Gender differences in the detection of carotid atherosclerosis: DUPLEX registry cross-sectional study results

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Abstract

The aim of this study was to assess the features of detecting carotid atherosclerosis depending on gender, age, the presence of arterial hypertension, other major diseases and conditions according to The Duplex Registry Database. The registry sequentially included the results of duplex scanning of the carotid arteries (DSCA) of all patients who underwent it at the United Hospital with Outpatient Department in 2013 (n=2548). The incidence of carotid atherosclerosis (CAS) was higher in men than in women (58.6% (n=763) *vs* 45.5% (n=568), p<0.0000001). This was noted in all categories according to the gradation of stenosis, including in the category of the most severe lesion (>70%): 2.9% (n=32) *vs* 1.0% (n=13), p=0.003. The presence of CAD significantly increased the chances of detecting CAS in men (OR 4.47 *vs* 2.6, p<0.0000001). Signs more significant in their influence in women compared to men were the following: age (OR 5.3 [4.12; 6.71] p<0.0000001); arterial hypertension (OR 2.7 [2.12; 3.39] p<0.0000001) and cerebrovascular disease (OR 1.63 [1.13; 2.36] p=0.004). The OR of CAS detection for the "acute cerebrovascular accident" diagnosis in men and women differed 2 times (OR 1.2, p=0.4 *vs* 2.4, p=0.15). The "hypercholesterolemia" diagnosis when referred for DSCA did not show itself as a predictor of CAS detection in all study groups. Disorders of autonomic nervous system, hearing loss and screening examination showed a significant decrease in the probability of CAS detecting for the whole group (OR 0.14 [0.08;0.24] p<0.0000001; OR 0.16 [0.02;0.66] p=0.004 and OR 0.3 [0.25 0.37] p<0.0000001, respectively), so and separately for males and females. The present study revealed significant gender differences in the prevalence of carotid atherosclerosis and in the influence of various signs on an increase in the chances of its detection. The most significant signs were (OR men vs women): gender (1.3 *vs* 0.8), age (4.2 *vs* 5.3), arterial hypertension (1.8 *vs* 2.7), CAD (4.4 *vs* 2.6), cerebrovascular disease (1.26 *vs* 1.63).

Introduction

The different prevalence of known risk factors for the development of cardiovascular diseases in men and women certainly have different effects on their influence on the development of atherosclerotic lesions of various vascular regions [1-4]. This is confirmed by gender differences in incidence and mortality from myocardial infarction and stroke in men and women, depending on the main risk factors [3-5]. Stroke is the leading cause of death in European countries in 26% of all deaths from cardiovascular diseases in women and 21% in men [1]. It is important to note that the role of the presence of even non-obstructive atherosclerotic lesions of the carotid arteries in the genesis of cryptogenic stroke in young people has been discussed [6].

There are available data on the presence of gender differences not only in the anatomy of the carotid arteries (CA), but also in the detection of carotid atherosclerosis (CAS). This was confirmed by

the analysis of data from the European Carotid Surgery Trial (ECST): atherosclerotic plaque (AP) of the carotid artery is more common in men, and an increase in IMT in the absence of stenosis is more common in women [7]. Similar results were obtained later in a relatively recent italian research [8], as well as in other european studies [9-11]. An in-depth analysis of these gender differences has received increasing attention in clinical observational studies. The medical scientific community has increasingly given an important role in this issue to the analysis of databases of large observational registries [5,12]. This study aimed to assess gender differences in carotid atherosclerosis depending on age, the presence of arterial hypertension, other major diseases and conditions according to the Duplex Registry Database.

Materials and Methods

The Duplex Registry Database was used to conduct this study. This registry sequentially included the results of duplex scanning of the carotid arteries (DSCA) of all patients who underwent outpatient and inpatient examination at the United Hospital with Outpatient Department in 2013. There were no exclusion criteria. All patients who underwent this study in 2013, regardless of the reason for referral to DSCA, were enrolled in this registry. The final database for analysis after excluding repeated studies during the year was 2548 primary patients.

