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Multimodality OCT, IVUS and FFR evaluation of coronary intermediate grade lesions in women vs. men

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Background: The pathophysiology of atherosclerotic plaque formation and its vulnerability seem to differ between genders due to contrasting risk profiles and sex hormones, however this process is still insufficiently understood. The aim of the study was to compare the differences between sexes regarding the optical coherence tomography (OCT), intravascular ultrasound (IVUS) and fractional flow reserve (FFR)-derived coronary plaque indices.

Methods: In this single-center multimodality imaging study patients with intermediate grade coronary stenoses identified in coronary angiogram (CAG) were evaluated using OCT, IVUS and FFR. Stenoses were considered significant when the FFR value was ≤0.8. Minimal lumen area (MLA), was analyzed by OCT in addition to plaque stratification into fibrotic, calcific, lipidic and thin-cap fibroatheroma (TCFA). IVUS was used for evaluation of lumen-, plaque- and vessel volume, as well as plaque burden.

Results: A total of 112 patients (88 men and 24 women) with chronic coronary syndromes (CCS), who underwent CAG were enrolled. No significant differences in baseline characteristics were present between the study groups. The mean FFR was 0.76 (0.73–0.86) in women and 0.78 ± 0.12 in men ($p = 0.695$). OCT evaluation showed a higher prevalence of calcific plaques among women than men $p = 0.002$ whereas lipid plaques were more frequent in men ($p = 0.04$). No significant differences regarding minimal lumen diameter and minimal lumen area were found between the sexes. In IVUS analysis women presented with significantly smaller vessel area, plaque area, plaque volume, vessel volume (11.1 ± 3.3 mm^2 vs. 15.0 ± 4.6 mm^2 $p = 0.001$, 6.04 ± 1.7 mm^2 vs. 9.24 ± 2.89 mm^2 $p < 0.001$, 59.8 ± 35.2 mm^3 vs. 96.3 (52.5–159.1) mm^3 $p = 0.005$, 106.9 ± 59.8 mm^3 vs. 153.3 (103–253.4) mm^3 $p = 0.015$ respectively). At MLA site plaque burden was significantly greater for men than women (61.50 ± 7.7% vs. 55.5 ± 8.0% $p = 0.005$). Survival did not differ significantly between women and men (94.6 ± 41.9 months and 103.51 ± 36.7 months respectively; $p = 0.187$).

Conclusion: The presented study did not demonstrate significant differences in FFR values between women and men, yet a higher prevalence of calcific plaques by OCT and lower plaque burden at the MLA site by IVUS was found in women vs. men.

KEYWORDS

coronary plaque, sex differences, OCT, FFR, IVUS, stable coronary artery disease

1. Introduction

The pathophysiology of atherosclerotic plaque formation and its vulnerability seem to be different between genders due to contrasting risk profiles and sex hormones (1–3). However, this process is still insufficiently understood. There is still a limited amount of data on sex associated differences in plaque morphology and their influence on blood flow dynamics, underscoring the need for further research.

The primary modality for diagnosing coronary artery disease (CAD) is coronary angiogram (CAG) (4–6). However, it has several widely acknowledged limitations (4–6). It is estimated that even 50% of patients who suffered from cardiac arrest did not experience any premonitory symptoms (7). Therefore, additional techniques have been developed in order to deepen the diagnostic process and optimize treatment strategy, i.e., intravascular ultrasound (IVUS), optical coherence tomography (OCT) and fractional flow reserve (FFR).

IVUS has a tissue penetration depth of up to 6 mm, enabling a full-thickness visualization of the vessel wall (8). Nevertheless, its resolution remains relatively low (axial 100–150 μm and lateral 150–300 μm, at 40 MHz) (9), as compared to infrared light-based OCT providing very high resolution (axial 10–20 μm and lateral 20–90 μm), though with a penetration depth of 1–2 mm (10–18).

Therefore, direct visualization of the artery wall is feasible, enabling a precise evaluation of plaque composition and its superficial layers (e.g., thin cap fibroatheroma – TCFA, plaque rapture) (19–21). Moreover, intravascular modalities are recognized to positively impact the clinical outcomes regarding CAD assessment and PCI guidance (10, 22). On the other hand, FFR/iFR remain the guideline-recommended invasive modalities to identify coronary lesions requiring interventional procedures to resolve myocardial ischemia (23, 24).

