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Sex differences in prevalence and outcomes of the different endotypes of chronic coronary syndrome in symptomatic patients undergoing invasive coronary angiography: Insights from the global ILIAS invasive coronary physiology registry

Caitlin E.M. Vink [a], Janneke Woudstra [a], Joo Myung Lee [b], Coen K.M. Boerhout [c], Christopher M. Cook [d,e], Masahiro Hoshino [f], Hernan Mejia-Renteria [g], Seung Hun Lee [h], Ji-Hyun Jung [i], Mauro Echavarria-Pinto [j], Martijn Meuwissen [k], Hitoshi Matsuo [i], Maribel Madera-Cambero [l], Ashkan Eftekhari [m], Mohamed A. Effat [n], Tadashi Murai [o], Koen Marques [a,c], Marcel A.M. Beijk [a,c], Joon-Hyung Doh [p], Jan J. Piek [c], Tim P. van de Hoef [a,c,q], Evald Høj Christiansen [m], Rupak Banerjee [r,s], Chang-Wook Nam [t], Giampaolo Niccoli [u], Masafumi Nakayama [i,v], Nobuhiro Tanaka [w], Eun-Seok Shin [x], Niels van Royen [y], Steven A.J. Chamuleau [a,c], Paul Knaapen [a,c], Javier Escaned [g], Tsunekazu Kakuta [o], Bon-Kwon Koo [z], Yolande Appelman [a,1], Guus A. de Waard [a,*,1]

[a] Department of Cardiology, Amsterdam UMC – Location VUmc, Amsterdam, the Netherlands
[b] Division of Cardiology, Department of Medicine, Heart Vascular Stroke Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
[c] Department of Cardiology, Amsterdam UMC – Location AMC, Amsterdam, the Netherlands
[d] The Essex Cardiothoracic Centre, Essex, United Kingdom
[e] Anglia Ruskin University, Essex, United Kingdom
[f] Gifu Heart Center, Department of Cardiovascular Medicine, Gifu, Japan
[g] Hospital Clínico San Carlos, IDISSC and Universidad Complutense de Madrid, Madrid, Spain
[h] Division of Cardiology, Department of Internal Medicine, Chonnam National University Hospital, Gwangju, Republic of Korea
[i] Sejong General Hospital, Sejong Heart Institute, Bucheon, Republic of Korea
[j] Hospital General ISSSTE Querétaro - Facultad de Medicina, Universidad Autónoma de Querétaro, Querétaro, Mexico
[k] Department of Cardiology, Amphia Hospital, Breda, the Netherlands
[l] Tergooi Hospital, Department of Cardiology, Blaricum, the Netherlands
[m] Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
[n] Division of Cardiovascular Health and Diseases, Department of Internal Medicine, University of Cincinnati, Cincinnati, OH, USA
[o] Tsuchiura Kyodo General Hospital, Department of Cardiology, Tsuchiura City, Japan
[p] Department of Medicine, Keimyung University Dongsan Medical Center, Daegu, South Korea
[q] Department of Cardiology, University Medical Center Utrecht, Utrecht, the Netherlands
[r] Mechanical and Materials Engineering Department, University of Cincinnati, Cincinnati, OH, USA
[s] Research Services, Veteran Affairs Medical Center, Cincinnati, OH, USA
[t] Department of Medicine, Inje University Ilsan Paik Hospital, Goyang, Republic of Korea
[u] Department of Cardiovascular Medicine, Catholic University of the Sacred Heart, Institute of Cardiology, Rome, Italy
[v] Cardiovascular Center, Toda Central General Hospital, Toda, Japan
[w] Department of Cardiology, Tokyo Medical University, Hachioji Medical Center, Tokyo, Japan
[x] Department of Cardiology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Republic of Korea
[y] Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands
[z] Department of Internal Medicine, Seoul National University Hospital, Cardiovascular Center, Seoul, Republic of Korea

* Corresponding author. Amsterdam UMC – location VUmc, Department of Cardiology, Room ZH 5 F013, De Boelelaan 1117, 1081 HV, Amsterdam, the Netherlands
  E-mail address: g.dewaard@amsterdamumc.nl (G.A. de Waard).
[1] These authors shared last authorship.

ARTICLE INFO

ABSTRACT

Background and aims: The management of chronic coronary syndrome (CCS) is informed by studies predominantly including men. This study investigated the relationship between patients sex and different endotypes of CCS, including sex-specific clinical outcomes.

Methods: In patients with CCS undergoing coronary angiography, invasive Fractional Flow Reserve (FFR) and Coronary Flow Reserve (CFR) were measured. Patients were stratified into groups: 1) obstructive coronary artery disease (oCAD) (FFR≤0.80, no revascularization), 2) undergoing revascularization, 3) non-obstructive coronary artery disease with coronary microvascular dysfunction (CMD) (FFR>0.80, CFR≤2.5), and 4) non-obstructive coronary artery disease without CMD (FFR>0.80 and CFR>2.5).

Results: 1836 patients (2335 vessels) were included, comprising 1359 (74.0%) men and 477 (26.0%) women. oCAD was present in 14.1% and was significantly less prevalent in women than in men (10.3% vs 15.5%, respectively $p < 0.01$). Revascularization was present in 30.9% and was similarly prevalent in women and men (28.2% *vs.* 31.9%, respectively $p = 0.13$). CMD was present in 24.2% and was significantly more prevalent in women than men (28.6% vs 22.6%, respectively $p < 0.01$). Normal invasive measurements were found in 564 patients (33.0% women vs 30.0% men, $p = 0.23$). Male sex was associated with an increased risk of target vessel failure compared to women (HR.1.89, 95% CI 1.12–3.18, $p = 0.018$), regardless of CCS-endotype.

Conclusions: Sex differences exist in the prevalence and outcomes of different endotypes of CCS in symptomatic patients undergoing invasive coronary angiography. In particular, oCAD (and subsequent revascularization) were more prevalent in men. Conversely, CMD was more prevalent in women. Overall, men experienced a worse cardiovascular outcome compared to women, independent of any specific CCS endotype.

