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ORIGINAL RESEARCH

The Association of Metformin With Heart Failure in Patients With Diabetes Mellitus Receiving Anthracycline Chemotherapy

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ABSTRACT

BACKGROUND The prevention of heart failure (HF) is an important issue in patients treated with anthracyclines. Metformin, widely used to treat diabetes mellitus (DM), protects from anthracycline-induced cardiotoxicity in vitro and in animal models.

OBJECTIVES The aim of our study was to test the association of metformin with the occurrence of symptomatic HF in patients with DM receiving anthracyclines.

METHODS A total of 561 patients with DM received new anthracycline therapy between 2008 and 2021 in a tertiary care center; propensity score matching was used to compare patients with or without metformin treatment. The primary outcome was new onset symptomatic HF occurring within 1 year of the initiation of anthracyclines.

RESULTS A total of 315 patients (65 ± 11 years of age, 33.7% male) were included. Patients with and without metformin were well matched for age, sex, type of cancer, medications, and cardiovascular risk factors. Six patients treated with metformin and 17 matched patients developed HF within 1 year of anthracycline initiation. The incidence of HF in patients treated with metformin was lower than patients without metformin within 1 year after anthracyclines (cumulative incidence: 3.6% vs 10.5%; $P = 0.022$; HR: 0.35; 95% CI: 0.14-0.90; $P = 0.029$). The use of metformin (HR: 0.71; 95% CI: 0.50-1.00; $P = 0.049$), was also associated with lower mortality.

CONCLUSIONS The use of metformin was associated with a lower incidence of HF and overall mortality in patients with DM receiving anthracyclines. Our findings should be further confirmed by randomized control trials. (J Am Coll Cardiol CardioOnc 2023;5:674–682) © 2023 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Although the risk for cardiotoxicity has been recognized for decades, anthracyclines remain the first-line therapy in many patients with cancer with superior overall cancer survival and response rate.[1-4] The prevalence of symptomatic heart failure (HF) associated with anthracyclines is approximately 3%,[5] but the occurrence of cardiac dysfunction is higher, up to 40% in some studies.[6-8] The cardiovascular mortality in patients with anthracycline-induced HF is high, 9% at 5 years and 24% at 10 years in a recent study.[9]

The existing HF treatments have demonstrated modest effects on cardiac dysfunction induced by anthracyclines. Several randomized studies report that angiotensin-converting enzyme inhibitors/angiotensin receptor blockers or beta-blockers either have no effect or attenuate the decline in left ventricular (LV) ejection fraction by 3% to 4%.[10] Additionally, these treatments may be difficult to initiate and maintain in patients already subjected to volume depletion.[11] Although dexrazoxane does significantly reduce the risk of HF and LV dysfunction, there have been potential concerns regarding secondary malignant neoplasm.[12-14]

Metformin is a widely used antidiabetic drug that lowers glucose by reducing hepatic gluconeogenesis.[15] Metformin had previously been contraindicated for use in diabetic patients with HF due to the rare occurrence of lactic acidosis.[16] However, several studies demonstrated that metformin was not associated with adverse outcomes and was associated with improved prognosis in patients with diabetes mellitus (DM) and HF.[17-20] Initial in vitro studies in murine cardiomyocytes demonstrated that metformin decreases doxorubicin-induced apoptosis.[21] Metformin treatment was also shown to decrease LV dysfunction in rats injected with doxorubicin.[22] These prior studies suggest the use of metformin will be associated with improved prognosis in patients treated with anthracyclines. In summary, the existing cardioprotective interventions in patients treated with anthracyclines have modest benefit and/or unacceptable side effects. Using propensity matching, our aim was to test the association of metformin, a widely available and safe treatment with experimentally proven cardioprotection, with the occurrence of symptomatic HF in patients treated with anthracyclines.

METHODS

IDENTIFICATION OF PATIENTS AND ENDPOINTS. This study was conducted at the Hospital of the University of Pennsylvania and was approved by the local Institutional Review Board. Adult patients with DM receiving new treatment with anthracyclines between November 2008 and July 2021 were retrospectively identified by using the medication records at the Hospital of the University of Pennsylvania. The exclusion criteria were the use of anthracyclines for chemoembolization, dialysis, significant valvular heart disease (more than or equal to moderate), or known cardiomyopathy or HF before the initiation of anthracyclines.

