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ORIGINAL ARTICLES
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Remote monitoring of outpatients discharged from the emergency cardiac care department

Garanin A. A.[1], Mullova I. S.[1,2], Shkaeva O. V.[1,2], Duplyakova P. D.[1,2], Duplyakov D. V.[1,2]

The coronavirus disease 2019 (COVID-19) pandemic has shown the need for the development of telemedicine technologies, especially remote follow-up using vital sign telemonitoring. In the Russian Federation, this approach is also justified by the remoteness factor with a shortage of medical workers in distant areas of the country.

Aim. To study the potential of remote monitoring in outpatients discharged after acute decompensated heart failure and acute coronary syndrome.

Material and methods. The study included 392 patients randomized to active follow-up groups with remote blood pressure (BP) monitoring (group 1, n=197) and standard management (group 2, n=195). The follow-up period lasted 3 months.

Results. During the follow-up period, patients managed with BP and heart rate telemonitoring tended to decrease in systolic BP from 132 (interquartile range (IQR), 121-139) mm Hg up to 125 (IQR, 115-130) mm Hg (p=ns). On the contrary, the 2nd group patients had a slight increase in systolic BP from 127 (IQR, 115-137) mm Hg up to 132 (IQR, 124-142) mm Hg (p=ns).

The patients of group 2 were more likely to receive diuretics and nitrates after 3-month follow-up, which can be considered a negative factor. This may indicate no improvement in the course of heart failure and chronic coronary artery disease with the absence of therapy correction over time. During follow-up, four patients from group 1 were hospitalized due to decompensated heart failure or an episode of acute coronary syndrome with a total duration of 30 days, compared with 13 hospitalizations for the same reasons in group 2 (p=0,027; OR 3,4; 95% CI 1,1-10,8). In total, six patients died during the follow-up period in group 1, and eleven patients died in group 2 (p=0,226; OR 1,9; 95% CI 0,7-5,3). At the same time, three patients in the 1st group and one patient from the 2nd group died during the follow-up period due to COVID-19. Thus, cardiovascular mortality consisted of 3 and 10 patients in groups 1 and 2, respectively (p=0,052; OR 3,5; 95% CI 0,9-12,9).

Conclusion. Three-month remote management of patients after decompensated heart failure or acute coronary syndrome, including BP monitoring, showed a significant reduction in the hospitalization rate and a trend towards a decrease in cardiovascular mortality.

Keywords: acute coronary syndrome, heart failure, blood pressure, telemedicine technologies, telemonitoring, cardiovascular mortality.

Relationships and Activities: none.

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Key messages

- Blood pressure monitoring in outpatients with HF helps to reduce the hospitalization rate.
- Remote management of patients after decompensated HF or acute coronary syndrome showed a trend towards a decrease in cardiovascular mortality.

The most important hemodynamic factor that determines the prognosis for a number of cardiovascular diseases (CVD) is the level of blood pressure (BP). Arterial hypertension (AH) is the considerable modifiable risk factor for the development of cardiovascular complications and death [1, 2]. At the same time, a negative effect of low BP on cardiovascular risk has also been found [3]. It has been shown that patients with AH have a J-dependent curve of blood pressure and cardiovascular outcomes [4].

Chronic heart failure (HF) remains a leading cause of disability and mortality with a high prevalence in the general population (7%). In the Russian Federation (RF), the average annual mortality is 6% in patients with functional class (FC) I-IV of HF, and 12% in patients with a pronounced clinical picture [5]. The increase in the prevalence of HF in the RF by 22% (from 6,7% to 8,2%) is of great concern, and that is clearly illustrated by the data of the recently completed EPOCH-CHF study [6]. The main reason of the formation of HF is acute and chronic forms of coronary artery disease (CAD). Obviously, an unfavorable prognosis in patients with HF is due to both the increase and the decrease in blood pressure, as well as the various forms of atrial and ventricular arrhythmias.

The pandemic of a new coronavirus infection has shown the unmet need for the development of telemedicine technologies, especially remote medical observation using telemonitoring of vital body functions. In the RF, this approach is also justified by the distance factor, when there is often a lack of medical workers in remote areas of our country.

The forecast of experts came true, who believed that mobile data traffic in Eastern Europe and Russia would have had six-fold increase by 2021 [7]. It is believed that more than 50% of patients going to the hospitals use the Internet resources to obtain data on their health status [8]. The significance of using telemedicine and its conceptual postulates are reflected in the official positions of international and major regional organizations (WHO, ESC, ACC/AHA) [9-11]. Taking into account the fact that CVD is diagnosed in more than half of the population in developed countries, and 46-57% of deaths are associated with them, and the cost of management of patients with this pathology is >70% of the healthcare budget, it can be assumed that telemedicine along with standard approaches can significantly affect CVD statistics [12].

Objective: to study the potential of remote monitoring in outpatients discharged after acute decompensated heart failure and acute coronary syndrome.

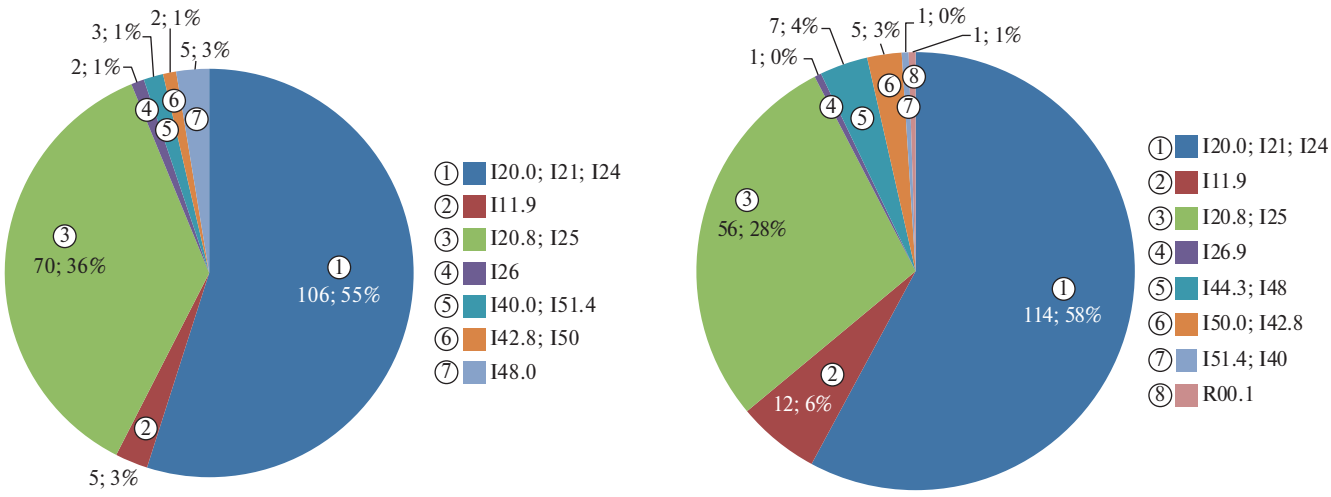
Material and methods

The open randomized prospective study was performed on the basis of two research centers of the third level (university hospitals). A total of 392 patients were included in the study. Group 1 comprised patients (n=197, mean age of 66,3 [59,7-73,5] years), incl. 94 women (49,3%) and 103 men (50,7%), who were actively controlled by remote BP monitoring (RBPM) using the oscillometric method. Monitoring was carried out with the certified INME-01 tonometer (LLC INME, Russia) with an integrated GSM module that allows BP and pulse rate measurement, and the ability to transmit the results via a cellular communication channel to a research center. Based on the results of the received data, the doctor could contact the patient and adjust the previously prescribed treatment. In order to obtain a more informative BP value, the patient was recommended to perform at least three measurements with an interval of at least 1 min on the dominant upper limb. An additional measurement was recommended whether a difference in blood pressure was more than 5 mm Hg. Thus, the recommended number of measurements per session was three, which were performed at least twice a day in the morning (from 6,00 to 12,00) and in the evening (from 18,00 to 24,00).

Patients of group 2 (n=195, mean age of 66,2 [61,0-74,0] years), incl. 95 women (49,5%) and 100 men (50,5%), were recommended to carry out self-monitoring of blood pressure, and drug treatment was adjusted by the district doctor. The duration of observation was 3 months.

Inclusion criteria for patients in the study:

1. Age over 18 years for both sexes.
2. Signed informed consent to participate in the study and consent to the processing of personal data.
3. Hospitalization for myocardial infarction (unstable angina) or acute decompensated HF, in the presence of HF symptoms equivalent to FC II-IV or ejection fraction <40%.
4. The ability to independently perform measurements of remotely controlled indicators.



A **B**

Figure 1. Quantitative and percentage ratio of nosological forms that caused the hospitalization in patients. **A**) in group 1; **B**) in group 2.

The informing procedure was carried out with face-to-face contact between the researcher and the patient, following which the latter signed a written consent.

Exclusion criteria for patients in the study:

1. Possible alternative diseases that can mimic the symptoms of HF in a patient, such as:
   — Chronic lung disease
   — Primary pulmonary hypertension
   — Chronic obstructive pulmonary disease with degree III-IV of bronchial obstruction.
2. Malignancy, other diseases/disorders or life-threatening conditions that may prevent the participant to complete the study.
3. Alcohol and drug abuse, serious mental disorder.
4. Lack of technical ability to transmit measurement results (living outside the zone of stable coverage of the cellular network, etc.).
5. Pregnancy and lactation period.
6. Patient life expectancy <3 months.
7. Patient's refusal to sign written informed consent to participate in the study.

Patients in the RBPM group received 4 visits. At visit 1, the patients were included in the study, informed consent was signed, and an individual registration card was filled out. Subsequently, medical telepatronage was carried out in the form of two visits performed in the mode of telemedicine video consultations after 1 and 2 months from the time of enrolment into the study. Wherein, complaints and anamnesis were collected, drug intake was monitored, and, if necessary, the previously prescribed treatment was corrected. It should be noted that if systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse values beyond the reference values were detected during RBPM, the doctor had the opportunity to contact the patient to correct therapy even outside the control visits. Visit 4 was performed after 3 months as a full-time appointment, during which the patient's clinical condition was assessed, and the effectiveness of therapy was monitored.

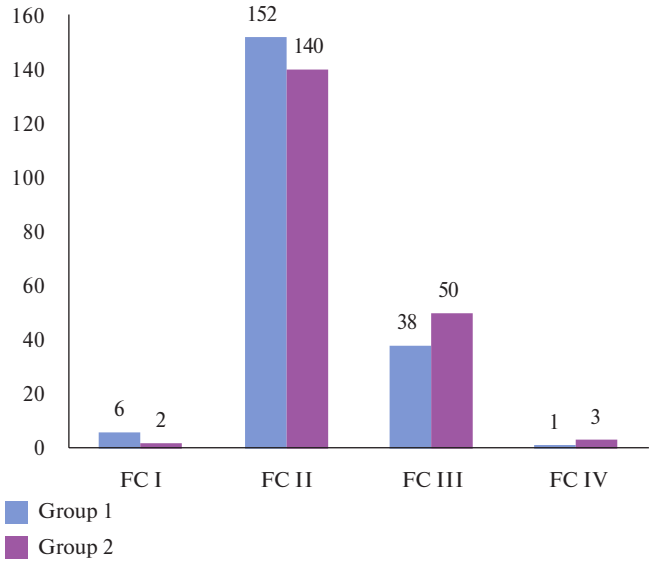


Figure 2. The number of patients with different FC of HF in the studied groups.
Abbreviation: FC — functional class.

Patients in the BP self-monitoring group received 2 visits. At visit 1, the patients were included in the study, informed consent was signed, and an individual registration card was filled out. Further management was carried out by the district doctor as needed; the patient independently went to the hospital in case of deterioration. Within 3 months the patient independently controlled the level of his

Table 1

The main baseline and final parameters in the studied groups

Parameter	Observed group		p
	Group 1	Group 2	
Age, years	66,27 [59,75-73,50]	66,15 [60,99-74,00]	0,29
Male, n (%)	103 (50,7)	100 (50,5)	0,46
EF, %	56 [48,75-60]	55 [46-62]	0,68
BMI1, kg/m^2	28 [24,48-32,22]	28,6 [26-33,45]	0,13
BMI4/2, kg/m^2	28 [24,03-31,93]	28,4 [25,83-33,0]	0,08
6MWT1, m	350 [301,25-390]	350 [255-400]	0,49
SBP1, mm Hg	130 [120-140]	130 [120-140]	0,18
DBP1, mm Hg	74 [65-80]	80 [70-80]	0,001
SBP4/2, mm Hg	125 [115-130]	130 [120-140]	0,001
DBP4/2, mm Hg	75 [70-80]	80 [70-85]	0,01
Puls1, n per 1'	72,5 [69-80]	70 [66-77]	0,008
Puls4/2, n per 1'	66 [63-73]	68 [64-74]	0,18
AF/AF, n (%)	47 (23,5)	53 (26,5)	1,0
CKD 4-5 st., n (%)	6 (3)	19 (9,5)	0,82
Type 2 DM, n (%)	38 (19)	43 (21,5)	0,77

Note: BMI1 — BMI at visit 1 in groups 1 and 2; BMI4/2 — BMI at visits 4 and 2 in groups 1 and 2, respectively; SBP1 and DBP1 — SBP and DBP at visit 1 in groups 1 and 2; SBP4/2 — SBP at visits 4 and 2 in groups 1 and 2, respectively; DBP4/2 — DBP at visits 4 and 2 in groups 1 and 2, respectively; Pulse1 — pulse rate at visit 1 in groups 1 and 2; Pulse4/2 — pulse rate at visits 4 and 2 in groups 1 and 2, respectively.

Abbreviations: DBP — diastolic blood pressure, BMI — body mass index, SBP — systolic blood pressure, DM — diabetes mellitus, 6MXT — 6-minute walk test, AF — atrial flutter, EF — ejection fraction, AF — atrial fibrillation, CKD — chronic kidney disease.

Table 2

Adherence to treatment in the studied groups

Drug group	Group 1			Group 2		
	Visit 1, n	Visit 4, n	%	Visit 1, n	Visit 2, n	%
Aspirin	172	171	99	149	140	94
Other antiplatelet agent	132	126	95	120	112	93
Anticoagulant	37	37	100	60	54	90
β-adrenoblocker	175	162	93	172	161	93
ACE inhibitor	119	116	97	93	86	92
Angiotensin receptor blocker	68	64	94	97	90	93
Nitrate	57	6	11*	64	56	93*
Calcium channel blocker	35	33	94	42	36	86
Diuretic	88	74	84*	96	94	98*
Statin	178	171	96	171	160	94

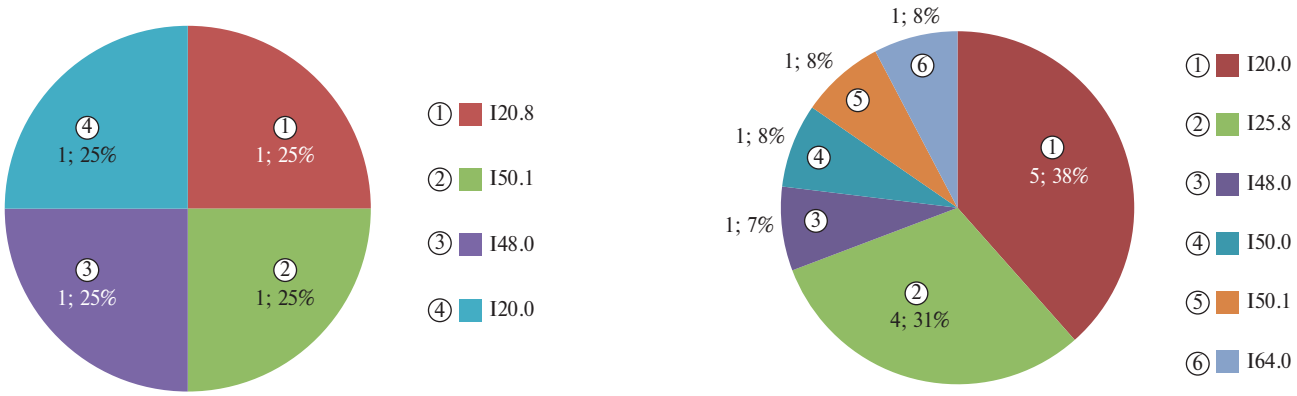
Note: * — p<0,05.

Abbreviation: ACE — angiotensin-converting enzyme.

pressure and pulse rate with a home tonometer. Visit 2 was carried out 3 months later in the form of a telemedicine consultation, during which the patient's clinical condition was assessed, and the effectiveness of therapy was monitored.

The study was conducted in accordance with the current version of the Helsinki Declaration, the provisions of the Russian National Standard GOST R52379-2005 on Good Clinical Practice of April 01, 2006, the Order 200n of the Russian Ministry of Healthcare of April 1, 2016 "On Approval of the Rules of Good Clinical Practice" and Good Clinical Practice (GCP) guidelines.

Statistical analysis was carried out using SPSS Statistics Version 26. The Kolmogorov-Smirnov test was used to determine the normality of the distribu-



A **B**

Figure 3. The reasons for hospitalization during the observation period. **A**) in group 1; **B**) in group 2.

tion. Normally distributed continuous variables were presented as the mean (M) ± standard deviation (σ). Abnormally distributed continuous variables were given as the median and interquartile range. Analytical statistics were performed using Student's t-test for quantitative data with a normal distribution or the Mann-Whitney/Kruskal-Wallis test for quantitative data with an abnormal distribution. Fisher's exact test was used to compare frequency scores between groups. Spearman's method was used to analyze the relationship between the studied parameters. The significance level for testing hypotheses was taken equal to 0,05.

Results

The nosological forms as the reasons for hospitalization in both groups are shown in Figure 1; more than 50% of those were acute and chronic forms of coronary artery disease.

Basically, both groups were comparable in age, gender, left ventricular ejection fraction, FC of HF, six-minute walk test distance, body mass index, SBP and DBP and heart rate (HR), the presence of comorbidities such as atrial fibrillation and flutter, diabetes mellitus, chronic kidney disease (Table 1, Figure 2).

During the follow-up period, there was a trend towards a decrease in SBP from 132 (interquartile range (IQR) 121-139) 125 (IQR 115-130) mm Hg (p=ns) in patients managed with BP and pulse telemonitoring. On the contrary, there was a slight increase in SBP from 127 (IQR 115-137) to 132 (IQR 124-142) mm Hg (p=ns) in group 2.

Evaluation of adherence to treatment in groups (Table 2) showed that group 1 had the best adherence for all groups of antihypertensive drugs, antiplatelet agents, anticoagulants and statins. However, there was a more frequent intake of diuretics and nitrates in group 2 during 3 months of follow-up. It could be regarded as a negative factor, since this may indicate the absence of positive dynamics in the course of HF and chronic coronary artery disease due to the absence of dynamic correction of treatment.

During follow-up, 4 patients from group 1 were hospitalized for HF decompensation or an episode of acute coronary syndrome with a total duration of 30 days, compared with 13 hospitalizations for the same reasons in group 2 (p=0,027; odds ratio (OR) =3,4; 95% confidence interval (CI) 1,1-10,8) with a total duration of 133 days (p=0,014). The distribution of hospitalized patients in the observation groups according to the diagnoses during the study is shown in Figure 3.

In total, 6 patients died during the follow-up period in group 1, and 11 patients died in group 2 (p=0,226; OR =1,9; 95% CI 0,7-5,3). At the same time, 3 patients in group 1 and one patient in group 2 died during the observation period from a new coronavirus infection. Thus, cardiovascular mortality was 3 people in group 1 (I25.1 — 2, I70.2 — 1) and 10 people in group 2 (G93.4 — 1, I25.1 — 3, I25.8 — 5, I21.1 — 1), p=0,052; OR =3,5; 95% CI 0,9-12,9.

In group 1, the analysis was also made of patients' adherence to a new method of BP and heart rate controlling with telemedicine technologies. A total of 34741 BP measurements were performed by patients with the RBPM technique, measurements were taken over a period of 10843 days. Thus, the average number of measurements was of 3,2 per day. The number of measurements was of 13102 in the first month, 10985 in the second month (decrease by 18,7% in relation to the first month) and 10654 measurements in the third month of observation (decrease by 3% in relation to the second month). The same trend continued for the number of days on which measurements were made — 4049, 3442 (15% decrease) and 3352 (2,6% decrease) for each month of observation, respectively. The decrease in

the total number of measurements could be due to a number of reasons: the death of several patients, their hospitalization, and also, to some extent, the loss of interest in the study. Meanwhile, the average number of measurements per day practically did not change during the follow-up and amounted to 3,24, 3,19, and 3,18, respectively, for 1, 2, and 3 months of follow-up, which was in line with the initial recommendations. The mean number of measurements per patient in group 1 was 176 (IQR 27-248); min 0, max 913; the average number of days of measurements was 55 (IQR 9-88); min 0, max 106.

During the observation period, 8569 (24,32%) episodes of high BP ⩾140 and 90 mm Hg were registered in the main group. Herewith, there was a tendency to reduce the number of such episodes during the study: 3850 cases were identified for the first month, 2449 ones were registered for the second month, and 1934 cases were revealed for the third month. The ratio of episodes of high BP to the total number of measurements for 1, 2 and 3 months of observation was 29,38%, 22,29% and 18,15%, respectively. The total number of episodes of hypotension (SBP ⩽90 mm Hg) was 658 measurements during the study period. Wherein, there was a trend towards a decrease in the number of such episodes during 1, 2 and 3 months, and that was 259, 204 and 197, respectively.

Episodes of tachycardia (HR ⩾100 bpm) and bradycardia (HR ⩽40 bpm) were also assessed. Tachycardia was noted in 963 cases during the entire observation period. In total, 403, 266, 293 episodes were registered for 1, 2 and 3 months of observation, respectively The overall number of episodes of bradycardia was 687 during the follow-up period, with a trend towards a decrease in the number of episodes of a rare pulse for 1, 2, and 3 months, and that was 255, 234 and 196 cases, respectively.

Discussion

Our data are comparable to a number of studies on the use of telemedicine technologies in the provision of medical care to patients with CVD. There was a higher probability of survival among patients in the intervention group compared with the control group after 1 year (adjusted relative risk (RR): 1,47, 95% CI 1,21-1,80, p<0,001) and 2 years (adjusted RR: 1,51, 95% CI 1,28-1,77, p<0,001), respectively. The authors made a fair conclusion that the probability of survival after 1 and 2 years was significantly higher in the active intervention group using telemedicine technologies [13].

A systematic review with direct meta-analysis of aggregated data using random effects models showed [14] that there was no difference in all-cause mortality between telemonitoring and conventional care. However, complex telemonitoring, which includes the transfer of patient data and analysis by specialists, reduces mortality from all causes (RR: 0,78, 95% CI 0,62-0,99; a total of 2885 people were analyzed in 12 randomized clinical trials (RCTs)). Evidence suggests that telemonitoring prevents HF-related hospitalizations (RR: 0,74; 95% CI 0,62-0,88; a total of 4001 people were included in 11 RCTs), structured telephone support reduces all-cause mortality (RR: 0,86; 95% CI 0,77-0,97; a total 9535 people in 24 RCTs) and HF-related hospitalizations (RR: 0,83; 95% CI 0,73-0,94; 7030 people were analyzed in 16 RCTs). The use of a mobile personal digital assistant prevents HF-related hospitalizations (RR: 0,58; 95% CI 0,44-0,77; a total of 674 people were included in 3 RCTs). The authors emphasize that clinicians should offer non-invasive monitoring using communication technologies to all patients with HF.

The long-term TEMA-HF study assessed whether an initial six-month telemonitoring program compared with conventional treatment would result in a reduction in all-cause mortality, hospitalizations for HF, and health care costs in long-term follow-up in patients with HF. The authors showed that this program led to a reduction in the number of days lost due to rehospitalization with heart failure [15].

A study based on comparing the effectiveness of office and home monitoring of 997 patients with HF using telemedicine technologies showed a 2-fold decrease in the number of hospitalizations in the group of patients with remote BP and ECG monitoring [16].

In Federal State Budgetary Institution "Almazov National Medical Research Centre" of the Ministry of Healthcare of the RF an analysis was made of the effectiveness of achieving targeted blood pressure and patient-oriented endpoints using telemonitoring in patients with hypertension. After 3 months, a significant decrease in "office" SBP and DBP was recorded in the telemonitoring group compared to the control group (p=0,002). By the end of the follow-up, BP parameters in the telemonitoring group decreased from 142±17 to 128±12 mm Hg (SBP), and from 88±8 to 79±6 mm Hg (DAD). Thus, a decline in SBP by -14±10 mm Hg (95% CI -11 to -17, r=0,819, p<0,0001) and DBP by -9±6 mm Hg (95% CI -7 to -11, r=0,647, p<0,0001) was achieved. There was also a decrease in the degree of anxiety and depression, according to Hospital Anxiety Depression Scale and the general condition of patients [17].

Federal State Budgetary Institution National Medical Research Center for Therapy and Preventive Medicine of the Ministry of Healthcare of the RF conducted an analysis of the economic feasibility of RBPM adoption using GPS-tonometers at

the regional level by modeling. The authors showed that in a region of 1 million people RBPM would have prevented 1940 deaths over 5 years with 90% coverage of RBPM in patients with hypertension, and with 30% coverage, 645 lives could have been saved. The mass RBPM adoption will reduce the burden on the healthcare system by preventing myocardial infarctions (95 cases with 90% monitoring coverage over 5 years), strokes (630 with 90% coverage over 5 years) and ambulance calls. RBPM is economically feasible, because the cost of its implementation is less than the expected economic effect due to the reduction in requests for medical care and the preservation of labor resources in the economy [18].

Federal State Budgetary Institution National Medical Research Center for Therapy and Preventive Medicine of the Ministry of Healthcare of the RF together with Federal State Budgetary Institution National Medical Research Centre of Cardiology of the Ministry of Health of the RF carried out a study that made it possible to evaluate the clinical effectiveness of various telemonitoring models in monitoring BP in patients with hypertension. The study included 225 patients divided depending on the method of observation into 4 groups: the RBPM group in a round-the-clock mode with automatic transmission of measurement results (50 patients); the RBPM group during doctor's working hours with automatic transmission of measurement results (50 patients); the RBPM group during doctor's working hours with manual transmission of measurement results (50 patients); and the group of self-control of blood pressure (75 patients). Initially, the groups did not differ by age and sex, BP values. Six-month follow-up revealed a decline in mean BP values in all observation groups. There were no significant differences in this parameter when comparing the groups with each other. A large number of refusals to continue observation until the completion of the study were noted in groups that used manual data entry [19].

Interesting data were obtained in patients with HF using a remote monitoring platform [20]. The authors determined the possibility of increasing the ability of patients to self-help and self-control using a remote monitoring platform based on a mobile application in patients with HF. The authors based the remote monitoring platform on the Russian version of the European scale for assessing the ability of patients to self-care, which includes 9 points related to self-control issues. A lower score reflects a better ability of patients with HF to self-care. The follow-up period was 6 months. After 6 months, the average score on the scale in the mobile application group decreased to 15±2,3. While in the control group the average score was 23,95±3,02, which indicates a significantly better ability to self-care in the group of patients using the mobile application ($p<0,001$).

In our opinion, the effectiveness of telemonitoring in outpatients with HF for its decompensation or acute coronary syndrome is due to a number of reasons, among which are of particular importance: the territorial separateness in our country, the lack of medical workers in some medical organizations and remote areas, low adherence to the treatment in patients with chronic non-communicable diseases causing HF, a progressive course of circulatory failure requiring regular dynamic monitoring of vital body functions.

Conclusion

Three-month remote management of patients after decompensated heart failure or acute coronary syndrome, including BP monitoring, showed a significant reduction in the hospitalization rate and the trend towards the decrease in cardiovascular mortality.

Relationships and Activities: none.

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Predictors of atrial fibrillation recurrence in patients with metabolic syndrome after pulmonary vein isolation

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Aim. To determine the role of biomarkers in predicting atrial fibrillation (AF) recurrence within 12 months after radiofrequency ablation (RFA) in patients with metabolic syndrome (MS).

Material and methods. The study included 245 patients with AF aged 35 to 65 years: patients without MS components (n=32), with 1-2 MS components (n=62) and patients with 3 or more MS components (n=153). All patients underwent a comprehensive clinical and anamnestic, anthropometric, laboratory and echocardiographic examinations. The prospective follow-up for 12 months included 135 patients with AF who underwent RFA.

Results. It was found that the presence of 3 or more MS components increased the risk of AF recurrence by 4,1 times within 12 months after RFA (relative risk (RR) =4,1, 95% CI 2,19-7,65, p<0,0001). According to binomial logistic regression, epicardial fat thickness (EFT) (OR =3,71, 95% CI 2,12-6,73, p=0,00001), the severity of left atrial fibrosis (OR =1,48, 95% CI 1,03-1,78, p=0,0006), concentrations of galectin-3 (OR =1,31, 95% CI 1,12-1,51, p=0,0001) and GDF-15 (OR =1,11, 95% CI 1,02-1,18, p=0,0002) in patients with AF and MS increase the risk of AF recurrence after RFA. For galectin-3, GDF-15, and EFT, using ROC analysis, the following threshold values were established, the excess of which had the greatest effect on the risk of AF recurrence after RFA in patients with MS: galectin-3 >11,0 ng/ml (RR =3,43, 95% CI 1,79-6,58, p=0,0001), GDF-15 >1380,7 pg/ml (RR =2,84, 95% CI 1,81-4,46, p<0,0001) and EFT >6,4 mm (RR =4,50, 95% CI 2,32-8,71, p<0,0001). In patients with excess of all three biomarker thresholds, the total risk of AF recurrence in patients with MS within 12 months after RFA increases by 3,2 times (RR =3,16, 95% CI 1,97-5,11, p<0,00001).

Conclusion. The risk of AF recurrence within 12 months after RFA in patients with three or more MS components is higher than in patients with 1-2 MS components. An increase in the blood concentration of profibrogenic biomarkers galectin-3, GDF-15 and an increase in the thickness of epicardial adipose tissue is associated with an increased risk of AF recurrence in patients with MS, and these biomarkers are likely to play a significant role in predicting recurrent episodes of AF after RFA.

Keywords: fibrosis, inflammation, recurrence of atrial fibrillation, radiofrequency ablation, metabolic syndrome.

Relationships and Activities: none.

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Key messages

- This paper expands understanding of why sinus rhythm control is not effective in patients with atrial fibrillation and metabolic syndrome after radiofrequency ablation.
- Established threshold values of novel biomarkers as galectin-3, GDF-15 and epicardial fat thickness make it possible to predict AF recurrence in patients, which can be used to personify antiarrhythmic management in patients with metabolic syndrome.

Metabolic syndrome (MS) is a cluster of pathological conditions that includes arterial hypertension (AH), abdominal obesity (AO), insulin resistance, and lipid metabolism disorders that all contribute to the development of cardiovascular diseases [1]. The prevalence of MS in the population of the Russian Federation is high and, according to the epidemiological ESSE-RF study, it is accounted for 33% in those examined at the age of 25-64 years [2]. Putting into clinical practice the MS criteria of the Joint Interim Societies, the Joint Interim Statement (JIS 2009) allows more frequently identifying this pathology and timely preventing of cardiovascular diseases [3]. Atrial fibrillation (AF) is the most common type of heart arrhythmia associated with an increased risk of stroke, systemic embolism, disability and mortality in the working-age population [4]. The main conditions of MS, such as AO, AH, and carbohydrate metabolism disorders, significantly increase the risk of developing AF, including younger generation [5]. The mechanisms of AF development in patients with MS are manifold and are caused by structural changes in the atria, a process known as remodeling. Anatomical atrial remodeling is accompanied by atrial dilatation due to an increased volume of circulating blood in patients with AO and an elevated filling pressure in the left ventricle (LV) in patients with AH [6, 7]. Impaired carbohydrate metabolism and diabetes mellitus (DM) jointly with visceral adipose tissue contribute to electrical and structural myocardial remodeling, which can lead to the formation of fibrosis. This, in turn, leads to the occurrence of micro-reentry as a substrate for the development of atrial fibrillation [8]. Recently the role of circulating biomarkers of fibrosis and inflammation has been actively studied in the manifestation of AF in various cohorts. Previously, increased galectin-3, procollagen types I and III expression has been revealed in patients with AF and MS, and the relationship between biomarkers and the severity of left atrial (LA) fibrosis has been established [9]. Epicardial adipose tissue, a biomarker of visceral obesity, promotes not only the systemic circulation of proinflammatory and profibrogenic cytokines, but also has a paracrine effect on the myocardium, which leads to the development of fibrosis and electrical remodeling [10]. Studying the role of various biomarkers exists due to the need to find out predictors not only for the risk of developing AF, but also for the progression of this arrhythmia, as well as for the effectiveness of drug and interventional therapy. According to the results of the study, it was found that elevated concentrations of galectin-3 and aldosterone was associated with an increased risk of recurrence of this rhythm disorder in patients with AF after radiofrequency ablation (RFA) [11]. In 2012, the results of a retrospective study were published, where MS was identified as a significant predictor of AF recurrence after RFA (relative risk (RR) =1,28, p=0,021). However, a comprehensive study of the role of various biomarkers has not been carried out yet [12]. The objective of this study was to evaluate the role of clinical, anthropometric, profibrogenic and pro-inflammatory factors as predictors of AF recurrence in patients with MS after RFA.

Material and methods

From 2014 to 2018, 245 (male of 55,9% and female of 44,1%, at the age of 35-65 years) patients out of 1307 patients with AF hospitalized in the therapeutic clinic of Federal State Budgetary Educational Institution of Higher Education "Academician I. P. Pavlov First St. Petersburg State Medical University" of the Ministry of Healthcare of Russian Federation were enrolled. The patients did not have any organic heart disease, clinical data for acute and chronic diseases. The study was approved by the local Ethics Committee of Institution. Informed written consent was obtained from all patients before their enrollment. The study included patients with paroxysmal (n=191) and persistent (n=54) forms of AF and a different number of MS components (JIS, 2009): no components or control group (n=30), 1-2 components (n= 62) and ⩾3 components (n=153). All the examined patients were assessed the anthropometric data, a set of laboratory and instrumental examinations: electrocardiogram (ECG), multi-day ECG monitoring ("Normocard", Kemerovo, Russia),

Table 1

Characteristics of methods and manufacturers of reagents for the evaluation of biomarker levels in blood samples

Biomarker	Technique	Company name	Country of origin
Aldosterone, pg/mL	ELISA	DBC Inc.	Canada
Galectin-3, ng/mL	ELISA	Human Galectin-3, Affymetrix, eBioscience	Austria
TGF-beta1, pg/mL	ELISA	ProcartaPlex Human TGF-beta1 Simplex, Affymetrix, eBioscience	Austria
CTGF, pg/mL	ELISA	Human CTGF High Sensitive, Aviscera Bioscience Inc	Austria
GDF-15, pg/mL	ELISA	BioVendor Human GDF-15/MIC-1	Czech Republic
PINP, pg/mL	ELISA	Cloud-Clone Corp.	USA
PIIINP, pg/mL	ELISA	Cloud-Clone Corp.	USA
CRP, mg/mL	IT	COBAS INTEGRA компании Roche Diagnostics GmbH.	Germany
CT-1, pg/mL	ELISA	RayBio® Human CT-1 (Cardiotrophin-1), RayBiotech	Austria
TNF-α, pg/mL	ELISA	Human TNF alpha High Sensitivity ELISA kit, Bender MedSystems	Austria
IL-6, pg/mL	ELISA	Human IL-6 High Sensitivity ELISA kit, Bender MedSystems	Austria

Abbreviations: IL-6 — interleukin-6, IT — immunoturbidimetry, ELISA — enzyme-linked immunosorbent assay, CRP — C-reactive protein, TNF-α — tumor necrosis factor alpha, TGF-beta1 — transforming growth factor-beta1, CT-1 — cardiotrophin-1, CTGF — Connective tissue growth factor, PIIINP — N-terminal propeptide of procollagen type III, PINP — N-terminal propeptide of procollagen type I, GDF-15 — growth differentiation factor-15.

echocardiography ("Vivid 7", GE, USA) with evaluation of epicardial fat thickness (EFT). All patients who underwent RFA received cardiorespiratory monitoring to find oud sleep-related respiratory disorders (SOMNOlab 2 (PG) Polygraphy system, Loewenstein Medical, Weinmann, Germany). All plasma and serum samples were centrifuged with subsequent storage at -40° C. The levels of biomarkers were determined using standard kits; their data are presented in Table 1.

