Closer Look

MEMORANDUM

JAMA analysis suggests current restriction against metformin in CKD is unnecessarily conservative - January 21, 2015

Executive Highlights

- A recent review article by Dr. Silvio Inzucchi et al. suggests that the current restriction against the use of metformin in patients with mild to moderate renal impairment is not consistent with the available evidence.
- The authors recommend a potential alternative approach that would allow cautious use of metformin in patients with an estimated glomerular filtration rate (eGFR) between 30 and 60 ml/min/1.73 m² with some dose adjustment.

A review article by Dr. Silvio Inzucchi (Yale University School of Medicine, New Haven, CT) et al. recently published in JAMA suggests that the current restriction against the use of metformin in patients with mild to moderate renal impairment may be overly cautious given existing clinical evidence. As a reminder, metformin's label includes a contraindication for patients with "renal disease or renal dysfunction," defined as serum creatinine ≥1.5 mg/dl for men and ≥1.4 mg/dl for females or abnormal creatinine clearance. This restriction exists due to concerns that metformin (which is partially cleared through the kidneys) would accumulate in the bloodstream of patients with impaired kidney function, putting them at risk for lactic acidosis. Following a review of 65 articles on the subject, the authors concluded that the available evidence does not support such restrictive guidelines. They found that while metformin clearance is reduced in patients with mild to moderate kidney disease, levels tend to remain within the therapeutic range in patients with an estimated glomerular filtration rate (eGFR) as low as 30 ml/min/1.73 m² (the lower limit for "moderate" renal impairment). Additionally, the slight elevation in plasma metformin concentration does not lead to any significant change in lactate levels. Observational studies investigating a potential link between metformin and lactic acidosis have found no significant relationship.

Notably, based on this evidence, the authors suggest a possible new guideline for prescribing metformin that would allow cautious use with some dose adjustment in patients with mild to moderate renal impairment (see the table below). As a key author of the most recent ADA/EASD position statement, Dr. Inzucchi holds weight in the diabetes care field and we imagine this suggested recommendation could (informally) enter clinical practice. As they note, these or other alternative recommendations should ideally be validated in a clinical trial setting. However, the incredibly low event rates for lactic acidosis would make such a trial highly impractical, and with metformin having gone generic many years ago it is unclear who would fund such a study. Given the extensive body of evidence considered in this analysis, it seems reasonable to conclude that metformin's current label is unnecessarily conservative. In addition, as the article notes, studies suggest that these guidelines are not consistently followed in real-world clinical practice with no apparent adverse effect. To the extent that they are followed, they may be depriving a significant number of patients with type 2 diabetes of a valuable therapeutic option: an analysis recently published in JAMA Internal Medicine found that only 48.6%-57.4% of patients with an eGFR of 30-60 ml/min/1.73 m² were treated with metformin compared to 90.4% of patients with an eGFR >90 ml/min/1.73 m². An expanded label that allows cautious and well-monitored use of metformin in these patients could resolve much of the uncertainty that clinicians currently face and allow more patients to take advantage of a product that is widely considered the standard first line therapy for type 2 diabetes.

- **A forthrightly worded accompanying research letter ended with an emphatic concluding sentence:** "The FDA is overdue to revisit the contraindication to metformin use in

patients with renal insufficiency, which may be worsening the care of almost 1 million patients with T2DM in the United States." Drs. James Flory (Weill Cornell Medical College, New York, NY) and Sean Hennessy (University of Pennsylvania, Philadelphia, PA), who wrote the research letter, are right to put the ball in the FDA's court. If the discussion involved a branded drug, then perhaps the drug manufacturer would consider funding a study exploring metformin use in patients with mild to moderate renal impairment. However, with metformin being generic, a study led by government agencies (perhaps centrally supported by the NIH or CDC with guidance on trial design from the FDA) may be the only hope to get the guidelines formally changed. Arguably, a small portion of the billions of dollars being spent on FDA-mandated CVOTs for the newest diabetes drugs would be better used to fund a study on metformin's safety in patients with renal impairment, a population of millions of patients in the US alone.

Table 1: Alternative prescribing guideline for metformin in renal impairment (Inzucchi et al.)

eGFR (ml/min/1.73 m²)	Maximum daily dose (mg)	Other Recommendations
≥60 (mild or no renal impairment)	2550	
45-60 (moderate renal impairment)	2000	Monitor kidney function; avoid if kidney function is/expected to become unstable
30-45 (moderate renal impairment)	1000	Don't initiate therapy but drug can be continued; monitor kidney function; avoid if kidney function is/expected to become unstable;
≤ 30 (severe renal impairment or end-stage kidney disease)	Do not use	

-- by Emily Regier, Manu Venkat, and Kelly Close