Editorials

Controversies in Family Medicine

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

No: Other Drugs Have Stronger Evidence of Benefit

Henry C. Barry, MD, MS, Michigan State University, East Lansing, Michigan

Allen F. Shaughnessy, PharmD, MMedEd, Tufts University School of Medicine, Boston, Massachusetts

Clinicians and patients were excited when research showed that metformin reduces mortality and decreases complications associated with type 2 diabetes mellitus. However, the initial enthusiasm has been tempered by further research that has yet to support these claims and by new medication options with greater promise.

Metformin quickly became the cornerstone of treatment following reports from the United Kingdom Prospective Diabetes Study (UKPDS) that stated that metformin decreased several outcomes (e.g., overall mortality, stroke), independent of its effect on serum blood glucose levels, compared with dietary advice alone.[1] The mortality benefit was found only in patients who were overweight.[2]

The UKPDS was the first to show the benefit of medication treatment on important clinical outcomes. However, the UKPDS has been criticized for its shortcomings.[3] The study began in 1977 with a small grant and later burgeoned into a 20-year study enrolling 5,102 people with newly diagnosed type 2 diabetes identified throughout the United Kingdom.[4] The study protocol was adjusted multiple times, including the addition of metformin after the trial was underway. The study was unblinded and did not have a control group. Only 342 adults who were overweight received metformin.[2]

The results of the UKPDS have not been reproduced. Several meta-analyses have not found metformin to be more effective than any other comparison in decreasing clinically important outcomes such as all-cause or cardiovascular mortality *(Table 1)*.[5-8] One of the analyses found that adding metformin to sulfonylureas *increased* all-cause mortality compared with sulfonylurea monotherapy.[5] A 2023 network meta-analysis of 816 randomized trials found that metformin is not convincingly different than standard treatments in decreasing mortality in patients with an average body mass index of 29.5 kg per m^2 or greater, with three or fewer cardiovascular risk factors, with more than three risk factors, or who are already diagnosed with cardiovascular disease.[8] Better options exist. This meta-analysis also found that sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists are most effective at reducing all-cause and cardiovascular mortality and other cardiac-related problems in patients with pre-existing cardiovascular disease. However, they were less effective in patients at lower risk.[8]

We now have a robust database, which has evolved over the past 20 years. The medical literature comprises at least four meta-analyses and many unique randomized trials. The evidence accumulated since the initial UKPDS does not show a clear advantage of using metformin to treat patients with type 2 diabetes.

As is common in medicine, guidelines have been slow to change. The 2023 American Diabetes Association guidelines on the treatment of type 2 diabetes continue to recommend metformin as first-line therapy. Previous versions of the guidelines have cited the UKPDS; however, the 2024 guideline released in January no longer recognizes the UKPDS but also does not mention the more recent meta-analysis.[9,10]

We are equally concerned about the overzealous extrapolation of research findings to include patients who differ from the original study populations. We have already seen this with metformin and caution against prematurely recommending the newer agents, which have been primarily studied in patients with preexisting cardiovascular disease, to all patients with type 2 diabetes.

Unfortunately, metformin, a safe, tolerable, inexpensive, and easy-to-use treatment, does not offer the benefits the UKPDS initially suggested. However, sodium-glucose cotransporter-2 inhibitors and glucagon-like peptide-1 receptor agonists have demonstrated benefit, especially in

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

See related editorial on page 200.

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

Author disclosure: No relevant financial relationships.

Downloaded from the American Family Physician website at www.aafp.org/afp. Copyright © 2024 American Academy of Family Physicians. For the private, noncommercial use of one individual user of the website. All other rights reserved. Contact copyrights@aafp.org for copyright questions and/or permission requests.

patients with established cardiovascular disease.[6] Tools are available to determine the benefits and harms (https://matchit.magicevidence.org/230125dist-diabetes1/#!/). Although these newer drug classes are not as well tolerated, easy to use, and affordable, the science supporting them is stronger, albeit in patients not representative of those we see in primary care. Clinicians need to exercise judgment in the care of patients: we should follow the evidence, balance