1. Introduction

Chronic coronary syndrome (CCS) remains the leading cause of death worldwide in both men and women [1–3]. CCS has multiple underlying pathophysiological mechanisms and clinical presentations. Classically, CCS has most frequently been associated with the presence of obstructive epicardial coronary artery disease (oCAD). However, more recently, there is an increasing understanding of the role of coronary microvascular dysfunction (CMD) in the pathophysiology, symptomatology and adverse clinical outcome of patients with CCS.

To date, the invasive diagnosis of CCS has focused mainly on the detection of oCAD, which is known to be more prevalent in men than women [4,5] irrespective of the presence of typical angina symptoms or positive non-invasive ischemia testing [5,6]. Despite this, there exists an apparent clinical outcome paradox, with women more frequently experiencing cardiovascular death in CCS compared to men [7].

One hypothesis to explain this differential outcome between the sexes in CCS may be that there is a higher prevalence of CMD, and thus adverse cardiovascular outcome [8], in women as compared to men [7, 9]. However, data supporting this rationale is currently lacking, owing to previous studies reporting on sex differences in the prevalence of CMD being small and in highly selected patient groups.

Accordingly, in order to adequately inform on the prevalence of CMD in symptomatic patients with CCS presenting to the catheterization laboratory, we investigated the relationship between patient sex and the different endotypes of CCS, as well as their association with long-term clinical outcomes in the large multicenter ILIAS registry.

2. Patients and methods

2.1. Study population

The ILIAS registry is a multi-center, global registry of patients with accompanying comprehensive invasive epicardial and microvascular physiological assessment and associated clinical outcomes. The registry consists of prospectively gathered from 20 expert medical institutes in the Netherlands, Korea, Japan, Denmark, Spain, Italy and the United States of America. Patients were enrolled into the ILIAS registry if they underwent clinically indicated coronary angiography and comprehensive invasive physiological assessment of at least one native coronary artery. Patients with hemodynamic instability, significant valvular pathology, prior coronary artery bypass graft surgery, as well as culprit vessels of acute coronary syndromes were excluded.

Individual patient data were collected and anonymously stored in a fully compliant cloud-based clinical data platform (Castor EDC, Amsterdam, The Netherlands). The ILIAS registry was registered at ClinicalTrials.gov (NCT04485234).

For the present study, the following inclusion criteria were applied: i) Invasive coronary angiogram performed to evaluate CCS, ii) both invasive Fractional Flow Reserve (FFR) and Coronary Flow Reserve (CFR) physiological indices were measured, and iii) individual patient outcome data were available.

2.2. Invasive coronary assessment

Invasive coronary assessment was performed according to standard techniques. Invasive physiologic measurements were performed using either separate pressure- (PressureWire, RADI medical – now Abbott Vascular, St Paul, MN, USA) and Doppler velocity sensor-equipped coronary guidewires (FloWire, Endosonics – now Philips-Volcano, San Diego, CA, USA), a dual pressure- and Doppler flow velocity-equipped guidewire (ComboWire, Volcano Corp. – now Philips-Volcano, San Diego, CA, USA), or a temperature-sensitive pressure sensor-equipped guidewire (PressureWire, St Jude Medical-now Abbott Vascular, St. Paul, MN, USA). Prior to physiological assessment, intracoronary nitroglycerine (100 or 200 μg) was administered in all cases. Baseline (bAPV) and hyperemic average peak flow velocities (hAPV) were obtained from Doppler velocity measurements. The inverse of the average basal (bTmn) and hyperemic mean transit times (hTmn) was derived from resting and hyperemic thermodilution curves as described previously [10]. Hyperemia was induced according to local standards by intravenous infusion of adenosine (140 μg/kg per min) or adenosine-triphosphate (ATP 150 μg/kg per min) through a peripheral or central vein, intracoronary bolus injection of adenosine (20-200mcg), or intracoronary bolus injection of nicorandil (3 mg).

FFR was calculated as the ratio between mean hyperemic distal coronary pressure and mean hyperemic aortic pressure, and FFR≤0.80 was considered abnormal [11]. CFR was calculated as the ratio between hyperemic and baseline coronary flow, and CFR≤2.5 was considered abnormal [12]. Microvascular resistance (MR) was calculated as the ratio of distal coronary flow and distal coronary pressure during hyperemia. For MR, the hyperemic microvascular resistance index (HMR) was derived from Doppler velocity measurements and the index of microcirculatory resistance (IMR) was derived from thermodilution measurements. HMR≥2.5 [13] and IMR≥25 were considered abnormal [14].

Table 1
Baseline characteristics.

