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Sex differences in independent factors associated with coronary artery disease

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Summary
Background Women undergoing coronary angiography (CA) due to chest pain are more likely to present with less extensive coronary artery disease (CAD) than men, which might be attributed to different effects of cardiovascular risk factors on coronary atherogenesis between sexes. The aim of the present study was to evaluate sex differences in independent factors associated with obstructive and non-obstructive CAD in a large consecutive cohort of patients undergoing elective CA.

Methods Data from 7819 patients (2653 women and 5184 men), including cardiovascular risk factors, clinical presentation, CAD severity and treatment decisions were analysed.

Results Women were older than men (65 ± 11 vs. 63 ± 11 years, $p<0.001$); low-density lipoprotein cholesterol (LDL; 125 ± 38 vs. 122 ± 37 mg/dL, $p<0.001$) and high-density lipoprotein cholesterol (HDL) cholesterol levels (62 ± 18 vs. 51 ± 15 mg/dL, $p<0.001$) were higher in women; and smokers were more frequently men (14.4 vs. 20.1 %, $p<0.001$). Men more frequently had an obstructive CAD (41.1 vs. 65.6 %, $p<0.001$). Multivariable analyses revealed age, HDL cholesterol, hypercholesterolaemia, diabetes mellitus, arterial hypertension and a positive family history being associated with *obstructive CAD* in both sexes, whereas smoking was independently associated with obstructive CAD only in women. The association of hypercholesterolaemia with obstructive CAD was stronger in men. For *non-obstructive CAD*, no sex-specific associated factors could be identified.

Conclusion The impact of smoking and hypercholesterolaemia on coronary atherosclerosis is different between women and men. This might be taken into account when planning individual interventions to reduce cardiovascular risk.

Keywords Sex differences · Coronary artery disease · Cardiovascular risk factors · Chest pain

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Geschlechtsunterschiede in mit koronarer Herzkrankheit unabhängig assoziierten Risikofaktoren

Zusammenfassung
Hintergrund Bei Frauen, die sich aufgrund von Brustschmerzen einer Koronarangiographie unterziehen müssen, findet sich im Vergleich zu Männern seltener eine relevante koronare Herzkrankheit (KHK). Dies könnte auf den unterschiedlichen Einfluss kardiovaskulärer Risikofaktoren auf die KHK bei Frauen und Männern zurückzuführen sein. Das Ziel der aktuellen Studie lag darin, geschlechtsspezifische Unterschiede in unabhängig mit signifikanter und nicht-signifikanter KHK assoziierten Faktoren in einem großen konsekutiven Patientenkollektiv, bei dem eine elektive Koronarangiographie durchgeführt wurde, zu untersuchen.

Methoden Von 7819 Patienten ($n=2653$ Frauen, $n=5184$ Männer) wurden kardiovaskuläre Risikofaktoren, die klinische Präsentation, die Schwere der KHK und therapeutische Entscheidungen analysiert.

Resultate Frauen waren älter als Männer (65 ± 11 vs. 63 ± 11 Jahre, $p<0{,}001$), LDL- (125 ± 38 vs. 122 ± 37 mg/dL, $p<0{,}001$) und HDL-Cholesterin Werte (62 ± 18 vs. 51 ± 15 mg/dL, $p<0{,}001$) waren höher bei Frauen, Rauchen fand sich häufiger bei Männern (14,4 vs. 20,1 %, $p<0{,}001$). Bei Männer wurde häufiger eine signifikante KHK diagnostiziert (41,1 vs. 65,6 %, $p<0{,}001$). In multivariablen Analysen waren das Alter, das HDL-Cholesterin, eine Hypercholesterinämie, ein Diabetes mellitus, eine arterielle Hypertonie und eine positive Familienanamnese mit dem Vorliegen einer signifikanten KHK bei beiden Geschlechtern assoziiert. Rauchen war nur bei Frauen unabhängig mit einer signifikanten KHK korreliert. Die Assoziation von Hypercholesterinämie mit einer signifikanten KHK war bei Männern stärker ausgeprägt. Für die nicht-signifikante KHK konnten keine Geschlechtsunterschiede in den unabhängig assoziierten Faktoren identifiziert werden.

