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# Diabetes & Cardiorenal Risk:
## The Evolving Role for GLP-1 Receptor Agonists - now in Primary Prevention

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We find ourselves in an era with more knowledge about Type 2 Diabetes (T2D) than we've ever had – more insights into the disease and more therapy choices. As much as finding the right path for patients should arguably be easier, the array of options can be understandably daunting. After our classic default of 1st-line metformin, DPP-4 inhibitors have become an almost 'routine' 2nd-line therapy - and with good reason – they've been proven safe and effective, with over a decade of prescriber comfort behind them. After metformin, DPP4i's are the most commonly used diabetes therapy in Canada.

> *"...as a series of priorities emerge among a growing array of therapies, we're forced to move away from our traditional 'go to' class"*

The complexity deepens when we consider the potential further advantages of newer classes of glucose lowering therapies: SGLT2 inhibitors (commonly empagliflozin, Jardiance; canagliflozin, Invokana; and dapagliflozin, Forxiga) and GLP-1 Receptor Agonists (commonly dulaglutide, Trulicity®; liraglutide, Victoza®; and semaglutide, Ozempic®). In addition to "safe and effective", these classes add the benefits of weight loss (typically 3-4kg) and reduced cardiovascular (CV) events in patients with known CV disease (Heart Failure events in SGLT2i's and MACE events among GLP-1 RA's). For these reasons, international (ADA/EASD) guidelines now encourage us to individualize therapy for T2D patients with cardiovascular disease: if ischemic events predominate, we should be ideally prioritizing GLP-1 RA's with proven efficacy (listed above). Where HF is the primary cardiac disease, we should be prioritizing SGLT2i's. For patients with established renal disease, both of these classes offer additional benefits, with the strongest evidence to date emerging from the recent CREDENCE trial evaluating canagliflozin in patients at high risk for renal events.

Our individual challenge as healthcare providers is that as a series of priorities emerge among a growing array of therapies, we're forced to move away from our traditional 'go to' class, which for a decade has been the DPP4i's.

**The majority of our T2D patients don't actually have CV disease but are often at high risk for it – Primary Prevention status.** To this point, our prior trials had focused on patients with established CV disease who had ~5% risk of a recurrent CV event each year. While some trials had included cohorts of patients who only had CV risk factors, none had produced definitive (statistically sound) conclusions sufficient to change guidelines for therapy.

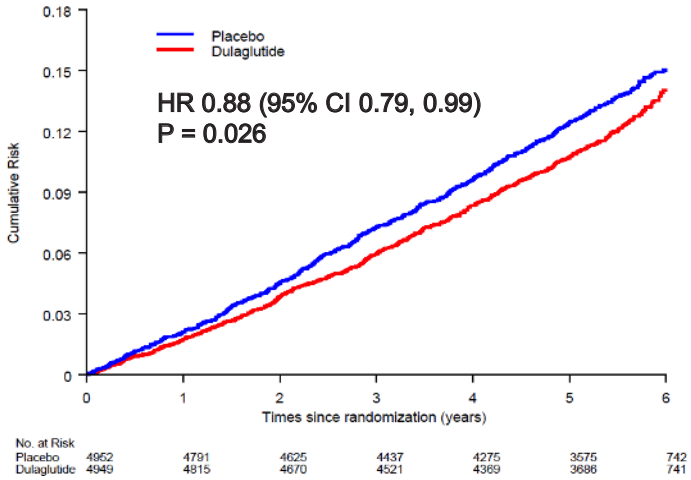
When it comes to Primary Prevention of CV disease using a diabetes therapy, our first firm findings of a benefit came in this summer's long-awaited presentation of the REWIND study at the ADA meetings in San Francisco and simultaneously published in the Lancet. The REWIND study explored whether participants with new or established T2D with additional CV risk factors would see a benefit in reducing serious CV outcomes with a weekly 1.5 mg injection of the GLP-1 RA dulaglutide compared to a weekly placebo injection, added to standard diabetes therapies. Over 9900 people were enrolled and followed for a mean of 5.4 years with a >97% retention rate and ~82% 'on drug' time. Participants came from 24 countries, including a large number from Canada, where our own LMC sites were able to contribute over 5% of the overall global cohort.