	Total	Women	Men	*p*-value
Total number of patients	n = 1836	n = 477 (26.0)	n = 1359 (74.0)	
Demographics				
Age, yrs	63.9 ± 10.3	65.7 ± 10.2	63.3 ± 10.2	<0.01
Ejection fraction	60.9 ± 9.4	63.6 ± 8.0	60.1 ± 9.6	<0.01
Coronary risk factors				
Hypertension, %	1099 (60.1)	293 (61.6)	806 (59.6)	0.45
Hyperlipidemia, %	1234 (67.4)	318 (66.8)	916 (67.6)	0.77
Positive family history, %	560 (32.4)	175 (38.6)	385 (30.1)	<0.01
Current smoking, %	399 (22.1)	76 (16.1)	323 (24.2)	<0.01
Diabetes mellitus, %	516 (28.2)	115 (24.2)	401 (29.6)	0.023
Prior myocardial infarction, %	378 (20.6)	63 (13.2)	315 (23.2)	<0.01
Prior coronary intervention, %	473 (28.2)	83 (18.4)	390 (32.0)	<0.01
Medication at hospital admission				
Beta-blocker, %	839 (50.2)	223 (49.5)	616 (50.5)	0.69
Nitrates, %	617 (37.8)	161 (38.2)	456 (37.7)	0.86
Calcium antagonist, %	699 (41.8)	183 (40.5)	516 (42.3)	0.51
ACE-inhibitors, %	748 (44.7)	180 (39.8)	568 (46.5)	0.014
Aspirin, %	1403 (83.9)	377 (84.6)	1026 (84.0)	0.83
Total number of vessels	**n = 2335**	**n = 596 (25.5)**	**n = 1739 (74.5)**	
Measurement technique				0.27
Doppler flow velocity, %	962 (41.2)	257 (43.1)	705 (40.5)	
Thermodilution, %	1373 (58.8)	339 (56.9)	1034 (59.5)	
Hyperemic stimulus				<0.01
Intravenous adenosine, %	528 (22.6)	103 (17.3)	425 (24.4)	
Intravenous ATP, %	347 (14.9)	80 (13.4)	267 (15.4)	
Intracoronary nicorandil, %	687 (29.4)	187 (31.4)	500 (28.8)	
Intracoronary adenosine, %	773 (33.1)	226 (37.9)	547 (31.5)	
Examined vessel				0.017
LAD, %	1378 (59.4)	381 (64.4)	997 (57.7)	
LCX, %	424 (18.3)	95 (16.1)	329 (19.0)	
RCA, %	518 (22.3)	116 (19.6)	402 (23.3)	
Hemodynamic parameters				
FFR, [IQR]	0.82 [0.76–0.91]	0.83 [0.78–0.92]	0.82 [0.76–0.90]	<0.01
CFR, [IQR]	2.63 [1.8–3.2]	2.50 [1.8–3.0]	2.68 [1.8–3.3]	<0.01
HMR, mmHg/cm/s, [IQR]	2.27 [1.62–2.75]	2.36 [1.71–2.73]	2.24 [1.58–2.76]	0.18
IMR, U, [IQR]	20.7 [12.6–24.1]	20.5 [12.4–24.0]	20.7 [12.6–24.1]	0.66
Reduced FFR (<0.80), %	851 (36.5)	184 (30.9)	667 (38.4)	<0.01
Reduced CFR (≤2.5), %	1213 (52.0)	331 (55.6)	882 (50.8)	0.04
Increased MR, %	563 (28.1)	148 (28.2)	415 (28.0)	0.94
Increased HMR (>2.5), %	321 (13.7)	91 (15.3)	230 (13.2)	0.39
Increased IMR (>25), %	240 (10.3)	56 (9.4)	184 (10.6)	0.63

Data presented as n(%), mean ± standard deviation or median [1st quartile – 3rd quartile].
yrs: years; ACE: angiotensin-converting enzyme; ATP: adenosine triphosphate; LAD: left anterior descending coronary artery; LCX: left circumflex coronary artery; RCA: right coronary artery; FFR: Fractional flow reserve; CFR: coronary flow reserve; HMR: hyperemic microvascular resistance index; IMR: index of microcirculatory resistance; IQR: interquartile range.

2.3. Clinical follow-up

To ascertain the occurrence of target vessel failure (TVF), clinical follow-up was obtained either at outpatient clinic visits or by telephone contact. TVF was a composite vessel-level endpoint, consisting of cardiac death, acute myocardial infarction not clearly attributable to a nontarget vessel, and clinically driven revascularization of the target vessel by means of CABG or PCI. All patient-reported adverse events were verified by evaluating hospital records or contacting the treating general practitioner or cardiologist.

2.4. Definition of different endotypes of CCS

Patients were classified into different endotype groups of CCS based upon i) their dichotomized FFR and CFR values, and ii) whether revascularization was performed. First, the undergoing revascularization group ('Revasc.' group) consisted of those vessels where revascularization was performed, regardless of the accompanying pre-PCI physiology values. Second, the hemodynamically significant obstructive CAD group ('oCAD' group) consisted of those vessels where FFR was ≤0.80, but no revascularization was performed. Third, the non-obstructive coronary

artery disease with coronary microvascular dysfunction group ('CMD' group) consisted of those vessels where FFR was >0.80 and CFR was ≤2.5. Fourth, the non-obstructive coronary artery disease without CMD group ('Normal') group consisted of vessels where FFR was >0.80 and CFR was >2.5 [15].

2.5. Statistical analyses

Descriptive data were analyzed on a per-patient basis for clinical characteristics, and on a per-vessel basis for all other calculations. Independence was assumed for vessel-level analyses. Normality of the distribution was tested with the Shapiro-Wilk statistic. Continuous variables are presented as mean ± SD or median [first quartile – third quartile], and were compared using the Student *t*-test or Mann–Whitney *U* test depending on whether data was distributed normally. Categorical variables were presented as number (%) and were compared using Pearson's chi-square test. For the vessel level analyses, robust linear and logistic regressions with Huber-White robust standard errors were used to adjust for clustering of vessels within patients, where appropriate. Event rates over time were presented using the Kaplan-Meier method. To compare the risk of the occurrence of adverse events between groups,

multivariable (marginal) Cox proportional hazard regression was used to calculate adjusted hazard ratios (HR) and 95% confidence interval (CI). All clinical characteristics were considered as co-variates in univariate Cox regression analysis, where variable significantly associated with TVF (p for inclusion<0.1) were used to adjust for confounding. Statistical analysis was performed using Stata version 14.1 (StataCorp, College Station, Texas). A p-value <0.05 was considered statistically significant.

3. Results

3.1. Patient population

Of the 2322 patients included in the ILIAS Registry, 1836 patients (2335 vessels) fulfilled study inclusion- and exclusion criteria. The study population included 477 women (26.0%), with a mean age of 65.7 ± 10.2 years, and 1359 men (74.0%) with a mean age of 63.3 ± 10.2 years (p < 0.01). Full baseline characteristics are presented in Table 1.

A statistically significant difference was found in left ventricular ejection fraction between women and men (63.6 ± 8.0% *vs.* 60.1 ± 9.6%, p < 0.01). Furthermore, women less often smoked tobacco compared to men (16.1% *vs.* 24.2%, p < 0.01), less often had diabetes mellitus (24.2% *vs.* 29.6%, p = 0.02), prior myocardial infarction (13.2% *vs.* 23.2%, p < 0.01) or prior percutaneous coronary intervention (PCI) (18.4% *vs.* 32.0%, p < 0.01). Conversely, women more often had a positive family history of cardiovascular disease compared to men (38.6% *vs.* 30.1%, p < 0.01) [Table 1].

Angiographic and physiological characteristics are also summarized in Table 1. The left anterior descending coronary artery (LAD) (59.4%) was most frequently examined. With regards to coronary flow assessment, 1373 vessels (58.8%) were evaluated with coronary thermodilution, and 962 vessels (41.2%) with Doppler flow velocity.

