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Improving the Approach to Risk Grading in Patients with Coronary Artery Disease in Combination with Type 2 Diabetes Mellitus and Preserved Left Ventricular Ejection Fraction

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Abstract

Purpose. Creation of a model for predicting the risk of the first cardiovascular event, based on the assessment of HbAc1 trajectories in patients with coronary heart disease with type 2 diabetes with preserved left ventricular ejection fraction, performed dynamically against the background of modern classes of antihyperglycemic drugs.
Materials and methods. A retrospective single-center comparative study. 130 patients with coronary heart disease with T2DM without signs of myocardial infarction (MI) less than three months ago and severe complications of T2DM were examined, who are being treated at the department of coronary heart disease of the Republican Specialized Scientific-Practical Medical Center of Cardiology of the Ministry of Health of the Republic of Uzbekistan. All patients underwent a complete clinical and laboratory examination. The presence of concomitant pathology was judged based on the analysis of medical records and the results of inpatient examination of patients.
Results. The dynamics of glycated hemoglobin was evaluated with the identification of risk stratification markers for the development of a model (software product) for predicting the 2-year risk of the first ACCS event in patients with coronary heart disease and T2DM (by introducing certain risk factors). The identified markers in the group of patients with CHD with T2DM with NBT with preserved LV LV at HbA1c >8.5% were the values: Total cholesterol ≥142 mg/dl (χ^2=74.5; P=0.000); TG>163 mg/dl and higher (χ^2=27.15; P=0.000); M >3.52 mg/dl, vitamin D<14.9 ng/ml χ^2=72.038; P=0.000); NT proBNP >1984 pg/ml (χ^2=52.80; P=0.000). In patients with preserved PV, the criterion of an increase in the risk of adverse events <57% (χ^2=13.846, P=0.000), increased MMLF >309 g (χ^2=65.54, P=0.000) and an increase in E/A >0.69 (χ^2=41.17, P=0.000) was determined. In addition, there was

a tendency to a higher incidence of LDL with unfavorable outcomes (2.5 times higher, versus 1.6 times with favorable outcomes).
Conclusion. An algorithm has been developed that allows to identify patients with CHD with T2DM with preserved LVEF with an unfavorable course with a high degree of accuracy. On the one hand, to recommend treatment that is more aggressive and possibly invasive interventions to the patient in a timely manner, and on the other hand, to limit themselves to medical treatment if it is impossible and inexpedient to implement invasive treatment methods.
Keywords: risk stratification, coronary heart disease, type 2 diabetes mellitus, software product, preserved left ventricular ejection fraction

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Совершенствование подхода к градации риска у пациентов с ишемической болезнью сердца, сахарным диабетом второго типа и сохраненной фракцией выброса левого желудочка

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Резюме

Цель. Создание модели прогнозирования на основании оценки траекторий HbAc1 у пациентов с ИБС, СД 2-го типа и сохраненной фракцией выброса левого желудочка, выполненное в динамике на фоне современных классов антигипергликемических препаратов.
Материалы и методы. Ретроспективное одноцентровое сравнительное исследование. Обследовано 130 пациентов с ИБС, СД 2-го типа без признаков инфаркта миокарда (ИМ) в течение трех последних месяцев и тяжелыми осложнениями СД, проходивших лечение на базе отделения ИБС РСНПМЦК МЗ РУз. Всем пациентам проводили полное клиническое и лабораторное обследование. О наличии сопутствующей патологии судили на основании анализа медицинских карт и результатов стационарного обследования пациентов.

Результаты. Выполнена оценка динамики гликированного гемоглобина с выявлением маркеров риск-стратификации для разработки модели (программный продукт) прогнозирования 2-летнего риска развития первого атеросклеротического сердечно-сосудистого заболевания у пациентов с ИБС и СД 2-го типа (путем ввода определенных факторов риска). Выявленными маркерами в группе пациентов с ИБС, СД 2-го типа и НБТ с сохраненной ФВ ЛЖ при HbA1c >8,5% оказались величины: ОХС ≥142 мг/дл (χ^2=74,5; P=0,000); ТГ >163 мг/дл и выше (χ^2=27,15; P=0,000); МИ >3,52 мг/дл, витамин D <14,9 нг/мл (χ^2=72,038; P=0,000); МНУП >1984 пг/мл (χ^2=52,80; P=0,000). У пациентов с сохраненной ФВ определен критерий роста риска развития нежелательных событий <57% (χ^2=13,846, P=0,000), повышенной ММЛЖ >309 г (χ^2=65,54, P=0,000) и повышения E/A >0,69 (χ^2=41,17, P=0,000). Помимо этого, регистрировалась тенденция к большей частоте встречаемости ДДЛЖ при неблагоприятных исходах (выше в 2,5 раза против 1,6 раза при благоприятных).