Schlussfolgerung Der Einfluss von Rauchen und Hypercholesterinämie auf eine KHK ist bei Frauen und Männern unterschiedlich. Dies könnte zukünftig bei der Planung von individuellen Interventionen zur Reduktion des kardiovaskulären Risikos berücksichtigt werden.

Schlüsselwörter Geschlechtsunterschiede · Koronare Herzkrankheit · Kardiovaskuläre Risikofaktoren · Brustschmerzen

Introduction

Women undergoing coronary angiography (CA) due to chest pain are more likely to present with less extensive coronary artery disease (CAD) than men [1, 2]. Patients with evidence of myocardial ischaemia and non-obstructive CAD are more likely to be women [3]. Compared with men, non-obstructive CAD is associated with higher risk for future acute coronary syndromes in women [4]. These findings might be attributed to different effects of cardiovascular risk factors on coronary atherogenesis between women and men, probably resulting in different treatment and cardiovascular risk management strategies between sexes. The aim of the present analysis was to evaluate whether sex differences in independent factors associated with obstructive and non-obstructive CAD exist in a large consecutive cohort of patients undergoing elective (non-acute) CA due to suspected CAD.

Patients, materials and methods

Data from 7819 consecutive elective patients referred to our institution (tertiary University Hospital) for CA for the evaluation of CAD were collected in a risk factor screening programme between February 2004 and March 2008. All patients routinely gave written informed consent for CA, which was performed according to standard Judkins' technique [5]. Patients referred for primary or acute percutaneous coronary intervention (PCI) as well as patients prior to planned organ transplantation (liver, kidney and lung) and patients with congenital heart disease, intended to undergo valve repair/replacement and after heart transplantation, were excluded from this analysis.

The study was performed according to the Declaration of Helsinki, and the study protocol was approved by the ethics committee of Innsbruck Medical University (EC number UN3266).

Risk factor assessment

Cardiovascular risk factors were assessed by questionnaire (filled out by the treating physician) and blood chemistry. Hypertension was defined as suggested by the seventh report of the "Joint National Committee" [6]. Diabetes mellitus was defined according to the criteria of the American Diabetes Association [7]. A positive family history for premature CAD was present when a first-degree relative suffered a myocardial infarction before the age of 55 years (male) or 65 years (female), respectively [8]. Smokers were defined as subjects who had smoked regularly within the previous 12 months. Hypercholesterolaemia was defined as being under statin therapy or if low-density lipoprotein cholesterol (LDL) cholesterol levels were ≥ 130 mg/dL. Total cholesterol, LDL, high-density lipoprotein cholesterol (HDL) and triglyceride levels were determined by routine blood chemistry as well as C-reactive protein (CRP) concentration by immunoturbidimetric assay (Roche Diagnostics). The height and weight were obtained to calculate the body mass index (BMI).

Medical history

The clinical presentation (stable/unstable angina pectoris according to the Canadian Cardiovascular Society (CCS) angina classification [9], atypical or no chest pain), the former medical history including recent (within 6 months) or prior (more than 6 months ago) myocardial infarctions or any revascularisations (PCI or coronary artery bypass grafting (CABG)) and prior valve repair/replacement and therapeutic decisions (optimal medical treatment alone, CABG, ad hoc PCI and ad hoc undefined) according to angiographic results were recorded.

Clinical presentation

Stable angina pectoris was defined as chest pain or discomfort that typically occurs with activity or stress—according to CCS angina class I, II or III.

Unstable angina pectoris was defined as new or increasing chest pain or discomfort that also occurs at

rest or with less exertion and that could be less responsive to medication—according to CCS angina class IV.

Pain located in a small area of the left chest or pain felt outside the chest (e.g. neck and jaw pain), not related to physical activity, was assumed to be atypical angina pectoris. Furthermore, weakness, fatigue, palpitations, nausea or dyspnoea were included in this definition [10].

History of myocardial infarction

Patients being referred for elective CA after conservative therapy of ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI) were defined as recent STEMI and recent NSTEMI. All patients with STEMI or NSTEMI in their medical history, which was not the current reason for referral to CA, were defined as prior myocardial infarction.

