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ORIGINAL ARTICLE

The influence of metformin and the presence of type 2 diabetes mellitus on mortality and hospitalisation in patients with heart failure

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Abstract

Background: Metformin is one of the antihyperglycaemic drugs, reducing the risk of major cardiovascular events, including fatal ones. Although it is formally contraindicated in moderate and severe functional stages of heart failure (HF), it is commonly used in patients with concomitant type 2 diabetes mellitus (T2DM).

Aim: We sought to evaluate the effect of metformin and T2DM on total mortality and hospitalisation rates in patients with HF.

Methods: This retrospective analysis included 1030 adult patients (> 18 years) with HF from the Polish section of the HF Long-Term Registry (enrolled between 2011 and 2014). Patients with T2DM (n = 350) were identified and divided into two groups: those receiving metformin and those not. Both groups were subjected to one-year follow-up.

Results: Mean patient age was 65.3 ± 13.5 years, with the predominance of male sex (n = 726) and obesity (mean body mass index 30.3 ± 5.5 kg/m^2) and mean left ventricular ejection fraction was 34.3% ± 14.1%. Among patients with T2DM (n = 350) only 135 (38.6%) were treated with metformin. During one-year follow-up, 128 patients with HF died, of whom 53 had T2DM (15.1% vs. 10.9%, hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.87–0.91, p = 0.045). Metformin was associated with a lower mortality rate compared to other antihyperglycaemic agents (9.6% vs. 18.6%, HR 0.85; 95% CI 0.81–0.89, p = 0.023). There were no significant differences in the hospitalisation rate, including that due to HF decompensation, among patients treated with metformin and the remainder (53.5% vs. 40.0%, respectively HR 0.93, 95% CI 0.82–1.04, p = 0.433).

Conclusions: Metformin treatment in patients with different degrees of HF and T2DM is associated with a reduction in mortality and does not affect the hospitalisation rate.

Key words: metformin, heart failure, type 2 diabetes mellitus, pharmacology

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INTRODUCTION

Heart failure (HF) is often an independent consequence of diabetes mellitus (DM), and it may also be a concurrent disorder. Yang et al. [1] have reported that after coronary artery disease, DM is the second most common pathology related to HF, doubling the risk of this disease. It has been suggested that HF is usually an initial manifestation of cardiovascular disease in patients with type 2 diabetes mellitus (T2DM) [2].

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Conversely, the severity of HF was associated with a slightly increased risk of developing DM [3].

Insulin resistance plays a pivotal role in the development of a varied cluster of metabolic abnormalities, including T2DM and associated cardiovascular diseases. It has been found that insulin resistance alters the systemic and neurohumoral environment, leading to the growth of fibrous tissue. This damaging process increases myocardial stiffness and contributes to left ventricular diastolic dysfunction, known as "diabetic cardiomyopathy" [4].

Metformin is the most widely used oral antihyperglycaemic agent and it is the preferred initial pharmacological agent for T2DM patients. It is well known that metformin improves insulin sensitivity, mainly in skeletal muscles and the liver, and in addition to its glucose-lowering effect, the drug appears to possess a cardioprotective potential. A number of experimental and clinical studies have demonstrated that metformin has a beneficial effect on lipid, atherothrombic, and inflammatory profiles, endothelial function, oxidative stress, and antiproliferative and neuroprotective properties [5].

Due to the risk of lactic acidosis, the Food and Drug Administration classified HF as a contraindication to metformin therapy [6]. However, a recent placebo-controlled trial suggests that a number of possible benefits may be derived from this drug with regard to its effect on HF and DM [7]. Therefore, the aim of this retrospective analysis was to assess whether metformin treatment and the presence of T2DM affect overall mortality and all-cause hospitalisation rates in patients with HF and T2DM during a one-year follow-up period.

METHODS

ESC HF Long-Term Registry

The data was obtained from a Polish population of the prospective, multicentre, observational study of the European Society of Cardiology (ESC) HF Long-Term Registry. A list of all participating centres is provided in Acknowledgements. The study was approved by the Bioethics Committee in 2011.

The study included 1126 patients with HF enrolled in the years 2011–2014. Patients with new onset, worsening, or chronic HF (CHF) were included by participating centre physicians after obtaining written informed patient's consent both in hospital (acute and worsening of HF) and outpatient clinics (CHF).

