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METFORMIN USE AND RISK FOR LACTIC ACIDOSIS

Although there are approximately 1 million patients in the United States with type 2 diabetes mellitus, many people are not able to follow the clinical guidelines of receiving metformin who have kidney disease for fear of exacerbating the existing kidney disease. Metformin is typically used as a first-line agent for the treatment of diabetes; however, 20% of patients with diabetes have existing kidney disease. FDA recently relaxed the metformin drug labeling. Previous dosing instructions indicated that metformin was contradindicated if the serum creatine label was greater than 1.5 mg/dL in men and greater than 1.4 mg/dL in women. Now the labeling recommends that metformin should not be initiated in patients with an eGFR less than 45 mL/min/1.73m^2. Current research has conflicting results about the safety of metformin in patients with diabetes and pre-existing kidney disease. The purpose of this article was to evaluate the relationship between metformin therapy and acidosis in patients across a wide variety of eGFR. If you need further information, please contact the Center for Healthcare Innovation and Patient Outcomes Research (CHIPOR) at chipor@samford.edu.

Lazarus B, Wu Aozhou, Shin J-I, et al. Association of metformin use with risk of lactic acidosis across the range of kidney function. JAMA Intern Med. 2018;178(7):903-910.

Introduction

- Over 380 million people worldwide have type 2 diabetes and 20% have an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73m^2.
- Metformin is typically used as a first-line treatment for diabetes, but until recently, it has been contraindicated in patients with reduced serium creatine.
- Large studies assessing the affect of metformin in patients with reduced renal function, have been conflicting.

Methods

- A community-based cohort of patients with diabetes and a serum creatinine measurement between January 1, 2004 and January 2017, being treated at Geisinger Health System, was identified.
- Patients were excluded with missing serum creatinine level, end-stage renal disease, or initial eGFRless than 15 mL/min/1.73m^2.
- The primary outcome was a hospitalized acidosis event, defined by the appropriate ICD-9 code.
- Metformin start time was evaluated via electronic prescription drug database.
- eFGR scores were stratified by the Kidney Disease Improving GlobalOutcome guideline (<30, 30-44, 45-59, 60-89, and ≥90 mL/min/1.73m^2.
- The following covariates were also assessed age, sex, race, smoking status, body mass index,serium bicarbonate, hemoglobin A1c, comorbid cardiovasacular disease, heart failure, hypertension, and medication use.
- Death was determined by searching the National Death Index.
- The results were compared to the MarketScan database. Medication use was obtained from pharmacy dispensing claims.

Results

- The total study population consisted of 75,413of Geisinger patients.
- The mean age of the patients was 60.4 (15.5) years, 51% were female, and the mean (SD) BMI was 34.1.
- A total of 14,662 patients had a eGFR < 60 mL/min/1.73 m^2 and 1765 had an eGFR <30 mL/min/1.73 m^2.
- Approximately 45% of patients were taking metromin at study enrollment (34,095), and 13781 patients were prescribed metformin during follow up.

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Results (continued)

- The median duration of metformin use was 2.8 years (IQR, 0.9-6.2 years).
- There were 2335 hospitalizations with acidosis over the 470,114 person years of follow-up. A total of 737 events occurred over 188,578 person-years of metformin useand 1598 events occurred over 281536 person-years of no metformin use.
- Only 29 patients had acidosis as a diagnostic code.
- The adjusted hazard ratio (HR) of acidosis during metformin use compared with nonuse was 0.98 (95% CI, 0.89-1.08).
- The risk of acidosis was higher with metformin at lower GFR; however, the risk was not stastically significant with metformin use at eGFR > 90 mL/min/1.73m^2 (adjusted HR,0.88; 95% CI, 0.73-1.05), eGFR 60 to 89 mL/min/1.73m^2 (adjusted HR, 0.87; 95% CI, 0.75-1.02), eGFR 45 to 59 mL/min/1.73m^2 (adjusted HR, 1.16; 95%CI, 0.95-1.41), and eGFR 30 to 44 mL/min/1.73 m^2 (adjusted HR, 1.09; 95% CI, 0.83-1.44).
- An increased risk of acidosis associated with metformin use at eGFR less than 30 mL/min/1.73m^2 (adjusted HR, 2.07; 95% CI, 1.33-3.22).
- When compared with the matching database, sulfonylurea use and metformin use had a similar correlation with acidosis (adjusted 0.91; 95% CI, 0.70- 1.18), and in eGFR 45 to 59 mL/min/1.73m^2 (adjusted HR, 1.03; 95% CI, 0.60-1.77) and eGFR 30 to 44 mL/min/1.73 m^2 (adjustedHR, 0.77;95%CI,0.29-2.05).

Discussion

- Metformin use in patients with eGFR of at least 30 mL/min/1.73m^2 was not associated with hospitalization for acidosis.
- The potential benefits associated with increasing the number of patients eligible for metformin therapy can have a considerable impact on patient care.
- Metformin therapy is associated with less weight gain, lower risk for myocardial infarction, and lower long-term mortality than those receiving other hypoglycemic therapies.

Summary

- Metformin therapy may be cautiouslyused in patients with type 2 DM and eGFR of at least 30 mL/min/1.73m^2.

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