We were able to include patients aged 50 and older, if they had T2D, using stable therapy for at least 3 months, and were using up to 2 oral therapies +/- basal insulin or GLP-1 RA. Interestingly, there was no minimum A1C (max of 9.5%) and BMI > 23 kg/m$^2$. Their CV status could include either established disease; or age 55 plus subclinical vascular disease (positive stress test/image, >50% stenosis, ABI<0.9; eGFR <60; hypertension + LVH, or albuminuria); or age 60 plus 2 CV risk factors (tobacco, lipid drug, LDL-C ≥ 3.4, HDL-C < 1.0 for men & < 1.3 for women or TG ≥ 2.3, ≥ 1 BP drug or SBP ≥ 140 or DBP ≥ 95, or waist:hip ratio >1.0 for men & > 0.8 for women).

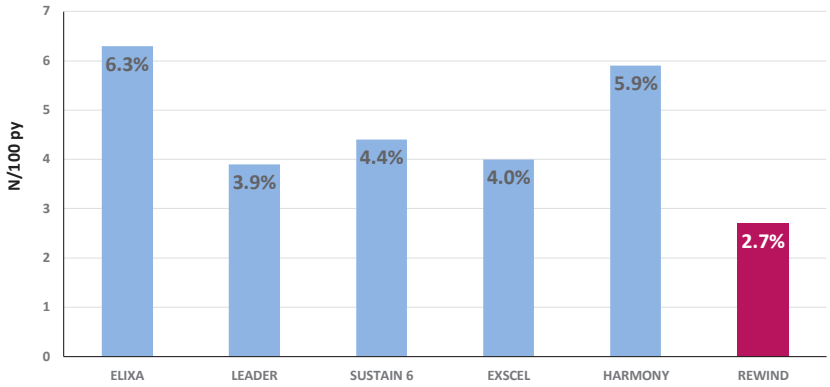
The resulting group of 9901 patients were quite typical of our Canadian practices, showing a mean A1C of 7.3%, quite a bit lower than ever seen in a prior CVOT trial in Diabetes. The majority were using metformin, sulfonylureas or DPP4i's and nearly 24% were also using basal insulin. Mean BMI was 32 (kg/m$^2$). The proportion of women was 46.4%, which is substantially higher than in prior CVOT's (typically low 30% range) and only 31.5% had existing CV disease, again, in contrast to our other CVOT trials.

## Dulaglutide's Effect on the CV Composite

Primary Outcome: 1st Occurence of Nonfatal MI, Nonfatal Stroke, CV Death




## Annual Placebo MACE Rates by Trial



Although both treatment arms could use other non-incretin diabetes therapies ad lib, there was a difference in A1C of 0.6% over the 5.4 years of mean follow-up, and a weight difference of 1.5kg, both favouring the dulaglutide group.

**The primary outcome was the classic composite MACE outcome of CV Death, nonfatal MI or nonfatal stroke was reduced by a significant 12% (HR 0.88, p=0.026, Figure 1) in the dulaglutide-treated arm. The effect was consistent across demographics: age (under and over 65), gender, ethnicity and duration of DM; and across health parameters: BMI and baseline A1C (under and over 7.2%). The high proportion of women included in the trial and the low mean A1C make the findings particularly meaningful.**

Similarly important, the effects were consistent in those with CV disease and in the larger cohort who were Primary Prevention status.

Interestingly, microvascular disease event rates were also reduced in the dulaglutide-treated arm, largely contributed by reduced rates of renal outcomes. Benefits in renal outcomes have been seen as secondary/exploratory findings in prior GLP-1 RA therapy trials, and now, the REWIND trial carries on that same pattern for dulaglutide. As with CV disease, this group of participants had a relatively low prevalence of pre-existing renal disease: 22.2% had eGFR below 60 ml/min/1.73m$^2$, 35% had albuminuria and 10.5% had both. At the end of the study, the dulaglutide-treated group had 18% lower rate of albuminuria ($p<0.001$) and a composite outcome of new renal events (new albuminuria, 30% fall in eGFR, or renal replacement therapy) was reduced by 15% ($p<0.0004$). Further declines in eGFR were also reduced in the dulaglutide-treated participants, reaching significance for a decline of 40% (30% lower risk, p=0.0004) and for a decline of 50% (44% lower risk, p=0.0002). The benefits for renal health were consistent across baseline GFR, baseline proteinuria, and ACEi/ARB usage.

Among incretins, we continue to pay special attention to specific outcomes that were suspected in animal models, among early entrants in the field. In the REWIND trial, pancreatitis events, as well as cancer and thyroid cancer events, were rare and were not different between the two groups. Severe hypoglycemia was rare (1.5 – 1.8%) and not different between the two groups.