The prospective 12-month follow-up included patients with clinically significant AF paroxysms (involving those with reduced quality of life due to this condition), resistant to drug antiarrhythmic therapy, who underwent pulmonary vein isolation ablation.

Scheduled outpatient visits after RFA were carried out at 3, 6, 9 and 12 months. AF recurrence after RFA was considered to be complaints of patients and recorded episodes of AF ⩾30 sec on ECG in the period from 3 to 12 months. All patients underwent 3-day ECG monitoring at 6 months after RFA and longer up to 7-day ECG monitoring at 12 months after RFA using the Normocard system (Kemerovo) to reveal/exclude AF paroxysms after the RFA procedure, which was considered effective in the absence of complaints and indications of AF paroxysms in the period from 3 to 12 months. Against the background of sinus rhythm, bipolar amplitude LA maps and local activation time estimation maps were performed before RFA of the pulmonary vein in an X-ray operating room using a non-fluoroscopic electrical and anatomical mapping system CARTO 3 (Biosense Webster, USA) and a catheter measuring the contact force with the LA myocardium (Smart Touch Thermocool, Biosense Webster, USA). The assessment of low voltage zones in the amplitude spectrum of 0,2-0,5 mV with the measurement of their area using the "area measurement" function of the CARTO 3 navigation system software was carried out in the "off line" mode [13]. The prevalence of fibrosis was assessed as a percentage of the area of fibrosis to the total area of the LA.

Statistical analysis was performed using licensed IBM SPSS Statistics software, version 22.0. The Kolmogorov-Smirnov test was carried out to evaluate the normality of the distribution. Normally distributed quantitative variables are presented as mean (M) ± standard deviation (σ). The parametric unpaired Student's t-test was used to compare the normally distributed quantitative variables of independent groups. Abnormally distributed quantitative variables are presented as medians (Me) with interquartile intervals (25-75%), and the nonparametric Mann-Whitney U-test was used to compare such variables in independent groups. The parametric analysis of variance (ANOVA) and the non-parametric Kruskal-Wallis test were used for multiple comparisons in groups (more than two). Binomial regression analysis was also used to predict the probability of event occurrence (odds ratio (OR)) and ROC-analysis to determine the cut-off value of biomarkers with the relative risk of events (RR) using a 2×2 contingency table.

Table 2

Clinical, laboratory and echocardiographic characteristics of the examined patients

Parameter		AF			Statistical significance, p
		0 MS components, n=30 (1)	1-2 MS components, n=62 (2)	⩾3 MS components, n=153 (3)	
Age, years		54,1±7,6	55,1±8,2	56,2±5,2	$p_{1,2,3}>0,05$
Gender, male/female		13/17	32/30	69/84	$p_{1,2,3}>0,05$
AF duration, years		4,7±1,8	4,7±1,8	4,2±2,2	$p_{1,2,3}>0,05$
AF form	Paroxysmal	26/30 (86,7%)	51/62 (82,3%)	113/153 (73,9%)	$p_{1,2,3}>0,05$
	Persistent	4/30 (13,3%)	11/62 (17,7%)	40/153 (26,1%)	$p_{1,2,3}>0,05$
BMI, kg/m^2		24,6±3,8	28,1±7,3	33,6±7,1	$p_{1,2}=0,01$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
WC, sm	Male	87,9±5,1	96,0±10,5	113,9±13,5	$p_{1,2}<0,001$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
	Female	74,9±3,1	86,3±10,5	107,2±13,5	$p_{1,2}<0,001$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
Total cholesterol, mmol/L		5,2±0,9	5,1±1,1	5,3±1,2	$p_{1,2,3}>0,05$
LDL cholesterol, mmol/L		3,1±0,3	3,1±0,3	3,1±0,4	$p_{1,2,3}>0,05$
HDL cholesterol, mmol/L	Male	1,3±0,3	1,4±0,3	1,1±0,4	$p_{1,2,3}>0,05$
	Female	1,6±0,3	1,6±0,3	1,3±0,4	$p_{1,2,3}>0,05$
TG, mmol/L		1,2±0,3	1,3±0,8	2,1±1,2	$p_{1,2}=0,671$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
Glucose, mmol/L		5,1±0,6	5,2±1,2	6,0±1,4	$p_{1,2}=0,871$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
LA diameter, mm		40,7±2,7	44,2±4,2	46,5±4,0	$p_{1,2}<0,001$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
LA volume, mL		68,2±9,4	80,9±16,6	88,9±19,4	$p_{1,2}<0,001$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
LA volume index, ml/m^2		36,9±4,9	41,5±9,7	43,5±11,2	$p_{1,2}<0,001$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
RA volume, mL		58,3±8,9	63,8±14,4	71,1±14,7	$p_{1,2}=0,01$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
RA volume index, ml/m^2		30,6±4,3	32,9±7,3	34,8±7,8	$p_{1,2}=0,01$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
LVMMi, g/m^2	Male	95,4±4,3	108,2±7,3	112,2±7,8	$p_{1,2}<0,001$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
	Female	82,3±5,1	88,7±7,3	102,5±7,8	$p_{1,2}<0,001$, $p_{1,3}<0,001$, $p_{2,3}<0,001$
LVEF, %		62,8±7,0	61,2±6,0	61,3±6,0	$p_{1,2,3}>0,05$
Epicardial fat thickness, mm		3,8±7,0	4,6±6,0	6,3±6,0	$p_{1,2}<0,001$, $p_{1,3}<0,001$, $p_{2,3}<0,001$

Abbreviations: BMI — body mass index, LVMMi — left ventricular myocardial mass index, LA — left atrium, HDL — high density lipoproteins, LDL — low density lipoproteins, MS — metabolic syndrome, WC — waist circumference, RA — right atrium, TG — triglycerides, LVEF — left ventricular ejection fraction, AF — atrial fibrillation.

Results

Patients with AF without MS components and with varies numbers of MS components were included. The studied groups were comparable by sex and did not differ statistically significantly by age. Patients with 1-2 MS components had higher body mass index (BMI) and waist circumference (WC) than those without MS components. However, these groups did not differ significantly in terms of lipid and carbohydrate metabolism parameters. The highest values of BMI, WC, and plasma glucose concentrations were found in patients with ⩾3 MS components, but lipid metabolism parameters were comparable with the comparison groups. Patients with AF and MS had significantly larger sizes of the left and right atria, greater values of the LV myocardial mass index (LVMMi) and EFT than patients with 1-2 components of MS and patients without MS. Bothe he dimension and volume of the LA and LVMMi were greater in patients with 1-2 MS components than in patients without MS. The examined groups were comparable in terms of LV ejection fraction and duration of AF. The main clinical, laboratory and instrumental characteristics of the examined patients are presented in Table 2.

Table 3 presents data on the serum and plasma biomarker concentrations of the patients. The levels of pro-fibrogenic and pro-inflammatory biomarkers have been established to be higher in patients with AF and MS than in those with AF and 1-2 MS components or without MS components. The concentrations of connective tissue growth factor, growth differentiation factor-15 (GDF-15), tumor necrosis factor alpha and interleukin-6 were greater in patients with AF and 1-2 components of MS than in patients with AF and without MS.

Table 3

Circulating blood levels of biomarkers of fibrosis and inflammation in patients with AF and MS, AF without MS, AF with 1-2 MS components

Biomarker	AF			Statistical significance, p
	0 MS components, n=30 (1)	0 MS components, n=30 (1)	0 MS components, n=30 (1)	
Aldosterone, pg/mL	90,2 (66,6-109,2)	95,5 (72,3-125,2)	134,2 (100,7-178,3)	$p_{1,2}$=0,145, $p_{1,3}$<0,001, $p_{2,3}$<0,001
Galectin-3, ng/mL	4,9 (4,3-7,1)	6,4 (4,8-7,6)	13,2 (6,8-16,8)	$p_{1,2}$=0,052, $p_{1,3}$<0,001, $p_{2,3}$<0,001
TGF-beta1, pg/mL	2155,4 (1678,3-3031,4)	2610,6 (2142,3-3355,5)	3572,5 (2468,5-5497,5)	$p_{1,2}$=0,09, $p_{1,3}$=0,001, $p_{2,3}$=0,001
CTGF, pg/mL	114,8 (64,7-169,7)	145,1 (115,1-178,2)	167,1 (121,6-224,3)	$p_{1,2}$=0,03, $p_{1,3}$<0,001, $p_{2,3}$=0,01
GDF-15, pg/mL	548,8 (450,7-801,2)	716,9 (586,9-847,7)	1256,3 (893,3-2235,1)	$p_{1,2}$=0,004, $p_{1,3}$<0,001, $p_{2,3}$<0,001
PINP, pg/mL	59,5 (46,2-89,1)	58,9 (50,9-83,3)	94,1 (61,6-127,3)	$p_{1,2}$=0,862, $p_{1,3}$<0,001, $p_{2,3}$<0,001
PIIINP, pg/mL	2777,9 (1654,1-3414,6)	2789,3 (2001,0-3663,5)	3488,4 (2352,1-4418,7)	$p_{1,2}$=0,572, $p_{1,3}$<0,001, $p_{2,3}$=0,01
CRP, mg/mL	1,1 (0,6-3,0)	2,1 (1,1-3,1)	3,5 (2,18-4,4)	$p_{1,2}$=0,068, $p_{1,3}$<0,001, $p_{2,3}$<0,001
CT-1, pg/mL	3,1 (2,1-4,1)	4,3 (3,1-6,7)	6,1 (3,2-12,4)	$p_{1,2}$=0,005, $p_{1,3}$<0,001, $p_{2,3}$=0,002
TNF-α, pg/mL	531,1 (451,8-802,1)	689,1 (490,9-852,7)	1032,1 (667,6-1495,3)	$p_{1,2}$=0,110, $p_{1,3}$<0,001, $p_{2,3}$<0,001
IL-6, pg/mL	0,9 (0,5-1,4)	1,3 (0,7-2,2)	2,8 (1,3-5,3)	$p_{1,2}$<0,001, $p_{1,3}$<0,001, $p_{2,3}$<0,001

Abbreviations: IL-6 — interleukin-6, MS — metabolic syndrome, CRP — C-reactive protein, TNF-α — tumor necrosis factor alpha, TGF-beta1 — transforming growth factor-beta1, CT-1 — cardiotrophin-1, CTGF — Connective tissue growth factor, PIIINP — N-terminal propeptide of procollagen type III, PINP — N-terminal propeptide of procollagen type I, GDF-15 — growth differentiation factor-15.

Table 4

Risk of AF recurrence 12 months after RFA in patients with different numbers of MS components

Number of MS components	N	AF recurrence, n (%)		RR	95% CI	Statistical significance, p
		+	-			
0	23	4 (17,4%)	19 (82,6%)	0,336	0,135-0,833	0,007
1	21	3 (14,3%)	18 (85,7%)	0,821	0,208-3,249	0,779
2	14	2 (14,3%)	12 (85,7%)	0,821	0,172-3,917	0,804
3	38	19 (50,0%)	19 (50,0%)	2,875	1,117-7,402	0,011
4	25	18 (72,0%)	7 (28,0%)	4,140	1,644-10,426	0,0001
5	14	12 (85,7%)	2 (14,3%)	4,929	1,972-12,318	0,0001

Abbreviations: CI — confidence interval, MS — metabolic syndrome, AF — atrial fibrillation, RR — relative risk.

The further prospective 12-month follow-up observation included patients with indications for RFA (n=135) without MS and various numbers of MS components: 0 MS components (n=23), 1-2 MS components (n=35), ⩾3 MS components (n=77). It was found that 42,9% of patients (n=58) had AF recurrence during follow-up period after RFA in the following ratio: 72,4% (n=49) of patients with ⩾3 MS components, 8,6% (n=5) of patients with 1-2 MS components and 6,9% (n=4) of patients without MS components. There were fewer patients with AF recurrence in those without MS components, than patients without recurrent AF episodes, and a low risk of AF recurrence after RFA was revealed (RR =0,34, 95% confidence interval (CI) 0,14-0,83, p=0,007). Patients with 1-2 MS components showed a trend towards an increased risk of AF recurrence, however, no statistically significant difference was found in comparison to patients without MS components (RR =0,82, 95% CI 0,21-3,25, p=0,779). In patients with ⩾3 MS components, there were more patients with recurrent AF than those without arrhythmia. Thus, the presence of MS increased the risk of AF recurrence by 4,1 times after RFA within 12 months (RR =4,11, 95% CI 2,19-7,65, p<0,0001). When analyzing the risk of AF recurrence after RFA in the examined patients based on the number of MS components, a statistically significant increase was observed in this parameter in patients with 3 or more components, and the maximum risk of recurrent episodes of AF after RFA was found in patients with 5 MS components (Table 4).

On binomial logistic regression, an increase in the number of MS components from 0 to 5 raised the likelihood of AF recurrence after RFA by 2,2 times (OR =2,16, 95% CI 1,61-2,89, p<0,0001). Data

Table 5

Clinical, anthropometric, laboratory and echocardiographic characteristics of patients with AF and MS with and without AF recurrence after RFA

Parameter		Without AF recurrence, n=28	With AF recurrence, n=49	Statistical significance, p
Age, years		56,3±4,2	55,1±3,2	p=0,357
Gender, male/female		13/15	21/28	p=0,345
AF duration, years		5,1±1,8	5,2±2,2	p=0,895
AF form	Paroxysmal	25/28 (89,3%)	39/49 (79,6%)	p=0,585
	Persistent	3/28 (10,7%)	10/49 (20,4%)	p=0,08
BMI, kg/m^2		31,3±3,9	33,1±4,3	p=0,104
WC, sm	Male	106,8±8,5	115,9±3,5	p=0,001
	Female	104,8±7,3	112,8±5,1	p=0,001
Total cholesterol, mmol/L			5,3±1,2	p=0,245
LDL cholesterol, mmol/L			3,1±1,1	p=0,497
HDL cholesterol, mmol/L	Male	1,2±0,3	1,1±0,4	p=0,607
	Female	1,5±0,3	1,3±0,4	p=0,103
TG, mmol/L			2,3±1,2	p=0,011
Glucose, mmol/L		5,9±0,9	6,0±1,1	p=0,907
Diabetes mellitus		3/28 (10,7%)	10/49 (20,4%)	p=0,001
Arterial hypertension		27/28 (96,4%)	49/49 (100%)	p=0,875
OSAS		8/28 (28,6%)	15/49 (30,6%)	p=0,105
LA diameter, mm		45,6±4,2	45,7±4,0	p=0,786
LA volume, mL		80,4±21,5	86,1±25,6	p=0,349
LA volume index, ml/m^2		40,2±9,7	41,4±10,4	p=0,649
RA volume, mL		68,8±14,4	68,3±6,7	p=0,831
RA volume index, ml/m^2		33,9±7,3	33,1±9,8	p=0,907
LVMMi, g/m^2	Male	109,6±7,3	116,1±5,8	p=0,01
	Female	90,2±6,1	101,1±6,3	p=0,001
Epicardial fat thickness, mm		4,6±1,3	6,7±1,7	p=0,00001
% of myocardial fibrosis to the total LA area		11,6 (10,4-22,2)	33,1 (23,9-43,6)	p=0,0018
ACE inhibitor/ARA		22/28 (78,5%)	37/49 (75,5%)	p=0,305
Statins		18/28 (64,3%)	34/49 (69,4%)	p=0,455
Hypoglycemic therapy		10/28 (35,7%)	16/49 (32,7%)	p=0,101
ADT after RFA		22/28 (78,6%)	39/49 (79,6%)	p=0,585

Abbreviations: ADT — antiarrhythmic drug therapy, ACE inhibitors/ARA — angiotensinconverting enzyme inhibitors/angiotensin receptor antagonists, LVMMi — left ventricular myocardial mass index, BMI — body mass index, LA — left atrium, HDL — high density lipoprotein, LDH — low density lipoprotein, RA — right atrium, RFA — radiofrequency ablation, OSAS — obstructive sleep apnea syndrome, TG — triglycerides, LV EF — left ventricular ejection fraction, AF — atrial fibrillation.

from patients with AF and 3 or more MS components underwent RFA were analyzed in more detail. Groups of patients with MS and AF with AF recurrence and without it after RFA were comparable distribution in age, BMI and sex. Having analyzed statistical data, WC in patients with recurrent AF has been found to be greater than in patients with effective RFA. Plasma triglyceride levels in patients with recurrent AF were higher than in patients without recurrent episodes of arrhythmias. Generally, the groups were comparable in terms of the prevalence of AO, AH, obstructive sleep apnea syndrome, but the frequency of DM in patients with recurrent AF after RFA was higher than in patients with the effective interventional therapy. The groups were matched for antiarrhythmic therapy after RFA. The patients received the following drugs: beta-blockers (32,6%), propafenone (31,9%), sotalol (25,9%), amiodarone (7,4%), allapinin (2,2%). It should be noted that the parameters characterizing the dilatation of both atria were comparable in groups. However, LVMMi was higher in patients with recurrent AF after RFA. EFT

Table 6

Circulating blood levels of biomarkers of fibrosis and inflammation in patients with AF and MS with and without AF recurrence after RFA

Biomarker	Without AF recurrence, n=28	With AF recurrence, n=49	Statistical significance, p
Aldosterone, pg/mL	112,1 (77,7-91,5)	128,2 (91,5-146,5)	p=0,401
Galectin-3, ng/mL	7,8 (4,8-13,1)	16,4 (12,8-19,6)	p=0,0003
TGF-beta1, pg/mL	2577,5 (2041,3-4777,9)	3232,1 (2165,3-4421,1)	p=0,594
CTGF, pg/mL	178,1 (129,7-187,3)	187,1 (153,6-231,3)	p=0,524
GDF-15, pg/mL	893,9 (674,9-986,7)	2603,3 (1516,3-3167,1)	p=0,0001
PINP, pg/mL	72,9 (57,1-96,2)	86,7 (57,7-131,1)	p=0,332
PIIINP, pg/mL	3184,9 (2316,0-4151,5)	3473,4 (2484,1-4321,7)	p=0,538
CRP, mg/mL	2,9 (1,8-3,5)	3,2 (1,1-6,7)	p=0,466
CT-1, pg/mL	6,5 (4,2-13,1)	9,8 (3,8-18,3)	p=0,417
TNF-α, pg/mL	795,1 (530,9-1001,7)	887,1 (599,8-1319,5)	p=0,183
IL-6, pg/mL	4,9 (3,4-6,3)	4,2 (1,6-6,1)	p=0,221

Abbreviations: IL-6 — interleukin-6, MS — metabolic syndrome, CRP — C-reactive protein, TNF-α — tumor necrosis factor alpha, AF — atrial fibrillation, TGF-beta1 — transforming growth factor-beta1, CT-1 — cardiotrophin-1, CTGF — Connective tissue growth factor, PIIINP — N-terminal propeptide of procollagen type III, PINP — N-terminal propeptide of procollagen type I, GDF-15 — growth differentiation factor-15.

and the severity of LA myocardial fibrosis were significantly higher in patients with recurrent episodes of AF after interventional therapy than in patients without it (Table 5).

On binomial logistic regression, greater values of EFT (OR =3,71, 95% CI 2,12-6,73, p=0,00001) and significant fibrosis (OR =1,48, 95% CI 1,03-1,78, p=0,0006) in patients with AF and MS increased the risk of recurrence of this arrhythmia after RFA. Having analyzed the concentrations of biomarkers of fibrosis and inflammation, it was found that the levels of galectin-3 and GDF-15 were higher in patients with AF and MS with recurrent AF after RFA than in patients with no recorded recurrent episodes of AF. The concentrations of other pro-fibrogenic and pro-inflammatory cytokines did not differ significantly in the groups (Table 6).

On binomial logistic regression, the levels of galectin-3 (OR =1,31, 95% CI 1,12-1,51, p=0,0001) and GDF-15 (OR =1,11, 95% CI 1,02-1,18, p=0,0002) in patients with MS increased the likelihood of AF recurrence within 12 months after RFA. For galectin-3, GDF-15, and EFT, ROC-analysis was used to calculate the predictive curves for the probability of AF recurrence in patients with MS within 12 months after RFA. The analysis revealed high areas under the curves, which correspond to a significant effect of these biomarkers on the likelihood of recurrence of AF after RFA in patients with MS (Figure 1). Based on ROC-analysis, the elevated levels of galectin-3 (>11,0 ng/mL; RR =3,43, 95% CI 1,79-6,58, p=0,0001), GDF-15 (>1380,7 pg/mL; RR =2,84, 95% CI 1,81-4,46, p<0,0001) and EFT (>6,4 mm; RR =4,50, 95% CI 2,32-8,71, p<0,0001) had the greatest effect on the risk of AF recurrence after RFA in patients with MS. If there was the excess of all three biomarker cut-off values, the total risk of AF recurrence in patients with MS within 12 months after RFA increased by 3,2 times (RR =3,16, 95% CI 1,97-5,11, p<0,00001). Sensitivity (Se — 75,5%) and

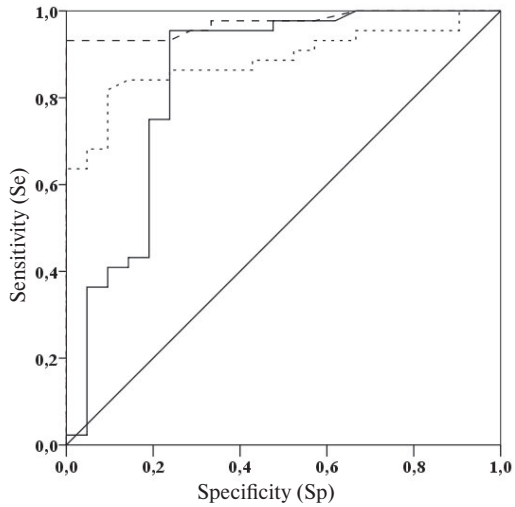

Figure 1. ROC curves of the blood levels of galectin-3 and GDF-15 and EFT for predicting the probability of AF recurrence in patients with MS within 12 months after RFA.
Abbreviations: EFT — epicardial fat thickness, AUC — area under the curve, GDF-15 — growth differentiation factor-15.

specificity (Sp — 96,4%) indicated the high significance of this model for predicting the probability of the event.

Discussion

AF is the most common arrhythmia worldwide. It is expected that the incidence of AF will increase significantly over the next few decades [14]. The mechanisms of development of this heart rhythm disorder are diverse and represent a whole system of changes, including electrical and structural remodeling with the formation of myocardial fibrosis, anatomical remodeling with the development of atrial dilatation and impaired contractile function, as well as changes in neurovegetative regulation [15]. MS components, such as hypertension, obesity, disorders of carbohydrate and lipid metabolism, are among the risk factors for the development of AF. The presence of a large number of MS components significantly increases the likelihood of developing this arrhythmia [16]. Sinus rhythm control with drug antiarrhythmic therapy and interventional treatments plays a substantial role in the up-to-date management strategy of patients with AF. Data from the prospective EAST-AFNET study showed that early control of sinus rhythm in patients with AF can reduce the risk of cardiovascular death and stroke, which makes antiarrhythmic drug therapy of patients with AF even more relevant [17]. Nevertheless, these facts such little amount of antiarrhythmic drugs, their insufficient effect or cardiovascular and other system adverse events limit the choice of drug therapy [18]. Current techniques of interventional treatment of AF, including, in particular, radiofrequency pulmonary vein isolation ablation make it possible to control sinus rhythm with high efficiency for a long time to a greater extent in patients with paroxysmal AF. However, this method of treatment has a rather high efficiency even in patients with a persistent form. The results of the CABANA study found that catheter ablation in AF was more effective in terms of sinus rhythm control compared to medical therapy, and both tactics were comparable in the risk reduction of cardiovascular complications [19]. In turn, the choice of antiarrhythmic tactics always requires personalized strategy, taking into account comorbid conditions. According to numerous studies, it has already been established that obesity, diabetes, uncontrolled hypertension can increase the risk of arrhythmia recurrence after RFA, which is probably due to persistent pathogenetic changes in structural remodeling and progressive myocardial fibrosis [12, 20].

One of the largest meta-analyses, including 23 studies and 12924 patients with AF, found that MS increased the risk of AF recurrence (RR =1,63, 95% CI 1,25-2,12) [21]. In our cohort study [20], it was revealed that the presence of 3 or more MS components increased the risk of AF recurrence after RFA by 4,1 times (RR =4,11, 95% CI 2,19-7,65, p<0,0001). It was proved that the increase in the number of MS components from 0 to 5 raised the risk of AF recurrence by 2,2 times. The obtained data confirmed the fact that worsening of RFA efficiency prediction was observed only in the occurrence of 3 or more MS components, i.e. in the presence of criteria for this syndrome. It is worth noting that the examined groups of patients with MS and recurrent AF were comparable in terms of the occurrence of AH. However, in patients with no effect of interventional therapy, DM and AO were more common.

The risk stratification of AF recurrence in patients with MS seems to be extremely relevant, because identification of predictors of insufficient effect of RFA will allow personalizing the strategy for managing patients with AF. In recent years, various biomarkers affecting myocardial fibrosis have been actively studied. It was previously established that the concentrations of such biomarkers as galectin-3, transforming growth factor-beta1, N-terminal propeptide of procollagen type I and III is increased in patients with MS and AF and are associated with the severity of LA myocardial fibrosis [22]. It has been found that the blood circulating levels of GDF-15 are associated with the severity of myocardial fibrosis and are likely to have an important prognostic value for patients with AF [23]. It was revealed that the increase in the concentrations of galectin-3 and aldosterone is associated with the increased risk of recurrence of this heart rhythm disorder in patients with AF in the study of biomarkers of fibrosis and inflammation in patients with AF and RFA [11].

Elevated serum levels of transforming growth factor-beta1 was an independent predictor of AF recurrence after RFA (OR =1,14, 95% CI 1,11-1,17, p=0,02) [24]. However, to date, studies on the comprehensive assessment of the role of biomarkers of fibrosis and inflammation in the development of AF relapses after RFA in patients with MS have not been published. However, to date, studies on the comprehensive assessment of the role of biomarkers of fibrosis and inflammation in the development of AF relapses after RFA in patients with MS have not been published. However, to date, studies on the comprehensive assessment of biomarkers of fibrosis and inflammation in the development of AF recurrence after RFA in patients with MS have not been published. It is worth noting that our examined patients with MS and AF had higher values of a large number of fibrosis biomarkers studied, in comparison with patients with AF and with 1-2 MS components. The peculiarity of our study is that patients with MS in the groups with and without AF recurrence

were comparable not only in age, BMI, duration of AF and received drug therapy, but they also did not differ significantly in the severity of both atria dilatation. Simultaneously, echocardiography showed a significantly higher EFT values in patients with recurrent AF after RFA, and, on binomial regression analysis, this biomarker was found to increase the risk of arrhythmia recurrence (OR =3,71, 95% CI 2,12-6,73, p=0,00001) [25, 26]. It is known that MRI and CT are the gold standard for imaging EFT assessment; however, echocardiography is a more accessible screening method for evaluating this parameter in real clinical practice. In our study, based on ROC analysis, a cut-off value of EFT of 6,4 mm was revealed. Exceeding this cut-off significantly increases the risk of AF recurrence after RFA (RR =4,50, 95% CI 2,32-8,71, p<0,0001). A greater increase in EFT in patients with recurrent AF after RFA might be associated with a more severe the degree of fibrosis with a comparable volume of LA in the comparison groups with MS. In turn, the severity of LA fibrosis increased the risk of AF recurrence in patients with MS (OR =1,48, 95% CI 1,03-1,78, p=0,0006). The study of pro-inflammatory and profibrogenic biomarkers revealed higher concentrations of galectin-3 and GDF-15 in patients with MS and recurrent AF. In recent years, various studies, including a large meta-analysis, have confirmed the association of galectin-3 with the risk of developing AF and myocardial fibrosis [27]. Pro-inflammatory cytokines activate macrophages and increase the production of galectin-3. Overexpression of galectin-3 induces fibroblasts to increase the secretion of collagen into the intercellular space, and therefore the highest concentrations of this biomarker are observed in patients with obesity and DM [28, 29]. It was found that the plasma concentration of galectin-3 >5,83 ng/mL in patients with persistent AF without structural heart disease increases the risk of arrhythmia recurrence after RFA (RR =1,28, 95% CI 1,072-1,529, p<0,006). In our cohort study, we studied the role of galectin-3 in predicting the risk of AF recurrence, predominantly in patients with paroxysmal arrhythmia in combination with MS. We also established the prognostic role of this biomarker, and the cut-off value of galectin-3 >11,0 ng/mL increased the risk of recurrence by more than 3 times (RR =3,43, 95% CI 1,79-6,58, p=0,0001). It can be assumed that the production of galectin-3 is significantly increased in the early stages of myocardial fibrosis formation. Nevertheless, given its significant prognostic role in patients with not only paroxysmal, but also persistent forms of AF, it is possible to believe that this biomarker acts as a predictor of more long-term prognosis in patients with AF.

As our study showed, the biomarker GDF-15 is no less important in terms of predicting AF recurrence after RFA in patients with MS. The results of numerous studies have established that this biomarker increases in inflammation, oxidative stress, hypoxia, and hyperglycemia. It probably determines its important integrative role as an indicator of adverse metabolic pathological processes in the body [30]. In patients with AF, the prognostic role of GDF-15 in the risk stratification of bleeding was well-studied in a large randomized trial ARISTOTLE, where GDF-15 was proved to be associated with the risk of cardiovascular death and bleeding [31]. In 2020, data on the role of GDF-15 in predicting AF recurrence was firstly published. It was found that exceeding the cut-off value of 1287,3 pg/ml increased the risk of AF recurrence (RR =1,053, 95% CI 1,007-1,1, p=0,022), however, this predictive model had low sensitivity (51,4%) and specificity (70,8%), and more than half of the patients in the study had persistent AF [32]. According to the results of our study, the GDF-15 biomarker also demonstrated a high prognostic role in predicting AF recurrence after RFA in a cohort of patients with MS, wherein the cut-off value of GDF-15 was higher (1380,7 pg/ml), and the increase in the risk of recurrence was found to be more degree (RR =2,84, 95% CI 1,81-4,46, p<0,0001).

The use of various biomarkers in actual clinical practice allows personalization of therapy to achieve a better result in reducing the risk of endpoint events. In particular, a comprehensive assessment of such prognostic biomarkers as galectin-3, GDF-15, and EFT in patients with AF and MS makes it possible to predict AF recurrence within 12 months after RFA with a high degree of sensitivity and specificity. The main practical significance of such personalized therapy is the timely identification of patients with an unfavorable prognosis of RFA. In those patients primary prevention such as the impact on risk factors of AF: weight loss, normalization of blood pressure and stabilization of the glycemic profile, identification and correction of respiratory disorders during sleep in preparation for an intervention therapy should be intensified. All that may improve the prognosis of the effectiveness of radiofrequency pulmonary vein isolation in patients with MS.

Conclusion

1. The presence of 3 and more MS components increases the risk of AF recurrence by 4,1 times within 12 months after RFA, and the highest risk of recurrent episodes of this arrhythmia was found in patients with 5 MS components.

2. On binomial logistic regression, independent predictors of AF recurrence such as EFT, severity

of LA fibrosis, elevated blood levels of galectin-3 and GDF-15 were identified in patients with MS during the first 12 months after RFA.

3. Cut-off values of the blood concentrations of galectin-3 (>11,0 ng/mL), GDF-15 (>1380,7 pg/mL) and EFT (>6,4 mm) have been established. The excess of those significantly affects the risk of AF recurrence after RFA in patients with MS.

Relationships and Activities: none.

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Comparison of open femoral exposure and percutaneous access in endovascular reconstruction of the thoracic aorta: a two-center retrospective study

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Aim. To analyze the efficacy and safety of the percutaneous transfemoral puncture technique for TEVAR (thoracis endovascular aortic repair).

Material and methods. The retrospective study included 89 patients with aortic pathologies, for whom endovascular repair was performed: 51 patients (57%) with aortic dissection (type I DeBakey — 30 cases (58,8%) and type III — 21 (41,2%)), 38 (43%) patients with aortic aneurism. 82% of patients were male, the median age was 57 years (minimum age 17 years, maximum age 75 years). All patients were divided into two groups: in the first group (48 patients) endovascular aortic repair was performed under endotracheal anesthesia with open femoral exposure of the common femoral artery (CFA), in the second group (41 patients) — by percutaneous puncture method under local anesthesia. Technical and clinical aspects of procedures were analyzed.

Results. Technical success of endovascular repair was achieved in 100% cases in both groups. The duration of the operation in the group with percutaneous access was statically significantly shorter (120 (94-150) minutes vs 87 (60-120) minutes, p=0,001). Also, the time spent by patients in the intensive care unit and the period of hospitalization (18 (14-22) hours versus 1 (0-3) hours, p=0,001; 5 (4-6) days versus 4 (3-5) days, p=0,03) was shorter. In the open access group 2 (4,2%) patients developed access-related complications — acute thrombosis of the common femoral artery and hematoma of the postoperative wound, which required additional surgical aid — thrombectomy from the CFA, the second patient had evacuation of the hematoma of the postoperative wound. Cite-related complications in the second group were not observed. No major complications including neurological deficits and hospital mortality were observed in both groups.

Conclusions. Thoracic endovascular aortic repair (TEVAR) using percutaneous access under local anesthesia in stable patients has proven to be safe and effective. The operation time is significantly reduced and this approach in most cases eliminates the need for the patient to stay in the intensive care unit in the early postoperative period. Possibility of early mobilization of the patient appears with reducing of the duration of hospitalization.

Keywords: endoprosthesis, thoracic aortic aneurysm, aortic dissection, femoral artery, local anesthesia, stent graft, endovascular aortic repair.

Relationships and Activities: none.

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Key messages

- Endovascular stent-grafting occupies a leading position in the treatment of patients with descending aortic dissection or aneurysm.
- The key to stent graft implantation is access to peripheral vessels.
- Studies comparing the direct percutaneous assess with open exposure of the common femoral artery in this pathology are rare and limited.
- This article presents the experience of two comparison centers of the above methods. In our experience, the percutaneous technique under local anesthesia has proven to be highly effective and safe.

Endovascular techniques have revolutionized the treatment of patients with various aortic pathologies, but despite significant technical progress in the manufacture of instruments, stent-graft delivery systems have a large diameter from 18F to 26F, which requires adequate access to the common femoral artery (CFA) and can be considered as a limiting factor for the percutaneous method [1-3]. For this reason, at the present stage, a number of centers prefer open surgical access. However, the open arteriotomy can lead to a number of serious complications such as formation of hematoma, lymphoma, seroma, lymphocele, postoperative scar and wound infection that results in the necessity of additional interventions and increasing the time of hospitalization of patients [4, 5].

