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## ABSTRACT

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## THE ROLE OF GAS6 IN LEFT VENTRICLE REMODELLING IN PATIENTS WITH CHRONIC HEART FAILURE OF ISCHEMIC ORIGIN AND CONCOMITANT TYPE 2 DIABETES MELLITUS AND OBESITY

**Introduction.** Chronic heart failure (CHF) remains a global pandemic, and the prognosis is particularly poor for patients with ischaemic CHF against a background of concomitant type 2 diabetes mellitus (T2DM) and obesity. A key process determining the progression of CHF is pathological remodelling of the left ventricle (LV). The protein GAS6 (Growth Arrest-Specific 6), a ligand of the TAM family of receptors, is involved in the regulation of inflammation, fibrosis and proliferation. The specific role of the GAS6/TAM system in the complex process of LV remodelling in this high-risk cohort of patients remains poorly understood. The relevance of the work is consistent with UN Sustainable Development Goal No. 3.

The **aim** is to study the role of GAS6 protein as a potential biomarker and pathophysiological mediator of left ventricle remodelling in patients with chronic heart failure at the background of coronary artery disease with concomitant type 2 diabetes mellitus and obesity.

**Materials and methods.** The study included 75 patients with CHF against the background of coronary artery disease (CAD), T2DM and obesity. The inclusion criteria were age over 18 years, presence of CAD with signs of CHF, T2DM, presence of overweight/obesity of 1-3 degrees or their absence, and written consent. Exclusion criteria included acute and oncological diseases, chronic renal failure with GFR < 35 ml/min/1.73 m<sup>2</sup>, and acute coronary/cerebral events within 6 months. Patients were divided into 2 subgroups: subgroup 1 – GAS6 < 31.64 ng/ml (n=36), subgroup 2 – GAS6 > 31.64 ng/ml (n=39). Echocardiography was performed, including assessment of ventricular-arterial coupling (VAC) as the ratio of effective arterial elasticity to end-systolic elasticity of the LV (Ea/Es). GAS6 levels were determined by enzyme-linked immunosorbent assay (ELISA).

**Results and Discussion.** The study demonstrated that structural and functional changes in the myocardium were most unfavourable in patients with higher GAS6 levels (subgroup 2). The following statistically significant differences ( $p < 0.05$ ) were found in the 2nd subgroup compared to the 1st: end-systolic volume was 42.47% higher, and end-diastolic volume was 28.84% higher; LV ejection fraction was significantly lower by 25.52%; LV myocardial mass and LV myocardial mass index were higher by 25.71% and 12.23%, respectively; the Ea/Es ratio was significantly higher by 35.09%, indicating severe cardiovascular dysfunction. Correlation analysis confirmed direct, statistically significant associations between GAS6 levels and most remodelling parameters, including a strong direct association with end-systolic dimension ( $r = 0.71$ ).

**Conclusions.** GAS6 protein levels  $> 31.64$  ng/ml are associated with a more pronounced dilated type of left ventricular remodelling, significantly reduced pumping function, and significant ventricular-arterial coupling impairment, emphasising its role as a potential marker of unfavourable chronic heart failure progression in conditions of polymorbidity.

**Keywords:** GAS6, left ventricular remodelling, chronic heart failure, coronary artery disease, type 2 diabetes mellitus, obesity, ventricular-arterial coupling.

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## РЕЗЮМЕ

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## РОЛЬ GAS6 У РЕМОДЕЛЮВАННІ ЛІВОГО ШЛУНОЧКА У ХВОРИХ З ХРОНІЧНОЮ СЕРЦЕВОЮ НЕДОСТАТНІСТЮ ІШЕМІЧНОГО ГЕНЕЗУ НА ТЛІ СУПУТНЬОГО ЦУКРОВОГО ДІАБЕТУ 2 ТИПУ ТА ОЖИРІННЯ

