Session Objective: The objective of this workshop is to assess the value of undertaking comparative effectiveness studies incorporating newer agents for treating patients with type 2 diabetes mellitus, with a focus on SGLT-2 inhibitors, DPP-4 inhibitors, and other agents, and to define the parameters for such research.

“This document was prepared for informational purposes only and should not be construed as medical advice or used for clinical decision making.”
Opportunity Snapshot

As part of PCORI’s efforts to fund high-impact and useful research on critical patient-centered health and healthcare issues, the Clinical Effectiveness Research (CER) program is hosting a multi-stakeholder workgroup to discuss second- and third-line therapies for type 2 diabetes. The objective of this workshop is to assess the value of undertaking comparative effectiveness studies incorporating newer agents for treating patients with type 2 diabetes mellitus, with a focus on sodium glucose cotransporter 2 (SGLT-2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, and other classes of agents. Potential parameters of comparative research in this area will also be discussed. The CER program intends to use the feedback from this workshop to determine whether an investment in patient-centered research in this area by PCORI could offer unique contributions.

The following materials are largely excerpted from previous PCORI briefs.1, 2

I. Background

Diabetes affects over 29 million Americans and continues to increase in prevalence, with 1.7 million new cases in 2012.3 As the seventh leading cause of death in the United States, diabetes may decrease life expectancy by as much as 10 to 15 years.3, 4 Beyond its impact on mortality, diabetes is a significant societal burden, with over $245 billion in annual costs. Much of this expense results from the devastating complications of diabetes, which include vision loss, kidney injury, lower extremity amputation, heart attacks, and strokes. Along with these complications, people with poorly controlled type 2 diabetes commonly experience decreased sense of well-being, impaired quality of life, cognitive impairment, depression, periodontal disease, and other effects.5

Treatment of type 2 diabetes typically begins with lifestyle modification and the prescription of metformin, a medication that lowers blood sugar by reducing glucose production in the liver and enhancing muscle glucose uptake. When lifestyle modification and metformin are insufficient to control blood sugar, additional medications are prescribed. The Surveillance Prevention and Management of Diabetes Mellitus (SUPREME-DM) study found that the addition of a second-line therapy is required in more than one-third (34 percent) of recently diagnosed type 2 diabetics within 6 months and in nearly half (45 percent) within 12 months.6 Further intensification of treatment by adding a third antidiabetic agent may be required when glucose control is insufficient with dual therapy.

While metformin is the consensus first-line pharmacologic treatment for type 2 diabetes, clinical guidelines provide less clarity regarding the choice of second- and third-line therapies. Numerous classes of drugs to treat type 2 diabetes exist, with varying benefits and risks associated with each class and further variance occurring between drugs in each class. These classes include: sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT-2 inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin.7, 8
In their 2015 position statement on the management of hyperglycemia in type 2 diabetes, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes recommend that second- and third-line glucose-lowering agents should be chosen from available options based on patient preferences as well as various patient, disease, and drug characteristics, but the position statement does not specify an order of preference among drug classes. In contrast, while the 2016 consensus statement by the American Association of Clinical Endocrinologists and the American College of Endocrinology on the comprehensive type 2 diabetes management algorithm also recommends tailoring the choice of therapies to patient preferences and needs, these recommendations suggest a hierarchy of usage for second-line treatments placing GLP-1 receptor agonists at the top of the list, followed by SGLT-2 inhibitors, DPP-4 inhibitors, and a number of other classes of drugs. The lack of clarity within and among existing guidelines and recommendations and the number of drug classes available make the selection of the appropriate second- and third-line therapies a challenge for patients and clinicians.

II. Current Research and Evidence Base

Ongoing comparative effectiveness studies may help to inform the choice of second- and third-line pharmacologic agents for type 2 diabetes. Chief among these studies is the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study. GRADE is a multicenter pragmatic trial designed to compare four medications commonly added to metformin: 1) glimepride (a sulfonylurea); 2) sitagliptin (a DDP-4 inhibitor); 3) liraglutide (a GLP-1 receptor agonist); and 4) glargine (long-acting insulin). The GRADE study’s primary outcome is time to treatment failure, which is defined as hemoglobin A1c ≥7% during the anticipated five-year observation period. Secondary outcomes include microvascular complications, adverse effects, tolerability, quality of life, and cost-effectiveness. Estimated enrollment is 5,000 participants, and study follow-up is expected to conclude in 2020.

Of note, GRADE does not include SGLT-2 inhibitors, as this newest class of drugs was not on the market at the time the GRADE study was planned. In the past three years, the FDA has approved three SGLT-2 inhibitors: canagliflozin, dapagliflozin, and empagliflozin. The introduction of the SGLT-2 inhibitor class to the market is of therapeutic interest as the class functions by inhibiting renal reabsorption of glucose and increasing excretion of glucose in the urine. Accordingly, SGLT-2 inhibitors function independent of insulin production and regulation and may be used at any stage of type 2 diabetes and in combination with other type 2 diabetes medications. In addition, they introduce the potential advantage of modest weight loss and the lowering of blood pressure. In late 2015, the findings of the EMPA-REG OUTCOME trial were published indicating that empagliflozin is beneficial for patients with type 2 diabetes at high risk for cardiovascular events. Trials evaluating cardiovascular outcomes among high-risk patients on canagliflozin and dapagliflozin are ongoing with findings anticipated in 2017 and 2019, respectively.
III. Research Areas of Interest

Given that: 1) the prevalence, morbidity, and costs of type 2 diabetes are increasing; 2) the comparative effectiveness of available second- and third-line medication for type 2 diabetes remains uncertain; and 3) GRADE will likely not conclude before 2020 and will not include all potentially relevant medication classes (namely, SGLT-2 inhibitors), further research comparing the effectiveness of second- and third-line therapies for type 2 diabetes will likely be informative.

PCORI is interested in potentially funding comparative effectiveness research that would:

- Complement and expand on existing and ongoing comparative effectiveness trials assessing second-line type 2 diabetes treatments;
- Include newly approved second-line type 2 diabetes treatments not currently included as a comparator in clinical effectiveness trials (i.e., SGLT-2 inhibitors); and
- Evaluate outcomes identified important by patients, clinicians, and other stakeholders.

References


