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Characteristics of aortic valve stenosis in urban population aged 35–69 years: prevalence, echocardiographic data, atrial fibrillation, biomarkers, lipoprotein(a)

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The aim of the study is to characterise the prevalence and echocardiographic (EchoCG) features of aortic valve stenosis (AVS) and to evaluate the associations of aortic valve area (AVA) with lipoprotein(a) (Lp(a)), the heart failure (HF) biomarker NT-proBNP and atrial fibrillation (AF) in an adult population.

Methods. We used data from the "Know your heart study" with a cross-sectional design, which included 2380 participants aged 35–69 years, recruited in 2015-2017. In 2328 respondents, the following were determined by EchoCG: mean pressure gradient (Gmean), mmHg, peak aortic blood flow velocity (Vmax), m/s. The presence of AS was confirmed by a ⩾15 mmHg and a Vmax at the valve ⩾2.5 m/s. In 2105 participants, AVA, cm^2 and the prevalence of severe AVS were determined by the continuous flow equation according to the criteria: AVA ⩽1.0 cm^2 and indexed AVA (iAVA) ⩽0.6 cm^2/m^2. Subtypes of AVS — high-gradient (HG) and low-gradient (LG) were distinguished according to EACI and ASE (2017) criteria. Structural and functional EchoCG parameters of the heart, disease history, biomarkers (troponin T, N-terminal prohormone of brain natriuretic peptide (NT-proBNP), Lp(a)) were used in the analysis.

Results. The prevalence of high gradient aortic valve stenosis (HGAVS) (Gmean ⩾15 mmHg) was 0.43% (n=10), 0.2% aged 40–59 years and 1.1% aged 60–69 years (p=0.007); 0.6% in men and 0.3% in women. The prevalence of severe low gradient aortic valve stenosis (LGAVS) was 0.9% (n=18, 61% men) and all had a left ventricular ejection fraction (LVEF) >50%. The formation of concentric LV remodelling was detected in those with HGAVS, and the predominance of diastolic dysfunction was found in those with severe LGAVS. AVA value was associated with male gender (ß=0.383, p<0.001), age (ß=-0.097, p<0.001) and Lp(a) (ß=-0.048, p=0.018). In patients with severe LGAVS, NT-proBNP levels were Me 158.4 (105.4; 260.8) pg/ml and were higher than those without AVS (p=0.005). NT-proBNP correlated with iAVA and AF correlated with age, HF and AVA.

Conclusion. The prevalence of mild to moderately severe HGAVS according to echocardiography in the population was 0.2% at the age of 40–59 years and 1.1% at the age 60–69 years. Severe LGAVS occurred in 0.9% of participants. AVA was negatively associated with Lp(a) when corrected for sex and age. NT-proBNP and AF were associated with AVA when corrected for HF, age and sex.

Keywords: high-gradient, low-gradient aortic stenosis, population, prevalence, lipoprotein(a), N-terminal prohormone of brain natriuretic peptide (NT-proBNP).

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Introduction

Due to an ageing population, the incidence of aortic valve stenosis (AVS) and its reconstructive surgery is increasing worldwide [1, 2]. A systematic review and meta-analysis of population-based studies conducted in European countries and North America showed that the prevalence of AVS in the elderly population (age ⩾75 years) is 12.4%, and severe AVS is present in 3.4% of elderly patients who are candidates for transcatheter aortic valve replacment (TAVR) [3]. In an epidemiological study conducted in Northern Norway (Tromsø), the prevalence of AVS was 0.2% in 50–59 year olds and 1.3% in 60–69 year olds [4]. It is noteworthy that the geographical distribution of AVS is heterogeneous. Regional clustering of AVS cases and observations of familial aggregation suggest that the genetic component contributes to the pathophysiology of AVS [5]. Researchers are currently focusing on lipoprotein(a) (Lp(a)), which is considered to be an important genetic risk factor for the development of atherosclerotic cardiovascular disease and AVS [6, 7].

