systemic embolization	12 (23)
Cerebral infarction	8 (67)
Acute thromboembolic limb ischemia	3 (25)
Renal infarction	3 (25)
Splenic infarction	1 (4)
Intracardiac embolic source	16 (31)
Left atrium thrombus	12 (75)
Aortic valve vegetation attributable to IE	2 (13)
Mitral valve vegetation attributable to NBTE	1 (6)
Valsalva sinus thrombus	1 (6)

Categorical variables are expressed as n (%). ASD indicates atrial septal defect; AF, atrial fibrillation; CE, coronary artery embolism; IE, infectious endocarditis; LAD, left anterior descending artery; LCx, left circumflex artery; LMT, left main trunk; NBTE, nonbacterial thrombotic endocarditis; and RCA, right coronary artery.

(34%) had paroxysmal AF and 25 (66%) had chronic AF. There were 30 (58%) patients with NVAF. Of the 6 patients with dilated cardiomyopathy, 2 (33%) had chronic AF, and the remaining 4 (67%) had no history of either chronic or paroxysmal AF. On the other hand, all 5 patients with hypertrophic cardiomyopathy had chronic AF. Notable causes of CE were paradoxical embolism via an atrial septal defect attributable to deep vein thrombosis (n=2, 4%), malignancy (n=5, 10%), and septic emboli attributable to infective endocarditis (n=2, 4%).

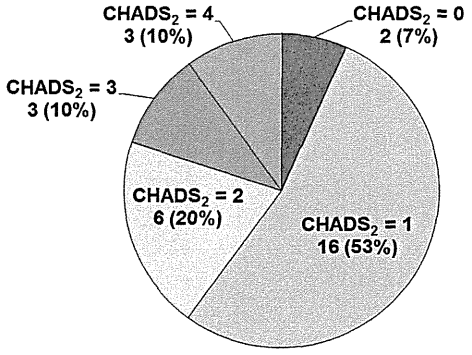

Figure 3. $CHADS_2$ scores in CE patients with nonvalvular atrial fibrillation (n=30). The $CHADS_2$ scoring system assigns 1 point each for heart failure, hypertension, age ≥75 years, and diabetes mellitus and 2 points each for previous stroke or transient ischemic attack. CE indicates coronary artery embolism.

There were no significant differences in the distribution of left anterior descending, left circumflex, and right coronary artery involvement. Coronary embolization at multiple sites was found in 8 patients (15%). Twelve (23%) patients presented with concomitant systemic embolization. Of these, 8 (67%) patients had stroke, 3 (25%) patients had acute lower limb ischemia, and 3 (25%) patients had renal infarction. An intracardiac embolic source was detected in 16 (31%) patients. Of these, 12 (75%) patients had left atrial thrombus and 2 (13%) patients had infected thrombi on the aortic valve. The diagnosis of intracardiac thrombi was made by transesophageal echocardiography in all patients, except 1 patient with end-stage lung cancer in whom a Valsalva sinus thrombus was detected by computed tomography angiography. All 12 patients with left atrial thrombus had AF (chronic AF, n=10; paroxysmal AF, n=2).

PCI Procedure for Patients With CE

A total of 29 (56%) patients underwent PCI; 28 of these 29 patients underwent initial thrombus aspiration and 1 patient was treated with balloon angioplasty alone. Of the 28 patients with initial thrombus aspiration, 5 (18%) patients underwent stent implantation and 4 (14%) patients underwent balloon angioplasty. Importantly, Thrombolysis in Acute Myocardial Infarction 3 flow was achieved in only 19 patients (66%). Reasons for failure in the remaining 10 patients included failure to cross into the distal lumen with the aspiration device owing to small vessel diameter (n=7) and residual distal thrombus after PCI (n=3).

Anticoagulation Status and $CHADS_2$/CHA_2DS_2-VAS Score in AF Patients

Of the 38 AF patients in the CE group, only 15 (39%) patients were treated with a vitamin K antagonist and their median international normalized ratio was 1.42 (range, 0.95–1.80) at the onset of CE. No patients were on non–vitamin K antagonist oral anticoagulants. Importantly, of the 30 patients with NVAF, 18 (60%) had a $CHADS_2$ score of 0 or 1 before the onset of CE (Figure 3). When those 18 patients with a low $CHADS_2$ score were reevaluated using the CHA_2DS_2-VASc score, 11 (61%) were categorized into a higher risk category (≥2) that would benefit from oral anticoagulation (Table 4).

Table 4. Reevaluation of Patients With a $CHADS_2$ Score of 0 or 1 Using the CHA_2DS_2-VASc Score

Age	Sex	Underlying Disease	$CHADS_2$ Score	CHA_2DS_2-VASc Score	HAS-BLED Score
77	F	–	1	4	1
88	F	–	1	3	1
74	F	Hypertensive cardiomyopathy	1	3	2
59	M	Alcoholic cardiomyopathy	1	2	2
73	M	–	1	2	1
71	M	–	1	2	1
70	M	–	1	2	1
81	M	–	1	2	1
64	M	HCM	1	2	0
66	M	–	1	2	1
58	F	HCM	1	2	2
43	M	DCM	1	1	0
64	M	–	1	1	0
45	M	DCM	1	1	1
64	M	HCM	1	1	0
43	M	–	1	1	0
55	F	–	0	1	0
50	M	–	0	0	0

DCM indicates dilated cardiomyopathy; F, female; HCM, hypertrophic cardiomyopathy; and M, male.

These patients did not have a high risk of bleeding based on the HAS-BLED score (<3).