Заключение. Разработан алгоритм, позволяющий с высокой степенью точности идентифицировать пациентов с ИБС, СД 2-го типа и сохраненной ФВ ЛЖ с неблагоприятным течением. С одной стороны, это позволит своевременно рекомендовать пациенту более интенсивное лечение с возможностью инвазивных вмешательств, а с другой – ограничиться медикаментозным лечением при невозможности и нецелесообразности реализации инвазивных методов лечения.

Ключевые слова: стратификация риска, ишемическая болезнь сердца, сахарный диабет 2-го типа, программный продукт, сохраненная фракция выброса левого желудочка

■ INTRODUCTION

The relevance of the issue of risk stratification for the development of cardiovascular complications (CVCs) in ischemic heart disease (IHD) patients has not lost its significance over many years. In light of the rapid increase in type 2 diabetes mellitus (T2DM) cases, in 2011, the United Nations adopted a political declaration, emphasizing the importance of T2DM as a leading cause of disability and mortality, with cardiovascular diseases (CVDs) occupying prominent positions among its complications. Hyperglycemia [1], one of the primary risk factors for CVCs in T2DM patients, is particularly significant for those with type 2 diabetes mellitus. Multicenter studies have demonstrated that lowering the level of glycated hemoglobin (HbA1c) [2] is associated with a decrease in specific vascular complications of T2DM. The Diabetes Control and Complications Trial (DCCT), conducted from 1982 to 1989, and its continuation, the Epidemiology of Diabetes Interventions and Complications Research Study (EDIC) [3], have shown that transitioning from traditional to intensive insulin therapy led to a decrease in the risk of developing and progressing vascular complications [4, 5]. The UKPDS (U.K. Prospective Diabetes Study) [6] is a large clinical study that identified the most significant risk factors for the development of ischemic heart disease (IHD) and its complications in patients with type 2 diabetes (in descending order of significance): elevated levels of LDL cholesterol, high blood pressure, smoking, low levels of HDL cholesterol, and elevated levels of HbA1c [7]. The study found that reducing HbA1c levels by approximately 1% in patients with type 2 diabetes led to a 14% reduction in the incidence of myocardial infarction (MI) and a 21% reduction in

overall mortality [2]. Conversely, increasing this indicator by 1% led to an 18% increase in cardiovascular disease [8]. The study also showed that in the treatment of type 2 diabetes, it is necessary to avoid high variability in blood glucose levels, which can be an independent predictor of worsening coronary atherosclerosis and increases the likelihood of ventricular arrhythmias in patients with type 2 diabetes mellitus [9, 10].

Clarifying the criteria for adverse disease progression in patients with IHD and concomitant type 2 diabetes using traditional risk factors and new well-interpreted parameters that reflect modern concepts of the pathogenesis of IHD destabilization [11] in patients with type 2 diabetes mellitus remains highly promising. The development of risk prediction models for cardiovascular disease in patients with type 2 diabetes mellitus is always at the center of research attention. At the same time, the results obtained on the regulation of blood glucose levels in patients with type 2 diabetes mellitus depending on the level of cardiovascular risk obtained in the ACCORD and VADT studies are ambiguous and continue to be studied [12]. To eliminate the imbalance of clinical data, effective prediction models are currently being developed that guarantee their reliability and accuracy, are user-friendly, and play a vital role in communication between doctors and patients. By using machine learning in the software model, recognizing patterns with logarithmic elements, and subsequently validating the prediction model, its overall performance can be improved, and decisions can be made based on new settings or situations [13].

■ PURPOSE OF THE STUDY

Creation of a model for predicting the risk of the first cardiovascular event, based on the assessment of HbAc1 trajectories in patients with coronary heart disease with type 2 diabetes with preserved left ventricular ejection fraction, performed dynamically against the background of modern classes of antihyperglycemic drugs.

■ MATERIALS AND METHODS

A retrospective, single-center, comparative study was performed. A total of 130 T2DM patients without myocardial infarction (MI) within three months and severe complications of diabetes, receiving treatment at the department of coronary heart disease of the Republican Specialized Scientific-Practical Medical Center of Cardiology of the Ministry of Health of the Republic of Uzbekistan, underwent comprehensive clinical and laboratory examination. The presence of comorbidities was determined based on medical records and hospital examination results.

