Abstract

***Aims*:** To provide multinational, multiethnic data on the clinical characteristics and prognosis of patients with microvascular angina (MVA).

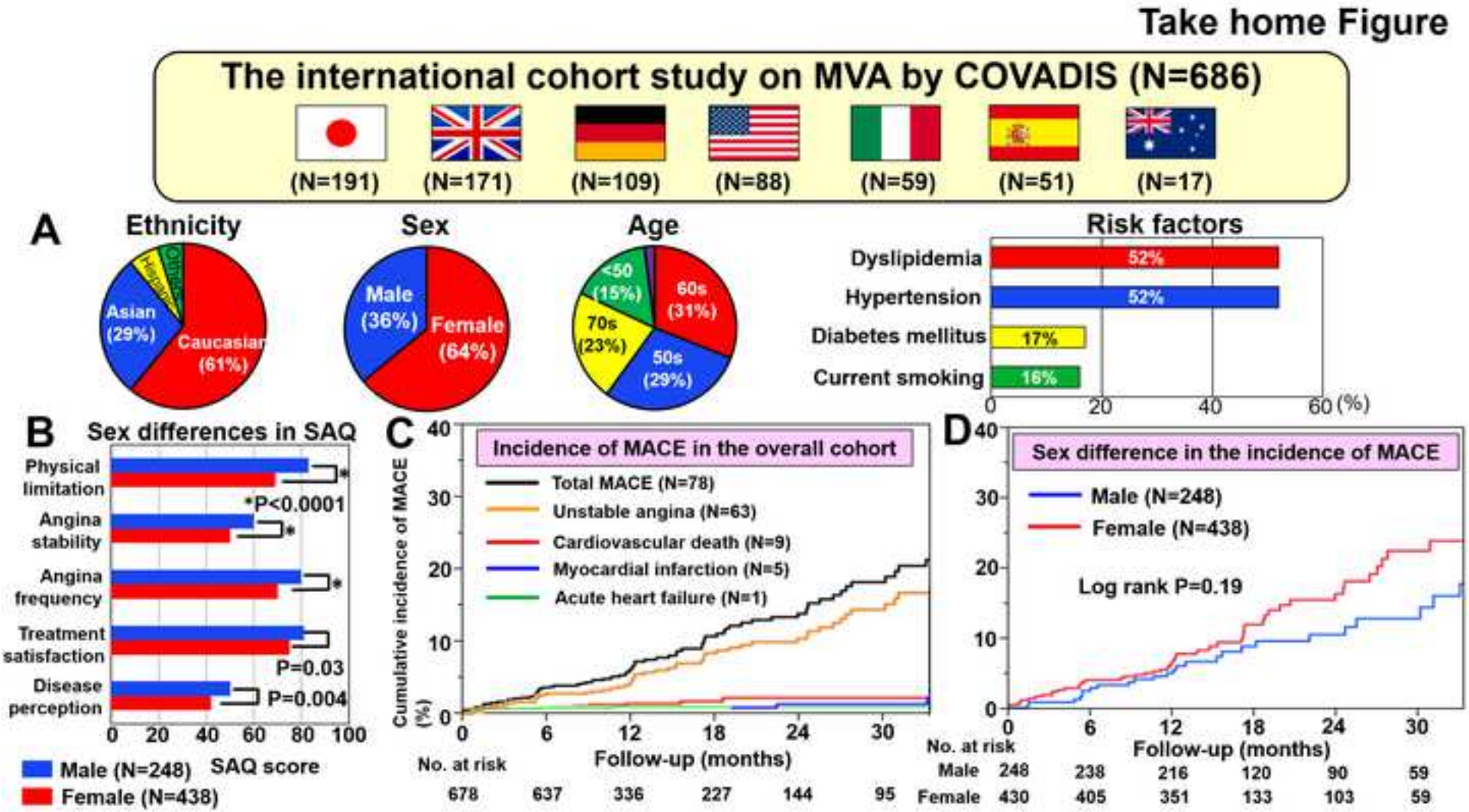
***Methods*:** The Coronary Vasomotor Disorders International Study (COVADIS) Group proposed the diagnostic criteria for MVA. We prospectively evaluated the clinical characteristics of patients according to these criteria and their prognosis. The primary endpoint was the composite of major cardiovascular events (MACE), verified by institutional investigators, which included cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization due to heart failure or unstable angina.

***Results*:** During the period from July 1, 2015 to December 31, 2018, 686 patients with MVA were registered from 14 institutes in 7 countries from 4 continents. Among them, 64% were female and the main ethnic groups were Caucasians (61%) and Asians (29%). During follow-up of a median of 398 days (IQR 365-744), 78 MACE occurred (6.4% in men vs. 8.6% in women, P=0.19). Multivariable Cox proportional hazard analysis disclosed that hypertension and previous history of coronary artery disease (CAD), including acute coronary syndrome and stable angina pectoris, were independent predictors of MACE. There was no sex or ethnic difference in prognosis, although women had lower Seattle Angina Questionnaire scores than men (P<0.05).

***Conclusions*:** This first international study provides novel evidence that MVA is an important health problem regardless of sex or ethnicity, that a diagnosis of MVA portends a substantial risk for MACE associated with hypertension and previous history of CAD, and that women have lower quality of life than men despite comparable prognosis.

（246/250 words）

Keywords: Microvascular angina, coronary microvascular dysfunction, prognosis



Clinical characteristics and prognosis of patients with microvascular angina

-An international and prospective cohort study by the Coronary Vasomotor Disorders International Study (COVADIS) Group-

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Total word count: 4,434/5,000 words

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Introduction

Angina pectoris has been considered to be mainly caused by atherosclerotic obstructive coronary artery disease (CAD).[1] However, up to 50% of patients undergoing diagnostic coronary angiography for typical chest pain have angiographically normal coronary arteries or non-obstructive CAD.[2] In such cases, coronary functional abnormalities are implicated, including epicardial coronary artery spasm and coronary microvascular dysfunction (CMD).[3] The latter is typically defined as increased susceptibility to vasoconstrictor stimuli resulting in microvascular spasm and/or impaired dilatation of coronary microvessels, with resultant inadequate increase in blood flow in response to stress.[4-6] Thus, CMD may be the underlying mechanism in a large proportion of angina patients.

The term microvascular angina (MVA), originally proposed by Cannon and Epstein in 1988,[7] is used for angina/myocardial ischemia attributable to CMD. Recently, several studies with either invasive or non-invasive techniques for assessment of coronary physiology have provided extensive data, improving what is known about CMD and microvascular ischemia.[8,9] In addition, as the COronary VAsomotor Disorders International Study (COVADIS) group, we have proposed the diagnostic criteria of MVA.[10] Briefly, the diagnosis of MVA is established based upon symptoms suggestive of myocardial ischemia in the absence of obstructive CAD (<50% diameter reduction and/or FFR >0.80) associated with objective evidence of myocardial ischemia and impaired coronary microvascular function defined by the following 4 findings; reduced coronary flow reserve (CFR), microvascular spasm, increased microvascular resistance, and/or coronary "slow flow phenomenon".[10]

To date, clinical studies have mainly been single center. Given the lack of evidence from international multicenter study, the clinical characteristics and prognosis of patients with MVA remain to be fully elucidated. Our first objective was to study the clinical

characteristics and health outcomes of patients with MVA, in a large, prospective, international registry. Our second objective was to assess for associations by sex and ethnicity. Thus, in the present study, we undertook a multinational, multicenter, multiethnic, prospective, observational, and longitudinal cohort study.

