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RESEARCH ARTICLE

Influence of Metformin Discontinuation on Readmission Rate in Patients With Acute Heart Failure☆,☆☆

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Abstract

Background: **The consequences of discontinuing metformin in patients with heart failure have not been determined. Knowing that acute exacerbation of chronic heart failure contributes to substantial increases in major adverse cardiovascular events (MACE), we proposed a retrospective study to examine whether discontinuing metformin in patients hospitalized with heart failure impacts mortality and readmission rates.**

Methods: **We conducted a retrospective analysis of patients admitted with a diagnosis of acute heart failure to hospitals in the HCA Healthcare System from 2020 to 2022. Included patients had a prior diagnosis of diabetes mellitus, acute heart failure, and were taking metformin prior to admission. After applying our exclusion criteria, a total of 7740 patients remained. The primary outcomes were 30-, 60-, and 90-day readmission rates and secondary outcomes were mortality and length of stay.**

Results: **Patients who were discharged without a prescription for metformin (NONDIS-MET) were 4.489 (95% CI 3.673−5.488, $p < 0.0001$) times more likely to have a MACE outcome in 30 days compared to patients who received a discharge order for metformin (DIS-MET). The findings were similar for 60-day and 90-day readmission rates, with NONDIS-MET patients 3.457 (95% CI 2.893−4.131, $p < 0.0001$) and 2.992 (95% CI 2.534−3.533 $p < 0.0001$) times more likely to have a MACE outcome than MET patients, respectively. However, when metformin was continued during the patients' hospital stay (CONT-MET) there was no significant association with MACE outcomes, readmission, or mortality rates.**

Conclusion: **We found that diabetic patients admitted with acute heart failure exacerbations had a higher incidence of major adverse cardiac events and were more likely to be readmitted when they were not prescribed metformin after discharge. Our findings agree with prior work showing the cardioprotective effects of metformin; however, continuing metformin during hospital admission did not affect our patients adverse outcomes.**

Keywords: Diabetes, Major adverse cardiovascular events, Mortality, MACE, Metformin

1. Introduction

Diabetes is a prevalent comorbidity in patients with heart failure, which can cause increased mortality and hospitalizations.[1] Metformin is the first-line oral medication for diabetes mellitus (DM) type II patients that lowers the risk of complications, diabetes-related death, and myocardial infarction.[2] Metformin was originally considered to be dangerous for people with heart failure since it can induce lactic acidosis.[3] More recently, it was shown that metformin can be administered safely in people with DM who are at risk of heart failure or already have heart failure as long as their estimated glomerular filtration rate is more than 30 ml/min/1.73 m^2.[4] Furthermore, metformin is known to have cardioprotective effects,[5] such that individuals taking metformin experienced fewer hospitalizations

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for heart failure exacerbations, and patients with diabetes and heart failure taking metformin had lower mortality rates.[6,7] It has not been determined whether discontinuing metformin in admitted patients with heart failure affects outcomes. Based on an understanding that acute exacerbation of chronic heart failure contributes to substantial increases in major adverse cardiovascular events (MACE),[8] we conducted a retrospective study to determine whether discontinuing metformin in patients hospitalized with heart failure impacts mortality and readmission rates for MACE. We hypothesized that diabetic patients admitted with acute heart failure exacerbations, who were discontinued from metformin therapy during hospitalization, would experience a higher incidence of MACE and readmission rates compared to patients who were not prescribed metformin after discharge.

2. Methods

We evaluated patient data from the HCA Healthcare Enterprise Data Warehouse. Our dataset was created from 186 HCA Healthcare hospitals in 21 states across the US. This research activity was conducted in compliance with the corporate requirements and determined to be exempt from Institutional Review Board (IRB) oversight in accordance with current regulations and institutional policy. The internal reference number for this determination is 2023-017.

The study cohort included patients 18 years and over who were admitted to the hospital with the diagnosis of diabetes mellitus (type 2) and acute heart failure. The study index date was defined as the date of hospitalization from January 1, 2016 to December 31, 2022. All included patients were taking metformin prior to admission. The study index date was defined as the date of hospitalization from January 1, 2016, to December 31, 2022. Patients less than 18 years of age and patients admitted for surgery were excluded from the study, enrolling a total of 7740 patients.