Despite equivalent mean angiographic diameter stenoses between the sexes (women: 49.4% *vs.* men: 52.1%, p = 1.00), FFR across the studied vessels was significantly higher for women *vs.* men (FFR 0.83 [0.78–0.92] *vs.* 0.82 [0.76–0.90], p < 0.01). Consequently, men more often demonstrated a hemodynamically significant FFR (≤0.80) compared to women (30.9% *vs.* 38.4%, p < 0.01). CFR was significantly lower for women *vs.* men (CFR 2.50 [1.8–3.0] *vs.* 2.68 [1.8–3.3], p < 0.01), and consequently, the prevalence of an abnormal CFR (≤2.5) was higher in women compared to men (55.6% *vs.* 50.8%, respectively p = 0.04). MR was equivalent between women and men, irrespective of either HMR or IMR methods of resistance quantification.

3.2. Endotypes of CCS by sex

Fig. 4 shows the patient-level prevalence of CCS endotypes. Within the study population, obstructive CAD occurred in 826 patients (45%) with 959 vessels (41%). Revascularization was performed in 567 patient (30.9%), and rates did not differ between women and men (28.1% *vs.* 31.9%, respectively p = 0.13). oCAD without revascularization occurred in 259 patients (4.1%). oCAD was more frequently observed in men compared to women (15.5% 10.3% respectively, p < 0.01). Women were more likely to have CMD compared to men (28.5% *vs.* 22.6% respectively, p < 0.01). Lastly, there was a similar occurrence of normal invasive physiologic measurements in both women and men (32.9% *vs.* 30.0% respectively, p = 0.23). Patient characteristics stratified according to CCS endotype are shown in Table 2.

Fig. 1 shows the prevalence of CCS endotypes per sex, on a per-vessel level. The analysis on a per-vessel level demonstrated consistent results with the per-patient level analysis. Supplementary Table 1 shows the CCS endotypes according to sex for CFR≤2.0 (the CFR threshold recommended by the recent European Society of Cardiology consensus document [16]). Analyses according to both CFR≤2.0 and CFR≤2.5 yielded similar and consistent results.

3.3. Long-term clinical outcomes determined by sex and CCS endotypes

During a 5-year follow-up period, one or more TVF events occurred in 146 vessels (8.0%). Overall, the incidence of TVF events was relatively low across all CCS endotypes.

Fig. 2A depicts the per-vessel Kaplan-Meier time to event curves for TVF, stratified by sex. Sex, age, diabetes mellitus, positive family history, previous myocardial infarction, use of beta-blockers, use of nitrates, and the method used to measure coronary flow were all associated with 5-year TVF. After adjustment for these potential co-founders, patient sex remained an independent predictor of TVF, where men had a higher risk for TVF than women (HR.1.89, 95% CI 1.12–3.18, p = 0.018). Likewise, men had a trend towards a shorter mean survival time (14.6 years, 95% CI 13.9–15.3) compared to women (15.4 years, 95% CI 14.4–16.3).

Fig. 2B depicts the per-vessel Kaplan-Meier time to event curves for TVF, stratified by CCS endotype (excluding the revascularization group). A significant difference in 5-year TVF rates was observed across CCS

Table 2
Baseline characteristics per CCS endotype.

	oCAD	Revasc	CMD	Normal
Total number of patients	n = 259 (14.1)	n = 567 (30.9)	n = 443 (24.2)	n = 564 (30.8)
Total number of vessels	n = 308 (13.2)	n = 651 (27.9)	n = 586 (25.1)	n = 787 (33.8)
Demographics				
Men, %	210 (81.1)	433 (76.4)	307 (69.3)	407 (72.2)
Age, yrs	62.6 ± 10.5	64.2 ± 10.3	65.4 ± 10.0	63.0 ± 10.2
Ejection fraction, %	61.3 ± 9.4	60.5 ± 9.5	60.5 ± 10.1	61.4 ± 8.6
Coronary risk factors				
Hypertension, %	155 (59.9)	345 (61.2)	269 (60.9)	329 (58.3)
Hyperlipidemia, %	193 (74.2)	392 (69.4)	289 (65.1)	361 (64.0)
Positive family history, %	95 (38.3)	165 (31.2)	137 (33.4)	166 (30.3)
Current smoking, %	60 (23.5)	140 (25.0)	79 (18.0)	121 (21.8)
Diabetes mellitus, %	77 (29.6)	180 (31.8)	115 (25.9)	144 (25.6)
Prior myocardial infarction, %	54 (20.8)	146 (25.8)	85 (19.1)	93 (16.5)
Prior coronary intervention, %	70 (29.3)	149 (29.6)	109 (28.1)	145 (26.7)
Medication at hospital admission				
Beta-blocker, %	122 (50.8)	294 (58.7)	185 (47.7)	240 (44.2)
Nitrates, %	106 (45.3)	182 (38.1)	140 (36.3)	192 (35.8)
Calcium antagonist, %	102 (42.5)	215 (42.7)	164 (42.2)	219 (40.3)
ACE-inhibitors, %	113 (47.1)	239 (47.6)	173 (44.5)	223 (41.0)
Aspirin, %	208 (87.4)	453 (90.1)	308 (79.2)	436 (80.2)

Data presented as n(%) or mean ± standard deviation.
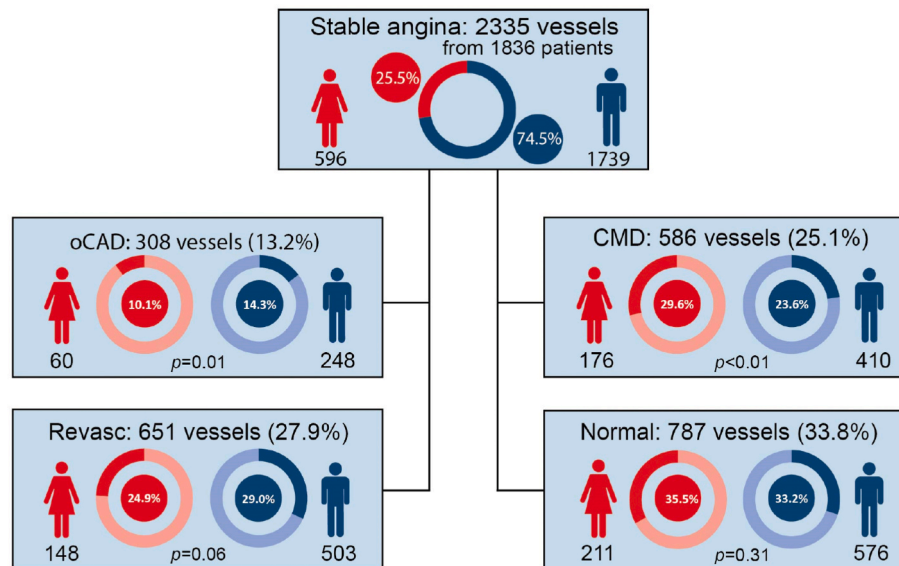yrs: years; ACE: angiotensin-converting enzyme.