Long-Term Outcomes of CE Patients

CE Recurrence and MACCE

Table 5 shows a summary of MACCE. During a median follow-up of 49 months (interquartile range, 19–93 months) with a 94.2% follow-up rate (n=49), 5 (10.4%) patients developed recurrent thromboembolic episodes: AMI attributable to CE in 2 patients (4.2%) and stroke in 3 patients (6.3%). All 5 patients with recurrent thromboembolism had AF (NVAF, n=3; valvular AF, n=2). The mean international normalized ratio at the time of the recurrent thromboembolism was 1.47±0.57. Figure 4A shows the Kaplan–Meier curves for survival free from the recurrence of CE or other thromboembolic events. After a primary CE event, the 5-year rate of recurrent CE or thromboembolism was 8.7%. The median time to a second episode of CE or thromboembolism was 35 months (interquartile range, 11–63 months).

Figure 4B shows the Kaplan–Meier curves for MACCE. Four patients experienced cardiac death (end-stage heart failure, n=3; sudden cardiac death, n=1), 2 had AMI, 3 developed stroke, and 2 experienced ventricular fibrillation (survived with bystander cardiopulmonary resuscitation and automated external defibrillation). The 5-year rate for MACCE was 27.1%.

Comparison of Long-Term Outcomes in Patients With CE Versus Non-CE AMI

We then compared the long-term outcomes between the CE and non-CE groups. Kaplan–Meier analysis showed a significantly higher incidence of all-cause death (hazard ratio [HR], 3.82; 95% CI, 2.06–6.48; $P<0.001$) and cardiac death (HR, 5.39; 95% CI, 2.38–10.6; $P<0.001$) in the CE group than in the non-CE group (Figure 5A and 5B). The 5-year rates of all-cause death and cardiac death in the CE group were significantly higher than those in the non-CE group (28% versus 7.6%, $P<0.001$; 17.5% versus 3.4%, $P<0.001$), respectively.

For further analysis, a propensity score–matched cohort consisting of 45 patients with CE and 45 patients without CE was selected (Table 2, model 1, and Tables II and III in the online-only Data Supplement). In this model that matched age; sex; history of DM, HT, and dyslipidemia; current smoking; and left ventricular ejection fraction, all-cause mortality (HR, 7.66; 95% CI, 1.65–35.45; $P<0.001$) and cardiac mortality (HR, 9.29; 95% CI, 1.13–76.5; $P<0.001$) were much

Table 5. Summary of MACCE During the Follow-up Period

MACCE	n (%)
Composite end point	11 (22.9)
Heart failure death	3 (6.3)
Sudden cardiac death	1 (2.1)
Ventricular fibrillation (successfully-resuscitated)	2 (4.2)
Recurrence of thromboembolism	5 (10.4)
CE resulting in AMI	2 (4.2)
Stroke	3 (6.3)
Other organs	0 (0)

Categorical variables are expressed as n (%). AMI indicates acute myocardial infarction; CE, coronary artery embolism; and MACCE, major adverse cardiac and cerebrovascular events (cardiovascular death, myocardial infarction, ventricular tachycardia/ventricular fibrillation, stroke, or recurrent thromboembolism including CE).

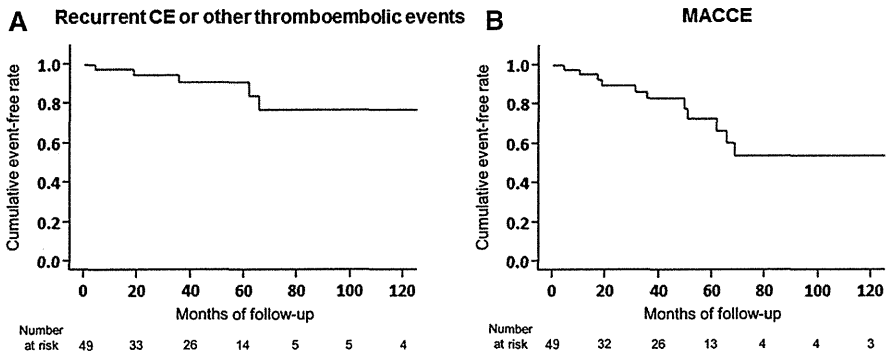

Figure 4. Kaplan–Meier curves for recurrent CE or other thromboembolic events and MACCE in patients with CE. Kaplan–Meier curves showing event-free survival with respect to recurrent CE or other thromboembolic events (**A**) and major adverse cardiac and cerebrovascular events (MACCE; **B**). MACCE include cardiac death, ventricular tachycardia/ventricular fibrillation, and recurrent thromboembolism >30 days after the onset of the initial CE event. The 5-year rate of recurrent CE or thromboembolism after a primary CE event was 8.7% (**A**). The 5-year rate for MACCE was 27.1% (**B**). CE indicates coronary artery embolism.

higher in the CE group than in the non-CE group. To further compare rates of cardiac and all-cause mortality between the 2 groups, an additional propensity score–matched cohort consisting of 30 patients with CE and 30 patients without CE was selected (Table 2, model 2, and Tables IV and V in the online-only Data Supplement). In this model that matched peak creatine kinase and history of STEMI in addition to all of the covariates in model 1, all-cause mortality (HR, 8.01; 95% CI, 1.42–45.13; P=0.018) and cardiac mortality (HR, 6.73; 95% CI, 1.07–42.28; P=0.042) were much higher in the CE group than in the non-CE group.

Discussion

The major findings of this study are as follows: (1) the prevalence of CE in patients with de novo AMI was 2.9%, (2) AF is the most frequent cause of CE; (3) 60% of NVAF patients in the CE group had low $CHADS_2$ scores; (4) the 5-year rate of thromboembolism, which includes CE recurrence, was 10.4% and the 5-year rate of MACCE was 27.1%. In addition, (5) although 30-day cardiovascular mortality in the CE group was significantly lower than that in the non-CE group, all-cause death and cardiac death during follow-up were significantly higher in the CE group than in the non-CE group. To the best of our knowledge, this is the first mechanistic study of the prevalence, clinical features, and prognosis of patients with AMI attributable to CE in the clinical setting.