Methods

Study population

Fourteen medical centers in 7 countries from 4 continents participated in the present study. Data collection was performed via a standardized electronic case report system established by the Japanese Coronary Spasm Association.[11] We enrolled patients who fulfilling the COVADIS diagnostic criteria for MVA as follows; (1) signs and/or symptoms of myocardial ischemia, (2) absence of obstructive CAD, (3) objective evidence of myocardial ischemia, and (4) evidence of impaired coronary microvascular function, as determined by the clinical site (**Figure 1, Table S1**).[10] Objective evidence of myocardial ischemia, impaired coronary microvascular function, and ischemic symptoms were determined by attending COVADIS site physicians using detailed criteria below. Clinical characteristics, cardiovascular risk factors (including body mass index, history of hypertension, dyslipidemia, diabetes mellitus, and current smoking), diagnostic approaches, and the trend of medical therapies for contemporary MVA patients, particularly in terms of the ethnic and sex differences were documented (**Supplementary methods**).

Obstructive CAD was defined as any coronary stenosis of >50% reduction in diameter by conventional angiography or computed tomography angiography, and those patients with obstructive CAD were excluded. Objective evidence of myocardial ischemia was evaluated using non-invasive stress testing. Evidence of myocardial ischemia was obtained by rest/stress ECG and/or by means of non-invasive imaging by assessing either myocardial perfusion with single photon emission computed tomography (SPECT), positron emission tomography (PET), cardiac magnetic resonance (CMR), and left ventricular wall motion abnormality with stress echocardiography.[10]

Non-invasive assessment of CMD was obtained by measuring CFR for the whole left

ventricle with PET, CMR or by measuring Doppler flow velocity reserve on the LAD coronary artery. The CFR cutoff was set at <2.5.[4,6]

CMD was assessed invasively by using coronary functional testing, including measurements of CFR and/or microvascular resistance and/or acetylcholine provocation testing for coronary microvascular spasm.[10] The CFR cutoff was defined at <2.0 for invasive measurement.[8-10,12] Abnormal microvascular resistance was defined as more than 25 units of index of microcirculatory resistance (IMR).[8-10] Coronary slow flow phenomenon was defined as TIMI frame count >25 at invasive coronary angiography.[8-10] Coronary microvascular spasm was defined as reproduction of symptoms, ischemic ECG changes, but no epicardial coronary spasm during acetylcholine provocation testing.[10] In the present study, definitive MVA was diagnosed if all 4 criteria were present, while suspected MVA was diagnosed if symptoms of ischemia were present with no obstructive CAD but one of the following only; objective evidence of myocardial ischemia or evidence of coronary microvascular dysfunction. Both definitive and suspected MVA were included in the present study. Seventy-five patients (11%) were diagnosed as having MVA by using non-invasive assessment alone, including exercise stress ECG (n=34), SPECT (n=18), PET (n=16), stress echocardiography (n=4) and cardiac MRI (n=3). At enrollment, we obtained study variables, including patient demographic profiles, cardiovascular risk factors, past history of CAD including acute coronary syndrome and stable angina pectoris, non-invasive diagnostic modalities for myocardial ischemia, invasive assessment of microvascular function, initial treatment after diagnosis and assessment of quality of life (QOL) by the Seattle Angina Questionnaire (SAQ) (**Supplementary methods**).[13]

During the period from July 1, 2015 to December 31, 2018, the participating centers prospectively enrolled 686 patients with MVA (**Figure 1**). All patients underwent clinical assessments and received usual medical care as determined by attending physicians. They

did not receive any investigational treatments for MVA before study enrollment and during the follow-up period. Follow-up of each patient was conducted at least once from study entry to the end of December 2019 either by a telephone call or a site visit, depending on the approach considered most practical and effective.

The ethics committee of Tohoku University Graduate School of Medicine approved the study protocol (No. 2015-1-188) followed by the ethics committee and/or sponsors at each participating institute, in compliance with the Declaration of Helsinki (UMIN000035177). All patients provided a written informed consent for research before study entry.

Study endpoints

The primary endpoint was the composite of major cardiovascular events (MACE), including cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke, and hospitalization due to heart failure or unstable angina (UA) determined by the institutional investigators at each COVADIS site or an independent clinical event committee. Definition of MI was based on the third universal definition,[14] and that of UA was based on the presence of ischemic chest pain and hospitalization within 24 hours of most recent symptoms, without elevation in cardiac biomarkers but with ischemic ECG changes.[15] Stroke was defined as neurological deficit due to an ischemic or hemorrhagic central nervous system event with residual systems >24 hours after onset or leading to death.[16] For each patient, a MACE was defined as the first occurrence of one of these events during follow-up period. The associations between baseline characteristics, including sex and medical history, and MACE were evaluated.

Statistical methods

Statistical methods appropriate for epidemiological studies were used for the analysis of the

collected data. Baseline continuous variables are presented as means ± SD or medians and interquartile range, depending on the distribution of the data that was tested by Shapiro-Wilk normality test. Categorical variables are presented as counts and percentages. We used the Wilcoxon rank-sum test to compare continuous variables and the Pearson chi-square test to compare categorical variables. Events were analyzed as time from enrolment to first occurrence of any event from the composite endpoint. We used the Kaplan-Meier method to provide survival estimates, which were assessed with a log-rank test. To reduce confounding effects, propensity score methods were used with potential confounding covariates, including age, sex, hypertension, dyslipidemia, diabetes mellitus, current smoking, previous history of CAD, and previous PCI. Additional supportive analyses included time to first occurrence of each component of the composite endpoint individually. Event rate of the composite endpoint and that of each of endpoint are reported separately at 1, 2, and 3 years since enrolment. To examine the determinants of primary endpoint, we used multivariable Cox proportional hazard model. A SAP was pre-specified before each interim analysis. Multivariable analysis was conducted to analyze outcomes by study variables.

Results

Baseline clinical characteristics

Patient enrollment and their follow-up are shown in **Figure 1**. From July 2015 to December 2018, a total of 686 patients with MVA (M/F 248/438, 61.2±11.8 [SD] yrs.) were finally enrolled, including 191 cases in Japan, 171 in UK, 109 in Germany, 88 in USA, 59 in Italy, 51 in Spain, and 17 in Australia (**Take home figure**). Follow-up rate was 97% (18 lost among 704 patients). Their pertinent clinical characteristics are summarized in **Table 1**. Approximately two thirds (64%) were female and the main ethnic groups were Caucasians (61%), Asians (29%), and Hispanics (6%). More than half of them had hypertension (52%) and/or dyslipidemia (52%), whereas relatively fewer patients had diabetes mellitus (17%) or were current smokers (16%). Although 233 patients (34%) had previous history of CAD, including acute coronary syndrome and stable angina pectoris, only 9% had undergone PCI previously. Considering risk factors for coronary atherosclerosis, current smoking, previous history of CAD, vasospastic angina, and previous PCI were more prevalent among men, whereas the prevalence of other risk factors were comparable in both sexes (**Table 1**).

Predominant symptoms were chest pain or chest discomfort (68%), especially at rest (36%), and shortness of breath on exertion (18%). Ischemic ECG changes during chest pain were documented in 26%, where the most frequent finding was ST-segment depression (24%). Of note, regarding SAQ scores, women had significantly lower scores compared with men in all items, indicating lower QOL in women (**Table 1) (Take home figure**). Of the 686 patients, 59% had objective evidence of myocardial ischemia during non-invasive stress testing, including exercise stress ECG (34%), Doppler/stress echocardiography (13%), cardiac MRI (10%), SPECT (6%), and PET (6%). Invasive assessments of coronary microvascular function were performed in 611 patients (89%); these showed that microvascular spasm was most frequent (42%), followed by impaired CFR (35%), abnormal

microvascular resistance (14%), and slow flow abnormalities (6%) (**Table 1**). In the present study, 261 patients (38%) had comorbid epicardial coronary spasm evaluated by acetylcholine provocation testing. For the initial treatment after the diagnosis of MVA was made, patients received oral treatment with statins (62%), nitrates (43%), calcium channel blockers (36%), and/or beta blockers (36%), as determined by attending physicians (**Table 1**).