The appearance on the market devices for percutaneous puncture suturing the arterial wall has made a revolution in the endovascular aortic reconstruction. The use of the Perclose Proglide (Abbott Vascular, Redwood City, CA, USA) devices is an important step in reducing the invasiveness of the procedure. Increasingly, the specialized literature gives examples of routine use of such devices. Unfortunately, many of them are not registered on the domestic market. Some authors note that in a number of clinics this technique is a full-fledged alternative to surgical isolation of the femoral artery [6]. Moreover, this group of patients is generally more satisfied with the treatment process due to reducing the time of the operation and the length of stay in the clinic [7, 8]. The use of local anesthesia for the puncture access contributes to not only early diagnostics of the neurological disorders such as ischemia of the spinal cord and brain, but also generally reduces the invasiveness of the procedure. During the process of endoprosthesis delivery, the aortic wall undergoes significant pressure, especially pronounced in the isthmus area. This may cause the discomfort which warns the surgeon about the danger of rupture or retrograde dissection of the aorta. A patient under general endotracheal anesthesia cannot inform about these senses [9, 10]. The study is aimed to compare the open and puncture access in endovascular reconstruction of thoracic aorta.

Material and methods

We made the retrospective analysis of the nine-year work experience of the Federal State Budgetary Institution "Federal Center for Cardiovascular Surgery" of the Ministry of Health of the Russian Federation (Astrakhan) and the Bashkir State Medical University for the period from 2012 to 2021. The study included the patients with aneurysm and dissection of thoracic aorta. The patients in acute phase of the pathological process and the patients treated with endovascular techniques were excluded. The total number of the included patients was 89, and 82% of them were men (73 patients). The median age was 57 years (the minimum age was 17 years, and the maximum was 75 years). Endoprosthetic repair of thoracic aorta aneurysms was performed in 38 patients (43%), thoracic aorta dissection — in 51 patients (57%). De Beiki type I was recorded in 30 cases (58,8%), III type — in 21 cases (41,2%). Stanford type A — 31 cases (61%), type B — 20 cases (39%).

The study includes two groups of patients. The first group includes 48 patients — aortic stent-graft implantation was performed under general endotracheal anesthesia and with traditional isolation of CFA. The second group includes 41 patients — the local anesthesia and percutaneous puncture method of endoprosthesis delivery were used.

These groups did not differ from each other in main demographic parameters and concomitant diseases (Table 1, Figures 1 and 2). More frequently, the puncture method was used in patients of more elderly age: the median age in the group with the open access was 56 years (46-61), while in the group with the percutaneous puncture method — 62 years (53-69), p=0,01. Because of small size sample

Table 1

General characteristics of the patients included in the study

Parameters	Open access (n=48)	Puncture access (n=41)	P-value
Age, years (Me (Q_1-Q_3))	56 (46-61)	62 (53-69)	0,01
Men, n (%)	40 (83,3)	33 (80,5)	0,7
Concomitant disease, n (%)			
NYHA III-IV FC, n (%)	8 (16,7)	10 (24,4)	0,4
IHD	14 (29,2)	9 (22,0)	0,4
Diabetes mellitus	6 (12,5)	6 (14,6)	0,9
Cardiac rhythm disturbances	7 (14,6)	2 (4,9)	0,1
CBS in anamnesis	7 (14,6)	6 (14,6)	1
PCI in anamnesis	5 (10,4)	2 (4,9)	0,4
AH	44 (91,7)	32 (78,0)	0,08
ACVA	6 (12,5)	2 (4,9)	0,3
COPD	10 (20,8)	11 (26,8)	0,5
CKD	14 (29,2)	7 (17,1)	0,1

Abbreviations: AH — arterail hypertension, ACVA — acute cerebrovascular accident, CBS — coronary bypass surgery, CKD — chronic kidney disease, COPD — chronic obstructive pulmonary disease, FC — functional class, IHD — ischemic heart disease, NYHA — New York Heart Association, PCI — percutaneous coronary intervention.

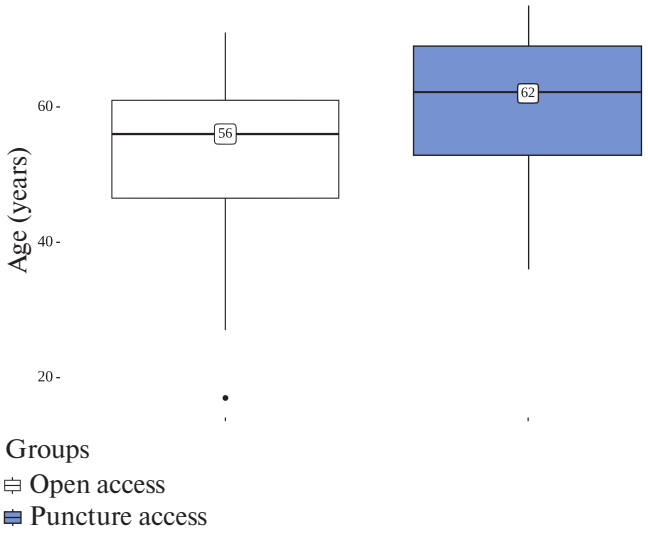

Figure 1. The age of patients included in the study, depending on the access.

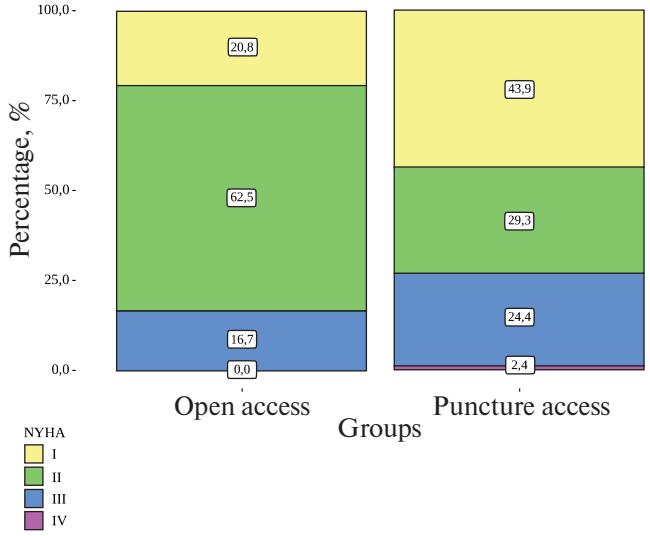

Figure 2. The analysis of the functional class parameter according to NYHA depending on the access.

we decided to refuse the conduction of propensity score matching and to perform the retrospective analysis despite of statistically significant difference in age. Severe heart failure of functional class III-IV according to New York Heart Association (NYHA) was met in both groups without a statistically significant difference (in 8 patients of the 1 group (16,7%) and in 10 patients of the 2 group (24,4%), p=0,4).

Technical aspects of interventions. To treat patients in both groups, the Medtronic & Ankura`s stent-grafts Valiant Captivia of Lifetech company were used. The diameter of the delivery device is 22-25F. The morphology of the vessels was precisely analyzed by contrast-enhanced multispiral computed tomography. In the group with open access, endoprosthetic repair of aorta was performed under general endotracheal anesthesia with surgical isolation of CFA. In the group with percutaneous puncture access, the endoprosthetic repair of aorta was performed under local anesthesia. The local anesthesia was performed by pricking the puncture site with 0,25% — 20 ml of lidocaine solution. If the adequate

Table 2

Intraoperative and postoperative parameters

Parameters	Open access (n=48)	Puncture access (n=41)	P-value
Duration of operation, min (Me (Q_1-Q_3))	120 (94-150)	87 (60-120)	0,001
Caliber of delivery device, Fr (Me (Q_1-Q_3))	24 (24-24)	24 (20-24)	<0,001
Time spent in ICU, hours (Me (Q_1-Q_3))	18 (14-22)	1 (0-3)	<0,001
Postoperative bed days, days (Me (Q_1-Q_3))	5 (4-6)	4 (3-5)	0,03
Local postoperative complications (hematoma, thrombosis), n (%)	2 (4,2)	0	0,497
Hospital lethality, n (%)	0	0	1

Abbreviation: ICU — intensive care unit.

local anesthesia was not achieved, intravenous bolus or continuous administration of 0,005% — 1,0-2,0 ml of fentanyl solution in dilution with NaCl was added. In puncture access, the suturing of the artery was performed using two Perclose Proglide (Abbott Vascular, Redwood City, CA, USA) devices according to adopted technique: after performing the puncture of the artery according to Seldinger technique and installing the introducer 6F, the suturing was performed by the two devices alternately (with angulation of the suturing systems at 90° relatively to each other) followed by re-installation of the introducer and further entry of rigid conduction and implantation of stent-graft. There were no conversions with transition to general endotracheal anesthesia and open access. During entire operation all the patients were conscious, and neurological monitoring for timely diagnostics of intraoperative circulatory disorders of the brain and spinal cord was continuously conducted.

Intraoperative angiography of the arteries of the lower extremities on the side of access was performed. In the postoperative period, all patients underwent puncture site monitoring and duplex ultrasound examination of the inguinal region and retroperitoneal space for early diagnostics of retroperitoneal hematoma.

Statistical analysis. The statistical analysis of the material was performed using a software package IBM SPSS Statistics 26 (Chicago, IL, USA), Jamovi (Version 1.6.9) (Computer Software). We verified all quantitative variables for the type of distribution using the Shapiro-Wilk criterion because the number of patients in both groups was <50. The quantitative parameters having a normal distribution were described using arithmetic means (M) and standard deviations (SD), the limits of the 95% confidence interval (95% CI). In case of the absence of a normal distribution, we described the quantitative data using the median (Me) and the lower and upper quartiles (Q1-Q3). The categorical data were described with absolute values (n) and percentages (%). The comparison of the two groups by a quantitative parameter having a normal distribution with unequal dispersions was performed using the Welch t-test. The comparison of the two groups by a quantitative parameter, the distribution of which differed from the normal one, was performed using the Mann-Whitney U test. The comparison of percentages in the analysis of four-field conjugacy tables was performed using Pearson's chi-squared test (with values of the expected phenomenon >10) and Fisher's exact test (with values of the expected phenomenon <10). The comparison of percentages in the analysis of multipole conjugacy tables was performed using Pearson's chi-square test. The critical significance level when checking statistical hypotheses was taken as 0,05.

Results

The technical success of the stent-graft implantation was achieved in 100% of cases in the investigated groups. The duration of the operation in the group with puncture access was statistically significant shorter (120 (94-150) min vs 87 (60-120) min, p=0,001). We recorded the reduction of the time spent by the patients in the intensive care unit (18 (14-22) hours vs 1 (0-3) hours, p=0,001); this led to a significant reduction of the overall hospitalization period (5 (4-6) days vs 4 (3-5), p=0,03). 2 (4,2%) patients in the first group had the access-associated complications — acute CFA thrombosis and postoperative wound hematoma that required the additional surgical manipulations — thrombectomy from CFA and evacuation of postoperative wound hematoma, respectively. There were no such complications requiring a surgical intervention in postoperative period in the second group. In 3 cases (7,3%), we observed unsatisfactory hemostasis directly after suturing by two Perclose Proglide systems, that required the use of additional closure device Angioseal 8F (Terumo). We did not find a statistically significant difference between the groups in the occurrence of complications depending on the

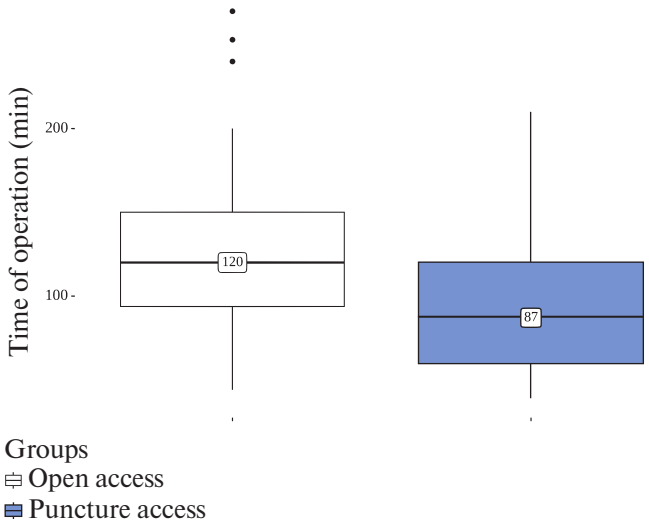

Figure 3. Duration of the operation depending on the access.

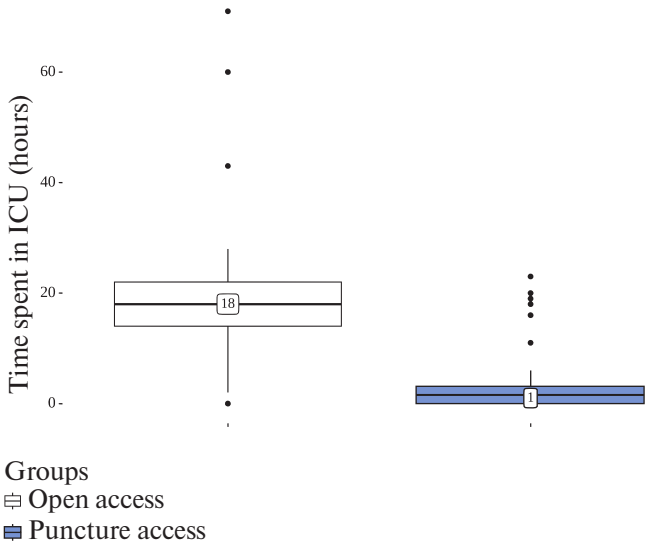

Figure 4. Time spent in the intensive care unit depending on the access.
Abbreviation: ICU — intensive care unit.

access. There were none of cases of the neurological deficit occurrence. The hospital lethality rate was 0 in both groups.

The intra- and postoperative data were shown in Table 2 and in Figures 3 and 4.

Discussion

The extension of indications for the use of percutaneous puncture access for large-caliber delivery devices does not lead to an increase in the number of access-associated complications, while maintaining the maximal technical success of the entire procedure. With the accumulation of experience with suturing devices in our clinics, the tactics for their use have been changed — we actively use a combination of devices with a different mechanism for the closure of an arterial defect. Currently, one system is always used first: Perclose Proglide. At the end of the operation, after tightening the node, the quality of hemostasis is evaluated. In case of major bleeding, we additionally use the second Perclose Proglide device. If the leakage from the puncture site remains, we add hemostasis by using the Angioseal 8F device. In the absence of such a device, it is acceptable to perform prolonged manual compression until complete hemostasis is achieved, that is actively used in a number of centers. In our opinion, the use of an additional device for complete hemostasis is the most reliable and allows you to confidently prevent bleeding in the postoperative period, especially when the patient begins to get up and move around. It should be noted that in our center, we use one suturing device while working with the instruments of no more than the 16F caliber. The importance to explore the effectiveness and safety of the use of number and types of suturing devices is caused by not only accumulation of the experience of the use but also by the appearance of new hemostasis systems and progressive decrease in the diameter of endovascular instrument delivery systems.

Monitoring the results of aortic prosthetic repair using the puncture access, exactly the obtaining a reliable reduction of the time spent by patients in the intensive care unit, led to a change in approaches to postoperative logistics. For instance, currently, after the operation, the patients are transferred immediately to the surgical ward, bypassing the intensive care unit, which is safer, more comfortable for patients and brings economic benefits for the clinic.

The important aspect of the present study is the analysis of the results of the treatment of patients under local anesthesia. This approach provides undeniable advantages because it gives the possibility of early diagnostics of serious complications, especially neurological deficits. Spinal cord ischemia is still one of the most severe complications of endovascular reconstruction of thoracic aorta, and the performing operations under local anesthesia is another step towards early diagnostics of spinal cord ischemia that allows to reduce its symptoms in case of the occurrence [9].

The limitations of the study. The limitation is retrospective analysis and inability to perform propensity score matching because of a small group of patients.

Conclusion

Routine use of percutaneous puncture method and local anesthesia in stable patients while perfor-

ming endoprosthetic repair of thoracic aorta, showed high efficiency and safety. The combination of local anesthesia and percutaneous puncture access in concerned with less number of complications that are typical of traditional surgical access under general endotracheal anesthesia. As a result, the duration of hospitalization and rehabilitation is reduced, and, together with other factors, all this is more favorable for the patients. Without general anesthesia, it is possible to conduct a constant neuromonitoring. This contributes to early detection of neurological complications. We believe that the most reliable closure of the arterial wall defect is carried out using a combination of suturing devices. This allows to safely apply the large caliber delivery devices up to 25F. The risks of cutaneous sensitivity disorders, lymphorrhea and infection are minimized. The duration of the operation is significantly reduced. In most cases, there is no need to monitor the patients in early postoperative period in the intensive care unit. And there is also the possibility of early mobilization of the patient. All these factors can significantly reduce the time of hospitalization and economic costs.

Relationships and Activities: none.

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Experience in implementing a program for basic life support and available automated defibrillation in a cancer center

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Unified approaches to ensuring the chain of survival can improve the patient's prognosis both in out-of-hospital and in-hospital cardiac arrest.

Aim. To discuss practical issues of introducing a program for the availability of automated external defibrillation in a cancer center.

Material and methods. For four years, our healthcare facility has been implementing a training program for basic and advanced life support according to the European Resuscitation Council standards, combined with the creation and development of an infrastructure for the availability of automatic defibrillation. A roadmap and infrastructure were developed for the project implementation.

Results. In 2018-2022, 229 employees (114 doctors, 85 nurses and 30 non-medical workers) were trained under the basic life support program. Fifteen defibrillators were placed in various units. During the specified period, first aid in case of sudden cardiac arrest using an automated external defibrillator before the resuscitation team arrival was independently provided by doctors and nurses of departments three times. To implement training in the continuous education system, the curriculum has passed the examination and accreditation in the edu.rosminzdrav system.

Conclusion. The development and implementation of such initiatives requires significant organizational and methodological work, including continuous education system. However, in our opinion, this is an extremely useful tool for improving the safety and quality of medical care.

Keywords: cardiopulmonary resuscitation, training, automated external defibrillator, basic life support, cardiac arrest.

Relationships and Activities: none.

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Key messages

- It is important to implement a systematic approach to educating healthcare professionals about first aid and emergency care.
- The educational approaches of the European Resuscitation Council at the level of a certain hospital allow this to be done.
- Placing automated defibrillators in the public areas of hospitals and outpatient departments, combined with trained healthcare professionals, allows the early rhythm analysis and defibrillation to be performed before the arrival of the resuscitation team or the ambulance team.

Sudden cardiac arrest (SCA) is one the most common causes of death nowadays. Despite the significant progress in the prevention and treatment of heart and vascular diseases achieved in the last decade, mortality from sudden cardiac arrest remains high [1]. For example, in USA, almost 400 thousand cases of SCA occur every year at the prehospital stage, and only 12% of these patients survive [2, 3]. The majority of out-of-hospital cardiac arrests (~80%) occur in houses and other residential premises [4, 5]. The numerous studies showed that early defibrillation and availability of a trained lifeguard who is able to recognize cardiac arrest and to start resuscitation measures before the arrival of qualified help, can increase survival rate in case of both out-of-hospital and intrahospital cardiac arrests [6-9]. One study evaluated the effectiveness of defibrillation in public places found that the percentage of patients surviving after SCA was significantly higher when the help on the street was provided by bystanders trained to do cardiopulmonary resuscitation (CPR) using an automated external defibrillator (AED) (23%), compared with situations where only chest compressions were performed (14%) [10]. The comparable data were obtained when analyzing the real practice of AED installation in schools and police cars [11-13]. That is why in many countries in public places (pharmacies, stadiums, beaches, shopping malls, museums, tourist attractions, etc.), public transport, cars of law enforcement agencies and rescue services, the AEDs are installed; and also extensive training of medical workers, firefighters, rescuers, police officers, teachers, airline employees and just concerned citizens is carried out. In the UK, the BLS certification course (Basic Life Support — basic CPR using AEDs) is a prerequisite for obtaining a graduation certificate of middle school[1]. In Denmark currently it is mandatory for all drivers to hold a valid BLS certificate and therefore, as of January 1, 2020, 1 million out of 4,8 million people aged 15 to 105 years have been the trained providers of basic resuscitation [14]. As an experiment, some countries have pilot launched projects with the delivery of AEDs to the accident scene using unmanned aerial vehicles [15, 16].

In our country, the currently existing legal limitations do not allow mass placement of AEDs in public places, since defibrillators are the medical devices, but it is possible within a medical facility. As for ambulatory subdivisions, taking into account the daily number of visits, many of them are actually a public place, and the availability of defibrillators and personnel capable of providing high-quality first aid increases the level of safety. According to the results of large-scale studies in Denmark and USA, it is economically reasonable to place the AEDs in areas where one cardiac arrest for a period from 2 to 5 years can be expected, and, for example, in Copenhagen, such a frequency of sudden cardiac arrests is recorded at train stations, in public parks and even pedestrian zones [17, 18]. With a high degree of probability, it can be assumed that medical organizations also fall into this category. That is why, since the late 1980s, even before the introduction of public accessibility programs, AEDs were initially installed in hospitals and outpatient centers in various countries [19]. This practice is still quite common in the European region. For example, in Denmark, 93% of hospitals are equipped with AEDs, which are placed in public spaces, non-clinical subdivisions, usual hospital departments and are intended for use by personnel until the arrival of specialized resuscitation teams [19]. This strategy provides the best survival rates even in intrahospital cardiac arrest but only if the first discharge is applied no later than 3 minutes from the moment of calling for help [20].

To provide the work of all elements of the survival chain, in addition to the equipment, standardization of training of medical workers according to the

[1] Education and Training (Welfare of Children) Act 2021. 29 April 2021. https://www.legislation.gov.uk/en/ukpga/2021/16/enacted (доступ 26.04.2022).

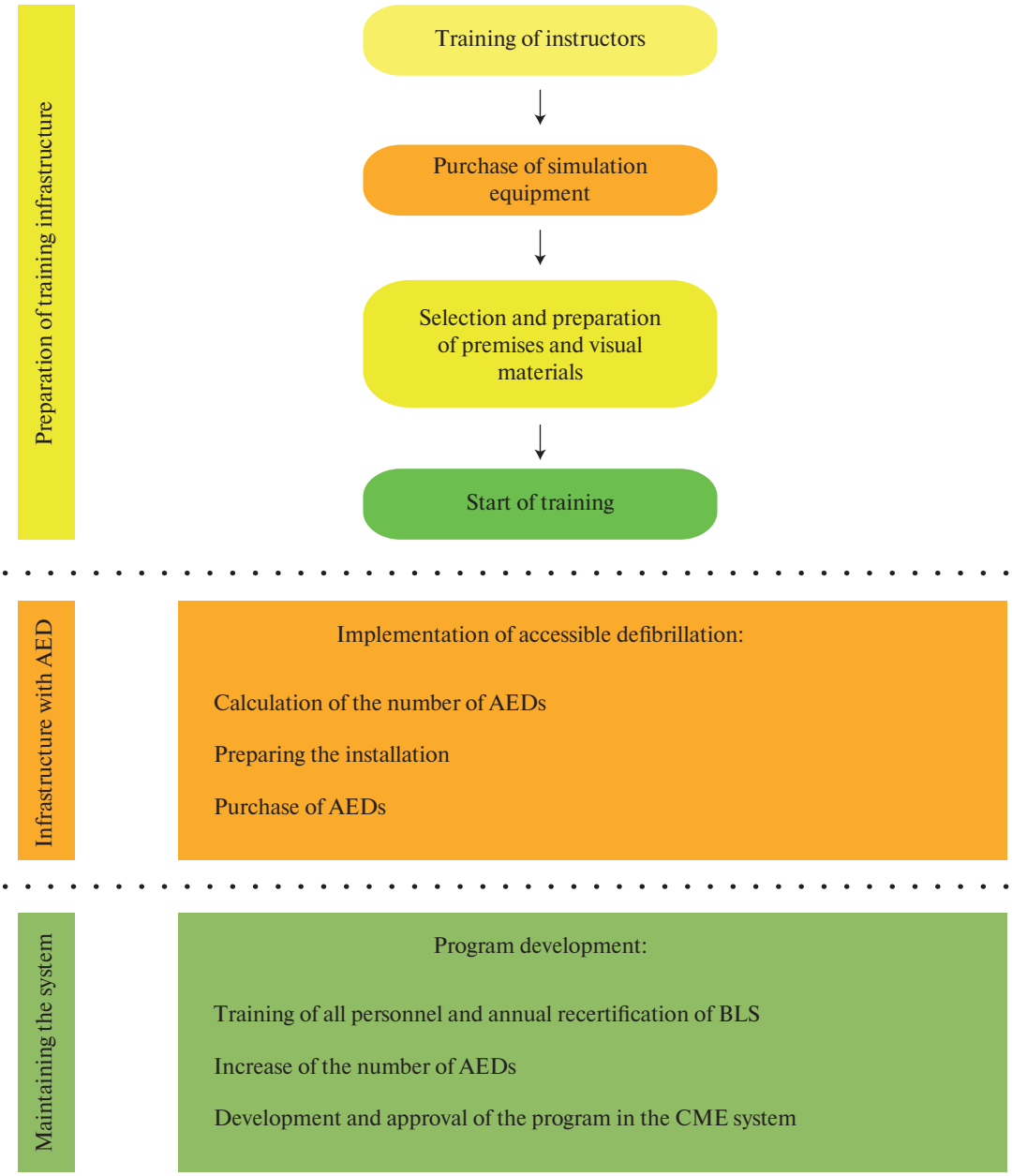

Figure 1. The stages of the implementing the program of accessible defibrillation.
Abbreviations: AED — automated external defibrillator, CME — continuing medical education, BLS — Basic Life Support.

algorithms adopted by the European Resuscitation Council (ERC) and the National Resuscitation Council (NRS) is extremely important [6, 7]. The first step in the training system is the BLS protocol [21]. In foreign countries, the course of basic resuscitation is mandatory curriculum component of medical schools and universities [22, 23]. The extended resuscitation programs — ALS (Advanced Life Support) in European countries or ACLS (Advanced Cardiac Life Support) — in the USA, UK and Canada are the mandatory component of residency training for doctors of all specialties [24].

The aim of the study: the present work is not a study in the classical sense; the authors tried to present and discuss their own experience of the AED accessibility program realization, implementing the training system for medical workers in concern with the Life Support strategy at different levels under oncological hospital conditions, as well as to identify those key points that should not be missed during the training, and difficulties that may arise during the implementation.

Material and methods

Since 2018 our medical organization (100-bed oncological hospital with departments of anesthesiology and intensive care, surgical oncology, general oncology and chemotherapy, radiation therapy, pediatric oncology; proton radiation therapy center with a 60-bed building; two outpatient polyclinic complexes with day hospitals; >80 free-standing diagnostic centers in the regions; nuclear medicine centers with a day hospital in Novosibirsk, Tomsk and Barnaul) has developed and has been implementing an AED accessibility program. The specificity of our organization is a large number of free-standing radiation diagnostic centers, where as a rule, there are only radiologists, radiologist technicians and medical registrars. In fact, they are the outpatient centers where, if necessary, the medical personnel have to provide the first and emergency care without any support of the resuscitation team and to call the city ambulance service therefore, it was necessary to train precisely these categories of medical workers.

At the discussion of the conception stage, we developed a roadmap which has undergone many changes over these years, but today it can be presented as follows (Figure 1).

As of 2018, there was only one NRS instructor working on a full-time basis, who, however, became the main organizer and motivator of the change implementation. Currently in Saint-Petersburg there are 890 employees in our organization (totally in the country >2000). Since, according to the ERS rules, the BLS training group consists of no more than eight students per a instructor, and the instructors are usually doctors who are primarily engaged in basic medical work, we had an urgent need for scale development of the simulation center. The purchase of equipment was carried out consistently, at the rate of one set per an instructor. The standard set for the basic resuscitation course includes a mannequin for simulating chest compressions and artificial inspirations (preferably with feedback), an Ambu bag, a training defibrillator, a vest for practicing manual skills of performing the Heimlich method. In our institution we used the mannequins Laerdal Resusci Anne QCPR of modification 2018, having a SkillGuide device to assess the depth, frequency of compressions and the effectiveness of artificial inspirations as well as the possibility to assess all these parameters with help of mobile application for smartphone, and also the training defibrillators Zoll AED plus and Philips Heartstart FRx.

The training is conducted by certified instructors in strict accordance with the training programs and clinical recommendations of the ERC and NRS. The training process is regulated by European Resuscitation Council: the class lasts 8 hours and includes theoretical blocks and practicing practical skills on simulators, both individually and at providing aid by two rescuers. From the moment of registration for the course until the course completion, the trainees receive the access to the course materials through an internal electronic platform — a course manual, videos, lecture material and a preliminary test task for self-preparation. The trainees who have successfully completed the practical exam issued the international certificate, and they receive the credit units in the system of continuing medical education (CME) in their personal account of the portal edu.rosminzdrav. To maintain skills and qualifications, the course should be repeated annually.

At the same time with the training, the concept of creating and promoting the infrastructure of the public-access AEDs was developed. At the initial stage, the main criterion to choose the addresses for AED installations was the presence of either department of anesthesiology and intensive care, or an anesthesiological group as well as the availability of outpatient consultations. Apart from that, a calculation method based on the data of NMRC named after A. N. Bakulev about the frequency of sudden coronary death in the Russian Federation amounting 150-450 thousand a year, i.e. approximately from 1 to 3 thousand per 1 million of population, was used. Thus, for example, if the patient flow through all oncological hospital subdivisions ~15 thousand people a year, there is a probability to meet approximately 15 sudden cardiac arrests hence, the AED installation appears reasonable. Since 2021, all the centers have been equipping with automatic defibrillators.

An extremely important point that can complicate the implementation of the defibrillator accessibility program is the choice of a source of financing for the purchase. The medical equipment standards of providing oncology and pediatric oncology medical care do not stipulate the availability of AEDs in the bed- and consultation departments. Therefore, a medical organization may purchase them either from extra-budgetary sources of financing or with the help of grants. Taking into account these specificities, both mechanisms were implemented in our organization — the first AEDs were purchased using own extra-budgetary funds of the hospital, then the grant support was received.

Results

In 2019-2022, 229 employees were trained according to the program (114 doctors, 85 specialists of the secondary medical staff and 30 non-medical workers). During the same period, after the first stage training, 15 doctors completed the ALS program,

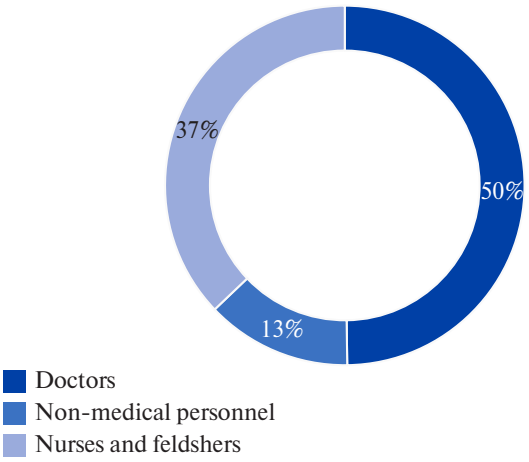

Figure 2. The structure of trainees according to profession/level of education.

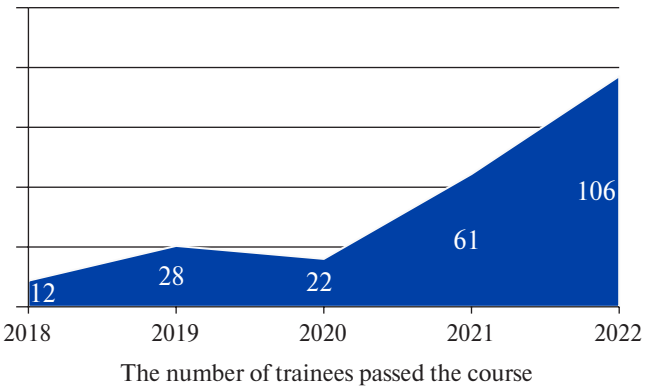

Figure 3. Dynamics of the number of trainees by years (2022 — data for the first quarter).

3 doctors, 2 feldshers and 2 nurses — Immediate Life Support program, and 2 doctors — International Trauma Life Support program. Besides, 36 radiologists, medical physicists and radiotherapists passed the non-standardized first aid course under World Restart Heart Day (CPR skills using the AEDs) without obtaining a BLS certificate. The program was also implemented to the ambulatory oncologic centers in Novosibirsk, Barnaul, Tomsk (23 employees passed the program). The average age of all the trainees was 36,5 ages (from 21 to 66), 75 men and 154 women. The structure of the trainees is shown in the Figure 2.

Most of all the trainees were radiologists 38% (n=43), next — anesthesiologists-resuscitators 14% (n=16), and on the third place — heads of departments 9% (n=10).

As planned, a significant percent was occupied by the doctors of the radiology departments, since under the conditions of a free-standing office, it is the radiologist who, if necessary, will be the team leader and must possess all the required skills. A considerable number of anesthesiologists is explained by the mandatory successful passage of Advanced Life Support course in the trajectories of their professional development, and BLS is the first stage of ALS course.

In the composition of secondary medical personnel, 38% were occupied by radiologist technicians (n=32), and nurses and feldshers together — 62% (n=53). The non-medical workers were represented by medical registrars 50% (n=15), engineers 13% (n=4) and office workers — accounting department, etc. 37% (n=11).

Since only one instructor was involved in training for a long time, just over 70 employees completed the course between 2018 and the third quarter of 2021. Another limiting factor was the novel coronavirus infection pandemic, in which regulators limited the conduct of face-to-face educational events, and the ERC made changes to the BLS algorithm, structure and rules of the lesson. Apart from that, many doctor (including future instructors), radiologist technicians, nurses and registrars worked in repurposed centers for a long time; this excluded the very possibility of their participation in the training process.

With the improvement of the epidemiological situation, starting from October 2021, 3 people completed the course for instructors (BIC — Basic Instructor Course) and the traineeships necessary to obtain the status of a "full-fledged instructor", additional simulation equipment was purchased, an electronic platform to register in the course with materials for self-training was created; all this made the possibility to abruptly intensify the process (Figure 3). The program itself became a resource for selecting potential instructors — during the course passage, the participants were evaluated, and the most active of them were invited to traineeships. Nowadays, the organization staff includes 4 full-fledged BLS instructors, 1 ALS candidate instructor and 1 International Trauma Life Support candidate instructor, but the development process of the simulation center continues, because the global goal is to train all employees without exception.

To harmonize the training program with the CME developmental strategy in 2022, we developed an additional professional education program "Basic Cardiopulmonary resuscitation of adults" (code V0002000-2022), which was examined and approved on the CME portal. Currently, medical workers are registered for the cycle and receive the credit units after successful completing the exam, that serves as additional motivation for them to pass the course. The development process is not complicated and

Figure 4. The standard wall packing with AED.

is about the preparation of the training program itself, the creation of materials for the test exam, the creation of an electronic platform for trainees, where educational materials (lectures, videos, sample test assignment) are placed. An important point is that the program should be implemented not only through a full-time simulation course, but also with the participation of distance learning technologies and e-learning. Since basic CPR is included in the block of general medical knowledge, the program is intended (and is included in educational and methodological complexes) for doctors and nurses of all specialties.