Proposed Criteria for the Clinical Diagnosis of CE

In general, the diagnosis of CE has been made based on conventional angiographic features specific for coronary occlusion such as globular filling defects,[16] horse-riding thrombi,[8] or multiple filling defects[33] plus a couple of the following characteristics: (1) no atherosclerotic findings in the coronary trees, (2) presence of predisposing factors or comorbidities (ie, AF, intracardiac prosthesis, infective endocarditis, mural thrombus, or cardiac tumor), or (3) absence of significant stenosis at the culprit lesion after thrombus aspiration.[3] In this study, we have integrated these conventional findings as major and minor criteria (Table 1). Because recent advances in thrombectomy devices allow for the aspiration of histological samples that can provide additional information for diagnosing CE,[3] we have added pathological examination of aspirated thrombus as part of the major inclusion and exclusion criteria. Moreover, to represent the nature of thromboembolism, we have included concomitant systemic embolization as another major criterion in the present diagnostic criteria. To minimize including atherosclerotic causes of AMI, we have added the following as a minor criterion: < 25% stenosis on coronary angiography outside of the culprit lesion. We have also included plaque disruption and coronary erosion detected by optic coherence tomography and intravascular ultrasound as exclusion criteria. AMI secondary to coronary erosion is not associated with any significant atherosclerotic findings or plaque rupture.[34]

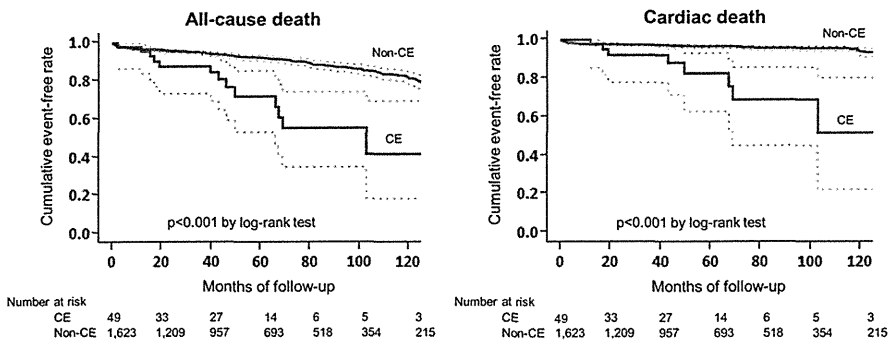

Figure 5. Comparison of long-term outcomes between AMI patients with and without CE. Kaplan–Meier curves showing the 5-year rate of survival free from all-cause death (**A**) and cardiac death (**B**). Kaplan–Meier analysis of all-cause and cardiac death demonstrated significantly poorer long-term outcomes in the CE group (solid red line) than in the non-CE group (solid blue line). The dotted lines indicate 95% confidence intervals. AMI indicates acute myocardial infarction; and CE, coronary artery embolism.

Prevalence of AF and Causes of CE

In the present study, we showed that the prevalence of de novo AMI attributable to CE according to our diagnostic criteria for CE was 2.9%. This is the first report on the prevalence of CE in AMI patients in a clinical setting. In comparison with a previous autopsy study that reported a CE prevalence of 13%,[2] the prevalence of CE in this study was relatively low. One possible explanation for this discrepancy may be attributable to the exclusion criteria used in this study. Because we intended to rigorously rule out atherosclerotic causes of AMI, we excluded patients with a history of coronary revascularization and ≥25% coronary stenosis under the new diagnostic criteria.

The cause of CE is multifactorial. In a 1978 autopsy-based study of 55 AMI patients, Prizel et al[2] reported that underlying diseases predisposing to CE included valvular heart disease (40%), cardiomyopathy (29%), coronary atherosclerosis (16%), and AF (24%). In another autopsy study, Charles et al[35] reported that the most common cause of CE was bacterial endocarditis; other causes included rheumatic heart disease, dilated cardiomyopathy, left atrial myxoma, arrhythmia, and myocardial infarction. In contrast to these previous autopsy reports, the present clinical study demonstrated that the most frequent underlying disease predisposing to CE was AF, and rheumatic or bacterial endocarditis constituted a small proportion of CE cases (Table 3). Decreases in the prevalence of rheumatic valvular heart disease and bacterial endocarditis with 3 decades of advances in medical therapy may have affected the prevalence of the underlying causes of CE. In addition, according to recent epidemiological studies in Europe and the United States, the prevalence of AF is ≈4% in individuals in their seventies, and ≈10% in those >80 years of age, indicating a significant increase with aging.[17]

Characteristics of CE

In this study, we found that CE patients have a lower prevalence of HT, DM, dyslipidemia, smoking, and total number of major coronary risk factors in comparison with non-CE AMI patients (Table 2). These findings may be related in part to the present exclusion criteria, even the minor criterion of <25% stenosis on coronary angiography outside the culprit lesion. Interestingly, in contrast to a previous autopsy study, there were no significant differences in the distribution of involved coronary vessels (Table 3). A previous autopsy study showed that CE occurs 3 to 4 times more often in the left coronary artery than in the right, and in the left anterior descending artery more often than in the left circumflex, because of their anatomic properties.[2] Such differences in the distribution of involved coronary vessels may be explained by bias related to the fact that arteries with larger territories are more likely to be involved in autopsy cases.