Scoring of coronary angiograms

Significant CAD was defined as ≥70 % lumen diameter reduction of more than one major epicardial coronary artery at visual estimation. Coronary angiograms were reviewed by an experienced interventional cardiologist as it is done in daily clinical practice. Patients were classified as having single vessel (1-VD), two vessel (2-VD) or multivessel (3-VD) disease, as having non-significant CAD (defined as lumen irregularities <70 % lumen diameter reduction) or non-CAD (no lumen irregularities).

Statistical analysis

All analyses were conducted with the use of statistical software (SPSS® for Windows, version 18 or 19). Data are expressed as means ± standard deviations or as frequencies (percentages). Due to the large sample size, histograms were used to test for normal distribution. To compare categorical variables, chi-square test was used. For continuous variables, Student's *t* test or Mann–Whitney *U* test were used as appropriate. A two-sided *p*-value <0.05 was considered statistically significant. Analyses were performed in the overall study population and after dividing the overall cohort in three groups: obstructive, non-obstructive and non-CAD. We predefined the following covariates that potentially influence the extent of CAD: age, female sex, total cholesterol, LDL cholesterol, HDL cholesterol, CRP, triglycerides, BMI and estimated glomerular filtration rate (eGFR); as dichotomous variable, hypercholesterolaemia, diabetes mellitus, arterial hypertension, smoking, positive family history, stable/unstable/atypical angina and prior statin use were employed. After bivariate correlation analyses, total cholesterol, which was correlated with LDL cholesterol, and prior statin use, which was correlated with hypercholesterolaemia, were excluded from multivariable analyses. In the first step, multivariable logistic regression analysis was used to assess the relation between sex and the presence of different extents of CAD (obstructive and non-obstructive CAD) adjusted for the aforementioned covariates, thereby estimating odds ratios (OR) and the accompanying 95 % confidence interval (CI). To test for possible effect modifiers, the interaction terms for sex with age, LDL cholesterol, HDL cholesterol, CRP, triglycerides, BMI, eGFR, hypercholesterolaemia, diabetes mellitus, arterial hypertension and smoking were assessed in the models.

In the second step, multivariable logistic regression analysis was used separately for women and men, with the aforementioned covariates (except sex) to assess the relation between these covariates and the extent of CAD. Cases with missing data were not included in multivariable analyses.

Results

The clinical and demographic characteristics, cardiovascular risk factors, angiographic results and treatment decisions of the overall study population are displayed in Table 1. Sex differences in risk factors were found for smoking and a positive family history for premature cardiovascular disease. Total, LDL and HDL cholesterol levels were higher in women, whereas no sex differences were found in CRP levels. Comparisons of the clinical presentation revealed that men more often had no angina pectoris and women reported more often atypical angina. At CA, men more frequently had a significant CAD. Hence, the overall PCI rate was higher in men.

Given the sex comparisons in the overall population, we separated patients with obstructive CAD from those with non-obstructive and non-CAD for further analyses. In patients with *obstructive CAD*, the rate of PCI and optimal medical treatment alone was similar in women and men, despite several differences in risk factors or clinical presentation (Table 2). The comparisons of clinical and demographic characteristics, cardiovascular risk factors, angiographic results and treatment decisions in patients with *non-obstructive and non-CAD* are also displayed in Table 2.

Obstructive vs. non-CAD

Multivariable analysis revealed that female sex, HDL cholesterol, BMI and atypical angina were inversely associated with obstructive CAD (Table 3). Age, CRP, the presence of hypercholesterolaemia, diabetes mellitus, arterial hypertension, smoking, a positive family history and unstable angina were found to be positively associated with obstructive CAD. When analysing women and men separately, age, HDL cholesterol, hypercholesterolaemia, diabetes mellitus, arterial hypertension, a positive family history, and atypical angina were independently associated with obstructive CAD in both sexes. Smoking was associated with obstructive CAD in women but

Table 1 Clinical characteristics and risk factors in the total study population and in women vs. men