ABBREVIATIONS AND ACRONYMS

AMPK = AMP-activated protein kinase
DM = diabetes mellitus
HF = heart failure
LV = left ventricular
ROS = reactive oxygen species

We defined the entry date as the date of initiation of anthracyclines and extracted baseline clinical characteristics including relevant medications and physical findings from the medical records. Preexisting cardiovascular risk factors and cardiovascular diseases were determined using the relevant International Classification of Diseases-Ninth Revision and/or International Classification of Diseases-Tenth Revision codes and confirmed by individual chart analysis. Anthracycline dose was calculated based on the following doxorubicin hematologic toxicity equivalence: daunorubicin, 1.0; idarubicin, 5.0; and mitoxantrone, 4.0.[23]

The primary outcome was new onset symptomatic HF and secondary outcome was all-cause mortality. Heart failure was identified by using the American College of Cardiology/American Heart Association outcome definition for clinical trials.[24] A symptomatic HF event was confirmed if an individual met all 3 criteria of: 1) symptoms; 2) objective evidence; and 3) initiation or intensification of treatment. HF symptoms were defined by at least 1 of the following: dyspnea at rest or on exertion, decreased exercise tolerance, fatigue, worsening end-organ perfusion, and volume overload. Objective evidence consisted of at least 2 physical examination findings (peripheral edema, ascites in the absence of hepatic disease, pulmonary crackles or rales, increased jugular venous pressure, S3 gallop, rapid weight gain related to fluid retention) or 1 physical examination and at least 1 laboratory finding of HF (increased B-type natriuretic peptide or N-terminal pro-B-type natriuretic peptide, radiological evidence of pulmonary congestion, Kerley B lines or pleural effusion, decreased LV ejection fraction). A change of treatment was defined as at least 1 of the following: augmentation in oral diuretic therapy, intravenous diuretic or vasoactive agent, or mechanical or surgical intervention. Two independent cardiologists (T.O. and B.L.) adjudicated symptomatic HF separately. The patients with disagreement between 2 readers were reassessed by a third cardiologist (M.S.-C.).

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TABLE 1 Baseline Characteristics of Patients Treated With Anthracyclines With or Without Metformin Exposure