Clinical Implications of $CHADS_2$ and CHA_2DS_2-VASc Scores

In this study, 60% of NVAF patients had a $CHADS_2$ score of 0 or 1 (Figure 3) before CE onset. When those patients were reevaluated by using CHA_2DS_2-VASc, ≈61% were reassigned to a higher risk category (≥2) that would benefit from oral anticoagulation therapy (Table 4). This is clinically important, because many patients at low risk according to $CHADS_2$ are not truly low risk and treatment guidelines are not conclusive for patients at intermediate risk. Recent studies have demonstrated that CHA_2DS_2-VASc performs better than $CHADS_2$ in predicting patients at high risk for stroke and thromboembolism.[18,19] Consistent with these reports, our results suggest that the CHA_2DS_2-VASc score, not the $CHADS_2$ score, may yield useful clinical information regarding CE.

Thrombectomy During PCI for CE Patients and In-hospital Outcomes

In the present study, 58% of patients underwent PCI, of which 97% had thrombus aspiration as the initial PCI strategy. Thrombus aspiration devices have been used widely in recent years in STEMI patients with angiographic evidence of thrombus. They have been shown to be a feasible and effective strategy for the treatment of AMI, including CE-related infarction.[3] Importantly, histological examination of the aspirated thrombus provides additional information for diagnosing CE.[3] Although thrombus aspiration appears to be a reasonable option for CE patients, Stoel et al[14] reported that the smaller inner lumen diameter of aspiration catheters makes them less useful for aspirating large thrombi. In addition, crossing into the distal lumen with the aspiration device is challenging; indeed, 42% of the present patients were treated conservatively because of far distal occlusion or the small diameter of the vessel with the culprit lesion.

In this study, although the CE group had a Thrombolysis in Acute Myocardial Infarction 3 flow achievement rate of 66%, they had significantly lower peak creatine kinase and similar LVEF in comparison with the non-CE group. In addition, cardiovascular death within 30 days was significantly lower in the CE group than in the non-CE group (Table 2). These findings may be related in part to the distribution of occlusive thrombi in the coronary system after thrombus aspiration or PCI; that is, occlusive thrombi moved more distally from the culprit lesion after intervention, and this phenomenon may have affected infarct size and 30-day mortality.

Long-Term Prognosis of CE

The 5-year rate of thromboembolism including CE recurrence was 8.7% and the 5-year rate of MACCE was 27.1% in the present study population (Figure 4). It is notable that recurrent CE occurred exclusively in AF patients with inadequate international normalized ratio. This finding highlights the need for adequate vitamin K antagonist therapy for preventing CE recurrence. In addition, in comparison with the non-CE group, the 5-year rates of all-cause death and cardiac death in the CE group were unexpectedly high (Figure 5A and 5B). These unfavorable outcomes in the CE group were more pronounced in the propensity score–matched cohort analysis. The unexpectedly higher mortality rates in the CE group may be related to comorbidities (ie, cardiomyopathy or valvular heart disease). It should be noted that approximately one-third of those particular patients with underlying heart disease had AF, which may affect hemodynamics and lead to the development of heart failure. In the CE group, malignancy was a characteristic comorbidity. It was associated with noncardiovascular

death within 30 days but not long-term prognosis in the present study. These findings suggest that CE events may be related to an advanced stage of malignancy.

Limitations

The present study has several limitations. First, the retrospective and single-site nature of this study and the small number of cardiac events observed might have resulted in a certain extent of bias. Second, because the proposed diagnostic criteria exclude patients with ≥25% coronary artery stenosis or a history of revascularization, some patients with CE plus coronary artery disease may have been excluded; thus, the prevalence of CE may have been underestimated. Finally, the rates of all-cause and cardiac mortality in the non-CE group (ie, de novo AMI subjects without CE) in this study were much lower than those in Western countries.[36,37] However, a recent large prospective registry study in Japan demonstrated that all-cause mortality at 2 years of follow-up was 6.3% in patients with acute coronary syndrome.[38] Our observed mortality rate was consistent with that result.

Conclusion

This study found that the prevalence of CE in patients with AMI was 2.9%, and AF was the most frequent cause. Long-term outcomes indicate that CE patients represent a high-risk subpopulation of patients with AMI and therefore require close follow-up.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Coronary artery embolism is an infrequent but important cause of acute myocardial infarction. It is a nonatherosclerotic entity whose clinical characteristics have not been elucidated. This retrospective single-center study evaluated the prevalence, clinical features, initial management, and early and late outcomes of 52 patients with coronary artery embolism with the use of our proposed diagnostic criteria. We found that atrial fibrillation with a low burden of atherosclerotic risk factors was the most frequent cause of coronary artery embolism. Only 39% of patients with atrial fibrillation were treated with vitamin K antagonists, but their median international normalized ratios were inadequate. Thrombus aspiration as the initial management strategy was useful for achieving Thrombolysis in Acute Myocardial Infarction 3 grade flow in select patients. Although early clinical outcomes (30-day mortality) were comparable to those for acute myocardial infarction with atherosclerotic etiologies, both cardiac and all-cause mortality were unexpectedly high during long-term follow-up. Coronary artery embolization recurred in 3.8% of patients, all with atrial fibrillation. These findings underscore the need for close follow-up in this high-risk patient population.

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Original Article

Calibration between the Estimated Probability of the Risk Assessment Chart of Japan Atherosclerosis Society and Actual Mortality Using External Population: Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN)

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Aim: In Japan Atherosclerosis Society guidelines for the prevention of atherosclerotic cardiovascular diseases 2012 (JAS2012), NIPPON DATA80 risk assessment chart (ND80RAC) was adopted to estimate the 10-year probability of coronary artery disease (CAD) mortality. However, there was no comparison between the estimated mortality calculated by ND80RAC and actual mortality in external populations. Accordingly, we used the large pooled database of cohorts in Japan, EPOCH-JAPAN, as an external population.