In addition to training, the second key point is the development of technical infrastructure of accessible AEDs. For the past 4 years, 12 AEDs have been installed in St. Petersburg and one in Novosibirsk, Tomsk and Barnaul. In Saint-Petersburg, they were installed in the greatest people concentration places and at the crossing of the main "routes" of staff and patients. This looks as follows: 3 defibrillators are placed in the oncological hospital (the hall of the first floor, the hall of the second floor, the registry of the radiotherapy building); 4 — in the proton radiation therapy center (the hall of the bed-building, the registry of the radiotherapy building, the hall of the day chemotherapy hospital, the hall of the positron emission tomography department), 3 — in outpatient departments, 1 — in the computed tomography center, 1 — in the magnetic resonance imaging center. The clinical subdivisions use Zoll AED plus, the free-standing diagnostic subdivisions — Philips Heartstart FRx. In accordance with European Resuscitation Council recommendations, each defibrillator is packed in a special bag containing reserve baby electrodes, sterile gloves, razors, gauze wipes, a breathing mask with a valve. The packing is placed in a wall cabinet with a transparent door and an identification mark. Above each cabinet with AED the signs indicating the emergency call number of the resuscitation team were mounted as well as a QR code that allows you to make an automatic call from a mobile phone by simply scanning with the built-in camera of a smartphone (Figure 4).

In 2018-2022, there were three cases when first aid for SCA using AED was independently provided by medical workers of treatment and diagnostic departments before the arrival of the resuscitation team. In two cases they performed effective CPR; the rhythm was potentially defibrillable, and the application of the discharge restored the electrical activity of the heart, in one case there was a spontaneous restoration of the rhythm. Besides, in one case to eliminate airway obstruction, the Heimlich technique was used; in dozens of cases, after assessing the level of consciousness and the presence of breathing, patients were placed to a lateral recovery position. The implemented infrastructure also allowed to increase the mobility of resuscitators on duty, since currently there is no need to carry a defibrillator to the place of the first aid providing.

Because of the small number of cases with the use of AEDs, it is still quite difficult to fully assess the pharmacoeconomical effectiveness of the program implementation; at the same time, it is possible to estimate the level of costs, as well as to calculate the costs of one effective CPR.

1. The expenses for training.

Training of one instructor in the Moscow, St. Petersburg or Tomsk certified centers costs ~15 thousand rubles. It is required to have one set of the training simulators and devices for each instructor. The cost of BLS equipment depends on the manufacturer; the average cost of a set (a mannequin, a training defibrillator with consumable materials, a device for training Heimlich method) is ~100 thousand rubles. Apart from that, the organizational and administrative expenses (meals for trainees, since the ERC rules stipulate this, registration of a certificate, rental of premises, stationery, gloves, masks, etc.) are ~2 thousand rubles per a trainee in average. Thus, the final cost of the course, including amortization of equipment and payment of the instructor's working time, ranges from 5 to 7,5 thousand rubles per a trainee. On one side, this seems large for the medical organization aiming to train all employees because these expenses are for hundreds of people. However, it is important to take into account that this course is a professional development, and if the program is approved in the CME system, the expenses for the training of medical workers may be taken from the compulsory medical insurance funds.

2. The expenses for the infrastructure of accessible defibrillation.

The cost of one AED Philips as 2021 is ~90 thousand rubles. The additional equipment (cabinet, packing, pediatric electrodes, etc.) raises main expenses up to 150 thousand rubles. Since currently AED are included in the equipment standards of only dental offices and ambulances, we have to find extra-budgetary sources of financing for infrastructure costs, and this, in our opinion, is the greatest organizational difficulty. Thus, the total costs for the program implementation for 4 years amounted to ~3,5 million rubles. In our case, the expenses for one effective CPR using AED when recalculating reached ~1 million rubles, which, in turn, is significantly lower than in foreign studies on pharmacoeconomics (the calculated QALY in which ranges from 30 to 50 thousand US dollars per defibrillator) [17].

Discussion

As the CME system has been gradually introducing in Russian healthcare since 2015, basic CPR has been included in the primary accreditation programs for all specialties [25]. At the same time, a medical worker passes primary accreditation only once, when receiving a specialty; hence, skills and knowledge that are not used in routine practice may be lost. That is why one of the ERC requirements is annual re-passing the BLS course [21]. This recommendation has a serious foundation and has been confirmed over the years by the results of various studies. Back in 2007, there was a study on a group of Birmingham University students, which evaluated the effectiveness of chest compressions on a mannequin with feedback directly during training and 6 weeks afterwards [19]. The obtained results were 58% and 43%, respectively. In 2021, the group of Spanish authors published the results of the study which evaluated the BLS knowledge survival among the students of medical colleges of the Almeria and Murcia universities [26]. The analysis included 479 trainees who were asked to undergo an assessment of theoretical knowledge and practical skills 6 months after completing the course. Only 60% of trainees showed satisfactory effectiveness of compressions (depth 67%, frequency 62,2%), and this allowed the authors to conclude that the training should be regular. For already working healthcare professionals, the situation may be even more critical. According to a multicenter study performed by Pakistani authors, the survival rate of skills among medical workers was 41,7% in average, and just 1 out of 140 respondents showed full knowledge of the BLS algorithm when tested [27]. At the same time, the study performed in the University of Pennsylvania showed that 6-11 months after the course completing the level of manual skills falls up to 74%, while in the period from 12 to 17 months — up to 71%, that looks quite optimistic [28]. In general, the majority of studies accepts that the training process should be constant and repetitive. In our opinion, it is the regular annual simulation training that allows medical professionals to make the correct algorithm of actions when meeting SCA. Undoubtedly, continuous training and regular re-certification require significant resources, but this is the only way to develop and maintain CPR skills using the AEDs.

An interesting issue is reasonability of the implementing automated defibrillation in a medical facility. At first glance, especially in the buildings having the anesthesiology-resuscitation departments or groups, this step seems excessive. However, the standard practice, including the world experience, shows that while meeting a patient with SCA, some time is spent on calling a duty doctor, then some time is spent on calling a resuscitator, and as a result, precious minutes are lost for the delivery of a manual defibrillator and the arrival of a specialist who is able to assess the patient's condition and adequately carry out resuscitation measures [20, 29]. Apart from that, the important restriction in use of biphasic defibrillator monitor (even if it is available in quick access) in manual mode is the fact is that rhythm assessment and decision-making for manual defibrillation require good skills to quickly read an electrocardiogram from a monitor screen, which is not always applicable to doctors and nurses of those specialties that do not involve daily work with an electrocardiogram. One of the solutions in Western hospitals was the formation of the so-called Code team — emergency resuscitation teams of doctors and nurses who are not employees of intensive care units, but have been certified for advanced resuscitation measures [30]. At the same time, the availability of such teams requires significant resources both for training and for the infrastructure development (resuscitation trolleys with defibrillators and packing of drugs and medical devices), that may not always be implemented in all departments. Thus, the ERC experts recommend to use AEDs in semi-automated mode in those hospital departments where is the risk of the delay of defibrillation for several minutes (more than 2-3 min), and where the workers who first react to SCA do not have an experience of manual defibrillation [21, 31, 32]. In general, intrahospital SCA are characterized by low survival rate which ranges within 10-20% [20]. If in the intensive care units this situation is explained by the structure of electrical rhythms of arrest (the predominance of potentially non-defibrillable arrests — electrome-

chanical dissociation and asystole), then in usual departments and public places of hospitals, the leading cause is delayed defibrillation [20]. That is why until now the practice of mass training of medical personnel and the installation of automated defibrillators is recognized by most researchers as adequate [20, 29].

As for free-standing units, the problem is even more acute, since qualified help in this case involves the call and arrival of an ambulance team. Even with strict time standards for the arrival of the brigade in megacities (~20 min) and the early start of chest compressions, the time interval before the first discharge can be tens of minutes, which negatively affects the further prognosis of patient survival. Psychological barriers, especially in secondary medical personnel, are also important moment. According to the results of the published in 2018 multicenter research, which carried out in three Canadian university clinics, 87,5% of nurses performed CPR at least once in their life but only 29% of them used defibrillator [29]. That is why in our practice, at the first stage, we concentrated on training nurses and radiologist technicians. Undoubtedly, the global goal — to train all employees — has not yet been achieved, but after 4 years of implementation, it became obvious to us that it is achievable.

Conclusion

The implementation and development of the AED accessibility program in combination with the training of personnel under the Life Support programs, is a useful and necessary process under the conditions of a medical organization. The employees trained to perform the measures of first and emergency care according to the standards, and the presence of the corresponding material and technical base form a certain safety culture.

The doctors and nurses who successfully passed the basic resuscitation course are the personnel reserve for the training extended resuscitation measures, the formation of emergency resuscitation teams and the expansion of the teaching staff of the simulation center.

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Relationships and Activities: none.

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LITERATURE REVIEWS
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Efficacy and safety of combined aspirin and warfarin therapy after heart valve replacement: a systematic review and meta-analysis of randomized clinical trials

Golukhova E. Z., Berdibekov B. Sh., Ruzina E. V.

Aim. To conduct a systematic review and meta-analysis of the efficacy and safety of combined oral anticoagulant therapy with vitamin K antagonists (VKA) and antiplatelet therapy with aspirin compared with VKA monotherapy in patients after mechanical valve replacement.

Material and methods. We searched the PubMed, Google Scholar databases for studies comparing the risk of thromboembolic events, major bleeding, and mortality in VKA monotherapy versus combined aspirin and VKA therapy in patients with mechanical valve replacement.

Results. Eight randomized clinical trials were selected for this systematic review and meta-analysis. In total, 4082 patients were included in the analysis (mean age, 50,8 years, men — 2484 (60,9%)). A meta-analysis showed that the addition of aspirin to VKA, compared with VKA monotherapy, significantly reduced the incidence of thromboembolic events (odds ratio (OR) 0,47; 95% confidence interval (CI): 0,33-0,67; p<0,0001) and mortality (OR 0,58; 95% CI: 0,38-0,88; p=0,01). The risk of major bleeding in the aspirin plus VKA group compared with VKA monotherapy tended to increase, without reaching a significant difference (OR 1,41; 95% CI: 0,99-2,01; p=0,06).

Conclusion. The addition of aspirin to VKA, compared with VKA monotherapy, reduces the risk of systemic embolism and death in patients after mechanical valve replacement. At the same time, the risk of major bleeding did not differ between the groups.

Keywords: warfarin, vitamin K antagonist, aspirin, prosthetic mechanical valve, thromboembolism, bleeding.

Relationships and Activities: none.

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Key messages

- The addition of aspirin to VKA, compared with VKA monotherapy, significantly reduces the risk of systemic embolism and death in patients after mechanical valve replacement.
- There were no significant differences in major bleeding between VKA monotherapy versus combined aspirin and VKA therapy.

Valvular heart defects is a great clinical problem in developing countries because of high incidence of rheumatic heart diseases and in Western countries because of high incidence of degenerative valve diseases [1]. Such patients often require the implantation of a valve prosthesis — mechanical or biological. These two types of the valves differ from each other in service life and thrombogenicity. Unlike the mechanical prosthesis, the biological one is less thrombogenic on the one side and has a shorter life duration on the other side.

The patients undergone the operation for the replacement of the heart valves by the mechanical prostheses are at the risk of developing thromboembolic complications, the most formidable of which are thrombosis of valve prostheses and disabling strokes, which, in turn, can lead to the death of a patient [2, 3]. Thromboembolism can be caused by the following: the occurrence of turbulent blood flow and blood stasis, which are created by the implanted valve itself, as well as high thrombogenicity of the mechanical prosthesis material [4]. It should be noted that the place of prosthetics plays an important role in the assessment of thrombogenic risk factors: unlike the aortic valve replacement, the mitral valve replacement has a higher risk of thromboembolic complications; this, in turn, leads to higher values of the target international normalized ratio (INR) and therefore, to an increased risk of bleeding [5]. Thus, antithrombotic therapy is necessary for everyone in this group of patients in the postoperative period. The antithrombotic drugs include indirect anticoagulants — vitamin K antagonists (VKA) (warfarin, acenocoumarol, phenprocoumarol) and antiplatelet agents (aspirin, dipyridamole and clopidogrel) [6, 7]. It is important to note that the effect of each of these drugs on clotting factors and on the degree of platelet aggregation predisposes to bleeding.

The major meta-analysis including 13 studies with 4122 patients was published in 2013 by Cochrane Collaboration. The research showed that compared to VKA alone, the addition of antiplatelet agent (aspirin/dipyridamole) not only reduced the risk of thromboembolic complications but also increased the risk of bleeding [8]. However, this meta-analysis had a number of significant limitations: first of all, the most studies were done before 1990, and the implanted prostheses had high rates of thrombogenicity; secondly, the research investigated relatively small sample size (the majority <200 people); thirdly, the studies contained many patients with concomitant ischemic heart disease that can explain the benefits of additional prescription of antiplatelet drugs. It should be noted that in 6 studies of 13 in the meta-analysis, dipyridamole was used as an antiplatelet agent, which is currently rarely used in clinical practice.

Thus, the optimal strategy for combined antithrombotic therapy in patients with mechanical prosthetic heart valves is still an open question.

The purpose of our systematic review and meta-analysis is to evaluate the efficiency and safety of combined oral anticoagulant therapy (VKA) and aspirin antiplatelet therapy in comparison with VKA monotherapy in patients after mechanical heart valve replacement.

Material and methods

Search for publications and selection of studies. The information retrieval algorithm was developed in accordance with the reporting requirements and regulations for systematic reviews and meta-analyses (PRISMA) [10, 11]. These recommendations help to describe the study so that it can be evaluated by editors, reviewers, readers, as well as other researchers engaged in meta-analysis. The literature was searched in databases MEDLINE/PubMed (www.ncbi.nlm.nih.gov/pubmed) and Google Scholar.

To search data in PubMed we used the following keywords: "warfarin" OR "vitamin k antagonists" AND "mechanical heart-valve" AND "aspirin" AND "thromboembolism". We also used a manual search in the links from the certain review articles, meta-analyses and consensus statements. To search data in Google Scholar we used the following: mechanical valve replacement, valvular heart disease, anticoagulation, vitamin K antagonists, warfarin, antiplatelet, aspirin, prosthesis, thromboembolism, bleeding, stroke, efficiency, safety. The selection of suitable studies for inclusion into this systematic review and meta-analysis was carried out by following: the two authors studied abstracts and full-text articles for compliance with the inclusion criteria independently from each other.

The last data search for inclusion into this analysis was done on 05.02.2022.

Criteria for inclusion/exclusion. The criteria for inclusion into the systematic review followed by meta-analysis were: only randomized clinical trials were included; the studies with access to full texts; all participants were adult (18 years old and above); the research which studied the group of patients after mechanical heart valve replacement, where was the comparison between addition of aspirin to VKA (warfarin) and VKA (warfarin) monotherapy. Apart from that, a prerequisite for the inclusion of the publications in the meta-analysis was the presentation of clinical outcome data, such as thromboembolic events, major bleeding and mortality. The minimum follow-up period in the study was 6 months. The articles in languages other than English, descrip-

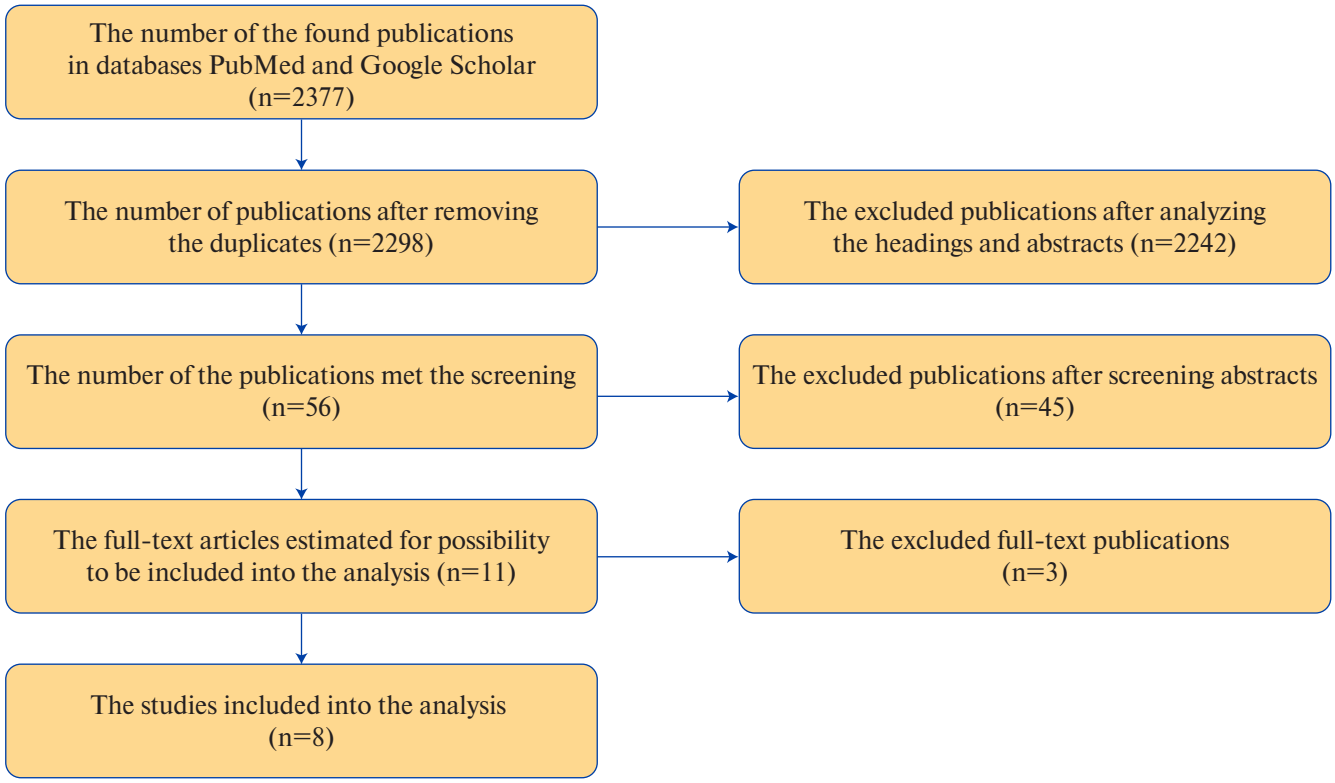

Figure 1. Flowchart of the selection of the studies included in the review.

tions of individual cases, preclinical studies, reviews and expert opinions, as well as studies whose results are published only in the form of abstracts, were excluded from the meta-analysis.

Besides, to describe the basic characteristics, the following data were taken from each study: mean follow-up period, average age of patients and gender distribution, target INR or prothrombin time ratio, aspirin dosage, type and location of the prosthetic valve.

Assessment of methodological quality. The systematic error (Risk of bias) was assessed in accordance with the Cochrane criteria for the assessment methodological quality of randomized clinical trials (RoB 2 tool) [12]. All discrepancies were eliminated by discussion between the authors of the work.

Statistical analysis. All types of statistical analysis were carried out using the program RevMan 5[1]. The main results are depicted graphically as forest plot or blobbogram. Statistical heterogeneity was evaluated using Pearson's chi-squared criterion, as well as the heterogeneity index I^2. The interpretation of the statistical heterogeneity assessment according to the index I^2 was carried out by following the recommendations of the Cochrane Collaboration, under which I^2=0-40% corresponds to weak heterogeneity; 30-60% — moderate heterogeneity; 50-90% — substantial heterogeneity; 75-100% — high heterogeneity. Also, statistical heterogeneity was assessed by p-value defined by criterion χ^2, where $p<0,1$ — presence of statistically significant heterogeneity, and $p\geqslant 0,1$ — absence of statistically significant heterogeneity. The effect was measured mainly using the odds ratio (OR) with 95% confidence interval (CI). The effect was considered statistically significant at $p<0,05$. For OR calculation to assess the effect we used a fixed effects model. The possibility of systematic errors associated with predominant publication of positive research results was analyzed by means of visual assessment of the funnel plot.

[1] Review Manager (RevMan) [Computer program]. Version 5.4.1, The Cochrane Collaboration. 2020.

Results

Literature search results. The total number of the publications found in databases PubMed and Google Scholar using the keywords was 2377. The number of publications after excluding the duplicates was 2298. After analyzing the headers and abstracts, only 56 publications matching the set goal remained. The most frequent reasons for the exclusion of the articles were the set goal mismatch and the absence of specified data; we also excluded the review articles, discussions, abstracts and reports. After full-text screening, 11 articles remained. However, two of them did not give the data of the number of outcomes

Table 1

Characteristics of the studies included in the systematic review. Location and type of mechanical prosthesis

Author	Year	N	Prosthesis MV (%)	Prosthesis AV (%)	Prosthesis MV+AV (%)	% mechanical prostheses	Type of prosthesis
Altman [16]	1976	122	74	26	0	100	Starr-Edwards valves (93%) and disc valves (7%)
Dale [17]	1977	148	0	100	0	100	Starr-Edwards valves (100%)
Turpie [18]	1993	370	44	46	10	76	n/d
Meschengieser [19]	1997	503	29	66	4	100	Starr-Edwards valves (26%), disc valves (65%), St. Jude Medical (4,5%), unknown (4,5%)
Laffort [20]	2000	229	60	0	40	100	St. Jude Medical (100%)
LIWACAP [21]	2007	198	27	63	10	100	Sorin Bicarbon (40%), St. Jude Medical (28%), Carbomedics (20%), others (12%)
Dong [22]	2011	1496	83	43	16	100	St. Jude Medical (36%), GK (China) (34%), Medtronic (30%)
Wang [9]	2014	1016	70	20	10	100	St. Jude Medical (34%), GK (China) (36%), Medtronic (20%)

Abbreviations: AV — aortic valve, MV — mitral valve, n/d — no data, N — the number of the patients included in the study.

Table 2

Main characteristics of the patients included in the study

Author	Year	N	Age (years)	Men (%)	Type of VKA	VKA (target INR)	VKA+aspirin (target INR)	Mean follow-up period (years)
Altman [16]	1976	122	n/d	75	Acenocoumarol	PT 1,8-2,3 times from normal	PT1,8-2,3 of normal	2
Dale [17]	1977	148	51	75	n/d	10% of normal thrombo-test	10% of normal thrombo-test	2
Turpie [18]	1993	370	58	51	Warfarin	3,0-4,5 (3,0)	3,0-4,5 (3,1)	2,5
Meschengieser [19]	1997	503	53	58	Warfarin	3,5-4,5 (3,98)	2,5-3,5 (3,11)	2 (mediana)
Laffort [20]	2000	229	63	50	Warfarin	2,5-3,5 (3,03)	2,5-3,5 (3,04)	1
LIWACAP [21]	2007	198	60	47	Warfarin	3,0-4,5 (3,7)	2,0-3,0 (2,5)	0,5
Dong [22]	2011	1496	34	92	Warfarin	1,8-2,5	1,8-2,5	2
Wang [9]	2014	1016	37	39	Warfarin	1,8-2,5	1,8-2,5	2

Abbreviations: VKA — vitamin K antagonist, INR — international normalized ratio, n/d — no data, PT — prothrombin time.

Table 3

Comparison between combination of VKA and aspirin and VKA monotherapy

Ouncomes	Number of trials (n)	Number of patients (n)	Total number of events	Statistical methods	Effect size
Thromboembolic events	8	4082	154 (3,8%)	OR, fixed effect model, 95% CI	0,47 [0,33-0,67]
Lethal cases	8	4082	97 (2,4%)	OR, fixed effect model, 95% CI	0,58 [0,38-0,88]
Hemorrhages	8	4082	136 (3,3%)	OR, fixed effect model, 95% CI	1,41 [0,99-2,01]

Abbreviations: OR — odds ratio, CI — confidence interval.

in the groups [13, 14], and one study [15] did not meet the criteria for a randomized trial because it was cohort, and therefore, these studies were also excluded from our analysis. Thus, 8 studies were finally selected for our review; the process of the selecting relevant studies is shown in Figure 1.

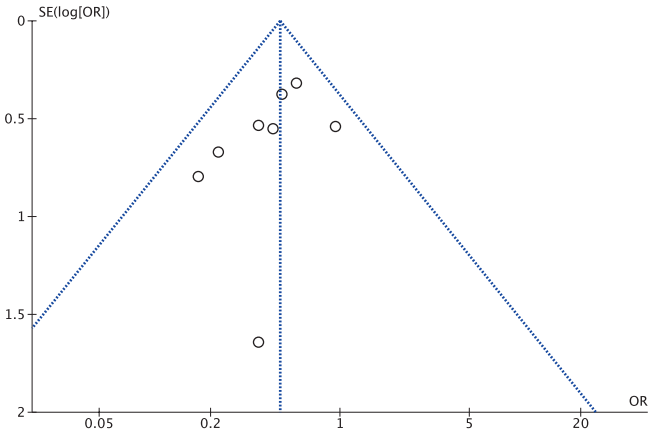

Figure 2. Funnel plot: aspirin + VKA versus VKA monotherapy. Thromboembolic risk.

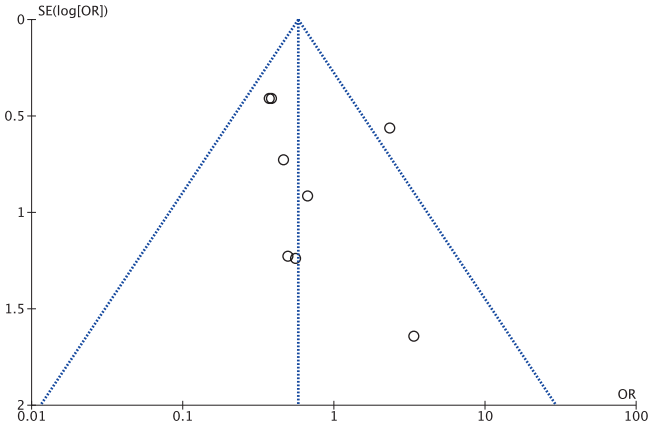

Figure 3. Funnel plot: aspirin + VKA versus VKA monotherapy. Lethal cases.

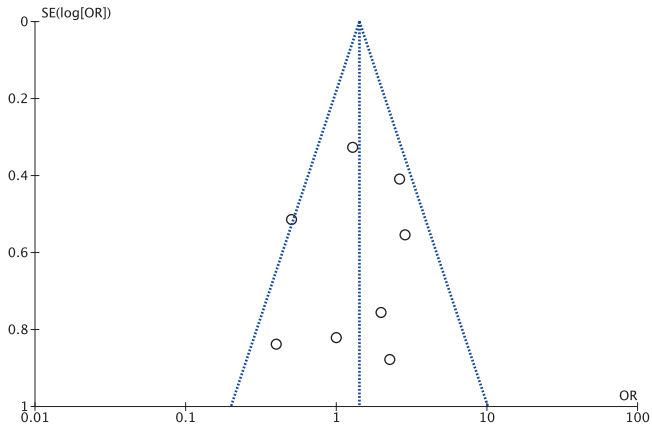

Figure 4. Funnel plot: aspirin + VKA versus VKA monotherapy. Hemorrhages.

General characteristics of study. For the present systematic review and meta-analysis, 8 randomized clinical trials were selected [9, 16-22]. The articles included in the systematic review and meta-analysis were published in the period from 1976 to 2014. The total number of patients was 4082. The average age of the patients was 50.8 years old, men — 2484 (60,9%). The average follow-up period was 1,75 years (Tables 1, 2).

In all included studies, the antiplatelet agent was aspirin at doses of 500 mg/day [16], 1000 mg/day [17], 200 mg/day [20], 100 mg/day [18, 19, 21], 75-100 mg/day [9, 22].

A number of studies preceded the appearance and widespread use of the INR value, and the target level of anticoagulation was estimated by an increase of prothrombin time 1,8-2,3 times as long as in normal [16] or 10% increase of thrombo-test relatively to normal [17]. It should be noted that in two studies, the target INR was 1,8 to 2,5 [9, 22]; in three studies, the high level of the target INR was from 3,0-3,5 to 4,5 [18, 19, 21]; and in one study, the target INR values were 2,5 to 3,5 [20].

Endpoints and adverse outcomes. One of the criteria for inclusion into the systematic review was the presence of the endpoint reports — thromboembolic events, bleeding and lethality. Of the main outcomes, the criteria for thromboembolic events or arterial thromboembolism were clearly defined for each trial. In the most trials, the definitions of thromboembolic complications were similar and included the following conditions: ischemic stroke or transient ischemic attack, other systemic thromboembolism confirmed by ultrasound and/or surgery. In one trial [20], non-obstructive thrombosis of mechanical prostheses and transient ischemic attack were considered as minor embolic events. However, for our meta-analysis, such outcomes were classified as major thromboembolic events.

The data of serious hemorrhagic complications in the included studies were less unambiguous. In the Meschengieser`s study 1997 [19], a major hemorrhagic event was defined as bleeding required hemotransfusion, hospitalization or if it was the cause of death. In Turpie`s study 1993 [18], major hemorrhage was defined as obvious bleeding associated with a drop in hemoglobin levels by >20 g/l, the need for transfusion of >2 units of blood, or any intracranial, intraocular, intra-articular or retroperitoneal hemorrhage. In LIWACAP study 2007 [21], the concept of major hemorrhage included the following: intracranial hemorrhage confirmed by computed tomography; retroperitoneal hemorrhage, also confirmed by computed tomography; intraocular hemorrhage, led to blindness; intra-articular hemorrhage; bleeding associated with a drop in hemoglobin levels by >20 g/l or the need for transfusion of >2 units of blood or required surgical intervention. In two studies [16, 17], there were no classification of hemorrhages into major and minor therefore, in our meta-analysis, we consi-

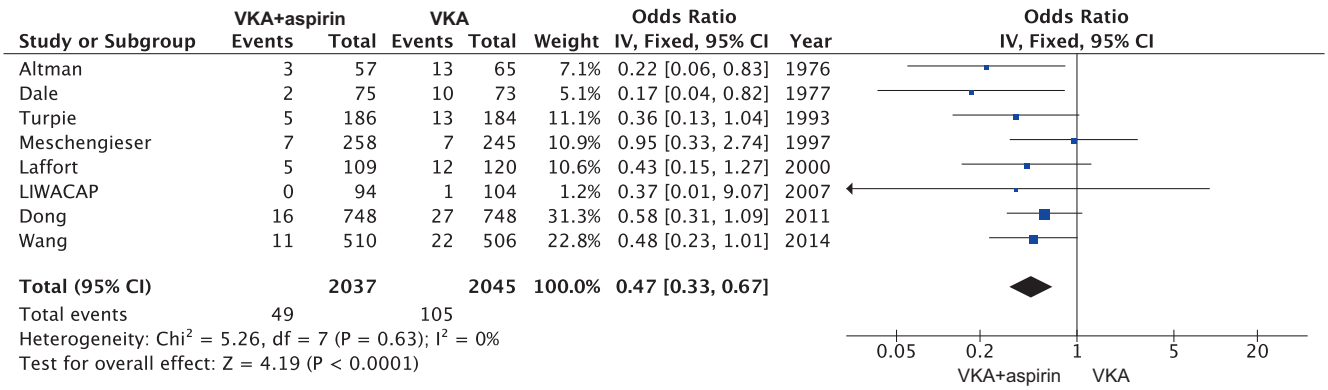

Figure 5. Forest plot OR (logarithmic scale) for thromboembolic risks depending on addition of aspirin to VKA compared with VKA monotherapy.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

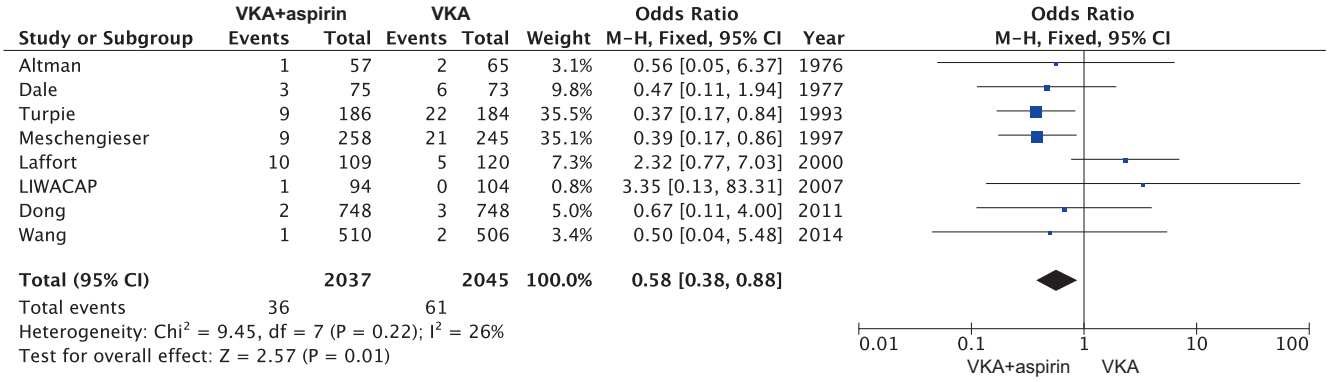

Figure 6. Forest plot OR (logarithmic scale) for lethal outcomes depending on addition of aspirin to VKA compared with VKA monotherapy.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

dered any cases of intracerebral and gastrointestinal hemorrhage, and also the episodes of hemoptysis, as significant hemorrhagic events. In Laffort`s study 2000 [20], hemorrhages were also classified into major and minor: major hemorrhage was defined as bleeding associated with a sudden drop in hemoglobin levels by >20 g/l or bleeding required transfusion of >2 units of blood or required surgical intervention as well as any intracranial hemorrhage. In two studies [9, 22], there were no definition of the concept of major and minor hemorrhages but were given the data of the bleeding localization therefore, for our meta-analysis, we considered significant bleeding as cerebral hemorrhage.

The data of lethality were available for all the trials and included general lethality. In one study only (LIWACAP 2007) [21], the concept "lethality" implied sudden cardiac death (death that occurred within an hour after the manifestation of symptoms and was not provoked by a non-vascular cause); the study did not report of any other cases of death.

Risk of systematic error in the included studies. The funnel plots for thromboembolic events, mortality and massive hemorrhages did not show any signs of publication systematic error (Figures 2, 3 and 4).

Thromboembolic events. The total number of thromboembolic events in the VKA with aspirin group was 49 (2,4% of 2037 patients), while in the VKA monotherapy group — 105 (5,1% of 2045 patients). The addition of aspirin to VKA led to a statistically significant decrease in thromboembolic complications. Compared with taking VKA only, the combination of VKA and aspirin significantly reduced the risk of thromboembolic complications by 2,1 times (OR: 0,47; 95% CI: 0,33-0,67; p<0,0001). The heterogeneity test was insignificant (p=0,63, I^2=0%) (Figure 5).