The main inclusion conditions in the study were: typical manifestations of new-onset or progressive angina according to the ESC recommendations (protracted anginal attack occurring at rest or with minor physical exertion, lasting at least 20 minutes, despite taking nitroglycerin; de novo angina or recent destabilization of stable angina reaching at least functional class III according to the Canadian classification); transient changes in the ST-T interval on the ECG, outside of a pain attack, without ST segment elevation and fresh Q waves [14].

Exclusion criteria from the study: presence of CHF III-IV functional class, period of acute myocardial infarction for 2 months, permanent or persistent form of atrial fibrillation (AF), lung diseases with respiratory failure, chronic kidney disease (CKD) stages 4–5, severe liver

dysfunction, left ventricular ejection fraction (LVEF) less than 50%, CKD 3B-4, retinopathy with blindness, previous amputations, polyneuropathy.

Among the examined patients, 42.3% had a history of acute MI with Q-wave, 33.8% had chronic kidney disease (CKD), 6.9% had coronary artery bypass grafting (CABG), 5.3% had a history of myocardial infarction (MI) without Q-wave, 100% had hypertension, 34.3% had dyslipidemia (high cholesterol levels >100 mg/dL), and 37.6% had a history of COVID-19. The duration of T2DM ranged from 7.27±3.7 years, and the duration of IHD was 8.94±5.72 years.

The study included a hospital stay (9–10 days) and follow-up periods of ambulatory care after the patient's discharge from the hospital (24 months). During the hospital stay, data on medical history, clinical and hemodynamic parameters, and electrocardiogram (ECG) were recorded. Laboratory tests included lipid profile, carbohydrate profile, electrolytes, C-reactive protein (CRP) using the biochemical method on the COBAS C 311 analyzer with closed system reagents, vitamin D levels in blood, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) using the immunoassay method on the COBAS E 411 analyzer. The metabolic index (MI) was used to indirectly assess insulin resistance, with the formula MI = [fasting triglycerides (mg/dL) / fasting HDL cholesterol (mg/dL)]. The higher the MI value, the more pronounced the insulin resistance. Echocardiographic examination was performed using the Acuson S2000 ultrasound system (Siemens, Germany) to assess diastolic dysfunction of the left ventricle (DDLV) in patients with preserved LVEF [15] [16], using the criteria specified in the 2016 EACVI recommendations [17].

All patients received antiplatelet therapy, beta-blockers, nitrates, calcium channel antagonists, renin-angiotensin-aldosterone system (RAAS) inhibitors, and statins. To manage glucose metabolism, all patients were taking metformin and incretins.

At the end of the two-year observation period, patients were divided into two groups:

- Favorable course (Group I, n=116, 89.3%).
- Unfavorable course (Group II, n=14, 10.7%).

Unfavorable outcomes included:

- Fatal myocardial infarction (FMI)
- Non-fatal myocardial infarction (NMI)
- Stroke
- Percutaneous coronary intervention (PCI)
- Coronary artery bypass grafting (CABG)
- Sudden death
- Rehospitalization due to emergency reasons.

RESULTS

The baseline characteristics of the included patients are presented in Table 1. The study population was balanced in terms of gender (p=0.130), duration of diabetes (p=0.878), ischemic heart disease (p=0.693), and age (p=0.607). All patients were receiving statins (100%), beta-blockers, and medications affecting the renin-angiotensin-aldosterone system (100%). However, patients differed in terms of body mass index (BMI, p=0.022), history of myocardial infarction (p=0.001), percutaneous coronary intervention (p=0.001), and coronary artery bypass grafting (p=0.001).

Table 1
Comparative characteristics of the compared subgroups of patients with coronary heart disease and type 2 diabetes mellitus with preserved ejection fraction (EF) in absolute values (%)

Options	Favorable outcomes, n=116	Adverse outcomes, n=14	p
Age	64.12±8.71	62.88±8.80	0.607
Gender (women)	51.33% (n=58)	62.50% (n=10)	0.130
IHD experience, year	8.69±0.49	9.28±0.56	0.693
SD experience, year	7.30±3.92	7.89±3.39	0.878
BMI	32.91±6.46	30.00±5.96	0.022
COVID-19, medical history	37.72% (n=43)	37.50% (n=6)	0.847
AF, medical history	6.14% (n=7)	0.00% (n=0)	
AMI, medical history	36.84% (n=42)	81.25% (n=13)	0.001
PCI, medical history	28.95% (n=33)	68.75% (n=11)	0.001
CABG, medical history	3.51% (n=4)	31.25% (n=5)	0.001
Stroke, medical history	6.14% (n=7)	0.00% (n=0)	