The aim of the study was to visualize and compare the imaging (OCT, IVUS) and functional indices of coronary lesions in women vs. men, taking into account such parameters as minimal lumen area (MLA), plaque characteristics (fibrotic, calcific, lipidic or TCFA), plaque burden and a functional index of FFR among patients undergoing CAG due to chronic coronary syndromes (CCS).

2. Material and methods

2.1. Study population

This was a single-center, prospective, observational, longitudinal, cohort study that enrolled patients with CCS ($n = 112$) who underwent CAG. Intermediate grade coronary stenoses were evaluated with FFR, OCT and IVUS (**Figure 1**). The relevance of the stenoses was found significant if FFR ≤ 0.8. The study protocol was approved by the local Ethics Committee.

The study inclusion and exclusion criteria have been previously published (25). In brief, the inclusion criteria comprised: chronic coronary syndrome, presence of chest pain ranked 2-3 in the Canadian Cardiovascular Society classification or positive ischemia test (exercise test, single photon emission tomography – SPECT), age >18 years, intermediate grade coronary stenoses of 40%–80% evaluated visually during angiography (26), FFR and OCT examination of the same lesion.

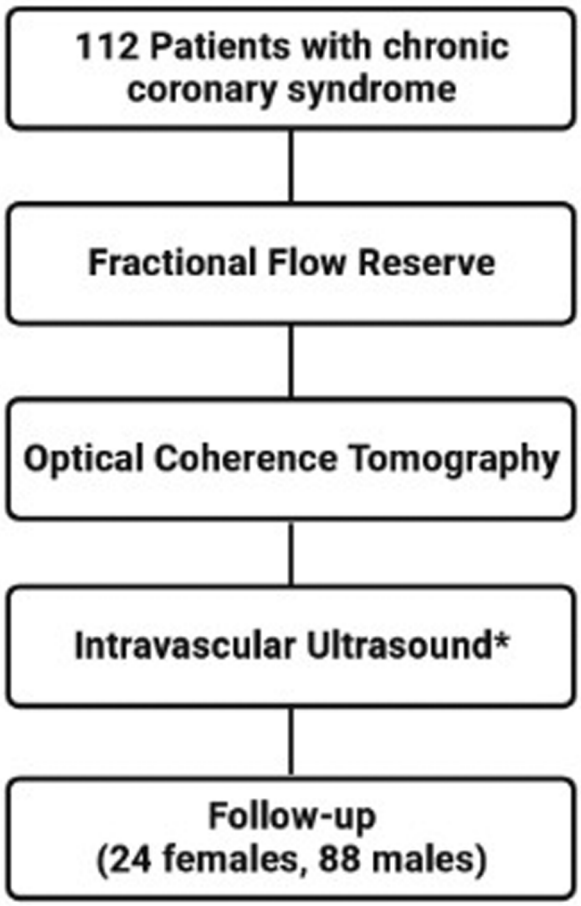

FIGURE 1
Study flow chart. Intravascular ultrasound was performed at the discretion of the operator (in 64 patients).

Exclusion criteria: left main disease, ostial right coronary lesion, bypass graft lesions, hemodynamic instability, acute or chronic renal insufficiency defined as serum creatinine level >1.5 mmol/L, contraindication for adenosine administration, pregnancy.

2.2. OCT

OCT recordings were obtained with a commercially available frequency domain OCT imaging system (Abbott, C7XR Dragonfly TM, LightLab Imaging Inc., MA, USA), using the non-occlusive technique (4, 10, 16, 22).