Clinical outcomes and prognostic factors

During the median follow-up period of 398 days (IQR 365, 744 days), there were 78 MACE in the overall cohort, including hospitalization for unstable angina (n=63), cardiovascular death (n=9), non-fatal myocardial infarction (n=5), and hospitalization for acute heart failure (n=1). The annual incidence of primary composite of MACE in the overall cohort was 7.7% per patient year (**Figure 2A**). Among these, the incidence of hospitalization for unstable angina (5.9% per patient year) was higher than that of the other adverse events, given that the rate of cardiovascular death was 1.0% per patient year and the rate of non-fatal myocardial infarction was 0.5% per patient year (**Figure 2B**).

Importantly, there was no significant sex difference in the incidence of MACE (male 6.4% vs. female 8.6% per patient year, P=0.19) (**Figure 3A**). Furthermore, the incidence of MACE was comparable even after propensity score matching (**Figure S1**). Considering MACE by ethnic group, Caucasians had higher risk of MACE than Asians (Caucasians 9.3% vs. Asians 4.5% per patient year, P=0.0002) (**Figure 3B**). However, after propensity score matching, there was no significant difference in the incidence of MACE between the 2 ethnicities **(Figure S2**).

Furthermore, multivariable Cox proportional hazard analysis showed that hypertension and previous history of CAD, including acute coronary syndrome and stable angina pectoris, were independent predictors for the occurrence of MACE in patients with MVA (**Table 2**).

Discussion

To the best of our knowledge, this is the first international and prospective study that focused on the clinical characteristics and prognosis of contemporary patients with MVA accurately diagnosed by established uniform criteria (**Take home figure**). We have found that patients with MVA are at substantial risk of MACE, especially hospitalization for unstable angina, and that hypertension and previous history of CAD were independent predictors of MACE, and that there were no sex differences in prognosis despite lower QOL in women (**Take home figure**). There were no differences in prognosis between ethnic groups.

Diagnosis of MVA

CMD can develop in variable clinical settings and can be triggered by multiple pathogenetic mechanisms.[5] MVA is attributable to varying degrees of disruption of normal coronary physiology, which may subsequently impair the capacity of myocardial blood flow to satisfy myocardial oxygen demand.[4] In the present study, all patients were registered based on objective evidence of myocardial ischemia and/or microvascular dysfunction according to the established diagnostic criteria for MVA by the COVADIS group.[10] Thus, employing the standardized criteria for MVA allowed us to utilize different diagnostic strategies, including non-invasive and invasive assessments in relation to their institutional feasibility and safety.

Clinical characteristics of patients with MVA

CMD has been associated with cardiovascular risk factors, including aging, hypertension, dyslipidemia, and diabetes mellitus,[17] although the prevalence of these conditions in patients with the MVA syndrome remains unknown. Moreover, CMD is also associated with clinical syndromes caused by cardiovascular disease, including LVH and HFpEF.[17] In the present

study, more than half of the patients with MVA had hypertension (52%) and/or dyslipidemia (52%), whereas relatively fewer patients had diabetes mellitus (17%) or were current smokers (16%). The prevalence of traditional coronary risk factors in our patients with MVA is consistent with a previous report that targeted patients with myocardial ischemia and non-obstructive CAD.[18]

Prognosis of patients with MVA

Previously, prognosis of patients with MVA has been suggested to be good,[19] however, the sample size was small, and a considerable proportion of patients lacked markers of potential worse outcome.[20] In the present study, the incidence of the primary composite of MACE in the overall cohort (7.7% per patient year) was comparable to that reported by Pepine et al.[20] Although the prevalence of atherosclerotic risk factors was comparable with that of the previous studies of non-obstructive CAD, the incidence of subsequent acute MI in the present study was lower than that reported before.[19,20]

Sex and ethnic differences in MVA

In previous studies, women, as compared with men, were more likely to have angina without significant coronary artery stenosis but had a comparable risk of cardiovascular events.[18,20] Of note, in the present study, there was no significant sex-related difference in the incidence of cardiovascular events even after propensity score matching with potential confounding factors. Additionally, as demonstrated in **Table 1,** women had significantly lower SAQ scores than men, indicating worse QOL in the former. To date, a few studies addressed sex-related differences in QOL in patients with chronic coronary syndromes, but they did not address the underlying mechanisms of ischemia.[21] Recently, the CorMicA randomized, controlled trial of stratified medicine reported improvements in anginal symptoms and QOL

in patients with CMD in general, but not specifically sex-related differences.[8] Female hormones are involved in sex differences in perception of chest symptoms in female patients with MVA.[18] Furthermore, while no previous study has addressed ethnic differences in patients with MVA, in the present study, the incidence of adverse cardiovascular events was significantly higher in Caucasians than in Asians (**Figure 3B)**, in part relating to differences in the burden of vascular risk factors since, after propensity score matching, the incidence of MACE was not different between the two ethnic groups (**Table S2**, **Figure S2**).

Treatment of MVA

The management of MVA represents a major unmet need because the lack of large, randomized studies with homogeneous patient group makes it difficult to generate evidence-based recommendations.[22] Two outcome trials are currently underway, the Women's IschemiA TRial to Reduce Events In Non-ObstRuctive CAD (WARRIOR) is a multicenter, prospective, randomized, blinded outcome evaluation (PROBE design) of a pragmatic strategy of intensive medical treatment vs. usual care (UC) in 4,422 symptomatic women with INOCA (NCT 03417388) and the International Coronary Microvascular Angina Trial (iCorMicA: NCT04674449) of stratified medicine in angina. Furthermore, the treatment of MVA has been empirical because its pathophysiology appears to be multifactorial with overlapping phenotypes that often coexist. Recent reports discussed management of MVA patients and suggested some potential treatment strategies.[18,22] Anti-atherothrombotic treatments with statins, angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), and low-dose aspirin may improve symptoms and outcomes of MVA patients.[23,24] Patients enrolled in the present study received oral treatment with statins (62%), nitrates (43%), ACE-I (25%), and ARB (17%) as determined by attending physicians after the diagnosis of MVA was made. Furthermore, conventional anti-anginal therapies,

including beta-blockers, calcium channel blockers, and nitrates, are reasonable first-line regimens for MVA patients given the underlying pathophysiology.[25,26] Regarding vasodilators, there was a sex difference in the present study as women received more frequently nitrates, whereas men received more frequently calcium channel blockers. More frequent use of nitrates in women might represent more frequent anginal attacks than in men, which is consistent with our observations of significantly lower SAQ scores in physical limitation and angina stability among women.

Study limitations

Although our study has multiple strengths (the first international study with multiple ethnicities and countries, large sample size, use of consensus diagnostic criteria for MVA, and high follow-up rate, etc.), several limitations should be mentioned. First, the present study was an observational study without a reference group. Second, the relatively small number of MACE during follow-up limits the statistical power of the present study and might have led to data overfitting. Third, the majority of MACE (90%) were hospitalization for unstable angina. However, the prevalence of hospitalization for unstable angina to total MACE was comparable with the previous reports.[9,27] Fourth, we excluded patients with obstructive CAD by conventional angiography or coronary computed tomography and have no data regarding functional relevance of coronary artery stenoses evaluated by physiological indices. Finally, we have no data regarding changes in or adherence to medical therapy, or symptoms and/or QOL (e.g. SAQ) during follow-up. These issues remain to be examined in future studies.

