American Heart Journal Plus: Cardiology Research and Practice 46 (2024) 100451

Contents lists available at ScienceDirect

American Heart Journal Plus: Cardiology Research and Practice

journal homepage: www.sciencedirect.com/journal/american-heart-journal-plus-cardiology-research-and-practice

Short communication

Age-specific sex differences in intravascular ultrasound based coronary atherosclerotic plaque characteristics

Jurgen Ligthart [a,1], Marie de Bakker [a,1,*], Karen Witberg [a], Folkert ten Cate [a], Hester den Ruijter [b], Joost Daemen [a], Nicolas M. Van Mieghem [a], Eric Boersma [a,*]

[a] Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[b] Laboratory of Experimental Cardiology, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Coronary artery disease
Sex differences
Plaque characteristics
IVUS
Intravascular ultrasound

ABSTRACT

Insights in age- and sex-specific coronary atherosclerotic plaque characteristics may contribute to a better understanding of coronary artery disease and, ultimately, to its prevention and treatment. In 307 women and 406 men aged 20 to 90 years undergoing intravascular ultrasound imaging, sex-based differences in coronary atherosclerotic plaque characteristics were mainly present in younger patients, while these differences were less pronounced at advanced age.

1. Introduction

It is well known that the genesis and manifestation of coronary artery disease (CAD) differ between women and men. For example, smoking, a common CAD risk factor, has a different impact in women as compared to men [1]. Also, CAD risk in women is influenced by female-specific factors, such as endogenous estrogen levels, and pregnancy-induced cardiometabolic complications [1]. Moreover, women develop symptomatic CAD approximately five to ten years later than men. As a consequence, sex-differences are expected in the lifetime development of coronary atherosclerotic plaques.

Over the past decades, intravascular ultrasound (IVUS) imaging has emerged as a valuable tool for studying atherosclerotic plaque characteristics *in vivo* [2]. Nonetheless, previous studies focusing on age-specific sex differences in atherosclerotic plaque characteristics using IVUS are scarce, generally performed in middle-aged or elderly populations, and women were typically underrepresented [3]. In the current study, we investigated the atherosclerotic plaque characteristics of 307 women and 406 men with an age-range of 20 to 90 years undergoing IVUS imaging. Insights in age- and sex-specific coronary atherosclerotic plaque characteristics may contribute to a better understanding of CAD and, ultimately, to its prevention and treatment.