OCT images were analyzed according to expert consensuses' definitions (27–30), by the analysts blinded to patient characteristics, IVUS and FFR result. Evaluation of the reference

lumen area was performed in the largest lumen proximal or distal to a stenosis (within 10 mm of the stenosis). Morphometric assessment of the plaque was done at the site of MLA in at least three consecutive frames. Plaques were stratified into fibrous, calcified, lipid-rich or mixed. Fibrous plaque is characterized by high backscattering and a relatively homogenous signal, calcified plaque comprises calcium visible as a signal poor heterogeneous region with sharply delineated border (27–30) (**Figure 2**). In addition, the calcium angle (the circumference of the calcium covering the lumen and presented in degrees) was assessed. Plaque was considered lipid-rich in case of inhomogeneous signal-poor region with diffused borders (28, 31). The lipid angle was computed as the arc of a low-signal region presented in degrees. Fibrous cap thickness (FCT) was defined as the distance between the arterial lumen and the inner border of the lipid or calcium pool. The FCT was assessed first at 0.2-mm intervals over the plaque and then 3 times at its thinnest part at each cross-section, and the average value was taken into the final analyses (31). TCFA was defined with minimal FCT < 65 μm.

2.3. FFR

Coronary pressure was obtained using a 0.014-inch pressure guide wire (St. Jude Medical, Minneapolis, MN, USA). Maximal hyperemia was induced by intravenous adenosine administration at 140 μg/kg/min through a large peripheral vein. The used formula for FFR calculations was mean hyperemic distal coronary pressure divided by mean aortic pressure. The stenosis was found significant in the case of a FFR ≤ 0.80 (32–34) (**Figure 3**).

2.4. IVUS

In order to acquire an IVUS image, the catheter was placed in the distal fragment of the vessel and a pullback was performed at a speed of 0.5 mm/s at 40 MHz (35). IVUS image assessment was performed in 0.5 mm intervals using a dedicated software by analyst blinded to patients characteristics, FFR and OCT results. The plaque burden at MLA site was calculated using the formula: (external elastic membrane area-lumen area)/external elastic membrane area × 100%.

2.5. Statistical analysis

Statistical analyses have been performed using the SPSS version 28.0 (IBM Corp, Armonk, NY, USA). The distribution was analyzed with the Kolmogorov–Smirnov test. Normally distributed data were presented with means and standard deviation (SD), whereas the non-parametric data were presented with median and percentiles 25th and 75th (interquartile range). Categorical variables were presented by percentages within each group. Between-group comparisons were carried out with a Student *t*-test or Mann-Whitney U test for continuous variables and Chi-square test or Fisher's exact test, as appropriate, for categorical variables. Kaplan-Meier analysis with log-rank test was conducted to compare the MACE-free survival and death