In individuals with AVS, the mean pressure gradient (Gmean) often does not correspond to the aortic valve opening area (AVA), which is determined by multiple factors, both valvular (aortic valve calcification) and non-valvular (arterial stiffness), independent of flow. Of importance is the assessment of the severity of AV calcification by computed tomography (CT), which is strongly associated with the severity of AVS [8]. The AVS syndrome is heterogeneous, and low-gradient (LG) and high-gradient (HG) subtypes of AVS have been identified. Patients with "classical" LGAVS with reduced left ventricular ejection fraction (LVEF) have the worst prognosis after TAVR, including one-year

survival, compared to patients with HGAVS and "paradoxical" LGAVS with preserved LVEF [9, 10]. This phenomenon can often be misdiagnosed, leading to underestimation of symptoms and inappropriate delay of AV replacement surgery [11]. However, not all risk factors and pathophysiological features of the heterogeneous group of LG subtypes of AVS are fully understood and require further investigation. Atrial fibrillation (AF) complicates the course of AVS in 32 % of cases, often in the asymptomatic period with preserved LVEF; according to current thinking, its negative role is due to the transition from the asymptomatic stage of AVS to the symptomatic stage and to the worsening of the prognosis of patients after valve replacement [12]. Therefore, the determination of AF frequency in a population sample in different AVS subtypes seems to be relevant.

The study of HF biomarker levels, N-terminal brain natriuretic peptide (NT-proBNP) propeptide, both in relation to the severity of LV and LA remodelling and in terms of prognostic assessment of the occurrence of myocardial dysfunction after AVS surgery, is reflected in the modern literature [13]. The prospectivity of the determination of high-sensitivity cardiac troponin (hs-Tn) as a biomarker of myocardial damage, which can predict the risk of HF and other adverse cardiovascular events long before the appearance of structural and functional changes in the heart as determined by imaging techniques, has been demonstrated [14]. It is valuable in population studies with regard to the possibility of applying individual preventive measures. The prevalence of AVS and its subtypes in the population of the region (Arkhangelsk) using modern echocardiography (EchoCG) has not been determined.

The aim of the study is to characterise the prevalence and EchoCG features of AVS and to evaluate the associations of AVA with Lp(a), the HF biomarker NT-proBNP and AF in an adult population.

Methods

Data were used from the "Know your heart study" with a cross-sectional design, which included 2380 participants aged 35–69 years recruited in 2015–2017. Information on the methods of sampling and data collection are described in detail in the article by Cook S. et al [15]. The sample was formed on the basis of the anonymised database of the Federal Compulsory Medical Insurance Fund (FOMS). The database, covering four districts of the city, contained addresses of OMS-insured citizens and information on age and sex. Addresses were randomly selected and men and women aged 35–69 living there were invited to participate in the study. Inclusion criteria: living at randomly selected addresses in Arkhangelsk, aged 35–69 years. Exclusion criteria: presence of a mental illness that precludes the possibility of conducting an interview (inability to understand the questions, to answer them adequately); presence of a disability that precludes the possibility of undergoing a medical examination in a polyclinic (not able to walk); refusal to sign an informed consent form. The response rate was 68 %. Participants were given a questionnaire and 98 % underwent a medical examination at the university polyclinic. The present analyzes include 2328 participants in this study (41.4 % male) who had a set of EchoCG parameters necessary to achieve the aim of the study.

To assess AV parameters and structural and functional characteristics of the heart, we used data from transthoracic EchoCG (Vivid q, GE HealthCare) using a phased array transducer 1.5–3.6 MHz, the technique is described by Cook S. et al. [15]. LVEF according to Simpson method, %; LV stroke volume (SV), ml; SV indexed to body surface area (BSA) (iSV), ml/m^2; maximum left atrial (LA) transverse diameter, mm; LA volume (LAV), ml; LAV indexed to BSA (iLAV), min and max, ml/m^2; LV diameter in systole and in diastole, mm; LV posterior wall thickness (PWT) in systole and in diastole, mm; interventricular septal thickness (IVST) in systole and in diastole, mm; relative wall thickness (RWT); LV myocardial mass index (LVMI), g/m^2; pulmonary capillary wedging pressure (PCWP), mmHg; E/é$_{mean}$ (LV early filling velocity by transmittal Doppler/early relaxation velocity by tissue Doppler) reflecting LV filling pressure were determined and used in the analysis.

To detect AVS and assess its severity, peak aortic blood flow velocity (Vmax), m/s, and maximum and mean percutaneous pressure gradient (Gmean), mmHg, were determined. The presence of AVS was confirmed by Gmean ⩾15 mmHg and Vmax at the valve ⩾2.5 m/s.