Methods: The participants of EPOCH-JAPAN without a history of cardiovascular disease (15,091 men and 18,589 women aged 40−74 years) were analyzed based on sex. The probability of a 10-year risk of CAD/stroke mortality was estimated by ND80RAC. The participants were divided into both decile of their estimated mortality and three categories according to JAS2012. The calibration between the mean estimated mortality and the actual mortality was performed by the Hosmer and Lemeshow (H-L) test.

Results: In both sexes, the estimated CAD mortality was higher than the actual mortality, particularly in higher deciles of estimated mortality, and the estimated stroke mortality was almost concordant with the actual mortality in low/moderate deciles of estimated mortality. As for the categories according to JAS2012, the estimated CAD mortality was higher than the actual mortality in both sexes; actual mortality in Category III was lower than that in Category II in women. However, it increased in the ascending order of category when we excluded the presence of diabetes from Category III.

Conclusions: The estimated CAD mortality by ND80RAC tended to be higher than the actual mortality in the population in which the baseline survey was more recently performed.

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Key words: External calibration, Cohort studies, Pooled analysis, Risk assessment Chart, Stroke, Coronary artery disease

Introduction

Cardiovascular disease (CVD) is one of the leading causes of mortality in the world as well as in Japan[1, 2]. To predict individuals at high risk for CVD, several risk prediction tools have been developed[3, 4]. Among them, the Framingham risk score (FRS) was widely accepted in Western countries because of its well-established validity[5-11]. The 2013 American College of Cardiology/American Heart Association recently updated cholesterol guidelines, which recommend the use of Pooled Cohort Equations to estimate the 10-year absolute risk for atherosclerotic cardiovascular disease (ASCVD)[12]. However, because FRS and ASCVD had been established among Caucasians, the risk for coronary artery disease (CAD) may be overestimated in Asians, especially Japanese population, which have extremely lower CAD mortality than the Western population[13].

The Japan Atherosclerosis Society (JAS) proposed comprehensive lipid and risk management guidelines for CAD in 2012. In the guideline, the 10-year absolute risk chart of CAD mortality was established using the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged 1980 (NIPPON DATA80) Risk Assessment Chart (ND80RAC)[14, 15]. In addition, JAS defined three categories for the prevention of CAD according to the presence of several diseases such as diabetes mellitus (DM). In the previous study, subclinical atherosclerosis of the carotid arteries has been reported to be concordant with the three categories defined by the JAS guidelines 2012[16]. However, there was no calibration study between the estimated mortality calculated by ND80RAC and actual mortality in the external populations and time-period.

The purpose of this study was to investigate the external calibration of ND80RAC using the large pooled database of the cohorts in Japan, the Evidence for Cardiovascular Prevention from Observational Cohorts in Japan (EPOCH-JAPAN).

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Methods

Study Design and Participants

The present study was a part of pooled project called EPOCH-JAPAN, one of the largest cohort dataset, which incorporates 14 both nationwide and regional cohort studies in Japan for meta-analyses. The details of the rationale, study design, and methods of EPOCH-JAPAN have been described elsewhere[17-24]. In brief, the criteria for a cohort recruitment of EPOCH-JAPAN were as follows: (i) collected health examination measures; (ii) had almost 10 years of follow-up; (iii) included >1,000 participants. Quality control of the collected cohort data was performed at the EPOCH-JAPAN study coordinating center. Permission to submit data from each cohort to the EPOCH-JAPAN study coordinating center was obtained from the relevant institutional review boards for ethical issues.

Of the 14 cohorts, two cohorts were excluded from the present analysis because of the absence of cause of death information and 12 cohorts were included (Tanno-Sobetsu, Ohsaki, Ohasama, Oyabe, YKK workers, Suita, RERF cohort, Hisayama, JACC, NIPPON DATA80, NIPPON DATA90 and Osaka). From 101,977 total participants, the participants of NIPPON DATA80 (n=9,442), the participants who had a history of cardiovascular disease at baseline (n=7,029) and who were <40 years or >75 years (n=13,747) were excluded. In addition, those with the missing values or outliers on systolic blood pressure, serum total cholesterol, blood glucose, and smoking status (n=38,079) were excluded. In this process, the dataset of 2 cohorts (Oyabe and JACC) were completely excluded due to the missing values of blood glucose. Finally, the remaining participants of 33,680 (15,091 men and 18,589 women) were included in the present study.

Risk Factors

Information of each participant's medical history and drinking/smoking status was obtained throughout questionnaires. Blood pressure was measured in the sitting position with a standard mercury sphygmomanometer, except for the Ohasama study in which the validated automatic monitor was used. The participants rested before measurement except in the Ohsaki study. Two (Ohasama and Suita studies) or three (Hisayama study) consecutive values, or otherwise one reading at the examination center was used in the analysis[17, 18, 24-26]. Non-fasting serum total cholesterol and blood glucose level were determined by automated enzymatic methods on venous blood samples.

Endpoints

The details of determining the endpoints in EPOCH-JAPAN have been reported elsewhere[19]. Shortly, a primary underlying cause of death was sought in great detail from the available sources such as death certificates, the National Vital Statistics, autopsy reports as well as medical records in each cohort study and coded according to the ninth revision of the International Classification of Disease (ICD-9) for National Vital Statistics based on the criteria proposed by the World Health Organization[27]. In the present study, the endpoints were mortality from CAD (ICD-9 codes 410-414, ICD-10 codes I-20-I25) and stroke (ICD-9 codes 430-438, ICD-10 codes I60-I69) during the 10 year follow-up.

NIPPON DATA80 Risk Assessment Charts

Risk charts for the probability over a 10-year period of mortality from CAD/stroke were constructed on the basis of a nationwide cohort study called NIPPON DATA80 and cited in the JAS guidelines 2012[14, 15]. The participants of NIPPON DATA80 were those in the National Survey on Circulatory Disorders 1980 and all household members aged ≥30 years in 300 randomly selected census tracts across Japan who agreed to cooperate in the survey.