**Вступ.** Хронічна серцева недостатність (ХСН) залишається глобальною пандемією, а особливо обтяжливим є прогноз для пацієнтів з ХСН ішемічного генезу на тлі супутнього цукрового діабету (ЦД) 2 типу та ожиріння. Ключовим процесом, що визначає прогресування ХСН, є патологічне ремоделювання лівого шлуночка (ЛШ). Протеїн GAS6 (Growth Arrest-Specific 6), ліганд рецепторів родини TAM, залучений до регуляції запалення, фіброзу та проліферації. Конкретна роль системи GAS6/TAM у комплексному процесі ремоделювання ЛШ у цій високоризиковій когорті пацієнтів залишається недостатньо вивченою.

**Мета** – вивчити роль протеїну GAS6 як потенційного біомаркера та патофізіологічного медіатора ремоделювання ЛШ у хворих з ХСН, що виникла на тлі ІХС з супутнім ЦД 2 типу та ожирінням.

**Матеріали та методи.** До дослідження було залучено 75 пацієнтів із ХСН на тлі ішемічної хвороби серця (ІХС), ЦД 2 типу й ожиріння. Критеріями включення були вік старше 18 років, наявність ІХС з ознаками ХСН, ЦД 2 типу, наявність надмірної маси тіла/ожиріння 1-3 ст. або їх відсутність, та письмова згода. Критерії виключення включали гострі та онкологічні захворювання, хронічна ниркова недостатність з ШКФ  $< 35$  мл/хв/1,73 м<sup>2</sup> та гострі коронарні/мозкові події протягом 6 місяців.

Пацієнтів розподілено на 2 підгрупи: 1-а підгрупа – GAS6 < 31,64 нг/мл (n=36), 2-а підгрупа – GAS6 > 31,64 нг/мл (n=39). Проводилось ехокардіографічне дослідження, включаючи оцінку серцево-судинного сполучення як співвідношення ефективної артеріальної еластичності до кінцево-систолическої еластичності ЛШ (Ea/Es). Рівень GAS6 визначали імуноферментним методом (ELISA).

**Результати та обговорення.** Проведене дослідження продемонструвало, що структурно-функціональні зміни міокарда були найбільш несприятливими у пацієнтів з вищим рівнем GAS6 (2-га підгрупа). Було виявлено наступні статистично значущі відмінності (p<0,05) у 2-й підгрупі порівняно з 1-ю: кінцево-систолический об'єм був більшим на 42,47 %, а кінцево-діастолічний об'єм – на 28,84 %; фракція викиду ЛШ була суттєво нижчою на 25,52 %; маса міокарда ЛШ та індекс маси міокарда ЛШ були більшими на 25,71 % та 12,23 % відповідно; співвідношення Ea/Es було значно вищим на 35,09 %, що свідчить про виражену дисфункцію серцево-судинного сполучення. Кореляційний аналіз підтвердив прямі, статистично значущі зв'язки між рівнем GAS6 та більшістю параметрів ремоделювання, включаючи сильний прямий зв'язок із кінцево-систолическим розміром (r=0,71).

**Висновки.** Рівень протеїну GAS6 > 31,64 нг/мл асоціюється з більш вираженим дилатаційним типом ремоделювання лівого шлуночка, значно зниженою насосною функцією та суттєвим порушенням серцево-судинного сполучення, підкреслюючи його роль як потенційного маркера несприятливого перебігу хронічної серцевої недостатності в умовах поліморбідності.

**Ключові слова:** GAS6, ремоделювання лівого шлуночка, хронічна серцева недостатність, ішемічна хвороба серця, цукровий діабет 2 типу, ожиріння, серцево-судинне сполучення.

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## INTRODUCTION

Chronic heart failure (CHF) is a global pandemic that significantly affects quality of life and is one of the leading causes of death worldwide [1, 2]. The prognosis for patients with ischaemic CHF is particularly poor, as coronary artery disease (CAD) is the most common cause of CHF [3, 4]. The key pathophysiological process determining the progression of CHF is left ventricular (LV) remodelling – a complex set of structural, functional and molecular changes in the myocardium, leading to chamber dilatation, wall hypertrophy and subsequent deterioration of pumping function [5, 6].

