

**SPECIAL
SUPPLEMENT**
July 2023

CANADIAN || **TODAY** PRIMARY CARE

Clinical Insights, Perspectives, and Disease Management

**THE URGENCY TO TREAT OPTIMALLY
AND TO TARGET: AVOIDING LONG-TERM
COMPLICATIONS IN TYPE 2 DIABETES WITH
A FOCUS ON GLP-1 RECEPTOR AGONISTS**

Lionel Noronha, MD

ABOUT THE AUTHOR

Lionel Noronha, MD

Dr. Lionel Noronha graduated from the University of Toronto medical school in 1990 and completed his family medicine residency there in 1992. He was awarded the Gaynor Dawn Memorial scholarship in family medicine. He is the medical director of the Stirling Manor and the lead physician for the Belleville family health organization. He has been a clinical investigator in numerous studies and also has published in peer-reviewed journals. He has a passion for CME and has given over 250 talks to other physicians as well as nurses, pharmacists and diabetic educators.



The urgency to treat optimally and to target: Avoiding long-term complications in type 2 diabetes with a focus on GLP-1 receptor agonists

Lionel Noronha, MD

Introduction

The wave of diabetes continues to increase in Canada and around the world. According to national data, 3.4 million Canadians were living with diabetes (type 1 and type 2 combined) in 2017–2018, compared to 1.3 million in 2000–2001.¹ It is well-accepted that diabetes is a major cause of death and is the leading cause of renal failure, lower limb amputations and blindness in adults.

Cardiovascular Outcomes: Clinical Trials Overview

A 2008 study demonstrated that long-term complications and mortality may be avoided in patients with type 2 diabetes (T2D). The STENO-2 study randomized 160 T2D patients with persistent microalbuminuria to receive either intensive (strict targets for A1C, blood pressure medication, lipid-lowering agents, renin-angiotensin system blockers, low-dose aspirin and formed behavioral modification) or conventional therapy consisting of insulin and formed behavioural modification. The mean treatment time for subjects in the study was 7.8 years with a subsequent observational follow-up for a mean of 5.5 years. In all, 24 patients in the intensive therapy group died (30%) and 40 patients in the conventional therapy group died (50%), which corresponded to a 20% absolute risk reduction in death ($P=0.02$). There was a 46% reduction in the overall hazard ratio for death with intensive therapy. Death from cardiovascular causes was reduced by 57% ($P=0.04$), and cardiovascular events were reduced by 59% ($P=0.001$) in the intensive therapy group compared with the conventional therapy group. Additionally, only 1 patient in the intensive therapy group needed dialysis versus 6 in the conventional therapy group.²

STENO-2 demonstrated that the rationale of multi-risk factor modification and lifestyle changes had a meaningful impact on outcomes for patients. Until the STENO-2 results, other studies had demonstrated reductions in mainly microvascular disease. Some of these studies included the Diabetes Control and Complications Trial (DCCT),³ UK Prospective Diabetes Study (UKPDS),⁴ Veterans Affairs Diabetes Trial (VADT),⁵ and Action in Diabetes and Vascular Disease: Preterax and Diamicon

Modified Release Controlled Evaluation (ADVANCE)⁶ trials. It is important to note that the metformin subgroup analysis arm of UKPDS, and later the extension studies of the UKPDS and DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC),⁷ did show macrovascular benefits.

After a landmark meta-analysis was published by Dr. Steve Nissen in 2007⁸ examining the effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes, in which researchers found a significant increase in the risk of myocardial infarction for patients treated with rosiglitazone, the call for inclusion of cardiovascular outcomes in diabetes trials increased. While essentially neutral cardiovascular outcomes had been seen for the Dipeptidyl Peptidase-4 (DPP-4) inhibitor class (TECOS,⁹ SAVOR-TIMI 53¹⁰ and CARMELINA¹¹), in 2016 the medical community started to rethink the approach to the management and treatment of people living with T2D. That year, the EMPA-REG¹² and LEADER¹³ studies were presented for the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin and for the glucagon-like peptide 1 receptor agonist (GLP-1RA) liraglutide, respectively.