	Total ($n=7819$)	Women ($n=2635$)	Men ($n=5184$)	p (Women vs. men)
Age (years)	64 ± 11	65 ± 11	63 ± 11	< 0.001
Arterial hypertension (%)	78.6	79.2	78.3	0.35
Hypercholesterolaemia (%)	60.7	60.3	60.9	0.57
Smoking (%)	18.1	14.4	20.1	< 0.001
Positive family history (%)	22.5	26.4	20.5	< 0.001
Diabetes mellitus (%)	17.1	17.5	17.0	0.58
Total cholesterol (mg/dL)	193 ± 45	200 ± 45	189 ± 44	< 0.001
LDL cholesterol (mg/dL)	123 ± 38	125 ± 38	122 ± 37	< 0.001
HDL cholesterol (mg/dL)	55 ± 17	62 ± 18	51 ± 15	< 0.001
Trigylcerides (mg/dL)	152 ± 121	135 ± 80	161 ± 135	< 0.001
C-reactive protein (mg/dL)	085 ± 2.1	0.77 ± 1.9	0.89 ± 2.15	0.57
Body mass index (kg/m^2)	26.9 ± 4.3	26.6 ± 4.9	27.2 ± 3.9	< 0.001
eGFR (MDRD2)	77.1 ± 23.0	72.7 ± 21.0	79.3 ± 23.6	< 0.001
Clinical presentation				
Available data (n)	5961	2034	3927	
No angina pectoris (%)	19.6	16.8	21.1	< 0.001
Stable angina (%)	51.9	52.9	51.3	
Unstable angina (%)	22.2	22.5	22.1	
Atypical angina (%)	6.3	7.8	5.5	
History of myocardial infarction				
Available data (n)	4597	1469	3128	
Recent STEMI (%)	10.1	9.0	10.7	0.08
Recent NSTEMI (%)	14.8	14.6	14.9	0.82
Prior myocardial infarction (%)	15.2	11.0	17.2	< 0.001
Results of CA				
1-Vessel disease (%)	24.0	20.3	25.9	< 0.001
2-Vessel disease (%)	16.3	10.4	19.3	
3-Vessel disease (%)	17.0	10.4	20.4	
Non-obstructive CAD	17.8	20.4	16.4	
Non-CAD	24.9	38.5	18.0	
Treatment decision				
Available data (n)	7667	2588	5097	
Optimal medical treatment alone (%)	57.2	67.8	51.8	< 0.001
CABG (%)	7.3	4.3	8.8	
Ad hoc undefined[a] (%)	7.4	7.7	7.3	
Ad hoc PCI (%)	28.1	20.2	32.1	

LDL low density lipoprotein, *HDL* high density lipoprotein, *eGFR* estimated glomerular filtration rate, *STEMI* ST-elevation myocardial infarction, *NSTEMI* non-ST-elevation myocardial infarction, *CA* coronary angiography, *CAD* coronary artery disease, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention

[a]Decision postponed as further testing is required (e.g. test for viability, contractility reserve or inducible ischaemia) or patient's request ad hoc uncertain

not in men. Unstable angina pectoris was independently associated with obstructive CAD only in men. For BMI, a trend towards a stronger association with obstructive CAD in women was found. In contrast, for CRP, a trend towards being independently associated with obstructive CAD in men was found. However, as for both variables, 95 % CI were overlapping, no clear sex differences can be claimed.

Interaction analyses revealed significant interactions of sex with smoking status ($p=0.009$) and hypercholesterolaemia ($p=0.001$). A subgroup analysis stratified by sex revealed for smoking an increased OR (95 % CI) for women (2.18 (1.51–3.14)) and a lower OR for men (1.29 (0.99–1.68)). ORs for hypercholesterolaemia increases for men (2.48 (1.961–3.128)) and decreases for women (1.36 (1.029–1.784)). ORs for unstable angina pecto-

Table 2 Sex-specific clinical characteristics and risk factors in patients with obstructive, non-obstructive and non-CAD