One of the practical end goals of this study involved constructing a mathematical model that, with a high probability of error-free prediction, would enable the identification of patients with concomitant type 2 diabetes mellitus (T2DM) who are at risk of adverse outcomes, i.e., individuals in need of mandatory consideration for more aggressive medical therapy. The model development comprised the following stages of data analysis:

Inter-group comparative assessment of baseline indicators to identify features that differentiate patients with well-controlled T2DM and poorly controlled T2DM with corresponding long-term outcomes, and evaluation of the dynamics of the analyzed features during the study observation period;

Identification of the most informative features that differentiate patients with well-controlled T2DM and poorly controlled T2DM with corresponding long-term (2-year) outcomes;

Construction of a mathematical model for recognizing patients with well-controlled T2DM and poorly controlled T2DM with corresponding long-term disease outcomes under medical therapy.

The first stage of this analysis, related to the identification of features differentiating patients with favorable and unfavorable outcomes, is reflected in Table 2.

These data were utilized to create mathematical models that predict the effectiveness of standard therapy as a component of optimizing drug therapy for patients with coronary heart disease and type 2 diabetes with preserved left ventricular ejection fraction. To achieve this, potentially informative features were selected that differentiate individuals with and without type 2 diabetes who have coronary heart disease. According to the principles of formal logic and pattern recognition theory, indicators that are most commonly found among individuals with type 2 diabetes and least commonly found among those without type 2 diabetes will be attributed to these features, and vice versa.

The identified parameters that demonstrated a high frequency of occurrence in the group of patients with coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) with preserved left ventricular ejection fraction (LVEF) and HbA1c >8.5% were as follows: OHB ≥142 mg/dL (χ^2=74.5; P=0.000); TG >163 mg/dL (χ^2=27.15; P=0.000); MI >3.52 mg/dL; vitamin D <14.9 ng/mL (χ^2=72.038; P=0.000); and MNUP >1984 pg/mL (χ^2=52.80; P=0.000).

Table 2
Comparative analysis of outcome parameters based on frequency of occurrence in the analyzed subgroups of patients with coronary artery disease and type 2 diabetes mellitus with preserved ejection fraction (abs %)

Indicators	Visit	Favorable outcomes, n=116	Unfavorable outcomes, n=14	Kruskal – Wallis P#
HbA1c, %	1	8.79±2.31	9.65±3.11	0.494
	2	7.93±1.87	8.57±2.12	0.249
TC, mg/dl	1	182.25±51.72	186.62±89.36	0.385
	2	168.20±50.45	172.25±76.32	0.573
MI, mg/dl	1	7.58±7.67	10.98±11.64	0.167
	2	5.74±4.19	20.40±36.09	0.074
Urinary acid, mg/dl	1	6.36±1.90	6.29±2.14	0.79
	2	5.93±1.72	5.90±1.17	0.924
Vitamin D, ng/ml	1	18.27±12.07	24.72±13.11	0.021
	2	25.59±14.41	27.88±10.18	0.245
NTproBNP, pg/ml	1	1848.12±1112.48	2287.60±829.62	0.05
	2	1507.74±889.79	1670.44±829.00	0.04
Sodium, mmol/l	1	149.4.98±4.98	147.69±5.80	0.85
	2	150.63±5.63	148.25±5.08	0.084
eGFR, ml/min/1.73 m^2	1	66.31±17.92	76.57±19.94	0.071
	2	68.86±20.0	68.86±22.7	0.622
LVEF, %	1	59.19±7.15	57.20±7.04	0.294
	2	58.36±7.44	53.07±9.43	0.043
LVmass, g	1	255.05±63.04	282.25±74.29	0.151
	2	245.04±65.21	249.56±68.91	0.699
E/A	1	0.84±0.30	0.73±0.19	0.083
	2	0.82±0.27	0.80±0.17	0.845
DTE	1	194.86±42.1	211.19±27.5	0.104
	2	191.33±37.0	202.69±24.2	0.316
e' septal	1	7.04±1.17	6.62±0.98	0.152
	2	7.23±0.99	7.09±0.75	0.473

Notes: HbA1c – Glycated hemoglobin; TC – Total cholesterol; MI – Metabolic index; NT-proBNP – Brain natriuretic peptide; eGFR – Calculated glomerular filtration rate; LVEF – Left ventricular ejection fraction; LVmass – Left ventricular mass; E/A – ratio of the early (E) to late (A) ventricular filling velocities; DTE – Time to peak; e' septal – Septal velocity.

