ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Metformin and CI-AKI Risk in STEMI: Evaluation Using Propensity Score Weighting Method

STEMI'da Metformin ve CI-AKI Riski: Propensity Skor Ağırlıklandırma Yöntemi Kullanılarak Değerlendirilmesi

ABSTRACT

Objective: Discontinuation of metformin therapy is a frequent clinical practice to reduce the risk of contrast-induced acute kidney injury (CI-AKI) in diabetic ST-segment elevation myocardial infarction patients using metformin. There is insufficient evidence in the literature to support this approach. The aim of this study is to determine whether the risk of contrast-induced acute kidney injury is different in diabetic ST-segment elevation myocardial infarction patients using metformin compared to those not taking metformin.

Methods: The study population consisted of patients with ST-segment elevation myocardial infarction admitted to the centers that participated in this study between 2014 and 2019 and underwent primary percutaneous intervention. Diabetic patients (n = 343) that met the study inclusion criteria were divided into 2 groups as who have been receiving metformin and who have not. Patients' creatinine values on admission and peak creatinine values were compared in order to determine whether they have developed contrast-induced acute kidney injury. The 2 groups were compared using conditional logistic regression analysis conducted with the inverse probability weighting method.

Results: Non-weighted classic multivariable logistic regression analysis revealed that metformin use was not associated with acute kidney injury. Weighted conditional multivariable logistic regression revealed that the increase in the risk of acute kidney injury was associated with baseline creatinine levels [odds ratio: 1.49 (1.06-2.10; 95% CI) $P=.02$] and that the increase in the risk of contrast-induced acute kidney injury was not associated with metformin usage [odds ratio: 0.92 (0.57-1.50, 95% CI) $P=.74$].

Conclusion: No statistically significant difference was found between the metformin and non-metformin users among the diabetic ST-segment elevation myocardial infarction patients who underwent primary percutaneous intervention in the risk of contrast-induced acute kidney injury.

Keywords: Contrast nephropathy, contrast-induced acute kidney injury, metformin, ST-segment elevation myocardial infarction

ÖZET

Giriş: Metformin kullanan diyabetik STEMI hastalarında kontrasta bağlı akut böbrek hasarı (CI-AKI) riskini azaltmak için metformin tedavisinin kesilmesi klinik pratikte sıklıkla kullanılan bir yaklaşımdır. Literatürde bu yaklaşımı destekleyecek yeterli kanıt yoktur. Bu çalışmanın amacı, metformin kullanan diyabetik STEMI hastalarında metformin kullanmayanlara göre CI-AKI riskinin farklı olup olmadığını belirlemektir.

Yöntemler: Araştırmanın evrenini 2014-2019 yılları arasında bu çalışmaya dahil olan merkezlerimize STEMI tanısı ile başvuran ve pPCI uygulanan hastalar oluşturmuştur. Dahil edilme kriterlerini karşılayan 343 diabetik hasta, metformin alanlar ve almayanlar olarak iki gruba ayrılmıştır. CI-AKI geliştirip geliştirmediklerini belirlemek için hastaların başvurudaki kreatinin değerleri ile pik kreatinin değerleri karşılaştırıldı. İki grup, 'inverse probability weighting' yöntemiyle yürütülen koşullu lojistik regresyon analizi kullanılarak karşılaştırıldı.

Bulgular: Ağırlıksız klasik çok değişkenli lojistik regresyon analizi, metformin kullanımının AKI ile ilişkili olmadığını ortaya koydu. Ağırlıklı koşullu çok değişkenli lojistik regresyon, AKI riskindeki artışın başlangıç kreatinin seviyeleriyle ilişkili olduğunu (OR: 1,49 [1,06-2,0 GA; %95]; $P=,02$) ve CI-AKI riskindeki artışın metformin kullanımı ile ilişkili olmadığını gösterdi (OR: 0,92 [0,57-1,50, GA: %95; $P=,74$]).

Sonuç: pPCI yapılan diyabetik STEMI hastalarında CI-AKI riskinde metformin kullanan ve kullanmayanlar arasında istatistiksel olarak anlamlı fark bulunmadı.

Anahtar Kelimeler: Kontrast nefropati, kontrasta bağlı akut böbrek hasarı, metformin, ST yükselmeli miyokard infarktüsü

ORIGINAL ARTICLE
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Received: April 5, 2022
Accepted: May 16, 2022

Cite this article as: Kalkan S, Karagöz A, Efe SÇ, et al. Metformin and CI-AKI risk in STEMI: Evaluation using propensity score weighting method. *Turk Kardiyol Dern Ars.* 2022;50(6):422-430.

