March 2016

Overview

On March 7, 2016, PCORI convened a multi-stakeholder workgroup to discuss current research and explore opportunities to fund comparative effectiveness research for second-line type 2 diabetes mellitus (T2DM) treatment. The meeting, which was chaired by Doug Owens, MD, MS of Stanford University, was audio-recorded and open to the public via webinar.

Workgroup members included patients, patient advocates, representatives of the pharmaceutical industry, representatives of public and private payers, and researchers from universities and federal agencies. The meeting was open to the public via webinar, and PCORI welcomed comments before, during, and after the meeting.

The objective of this workshop was to assess the value of undertaking comparative effectiveness studies incorporating newer agents for treating patients with T2DM, with a focus on sodium/glucose cotransporter 2 inhibitors (SGLT-2 Inhibitors), dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), and other agents, and to define the parameters of such research.

Prior to the meeting, attendees were requested to review a PCORI Topic Brief that summarized the current landscape of research in this area. Attendees were tasked with considering whether additional research funded by PCORI in this clinical area is needed and what such research might look like. PCORI will use this information to determine whether the development of a PCORI funding announcement in this area is appropriate.
Background

Because of the burden that T2DM places upon patients and the healthcare system, effective treatment is a topic of great interest to many stakeholders in the healthcare system. While there is general consensus that metformin should be the first-line treatment after lifestyle modification, the path toward choosing the optimal second-line approach is less clear. Given the decisional dilemma faced by clinicians and patients when choosing a second-line treatment, this area is ripe for comparative effectiveness research.

PCORI’s Executive Director Joe Selby, MD, MPH, summarized current recommendations for T2DM management from the major international medical societies. The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) position statement on the management of hyperglycemia in T2DM does not specify an order of preference among drug classes. The American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) consensus algorithm suggests a hierarchy of second- and third-line T2DM treatments.

Both sets of guidelines, however, recommend tailoring the choice of second- and third-line treatment to patient preferences and needs—indicating the current lack of clarity about which medications are better for which patients. With insufficient evidence to support the selection of one class of drugs over another, or to indicate which patients will do better on which medications, the choice of a second- or third-line treatment is often a difficult one for patients and clinicians to face.

Current Research Landscape: GRADE

Judith Fradkin, MD, Director, Division of Diabetes, Endocrinology, and Metabolic Diseases at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) presented a summary of the Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) Study. GRADE is a multicenter randomized controlled 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).

GRADE is the first comprehensive comparative effectiveness study of the major second-line pharmacologic treatments for T2DM, and is long enough in duration to be clinically relevant. The focus on demographic, clinical, and metabolic factors that are associated with response to and failure of the different treatments will promote understanding of how to individualize therapy.

Patients enrolled in GRADE will be followed for an average of four years (range three to seven years). The trial expects to recruit 5,000 patients at 45 sites across the country. As GRADE is meant to be representative of patients at a relatively early stage of diabetes, participants must have been diagnosed less than 10 years ago. GRADE began enrolling patients in 2013 and is projected to end in 2020, with results available in 2021.
Dr. Fradkin noted that 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.

Workshop participants discussed specifics of the trial, asking primarily about the age distribution of the participants and the monitoring of adherence, patient satisfaction, and quality-of-life outcomes among participants. Dr. Fradkin noted that the patient population enrolled in GRADE skews toward younger individuals, given the requirement that patients be relatively recently diagnosed, and is reflective of the diversity of the US population (approximately 23 percent African-American and 20 percent Hispanic).

Dr. Fradkin noted that there may be a possibility of continued follow-up of participants in GRADE, allowing the assessment of symptoms and complications of greatest importance to patients emerge over a longer period of time. When asked if the investigators had considered adding an arm now to look at SGLT-2 inhibitors, Dr. Fradkin said the possibility had been discussed, but was considered too difficult to pursue at the point it became a possibility, as it would require a significant increase in sample size and restructuring of the trial.

