services, including ventilator support, for 2 principal reasons: For these conditions, mortality rates have decreased and the quality of life improved in recent years, and, with either condition, outcomes are vastly different depending upon individual patients, their comorbidities, and the specific cause of either CKD or ESRD.

Gaurav Jain, MD
Division of Nephrology
University of Alabama at Birmingham

Potential Competing Interests: The authors report no competing interests.


Comparison of Outcomes With Metformin and Sulfonylureas in Chronic Kidney Disease

To the Editor: The article by Whitlock et al1 was a welcome addition to literature regarding treatment of patients with diabetes and stage 3-4 renal disease. As renal function diminishes, some patients with conditions previously controlled on oral agents must forgo them due to inefficacy, hypoglycemia, and metabolic complications and may ultimately require insulin. Patients with estimated glomerular filtration rates (eGFRs) less than 30 mL/min per 1.73 m² are often excluded from clinical trials. With respect to metformin therapy in the Manitoba study, only 247 patients had eGFR of less than 30 mL/min per 1.73 m². Of these, 90 were on metformin and represented 0.5% of the total study group. One hundred fifty-seven (7.8%) patients were on sulfonylureas. This observation adds to the evaluation of the international Ticagrelor in Patients With ST Elevation Myocardial Infarction Treated With Pharmacological Thrombolysis (TREAT) trial2 from the same period that noted 75 patients with similar loss of kidney function who were prescribed metformin among 2515 (3%) of North American patients in the trial, although rates of metformin use were slightly higher in Eastern Europe/Russia (4.3%), Western Europe/Australia (6.5%), and Latin America (5.3%). The total of patients with eGFR less than 30 mL/min per 1.73 m² in the TREAT study was 153 of 4038. In the single-center, Joslin Diabetes Center records only 10 of 4625 (0.2%) patients with eGFR less than 30 mL/min per 1.73 m² were on metformin.3 Clearly there is geographic variability in use of metformin (as well as sulfonylureas) among patients with stage 4 renal disease at greatest risk for hypoglycemia.

With respect to sulfonylureas, those used in the Manitoba analysis were chlorpropamide, tolbutamide, glyburide, glimepiride, and glipizide, for which 50% to 90% of the active metabolites/drug are excreted in the urine. We were surprised that there was no mention of glipizide which is virtually all metabolized through the liver. The sulfonylurea drugs mentioned could be expected to have a higher complication rate than either glipizide or metformin. It would be helpful to use glipizide as the comparator. Unfortunately, none of the above studies have addressed this point. Given the relatively small numbers of patients with stage 4 renal disease who receive either metformin or sulfonylurea, additional information on glipizide would be of clinical importance. Until this is available, we would continue to exercise caution with the use of either sulfonylureas or metformin in patients with stage 4 chronic kidney disease.

Larry A. Weinrauch, MD
Harvard Medical School
Watertown, MA
Joslin Diabetes Center
Boston, MA

John A. D’Elia, MD
Joslin Diabetes Center
Boston, MA

Potential Competing Interests: The authors report no competing interests.
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In Reply — Comparison of Outcomes With Metformin and Sulfonylureas in Chronic Kidney Disease

To the Editor: We thank Weinrauch et al1 for their letter in response to our article. The authors raise an interesting point regarding the absence of glipizide from the sulfonylurea group in our study and in the other studies they cited in their letter. Unfortunately, there were no prescriptions of glipizide in Manitoba during our study period. We agree that the safety of glipizide in individuals with an estimated glomerular filtration rate (eGFR) less than 30 mL/min per 1.73 m² is an important evidence gap that should be addressed given that, unlike other sulfonylureas, they are primarily excreted through the liver rather than the kidneys. We also agree with the authors that metformin use is associated with a higher risk of lactic acidosis in patients with an eGFR less than 30 mL/min per 1.73 m² compared with alternative diabetes management.2,3

However, it is also the case that sulfonylureas, including glipizide, are associated with a higher absolute risk of major hypoglycemic episodes compared with other oral agents.3,4 Furthermore, current guidelines suggest that newer therapies with a more favorable safety profile such as sodium/glucose cotransporter 2 inhibitors and glucogen-like peptide 1 receptor agonists should not be initiated in patients in later stages of chronic kidney disease.3,5 This leaves clinicians with very few options in this population when starting a diabetes treatment regimen. As such, we recommend an individualized approach which balances the more frequent risks of cardiovascular events and major hypoglycemic episodes of sulfonylureas versus the rare but likely real risk of lactic acidosis with metformin in patients with an eGFR less than 30 mL/min per 1.73 m².

Navdeep Tangri, MD, PhD, FRCPC
University of Manitoba
Winnepeg, Canada

Reid Whitlock, MSc
Seven Oaks Hospital
Winnepeg, Manitoba, Canada


https://doi.org/10.1016/j.mayocp.2020.04.034

Angiotensin-Converting Enzyme 2 and the Resolution of Inflammation: In Support of Continuation of Prescribed Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

To the Editor: The coronavirus disease 2019 (COVID-19) pandemic has resulted in a debate on potential risks vs benefits of certain pharmaceuticals—angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs). A recent letter to the editor, published in the Journal of Travel Medicine,1 outlined a hypothesis stating that the use of ACEIs and ARBs may increase the risk of severe disease in patients with COVID-19. Data suggested that the intravenous infusion of ACEIs and ARBs in experimental animals increased the numbers of angiotensin-converting enzyme 2 (ACE2) receptors in the cardiopulmonary circulation. It is acknowledged that ACE2 receptors are widely dispersed, including lung alveolar epithelial cells, gastrointestinal tract enterocytes, the vascular system, the nasopharynx, kidney, and brain.2 Based on those preclinical data, recognizing that ACE2 receptors are binding sites for coronavirus entry into the body, an increased number of ACE2 receptors was hypothesized to increase the risk of severe