Analysis of the effect of metformin use and the presence of T2DM

Our retrospective analysis comprised 1030 patients (726 men, mean age 65.3 ± 13.5 years) in various New York Heart Association (NYHA) functional classes. All patients who were enrolled in hospital and died before discharge or patients lost to follow-up were excluded from analysis (n = 96).

Heart failure diagnosis was based on symptoms, physical examination, documented aetiology (ischaemic, hypertension, dilated cardiomyopathy, valve disease, tachycardia-related cardiomyopathy, and others), and echocardiography according to the clinical judgement of the physicians from participating centres. No specific exclusion criteria were given in the HF Long-Term Registry protocol, except age under 18 years. Exercise tolerance was estimated according to the NYHA classification.

A detailed history of HF, comorbidities, and actual treatment was collected from each patient during first contact. Additionally, physical examination, measurement of basic anthropometric and laboratory parameters and blood pressure, electrocardiography (ECG), and echocardiography were performed. Patients were asked about the presence of glucose metabolism disorders. T2DM was diagnosed on the basis of medical documentation, used antihyperglycaemic agents (insulin, metformin, glitazones, incretins, sulphonylurea, and others) or diagnostic procedure during the first contact with the patient, according to the current guidelines of the Polish Diabetes Association. Chronic kidney dysfunction and hepatic dysfunction were diagnosed on the basis of medical documentation.

Patients with and without T2DM were identified (T2DM and non-T2DM groups, respectively). The former group was further subdivided as follows: group 1 — patients receiving metformin in monotherapy or in combination with other antihyperglycaemic drugs (T2DM-M); group 2 — patients treated with antidiabetic agents other than metformin (T2DM-NM).

Patients were included in the metformin group if they had been treated with it in an outpatient clinic, during hospitalisation, or after discharge from hospital.

Participants were subjected to one-year follow-up. The follow-up data were collected by phone, during a visit in an outpatient clinic or during hospitalisation. A detailed history of rehospitalisations and vital status was collected. Hospitalisation rates were divided into five categories: related to HF, non-HF cardiac cause, vascular cause (peripheral vascular disease, stroke, embolism, aneurysms), renal dysfunction, and other causes.

Statistical analysis

Statistical analyses were performed with STATISTICA 12 Software (StatSoft Inc., Tulsa, OK, USA). Probability distribution of continuous values was tested with Lillefors and Shapiro-Wilk tests. Because the distribution was found to be non-normal, the Mann-Whitney U test was performed to analyse the investigated values. The χ^2 test was used to compare non-parametric values, including NYHA classification, while univariate regression analysis was performed for parametric values. Data were presented as mean ± standard deviation, and p-values < 0.05 were considered statistically significant.

RESULTS

Demographic and baseline clinical data

Out of 1030 patients with HF, 350 were identified as having T2DM. The whole population had mean body mass index (BMI) of 30.3 ± 5.5 kg/m^2 and mean value of left ventricular

Table 1. Baseline parametric characteristics of the study population selected by the presence of type 2 diabetes mellitus and metformin treatment

	T2DM-NM	T2DM-M	N-T2DM	p (T2DM-NM vs. T2DM-M)	p (N-T2DM vs. T2DM)
Age [years]	68.1 ± 10.8	64.5 ± 10.5	62.3 ± 14.5	0.051	< 0.001
Height [cm]	168.4 ± 8.5	169.1 ± 9.8	170.5 ± 8.3	0.465	0.003
Weight [kg]	84.0 ± 15.3	90.2 ± 19.1	80.2 ± 16,.5	0.003	< 0.001
BMI [kg/m^2]	29.6 ± 5.1	31.4 ± 6.0	27.5 ± 4.7	0.003	< 0.001
Heart rate [bpm]	82.3 ± 20.3	80.7 ± 19.2	80.3 ± 21.9	0.528	0.375
Systolic BP [mmHg]	127.3 ± 24.0	128.8 ± 26.7	122.9 ± 20.5	0.584	0.002
Diastolic BP [mmHg]	76.1 ± 12.9	77.6 ± 14.7	75.8 ± 12.1	0.357	0.327
Last known LVEF [%]	33.1 ± 14.2	36.2 ± 13.8	35.6 ± 13.8	0.072	0.229

Data are shown as mean ± standard deviation. BMI — body mass index; BP — blood pressure; LVEF — left ventricular ejection fraction; T2DM — type 2 diabetes mellitus; T2DM-M — patients with type 2 diabetes mellitus treated with metformin; T2DM-NM — patients with type 2 diabetes mellitus treated without metformin; N-T2DM — patients without type 2 diabetes mellitus

ejection fraction (LVEF) was 34.3% ± 14.1% (Table 1). In both groups with HF: T2DM and non-T2DM (N-T2DM), the male population prevailed, and sex distribution was similar (n = 488, 71.8% and n = 238, 68.0%, respectively, p = 0.254) (Table 2).

