

Metformin Use in Patients With Diabetes and Heart Failure: Cause for Concern?

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Patients with type 2 diabetes are 2.5 times more likely to develop heart failure than those without diabetes,¹ and > 30% of patients with heart failure have concurrent diabetes.² Biguanides, namely phenformin and metformin, have been used for the treatment of diabetes for decades. In certain clinical situations, however, the use of biguanides can result in an accumulation of lactic acid, which may result in a rare condition known as acute lactic acidosis (ALA), which is fatal in ~ 50% of cases.^{3,4} In most instances, the development of ALA arises secondary to conditions predisposing patients to hemodynamic compromise and overt tissue hypoxia, such as acute myocardial infarction (MI), acute uncompromised heart failure, or sepsis.^{5,6}

Phenformin was removed from the market in 1976 because of reports of both fatal and nonfatal phenformin-associated lactic acidosis (PALA).⁷ The incidence of PALA at the time was estimated to be between 40 and 64 cases per 100,000 patient-years, or four to six times that seen in patients with diabetes who were not on phenformin.^{8,9} Unlike phenformin, which is metabolized through the liver via hydroxylation, metformin is excreted unchanged in the urine.¹⁰ Therefore, metformin is less likely to inhibit hepatic lactate clearance and lead to ALA. The estimated incidence of metformin-associated lactic acidosis (MALA) in patients with diabetes is between 3 and 9 cases per 100,000 patient-years, roughly the same as that reported in patients with diabetes who are not taking a biguanide.^{4,7,11-13}

Epidemiological data reveal that metformin is often used in patients with heart failure. Prospective and retrospective cohort studies have evaluated health care databases of hospitalized and outpatient diabetic populations to determine metformin usage in patients with concurrent International Classification of Diseases-9 (ICD-9) codes for heart failure. Heart failure, described generally as cardiac failure or specifically as New York Heart Association (NYHA) heart failure class II-IV, was noted to be a primary contraindication to metformin therapy in 2-39% patients ($n > 16,000$).^{12,14-17} Despite the use of metformin in some patients with notable contraindications, the rate of reported MALA has not increased in the 13 years since metformin was first approved. In fact, most reported cases of MALA ($n > 330$) have occurred in patients with changing or worsening renal function or underlying risk factors for the development of lactic acidosis.^{5,6,18}

In 2006, the U.S. Food and Drug Administration approved changes to metformin product labeling listing heart failure as a precaution rather than a contraindication.³ Despite this labeling change, concern still exists for its use in this population because of the potential for the development of MALA. Current guidelines from the American Diabetes Association state the use of metformin is contraindicated in patients treated for congestive heart failure.¹⁹ In these instances, health care providers are left to weigh the risks and benefits of using metformin in patients with diabetes and concurrent heart failure. This article reviews the evidence

for the use of metformin in such patients.

Methods

A Medline search was conducted for English-language articles published from January 1966 to May 2008. A manual search of references was also conducted to complete the search. Key search terms included: metformin, lactic acidosis, heart failure or congestive heart failure, and diabetes mellitus type 2. The intent of the search was to find randomized controlled trials or meta-analyses; however, the evidence from observational cohorts is discussed when a higher level of evidence is lacking. Case reports and case series of MALA were excluded. Only studies evaluating patients on metformin with preexisting heart failure were reviewed.

Clinical Evidence

Major prospective studies evaluating the use of metformin in patients with diabetes excluded patients with known heart failure. However, one randomized controlled trial and three retrospective cohort studies have evaluated the use of metformin in patients with preexisting heart failure.

Randomized controlled trial results

Patients on metformin ($n = 392$) hospitalized with one or more contraindications to metformin use including heart failure ($n = 91$) were randomized to either continue or stop metformin.²⁰ Patients were followed through annual visits or data from hospitalizations for up to 4 years. Study participants were an average age of 64 years, were

52% male, and had a mean A1C of 8.6%. Additionally, the mean serum creatinine was 1.8 mg/dl, and patients with heart failure were classified as having NYHA class III or IV. Patients with liver cirrhosis, acute MI, pulmonary edema in the past 30 days, a history of carbon dioxide narcosis, or malignancy were excluded.