	Total Cohort (N = 561)	Metformin (n = 310)	No Metformin (n = 251)	*P* Value	Standardized Difference
Age, y	64.0 (56.0-70.0)	63.0 (55.8-69.0)	65.0 (56.0-72.0)	0.18	0.06
Sex				0.067	0.16
Female	378 (67.4)	219 (70.7)	159 (63.4)		
Male	183 (32.6)	91 (29.4)	92 (36.7)		
Body mass index, kg/m^2	30.1 (26.3-31.4)	31.0 (26.7-35.6)	29.2 (25.9-35)	0.026	0.37
Sulfonylureas	102 (18.0)	72 (23.2)	30 (12.0)	<0.001	0.30
DPP-4 inhibitors	48 (8.6)	36 (11.6)	12 (4.8)	0.003	0.25
GLP-1 agonists	14 (2.5)	8 (2.6)	6 (2.4)	0.89	0.01
Meglitinide	4 (0.7)	1 (0.3)	3 (1.2)	0.22	0.11
SGLT2 inhibitors	14 (3.0)	9 (2.9)	5 (2.0)	0.49	0.06
Thiazolidine	10 (1.8)	8 (2.6)	2 (0.8)	0.098	0.14
Insulin	204 (36.3)	81 (26.1)	123 (49.0)	<0.001	0.49
Anthracycline total dose, mg/m^2	225 (127-257)	240 (150-270)	200 (100-243)	<0.001	0.30
Type of cancer					
Lymphoma	169 (30.1)	94 (30.3)	75 (29.9)	<0.001	0.01
Leukemia	55 (9.8)	23 (7.4)	32 (12.8)		0.18
Breast cancer	156 (27.8)	108 (34.8)	48 (19.1)		0.36
Sarcoma	6 (1.1)	3 (1.0)	3 (1.2)		0.02
Others	175 (31.2)	82 (26.5)	93 (37.1)		0.23
Glycosylated hemoglobin, %	6.8 (6.1-7.9) (n = 389)	6.9 (6.2-7.9) (n = 212)	6.8 (6.1-7.8) (n = 180)	0.93	0.03
Systolic BP, mm Hg	130 (118-142)	131 (120-144)	129 (117-140)	0.16	0.12
Diastolic BP, mm Hg	74 (67-81)	76 (68-82)	73 (66-80)	0.014	0.19
Heart rate, beats/min	83 (72-95)	83 (73-94)	82 (72-97)	0.94	0.04
ACE inhibitor/ARB	310 (55.2)	178 (57.4)	132 (52.6)	0.25	0.10
β-blockers	223 (39.8)	118 (38.1)	105 (41.8)	0.36	0.08
Statins	359 (64.0)	215 (69.4)	144 (57.4)	0.003	0.25
Aspirin	258 (46.0)	141 (45.5)	117 (46.6)	0.79	0.02
Hypertension	455 (81.1)	255 (82.3)	200 (79.7)	0.44	0.07
Hyperlipidemia	389 (69.3)	221 (71.3)	168 (66.9)	0.27	0.10
CAD	83 (14.8)	44 (14.2)	39 (15.5)	0.66	0.04
Atrial fibrillation	33 (5.7)	17 (5.5)	16 (6.4)	0.66	0.04
COPD	44 (7.8)	27 (8.7)	17 (6.8)	0.39	0.07
CVD	334 (6.0)	26 (8.4)	33 (13.2)	0.069	0.13
PAD	59 (8.6)	27 (8.7)	21 (8.4)	0.89	0.01
CKD	166 (15.7)	85 (27.4)	81 (32.3)	0.21	0.11
Creatinine, mg/dL	0.85 (0.69-1.08)	0.81 (0.68-1.00)	0.89 (0.71-1.22)	<0.001	0.36
Echo screening	398 (70.9)	213 (68.7)	185 (73.7)	0.19	0.11
LVEF, %	65.0 (60.0-66.0)	65.0 (60.0-66.0)	65.0 (60.0-65.5)	0.91	0.03
Entry year					
2010	4 (0.7)	1 (0.3)	3 (1.2)	0.092	0.10
2011	17 (3.0)	10 (3.2)	7 (2.8)		0.02
2012	15 (3.0)	6 (1.9)	9 (3.6)		0.10
2013	21 (3.7)	14 (4.5)	7 (2.8)		0.09
2014	45 (8.0)	29 (9.4)	16 (6.4)		0.11
2015	49 (8.7)	31 (10.0)	18 (7.2)		0.10
2016	53 (9.4)	36 (11.6)	17 (6.8)		0.17
2017	92 (16.4)	48 (15.5)	44 (17.5)		0.05
2018	87 (15.5)	41 (13.2)	46 (18.3)		0.14
2019	68 (12.1)	35 (11.3)	33 (13.2)		0.06
2020	75 (13.3)	45 (14.5)	30 (12.0)		0.07
2021	35 (6.2)	14 (4.5)	21 (8.4)		0.16

Values are median (IQR) or n (%), unless otherwise indicated.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BP = blood pressure; CAD = coronary artery disease; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CVD = cerebrovascular disease; DPP = dipeptidyl-peptidase; GLP1 = glucagon-like peptide 1; LVEF = left ventricular ejection fraction; PAD = peripheral arterial disease, SGLT2 = sodium-glucose cotransporter-2.

STATISTICAL ANALYSIS. Categorical variables are presented as frequencies and continuous variables are presented as the mean ± SD or median (IQR). Normality was determined by using the Shapiro-Wilk test. Continuous variables were compared using standardized differences and a 2-sample *t* test or the Mann-Whitney *U* test according to the data distribution. Differences between proportions were assessed using standardized differences and chi-square analysis. Logistic regression analysis was used to calculate a propensity score by examining the association of metformin treatment with baseline characteristics and including potential confounders of the association between metformin exposure and HF. The variables included in the regression model were age, sex, body mass index, the use of sulfonylureas, dipeptidyl-peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, insulin, angiotensin-converting enzyme inhibitors or angiotensin receptor blocker, beta-blockers, statins, type of cancer, systolic and diastolic blood pressure, coronary arterial disease, atrial fibrillation, cerebrovascular disease, peripheral arterial disease, creatinine, echocardiographic screening, and entry year. Using nearest-neighbor matching with a caliper width of 0.2 SD, the patients were distributed into patients with or without metformin. Because of the occurrence of death as a competing risk, the cumulative incidence function for HF over 1- and 5-year follow-up was compared using Gray's method. Univariable Fine-Gray regression models were used to calculate the HR and 95% CI between metformin use and incident HF adjusting for matched pairs by using a robust sandwich covariance estimate. The incidence of HF was analyzed within 1 and 5 years of the initiation of anthracyclines to increase the probability that the HF was due to anthracycline toxicity. Patients were censored at the earliest occurrence of the date of 1 year (or 5 years for the analysis at 5 years) after initiating anthracyclines, or the date of last encounter (before October 31, 2021). The association of metformin with the occurrence of death within the full follow-up period was determined using Cox proportional hazards analysis and presented as HR with 95% CI. Kaplan-Meier curves using the log-rank test were used to assess differences in mortality. A *P* value <0.05 was considered significant and all analyses were considered exploratory. Statistical analyses were performed by SPSS version 16.0 (IBM Corporation), JMP pro 16.0 (SAS Institute), and R version i386 3.5.0 (R Foundation for Statistical Computing).