Duplex scanning was carried out on a Vivid 7 device (General Electric) according to the standard technique using multi-section linear sensors (L9, L12, 9-12 MHz). Both common CA (CCA) were examined in longitudinal and transverse projections in order to determine the section where AP had the largest size. CCA bifurcations on both sides, internal and external CA, vertebral arteries, subclavian arteries were also thoroughly investigated. IMT was determined in B-mode (the norm was up to 1.0 mm) at three points of the distal part of both CCA at a distance of 1.0 cm from the bifurcation (the maximum value was chosen for each CA). If AP was verified in CCA, IMT was determined in an area free from AP (in the intact area). The percentage of stenosis was determined in the area of maximum narrowing of the lumen of the artery according to the ECST criteria (in% of the diameter and area of the vessel lumen) [13] in accordance with the guidelines for performing duplex scanning [14]. The linear blood flow velocities (LBFV) in the carotid arteries were measured; in the assessment of hemodynamically significant stenoses LBFV gradients were taken into account. Lack of blood flow in the CA lumen was considered occlusion.

DSCA was performed by two highly qualified specialists with more than 20 years of experience using a single unified protocol, which made it possible to minimize the level of inter-operator variability between operators.

All patients initially signed a written consent to examination and informed consent to the processing of personal data. Additional written informed consent for each participant was not required for such a retrospective study. All patient record's information were anonymized before analysis.

All registry patients were divided into 5 grades depending on the degree of carotid atherosclerosis (CAS) detected: 0 - no atherosclerotic plaque (AP) was detected in the carotid arteries during duplex scanning; 1 - AP, stenosing the lumen from 20 to 49%; 2 - AP, stenosing the lumen from 50 to 69%; 3 - AP, stenosing the lumen from 70 to 99%; 4 - occlusion detected. Verification of Duplex registry patients for ICD-10 diagnoses preceding the referral for DSCA was carried out on the basis of the diagnosis code in the direction of the study during the previous medical examination.

Statistical analysis

OpenEpi Version 3 and Statistica 10 software packages were used for statistical analysis, data processing and graphical transformation. Data of groups presented as absolute numbers and percentages (or, if applicable, mean and standard deviation). Standard descriptive statistics methods were applied. Comparison of two independent groups for quantitative variables was carried out using the Wald-Wolfowitz test and the Mann-Whitney U-test. The Levene test was used to test whether the studied samples have equal variances. The chi square test was used to compare groups for categorical variables (if necessary, Fisher's exact test was applied depending on the size of the subgroups). An approach based on the adjusted Mantel-Hensel ratio using two-by-two tables was applied to calculate the odds ratio with the adjusted point estimate and the confidence interval (the Taylor series approach was applied for confidence intervals) [15,16]. The odds ratio (OR) and 95% confidence interval (CI) were calculated to determine the influence of various factors on the likelihood of detecting carotid atherosclerosis, confirmed by the presence of atherosclerotic plaque stenosing the lumen of the carotid artery by 20% or more (which corresponds to 1-4 grading's level). Differences were considered statistically significant when p<0.05.

Results

The general characteristics of study group participants for ICD-10 diagnoses preceding referral to DSCA are presented in Table 1.

The analysis of the prevalence of the main risk factors in both genders was carried out with regard to hypercholesterolemia (HCHL) and arterial hypertension (AH). Arterial hypertension was registered in 45.64% of the study participants (n=1163). Moreover, in men it was registered in a slightly higher percentage of cases: 47.88% (n=624) vs 43.22% (n=539) (p=0.02). The prevalence of HCHL (according to the total cholesterol criterion >5 mmol / L) in men and women was 69.07% and 72.03% respectively (p=0.2267).

