Editorials

Controversies in Family Medicine

Should Metformin Continue as First-Line Pharmacotherapy for Patients With Type 2 Diabetes?

Yes: Metformin Is Still the Best Choice

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Metformin has been the first-line treatment for type 2 diabetes mellitus for decades. The glucose-lowering effects of metformin were first discovered in the 1920s.[1] After extensive use throughout Europe, the U.S. Food and Drug Administration (FDA) approved metformin for the treatment of type 2 diabetes with a 1995 randomized controlled trial demonstrating metformin's safety and efficacy.[2] Following two decades of widespread use in the United States, extended-release and combination formulations were introduced.

Adding to the known glycemic effects of metformin, the 10-year United Kingdom Prospective Diabetes Study found improvement in patient-oriented outcomes, specifically diabetes-related endpoints, stroke, and mortality.[3] Of note, 85% of participants randomized to protocols including metformin had their dosage titrated up to a maximum of 2,550 mg per day. A follow-up randomized controlled study in 2008 showed a long-term benefit with early initiation of metformin, with risk reductions in diabetes-related endpoints, diabetes-related death, myocardial infarction, and death from any cause.[4] This study shifted primarily sulfonylurea-based regimens to metformin-first regimens for the treatment of non–insulin-dependent diabetes. Subsequent studies demonstrating reduced mortality in populations with atherothrombosis or heart failure and its affordable cost further solidified metformin as the preferred initial treatment for diabetes.[5,6] Metformin is the most commonly prescribed glucose-lowering medication worldwide and the recommended initial pharmacologic option in major clinical guidelines, including those from the International Diabetes Federation, American Association of Clinical Endocrinology, and American College of Physicians.[7-9]

A recent network meta-analysis joined a growing body of literature questioning the best initial strategy for managing type 2 diabetes.[10] Some contend that metformin should be de-emphasized in favor of newer treatments. However, a closer look at the trials leading to this conclusion is needed. Notably, the FDA published guidance in 2008 requiring drug companies to evaluate the arteriosclerotic cardiovascular disease (ASCVD) benefits and harms of new diabetes therapies.[11] Metformin, having long been approved for diabetes management, was not subject to this requirement.

During the years the FDA guidance was in effect (2008 to 2020), two novel classes of medications were developed, studied, and marketed: sodium-glucose cotransporter-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. Both have been shown to reduce ASCVD events in patients with type 2 diabetes, leading to questions about whether they should be considered first-line therapy.[12-16] However, these trials focused on patients with a history of ASCVD or at high risk for a first ASCVD event, which may not apply to all patients with diabetes who present in primary care settings.

For example, the LEADER trial evaluated the ASCVD effects of liraglutide.[15] In this trial, patients had established ASCVD and were 50 years or older with at least one coexisting cardiovascular condition or 60 years or older with at least one cardiovascular risk factor. Although liraglutide showed benefit in patients with established ASCVD (hazard ratio [HR] = 0.83; 95% CI, 0.74 to 0.93), there was no benefit for those without ASCVD (HR = 1.20; 95% CI, 0.86 to 1.67). Empagliflozin (Jardiance) was studied in the EMPA-REG trial, in which all participants had established ASCVD.[12] Although treatment showed benefit for the primary composite outcome (10.5% vs. 12.1%; HR = 0.86; 95% CI, 0.74 to 0.99), the only individual outcome of the composite to show a benefit was cardiovascular death, which was determined by presumed cardiovascular death and worsening heart failure. Because many meta-analyses are based on composite outcomes of included trials instead of individual-level patient data, nuances like these do not make the headlines.

This is one in a series of pro/con editorials discussing controversial issues in family medicine.

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A collection of Editorials: Controversies in Family Medicine published in *AFP* is available at https:// www.aafp.org/afp/pro-con.

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A 2022 consensus report from the American Diabetes Association and European Association for the Study of Diabetes removed metformin as first-line therapy and focused on goal-based therapy, such as secondary ASCVD reduction in patients with established ASCVD, preventing the progression of chronic kidney disease, and weight management.[17] However, selecting therapy to meet patient goals is the approach every clinician should use for those with type 2 diabetes; this does not automatically exclude the use of metformin. The goals for each patient are different and include considerations such as costs, adverse effects, and administration. Metformin's established safety and effectiveness at A1C reduction—in addition to its relatively low cost and widespread availability to patients—make it an ideal first-line option for many patients with diabetes. Because of safety concerns, metformin is preferred over other older and inexpensive options such as sulfonylureas and thiazolidinediones.[9]

Metformin should be included in first-line medication regimens. Whether additional therapies are started concurrently or deferred depends on individual patient goals. Primary care physicians should not overstate the ASCVD benefits of SGLT-2 inhibitors and GLP-1 receptor agonist medications.

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References

1. Bailey CJ. Metformin: historical overview. *Diabetologia*. 2017;60(9):1566-1576.
2. DeFronzo RA, Goodman AM; The Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. *N Engl J Med*. 1995;333(9):541-549.
3. UK Prospective Diabetes Study Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34) [published correction appears in *Lancet*. 1998;352(9139):1558]. *Lancet*. 1998;352(9131):854-865.
4. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med*. 2008;359(15):1577-1589.
5. Roussel R, Travert F, Pasquet B, et al.; Reduction of Atherothrombosis for Continued Health Registry Investigators. Metformin use and mortality among patients with diabetes and atherothrombosis. *Arch Intern Med*. 2010;170(21):1892-1899.
6. Clarke P, Gray A, Adler A, et al.; United Kingdom Prospective Diabetes Study. Cost-effectiveness analysis of intensive blood-glucose control with metformin in overweight patients with type II diabetes. *Diabetologia*. 2001;44(3):298-304.
7. International Diabetes Federation. IDF clinical practice recommendations for managing type 2 diabetes in primary care. 2017. Accessed October 22, 2023. https://idf.org/media/uploads/2023/05/attachments-63.pdf
8. Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology consensus statement: comprehensive type 2 diabetes management algorithm - 2023 update [published corrections appear in *Endocr Pract*. 2023;29(9):746 and *Endocr Pract*. 2023;29(12):1025]. *Endocr Pract*. 2023;29(5):305-340.
9. Qaseem A, Barry MJ, Humphrey LL, et al. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians. *Ann Intern Med*. 2017;166(4):279-290.
10. Shi Q, Nong K, Vandvik PO, et al. Benefits and harms of drug treatment for type 2 diabetes: systematic review and network meta-analysis of randomised controlled trials. *BMJ*. 2023;381:e074068.
11. U.S. Food and Drug Administration. Guidance for industry on diabetes mellitus-evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes; availability. December 18, 2008. Accessed February 7, 2024. https://www.federalregister.gov/documents/2008/12/19/E8-30086/guidance-for-industry-on-diabetes-mellitus-evaluating-cardiovascular-risk-in-new-antidiabetic
12. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
13. Neal B, Perkovic V, Mahaffey KW, et al.; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657.
14. Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.
15. Marso SP, Daniels GH, Brown-Frandsen K, et al.; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311-322.
16. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121-130.
17. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2022;45(11):2753-2786. ■