In 2105 participants, AVA, cm^2 was determined using the continuous flow equation and the incidence of severe AVS was assessed using the criteria: AVA ⩽1.0 cm^2 and indexed AVA to BSA (iAVA) ⩽0.6 cm^2/m^2.

An attempt has been made to distinguish between four subtypes of severe AVS according to the current guidelines [16]:

Normal/preserved LVEF (pEF), HGAVS (NEF HGAVS) (pEF HGAVS): LVEF ⩾ 50 %, aortic Vmax ⩾4 m/s or Gmean ⩾ 40 mmHg, AVA ⩽ 1.0 cm^2;

Low/reduced LVEF (rEF), HGAVS (LEF HGAVS) (rEF HGAVS): LVEF<50 %, aortic Vmax ⩾4 m/s or Gmean⩾40 mmHg and AVA⩽1.0 cm^2.

Low/reduced LVEF, LGAVS ("classic" low-flow, low-gradient) (LEF LGAVS) (rEF LGAVS): LVEF<50 %, Vmax<4 m/s and G_{mean}<40 mmHg, AVA⩽1.0 cm^2, and SV ⩽35 ml/m^2.

Normal/preserved LVEF, LGAVS ("paradoxical" low-flow, low-gradient) (NEF LGAVS) (pEF LGAVS): LVEF⩾50 %, aortic Vmax<4 m/s and Gmean<40 mmHg, AVA⩽1.0 cm^2 and iAVA⩽0.6 cm^2/m^2 and SV⩽35 ml/m^2.

Information on medical history (arterial hypertension (AH), diabetes mellitus (DM), HF, AF) was obtained by questionnaire and screening examination.

Laboratory tests included: high-sensitivity troponin T (hs-Tn), ng/mL; N-terminal propeptide of brain natriuretic peptide (NT-proBNP), pg/mL; and Lp(a), mg/dL. Hs-Tn and NT-proBNP were determined by the immunoelectrochemiluminescence method (Cobas e411 analyzer; Roche Diagnostics GmbH, Hitachi, Japan), Lp(a) by the particle amplification immunoturbidimetric assay (AU 680; Beckman Coulter chemistry system) [15].

Ethical approval. The study was performed in accordance with the standards of Good Clinical Practice and the principles of the Declaration of Helsinki. The protocol of the "Know your heart study" was approved by the local ethical committees of the London School of Hygiene and Tropical Medicine, London, UK (protocol No. 8808, 2015) and the Russian University (protocol No. 01/01-15, 2015). All study participants signed informed voluntary consent.

Statistical analysis. Descriptive data are presented as means (M) with standard deviations (SD) or medians (Me) with quartiles (Q1; Q3). Categorical variables are presented as absolute values and percentages. Comparisons between groups for continuous variables were made using the independent samples t-test. Continuous variables with skewed distributions were analyzed by ln transformation. Comparisons between groups on categorical variables were made using the chi-squared (x2) Pearson test. Associations of continuous variables (AVA, NT-proBNP) with age and sex and a number of other indices were determined using multivariate linear regression. Results of linear regression analysis are presented as standardised β-coefficients. Associations of AVS with dichotomous characteristics (medical history) were examined using multivariate logistic regression analysis with correction for sex and age, with results presented as odds ratios (OR) with 95% confidence intervals (CI). IBM SPSS Statistics 29 software was used for statistical analysis.

Results

The prevalence of AVS according to the Gmean ⩾15 mmHg criterion in the study sample was 0.43 %. The prevalence of HGAVS (mild and moderate) was 0.6 % in men and 0.3 % in women (p=0.489). There were no individuals with severe HGAVS in this sample (Table 1). The age of participants with HGAVS in both sexes was 63.0±9.1 years compared to 53.8±9.7 years

