RESEARCH LETTER

Metformin and cardiac injury after acute coronary syndrome in diabetic patients with no history of cardiovascular disease: data from the PL-ACS registry

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Introduction Cardiovascular disease (CVD) is the most common complication of diabetes. Myocardial infarction occurs in every sixth patient within 10 years after diabetes has been diagnosed.[1] Although postinfarction mortality has decreased, it is still relatively high.[2] Multifactorial intervention including normalization of glycemia, blood pressure, lipid levels, and body weight is related to a 50% lower risk of myocardial infarction.[3] Additionally, some data have shown the specific cardioprotective effect of antidiabetic drugs.[4]

Metformin is the first-line drug in antihyperglycemic treatment of diabetes.[5] Its additional cardioprotective effect has been well documented.[6] There are limited data on cardiac injury in diabetic patients who experienced myocardial infarction, which would specify whether they were treated with metformin or not. Therefore, we searched the PL-ACS registry (Polish Registry of Acute Coronary Syndromes) for information about antidiabetic treatment received by patients with acute coronary syndrome (ACS). In the present analysis, we included diabetic patients with no history of CVD prior to the reported episode who were treated with percutaneous coronary intervention (PCI). Selected patients were divided into 2 groups: treated or not treated with metformin before admission to the hospital.

We analyzed patients' metabolic status (glycated hemoglobin [HbA_{1c}] and lipid profile) on admission and ejection fraction (EF) at discharge.

Patients and methods Among 387 125 individuals recorded in the PL-ACS registry in the years 2011 to 2019, we identified 209 228 patients with diabetes, 48 073 of whom were treated with metformin before admission. The study patients were matched to achieve similar age and duration of symptoms before admission and to enable comparisons. Data were matched using the Mahalanobis distance within propensity score calipers. The caliper radius was set to 0.2 * sigma for diabetic subjects not treated with metformin. Finally, each of the propensity score–matched groups included 1199 individuals. The median (interquartile range [IQR]) age of patients was 70 (63–77) years in both groups. There were 56% of men in the metformin group and 57% of men in the group not receiving metformin. The median (IQR) body mass index in these groups was 29 (26–32) and 29 (26–32) kg/m^2, respectively.

Ethics Study data were obtained from the PL-ACS registry. Ethics committee approval and patient informed consent were not required.

Statistical analysis Data were presented as median (IQR) or number and percentage as appropriate. The study groups were compared using the Mann–Whitney test or the χ^2 test.

Results Diabetes duration, coexistence of hypertension, dyslipidemia as well as antihypertensive and lipid-lowering treatment were similar in both study groups. Metabolic control expressed by HbA_{1c} and lipid levels was also comparable in both groups. The mean EF was similar in both groups, but the number of patients with EF

TABLE 1 Clinical characteristics of diabetic patients after acute coronary syndrome, with no history of cardiovascular disease, and treated with percutaneous coronary intervention depending on antihyperglycemic treatment on admission

Parameter	Patients on metformin (n = 1199)	Patients receiving other antidiabetic drugs (n = 1199)	*P* value
Age, y	70 (63–77)	70 (63–77)	0.41
Symptom duration, h	3.81 (2.11–6.65)	3.60 (2–6)	0.11
HbA_{1c}, mmol/mol	54 (43.2–67.2)	51.9 (44.3–65)	0.69
HbA_{1c}, %	7.1 (6.1–8.3)	6.9 (6.2–8.1)	0.69
Total cholesterol, mmol/l	4.47(3.7–5.48)	4.55 (3.75–5.4)	0.81
LDL cholesterol, mmol/l	2.63 (1.99–3.49)	2.77 (2–3.35)	0.34
HDL cholesterol, mmol/l	1.11 (0.93–1.3)	1.11 (0.96–1.34)	0.34
Triglycerides, mmol/l	1.6 (1.17–2.19)	1.56 (1.09–2.19)	0.29
EF at discharge, %	48 (42–55)	47 (40–55)	0.95
EF at discharge <40%, n (%)	143 (12)	207 (17)	<0.001

Data are presented as median (interquartile range) unless otherwise indicated.

Abbreviations: EF, ejection fraction; HbA_{1c}, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein

below 40% was significantly smaller in metformin users compared with patients treated with other hypoglycemic drugs. Detailed study results are presented in **TABLE 1**.

Discussion Results obtained from a population of diabetic patients with no history of CVD who were treated with PCI showed that those on metformin on admission due to ACS had a significantly lower prevalence of remarkable postinfarction cardiac injury. We selected patients with no history of CVD who were matched for age and symptom duration and, as a result, similar levels of HbA_{1c} and lipids were observed in both study groups. This selection was performed to avoid potential bias due to known influence of these factors on EF. Although metformin is the first-line treatment in type 2 diabetes, a considerable number of patients still remain on treatment with other drugs, which was also shown in our analysis: only 48 073 diabetic patients (23%) in the registry were treated with metformin. The registry design did not allow us to determine why metformin was not used in so many patients.