Analysis of the lipid-lowering therapy (LLT) performed in men and women showed in general its rather low level of use, however men took statins significantly more often than women (27.8% vs 17.7%, p=0.000008).

The average total cholesterol level in men and women was 5.73±1.22 and 5.89±1.13 mmol/l, respectively. Statistical analysis gave contradictory results in relation to group comparison: the application of the Wald-Wolfowitz test did not give significant differences (p=0.72) in contrast to the Mann-Whitney test (p=0.035). In this connection, analysis using Levene test was performed to check whether the data samples have equal variances. The following result was obtained: Levene F (1, ss) = 3.612165, p=0.05758.

Comparison of male and female groups depending on the CAS degree grading are presented in Figure 1. The incidence of CAS was higher in men than in women [58.6% (n=763) vs 45.5% (n=568), p<0.0000001]. This was noted in all categories according to the grading of stenosis, including in the category of the most severe lesion [grade 3 + grade 4: 2.9% (n=32) vs 1.0% (n=13), p=0.003]. Hemodynamically significant lesions of the carotid arteries with stenosis from 70 to 99% (grade 3) differed between genders by almost 2 times [1.9% (n=25) vs 1.0% (n=13)]. The presence of carotid artery occlusions was found only in males (n=7).

Table 1. General characteristics of Duplex registry patients in the according to ICD-10 diagnoses prior to referral to duplex scanning of the carotid arteries.

	ICD-10	n	% in the whole group	CAS grading in subgroups	% in the subgroup
Hypertension					
	I11	n=1163	45.6%	0 – 433	37.2%
				1 – 633	54.4%
				2 – 76	6.5%
				3 – 18	1.5%
				4 – 2	0.08%
Cerebrovascular diseases		n=195	7.65%		
incl.:	I67.2	n=3	0.12%	0 – 80	41.0%
	I67.8	n=118	4.63%	1 – 95	48.7%
	I67.9	n=74	2.9%	2 – 13	6.7%
				3 – 5	2.6%
				4 – 2	1.0%
Acute cerebrovascular accident		n=14	0.54%		
	I61-64	n=7	0.27%	0 – 5	35.7%
	G45	n=7	0.27%	1 – 8	57.1%
				2 – 1	7.1%
				3 – 0	0
				4 – 0	0
Hypercholesterolemia					
	E78	n=144	5.65%	0 – 77	53.5%
				1 – 65	45.1%
				2 – 2	1.4%
				3 – 0	0
				4 – 0	0
Coronary artery disease		n=161	6.32%		
incl.:	I21	n=6	0.24%	0 – 32	22.2%
	I25.2	n=49	1.92%	1 – 103	71.5%
	I25.8	n=106	4.16%	2 – 19	13.2%
				3 – 5	3.5%
				4 – 2	1.4%
Atherosclerosis		n=40	1.6%		
incl.:	I70	n=3	0.12%	0 – 5	12.5%
	I70.0	n=1	0.04%	1 – 17	42.5%
	I70.2	n=4	0.16%	2 – 13	32.5%
	I70.8	n=6	0.24%	3 – 4	10.0%
	I70.9	n=26	1.02%	4 – 1	2.5%
Disorders of autonomic nervous system					
	G90.8	n=122	4.78%	0 – 104	85.2%
				1 – 18	14.8%
				2 – 0	0
				3 – 0	0
				4 – 0	0
Diabetes mellitus					
	E11	n=27	1.06%	0 – 12	44.4%
				1 – 14	51.9%
				2 – 1	3.7%
				3 – 0	0
				4 – 0	0
Atrial fibrillation					
	I48	n=26	1.02%	0 – 11	42.3%
				1 – 15	57.7%
				2 – 0	0
				3 – 0	0
				4 – 0	0
Obesity					
	E66	n=5	0.2%	0 – 3	60.0%
				1 – 2	40.0%
				2 – 0	0
				3 – 0	0
				4 – 0	0

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The odds ratio (OR) and 95% confidence interval (CI) were calculated to determine the influence of various factors on the probability of CAS detecting, taking into account the purpose of this study (Figure 2). Important gender differences in CAS detection were obtained in the present study: male gender (as opposed to female) significantly increased the chances of CAS detecting [OR 1.3 (1.13;1.48) p=0.000008 *vs* OR 0.8 (0.67;0.88) p=0.00005].