Conclusions

This first international study provides evidence on the prognostic impact of MVA and novel

insights into sex and ethnicity. Female patients have lower QOL than male patients despite comparable prognosis. Vascular risk factors are prevalent and a target for therapy. Further studies are needed to address knowledge gaps including risk stratification and effective treatments of patients with MVA.

Acknowledgments

We thank all the staff who supported this study, including Chassidi Garrett, Sonoka Goto, Koichi Kaikita, Hideki Kawai, Sarah Long, Jenna Maughn, Valeria Martínez Pereyra, Sabine Nägele, Andreas Seitz, Chrisandra Shufelt, and Janet Wei.

Funding: The Japanese Coronary Spasm Association (funded by the Japan Heart Foundation). CB received funding from the British Heart Foundation (PG/17/2532884; RE/18/6134217). CNBM and CJP received funding from contracts from the National Heart, Lung and Blood Institutes nos. N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, grants U0164829, U01 HL649141, U01 HL649241, K23HL105787, T32HL69751, R01 HL090957, 1R03AG032631 from the National Institute on Aging, GCRC grant MO1-RR00425 from the National Center for Research Resources, the National Center for Advancing Translational Sciences Grant UL1TR000124 and UL1TR000064. JB received funding from The Hospital Research Foundation. PO and US received funding from the Berthold-Leibinger-Foundation, Germany.

Conflict of interest: F.C. reports speaker fees from AstraZeneca, Amgen and Servier and institutional agreements between his employer, the Catholic University, and Biotronik, Boheringer Ingelheim. C.N.B.M. reports lecturer fees from Abbott Diagnostics, board director fees from iRhythm, consulting fees from Caladrius, and advisory board fees from Bayer. C.B. declares institutional agreements between his employer, the University of Glasgow, and AbbottVascular, AstraZeneca, Boehringer Ingelheim, Coroventis, DalCor, GSK, HeartFlow, Novartis, and Philips. P.G.C. reports speaking honoraria from Servier and Abbott. P.O. reports personal fees from Bayer Healthcare, Pfizer and Philips/Volcano. U.S. reports speaker and consulting fees from Amgen, Bristol-Myers Squibb, Boehringer-Ingelheim, Abbott, Servier, Astra-Zeneca, Bayer, and Pfizer. T.F. has acted as a speaker for Abbott Vascular, Boehringer Ingelheim and Novartis. None of the declared interests regard the submitted work. All other authors have nothing to disclose.

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Figure legends

Figure 1. Patient enrollment and follow-up

Figure 2. Kaplan-Meier curves for MACE in the overall cohort

(**A**) Kaplan-Meier curve for primary composite outcome

(**B**) Kaplan-Meier curve for each component of composite outcome

Figure 3. Kaplan-Meier curves for MACE by patient group

(**A**) Sex difference in the incidence of MACE

(**B**) Ethnic difference in the incidence of MACE (Caucasian vs. Asian)

Take home figure

The international cohort study on MVA by COVADIS (14 institutes in 7 countries, N=686).

(A) Prevalence of ethnicity, sex, age, and risk factors in the present MVA cohort.

(B) The incidence of MACE in overall cohort.

(C) The incidence of MACE by sex.

(D) Sex differences in SAQs.

Tables

Table 1. Baseline clinical characteristics of patients with MVA

Characteristics	Total cohort (N=686)	Male (N=248)	Female (N=438)	P value
Age (mean, yrs.)	61.7±11.8	61.6±12.7	60.9±11.2	0.45
Race or ethnic group, n (%)				
Caucasian	419 (61)	111 (45)	308 (70)	<0.0001
Asian	199 (29)	113 (46)	86 (20)	<0.0001
Hispanic	40 (6)	21 (8)	19 (4)	0.03
Black	16 (2)	1 (0.4)	15 (3.4)	0.004
Others	12 (2)	2 (0.8)	10 (2)	0.04
Body mass index (mean)	26.1±5.9	25.9±4.4	26.3±6.7	0.48
Hypertension, n (%)	358 (52)	139 (56)	219 (50)	0.13
Dyslipidemia, n (%)	358 (52)	119 (48)	239 (55)	0.09
Diabetes mellitus, n (%)	116 (17)	51 (21)	65 (15)	0.06
Current smoking, n (%)	108 (16)	49 (20)	59 (13)	0.03

Previous history of CAD, n (%)	233 (34)	70 (28)	163 (37)	0.02
Previous PCI, n (%)	65 (9)	46 (19)	19 (4)	<0.0001
LVEF (mean, %)	65.6±10.2	64.3±11.3	66.6±9.2	0.07
Symptoms				
Angina, n (%)	465 (68)	154 (62)	311 (71)	0.0003
Rest angina, n (%)	245 (36)	94 (38)	151 (34)	0.37
Effort angina, n (%)	99 (14)	39 (16)	60 (14)	0.47
Rest and effort angina, n (%)	121 (18)	21 (8)	100 (23)	<0.0001
Shortness of breath, n (%)	125 (18)	23 (9)	102 (23)	<0.0001
Others, n (%)	135 (19)	55 (22)	80 (18)	0.0003
Ischemic ECG changes during angina attack	177 (26)	94 (38)	83 (19)	<0.0001
ST-segment elevation, n (%)	13 (2)	12 (5)	1 (0.2)	<0.0001
ST-segment depression, n (%)	164 (24)	82 (33)	82 (19)	<0.0001
Seattle Angina Questionnaire score (median, IQR)				
Physical limitation	75 (53-93)	83 (64-97)	69 (50-89)	<0.0001
Angina stability	50 (25-75)	75 (50-100)	50 (25-75)	<0.0001
Angina frequency	70 (50-90)	80 (60-100)	70 (50-80)	<0.0001

Treatment satisfaction	75 (63-88)	81 (63-94)	75 (56-88)	0.01
Disease perception	50 (25-67)	50 (33-67)	42 (25-58)	0.002
Objective evidence of myocardial ischemia in non-invasive tests	402 (59)	129 (52)	273 (62)	0.009
Exercise stress ECG, n (%)	231 (34)	79 (32)	152 (35)	0.45
Doppler / Stress echocardiography, n (%)	86 (13)	38 (15)	48 (11)	0.10
Cardiac MRI, n (%)	68 (10)	10 (4)	58 (13)	<0.0001
SPECT, n (%)	42 (6)	14 (6)	28 (6)	0.69
PET, n (%)	41 (6)	5 (2)	36 (8)	0.0004
Evidence of impaired microvascular function, n (%)				
Microvascular spasm, n (%)	288 (42)	100 (40)	188 (43)	0.51
Impaired coronary flow reserve, n (%)	241 (35)	100 (40)	141 (32)	0.51
Abnormal coronary microvascular resistance, n (%)	99 (14)	46 (19)	53 (12)	0.03
Slow flow / TIMI frame count abnormalities, n (%)	45 (6)	20 (8)	25 (6)	0.24
Initial treatment after diagnosis				
Statin, n (%)	424 (62)	141 (57)	283 (65)	0.04
Nitrate, n (%)	295 (43)	83 (33)	212 (48)	0.0001
Calcium channel blocker, n (%)	249 (36)	106 (43)	143 (33)	0.009

Beta blocker, n (%)	249 (36)	83 (33)	166 (38)	0.25
Angiotensin-converting enzyme inhibitor, n (%)	169 (25)	57 (23)	112 (26)	0.49
Angiotensin Ⅱ receptor blocker, n (%)	117 (17)	41 (17)	76 (17)	0.78

CAD, coronary artery disease; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; MVA, microvascular angina; PCI, percutaneous coronary intervention; PET, positron emission tomography; SAQ, Seattle angina questionnaire; SPECT, single photon emission computed tomography; TIMI, thrombolysis in myocardial infarction.

