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Patients With Non-Obstructive Coronary Artery Disease and Polyvascular Disease. Sub-Analysis of the Real-World Registry KAMMA (Clinical Registry on Patient Population With Polyvascular Disease in the Russian Federation and Eurasian Countries)

Aim	To study the clinical status and data of laboratory and instrumental examination of patients with non-obstructive ischemic heart disease (IHD) and multifocal atherosclerosis (MFA) included in the KAMMA registry.
Material and methods	The subanalysis included 1,893 IHD patients who underwent coronary angiography (CAG) and ultrasonic examination of peripheral arteries. Based on the CAG data, patients were divided into two groups: group 1, patients with obstructive coronary atherosclerosis (CA) (maximum stenosis ≥50% and/or history of percutaneous coronary intervention/coronary artery bypass grafting, n=1728; 91.3%) and group 2, patients with non-obstructive CA (maximum stenosis <50%, n = 165; 8.7%).
Results	A comparative analysis based on the degree of coronary obstruction in patients with verified IHD who were included in the KAMMA registry showed that 8.7% of them had coronary artery stenosis of less than 50%. The overwhelming majority of patients with non-obstructive CA had MFA affecting the brachiocephalic arteries in 94.3% and the lower extremity arteries in 40.2%. Among patients with non-obstructive IHD, women predominated; risk factors such as smoking and type 2 diabetes mellitus were less frequent in this group than in the obstructive IHD group. Patients with non-obstructive CA more frequently had a history of dyslipidemia; they had higher total cholesterol and non-high-density lipoprotein cholesterol; and they more frequently received moderate-intensity statin therapy than patients with obstructive CA (55.8% vs. 34.5%). Characteristic features of patients with non-obstructive CA were less severe IHD and less frequent history of acute coronary syndrome. However, the incidence of stroke, peripheral arterial thrombosis, and chronic arterial insufficiency of the lower extremities did not differ in groups 1 and 2, whereas the incidence of paroxysmal atrial fibrillation was higher in the non-obstructive IHD group.
Conclusion	IHD patients without coronary obstruction also require assessment of the peripheral arterial status, as they may have advanced MFA, which should be taken into account when choosing the «aggressiveness» of therapy.

Keywords	Ischemic heart disease; multifocal atherosclerosis; obstructive coronary atherosclerosis; non-obstructive coronary atherosclerosis; real-world evidence registry
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Introduction

A considerable number of routine coronary angiography (CAG) procedures are conducted on a daily basis worldwide. However, from 40% to 70% of patients who have undergone invasive CAG do not have coronary artery obstruction [1, 2]. The novel evidence suggests that many, perhaps most, cases of chronic coronary heart disease (CHD) may occur in patients with nonstenotic coronary arteries [3]. The potential mechanisms include coronary microvascular dysfunction (MVD), epicardial and microvascular vasoconstriction, and a combination of these mechanisms with coronary atherosclerosis [4]. These patients are at an elevated risk of adverse cardiovascular events and increased all-cause mortality compared to individuals with normal coronary arteries [5].

A recently published expert consensus document of the European Association of Percutaneous Cardiovascular Interventions and the European Society of Cardiology (ESC) Working Group on Coronary Pathophysiology and Microcirculation has emphasized the significance of non-obstructive forms of CHD and the imperative for larger-scale studies and registries to advance our comprehension and

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treatment of this underdiagnosed and intricate condition that is associated with unfavorable outcomes [1].

Objective

The objective of the present study was to examine the distinctive characteristics of the clinical status and laboratory data of patients with non-obstructive CHD and multifocal atherosclerosis (MFA) enrolled in the KAMMA registry.