The N-T2DM patients demonstrated a lower NYHA class at discharge from hospital, at first visit to the outpatient clinic and at one-year follow-up. Additionally, while this score was similar in both T2DM subgroups at discharge from hospital, at first visit to the outpatient clinic, and at the one-year follow-up, the T2DM-M group presented a lower NYHA class on admission to hospital (Table 3).

Most of the results were obtained from hospitalised T2DM patients (135 of 350, 38.6%) treated with metformin. Metformin was more frequently used on inpatients than on those in outpatient clinics (65% vs. 35%) (Fig. 1).

Interfering factors

The T2DM patients tended to be older with lower height, systolic blood pressure, body weight, and BMI than N-T2DM patients (Table 1). Moreover, this study group demonstrated a more frequent history of myocardial infarction or angina, peripheral vascular disease, valvular surgery, hypertension treatment, chronic kidney dysfunction (CKD), and current malignant disease than the N-T2DM group with HF (Table 2).

In the T2DM group, those receiving metformin demonstrated a lower prevalence of CKD (n = 27, 20.0% vs. n = 80, 37.2%; p < 0.001) and hepatic dysfunction (n = 2, 6.5% vs. n = 14, 1.5%; p = 0.028), and higher body mass (90.2 ±19.1 kg vs. 84.0 ± 15.3 kg; p = 0.003) and BMI (31.4 ± 6.0 kg/m^2 vs. 29.6 ± 5.1 kg/m^2, p = 0.003) than T2DM-NM patients (Table 2).

Mortality and hospitalisation rates

Of the whole HF population 128 (12.4%) patients had died by the time of the one-year follow-up. More patients with T2DM (n = 53, 15.1%) had died than N-T2DM patients (n = 75, 10.9%, hazard ratio [HR] 0.89; 95% confidence interval [CI] 0.87–0.91; p = 0.045).

Metformin treatment was associated with lower mortality rates: 9.6% (n = 13) for treated patients compared to 18.6% (n = 40) for T2DM-NM patients (HR 0.85; 95% CI 0.81–0.89; p = 0.023; Fig. 2, Table 4).

Hospitalisation rates were lower for T2DM patients for 12 months, at 92.8% (n = 325), compared to 78.2% for N-T2DM patients (n = 200, p = 0.01), with no significant differences regarding hospitalisation rates by cause of hospitalisation (Table 4).

For the T2DM-M and T2DM-NM subgroups total hospitalisation rates were similar, but the hospitalisation rate due to non-HF cardiac cause was higher in the metformin group (n = 43, 31.9%) than in the non-metformin group (n = 36, 16.7%; p = 0.042; Fig. 3, Table 4).

There was no difference in mortality rates in terms of presence of CKD and hepatic dysfunction in N-T2DM patients. Likewise, in T2DM-M patients the analysis showed that these mortality rates were similar. However, we found that they were higher in T2DM-NM patients with CKD (n = 14, 23.8% vs. n = 21, 15.6%; p = 0.012) and hepatic dysfunction (n = 5, 35.7% vs. n = 35, 17.4%; p = 0.01; Table 5).

DISCUSSION

Metformin has long been considered as an initial pharmacotherapy in the treatment of hyperglycaemia in patients with T2DM recommended by all diabetes associations. Miura et al. [8] found that about 44% of patients with CHF were treated with antidiabetic drugs such as metformin, and 11.5% had various forms of insulin regimens. In our study, 38.6% of patients with T2DM, mainly requiring hospitalisation, were treated with metformin. It should be emphasised that the majority of these patients were not using metformin.