	Patients with obstructive CAD			Patients with non-obstructive CAD			Patients with non-CAD		
	Women	Men	*p* (Women vs. men)	Women	Men	*p* (Women vs. men)	Women	Men	*p* (Women vs. men)
n	1083	3401		537	851		1015	932	
Age (years)	67 ± 10	64 ± 10	< 0.001	68 ± 9	64 ± 10	< 0.001	61 ± 11	57 ± 12	< 0.001
Arterial hypertension (%)	87.8	81.8	< 0.001	82.9	79.2	0.09	68.1	64.5	0.09
Hypercholesterolaemia (%)	62.9	65.0	0.22	63.1	57.2	0.03	56.0	49.7	0.01
Smoking (%)	16.3	20.3	0.004	12.8	19.3	0.002	13.1	20.0	< 0.001
Positive family history (%)	29.4	21.7	< 0.001	27.9	19.0	< 0.001	22.5	17.5	0.01
Diabetes mellitus (%)	24.8	18.7	< 0.001	16.4	19.0	0.21	10.1	8.8	0.31
Total cholesterol (mg/dL)	198 ± 48	188 ± 44	< 0.001	201 ± 43	190 ± 43	< 0.001	202 ± 44	193 ± 44	< 0.001
LDL cholesterol (mg/dL)	125 ± 40	121 ± 38	0.011	125 ± 37	123 ± 37	0.27	126 ± 38	124 ± 34	0.18
HDL cholesterol (mg/dL)	58 ± 16	49 ± 14	< 0.001	62 ± 17	53 ± 17	< 0.001	66 ± 19	55 ± 17	< 0.001
Trigylcerides (mg/dL)	146 ± 92	162 ± 118	< 0.001	139 ± 78	163 ± 136	0.002	122 ± 74	157 ± 185	< 0.001
C-reactive protein (mg/dL)	0.95 ± 2.0	1.01 ± 2.39	0.014	0.66 ± 1.51	0.70 ± 1.51	0.13	0.64 ± 1.94	0.65 ± 1.65	0.15
Body mass index (kg/m²)	26.5 ± 4.8	27.2 ± 3.8	< 0.001	27.0 ± 5.0	27.2 ± 4.1	0.29	26 ± 5	27 ± 4	< 0.01
eGFR (MDRD2)	71.2 ± 22.0	78.2 ± 24.6	< 0.001	70.2 ± 20.7	78.7 ± 21.5	< 0.001	76 ± 20	84 ± 21	< 0.001
Clinical presentation									
Available data (*n* (%) of all patients)	850 (78.5)	2632 (77.4)		471 (87.7)	674 (79.2)		713 (70.2)	621 (66.6)	
No angina pectoris (%)	15.7	15.1	0.78	13.4	23.1	< 0.001	15.1	25.6	< 0.001
Stable angina (%)	38.7	40.2	0.18	57.3	52.1	0.08	54.4	47.8	0.02
Unstable angina (%)	21.4	19.5	0.22	20.8	17.5	0.16	18.0	13.8	0.04
Atypical angina (%)	2.7	2.6	0.88	8.5	7.3	0.45	12.5	12.7	0.90
History of myocardial infarction									
Available data (n)	730	2238		308	491		431 (42.5)	399 (42.8)	
Recent STEMI (%)	15.8	14.3	0.32	2.9	1.8	0.31	1.9	1.5	0.69
Recent NSTEMI (%)	21.5	18.1	0.04	9.4	7.5	0.35	6.7	5.8	0.57
Prior myocardial infarction (%)	16.8	21.0	0.01	8.1	12.2	0.07	3.0	2.0	0.35
Results of CA									
1-Vessel disease (%)	49.4	39.5	< 0.001						
2-Vessel disease (%)	25.3	29.4							
3-Vessel disease (%)	25.3	31.1							
Treatment decision									
Available data (n (%) of all patients)	1062 (98.1)	3346 (98.4)		532 (99.1)	839 (98.6)		994 (97.9)	894 (95.9)	
Optimal medical treatment alone (%)	33.7	31.2	0.13	94.2	93.6	0.65	90.0	89.8	0.87
CABG (%)	10.4	13.4	0.01	0	0		0	0	
Ad hoc undefined[a] (%)	6.7	6.8	0.91	5.8	6.4	0.76	10.0	10.2	0.87
Ad hoc PCI (%)	49.2	48.6	0.72	0	0		0	0	

LDL low density lipoprotein, *HDL* high density lipoprotein, *eGFR* estimated glomerular filtration rate, *STEMI* ST-elevation myocardial infarction, *NSTEMI* non-ST-elevation myocardial infarction, *CA* coronary angiography, *CAD* coronary artery disease, *CABG* coronary artery bypass graft, *PCI* percutaneous coronary intervention

[a]Decision postponed as further testing is required (e.g. test for viability, contractility reserve or inducible ischaemia) or patient's request ad hoc uncertain

ris ($p = 0.006$) increases in men (2.04 (1.47–2.83)) and decreases in women (0.98 (0.67–1.43)). The same was found for stable angina pectoris ($p = 0.013$; women: 0.73 (0.52–1.02); men: 1.25 (0.97–1.62)).