It was determined that the risk of adverse events (the edge of the indicator) is significantly higher at the LVEF level <57% (χ^2=13.846, P=0.000), with increased left ventricular mass index (LVMI) >309 g (χ^2=65.54, P=0.000) and an increased E/A ratio >0.69 (χ^2=41.17, P=0.000). The analysis of the frequency of occurrence of diastolic dysfunction with unfavorable outcomes was 2.5 times higher than with favorable outcomes, respectively, but it was not statistically significant (χ^2=0.556; P=0.456) in both the outcome and observation stages (χ^2=0.020; P=0.889).

Based on the selected features for each patient, taking into account the basic therapy and antihyperglycemic drugs, logistic function equations were constructed using all control data in complex combinations. A single algorithm was used to form the models.

Based on the results obtained, a software product was created, "Forecasting the Risk of Adverse Cardiological Complications in Patients with CHD, Hypertension, and Type 2

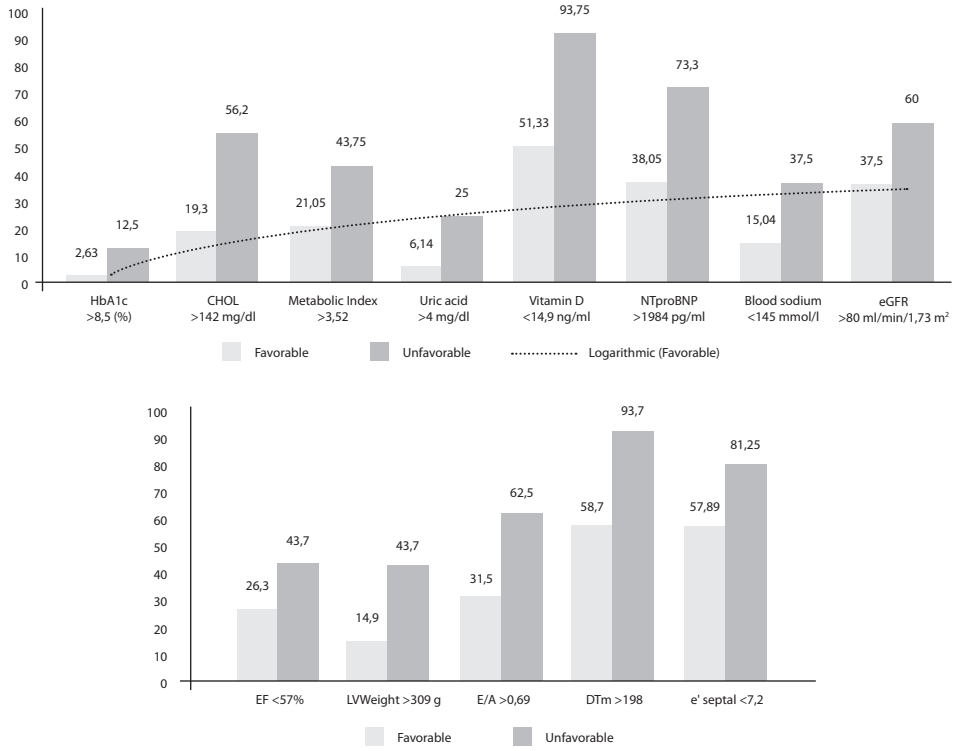

Fig. 1. Frequency of laboratory hemodynamic signs discriminating patients with coronary heart disease and type 2 diabetes mellitus with different outcomes

Notes: HbA1c – Glycated hemoglobin, CHOL – Total cholesterol, MI – Metabolic index, NT-proBNP – Brain natriuretic peptide, eGFR – Calculated glomerular filtration rate, BMI – Body mass index; LVEF – Left ventricular ejection fraction, DTm – Time to peak, e' septal – Septal velocity.

Diabetes Mellitus" (DGU 23738) [18], which is an algorithm that can identify patients with an unfavorable (lethal) outcome.

