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Dr. Jan Hux
President, Diabetes Canada

January 30, 2018

Therapeutics Initiative
2176 Health Sciences Mall
Vancouver, BC
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Re: Therapeutics Initiative's assessment of the EMPA-REG OUTCOME trial

To whom it may concern,

Diabetes Canada appreciates the opportunity to comment on the Therapeutics Initiative's assessment of the EMPA-REG OUTCOME trial. We are concerned with several points made in Therapeutics Letter 107 and with the overall tone and message of the review. It gives the impression of a bias against medication use in people with diabetes. This is a position we patently disagree with. We believe that people living with diabetes deserve every available opportunity to achieve their full health potential. This includes having access both to medications and to nonpharmacologic interventions that could improve their outcomes and reduce their risk of disease-related complications. It is important for Therapeutics Initiative reviewers to declare their perspectives against medications and specific populations up-front when writing editorials about clinical trials and medical therapy. There are significant policy implications to a publicly funded institution taking a position that appears biased against people living with a progressive, chronic condition with no known cure.

1. In interpreting the EMPA-REG OUTCOME trial results, the authors posit that "the more aggressive use of other glucose-lowering medications in the placebo group increases mortality and serious adverse events". As the authors likely know, the Food and Drug Administration (FDA), through its 2008 guidance document[i], mandated that all the cardiovascular outcome trials (CVOTs) with antihyperglycemic agents be carried out with a design of glycemic equipoise (both the drug and placebo arms should continue to be treated during the trial to standard of care and HbA1c targets according to local guidelines in every country). All CVOTs, since this regulation was applied, have had an increased utilization of glucose lowering agents in the placebo and comparator arms of the trials and resulted in minimal HbA1c difference between the two arms (ranging from 0.2%-0.3%). This is relevant because the HbA1c effects are minimized between the groups and unlikely to be the reason for differences in serious adverse events.

2. Empagliflozin was noted to cause harm to study participants, in the form of genital infections for 1 in 29 men and 1 in 14 women over a three year period, and that this adversely affected their quality of life. Indeed, increased risk of genitourinary infections is a known side effect of empagliflozin. It is an effect that many people living with diabetes would be willing to chance and/or to bear for an opportunity at longer life. Decreased risk of cardiovascular mortality – i.e. survival – is the most important outcome for the majority of people with diabetes. However, we strongly support patients being informed of the potential benefits and harms of therapy and being part of the decision-making for their own treatment.

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3. The FDA's rejection of the claim that empagliflozin reduces the risk of nephropathy was also noted in the Therapeutics Letter as another "reason for scepticism". We agree that this evidence should direct regulatory approval and clinical recommendations. In a 2016 update to Diabetes Canada's 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada, empagliflozin was recommended as a treatment for suboptimal glycemic control in people with type 2 diabetes and clinical cardiovascular disease. Though the potential microvascular benefits of the drug are recognized, the guidelines suggest the addition of empagliflozin specifically for its cardioprotective effects, as follows: "In adults with type 2 diabetes with clinical cardiovascular disease in whom glycemic targets are not met, an antihyperglycemic agent with demonstrated cardiovascular outcome benefit should be added to reduce the risk of major cardiovascular events (Grade 1, Level 1A for empagliflozin)."

   The lack of demonstrated clinical benefit to reduce the risk of nephropathy does not negate the demonstrated cardiovascular outcome benefits.

4. The conclusion states that "the EMPA-REG OUCTOME Trial tested the addition of empagliflozin to a 'standard of care' for T2DM whose impact on clinically important outcomes is currently unknown". Recommendations for current standards of care are based on trials that have measured HbA1c. Glycemic control measured by HbA1c is a surrogate outcome used in clinical trials that has been a standard metric for decades. In the absence of outcome data, HbA1c is useful to guide decision making. Therapeutics Initiative reviewers have previously questioned the validity of HbA1c as a surrogate outcome. Now that health outcome data are available, these data are also being discarded. The reviewers seem to be systematically biased against people with diabetes having access to medications that can improve their health outcomes.

Diabetes Canada asserts that education, behavioural interventions and support are essential for optimal diabetes management. Medications can be added to therapy as an important adjunct to the care regimen for many Canadians. Therapy must always be individualized, and should include evidence-based options for people living with this disease. Diabetes Canada highlights that the evidence for the role of empagliflozin in the population with type 2 diabetes and clinical cardiovascular disease is robust and we continue to recommend this medication as a choice for those clinicians and patients who wish to access it. We would welcome a discussion with you about these very important issues and the evidence that supports this position.

Sincerely,

Dr. Jan Hux

[i] U.S. Food and Drug Administration. Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008, Center for Drug Evaluation and Research. Available from https://www.fda.gov/downloads/Drugs/Guidances/ ucm071627.pdf.

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