Fig. 1. Prevalence of endotypes of CCS per sex on per-vessel level.
Prevalence of endotypes of CCS per sex on per-vessel level, with the highest prevalence of normal coronary arteries in women and the highest prevalence of revascularization in men. oCAD: obstructive coronary artery disease; CMD: coronary microvascular dysfunction; Revasc: revascularization-group.

endotypes (log rank p for trend <0.01). Compared with the normal endotype, oCAD had the highest risk for TVF [HR 4.97, 95% CI 3.01–7.99, $p < 0.01$], which was higher than the TVF risk observed in vessels with CMD [HR 1.9, 95% CI 1.28–2.89, $p < 0.01$ *vs.* OCAD]. CMD was, however, associated with increased TVF compared with physiologically normal coronary arteries (HR 2.58, 95% CI 1.62–4.44, $p < 0.01$ for CMD *vs.* normal). Correspondingly, mean survival time was 11.5 years (95% CI 10.5–12.5) for the oCAD group, 14.1 years (95% CI 13.0–15.1) for the revascularization group and 15.6 years (95% CI 14.5–16.6) for the normal coronary artery group.

Fig. 3 depicts Kaplan-Meier time to event curves for TVF, stratified by sex according to the following CCS endotypes. Fig. 3A compares oCAD *vs.* revascularization. Fig. 3B depicts CMD, and Fig. 3C depicts normal coronary arteries. A difference in 5-year TVF rate was found between sexes in the normal coronary artery group, with a higher risk for TVF in women compared to men (HR 4.5, 95% CI 1.07–19.3, $p = 0.041$). No sex difference was found in 5-year TVF rate in the other endotypes. However, men who underwent revascularization had a significant lower risk for TVF compared to men with obstructive CAD who did not undergo revascularization (HR 0.60, 95% CI 0.38–0.93, $p = 0.022$). Conversely, this difference in risk for TVF was not found in women who underwent revascularization compared to women with obstructive CAD whom did not undergo revascularization (HR 0.88, 95% CI 0.41–1.89, $p = 0.74$). Results were consistent when the CFR cut-off value of 2.0 was used instead of the CFR cut-off value of 2.5 (Supplementary Figures 1 through 3).

4. Discussion

The present study describes the sex-specific prevalence and clinical outcome of the different endotypes of symptomatic CCS patients referred for clinically indicated invasive coronary angiography in a large global patient cohort. The endotypes of CCS were comprehensively characterized by combined assessment of intracoronary pressure and flow to distinguish obstructive CAD, CMD and physiological normal endotype groups (Fig. 4).

The main study findings were as follows: In patients referred for invasive coronary angiography for the evaluation of CCS: 1) oCAD was significantly less prevalent and CMD was significantly more prevalent in women compared to men; 2) long-term cardiovascular outcomes

(defined as TVF) were sequentially worst for patients with obstructive CAD, followed by patients with CMD. Conversely, patients with physiologically normal coronary arteries had the best long-term cardiovascular outcomes; 3) men experienced a worse 5-year TVF rate compared to women; 4) no sex-specific differences in prognosis was observed in the obstructive CAD, revascularization and CMD groups; and, 5) in the presence of oCAD (FFR≤0.80), men who underwent revascularization had lower risk of TVF at 5 years than men in whom revascularization was not performed. Conversely, this impact of revascularization was not identified in women.

4.1. Invasive coronary physiological assessment in men and women

Earlier studies have shown that women experience angina differently, have less extensive atherosclerosis and suffer from obstructive CAD less frequently compared to men [17,18]. Yet, the prevalence of the distinct CCS endotypes across sexes encountered in catheterization laboratory in daily clinical practice is poorly understood. In the present large study, obstructive CAD was indeed less prevalent in women compared to men presenting with stable angina (15.5%, 210/1359 *vs.* 10.3%, 49/477). Additionally, we found a trend towards less revascularization in women compared to men (28.2%, 134/477 *vs.* 31.9%, 433/1359) suggesting an excess of obstructive CAD in men referred to the catheterization laboratory for suspected stable ischemic heart disease.