DOI:10.5543/tkda.2022.22430

ST-segment elevation myocardial infarction (STEMI) is one of the leading causes of death worldwide and requires urgent administration of reperfusion therapy.[1] Diabetic patients constitute a significant portion of STEMI patients, and the risk of contrast nephropathy in diabetic patients who are to undergo primary percutaneous intervention (pPCI) poses a serious problem. The risk of contrast-induced acute kidney injury (CI-AKI) following pPCI in STEMI patients ranges from 6.4% to 27.7%,[2] and it is known that cardiovascular morbidity and mortality risk increase in patients who develop CI-AKI.[3] In addition, CI-AKI may cause long-term loss of renal function.[4,5]

Type 2 diabetes mellitus (T2DM) is a major risk factor for coronary artery disease (CAD) and acute coronary syndrome.[6] Metformin is the most commonly used oral antidiabetic agent in patients with T2DM since it effectively reduces cardiovascular mortality. In parallel, approximately one-third of diabetic patients receive metformin therapy.[7,8] Metformin stabilizes the blood glucose level by reducing insulin resistance as well as hepatic glycogenolysis and gluconeogenesis.[9] Contrast media (CM) administered during pPCI may increase the risk of CI-AKI in STEMI patients. It has also been claimed that metformin may increase the risk of acute renal failure in diabetic patients using metformin by reducing gluconeogenesis and causing lactic acid accumulation as a result.[10] Metformin, which is largely (90%) excreted by the kidney,[11] does not have a direct nephrotoxic effect.[12] Nevertheless, the risk of nephropathy and lactic acidosis observed in association with its precursor, that is, phenformin,[13] has raised the suspicion that metformin may also be associated with an increased risk of contrast nephropathy. In parallel, despite the lack of general consensus and insufficient evidence in that regard, discontinuation of metformin treatment before pPCI and during hospitalization has become a routine practice with a view to reducing the risk of metformin-induced lactic acidosis (MALA) and CI-AKI.[9]

It remains unclear whether metformin treatment should be continued in patients who are to undergo pPCI, and there is also no clear recommendation in current guidelines in that regard.[6,14] In addition, it is known that the risk of CI-AKI is higher in STEMI patients who require urgent pPCI compared to other STEMI patients who are to be administered CM intravenously.[15,16] A few studies involving only a limited number of patients have addressed the renal effects of metformin in patients with STEMI who underwent pPCI, but these studies did not employ weighted methods based on the patients' metformin use at admission, which may cause bias. In view of the foregoing, the aim of this study is to evaluate the effect of chronic metformin treatment on the risk of contrast nephropathy following pPCI in diabetic STEMI patients.

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
ARB	Angiotensin II receptor blocker
CAG	Coronary angiography
CAD	Coronary artery disease
CI-AKI	Contrast-induced acute kidney
CIN	Contrast-induced nephropathy
CM	Contrast media
CRP	C-reactive protein
DM	Diabetes mellitus
GFR	Glomerular filtration rate
HT	Hypertension
IA	Intra-arteriel
IPW	Inverse probability weighting
IV	Intravenous
LVEF	Left ventricular ejection fraction
MALA	Metformin-induced lactic acidosis
pPCI	Primary percutaneous intervention injury
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction

Methods

Study Group

The population of the study consisted of patients who applied to the healthcare centers covered by this study with the diagnosis of STEMI and underwent pPCI between 2014 and 2019. These 3069 patients were reviewed retrospectively, and 343 diabetic patients met the study inclusion criteria. Due to finding a non-biased estimate, we only included diabetic patients. The study group was further divided into 2 groups as the group of patients who have been receiving metformin and the group of patients who have not. The Median age of the study group was 61 years. Twenty-nine percent of the patients included in the study group were female.

Study inclusion criteria were determined as having diabetes, having presented to the hospital with the complaint of chest pain in the first 12 hours of the onset of chest pain, having ST elevation of at least 1 mm (2 mm for V1-V3) in 2 or more adjacent leads, or having new-onset left bundle branch block.[6]

On the other hand, study exclusion criteria were determined as having signs of active infection, active malignancy, and severe renal failure [glomerular filtration rate (GFR) <30 mL/min/1.73 m^2] at admission or having been treated with hemodialysis.

Patients' baseline demographic and clinical characteristics including their diabetes mellitus (DM), hypertension (HT), dyslipidemia, smoking, and CAD history were obtained from the hospital records. All patients included in the study were performed electrocardiography on admission, immediately after the pPCI procedure, 60 minutes after the pPCI procedure, and daily thereafter.

The blood samples of the patients were taken via the antecubital vein at admission and before the administration of any heparin therapy or reperfusion procedure. Complete blood cell counts and plasma levels including blood glucose, serum albumin, uric acid and creatinine levels, and hemogram and lipid profile were determined for all the patients. C-reactive protein (CRP) levels were measured using a Beckman Coulter's nephelometry analyzer. Characteristic data were collected during hospitalization. The clinical presentation including the heart rate and the Killip class was assessed upon admission by the attending physician. Routine biochemistry tests and creatinine measurements were completed in the first 24 hours of admission and repeated every 24 hours thereafter.

Outcome variable: Contrast-induced acute kidney injury[17]

Definitions

Contrast-induced acute kidney injury was defined as having an increase of 0.5 mg/dL in plasma creatinine levels or a 25% increase in basal creatinine levels within 72 hours after

the completion of the pPCI procedure in accordance with the European Society of Urogenital Radiology recommendations.[18,19] Taking into consideration the urgency of performing the pPCI procedure, metformin treatment was not stopped prior to pPCI but was usually discontinued after the completion of the pPCI procedure. Subsequently, blood glucose levels were controlled in accordance with the current consensus statement.[20]

All patients were performed postprocedural transthoracic echocardiography (Vivid 5 or Vivid 7; GE Vingmed Ultrasound AS, Horten, Norway) during hospitalization. The left ventricular ejection fraction (LVEF) was calculated using the biplane Simpson method.