Data on the effect of metformin on postinfarct myocardial injury in clinical practice are limited. Lexis et al[7] performed a retrospective analysis of the infarct size expressed by the peak activity of cardiac enzymes. They found that the peak activity of these indicators was significantly lower in patients treated with metformin. In contrast, Basnet et al[8] found no difference in enzymes and EF at hospital discharge in patients with ST-segment elevation myocardial infarction receiving metformin.[8] They did not report whether patients evaluated in their study had a history of CVD. From the clinical point of view, EF is the key indicator of cardiac injury. Our study showed that treatment with metformin was associated with a lower percentage of patients with clinically relevant EF decrease reported at discharge from the hospital after an ACS episode.

A meta-analysis of animal studies assessing the impact of metformin on cardiac injury showed that the drug use was related to a significantly smaller extent of postinfarct myocardial injury,[9] which is in line with our data from the human population. Our patients had no history of CVD, which excludes myocardial injury associated with a prior ischemic episode. Additionally, glycemic control, expressed by HbA_{1c} and lipid levels measured on admission as a potential confounder, was similar in both study groups, which strongly supports the concept of a cardioprotective effect of metformin.

The mechanism underlying this effect is unclear. Most likely, metformin influences the activation of intracellular enzymatic pathways and increases glucose utilization in cardiomyocytes.[10] Among other well-established risk factors, epicardial fat being part of visceral fat plays an active paracrine and endocrine role in CVD. An increased volume of epicardial fat and its dysfunctional profile of gene expression as well as decreased expression of cardioprotective fibroblast growth factor 21 (FGF21) were found in patients with multivessel coronary artery disease and diabetes.[11] Treatment with metformin is associated with a significantly increased FGF21 expression. By inhibiting mitochondrial respiratory chain complex I, metformin leads to production of reactive oxygen species and generates integrated stress response through activation of transcription factor 4, which stimulates FGF21.[12]

In conclusion, metformin treatment protects diabetic patients from cardiac injury after ACS. Our results confirm the strong position of metformin as the first-line hypoglycemic treatment in diabetes.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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REFERENCES

1 UKPDS Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352: 837-853.

2 Gąsior M, Pres D, Wojakowski W, et al. Causes of hospitalization and prognosis in patients with cardiovascular diseases Secular trends in the years 2006-2014 according to the SILesian CARDiovascular (SILCARD) database. Pol Arch Med Wewn. 2016; 126: 754-762.

3 Gæde P, Oellgaard J, Carstensen B, et al. Years of life gained by multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: 21 years follow-up on the Steno-2 randomised trial. Diabetologia. 2016; 59: 2298-2307.

4 Komaru J, Takeuchi T, Suzuki L, et al. Recurrent cardiovascular events in patients with newly diagnosed acute coronary syndrome: Influence of diabetes and its management with medication. J Diabetes Complications. 2020; 34: 107511.

5 Davies M, D'Alessio D, Fradkin J, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2018; 61: 2461-2498.

6 Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. Arch Intern Med. 2009; 169: 616-625.

7 Lexis CPH, Deursen HB, Lipsic P, et al. Chronic metformin treatment is associated with reduced myocardial infarct size in diabetic patients with ST-segment elevation myocardial infarction. Cardiovasc Drugs Ther. 2014; 28: 163-171.

8 Basnet S, Kozikowski A, Makaryus AN, et al. Metformin and myocardial injury in patients with diabetes and ST-segment elevation myocardial infarction: a propensity score matched analysis. J Am Heart Assoc. 2015; 22; 4: e002314.

9 Hesen NA, Riksen NP, Aalders B, et al. A systematic review and meta-analysis of the protective effects of metformin in experimental myocardial infarction. PLoS One. 2017; 23; 12: e0183664.

10 Bhamra GS, Hausenloy DJ, Davidson SM, et al. Metformin protects the ischemic heart by the Akt-mediated inhibition of mitochondrial permeability transition pore opening. Basic Res Cardiol. 2008; 103: 274-284.

11 Haberka M, Machnik G, Kowalówka A, et al. Epicardial, paracardial, and perivascular fat quantity, gene expressions, and serum cytokines in patients with coronary artery disease and diabetes. Pol Arch Intern Med. 2019; 29; 129: 738-746.

12 Wróbel MP, Marek B, Kajdaniuk D, et al. Metformin – a new old drug. Endokrynol Pol. 2017; 68: 482-496.