Demographic data including age, sex and race, pharmacy, clinic, laboratorial, and comorbidities data were extracted for each patient on the date of admission. Relevant comorbid conditions identified were hypertension, asthma, chronic kidney disease, acute kidney failure, and heart failure.

Data were analyzed using SAS 9.4 (SAS Institute, Cary, NC) and IBM Statistical Package for Social Sciences (SPSS), version 24 (IBM Corp., Armonk, NY). The primary outcomes were 30-, 60-, and 90-day readmission rates and secondary outcomes were mortality and length of stay. The independent variable in this study was the discontinuation of metformin therapy, with patients initially categorized into groups based on whether they continued metformin after admission (CONT-MET) or discontinued it after admission (NONCONT-MET). The patients were further grouped by whether they had an order for metformin on discharge (DIS-MET) or did not have an order for metformin on discharge (NODIS-MET). Binary logistic regression was performed to determine the association between predictor variables, metformin discontinuation, and patient readmission for a MACE outcome. An alpha level of 0.05, with correction for multiple comparisons, was used for the type I error rate.

3. Results

The study cohort included 7740 patients admitted to the hospital with a diagnosis of acute heart failure who also had a prior diagnosis of diabetes mellitus. A substantially higher proportion of patients had metformin discontinued after admission (NONCONT-MET, n = 6991) compared to those who were continued on metformin (CONT-MET, n = 749, Table 1). The NONCONT-MET group had a median age 71 (IQR 16.0) and the CONT-MET group age was 70 (16.0, P = 0.47) of with a median age of 71 with an IQR of 16 years. There was no significant difference in the distribution of gender, race, or smoking status between the NONCONT-MET and CONT-MET groups (Table 1). On admission, hypertension (HTN), chronic kidney failure, and acute kidney failure were significantly higher (%) in the NONCONT-MET group while the proportion of asthma was higher in the CONT-MET group (Table 1).

Metformin was recommended at discharge for 66.7% (n = 5162) of all patients with a significantly ($p < 0.001$) higher proportion of CONT-MET patients who had metformin recommended at discharge (79.1%, n = 593) than in the NONCONT-MET group (65%, n = 4569). Thus, we created an additional sub-grouping of DIS-MET patients (n = 5162) and NONDIS-MET patients (n = 2578), which was included as a variable in our logistic regression (Fig. 1).

Fig. 2 shows the forest plot of our logistic regression analysis of 30-, 60-, and 90-day MACE readmissions in the context of inpatient metformin discontinuation. There was no statistically significant association between NONCONT-MET and CONT-MET (reference) and MACE readmission at any of the three time points.

Fig. 3 shows the forest plot for 30-, 60-, and 90-day MACE outcomes in the context of metformin after

Table 1. Demographic data for patients in the metformin discontinued during hospitalization (NON-CONT MET, n = 6001), and metformin continued during hospitalization (CONT-MET, n = 749), groups.

		Total	NONCONT-MET N = 6991	CONT-MET = 749	P-value
Sex	**Female**	3160 (40.83%)	2835 (40.55%)	325 (43.39%)	0.1330
	Male	4580 (59.17%)	4156 (59.45%)	424 (56.61%)	Chi square
Age Median (IQR)		71.00 (16.00)	71.00 (16.00)	70.00 (16.00)	0.0471
					Mann Whitney
Race	**Black**	1375 (17.76%)	1232 (17.62%)	143 (19.09%)	0.6041
	Other	906 (11.71%)	819 (11.72%)	87 (11.62%)	Chi square
	White	5459 (70.53%)	4940 (70.66%)	519 (69.29%)	
HTN		5022 (64.88%)	4456 (63.74%)	566 (75.57%)	<0.0001
					Chi square
Asthma		1548 (20.00%)	1376 (19.68%)	172 (22.96%)	0.0329
					Chi square
CKD		723 (9.34%)	670 (9.58%)	53 (7.08%)	0.0250
					Chi square
Acute Kidney Failure		3300 (42.64%)	3103 (44.39%)	197 (26.30%)	<0.0001
					Chi square
Heart Failure Category					
Combined		1297 (16.76%)	1194 (17.08%)	103 (13.75%)	0.0064
Diastolic		3685 (47.61%)	3290 (47.06%)	395 (52.74%)	Chi square
Systolic		2758 (35.63%)	2507 (35.86%)	251 (33.51%)	
Metformin Recommended at Discharge		5162 (66.69%)	4569 (65.36%)	593 (79.17%)	<0.0001
					Chi square

discharge. NONDIS-MET was associated with 4.489 higher odds of a 30-day readmission for MACE, 3.457 higher odds of 60-day readmission for MACE, and 2.995 higher odds of a 90-day readmission for MACE than the DIS-MET patients.