Thrombolysis in myocardial infarction (TIMI) was defined as having the number of cine-frames needed for contrast to reach the standardized distal landmarks of coronary arteries.[21]

The amount of opaque used was divided by the weight of the patient, and the body weight-adapted contract media value was obtained in mL/kg.

Diseased vessel number was defined as the presence of a greater than 50% diameter stenosis in major epicardial arteries.

Angiographic Analyses

The coronary angiography (CAG) was performed using a Siemens Artis floor angiography device. All patients underwent pPCI procedure for culprit lesion. Coronary interventions were performed in accordance with the current guidelines.[6,22] All patients were given 300 mg chewable aspirin and a loading dose of 600 mg clopidogrel on admission and 70 U/kg standard heparin before the procedure. All pPCI procedures were performed by experienced interventional cardiologists using a femoral approach. The patients were subjected to direct stenting, conventional stenting, or only balloon dilation depending on the coronary anatomy and lesion characteristics. After the pPCI, patients were given 100 mg/day aspirin and 75 mg/day clopidogrel or ticagrelor or prasugrel. This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the Kartal Koşuyolu Yüksek İhtisas Eğitim ve Araştırma Hastanesi (2020/KK/141).

Statistical Analyses

Continuous research data were expressed as mean and standard deviation values, whereas the categorical data were expressed as absolute and percentage values. Independent samples *t*-test and Mann–Whitney *U* test were used for the comparisons of independent continuous data groups, and Pearson''s chi-squared or Fisher''s exact test was used used for the comparisons of categorical data groups. Crude univariate and adjusted multivariate regression analyses were used to determine the independent predictors of the dependent (CI-AKI) variable. We have inputed continuous predictor variable with lower than 10% and cathegoric variable lower than 5% using "Hmisc r package" with "areg" function.

Statistical Modelling

Inverse probability weighting (IPW) methods are used to decrease bias. Accordingly, in this study, IPW methods were used to adjust for confounders. The following covariates of age, gender, hemoglobin A1c (HbA1c), admission creatinine, hypertension (HT), and previous myocardial infarction (MI) were selected based on prior studies as the outcome condition in the logistic regression model for metformin and the medications used, that is, angiotensin-converting enzyme (ACE)/angiotensin II receptor blocker (ARB) inhibitors and statin, were taken into account in the model.[23,24] The probabilities estimated by the model were used to calculate stabilized IPW weights, which were then used to weigh each individual's contribution to the AKI and the logistic regression model. The model was adjusted to the plausible confounders, that is, age, creatinine, HbA1c, spontaneous bacterial peritonitis, hemoglobin, body weight-adapted CM, and metformin usage (double robust method). Model's coefficient was represented using odds ratio (OR), and CI was taken as 95%.[17]

For all statistical analyses, 2-tailed probability (*P*) values less than .05 were deemed to indicate statistical significance. All statistical analyses were performed using R 4.01 software (Vienna, Austria) with "ipw," "ggplot," "rms" packages.

Results

The median age of the patients included in the study was 61 (min. 54, max. 72) years (IQR: 25th-75th). Of the 343 patients, 100 (29.1%) were female. Patients were divided into 2 groups according to whether they have been using metformin or not. The baseline characteristics of patients that have and have not been using metformin are shown in Table 1. There was statistically significant difference between the groups in terms of HT presence [133 (68.2%) vs. 85 (57.4%), $P = .04$], basal creatinine levels [1.03 (0.50) vs. 1.01 (0.74), $P < .001$], ACE/ARB usage [48 (24.6%) vs. 64 (43.2%), $P < .001$], antiagregan usage [39 (20%) vs. 56 (37.8%), $P < .001$], beta-blocker usage [39 (20%) vs. 48 (32.4%), $P < .001$], and statin usage [26 (13.3%) vs. 44 (29.7%), $P < .001$]. On the other hand, no statistically significant difference was found between the groups in terms of age, gender, systolic blood pressure, diastolic blood pressure, and smoking status. Additionally, there was no significant difference between the groups in terms of the following laboratory findings of albumin, CRP, triglyceride, total cholesterol, lymphocyte count, glucose, uric acid, neutrophil and hemoglobin, low-density lipoprotein, and platelet count. There was no significant difference between the groups also in terms of LVEF, body weight-adapted CM, body mass index, Killip classification, and in-hospital mortality (Table 1). Study inclusion criteria are presented in Figure 1 in the consort flowchart.