Statistical Methods

Sex-specific analyses were performed. From the risk assessment charts in JAS guidelines 2012, the equation $1-S(10:x)=1-[S_0(10:\bar{x})]^{\exp(\beta(\bar{x}-x))}$ estimated the probability of the 10-year risk for CAD/stroke mortality, where x: risk factors at baseline in EPOCH-JAPAN, $\bar{x}$: mean values of risk factors at baseline in NIPPON DATA80, β: regression coefficients for the risk factors of NIPPON DATA80, and $S_0(10:\bar{x})$: the survival probability of 10-year risk with risk factors $\bar{x}$. The risk factors in this model were as follows: age, systolic blood pressure (SBP), total cholesterol, smoke status (current or not), and casual glucose level (≥200 mg/dL or <200 mg/dL)[15]. To calibrate the mean estimated CAD/stroke mortality in ND80RAC and the actual cumulative mortality in EPOCH-JAPAN, the participants were divided into decile of their estimated probability, and the mean estimated probability was calculated in each decile. Furthermore, the actual cumulative mortality of CAD/stroke in each decile was calculated as the number of deceased participants divided by the number of all participants in the decile. Hosmer and Lemeshow test was conducted to perform the difference between the estimate CAD/stroke mortality and the actual cumulative mortality.

The participants were also categorized according to the JAS guidelines 2012 with four exceptions: (i) none of the study participants had a history of non-cardiogenic cerebral infarction because a history of any type of stroke was excluded from the cohort; (ii) a family history of premature CAD was not assessed because we have not been collected; (iii) there was no information about HDL (high density lipoprotein) cholesterol; and (iv) there was also no information about chronic kidney disease (CKD). Finally, the participants were defined in three categories: Category I (low risk, probability of CAD mortality <0.5%), Category II (intermediate risk, probability of CAD mortality ≥0.5% and <2.0%), and Category III (high risk, probability of CAD mortality ≥2.0% or having DM)[14]. In addition, the participants were classified into three risk categories according to the probability of CAD mortality mentioned above, without considering the presence of DM in Category III.

The analyses were performed using the SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

Results

The mean age of the participants was 56 years (standard deviation: 10 years) and the mean follow-up period was 9.4 years. During the 10-year follow-up, we observed 120 deaths from CAD and 186 deaths from stroke (cerebral infarction: 65, hemorrhagic stroke: 42 and subarachnoidal hemorrhage: 39).

Table 1 shows the baseline characteristics of the participants defined by the three categories of JAS guidelines 2012. Category III accounted for a majority of the CAD/stroke mortality.

Fig. 1 shows the mean estimated CAD mortality and its actual cumulative mortality according to the decile of estimated CAD mortality. In men, the actual mortality increased as the mean estimated mortality increased. In lower decile groups, the mean estimated mortality fairly predicted the actual mortality. Meanwhile, in higher decile groups, the mean estimated mortality was predicted to be higher than the actual mortality, especially in the 8th, 9th, and 10th decile. In women, the results were almost similar with those in men, while the number of CAD mortality in women was fewer than that in men. In the 10th decile, the mean estimated mortality was particularly higher than the actual mortality. Homer and Lemeshow test showed the significant difference in both men ($p<0.001$) and women ($p<0.001$).

Fig. 2 shows the mean estimated stroke mortality and its actual cumulative mortality according to the decile of estimated stroke mortality. In men, the actual mortality increased as the estimated mortality

Table 1. Baseline Characteristics of EPOCH-JAPAN distinguished by Japan Atherosclerosis Society (JAS) classification

	Category for LDL-c management proposed by JAS Guidelines 2012[1)]					
	Men			Women		
	I	II	III	I	II	III
Age, years (SD)	46 (5)	58 (6)	57 (10)	51 (7)	67 (3)	58 (10)
Person year (SD)	9.8 (0.9)	9.5 (1.5)	9.3 (2.0)	9.8 (0.9)	9.6 (1.5)	9.4 (2.0)
Systolic blood pressure, mmHg (SD)	121 (15)	131 (18)	133 (19)	126 (19)	137 (20)	131 (20)
Total cholesterol, mg/dL (SD)	186 (30)	200 (34)	199 (36)	210 (37)	227 (38)	213 (37)
Blood glucose, mg/dL (SD)	96 (13)	101 (19)	106 (32)	95 (13)	102 (19)	103 (28)
% of those having glucose ≥ 200 mg/dL	0	0	2.2	0	0	1.7
Current Smoker (%)	56.6	55.4	53.0	8.3	11.5	6.7
Number of Stroke	0	8	81	4	8	85
Number of Ischemic Stroke	0	2	33	1	4	25
Number of Hemorrhagic Strokes	0	2	24	1	3	12
Number of Subarachnoid hemorrhage	0	3	13	0	1	22
Number of Coronary Artery Disease	1	10	69	1	8	31

1) Category I: < 0.5%, Category II: ≥ 0.5% < 2.0%, Category III: ≥ 2.0% or Diabetes Mellitus

increased. In low/moderate decile groups, the mean estimated mortality fairly predicted the actual mortality. Meanwhile, in the higher decile group, the mean estimated mortality was predicted to be higher than the actual mortality, particularly in the 9th and 10th decile. In women, the results were almost similar with those in men. In the 9th and 10th decile, the mean estimated mortality was particularly higher than the actual mortality. Homer and Lemeshow test showed the significant difference in both men ($p<0.001$) and women ($p<0.001$).