Material and Methods

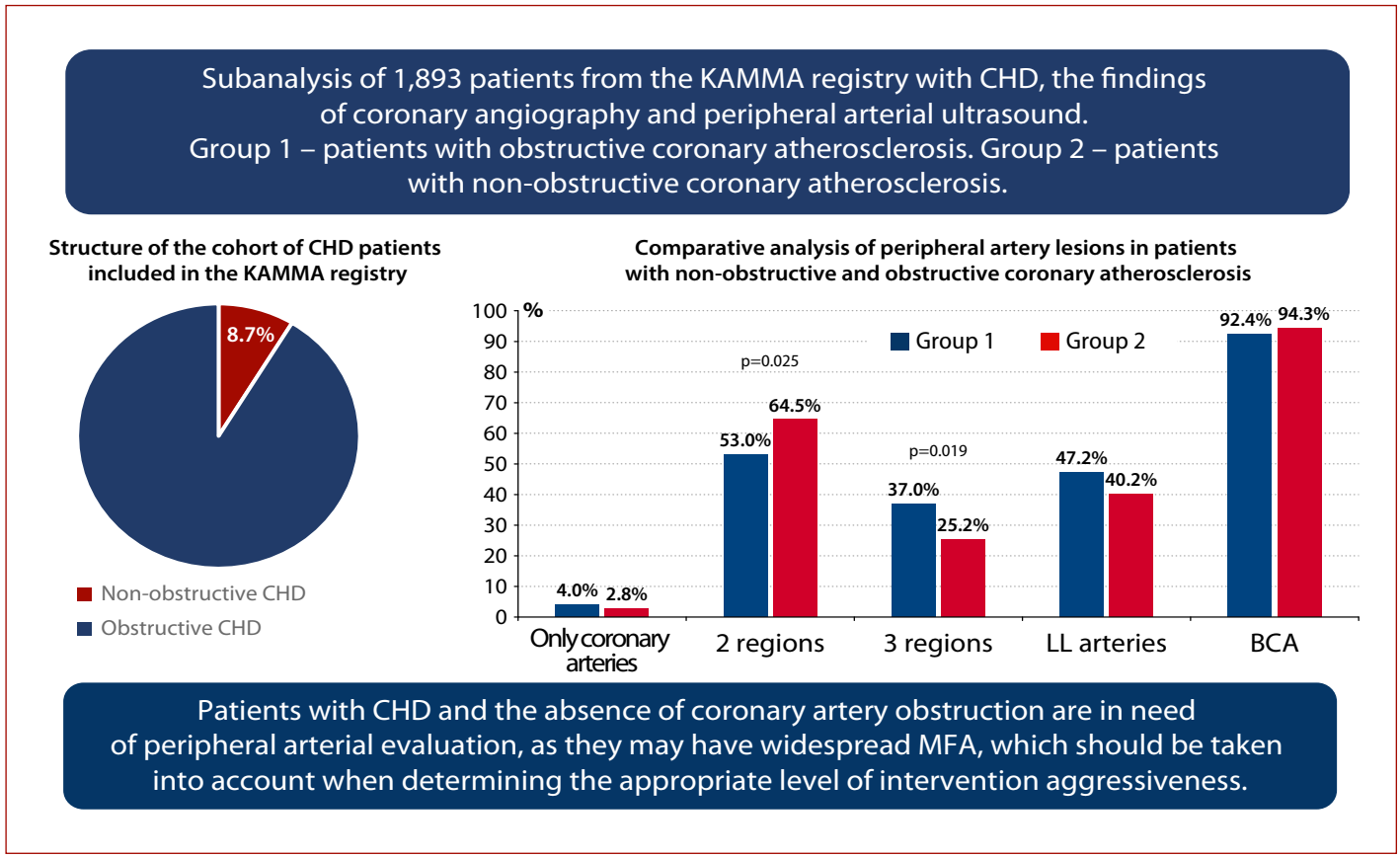
KAMMA (ClinicalTrials.gov: NCT05189847) is an international, multicenter, non-interventional, prospective registry of real-world clinical practice. The Eurasian Association of Therapists is responsible for the organization and conduct of the registry. The initial cohort of the registry comprised male and female subjects aged 18 years and older with confirmed atherosclerosis in two or more arterial beds, as well as with the presence of one or more risk factors for atherosclerosis, including excessive body weight, carbohydrate and/or lipid metabolism disorders, smoking, and chronic kidney disease stage 3a and above. The registry included patients who had been treated by outpatient cardiologists.

The second branch of the register, designated KAMMA-cardio, was constituted for the purpose of including patients exhibiting atherosclerotic lesions of the coronary system, as confirmed by CAG, as well as one or more clinical variants of CHD, including typical angina pectoris, acute coronary syndrome (ACS), and coronary artery revascularization.

The recruitment of patients commenced on February 1, 2022, and concluded on November 27, 2022. The planned follow-up period was one year. The 28 investigational sites were situated in seven federal districts of the Russian Federation (Volga, Northwestern, North Caucasian, Siberian, Ural, Central, and Southern), as well as in the Republic of Kazakhstan, the Republic of Uzbekistan, and the Republic of Belarus.

A detailed account of the KAMMA registry design can be found in a previous publication [6]. The present study was approved by the local ethics committee of N. I. Pirogov Russian National Research Medical University for research centers in the Russian Federation (minutes #212, dated November 11, 2021) and by the local ethics committees

Central illustration. Patients With Non-Obstructive Coronary Artery Disease and Polyvascular Disease. Sub-Analysis of the Real-World Registry KAMMA (Clinical Registry on Patient Population With Polyvascular Disease in the Russian Federation and Eurasian Countries)



BCA, brachiocephalic arteries; LL, lower limb.
Group 1 – obstructive coronary atherosclerosis (maximal stenosis ≥50% and/or a history of PCI/CABG) (n = 1,728; 91.3 %);
Group 2 - non-obstructive coronary atherosclerosis (maximal stenosis < 50 %) (n = 165; 8.7 %).

of corresponding investigational sites outside the Russian Federation. Prior to their inclusion in the study, the subjects were required to provide written informed consent. An analysis of the patient population within the primary branch of the KAMMA registry revealed that it comprises 91.6% of patients diagnosed with CHD. In light of these considerations, the investigational team opted to integrate the data of 91.6% of patients with CHD from the primary branch of the KAMMA registry with the data of patients from the KAMMA-cardio branch.