Metformin not only has an antihyperglycaemic effect, but also other important effect, especially on the cardiovas-

Table 2. Baseline characteristics of the study population with heart failure, selected by the presence of type 2 diabetes mellitus and metformin treatment

	T2DM-NM (n = 215)	T2DM-M (n = 135)	N-T2DM (n = 680)	p (T2DM-NM vs. T2DM-M)	p (N-T2DM vs. T2DM)
Sex:				0.605	0.254
Female	71 (33.0)	41 (30.4)	192 (28.2)		
Male	144 (67.0)	94 (69.6)	488 (71.8)		
Comorbidities:					
MI/angina	129 (60.0)	80 (59.3)	319 (46.9)	0.891	< 0.001
CABG	24 (11.1)	19 (14.1)	69 (10.1)	0.419	0.255
PCI	66 (30.7)	47 (34.8)	186 (27.4)	0.314	0.267
Stroke/TIA	28 (13.0)	15 (11.1)	68 (10.0)	0.596	0.224
Peripheral vascular disease	41 (19.1)	25 (18.5)	70 (10.3)	0.898	< 0.001
Valvular surgery	8 (3.7)	8 (5.9)	69 (10.2)	0.336	0.001
Hypertension treatment	164 (76.3)	101 (74.8)	385 (56.6)	0.677	< 0.001
VTE	10 (4.7)	7 (5.2)	38 (5.6)	0.821	0.705
COPD	40 (18.6)	16 (11.9)	94 (13.8)	0.093	0.539
CKD	80 (37.2)	27 (20.0)	135 (19.9)	< 0.001	< 0.001
Current malignant disease	13 (6.1)	3 (2.2)	16 (2.3)	0.095	0.046
Hepatic dysfunction	14 (6.5)	2 (1.5)	35 (5.1)	0.028	0.731
Sleep apnoea	11 (5.1)	11 (8.1)	32 (4.7)	0.373	0.275
Depression	11 (5.1)	6 (4.4)	30 (4.4)	0.776	0.723
Parkinson's disease	4 (1.9)	0	4 (0.6)	0.111	0.324
Rheumatoid arthritis	13 (6.1)	3 (2.2)	20 (2.9)	0.095	0.161
Thyroid dysfunction	40 (18.4)	23 (17.0)	88 (13.0)	0.733	0.693

Data are shown as number (percentage). CABG — coronary artery bypass graft; CKD — chronic kidney dysfunction; COPD — chronic obstructive pulmonary disease; MI — myocardial infarction; PCI — percutaneous coronary intervention; TIA — transient ischaemic attacks; VTE — venous thromboembolism; other abbreviations — see Table 1

Table 3. New York Heart Association (NYHA) class at admission to hospital, at discharge/first visit in outpatient clinic, and at one-year follow-up in heart failure patients

	NYHA class				p (T2DM-NM vs. T2DM-M)	p (N-T2DM vs. T2DM)
	I	II	III	IV		
Admission to the hospital:						
T2DM-NM	0	32 (15)	103 (48)	80 (37)	0.008	0.073
T2DM-M	0	46 (34)	49 (36)	41 (30)		
N-T2DM	0	170 (25)	306 (45)	204 (30)	–	
Discharge/outpatient:						
T2DM-NM	11 (5)	118 (55)	80 (37)	6 (3)	0.169	0.002
T2DM-M	5 (4)	88 (65)	41 (30)	1 (1)		
N-T2DM	54 (8)	422 (62)	190 (28)	14 (2)	–	
12-month follow-up:						
T2DM-NM	17 (8)	69 (57)	69 (32)	6 (3)	0.566	0.004
T2DM-M	9 (7)	84 (62)	39 (29)	3 (2)		
N-T2DM	88 (13)	415 (61)	156 (23)	20 (3)	–	

Data are shown as number (percentage). Abbreviations — see Table 1

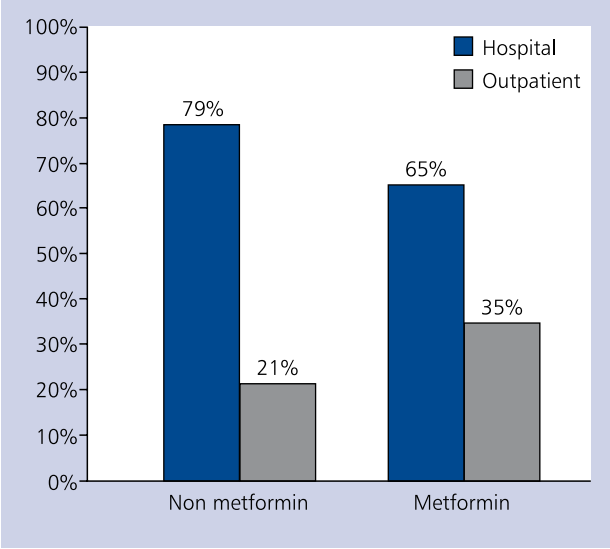

Figure 1. Metformin treatment in heart failure patients with type 2 diabetes mellitus during the first medical contact in hospital or the outpatient clinic