The comparison of the clinical and procedural characteristics of the patients is given in Table 2. Accordingly, CI-AKI, CHA_2DS_2-VASc [congestive heart failure, HT, age ≥75 years (doubled), DM, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65-74 years, sex category] score, no-reflow, TIMI score, diuretic usage at admission, multivessel PCI, in-hospital hemofiltration or dialysis, previous MI, disease vessel number, and IPW score were similar between the groups (Table 2). On the other hand, no-reflow was found to be higher in the group of patients who have not been using

Table 1. Baseline Clinical and Laboratory Variables Comparison Between Users or Non-users of Metformin

Variables	Metformin− (n = 195)	Metformin+ (n = 148)	*P*
Age (years)	63.7 (12.5)	61.3 (11.9)	.06
Gender (n, %) (female)	58, 29.7 %	42, 28.4%	.78
HT (n, %)	133, 68.2%	85, 57.4%	.040
Systolic blood pressure (mm Hg)	131.6 (30.5)	139.2 (34.1)	.87
Diastolic blood pressure (mm Hg)	77.5 (16.3)	78.6 (16.8)	.55
Smoking (n, %)	122, 62.6%	85, 57.4%	.336
Glucose (mg/dL)	170.3 (116)	177 (97)	.56
Creatinine (mg/dL)	1.03 (0.50)	1.01 (0.74)	<.001
Uric acid (mg/dL)	6.4 (1.9)	6.0 (1.7)	.06
Albumin (g/L)	3.72 (0.42)	3.73 (0.36)	.88
CRP (mg/L)	0.8 (0.4-2.9)	0.6 (0.3-1.6)	.05
Triglyceride (mg/dL)	142 (99-200)	152 (105-201)	.38
LDL (mg/dL)	114 (36)	117 (38)	.48
Total cholesterol (mg/dL)	180 (49)	185 (47)	.40
Neutrophile ($\times 10^3$/μL)	9.58 (5.16)	9.09 (4.32)	.35
Lymphocyte ($\times 10^3$/μL)	1.82 (1.0)	2.01 (1.1)	.10
Hemoglobin (g/dL)	13.3 (2.0)	13.7 (2.0)	.14
Platelet (per cubic mm^3)	237 (66)	246 (75)	.27
EF%	44.5 (11.3)	43.6 (11.2)	.47
Body weight-adapted contrast agent (mL/kg)	1.76 (1.02)	1.80 (1.1)	.69
BMI (kg/m^2)	28.9 (4.6)	29.5 (5.6)	.29
Killip class I	175 (89.7)	120 (81.1)	.12
II	6 (3.1)	6 (4.1)	
III	8 (4.1)	11 (7.4)	
IV	6 (3.1)	11 (7.4)	
In-hospital mortality (n, %)	23, 11.8%	20, 13.5%	.63
ACE/ARB (n, %)	48, 24.6 %	64, 43.2%	<.001
Antiplatelet usage (n, %)	39, 20 %	56, 37.8%	<.001
Beta blocker (n, %)	39, 20 %	48, 32.4%	<.001
Statin (n, %)	26, 13.3 %	44, 29.7%	<.001

CRP, C-reactive protein; LDL, low-density cholesterol; EF, ejection fraction; BMI, body mass index; ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; smoking, active and ex-smoker.

metformin [22 (11.3%) vs. 7 (4.8%); *P* = .03]. Stabilized weighting density plot between the groups of patients who have and have not been using metformin is shown in Figure 2.

Non-weighted classic multivariable logistic regression analysis revealed that metformin use was not associated with AKI [OR: 0.91 (0.56-1.49, 95% CI); *P* = .75] (Table 3). On the other hand, weighted conditional multivariable logistic regression revealed that the increase in the risk of AKI was associated with baseline creatinine levels [OR: 1.49 (1.06-2.10, 95% CI); *P* = .02] and that the increase in the risk of CI-AKI was not associated with metformin usage [OR: 0.92 (0.57-1.50, 95% CI; *P* = .74] or hemoglobin levels [OR: 1.01 (0.89-1.20, 95% CI; *P* = .92] (Table 4). The adjusted variable plot indicated the association between baseline creatinine and metformin on AKI as demonstrated in Figure 3.