According to the methodology requirements, the evaluation of the effectiveness (informativeness) of the developed model requires testing on a separate independent sample of patients (the so-called "examination group") to confirm the results obtained in the so-called "training group". This sample (i.e., the "examination group") was formed based on the emergency cardiology department (EC-1) of the Republican Specialized Scientific-Practical Medical Center of Cardiology of the Ministry of Health of the Republic of Uzbekistan under observation of the scientific department of laboratory AMI (n=150), comparable to the "training group". The data were selected during a 1-year observation period.

There were no significant differences in the nosological characteristics between the "training" and "examination" groups, except for some predominance of patients with stable angina pectoris FC 2 in the training group (Table 3).

Table 3
Comparative characteristics of the risk factor profile in the exam group and the learning group (m±δ)

Index	Training group n=130 (m±δ)	"Exam" group n=150 (m±δ)	P # Kruskal – Wallis
Age	63.9±8.8	61.8±6.5	0.48
Husband/wives	66 (48.9%) / 69 (51.1%)	74 (49.4%) / 76 (50.6%)	0.81/0.69
Weight, cm	88.7±16.7	86.2±14.9	0.34
Height, kg	164.4±12.5	167.1±11.8	0.27
BMI	32.6±6.4	30.9±5.7	0.15
St St FC II	7 (4.7%)	1 (0.66%)	0.02
St St FC III	123 (91.1%)	149 (99.4%)	0.02
COVID-19, medical history	49 (36.3%)	58 (38.6%)	0.91
IHD experience, year	9.69±0.49	12.44±0.72	0.11
SD experience, year	7.3±3.9	7.5±4.2	0.84
AF/T, medical history	8 (5.9%)	5 (3.3%)	0.26
AMI, medical history	59 (43.7%)	63 (42.0%)	0.57
PCI, medical history	44 (32.6%)	48 (32.0%)	0.74
CABG, medical history	10 (7.4%)	11 (7.3%)	0.91

Note: Differences are significant at p≤0.05.

The structure of risk factors for an unfavorable course in patients of this sample (Table 3) was as follows: a history of myocardial infarction (MI) was present in 63 (42.0%) patients, concomitant arterial hypertension (AH) was detected in 73 (48.4%), dyslipidemia in 118 (76.56%), and 70 (47%) were smokers. Elderly patients (65 years and older) accounted for 31 (20.31%) of the sample, 35 (23.44%) suffered from obesity (BMI >30), and left ventricular hypertrophy was documented in 57 (37.5%) patients.

Uncontrolled integral hemodynamic parameters upon admission to the hospital, namely, high systolic blood pressure (SBP >160 mmHg) and diastolic blood pressure (DBP >100 mmHg), as well as tachycardia (heart rate >90 bpm), were found in 47 (31.25%), 52 (34.38%), and 66 (43.75%) patients, respectively.

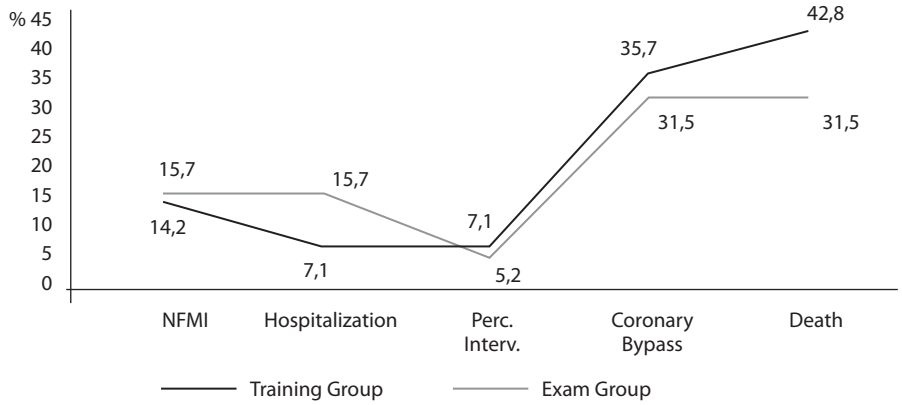

Fig. 2. Distribution of adverse outcomes in patients with coronary heart disease and type 2 diabetes with preserved left ventricular ejection fraction, used to validate the algorithm

The distribution of recorded adverse outcomes was as follows: death 31.5% (n=6), non-fatal recurrent MI 15.7% (n=3), readmission 15.7% (n=3), stroke 5.2% (n=1), and congestive heart failure 31.5% (n=6).