Study or Subgroup	VKA+aspirin Events	Total	VKA Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Altman	5	57	3	65	4.9%	1.99 [0.45, 8.71]	1976
Dale	13	75	5	73	8.1%	2.85 [0.96, 8.46]	1977
Turpie	24	186	19	184	32.1%	1.29 [0.68, 2.44]	1993
Meschengieser	6	258	11	245	21.2%	0.51 [0.18, 1.39]	1997
Laffort	21	109	10	120	14.8%	2.63 [1.18, 5.86]	2000
LIWACAP	4	94	2	104	3.5%	2.27 [0.41, 12.67]	2007
Dong	2	748	5	748	9.6%	0.40 [0.08, 2.06]	2011
Wang	3	510	3	506	5.8%	0.99 [0.20, 4.94]	2014
Total (95% CI)		**2037**		**2045**	**100.0%**	**1.41 [0.99, 2.01]**	
Total events	78		58				

Heterogeneity: Chi² = 10.89, df = 7 (P = 0.14); I² = 36%
Test for overall effect: Z = 1.91 (P = 0.06)

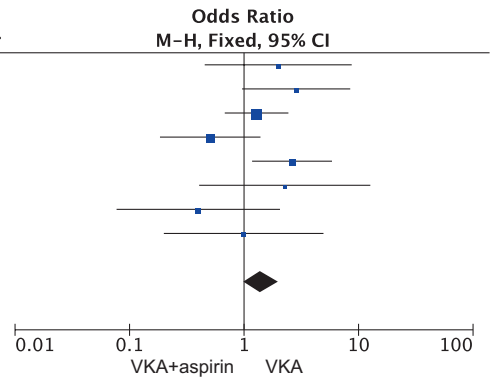

Figure 7. Forest plot OR (logarithmic scale) for major hemorrhages depending on addition of aspirin to VKA compared with VKA monotherapy.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

Study or Subgroup	VKA+aspirin Events	Total	VKA Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Meschengieser	6	258	11	245	85.8%	0.51 [0.18, 1.39]	1997
LIWACAP	4	94	2	104	14.2%	2.27 [0.41, 12.67]	2007
Total (95% CI)		**352**		**349**	**100.0%**	**0.76 [0.33, 1.74]**	
Total events	10		13				

Heterogeneity: Chi² = 2.17, df = 1 (P = 0.14); I² = 54%
Test for overall effect: Z = 0.66 (P = 0.51)

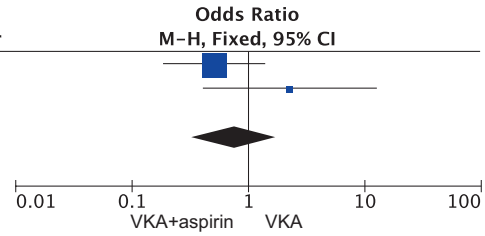

Figure 8. Forest plot OR (logarithmic scale) for major hemorrhages in the studies of high-intensity warfarin therapy.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

Study or Subgroup	VKA+aspirin Events	Total	VKA Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Meschengieser	7	258	7	245	83.1%	0.95 [0.33, 2.74]
LIWACAP	0	94	1	104	16.9%	0.37 [0.01, 9.07]
Total (95% CI)		**352**		**349**	**100.0%**	**0.85 [0.31, 2.30]**
Total events	7		8			

Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.32 (P = 0.75)

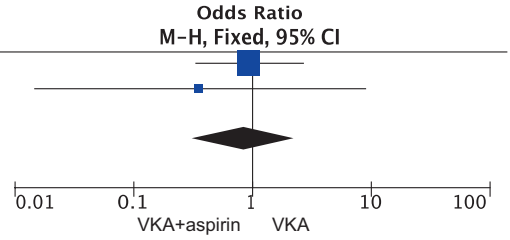

Figure 9. Forest plot OR (logarithmic scale) for thromboembolic events in the studies of high-intensity warfarin therapy.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

Lethality. The total number of lethal cases in the VKA + aspirin group was 36 (1,8% of 2037 patients), while in the VKA monotherapy group — 105 (3,0% of 2045 patients). The combined analysis of lethal events showed that the total mortality was 1,7 times statistically significant lower in the aspirin + VKA group versus VKA monotherapy (OR: 0,58; 95% CI: 0,38-0,88; p=0,01). The heterogeneity test was insignificant (p=0,22, I^2=26%) (Figure 6).

Major hemorrhages. The total number of the cases of bleeding occurrence in the VKA + aspirin group was 78 (3,8% of 2037 patients), while in the VKA monotherapy group — 58 (2,8% of 2045 patients). The meta-analysis showed that the frequency of the major hemorrhages increased with combined therapy VKA + aspirin versus VKA monotherapy but these differences did not reach statistical significance (OR: 1,41; 95% CI: 0,99-2,01; p=0,06). The heterogeneity test was insignificant (p=0,14, I^2=36%) (Figure 7).

The table 3 shows the summarized results reflected the occurrence of the main clinical out-

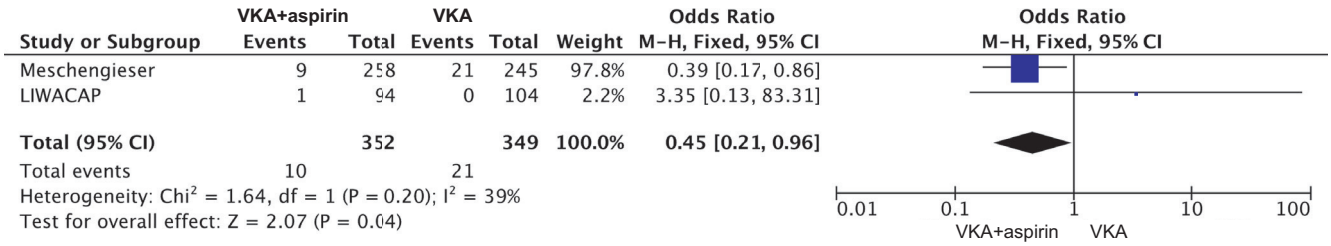

Figure 10. Forest plot OR (logarithmic scale) for lethal outcomes in the studies of high-intensity warfarin therapy.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

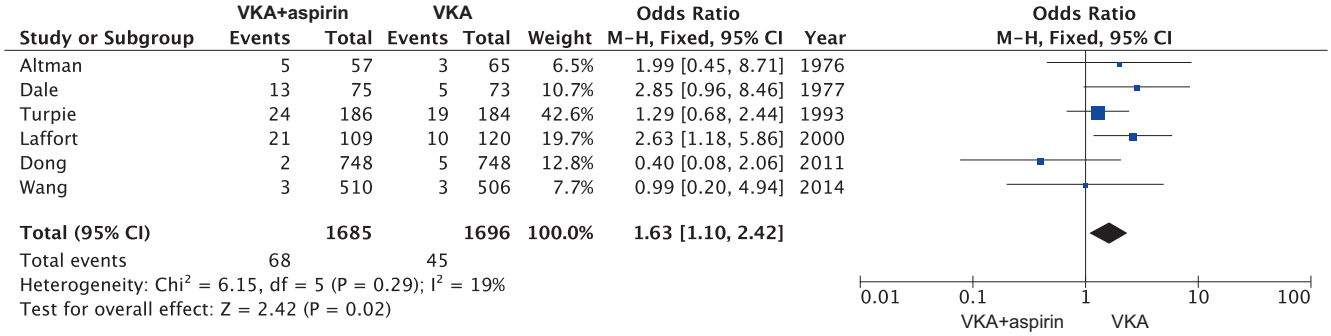

Figure 11. Forest plot OR (logarithmic scale) for major hemorrhages depending on addition of aspirin to VKA compared with VKA monotherapy. The Meschengieser 1997 and LIWACAP 2007 studies are excluded.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

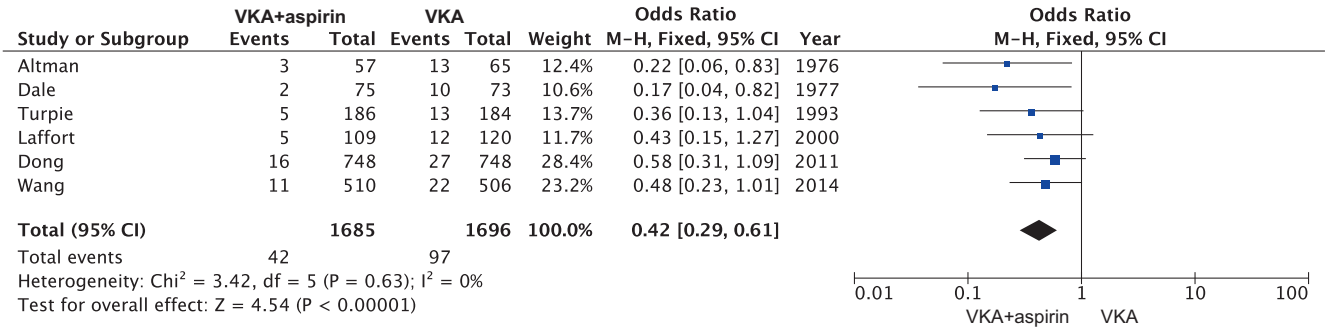

Figure 12. Forest plot OR (logarithmic scale) for thromboembolic risks depending on addition of aspirin to VKA compared with VKA monotherapy. The Meschengieser 1997 and LIWACAP 2007 studies are excluded.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

comes in the patients after mechanical heart valve replacement in comparison groups between VKA + aspirin therapy and VKA monotherapy.

Analysis of subgroups depending on the intensity of anticoagulant therapy. As it is known, the increase of INR greater than the target values against the background of taking VKA increases the risk of bleeding. Our meta-analysis includes two studies [19, 21], in which for the VKA monotherapy group, the higher target values of INR were defined (from 3,0-3,5 to 4,5), while in the aspirin + VKA group, the target values of INR were from 2,5 to 3,5. The total number of the cases of bleeding occurrence in the aspirin + VKA group was 10 (2,8% of 352 patients), while in the VKA monotherapy group — 13 (3,7% of 349 patients). The

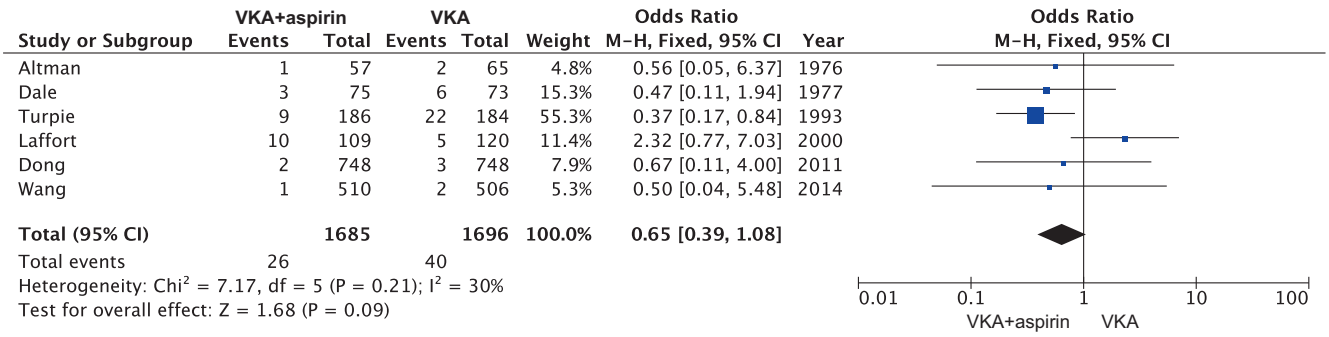

Figure 13. Forest plot OR (logarithmic scale) for lethal outcomes depending on addition of aspirin to VKA compared with VKA monotherapy. The Meschengieser 1997 and LIWACAP 2007 studies are excluded.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

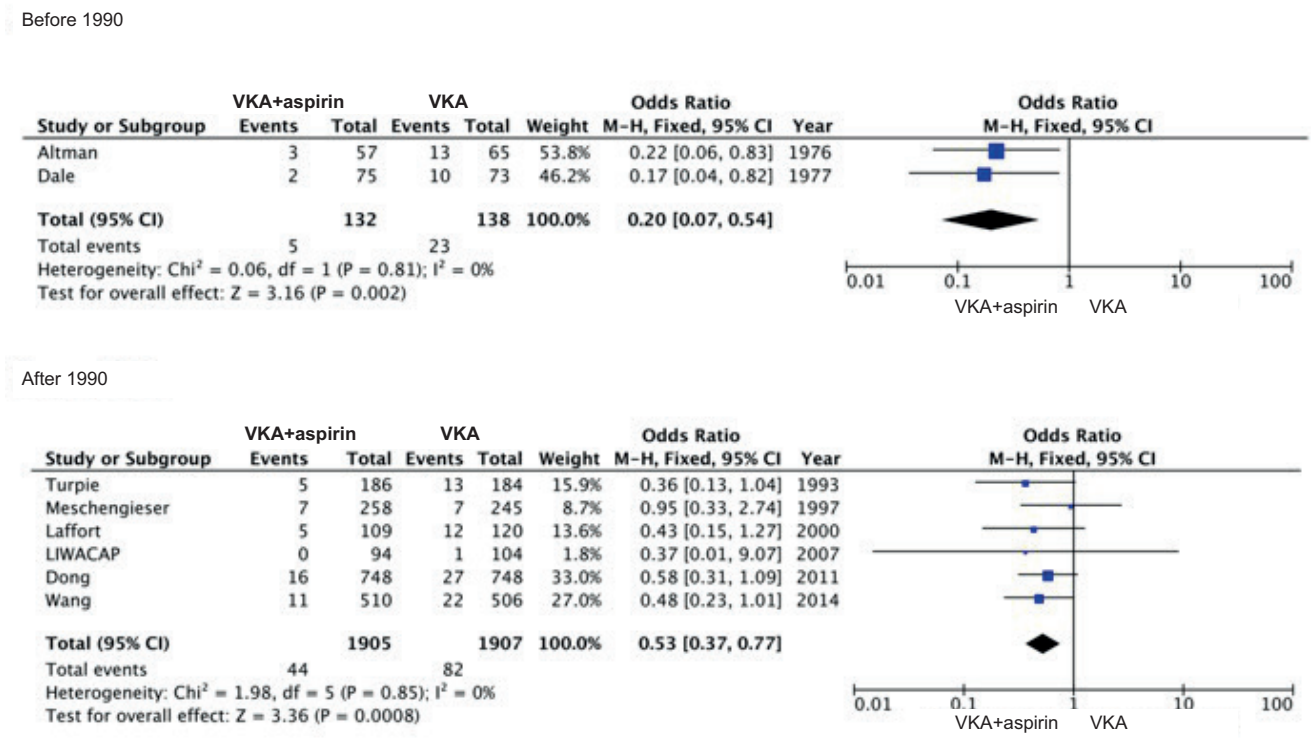

Figure 14. Forest plot OR (logarithmic scale) for thromboembolic risks depending on addition of aspirin to VKA compared with VKA monotherapy. The analysis of subgroups that include the studies performed before and after 1990.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

meta-analysis showed that the risk of major hemorrhages did not differ between the groups (OR: 0,76; 95% CI: 0,33-1,74; p=0,51) (Figure 8).

We also analyzed the influence of these two studies [19, 21] on the endpoints of death and thromboembolic complications. The total number of thromboembolic events in the VKA + aspirin group was 7 (2,0% of 352 patients), while in the VKA monotherapy group — 8 (2,3% of 349 patients), lethal outcomes — 10 (2,8% of 352 patients) and 21 (6,0% of 349 patients), respectively. The meta-analysis showed that the risk of thromboembolic events did not differ statistically significant in the VKA + aspirin group versus the VKA monotherapy group (OR: 0,85; 95% CI: 0,31-2,30; p=0,75); at the same time, the frequency of the lethal outcomes statistically significant decreased (OR: 0,45; 95% CI: 0,21-0,96; p=0,04) (Figures 9, 10).

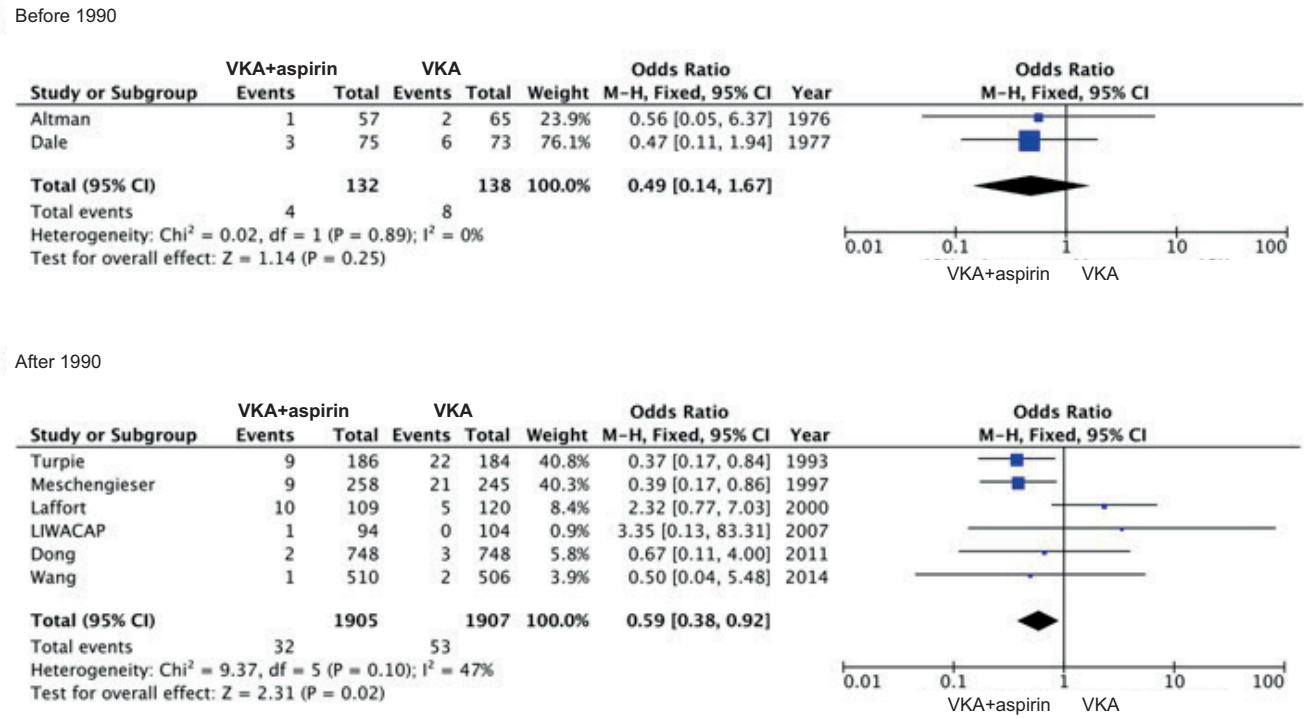

Figure 15. Forest plot OR (logarithmic scale) for lethal outcomes depending on addition of aspirin to VKA compared with VKA monotherapy. The analysis of subgroups that include the studies performed before and after 1990.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

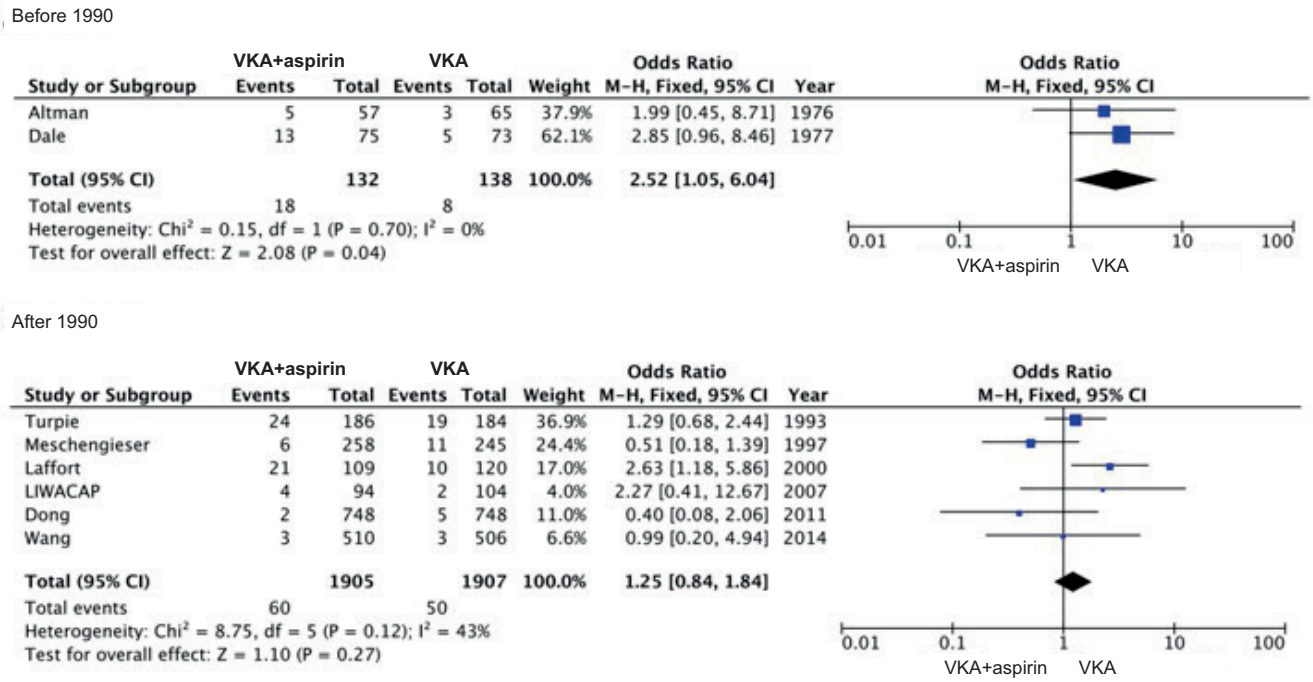

Figure 16. Forest plot OR (logarithmic scale) for major hemorrhagic events depending on addition of aspirin to VKA compared with VKA monotherapy. The analysis of subgroups that include the studies performed before and after 1990.
Note: The center of each line represents the OR for each study, and the ends of the horizontal lines represent 95% CI. A continuous vertical line represents an OR equal to 1.
Abbreviations: VKA — vitamin K antagonist, CI — confidence interval, OR — odds ratio.

Therefore, for the verification of the possible impact on the overall results of the meta-analysis, the studies with high values of target INR (Meschengieser 1997 [19] and LIWACAP 2007 [21]) were excluded in the general analysis.

The total number of the cases of major hemorrhages in VKA + aspirin group was 68 (4,0% of 1685 patients), while in VKA monotherapy group — 45 (2,7% of 1696 patients). After excluding the above studies, the meta-analysis showed that the risk of bleeding statistically significant increased with the addition of aspirin to VKA versus VKA monotherapy (OR: 1,63; 95% CI: 1,1-2,42; p=0,02) (Figure 11). We also analyzed the influence of the exclusion of these studies on the endpoints of death and thromboembolic complications. The total number of thromboembolic events in the VKA + aspirin group was 42 (2,5% of 1685 patients), while in the VKA monotherapy group — 97 (5,7% of 1696 patients), lethal outcomes — 26 (1,5% of 1685 patients) and 40 (2,4% of 1696 patients), respectively. The meta-analysis showed that the risk of thromboembolic events statistically significant decreased in the VKA + aspirin group versus VKA monotherapy (OR: 0,42; 95% CI: 0,29-0,61; p<0,00001); at the same time, the frequency of the lethal outcomes did not differ statistically significant between the groups (OR: 0,65; 95% CI: 0,39-1,08; p=0,09) (Figures 12, 13).

Analysis of subgroups depending on the monitoring method of the anticoagulant therapy effectiveness

As already noted, until 1990, there was no standardized assessment of the effectiveness of VKA therapy after mechanical heart valve replacement. In our meta-analysis, we analyzed the subgroups which were formed in accordance with the era of research — before and after 1990 (the year of the beginning of widespread use of standardized INR). Before 1990, there were just two studies — Altman [16] and Dale [17], where 270 patients were included. The six studies were published after 1990 (Turpie [18], Meschengieser [19], Laffort [20], LIWACAP [21], Dong [22], Wang [9]); the total number of the included patients were 3812. The risk of thromboembolic events statistically significant decreased in both subgroups (before and after 1990) in the VKA + aspirin group versus VKA monotherapy (before 1990: OR: 0,20; 95% CI: 0,07-0,54; p=0,002; after 1990: OR: 0,53; 95% CI: 0,37-0,77; p=0,0008) (Figure 14). In our meta-analysis, the number of the lethal outcomes in the subgroup before 1990 does not differ significantly in the VKA + aspirin group versus VKA monotherapy (OR: 0,49; 95% CI: 0,14-1,67; p=0,25); on the contrary, in the subgroup after 1990 the risk of lethal outcomes statistically significant decreased in the VKA + aspirin group (OR: 0,59; 95% CI: 0,38-0,92; p=0,02) (Figure 15). The meta-analysis showed that in the subgroup before 1990, the risk of major hemorrhage occurrence was statistically significant higher in the VKA + aspirin group versus VKA monotherapy (OR: 2,52; 95% CI: 1,05-6,04; p=0,04), while in the subgroup after 1990 there were no significant differences (OR: 1,25; 95% CI: 0,84-1,84; p=0,27) (Figure 16). Probably, the obtained results regarding the increase of the risk of major hemorrhage occurrence in the dual therapy group are associated not only with the absence of standardized assessment of the VKA therapy effectiveness but also with the use of aspirin in large doses when added to VKA: in the Altman`s study [16] the dose was 500 mg/day, in Dale`s study [17] — 1000 mg/day.

Discussion

The 2020 guideline of American College of Cardiology (ACC)/American Heart Association (AHA) [23] on managing patients with heart failure reported of the decrease of the recommendation class and the level of evidence for adding aspirin to VKA for patients after mechanical heart valve replacement (class 2b, level B-R). It should be recalled that the previous ACC/AHA guideline on managing patients with heart failure (2017) recommended to add aspirin at doses 75-100 mg to VKA therapy for all patients with mechanical heart valve prostheses (1A) [24]. It should be noted that this recommendation was based mainly on the results of two small studies (Turpie, Meschengieser), performed in 1993 and 1997, respectively [18, 19]. The Turpie`s study 1993 included 370 patients, the majority of which had ischemic heart disease therefore, the prescription of aspirin in addition to warfarin naturally led to the decline in mortality from cardiovascular causes unlike with warfarin monotherapy, while the risk of major hemorrhage in the groups was comparable. However, when studying the structure of the occurred hemorrhages, it was obvious that such a severe complication as intracranial hemorrhage occurred in 8 patients who took aspirin together with VKA, and in just 3 patients who took VKA only. The Meschengieser`s study 1997 [19] which included 503 patients, compared VKA monotherapy against the background of the maintenance of high INR values (3,5-4,5) and the addition of aspirin to warfarin against the background of the INR values from 2,5 to 3,5. It is notable that the frequency of thromboembolic events in VKA monotherapy group compared with the aspirin + VKA group was the same (2,8% and 2,7%, respectively); similarly, the frequency of major hemorrhages in the groups did not differ (4,5% and 2,3%, respectively). As in the previous study, when investigating the structure of the occurred hemorrhages, it was found that in the

warfarin monotherapy group against the background of high INR values, 3 intracranial hemorrhages occurred, whereas none in the combination therapy group.

The decrease of the class and the level of evidence for adding aspirin to VKA for patients after mechanical heart valve replacement in the recommendations of ACC/AHA 2020 is based on the results of a major systematic review and meta-analysis published in 2013 by Cochrane Collaboration (Cochrane Database of Systematic Reviews). The analysis included 13 studies with total number of patients 4122 in the period from 1971 to 2011. Compared with VKA monotherapy, the addition of antiplatelet agent (apirin/dipyridamol) was associated with statistically significant decrease of the risk or thromboembolic events by 2,3 times (OR: 0,43; 95% CI: 0,32-0,59; p<0,00001) and total mortality by 1,7 times (OR: 0,57; 95% CI: 0,42-0,78; p=0,0004). However, at the same time, the risk of major hemorrhage also statistically significant increased (OR: 1,58; 95% CI: 1,14-2,18; p=0,006), that, apparently, was the reason for the decrease in the class and level of evidence of the recommendations [8].

It should be noted that the quality of the most studies included in this systematic review, was low that perhaps reflected the era when some of them were performed (1970s and 1980s i.e. before the appearance of widespread use of standardized INR) [25].

In our meta-analysis, we investigated the addition of aspirin to VKA as the most common antiplatelet agent used in clinical practice. The obtained results regarding to statistically significant decrease of the frequency of thromboembolic events convince us in undoubted benefit of the addition of aspirin to VKA. However, the safety profile issue of the combination of aspirin and VKA remains controversial. For instance, in our work, the combined analysis of all the eight studies showed the absence of statistical significance in the frequency of the major hemorrhage occurrence against the background of aspirin + VKA therapy compared with VKA monotherapy, whereas the Cochrane Collaboration meta-analysis 2013 showed statistically significant increase in the frequency of hemorrhagic events in the dual therapy group. Probably, the results we obtained are associated with addition of Wang`s study 2014 [9] included quite a large number of patients (N=1016) into the meta-analysis. Apart from that, when added aspirin to VKA, the low dosage was used (75-100 mg/day), and the target INR was within the limits from 1,8 to 2,5. It is also important to note that during heart valve replacement surgery, the modern mechanical prostheses with low thrombogenic profile were used, that allowed to maintain low values of INR and thereby, to decrease the risk of bleeding. For instance, in the Wang`s study 2014, the frequency of thromboembolic complications in the group with combination of OAC and low-dose aspirin was 2,2% compared with 4,3% when use OAC only (OR: 0,48; 95% CI: 0,23-1,01). The frequency of major hemorrhagic events was comparable, and in both groups it was 0,6% (OR: 0,99; 95% CI: 0,20-4,94).

Conclusion

The addition of aspirin to VKA versus VKA monotherapy showed statistically significant risk reduction of systemic embolism and death in patients with mechanical heart valve prostheses, in the absence of statistically significant differences in the frequency of major hemorrhages. The results we obtained require further verification and conducting large-scale research with use of the modern mechanical heart valve prostheses with low thrombogenic profile and possible maintenance of lower target INR values when taking VKA together with aspirin to assess the efficiency and safety of this combination of drugs.

Relationships and Activities: none.

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LITERATURE REVIEWS
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Thrombolysis versus unfractionated heparin for hemodynamically stable patients with pulmonary embolism: a systematic review and meta-analysis

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Currently, thrombolytic therapy (TLT) for pulmonary embolism (PE) is recommended only for patients with high-risk PE. At the same time, in real practice, TLT is often performed in hemodynamically stable patients. The main contradiction arises due to the different risk-benefit ratio of TLT in comparison with anticoagulant monotherapy.

Aim. To assess the benefits of TLT, compared with unfractionated heparin (UFH) monotherapy, in hemodynamically stable patients with PE in reducing mortality, recurrence of PE and risk of bleeding.

Material and methods. Randomized controlled trials were searched in PubMed, Embase, and Cochrane Library databases. Of the 3050 publications found, 100 papers were selected for a detailed study. As a result of detailed analysis, 7 randomized clinical trials (n=1611) remained according to established criteria.

Results. TLT in hemodynamically stable patients with PE, in comparison with UFH, showed a tendency to decrease in the inhospital death rate: 2,39% vs 3,68 (odds ratio (OR): 0,73; 95% confidence interval (CI): 0,34-1,57), and a decrease in the composite endpoint (death and/or recurrent PE): 3,14% vs 5,15% (OR: 0,61; CI: 0,37-1,01). There was a significant increase in the number of major bleeding: 8,81% vs 2,70% (OR: 3,35; 95% CI: 2,06-5,45). TLT in hemodynamically stable patients with PE to a greater extent can reduce the pulmonary blood pressure, perfusion defects according to lung scintigraphy, as well as the need for therapy intensification. However, the heterogeneity of studies and the small number of participants require caution when interpreting their results.

Conclusion. TLT in patients with PE and stable hemodynamics tends to reduce mortality and/or recurrence of PE, but increases the incidence of major bleeding. Further studies need to determine the phenotypes of hemodynamically stable patients with PE who would benefit from TLT.

Keywords: pulmonary embolism, intermediate risk, thrombolytic therapy, unfractionated heparin, meta-analysis.

Relationships and Activities: none.

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Key messages

- Thrombolytic therapy in patients with pulmonary embolism and stable hemodynamics, compared with unfractionated heparin, tends to reduce inhospital mortality rate (2,39% vs 3,68% (OR: 0,73; 95% CI: 0,34-1,57)) and composite endpoint — death and/or recurrent PE: 3,14% vs 5,15% (OR: 0,61; CI: 0,37-1,01).
- There was a significant increase in major bleeding as follows: 8,81% vs 2,70% (OR: 3,35; 95% CI: 2,06-5,45).

Currently, thrombolytic therapy (TLT) for pulmonary embolism (PE) is recommended only for patients with high-risk PE (evidence level IA), because hospital lethality in this category of patients may exceed 40% [1]. The reasonability of TLT in patients with PE and stable hemodynamics at hospitalization has been discussed over the past three decades. The patients of this group have a significantly less risk of intrahospital death [2]. The main contradiction is in the different ratios of risk and benefit of thrombolysis in comparison with anticoagulant monotherapy in randomized controlled trials (RCTs) [1].

The meta-analysis is aimed to evaluate the benefits associated with TLT in the decrease in lethality, recurrent PE and the risk of bleeding compared with anticoagulant monotherapy in hemodynamically stable patients with PE.

Material and methods

Search for publications and selection of studies. At first stage of the work, we performed the search for relevant sources in several electronic databases including PubMed, Embase, Cochrane Library for the period from 01.01.1970 to 31.12.2021 (last message). The search terms were — thrombolysis, thrombolytic therapy, pulmonary embolism, reperfusion, intermediate risk PE, hemodynamically stable PE, submassive PE. The language of publications is English. The information retrieval algorithm was developed in accordance with the reporting requirements and regulations for systematic reviews and meta-analyses (PRISMA) [3]. Abstracts of reports, protocols of meetings, monographs, clinical cases and series of cases were not included in the analysis. The selection process of the studies is shown in Figure 1.

Criteria for inclusion/exclusion. We included the RCTs that met the following criteria in the analysis: a) PE with stable hemodynamics/intermediate risk at hospitalization; b) the conduction of systemic thrombolysis; c) the use of unfractionated heparin (UFH) as a comparison anticoagulant; d) 18 years of age and older.

Initially, while selecting using the search queries described above, we obtained 2489 publications by PubMed, 366 publications — Cochrane Library, 195 publications from Embase.

The studies with participation of patients having high-risk PE/hemodynamically unstable, those concerning the catheter methods of administering thrombolytic agents, or comparing two different thrombolytic agents, or evaluating the different doses of the same drug, or about the use of low molecular weight heparins were excluded from the analysis.

From 3050 found publications, 100 articles were selected for a detailed analysis. It should be emphasized that the number of the patients included in the studies was not a determining factor of the selection. The access to the full-text version of the article was also necessary.

After analyzing the headings and their annotations, we found 81 articles that met the goal; then 19 repetitive publications were excluded. After evaluating full-text copies, we took 19 publications dedicated to RCTs about the use of systemic TLT for PE to analyze. Further, 8 publications included patents with high-risk PE [4-11], two studies about the use of 50% of TLT dose [12, 13], one study about the use of low molecular weight heparins as an anticoagulant [14], and one study concerning the comparison of different methods of administering thrombolytic drug [15] were excluded from them. Finally, 7 publications met to primarily established criteria were left for analysis.