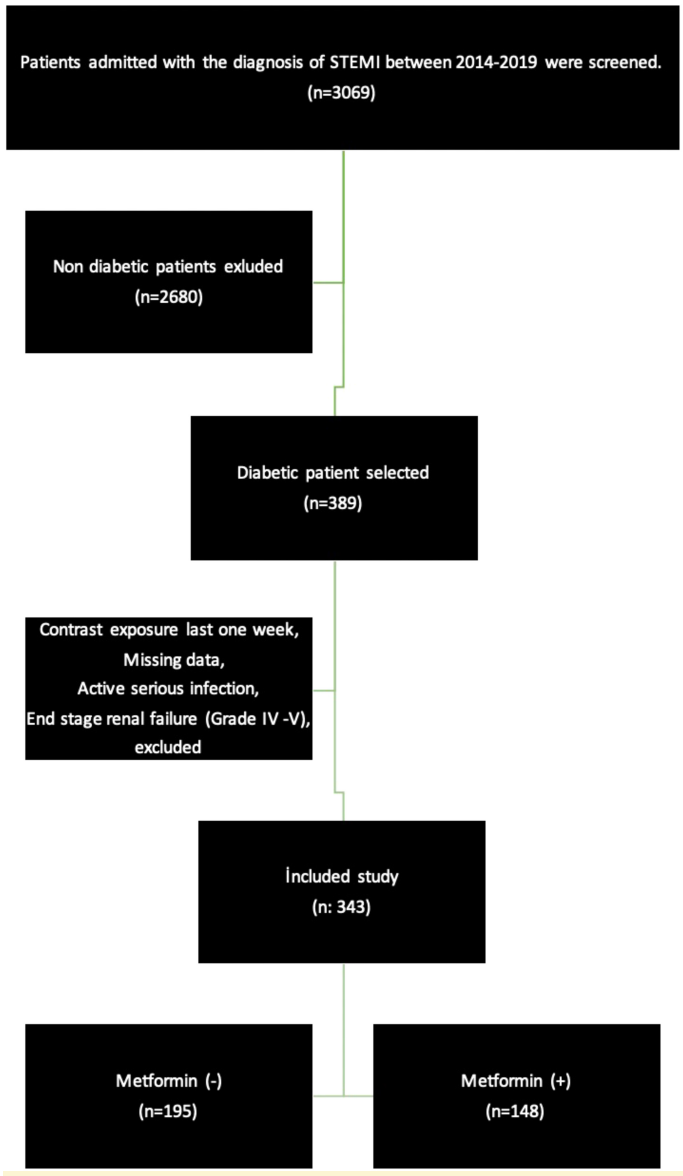

Figure 1. Consort flow diagram for inclusion to the study.

Discussion

The findings of this study revealed that the increase in the risk of AKI was associated with baseline creatinine levels (OR: 1.49, 1.06-2.10, 95% CI) but not with metformin usage (OR: 0.92, 0.57-1.50, 95% CI) in diabetic patients who were admitted to the healthcare centers with the diagnosis of STEMI and

Table 2. Clinical and Procedural Charecteristics of Patients

Variables	Metformin− (n=195)	Metformin+ (n=148)	P
CHADS VASc	2.96 (1.44)	2.67 (1.41)	.06
CI-AKI (n, %)	58, 29.7%	43, 29.1%	.89
No reflow (n, %)	22, 11.3%	7, 4.8 %	.03
TIMI admission 0	145, 74.4%	100, 68%	.39
1	17, 8.7%	11, 7.5%	
2	15, 7.7%	16, 10.9%	
3	18, 9.2%	20, 13.6%	
During admission diuretic usage (n, %)	20, 10.3%	14, 9.5%	.82
Multivessel PCI (n, %)	6 (3.2)	11, 7.8%	.14
In-hospital hemofiltration or dialysis (n, %)	3, 1.5%	1, 0.7%	.63
Previous MI (n, %)	41, 21%	28, 18.9%	.63
Disease vessel number (>%50 narrow) (n, %)			.49
1	96 (49.3)	73 (49.3)	
2	63 (32,3)	42 (28.4)	
3	36 (18.5)	33 (22.3)	
Inverse probability weighting score	1.0 (0.16)	0.99 (0.20)	.88

CHADS VASc, CHADS VASc score; CI-AKI, contrast-induced acute kidney injury; MI, myocardial infarction; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

underwent pPCI. The results of the classical and IPW logistic regression analyses indicated that the risk of CI-AKI have not differed in diabetic STEMI patients based on whether they have been using metformin or not, that is, metformin usage did not increase the risk of CI-AKI.

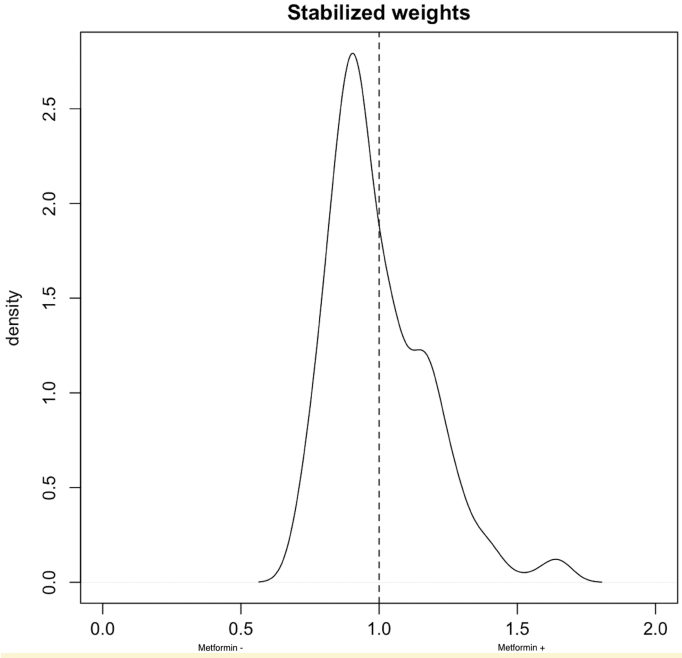

Figure 2. Stabilized weighting density plot between metformin user and non-user group.