This observation of the presence of exertional angina in the absence of obstructive CAD has been suggested by the Women's Ischemia Syndrome Evaluation (WISE) study as being potentially related to a higher prevalence of CMD in women compared to men [5,19]. However, the WISE-study is limited in its scope owing to its inclusion of only women. Accordingly, our study addresses this limitation by the inclusion of a multiethnic cohort of both men and women across multiple centers. Within this wider, clinically-representative, patient population, CMD was indeed significantly more prevalent in women compared to men (28.5% *vs.* 22.6%). Our findings are also consistent with a recent meta-analysis by Meliva et al. [20], which similarly demonstrated a high pooled prevalence of CMD in ANOCA patients 41% (95% CI: 36–47%), with CMD being more prevalent in women compared to men (risk ratio 1.45). Our study complements the study of Meliva, which suffers from inherent limitations as a systematic review such as the a large
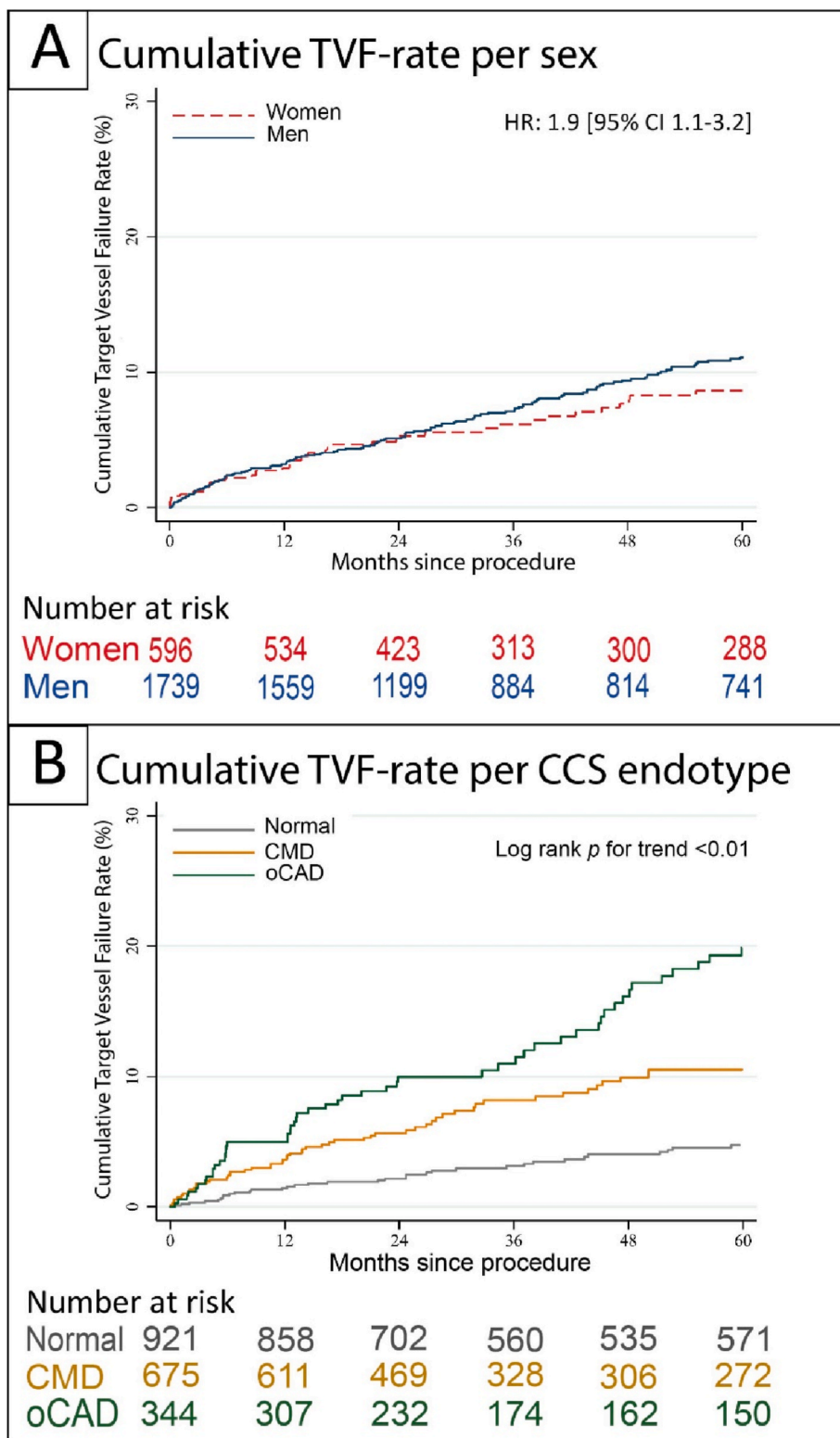
Fig. 2. Cumulative TVF-event rate per sex in overall population on per-vessel level.

Kaplan Meier-curve of total population per sex and per CCS endotype. (A) Kaplan Meier-curves of CCS per sex, with a mean survival time men *vs.* women: 14.6 *vs.* 15.4 years. (B) Kaplan Meier-curves of CCS per endotype, excluding the revascularization-group, with a mean survival time of normal *vs.* CMD *vs.* oCAD: 15.6 *vs.* 14.1 *vs.* 11.5 years. TVF; target vessel failure, CCS; chronic coronary syndrome; HR: hazard-ratio; CI: confidence-interval; CMD: coronary micro-vascular dysfunction; oCAD: obstructive coronary artery disease.

heterogeneity in the incorporated studies, regarding prevalence of CMD, different inclusion criteria and methods to calculate CFR according to the studies.