Non-obstructive vs. non-CAD

Variables associated with non-obstructive CAD were age, hypercholesterolemia, diabetes mellitus, arterial hypertension, smoking and a positive family history (Table 3).

Table 3 Multivariable analyses evaluating independent factors associated with obstructive vs. non-CAD and non-obstructive vs. non-CAD in overall patients, in women and men

	Overall patients ($n=5345$)		Women ($n=1813$)		Men ($n=3532$)	
	OR (95 %CI)	*p*	OR (95 %CI)	*p*	OR (95 %CI)	*p*
Obstructive vs. non-CAD						
Age (per year)	1.07 (1.06–1.07)	<0.001	1.06 (1.05–1.08)	<0.001	1.07 (1.05–1.08)	<0.001
Female sex	0.25 (0.21–0.29)	<0.001				
LDL-cholesterol (per mg/dL)	0.99 (0.97–1.0)	0.28	1.0 (1.0–1.0)	0.86	1.0 (1.0–1.0)	0.3
HDL-cholesterol (per mg/dL)	0.98 (0.97–0.98)	<0.001	0.98 (0.97–0.99)	<0.001	0.97 (0.97–0.98)	<0.001
C-reactive protein (per mg/dL)	1.08 (1.01–1.15)	0.03	0.99 (0.91–1.08)	0.87	1.19 (1.06–1.32)	<0.01
Triglycerides (per mg/dL)	1.0 (1.0–1.0)	0.41	1.0 (1.0–1.0)	0.14	1.0 (1.0–1.0)	0.99
Body-mass index (per kg/m^2)	0.97 (0.96–0.99)	<0.01	0.96 (0.94–0.99)	0.002	0.99 (0.96–1.01)	0.26
eGFR (per mL/min/1.73m^2)	1.0 (0.99–1.0)	0.35	1.0 (0.99–1.0)	0.84	1.0 (0.99–1.0)	0.16
Hypercholesterolaemia (yes vs. no)	1.96 (1.64–2.33)	<0.001	1.36 (1.03–1.78)	0.03	2.48 (1.96–3.22)	<0.001
Diabetes mellitus (yes vs. no)	1.87 (1.49–2.35)	<0.001	2.0 (1.45–2.77)	<0.001	1.92 (1.38–2.67)	<0.001
Arterial hypertension (yes vs. no)	2.07 (1.72–2.49)	<0.001	2.5 (1.81–3.46)	<0.001	1.99 (1.5–2.4)	<0.001
Smoking (yes vs. no)	1.55 (1.26–1.92)	<0.001	2.18 (1.51–3.14)	<0.001	1.29 (0.99–1.68)	0.06
Positive family history (yes vs. no)	1.46 (1.22–1.74)	<0.001	1.48 (1.14–1.91)	0.003	1.42 (1.11–1.82)	0.01
Atypical angina vs. no angina	0.34 (0.24–0.47)	<0.001	0.23 (0.14–0.4)	<0.001	0.4 (.27–0.61)	<0.001
Unstable angina vs. no angina	1.51 (1.19–1.94)	0.001	0.98 (0.67–1.43)	0.92	2.04 (1.47–2.83)	<0.001
Stable angina vs. no angina	1.04 (0.85–1.27)	0.7	0.73 (0.52–1.02)	0.06	1.25 (0.97–1.62)	0.09
Non-obstructive vs. non-CAD						
Age (per year)	1.06 (1.05–1.07)	<0.001	1.06 (1.05–1.08)	<0.001	1.05 (1.04–1.06)	<0.001
Female sex	0.52 (0.43–0.63)	<0.001				
LDL-cholesterol (per mg/dL)	1.0 (0.98–1.0)	0.7	1.0 (1.0–1.0)	0.42	1.0 (1.0–1.0)	0.99
HDL-cholesterol (per mg/dL)	0.99 (0.98–1.0)	<0.001	0.99 (0.98–0.99)	0.001	0.99 (0.99–1.0)	0.16
C-reactive protein (per mg/dL)	0.98 (0.9–1.07)	0.71	0.9 (0.79–1.03)	0.12	1.09 (0.96–1.24)	0.2
Triglycerides (per mg/dL)	1.0 (1.0–1.0)	0.08	1.0 (1.0–1.0)	0.14	1.0 (1.0–1.0)	0.3
Body-mass index (per kg/m^2)	0.99 (0.97–1.01)	0.50	1.0 (0.97–1.0)	0.7	1.0 (0.96–1.03)	0.75
eGFR (per mL/min/1.73m^2)	0.99 (0.99–1.0)	0.32	1.0 (0.99–1.0)	0.74	1.0 (0.99–1.0)	0.28
Hypercholesterolaemia (yes vs. no)	1.4 (1.14–1.72)	0.001	1.36 (1.0–1.85)	0.05	1.54 (1.17–2.03)	<0.01
Diabetes mellitus (yes vs. no)	1.61 (1.24–2.08)	<0.001	1.29 (0.89–1.87)	0.19	1.95 (1.34–2.83)	<0.001
Arterial hypertension (yes vs. no)	1.64 (1.31–2.04)	<0.001	1.42 (1.01–2.0)	0.04	1.76 (1.32–2.36)	<0.001
Smoking (yes vs. no)	1.49 (1.16–1.92)	0.002	1.81 (1.2–2.74)	0.01	1.3 (0.95–1.79)	0.1
Positive family history (yes vs. no)	1.29 (1.05–1.58)	0.02	1.33 (1.0–1.78)	0.05	1.24 (0.92–1.67)	0.16
Atypical angina vs. no angina	0.71 (0.50–1.0)	0.05	0.79 (0.46–1.36)	0.4	0.71 (0.44–1.13)	0.71
Unstable angina vs. no angina	1.14 (0.86–1.53)	0.37	1.1 (0.70–1.75)	0.67	1.33 (0.9–1.97)	0.16
Stable angina vs. no angina	1.05 (0.83–1.34)	0.68	1.2 (0.81–1.88)	0.38	1.05 (0.77–1.42)	0.78