Statistical analysis

The data obtained were processed using Python statistical packages, specifically statsmodels, stats, and matplotlib. As all numerical variables analyzed within the framework of this paper deviated significantly from the normal distribution, as indicated by graphical analysis and the Shapiro-Wilk test, nonparametric tests were subsequently employed. Descriptive statistics for numeric variables included medians (Me) and ranges (inter-quartile and min-max), while frequencies were employed for categorical variables. The analysis of relationships between categorical variables was conducted using the chi-squared test, while the analysis of relationships between numerical variables was performed using Spearman's rank correlation coefficient. The comparison of independent groups by numerical indicators was conducted using the Mann-Whitney test, and in cases where there were three or more groups, the Kruskal-Wallis test was employed. All comparisons were made with a significance level of $p = 0.05$. Post hoc comparisons were conducted in accordance with the Holm method. The final stage was the construction of a multivariate model. A random forest model (Python module sklearn.ensemble.RandomForestClassifier: predictors were evaluated by the effect on the Gini index (mean decrease in impurity), and stepwise logistic regression (ten-fold iterative rebuilding of the model on different portions of the sample) were employed to select variables. The final prognosis was also generated using the logit model in IBM SPSS Statistics 25, with an additional division of the sample into training and test sets (70%/30%).

Results

A total of 1,893 patients with CHD who underwent CAG and peripheral arterial ultrasound were included in the subanalysis. Patients were divided into two groups based on CAG data: Group 1, which included patients with obstructive coronary atherosclerosis (maximal stenosis ≥ 50% and/or a history of percutaneous coronary intervention/coronary artery bypass grafting) (n = 1,728; 91.3%), and Group 2, which included patients with non-obstructive coronary atherosclerosis (maximal stenosis < 50%) (n = 165; 8.7%) (Table 1).

Cardiovascular risk factors in patients with non-obstructive and obstructive coronary atherosclerosis

There was no significant difference in age between patients in Groups 1 and 2 (Table 1). Among patients with non-obstructive CHD, there was a prevalence of female patients (57.6% female and 42.4% male), while among patients with obstructive CHD, there was a predominance of male patients (31.7% female and 68.3% male). In the cohort of patients with non-obstructive coronary atherosclerosis, there was a predominance of individuals with higher education (49.7% and 36.7%, $p = 0.001$).

In the cohort of patients with non-obstructive CHD, compared to those with obstructive CHD, risk factors such as smoking (40.2% vs. 50.4%, $p = 0.013$) and type 2 DM2 (24.2% vs. 34.5%, $p = 0.008$) were less prevalent. The prevalence of hypertension was comparable between the two cohorts, with a frequency of 98.2% in the non-obstructive CHD group and 96.4% in the obstructive CHD group. (Table 1).

Patients with non-obstructive coronary atherosclerosis were more likely to have a history of dyslipidemia (LDL) (35.8% vs. 24.3%, $p = 0.001$), but the prevalence of confirmed familial hypercholesterolemia was similar in Groups 1 and 2 (3.9% and 3.8%, respectively). The levels of total cholesterol (TC) and non-high-density lipoprotein cholesterol (non-HDL–C) were higher in patients with non-obstructive coronary atherosclerosis (Table 2).

Comparative analysis of peripheral artery lesions in patients with non-obstructive and obstructive coronary atherosclerosis

Isolated lesions of the coronary arteries were observed infrequently in patients with obstructive and non-obstructive coronary atherosclerosis (4.0% and 2.8%, respectively) (Figure 1). Patients with non-obstructive coronary atherosclerosis exhibited a higher prevalence of atherosclerosis in two vascular beds (64.5% vs. 53.0%, $p = 0.025$) and a lower prevalence in three vascular beds (25.2% vs. 37.0%, $p = 0.019$).

In patients with non-obstructive and obstructive coronary atherosclerosis, the brachiocephalic arteries were affected in 94.3% and 92.4% of cases, respectively, while the lower limb arteries were affected in 40.2% and 47.2% of cases, respectively.