Table 1. **Assessment of AVS frequency and severity, (n=2328)**

AVS gradation By Gmean, mmHg	Both sexes, abs. number, (%)	Males, abs. number, (%)	Females, abs. number, (%)	p	Age (years), both sexes, M±SD	p
No AVS, Gmean<15 mmHg	2318 (99.6)	958 (99.4)	1360 (99.7)	χ^2 (2) = 1.431 p=0.489	53.8±9.7	P_{1-2} 0.022 P_{1-3} 0.365
Mild AVS, Gmean 15–19 mmHg	5 (0.2)	3 (0.3)	2 (0.15)		65.5±6.8	
Moderate AVS, Gmean 20–39 mmHg	5 (0.2)	3 (0.3)	2 (0.15)		60.5±11.3	
Severe AVS, Gmean⩾40 mmHg	0 (0)	0 (0)	0 (0)		—	
Distribution of participants with AVS (Gmean ⩾15 mmHg) in different age groups						
Age groups	**Absolute number of the participants**		**AVS. abs. number, (%)**			**P**
35-39 years	222		0 (0)			x^2 (6) = 17.719 p=0.007
40-49 years	656		1 (0.2)			
50-59 years	698		1 (0.2)			
60-69 years	752		8 (1.1)			

Table 2. **Distribution of the participants by the severity of AVS assessed by AVA, (n=2105)**

AVS gradation by AVA, cm^2	Both sexes Abs. number, (%)	Females, Abs. number, (%)	Males, Abs. number, (%)	p	Age (years), both sexes, M±SD	p
No/mild AVS, AVA>1.5 cm^2	1989 (94.5)	1136 (92.4)	853 (97.37)	χ^2 (2) = 38.931 p<0.001	53.7±9.7	P_{1-2}= 0.051 P_{1-3}= 0.004
Moderate AVS, AVA 1.0–1.5 cm^2	98 (4.7)	86 (7.0)	12 (1.37)		56.1±10.6	
Severe AVS, AVA≤1.0 cm^2	18 (0.9)	7 (0.6)	11 (1.26)		61.1±10.3	

in those without AVS, p=0.003; participants with mild stenosis were older and their age was significantly different from those without AVS (p=0.022). No differences were found in the age of participants with moderate AVS compared to those without AVS (p=0.365).

The distribution of the participants with AVS (Gmean ≥15 mmHg) in different age groups had a significant difference (p=0.007) (Table 1).

Analyzes of the distribution of participants by aortic Vmax also showed the absence of individuals with severe HGAVS (aortic Vmax≥4.0 m/s). We identified 10 individuals (6 men) who had mild to moderate HGAVS according to both criteria (Gmean and aortic Vmax); all 10 had pLVEF ≥50 %.

AVA 1.0-1.5 cm^2 was detected in 4.7 % of participants, with 7 % in females and only 1.37 % in males, AVA ≤1.0 cm^2 was detected in 0.9 % of participants, corresponding to severe AVS, the prevalence of which was higher in males 1.26 % vs. 0.6 % in females (p<0.001) (Table 2). Among those with severe AVS, males predominated with 61.1 %. The mean age was highest in individuals of both sexes with severe AVS, 61.1±10.3 years, and significantly different from that of participants without AVS (P_{1-3}=0.004).

The distribution of participants with severe AVS (AVA≤1.0 cm^2) in different age groups was as follows: 35–39 years (n=199) — 1 participant (0.5 %), 40–49 years (n=591) — 2 people (0.3 %), 50–59 years (n=627) — 1 participant (0.2 %), 60–69 years (n=688) — 14 people (2.0 %), χ^2 (6)=27.284, p<0.001.

All participants with AVA≤1.0 cm^2 had pEF (≥50 %). However, Gmean and Vmax in the aorta did not meet the criteria for severe HGAVS. Gmean was 11.6±7.5 mmHg. To classify these participants into specific subtypes of severe LGAVS, SV (n=15) was also assessed, which was 24.6±7.5 ml/m^2. SV index was≤35 ml/m^2 in 93.3 % (n=14) of participants, corresponding to severe "paradoxical" low-flow LGAVS and pEF. There were no participants with "classic" LGAVS and rEF. Three patients with LGAVS and pEF had missing SV data. One participant with severe LGAVS and SV was 36.8 ml/m^2, i.e. AVS with normal flow/LG and pEF (Appendix 1).

EchoCG parameters of individuals with HGAVS (mild and moderate) were higher than those of individuals with Gmean<15 mmHg. They had higher interventricular septal thickness in diastole (12.5±1.5 mm vs. 10.6±1.6 mm in the comparison group, p<0, 001) and LVMI (146.1±38.8 g/m^2 vs 111.6±28.7 8 g/m^2, p<0.001). LA diameter in systole (43.0±7.1 mm vs 37.3±4.5 mm, p<0.001), iLAV max (39.7±15.0 ml/m^2 vs 27.4±7.4 ml/m^2, p<0.001) were also higher. Moreover, hs-Tn concentration was higher in those with HGAVS (12.44±8.35 pg/ml vs. 7.46±5.59 pg/ml in the comparison group, p=0.002). No differences in diastolic function indices (PCWP and E/é ratio) were found between the comparison groups (Table 3).

