Sex-related differences in plaque characteristics and endothelial shear stress related plaque-progression in human coronary arteries

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ABSTRACT

Background and aims: Clinical atherosclerosis manifestations are different in women compared to men. Since endothelial shear stress (ESS) is known to play a critical role in coronary atherosclerosis development, we investigated differences in anatomical characteristics and endothelial shear stress (ESS)-related plaque growth in human coronary arteries in men compared to women.

Methods: 1183 coronary arteries (male/female: 944/239) from the PREDICTION study were studied for differences in artery/plaque and ESS characteristics, and ESS-related plaque progression (6-10 months follow-up) among men and women and after stratification for age. All characteristics were derived from IVUS-based vascular profiling and reported per 3 mm-segments (13,030 3-mm-segments (male/female: 10,465/2,565)).

Results: Coronary arteries and plaques were significantly smaller in females compared to males; but no important differences were observed in plaque burden, ESS and rate of plaque progression. Change in plaque burden was inversely related to ESS (p<0.001) with no difference between women versus men (β: -0.62 ± 0.13 vs -0.68 ± 0.05, p=0.62). However, stratification for age demonstrated that ESS-related plaque growth was more marked in young women compared to men (<55 years, β: -2.02 ± 0.61 vs -0.33 ± 0.10, p=0.007), reducing in magnitude over the age-categories up till 75 years.

Conclusions: Coronary artery and plaque size are smaller in women compared to men, but ESS and ESS-related plaque progression were similar. Sex-related differences in ESS-related plaque growth were evident after stratification for age. These observations suggest that although the fundamental processes of atherosclerosis progression are similar in men versus women, plaque progression may be influenced by age within gender.

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1. Introduction

Although coronary artery disease is the leading underlying cause of mortality in both men and women, clinical presentation of the disease is very different. Men are more likely to present with sudden death and acute myocardial infarction, whereas women display atypical symptoms and/or angina pectoris [1]. Atherosclerosis manifests differently in women compared to men in terms of atherosclerotic plaque size, composition and rupture risk [2]. In general, coronary plaques of women are smaller in size and display fewer features of plaque vulnerability [3–5]. Furthermore, women more often exhibit non-obstructive coronary disease, which is associated with coronary microvasculature abnormalities [6]. Despite the often mentioned sex-related differences in plaque distribution in coronary arteries, no systematic, detailed analysis has been previously performed.

Endothelial shear stress (ESS), the frictional force of blood flowing along endothelial cells, is recognized for its influence on endothelial cell function and thereby on plaque distribution and progression. Low ESS causes inflammation-driven endothelial cell dysfunction [7,8] and is unevenly distributed over the vasculature with pronounced low ESS areas close to side branches, on inner aspects of artery curvature, outer waists of artery bifurcations, and up- and down-stream from a...
flow-limiting obstruction. Based on longitudinal studies, we and other researchers have demonstrated that low ESS is one of the main determinants of plaque localization and influences plaque size [9–11], composition [12–14] and progression [13–15].

To explain the observed sex-related differences in plaque size and distribution, we hypothesized that coronary arteries of females show different ESS patterns compared to coronary arteries in males or that ESS-related plaque progression is different over time. We also hypothesized that rates of plaque progression were related to age and sex: i.e., that men display more marked ESS-related progression at a younger age compared to women, but that men and women display similar rates of ESS-related progression at an older age.

Therefore, the aim of this study was to investigate differences in coronary artery size; plaque size, characteristics, and distribution; and coronary flow and ESS characteristics in coronary arteries from men and women. Furthermore, we studied differences in the role of local ESS in plaque distribution and progression between men and women, and at different age ranges. We utilized the PREDICTION data set which included information on clinical characteristics (including the sex and age of the patient), and ESS distribution, plaque morphology and plaque progression over time in all major coronary arteries.