Table 3. Non-weighted Classic Multivariable Logistic Regression Analysis

Variables	Odds Ratio	95% CI	P
Age (years)	1.00	0.98-1.02	.66
Admission creatinine (mg/dL)	1.56	1.06-2.29	.02
Body weight-adapted contrast agent (mL/kg)	0.83	0.65-1.05	.12
HgA1c (%)	1.09	0.98-1.22	.13
Hemoglobin (g/dL)	1.02	0.90-1.15	.74
Admission systolic blood pressure (mm Hg)	1.00	0.99-1.01	.69
Metformin usage yes/no	0.91	0.56-1.49	.75

Metformin was first synthesized in 1922 and has been in use for nearly 60 years in order to control hyperglycemia in patients with T2DM.[25] Metformin is excreted by the kidneys as it is, most likely through both glomerular filtration and tubular excretion. Approximately, 90% of the absorbed metformin is eliminated through the renal route within the first 24 hours. Metformin is contraindicated in patients with estimated glomerular filtration rate (eGFR) of less than 30 mL/min.[26]

A significant portion of STEMI patients are diabetic patients and hence CI-AKI poses a significant problem in this patient group who underwent pPCI. It has been claimed that metformin, which is used as the first-line treatment in T2DM patients, may increase the risk of CI-AKI and MALA in this patient group. In parallel, it has been suggested in many studies that addressed the elective PCIs that metformin treatment should be discontinued before the pPCI procedure to reduce the risk of CI-AKI and MALA.[27-29]

Contrast-induced acute kidney injury, formerly known as contrast-induced nephropathy (CIN), describes the sudden deterioration of renal function after exposure to intravascular ionized contrast. It is demonstrated by a more than 25% rise in serum creatinine levels 48 hours after a 0.5 mg/dL contrast exposure absolute rise in creatinine levels.[30] The pathophysiological mechanisms underlying CK-AKI have not been fully elucidated.[3] The

Table 4. Inverse Probability Weighted Conditional Multivariable Logistic Regression Analysis

Variables	Odds Ratio	95% CI	P
Age (years)	0.99	0.97-1.01	.66
Admission creatinine (mg/dL)	1.49	1.06-2.10	.02
Body weight-adapted contrast agent (mL/kg)	0.82	0.64-1.04	.10
HgA1c (%)	1.07	0.95-1.20	.23
Hemoglobin (g/dL)	1.01	0.89-1.13	.92
Admission systolic blood pressure (mmHg)	1.00	0.99-1.01	.59
Metformin usage yes/no	0.92	0.57-1.50	.74

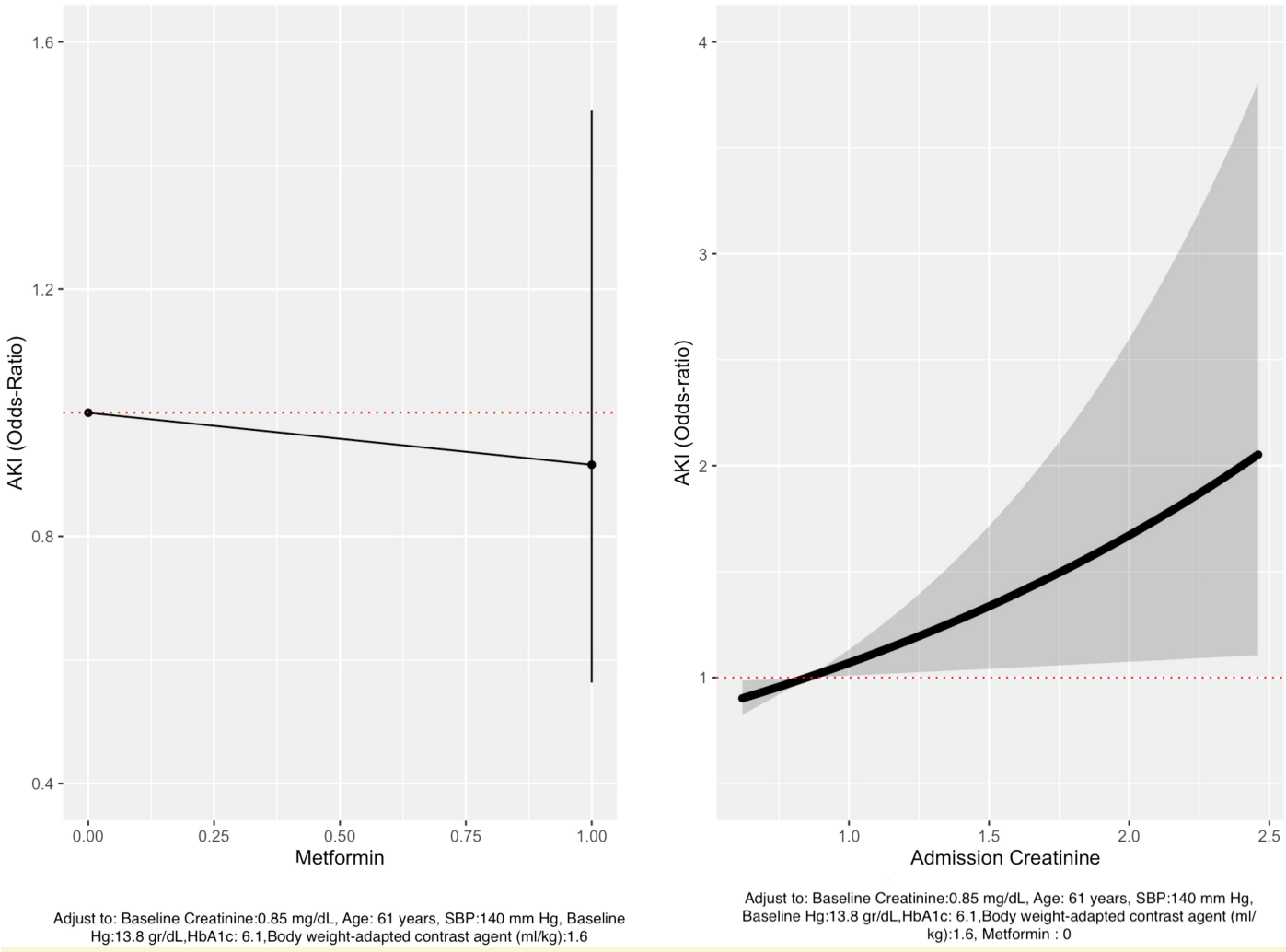

Figure 3. Adjusted variable plot for predicting contrast induced-acute kidney injury according to metformin and admission creatinine.