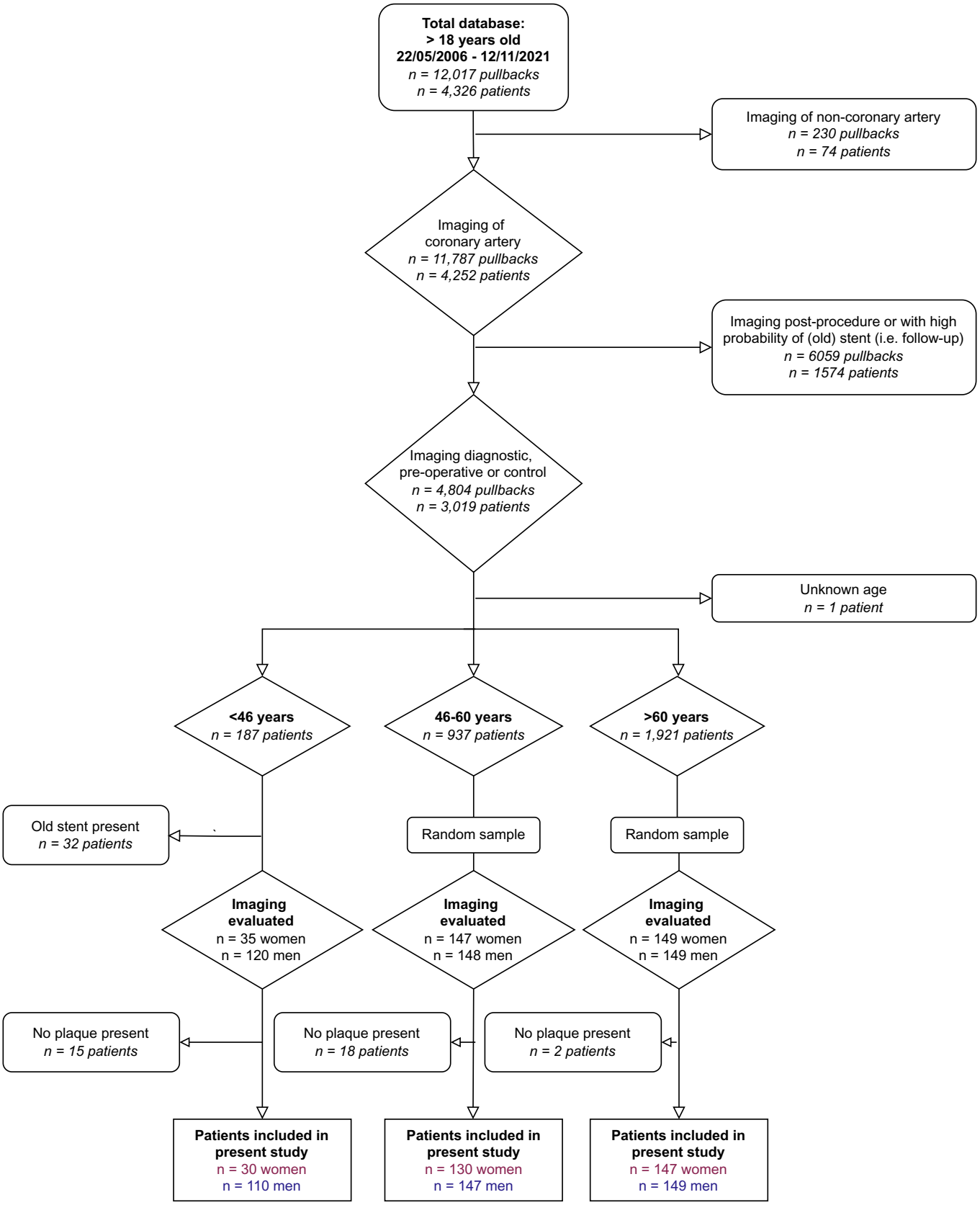
2. Methods

Between May 2006 and November 2021, 3019 patients with presumed or established CAD, aged ≥18 years, underwent invasive IVUS imaging of a non-culprit or yet to be treated coronary artery in our academic tertiary referral hospital. We stratified these patients into three pragmatically determined age groups: <46, 46 to 60 and >60 years. For each age group we then selected all available women and men, or a random selection of $N = 150$ from both sexes (Fig. 1). Imaging data were collected during routine practice. All patients provided written informed consent for use of their data in future analyses.

Greyscale IVUS examination was performed with 20 mHz to 60 mHz IVUS catheters, and motorized pullbacks were performed at 0.5 to 2.5 mm/s. Average length of the imaged sections was 6.1 cm. IVUS analysis was performed by two experienced observers (KW and JL), who reached consensus. If multiple pullbacks were performed, only the first was analyzed, and if multiple arteries were imaged, the culprit-containing artery was analyzed. Patients devoid of any atherosclerotic plaque in the analyzed pullbacks were excluded from current analyses. Plaque characteristics throughout the entire length of each pullback were scored as 'present' or 'absent', regardless of their frequency, while the length of the imaged segment was considered in the statistical models. Plaques were classified in accordance with definitions in the American

* Corresponding author at: Department of Cardiology, Erasmus MC, University Medical Center Rotterdam, Room Na-317, P.O. Box 2040, 3000 CA Rotterdam, the Netherlands.
E-mail address: h.boersma@erasmusmc.nl (E. Boersma).
[1] The first two authors contributed equally to the study.

https://doi.org/10.1016/j.ahjo.2024.100451
Received 6 June 2024; Accepted 28 August 2024
Available online 30 August 2024



(caption on next page)