2. Patients and methods

2.1. Patient population

The PREDICTION study was an anatomic natural history study performed in Japanese clinical sites and has been previously described [15]. Written informed consent was obtained from each patient included in the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and the study protocol has been priorly approved by the institution’s ethics committee on research on humans. In brief, 506 patients presenting with an acute coronary syndrome underwent intravascular ultrasound imaging (IVUS) and bi-plane angiography of all major coronary arteries (average 2.7 per patient) at baseline and by study design 374 patients invasive imaging was repeated 6–10 months later. From the 506 patients enrolled in the PREDICTION study, vascular profiling methods of 3-D coronary artery reconstruction and computational fluid dynamics were successful in 496, of which 479 had a complete data set that could be included in the analysis.

2.2. Vascular profiling methods

Arterial and plaque characteristics, and ESS measures were derived from vascular profiling methods as previously described [15]. Vascular profiling utilizes a three-dimensional (3D) reconstruction of the coronary artery as input for computational fluid dynamics. 3D-reconstructions were obtained by combining information on lumen and outer vessel wall segmented from end-diastolic intravascular ultrasound (IVUS) frames with information on the 3D-arterial geometry centerline derived from biplane angiography. This process provided the anatomical dimensions and characteristics of the arteries (lumen, wall, plaque area, plaque thickness). Coronary blood flow was calculated from the time that radiopaque material after injection traveled from the beginning to the end of the reconstructed lumen region of interest using x-ray coronary angiography. The 3D-reconstruction of the lumen and the flow were fed into a finite element software package to calculate the local ESS (Phoenix CHAM, England). The ESS was calculated as the product of the local gradient of the blood velocity at the vessel wall and the viscosity, which was derived from the patient-specific hematocrit at each invasive procedure.

2.3. Data analysis and definitions

To allow detailed, serial analysis of differences in anatomical/plaque characteristics and ESS of men versus women, the coronary 3D reconstructions were subdivided longitudinally into consecutive 3-mm segments starting from the ostium. A number of geometrical and ESS parameters were calculated for each 3-mm segment: average lumen area (LA), minimal lumen area (Lamin), average plaque area (PA), average vessel area (VA, i.e. the area circumscribed within the external elastic lamina) and plaque burden (PB, average PA/average VA) were calculated. Within each 3-mm segment, the maximal and minimal plaque thickness (PTmax and PTmin) were determined within a moving 90◦ arc and used to calculate the plaque eccentricity index (EI), as the ratio of PTmax to PTmin. A plaque was defined as a region with ≥3 consecutive segments with a PTmax > 0.5 mm. For each artery and plaque, the minimal Lamin, the maximal PTmax, the maximal EI and the maximal