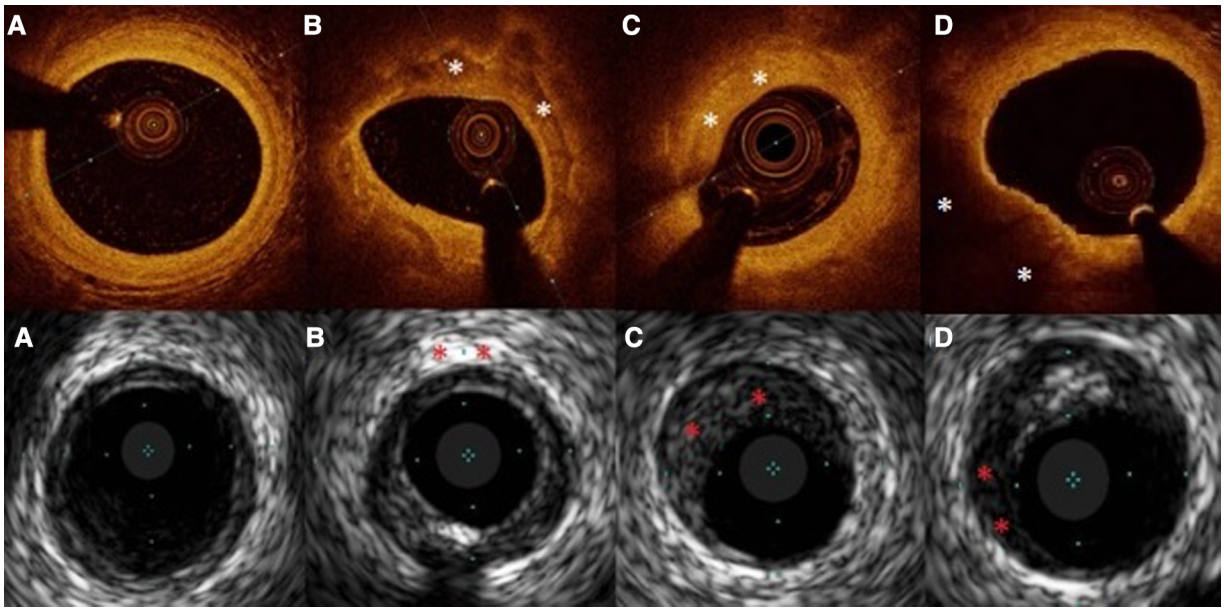

FIGURE 2
Examples of OCT and IVUS obtained images. In capital letters (**A–D**) OCT images, in small letters (**a–d**) IVUS images. Plaques marked with "*". (**A**), (**a**)-healthy vessel, (**B**) calcific plaque, (**b**)- calcification, (**C**) fibrous plaque, (**c**)- fibrous plaque, (**D**) lipidic plaque, (**d**)-lipidic area in plaque.

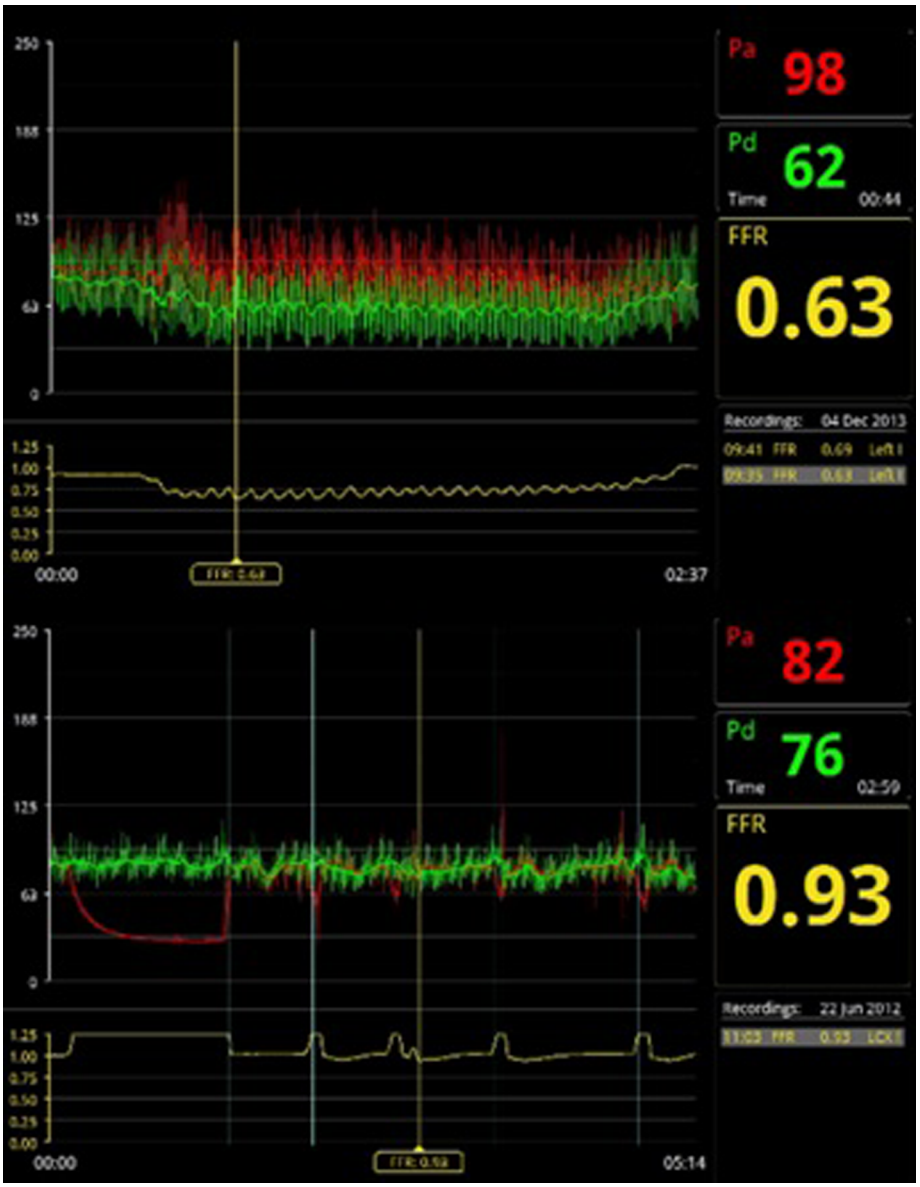

FIGURE 3
Examples of FFR measurements. On the top panel a significant FFR value of 0.63, on the bottom panel a non-significant FFR value of 0.93.

probability between the sexes. The results were considered significant for $p < 0.05$.