There is continued debate on the optimal invasive CFR cut-off value to define an abnormal result. Specifically, a recent ESC consensus paper [16] recommends CFR≤2.0, whereas CFR ≤2.5 may better relate to pathophysiological changes in the coronary circulation and prognosis in ANOCA patients [16,21,22]. Cognizant of these variations in CFR cut-off value, we performed our analysis according to both CFR≤2.0 and CFR≤2.5. Our results remained unchanged independent of the CFR cut-off value used. Therefore, regardless of the CFR-derived definition for CMD, CMD was more prevalent in women presenting with CCS compared to men. This consistent finding underscores the importance of detailed physiological interrogation of the coronary microcirculation for diagnostic purposes in both sexes once obstructive CAD has been ruled out.
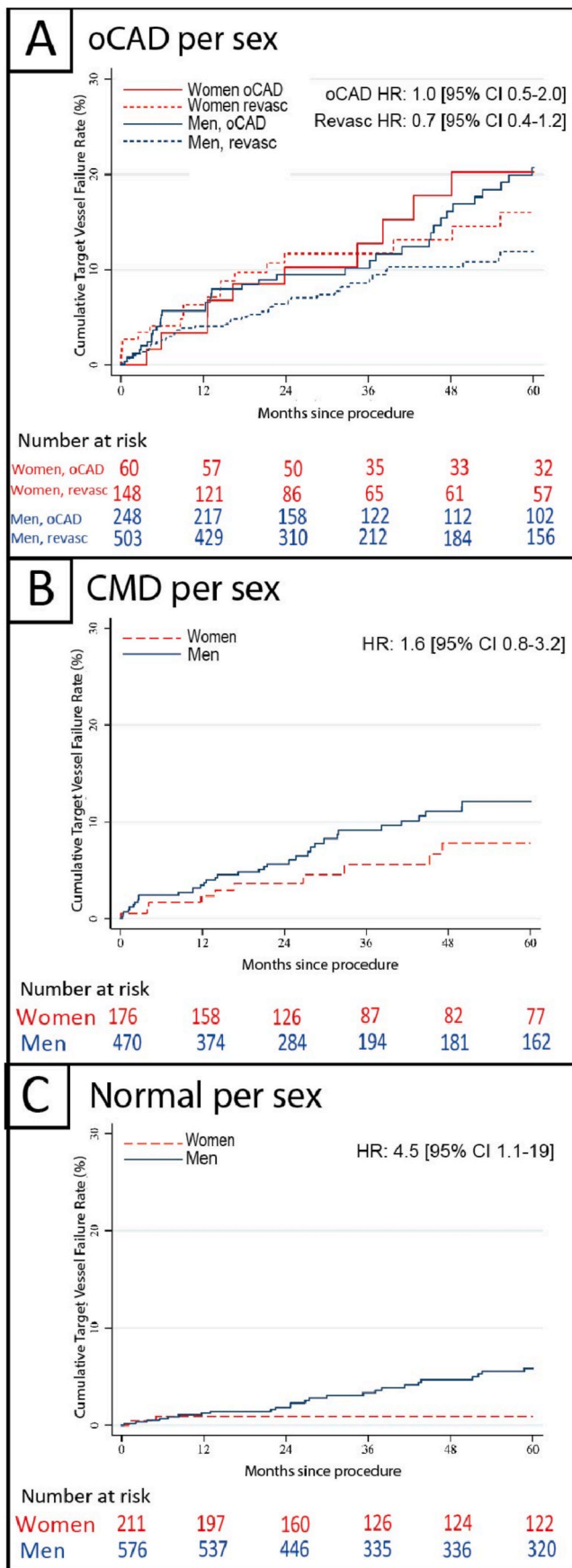
Fig. 3. Cumulative TVF-event rate per sex.
(A) Kaplan Meier-curves of oCAD per sex, with a mean survival time men *vs.* women in oCAD: 10.1 *vs.* 12.4 years, and men *vs.* women in revascularization: 14.0 *vs.* 13.5 years. (B) Kaplan Meier-curves of CMD per sex, with a mean survival time men *vs.* women: 14.6 *vs.* 13.2 years. (C) Kaplan Meier-curves of normal coronary arteries per sex, with a mean survival time men *vs.* women: 15.2 *vs.* 16.6 years. HR: hazard-ratio; CI: confidence-interval; oCAD: obstructive coronary artery disease; CMD: coronary microvascular dysfunction; Revasc: revascularization-group.

4.2. Prognostic values according to sex and CCS-endotypes

In our study sex was an independent predictor of TVF at 5-year follow-up, with men demonstrating a worse prognosis compared to women. Presumably, this finding is driven by both an over-representation of men in the obstructive CAD and revascularization groups, as well as men having a worse prognosis in the normal coronary artery group compared to women. According to our results, men seem to benefit more from a revascularization compared to women. With respect to the finding that obstructive CAD and revascularization were more prevalent in men, this might be related to sex differences in athero-sclerotic plaque size, composition and the propensity to rupture. Another hypothesis could be that women suffer from CMD after revas-cularization, in which the relationship between underlying CMD and coronary arteriosclerosis mediate a worse outcome [23]. A recently published meta-analysis of Kelshiker et al. has shown that a reduced CFR is strongly associated with an increased risk of all-cause mortality and MACE across a broad range of patient groups and different pathologies [29].

4.3. CCS-endotypes

Of the total population, 30.8% of the patients had no evidence of abnormal coronary physiology as identified by combined pressure and flow measurements. There are several explanations for the angina-like symptoms in the absence of epicardial or microcirculatory disease. Vasomotor dysfunction presenting as coronary vasospasm can be caused by hyper reactivity of the vascular smooth muscle cells and encompasses focal or diffuse epicardial and microvascular vasospasm. Another cause of vasospasm is the acute activation of coronary mast cells. Mast cells play a role in regulating vascular function by producing vasoactive substance, such as histamine. The effect of histamine is mediated through activation of H1 and H2 coronary receptors. Coronary arteries can be hypersensitive to histamine, leading to vasoconstriction [24,25]. Vasospasm can be assessed using acetylcholine reactivity testing [16]. Coronary vasospasm is highly prevalent in patients with non-obstructive CAD as assessed by intracoronary acetylcholine provocation testing and is more prevalent in women compared to men [26]. Non-cardiac chest pain such as pulmonary or gastrointestinal disorders are another explanation for the non-diagnostic coronary angiograms in our study [27].

4.4. Limitations

The results from the present study should be interpreted with several limitations in mind. First, this is an observational study consisting of multiple prospective registries from different expert centers across the world. Hence, inherent heterogeneity in the study protocols may have influenced the study and its findings. However, conversely, our study cohort represents a large collection of multiethnic CCS patients from multiple centers and thus significant external validation and generaliz-ability to our findings. Second, medication use was not registered in all patients and medication changes after ICA were not considered as part of our analysis. Since it is recognized that women are more likely to be underdiagnosed and undertreated in CCS, medication could be a
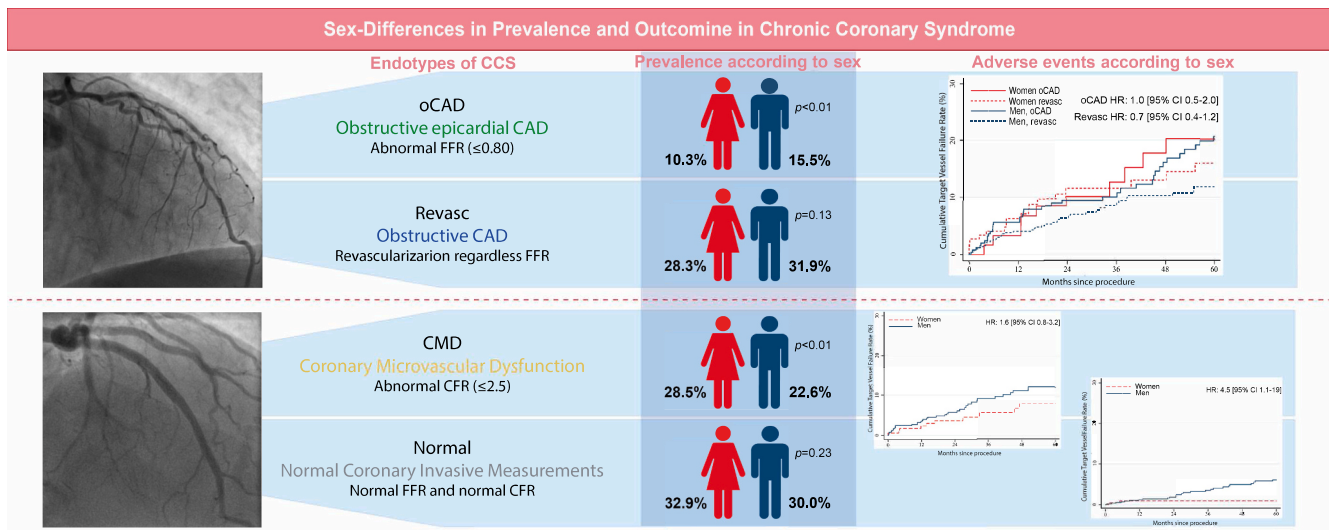
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Fig. 4. Prevalence of endotypes of CCS per sex on per-patient level, with the highest prevalence of normal coronary arteries in women and the highest prevalence of revascularization in men.