**SGLT-2 Inhibitors: EMPA-REG OUTCOME, CANVAS, and DECLARE**

Dr. Owens provided more information about SGLT-2 inhibitors, including their mechanism of action, potential benefits, and adverse effects. There are numerous ongoing and completed post-market trials of all three FDA-approved SGLT-2 inhibitors, including placebo-controlled trials exploring cardiovascular outcomes in high-risk patients for each drug.

Of these, only the trial for empagliflozin (EMPA-REG OUTCOME) has been completed. Similar trials, the Canagliflozin Cardiovascular Assessment Study (CANVAS; NCT01032629) and the Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events (DECLARE; NCT01730534), are scheduled to conclude in March 2017 and April 2019, respectively.

In late 2015, the findings of the EMPA-REG OUTCOME trial were published indicating that empagliflozin is associated with significant reduction in death from cardiovascular causes as well as death from all causes and hospitalization for heart failure in patients with T2DM at high risk for cardiovascular events. The trial was halted early because of the significant benefits found in the intervention group. Notably, the patient population included in EMPRA-REG OUTCOME was quite different than that included in GRADE. The mean age of EMPA-REG OUTCOME’s 7,000 participants was 63; 72 percent were male; 72 percent were white, and 57 percent had been diagnosed more than 10 years prior to enrolling in the trial.

Workshop participants discussed the EMPA-REG OUTCOME trial and brainstormed questions about SGLT-2 inhibitors that remain, including if similar cardiovascular effects are likely to be seen in a lower-risk or more diverse population. Questions regarding the mechanism of empagliflozin’s action were also raised, as was a discussion of whether the effects seen in EMPA-REG OUTCOME are unique to this agent or common among other SGLT-2 inhibitors. The ongoing CANVAS and DECLARE trials may answer some of these questions.
Discussion

Dr. Owens then posed the first key discussion question to workgroup participants: Is a study that compares the effectiveness of SGLT2 inhibitors as a second-line T2DM treatment to other second-line T2DM treatments needed?

Attendees were in agreement that such a study would be beneficial, but acknowledged that a single pragmatic study is rarely sufficient to answer all of the relevant questions. There was general consensus in the room that studies evaluating the effects of SGLT-2 inhibitors on cardiovascular outcomes in a broader, lower-risk population would be beneficial.

Participants were in agreement that any pragmatic trial should consider the questions that patients have, and assess outcomes relevant to patients. They pointed out the need for PCORI to fund studies that won’t be funded by other entities, such as pharmaceutical companies.

Dr. Owens also asked the group to discuss how prescriptive PCORI should be in framing these aspects of specific research questions:

1. Patient population and characteristics
2. Comparators
3. Outcomes

Workgroup participants provided input on each of these considerations based on informational needs that will not be met by the GRADE study. Participants were also asked to discuss the magnitude of such a trial, particularly relating to its timeline, cost, and scope.

Patient Population and Characteristics

The group discussed what the target patient population and characteristics (e.g., age, stage of disease, cardiovascular risk) of such a trial should be. Workshop participants noted that the EMPA-REG OUTCOME trial looked at a very particular type of patients—those who are older, sicker, and less reflective of the diversity of the growing US population with diabetes.

Participants noted that it will be important to determine if the findings of the EMPA-REG OUTCOME trial are replicable in younger patients who are not at high-risk for cardiovascular events. They also noted that the diversity of the patient population is important, especially since T2DM is increasingly prevalent in racial and ethnic minority patients. Most participants favored mirroring the patient population of the GRADE study, noting that doing this would yield more comparable findings.

Participants noted, however, that having sufficient power to assess some of the outcomes of interest (e.g., cardiovascular outcomes) in a low- to moderate-risk population requires a large sample size. Likewise, being powered to look at heterogeneity of treatment effect across important subgroups of
patients may also require an increase in scope. Participants noted that these tensions will have to be addressed when developing the parameters of a potential trial.