Table 1
Demographics stratified by sex (all patients; n = 506).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Male (N = 404)</th>
<th>Female (N = 102)</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>63.5 (56.7–71.1)</td>
<td>69.4 (64.4–75.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>247 (61.1)</td>
<td>74 (72.5)</td>
<td>0.033</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL &gt;100 mg/dL, n (%)</td>
<td>292 (72.3)</td>
<td>82 (80.4)</td>
<td>0.095</td>
</tr>
<tr>
<td>HDL &lt;40 mg/dL, n (%)</td>
<td>171 (42.3)</td>
<td>25 (24.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(within last 2 yrs), n (%)</td>
<td>229 (56.7)</td>
<td>20 (19.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>147 (36.4)</td>
<td>32 (31.4)</td>
<td>0.344</td>
</tr>
<tr>
<td>Insulin dependent, n (%)</td>
<td>10 (2.5)</td>
<td>5 (4.9)</td>
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</tr>
<tr>
<td>Family history of premature CAD, n (%)</td>
<td>27 (6.7)</td>
<td>5 (4.9)</td>
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</tr>
<tr>
<td>Previous CAD history, n (%)</td>
<td>50 (12.4)</td>
<td>9 (8.8)</td>
<td>0.318</td>
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<tr>
<td>ACS presentation</td>
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<tr>
<td>Unstable angina, n (%)</td>
<td>119 (29.5)</td>
<td>36 (35.3)</td>
<td>0.376</td>
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<tr>
<td>Non-ST elevation MI, n (%)</td>
<td>51 (12.6)</td>
<td>9 (8.8)</td>
<td></td>
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<td>ST elevation MI, n (%)</td>
<td>234 (57.9)</td>
<td>57 (55.9)</td>
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<td>Physical exam</td>
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<tr>
<td>Heart rate, bpm</td>
<td>69 (62–78)</td>
<td>70 (64–76)</td>
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<td>Systolic blood pressure, mmHg</td>
<td>126 (111–140)</td>
<td>128 (112–146)</td>
<td>0.183</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>72 (65–81)</td>
<td>70 (62–80)</td>
<td>0.039</td>
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<tr>
<td>Laboratory data</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>40 (36–43)</td>
<td>35 (33–39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL, mg/dl</td>
<td>107 (86–130)</td>
<td>117 (98–138)</td>
<td>0.029</td>
</tr>
<tr>
<td>HDL, mg/dl</td>
<td>42 (34–50)</td>
<td>49 (42–60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>175 (148–210)</td>
<td>190 (171–230)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>114 (76–157)</td>
<td>99 (69–143)</td>
<td>0.097</td>
</tr>
<tr>
<td>C-reactive protein, mg/dl</td>
<td>0.4 (0.1–1.1)</td>
<td>0.3 (0.1–1.0)</td>
<td>0.826</td>
</tr>
</tbody>
</table>
Fig. 1. Distribution of male and female coronary arteries.
(A) Distribution of studied number of arteries and of 3 mm segments (seg) at baseline and follow-up over the different vessel types stratified to sex. (B) Distribution of studied number of plaques at baseline and follow-up over the different vessel types and stratified to sex.
PB were also determined. Calculated ESS variables included average ESS, minimal ESS (ESSmin: the 90° arc with the lowest ESS) and maximal ESS (ESSmax: the 90° arc with the highest ESS) per segment. Also, per artery and per plaque, the minimal ESSmin and the maximal ESSmax were calculated. To account for the patient specific flow, the ESS were also normalized by the flow and compared between men and women. For the serial analyses, the changes in these parameters over time were calculated (Δ = follow-up–baseline).

2.4. Statistics

Categorical variables were presented as count/percentages and continuous variables as mean ± SEM for variables with normal distribution, median (25 percentile – 75 percentile) for variables that are not-normally distributed or estimated means and standard error if derived from the mixed linear models. To test differences of the baseline characteristics or frequency distribution comparing men and women in the study population Kruskal Wallis test and $\chi^2$ test was used respectively.

For the other statistical analysis, ANOVA, mixed effect linear regression models or mixed effect logistic regression models with patient (and artery) as random factors were used where appropriate. For detailed description see supplement. For the ESS-related plaque progression the mixed-effects regression analysis was used and repeated after stratification for 4 different age ranges (<55 years, 55–65 years, 65–75 years, >75 years). For all the statistical analysis IBM SPSS statistics version 24 was used. A $p$ value < 0.05 was considered as significant.

3. Results

Among the 479 total patients included in the baseline analysis of plaque characterization there were 384 men and 95 women, who contributed 944 male and 239 female coronary arteries (total 1183 arteries, mean 2.5 per patient). Among the 324 patients included in the follow-up plaque progression analysis, there were 262 men and 62 women, contributing 613 male arteries and 150 female arteries. Table 1 shows the demographics of the total patient population. In general, female patients were significantly older (69.4 [64.4–75.5] vs 63.5 [56.7–71.1] years, $p < 0.001$) presented more often with hypertension (73% vs 61%, $p = 0.033$), and were less often smokers or former smokers (19.6% vs 56.7%, $p < 0.001$). Cholesterol levels were significantly higher in female patients compared with male patients (LDL: 117 [95–138] vs 107 [86–135] mg/dl, $p = 0.029$, HDL: 49 [42–60] mg/dl vs 42 [34–50], $p < 0.001$), total cholesterol: 190 [171–230] vs 175 [148–210] mg/dl, $p < 0.001$). The detailed vascular analysis included a total of 13,030 segments (10,465 in male and 2,565 in female patients) from 1183 arteries, and 1041 plaques. Fig. 1 illustrates the details of coronary artery distribution, 3-mm arterial segments, and plaques.