Fig. 1. Flow chart of patient selection.
Between May 2006 and November 2021, 4326 patients aged ≥18 years underwent invasive IVUS imaging in our academic tertiary referral hospital, with subsequent storage of images in a dedicated database for offline analysis. We used the data to select patients who underwent invasive IVUS imaging of a non-culprit or yet to be treated coronary artery (*i.e.*, pullbacks that were labeled as 'diagnostic', 'pre-operative' or 'control' imaging of a coronary artery). Conversely, those who underwent invasive IVUS imaging of treated coronary arteries or exhibited a high probability of an old stent presence were excluded (*i.e.*, pullback that were labeled as 'post-operative' or 'follow-up'). Subsequently, patients were stratified into three pragmatically determined age groups: <46, 46 to 60 and >60 years. A sample size of 150 women and 150 men per age group was deemed necessary to achieve a statistically significant level of power, while effectively minimizing the risk of type II errors. As such, we included all available women and men (<46 years), or a random selection of $N = 150$ from both sexes (46 to 60 years and >60 years) per age group. The selected images were analyzed by two experienced observers. Finally, patients devoid of any atherosclerotic plaque in the analyzed pullbacks were excluded from in the current study.

College of Cardiology (ACC) expert consensus document of IVUS[2] as calcified, soft (echolucent) and/or fibrous, whereas the presence of thrombus and plaque rupture was assessed (Fig. 2). Clinical data were obtained from hospital patient files.

To investigate potential sex differences in atherosclerotic plaque characteristics across the three age groups, logistic regression models were performed. Interaction terms (sex * age group) were used to estimate the associations in the three age groups separately. Analyses were adjusted for smoking status, hypertension, family history, estimated glomerular filtration rate, clinical presentation, year of imaging procedure, and length of the imaged segment. Statistical analyses were performed using R version 4.1.2. A two-sided *p*-value <0.05 was considered statistically significant.

3. Results

Clinical characteristics were largely similar between women and men (Table 1), except that women had a lower estimated glomerular filtration rate (76 *versus* 83 mL/min/1.73 m^2, $P = 0.001$), were less often smokers (27 % *versus* 34 %, $P = 0.037$), and more often had hypertension (65 % *versus* 51 %, $P < 0.001$). These differences were most evident in the youngest patients (aged <46 years). Patients in the higher age groups had a higher proportion of comorbidities, such as hypertension and dyslipidemia, in both sexes.

The age-specific sex differences in atherosclerotic plaques are illustrated in Fig. 2. The presence of calcification was higher in the higher age groups (*i.e.*, 46 to 60 years *versus* <46 years as well as >60 years *versus* 46 to 60 years) in both sexes. Yet, the prevalence of calcification was higher in men than in women aged <46 years and 46 to 60 years, but these sex-related differences were not seen in patients >60 years. The presence of fibrous and soft (echolucent) plaques was numerically higher in men at young age as compared to women at young age, but sex differences did not reach statistical significance. The presence of intracoronary thrombus was similar in women and men aged <46 years, and significantly more prevalent in men compared to women aged 46 to 60 years and >60 years. The presence of plaque rupture was significantly different between women and men aged 46 to 60 years, with men showing more plaque ruptures than women.

Results were similar when patients were stratified based on their clinical presentation (*i.e.*, stable CAD *versus* acute coronary syndrome [ACS]), and when only the culprit vessel was studied (data not shown). Moreover, when patients were stratified based on relatively older age (≤75 years and >75 years), no significant differences were observed (Supplemental Fig. S1).

4. Discussion

In this study of patients undergoing IVUS imaging of an untreated coronary segment, calcified plaques were more frequently observed in men than in women in both groups aged 60 years and younger, and thrombi and plaque ruptures were more frequently observed in men aged between 46 and 60 years. In addition, below the age of 46, fibrous and soft (echolucent) plaques were numerically more often seen in men than in women. In patients older than 60 years, sex differences in plaque composition were less pronounced, although the presence of thrombus remained higher in men. These findings are largely in agreement with previous imaging studies using various (intravascular) techniques, showing sex-based differences in atherosclerotic plaque composition in younger patients with CAD, while these differences disappeared at older age [3–5]. Nonetheless, previous studies are generally performed in middle-aged or elderly populations, and women are typically underrepresented. To the best of our knowledge, this is the first study that encompasses such a broad age range in both women and men and that included a substantial portion (40 %) of women. A recent study in patients with an ACS, who underwent optical coherence tomography imaging of the culprit lesion, reported an age-related increase of vulnerable plaque characteristics in women, but not in men [6]. We and Sing et al. reported similar age-related trends in atherosclerotic plaque composition of patients with peripheral or carotid artery disease, respectively [7,8].