The situation is significantly complicated by the presence of concomitant pathologies, in particular type 2 diabetes mellitus (T2DM) and obesity, which are powerful risk factors for the development and

progression of CHF [7]. T2DM and obesity contribute to microvascular dysfunction, chronic systemic inflammation, and insulin resistance, which exacerbates ischaemic myocardial damage and accelerates its remodelling [8, 9]. Thus, the cohort of patients with ischaemic CHF against the background of T2DM and obesity represents a clinical challenge that requires the search for new, more accurate diagnostic and prognostic markers, as well as targeted treatment strategies.

In recent years, considerable attention has been drawn to the role of GAS6 (Growth Arrest-Specific 6) protein, a vitamin K-dependent protein that functions as a ligand for the Tyro3, Axl, and MerTK (TAM) family of receptors [10]. The GAS6/TAM receptor system is involved in the regulation of numerous cellular processes, including cell survival, phagocytosis, adhesion and, particularly important in the context of

cardiovascular pathology, inflammation, fibrosis and smooth muscle cell proliferation [11].

Numerous studies confirm the link between impaired GAS6 expression and the development of atherosclerosis, thrombosis and arterial hypertension. It has been shown that GAS6 can have both a protective (by inhibiting cardiomyocyte apoptosis) and a profibrotic effect (by activating fibroblasts and enhancing vascular remodelling) [12, 13].

GAS6 levels have been found to be associated with insulin resistance, dyslipidaemia and microvascular complications of T2DM, indicating its potential involvement in the pathogenesis of diabetic cardiomyopathy, which is also a component of CHF in patients with T2DM [14].

Despite the accumulated data, the specific role of the GAS6/TAM receptor system in the complex process of LV remodelling in patients with ischaemic CHF complicated by comorbid T2DM and obesity remains insufficiently studied. Existing studies often focus on a single type of pathology, ignoring the synergistic effect of comorbidities, which significantly complicates the interpretation of the results obtained and their transfer into clinical practice [15]. There is a critical lack of data on how GAS6 levels correlate with the dynamics of structural and functional indicators of the LV, as well as whether GAS6 can serve as an integral marker of the risk of adverse remodelling in this high-risk group of patients.

The relevance of the work carried out is consistent with the UN Sustainable Development Goals (SDGs), in particular SDG No. 3. By identifying GAS6 as an integral risk biomarker and potential therapeutic target, the study lays the foundation for improving early risk stratification and developing targeted treatment approaches, which are critical for slowing the progression of CHF and effectively reducing premature mortality from non-communicable diseases [16].

**Objective:** to study the role of GAS6 protein as a potential biomarker and pathophysiological mediator of left ventricular remodelling in patients with chronic heart failure against the background of coronary artery disease with concomitant type 2 diabetes mellitus and obesity.

#### MATERIALS AND METHODS

The study involved 75 patients with CHF against the background of IHD, type 2 diabetes mellitus and obesity, who were treated in the cardiology department of the Municipal Clinical Hospital No. 27 of the Kharkiv City Council. Patients were divided into two subgroups depending on the mean GAS6 value: subgroup 1 included 36 patients with a GAS6 level <31.64 ng/ml, and subgroup 2 included 39 patients with a GAS6 level >31.64 ng/ml. All subjects were matched

for mean age and gender, which ensured the accuracy of the subsequent comparative analysis.

The standard patient examination procedure included clinical and laboratory-instrumental examinations in accordance with the recommendations of the European Society of Cardiology (ESC) 2021, the American Diabetes Association 2019, and the International Diabetes Federation 2018. Laboratory and instrumental examinations were conducted at the Municipal Clinical Hospital No. 27 of the Kharkiv City Council and the Central Research Laboratory of the Kharkiv National Medical University.