TABLE 2 Baseline Characteristics of Patients Treated With Anthracyclines With or Without Metformin Exposure in Propensity-Matched Cohort

	Metformin (n = 175)	No Metformin (n = 175)	*P* Value	Standardized Difference
Age, y	65.0 (58.0-70.0)	66.0 (56.0-71.0)	0.99	0.01
Sex[a]			0.82	0.03
Female	117	115		
Male	58	60		
Body mass index, kg/m^2[a]	29.9 (25.6-35.2)	29.8 (26.6-35.2)	0.77	0.01
Sulfonylureas[a]	8 (16.0)	26 (14.9)	0.77	0.03
DPP-4 inhibitors[a]	9 (5.2)	11 (6.3)	0.64	0.01
SGLT2 inhibitors[a]	4 (2.3)	5 (2.9)	0.74	0.04
Insulin[a]	63 (36.0)	68 (38.9)	0.58	0.06
Anthracycline total dose, mg/m^2	231 (148-297)	220 (130-250)	0.12	0.18
Type of cancer[a]				
Lymphoma	56 (32.0)	54 (30.9)		0.02
Leukemia	17 (9.7)	21 (12.0)		0.07
Breast cancer	46 (26.3)	44 (25.1)	0.97	0.03
Sarcoma	1 (0.6)	1 (0.6)		0.00
Others	55 (31.4)	55 (31.4)		0.00
Systolic BP, mm Hg[a]	130 (118-141)	130 (118-141)	0.99	0.02
Diastolic BP, mm Hg[a]	74 (67-81)	74 (66-80)	0.69	0.02
ACE inhibitor/ARB[a]	96 (54.9)	97 (55.4)	0.91	0.01
Beta-blockers[a]	72 (41.1)	68 (38.9)	0.66	0.04
Statins[a]	110 (62.9)	114 (65.1)	0.66	0.05
CAD[a]	28 (16.0)	28 (16.0)	1.00	0.00
Atrial fibrillation[a]	9 (5.1)	11 (6.3)	0.64	0.05
CVD[a]	19 (10.9)	21 (12.0)	0.74	0.03
PAD[a]	15 (8.6)	18 (10.3)	0.58	0.06
Creatinine, mg/dl[a]	0.86 (0.71-1.03)	0.86 (0.71-1.13)	0.51	0.08
Echo screening[a]	126 (72.0)	125 (71.4)	0.91	0.01
Entry year[a]				
2010	1 (0.6)	1 (0.6)	0.99	0.00
2011	4 (2.3)	4 (2.3)		0.00
2012	6 (3.4)	5 (2.9)		0.03
2013	7 (4.0)	7 (4.0)		0.00
2014	12 (6.9)	14 (8.0)		0.04
2015	16 (9.2)	11 (6.3)		0.11
2016	16 (9.2)	17 (9.7)		0.02
2017	30 (17.1)	34 (19.4)		0.06
2018	27 (15.4)	24 (13.7)		0.05
2019	22 (12.6)	22 (12.6)		0.00
2020	22 (12.6)	26 (14.9)		0.07
2021	12 (6.9)	10 (5.7)		0.05