A comparative analysis of EchoCG parameters between participants with severe LGAVS (AVA≤1.0 cm^2) and those with AVA>1.0 cm^2 showed that this variant of AVS differed only in systolic IVST (16.6±1.9 mm vs. 15.4±2.3 mm, p=0.020) and diastolic function parameters: iLAV min (14.7±8.8 ml/m^2 vs. 11.9±4.4 ml/m^2, p=0.009), pulmonary capillary wedge pressure (14.7±4.4 vs. 11.3±3.0 mmHg, p<0.001), LV filling pressure (E/é), 10.32±3.56 vs. 7.55±2.43 in the control group, (p<0.001). The other parameters assessed were not significantly different from the group with AVA>1.0 cm^2. In contrast to HGAVS, diastolic function was significantly impaired in patients with LGAVS. Respondents with AVA≤1.0 cm^2 also had higher hs-Tn levels (9.50±5.98 pg/ml vs. 7.46±5.35 pg/ml in the control group, p=0.027) (Table 3).

Lp(a) levels had a skewed distribution: Me 9.9 (4.8–23.8) mg/dl; percentiles: 90th, 59.2 mg/dl; 95th, 83.9 mg/dl; 99th, 129.4 mg/dl.

Univariate linear regression analysis showed that male sex was positively associated with ln-AVA (p<0.001), whereas age (p<0.001), Lp(a) (p=0.004) were negatively correlated with this index. Significant associations of Lp(a) were also maintained in multivariate linear regression (p=0.018) after correction for sex and age (Table 4).

In participants with severe LGAVS, the NT-proBNP concentration was 158.4 (105.4–260.8) pg/ml. In 61 % of participants, NT-proBNP was >125 pg/ml, consis-

Table 3. **Echocardiographic parameters and hs-Tn levels in responders with high-gradient (G_{mean}≥15 mmHg) and low-gradient (AVA≤1.0 cm²) AVS, both sexes**

Parameter	HGAVS		p	LGAVS		p
	G_{mean}≥15 mmHg	G_{mean}<15 mmHg		AVA≤1.0 mm²	AVA>1.0 mm²	
	M±SD			M ± SD		
Mean pressure gradient, mmHg	17.7±2.0* 23.9±6.2#	3.7±1.4	<0.001	11.6±7.5	3.7±1.5	<0.001
AVA, cm²	1.2±0.3	2.4±0.6	<0.001	0.9±0.1	2.4±0.6	<0.001
LA diameter in systole, mm	43.0±7.1	37.3±4.5	<0.001	39.1±4.2	37.3±4.5	0.083
LA volume, ml	33.1±11.7	22.5± 9.5	0.002	26.3±14.5	22.3±9.2	0.069
LA volume index (min), ml/m²	17.2±5.6	12.0±4.7	0.002	14.7±8.8	11.9±4.4	0.009
LA volume index (max)**, ml/m²	39.7±15.0	27.4±7.6	<0.001	31.3±12.0	27.4±7.4	0.071
LVEF, %	57.0±4.3	56.7±5.9	0.926	56.1±4.1	56.8±5.9	0.620
LV diameter in systole, mm	31.3±3.2	30.9±4.1	0.789	30.1±5.1	30.9±4.1	0.428
LV diameter in diastole, mm	52.9±5.3	50.4±4.6	0.086	50.4±5.6	50.3±4.6	0.970
LV posterior wall thickness in systole, mm	16.1±2.2	13.9±2.5	0.002	13.4±2.1	13.9±2.5	0.419
LV posterior wall thickness in diastole, mm	9.8±1.2	8.6±1.4	0.011	8.7±1.4	8.7±1.4	0.788
Interventricular septal thickness in systole, mm	17.5±1.7	15.4±2.3	0.002	16.6±1.9	15.4±2.3	0.020
Interventricular septal thickness in diastole, mm	12.5±1.5	10.6±1.6	<0.001	10.6±1.6	10.9±1.0	0.479
LV relative wall thickness	0.42±0.05	0.38±0.05	0.025	0.39±0.05	0.38±0.06	0.479
LV myocardial mass index, g/m²	146.1±38.8	111.6 ±28.7	<0.001	117.3±26.8	111.6±28.6	0.394
LV filling pressure, E/é	8.45±2.25	7.48±2.43	0.294	10.32±3.56	7.55±2.43	<0.001
Pulmonary capillary wedge pressure, mmHg	12.4±2.2	11.2±3.0	0.294	14.7±4.4	11.3±3.0	<0.001
hs-Tn*, ng/l	12.44±8.35	7.46±5.59	0.002	9.50±5.98	7.46±5.35	0.027