3. Results

3.1. Patients characteristics

A total of 112 patients (132 lesions) that underwent CAG were included in this study. This group comprised 24 women (21.4%) and 88 men (78.6%). The prevalence of coexisting conditions was high with the two most common, hypertension and hypercholesterolemia, present in 84.0% and 66.0% of patients respectively. There were no significant differences between genders in terms of age and comorbidities in the analyzed cohort. No differences in prior medication use were recorded either (Table 1).

There were no differences in plaque localization between men and women. Most frequently lesions were located in left anterior descending (LAD), which was the case for 20 women and 58 men. The mean FFR was 0.76 (0.73–0.86) for women and 0.78 ± 0.12 for men and did not differ significantly (Table 2).

3.2. IVUS

In a subset of 64 patients (16 women and 48 men) parameters were assessed using IVUS (Table 3). Women had a significantly smaller vessel area and plaque area. There were no significant differences in lumen volume, but plaque volume and vessel

TABLE 1 Baseline patient characteristics.

Characteristic	Women ($n = 24$)	Men ($n = 88$)	p-value
Age – mean years	65.17 ± 9.9	64.74 ± 9.6	0.425
Coexisting conditions – no. (%)			
Atrial fibrillation	4 (16.7)	13 (14.8)	0.758
Hypertension	22 (91.7)	72 (81.8)	0.353
Hypercholesterolemia	18 (75.0)	56 (63.6)	0.297
Diabetes mellitus	9 (37.5)	27 (30.7)	0.526
Chronic Kidney Disease	1 (4.2)	11 (12.5)	0.456
Peripheral Artery Disease	3 (12.5)	8 (9.1)	0.700
Heart failure	1 (4.2)	7 (8.0)	1.000
Previous stroke or transient ischemic attack	1 (4.2)	2 (2.3)	0.519
Previous myocardial infarction	15 (62.5)	46 (52.3)	0.373
Active smokers – no. (%)	3 (12.5)	16 (18.2)	0.760
Previous intervention – no. (%)			
Percutaneous Coronary Intervention	19 (79.2)	63 (71.6)	0.458
Coronary Artery Bypass Grafting	0	4 (4.5)	0.576
Medications – no. (%)			
β-blockers	23 (95.8)	84 (95.5)	1.000
Calcium channel blockers	8 (33.3)	23 (26.1)	0.485
ACE-inhibitors	17 (70.8)	59 (67.0)	0.725
ARB	6 (25.0)	17 (19.3)	0.573
Aspirin	22 (91.7)	87 (98.9)	0.115
Clopidogrel	16 (66.7)	55 (62.5)	0.784
Statin	23 (95.8)	85 (96.6)	1.000
NOAC	0	1 (1.1)	1.000
VKA	2 (8.3)	11 (12.5)	0.731

ARB, angiotensin II receptor blocker; NOAC, non-vitamin K antagonist oral anticoagulants; VKA, vitamin K antagonists.

TABLE 2 Angiographic findings.

Plaque location – no. (%)	Women ($n = 27$)	Men ($n = 105$)	p-value
Left main stem	0 (0.0)	5 (4.8)	0.583
Left anterior descending	20 (74.1)	58 (55.2)	0.076
Circumflex	2 (7.4)	13 (12.4)	0.735
Marginal branch	1 (3.7)	5 (4.8)	1.000
Right coronary artery	4 (14.8)	24 (22.9)	0.362
FFR	0.76 (0.73–0.86)	0.78 ± 0.12	0.695

FFR, fractional flow reserve.

volume were significantly greater in men. MLA did not differ between genders. At the MLA site, plaque burden was significantly greater for men than women. The same was true for vessel area, plaque area and average intimal thickness at MLA site.