TABLE 1

Comparison of Mortality Outcomes for Type 2 Diabetes Mellitus Treatments

Study	Number of trials (number of participants)	Comparisons (subsections are for selected comparisons with adequate data)	Risk ratio for metformin outcomes (95% CI)*	Comments
Boussageon 2012[5]	13 RCTs (13,110)	Metformin plus sulfonylureas vs. sulfonylureas	All-cause mortality: 1.53 (1.02 to 2.31)	Included UKPDS; data were heterogeneous, which resolved after removing UKPDS
Madsen 2019 (Cochrane review)[6]	32 RCTs (28,746)	Metformin plus sulfonylureas vs. metformin monotherapy or other glucose-lowering interventions	No trial compared metformin with placebo or no intervention	Excluded UKPDS because it "did not compare interventions of interest"
		Metformin plus sulfonylureas vs. glucagon-like peptide-1 receptor agonists	All-cause mortality: 1.15 (0.49 to 2.67)	—
		Metformin plus sulfonylureas vs. dipeptidyl-peptidase-4 inhibitors	All-cause mortality: 1.32 (0.76 to 2.28) Cardiovascular mortality: 1.54 (0.63 to 3.79)	—
		Metformin plus sulfonylureas vs. sodium-glucose cotransporter-2 inhibitors	All-cause mortality: 0.96 (0.44 to 2.09) Cardiovascular mortality: 1.22 (0.33 to 4.41)	—
Gnesin 2020 (Cochrane review)[7]	18 RCTs (10,680)	Metformin monotherapy vs. placebo, no intervention, diet, other hypoglycemic agents	No trial compared metformin with placebo or no intervention	Included UKPDS
		Metformin vs. sulfonylureas	All-cause mortality: 0.99 (0.61 to 1.62) Cardiovascular mortality: 0.50 (0.15 to 1.65)	—
		Metformin vs. thiazolidinediones	All-cause mortality: 0.88 (0.55 to 1.39) Cardiovascular mortality: 0.71 (0.21 to 2.39)	—
Shi 2023[8]	816 RCTs (471,038); 92 used metformin as first-line therapy	All drug treatments for patients with type 2 diabetes, in combination or as monotherapy (13 different drug classes)	All-cause mortality: 0.84 (0.67 to 1.04) Cardiovascular mortality: 0.95 (0.48 to 1.88)	Included UKPDS

RCT = randomized controlled trial; UKPDS = United Kingdom Prospective Diabetes Study.

*—Even after pooling, the data for some comparisons were too few to estimate cardiovascular mortality.

Information from references 5-8.

benefits and harms, weigh the economic and implementation costs, and change practices when better and more relevant data are presented.

Editor's note: Dr. Shaughnessy is an assistant medical editor for *AFP*.

Address correspondence to Henry C. Barry, MD, MS, at henbarry@gmail.com. Reprints are not available from the authors.

References

1. McCormack J, Greenhalgh T. Seeing what you want to see in randomised controlled trials: versions and perversions of UKPDS data. United Kingdom Prospective Diabetes Study. *BMJ*. 2000;320(7251):1720-1723.
2. UK Prospective Diabetes Study (UKPDS) 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.
3. Ewart RM. The UKPDS: what was the question? *Lancet*. 1999;353(9167):1882.
4. Holman RR. Brief history of the UK Prospective Diabetes Study. *Br J Diabetes*. 2022;22(suppl 1):S32-S35.
5. Boussageon R, Supper I, Bejan-Angoulvant T, et al. Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials. *PLoS Med*. 2012;9(4):e1001204.
6. Madsen KS, Kähler P, Kähler LKA, et al. Metformin and second- or third-generation sulphonylurea combination therapy for adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2019;(4):CD012368.
7. Gnesin F, Thuesen ACB, Kähler LKA, et al. Metformin monotherapy for adults with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2020;(6):CD012906.
8. 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.
9. ElSayed NA, Aleppo G, Aroda VR, et al.; American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2023. *Diabetes Care*. 2023;46(suppl 1):S140-S157.
10. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: standards of care in diabetes-2024. *Diabetes Care*. 2024;47(suppl 1):S158-S178. ■