Clinical manifestations of atherosclerotic lesions of coronary and peripheral arteries

Patients with non-obstructive coronary atherosclerosis were less likely to have a history of ACS than patients with obstructive atherosclerosis (21.2% vs. 62.1%, $p < 0.001$); severe heart failure class III–IV was less frequently observed in patients with non-obstructive coronary atherosclerosis (10.9% vs. 24.4%, $p < 0.001$) (Table 1). It is noteworthy,

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Table 1. (start of table). Demographic characteristics and clinical status of patients depending on the degree of coronary obstruction

Parameter	Obstructive coronary atherosclerosis (n = 1,728; 91.3 %)	Non-obstructive coronary atherosclerosis (n = 165; 8.7 %)	*OR [95% CI]	p.ratio	p.overall	n
Age	65 [59; 73]	65 [59; 71]	–	–	0.642	1893
Sex					<0.001	1893
Females	548 (31.7%)	95 (57.6%)	Ref.	Ref.		
Males	1180 (68.3%)	70 (42.4%)	2.92 (2.11–4.04)	<0.001		
Education					0.001	1893
Higher	635 (36.7%)	82 (49.7%)	0.42 (0.25–0.70)	0.001		
Alcohol consumption					0.008	1752
No	1260 (79.1%)	112 (70%)	Ref.	Ref.		
Yes	332 (20.9%)	48 (30%)	0.61 (0.43–0.88)	0.012		
Smoking					0.013	1852
No	837 (49.6%)	98 (59.8%)	Ref.	Ref.		
Yes	851 (50.4%)	66 (40.2%)	1.51 (1.09–2.09)	0.014		
History of dyslipidemia					0.001	1824
No	1258 (75.7%)	104 (64.2%)	Ref.	Ref.		
Yes	404 (24.3%)	58 (35.8%)	0.58 (0.41–0.81)	0.002		
Hypertension, grade					0.083	1892
0	62 (3.6%)	3 (1.8%)	Ref.	Ref.		
1	265 (15.3%)	15 (9.1%)	0.85 (0.24–3.04)	1		
2	494 (28.6%)	54 (32.7%)	0.44 (0.13–1.46)	0.256		
3	906 (52.5%)	93 (56.4%)	0.47 (0.15–1.53)	0.265		
Documented FH					0.972	1756
No	1537 (96.1%)	151 (96.2%)	Ref.	Ref.		
Yes	62 (3.9%)	6 (3.8%)	1.02 (0.43–2.39)	1		
Type 2 diabetes					0.008	1893
No	1132 (65.5%)	125 (75.8%)	Ref.	Ref.		
Yes	596 (34.5%)	40 (24.2%)	1.65 (1.14–2.38)	0.007		
History of ACS					<0.001	1888
No	653 (37.9%)	130 (78.8%)	Ref.	Ref.		
Yes	1070 (62.1%)	35 (21.2%)	6.09 (4.14–8.95)	<0.001		
AF / AFL**					0.007	1892
• Paroxysmal	82 (4.7%)	18 (10.9%)	0.4 (0.24–0.69)	0.003		
• Persistent	30 (1.7%)	2 (1.2%)	1.33 (0.31–5.63)	1		
• Permanent	70 (4.1%)	8 (4.8%)	0.78 (0.37–1.65)	0.524		
CHF (class I-IV)					0.686	1891
No	262 (15.2%)	27 (16.4%)	Ref.	Ref.		
Yes	1464 (84.8%)	138 (83.6%)	1.09 (0.71–1.69)	0.652		
Class 1–2					0.002	–
No	684 (39.6%)	45 (27.3%)	Ref.	Ref.		
Yes	1042 (60.4%)	120 (72.7%)	0.57 (0.4–0.82)	0.002		
Class 3–4					<0.001	–
No	1304 (75.6%)	147 (89.1%)	Ref.	Ref.		
Yes	422 (24.4%)	18 (10.9%)	2.64 (1.6–4.36)	<0.001		
Chronic arterial insufficiency of the lower limbs					0.812	1815
No	1325 (80.2%)	132 (81.0%)	Ref.	Ref.		
Yes	327 (19.8%)	31 (19.0%)	1.05 (0.7–1.58)	0.918		
History of stroke					0.057	1890
No	1513 (87.7%)	153 (92.7%)	Ref.	Ref.		
Yes	212 (12.3%)	12 (7.3%)	1.79 (0.98–3.27)	0.059		
Surgical amputation of extremity					0.327	1893
No	1718 (99.4%)	165 (100%)	–	–		
Yes	10 (0.6%)	0 (0%)				

Table 1 (end of table). Demographic characteristics and clinical status of patients depending on the degree of coronary obstruction

Parameter	Obstructive coronary atherosclerosis (n = 1,728; 91.3 %)	Non-obstructive coronary atherosclerosis (n = 165; 8.7 %)	*OR [95% CI]	p.ratio	p.overall	n
History of peripheral arterial thrombosis					0,691	1849
No	1646 (97.7%)	161 (98.2%)	Ref.	Ref.		
Yes	39 (2.3%)	3 (1.8%)	1.27 (0.39–4.16)	1.000		
History of COVID-19 (confirmed)					<0.001	1670
No	721 (47.5%)	35 (23%)	Ref.	Ref.		
Yes	797 (52.5%)	117 (77%)	0.33 (0.22–0.49)	<0.001		

* OR, odds ratio for the presence of obstructive coronary atherosclerosis; ** OR calculated in relation to patients without AFL/AF; p.ratio, the level of statistical significance for OR; p.overall, the level of statistical significance for intergroup differences; Ref, reference level. The data are presented as n (%) и Me [25; 75]; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; CHD, coronary heart disease; MI, myocardial infarction; MFA, multifocal atherosclerosis; SBP, systolic blood pressure; FH, familial hypercholesterolemia; CHF, chronic heart failure.