The lower prevalence of coronary calcifications that we observed in women aged 60 years and younger, in particular in those below the age of 46, may likely be explained by high levels of endogeneous estrogen until early after menopause [9]. Beside the loss of cardioprotective effects of female sex hormones after menopause, risk factors such as hypertension and chronic kidney disease are more prevalent in elderly individuals, which might enhance the development of calcified plaques [10]. Moreover, a higher prevalence in the presence of thrombus and plaque ruptures was observed in women aged 60 years and older compared to women aged 45 to 60 years, suggesting an age effect, while such a pattern was not observed in men. No differences in the presence of thrombus were observed between women and men at younger ages. Burke et al. reported that plaque erosion, the major substrate for thrombosis in premenopausal women, does not appear to be inhibited by estrogen [11]. Presumably this could explain why we did not find any differences in the presence of thrombus between young men and women. Nonetheless, it should be kept in mind that differences in the prevalence of thrombus and plaque ruptures between women and men may be linked to differences in clinical presentation. In patients experiencing an ACS, coronary arteries are more inclined to exhibit vulnerable plaque attributes, such as thrombi and plaque ruptures, compared to those with stable CAD [12]. Nevertheless, the age-specific sex differences in plaque composition observed in the current study persisted when patients were stratified based on their clinical presentation, and when only the culprit vessel was studied.

The key strength of this study is that it provides an IVUS based analysis of sex differences in atherosclerotic coronary plaque characteristics over the young to late adulthood life course. To the best of our knowledge, this is the first study that encompasses such a broad age range in both women and men. Also, in contrast to other landmark studies in the field [3–5], a substantial portion (40 %) of women was included. Nonetheless, our study has inherent limitations. First, patients in the current study were referred for invasive coronary imaging during routine practice, and IVUS use was per operator discretion. Nonetheless, it's important to highlight that all patients undergoing IVUS in our hospital have been systematically included in our database since 2006, without any exclusion criteria. This practice ensures that our dataset encompasses a comprehensive representation of patients undergoing IVUS, minimizing the risk of selection bias. All in all, generalization of our findings beyond a clinical setting that is less IVUS-oriented should be

