

[ORIGINAL ARTICLE]

Differences in Clinical Features in Patients with Acute Coronary Syndrome and Stroke: Japanese Multicenter Registry Results

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on behalf of the PACIFIC Investigators and the EVEREST Investigators

Abstract:

Objective Coronary artery and cerebrovascular disease are the main causes of non-communicable diseases. In particular, acute coronary syndrome (ACS) and ischemic stroke are the most serious conditions of coronary artery disease and cerebrovascular disease, respectively. Therefore, it is important to prevent these conditions by identifying populations at high risk of these diseases. We sought to investigate the differences in the clinical features of patients with these atherothrombotic diseases in nationwide Japanese multicenter registries. Gender differences were also examined.

Methods The dataset of the two nationwide multicenter registries for ACS [Prevention of Atherothrombotic Incidents Following Ischemic Coronary (PACIFIC)] and ischemic stroke [Effective Vascular Event REDuction after STroke (EVEREST)] was analyzed. Clinical features were examined and compared using datasets from the two registries.

Results A total of 6,878 patients (PACIFIC: n=3,426, EVEREST: n=3,452) were evaluated. The patients' background characteristics were significantly different between the two populations. Patients with ACS tended to be younger, had a higher body mass index, had a greater prevalence of diabetes mellitus and dyslipidemia, were current smokers, and more often had a prior history of ischemia heart disease than patients with a stroke. Hypertension was more prevalent in patients with stroke than in those with ACS. The differences in patients' background characteristics between ACS and stroke in men were similar to those in the whole sample. However, the prevalence of hypertension in women was similar between the ACS and stroke groups, in contrast to the results from the whole sample.

Conclusion Patients' background characteristics were significantly different between those with ACS and stroke. Gender differences were also observed.

Key words: acute coronary syndrome, ischemic stroke, clinical features, gender differences, nationwide registry data

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Introduction

Non-communicable diseases, such as heart disease, lung disease, cancer, and diabetes, account for approximately 60% of all-cause death worldwide (1). Coronary artery and cerebrovascular disease are the main causes of non-

communicable diseases (2). A report from the Japanese Ministry of Health, Labor and Welfare demonstrated that the number of deaths associated with cardiac and cerebrovascular diseases was 196,925 and 114,204, respectively, in 2014, making these diseases the second-most common cause of death in Japan (2). In particular, acute coronary syndrome (ACS) is the most serious condition among patients with

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coronary artery diseases (3, 4), and that of patients with cerebrovascular diseases is stroke (5, 6). Therefore, it is important to prevent these diseases by identifying populations at high risk. However, coronary artery disease and cerebrovascular disease are two distinct diseases with different risk factors (7-9).

The aim of this study was to investigate differences in the clinical features between patients with ACS and those with stroke using data from nationwide multicenter registries. Gender differences between the clinical features of these diseases were also examined.

Materials and Methods

We analyzed a database that consisted of two nationwide multicenter registries.

The Prevention of Atherothrombotic Incidents Following Ischemic Coronary attack (PACIFIC) registry is a prospective, two-year observational study of a large cohort of Japanese patients hospitalized for any ACS [ST elevation myocardial infarction (STEMI), non-STEMI (NSTEMI) or unstable angina (UA)] (10). Hospitalized ACS patients ≥ 20 years of age were enrolled from 96 Japanese regional core hospitals with facilities for advanced interventional therapy between May 2008 and May 2009. Complete definitions for STEMI, NSTEMI and UA were provided in the protocol paper (11). In brief, for a diagnosis of STEMI, patients had to have chest symptoms, ST segment elevation ≥ 1 mV in ≥ 2 limb leads or ≥ 2 contiguous precordial leads or left bundle branch block and elevated biochemical markers of myocardial necrosis (troponin T ≥ 0.1 ng/mL or creatine phosphokinase 2-fold above the normal range). For a diagnosis of NSTEMI, patients had to have chest symptoms, ST-segment depression ≥ 0.05 mV or T-wave inversion ≥ 0.3 mV or transient < 0.05 -mV ST-segment elevation and elevated biochemical markers of myocardial necrosis (and no electrocardiogram abnormalities for STEMI). UA was diagnosed in patients with persistent resting or nocturnal chest pain along with additional findings described in the protocol paper (11). Patients with chest pain and coronary artery disease that occurred as a consequence of other serious diseases, traumatic events or revascularization procedures were excluded from the study. Participating institutions were requested to enroll 40-80 patients consecutively. Patients were evaluated at baseline for demographic and clinical characteristics, and the treatment strategy for ACS, including coronary interventions and pharmacological treatments, was also recorded.