Note. * — When comparing groups, the variable was included in the analysis in ln-transformed form, ** — in individuals with mild AVS, # — in individuals with moderate AVS.

Table 4. **Relationship between AVA (cm²) and lipoprotein(a), sex and age**

Parameter	Univariate analysis*		Multivariate analysis**	
	β	p	β	p
Lipoprotein(a)***	−0.063	0.004	−0.048	0.018
Age	−0.100	<0.001	−0.097	<0.001
Sex, males — 1, females — 0	0.384	<0.001	0.383	<0.001

Note. *— one-factor linear regression; ** — multiple linear regression; *** — the parameter is used in ln-transformed form.

Table 5. **Relationships between ln-NT-proBNP and indexed AVA, HF, sex and age**

Parameter	Multivariate analysis*	
	β	p
iAVA, cm/m²	−0.065	0.001
History of HF (1 — present, 2 — none)	−0.070	<0.001
Age, years	0.398	<0.001
Sex, female.	0.175	<0.001

Note. * — multiple linear regression.

Table 6. **Relationship between AF and the different degrees of AVS**

AVS	AF		Total
	Yes Abs. number, (%)	No Abs. number, (%)	
AVS, defined by AVA*			
Mild/none (AVA >1.5 cm²)	33 (1.7 %)	1950 (98.3 %)	1983 (100 %)
Moderate (AVA 1.0–1.5 cm²)	3 (3.1 %)	95 (96.9 %)	98 (100 %)
Severe (AVA <1.0 cm²)	3 (16.7 %)	15 (83.3 %)	18 (100 %)
Total	39 (1.9 %)	2060 (98.1 %)	2099 (100 %)
AVS, defined by Gmean#			
No AVA stenosis, G_{mean} <15 mmHg	43 (1.9 %)	2266 (98.1 %)	2309 (100 %)
Mild AVA stenosis, G_{mean} 15–19 mmHg	2 (40 %)	3 (60 %)	5 (100 %)
Moderate AVA stenosis, G_{mean} 20–39 mmHg	2 (40 %)	3 (60 %)	5 (100 %)
Total	47 (2.0 %)	2272 (98.0 %)	2319 (100 %)

Note. * — χ^2 (2) = 22,607; p<0,001; # — χ^2 (2) = 72,934; p<0,001.

tent with HF. There was a significant difference in the mean ln-NT-proBNP concentration in participants with different degrees of AVS. The ln-NT-proBNP level was highest in the group with severe AVS (5.18±0.78) and differed significantly from the group with no/mild AVS: 4.40±0.02 (p=0.005), and the latter group differed significantly from the group with moderate AVS: ln-NT-proBNP 4.40±0.02 vs. 4.71±0.10 (p=0.014).

A significant negative correlation of ln-NT-proBNP with iAVA was shown (p=0.001) when adjusted for the presence of HF history, sex and age (Table 5).

The frequency of AF was 16.7 % in participants with severe LGAVS and 40 % in those with HGAVS (Table 6).

Table 7. **Associations of AF with medical history, AVA, age and sex**

Parameter	OR*	95 % CI OR	p	OR adjusted**	95 % CI OR adjusted	p
Age, years	0,92	0,89–0,96	<0,001	0,95	0,91–0,99	0,019
Sex, male	1,05	0,58–1,89	0,880	—	—	
AH	0,31	0,16–0,61	0,001	—	—	
DM	0,43	0,20–0,94	0,034	—	—	
HF	0,17	0,09–0,31	<0,001	0,24	0,12–0,47	<0,001
AVA***, cm^2	1,89	1,65–14,98	0,004	3,76	1,23–11,47	0,020

Note. * — one-factor linear regression; ** — multiple linear regression; *** — the parameter is used in ln-transformed form.