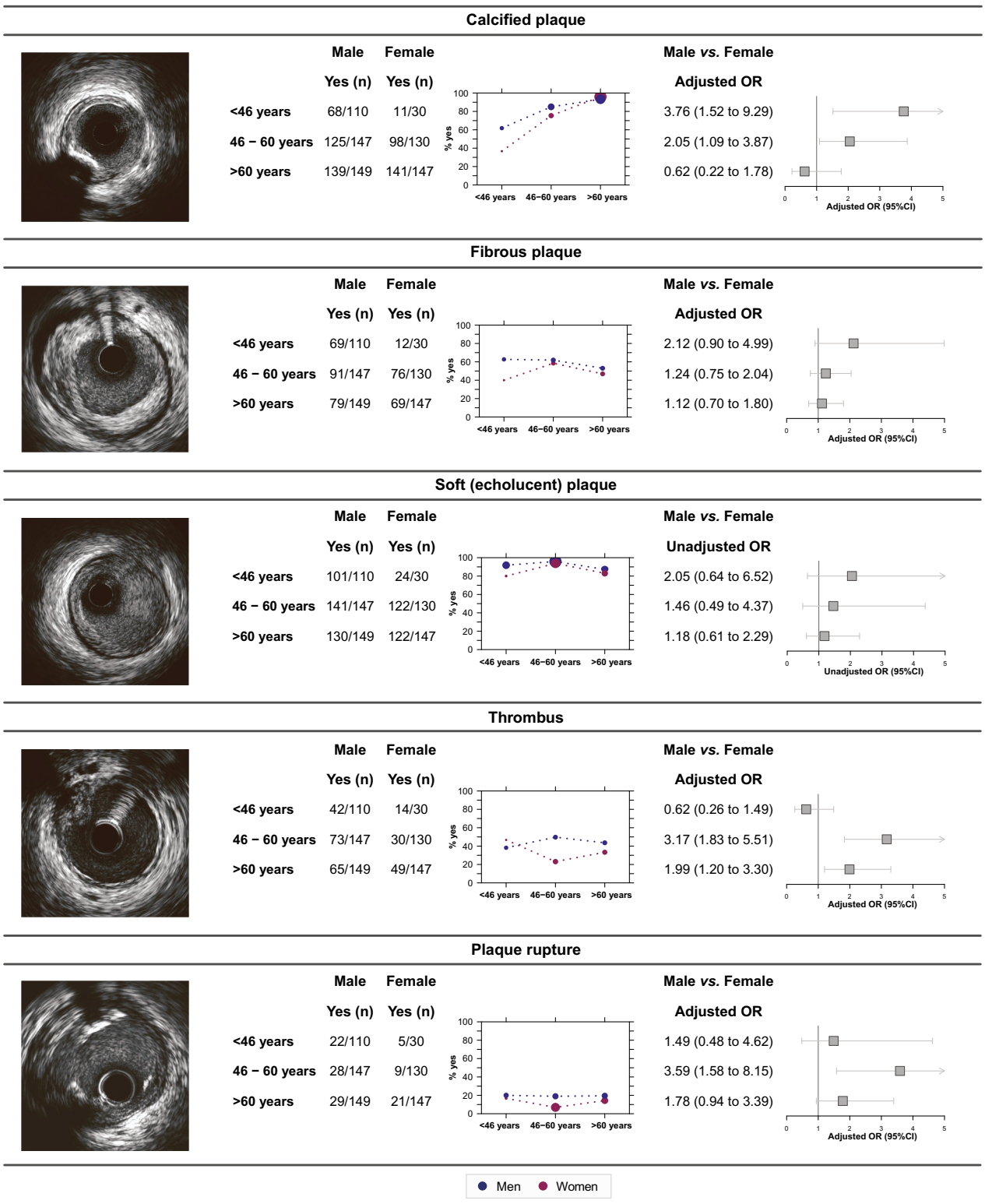


Fig. 2. Sex differences in coronary atherosclerotic plaque characteristics across age groups.
Analyses were adjusted for smoking status, hypertension, family history, estimated glomerular filtration rate, clinical presentation, year of imaging procedure, and length of imaged segment. To avoid risk of overfitting, the association between sex and the presence of fibrous plaques was only adjusted for year of imaging procedure and length of imaged segment. The size of data points is depicted relative to 1 divided by the standard error, where larger points indicate relatively less variance, while smaller points represent relatively higher variance.

done with caution. Second, while our study included all women below the age of 46, it cannot fully be excluded that a lack of statistical power may have contributed to the potential underestimation of sex-based differences within this age group. Third, although IVUS imaging was standardized and conducted according to the ACC expert consensus standards, the procedure was not performed for the very purpose of this study, and, consequently, sex-based differences in coronary plaque characteristics may have remained undetected. Moreover, although the

Table 1
Clinical characteristics of patient population.