3.1. Sex-related differences in coronary artery anatomic characteristics and ESS

Sex-related differences in artery characteristics are reported in Supplementary Table S1 for the LAD, LCX and RCA, respectively. In general, coronary arteries in women were significantly smaller in size, as reflected by the smaller LA and smaller VA with smaller plaque area and smaller average PTmax compared to coronary arteries in men (Supplementary Table S1). This difference in PTmax was also clearly observed in the distribution of PTmax in male compared to female coronary arteries (Fig. 2 A and B, $p < 0.001$). Even though plaques were eccentric with PTmax approximately 2 times higher than PTmin, no sex-related
differences in plaque eccentricity were observed. Of note, PB was not different for the LAD and LCX, but there was a small, but significant, difference for RCA between men and women, respectively. Also, the distribution in PB (Fig. 2C and D, \( p < 0.001 \)) was significantly different among men and women. Compared to men, coronary arteries in women tended to have lower coronary blood flow (Supplementary Table S1 A-C) which, in combination with the smaller artery size in women, resulted in similar exposure to average ESS, ESSmin and ESSmax values (Supplementary Table S1), which was also true after normalization for the flow.

3.2. Sex-related differences in plaque distribution at the proximal and mid-distal portion of coronary arteries

In all coronary arteries, the PTmax and PB were significantly larger at the proximal portion compared to the mid-distal portion (\( p < 0.001 \)) (Supplementary Figs. 1 and 2). At both locations, the PTmax was significantly smaller in coronary arteries from women compared to men, however, for PB these sex-related differences were much less clear. These observations were also reflected by the observed differences in the frequency of affected segments with PTmax > 1.0 mm or PB > 40% (Figs. 3 and 4); the proximal portion of the LAD and RCA in women were less often affected with large plaques (PTmax > 1.0 mm) compared to the LAD and RCAs in men.
3.3. Sex-related differences in per-plaque anatomic characteristics and ESS

1041 plaques were studied for their differences in characteristics comparing 187 female and 854 male plaques. The average length of the plaques and the location, expressed as the distance from the ostium, were similar for plaques located in coronary arteries from women and men (Table 2). The average PA and VA were respectively 15% ($p < 0.001$) and 14% ($p < 0.001$) smaller in women compared to men, which was also reflected by the 8% smaller PTmax of female plaques ($p=0.002$). No differences in plaque eccentricity were observed comparing male and female plaques (2.40 ± 0.04 vs 2.45 ± 0.07, $p = 0.56$). Although the lumen size was 13% smaller in female compared to male coronary arteries, the average ESS over the plaque was not different, but normalization of the ESS with the flow revealed a higher average and minimal ESS in women ($p = 0.049$, $p = 0.024$, Table 2). Interestingly, the ESSmin that female plaques were exposed to was 17% higher than for male plaques ($p=0.037$).

3.4. Sex-related differences in plaque growth and changes in ESS

The studied plaques demonstrated significant plaque regression over time with respect to PA and VA (Supplementary Table S2). However, these plaque changes were not different in coronary arteries in men versus women (Supplementary Table S2). Although at baseline the ESS surrounding the plaque was not different between men and women, the change in average ESS and maximum ESSmax over time tended to be higher for plaques in coronary arteries of women compared to men.

Fig. 4. Frequency of plaque burden >40% proximal versus distal portion of the coronary artery. Frequency of segments affected with plaque burden >40% in the proximal (<30 mm distance from the ostium) versus distal (30–60 mm from the ostium) portion of the LAD, LCX and RCA stratified for sex.
ESS-related plaque growth showed the previously reported significant inverse relationship between changes in PB and the baseline ESSmin (β = −0.68 ± 0.04, p < 0.001) and changes in PTmax and the baseline ESSmin (β = −0.01 ± 0.001, p < 0.001). However, no differences in ESS-related plaque growth were observed comparing coronary arteries from women and men (PB: \( \beta = -0.62 \pm 0.13 \) vs \( \beta = -0.68 \pm 0.05, p=0.62 \); PTmax: \( \beta = -0.011 \pm 0.004 \) vs \( \beta = -0.01 \pm 0.001, p = 0.63 \)), and similarly after adjustment for baseline plaque characteristics (Supplementary Table S3).