For the first time in diabetes trials, researchers reported outcome data showing reductions in cardiovascular death and in overall mortality in patients within 3–5 years of follow-up. Specifically, researchers observed a 38% relative risk reduction in death from cardiovascular causes between the active arm and the placebo arm in the EMPA-REG study.¹² In the LEADER study, there was a reported 22% reduction in death from cardiovascular causes ($P=0.007$) along with a lower rate of death from any cause ($P=0.02$). The rates of non-fatal myocardial infarction, non-fatal stroke and hospitalization for heart failure were non-significantly lower in the liraglutide group than in the placebo group.¹³ Following these two landmark studies, clinicians embraced the growing urgency for both a multi-risk factor approach in the management and treatment of people living with T2D, as well as the specific selection of agents with a proven track record of delivering meaningful cardiovascular outcomes within a short time frame.

The CANVAS¹⁴ and DECLARE¹⁵ studies for the SGLT2 inhibitors canagliflozin and dapagliflozin, respectively,

Agent (outcome trial)	Population	Clinical outcomes (HR [95% CI] vs placebo)						
		MACE	CV mortality	All-cause mortality	Fatal/nonfatal MI	Fatal/nonfatal stroke	Hosp HF	Progression of CKD
GLP-1RA								
Exenatide (EXSCEL)	CVD (73%) or CV risk factors	0.91 (0.83–1.00)	0.88 (0.76–1.02)	0.86 (0.77–0.97)	0.97 (0.85–1.10)	0.85 (0.70–1.03)	–	–
Liraglutide (LEADER)	CVD (72%) or CV risk factors	0.87 (0.78–0.97)	0.78 (0.66–0.93)	0.85 (0.74–0.97)	0.86 (0.73–1.00)	0.86 (0.71–1.06)	–	–
Semaglutide SC (SUSTAIN-6)	CVD (59%) or CV risk factors	0.74 (0.58–0.95)	0.98 (0.65–1.48)	1.05 (0.74–1.50)	0.74 (0.51–1.08)	0.61 (0.38–0.99)	–	–
Semaglutide Oral (PIONEER 6)	CVD (85%) or CV risk factors	0.79 (0.57–1.11)	0.49 (0.27–0.92)	0.50 (0.31–0.84)	0.18 (0.73–1.90)	0.74 (0.35–1.57)	–	–
Dulaglutide (REWIND)	CVD (31.5%) or CV risk factors	0.88 (0.79–0.99)	0.91 (0.78–1.06)	0.90 (0.80–1.01)	0.96 (0.79–1.16)	0.76 (0.61–0.95)	–	–
Albiglutide (HARMONY) (withdrawn from market)	CVD or PVD	0.78 (0.68–0.90)	0.93 (0.73–1.19)	0.95 (0.79–1.16)	0.96 (0.79–1.15)	0.76 (0.62–0.94)	–	–

Table 1: Reviewing, adjusting or advancing therapy in type 2 diabetes for GLP-1RAs.

Adapted from *Diabetes Canada Practice Guidelines, 2020*. MACE: major adverse cardiovascular events, CV: cardiovascular, MI: myocardial infarction, Hosp: hospitalization, HF: heart failure, CKD: chronic kidney disease, CVD: cardiovascular disease

further strengthened the value of the SGLT2 inhibitor class. Data from both of these studies along with the EMPA-REG study revealed benefits with the use of these agents specifically in patients with congestive heart failure and for nephroprotection. As a result, further studies in congestive heart failure patients were designed to examine the nephroprotective benefits of these agents. Some endocrinologists, primary care practitioners, internists, cardiologists, and nephrologists have modified their treatment of these types of patients in light of this published and continually emerging data.

The SGLT2 inhibitor and GLP-1RA classes both have clear benefits beyond glycemic lowering. The two commonly-used GLP-1RAs, semaglutide and dulaglutide, are once-weekly injectables, unlike liraglutide which is injected daily. Semaglutide is also available as an oral tablet.

According to the 2020 Diabetes Canada Clinical Practice Guidelines,¹⁶ “there is substantial evidence that GLP-1RAs (with the exception of lixisenatide) are associated with a significant reduction in risk of major adverse cardiovascular events (MACE) among patients with T2D and established cardiovascular disease (CVD) (**Table 1**). The most reliable evidence for cardiovascular benefit from individual clinical trials is for liraglutide, dulaglutide and semaglutide.” The most recent update to the guidelines also states that there is now “evidence suggesting GLP-1RAs, particularly dulaglutide, can reduce the risk of MACE in people without established CVD. This evidence has led to a recommendation that a GLP-1RA with proven cardiovascular outcome benefits can be considered in patients aged 60 years or older with at least two cardiovascular risk factors, with the strongest evidence for dulaglutide followed by liraglutide and subcutaneous semaglutide.”