Lactate levels were measured, but no overt cases of ALA occurred in either study group. Notably, increases in lactate levels from baseline correlated with renal function and BMI, but not with metformin therapy. There were no statistically significant differences in cardiovascular events (55 vs. 55%), cardiovascular mortality (26 vs. 26%), or all-cause mortality (32 vs. 34%) between those who continued and those who stopped metformin therapy, respectively. A noteworthy limitation to this study is that randomization and outcomes for the subgroup of patients with heart failure were not reported; therefore, the impact of this specific contraindication in patients taking metformin is unclear. In addition, the overall high mortality rate observed during the study brings into question the external validity of these outcomes.

Results of retrospective observational cohort studies

Two retrospective cohort studies evaluated the use of metformin as monotherapy ($n = 2,069$) or in combination with other oral hypoglycemic agents (sulfonylurea [SU] or thiazolidinedione [TZD]) or insulin ($n = 1,113$) in hospitalized patients with a concurrent ICD-9 code for heart failure.^{21,22} An additional study evaluated the use of metformin in a pre-specified subgroup of patients with a primary diagnosis of acute MI who also had either an impaired ejection fraction or heart failure/pulmonary edema on chest radiograph on admission ($n = 2,670$).²³ Study participants were an average age of 72–77 years, and 39–57% were male. No cases of ALA occurred in any of the studies. However, one study noted a non-significant decrease in generalized metabolic acidosis readmissions in patients on metformin compared to

those not on metformin or a TZD (2.3 vs. 2.6%).²²

In two of the studies, metformin use was associated with a statistically significant decrease in 1-year mortality compared to nonmetformin-containing regimens (11–24.7 vs. 26–36%, $P < 0.05$).^{21,22} In the third study, no significant difference was found in 1-year all-cause mortality between metformin monotherapy and the SU/insulin group (hazard ratio [HR] 0.92–0.96; 95% CI 0.72–1.19).²³ Unadjusted data from both studies, which evaluated all-cause readmission or hospitalization at 1 year, suggested metformin had a statistically significant benefit; however, the significance did not persist after the data were adjusted (49–51 vs. 53%)²¹ (HR 0.94; CI 0.89–1.01).²² After 2.5 years of follow-up, metformin maintained a statistically significant benefit for all-cause mortality (31–33 vs. 52%, $P < 0.05$) but not for hospitalization rates (69–74 vs. 70%, $P = \text{NS}$), compared to nonmetformin therapies.²¹ Use of metformin with a TZD appeared to decrease 1-year all-cause readmissions (adjusted HR 0.82; CI 0.69–0.96).²²

A recent meta-analysis²⁴ pooled outcomes for 1-year all-cause hospitalization from two of the above trials.^{21,22} The pooled analysis confirmed that metformin, alone or in combination with a TZD, decreased 1-year all-cause hospitalization (HR 0.85; CI 0.76–0.95). However, the same meta-analysis could not be performed on the data for all-cause mortality because of the degree of statistically significant heterogeneity found between the studies.

Given the populations included in these studies, these data may not be generalizable to younger patients. In addition, it is possible that patients with more severe heart failure were not taking metformin because of their providers' concerns about MALA. Thus, a potential for selection bias exists in all of these trials. Although the investigators adjusted for many factors, such as age, sex, concurrent use of select heart failure medications, and mean A1C levels, other variables, such as metformin doses, other diabetes medication doses, serum

creatinine levels, left ventricular ejection fraction, and NYHA heart failure classes were not consistently reported in the trials. Therefore, it is difficult to ascertain the effects of both glycemic control and functional capacity of patients with heart failure on the outcomes reported.

Conclusion

There is concern that metformin use in patients with heart failure can lead to MALA. Epidemiological data, however, describe the frequent use of metformin in patients with heart failure despite the preexisting precaution, but they do not reveal new MALA cases in this population. Despite these encouraging findings, it would be unlikely that trials with relatively small sample sizes and shorter durations of follow-up would be able to identify such a rare occurrence, given the reported MALA incidence of ~ 1 case per 10,000 patient-years. In the absence of prospective, controlled trials that account for NYHA heart failure class, severity of illness, and drug dosages, health care providers are advised to continue to weigh the potential risks and benefits of using metformin in individual patients with heart failure.

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