Data collection and analysis. To assess the risk of systematic errors in RCTs, we used an adapted and validated questionnaire in our work [16]. The risk of systematic errors was assessed as low (1 score), high (2 scores) and indefinite (0 scores). We assessed the effectiveness and safety of the intervention (TLT versus UFH therapy), using the odds ratio (OR) with 95% confidence interval (CI). The calculations were based on the random effects models at $I^2 > 40\%$, $P<0,10$ and on the fixed effects model at $I^2 \leqslant 40\%$, $P\geqslant 0,10$. The main endpoints we interested were death during hospitalization period, major bleeding and composite endpoint (death during hospitaliza-

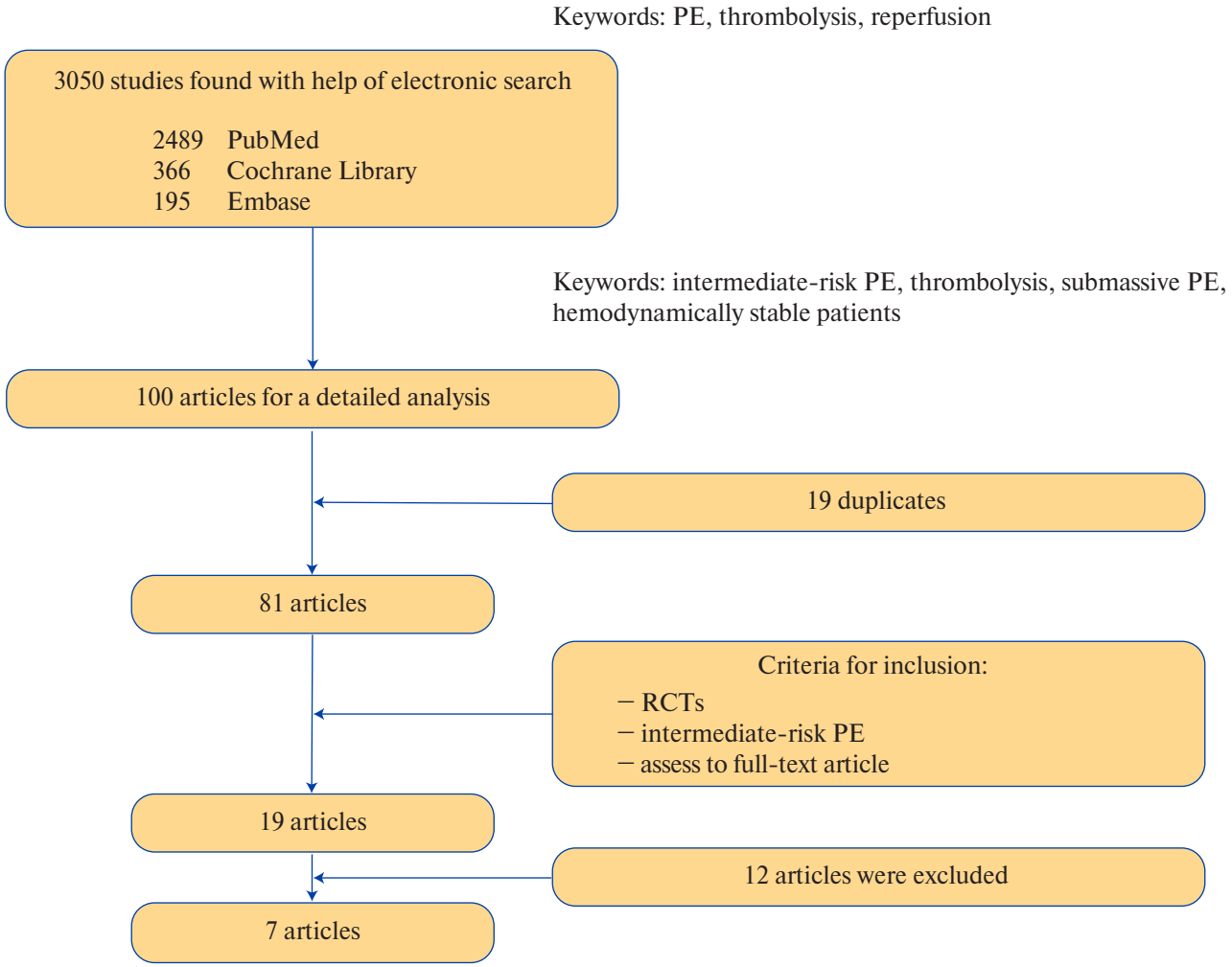

Figure 1. The selection process of the studies included in the meta-analysis.
Abbreviations: RCT — randomized controlled trial, PE — pulmonary embolism.

tion period from all causes and/or recurrent PE). The analysis was performed using Review Manager (RevMan) version 5.4.

Results

The main characteristics of RCTs met to the criteria of inclusion are shown in Table 1; the risk of bias of the studies included in the meta-analysis is given in Table 2.

The last RCT performed in this group of patients is dated 2014, and the later RCTs included either a half dose of a thrombolytic drug [13], or low molecular weight heparins as a comparison anticoagulant [14], or analyzed catheter administration of thrombolytic drugs immediately into pulmonary artery [17-20].

The total number of patients included in our meta-analysis was 1611. The number of centers in RCTs varied from 3 to 76. In 4 studies, recombinant tissue plasminogen activator (r-tPA) was used as a thrombolytic drug, in 3 studies — tenecteplase. All RCTs excepting the study of Meyer G, et al. [21], included a small number of patients therefore, mortality was a part of the composite endpoint.

The meta-analysis showed that TLT in patients with PE and stable hemodynamics had a tendency to decrease the frequency of hospital lethality (Figure 2): 2,39% vs 3,68% (OR: 0,73; 95% CI: 0,34-1,57) and to decrease the composite endpoint — death and/or recurrent PE (Figure 3): 3,14% vs 5,15% (OR: 0,61; CI: 0,37-1,01). At the same time, there was a statistically significant increase in the number of major bleeding events (Figure 4): 8,81% vs 2,70% (OR: 3,35; 95% CI: 2,06-5,45).

Previously, it was shown that the administration of a thrombolytic drug reduces pressure in the pulmonary artery (assessed by echocardiography [22-24] and angiopulmonography [25]), reduces the

Table 1

Characteristics of the studies included in the systematic review

Serial number of the study	First author, year of publication	(n) patients (study/ control)	N of centers	Study design	Comparison drugs	Endpoints
1	S. Dalla-Volta [25], 1992	36	8	Randomized, multicenter, open, parallel	r-tPA+UFH vs UFH	1) efficiency: mean pulmonary pressure and degree of obstruction; 2) efficiency: death; 3) safety: moderate and major bleeding.
2	S. Z. Goldhaber [22], 1993	101	nd	Randomized, multicenter	r-tPA+UFH vs placebo+UFH	1) efficacy: assessment of the RV wall excursion, end-diastolic volume of RV assessed by EchoCG in 3 and 24 hours, angiography in 24 hours; 2) unfavorable outcome: recurrence of PE, death, massive bleeding.
3	S. Konstantinides [26], 2002	246	49	Randomized, multicenter, prospective, double-blind placebo-controlled	r-tPA+UFH vs placebo+UFH	1) death in hospital or clinical worsening; 2) recurrent PE, major bleeding and ischemic stroke.
4	C. Becattini [23], 2010	58	15	Randomized, multicenter, double-blind placebo-controlled	Tenecteplase+ UFH vs placebo+UFH	1) efficiency: decrease in RV dysfunction (assessed by EchoCG in 24 hours); 2) efficiency: decrease in RV dysfunction 7 days after randomization or upon discharge from the hospital (depending on what comes first); clinical worsening requiring escalation of treatment within 7 days or before discharge; PE recurrence or death 30 days after randomization; 3) safety: massive bleeding.
5	S. Fasullo [24], 2011	72	3	Randomized, multicenter, double random blind controlled	r-tPA+UFH vs placebo+UFH	1) effeciency: decrease in RV dysfunction (assessed by EchoCG at admission, before discharge and on 180th day); 2) recurrence of PE, death or clinical worsening during hospitalization and in 180 days; 3) safety: major bleeding and side effects.
6	G. Meyer [21], 2014	1005	76	Randomized, multicenter	Tenecteplase+ UFH vs UFH	1) the totality of death from any cause or hemodynamic collapse within 7 days after randomization.
7	J. A. Kline [27], 2014	83	8	Randomized, multicenter, double-blind placebo-controlled	Tenecteplase+ UFH vs placebo+UFH	1) death, circulatory shock, severe bleeding within 5 days, recurrence of PE, intubation, RV dysfunction with shortness of breath at rest or physical load intolerance.

Abbreviations: nd — no data, UFH — unfractioned heparin, RV — right ventricle, r-tPA — recombinant tissue plasminogen activator, PE — pulmonary embolism, echoCG — echocardiography.

perfusion defects (assessed by lung scintigraphy [22] and angiopulmonography [25]) and reduces the need in therapy escalation [21, 26] to a greater extent than UFH monotherapy. However, the heterogeneity of the studies and the small number of participants require to be cautious in interpreting the results of such publications.

For instance, in the study of Dalla-Volta C, et al. [25], the degree of pulmonary obstruction according to the Miller index, assessed by angiography of

Table 2

Domains of occurrence of systematic errors

Serial number of the study	The studies	1 domain: randomization method	2 domain: concealment of randomization sequence	3 domain: "blinding" patients and medical staff during treatment	4 domain: "blinding" doctors when evaluating the effect of intervention	5 domain: withdrawal of patients from the study	6 domain: presentation of results in publication	7 domain: other risks of systematic error
1	Becattini, 2009	1	1	1	1	1	0	1, small sample size may be the source of other errors
2	Dalla-Volta, 1992	1	1	1	1	1	1	1, small sample size may be the source of other errors
3	Fasullo, 2011	0	1	0	0	0	0	1, small sample size may be the source of other errors
4	Goldhaber, 1993	0	0	2	2	0	1	1, small sample size may be the source of other errors
5	Kline, 2014	0	1	0	0	1	0	2, 1, funding of the study through a grant from Genentech, Inc.
6	Konstantinides, 2002	0	1	0	0	1	1	1, small sample size may be the source of other errors
7	Meyer, 2014	0	0	0	0	0	0	2, Although the authors of the study state: "None of the sponsors of the study took any part in the development or conduction of the study, data analysis or preparation of the manuscript," some authors of the study were hired or received funds or personal fees from related companies

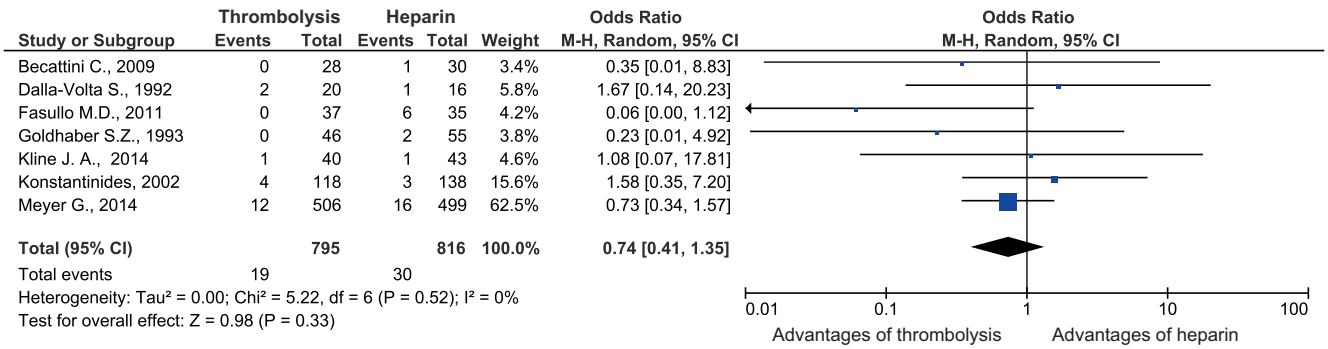

Figure 2. Hospital lethality.

the pulmonary artery significantly decreased in the patients who received r-tPA from 28,3±2,9 mm Hg to 24,8±5,2 mm Hg (p<0,01), whereas in the UFH group there was no reliable dynamics. Mean pulmonary pressure decreased from 30,2±7,8 mm Hg to 21,4±6,7 mm Hg in the r-tPA group and even increased in the UFH group: from 22,3±10,5 to 24,8±11,2 mm Hg (p<0,01).

In the study of Goldhaber SZ, et al. [22], in the TLT group there was the improvement in the right ventricular (RV) wall excursion in 24 hours compared with the initial level in 39% of patients (16 patients), worsening — in 2% (1 patient). The same indicators in the UFH group were — 17% (8 patients) and 17% (8 patients), respectively (p=0,005). In patients who received r-tPA, a significant improvement in pulmonary perfusion was recorded. The volume of non-perfused lung areas decreased by 14,6% (from 42,9% to 28,3%) compared with the decrease by 1,5% in the group of patients who received UFH (from 36,0% to 34,5%, p<0,0001).

In the study of Konstantinides S, et al. [26], the frequency of the primary endpoint (hospital death or escalation of treatment) was significantly higher in the UFH plus placebo group than in the UFH plus alteplase (24,6% (34 patients) vs 11,0% (13

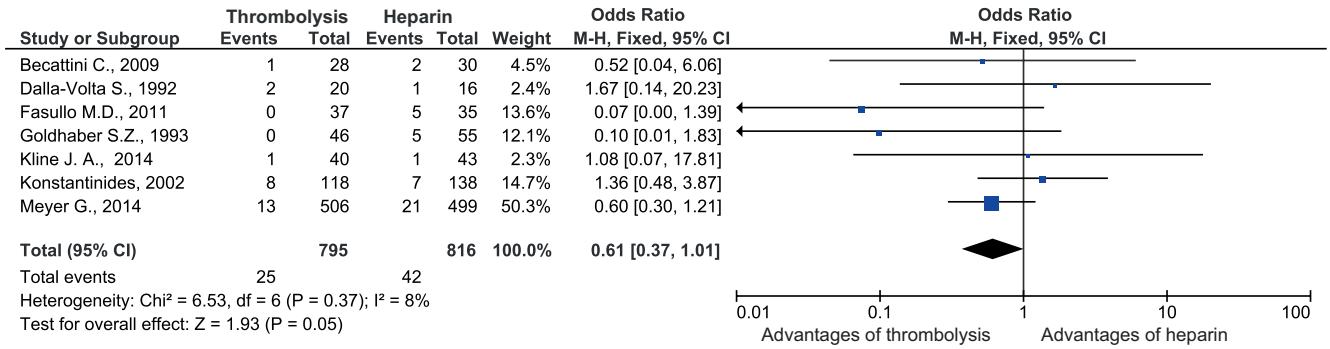

Figure 3. Hospital lethality and/or PE recurrence.

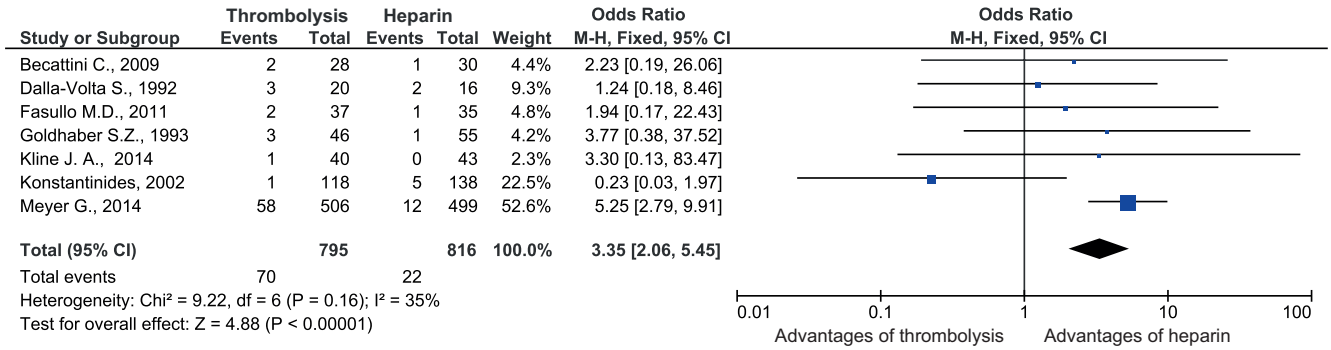

Figure 4. Major bleeding events.

patients), p=0,006). The escalation of treatment meant the need for infusion of inotropic drugs due to persistent arterial hypotension or shock; repeated or "life-saving" thrombolysis; endotracheal intubation; cardiopulmonary resuscitation; and emergency surgical embolectomy or catheter thrombectomy. Probability of 30-day survival (according to Kaplan-Meyer analysis) was higher in the UFN+alteplase group (p=0,005). This difference was associated with a higher frequency of treatment escalation in the UFH+placebo group (24,6% vs 10,2%, p=0,004) because the hospital lethality was low in both groups (3,4% in the TLT group and 2,2% in the UFH+placebo group, p=0,71).

The study performed by Becattini C, et al. [23] showed that the decrease in the ratio of the end-diastolic volume of the right ventricle to the left ventricle in 24 hours in the TLT group was 0,31±0,08, while in the placebo group — 0,10±0,07 (p=0,04).

The study of Fasullo MD, et al. [24] showed that the use of TLT was accompanied by early decrease of the RV size (in 48 hours in the UFH group from 48±2,3 mm to 39±1,2 mm, in the TLT group — from 49±2,4 mm to 35±1,2 mm, p=0,0001; in 3 months in the UFH group — 27±1,3 mm, in the TLT group — 23±0,6 mm, p=0,001) and by a more favorable tendency in clinical outcomes. Also, in the TLT group, the decrease in systolic pulmonary artery pressure was more pronounced (from 57±18 mm to 38±7 mm in 48 hours and 12±3 mm in 6 months, p<0,001) than in the UFH group (from 58±19 mm to 47±11 mm in 48 hours and 18±2 in 6 months).

According to the data obtained by Meyer G, et al. [21], the hemodynamic disorders or acute heart failure occurred in 1,6% of patients while using TLT and in 5% in the UFH group (p=0,002).

The study of Kline JA, et al. [27] reported about at least one adverse outcome: death, intubation, fatal intracranial hemorrhage in 37% of patients who received placebo+UFH and in 15% of patients who received TLT+UFH during 90 days of monitoring (p=0,017).

Discussion

The performed meta-analysis showed that the decrease in mortality and/or the frequency of PE recurrences by the use of TLT in patients with PE and stable hemodynamics is unreliable but the increase in frequency of bleeding events by the use of TLT is statistically significant. It should be especially noted that these data were obtained by the studies included a small number of patients, and the authors

needed to create the composite endpoints to evaluate the benefit/risk of the interventions in both groups [22-27].

Actually, the only RCT that included >1 thousand intermediate-high risk patients with PE was Pulmonary Embolism Thrombolysis (PEITHO) [21]. In the PEITHO study, the benefits of TLT using tenecteplase (OR 0,44; 95% CI 0,23-0,87) were leveled by a significant increase in the number of major bleeding events (6,3% in the TLT group vs 1,5% in the group without TLT). This study was a landmark, after which in the recommendations of the European Society of Cardiology in 2019 [1] the place of reperfusion therapy in intermediate-risk PE was defined only as a "life-saving" procedure for patients with worsening hemodynamics against the background of anticoagulant therapy. The performed RCTs [22-25] confirmed the important role of TLT in the ability to reduce right ventricular dysfunction in intermediate-risk PE.

Clearly, TLT is not a method to treat all patients with intermediate-risk PE. And it is necessary to concentrate on finding predictors of hemodynamic worsening before the occurrence of obstructive shock in a patient, using the ability of TLT to quickly reduce the load on the right ventricle. Thus, the recommendations of the American College of Chest Physicians in 2021 [28] set out the position to begin the systemic TLT in patients with PE and an acceptable risk of bleeding, whose condition worsens after the start of anticoagulant therapy before the occurrence of shock or hypotension (weak recommendation, evidence with a low degree of reliability). It is suggested to conduct anticoagulant therapy to these patients, monitoring the signs of clinical worsening (decrease in systolic blood pressure, increase in heart rate, deterioration of gas exchange, the signs of insufficient perfusion, deterioration of RV function or increase in cardiac biomarkers).

The same conclusions were obtained in previously performed meta-analyses [29-34]. For instance, in 2009, Tardy B, et al. performed meta-analysis which included 5 RCTs [29] to compare the use of r-tPA vs UFH momotherapy in 464 hemodynamically stable patients with acute PE. The generalized assessment revealed statistically insignificant decrease in mortality associated with PE or recurrent PE while using r-tPA in comparison with UFH (3,5% vs 4,6%, p=0,73). Also, in the r-tPA group compared with UFH there was no significant increase in the number of major bleeding events (4,9% vs 4,6%, risk ratio (RR): 0,94; 95% CI: 0,39-2,27). The same results were obtained when taking only those studies that included the patients with echocardiographic signs of RV dysfunction. There was no decrease in either mortality due to PE, or the frequency of PE recurrences against the background of the administration of r-tAP compared with UFH in patients with stable hemodynamics.

In 2014, at once 4 meta-analyses to assess the effectiveness of TLT in the treatment of hemodynamically stable patients with PE were performed [30-33].

Chen H, et al. [30] included 15 RCTs in meta-analysis (totally 1247 patients), which compared UFN with various thrombolytic drugs (urokinase/alteplase/tenecteplase). TLT was associated with significant decrease in the frequency of PE recurrences or death (1,94% vs 5,87%, OR: 0,37; 95% CI: 0,21-0,66; without statistically significant heterogeneity between studies, P=0,49) with an unreliable increase in the number of major bleeding events (3,57% vs 2,67%, OR: 1,34; 95% CI: 0,70-2,58), but with significant increase of minor bleeding events (12,78% vs 3,65%, OR: 4,12; 95% CI: 2,37-7,17). However, unlike our study, that meta-analysis also included the studies with high-risk PE and 50% of dose of a thrombolytic drug.

Liu Y, et al. [31] compared r-tPA with UFH monotherapy (n=594 patients) in the meta-analysis based on 7 RCTs. The use of r-tPA was associated with insignificant decrease in mortality (2,75% vs 3,96%, p=0,520); PE recurrences (2,13% vs 3,34%, RR: 0,70; 95% CI: 0,28-1,73); insignificant (unreliable) increase in the number of major bleeding events (5,15% vs 4,29%, RR: 1,06; 95% CI: 0,520-2,150). The same results were obtained when analyzing the subgroup of patients with echocardiographic signs of RV dysfunction. On the contrary, the use of r-tPA compared with UFH was associated with a significant decrease in the necessity of therapy escalation in the studies that also included the patients with the RV dysfunction (6,56% vs 19,7%; RR: 0,34; 95% CI: 0,20-0,65). The meta-analysis concluded that there is no data showing the advantage of r-tPA compared with UFH for the staring treatment of absolutely all hemodynamically stable patients with acute PE but r-tPA can be useful in the treatment of patients with RV dysfunction.

The meta-analysis performed by Marti K, et al. [32] (2057 patients, 15 RCTs) concluded that compared with UFH, TLT was associated with the reliable decrease in the total mortality (OR: 0,59; 95% CI: 0,36-0,96). However, this decrease turned out to be statistically insignificant after the exclusion of patients with high-risk PE from the pool of studies (OR: 0,64; 95% CI: 0,35-1,17). Thrombolysis was associated with a significant decrease in composite endpoint and/or therapy escalation (OR: 0,34, 95% CI: 0,22-0,53), with PE-related mortality (OR: 0,29; 95% CI: 0,14-0,60) and recurrent PE-related mortality (OR: 0,50; 95% CI: 0,27-0,94). Major

bleeding (OR: 2,91; 95% CI: 1,95-4,36) and lethal or intracranial hemorrhage (OR: 3,18; 95% CI: 1,25-8,11) were significantly more frequent in patients who received TLT.

The meta-analysis performed by Nakamura S, et al. [33] included 1510 patients. They did not obtain any significant differences in composite endpoint of death from all causes and/or PE recurrence between the TLT group and the group received only UFH (3,1% vs 5,4%; RR: 0,64; CI: 0,32-1,28). TLT has significantly decreased the frequency of the composite endpoint of death from all causes or clinical worsening (3,9% vs 9,4%; RR: 0,44; CI: 0,29-0,67). There were no statistically significant differences in the occurrence of major bleeding when comparing TLT with UFH monotherapy (6,6% vs 1,9%; RR: 0,44; 95% CI: 0,58-7,35). This meta-analysis also showed that reperfusion therapy does not significantly reduce the risk of mortality or PE recurrence in patients with acute submassive PE, but TLT prevents clinical worsening requiring escalation of treatment in patients with acute submassive PE. The assessment of bleeding risk can be the most successful approach for the improvement of clinical outcomes and patient-specific benefits of TLT.

The last, largest meta-analysis performed by Zuo Z, et al. [34] and published in 2021 included 21 studies, totally 2401 patients, among them the patients with massive PE and surgical interventions. The authors concluded that TLT may increase the risk of death from acute PE compared with UFH (OR: 0,58; 95% CI: 0,38-0,88); however, its efficiency was mainly caused by the studies performed in patients with high-risk PE. It is shown that TLT may be useful to reduce the risk of recurrent PE (OR: 0,54; 95% CI: 0,32-0,91) but it may cause major (OR: 2,84; 95% CI: 1,92-4,20) and minor bleeding events (OR: 2,97; 95% CI: 1,66-5,30) including hemorrhagic stroke (OR: 7,59; 95% CI: 1,38-41,72). In the article, the authors emphasize that these evidences are characterized by a low degree of reliability due to the high risk of bias of the RCTs included in the analysis.

Thus, nowadays, the TLT advantages in the decrease of hospital lethality and PE recurrences compared with the risk of bleeding in patients with high-risk PE have been proven, and this pattern is clearly visible even in the studies with a small number of patients [4-11]. In patients with PE and stable hemodynamics, not everything is so unambiguous. In our opinion, the use of TLT is justified in a narrow circle of patients with a low risk of bleeding and with criteria for the beginning hemodynamic deterioration for the purpose to timely unload the small circle of blood circulation, before the occurrence of obstructive shock. To confirm this hypothesis, it is advisable to conduct a planned RCT with a clear design and narrow inclusion criteria in patients with intermediate-high risk PE.

Limitations of the study. The present meta-analysis did not include the studies where low-molecular-weight heparins or direct oral anticoagulants were used as anticoagulant therapy.

Conclusion

Our meta-analysis showed that TLT in patients with PE and stable hemodynamics tends to reduce mortality and/or the frequency of PE recurrences, but increases the frequency of major bleeding events. Systemic administration of thrombolytic drugs leads to faster lysis of thrombus than UFH monotherapy, thereby reducing pressure in the pulmonary artery, improving RV function and pulmonary hemodynamics. In further studies, it is necessary to determine the phenotypes of patients with PE and stable hemodynamics who will benefit from TLT.

Relationships and Activities: none.

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LITERATURE REVIEWS
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Prognostic value of left ventricular global longitudinal strain and mechanical dispersion by speckle tracking echocardiography in patients with ischemic and nonischemic cardiomyopathy: a systematic review and meta-analysis

Golukhova E. Z., Bulaeva N. I., Mrikaev D. V., Aleksandrova S. A., Berdibekov B. Sh.

Aim. To conduct a systematic review and meta-analysis in order to evaluate the prognostic value of left ventricular global longitudinal strain (LV GLS) and LV mechanical dispersion (LVMD) in ischemic and nonischemic cardiomyopathy.

Material and methods. We searched PubMed, Google Scholar and EMBASE for studies on the prognostic value of LV GLS and LVMD in ischemic and nonischemic cardiomyopathy. Hazard ratios (HR) from included studies were pooled for meta-analysis.

Results. Twelve studies were selected from 314 publications for this systematic review and meta-analysis. In total, 2624 patients (mean age, 57,3 years; mean follow-up, 40,8 months) were included in the analysis. Meta-analysis showed that decreased LV GLS was associated with an increased risk of ventricular arrhythmias (VAs) (adjusted HR: 1,10 per 1% of GLS; 95% CI: 1,01-1,19; p=0,03) and major adverse cardiovascular events (MACE): adjusted HR: 1,22 per 1% of GLS; 95% CI: 1,11-1,33; p<0,0001). Patients with VAs had greater LVMD than those without it (weighted mean difference, 33,69 ms; 95% CI: -41,32 to -26,05; p<0,0001). Each 10 ms increment of LVMD was significantly and independently associated with VA episodes (adjusted HR: 1,18; 95% CI: 1,08-1,29; p=0,0002).

Conclusions. LV GLS and LVMD assessed using speckle tracking provides important predictive value and can be used as an effective tool for stratifying risk in patients with ischemic and nonischemic cardiomyopathy.

Keywords: ischemic cardiomyopathy, non-ischemic cardiomyopathy, speckle tracking echocardiography, myocardial strain, predictive value, prognosis.

Relationships and Activities: none.

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Ischemic and nonischemic cardiomyopathies are currently the main causes of chronic heart failure (HF) with reduced left ventricle (LV) ejection fraction (EF) [1]. It is associated with significant morbidity and premature mortality, primarily, due to the development of decompensated HF and sudden cardiac death (SCD) [1, 2]. The current risk stratification criteria are far from being perfect. There is a need for new risk stratification tools, since the majority of patients who, in particular, are implanted with the cardioverter-defibrillator for primary prevention of SCD, do not experience motivated device activations [3].

The emergence of myocardial deformation estimation methods by the technology of tracking the movement of gray scale spots in a two-dimensional image (speckle tracking echocardiography (STE)) made it possible to assess early ventricular dysfunction in the absence of obvious structural changes in the myocardium [4]. Over the past decade, there has been an increasing number of studies on the role of left ventricular global longitudinal strain (LV GLS) estimated by 2D STE to predict adverse events in patients with HFrEF [5]. Most of these studies have shown that deterioration of LV GLS is associated with the development of adverse cardiovascular events. It should be noted that not only LV GLS, but also left ventricular mechanical dispersion (LV MD) has proved to be a surrogate marker of delayed and inhomogeneous conduction in the myocardium and has been associated with the risk of arrhythmic events both in ischemic and nonischemic cardiomyopathy [6]. However, the use of these new echocardiographic markers is currently limited to only small, single-centre, observational clinical trials with little sample sizes and few events.

In light of these shortcomings, a systematic review and meta-analysis of studies on the prognostic role of LV GLS and MD in patients with ischemic and nonischemic cardiomyopathy were carried out.

Material and methods

Search for publications and selection of studies. The information retrieval algorithm was developed in accordance with the reporting requirements and regulations for systematic reviews and meta-analyses (PRISMA) [7] in the PubMed, Google Scholar and EMBASE databases. The last data search for inclusion in this analysis was performed on February 4, 2022. We used the following keywords to search PubMed and EMBASE databases: ((dilated cardiomyopathy) OR (non-ischemic dilated cardiomyopathy) OR (ischemic dilated cardiomyopathy) OR (Heart Failure)) AND ((Echocardiography) AND (speckle tracking) OR (Strain) OR (Global Longitudinal Strain) OR (Myocardial strain) OR (dyssynchrony) OR (dispersion)) AND ((risk assessment) OR (predictive value) OR (prognostic value)). The following query was used to search the Google Scholar database: speckle tracking echocardiography, Global Longitudinal Strain, dispersion, Nonischemic Dilated Cardiomyopathy, Ischemic Dilated Cardiomyopathy, Heart Failure, prognostic value, hazard ratio cox regression.

Two authors independently reviewed abstracts and full-text articles for inclusion criteria to select eligible studies for this systematic review and meta-analysis.

Inclusion/exclusion criteria. The inclusion criteria of primary studies in a systematic review followed by meta-analysis were: the access to full-text studies; all participants were adults (18 years or over); the studies with adequately presented baseline data, mainly data on the longitudinal strain and/or LV MD values measured by STE. In addition, the mandatory criteria to include publication in the meta-analysis were both the data on clinical outcomes and the results of univariate and/or multivariate Cox regression analysis with hazard ratio (HR). The lower observation period threshold of patients was set at 12 months (the average period). The articles in languages other than English, case reports, preclinical studies, reviews, and expert opinions were excluded from the meta-analysis.

Assessment of the methodological quality. The quality of the studies was evaluated on Newcastle-Ottawa quality assessment scale [8]. The evaluation of studies was carried out based on of the following main criteria: selection of research groups; group comparability; and setting the outcome of interest. All inconsistencies were eliminated by authors' discussion of this work.

Statistical analysis. Statistical data processing was performed using Review Manager (RevMan), version 5.4.1 (The Cochrane Collaboration, 2020) and Comprehensive Meta-Analysis 3.0 (Biostat, NJ). Meta-analysis was carried out according to the random effects model, using the inverse dispersion method. Graphically, the main results are presented in a "forest" diagram (forest plot). Statistical heterogeneity was assessed by Pearson's chi-square test and heterogeneity index I^2. Interpretation of the statistical heterogeneity assessment with the I^2 index was carried out according to the recommendation of Cochrane Collaboration. A guide to interpretation of I^2 index is as follows: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% may represent considerable heterogeneity. The baseline values for meta-analysis of survival rates were used the unadjusted (obtained for a single-factor model) and adjusted

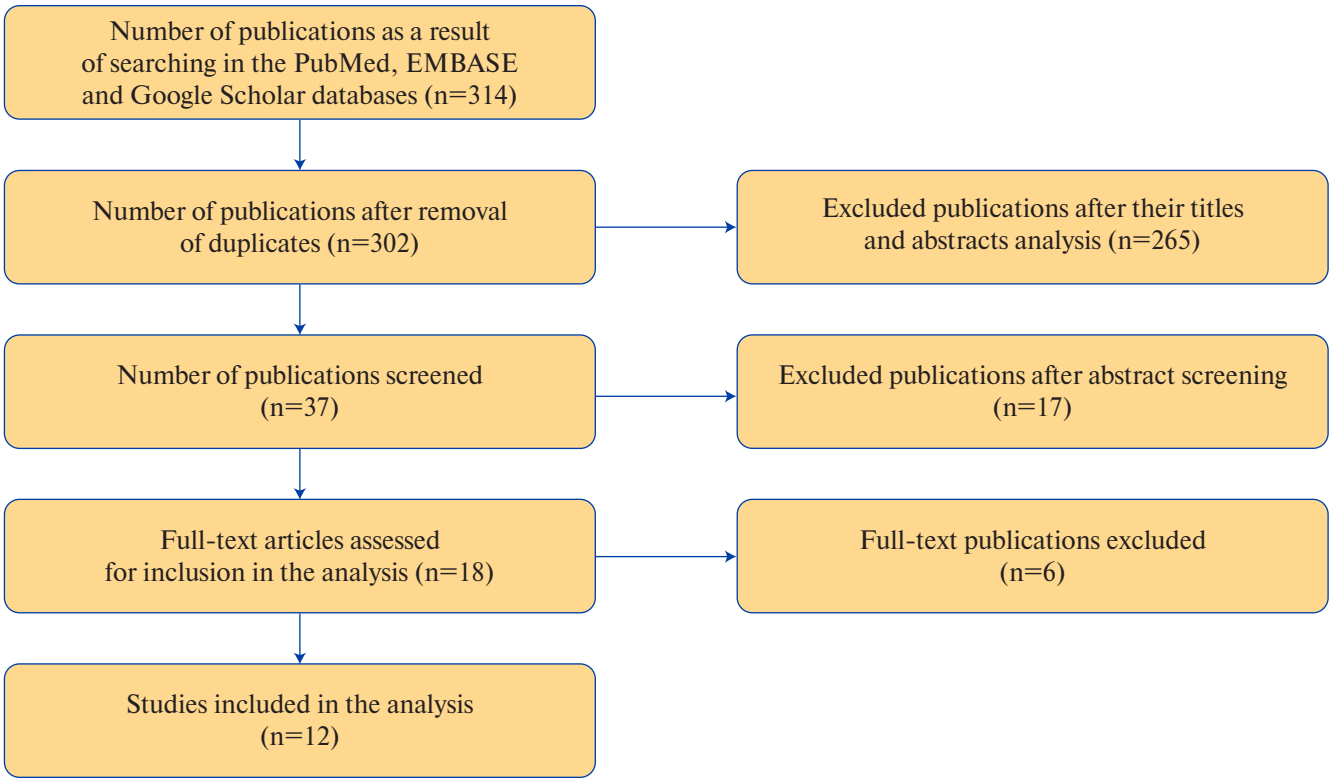

Figure 1. Study selection flowchart.

(obtained for a multivariate model) HR, determined for changes in LV GGL and MD per 1% and 10 ms, respectively. Publication bias was assessed by the Egger test. The effect was considered statistically significant at p<0,05.