The presence of CAD significantly increased the chances of CAS detecting in men than in women (OR 4.47 *vs* 2.6, p<0.0000001). Signs more significant in their influence for women in comparison with men were age [OR 5.3 (4.12; 6.71) p<0.0000001]; arterial hypertension (AH) [OR 2.7 (2.12;3.39) p<0.0000001] and cerebrovascular disease (CEVD) [OR 1.63 (1.13 2.36) p=0.004].

ACVA diagnosis (combining stroke and TIA; n=14) for the whole group also increased the chances of CAS detecting by 1.6 times but did not reach statistical significance [OR 1.6 (0.55;5.0) p=0.18]. It should be noted that the OR of CAS detection of this diagnosis in men and women differed 2 times (OR 1.2 *vs* 2.4), but these differences were not statistically significant (probably due to the small sample size of these subgroups). At the same time, a significant criterion for the whole group was the diagnosis of stroke, which significantly increased the chances of CAS detecting, despite the extremely small size of the group (n=7): OR 5.5 (0.7; 45.7) p=0.04. (*Authors' note: Descriptions of these groups, as well as other groups with other diagnoses with a small number of participants (n<10), are not given in the summary table (Figure 2).*

The presence of a diagnosis of diabetes mellitus (DM) and atrial fibrillation (AF) increased the chances of CAS detecting only in women by 1.4 and 2 times respectively, without reaching the level of statistical significance.

The diagnosis of hypercholesterolemia (HCHL) when referred for DSCA did not show itself as a predictor of CAS detection in any of the study groups: the whole group (OR 0.78), women (OR 0.85), men (OR 0.5).

Referring diagnoses such as disorders of autonomic nervous system (DANS), hearing loss and screening examination (according to this study showed a significant decrease in the likelihood of CAS detecting for the whole group [OR 0.14 (0.08;0.24) p<0.0000001; OR 0.16 (0.02;0.66) p=0.004 and OR 0.3 (0.25;0.37) p<0.0000001, respectively], and separately for males and females.

Discussion

Gender differences in the influence of various signs and conditions on CAS detection were confirmed in this study in a large cohort of patients (n=2548). We also obtained data on the prevalence and severity of CAS in men. The results obtained largely confirm the data of previous studies, but at the same time there are certain discrepancies in the significance of the influence of various signs in men and women.

The PESA study (n=3860) showed that the plaque burden was higher in men than in women [63.4 mm^3 (23.8;144.8) *vs* 25.7 mm^3 (11.5;61.6) p<0.001] [9].

In the ATHEROGEN study (n= 100), it was also revealed that all manifestations of CAS in men were significantly more pronounced than in women, both according to the criterion of the average maximum stenosis [27% (0-34) *vs* 22% (0-58), p=0.000] and total stenosis [48% (0-90) *vs* 22% (0-31), p=0.000] [11].

Table 1. Continued from previous page.

	ICD-10	n	% in the whole group	CAS grading in subgroups	% in the subgroup
Conductive and sensorineural hearing loss					
	H90	n=13	0.5%	0 – 11	84.6%
				1 – 0	0
				2 – 0	0
				3 – 2	15.4%
				4 – 0	0
Migraine					
	G43	n=5	0.2%	0 – 4	80.0%
				1 – 1	20.0%
				2 – 0	0
				3 – 0	0
				4 – 0	0
Syncope					
	R55	n=6	0.23%	0 – 4	66.8%
				1 – 1	16.6%
				2 – 1	16.6%
				3 – 0	0
				4 – 0	0
Examination and observation for other specified reasons					
	Z01.8	n=622	24.41%	0 – 431	69.4%
	Z03.5			1 – 180	28.9%
	Z04.8			2 – 7	1.1%
	Z13.6			3 – 4	0.6%
	Z13.8			4 – 0	0
Total		2548	100%		