It is worth noting that the exam group did not differ from the learning group in terms of the factors that led to an unfavorable outcome (as shown in Table 4) [19]. This can be attributed to the use of identical inclusion and exclusion criteria, which indicates that the exam group was appropriately formed. During the observation period, 19 patients were classified as having an unfavorable outcome, while 131 individuals remained in the favorable outcome subgroup.

For evaluating the validity of the developed algorithm and diagnostic tables in patients from the examination group, the structure of predictive conclusions obtained using the

Table 4
Comparative analysis of risk factor profile in groups with adverse outcomes (exam group and education group)

Signs	"Training" group Negative forecast, n=14 (%)	"Exam" group Unfavorable forecast, n=19 (%)	χ^2	P#
HbA1c >8.5 (%)	2 (12.50%)	3 (15.79%)	0.014	0.906
TC >142 mg/dl	9 (56.25%)	11 (57.89%)	0.138	0.710
Metabolic index (MI) (TG/HDL) >3.52	6 (43.75%)	9 (47.37%)	0.066	0.797
Urinary acid >4 mg/dl	4 (25.00%)	5 (26.32%)	0.021	0.886
Vitamin D <14.9 ng/ml	13 (93.75%)	18 (94.74%)	0.049	0.824
NTproBNP >1984 pg/ml	10 (73.33%)	14 (73.68%)	0.021	0.886
Blood sodium <145 mmol/l	5 (37.50%)	7 (36.84%)	2,460	0.117
eGFR >80 ml/min/1.73 m^2	9 (60.00%)	12 (63.16%)	0.004	0.947
EF <57%	6 (43.75%)	11 (57.89%)	0.732	0.393
LVmass >309 g	6 (43.75%)	8 (42.11%)	0.002	0.966
E/A >0.69	9 (62.50%)	12 (63.16%)	0.004	0.947
DTE >198	13 (93.75%	17 (89.47%)	0.114	0.736
e' septal <7.2	11 (81.25%)	16 (84.21%)	0.171	0.680

Table 5
Sequence of calculations for the informativeness (validity) parameters of the algorithm for predicting the course of coronary heart disease using a four-field table and standard formulas [20]

		Number of reference conclusions on BT IHD		Calculating the algorithm's predictive value (PV)	
		Present	Absent		
Number of forecast conclusions based on the algorithm	BT	a=103 (68.7%)	b=21 (14%)	(a+b)=124	+PV=a/a+b)=83.0%
	NBT	c=19 (12.5%)	d=7 (4.6%)	(c+d)=26	–PV=c/(c+d)=73.0%
Progress of algorithm sensitivity and specificity calculations (Sen, Spec)		(a+c)=122	(b+d)=28		
		Sen=a/ (a+c)*100%=84.4%	Spec =b/ (b+d)*100%=75%		

Note: Sen refers to sensitivity, Spec refers to specificity, +PV and PV– refer to the positive and negative predictive value of predicting coronary heart disease (CHD) using biomarkers.

developed algorithm was compared with the structure of evaluative conclusions of actual outcomes, which were obtained through observing patients for a period of one year.

The ratio (frequency) of favorable and unfavorable outcomes according to the predictive conclusions is shown in Table 5.

Following the evaluation of predictive conclusions using an algorithm for distributing diabetic patients with ischemic heart disease (IHD) and type 2 diabetes mellitus (T2DM), the following results were obtained:

Prediction for patients with stable angina (SA) was 124 (82.6%).

Prediction for patients with unfavorable outcomes (including patients not recognized by the algorithm) was 26 (17.3%). The number of patients not recognized by the algorithm was 12 (8.0%).

Analysis showed that predictive conclusions (determined using the developed algorithm) regarding the development of IHD in combination with T2DM and preserved left ventricular function (LVF) matched the actual (reference) results in 124 (83.0%) patients.

Calculated performance metrics (validity) according to standard formulas (Table 5) for the algorithm were as follows: sensitivity of the predictive algorithm was 84.4%, specificity was 75.0%. The predictive value of conclusions regarding SA was 83.2%, regarding non-SA IHD was 72.7%.

■ DISCUSSION

Currently, there is an increase in two global non-infectious epidemics, such as chronic kidney disease (CKD) and T2DM [21]. The relationship between T2DM and cardiovascular disease (CVD) is non-linear and represents a multi-factorial problem. A one-sided, glucocentric view of managing this category of patients by endocrinologists is outdated, and a personalized multi-factorial approach is now in the forefront. Diabetic cardiomyopathy, considered as a separate nosological entity, plays a significant role in the development and progression of CVD in patients with T2DM [22, 23].