The Effective Vascular Event REduction after STroke (EVEREST) registry was established to evaluate the one-year rates of atherothrombotic vascular events in patients with recent non-cardioembolic ischemic stroke receiving at least one oral antiplatelet agent and to assess the risk factors for recurrent ischemic stroke in this population (12). This prospective cohort study was conducted between January 2007 and July 2009 at 313 hospitals in Japan. The study group collected the data on patients from the physicians of

the participating institutions. Outpatients who were at least 45 years of age were eligible for the study if they had had ischemic stroke within 2 weeks to 6 months before enrollment, and the participating institutions were general hospitals with at least 100 beds or hospitals that had a department of neurology. Institutions were selected from all over Japan to ensure that the study population represented the entire Japanese patient population. Physicians at each institution were required to enroll 5 to 50 consecutive outpatients between January 2007 and May 2008.

Study participants younger than 45 years of age in the PACIFIC registry were excluded from the analysis, because the EVEREST registry recruited patients ≥ 45 years of age.

The data that support the findings of this study are available from Sanofi, but restrictions apply to the availability of these data, which were used under license for the current study and so are not publicly available. The data are, however, available from the authors upon reasonable request and with permission of Sanofi.

Purpose of study

We used data from a large Japanese cohort, including the PACIFIC ACS registry and the EVEREST stroke registry, to investigate differences in the clinical features of patients with ACS and those with stroke. Furthermore, we examined the clinical features of the two patient populations for gender differences, as men and women are two distinct populations with different characteristics.

Ethics

The PACIFIC study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committees of every participating institution. All subjects provided their written informed consent. The EVEREST study was conducted in accordance with the Declaration of Helsinki. Its protocol was reviewed and approved by the ethics committee of Keio University Hospital, the institution to which the principal investigator belongs.

Data analyses

The data of the PACIFIC and the EVEREST registry were merged by a statistician of Juntendo University who was unaffiliated with either of the registries.

Statistical analyses

Continuous variables are expressed as the median value with interquartile range. Categorical data are expressed as the frequency and percentage. Continuous variables were compared using the Mann-Whitney U test because the distribution of all continuous variables was skewed. Categorical variables were analyzed with the chi-squared test or Fisher's exact probability test. A two-sided probability of below 0.05 was considered statistically significant. Statistical analyses were conducted using the JMP software program, version 10.0 for Windows (SAS Institute, Cary, USA).

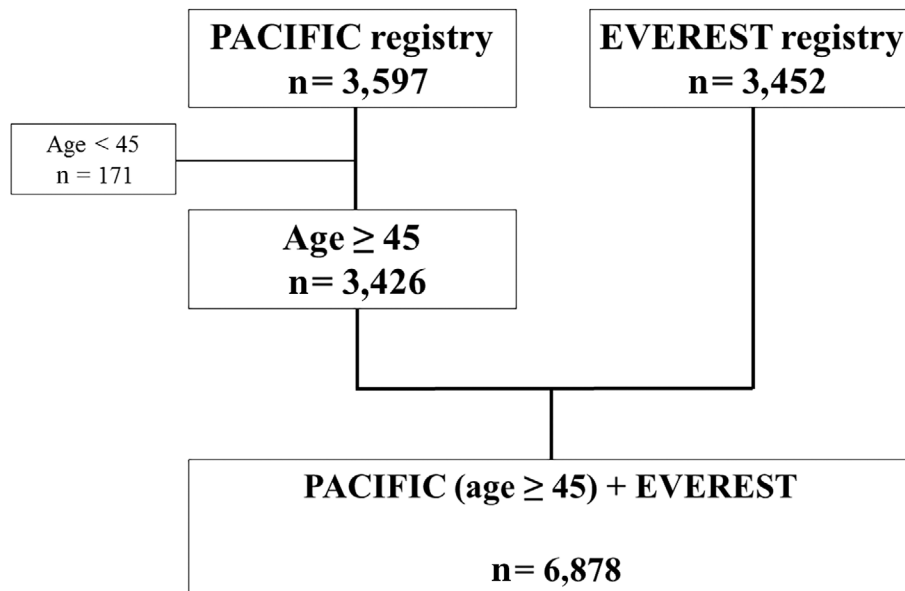


Figure 1. A flow chart of the study population. Of the 7,049 total patients enrolled from the PACIFIC and EVEREST registries, 171 younger than 45 years of age were excluded from the PACIFIC registry. The data of 6,878 patients were ultimately analyzed in this study.