In the univariate logistic regression models, AF was significantly associated with age (p<0.001), history, AH (p=0.001), DM (p=0.034), HF (p<0.001) and ln-AVA (p=0.004). In the multivariate model (Table 7), significant associations of AF with age, history of HF and ln-AVA remained (OR=3.76, p=0.020).

Discussion

In the «Know your heart» study, the prevalence of HGAVS was 0.2 % in the age group of 40–59 years and 1.1 % in the age group of 60–69 years, which is comparable to data from an epidemiological study conducted in northern Norway (Tromsø) using the same assessment criterion, Gmean ⩾15 mmHg. In the Tromsø study, the prevalence of AVS was 0.2 % in the 50–59 year age group and 1.3 % in the 60–69 year age group [4]. In the series of population-based studies by Nkomo V. T. et al, the prevalence of AVS was closely related to age, with an OR of 2.5 (95 % CI 2.0–3.1) for each 10-year increase in age [18].

In our sample of participants, mild and moderate HGAVS were detected; there was no severe HGAVS in individuals under 70 years of age. Moderate AVS, defined by an AVA of 1.0–1.5 cm^2, was found in 4.7 % of participants and severe (low-grade) in 0.9 %. The incidence of severe LGAVS was 10 times higher in the 60–69 years age group compared to the 40–49 and 50–59 years groups and was 2.0 %. Participants with LGAVS require reassessment and additional diagnostic techniques, particularly determination of the extent of AV calcinosis by CT scan [17]. Snir A. D. et al. analyzed a large EchoCG database [2] and found that of 192060 patients with native AV, 12013 patients (6.3 %) had severe AVS. Of these, 5601 (46.6 %) had severe high-gradient AVS, whereas 6412 (53.4 %) had severe low-gradient AVS. In 2561 patients with low gradient who had data on SV and/or LVEF, the prevalence of different subgroups of AVS was estimated in them, which were LGAVS and pEF 19.2 %, "paradoxical" (low flow, LG, pEF) 20.8 %, "classical" (low flow, LG, rEF) severe AVS 13.3 %. It should be noted that the average age of the participants in the sample was 75 years.

HGAVS and severe LGAVS in the age group we analyzed (35–69 years) was more common in men, but among participants with AVA of 1.0–1.5 cm^2 corresponding to moderate AVS, 87.8 % were women. Although the literature suggests that women with AVS have several distinctive characteristics compared to men [19], gender differences in the prevalence and developmental features of AVS were not considered in our article. We also concluded that male gender was positively associated with AVA, while the age was negatively associated.

Lp(a) is a new risk factor for AVS [7, 20]. Its high level is associated with both microcalcification and macrocalcification of AV, especially in relatively young healthy people (45–54 years) [7]. We also obtained a negative association of Lp(a) with AVA in the 35–69 years age group, which remained significant after adjustment for sex and age. Lp(a) is very rarely evaluated in routine clinical practice in Russia. According to the European Atherosclerosis Society document [7], it is recommended to check Lp(a) concentration at least once in adults; multiple testing is of potential value in familial hypercholesterolaemia, as well as in a family or individual history of (very) high Lp(a) levels or premature CVD.

Characteristics of HGAVS include significant structural changes in the LV and LA myocardium, the development of concentric remodelling (tendency to higher mean RWT) and LV hypertrophy, and higher levels of hs-Tn. A circulating biomarker, hs-Tn, is now considered a highly sensitive indicator of myocardial damage, increased apoptosis, low-grade systemic inflammation and fibrosis formation, as the small increase in hs-Tn independently predicts the occurrence of HF, other adverse events and higher mortality [14]. Structural changes of the LV and LA myocardium in individuals with severe "paradoxical"

LGAVS were less severe, and less high levels of hs-Tn were observed. However, these individuals showed signs of diastolic dysfunction and high levels of NT-proBNP, suggesting the presence of latent HFpEF. "Paradoxical" low-flow LGAVS shares many pathophysiological and clinical similarities with HFpEF [21, 22]. The prevalence of this AVS subtype increases with age, and is more common in women and individuals with the presence of concomitant systemic AH. This variant of AVS is also characterised by restrictive physiology, the development of fibrosis, resulting in markedly reduced LV pumping function and hence SV, despite the preserved LVEF. In the analyzed sample, presumably 0.9 % of participants had "paradoxical" low-flow, LGAVS. Severe "paradoxical" LGAVS is characterised by a high prevalence of AF, chronic HF and reduced survival, while AV replacement is associated with improved survival. These findings have implications for the evaluation and subsequent treatment of severe LGAVS, as older adults with a high number of comorbid conditions are the candidates for TAVR [22].