Verification of the diagnosis of CAD was carried out in accordance with the standards of the ESC, the Association of Cardiologists of Ukraine, and the protocols of the Ministry of Health of Ukraine (Unified Clinical Protocol for Primary, Secondary (Specialised) and Tertiary (Highly Specialised) Medical Care «Stable Ischemic Heart Disease» dated 23 December 2021 No. 2857). The presence of CHF was determined according to the classification of the Working Group on Heart Failure of the Ukrainian Scientific Society of Cardiologists, and the functional class was assessed according to the criteria of the New York Heart Association (NYHA). The diagnosis of T2DM was established according to the criteria of the unified protocol for the provision of medical care «Diabetes mellitus» (Order of the Ministry of Health of Ukraine dated 24 July 2024 No. 1300).

Patients underwent transthoracic echocardiography in accordance with generally accepted standards (Feigenbaum H., 1999) using a RADMIR (Ultima PRO 30) ultrasound machine (Kharkiv, Ukraine). Particular attention was paid to the assessment of ventricular-arterial coupling (VAC), which is an important indicator of myocardial efficiency and interaction between the LV and the arterial system. For this purpose, the CVC coefficient was calculated as the ratio of effective arterial elasticity (Ea) to end-systolic elasticity of the LV (Es):  $VAC = Ea/Es$ . The Ea and Es indices were calculated non-invasively based on echocardiographic data, which allowed us to assess the interaction of the LV volume-pressure curve with arterial load capacity.

$$Ea = ESP/SV,$$

where ESP is the end-systolic pressure, SV is the stroke volume

ESP was calculated using the formula:

$$ESP = 0.9 \times SBP$$

where SBP is systolic blood pressure.

$$Es = ESP/ESV$$

Where ESP is end-systolic pressure, ESV is end-diastolic volume

The Ea/Es ratio within the range of 0.6 to 1.2 under physiological conditions was taken as an indicator

reflecting the optimal interaction between the arterial system and the LV.

To determine the level of GAS6 (ng/ml), an immunoenzymatic method was used with the Human Growth arrest-specific protein 6 (GAS6) ELISA kit (Cusabio, USA). The study was conducted on a Labline-90 immunoenzymatic analyser (Austria Lab Technologies, Austria) at the biochemical department of the Central Research Laboratory of Kharkiv National Medical University of the Ministry of Health of Ukraine in accordance with the instructions accompanying the kit.

All patients involved in the study received optimal medical therapy for CHF in accordance with the current recommendations of the European Society of Cardiology, which included ACE inhibitors or ARBs (or ARNIs),  $\beta$ -blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors. Carbohydrate metabolism was corrected using modern hypoglycaemic drugs (metformin and SGLT2 inhibitors). Statistical analysis of baseline characteristics revealed no significant differences between the groups in terms of systolic and diastolic blood pressure, duration of CHF history, and degree of diabetes compensation (HbA1c level), which ensured high comparability of the groups and minimised the impact of these factors on the study results.

The results of the study were statistically processed using parametric analysis methods. The accumulation, correction, systematisation of the initial information and visualisation of the results obtained were carried out in Microsoft Office Excel 2010 spreadsheets. The

description and comparison of quantitative indicators were performed taking into account the distribution, the normality of which was assessed using the Kolmogorov-Smirnov criterion.

When the normality of the distribution was confirmed, the quantitative data were presented as the arithmetic mean (M) and the standard error of the mean (m). Fisher's F-test was used to assess the significance of the differences between the indicators of the studied groups. The degree of correlation between the studied samples was determined using Spearman's correlation coefficient (r). The critical level of significance for testing statistical hypotheses was set at  $p < 0.05$ .

The studies were approved by the Ethics and Bioethics Committee of the Kharkiv National Medical University, as indicated in Protocol No. 2 dated 12 October 2022, and conducted with the written consent of the participants and in accordance with the principles of bioethics set out in the Helsinki Declaration «Ethical Principles for Medical Research Involving Human Subjects» and the "Universal Declaration on Bioethics and Human Rights (UNESCO)".