Table 2. Parameters of lipid profile in patients with obstructive and non-obstructive coronary atherosclerosis

Parameter, mmol/L	Obstructive coronary atherosclerosis (n = 1,728; 91.3 %)	Non-obstructive coronary atherosclerosis (n = 165; 8.7 %)	p.overall (Mann–Whitney U-test)	n
Total cholesterol	4.84 [3.90; 5.87]	5.30 [4.36; 6.30]	< 0.001	1691
LDL-C	2.68 [2.00; 3.60]	2.41 [1.78; 3.52]	0.069	1518
HDL-C	1.16 [0.98; 1.40]	1.3 [1.10; 1.65]	< 0.001	1435
Triglycerides	1.5 [1.10; 2.10]	1.42 [1.07; 2.00]	0.417	1468
Non-HDL-C	3.54 [2.63; 4.44]	3.74 [3.00; 4.78]	0.01	1429

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; non-HDL-C, non-high-density lipoprotein cholesterol.

Table 3. Logistic regression coefficients obtained on the training sample

Parameter	Significance of a variable	Coefficient (B)	Exp (B) is the multiplicative effect of a variable on the odds of an outcome
History of ACS	0.000	1.984	7.268
Higher education	0.002	–0.736	0.479
Female	0.000	–1.088	0.337

ACS, acute coronary syndrome

however, that there was no significant difference in the incidence of stroke, peripheral arterial thrombosis, or the prevalence of chronic arterial insufficiency of the lower limbs between patients in Groups 1 and 2.

Paroxysmal atrial fibrillation (AF) was more frequently observed in patients with non-obstructive atherosclerosis (Table 1), but persistent and permanent forms of AF occurred with equal frequency in patients of Groups 1 and 2.

Multivariate comparative analysis

A list of potential predictors of non-obstructive atherosclerosis was generated on the basis of univariate correlation analysis (Table 2). A multivariate analysis was conducted using random forest modeling. The three most significant variables were a history of ACS as a factor decreasing the probability of non-obstructive atherosclerosis; female sex and higher education, which were identified as increasing factors (Table 3).

Lipid-lowering therapy

The administration of statins was observed in patients with non-obstructive and obstructive coronary atherosclerosis with similar frequencies (92.7% and 95.4%, respectively) (Figure 2). Omega-3 polyunsaturated fatty acids were the second most frequently administered drug, with patients with non-obstructive coronary atherosclerosis taking it more frequently than those with obstructive atherosclerosis (23.6% vs. 12.0%, p < 0.001).

Ezetimibe was administered to only 9.3% of patients with non-obstructive atherosclerosis and 10.3% with obstructive atherosclerosis. Fibrates were taken by only 4.3% and 3.3% of patients with non-obstructive and obstructive coronary

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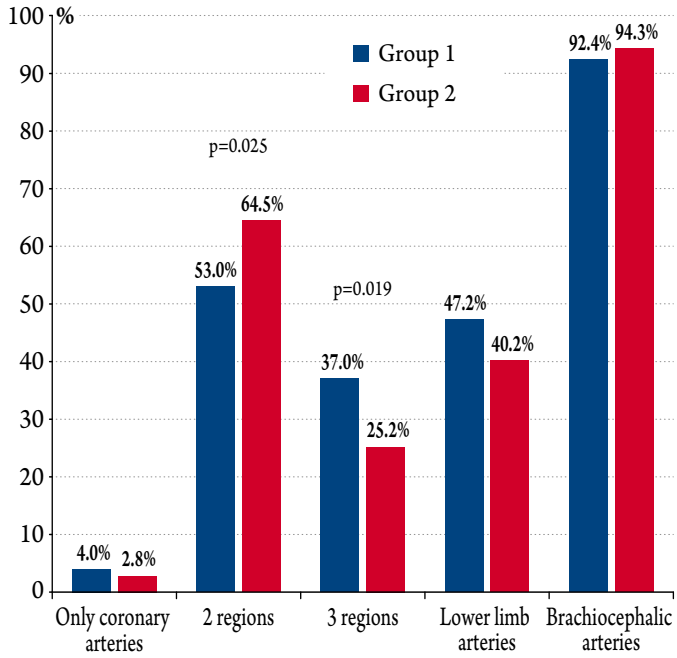
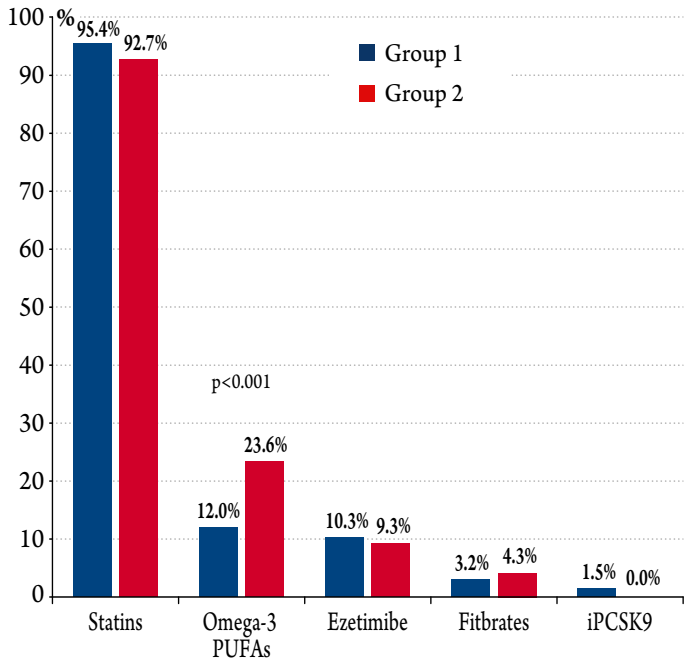
Figure 1. Comparative analysis of peripheral artery lesions in patients with non-obstructive and obstructive coronary atherosclerosis