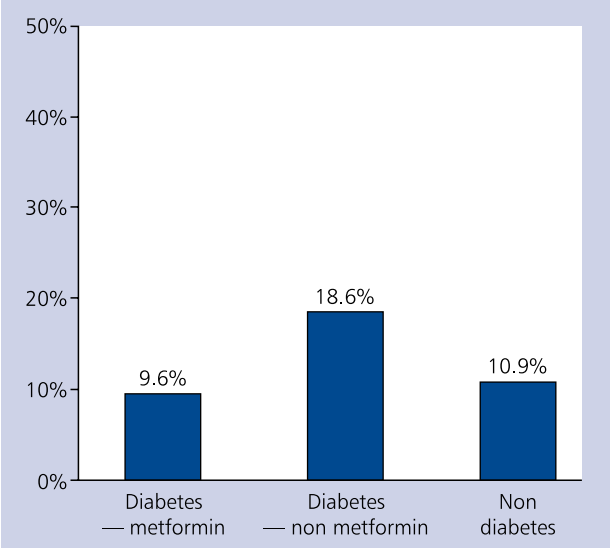

Figure 2. Mortality rates at one-year follow-up in heart failure patients

Table 4. Mortality and hospitalisation rates at one-year follow-up in heart failure patients, including type 2 diabetes mellitus patients treated with or without metformin

Major cause	T2DM-NM	T2DM-M	N-T2DM	p (T2DM-NM vs. T2DM-M)	HR (95% CI) T2DM	p (N-T2DM vs. T2DM)	HR (95% CI) N-T2DM
Mortality rates:							
Total	40 (18.6)	13 (9.6)	75 (10.9)	0.023	0.84 (0.81–0.88)	0.045	0.88 (0.86–0.90)
12-month hospitalisation rates:							
Total	200 (93.0)	125 (92.6)	532 (78.2)	0.996	0.93 (0.82–1.04)	0.010	0.83 (0.77–0.89)
Heart failure	115 (53.5)	54 (40.0)	208 (30.6)	0.433	0.48 (0.38–0.58)	0.060	0.83 (0.77–0.89)
Non-HF cardiac disease	36 (16.7)	43 (31.9)	157 (23.1)	0.042	0.23 (0.17–0.28)	0.511	0.23 (0.20–0.27)
Renal dysfunction	9 (4.2)	0	13 (1.9)	0.280	0.025 (0.002–0.049)	0.564	0.021 (0.008–0.034)
Vascular disease	6 (2.8)	8 (5.9)	13 (1.9)	0.348	0.04 (0.01–0.07)	0.211	0.03 (0.02–0.04)
Non-cardiac	30 (14.0)	20 (14.8)	84 (12.4)	0.701	0.14 (0.10–0.19)	0.107	0.13 (0.10–0.16)

Data are shown as number (percentage). CI — confidence interval; HR — hazard ratio; other abbreviations — see Table 1

cular system. Therefore, while choosing a drug for patients with T2DM it is essential to bear in mind that in addition to antihyperglycaemic action it can also affect comorbidities like HF.

Many of the biochemical pathways of metformin action are well known. It has been suggested that its pleiotropic effect is associated with its impact on mitochondria: specifically, its inhibition of mitochondrial respiratory-chain complex 1. Metformin also reduces glucose absorption, suppresses hepatic gluconeogenesis, amplifies the insulin suppression of glucose production, and improves glucose utilisation by skeletal muscle and adipose tissue [9]. Additionally, metformin improves