3.3. OCT

Plaques were classified into calcified, fibrous, mixed and lipidic. The most common type overall was calcified plaque, which was observed in 49 lesions – 17 in women and 32 in men. This plaque type was more common in women than men. Lipidic plaques on the other hand were more prevalent in men than women, but the type most frequently found in men was fibrous type – 37 plaques accounting for 35.9% of plaques (Table 4).

TABLE 3 Lesion characteristic by IVUS.

Variables	Women ($n = 16$)	Men ($n = 48$)	p-value
Lumen volume mm^3	47.1 ± 26.4	56.2 (32.8–97.9)	0.097
Plaque volume mm^3	59.8 ± 35.2	96.3 (52.5–159.1)	0.005
Vessel volume mm^3	106.9 ± 59.8	153.3 (103.0–253.4)	0.015
Lumen area mm^2	5.02 ± 2.16	5.17 (4.09–6.90)	0.198
Vessel area mm^2	11.1 ± 3.3	15 ± 4.6	0.001
Plaque area mm^2	6.04 ± 1.7	9.24 ± 2.89	<0.001
Plaque burden %	55.5 ± 8	61.5 ± 7.7	0.005
At minimal lumen area			
Minimal lumen area mm^2	2.76 (2.1–4.71)	3.12 (2.39–3.96)	0.768
Vessel area mm^2	10.04 ± 3.3	14.22 ± 5.02	0.001
Plaque area mm^2	6.42 ± 2.08	10.67 ± 4.2	<0.001
Plaque burden %	65.03 ± 10.12	74.0 ± 9.26	<0.001
Average intimal thickness mm	0.70 ± 0.18	0.99 ± 0.29	<0.001

The values are provided as mean ± SD or median (IQR).

The lesion characteristics by OCT are presented in Table 5. The length of the lesion did not differ significantly between men and women. Minimal lumen diameter and minimal lumen area did not show any significant differences as well. There were no significant differences in mean, minimal or maximal angle of calcium.

3.4. Follow-up

The clinical follow-up was present for 94 patients (median follow up 122 months, IQR = 107–122 months). Out of them, 25 patients died (26.6%) – 7 women and 18 men, no difference in the overall mortality was found for women vs. men (31.8% vs. 25%, $p = 0.526$). Average survival (in months) did not differ significantly between women and men (94.6 ± 41.9 and 103.51 ± 36.7 respectively; $p = 0.187$). Similarly, there were no significant differences in the number of major adverse cardiac event (MACE), defined as: all-cause death, myocardial infarction, repeated revascularization, stroke and hospitalization due to heart failure (Supplementary Table S1).

There were no significant differences in the mortality rates and survival probability (Figure 4) between men and women. MACE occurrence also did not differ significantly between sexes.

4. Discussion

Enriching a standard CAG with intravascular imaging modalities such as OCT or IVUS allows a more thorough lesion

TABLE 4 Plaque categories by OCT.

Plaque type – no. (%)	Women ($n = 27$)	Men ($n = 103$)	p-value
Calcified	17 (63.0)	32 (31.1)	0.002
Fibrous	8 (29.6)	37 (35.9)	0.541
Mixed	2 (7.4)	19 (18.4)	0.242
Lipidic	0 (0.0)	15 (14.6)	0.04

TABLE 5 Lesion characteristic by OCT.

Variable	Women ($n = 27$)	Men ($n = 105$)	p-value
Length mm	15.57 ± 8.3	11.6 (6.4–17.65)	0.089
Minimal lumen diameter mm	1.39 (0.92–1.48)	1.30 (1.1–1.58)	0.299
Mean lumen area mm^2	3.25 ± 1.23	3.62 (2.81–4.86)	0.035
Minimal lumen area mm^2	1.82 ± 0.83	1.88 (1.46–2.66)	0.131
Mean cap thickness over calcium mm	0.081 ± 0.048	0.12 ± 0.076	0.006
Mean angle of calcium	119 ± 56	95 (69–131)	0.277
Maximal angle of calcium	128 ± 67	96.8 (73.5–172)	0.681
Minimal angle of calcium	112 ± 50	81 (60–112)	0.07
Thrombus no.	3	11	1.000
Cholesterol crystals no.	3	17	0.736
Macrophages no.	3	13	1.000
Presence of TCFA no.	4	19	0.783

analysis and an identification of factors that worsen patients' prognosis e.g., TCFA (20, 21), macrophage infiltration (36) or lipid rich plaques (37).