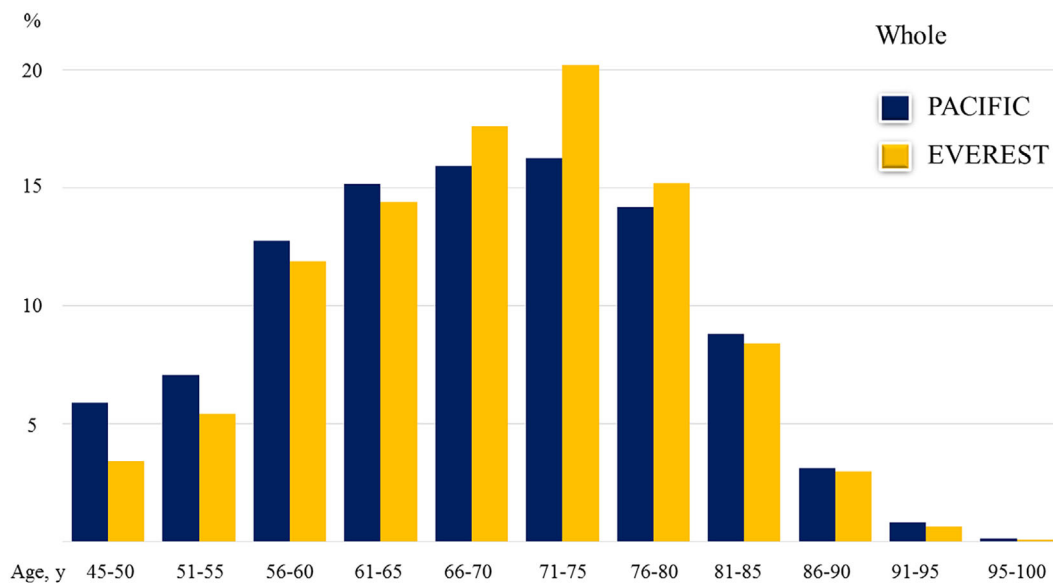


Figure 2. The distributions of the age at enrollment are shown for the PACIFIC and EVEREST registries. The distributions of age differed between the registries.

Results

A flow chart of the combined population is described as Fig. 1. Data from 6,878 people (PACIFIC, n=3,426, EVEREST, n=3,452) were analyzed. The ACS group tended to be younger and included a greater percentage of men than the stroke group. The age distribution differed between groups (Fig. 2). Body size parameters, including height, weight, waist circumference and body mass index (BMI), were greater in the ACS group than in the stroke group (Table 1).

Comorbidities

The prevalence of diabetes mellitus, dyslipidemia, current smoking and a history of ischemic heart disease was significantly higher in the ACS group, while the prevalence of hypertension was higher in the stroke group. The systolic and diastolic blood pressure were also higher in the stroke group. In addition, a greater percentage of patients had 3, 4 or 5 atherosclerotic risk factors in the ACS group than in the stroke group (Table 1). The prevalence of atrial fibrillation was greater in the ACS group, as was the percentage of patients with an ankle-brachial index (ABI) below 0.9. The

Table 1. Baseline Characteristics.

