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).

Supplementary references

1. Williams B, Mancia G, Spiering W, Rosei EA, Azizi M, Burnier M, Clement DL, Coca A, Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018;**39**:3021–3104.
2. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, Huikuri HV, Johansson I, Juni P, Lettino M, Marx N, Mellbin LG, Ostgren CJ, Rocca B, Roffi M, Sattar N, Seferovic PM, Uva MS, Valensi P, Wheeler DC. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular disease developed in collaboration with EASD. *Eur Heart J* 2020;**41**:255–323.
3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188.
4. Ibanez B, James S, Agewell S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio AL, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Windimsky P. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2018;**39**:119–177.
5. Collet Jp, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dandale P,

Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the task force for the managemant of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2020 doi:10.1093/eurheart/ehaa57.

6. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimogli M, Achenbach S, Bax JJ. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndrome. *Eur Heart J* 2020;**41**:407–477.
7. Ong P, Camici PG, Beltrame JF, Crea F, Shimokawa H, Sechtem U, Kaski JC, Merz CNB. International standardization of diagnostic criteria for microvascular angina. *Int J Cardiol* 2018;**250**:16–20.
8. Suda A, Takahashi J, Beltrame JF, Berry C, Camici PG, Crea F, Escaned J, Ford T, Kaski JC, Kiyooka T, Metha PK, Ong P, Ozaki Y, Pepine C, Rimoldi O, Safdar B, Sechtem U, Tsujita K, Yii E, Merz CNB, Shimokawa H. International prospective cohort study of microvascular angia -Ratinale and design. *Int J Cardiol Heart Vasc*;2020;**31**:100630 Doi:10.1016/j.ijcha.2020.100630.
9. Spertus JA, Winder JA, Dewhurst TA, Deyo RA, Prodzinski J, Mcdonell M, Fihn SD. Development and evaluation of the Seattle Angina Questionnaire: A new functional status measure for coronary artery disease. *J Am Coll Cardiol* 2015;**25**:333–341.

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.

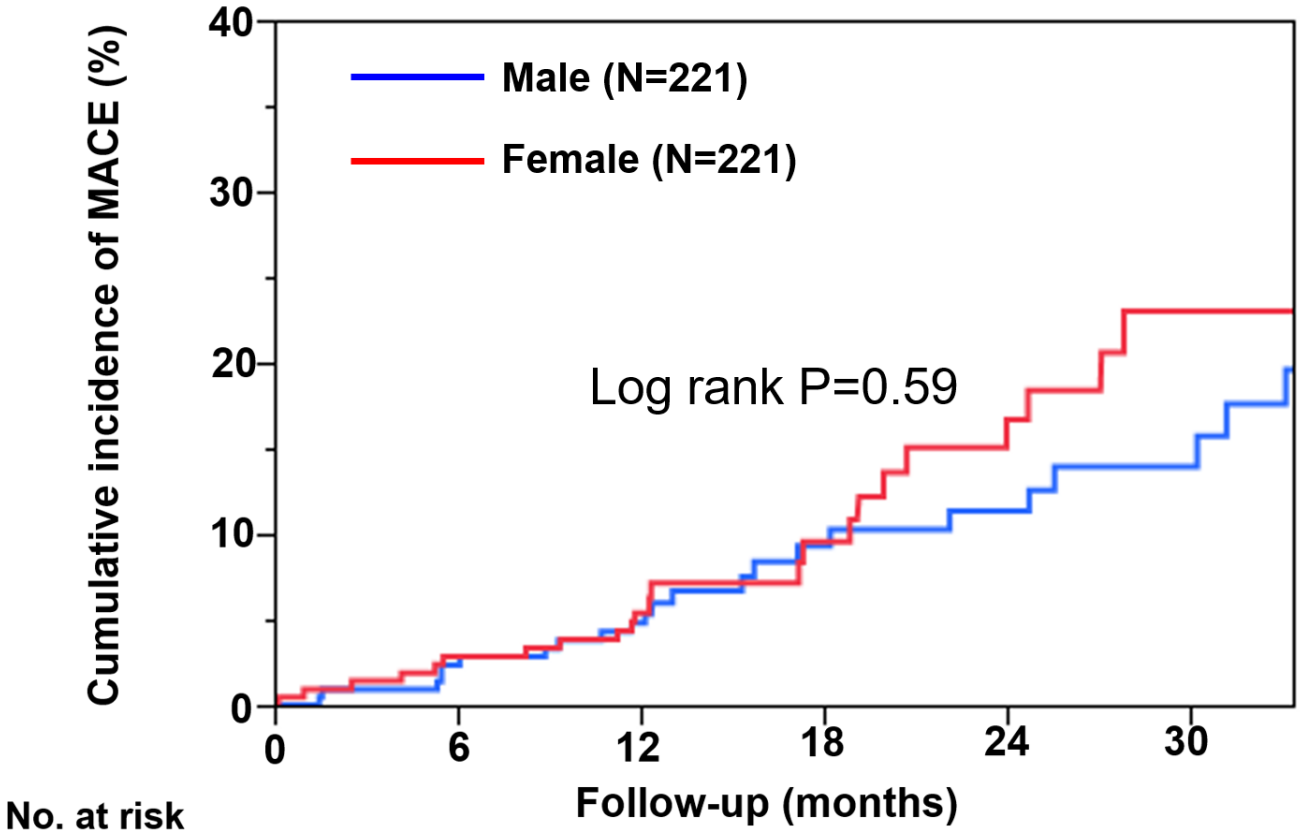
Supplementary table 2. Comparison of baseline clinical characteristics between Caucasian and Asian

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