4. Discussion

The primary finding in our study was that discontinuing metformin at discharge in patients with heart failure led to a significantly higher readmission rate for MACE. The strength of this association decreased somewhat over time (from 30 to 90 days) but remained substantial even at 90 days (OR 2.995). In a prior study, the continued use of metformin was linked to a decrease in overall mortality rates and an observed reduction in CHF hospital readmissions.[9] Despite the comorbidities being relatively similar between DIS-MET and NONDIS-MET groups, we acknowledge the possibility that patients in the NONDIS-MET group had a had a heightened risk profile compared to the DIS-MET group. This elevated risk could stem from an increased frequency of AKI or could be related to the increased severity of their existing comorbidities.

The literature advises against the use of metformin in patients who have conditions that increase their risk of lactic acidosis. Such conditions include an estimated glomerular filtration rate <30, acute heart failure, compromised tissue perfusion, and hemodynamic instability, whether induced by infections or other factors.[4,10] Despite these contentions, we found that discontinuation of metformin during the inpatient stay was not associated with MACE readmission in any of the models. While

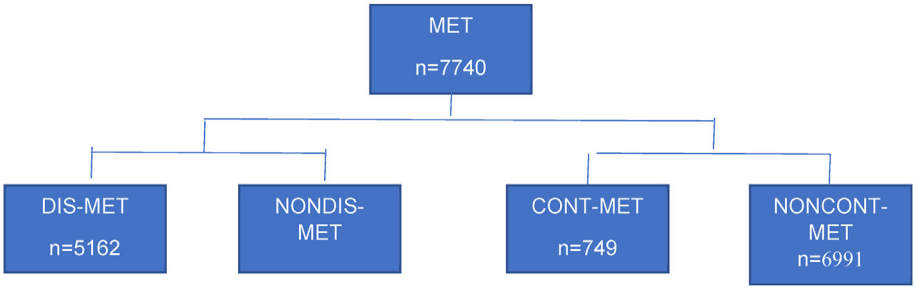

Fig. 1. We created an additional sub-grouping of DIS-MET patients (n = 5162) and NONDIS-MET patients (n = 2578), which was included as a variable in our logistic regression. NONDIS-MET = patients who were discharged without a prescription for metformin. DIS-MET = patients who received a discharge order for metformin.

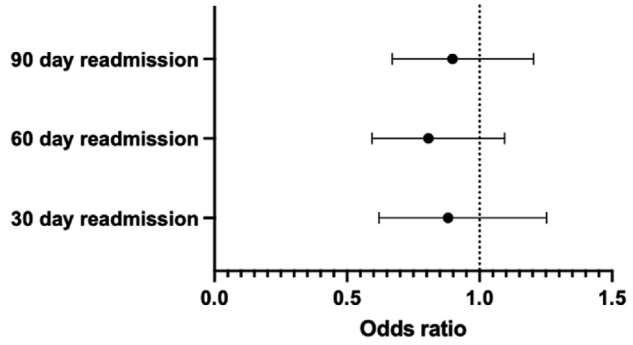

Fig. 2. Forest plot for the logistic regression analysis showing the association (NS) between NONCONT-MET (CONT-MET reference) and 30-, 60-, and 90-day readmission for MACE.

there are no existing studies directly linking inpatient metformin use to MACE, metformin's anti-inflammatory properties have been highlighted in prior research. These authors found that metformin led to milder disease progression, resulting in shorter hospital stays and a reduced rate of in-hospital mortality.[11–13] Our data suggest that decisions made regarding metformin use during the inpatient stay do not appear to have a measurable effect on MACE readmission outcomes. However, choosing to resume metformin use at discharge appears to have a significant effect on MACE outcomes.