	PACIFIC n=3,426	EVEREST n=3,452	P
Age, year	68 [60, 76]	70 [62, 76]	<0.0001
Male gender, n (%)	2,609 (76.2)	2,307 (66.8)	<0.0001
Height, cm	163 [156, 168]	160 [153, 166]	<0.0001
Weight, kg	62 [54.7, 70]	60 [52.3, 67]	<0.0001
BMI, kg/m ²	23.7 [21.6, 25.9]	23.4 [21.3, 25.5]	<0.0001
Waist circumference, cm	86 [80, 91]	85 [78, 90]	<0.0001
Systolic blood pressure, mmHg	133 [117, 152]	138 [126, 150]	<0.0001
Diastolic blood pressure, mmHg	76 [65, 88]	80 [70, 87]	<0.0001
Hypertension, n (%)	2,520 (73.6)	2,616 (75.8)	0.01
Diabetes mellitus, n (%)	1,219 (35.6)	908 (26.3)	<0.0001
Dyslipidemia, n (%)	2,289 (66.8)	2,100 (60.8)	<0.0001
Current smoking, n (%)	1,366 (39.9)	781 (22.7)	<0.0001
Number of risk factors*	2 [2, 3]	2 [1, 3]	<0.0001
3, n (%)	1,665 (49.6)	1,317 (38.2)	<0.0001
4, n (%)	683 (20.4)	403 (11.7)	<0.0001
5, n (%)	126 (3.8)	46 (1.3)	<0.0001
Prior MI, n (%)	379 (11.3)	89 (2.6)	<0.0001
Prior UAP, n (%)	293 (8.7)	48 (1.4)	<0.0001
Prior SAP, n (%)	427 (12.8)	93 (2.7)	0.067
Prior CABG, n (%)	76 (2.3)	24 (0.7)	<0.0001
Prior PCI, n (%)	454 (13.5)	72 (2.1)	<0.0001
ABI<0.9	103 (3.0)	17 (0.5)	<0.0001
Maximum intima-media thickness, mm	1.2 [0.9, 1.8]	1.3 [0.9, 1.9]	0.13
Region of Classification			<0.0001
Hokkaido	97 (2.8)	159 (4.6)	
Tohoku	350 (10.2)	176 (5.1)	
Kanto	1,004 (29.3)	11.35 (32.9)	
Chubu	539 (15.7)	503 (14.6)	
Kinki	608 (17.8)	56 (16.4)	
Chugoku	282 (8.2)	348 (10.1)	
Shikoku	161 (4.7)	172 (5.0)	
Kyushu/Okinawa	385 (11.2)	393 (11.4)	

*Risk factor: hypertension, diabetes mellitus, dyslipidemia, current smoking, BMI \geq 25

maximum intima-media thickness of the carotid arteries was not statistically different between the groups.

Gender differences in baseline characteristics

Patients' characteristics were separated by gender and shown in Table 2. The median age of men was significantly higher in the stroke group than in the ACS group, whereas the opposite finding was observed in women. In addition, the patterns of age distribution in the ACS and stroke groups differed according to gender in the combined registry data. Specifically, a higher prevalence of ACS than stroke was observed among men 45-65 years of age, and the opposite finding was seen among those \geq 66 years of age. In women, the prevalence of stroke was higher than that of ACS between patients 55-80 years of age, while the prevalence of ACS was higher in women \geq 81 years of age (Fig. 3). The men in the ACS group had greater body size parameters, including height, weight, waist circumference and BMI, than those in the stroke group, while no marked differences were observed between groups among women. The systolic and

diastolic blood pressures were higher in the stroke group than in the ACS group, regardless of sex. The number of atherosclerotic risk factors was higher in the ACS group than in the stroke group, also regardless of sex. In men, the prevalence of traditional risk factors was significantly different between the two registries, which was similar to those in the whole sample in terms of the higher prevalence of hypertension in the stroke group and the higher prevalence of diabetes mellitus, dyslipidemia, current smoking status and a history of coronary artery disease in the ACS group. Among women, the prevalence of hypertension was similar between the groups, while that of diabetes mellitus, dyslipidemia, current smoking and a history of coronary artery diseases was similar to that in men. The men in the ACS group had a higher frequency of atrial fibrillation than those in the stroke group, whereas women in the ACS group only showed a trend toward such a finding.

Table 2. Gender-specific Patients' Characteristics between the PACIFIC- and the EVEREST Registries.