Table 2. Prognostic factors for MACE in patients with MVA (Cox proportional hazard model)

	Univariable analysis			Multivariable analysis		
	HR	95% CI	P value	HR	95% CI	P value
Age	0.987	0.970 – 1.004	0.14			
Female sex	1.358	0.857 – 2.152	0.19			
Hypertension	1.802	1.148 – 2.831	0.01	1.692	1.067 – 2.681	0.03
Dyslipidemia	1.362	0.877 – 2.115	0.17			
Diabetes mellitus	1.461	0.887 – 2.407	0.14			
Current smoking	0.868	0.479 – 1.572	0.64			
Previous history of CAD	2.233	1.448 – 3.442	0.005	2.032	1.312 –3.147	0.001
Family history of CAD	1.700	1.093 – 2.645	0.02			

CAD, coronary artery disease including acute coronary syndrome and stable angina pectoris; MVA, microvascular angina.

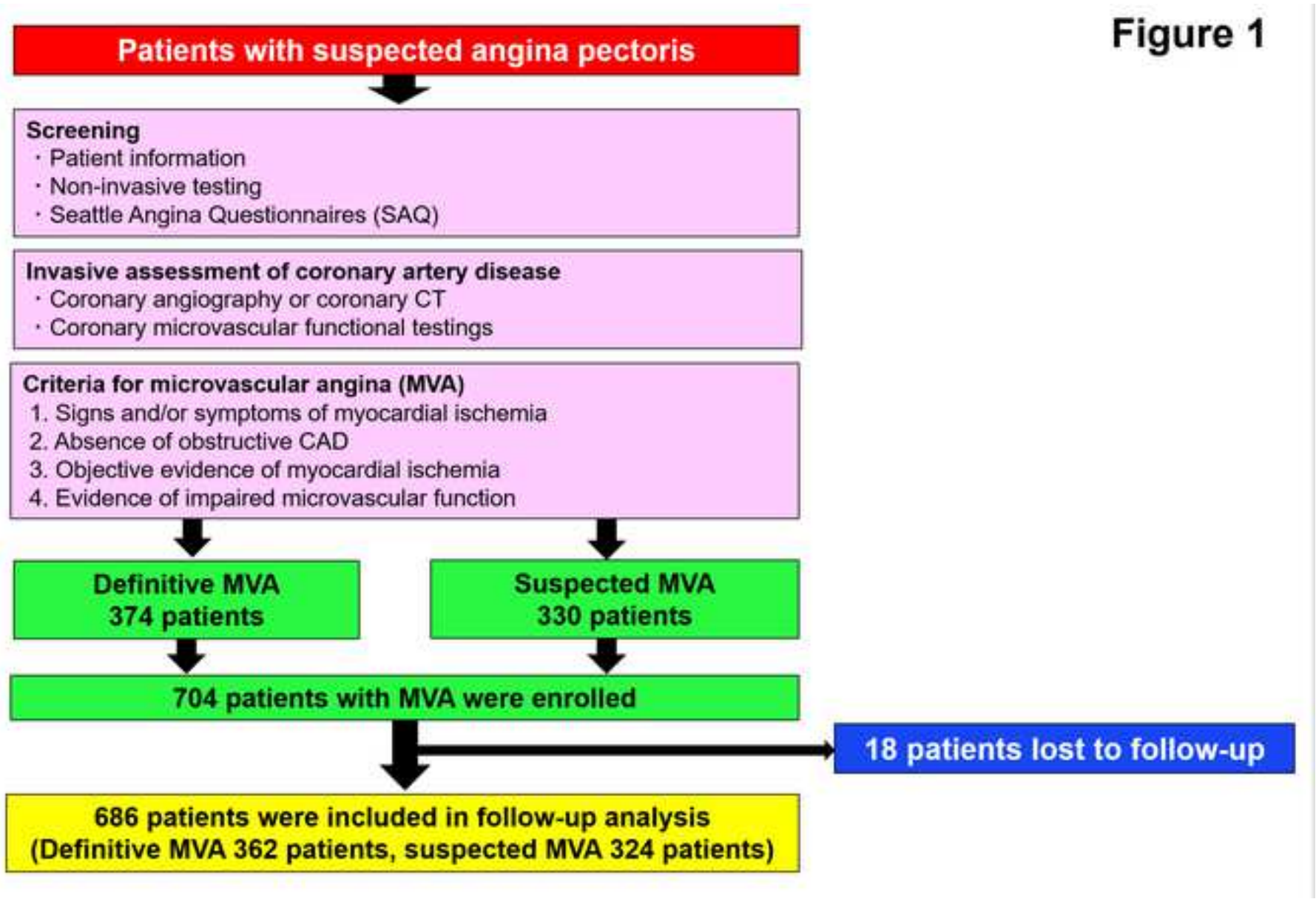


Figure 2

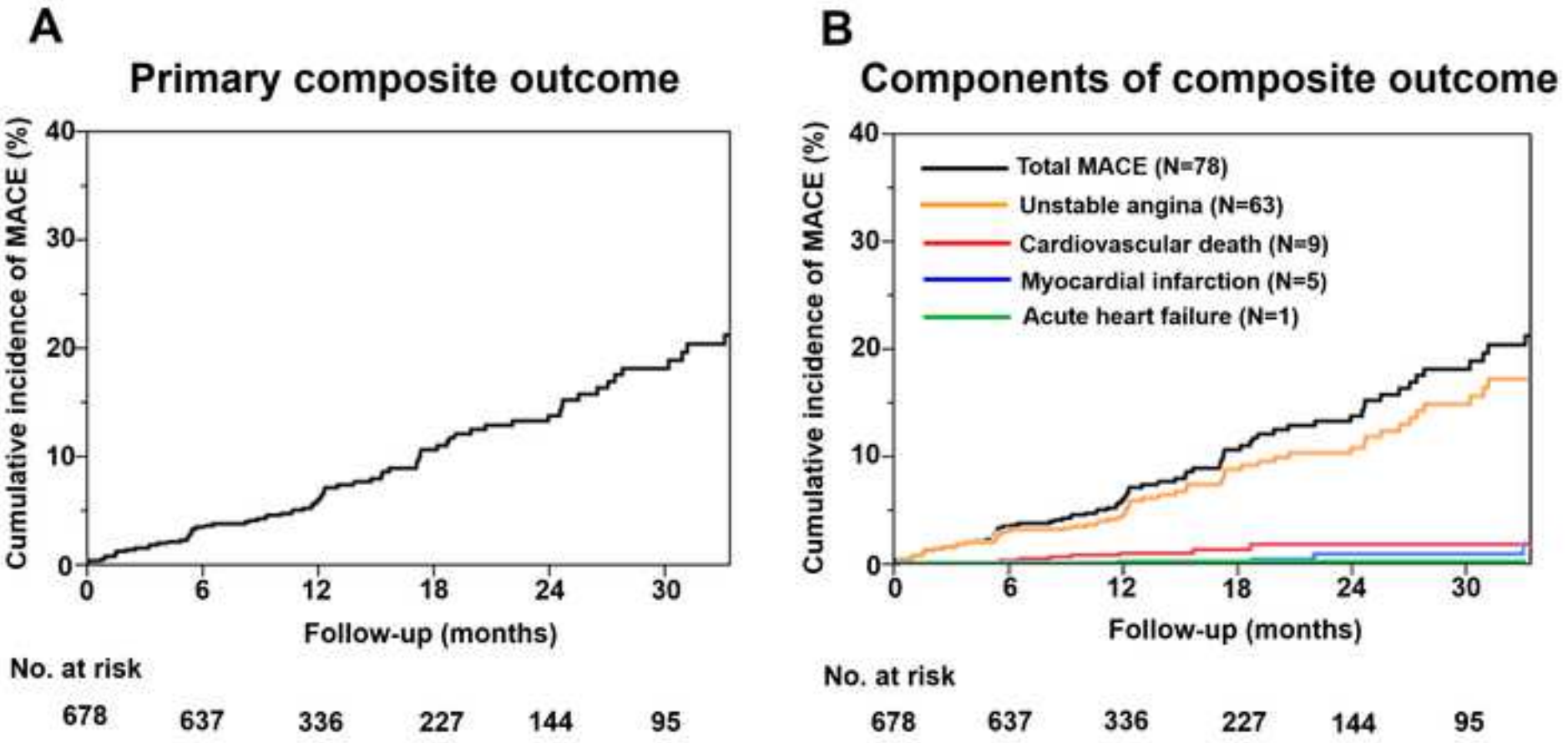
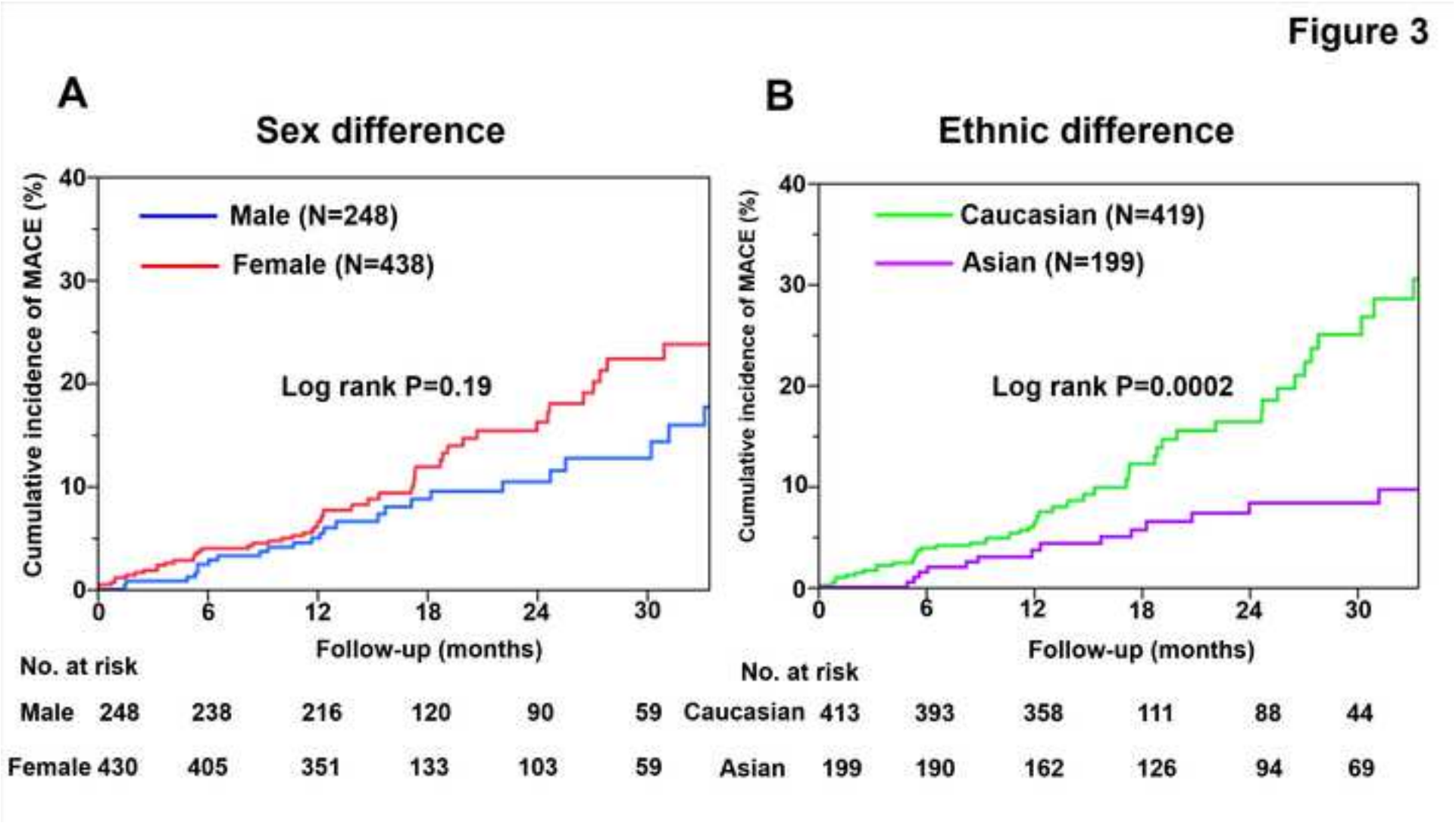


Figure 3



Clinical characteristics and prognosis of patients with microvascular angina

-An international and prospective cohort study by the Coronary Vasomotor Disorders International Study (COVADIS) Group-

Supplementary appendix

Supplementary methods

Definitions

1. Cardiovascular risk factors

We adopted the international criteria for definitions of cardiovascular risk factors including hypertensions[1], diabetes[2] and hyperlipidemia.[3]

2. Coronary artery disease

In terms of past and family history of coronary artery disease, we adopted the international criteria for definitions of acute coronary syndrome[4,5] and stable coronary artery disease.[6]

3. Diagnosis of microvascular angina

We diagnosed patients as having microvascular angina by using the COVADIS diagnostic criteria as follows; (1) signs and/or symptoms of myocardial ischemia, (2) absence of obstructive CAD, (3) objective evidence of myocardial ischemia, and (4) evidence of impaired coronary microvascular function, as determined by the clinical site (**Table S1**).[7]

Data collection