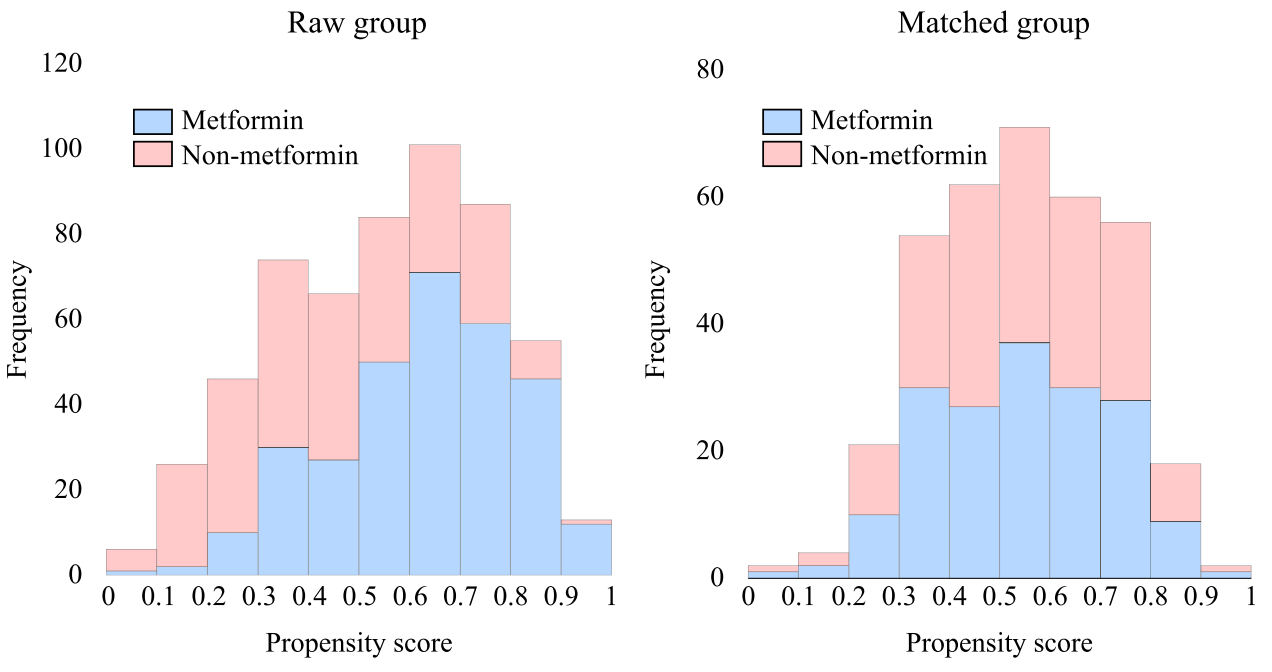
Values are median (IQR), n, or n (%). [a]Used to generate propensity score. Pre-existing cardiovascular disease: CAD or atrial fibrillation or PAD.

Abbreviations as in Table 1.

RESULTS

PATIENTS CHARACTERISTICS AND PROPENSITY SCORE MATCHING. Of 561 patients with DM (183 men, median age 64 [IQR: 56-70] years) who received new anthracycline treatment between November 2008 and July 2021, 310 patients were

FIGURE 1 Stacked Histogram of Propensity Score



(Left) The stacked histogram of the propensity score in the raw group (n = 561). (Right) The stacked histogram in the matched group.

treated with metformin. Baseline clinical characteristics of the entire cohort and of the patients treated with metformin at the initiation of anthracyclines are presented in Table 1. The proportion of women was slightly higher in metformin users (71.0% in metformin users and 63.0% in nonmetformin users; $P = 0.067$; standardized difference = 0.16). Metformin users had a greater body mass index (31.0 kg/m^2 vs 29.2 kg/m^2; $P = 0.026$), had higher prevalence of breast cancer, and were treated with more sulfonylureas, dipeptidyl-peptidase 4 inhibitors, thiazolidine, and statins (69.0% vs 57.0%; $P = 0.003$) than nonmetformin users. The dose of anthracyclines was higher in metformin users (240 mg/m^2 vs 200 mg/m^2; $P < 0.001$). Nonmetformin users were treated with more insulin and had lower diastolic blood pressure (76 mm Hg vs 73 mm Hg; $P = 0.014$), creatinine ($P < 0.001$), and prevalence of leukemia and cerebrovascular disease than metformin users. More nonmetformin users received echocardiography at the initiation of chemotherapy (74.0% vs 69.0%; $P = 0.19$; standardized difference = 0.11), and there were differences in the distribution of the entry year of chemotherapy without a specific pattern.