	Male		p	Female		p
	PACIFIC (n=2,609)	EVEREST (n=2,307)		PACIFIC (n=817)	EVEREST (n=1,145)	
Age, year	67 [59, 74]	68 [61, 75]	<0.0001	74 [66, 81]	72 [65, 78]	<0.0001
Height, cm	165 [160, 170]	164 [160, 168]	<0.0001	150 [146, 155]	150 [145.5, 154.8]	0.066
Weight, kg	64.9 [58, 72]	63 [57, 70]	<0.0001	52 [46, 58.5]	52 [46, 58.3]	0.86
BMI, kg/m ²	23.8 [21.9, 26]	23.5 [21.5, 25.4]	<0.0001	22.9 [20.8, 25.7]	23.1 [20.8, 25.6]	0.63
Waist circumference, cm	86 [82, 91]	85 [80, 90]	<0.0001	83 [76, 90]	82 [74, 89]	0.01
Systolic blood pressure, mmHg	134 [118, 152]	138 [126, 150]	<0.0001	132 [115, 151]	138 [126, 150]	<0.0001
Diastolic blood pressure, mmHg	77 [66, 89]	80 [70, 88]	<0.0001	72 [60, 84]	79 [70, 85.5]	<0.0001
Hypertension, n (%)	1,882 (72.1)	1,736 (75.3)	0.0038	638 (78.1)	880 (76.9)	0.52
Diabetes mellitus, n (%)	922 (35.3)	658 (28.5)	<0.0001	297 (36.4)	250 (21.8)	<0.0001
Dyslipidemia, n (%)	1,750 (67.1)	1,403 (60.8)	<0.0001	539 (66.0)	697 (60.9)	0.02
Current smoking, n (%)	1,233 (47.3)	717 (31.2)	<0.0001	133 (16.3)	64 (5.6)	<0.0001
Number of risk factors	3 [2, 3]	2 [1, 3]	<0.0001	2 [2, 3]	2 [1, 3]	<0.0001
3, n (%)	1,345 (52.3)	956 (41.5)		320 (40.8)	361 (31.6)	<0.0001
4, n (%)	567 (22.1)	316 (13.7)		116 (14.8)	87 (7.6)	<0.0001
5, n (%)	106 (4.1)	45 (2.0)		20 (2.6)	1 (0.1)	<0.0001
Prior MI, n (%)	301 (11.8)	70 (3.1)	<0.0001	78 (9.8)	19 (1.7)	<0.0001
Prior UAP, n (%)	230 (9.0)	33 (1.5)	<0.0001	63 (7.9)	15 (1.3)	<0.0001
Prior SAP, n (%)	337 (13.2)	70 (3.1)	<0.0001	90 (11.4)	23 (2.1)	<0.0001
Prior CABG, n (%)	65 (2.5)	18 (0.8)	<0.0001	11 (1.4)	6 (0.5)	0.052
Prior PCI, n (%)	364 (14.2)	61 (2.7)	<0.0001	91 (11.2)	11 (1.0)	<0.0001
Atrial fibrillation, n (%)	116 (4.5)	48 (2.1)	<0.0001	36 (4.4)	29 (2.5)	0.078
ABI<0.9	75/677 (11.1)	13/2,084 (0.6)	<0.0001	28/186 (15.1)	4/1,040 (0.4)	<0.0001
Maximum intima-media thickness, mm	1.2 [0.9, 1.8] (n=385)	1.3 [0.9, 2.0] (n=1,045)	0.06	1.1 [0.89, 1.7] (n=94)	1.2 [0.9, 1.7] (n=435)	0.67

*Risk factor: hypertension, diabetes mellitus, dyslipidemia, current smoking, BMI \geq 25

Discussion

The main results of this study were that patients' background characteristics were significantly different between those with ACS and those with stroke. Specifically, patients with ACS tended to be younger, were more often men, had a higher BMI, had a higher prevalence of diabetes mellitus and dyslipidemia, were current smokers and had a history of ischemia, while hypertension was more prevalent in those with stroke. In men, the ACS group tended to be significantly younger than the stroke group, while the opposite finding was seen in women.

Differences in the risk profiles between patients with ACS and stroke have been previously reported (13). A nationwide multicenter cohort of Japanese patients with myocardial infarction (MI; n=2,291), ischemic or hemorrhagic stroke (n=3,554) and non-valvular atrial fibrillation (n=2,242) was conducted as the Japanese Thrombosis Registry for Atrial Fibrillation, Coronary, or Cerebrovascular Events (J-TRACE) between January 2005 and December 2006. The authors reported distinct differences in the risk factor profiles among patients with MI and stroke. In detail, hypertension and a history of stroke were more frequent in patients with stroke (74.4% and 14.7%) than in those with MI (62.0% and 6.6%), while patients with MI were more likely