No significant differences were found on target vessel failure outcome. oCAD: obstructive coronary artery disease; FFR: fractional flow reserve; CMD: coronary microvascular dysfunction; CFR: coronary flow reserve, Revasc: revascularization-group; HR: hazard ratio; CI: confidence-interval.

confounder on the effect of sex differences and prognosis after ICA [7]. Third, the ILIAS-registry did not contain information on the character of anginal symptoms. This could be important, since it has been described that women and patients with CMD frequently present their symptoms differently to men and patients with obstructive CAD [7,28]. Fourth, clinical endpoints relevant to chronic coronary syndrome, such as hospitalization and reduced angina-burden, were not available. Lastly, this study might have oversimplified the complexity of vasomotor pathophysiology by using cut-off values derived from continuous variables to stratify into the different endotypes. However, this approach adheres to contemporary clinical and scientific practice.

4.5. Conclusion

In this large global registry of symptomatic CCS patients referred for coronary angiography, we observed a clinically relevant sex difference in the prevalence of CCS-endotypes between women and men using invasive physiological testing. While women had a higher prevalence of CMD, men had a higher prevalence of significant obstructive CAD. Men had a worse 5-year TVF rate compared to women, likely attributable to the observed higher prevalence of obstructive CAD.

In summary, because CMD was present in 29% of women and 23% of men (and is associated with a worse prognosis compared to patients with physiologically normal coronary arteries), our findings underscore the class IIB recommendation from the ESC/EAPCI guidelines [16] to perform guidewire based CFR-measurements once obstructive CAD is ruled out in CCS patients referred to the catheterization laboratory.

Clinical trial registration

Inclusive invasive physiological assessment in angina syndromes registry (ILIAS Registry), NCT04485234.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:
Tvdh has received speaker fees and institutional research grants from Abbott and Philips. JML received research grants from Abbott and Philips. MEP has received speaker fees from Abbott and Philips. BKK has received institutional research grants from Abbott Vascular and Philips

Volcano. JJP has received support as consultant for Philips/Volcano, and has received institutional research grants from Philips. The other authors report no relationship with industry related to this work.

CRediT author statement

Caitlin E.M. Vink, Conceptualization, Writing - Original Draft, Methodology, Visualization, Formal analysis. Janneke Woudstra, Writing - Review & Editing, Visualization, Formal analysis. Joo Myung Lee, Writing - Review & Editing, Investigation. Coen K.M. Boerhout, Writing - Review & Editing, Data Curation, Validation. Christopher M. Cook, Review & Editing. Masahiro Hoshino, Writing - Review & Editing, Investigation. Hernan Mejia-Renteria, Writing - Review & Editing, Investigation. Seung Hun Lee, Writing - Review & Editing, Investigation. Ji-Hyun Jung, Writing - Review & Editing, Investigation. Mauro Echavarria-Pinto, Writing - Review & Editing, Investigation. Martijn Meuwissen, Writing - Review & Editing, Investigation. Hitoshi Matsuo, Writing - Review & Editing, Investigation. Maribel Madera-Cambero, Writing - Review & Editing, Investigation. Ashkan Eftekhari, Writing - Review & Editing, Investigation. Mohamed A. Effat. Writing - Review & Editing, Investigation. Tadashi Murai, Writing - Review & Editing, Investigation. Koen Marques, Writing - Review & Editing, Investigation. Marcel A.M. Beijk, Writing - Review & Editing, Investigation. Joon-Hyung Doh, Writing - Review & Editing, Investigation. Jan J. Piek, Writing - Review & Editing, Investigation. Tim P. van de Hoef, Writing - Review & Editing, Project administration, Data Curation, Investigation, Formal analysis, Validation, Methodology. Evald Høj Christiansen, Writing - Review & Editing, Investigation. Rupak Banerjee; Writing - Review & Editing, Investigation. Chang-Wook Nam, Writing - Review & Editing, Investigation. Giampaolo Niccoli, Writing - Review & Editing, Investigation. Masafumi Nakayama, Writing - Review & Editing, Investigation. Nobuhiro Tanaka, Writing - Review & Editing, Investigation. Eun-Seok Shin, Writing - Review & Editing, Investigation. Niels van Royen, Writing - Review & Editing, Investigation. Steven A.J. Chamuleau, Writing - Review & Editing, Investigation. Paul Knaapen, Writing - Review & Editing, Investigation. Javier Escaned, Writing - Review & Editing, Investigation. Tsunekazu Kakuta, Writing - Review & Editing, Investigation. Bon-Kwon Koo, Writing - Review & Editing, Investigation. Yolande Appelman, MD, PhD; Supervision, Conceptualization, Writing - Review & Editing, Methodology. Guus A. de Waard, Supervision, Conceptualization, Writing - Review & Editing,

Investigation, Formal analysis, Validation, Methodology.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2023.06.073.

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