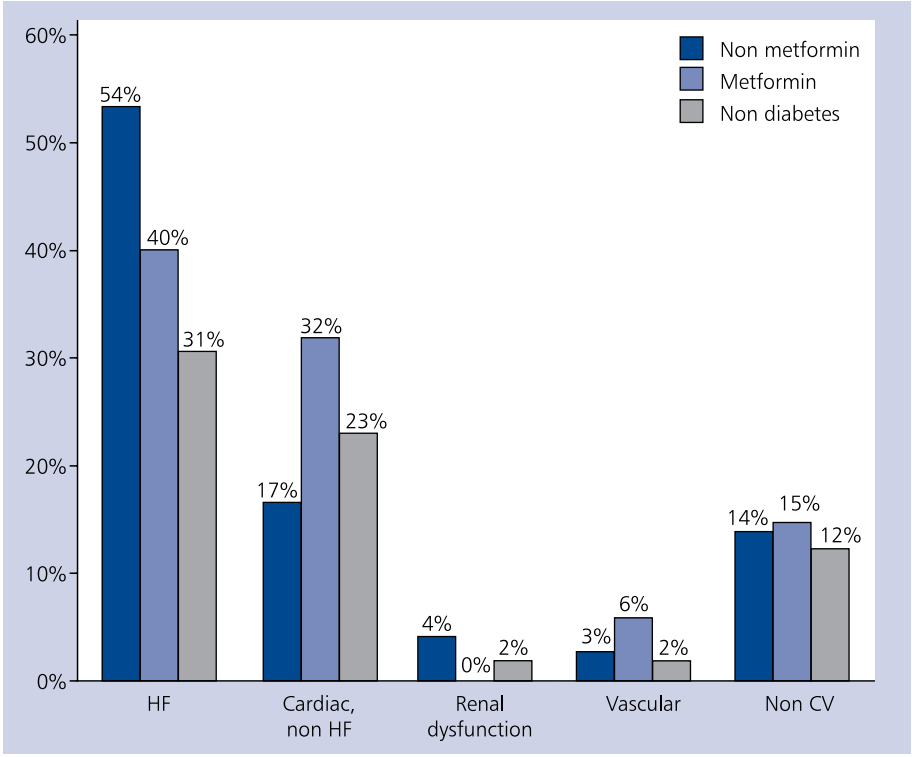

Figure 3. Hospitalisation rates at one-year follow-up in heart failure (HF) patients; CV — cardiovascular

Table 5. Mortality rates at one-year follow-up in heart failure patients with chronic kidney dysfunction (CKD) and hepatic dysfunction, including type 2 diabetes mellitus patients treated with or without metformin

Treatment	Mortality rates		p
	CKD (n = 60)	Without CKD (n = 68)	
T2DM-NM	14 (23.8)	21 (15.6)	0.012
T2DM-M	13 (22.2)	8 (7.4)	0.453
N-T2DM	16 (25.9)	39 (7.3)	0.271
	Hepatic dysfunction (n = 14)	Without hepatic dysfunction (n = 114)	p
T2DM-NM	5 (35.7)	35 (17.4)	0.010
T2DM-M	0 (0)	13 (9.8)	0.356
N-T2DM	9 (25.7)	66 (10.2)	0.301

Data are shown as number (percentage). Chronic kidney dysfunction and hepatic dysfunction were diagnosed on the basis of medical documentation. Abbreviations — see Table 1

glucose homeostasis through the action of glucagon-like peptide 1 [10] and opposes the action of the counter-regulatory hormone glucagon to inhibit hepatic glucose production [11]. Furthermore, metformin induces improvements in insulin action through alterations in hepatic lipid homeostasis via the inhibition of phosphorylation of acetyl CoA carboxylase by AMP-activated protein kinase (AMPK) [12].

AMPK activation by metformin or other activators can stimulate cardiac glucose uptake and glycolysis independently of insulin, bypassing insulin resistance in insulin-resistant cardiomyocytes [13]. Additionally, metformin is able to attenuate fibrosis in a canine model of HF, presumably via AMPK activation and its inhibitory action on transforming growth factor-β expression [14]. It has also been established that metformin inhibits myofibroblast differentiation by suppressing reactive oxygen species generation via the inhibition of the NADPH oxidase pathway, a process that is probably mediated by AMPK [15]. Metformin may also, through af-

fecting mitochondrial membrane potential and respiratory function, improve function of cardiomyocytes in HF after myocardial infarction [16].

Currently, although metformin is seen as a safe and well-tolerated drug with the most adverse effects associated with the gastrointestinal system (diarrhoea, nausea, and vomiting), it is contraindicated in patients with renal or hepatic insufficiency and in patients with conditions of circulatory dysfunction such as CHF, due to lactic acidosis. Salpeter et al. [17] reviewed published reports of controlled trials involving metformin that lasted one month or more and were reported in November 2002. They found no cases of lactic acidosis in 36,000 patient-years of exposure to metformin and concluded that there was no evidence to support a role for metformin in the development of lactic acidosis. A meta-analysis of observational studies by Eurich et al. [18] found that metformin treatment in patients with HF was not associated with any increased risk of lactic acidosis.