TABLE 3 Raw Number and Outcomes Frequencies in Patients Treated With Anthracyclines With or Without Metformin Exposure in the Propensity-Matched Cohort

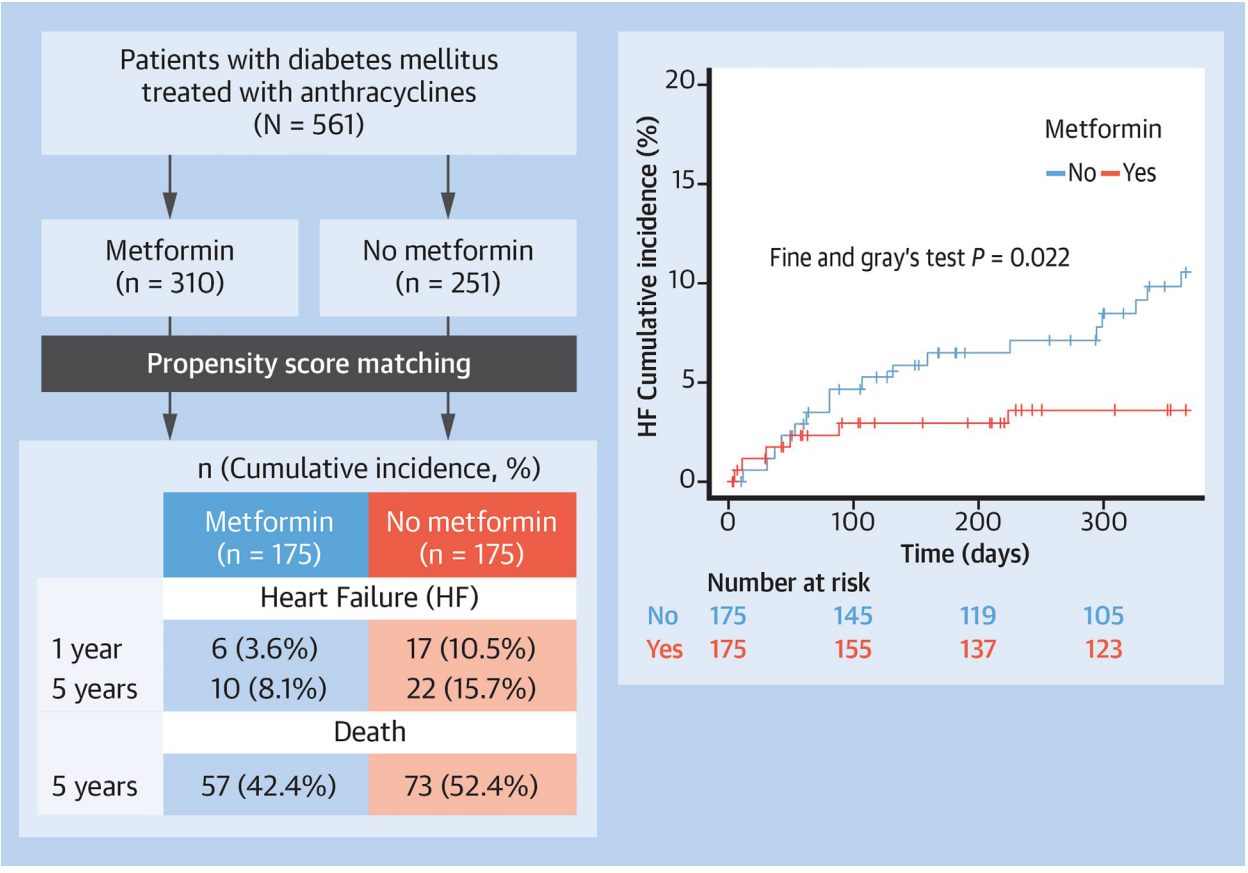
	Metformin (n = 175)	No Metformin (n = 175)	*P* Value
Heart failure within 1 y	6 (3.4)	17 (9.7)	0.016
Time to heart failure within 1 y, d	40 (10-122)	107 (48-296)	0.059
Heart failure within 5 y	10 (5.7)	22 (12.6)	0.024
Time to heart failure within 5 y, d	156 (25-1,060)	192 (60-340)	0.89
Death	60 (34.3)	77 (44.0)	0.062
Death within 5 y	57 (32.6)	73 (41.7)	0.076
Time to death, d	326 (159-679)	298 (104-684)	0.45
Follow-up period, d	661 (234-1,447)	515 (181-1,164)	0.072

Values are n (%).