## RESULTS AND DISCUSSION

The study demonstrated pronounced changes in the structural and functional state of the LV myocardium in patients with ischemic CHF, with these changes being most unfavourable in patients with GAS6 levels  $< 31.64$  ng/ml (Table 1). When comparing the structural and functional parameters of the myocardium of the two subgroups, the following statistically significant differences were found ( $p < 0.05$ ).

**Table 1**

**Structural and functional parameters of the myocardium in patients with chronic heart failure against the background of coronary artery disease with concomitant type 2 diabetes mellitus and obesity, depending on the level of GAS6**

Indicator, Unit Measurement	Observation groups		p
	1 subgroup GAS6<31.64 (n=36)	Subgroup 2 GAS6>31.64 (n=39)	
ESD, cm	4.46	5.26±0.16	<0.05
EDD, cm	6.51±0.18	6.61±0.28	>0.05
LWPWd, cm	1.29±0.01	1.29±0.03	>0.05
IVS, cm	1.25±0.01	1.25±0.03	>0.05
RWT	0.48±0.0	0.48±0.02	>0.05
LVMi, g/cm <sup>2</sup>	161.75±9.63	181.53±10.16	<0.05
LVM, g	278.03±12.26	349.71±9.44	<0.05
ESV, ml	83.78±11.12	119.36±9.83	<0.05
EDV, ml	167.94±9.53	216.38±8.67	<0.05
LVEF, %	48.91±3.09	36.43±4.05	<0.05
LA, cm	4.48±0.10	5.38±0.08	<0.05
RA cm	3.57±0.04	4.43±0.06	<0.05
Ea/Es	1.71±0.04	2.31±0.05	<0.05

Patients with low GAS6 levels (subgroup 1) had significantly worse remodelling parameters, indicating marked LV cavity dilatation and poorer systolic function. In subgroup 1, end-systolic volume (ESV) was 42.47% lower, EDV was 28.84% lower, and end-systolic dimension (ESD) was 17.94% smaller compared to the same indicators in subgroup 2. The left ventricular ejection fraction (LVEF) was significantly lower in the second subgroup – by 25.52%, reflecting a more significant impairment of the heart's pumping function in patients with lower GAS6 values. The left ventricular myocardial mass (LVM) was 25.71% higher in subgroup 2, and the left ventricular myocardial mass index (LVMI) exceeded that in subgroup 1 by 12.23%. Regarding the indicators reflecting the size of the atria and the SSS, it was found that the size of the left atrium (LA) was significantly larger in the second subgroup – by 20.09% compared to the first subgroup, and the size of the right atrium (RA) exceeded that in the first subgroup by 24.09%. The ratio of effective arterial elasticity to end-systolic elasticity of the LV (Ea/Es) was also significantly higher in the second subgroup by 35.09% and, taking into account the physiological norm of 0.6-1.2, indicates a pronounced dysfunction of the cardiovascular connection in both groups, but with the most severe impairment in the group with lower GAS6 values. The parameters, which did not have a statistically significant difference between the groups ( $p>0.05$ ),

included end-diastolic dimension (EDD), left ventricular posterior wall diameter in diastole (LVPWd), interventricular septal thickness (IVS), and relative left ventricular wall thickness (RWT). Thus, patients with higher GAS6 levels are associated with more pronounced dilated LV remodelling, significantly reduced pumping function, and significant CVC impairment, emphasising the role of GAS6 as a potential marker of unfavourable CHF progression.