CI confidence interval, *LDL* low density lipoprotein, *HDL* high density lipoprotein, *eGFR* estimated glomerular filtration rate, *CAD* coronary artery disease, *OR* odds ratios

The only negatively associated factors were female sex and HDL cholesterol. Analysing sex-specific factors associated with non-obstructive CAD revealed following differences: in women, age, arterial hypertension, hypercholesterolaemia, smoking and a positive family history were associated with increased risk of non-obstructive vs. non-CAD; high HDL cholesterol levels were associated with decreased risk. In men, age and the presence of diabetes, hypercholesterolaemia and hypertension were associated with non-obstructive CAD. However, as interaction analyses revealed no statistically significant effect modifiers for sex and the 95 % CI of all of these variables were overlapping between sexes, no clear sex-specific factors associated with non-obstructive CAD could be determined.

Discussion

The present analyses of a prospective single-centre registry including almost 8000 patients referred for elective non-acute CA revealed intriguing sex differences in factors independently associated with obstructive CAD. For non-obstructive CAD, no distinct sex-specific factors could be determined.

Analysing the overall study cohort, no unexpected sex differences in risk factor profile were observed: as described before, women were older [11, 12], men were more often smokers and the prevalence of hyperlipidaemia and diabetes mellitus was similar between sexes [11, 13, 14]. However, in patients with obstructive CAD, diabetes mellitus and arterial hypertension were more prevalent in women. This findings are in accordance with results recently published by the ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease (CLARIFY) investigators [15]. The aforementioned cardiovascular risk factors remained independently associated with obstructive CAD in both women and men. In patients with non-obstructive CAD, arterial hypertension remained independently associated with CAD in both sexes, whereas diabetes was associated with non-obstructive CAD only in men. Interestingly, although more men than women were smoking, this risk factor was more strongly associated with obstructive CAD in women, supporting earlier findings that women might be more sensitive to the damaging effects of smoking [16]. As recent analyses revealed that in some European countries, the smoking prevalence between adolescent boys and girls were about the same [17, 18], or even higher in girls [19], one might expect an increase in the prevalence of CAD in women.