to be men, have diabetes mellitus, have hypercholesterolemia, have a BMI >25, smoke cigarettes and have a history of MI (78.5%, 35.1%, 56.1%, 34.5%, 33.3% and 7.6%, respectively) than those with stroke (69.3%, 22.4%, 35.7%, 28.5%, 19.7% and 2.6%, respectively). Our findings of the ACS group having a higher prevalence rate of hypertension in the stroke group and a higher proportion of men, higher prevalence rates of diabetes mellitus and dyslipidemia, higher proportion of current smokers, greater BMI and a higher frequency of a history of MI than the stroke group were consistent with these previous results, although information regarding the history of stroke were not available in our study. In addition, the number of atherosclerotic risk factors per patient was greater in the ACS group than in the stroke group in this study, which was also reported in the J-TRACE registry. Since our cohort consisted of patients recruited between 2007 and 2009, it seems that the differences in atherosclerotic risk factors between acute coronary events and stroke did not change significantly from those seen between 2005 and 2006.

Previous epidemiological studies have suggested that the extent of atherosclerotic risk factors differ between coronary artery and cerebrovascular events. A large-scale observational study investigating the relationship between blood pressure and the incidence of stroke or MI in Japanese patients with hypertension demonstrated that the incidence rate

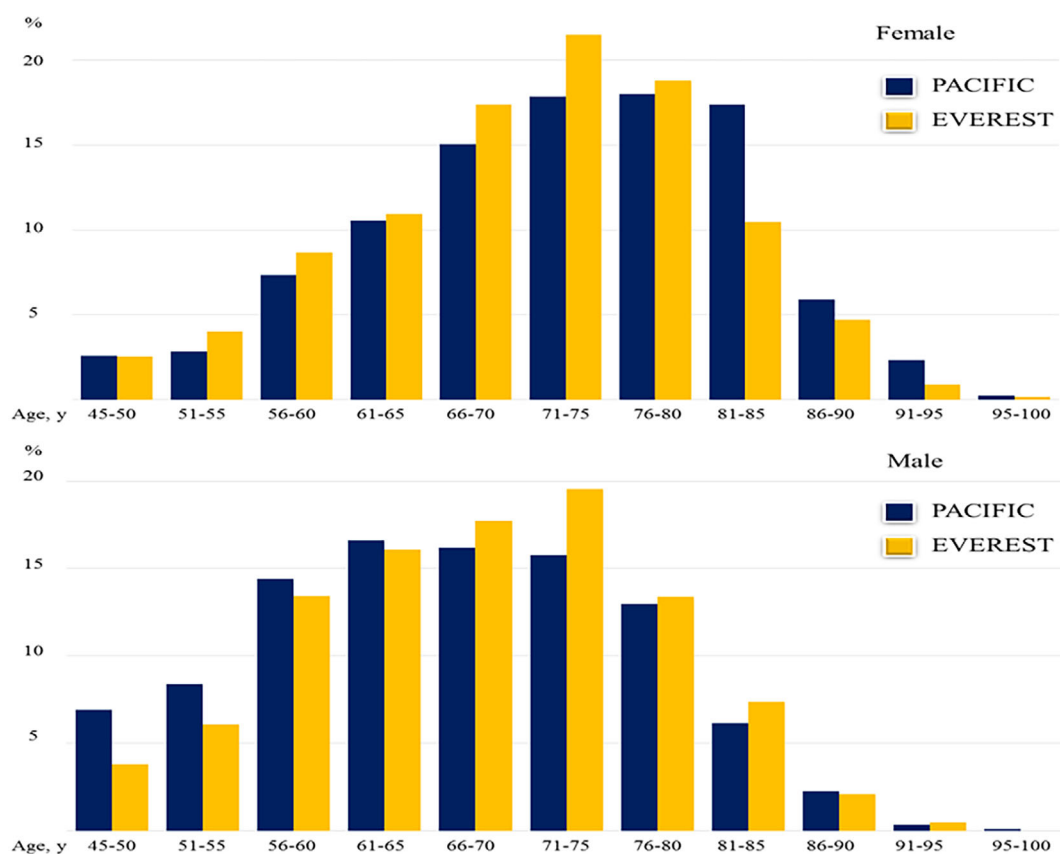


Figure 3. The distributions of the age at enrollment are shown for the PACIFIC and EVEREST registries separately for each gender (a: women, b: men). A higher prevalence of ACS than stroke was observed among men 45-65 years of age, and the opposite finding was seen among those ≥ 66 years of age. In women, the prevalence of stroke was higher than that of ACS between patients 55-80 years of age, while the prevalence of ACS was higher in women ≥ 81 years of age.

