The Right Diabetes Medication for the Right Patient for the Right Outcome: Can a Network Meta-analysis Help Us Decide?

The landscape of diabetes care has grown increasingly complex for patients with type 2 diabetes. Guidelines recognize the need to account for heterogeneous characteristics of patients (such as diabetes duration, cardiovascular risk, risks for adverse drug effects, and comorbidities) so that patients can be put at the center of care and treatment targets and goals can be individualized (1, 2). Since the U.S. Food and Drug Administration issued guidance in December 2008 requiring trial designs and outcomes for new type 2 diabetes therapies to demonstrate cardiovascular safety, evidence has expanded for new drug classes (sodium–glucose cotransporter-2 [SGLT-2] inhibitors and glucagon-like peptide-1 receptor agonists [GLP-1 RAs]) showing benefits beyond glycemic control for both cardioprotection and renoprotection, which has made the selection of drugs for different therapeutic goals more challenging. Furthermore, there is a paucity of head-to-head trials of these newer medications against others. A key clinical question that remains even today is whether any of these newer medications can be used as initial monotherapy and provide better efficacy than metformin in lowering glucose levels and preventing mortality and cardiovascular disease. There is also uncertainty as to whether patients with type 2 diabetes at low cardiovascular risk will benefit more from an SGLT-2 inhibitor or a GLP-1 RA when added to metformin and other diabetes medications.

There are growing attempts to fill such knowledge gaps from trials using network meta-analyses (NMAs), which provide estimates for indirect comparisons of interventions that were not directly compared in the actual trials (3). In their article, Tsapas and colleagues (4) have attempted NMAs of randomized controlled trials to generate evidence to guide the pharmacologic management of type 2 diabetes for different patient risk profiles and outcomes. They searched for randomized controlled trials in adults with type 2 diabetes that evaluated the effect of diabetes medications on different outcomes and, after review and agreement by independent reviewers, included data from 453 randomized controlled trials with an intervention duration of at least 24 weeks.

The results presented on the glycemic effects of diabetes medications from both the pairwise and network analyses are largely known. Diabetes drugs in all classes in both drug-naive and metformin-treated patients are more effective in lowering hemoglobin A_{1c} levels than placebo, albeit with greater confidence in estimates for the latter group. For other outcomes, the results with moderate to high confidence pertain to patients with type 2 diabetes who were already using metformin and had high cardiovascular risk. Compared with placebo, certain GLP-1 RAs and SGLT-2 inhibitors significantly decreased the risks for all-cause and cardiovascular mortality. Empagliflozin, liraglutide, and oral semaglutide significantly lowered the risks for both all-cause and cardiovascular mortality, whereas dapagliflozin and extended-release exenatide were efficacious in lowering the risk for all-cause mortality. With the indirect comparisons, empagliflozin decreased the risk for cardiovascular mortality compared with all other diabetes drugs except oral semaglutide. All SGLT-2 inhibitors lowered the risk for heart failure hospitalization compared with placebo, whereas pioglitazone seemed to confer a higher risk for heart failure hospitalization compared with placebo and all other diabetes drugs.

Unfortunately, in the NMA for drug-naive patients with type 2 diabetes, problems with network consistency and low confidence in estimates do not allow conclusions to be made for the head-to-head comparison of diabetes medications used for initial monotherapy in lowering glycemia, and the confidence in estimates for preventing mortality and cardiovascular outcomes was very low. Similarly, NMAs of trials with patients with type 2 diabetes who were using metformin and had low cardiovascular risk also had very low confidence in estimates to make conclusions on both the efficacy and comparison of diabetes medications for mortality, cardiovascular disease, and microvascular disease. Even the confidence in effect estimates for retinopathy, amputation, and end-stage renal disease was low for patients with type 2 diabetes at high cardiovascular risk.

Although other NMAs of trials studying medications for type 2 diabetes have been published (5, 6), the strength of this report is that it includes the greatest number of randomized clinical trials; attempts to evaluate outcomes beyond glycemia, mortality, and cardiovascular outcomes; and includes stratification not only by initial diabetes drug versus add-on to metformin but also by low versus high cardiovascular risk. There was rigorous and transparent reporting of methods and findings in accordance with PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) NMA guidance (7). They also contributed new findings from NMAs providing at least moderate confidence in estimates for many indirect drug comparisons for mortality and cardiovascular outcomes using trials of patients with type 2 diabetes who were using metformin and had high cardiovascular risk.

Given the approach, there are limitations to this analysis. The NMA estimates were limited in their attempt to answer some of the pressing clinical questions to date. Low confidence in estimates from networks of trials of initial drug therapy does not allow for answering whether any of the newer diabetes medications will be better initial monotherapy agents than metformin

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for lowering glycemia or reducing the risks for mortality and cardiovascular disease. The conduct of most randomized clinical trials of the newer drug classes in patients with type 2 diabetes at high cardiovascular risk also made it difficult to generate more comparative evidence for the population with low cardiovascular risk. Despite the patient-important outcomes like amputation, diabetic eye disease, and sexual dysfunction outlined in the mixed-methods article used to guide their selection of outcomes (8), the limited number of events and trials collecting such outcomes has made conclusive comparisons of diabetes medications through NMA for these outcomes impossible.

Guidelines emphasize the need for individualizing treatment targets and therapies (1, 2). To facilitate more robust and consistent NMAs for comparative effectiveness research that can inform individualized care, clinical trials should attempt to enroll a more heterogeneous patient population that includes the full range of cardiovascular risk and diabetes duration and should try to categorize these factors similarly. Furthermore, the use of a core set of standard secondary outcomes that include patient-important outcomes would also facilitate comparisons for outcomes of greatest relevance to our patients. Although underpowered to analyze in individual trials, the richness of such trial data will facilitate evidence generated from burgeoning methods of analysis that leverage these trials, such as predictive heterogeneity of treatment effect analyses and NMA of select subgroups, to inform efficacy of individualized treatment approaches (3, 9).

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