Age and AH were associated with CAS regardless of gender in our study, but in women the significance of these signs was more pronounced [OR 5.3 (4.12;6.71) *vs* OR 4.2 (3.53; 4.94) and OR 2.7 (2.12;3.39) *vs* OR 1.8 (1.45;2.38), respectively]. A study carried out by Ojima *et al.* also found that AH was the only common risk factor for both genders to detect a high IMT and a high carotid plaque score [17].

As for the more significant influence of the age factor in women, we can assume a significant role that menopause and hormonal changes may have contributing to the development of ACVD in the fourth-fifth decade of life in women. These assumptions were confirmed by Li *et al.* [18]. Menopause was significantly associated with the risk of developing carotid plaques [HR 1.93, (1.05; 3.54) p=0.03] [18].

Diagnosis of HCHL and DM did not show itself as a sign associated with CAS in our work compared to another recent Russian study [19]. The percentage of lipid-lowering therapy in patients with "hypercholesterolemia" diagnosis in our study was only 32.17%. Such a low percentage of LLT prescription can probably be explained by the fact that a practitioner made this diagnosis as the main when referring to DSCA to a patient without a confirmed CVD history and referred to DS in order to re-stratify the level of cardiovascular risk and the subsequent decision to initiate statin therapy. In addition, this can be explained by the fact that there is evidence that dyslipidemia and DM may manifest themselves as more significant factors in relation to atherosclerosis of other localizations. In the AWHS study OR of CAS detection depending on the presence of dyslipidemia, AH and DM, significantly differed in their influence on predicting the detection of coronary and femoral atherosclerosis [20]. Dyslipidemia, AH and DM appeared to be more significant factors in relation to the detection of femoral and coronary atherosclerosis in comparison with CAS: OR 1.46 (1.17;1.83), 1.24 (0.99;1.55) *vs* 1.2 (0.96;1.96); OR 1.66 (1.31;2.1), 1.69 (1.34;2.13) *vs* 1.41 (1.12;1.78) and OR 2.11 (1.2;3.7), 1.29 (0.79;2.1) *vs* 1.19 (0.73;1.94), respectively [20].

Somewhat similar, but at the same time with certain differences, the results were obtained in the PESA study. Age, gender and HCHL were more strongly associated with femoral atherosclerosis than with CAD, whereas AH and DM showed no territorial differences [9]. Another explanation for the absence of a signifi-
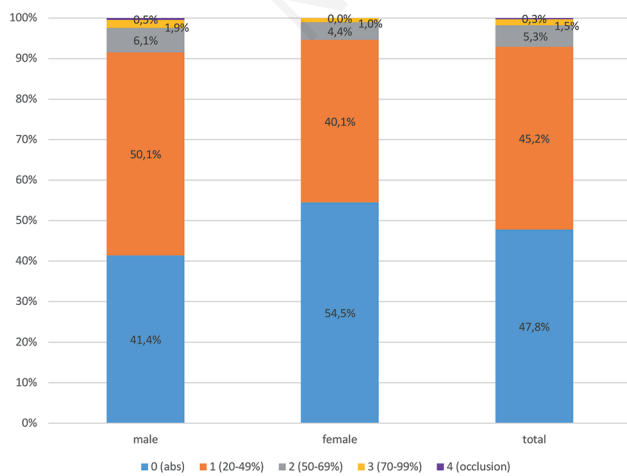
cant effect of HCHL on predicting of CAS detection is that this sign manifests its role at earlier stages of the development of the cardiovascular continuum even before the formation of ACVD [21]. On the other hand, there is evidence that not just HCHL, but a more accurate characterization of dyslipidemia as a high level of LDLc/HDLc can be significantly associated with the presence of carotid plaques, which was confirmed in a Chinese study in patients at high risk of stroke [22].