Comparators

The group then considered various possible comparisons to study in a pragmatic trial. Most participants favored a trial that compares an SGLT-2 inhibitor as an add-on to metformin to another class of drug (or drugs) as an add-on to metformin as a second-line treatment when glycemic control cannot be maintained on metformin alone. A robust discussion of what class or classes of drugs should be compared to SGLT-2s occurred.

Two classes emerged as likely comparators: DPP-4 inhibitors and GLP-1 receptor agonists. These specific classes were highlighted as they have similar cardiovascular risk profiles, effect on patient weight, and risk for hypoglycemia as SGLT-2 inhibitors. Some participants favored including a DPP-4 inhibitor over a GLP-1 receptor agonist as both SGLT-2 inhibitors and DPP-4 inhibitors are oral drugs, while GLP-1 receptor agonists are delivered via injection. Potential concerns about the patient acceptability of being randomized to an injectable drug were raised. The idea of adding an arm that allows patients to select from among a set number of classes was also discussed.

While most of the discussion focused on comparisons that involve newer classes of drugs, one attendee speaking from a payer perspective, pointed out that the lack of evidence for newer classes of T2DM drugs sometimes prevents payers from including them on drug formularies or recommending one over another. Payers also want to see comparisons of these new drugs to older drugs for which we have long-term data.

In addition to discussing which classes of drugs should be included in a comparison, participants discussed whether PCORI should simply define classes to be compared or specify drugs within each class. A number of participants highlighted that evidence indicates that there may be variation in the effectiveness, risks, and benefits of drugs within each class, suggesting that it may be more appropriate to define specific drugs to be compared rather than classes to be compared.

Finally, while most of the discussion regarding comparators focused on second-line treatments, the idea of comparing SGLT-2 inhibitors to metformin as a first-line treatment was raised. It was concluded, however, that this was more of an idea for an efficacy study than a comparative effectiveness trial.

Outcomes

The stakeholders discussed outcomes that they would like to see the study measure. They discussed that time to glycemic failure—the primary endpoint in GRADE—is generally not a top concern for patients. Patients are more focused on quality of life, treatment satisfaction, and the tolerability of medications.

Patient, clinician, and researcher participants all highlighted the tolerability of diabetes medications as key concerns of patients. Participants discussed that while SGLT-2 inhibitors do not carry the same risk of hypoglycemia and weight gain as some of the older drugs, they do come with the risk of side effects.
such as hypotension (which can be associated with dizziness and falls) and an increased occurrence of genital and urinary tract infections, especially in women. Participants noted that including an assessment of these and other side effects is important.

Cardiovascular outcomes and macrovascular complications were also highlighted as of great interest to patients, clinicians, and the health system more broadly, as were microvascular complications. In addition to amputation, retinopathy, macular degeneration, and other eye problems, as well as neuropathy can have severe effects on patients’ activities of daily living. A patient participant noted that cognitive outcomes such as memory and concentration were a pressing concern.

Participants highlighted that clinicians and patients would benefit from knowing whether earlier intensification of treatment improves clinical outcomes and discussed the need to know more about the relationship between clinical outcomes and treatment adherence or symptom management. More information about durability of treatment—or how long the intervention is effective—may also assist clinicians and patients in making clinical decisions.

Productivity, time away from work, absenteeism and “presenteeism” (defined as working while sick or staying at work despite compromised job performance) affect patients, employers, and the economy as a whole. Evaluating these outcomes, in addition to the out-of-pocket costs of treatment for patients, the total burden of disease, and resource utilization (pulled from electronic health records, claims data, or patient report) were also mentioned as outcomes of interest.

Closing and Moving Forward

Dr. Owens provided a synopsis of the discussion from the day, highlighting the general points of consensus within the group on the patient population, comparisons, and outcomes of interest. Dr. Selby and PCORI staff then adjourned the meeting with thanks to all the participants. Deliberations from the workshop will be shared with PCORI leadership and PCORI’s Science Oversight Committee, who will determine next steps.