Results

Flowchart of literature review

A total of 314 publications were found on the search results for those keywords in the PubMed, Google Scholar and EMBASE databases. The number of publications after the removal of duplicates was 302. Thirty seven publications corresponded to the goal after their titles and abstracts analyzed. The most common reasons to exclude an article were inconsistency with the goal and the lack of given data. The review articles, discussions, abstracts and reports were also excluded. Full-text screening of 20 publications was performed.

Three studies did not present comparative analysis of LV GLS parameters in patients with and without endpoints, or Cox regression analysis with calculated HR. Therefore these studies were excluded from our analysis [9-11]. In one study, LV GLS and MD were presented as binary data with a diagnostic cut-off values that prevented us to include this study for a pooled analysis of continuous data [12]. Another study presented highly heterogeneous groups of patients with hypertrophic cardiomyopathy and cardiac sarcaidosis, along with ischemic and nonischemic dilated cardiomyopathies, and therefore this study was also eliminated from our analysis [13]. Thus, 12 studies were finally included in our review; Figure 1 shows the selection process for relevant studies.

General characteristics of studies

In total, 2624 patients with HFrEF caused by ischemic or nonischemic cardiomyopathies were enrolled in this analysis. All patients underwent assessment of LV GLS and/or MD by STE. The mean age of the patients was of 57,9 years. The mean follow-up period was of 40,8 months. Data on study design, baseline patient characteristics are summarized in Table 1.

Echocardiography data

The echocardiography data were obtained on expert-class ultrasound device (General Electric, Philips, Siemens and Toshiba). In most studies (8 publications) the data were post-processed on EchoPAC workstations (GE), in one study the data were obtained on TomTec workstations (TomTec Imaging Systems) [19], in one study the data were

Table 1

Summary of studies included in the systematic review

Study (1st author)	(n) of patients	Study design	Age (years)	Male, %	Population	CAD (n, %)	Follow-up period, months	LV EF, %
Haugaa, 2012 [14]	94	Prospective	47±14	76 (81)	NICM	0	22	NR
Motoki, 2012 [15]	194	Prospective	57±14	140 (72)	NICM and ICM ИКМП	80 (41)	60	26±6
Goebel, 2014 [16]	87	Prospective	51±13	75 (116)	NICM	0	39±11	NR
Negishi, 2015 [17]	124	Prospective	56±13	67 (54)	NICM	0	45,6	31,4+9,9
Kosiuk, 2015 [18]	20	Prospective	62±11	15 (75)	NICM	0	70±40	32±6
Biering-Sørensen, 2016 [19]	1064	Prospective	64±11	799 (75)	NICM and ICM	592 (56)	34,8	29,2±3,4
Chimura, 2017 [20]	179	Retrospective	61±15	121 (68)	NICM	0	45,6	33±9,0
Mornoş, 2017 [21]	340	Prospective	63±12	111 (33)	NICM and ICM	215 (63)	36±9	–
Santos, 2019 [22]	31	Prospective	56,1±4,8	15 (48)	NICM	0	18,2	34,5±11,2
Jung, 2020 [23]	160	Retrospective	64±15	108 (67)	NICM	0	37,3±21,7	26,8±7,5
Kažukauskienė, 2021 [24]	41	Prospective	47±12	33 (80)	NICM	0	60	25 [20-34]
Melichova, 2021 [25]	290	Prospective	67±13	216 (74)	NICM	0	22	31±6

Abbreviations: CAD — coronary artery disease, ICM — ischemic cardiomyopathy, NICM — nonischemic cardiomyopathy, LV EF — left ventricle ejection fraction, NR — not reported.

Table 2

Characteristics (specification) of ultrasonic equipment used in research

Study (1st author)	Ultrasound scan system	Workstation	Frame rate, fps
Haugaa, 2012 [14]	GE	EchoPAC; GE Healthcare	>70
Motoki, 2012 [15]	Phillips и Siemens	Syngo Dynamics 9.0 software, Siemens	NR
Goebel, 2014 [16]	GE	EchoPAC; GE Healthcare	NR
Negishi, 2015 [17]	GE	EchoPAC; GE Healthcare	50±20
Kosiuk, 2015 [18]	GE	NR	>60
Biering-Sørensen, 2016 [19]	NR	TomTec Imaging Systems	NR
Chimura, 2017 [20]	Toshiba	2DST software (Toshiba Medical Systems)	NR
Mornoş, 2017 [21]	GE	EchoPAC; GE Healthcare	NR
Santos, 2019 [22]	GE	EchoPAC; GE Healthcare	NR
Jung, 2020 [23]	GE	EchoPAC; GE Healthcare	NR
Kažukauskienė, 2021 [24]	GE	EchoPAC; GE Healthcare	50-70
Melichova, 2021 [25]	GE	EchoPAC; GE Healthcare	>60

Abbreviation: NR — not reported.

evaluated on Syngo Dynamics 9.0 software machine (Siemens) [15], and in one more study the data were assessed on 2DST software (Toshiba Medical Systems) [20]. LV GLS was evaluated by 2D STE technology. The main characteristics of echocardiographic equipment and software are presented in Table 2.

Endpoints and adverse outcomes

The main endpoints in studies assessing LV GLS and/or MD were "arrhythmic" events (5 studies) [14, 18, 19, 21, 25], major cardiovascular adverse events (MACEs) (5 studies) [15, 16, 20, 22, 24] and reverse LV remodeling (1 study) [23].

The "arrhythmic" endpoints included a variety of events (sustained ventricular tachycardia, ventricular fibrillation, implantable cardioverter-defibrillator motivated activations, SCD). Most of the studies presented a composite endpoint defined as cardiovascular death, heart transplantation, hospitalization for decompensated heart failure, or implantation

Table 3

LV strain and MD indices included in the systematic review of publications

Study (1st author)	LV strain indices	Outcome -	n	Outcome +	n	Endpoints
Haugaa, 2012 [14]	GLD, %	-12,3±5,2	82	-6,4±3,3	12	Sustained VT or cardiac arrest
	MD, ms	56±18		98±43		
Motoki, 2012 [15]	GLS, %	-7,8±3,4	116	-6,0±2,9	78	Death, heart transplant, hospitalization for decompensated HF
Goebel, 2014 [16]	GLS, %	-12±4	37	-8±3	50	Death, heart transplant, hospitalization for decompensated HF
	MD, ms	78±79		140±134		
Negishi, 2015 [17]	GLS, %	-9,4±3,2	88	-8,2±3,8	36	Motivated ICD activation
Kosiuk, 2015 [18]	MD, ms	50±16	9	84±31	11	VT or VF
Biering-Sørensen, 2016 [19]	GLS, %	-9,1±2,9	810	-8,1±2,7	254	VT or VF
Chimura, 2017 [20]	GLS, %	-9,6±4,0	139	-5,8±2,9	40	Cardiac death, heart transplant, hospitalization for decompensated heart failure, or implantation of LV mechanical support devices
Mornoş, 2017 [21]	GLS, %	-18,1±6,5	292	-11,1±6,5	48	VT, VF, SCD
	MD, ms	39,7±33,1		72,3±27,6		
Santos, 2019 [22]	GLS, %	-12,7±4,3	25	-10,2±3,9	6	Cardiac death, heart transplant, hospitalization for decompensated HF
Jung, 2020 [23]	GLS, %	-8,2±2,9	115	-11,9±1,6	45	Reverse LV remodeling
Kažukauskienė, 2021 [24]	GLS, %	-9,9±2,8	21	-6,2±3,7	20	Cardiac death, heart transplant, hospitalization for decompensated HF, or implantation of LV mechanical support devices
Melichova, 2021 [25]	GLS, %	-10,7±3,1	252	-9,3±3,8	32	Sustained VT, cardiac arrest, SCD

Abbreviations: SCD — sudden cardiac death, GLS — global longitudinal strain, VT — ventricular tachycardia, ICD — implantable cardioverter-defibrillator, LV — left ventricle, MD — mechanical dispersion, HF– heart failure, VF — ventricular fibrillation.

Table 4

Estimated changes of LV GLS and MD with the HRs calculated from the univariate Cox regression model

Study (1st author)	LV strain indices	HR	95% CI	p	Log HR	SE	Endpoints
Haugaa, 2012 [14]	GLS (1%)	1,37	1,15-1,62	<0,001	0,315	0,087	"Arrhythmic" endpoint
	MD (10 ms)	1,39	1,21-1,58	<0,001	0,329	0,068	
Motoki, 2012 [15]	GLS (1%)	1,55	1,21-2,00	<0,001	–	–	MACE
	GLS (1%)	1,14	1,059-1,231	<0,001	0,131	0,038	
Negishi, 2015 [17]	GLS (1%)	1,09	1,01-1,19	0,037	0,086	0,041	"Arrhythmic" endpoint
Chimura, 2017 [20]	GLS (1%)	1,34	1,19-1,56	<0,0001	0,293	0,068	MACE
Mornoş, 2017 [21]	GLS (1%)	1,16	1,11-1,22	<0,001	0,148	0,025	"Arrhythmic" endpoint
	MD (1 ms)	1,02	1,01-1,03	<0,001	–	–	
	MD (10 ms)	1,22	1,105-1,344	<0,001	0,199	0,050	
Santos, 2019 [22]	GLS (1%)	0,879	0,784-0,985	0,026	-0,129	0,058	MACE
Jung, 2020 [23]	GLS (1%)	1,41	1,24-1,61	<0,001	–	–	"Arrhythmic" endpoint
Kažukauskienė, 2021 [24]	GLS (1%)	1,41	1,18-1,68	<0,0001	0,344	0,090	MACE

Abbreviations: CI — confidence interval, GLS — global longitudinal strain, LV — left ventricle, MD — mechanical dispersion, HR — hazard ratio, MACE — major adverse cardiovascular event, SE — standard error.

of LV mechanical support devices. We calculated the totality of these events as large MACEs for the further meta-analysis. Most of the studies enrolled in our analysis presented data on LV GLS [14-17, 19-25], three studies [14, 16, 21] also reported on LV MD, and in one study [18] only LV MD values

Table 5

Estimated changes of LV GLS and MD with the HRs calculated from the multivariate Cox regression model

Study (1st author)	LV strain indices	HR	95% CI	p	Log HR	SE	Covariates in a multivariate model
Haugaa, 2012 [14]	GLS (1%)	1,26	1,03-1,54	0,02	0,231	0,103	QRS, GLS, MD
	MD (10 ms)	1,20	1,03-1,40	0,02	0,182	0,078	
Motoki, 2012 [15]	GLS (%) per 1 SD	1,45	1,05-2,03	0,02	–	–	GSC
	GLS (1%)	1,12	1,015-1,236	0,02	0,113	0,050	
Negishi, 2015 [17]	GLS (1%)	1,11	1,01-1,22	0,03	0,104	0,048	Age, sex, implantation of CRT-D
Chimura, 2017 [20]	GLS (1%)	1,27	1,12-1,44	0,0001	0,239	0,064	GLS, FC by NYHA, BNP, LV EDV
Mornoş, 2017 [21]	GLS (1%)	1,01	0,93-1,09	0,91	0,010	0,040	
	MD (1 ms)	1,00	0,97-1,02	0,13	–	–	
	MD (10 ms)	1,01	0,74-1,22	0,13	0,010	0,127	
Santos, 2019 [22]	GLS (1%)	1,365	1,106-1,6862	0,003	0,311	0,108	E/e', LV EF
Jung, 2020 [23]	GLS (1%)	1,47	1,17-1,85	0,001	–	–	Age, sex, LBBB, iACE/ARB, MRA, ivabradine, LV EDD, LV ESD, LF EF, LA volume, E/e'
Kažukauskienė, 2021 [24]	GLS (1%)	1,25	1,01-1,55	0,04	0,223	0,109	BNP, Troponin T1
Melichova, 2021 [25]	GLS (1%)	1,14	1,00-1,30	0,04	0,131	0,067	Age, sex, LV EDD, LV ESD, LF EF, LA volume
	MD (1 ms)	1,02	1,00-1,03	0,01	–	–	
	MD (10 ms)	1,22	1,05-1,34	0,01	0,1989	0,062	

Abbreviations: MRA — mineralocorticoid receptor antagonists, LBBB — left bundle-branch block, ARB — angiotensin II receptor blockers, GLS — global circumferential strain, GSC — global circumferential strain, CI — confidence interval, iACE — angiotensin-converting enzyme inhibitors, EDV — end-diastolic volume, EDD — end-diastolic dimension, ESD — end-systolic dimension, LV — left ventricle, LA — left atrium, MD — mechanical dispersion, HR — hazard ratio, CRT-D — cardiac resynchronization therapy defibrillator, LV — left ventricle, FC — functional class, BNP — B-type natriuretic peptide, MACE — major adverse cardiovascular event, NYHA — New York Heart Association, SE — standard error, SD — standard deviation.

were assessed. Table 3 presents the main values of GLS and LV MD parameters, as well as data on endpoints and the number of events in each group. Tables 4 and 5 show the HRs for the endpoint development obtained as a result of univariate and multivariate regression analysis by the Cox method after the inclusion of continuous variables such as LV GLS and/or LV MD values as predictors. Studies where a similar score criterion (changes in LV GLS and LV MD per 1% and per 10 ms, respectively) was available by endpoint were pooled together in a meta-analysis.

The "arrhythmic" endpoint

Mean values of LV GLS depending on the "arrhythmic" endpoint development were presented in five studies. We performed a meta-analysis of the difference between the mean values of LV GLS in patients with and without the "arrhythmic" endpoints (Figure 2). Figure 2 shows that patients with ventricular arrhythmias (VA) had worse LV GLS values than those without it, so the weighted mean difference in LV GLS values was of 3,12% (95% confidence interval (CI): -5,13, -1,11%), these differences were statistically significant (p=0,002). The Egger test score were found to be statistically negligible, t=1,37; df=3,0; p=0,26.

A meta-analysis was also performed on the difference between the mean values of LV MD in patients with and without the "arrhythmic" endpoints (Figure 3). Figure 3 presents that patients with the arrhythmic endpoint had greater LV MD values compared to patients without it, so the weighted mean difference of LV MD was of 33,69 ms (95% CI: -41,32; -26,05), these differences were statistically significant (p<0,0001). The Egger test score were also found to be statistically negligible, t=1,08; df=1,0; p=0,48.

The univariate risk analysis data of the "arrhythmic" endpoints using continuous estimates of the LV GLS value as a predictor were presented in three studies [14, 17, 21]. These studies were comparable due to the same predictor score (changes per 1%), and that allowed to performed a meta-analysis of these publications. The number of the "arrhythmic" endpoints in these studies was of 96 (17,2% of 558 patients), the average follow-up period was of 29,8

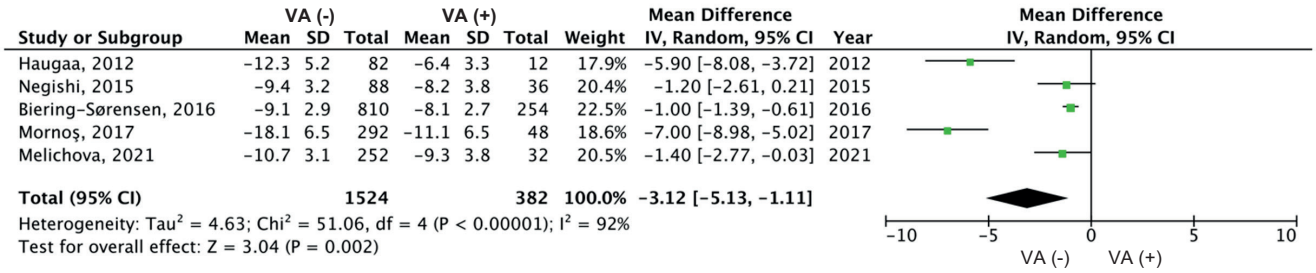

Figure 2. Results of a meta-analysis of the difference between the mean LV GLS values in the group with VAs and without it.
Note: the green squares show weighted effect sizes for each specific study (the green square sizes represent weights of studies), the black line segments show 95% CI, the black rhombus shows weighted average of GLS mean difference. The color figure is available in the electronic version of the journal.
Abbreviations: GLS — global longitudinal strain, CI — confidence interval, VA — ventricular arrhythmias.

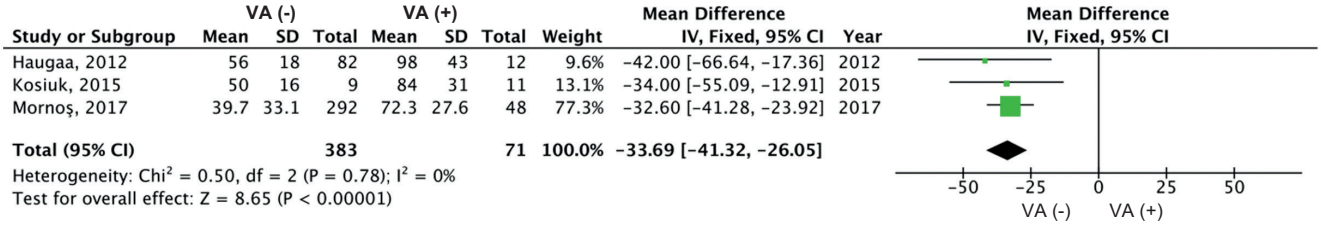

Figure 3. Results of a meta-analysis of the difference between the mean LV MD values in the group with VAs and without it.
Note: the green squares show weighted effect sizes for each specific study (the green square sizes represent weights of studies), the black line segments show 95% CI, the black rhombus shows weighted average of GLS mean difference. The color figure is available in the electronic version of the journal.
Abbreviations: MD — mechanical dispersion, CI — confidence interval, VA — ventricular arrhythmias.

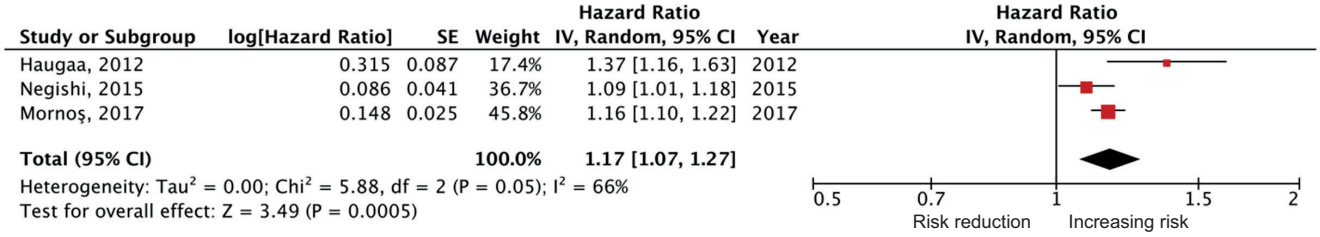

Figure 4. Results of a meta-analysis of the unadjusted HR for "arrhythmic" endpoints per each 1% decline of LV GLS.
Note: the red squares show the weighted effect size for each particular study (the red square sizes represent weights of studies), the red line segments show 95% CI, the black rhombus shows weighted average of HR. The color figure is available in the electronic version of the journal.
Abbreviations: CI — confidence interval, HR — hazard ratio.

months. In a pooled analysis, the deterioration of LV GLS was associated with a statistically significant increase in the weighted average risk of the VA development (HR: 1,17 per each 1% of LV GLS deterioration; 95% CI: 1,07-1,27; p=0.0005) (Figure 4). The Egger test score were also found to be statistically negligible, t=0,63; df=2,0; p=0,59.

The univariate risk analysis data of the VA development using continuous estimates of LV MD value as a predictor were presented only in two studies when [14, 21]. These studies were comparable due to the same predictor score (changes per 10 ms), that allowed to performed a meta-analysis of these publications. The number of the "arrhythmic" endpoints in these studies was of 60 (13,8% of 434 patients), the average follow-up period was of 29 months. In a pooled analysis, an increment of LV MD was associated with a statistically significant increase in the weighted average risk of the VA development (HR: 1,29 per each 10 ms of LV MD increment; 95% CI: 1,14-1,47; p<0,0001) (Figure 5).

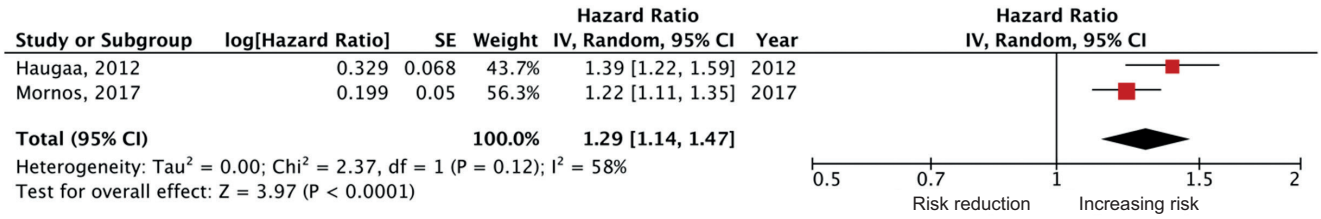

Figure 5. Results of a meta-analysis of the unadjusted HR for "arrhythmic" endpoints per each 10 ms increment of LV MD.
Note: the red squares show the weighted effect size for each particular study (the red square sizes represent weights of studies), the red line segments show 95% CI, the black rhombus shows weighted average of HR. The color figure is available in the electronic version of the journal.
Abbreviations: CI — confidence interval, HR — hazard ratio.

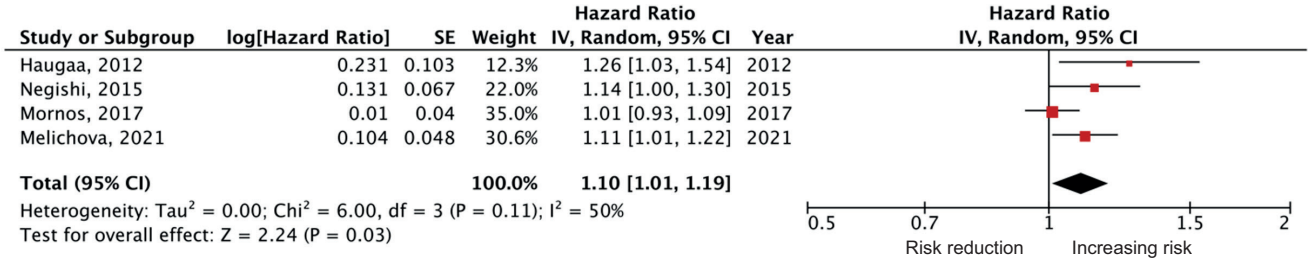

Figure 6. Results of a meta-analysis of the adjusted HR for "arrhythmic" endpoints per each 1% decline of LV GLS.
Note: the red squares show the weighted effect size for each particular study (the red square sizes represent weights of studies), the red line segments show 95% CI, the black rhombus shows weighted average of HR. The color figure is available in the electronic version of the journal.
Abbreviations: CI — confidence interval, HR — hazard ratio.

The multivariate risk analysis data of the "arrhythmic" endpoint development using continuous estimates of the LV GLS value as a predictor were presented in four studies [14, 17, 21, 25]. These studies were comparable due to the same predictor score (changes per 1%), that allowed to perform a meta-analysis of these publications. The number of the "arrhythmic" endpoints in these studies was of 128 (15,1% of 848 patients), the average follow-up period was of 31,4 months. In a pooled analysis, LV GLS deterioration was associated with a statistically significant increase in the weighted average risk of the VA development (adjusted HR: 1,10 per each 1% decline of LV GLS; 95% CI: 1,01-1,19; p=0,03) (Figure 6). The Egger test score were also found to be statistically negligible, t=2,82; df=2,0; p=0,106.

The multivariate risk analysis data of the "arrhythmic" endpoint development using continuous estimates of the value of LV MD as a predictor were presented in three studies [14, 21, 25]. These studies were comparable due to the same predictor score (changes per 10 ms), that allowed to carry out a meta-analysis of these publications. The number of the "arrhythmic" endpoints in these studies was of 92 (12,7% of 724 patients), the average follow-up period was of 26,6 months. In a pooled analysis, the increase of LV MD was associated with a statistically significant increment of the weighted average risk of the VA development (adjusted HR: 1,18 per each 10 ms of LV MD increase; 95% CI: 1,08-1,29; p=0,0002) (Figure 7).

Major adverse cardiovascular events

Mean values of LV GLS parameters depending on the MACE development were presented in 5 studies. We performed a meta-analysis of the difference between the mean values of LV GLS in patients with and without MACE (Figure 8). Patients with MACE had worse LV GLS compared to those without it, so the weighted mean difference in LV GLS values was of -3,15% (95% CI: -4,27; -2,03%), these differences were statistically significant (p<0,0001).

The univariate risk analysis data of MACE development using continuous estimates of LV GLS as a predictor were presented in four studies [15, 20, 22, 24] (Table 4). A similar score criterion (changes per 1%) was available in these studies, that allowed them to be pooled in a meta-analysis. In these studies, 144 patients experienced MACEs (31,7% of 454). The mean follow-up period was of 45,7 months. According to the results of the analysis, there was no statistically significant association between the LV GLS deterioration and the development of MACEs (HR: 1,17 per each 1% of LV GLS deterioration; 95% CI: 0,96-1,41; p=0,11) (Figure 9). The Egger test

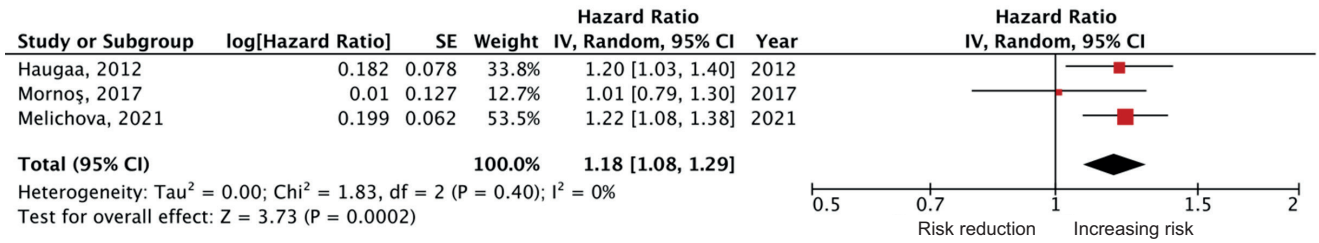

Figure 7. Results of a meta-analysis of the adjusted HR for "arrhythmic" endpoints per each 10 ms increment of LV MD.
Note: the red squares show the weighted effect size for each particular study (the red square sizes represent weights of studies), the red line segments show 95% CI, the black rhombus shows weighted average of HR. The color figure is available in the electronic version of the journal.
Abbreviations: CI — confidence interval, HR — hazard ratio.

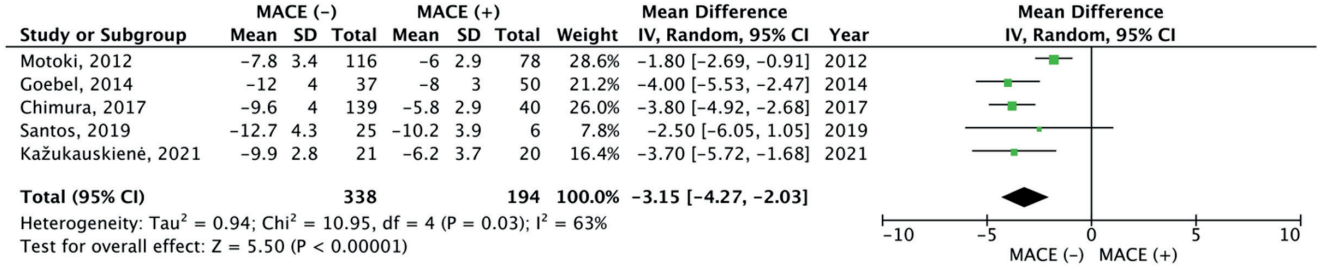

Figure 8. Results of a meta-analysis of the difference between the mean LV GLS values in the group with MACEs and without it.
Note: the green squares show weighted effect sizes for each specific study (the green square sizes represent weights of studies), the black line segments show 95% CI, the black rhombus shows weighted average of GLS mean difference. The color figure is available in the electronic version of the journal.
Abbreviations: GLS — global longitudinal strain, CI — confidence interval, MACE — major adverse cardiovascular event.

score were also found to be statistically negligible, t=0,48; df=2,0; p=0,67. It should be noted that the results of the meta-analysis were associated with the Santos' study inclusion, 2019 [22], where conflicting data were presented. Thus, it was shown that LV GLS deterioration was associated with a decrease in the rate of MACE development according to one-way analysis (HR: 0,879; 95% CI: 0,784-0,985; p=0,026). At the same time, according to multivariate analysis, LV GLS decline was associated with an increased risk of MACE development (adjusted HR: 1,365; 95% CI: 1,106-1,686; p=0,003).

Therefore, we excluded the Santos' study, 2019 [22] from the further meta-analysis. In the studies that were subsequently pooled [15, 20, 24], the MACE endpoint was reached in 138 patients (33,3% of 414). The mean follow-up period was of 55,0 months. A meta-analysis showed that LV GLS deterioration was associated with a statistically significant increase in the weighted average risk of MACE development (unadjusted RR: 1,27 per each 1% of GLS decline; 95% CI: 1,11-1,46; p=0,0008) (Figure 10). The Egger test score were found to be statistically negligible, t=5,8; df=1,0; p=0,11.

The multivariate risk analysis data of MACE development using continuous estimates of the LV GLS values as a predictor were presented in four studies [15, 20, 22, 24]. These studies were comparable due to the same predictor score (changes per 1%), that allowed to carry out a meta-analysis of these publications. In these studies, the MACEs were registered in 144 patients (31,7% of 454). The mean follow-up period was of 45,7 months. In a pooled analysis, LV GLS deterioration was associated with a statistically significant increase in the weighted average risk of MACE (adjusted RR: 1,22 for each 1% worsening of LV GLS; 95% CI: 1,11-1,33; p<0,0001) (Figure 11). The Egger test score were also found to be statistically negligible, t=1,73; df=2,0; p=0,22.

Discussion

Nowadays, the current strategies of risk stratification in patients with chronic HF with reduced EF caused by ischemic or non-ischemic cardiomyopathy are far from being perfect. There is still a clinical need to identify new markers to help in risk stratification. LV EF is a global assessment of LV systolic function, which is not always associated with myocardial injury and electrophysiological disturbances underlying electrical myocardial instability. All mentioned above highlights the need to use other additional parameters for risk stratification.

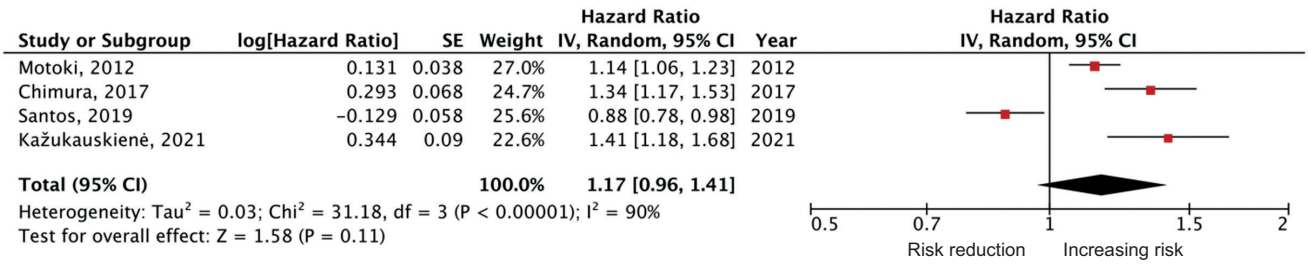

Figure 9. Results of a meta-analysis of the unadjusted HR for MACEs per each 1% decline of LV GLS.
Note: the red squares show the weighted effect size for each particular study (the red square sizes represent weights of studies), the red line segments show 95% CI, the black rhombus shows weighted average of HR. The color figure is available in the electronic version of the journal.
Abbreviations: CI — confidence interval, HR — hazard ratio.

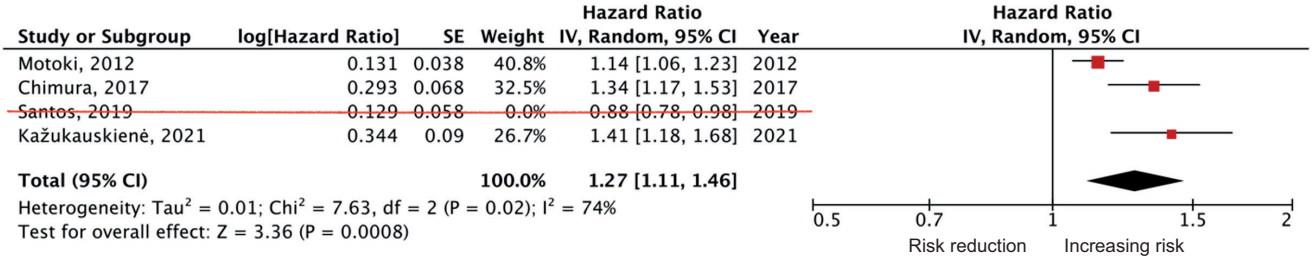

Figure 10. Results of a meta-analysis of the unadjusted HR for MACEs per each 1% decline of LV GLS (without Santos' study, 2019).
Note: the red squares show the weighted effect size for each particular study (the red square sizes represent weights of studies), the red line segments show 95% CI, the black rhombus shows weighted average of HR. The color figure is available in the electronic version of the journal.
Abbreviations: CI — confidence interval, HR — hazard ratio.

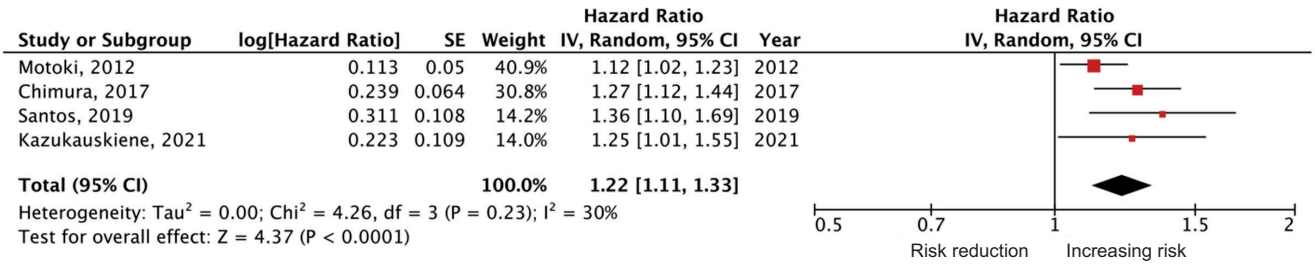

Figure 11. Results of a meta-analysis of the adjusted HR for MACEs per each 1% decline of LV GLS.
Note: the red squares show the weighted effect size for each particular study (the red square sizes represent weights of studies), the red line segments show 95% CI, the black rhombus shows weighted average of HR. The color figure is available in the electronic version of the journal.
Abbreviations: CI — confidence interval, HR — hazard ratio.

At the time of this writing, we could not find published meta-analyses regarding the prognostic role of LV GLS in patients with ischemic and nonischemic cardiomyopathy.

In this article, the patients developed VAs and MACEs have been shown to possess statistically significantly LV GLS decline than those without it. In addition, LV GLS has been established to be an independent predictor of adverse arrhythmic events and MACEs. Thus, according to the results of the pooled analysis, LV GLS deterioration per each 1% has been shown to be associated with a statistically significant increase in the weighted average risk of the "arrhythmic" endpoint and MACE development by 10% and 22%, respectively.