All patients who met the eligibility criteria determined at the site were registered following the site ethical review board approval. Data collection was performed through the use of the electronic case report form established by the Japanese Coronary Spasm Association.[8] The investigators at each study site registered information on demographics, relevant medical history, cardiovascular risk factors, quality of life (e.g. Seattle Angina Questionnaire, SAQ),[9] diagnostic approaches for myocardial ischemia, anatomical and/or functional status of epicardial coronary arteries and coronary microcirculation, and medications. Follow-up of

each patient was conducted at least once from study entry to the end of December 2019 either by a telephone call or personal visit, depending on the approach considered most practical and effective.

Study variables

Study variables obtained at enrolment included patient demographics (sex, age, height, weight), cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, smoking, menopause), past and family history of coronary artery disease (CAD) including acute coronary syndrome and stable angina pectoris, type of angina episodes (effort, rest, or mixed), circadian distribution of angina attacks, ECG leads of ST-segment elevation or depression at rest, arrhythmias during spontaneous attack, use of non-invasive diagnostic modalities for myocardial ischemia (SPECT, PET, CMR, stress echocardiography or electrocardiography), information regarding interventional diagnostic procedures for assessment of coronary vasodilatation (e.g. coronary flow reserve, index of microcirculatory resistance, hyperemic microvascular resistance) or assessment for propensity to coronary vasoconstriction (e.g. spasm provocation testing), medications (calcium channel blocker, nitrate, statin, ACE-I, ARB, and beta-blocker), patient-reported angina status assessed by the SAQ. During the follow-up period, clinical outcomes (cardiovascular death, non-fatal MI, non-fatal stroke, hospitalization due to heart failure, and UA) were collected.