The presence of CAD increased the OR of CAS detection both for the whole study group and separately in men and women in the present study [4.0 (2.67; 5.9), 4.4 (2.75; 6.9) *vs* 2.6 (1.24; 5.73)]. Contradictory data on the correlations between CAS and CAD were obtained in a recent Korean study. A significant proportion of patients had a discrepancy between the presence of AP in carotid artery and CAD. Male gender [OR 1.71 (1.20; 2.41) p=0.003], age OR [1.03 (1.01; 1.04) p=0.002] and end-diastolic blood flow

Figure 1. Features of carotid atherosclerosis detection depending on gender.

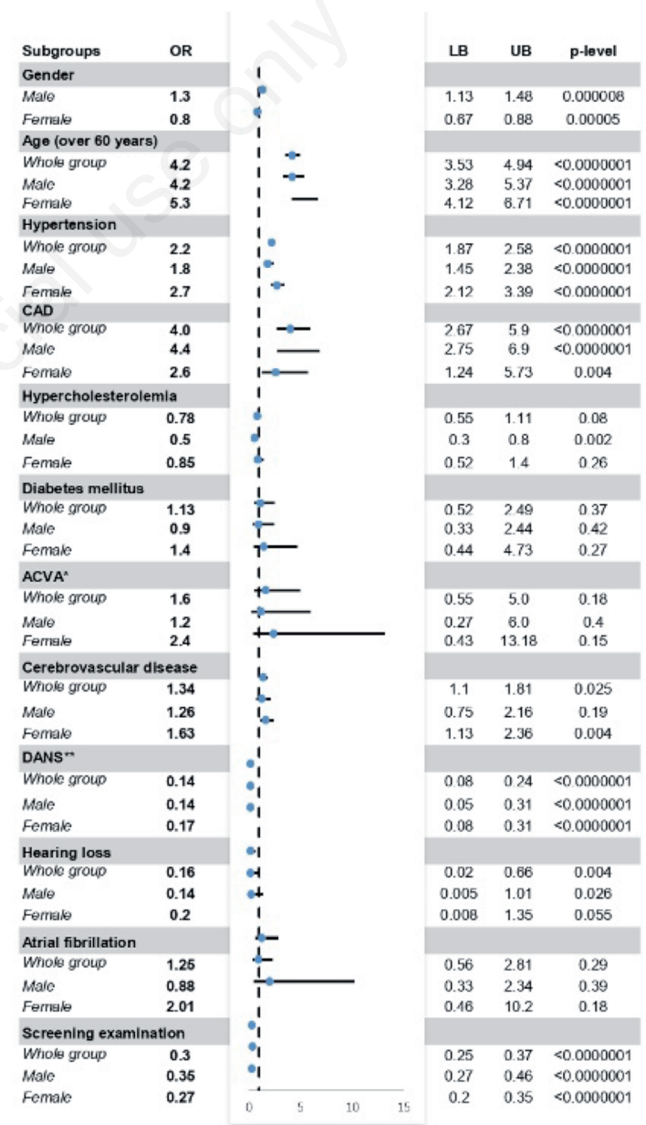| Subgroups	OR		LB	UB	p-level
Gender					
Male	1.3		1.13	1.48	0.000008
Female	0.8		0.67	0.88	0.00005
Age (over 60 years)					
Whole group	4.2		3.53	4.94	<0.0000001
Male	4.2		3.28	5.37	<0.0000001
Female	5.3		4.12	6.71	<0.0000001
Hypertension					
Whole group	2.2		1.87	2.58	<0.0000001
Male	1.8		1.45	2.38	<0.0000001
Female	2.7		2.12	3.39	<0.0000001
CAD					
Whole group	4.0		2.67	5.9	<0.0000001
Male	4.4		2.75	6.9	<0.0000001
Female	2.6		1.24	5.73	0.004
Hypercholesterolemia					
Whole group	0.78		0.55	1.11	0.08
Male	0.5		0.3	0.8	0.002
Female	0.85		0.52	1.4	0.26
Diabetes mellitus					
Whole group	1.13		0.52	2.49	0.37
Male	0.9		0.33	2.44	0.42
Female	1.4		0.44	4.73	0.27
ACVA^					
Whole group	1.6		0.55	5.0	0.18
Male	1.2		0.27	6.0	0.4
Female	2.4		0.43	13.18	0.15
Cerebrovascular disease					
Whole group	1.34		1.1	1.81	0.025
Male	1.26		0.75	2.16	0.19
Female	1.63		1.13	2.36	0.004
DANS**					
Whole group	0.14		0.08	0.24	<0.0000001
Male	0.14		0.05	0.31	<0.0000001
Female	0.17		0.08	0.31	<0.0000001
Hearing loss					
Whole group	0.16		0.02	0.66	0.004
Male	0.14		0.005	1.01	0.026
Female	0.2		0.008	1.35	0.055
Atrial fibrillation					
Whole group	1.25		0.56	2.81	0.29
Male	0.88		0.33	2.34	0.39
Female	2.01		0.46	10.2	0.18
Screening examination					
Whole group	0.3		0.25	0.37	<0.0000001
Male	0.35		0.27	0.46	<0.0000001
Female	0.27		0.2	0.35	<0.0000001