However, significant differences in ESS-related plaque growth were observed between men and women after stratification for age (Fig. 5). Fig. 5A shows the relationships between plaque burden and ESS for the different age categories, whereas Fig. 5B gives an overview of the different slopes (β) as estimated for women and men for the various age categories. Interestingly, among the youngest patients (<55 years), low ESS-related plaque growth was much more pronounced in women compared to men (PB: \( \beta = -2.02 \pm 0.61 \) vs \( \beta = -0.33 \pm 0.10; p = 0.007 \); PTmax: \( \beta = -0.054 \pm 0.02 \) vs \( \beta = 0.0008 \pm 0.003; p = 0.005 \), Supplementary Fig. 4A). Among patients aged between 65 and 75 years a small, but significant, difference in ESS-related plaque growth was also observed comparing women and men, but only for change in PB (β = −0.27 ± 0.17 vs β = −0.79 ± 0.10; p = 0.008). The number of segments, vessels and patients per age-category are listed in Supplementary Table S4.

Women showed a continuous change in magnitude of ESS-dependent plaque growth over the different age categories (p < 0.001). The clearest significant trend was the reduction in magnitude of ESS-related plaque growth (β) up till 75 years of age (Fig. 5B). This changing age-dependent plaque growth rate among women persisted after adjustment for baseline plaque characteristics (Supplementary Figs. 3 and 4B). In contrast, ESS-dependent plaque growth in coronary arteries in men (>55 years) was generally consistent throughout the age groups (Fig. 5 and Supplementary Figs. 3).

### 4. Discussion

We investigated sex-related differences in both anatomic and ESS parameters in human coronary arteries both at the per-artery and per-plaque level. Coronary arteries in women were smaller in size and contained smaller plaques compared to coronary arteries in men. Proximal coronary artery regions were most often affected with coronary disease in both men and women and the frequency of larger plaques (>1 mm PTmax or >40% PB) was significantly lower in women compared to men. Furthermore, since coronary blood flow was lower in coronary arteries in women, no differences in ESS were observed among coronary arteries from men and women. Interestingly, plaques in women were exposed to higher ESSmin than plaques in coronary arteries of men. The frequently observed inverse relationship between plaque progression and ESSmin was confirmed, but no differences in ESS-related plaque progression were observed comparing coronary arteries from men and women. When stratified for patient age at baseline, however, young women exhibited more marked plaque progression than men at a young age (<55 years). Women demonstrated a clear reduction in magnitude of the ESS-related plaque progression (β) up till 75 years of age.

Even though sex-hormones and gender have been known to influence the development of atherosclerotic plaques and clinical presentation and cardiovascular events [1,16,17], only recent imaging technology enabled refined, detailed analysis of the vessel wall and allowed for comparison of plaque size, growth and composition in coronary arteries of men and women [3,4]. Plaques imaged in coronary or carotid arteries from women presented less often with signs of plaque vulnerability compared to plaques in men [3,18]; such observations were also supported by studies on endarterectomy-derived histological specimens obtained from carotid arteries [19]. Although local plaque development and changes in plaque composition have been shown to be associated with blood flow-induced ESS, there have been no studies that investigated sex-related differences in ESS-related plaque development. There is also no information on the ESS distribution in the different coronary arteries stratified for sex. We investigated whether the magnitude of ESS itself could be the reason for the observed differences in plaque size and
composition in coronary arteries of women and men, but found no evidence to support that hypothesis. The only difference that we found was the higher ESSmin that plaques from women were exposed to compared to plaques from men. Whether the small difference can explain the large differences observed in atherosclerosis manifestation needs further research.