The variables entered in the logistic regression analysis performed to estimate the propensity scores are marked by superscript letters in Table 2. The baseline characteristics of 175 matched pairs are summarized in Table 2. In the matched cohort, cardiovascular risk factors and diabetic medications were well balanced (Figure 1). Patients were followed for a median of 1.7 (IQR: 0.6-3.5) years.

Incidence of HF. A total of 23 of the 350 matched patients developed HF within 1 year of anthracycline initiation including 6 patients treated with metformin and 17 matched patients (Table 3). The cumulative incidence at 1 year calculated by Gray's method was

CENTRAL ILLUSTRATION Study Design and Outcomes



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(Left) Flowchart of the study and outcomes. Of 561 diabetic patients receiving anthracyclines, 310 patients were treated with metformin. A total of 175 diabetic patients receiving anthracycline chemotherapy and treated with metformin were matched with 175 non–metformin-treated diabetic patients receiving anthracycline chemotherapy. Six patients treated with metformin and 17 patients without metformin developed heart failure (HF) within 1 year (cumulative incidence: 3.6% vs 10.5%). Ten patients treated with metformin and 22 patients without metformin developed HF within 5 years (cumulative incidence: 8.1% vs 15.7%). (Right) The cumulative incidence of symptomatic HF within 1 year in patients with metformin exposure was lower than in the nonmetformin group.

3.6% in metformin group and 10.5% in nonmetformin group ($P = 0.022$) (**Central Illustration**). A competing-risks model of HF incidence confirmed that the use of metformin was associated with a lower incidence of HF within 1 year of anthracycline initiation (HR: 0.35; 95% CI: 0.14-0.90; $P = 0.029$). Nine patients discontinued metformin treatment within 1 year (2 patients within 1 month and 2 additional patients within 3 months). None of the patients who stopped taking metformin developed HF.

Metformin use was also associated with a lower cumulative incidence of HF within the 5-year follow up period (8.1% in the metformin group and 15.7% in the nonmetformin group; $P = 0.026$). A competing-risks model of HF incidence confirmed that the use of metformin was associated with lower HF within 5 years of anthracycline initiation (HR: 0.44; 95% CI: 0.21-0.93; $P = 0.031$).

All-cause mortality. A total of 57 patients in the metformin group and 73 patients in the non-metformin group died within 5 years. Cumulative incidence of mortality throughout the follow-up period was 42.4% in the metformin group and 52.4% in the nonmetformin group (HR: 0.71; 95% CI: 0.50-1.00; $P = 0.049$) (**Figure 2**).

DISCUSSION

This single-center cohort study using propensity score matching demonstrates that in patients with

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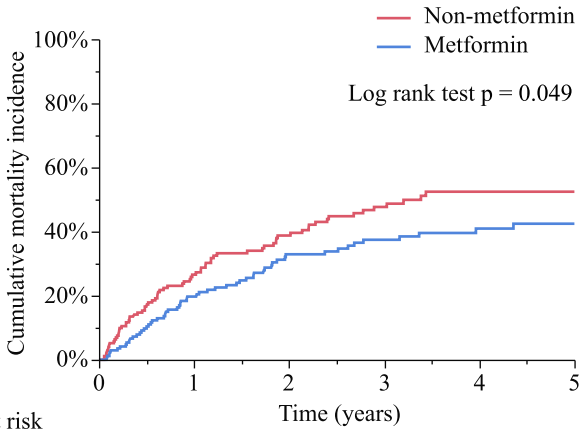
FIGURE 2 Kaplan-Meier Estimates for Survival in Patients With or Without Metformin



Number at risk						
Non-metformin	175	105	74	52	29	19
Metformin	175	117	80	65	44	29

A total of 175 diabetic patients receiving anthracycline chemotherapy and treated with metformin were matched to 175 non-metformin-treated diabetic patients receiving anthracycline chemotherapy. Kaplan-Meier estimates for survival of patients receiving anthracyclines with or without metformin exposure are presented. Patients treated with metformin had a higher survival rate than the nonmetformin group.

cancer and DM, the use of metformin at the initiation of anthracycline treatment was associated with a reduced incidence of HF within 1 year and 5 years and with an increased survival time within the follow-up period (**Central Illustration**).