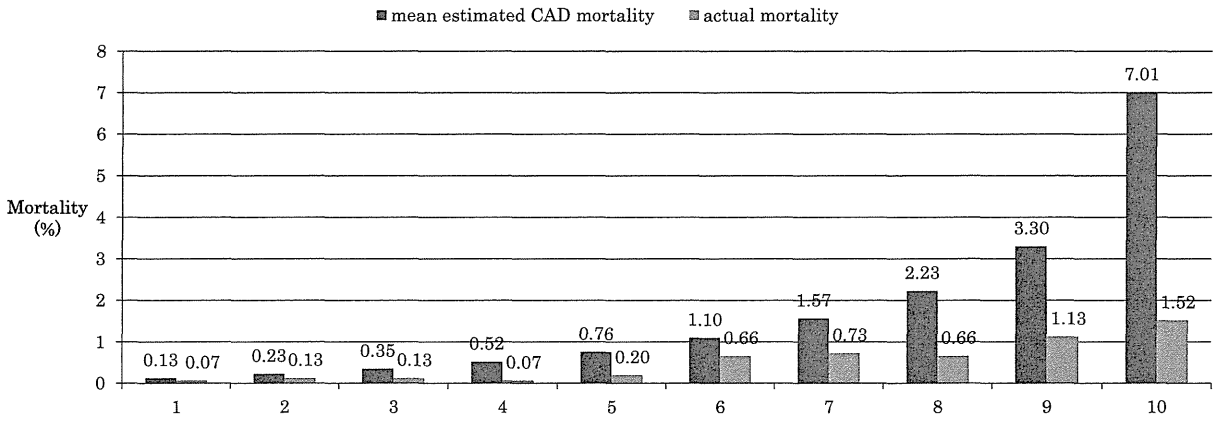
Supplemental Figures show the cohort-specific analysis between the mean estimated CAD/stroke mortality and its actual mortality by the quintile of estimated mortality. Based on their sample size and actual mortality, Suita cohort and Osaki cohort were selected as a representative of high and low age-adjusted CAD mortality rate (Suita: 474, Osaki: 273/100,000 population), respectively. In addition, NIPPON DATA90 was selected because it was performed under the similar protocol (sampling scheme of study participants) 10 years after NIPPON DATA80. In both men and women, the actual CAD/stroke mortality increased as the estimated morality increased. In higher quintile groups, i.e., 4th and 5th quintile, the mean estimated CAD/stroke mortality was higher than its actual mortality. These results were similar to the above-mentioned whole population analysis (**Fig. 1** and **2**).

Fig. 3 shows the mean estimated CAD mortality and its actual mortality according to the three categories of JAS guidelines 2012. The mean estimated mortality was higher than its actual mortality in all categories. In men, while the mean estimated mortality increased in the ascending order of category, its actual mortality in Category III did not increase significantly from that in Category II. The mean estimated mortality was higher than its actual mortality in Category III. In women, both the mean estimated mortality and actual mortality in Category III were lower than those in Category II. The Homer and Lemeshow test showed the significant difference in both men ($p<0.001$) and women ($p<0.001$).

Fig. 4 shows the mean estimated CAD mortality and its actual mortality according to the three categories of JAS guidelines 2012, without considering the presence of DM in risk classification. The mean estimated mortality was higher than its actual mortality in all categories. Compared to **Fig. 3**, the mean estimated mortality was higher than its actual mortality in Category III in **Fig. 4**. In men, both the mean estimated mortality and actual mortality increased in the ascending order of category, and the mean estimated mortality was higher than its actual mortality in Category III. In women, the results were almost the same as those in men. The Homer and Lemeshow test showed the significant difference in both men ($p<0.001$) and women ($p<0.001$).

Discussion

In the present study, we calibrated ND80RAC using one of the largest pooled cohort study, EPOCH-JAPAN. For CAD, in low mortality groups, the abso-

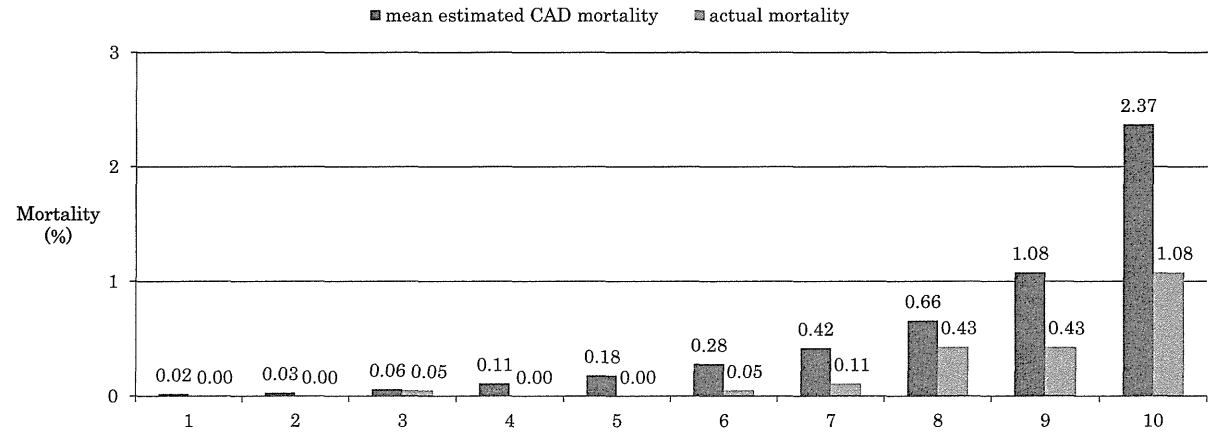


	1	2	3	4	5	6	7	8	9	10
Difference between two mortality [2]	0.06	0.10	0.22	0.45	0.56	0.44	0.84	1.57	2.17	5.49
Number of participants	1509	1509	1509	1509	1509	1509	1509	1508	1508	1512
Number of deaths	1	2	2	1	3	10	11	10	17	23

