Metformin in People With Diabetes and Advanced CKD: Should We Dare?

Jung-Im Shin, Antoine Créon, and Juan-Jesus Carrero

Metformin is first-line therapy for glycemic control in people with type 2 diabetes. It is effective, safe, inexpensive, and widely available, and may reduce cardiovascular events and mortality.[1] However, metformin is cleared by the kidneys and it has historically been contraindicated in patients with chronic kidney disease (CKD) because of concerns of lactic acidosis with drug accumulation. A series of observational studies during the early 2000s demonstrated the rarity of this adverse event across metformin users with CKD G3 (estimated glomerular filtration rate [eGFR] = 30-59 mL/min/1.73 m^2),[2-5] and this led in 2016 to a label change by the US Food and Drug Administration and European medicine agency expanding the indication of metformin use to CKD G3.[6,7] However, there is an increased relative risk of hospitalization owing to lactic acidosis with metformin in people with CKD G4/5 (ie, eGFR <30 mL/min/1.73 m^2),[8] and current regulatory and professional society guidelines recommend that metformin should neither be initiated nor be continued in these patients.[6,7,9,10] What is the risk-benefit ratio of metformin in CKD G4/5? May long-term benefits exceed the harms of possible lactic acidosis?

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In this issue of *AJKD*, Lambourg et al[11] conducted a target trial emulation study to compare the outcomes of patients who continued versus stopped metformin after developing CKD G4/5. They used routinely collected health data from the Scottish Diabetes Research Network – National Diabetes Study. A total of 4,278 metformin users reached CKD G4/5 while on therapy and had a history of good adherence to therapy. These patients experienced frequent changes in their metformin prescription during follow-up, likely reflecting uncertainty and hesitation on best practices by the physicians: 40% stopped metformin within 6 months, but 4% of them restarted metformin shortly after; among the 60% who continued with metformin, about half stopped at some point.

People who discontinued metformin had worse health profiles than those who continued with the treatment: Stoppers had lower eGFR and worse glycemic control, were more likely to have conditions like chronic lower respiratory diseases or a more frequent history of hospitalizations, and were less likely to be on renin-angiotensin system inhibitors or lipid-lowering agents. Using state-of-the-art statistical approaches to balance this confounding, they compared the clinical "impact" of stopping versus continuing treatment. They observed that stopping metformin was associated with a 23% higher risk of 3-year all-cause mortality compared with continuing (a 7% absolute survival benefit with continuing metformin). However, the risk of major adverse cardiovascular events (MACE) was similar between the 2 strategies. They conclude that the lower rate of all-cause mortality may support continuing with this treatment when eGFR drops below 30 mL/min/1.73 m^2.

Readers may wonder whether continuing with (vs stopping) metformin impaired safety (ie, risk of lactic acidosis), improved glycemic control, or delayed kidney failure, but these outcomes were not addressed, possibly because of limited statistical power with small sample/event size. Yang et al[12] recently investigated the same research question using health data from Hong Kong, comparing a variety of clinical outcomes between 7,500 (22%) patients who stopped metformin therapy within 6 months of incident CKD G4/5 and 26,086 (78%) similar patients who continued with metformin. In that study, stopping metformin (vs continuing) was associated with a 22% higher risk of death, a 40% higher risk of MACE, and a 52% higher risk of kidney failure. Within a smaller subset (n = 3,235) in which measures of pH and lactate were available, there was no difference between treatment strategies regarding the occurrence of lactic acidosis.[10]

From a methodological perspective, both studies used the target trial emulation framework to adequately design their study and minimize classic biases in pharmacoepidemiology such as selection biases or immortal time biases. Lambourg et al emulated a target trial using the clone-censor-weight approach, which is useful when the strategy adopted by a given patient cannot be determined at "enrollment" (ie, we cannot know if the patient continued treatment after incident CKD G4/5 until a new record of metformin prescription appears in their medical records). Yang et al[12] adopted a landmark design to classify stoppers or continuers of metformin at 6 months from incident CKD G4/5. This design is less granular, conditional on survival during the first 6 months of follow-up, and what it does is to look "statically" at the presence of a prescription record at that point.

While the use of target trial emulation studies is gaining momentum in nephrology, they are not meant to replace clinical trials. Target trial emulation studies continue to be observational studies and, as such, are inevitably dependent on the quality of the information available in the data source. As illustrated by worse health profiles, stopping treatment is likely not random, but rather a decision influenced by worsening clinical features such as rapidly decreasing eGFR, overall burden of illness, insufficient glycemic control, or anticipated low compliance. Some of

these issues cannot be easily captured by claims data. To circumvent this, the studies used advanced techniques that capture baseline as well as time-varying confounding. This is because the observed association of metformin discontinuation with outcomes may be confounded by indication (ie, characteristics prior to treatment change) but also by the other therapy changes besides or around metformin, such as simultaneous initiation of potentially harmful drugs like sulfonylureas, or substitution for other treatments like glucagon-like peptide-1 receptor agonists (GLP1-RA) or sodium/glucose cotransporter 2 (SGLT2) inhibitors. We note that whereas Yang et al did adjust for these novel medications, Lambourg et al did not. We speculate that this may explain, in part, the difference in associations with MACE risk between the studies. However, we acknowledge that data collection in both cohorts occurred during 2010-2019, an era where SGLT2 inhibitor users may have been few and use of GLP1-RA still moderate.

Can results from these 2 studies increase our confidence in prescribing metformin to people with CKD G4/5? They are telling us that despite guideline recommendations, many patients/practitioners decide to continue with the therapy: 80% of patients continued with metformin in Hong Kong and 60% did so in Scotland. Observational studies in the routine care settings indeed offer a different perspective of practice patterns and medication risk-benefits than the controlled settings of clinical trials (ie, with patients being enrolled and managed according to guidelines, strictly monitored for compliance, efficacy, and safety). If death is the ultimate outcome of medication safety and efficacy, both studies report strikingly similar effect estimates (22%-23% higher risk if stopping metformin). Playing devil's advocate, residual confounding may persist in any observational study. Although Lambourg et al did not evaluate this, Yang et al found no evidence of large residual confounding when using upper gastrointestinal bleeding as a negative control outcome, and thus results appear robust.

Certainly, we would like to have clinical trials to resolve every conundrum in medicine, but it may be difficult that trials with an out-of-patent medication like metformin are conducted in the short term. Until then, we argue that informed patients and physicians always make better shared decisions, and this rigorous observational study helps us understand the potential benefits of continued metformin use in CKD G4/5. Fortunately, metformin is no longer the sole first-line therapy for the management of diabetes and CKD.[9,10] Albeit more expensive, treatments such as GLP1-RA and SGLT2 inhibitors have no known or low absolute risks of lactic acidosis and additional cardiorenal-protective effects. We are finally leaving behind decades of therapeutic uncertainty and nihilism in the care of people with advanced CKD.

Article Information

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