A number of clinical trials have assessed the value of metformin in the treatment of T2DM in patients with various degrees of HF. Eurich et al. [19] recorded fewer deaths among subjects receiving metformin than those receiving sulphonylurea therapy: 404 (52%) for sulphonylurea monotherapy compared to 69 (33%) for metformin monotherapy and 263 (31%) for combination therapy. In addition, fewer deaths or hospitalisations were also observed: 658 (85%) for sulphonylurea monotherapy vs. 160 (77%) for metformin monotherapy and 681 (80%) for combination therapy. However, they reported no difference in time to first hospitalisation between the study groups [19]. MacDonald et al. [20] reported lower mortality in patients receiving metformin monotherapy or metformin with other antidiabetic agents than in patients who were not administered antidiabetic drugs; however, the use of other antidiabetic drugs or insulin was not associated with all-cause mortality. In the present study, the patients administered metformin demonstrated significantly lower mortality rates than those who were not. Additionally, no differences were observed regarding total hospitalisation rates. However, it should be highlighted that the hospitalisation rate due to non-HF cardiac causes was higher in patients treated with metformin.

Our results indicate that patients on metformin therapy demonstrated higher values of NYHA classification on admission to hospital. A study by Lexis et al. [21] found LVEF to be 53.1% in a group treated with metformin and 54.8% in a placebo group after four months, with no significant differences observed between the groups regarding creatinine or glycated haemoglobin concentration, and, what is also important, there was no case of lactic acidosis. Lapina et al. [22] examined the safety of therapy with metformin and its effect on clinical, haemodynamic, functional, and neurohumoral status in patients with CHF and T2DM. Patients with light and moderate NYHA functional class II–III CHF, LVEF < 45%, and T2DM were included in the study, and the total duration of the period of treatment and supervision was 12 months. The results confirm that metformin is acceptably safe: throughout the follow-up period, no cases of lactic acidosis were revealed by various comparative analyses. The lack of a positive influence of metformin on glycaemia at its initial low level was accompanied by an improvement of NYHA class, better central haemodynamic parameters, improved functional capacities of patients, improved quality of life, fewer CHF decompensations, and a reduced degree of sympathetic adrenergic system activation [22].

The results of our study confirm previous observations suggesting that metformin treatment is associated with a lower mortality in T2DM and HF patients. This can be partially explained by the reduction in mortality in patients with T2DM in general, but there are reports that metformin can also improve the function of cardiomyocytes through changes in myocardial metabolic and reconstruction processes. Furthermore, the presence of CKD did not affect mortality in patients treated with metformin.

Therefore, we support the view of other authors that contraindications for metformin should be reconsidered. It should be noted that the existing ESC recommendations state that metformin is safe for use in patients with HF with reduced LVEF and should be the treatment of choice in patients with HF, but it is contraindicated in patients with severe renal or hepatic impairment because of the risk of lactic acidosis [23, 24].

However, our results have some limitations due to the observational design of the registry study and protocol. First of all, the decision to diagnose HF and DM depended on locally used diagnostic methods and practice. The presence of oedema in patients with acute HF at first medical contact could falsify body weight and BMI differences. The differences in incidences of renal and hepatic dysfunctions could result from contraindications to metformin, and evaluation of the effect of concurrent hepatic insufficiency on metformin therapy was unreliable due to the small number of groups. Similarly, large differences in the group size did not allow a reliable assessment of the effect of other antidiabetic drugs on mortality and hospitalisations. Moreover, the registry does not collect information about the duration of DM.

In conclusion, the results confirm previous observations that the use of metformin in patients with different degrees of HF and T2DM is associated with a reduction in the risk of death and does not increase the number of hospitalisations. However, the presence of other contraindications to this drug, such as renal failure or liver dysfunction, which increase the frequency of hospitalisation, should be considered. These findings support increasing calls to reduce contraindications for metformin.

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WHAT IS NEW?

Despite previous concerns about lactic acidosis associated with the use of metformin, which were reflected in label contraindications, some studies suggest that antidiabetic treatment with metformin is safe in patients with heart failure. The results of this analysis indicate that metformin treatment is also associated with reduced mortality in heart failure patients. Although the incidence of all-cause hospitalisation was similar in both compared groups, the results of this study may affect the position of metformin in the pharmacotherapy of diabetics with heart failure and will set the foundation for future research.