Group 1 – obstructive coronary atherosclerosis (maximal stenosis ≥50% and/or a history of percutaneous coronary intervention/coronary artery bypass grafting) (n = 1,728; 91.3 %); Group 2 – non-obstructive coronary atherosclerosis (maximal stenosis < 50 %) (n = 165; 8.7 %).

Figure 2. Comparative analysis of lipid-lowering therapy in patients with non-obstructive and obstructive coronary atherosclerosis



Group 1 – obstructive coronary atherosclerosis (maximal stenosis ≥50% and/or a history of percutaneous coronary intervention/coronary artery bypass grafting) (n = 1,728; 91.3 %); Group 2 – non-obstructive coronary atherosclerosis (maximal stenosis < 50 %) (n = 165; 8.7 %).

atherosclerosis, respectively. PCSK9 inhibitors were administered to a mere 1.5% of patients with obstructive coronary atherosclerosis.

A comparative analysis of statin doses (Figure 3) revealed that patients with non-obstructive coronary atherosclerosis received moderate-intensity therapy more frequently than patients with obstructive atherosclerosis (55.8% vs. 34.5%, $p < 0.001$). The atorvastatin dose of 20 mg was the most frequently administered, followed by rosuvastatin at a dose of 10 mg. Atorvastatin doses of 40 mg and 80 mg, as well as rosuvastatin doses of 20 mg, were less commonly administered.

Discussion

A comparative analysis of patients with CHD, verified by anamnestic data (history of ACS/myocardial infarction (MI)/coronary artery revascularization) or stress tests, included in the KAMMA registry, revealed that 8.7% of patients exhibited coronary artery stenosis of less than 50%. Other studies have indicated that up to 40% of patients with a positive noninvasive stress test who are undergoing elective CAG do not demonstrate signs of epicardial coronary artery obstruction [7]. In the ISCHEMIA study [5], among 3,612 patients with stress test-confirmed moderate to severe ischemia who had undergone coronary computed tomography angiography, 476 (13%) patients exhibited no obstructive atherosclerosis of the coronary arteries.

In the present study, we elucidate the low prevalence of non-obstructive atherosclerosis among patients with CHD by the aforementioned criterion for inclusion in the main branch of the KAMMA registry, namely, the confirmation of atherosclerosis in two or more arterial beds [6]. In accordance with the design of the KAMMA registry, a characteristic feature of patients with non-obstructive coronary atherosclerosis included in the registry was the high prevalence of MFA lesions in both brachycephalic arteries (94.3%) and lower limb arteries (40.2%), which did not differ from the prevalence of peripheral artery lesions in patients with obstructive coronary atherosclerosis. The only difference between patients with non-obstructive atherosclerosis was a lower frequency of involvement of three vascular beds.

A review of the available literature revealed no description of a cohort of patients with this particular presentation. In a study by Sardu C. et al. [8], the prevalence of MFA in patients with non-obstructive coronary atherosclerosis was 9.7%, which was lower than in patients with coronary artery obstruction (31.4%).