CM may exert a direct cytotoxic effect on the tubular epithelial due to increased reactive oxygen radicals and decreased nitric oxide activity.[31] In addition, acute tubular necrosis, hypoxia, and medullary vasoconstriction may occur through vasoconstrictor mediators.

Contrast-induced nephropathy is associated with long-term loss of renal function and increased in-hospital mortality risk,[32] and lactic acidosis developed secondary to metformin usage can result in mortality in up to 50% of the cases.[4] For this reason, it is very important to identify patients with high CIN and lactic acidosis risks and to prevent the clinical conditions in question. On the other hand, discontinuation of metformin therapy in diabetic patients may worsen glycemic control during hospitalization giving rise to acute effects and increasing cardiovascular risks in the long term.[33]

Patients who underwent cardiac angiography constitute the majority of the CI-AKI cases reported in the literature in recent years. Cardiac angiography differs from intravenous (IV) administration in that the contrast injection is intra-arterial and suprarenal, the injection is administered with a catheter which may cause atheroembolism, and the kidneys are suddenly exposed to high contrast.[15,16] Although there is no evidence of a dose–toxicity relationship in IV administration when used at diagnostic doses,[34] the nephrotoxic effect of iodinated CM may be dose-related in cardiac angiographic procedures. This may be the reason why the overall incidence of CI-AKI in studies that address cardiac angiographic procedures is higher than the overall incidence of CI-AKI in patients that receive iodinated CM intravenously.[15,35] In this context, the patient group who underwent arterial and coronary interventions should be addressed also in terms of the risk of CI-AKI.

The risk of CI-AKI in STEMI patients using metformin has been assessed in a limited number of studies available in the literature. In one of these studies, which included 372 STEMI patients who underwent pPCI, it was determined that chronic metformin use did not have any negative effect on renal functions following pPCI and even that it had a protective effect against the development of CI-AKI. In the same study, lactic

acidosis was not observed in any of the patients included in the study.[3]

In another study, the safety of metformin usage together with CM administration was investigated on 379 STEMI patients without T2DM or chronic kidney disease. The patients included in the said study were randomized to receive metformin or placebo twice daily after primary pPCI for 4 months. Consequentially, no significant difference was found between the 2 groups that received metformin or placebo over the study period in terms of eGFR, and it was determined that the patients that received metformin were not at increased risk for CI-AKI.[36]

Additionally, in another study, the safety of peri-procedural metformin usage with respect to the development of CIN and MALA was demonstrated in patients with normal or mildly impaired renal functions (eGFR >60 mL/min/1.73 m^2), who were scheduled for elective CAG, and have been using metformin for T2DM treatment. In addition, the eGFR values measured 48 hours after CAG in patients in whom metformin treatment was not discontinued were found to be better than in patients in whom metformin treatment was discontinued. This result was attributed to the renoprotective effect of metformin in the setting of contrast exposure.[37]

The most important side effect of metformin treatment is the risk of developing MALA. Metformin-induced lactic acidosis is characterized with blood lactate levels above 5 mmol/L, decreased pH levels, and increased bicarbonate anion gap. Metformin doses are usually above the therapeutic range of 2-4 mg/L in patients who develop MALA and can be toxic at high doses. Metformin increases anaerobic respiration by inhibiting the mitochondrial respiratory chain enzyme and the mitochondrial glycerophosphate dehydrogenase enzyme, and the increased pyruvate is converted to lactate within the Krebs cycle.[38] The increased lactate due to the metformin-induced reduction in gluconeogenesis in the liver may not be reduced by glucose production.[39] As a result, lactic acidosis develops due to both increased production and decreased consumption.[40]

It is estimated that this condition occurs in up to 0.084 cases per 1000 patient-years. This incidence may not seem high, but the mortality rate associated with this condition is about 50%, which is very high. It has been reported that lactic acidosis occurred since one or more patient-associated contraindications for the medication were overlooked in almost all reported cases.[34] It was demonstrated in many studies and meta-analyses that the risk of lactic acidosis is very low and is associated primarily with the underlying diseases such as hypoxic conditions in particular[41] and other possible comorbidities rather than metformin usage.[42,43] Interestingly, in critically ill patients suffering from severe MALA, the prognosis of the patients that have been using metformin was significantly better than that of the patients who have not been using metformin.[44] In comparison, in this study, none of the patients has developed MALA.