The results obtained using OCT show a statistically significant difference in the most common type of plaque between sexes. In our study 63% of enrolled women had a calcified plaque, whereas among men such a plaque was present in 31.1% of the cases ($p = 0.002$). Furthermore, lipidic plaque was more common in men ($p = 0.04$).

The prevalence of each plaque type in women vs. men varies between the hitherto studies. A study by Mariani et al. analyzing coronary arteries by OCT in patients with stable CAD (138 men and 42 women) showed a higher percentage of lipid rich plaques and macrophages in women (38). On the other hand, in a study by Giordana et al., women presenting with non-ST segment elevation myocardial infarction (NSTEMI) had a lower prevalence of lipid plaques (39). Similar conclusions were drawn from a study that analyzed 187 non-culprit lesions among patients with CAD, women had overall a lower lipid index and less lipid-core length (40), which is consistent with our findings. In our study the mean age for women and men is 65.17 and 64.74 years respectively. A study by Sato et al. showed, that in the case of a group of patients below the age of 70 years calcifications are present more often among women (41), what is consistent with our results. A study by Kataoka et al. evaluated differences between genders in stable CAD and acute coronary syndromes (ACS) regarding OCT indices. A total number of 320 and 115 lesions in CCS and ACS respectively, were taken into consideration. In women presenting with CAD and ACS a lower prevalence of cholesterol crystals and calcifications was observed (42). The results of the above-mentioned studies and our findings are often contrary, thus proving the need for a more thorough assessment on a larger patients sample in order to develop a more gender specific approach in CAD treatment resulting in better clinical outcomes.

Previous studies concerning gender differences in IVUS plaque morphology have reached similar conclusions. Vessel area has been repeatedly found to be smaller in women than men (43, 44). A study by Kang et al. assessed vessel area and plaque burden at

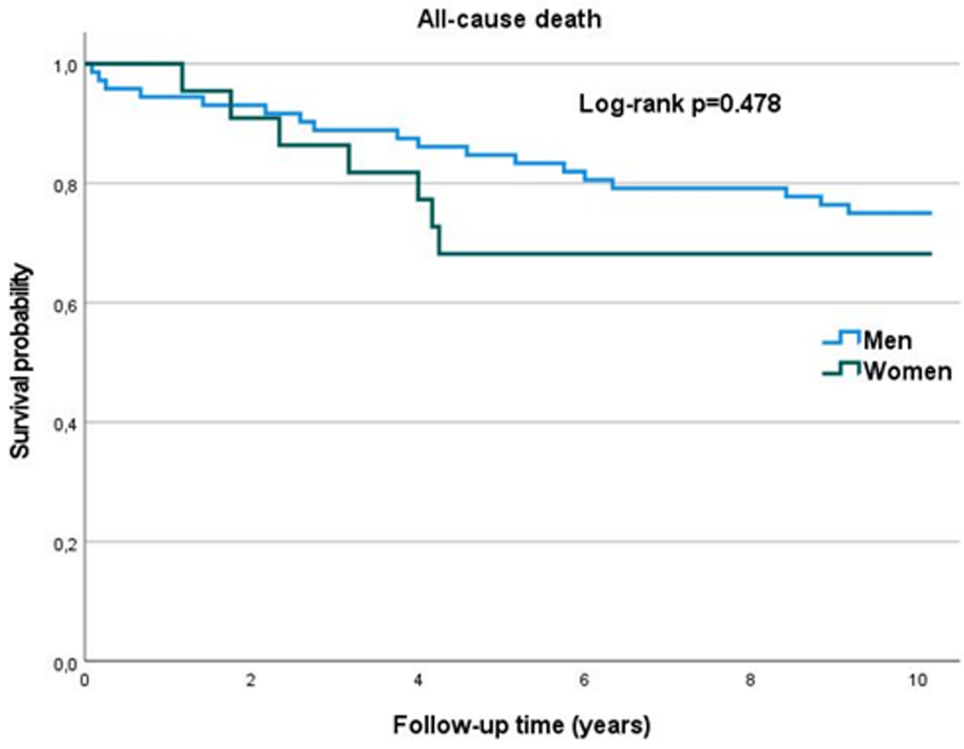

FIGURE 4
Kaplan-Meier curve – overall survival (years).