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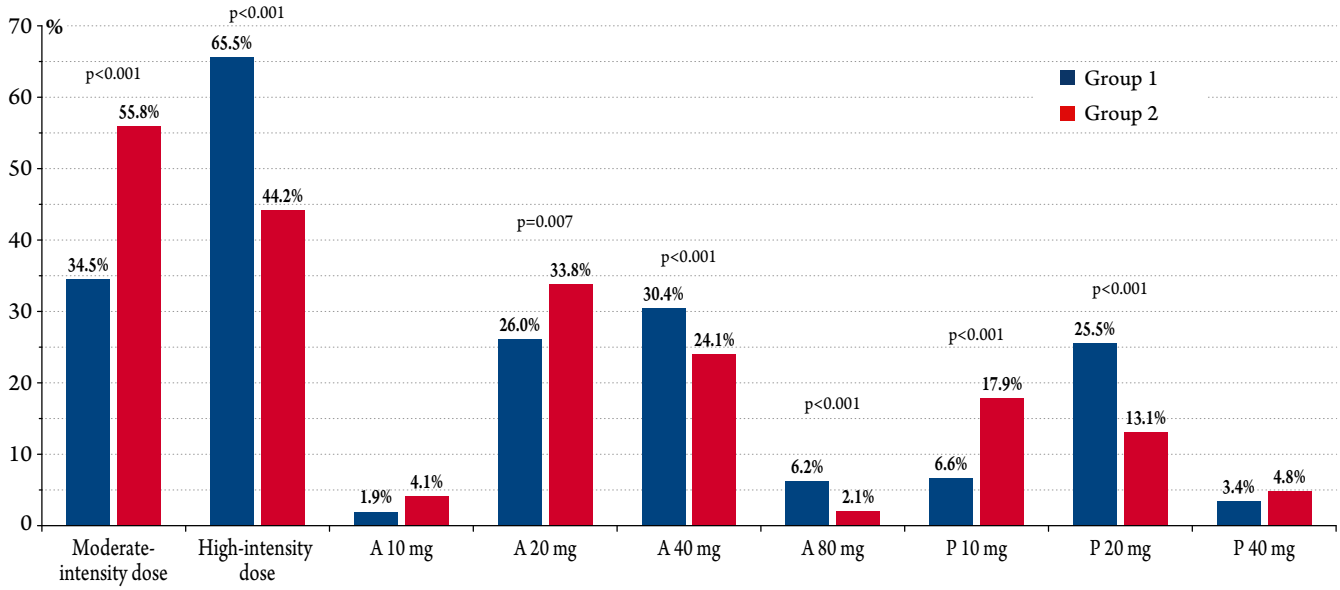
In the study by Jung J. et al. [9], the prevalence of MFA was 8.9% in patients with non-obstructive coronary atherosclerosis.

Despite the significant differences between our population of patients with non-obstructive coronary atherosclerosis and other studies, the most typical feature remained, namely the predominance of female patients (57.6% vs. 31.7% in patients with coronary artery obstruction). In multivariate analysis, female sex and higher education were independent factors that increased the odds of non-obstructive coronary artery disease. According to data from almost all studies of CHD without coronary artery obstruction, women predominate in this category of patients [7, 10]. Data from more than 750 US hospitals from 2007 to 2014 show that MI without coronary artery obstruction occurs in 10.5% of women with MI, compared with 3.4% of men [11]. Aziz A. et al. [12] examined 1,379 patients with stable angina pectoris and non-obstructive CHD. According to the data from this study, sex differences were significant in the multivariate logistic regression model: the odds ratio for MVD and epicardial vasospasm in women and men was 4.2 (95% CI: 3.1–5.5; p < 0.001) and 2.3 (95% CI: 1.7–3.1, p < 0.001), respectively. Women were more sensitive to acetylcholine than men, with vasomotor dysfunction occurring at lower doses of the drug. According to Waheed N. et al [13], unique risk factors such as pregnancy-related disorders, autoimmune dysfunction, chronic inflammation, autonomic and neuroendocrine dysfunction, and psychological risk factors contribute to the development of MVD and vasospasm in women.

The KAMMA registry indicates that risk factors such as smoking and diabetes mellitus type 2 were less prevalent among patients with non-obstructive CHD than those with obstructive CHD, a finding consistent with that of other studies [5]. In a Chinese registry of patients with angina pectoris (n = 10,940) [14], DM was observed in 22.3% of patients with non-obstructive coronary artery disease and 38.1% of patients with obstructive coronary artery disease. In addition, according to this registry, arterial hypertension, DLP, active smoking and family history of CHD were more common in patients with increasing degrees of coronary artery obstruction. Despite the lower prevalence in patients with non-obstructive CHD, DM has an extremely negative impact on the prognosis in this form of CHD [14], as prolonged hyperglycemia directly contributes to the development of MVD and vasospasm [1].