Clinical Trials Safety Data

Cardiovascular safety studies on semaglutide have been published for both its weekly injectable and daily oral formulations. The SUSTAIN-6 trial for the injectable form of semaglutide was a 104-week study of 3,297 patients with T2D who were randomly assigned to receive semaglutide (0.5 mg or 1.0 mg) vs placebo. At baseline, 83% of subjects had established atherosclerotic cardiovascular disease, chronic kidney disease, or both. The primary outcome was a composite of the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke, with a 26% reduction seen in the semaglutide arm (hazard ratio, 0.74; 95% confidence interval [CI], 0.58 to 0.95; $P < 0.001$ for non-inferiority; $P = -0.02$ for superiority). Additionally, a 39% reduction favouring the semaglutide arm was seen for the secondary endpoint of non-fatal stroke (hazard ratio, 0.61; 95% CI 0.38 to 0.99; $P = 0.04$).¹⁷

Safety data on oral semaglutide from the PIONEER 6 study has also been published.¹⁸ In this study, 3,183 T2D patients were enrolled with a primary endpoint of the first occurrence of a major adverse cardiovascular event (death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke). The published data show that the primary endpoint occurred in 61 of 1,591 patients (3.8%) in the oral semaglutide group and 76 of 1,592 (4.8%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.57 to 1.11; $P < 0.001$ for non-inferiority).

The primary takeaway from these cardiovascular outcome and safety data is that there is clearly an urgent need to focus on cardiovascular health for patients with T2D by choosing therapeutic agents with proven benefit for MACE, cardiovascular death, overall mortality, nephroprotection, and stroke reduction.

In a post-hoc analysis of the PIONEER 1 study, which randomized 703 patients with T2D to oral semaglutide for 26 weeks vs placebo, researchers found that “oral semaglutide monotherapy demonstrated superior and clinically relevant improvements in A1C (at all doses) and body weight loss (at the 14 mg dose) [-2.6 kg; P=0.001] versus placebo, with a safety profile consistent with other GLP-1RAs.” Statistically significantly greater body weight loss was seen at the 7 mg dose (-1.0 kg; P=0.01) as well.¹⁹

Role of Early Intervention

Early glycemic control in patients living with T2D was found to have benefits with respect to future complications based on data from the UKPDS-Legacy study. Compared with patients whose A1C was 6.5% from the early exposure cohort (0 to 1 year period), those whose A1C levels were 6.5% to < 7 % had a 20% higher rate of microvascular complications (95% CI 1.063 to 1.365). Further, those whose A1C was 7.0% to < 8.0% had a 29% increased mortality rate. This suggests that earlier achievement of lower glycemic targets provides benefits that may be seen decades later.²⁰

Similarly, early intensive control for patients with type 1 diabetes (T1D) was studied in the DCCT/EDIC trial. Statistical modelling was used to estimate the 20-year cumulative incidence (absolute risk) and the 20-year relative risk of cardiovascular disease and reduced estimated glomerular filtration rate (eGFR) over the first 20 years of EDIC follow-up as a function of the mean A1C. A hypothetical patient treated earlier with 10 years at a mean A1C of 7%, followed by 10 years at a mean of 9%, would have a 33% reduction in cardiovascular disease and a 52% reduction in reduced eGFR, vs a patient who had an initial 10 years of treatment with a mean A1C of 9%, followed by 10 years with a mean A1C of 7%. Although both scenarios involve equal glycemic exposure, the patient with 10 years of aggressive control initially targeting an A1C level of 7% had a lower risk of long-term complications.²¹

Having treated many people living with T2D for over 30 years, the introduction of SGLT2 inhibitors and GLP-1RAs in patients with T2D has resulted in a reduction in the use of insulin therapy in my practice. I believe that SGLT2

inhibitors and GLP-1RAs may delay the natural history of T2D indefinitely and therefore the need for the addition of insulin therapy. As a result of the GLP-1RA efficacy and safety benefits, along with long-term data on microvascular and macrovascular complications, I rarely use DPP-4 inhibitors.