The observation that coronary arteries in women are smaller in size, contain smaller plaques and have lower wall thickness, compared to coronary arteries in men, confirm earlier studies on sex-related differences in the cardiovascular system and cardiovascular disease [2, 4]. Even though plaques in women were smaller in size, they presented with the same plaque burden as plaques in coronary arteries of men (Table 2). Only minor sex differences in plaque burden became evident when the location (proximal or distal) was taken into consideration (Supplementary Fig. 2 and Fig. 4). These differences were more evident if PTmax was compared (Supplementary Fig. 1 and Fig. 3). Interestingly, the PROSPECT study also did not demonstrate any difference in plaque burden comparing plaques in coronary arteries of men and women [2].

Fig. 5. Shear stress related plaque burden progression stratified for AGE. (A) Plaque burden (PB) versus shear stress (ESSmin) with sex as fixed factor stratified for age using a linear mixed model with vessel and patient as random factors. (B) Estimated slopes ($\beta$) of the association between plaque burden (PB) and shear stress (ESSmin) with sex as fixed factor stratified for age using a linear mixed model with vessel and patient as random factors. * $p < 0.05$ MEN vs WOMEN; within MEN: #: <55 years are significantly different from 55–65, 65–75, >75 years; within WOMEN: $\$: <55 years is different from 55–65, 65–75 years, $+$: 65–75 years is different from <55, >75 years.

<table>
<thead>
<tr>
<th>Age</th>
<th>MEN</th>
<th>WOMEN</th>
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<tr>
<td>&lt;55</td>
<td>1505</td>
<td>177</td>
</tr>
<tr>
<td>55-65</td>
<td>2389</td>
<td>400</td>
</tr>
<tr>
<td>65-75</td>
<td>1926</td>
<td>608</td>
</tr>
<tr>
<td>&gt;75</td>
<td>816</td>
<td>316</td>
</tr>
</tbody>
</table>

WITHIN SEXES
MEN :
#: $p<0.05$; <55 vs 55-65, 65-75, >75 years
WOMEN:
$: $p<0.05$; <55 vs 55-65, 65-75 years
$+$: $p<0.05$; 65-75 vs >75 years
An explanation for this observation might be that even though women manifest smaller plaques compared to men, they are also located in smaller coronary arteries, resulting in similar plaque burden.

ESS was not different among men and women for each of the coronary arteries even after normalization for flow. Plaques were exposed to higher ESS in women, but only by about 0.1 Pa, which is probably not biological signifi cant (Table 2). Although there are no previous studies investigating sex-related differences in ESS in coronary arteries, an ultrasound study by Samijo in carotid arteries also reported that the time-average ESS was similar in men and women [20]. Of note, however, the peak ESS over the cardiac cycle in the carotid arteries was significantly higher in men than women.

The data from the PREDICTION trial are unique in that its large size allowed us for the first time to investigate differences in ESS-related plaque progression among men and women as a function of age. Since this study was not designed for that purpose our data should be considered as an exploratory post-hoc analysis. We expected to find a lower rate of ESS-related plaque progression in younger women (<55 years), since estrogen in pre-menopausal women is known to improve endothelial function and thereby prevent ESS-related atherosclerotic plaque build-up [17,21]. We observed, however, that younger women in our study group (<55 years) exhibited substantially larger ESS-related plaque progression over time than men as re ected by the larger, more negative β. Although the number of female patients in PREDICTION was limited, the trend of more robust ESS related progression at a young age was clearly evident (Fig. 5). Moreover, we noticed in women a trend that with age (up till 75) the magnitude of ESS-related progression diminished even after adjustment for baseline plaque size. A larger group of women may be necessary to con rm these observations. The observed sex-related differences in this young age group could be attributed to other confounding lifestyle or risk factors that might have contributed to the early manifestation of an ACS in these women or to the earlier described ‘catch up’ phenomena after menopause [21]. Unfortunately, we have no information concerning the age of menopause in these women nor the duration from the onset of menopause to the time of their clinical manifestations of coronary disease. Also no information was available regarding the prevalence of pre-eclampsia in this patient group, known to be one of the new female risk factors of atherosclerosis [22]. The decline in high ESS-related plaque progression with age compared to age-matched men may re ect increased medical interventions, such as initiation of statin therapy and antiplatelet agents for women following menopause, which would moderate the magnitude of this catch-up phenomenon. For older women we did not anticipate any difference in ESS-related plaque progression with men of similar age since estrogen is signi cantly reduced in older women and thus their protection from atherosclerosis is no longer present. Our results con rm the similar rate of plaque progression in older men and women. For men ESS-related plaque growth is much more consistent above 55 years.