The correlation analysis of GAS6 protein levels with indicators of the morphological and functional state of the myocardium is shown in Table 2. It was found that most of the structural and functional parameters of the LV have direct, statistically significant correlations with GAS6 levels ( $p<0.05$ ). A strong direct correlation was found between GAS6 levels and ESD ( $r=0.71$ ,  $p<0.05$ ). Moderate direct correlations were established with EDD ( $r=0.69$ ,  $p<0.05$ ), LVMI ( $r=0.54$ ,  $p<0.05$ ) and LVEF ( $r=0.50$ ,  $p<0.05$ ). Moderate direct correlations were also found with LVM ( $r=0.47$ ,  $p<0.05$ ), LA ( $r=0.39$ ,  $p<0.05$ ), RA ( $r=0.37$ ,  $p<0.05$ ), ESV ( $r=0.36$ ,  $p<0.05$ ), EDV ( $r=0.34$ ,  $p<0.05$ ) and the Ea/Es ratio ( $r=0.34$ ,  $p<0.05$ ). It should be noted that the indicators of LVPWd, ISV and RWT did not reach statistical significance ( $p>0.05$ ). The direct correlations found demonstrate that an increase in GAS6 concentration is closely associated with an increase in LV size, its hypertrophy and pathological remodelling.

Table 2

**Correlations between GAS6 levels and parameters of the morphofunctional state of the myocardium ( $r_{crit}=0.24$ )**

Parameter	r	p
ESD, cm	0.71	<0.05
EDD, cm	0.69	<0.05
LVPWd, cm	0.20	>0.05
IVS, cm	0.36	>0.05
RWT	0.13	>0.05
LVMI, g/cm <sup>2</sup>	0.54	<0.05
LVM, g	0.47	<0.05
ESV, ml	0.36	<0.05
EDV, ml	0.34	<0.05
LVEF, %	0.50	<0.05
LA, cm	0.39	<0.05
RA, cm	0.37	<0.05
Ea/Es	0.34	<0.05

This confirms the hypothesis that higher GAS6 levels are associated with more pronounced dilated LV remodelling and significant CVC impairment.

Our data are fully consistent with the results reported by other researchers, since such structural and functional changes are a classic reflection of

decompensated systolic dysfunction and progressive dilated LV remodelling, which is typical for patients with combined cardiometabolic pathology.

A key aspect of our study was the finding that higher GAS6 protein levels ( $>31.64$  ng/ml) are associated with a more unfavourable structural and functional state of

the myocardium. In the study by Zhao YF et al. [17], a pressure overload model (aortic banding) was used to induce hypertrophy, which is generally equivalent to our clinical cohort – patients with CHF, T2DM and obesity by definition had high levels of arterial stiffness and cardiovascular disorders, and therefore are in a state of chronic pressure overload. The researchers found that GAS6 inactivation led to less severe manifestations of hypertrophy, fibrosis, and dysfunction, while its overexpression exacerbated these negative effects. It has been described that GAS6 impairs ventricular adaptation by activating the MAPK/ERK (mitogen-activated protein kinase kinase 1/2–extracellular signal-regulated kinase 1/2) signalling pathway, which is central to the stimulation of cardiomyocyte and fibroblast proliferation, leading to hypertrophy and fibrosis. At the same time, our study demonstrated that high GAS6 exacerbates the pathological process of LV remodelling under conditions of chronic cardiac stress.

The work of Prouse T et al. [12] emphasises that GAS6 plays a key role in vascular remodelling through its influence on the migration, proliferation and survival of endothelial cells and vascular smooth muscle cells, which is consistent with the correlations we found between GAS6 levels and the Ea/Es ratio.

A review by Wen L et al. [18] details how GAS6, by binding to its receptor Axl, activates intracellular signalling pathways such as MAPK/ERK, which are major triggers of cardiomyocyte hypertrophy and fibrosis, and also has pro-inflammatory effects. The results of our study, which show direct correlations between GAS6 and remodelling parameters (ESV, EDV, LVMi, LVEF), are clinical evidence that the described molecular mechanisms are actively functioning in our cohort of patients. Thus, higher GAS6 levels are a prognostically unfavourable biomarker reflecting the progression of maladaptive changes in the heart and blood vessels.

According to Ürkmez YC et al. [19], GAS6/Axl is involved in the development of diabetic vascular complications and diabetic nephropathy. Our patients with T2DM also have this pathway activated, which exacerbates systemic inflammation and vascular damage.