of stroke was 3.9-fold higher than that of MI. In addition, blood pressure was positively correlated with the incidence of stroke (14). These results, as well as those from previous studies (7-9), support our findings that the prevalence of hypertension in patients with stroke is higher than that of patients with ACS. Kastorini et al. reported that smoking was more significantly associated with ACS than stroke, and that hyperlipidemia tended to be associated with ACS (15), which were also observed in our study. Considering these results, dyslipidemia may be more strongly associated with coronary artery events than cerebrovascular events. It should be noted that patients with ACS presented with a greater number of atherosclerotic risk factors than those with stroke in our study. Similar findings have been reported in previous studies from France, in which patients with ACS had more comorbid conditions, such as hypercholesterolemia, diabetes mellitus, and obesity, than those with stroke (16, 17).

Our data showed that the prevalence of atrial fibrillation was greater in the ACS group than in the stroke group, which might have been affected by the study design, as the population of the EVEREST registry were patients with recent non-cardioembolic ischemic stroke.

Gender-specific differences in patients' characteristics between ACS and stroke

To our knowledge, this is the first report to describe gender-specific differences in atherosclerotic risk profiles between patients with ACS and stroke. Because most of the patients in the present study were men, the patient characteristics of the whole population tended to reflect those of the men enrolled in our study. Therefore, risk profiles should be investigated separately for each gender. In addition, it is of interest that the difference in the age of men and women was greater in the ACS group than in the stroke group (6.3 and 3.1 years, respectively). Patterns of age distribution in the ACS and stroke groups also differed based on sex: a higher prevalence of ACS than stroke was observed among men 45-65 years of age, and the opposite finding was seen among those ≥ 66 years of age. In women, the prevalence of stroke was higher than that of ACS between patients 55-80 years of age, while the prevalence of ACS was higher in women ≥ 81 years of age. The prevalence of hypertension was not significantly different between the ACS and stroke groups in women, which was not consistent with that in men. That might be explained by the fact that the median age in the ACS group was older than that in the stroke

group in women. The number of atherosclerotic risk factors was higher in the ACS group than in the stroke group, regardless of sex. These results suggest that younger men are more likely to be exposed to risk factors associated with ACS than stroke, by the accumulation of multiple risk factors.

We acknowledge that this study has several limitations that are inherent to the study design. First, the dataset consisted of two registries in which the timing of patient enrollment, the participating institutes and the study registration period differed, resulting in selection bias in this study. The PACIFIC registry included patients with acute-phase ACS, while the EVEREST registry included patients with ischemic stroke within two weeks to six months of enrollment. Therefore, the patients' characteristics were significantly different between the two registries in terms of the medication use and results of blood examination tests. Second, we excluded patients <45 years of age in the PACIFIC registry because the EVEREST registry recruited patients with stroke ≥ 45 years of age. Although the excluded patients accounted for 4.8% of the whole sample in the PACIFIC registry, the results of the patients' characteristics failed to reflect the overall perspective of patients with ACS in Japan. Third, the definitions of atherosclerotic risk factors were not consistent between the registries due to the different protocols used. In the EVEREST registry, the diagnostic criteria of atherosclerotic risk factors were as follows, diabetes mellitus, fasting blood glucose of ≥ 126 mg/dL; hyperlipidemia, under medical treatment for hyperlipidemia and hypertension, under medical treatment for hypertension. In contrast, these atherosclerotic risk factors were determined based on an evaluation of the medical history in the PACIFIC registry. This issue may have resulted in some degree of incomparability of the two datasets. Consequently, the differences in patients' characteristics between the ACS and stroke patients were affected not only by differences between the two diseases but also by our study design that merged the two different registries. Based on these limitations, our results should be interpreted with caution. Gender-specific differences in patients' characteristics might be related to atherosclerotic risk factors that are unique to women, including menopause, gestational hypertension and diabetes mellitus (18). However, data on sex hormone levels and information regarding menstruation and pregnancy were not available in this study.

Conclusion

Patients' background characteristics were significantly different between those with ACS and those with stroke, with different trends also noted between men and women in this Asian population.

The authors state that they have no Conflict of Interest (COI).

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