4.1. Limitations of the study

An important limitation is the imbalance in the number of female (N = 102) compared to the male (N = 404) patients. In this study, we used data from every patient included in the PREDICTION study in an unbiased manner, but there were many fewer women enrolled compared to men. The PREDICTION Study is unique and the most appropriate dataset to perform this post-hoc analysis, since it is the largest study of male and female ACS patients with comprehensive and serial invasive coronary imaging and data on local ESS, plaque characteristics and progression of all three major coronary arteries. Clinical studies of CAD inevitably include fewer number of females than males for a variety of behavioral and socio-economic reasons [23].

Another limitation of the study is the unavailability of the body surface area value for each patient. Since female patients are in general smaller than males, correction of the data for BSA would have been preferable, so that our study observations would be independent of the well-known size-differences. However, such data were not available in the PREDICTION study, and the observed differences do re ect the daily practice differences in geometry and plaque size.

In this study, we had no access to the hormonal status of the patients and the duration of the post-menopausal status of the women. Unfortunately, differences in plaque growth and ESS-related plaque growth among men and women could not be related to individual hormone levels. Since estrogen is known to in uence endothelial function [17] it can be anticipated that information on hormone levels explains some of the observed variation especially in the younger age group. Future research should include that information into the analysis.

This study was performed in an Asian population only. Since Asian compared to Caucasian patients showed clear differences in vessel size, plaque morphology and composition [24,25], these data cannot be translated one-to-one to the general (multi-ethnic) population. With higher plaque burdens at baseline compared to Caucasian individuals, ESS-related plaque progression might be higher in Japanese patients than in Caucasians. However even after adjustment of baseline plaque size the observed differences remained. Moreover, in our study we found similar trends as reported based on studies that had a more multi-ethnic character [4].

Lastly, although we used state-of-the art methodology to calculate the ESS, a number of assumptions/simpli cations are generally needed to allow computation of the local ESS. For instance, we calculated the viscosity based on the hematocrit only. However, other parameters (e.g. proteins in the serum) may have a minor effect on blood viscosity as well. Thus there may still be minor differences in viscosity that we did not take into account. Furthermore, we assumed that the arteries were rigid, however elasticity was shown to minimally in uence ESS [26]. Since for the ESS calculation in coronary arteries of men and women utilized the same methodology, the absence in sex-related differences in ESS is presumably not in uenced by those assumptions.

4.2. Conclusion

Coronary arteries in women were smaller and contained smaller plaques than coronary arteries in men, although plaque burden was similar. Coronary blood flow was lower in women resulting in similar ESS in the coronary arteries of women compared to men. ESS-related plaque progression was not different between men and women in general, but the youngest female patients (<55 years) exhibited much more marked ESS-related plaque growth compared to men of similar age. Men generally demonstrated a consistent ESS-related plaque progression across the age-categories studied, whereas plaque progression in women evolved, with marked ‘catch-up’ of plaque progression early, to eventually get a similar plaque progression as men later in life. The pathophysiology of atherosclerosis progression is in uenced by gender and age, and may provide opportunities for different prognostic and therapeutic management strategies for male and female patients dependent on their age.

CRediT authorship contribution statement

Jolanda J. Wentzel: Conceptualization, statistics, drafting and revision manuscript.
Michail I. Papafaklis: Formal analysis, data analysis, statistics, revision manuscript.
Antonios P. Antoniadis: Formal analysis, data analysis, revision manuscript.
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Ahmet U. Coskun: Formal analysis, data analysis, revision manuscript.
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Declaration of competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A

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References