At the same time, Holden RM et al. [20] found that in patients with high metabolic risk, higher GAS6 was associated with fewer atherosclerotic plaques. Similar results were also obtained by Fan H et al. [15]. In patients with T2DM and atherosclerosis, GAS6 levels were significantly lower in patients ( $9.64 \pm 1.41$  ng/ml) compared to patients without atherosclerosis ( $11.38 \pm 2.08$  ng/ml) and healthy individuals ( $13.64 \pm 2.61$  ng/ml), and binary logistic regression analysis showed that reduced GAS6 ( $\beta = -0.400$ ) is an independent risk

factor for atherosclerosis in patients with T2DM (OR 0.670;  $p=0.027$ ). This contradiction may be due to differences in the patient groups studied. The analysed studies focus on carotid artery atherosclerosis, while our study involved complex polymorbid pathology. A review of the literature confirms that GAS6 may have both a protective (through inhibition of cardiomyocyte apoptosis) and profibrotic (through activation of fibroblasts) effect [21, 22, 12]. Its role probably varies depending on the stage of the disease and the type of affected tissue. Thus, in conditions of stable CAD and atherosclerosis, it can contribute to plaque stabilisation, and in decompensated CHF with metabolic comorbidity, its profibrotic effect in the myocardium becomes dominant and pathological. Despite the discrepancies, this study confirms the association of high GAS6 levels with adverse cardiovascular risk factors such as diabetes and obesity. Thus, it can be noted that the role of GAS6 changes from protective at the vascular level to pathologic at the myocardial level and may serve as an indicator of the depletion of protective mechanisms in conditions of extreme metabolic stress.

Therefore, GAS6 is not just a marker, but an active participant in molecular processes that lead to dilated myocardial remodelling in a high-risk cohort of patients with polymorbidity, when the pathological, profibrotic effect of GAS6 on the myocardium becomes dominant and clinically significant.

**Limitations of the study.** This study had certain limitations. First, although the groups were comparable in terms of baseline characteristics, we did not perform a separate multivariate analysis of the effect of specific drug doses (in particular, SGLT2 and ARNI inhibitors) on changes in GAS6 levels. Second, the duration of CHF history and variability in glycaemic control (HbA1c) could have had a potential impact on myocardial remodelling processes, but due to the limited sample size, these factors were considered as confounding constants. Further studies involving a larger number of patients will allow for a more in-depth subgroup analysis of the effect of drug therapy on the biomarkers studied.

## CONCLUSIONS

It has been established that a GAS6 protein level  $> 31.64$  ng/ml is associated with a more unfavourable structural and functional state of the left ventricular myocardium. Patients with higher GAS6 levels had significantly higher end-systolic volume (by 42.47%) and end-diastolic volume (by 28.84%), lower ejection fraction (by 25.52%), an increase in left ventricular myocardial mass (by 25.71%) and left ventricular myocardial mass index (by 12.23%), right and left atrial dimensions (by 24.09% and 20.09%, respectively), as

well as an increase in the ratio of effective arterial elasticity to end-systolic elasticity was significantly higher in the high GAS6 group (by 35.09%) compared to the low GAS6 group. The results are also confirmed by established reliable correlations with most structural and functional parameters of the left ventricle. Thus,

higher GAS6 levels are associated with a more pronounced dilated type of left ventricular remodelling, significantly reduced pumping function and significant cardiovascular impairment, emphasising its role as a potential marker of unfavourable chronic heart failure in polymorbid patients.

## PROSPECTS FOR FUTURE RESEARCH

Conducting long-term prospective cohort studies to determine whether high GAS6 levels are an independent predictor of Major Adverse Cardiac Events (MACE), cardiac death and the frequency of rehospitalisation in patients with chronic heart failure, type 2 diabetes mellitus and obesity, as well as to determine the optimal GAS6 threshold for risk stratification in this high-risk cohort.

## AUTHOR CONTRIBUTIONS

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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