Substantial controversies exist between the recommendations of international guidelines on CM administration in patients receiving metformin and on the discontinuation of metformin.[14,45-47] For example, it is recommended in the current European Society of Cardiology guidelines that the renal function is to be checked for at least 3 days after angiography and that metformin is to be discontinued in the event that renal function deteriorated.[6] On the other hand, it is recommended in the current U.S. Food and Drug Administration guidelines that metformin is to be discontinued before CM administration because of the perceived risk of CI-AKI.[3] Additionally, it is recommended in the current European Society of Radiology guidelines that metformin is to be discontinued in the event of CM administration and that metformin is to be administered to patients with eGFR values of <30 mL/min/1.73 m^2 receiving IV CM or intra-arteriel (IA) CM with second-pass renal exposure as well as to all patients receiving IA CM with first-pass renal exposure or who have AKI.[14]

Similarly, in the current guidelines of the American College of Radiology, it is stated that there is no need to discontinue metformin in patients who do not have a history of severe renal failure or AKI (GFR >30 mL/min) and who underwent IV CM. Additionally, it is emphasized that metformin should only be temporarily discontinued in patients with a known history of AKI, severe renal failure (GFR <30 mL/min), or CM exposure due to arterial catheterization and that renal functions are to be evaluated 48 hours later.[34]

The key benefit of IPTW is that all patients who are included in the study can be analyzed, additionally, using a doubly robust method like combining propensity score weighting and covariable adjustment for outcome estimation produces more reliable results.[48] Due to without conditioned to metformin in Zeller et al[3] results in may give biased result.

In summary, the findings of this study indicated that the intake of metformin in STEMI patients did not increase the risk of CI-AKI. This is a finding that would relieve the clinicians in terms of administration of metformin to the STEMI patients who underwent pPCI and had intra-arterial exposure to CM. In this way, the acute and long-term side effects associated with the discontinuation of metformin would also be prevented.

Apart from its strengths mentioned throughout the text, there were also some limitations to this study. The first limitation is that it was carried out retrospectively. Secondly, patients who were admitted to 2 healthcare centers only were included in the study. Thirdly, the data on the long-term renal functions of the patients were not taken into account within the scope of the study. Lastly, as per the nature of the regression method, some confounders might not have been calculated or included in the regression model. Nevertheless, it would be possible to reach a final conclusion based on the results of large-scale studies conducted with this patient group.

Conclusion

Metformin usage was not found to be associated with an increased risk for CI-AKI in diabetic STEMI patients who underwent pPCI and were exposed to CM. This finding indicates that the metformin therapy might be continued in STEMI patients without interruption. Despite the fact that IPW method was used in this study, further large-scale studies are needed in order to reach a final conclusion.

Visual summary of the article can be seen in Figure 4.

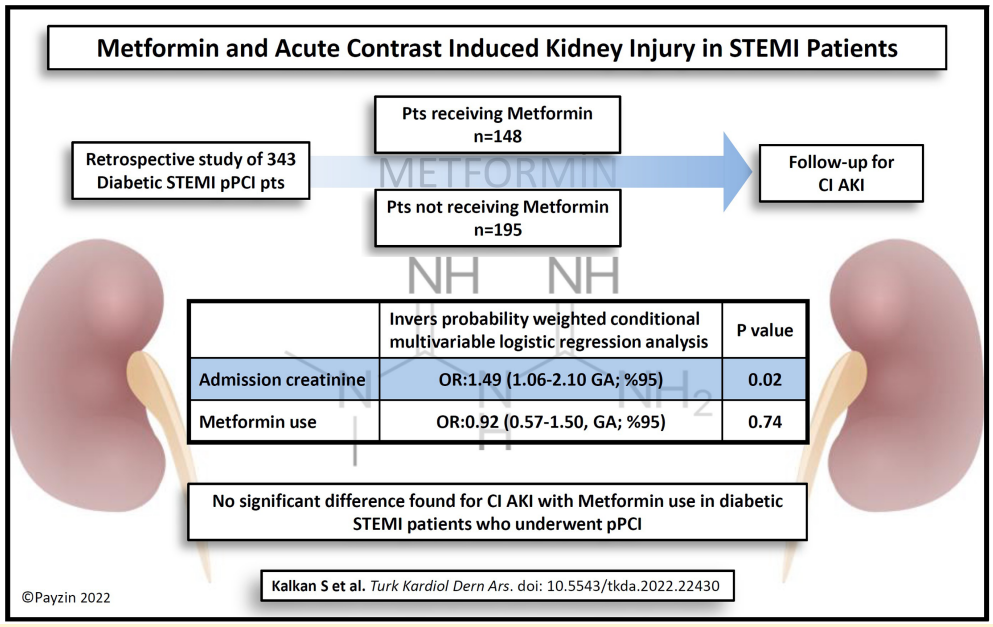

Figure 4. A visual summary of the article.

Ethics Committee Approval: The study approved by the ethics committee of Koşuyolu Kartal Heart Training and Research Hospital (approval no: 2022/11/616).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.K., C.Y.K., I.H.T.; Design – S.K., A.K.; Supervision – I.H.T., V.O.; Materials – S.Ç.E, A.S.; Data Collection and/or Processing – M.F.Y., U.B., S.K., B.S., A.S.; Analysis and/or Interpretation – S.K., A.K.; Literature Review – F.Y., U.B.; Writing – S.K., A.K.; Critical Review – C.K., C.Y.K.

Declaration of Interests: The authors declare that they have no competing interest.

Funding: This study received no funding.

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