As expected, in our study, patients treated with metformin had DM and a higher prevalence of cardiovascular risk factors and comorbidities compared with other cohorts of patients treated with anthracyclines.[5] Consequently, after matching patients treated with metformin with nonmetformin users, the resulting cohort studied developed a higher incidence of HF (23 of 350 patients developed HF; cumulative incidence based on Fine-Gray regression: 7.1% at 1 year) than that reported in other populations of patients receiving anthracyclines (2.0%-5.0% with longer follow-up periods).[5,25] We assessed the incidence of HF within 1 and 5 years of anthracycline initiation. The majority of anthracycline-induced complications were identified during the first year after treatment.[26,27] We confirmed the persistent association of metformin with HF within 5 years, a time point chosen in other studies.[28]

A recent small study reported that sodium-glucose transporter-2 inhibitors may be cardioprotective in patients treated with anthracyclines.[29] The present larger study suggests that patients treated with metformin may also have partial protection from anthracycline-induced HF. The mechanisms of anthracycline-induced cardiotoxicity are still under investigation, and involve multiple processes, including inhibition of topoisomerase IIb and DNA damage leading to transcriptional alterations, oxidative stress and generation of reactive oxygen species (ROS), and impairment of mitochondrial functions.[30] The AMP-activated protein kinase (AMPK) signal pathway and inflammation through toll-like receptor activation have also been implicated in the mechanisms underlying cardiotoxicity.[31-35]

Metformin suppresses inflammation, activates AMPK, and inhibits ROS generation.[15,36] Initial in vitro studies in murine cardiomyocytes demonstrated that metformin decreases doxorubicin-induced apoptosis, a hypothesized effect that appeared at least partially mediated by AMPK activation and adiponectin pathways.[21] Free iron pools implicated in oxidative stress were reduced by metformin through nuclear factor kappa B-mediated ferritin heavy chain upregulation.[37] In a rat model of doxorubicin-induced cardiotoxicity, metformin normalized autophagy makers such as LC3B-II and p62.[38,39] Our findings are consistent with recent in vitro and animal studies, which revealed beneficial effects of metformin on anthracycline-induced cardiomyopathy by suppressing inflammation, activating AMPK, and inhibiting ROS generation.[15,36] As the mechanisms of anthracycline-induced cardiomyopathy involve these pathways, metformin may be a specific therapy for anthracycline-induced cardiomyopathy than conventional therapy. Our results also showed that the use of metformin was associated with an increase in survival in these patients with cancer. Several studies have indicated the possibility of antitumor effects of metformin in patients with various types of cancer.[40-44] This association merits further investigation.

STUDY LIMITATIONS. Our data only included patients with DM. If the implementation of metformin is expanded in patients without DM, the risk of hypoglycemia has to be considered. However, metformin rarely produces hypoglycemia because it is not a secretagogue.[45] Further prospective studies are needed to investigate the efficiency and safety of metformin in the population of patients treated with anthracyclines. Even though we collected data for 5,598 patients treated with anthracyclines, our final cohort of matched patients was relatively small. Our data were collected retrospectively, and medical information could have been misclassified. However, HF was adjudicated by several cardiologists independently and derived from medical chart review. Additionally, the information regarding DM and

medications could not be assessed completely. Medication compliance could not be assessed. Patients who started taking metformin after initiation of anthracyclines were not included. Even though we carefully conducted propensity score matching, there may still be unmeasured confounding. Finally, this retrospective study does not allow to identify the mechanisms involved in the beneficial effect of metformin. Prospective randomized controlled trials and further experimental studies are required to overcome these limitations.

CONCLUSIONS

The present study demonstrates that the use of metformin in patients with cancer is associated with a decreased incidence of HF in the year following anthracycline chemotherapy. Our findings are consistent with previous experimental studies and provide impetus to develop further randomized controlled trials investigating the benefits of metformin in anthracycline-induced cardiotoxicity.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Metformin is associated with a decreased incidence of HF in patients treated with anthracyclines.

TRANSLATIONAL OUTLOOK: In this retrospective analysis, the use of metformin in patients with cancer is associated with a decreased incidence of HF in the year following anthracycline chemotherapy. Prospective studies are needed to confirm the potential cardioprotective effects of metformin.

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