We have conducted an assessment of the dynamics of glycated hemoglobin (HbA1c) with the identification of risk stratification markers for developing a model (software product) predicting a two-year risk of the first cardiovascular event in patients with IHD and T2DM (by inputting specific risk factors).

The identified markers in the group of patients with coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) with preserved left ventricular ejection fraction (LVEF) at HbA1c>8.5% were as follows: glucose levels (OGTT) ≥142 mg/dL (χ^2=74.5; P=0.000); triglycerides (TG) >163 mg/dL and above (χ^2=27.15; P=0.000); microalbuminuria (MI) >3.52 mg/dL, vitamin D <14.9 ng/mL (χ^2=72.038; P=0.000); N-terminal prohormone of brain natriuretic peptide (NT-proBNP) >1984 pg/mL (χ^2=52.80; P=0.000). In patients with preserved LVEF, a criterion for increased risk of adverse events was determined to be <57% (χ^2=13.846, P=0.000), increased left ventricular mass (LVM) >309 g (χ^2=65.54, P=0.000), and E/A ratio >0.69 (χ^2=41.17, P=0.000). In addition, there was a trend towards a higher frequency of occurrence of major adverse cardiac events (MACE) in unfavorable outcomes (2.5 times higher, as opposed to 1.6 times in favorable outcomes) [24]. In addition to the mentioned signs, baseline therapy and antihyperglycemic agents were taken into account.

The effectiveness of the logistic regression model was measured using the C-Index (also known as ROC AUC) [25–28]. Theoretically, AUC varies from 0 to 1.0, with higher

values indicating better model quality. The developed algorithm has a C-Index of 0.953, which characterizes the model as excellent.

Thus, the developed algorithm allows for a high probability of correct prediction and identifies patients with IHD and T2DM with preserved LVF and unfavorable outcomes [29, 30], enabling timely and appropriate treatment recommendations, including invasive interventions, or limiting treatment to medication alone when invasive methods are not possible or not advisable. Based on the obtained results, a software product "Risk of Developing Unfavorable Cardiological Outcomes in Patients with IHD, T2DM, and Diabetic Kidney Disease [30]" DGU 23738 was created, which represents an algorithm for identifying patients with unfavorable (lethal) outcomes.

The following factors have the greatest predictive value in terms of unfavorable disease progression in patients with coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) with preserved left ventricular ejection fraction (LVEF): elevated levels of total cholesterol ≥142 mg/dL (χ^2=74.5; P=0.000), triglycerides >163 mg/dL (χ^2=27.15; P=0.000), metabolic index >3.52 mg/dL, brain natriuretic peptide >1984 pg/mL (χ^2=52.80; P=0.000), as well as decreased levels of vitamin D <14.9 ng/mL (χ^2=72.038; P=0.000).

An algorithm has been developed that allows for the accurate identification of patients with CHD and T2DM with preserved LVEF who have an unfavorable disease progression. This algorithm can recommend more aggressive treatment and possibly invasive interventions when appropriate, while limiting treatment to medication only when invasive methods are not feasible or appropriate.

A software product called "Risk Prediction of Adverse Cardiac Complications in Patients with CHD, Hypertension, and Type 2 Diabetes Mellitus" (DGU 23738) has been created. This algorithm can identify patients with an unfavorable (lethal) outcome.

■ CONCLUSIONS

1. The following factors have the greatest predictive value in terms of unfavorable disease progression in patients with coronary heart disease (CHD) and type 2 diabetes mellitus (T2DM) with preserved left ventricular ejection fraction (LVEF): elevated levels of total cholesterol ≥142 mg/dL (χ^2=74.5; P=0.000), triglycerides >163 mg/dL (χ^2=27.15; P=0.000), metabolic index >3.52 mg/dL, brain natriuretic peptide >1984 pg/mL (χ^2=52.80; P=0.000), as well as decreased levels of vitamin D <14.9 ng/mL (χ^2=72.038; P=0.000).
2. An algorithm has been developed that allows for the accurate identification of patients with CHD and T2DM with preserved LVEF who have an unfavorable disease progression. This algorithm can recommend more aggressive treatment and possibly invasive interventions when appropriate, while limiting treatment to medication only when invasive methods are not feasible or appropriate.
3. A software product called "Risk Prediction of Adverse Cardiac Complications in Patients with CHD, Hypertension, and Type 2 Diabetes Mellitus" (DGU 23738) has been created. This algorithm can identify patients with an unfavorable (lethal) outcome.

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