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each decile

Fig. 1A. Decile of mean estimated CAD mortality of men in NIPPON DATA80 and actual mortality of men in EPOCH-JAPAN.[1] Hosmer–Lemeshow test (χ^2 statistic=134.18 d.f.=8, $P<0.001$)

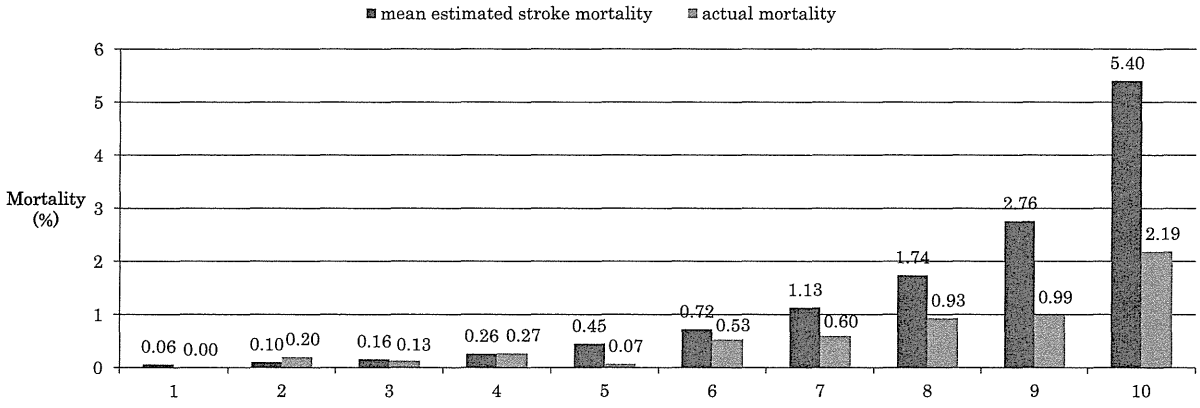


	1	2	3	4	5	6	7	8	9	10
Difference between two mortality [2]	0.02	0.03	0.01	0.11	0.18	0.23	0.31	0.23	0.65	1.29
Number of participants	1858	1859	1859	1859	1859	1859	1859	1859	1859	1859
Number of deaths	0	0	1	0	0	1	2	8	8	20

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated CAD mortality and the actual cumulative mortality in each decile

Fig. 1B. Decile of mean estimated CAD mortality of women in NIPPON DATA80 and actual mortality of women in EPOCH-JAPAN.[1] Hosmer–Lemeshow test (χ^2 statistic=36.38, d.f.=8, $P<0.001$)

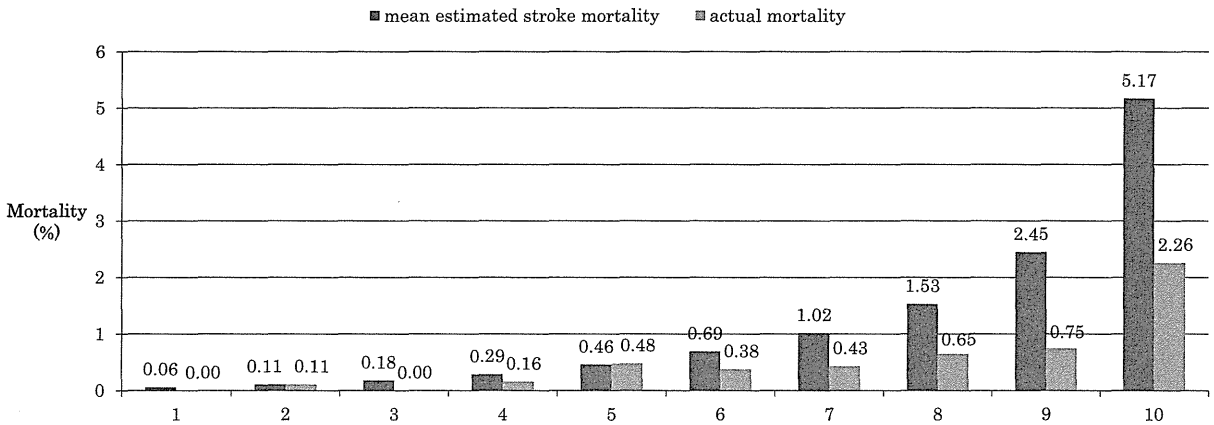


Difference between two mortality [2]	0.06	0.10	0.03	0.01	0.38	0.19	0.53	0.81	1.77	3.21
Number of participants	1509	1509	1509	1509	1509	1509	1509	1509	1509	1509
Number of deaths	0	3	2	4	1	8	9	14	15	33

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated stroke mortality and the actual cumulative mortality in each decile

Fig. 2A. Decile of mean estimated stroke mortality of men in NIPPON DATA80 and actual mortality of men in EPOCH-JAPAN.[1] Hosmer–Lemeshow test (χ^2 statistic=65.87, d.f.=8, $P<0.001$)



Difference between two mortality [2]	0.06	0.00	0.18	0.13	0.02	0.31	0.59	0.88	1.70	2.91
Number of participants	1858	1858	1860	1859	1859	1859	1859	1859	1857	1861
Number of deaths	0	2	0	3	9	7	8	12	14	42

1) Estimated from NIPPON DATA80 risk chart

2) Calculated the difference between the mean estimated stroke mortality and the actual cumulative mortality in each decile

Fig. 2B. Decile of mean estimated stroke mortality of women in NIPPON DATA80 and actual mortality of women in EPOCH-JAPAN.[1] Hosmer–Lemeshow test (χ^2 statistic=78.84, d.f.=8, $P<0.001$)