Ethics approval

The present study was performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Conference on Harmonization of Good Clinical Practice guidelines, and the applicable legislation on non-interventional studies. The final protocol was approved by the site ethics committee. An investigator at each site ensured that

the patient was given full and adequate oral and written information in the local language about the nature, purpose, possible risk, and benefit of the present study.

Study organization

The Coronary Vasomotor Disorder International Study (COVADIS) group was established in 2012 to define the nomenclature and stimulate interest into coronary vasomotor disorders. The COVADIS Steering Committee served as the principal investigators for the COVADIS Microvascular Angina Registry, including the Steering Committee co-chairs and the data coordinating center (DCC). The Steering Committee members are as follows; John Beltrame (COVADIS co-chair, Australia), Colin Berry (PI, United Kingdom), Paolo Camici (PI, Italy), Filippo Crea (PI, Italy), Juan Carlos Kaski (PI, United Kingdom), C. Noel Bairey Merz (COVADIS co-chair, USA), Peter Ong (PI, Germany), Carl J Pepine (PI, USA), Udo Sechtem (PI, Germany), and Hiroaki Shimokawa (Study Chair, DCC, Japan).

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Supplementary tables

Supplementary table 1. Criteria for microvascular angina (MVA) by COVADIS (Ref. 7)

1. **Symptoms of myocardial ischemia**
   a. Effort and/or rest angina
   b. Angina equivalents (i.e. shortness of breath)
2. **Absence of obstructive coronary artery disease** (< 50% diameter reduction or FFR > 0.80) by
   a. Coronary CTA
   b. Invasive coronary angiography
3. **Objective evidence of myocardial ischemia**
   a. Ischemic ECG changes during an episode of chest pain
   b. Stress-induced chest pain and/or ischemic ECG changes in the presence or absence of transient/reversible abnormal myocardial perfusion and/or wall motion abnormality
4. **Evidence of impaired coronary microvascular function**
   a. Impaired coronary flow reserve (cut-off values depending on methodology use between < 2.0 and < 2.5)
   b. Coronary microvascular spasm, defined as reproduction of symptoms, ischemic ECG changes but no epicardial spasm during acetylcholine provocation test
   c. Abnormal coronary microvascular resistance indices (e.g. IMR > 25)
   d. Coronary slow flow phenomenon, defined as TIMI frame count > 25

Definitive MVA: all four criteria are present for a diagnosis of microvascular angina.

Suspected MVA: symptoms of ischemia are present with no obstructive coronary artery disease but only objective evidence of myocardial ischemia, or evidence of impaired coronary microvascular function alone.

CTA, computed tomographic angiography; ECG, electrocardiogram; FFR, fractional flow reserve; IMR, index of microcirculatory resistance; TIMI, thrombolysis in myocardial infarction.

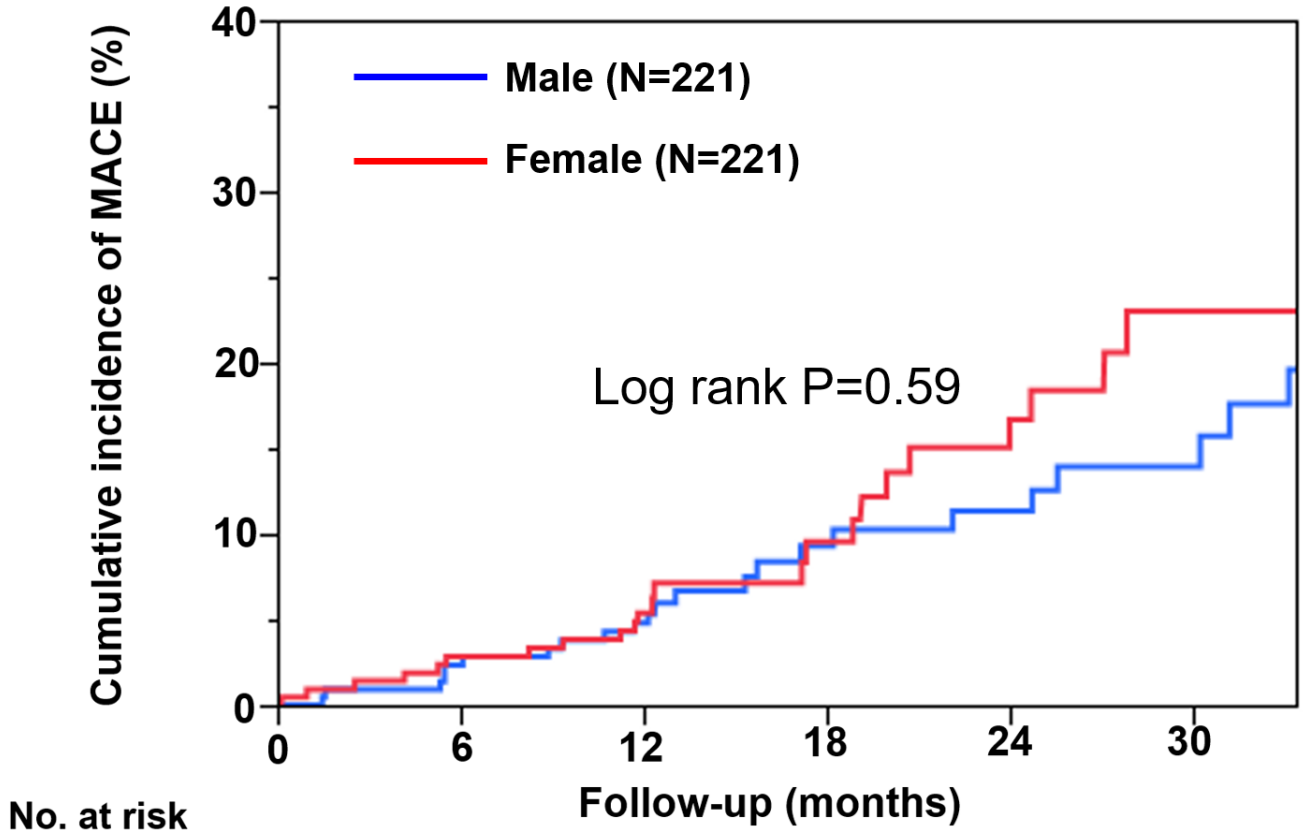
Supplementary table 2. Comparison of baseline clinical characteristics between Caucasian and Asian

Characteristics	Total cohort (N=686)	Caucasian (N=419)	Asian (N=199)	P value
Age (mean, yrs.)	61.7±11.8	60.8±10.8	62.6±13.1	0.02
Female, n (%)	438 (64)	308 (74)	86 (43)	<0.0001
Body mass index (mean)	26.1±5.9	26.9±5.8	24.0±4.0	<0.0001
Hypertension, n (%)	358 (52)	221 (53)	95 (48)	0.24
Dyslipidemia, n (%)	358 (52)	254 (61)	77 (39)	<0.0001
Diabetes mellitus, n (%)	116 (17)	55 (13)	41 (21)	0.02
Current smoking, n (%)	108 (16)	57 (14)	41 (21)	0.03
Previous history of CAD, n (%)	233 (34)	161 (38)	36 (18)	<0.0001
Previous PCI, n (%)	65 (9)	23 (5)	26 (13)	0.002
LVEF (mean, %)	65.6±10.2	65.5±9.9	66.6±10.4	0.29
Symptoms				
Angina, n (%)	465 (68)	271 (65)	142 (71)	0.25
Rest angina, n (%)	245 (36)	125 (30)	100 (50)	<0.0001
Effort angina, n (%)	99 (14)	61 (15)	23 (12)	0.30
Rest and effort angina, n (%)	121 (18)	85 (20)	19 (10)	0.0005