Severe AVS with normal flow/low gradient and pEF can be assumed in one study participant. According to the literature, early surgical AV replacement and surveillance and conservative treatment strategy show similar survival in symptomatic patients with similar subtype of AVS [23]. Vigilant surveillance with timely surgical intervention should be considered as the optimal management tactic.

One of the serious complications of AVS is atrial fibrillation, which, according to modern concepts, is primarily a consequence of the development of LA stiffness, changes in its longitudinal deformation and contributes to the worsening of haemodynamics, clinical symptoms and prognosis [12]. In our study, atrial fibrillation was present in 40 % cases of HGAVS and 16.7 % of severe LGAVS cases. In a multivariate logistic regression model, age, history of HF and AVA were found to be associated with AF. In 2022, Ahn Y. et al [24] presented factors associated with major cardiac and cerebrovascular events after surgical AV replacement in a scientific report. Those were: AF before surgery, high NT-proBNP level, "classic" LGAVS, smaller aortic root size. It was shown that all-cause mortality during 3-year follow-up after surgical valve replacement was significantly higher in patients with "classic" LGAVS (33.3 %) compared with HGAVS (13 %) and "paradoxical" LGAVS (14.5 %) [24]. The prognostic value of a high NT-proBNP concentration before AV surgery (more than 2000 pg/ml) is also suggested by the publications by Russian authors [13].

Thus, understanding the prevalence, severity and subtypes of AVS in the population, evaluating EchoCG and CT parameters of AV, determining functional and structural remodelling of the heart and clinical characteristics of AVS will allow competent selection for different types of aortic valve replacement and prediction of outcomes (complications and survival) after interventions, especially in the elderly.

Study limitations. The «Know your heart» study included participants aged 35–69 years, whereas the incidence of AVS in the elderly population increases significantly after the age of 75 years. The prevalence of aortic valve stenosis is low according to population-based studies, so the groups for analysing the characteristics of HGVAS and LGAVS were small, limiting the statistical power of the study to identify associations between the variables studied.

Conclusion

The prevalence of mild to moderate HGAVS and EF >50 % by echocardiography in the population aged 35–69 years was 0.43 % and increased with age (0.2 % in 40–59 years and 1.1 % in 60–69 years). There were no cases of severe HGAVS. Severe LGAVS and LVEF > 50 % occurred in 0.9 % of participants. Males predom-

Appendix 1

Parameters of a participant with a severe LGAVS with normal flow/LG and preserved LVEF

Parameter	Factual data
Sex, age	Female, 69 years
Anthropometric data	Height 151 cm, weight 58.8 kg, BSA — 1.54 m^2, (the woman is of a «small size»).
Comorbidities, (from questionnaire data)	AH, AF, CHD with angina rpisodes, chronic kidney disease, osteoarthritis, depression
EchoCG parameters	**Aortic valve:** AVA — 0,94 cm^2, iAVA — 0,61 cm^2/m^2, Gmean — 4,4 mmHg, Vmax 1,55 — m/s, and SV — 36,8 ml/m^2. **LA:** diameter — 48,9 mm, LAV — 65,5 ml, iLAV — 42,4, ml/m^2; **LV:** severe LV hypertrophy — LVMI — 142 g/m^2; LVEF — 56 %. **Diastolic dysfunction:** PCWP — 21,6 mmHg, E/é ratio — 15,7;
Biomarkers	NT-proBNP — 263 pg/ml, hs-Tn — 8,55 ng/l

inated among participants with HGAVS and severe LGAVS.

AVA was independently negatively associated with Lp(a) after THE adjustment for sex and age. AF occurred in 40 % of participants with HGAVS and 16.7 % of participants with severe LGAVS and LVEF >50 %. AF and NT-proBNP were independently associated with AVA in a population-based sample after adjustment for HF history, sex and age.

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