When initiating a GLP-1RA for a patient on an existing DPP-4 inhibitor, the DPP-4 inhibitor should be discontinued. Based on the rationale presented in this review article, clinicians may wish to consider using GLP-1RAs much earlier in the treatment course for patients living with diabetes. If a history of heart failure or renal failure is present, initiating an SGLT2 inhibitor post the initiation of metformin is a sound approach. In my opinion, it is practical to have access to an oral GLP-1RA (oral semaglutide). This allows patients who prefer a non-injectable formulation to gain the benefits of this class of agent.

Conclusion

There is currently extremely robust data on new classes of drugs to treat diabetic patients which demonstrate both excellent glycemic control and long-term improvements in microvascular and macrovascular complications. It is incumbent upon clinicians to use these therapies to manage the ever-growing diabetes epidemic in Canada in order to provide patients maximal benefit and improve their outcomes.

Correspondence

Dr. Lionel Noronha
Email: sempermater@yahoo.com

Financial Disclosures

Speaking Fees: Eli Lilly, AstraZeneca, Pfizer, Janssen, Bayer, Amgen, Novo Nordisk, Boehringer Ingelheim, Takeda, Eisai

Advisory Boards: Novo Nordisk, Eli Lilly, Amgen, Bristol Myers Squibb, Takeda, Eisai, Valeo, Cipher, Pfizer, Otsuka, Abbott, GSK, Khure, Boehringer Ingelheim.

CME Development: Eli Lilly, Novo Nordisk, Takeda, Bausch Health, Takeda.

References

1. Public Health Agency of Canada. Canadian Chronic Disease Surveillance System (CCDSS) [Internet]. Public Health Agency of Canada. 2017 [accessed 2019 Sept 2013].
2. Gaede P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med*. 2008 Feb 7;358(6):580-591.
3. DCCT Research Group. Diabetes control and complications trial (DCCT): update. *Diabetes Care*.1990;427-433.
4. King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *Br J Clin Pharmacol*. 1999;48(5):643.
5. Duckworth W, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360;2:129-139.
6. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560-2572.
7. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med*. 2005;353(25): 2643-2653.
8. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356(24):2457-2471.
9. Green JB, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2015;373(3):232-242.
10. Scirica BM, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317-1326.
11. Rosenstock J, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: the CARMELINA randomized clinical trial. *JAMA*. 2019;321(1):69-79.
12. Zinman B, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
13. Marso SP, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016;375(4):311-322.
14. Neal B, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657.
15. Wiviott SD, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.
16. Lipscombe L, et al. Pharmacologic glycemic management of type 2 diabetes in adults: 2020 update. *Can J Diabetes*. 2020;44(7):575-591.
17. Marso SP. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375:1834-1844.
18. Husain, M, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381(9): 841-851.
19. Aroda VR. Randomized clinical trial of the efficacy and safety of oral semaglutide monotherapy in comparison with placebo in patients with type 2 diabetes. *Diabetes Care*. 2019;4 (9):1724-1732.
20. Laiteerapong N. The legacy effect in type 2 diabetes: impact of early glycemic control on future (The Diabetes and Aging Study). *Diabetes Care*. 2019;42(3):416-426.
21. Lachlin JM. The beneficial effects of earlier versus later implementation of intensive therapy in type 1 diabetes. *Diabetes Care*. 2021;44(10):2225-2230.



Canadian Primary Care Today
Science for the Real World

canadianprimarycareday.com

Canadian Primary Care Today is published three times per year in English and in French (ISSN 2817-4186 imprimé; ISSN 2817-4194 en ligne) under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) license by Catalytic Health in Toronto, Ontario, Canada.

© 2023 Canadian Primary Care Today.

**SPECIAL
SUPPLEMENT**
July 2023

CANADIAN || **TODAY** PRIMARY CARE

Clinical Insights, Perspectives, and Disease Management

**THE URGENCY TO TREAT OPTIMALLY
AND TO TARGET: AVOIDING LONG-TERM
COMPLICATIONS IN TYPE 2 DIABETES WITH A
FOCUS ON GLP-1 RECEPTOR AGONISTS**

Lionel Noronha, MD