Shortness of breath, n (%)	125 (18)	109 (26)	4 (2)	<0.0001
Others, n (%)	135 (19)	77 (18)	39 (19)	0.27
SAQ score (median, IQR)				
Physical limitation	75 (53-93)	67 (44-86)	89 (72-100)	<0.0001
Angina stability	50 (25-75)	50 (25-75)	50 (50-75)	0.83
Angina frequency	70 (50-90)	70 (50-80)	80 (70-100)	<0.0001
Treatment satisfaction	75 (63-88)	75 (56-88)	75 (63-81)	0.26
Disease perception	50 (25-67)	42 (25-67)	50 (33-58)	0.38
Initial treatment after diagnosis				
Statin, n (%)	424 (62)	317 (76)	60 (30)	<0.0001
Nitrate, n (%)	295 (43)	237 (57)	39 (20)	<0.0001
Calcium channel blocker, n (%)	249 (36)	74 (18)	160 (80)	<0.0001
Beta blocker, n (%)	249 (36)	175 (42)	33 (17)	<0.0001
Angiotensin-converting enzyme inhibitor, n (%)	169 (25)	124 (30)	18 (9)	<0.0001
Angiotensin Ⅱ receptor blocker, n (%)	117 (17)	83 (20)	18 (9)	0.0004

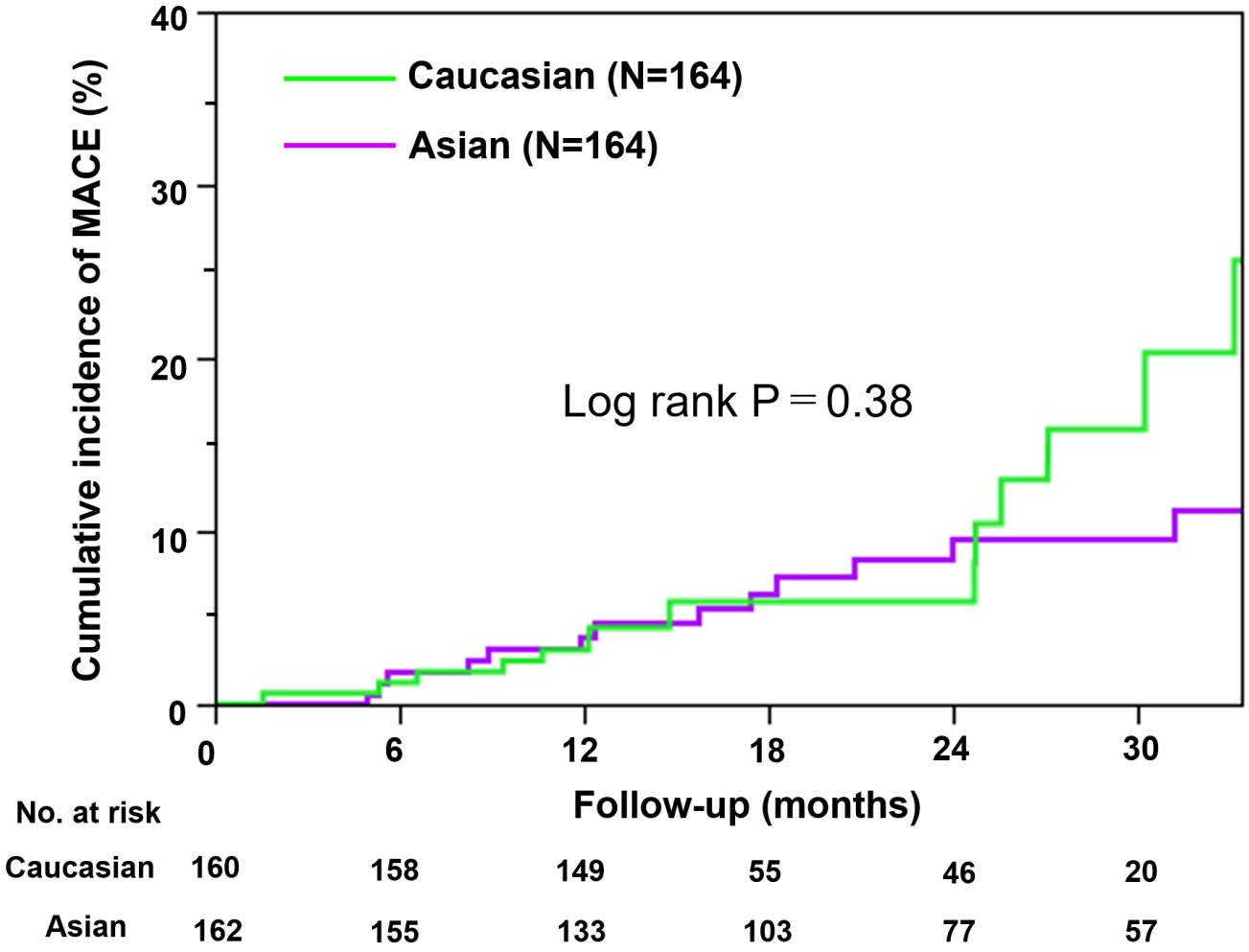
CAD, coronary artery disease; LVEF, left ventricular ejection fraction; magnetic resonance imaging; PCI, percutaneous coronary intervention, SAQ, Seattle angina questionnaire.

Supplementary figure 1. Sex difference in the incidence of primary composite outcome after propensity score matching



No. at risk						
Male	214	207	188	98	77	51
Female	211	203	179	72	53	26

Supplementary figure 2. Ethnic difference in the incidence of primary composite outcome after propensity score matching



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Funding: The Japanese Coronary Spasm Association (funded by the Japan Heart Foundation). CB received funding from the British Heart Foundation (PG/17/2532884; RE/18/6134217). CNBM and CJP received funding from contracts from the National Heart, Lung and Blood Institutes nos. N01-HV-68161, N01-HV-68162, N01-HV-68163, N01-HV-68164, grants U0164829, U01 HL649141, U01 HL649241, K23HL105787, T32HL69751, R01 HL090957, 1R03AG032631 from the National Institute on Aging, GCRC grant MO1-RR00425 from the National Center for Research Resources, the National Center for Advancing Translational Sciences Grant UL1TR000124 and UL1TR000064. JB received funding from The Hospital Research Foundation. PO and US received funding from the Berthold-Leibinger-Foundation, Germany.

Conflict of interest: F.C. reports speaker fees from AstraZeneca, Amgen and Servier and institutional agreements between his employer, the Catholic University, and Biotronik, Boheringer Ingelheim. C.N.B.M. reports lecturer fees from Abbott Diagnostics, board director fees from iRhythm, consulting fees from Caladrius, and advisory board fees from Bayer. C.B. declares institutional agreements between his employer, the University of Glasgow, and AbbottVascular, AstraZeneca, Boehringer Ingelheim, Coroventis, DalCor, GSK, HeartFlow, Novartis, and Philips. P.G.C. reports speaking honoraria from Servier and Abbott. P.O. reports personal fees from Bayer Healthcare, Pfizer and Philips/Volcano. U.S. reports speaker and consulting fees from Amgen, Bristol-Myers Squibb, Boehringer-Ingelheim, Abbott, Servier, Astra-Zeneca, Bayer, and Pfizer. T.F. has acted as a speaker for Abbott Vascular, Boehringer Ingelheim and Novartis. None of the declared interests regard the submitted work. All other authors have nothing to disclose.