> *"The REWIND trial now marks the first diabetes therapy to show a proven benefit in primary prevention of CV disease in people with T2D"*

The REWIND trial now marks the first diabetes therapy to show a proven benefit in primary prevention of CV disease in people with T2D. Whereas other trials had included small subgroups of primary prevention patients, in which consistent findings were seen, these were secondary endpoints and not eligible for statistical significance evaluation. It's important to recognize that this population had relatively low rates of CV disease (2.7% annually) compared to other trials (3.9 – 6.3% annually, Figure 2). The further strength of the REWIND trial includes its generalizability to our typical T2D populations with its relatively high proportion of women and relatively low A1C. The exploratory benefits to renal disease outcomes in this population are also very encouraging.

## What does it mean for our patients?

The last decade has seen our therapy class choices for T2D care expand dramatically. With our new and developing insights into the respective benefits of these therapy classes, we need to reconsider our long-standing routines of T2D care and consider the individual parameters of each of our patients to determine which agent should follow metformin. Where patients with CV disease are now already mandated a clear priority for GLP-1 RA or SGLT2i therapy, many of our T2D patients at increased CV risk will now need to be considered for dulaglutide/GLP1 RA therapy as 2nd line therapy.

## REFERENCES


Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. DOI:https://doi.org/10.1016/S0140-6736(19)31149-3

Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. DOI:https://doi.org/10.1016/S0140-6736(19)31150-X

# REWIND Q&A:

## Perspectives from LMC's Primary Investigators

After nearly 20 years in clinical research, LMC had an unprecedented impact on the REWIND trial contributing and supporting over 5% of patient enrolment globally. Including Dr. Aronson, 8 LMC primary investigators participated across 7 sites in 3 Canadian provinces, and we are happy to share their perspectives. We asked each of them:

As a Canadian Primary Investigator for the REWIND trial, which one key clinically significant finding do you think is most important to share with your primary care colleagues?

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**DR. HARPREET S. BAJAJ**
**LMC Brampton**

"The primary composite cardiovascular outcome (MACE) benefit observed with dulaglutide in REWIND sets this trial apart from other CVOTs in two ways:

1. Broadest inclusion criteria to date, with a generalizability of 42% (i.e. more than 3 times the generalizability than LEADER or SUSTAIN-6 trials) to adult US type 2 diabetes population – hence making the results broadly applicable to the majority of older adults with type 2 diabetes who visit outpatient clinics. No wonder REWIND was one of the easiest trials to recruit at LMC (our 7 REWIND sites randomized 529 participants)!

2. No new adverse effects (AE) signal observed (as expected, only gastrointestinal AEs were increased with dulaglutide) - a total of 53,465 patient-years of follow-up in the REWIND trial provides the best safety information for dulaglutide within the GLP-1 RA class, to date."

**DR. RONALD GOLDENBERG**
**LMC Vaughan**

"REWIND is the first CVOT to demonstrate a reduction in major adverse cardiovascular events with an antihyperglycemic agent in patients with T2D and risk factors but without CVD. This landmark trial has important implications for prioritizing add-on dulaglutide in T2D patients typically seen in a primary care practice."

**DR. HASNAIN KHANDWALA**
**LMC Etobicoke**

"Dulaglutide is the first GLP-1 RA to show a reduction in cardiovascular events in patients with and without pre-existing cardiovascular disease and thus is an attractive therapeutic option in both primary and secondary prevention patient populations."

**DR. BUKI AJALA – LMC Calgary**

"The reduction in CVD events was impressive particularly as glycemic control was fairly good in this large cohort of patients and in the majority, cardiovascular disease had not been detected at baseline."

**DR. STUART ROSS – LMC Calgary**

"Cardiovascular disease is a major complication of Type 2 diabetes.The REWIND trial has shown impressive results in actually preventing progression of cardiovascular disease in those patients without obvious clinical features of cardiovascular disease."

**DR. DAVID Y. TWUM-BARIMA**
**LMC Oakville**

"The results of REWIND confirms that as a class, the GLP1a are not only effective in glucose lowering but also offer significant cardiovascular protection not only in the setting of secondary prevention (as shown by earlier trials) but also in patients without prior CVD event. GLP1a's should therefore be considered early on in the management of diabetes by primary care physicians."

**DR. ZEINA YARED**
**LMC Montreal - Ville St Laurent**

"The Rewind trial confirmed to me that by adding dulaglutide, a safe and well tolerated once weekly injection, to my patients with type 2 diabetes for both primary or secondary cardiovascular prevention, I will help them achieve several positive clinical outcomes and reduce their 5 year risk of non fatal stroke. The reduction in renal outcomes is very promising but needs to be confirmed."

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