As noted, LV MD is a marker of delayed and inhomogeneous conduction in the myocardium and can be used as a predictor of the VA development. A recent meta-analysis of 3198 patients by Kawakami and colleagues found that patients with VAs had higher LV MD values compared to those without it, so the weighted mean difference in LV MD

values was of 20,3 ms (95% CI: 27,3-13,2; p<0,01). According to the results of the meta-analysis, each 10 ms increment of LV MD was associated with a statistically significant increase in the weighted average risk of VA development (adjusted HR: 1,19; 95% CI: 1,09-1,29; p<0,01). Moreover, the predictive value of LV MD was higher than the estimate of LV EF or LV GLS. It should also be noted that this meta-analysis included patients with both preserved and reduced LVEF, and most patients had prior myocardial infarction.

In our line of work, patients with ischemic and nonischemic cardiomyopathy with VAs have been established to have a statistically significantly higher LV DM values than those without "arrhythmic" endpoints. LV MD has also been shown to be an independent predictor of VA development. According to the results of the pooled analysis, each 10 ms increase of LV MD was associated with a statistically significant increase in the weighted average risk of "arrhythmic" endpoints by 18%. Thus, the assessment of LV GLS and LV MD by STE can be used as an effective tool for risk stratification in patients with HFrEF.

Study limitations. Firstly, a small number of studies were included in our systematic review and meta-analysis. Furthermore, as with any meta-analysis of observational studies, differences in inclusion criteria and endpoints are potential sources of study heterogeneity. Given the limited number of studies and patients, we are currently unable to perform a meta-analysis separately for groups with ischemic and nonischemic dilated cardiomyopathy, because some studies included a mixed population of patients with both types of cardiomyopathy and did not provide subgroup analysis data. Secondly, in the analysis we included the HR data obtained for LV GLS and/or LV MD, according to the data of both univariate and multivariate Cox regression analysis with calculated adjusted HR values.

However, in the latter case, the multivariate analysis included diverse covariates (age, gender, LV EF, LV end-diastolic volume, GPP, etc.) in various studies in addition to LV GLS and/or LV MD. Thirdly, although a similar score criterion was available (changes in LV GLS and LV MD values per 1% and 10 ms, respectively), that allowed them to be combined in a meta-analysis depending on the endpoint of the study. It should be remembered that the quality of the echocardiographic imaging and the appropriate imaging settings are crucial to assess myocardial strain (e.g., frame rate between 50 and 70 fps). In addition, it should be noted that in the studies, the assessment of echocardiographic parameters was carried out with various devices and software used for data post-processing, as well as by various operators.

Conclusion

LV GLS and LV MD assessed using speckle tracking provides important predictive value in patients with ischemic and nonischemic cardiomyopathy. Prospective multicenter studies with a large patient population and longer follow-up period are needed to validate the results and assess the feasibility of implementation in clinical decision-making.

Relationships and Activities: none.

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LITERATURE REVIEWS
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Electrocardiographic parameters and features of ventricular arrhythmias in various arrhythmogenic cardiomyopathy forms in the pediatric population: a systematic review and meta-analysis

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Arrhythmogenic cardiomyopathy (ACM) is a rare genetic disease characterized by the development of life-threatening ventricular arrhythmias and impaired ventricular systolic function due to fibrofatty infiltration of the myocardium. Currently, the Task Force 2010 criteria and the Padua criteria are proposed for the diagnosis of this disease. However, despite the multiparametric approach, there are certain limitations of the presented algorithms for disease establishment, especially in children. Carrying out such high-tech diagnostic methods as endomyocardial biopsy and magnetic resonance imaging is extremely difficult in the pediatric population. In this regard, the study and application of electrocardiography becomes extremely relevant in children. In addition, there are no data on the features of ventricular arrhythmias in ACM in the pediatric population. In this systematic review with meta-analysis, we studied the features of ventricular arrhythmias and electrocardiographic parameters in various ACM types.

Keywords: arrhythmogenic cardiomyopathy, sudden cardiac death, electrocardiography, ventricular arrhythmias, children.

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Key messages

- The limitations of developed criteria for arrhythmogenic cardiomyopathy (ACM) in children is shown.
- A systematic review with a meta-analysis of electrocardiographic parameters and features of ventricular arrhythmias in various forms of ACM in the pediatric population was carried out.
- The study results demonstrate the prospect of studying and using electrocardiographic parameters in the diagnosis of ACM in children.

Arrhythmogenic cardiomyopathy (ACM) is a genetic disease characterized by impaired ventricular systolic function due to progressive fibrofatty replacement of normal heart tissue and associated with development of ventricular arrhythmias (VAs) [1, 2]. Initially, it was regarded as a right-sided ventricular disease, which was reflected in its name: arrhythmogenic right ventricular (RV) dysplasia [3]. But later, biventricular (BV) and left-dominant types of the disease were recognized. In 2019, the working group of the Heart Rhythm Society adopted the common term of the disease as ACM and proposed updated recommendations for the diagnosis, risk stratification and treatment of this nosology [4, 5]. In the presented systematic review, we will use the term ACM with its form in order to avoid confusion in terminology.

The first diagnostic criteria for right-dominant ACM form were proposed in 1994 (Task Force) [6]. The last revision of these criteria was performed in 2010. According to the International Task Force 2010 criteria, family history data, electrocardiography (ECG), echocardiography (EchoCG), magnetic resonance imaging (MRI), 24-hour ECG monitoring, histological and genetic examinations are evaluated [7]. All criteria are divided into major and minor, depending on their specificity for the disease. To make a diagnosis, it is enough to have 2 major criteria, or 1 major and 2 minor criteria, or 4 minor ones. The diagnosis is considered possible in the presence of 2 minor criteria or 1 major, or 1 major and minor, or 3 minor criteria.

Despite the multiparametric approach, there are certain limitations of the presented diagnostic criteria. Thus, they do not allow assessment of other phenotypic variants other than RV dominance. A group of international experts pointed this out in 2019, and the updated Padua criteria were presented in 2020 [8, 9]. Currently, these criteria are not included in the recommendations for the diagnosis of ACM. According to these criteria, not only RV, but also LV involvement is taken into account. There are major and minor criteria and, depending on the quantitative correspondence, the diagnosis is considered definite, possible or borderline. Both EchoCG and MRI data are used as imaging methods in compliance with the Padua criteria. Unlike the Task Force 2010 criteria, where the sizes of the right heart chambers and ejection fraction values were indicated [7], the Padua criteria take into consideration the indexed dimensions of RV and LV cavities estimated by EchoCG and MRI taking into account body surface area, age, gender, and in accordance to the nomograms presented by the International Society for Cardiovascular Imaging [8]. There are certain difficulties in disease establishment of ACM, especially in the left-dominant form [10]. Thus, neither the Task Force 2010 nor the Padua criteria took into account the possibilities of diagnostic search in pediatric population. Complexities of the diagnosis of various ACM forms in children have been noted by many authors [11-13]. The absence of individual criteria for children with ACM complicates the diagnosis in pediatric practice. In addition, the questions of the originality of the clinical course of various ACM forms remain unclear.

ECG changes often precede morphological myocardial remodeling and make the diagnosis of ACM suspected. However, the use of ECG criteria is very limited in pediatric practice due to age characteristics. In particular, certain difficulties are caused by the interpretation of changes in the repolarization processes in children. Inverted T-wave in the right precordial leads V1-3 on ESG is a major criterion and is considered the most common, sensitive, and specific marker. It is generally recognized that this parameter is a normal phenomenon in pediatric patients under the age of 14 [14, 15]. The Epsilon wave as the major criterion of the disease in conformity with the Task Force 2010 criteria is observed in the right precordial leads and is a characteristic feature of ACM, and corresponds to a delay in depolarization of the RV free wall and the outflow tract. It occurs predominantly in advanced cases of ACM and is extremely rare in children and adolescents [16, 17]. All this potentially leads to the exclusion of two important ECG criteria in the diagnosis of ACM in the pediatric population. The presence of late potentials (minor criterion) is also not typical in pediatric patients [16].

In addition, the implementation of such high-tech diagnostic methods as endomyocardial biopsy and MRI is extremely arduous in the pediatric population. In this regard, the study of ECG features of ACM in children becomes extremely relevant in the diagnosis of this disease, which is primarily driven by the availability, ease of use and safety of these examination methods.

Moreover, the lack of data on the features of ventricular arrhythmias and ECG parameters in various phenotypic ACM types in the pediatric population prompted this systematic review with meta-analysis.

Thus, the objective of this systematic review with meta-analysis was to study the features of ventricular arrhythmias and electrocardiographic parameters in various ACM forms in pediatric patients.

Material and methods

Search for publications and selection of studies. The systematic review and meta-analysis were performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses

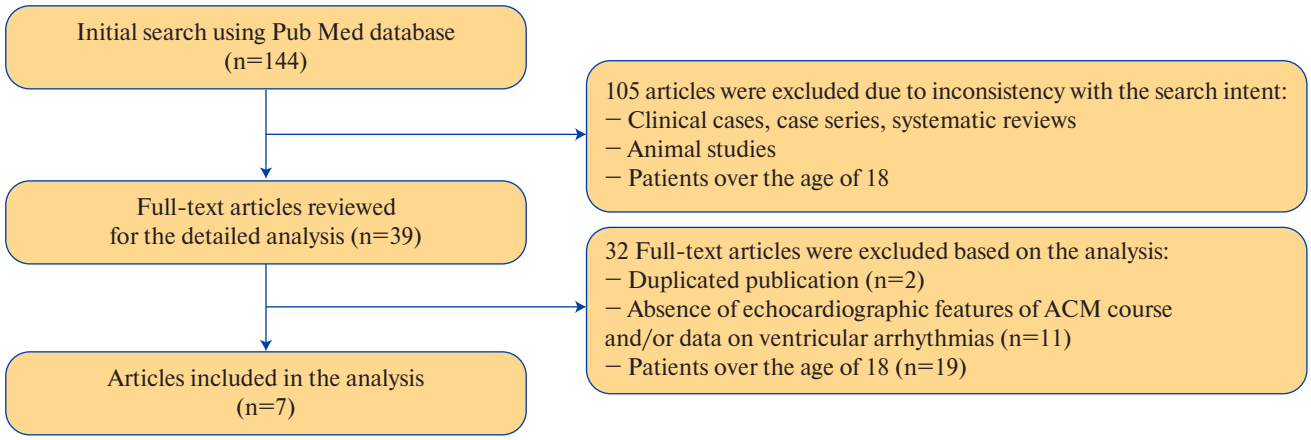

Figure 1. Selection algorithm of publications.
Abbreviation: ACM — arrhythmogenic cardiomyopathy.

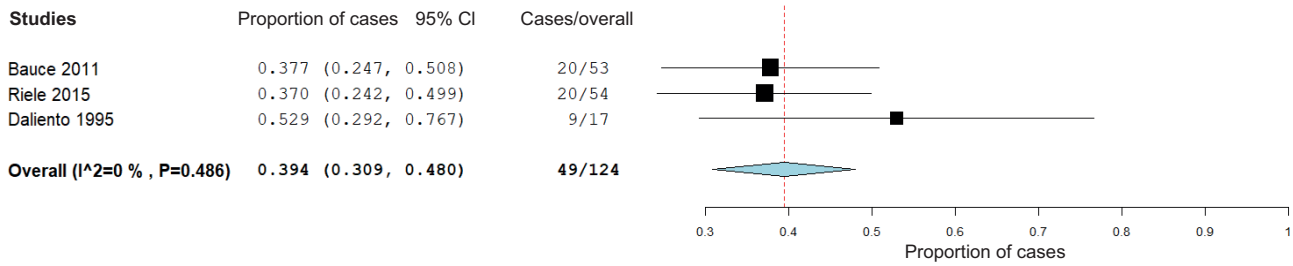

Figure 2. The meta-analysis of the frequency of late potentials on ECG in patients with right-dominant ACM.
Abbreviation: CI — confidential interval.

Table 1

Studies included in the systematic review

Author, year	Number of patients (n)	Age±SD, years	Follow-up period±SD, years	Male (n)	ACM forms		
					RD (n)	LD (n)	BV (n)
Cicenia, 2021	21	13,9±2	5,46±3,17 (1,13-12,43)	6	8	1	12
DeWitt, 2016	32	15,1±3,8	4,9±3,0	18	16	7	9
Surget, 2022	61	11,5±2,5	33	51	41	13	7
Bauce, 2011	53	12,3±3,9	9±7	31	53	–	–
Riele, 2015	75	15,3±2,4	8,4±7,5	41	75	–	–
Etoom, 2015	23	11,8±3,6	–	17	23	–	–
Daliento, 1995	17	14,9±4,9	7±3,7	12	17	–	–
Total	282	13,5±3,3	11,3±9,7	176, 62,4%	233, 82,6%	21, 7,45%	28, 9,93%

Abbreviations: ACM — arrhythmogenic cardiomyopathy, BV — biventricular, LD — left-dominant, DR — right-dominant.

(PRISMA) Statement. The search was carried out in the PubMed electronic database without restrictions on the date of issuing of publications and ended on March 8, 2022. Three independent investigators separately searched and selected studies using predefined search terms, keywords (including MeSH) and logical operators: "arrhythmogenic cardiomyopathy" and "Padua criteria" and "children" or "Phenotype" and "arrhythmogenic cardiomyopathy" and "children" or "right ventricular arrhythmogenic dysplasia and pediatric population". Any disagreements were resolved through discussion between them or with the involvement of a fourth researcher, if the disagreement persisted. The search was limited to English-language articles. We included studies that 1) compared ECG parameters and features of VAs

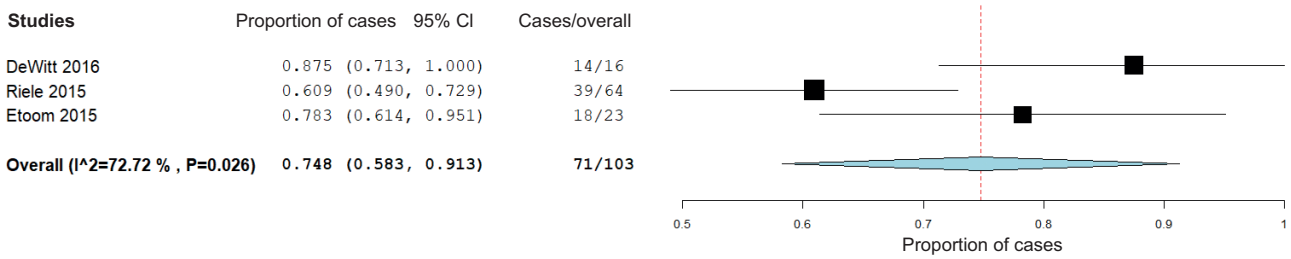

Figure 3. The meta-analysis of the frequency of depolarization changes on ECG in patients with right-dominant ACM.
Abbreviation: CI — confidential interval.

Table 2

ECG features in patients included in the systematic review

Repolarization changes, abs./n, %	Tot.	12/20, 60	22/25, 88	16/61, 26		58/64, 91	1/75, 4,35	9/17, 52,9	118/262, 45,0
	BV	–	8/9, 88,9	–	–	–	–	–	8/9, 88,9
	RD	–	16/16, 100	–	–	58/64, 91	1/75, 4,35	9/17, 52,9	84/256, 32,8
Depolarization change, abs./n, %	Tot.		20/25, 80		–	39/64, 61	18/23, 78,3		77/112, 68,8
	BV	–	6/9, 66,7	–	–	–	–	–	6/9, 66,7
	RD	–	14/16, 87,5	–	–	39/64, 61	18/23, 78,3	–	71/103, 68,9
delayed intraventricular conduction, abs./n, %	Tot.	–	–	–	–	26/64, 41	–	10/17, 58,8	36/81, 44,4
	BV	–	–	–	–	–	–	–	–
	RD	–		–	–	26/64, 41,0	–	10/17, 58,8	36/81, 44,4
Low voltage, abs./n, %	Tot.	–			3/53, 5,66	–	–	–	3/53, 5,66
	BV	–		–	–	–	–	–	
	LD	–		–	–	–	–	–	
	RD	–			3/53, 5,66	–	–	–	3/53, 5,66
Study		Cicenia, 2021	DeWitt, 2016	Surget, 2022	Bauce, 2011	Riele, 2015	Etoom, 2015	Daliento, 1995	Total, n/abs., %

Abbreviations: BV — biventricular, LD — left-dominant, DR — right-dominant.

in pediatric patients with various phenotypic ACM forms; 2) described ECG signs and features of VAs in confirmed ACM in children. The studies representing animal trials, abstracts, minutes of meetings, books, clinical cases and case series were excluded. The eligibility of each work being included was checked in 2 steps: 1) review of the title and abstract, and 2) review of the full text.

Research data extraction and synthesis. The following data were recorded for each study: first author, year of publication, study population, number of cases, age of ACM onset, gender and the ensuing features based on Task Force 2010 or the Padua criteria: changes in the processes of depolarization and repolarization (inverted T-wave in the right precordial leads (V1-3), Epsilon wave in the right precordial leads (V1-3), late ventricular potentials, delayed intraventricular conduction, etc.), VAs and their morphological characteristics. Any disagreements were resolved through discussion.

Statistical analysis. Data meta-analysis was carried out using the free Open Meta-Analyst software. Given the significant statistical heterogeneity of most parameters, a random effects model was used when the data from individual studies summarized. Percentages with 95% confidence intervals (CI) were calculated using the Der Simonian-Laird method [18]. The results of meta-analysis were presented as a blobbogram (forestplot).

Comparison of the data of dominant-right ACM to BV and dominant-left types was performed by calculating the generalized frequency of pathological conditions with a preliminary addition of the number of cases and the number of patients studied in separate publications. Next, the statistical significance of differences in parameters was assessed using Pearson's chi-square test, and the odds ratio with 95% CI was calculated. Differences were considered statistically significant at $p<0,05$.

Table 3

The comparison results of the frequency of changes in ventricular depolarization on ECG in various ACM forms

Pathological condition	RD		BV		p
	abs./n	%	abs./n	%	
Depolarization changes	71/103	68,9	6/9	66,7	1,0

Abbreviations: BV — biventricular, RD — right-dominant.

Results

The initial electronic search identified 144 studies. In total, 39 papers remained after the removal of duplicated articles, clinical cases, studies on patients over the age of 18. Three independent researchers reviewed the full-text versions of the remaining publications and identified 5, 7, and 9 articles, respectively. Seven articles were selected for analysis after a collegial discussion and the involvement of the fourth researcher. The search algorithm is shown in Figure 1.

The number of children in 7 studies included in the analysis varied from 17 to 75; follow-up period varied from 1 year to 33 years.

We were unable to conduct a meta-analysis of data on the frequency of VAs and ECG features in "non-classical" ACM forms because the information was provided in single studies. At the same time, the meta-analysis was performed for cases of right-dominant ACM and the overall frequency of cases of VAs and ECG signs. Table 1 shows the characteristics of the studies included in the analysis [17, 19-24].

ECG features. ECG abnormalities as changes in the processes of repolarization and depolarization were described in 6 studies. The most frequently recorded ECG parameter of repolarization was inverted T-wave in leads V1-3, which was described in half of the patients (n=197, 50,8%). Wherein, the frequency of this criterion occurrence taking into account ACM forms was presented in 5 out of 6 studies and, regardless of the phenotypic variant, was observed in half of the cases both in patients with BV (55,6%) and right-dominant (50,3%) ACM.

Among the changes in the processes of depolarization, the late ventricular potentials were the most common ones (in 49 cases out of 124). Quantitative data on those ventricular potentials were presented in 3 studies, and only in patients with right-dominant ACM. The results of the meta-analysis of the prevalence of the late ventricular potentials based on ECG data are presented in Figure 2.

In accordance with the data obtained, the frequency of disclosure of the late potentials was 39,4% (95% CI: 30,9-48,0). The parameter had low heterogeneity (I^2=0%, p=0,486), ranging from 37,0 (Riele, 2015) to 52,9% (Daliento, 1995).

Data on changes in depolarization were presented in 3 papers. The number of patients with right-dominant ACM who had this sign was 71 ones, when a total number of analyzed patients were 103. The results of the meta-analysis are shown in Figure 3.

As follows from the obtained blobbogram, the prevalence of changes in depolarization varied from 60,9 (Riele, 2015) to 87,5% (DeWitt, 2016) in different studies featuring in significant heterogeneity (I^2=72,7%, p=0,026). The composite rate was 74,8% (95% CI: 58,3-91,3).

DeWitt (2016) presented data on the frequency of detection of depolarization changes in BV ACM. The parameter was of 66,7% (6 cases out of 9 studies), which corresponded to the frequency of the symptom in dominant-right ACM.

The Epsilon wave was rare and was described in 5 papers, which corresponds to 4,86%. The distribution of this symptom was presented in 4 studies depending on ACM form: it occurred in 5 (5,0%) patients with RV damage and in one (11,9%) with BV form.

The detailed description of the ECG features is presented in Table 2.

The comparison results of the frequency of changes in ventricular depolarization on ECG data in patients with right-dominant ACM with the parameter in BV form presented in the study by DeWitt (2016) are shown in Table 3. In accordance with the table, the frequency of depolarization changes was of 68,9% in right-dominant ACM based on the generalized data of 3 studies, and it was of 66,7% in BV ACM in compliance with the results of the study by DeWitt (2016). The values of the parameters were comparable (p=1,0).

Ventricular arrhythmia (VA). VAs were described in all the papers included in the systematic review, however, their quantitative characteristics are presented in 6 ones. Data on the frequency of this symptom in any ACM form are presented in Table 4.

Thus, VAs were registered in 126 out of 210 (60,0%) patients, i.e. in more than half of the cases. In the meta-analysis, the overall incidence of VAs was of 61,4% (95% CI: 37,0-85,7). The data were highly heterogeneous (I^2=95,6%, p<0,001).

Table 4

The frequency of VA in ACM of any localization

Pathological condition	Total number of cases/ number of patients (%)	Meta-analysis results	Heterogeneity	
		Proportion of cases (95% CI), %	I^2, %	p
VA	126/210 (60,0%)	61,4 (37,0-85,7)	95,6	<0,001
Of these, VT, including:	126/250 (50,4)	46,7 (28,5-64,8)	89,3	<0,001
— non-sustained VT	29/102 (28,4)	28,2 (16,8-39,5)	36,4	0,207
— sustained VT	44/197 (22,3)	22,9 (11,6-34,3)	73,4	0,005

Abbreviations: CI — confidential interval, VA — ventricular arrhythmias, VT — ventricular tachycardia.

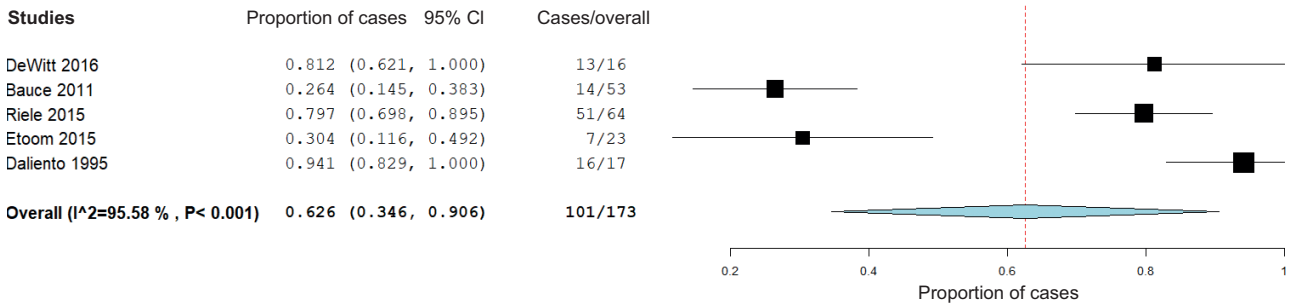

Figure 4. The meta-analysis of the frequency of VA in patients with right-dominant ACM.
Abbreviation: CI — confidential interval.

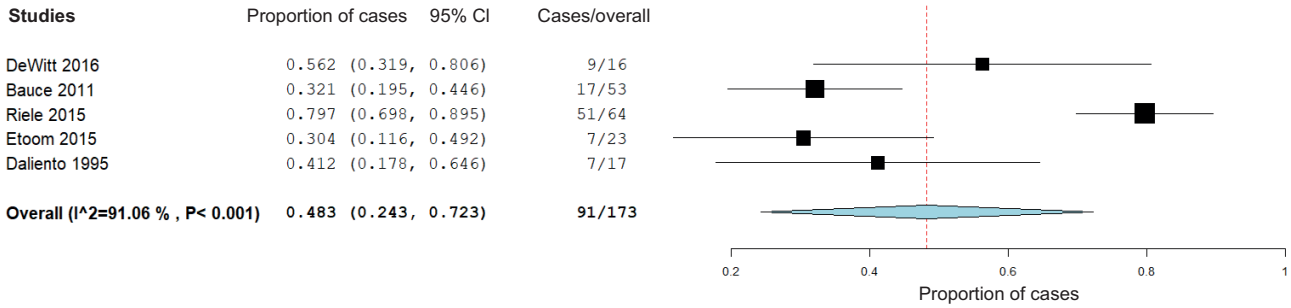

Figure 5. The meta-analysis of the frequency of VA in patients with right-dominant ACM.
Abbreviation: CI — confidential interval.

The proportion of identified ventricular tachycardia (VT) was of 46,7% in the meta-analysis of the studies on ACM of any localization including non-sustained ventricular tachycardia of 28,2%, and sustained VT of 22,9%.

According to the study by DeWitt (2016), VA was characteristic of all patients with both left-dominant and BV forms. Whereas, in the "classic" form of the disease described in 5 publications, VAs occurred in 101 out of 173 cases. The results of the meta-analysis of the frequency of VA in right-dominant ACM are presented in Figure 4.

The blobbogram above shows that the total proportion of patients with VAs was of 6,6% (95% CI: 34,6-9,6) in right-dominant ACM. The parameter, as well as in the analysis of ACM of any localization, was highly heterogeneous (I^2=95,6%, p<0,001).

Holter monitoring was performed in all studies. However, data on the quantitative characteristics of ventricular ectopic complexes >500 per day were presented only in 2 papers out of 7 and were described in the vast majority of children 55 (77,5%). Four studies showed the morphological characteristics of the VAs. Based on the data presented, enumeration was only possible in 3 studies.

Thus, VAs were registered in a third of patients as left bundle-branch block in 35,2% of cases and much less frequently as right bundle-branch block in 8,79% of cases. The correct numerical characteristic of the VT morphology was described in one paper presented only right-dominant ACM form. Thus, VT with the morphology of left bundle-branch block with the lower axis was recorded in 5 (9,43%) patients, and left bundle-branch block

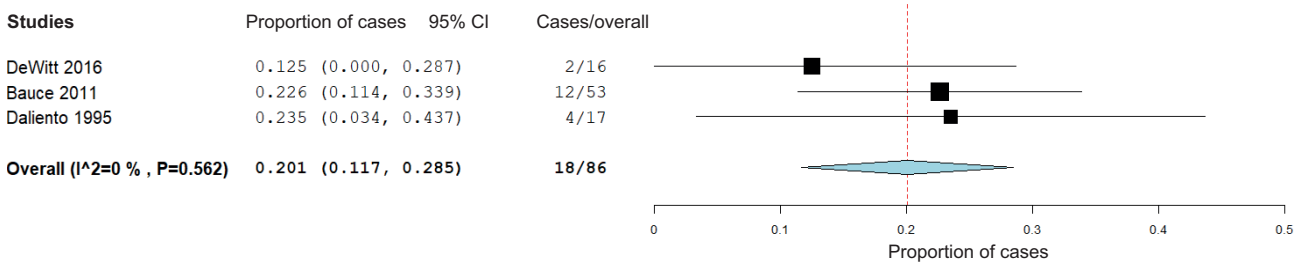

Figure 6. The meta-analysis of the frequency of non-sustained VT in patients with right-dominant ACM.
Abbreviation: CI — confidential interval.

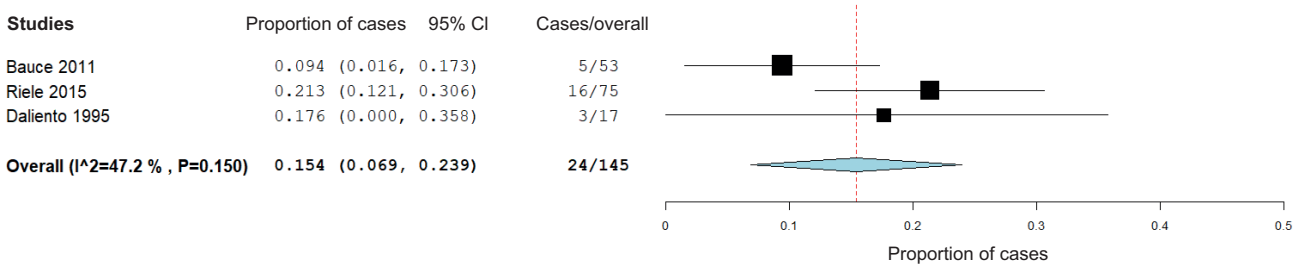

Figure 7. The meta-analysis of the frequency of sustained VT in patients with right-dominant ACM.
Abbreviation: CI — confidential interval.

with the upper axis was registered in 4 (7,55%) patients.

When assessing the frequency of VT in patients with right-dominant ACM, this symptom was observed in 91 patients out of 173. As the result of the meta-analysis, the following blobbogram was obtained (Figure 5).

According to the data obtained, the incidence of VT was of 48,3% (95% CI: 24,3-72,3) in patients with right-dominant ACM. The parameter was highly heterogeneous (I^2=91,1%, p<0,001), ranging from 30,4% (Etoom, 2015) to 79,7% (Riele, 2015).

Non-sustained VT was observed in 18 out of 86 cases in right-dominant ACM. The results of the meta-analysis of this parameter are presented in Figure 6.

The meta-analysis of 3 studies found that the incidence of non-sustained VT was of 20,1% (95% CI: 11,7-28,5). The parameter had a insignificant heterogeneity (I^2=0%, p=0,562), which corresponded to close values of the frequency of non-sustained VT in right-dominant ACM obtained by different researchers: from 12,5% (DeWitt, 2016) to 23,5% (Daliento, 1995).

Eventually, sustained VT in right-dominant ACM was observed in 24 patients out of 145 described in 3 studies. Based on the results of the meta-analysis, the following blobbogram was obtained (Figure 7).

The reported rate was of 15,4% (95% CI: 6,9-23,9). The range of values corresponding to different studies accounted from 9,4 to 21,3%, the parameter was moderately heterogeneous (I^2=47,2%, p=0,15).

We also compared the frequency of VA, VT, and non-sustained VT depending on the phenotypic forms of ACM. As in previous cases, data on the frequency of these conditions for left-dominant and BV ACM were taken from the study by DeWitt (2016). The results obtained are reflected in Table 5. This table shows that the frequency of VA in patients with the left-dominant and BV ACM forms, reaching 100% in both cases, was significantly higher than in those with right-dominant ACM, which was of 58,4% (p=0,043 and p=0,012, respectively). On the contrary, the rate of VT was higher in right-dominant ACM (up to 52,6%), whereas the rate was of 42,9% in left- dominant ACM, and it was of 22,2% in the BV form. Despite the fact that the incidence of VT was over twofold higher in the right-dominant form than in the BV form, the difference was not statistically significant (p=0,095). There were also no statistically significant differences between left-dominant and right-dominant ACM (p=0,711).

In the analysis of the frequency of non-sustained VT, right-dominant ACM form this symptom was found to occur only in 20,9% of the subjects. Among patients with a left-dominant form of the disease, the incidence of non-sustained VT was almost threefold higher, up to 57,1%, and it was 3,7-fold higher in BV ACM patients, up to 77,8%. The differences were

Table 5

The comparison results of the frequency of VA in various ACM forms

Pathological condition	1) RD		2) LD		3) BV		p
	abs./n	%	abs./n	%	abs./n	%	
VA	101/173	58,4	7/7	100,0	9/9	100,0	p_{1-2}=0,043* p_{1-3}=0,012*
VT	91/173	52,6	3/7	42,9	2/9	22,2	p_{1-2}=0,711 p_{1-3}=0,095
Non-sustained VT	18/86	20,9	4/7	57,1	7/9	77,8	p_{1-2}=0,052 p_{1-3}=0,001*

Note: * — statistically significant differences (p<0,05).
Abbreviations: BV — biventricular, VA — ventricular arrhythmias, VT — ventricular tachycardia, LD — left-dominant, DR — right-dominant.

characterized by p=0,052 when comparing right-dominant and left-dominant ACM forms, which suggests a certain relationship between the morphological forms of ACM and the frequency of non-sustained VT. The parameter statistically significantly exceeded the frequency of non-sustained VT in BV ACM than in right-dominant ACM (p=0,001).

Thus, a significantly higher incidence of VA in general, as well as non-sustained VT, was found in patients with left-dominant and BV ACM forms compared to dominant-right ACM.

Discussion

Our systematic review with meta-analysis demonstrates the features of VA and ECG parameters in children with various ACM forms, and also gives a general idea of the characteristics of the above parameters.

More than half of the patients had VA. Wherein, compared to right-dominant ACM, the number of patients with VAs significantly prevailed in "non-classical" one. A significantly higher incidence of non-sustained VT was also established in patients with left-dominant and BV ACM forms than in those with right-dominant ACM. However, as per literature, VA is the main manifestation of ACM, regardless of the phenotype [25, 26].

ECG criteria of the disease are known to include both changes in the processes of depolarization and repolarization. At the same time, their relevance in the diagnosis of only right-dominant and BV forms should be taken into account.

The results of this work revealed that the change in depolarization such as the Epsilon wave is quite rare, regardless of the ventricle involvement. Our conclusions correlate with the literature data: the Epsilon wave is extremely rare, mainly in the late stages of the disease, and the detection of the Epsilon wave on ECG is a minor criterion in the updated Padua criteria [4, 27]. This is probably due to the fact that this sign manifests itself at later stages of the disease, when there is a significant structural pathology of the heart [7, 28]. In addition, it is known that this pattern on the ECG may be transient and not manifest during repeated examinations [29]. The late ventricular potentials have been described to also depend on the progression of the disease, but they are much more common than the Epsilon wave [16]. So according to our data, the late ventricular potentials were recorded in more than a third of cases with right-dominant form. In addition, the frequency of depolarization changes in both right-dominant and BV forms did not differ significantly and was observed in a significant number of patients. This observation is warranted further research and study of this phenomenon.

Among the repolarization changes, the most common, sensitive and specific marker is inverted T-wave in the right precordial leads V1-3, which is a major diagnostic criterion for ACM. It should be noted that this criterion cannot be used in children under 14 years of age, because it is the age norm [14, 15]. In our study, these changes were described in more than a third of patients, but, unfortunately, they did not carry any diagnostic value, because the average age of the children included in the study was of 13,5 years.

Thus, our systematic review with meta-analysis concludes that VA is the leading sign of ACM in the pediatric population. Wherein, non-sustained VT is recorded much more often in "non-classical" forms than in right-dominant ACM. Among the ECG parameters that should be paid attention to in children, one can single out the changes in depolarization processes. At the same time, the late ventricular potentials can be considered as a promising diagnostic criterion for RV involvement in children.

Study limitations. Our study has several limitations. ECG parameters were not clearly presented in most cases, which made it difficult to perform the meta-analysis in many ways. The heterogeneity in

the range of the described VA characteristics should be noted as a complication of the analysis.

Conclusion

The publications included in our systematic review with meta-analysis demonstrated the promising prognostic value of a number of ECG parameters. Taking into account the absence of specific ECG signs in children, it is necessary to provide dynamic monitoring of patients with VAs and continue further research to study the ECG parameters and features of VA in order to develop diagnostic criteria for ACM in the pediatric population.

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