Recent studies highlight that metformin-treated patients experienced notably reduced all-cause mortality rates.[14] These findings raise the possibility that metformin could offer protection outside the realm of glycemic control. Metformin has been identified as a safe option for those with both diabetes mellitus and advanced heart failure, often resulting in improved survival outcomes.[15] A retrospective examination of diabetes mellitus patients, post-hospitalization due to heart failure,

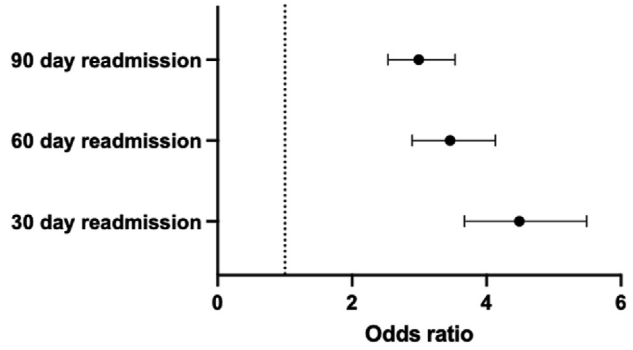

Fig. 3. Forest plot for logistic regression analysis showing the association (P < 001) between DIS-MET (NONDIS-MET reference) and 30-, 60-, and 90-day readmission for MACE.

showed that those treated with metformin had fewer hospital readmission and a marked decrease in death risk after one year.[16] A retrospective analysis comparing new oral antidiabetic medication users with heart failure showed that those on metformin alone faced a significantly reduced risk of death or hospitalization compared to those on sulfonylurea alone.[17]

A comprehensive meta-analysis of 39 studies showed that the use of metformin in the management of patients diagnosed with diabetes who have concomitant heart failure, could markedly diminish the risk of hospitalization.[18] The underlying mechanisms are known to be multifaceted. Metformin is known to improve glycemic control, exhibit favorable effects on the lipid profile, and exhibit anti-inflammatory properties.[19–21] Collectively, these factors might contribute to cardiovascular stability, thereby reducing acute cardiac decompensations that require hospital admissions. In support of this contention, the UK Prospective Diabetes Study (UKPDS) has highlighted that metformin, compared to other conventional treatments, was associated with a reduction in diabetes-related endpoints, diabetes-related deaths, and all-cause mortality in overweight patients.[22] Additionally, a study by Eurich et al. found that metformin was associated with a decreased risk of heart failure-related death, hospitalization, and all-cause mortality when compared to sulfonylureas.[23]

Based on our observational findings, discontinuation of metformin at discharge may lead to increased adverse outcomes. The disparity between the metformin-continued and metformin-discontinued groups can be attributed to the standard practice of discontinuing metformin in patients who are acutely ill, particularly those presenting with conditions such as CHF exacerbations or acute kidney injury (AKI).

However, further research is needed to determine a causal link between metformin discontinuation at discharge and increased MACE events, hospital readmission, as well as metformin's potential to improve myocardial function in chronic heart failure. Lastly, future researchers should consider accounting for the possibility of primary care physicians reinstating metformin therapy after patient discharge.

5. Conclusion

Based on our analysis of 7740 diabetic patients admitted with acute heart failure exacerbations, patients who were not resumed on metformin at discharge appear to have a higher incidence of

major adverse cardiac events and increased readmission rates. Further prospective research studies including randomized controlled trials with a larger sample size are warranted to understand the association between metformin discontinuation in acute heart failure.

6. Limitations

Patients were excluded from the study due to missing data/labs, preexisting renal disease, presence of MACE on admission, which might introduce selection bias. It's possible that our cohort had a preexisting high risk for MACE readmission, perhaps due to their overall health status, which may be a confounding variable. In addition, the retrospective nature of this study introduces the potential for inherent biases including information bias. Another limitation is that our dataset only accounted for patient readmissions when they returned to an HCA Healthcare facility. Lastly, we don't have access to data on whether the patient followed up with primary care or what changes were made at a PCP visit.

Ethics information

This research activity was conducted in compliance with the corporate requirements and determined to be exempt from Institutional Review Board (IRB) oversight in accordance with current regulations and institutional policy.

HCA Disclaimer

This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare-affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

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Conflict of interest

None to declare.

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