minimum lumen area (MLA) site with both measurements greater in men (44). The same study as well as Bharadwaj et al. study found that plaque burden was greater in men in reference vessel area (44, 45). The results in our study are consistent with the above. Vessel area and plaque area overall were found to be greater in men than women. At minimal lumen area vessel area, plaque area and plaque burden were also significantly greater in men than women. Moreover, this study has found the average intimal thickness at MLA to be greater in men than women, which was not reported in any previous study concerning this issue.

The main finding of our study concerning FFR was that on average the FFR in patients undergoing CAG due to CAD does not differ significantly by gender. FFR-guided PCI is superior to classical coronary angiography. It allows to identify the hemodynamically significant lesions and therefore, to choose a more adequate treatment strategy (46–48). It was already established, that it is equally beneficial for both male and female patients with CAD, although the FFR below 0.8 has a higher positive prognostic value in men (49). Moreover, the FFR values below 0.8 are associated with a higher risk of death or MI in female patients (50).

The studies to date suggest that with the same grade of stenosis in coronary arteries, women tend to have higher values of FFR (44, 51), which seems to be associated with the size of the body and hence the mass of the heart, and not as it was previously suspected with microvascular dysfunction (44, 52, 53). The composition of the plaque may also impact FFR value. Non-calcified and low-density plaques are associated with lower FFRs in both patients with and without hemodynamically significant narrowing of the vessel (54). A recent study showed that after adjustment for left ventricle mass and plaque characteristics, sex is not an independent factor of FFR value (53). In our population, there were no significant differences in baseline characteristics between genders, including the factors associated with the progression of CAD such as age, HT, or dyslipidemia, which is different in comparison with previously conducted studies. This would stay in line with the conclusions that gender is not an independent factor of FFR values and the higher FFR values in women (49) are due to other differences in populations' characteristics. Even though the plaque composition differed significantly in terms of calcification, the FFR remained on the same levels between sex groups which may suggest that the calcification grade did not significantly impact the outcomes.

It should be noted that our findings have limitations. We conducted a single-center and non-randomized study; thus, it is imperative that further research include more centers and randomization. Moreover, there is a high disproportion between genders as women comprise only 21.4% of the investigated group, thus future research should focus on minimizing that disparity.

Performing a vessel analysis by both OCT and IVUS requires two separate catheters. It is associated with difficulties in an accurate lesion analysis due to an imperfection of image overlapping and carries a higher risk of side effects (55, 56). However, both modalities are complementary with each other, therefore combined catheters were designed, which perform an evaluation of the same area at the same time, enabling a complete vessel wall visualization and precise evaluation (19, 56). Furthermore, during the last few years new diagnostic techniques have been developed in order to assess coronary blood flow disturbances and estimate FFR without using a pressure wire. Such modalities build a three-dimensional artery model based on CAG images. Recent studies proved similar sensitivity and specificity of these techniques in comparison to pressure wire-based FFR (57–61).

5. Conclusions

The presented study did not demonstrate significant differences in FFR values between women and men, yet a higher prevalence of calcific plaques by OCT and lower plaque burden at the MLA site by IVUS was found in women as compared to men.

Data availability statement

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Medical University of Warsaw Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PB and AdP contributed to the conception and design of the study, literature review, writing the initial and final version of the manuscript, data collection, analysis and/or interpretation of data. KG, AB, PD contributed to the literature review, data collection, analysis and/or interpretation of data. MGł, KS, DO contributed to the critical revision of the manuscript, analysis and/or interpretation of data. AR, ArP contributed to the data collection and the critical revision of the manuscript. MGr, JK were responsible for the supervision of the study. MT contributed to the conception and design of the study, critical revision of the manuscript, writing of the final version of the manuscript and was responsible for the supervision of the study. All authors approve the final version and agree to be accountable for all aspects of work ensuring integrity, and accuracy.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2023.1021023/full#supplementary-material

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