The comparison of lipid levels between sexes revealed higher total, LDL and HDL cholesterol but lower triglyceride concentrations in women in all analysed subgroups. As population studies reported higher cholesterol levels in men until the fifth decade, with women having higher concentrations at later stages of life [20], this differences in cholesterol levels might be partially attributed to the older age of women. In multivariable analyses, the presence of hypercholesterolaemia was strongly associated with obstructive CAD in men than in women. In accordance with a recent meta-analyses revealing that lipid-lowering therapy with statins reduces the risk of coronary heart disease events in men but not in women [21], our study results emphasise a strict lipid-lowering strategy for CAD prevention especially in men.

Among a myriad of inflammatory markers [22–24], CRP has been extensively studied in atherogenesis. CRP has been shown to be an independent predictor of cardiovascular events in both women and men [25, 26]. Its association with the prevalence of CAD in stable patients is less well investigated and obvious [27]. In our study, higher serum CRP levels were found in men than in women with obstructive CAD, whereas in the overall as well as in the subgroup with non-obstructive or non-CAD, CRP levels were comparable between sexes. In women with chronic stable angina, higher CRP levels were reported compared with men [28, 29]. However, as we also included patients with unstable angina and even prior or previous myocardial infarctions, results are not directly comparable. We recently demonstrated in a large cohort of more than 5000 patients undergoing CA that CRP was independently associated with the presence of CAD only in men but not in women [27]. Comparing patients with obstructive and non-CAD, the present analyses confirmed our previous results that CRP might be strongly associated with obstructive CAD in men than in women. Although some data suggest that in patients with a high risk for cardiovascular disease, CRP seems to be more predictive for coronary artery calcium in women [30, 31], our data indicate that in consecutive patients who are referred for elective CA, CRP seems to be strongly associated with obstructive CAD in men.

Atypical angina pectoris was associated with a lower risk of obstructive CAD in both sexes, suggesting that symptoms considered being “atypical” often do not have a cardiac origin in women and men. The presence of stable angina was not associated with obstructive CAD in both sexes, whereas unstable angina was strongly associated with obstructive CAD in men but not in women. A possible explanation for this finding might be that women often report chest pain differently compared with men [32, 33], and especially in patients with an acute coronary syndrome, physicians consider chest pain being typical less frequently in women [34].

Studies have repeatedly reported that PCI and CABG rates are higher in men than in women [35, 36]. In our overall study cohort, we also found a higher PCI rate in men and accordingly a higher isolated medical treatment rate in women. This sex difference can be explained by the higher presence of significant 1-, 2- or 3-VD in men. When analysing only patients with significant CAD, no sex differences in the rate of PCI respectively optimal medical treatment alone remained. This was also described by Ghali et al. [37], who found that sex differences in the rates of revascularisation disappeared once demographic and especially clinical characteristics are taken into account. In our analyses, men with significant CAD were more often referred for CABG than women with significant CAD. Reasons commonly given for lower CABG rates in women include higher comorbidity and smaller coronary arteries [38], facts that may reflect greater technical challenges and increase the potential for incomplete revascularisation.

Study limitations

The present study has all the limitations inherent to registries while reflecting the real-world setting of elective patients referred for CA [39]. Furthermore, as all patients were referred for invasive evaluation of CAD, a referral bias may be present. Therefore, our results cannot be extrapolated to the general population.

Conclusion

In patients referred for non-acute CA, smoking was strongly associated with obstructive CAD in women than in men, whereas hypercholesterolaemia was strongly associated with obstructive CAD in men. For non-obstructive CAD, no distinct sex differences in associated risk factors were observed. These findings might be taken

into account when planning individual interventions to reduce cardiovascular risk. Sex differences in therapeutic decisions met in the catheterisation laboratory in patients with obstructive CAD seem to be eliminated today.

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Conflict of interest
All authors declare that they have no conflict of interest.

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