Patient characteristics	All	All	P-value	<46 years	<46 years	P-value	46–60 years	46–60 years	P-value	>60 years	>60 years	P-value
	Men	Women		Men	Women		Men	Women		Men	Women	
	n = 406	n = 307		n = 110	n = 30		n = 147	n = 130		n = 149	n = 147	
Age (years)	57.1 (13.5)	62.4 (12.9)	**<0.001**	41.2 (5.4)	40.6 (5.8)	0.592	54.4 (4.4)	54.7 (4.1)	0.49	71.5 (7.1)	73.6 (6.9)	**0.011**
Body mass index (kg/m^2)	27.9 (4.7)	27.3 (5.1)	0.156	27.8 (5.2)	27.9 (4.8)	0.952	28.2 (4.7)	27.5 (5.4)	0.322	27.7 (4.3)	27.0 (4.8)	0.251
eGFR, median [IQR]	83.0 (22.2)	76.0 (24.2)	**0.001**	97.0 (22.0)	87.5 (27.7)	0.078	86.6 (17.0)	83.2 (21.7)	0.195	69.2 (19.1)	65.6 (21.8)	0.207
Smoker (% yes)	138 (34.2)	81 (26.6)	**0.037**	65 (59.1)	9 (31.0)	**0.013**	61 (42.1)	51 (39.5)	0.762	12 (8.1)	21 (14.4)	0.129
Diabetes mellitus (% yes)	72 (17.9)	68 (22.4)	0.164	12 (10.9)	8 (27.6)	**0.048**	27 (18.6)	26 (20.2)	0.867	33 (22.3)	34 (23.3)	0.949
Hypertension (% yes)	202 (50.5)	198 (65.3)	**<0.001**	36 (33.6)	16 (55.2)	0.057	69 (47.6)	75 (58.6)	0.09	97 (65.5)	107 (73.3)	0.189
Dyslipidemia (% yes)	180 (45.2)	151 (50.5)	0.192	42 (39.6)	9 (31.0)	0.529	61 (42.1)	61 (48.4)	0.355	77 (52.4)	81 (56.2)	0.586
Family history (% yes)	144 (35.7)	86 (28.6)	0.054	58 (52.7)	11 (39.3)	0.290	51 (35.2)	54 (42.2)	0.287	35 (23.6)	21 (14.5)	0.065
Clinical presentation												
Clinical presentation (%)			0.405			0.065			0.504			0.123
§ Stable	230 (56.8)	183 (60.2)		46 (42.2)	19 (63.3)		81 (55.1)	76 (59.8)		103 (69.1)	88 (59.9)	
§ ACS	175 (43.2)	121 (39.8)		63 (57.8)	11 (36.7)		66 (44.9)	51 (40.2)		46 (30.9)	59 (40.1)	
Diagnosis (%)			0.126			**0.012**			0.195			**0.021**
§ Stable AP	152 (44.8)	115 (44.4)		35 (31.8)	19 (63.3)		50 (46.3)	50 (49.5)		67 (55.4)	46 (35.9)	
§ UAP	24 (7.1)	28 (10.8)		14 (12.7)	5 (16.7)		3 (2.8)	10 (9.9)		7 (5.8)	13 (10.2)	
§ STEMI	82 (24.2)	44 (17.0)		39 (35.5)	4 (13.3)		24 (22.2)	19 (18.8)		19 (15.7)	21 (16.4)	
§ NSTEMI	51 (15.0)	42 (16.2)		17 (15.5)	2 (6.7)		21 (19.4)	13 (12.9)		13 (10.7)	27 (21.1)	
§ Other	30 (8.8)	30 (11.6)		5 (4.5)	0 (0.0)		10 (9.3)	9 (8.9)		15 (12.4)	21 (16.4)	
Imaging and vessel characteristics												
Moment of imaging (%)			0.973			0.637			**0.008**			0.398
§ Diagnostic	161 (39.7)	123 (40.1)		59 (53.6)	14 (46.7)		58 (39.5)	73 (56.2)		44 (29.5)	36 (24.5)	
§ Pre-procedure	245 (60.3)	184 (59.9)		51 (46.4)	16 (53.3)		89 (60.5)	57 (43.8)		105 (70.5)	111 (75.5)	
Vessel (%)			0.227			0.303			0.305			0.124
§ LAD	240 (59.1)	185 (60.3)		63 (57.3)	20 (66.7)		92 (62.6)	70 (53.8)		85 (57.0)	95 (64.6)	
§ LCX	93 (22.9)	56 (18.2)		25 (22.7)	3 (10.0)		28 (19.0)	28 (21.5)		40 (26.8)	25 (17.0)	
§ RCA	73 (18.0)	66 (21.5)		22 (20.0)	7 (23.3)		27 (18.4)	32 (24.6)		24 (16.1)	27 (18.4)	
Culprit vessel (% yes)	258 (63.7)	187 (60.9)	0.494	55 (50.0)	16 (53.3)	0.906	98 (67.1)	60 (46.2)	0.001	105 (70.5)	111 (75.5)	0.398

A P-value <0.05 is considered statistically significant and presented in bold typeface. Abbreviations: ACS, acute coronary syndrome; AP, angina pectoris; eGFR, estimated glomerular filtration rate; LAD, left anterior descending; LCX, left circumflex artery; UAP, unstable angina pectoris; RCA, right coronary artery. Missingness <5 % for all variables, except for body mass index (22.6 %), eGFR (23.7 %), and diagnosis (16.1 %).

analyses were adjusted for the length of the imaged segment, data on plaque burden were not available in the current study. Therefore, it cannot be excluded that differences in plaque characteristics may be due to variations in plaque burden. Finally, the findings in the current study are based on a single assessment per patient, while repeated measurements over the life course could provide additional insights into the sex-specific effects of aging on coronary atherosclerotic plaque compositions.