According to the KAMMA registry, patients with non-obstructive coronary atherosclerosis were more likely to have anamnestic data on DLP, and levels of TC and non-HDL–C were higher in patients with non-obstructive coronary atherosclerosis. Other studies have reported that DLP is equally prevalent in obstructive and non-obstructive CHD [15, 16]. The expert consensus document on non-obstructive ischemia of coronary arteries [1] indicates that the correlation between coronary artery disease and DLP in non-obstructive CHD is less pronounced. However,

Figure 3. Comparative analysis of statin doses in patients with non-obstructive and obstructive coronary atherosclerosis



A, atorvastatin; R, rosuvastatin.
Group 1 – obstructive coronary atherosclerosis (maximal stenosis ≥50% and/or a history of percutaneous coronary intervention/coronary artery bypass grafting) (n = 1,728; 91.3 %); Group 2 – non-obstructive coronary atherosclerosis (maximal stenosis < 50 %) (n = 165; 8.7 %).

the document recommends that DLP be considered a risk factor and corrected in this form of coronary artery disease. The more pronounced DLP observed in patients with non-obstructive CHD in the KAMMA registry can be attributed to the fact that patients with non-obstructive coronary atherosclerosis were more likely to receive moderate-intensity statin therapy than patients with obstructive atherosclerosis (55.8% vs. 34.5%). The fact that patients without obstructive CHD are less likely to receive effective hypolipidemic therapy than patients with obstructive CHD has been repeatedly reported in several studies, which is consistent with our findings [5, 10, 17].

Our data indicate that patients with non-obstructive coronary atherosclerosis were more likely to have paroxysmal AF, a finding that is consistent with the results reported by other researchers [9]. The results of the study conducted by Lopez-Pais J. et al. [18] indicate that AF was twice as frequent in MI with non-obstructive coronary arteries (14.7% vs. 7.3%; p=0.016), which be attributed by the authors to a more pronounced proinflammatory status in this category of patients.

The KAMMA registry data indicate that patients with non-obstructive coronary atherosclerosis had less severe manifestations of CHD. However, there was no significant difference in the incidence of stroke, peripheral arterial thrombosis, or the prevalence of chronic limb ischemia between Groups 1 and 2. In multivariate analysis, a history of ACS was identified as a significant predictor of the likelihood of non-obstructive coronary artery disease. These findings are in accordance with the results of a large five year prospective observational study of patients with non-obstructive CHD [9], in which the elevated risk of major vascular events in this patient cohort was predominantly attributed to stroke rather than coronary events. The authors attribute this to the inferior quality of hypotensive and lipid-lowering therapy in patients with non-obstructive CHD, among whom younger patients, women with an atypical clinical presentation, and obese patients without DM are most prevalent.

Limitations

The KAMMA register comprises data of the real-world clinical practice. In certain instances, data pertaining to particular variables were entered on an «if known» basis, rendering them unnecessary. It was inevitable that a certain degree of data loss would occur during the data entry process conducted by the investigating physicians. Furthermore, it is essential to consider the decision of the medical committee of the registry to integrate the data on patients with CHD from the two branches into a unified population, given that CHD was present in the overwhelming majority of patients (91.6%) from the primary branch.

Conclusion

A comparative analysis of the degree of coronary artery obstruction in patients with verified CHD included in the KAMMA registry revealed that 8.7% of patients had coronary artery stenosis of less than 50%. A distinctive feature of patients with non-obstructive coronary atherosclerosis included in the registry was the high prevalence of MFA lesions in both brachycephalic arteries (94.3%) and lower limb arteries (40.2%). A significant prevalence of female patients with non-obstructive CHD was observed. The prevalence of risk factors such as smoking and DM type 2 was found to be lower in this group of patients than in patients with obstructive CHD. Patients with non-obstructive coronary atherosclerosis were more likely to have a history of DLP, to have higher levels of TC and non-HDL–C, and to receive moderate-intensity statin therapy more frequently than patients with obstructive atherosclerosis (55.8% vs. 34.5%). A distinctive feature of patients with non-obstructive atherosclerosis was the relatively milder clinical manifestations of CHD. The history of ACS was less frequent in this group, yet the prevalence of strokes, peripheral arterial thrombosis, and chronic arterial insufficiency of the lower limbs did not differ between patients in Groups 1 and 2. The prevalence of paroxysmal AF was higher in the non-obstructive form of CHD.

Consequently, patients with CHD and the absence of coronary artery obstruction are also in need of peripheral arterial evaluation, as they may have widespread MFA, which should be taken into account when determining the appropriate level of intervention aggressiveness. A new paradigm for the management of patients with stable CHD is required, one that takes into account the multitude of pathogenetic mechanisms responsible for angina and ischemia, as well as the generalized lesion of the arterial bed, which is present in the majority of patients. This new paradigm is necessary to establish diagnostic and therapeutic approaches that can more effectively tailor the appropriate treatment of obstructive and non-obstructive causes of myocardial ischemia to the individual characteristics of the patient [3].

Information and ethical compliance during the study

The study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The study was approved by the Ethics Committee of the N.I. Pirogov Russian National Research Medical University for investigational sites in the Russian Federation (minutes #212, dated November 22, 2021) and local ethics committees of foreign investigational sites. ClinicalTrials.gov registration number: NCT05189847. Information regarding the registry is accessible on the websites designated for physicians (https://promfa.ru/) and patients (https://mfainfo.ru/).

No conflict of interest is reported.

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