Figure 2. The odds ratio of CAS detecting depending on gender, age, presence of arterial hypertension, other diseases and conditions according to the DUPLEX registry. *ACVA, acute cerebrovascular accident; **DANS, disorders of autonomic nervous system.

velocity in the common carotid artery (CCA-EDV) [OR 0.97 (0.95;0.99) p=0.005] were independently associated with the presence of CAD in patients without CAS [3].

This can be explained by the fact that ethnic and racial differences in patients can have a significant impact on the results of studies even at the level of one population of a particular geographic region [12,23], and even more so carried out in different countries.

It is worth noting the limitations of this study. Patient diagnosis verification was carried out on the basis of the diagnosis according to the ICD code entered in the Duplex Registry Database and was based on the diagnosis indicated in the medical report when the patient was referred for duplex scanning. Of course, this could not take into account the problem of patients' polymorbidity, but this approach is now generally accepted in clinical trials, when the patient's diagnosis is verified using the ICD diagnosis code registered in the electronic database [24-26].

Another limitation of this study is to consider the effect of lipid-lowering therapy on the potential bias of data, as it is known that statins have an influence on the development and formation of atherosclerotic plaque in the carotid artery. However, the fact that the LLT prescription in the present study was low (23%) and the total cholesterol level did not reach the target values (the average total cholesterol level in the group was 5.81±1.18 mmol/l) suggests that the influence of this factor the bias in the data was minimal and could not influence the conclusions reached in the present study.

Conclusions

Significant gender differences were identified in the present study in the higher prevalence of stenosing atherosclerosis of the carotid arteries among men compared to women, including severe hemodynamically significant lesions. Gender differences were also revealed in the influence of various diseases / conditions on an increase in the chances of CAS detecting (OR men *vs* women): i) signs with a high level of statistical significance - age over 60 years (1.3 *vs* 0.8), AH (1.8 vs 2.7), CAD (4.4 *vs* 2.6), CEVD (1.26 *vs* 1.63); ii) signs that did not confirm statistical significance - DM (0.9 *vs* 1.4), ACVA (1.2 *vs* 2.4), AF (0.8 *vs* 2.0). Baseline diagnoses such as HCHL, DANS, hearing loss and screening examination showed a decrease in the likelihood of CAS detecting according to this study. The obtained results can be useful in setting up patients' examination in real clinical practice, including when they are referred to DSCA.

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