In conclusion, sex-based differences in coronary atherosclerotic plaque characteristics are mainly observed in younger patients and were less pronounced at advanced age.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2024.100451.

Ethical statement

All procedures were performed in compliance with relevant laws and institutional guidelines. Data were collected during routine practice and all patients provided written informed consent for use of their data in future analyses.

CRediT authorship contribution statement

Jurgen Ligthart: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review & editing. **Marie de Bakker:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Karen Witberg:** Conceptualization, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review &

editing. **Folkert ten Cate:** Conceptualization, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Hester den Ruijter:** Conceptualization, Writing – review & editing. **Joost Daemen:** Conceptualization, Writing – review & editing. **Nicolas M. Van Mieghem:** Conceptualization, Writing – review & editing. **Eric Boersma:** Conceptualization, Formal analysis, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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.

References

[1] Y. Appelman, B.B. van Rijn, M.E. ten Haaf, E. Boersma, S.A.E. Peters, Sex differences in cardiovascular risk factors and disease prevention, Atherosclerosis 241 (1) (2015) 211–218.

[2] G.S. Mintz, S.E. Nissen, W.D. Anderson, S.R. Bailey, R. Erbel, P.J. Fitzgerald, et al., American College of Cardiology Clinical Expert Consensus Document on standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies (IVUS). A report of the American College of Cardiology Task Force on clinical expert consensus documents, J. Am. Coll. Cardiol. 37 (5) (2001) 1478–1492.

[3] J. Chandrasekhar, R. Mehran, Sex-based differences in acute coronary syndromes: insights from invasive and noninvasive coronary technologies, JACC Cardiovasc. Imaging 9 (4) (2016) 451–464.

[4] L. Wang, G.S. Mintz, B. Witzenbichler, D.C. Metzger, M.J. Rinaldi, P.L. Duffy, et al., Differences in underlying culprit lesion morphology between men and women, JACC Cardiovasc. Imaging 9 (4) (2016) 498–499.

[5] S.H. Ann, C. De Jin, G.B. Singh, K.H. Lim, J.W. Chung, S. Garg, et al., Gender differences in plaque characteristics of culprit lesions in patients with ST elevation myocardial infarction, Heart Vessel. 31 (11) (2016) 1767–1775.

[6] L.M. Seegers, M. Araki, A. Nakajima, T. Yonetsu, Y. Minami, J. Ako, et al., Sex differences in culprit plaque characteristics among different age groups in patients with acute coronary syndromes, Circulation: Cardiovasc. Interv. 15 (6) (2022) e011612.

[7] M. de Bakker, N. Timmerman, I.D. van Koeverden, D.P.V. de Kleijn, G.J. de Borst, G. Pasterkamp, et al., The age- and sex-specific composition of atherosclerotic plaques in vascular surgery patients, Atherosclerosis 310 (2020) 1–10.

[8] N. Singh, A.R. Moody, B. Zhang, I. Kaminski, K. Kapur, S. Chiu, et al., Age-specific sex differences in magnetic resonance imaging-depicted carotid intraplaque hemorrhage, Stroke 48 (8) (2017) 2129–2135.

[9] H.J. Woodward, D. Zhu, P.W.F. Hadoke, V.E. MacRae, Regulatory role of sex hormones in cardiovascular calcification, Int. J. Mol. Sci. 22 (9) (2021).

[10] F. Giallauria, C. Vigorito, N. Ferrara, L. Ferrucci, Cardiovascular calcifications in old age: mechanisms and clinical implications, Curr. Transl. Geriatr. Exp. Gerontol. Rep. 2 (4) (2013) 255–267.

[11] A.P. Burke, A. Farb, G. Malcom, R. Virmani, Effect of menopause on plaque morphologic characteristics in coronary atherosclerosis, Am. Heart J. 141 (2 Suppl) (2001) S58–S62.

[12] H. Myeong-Ki, S.M. Gary, L. Cheol Whan, K. Young-Hak, L. Seung-Whan, S. Jong-Min, et al., Comparison of coronary plaque rupture between stable angina and acute myocardial infarction, Circulation 110 (8) (2004) 928–933.