Journal Club
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Title: Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

Authors: Gerstein HC, Colhoun HM, Dagenais GR, et al

Source: *Lancet* 2019;394(10193):121-130

Background: Currently, the American Diabetes Association guidelines recommend that metformin be used as first line therapy.[2] What medication providers choose next varies based on patient specific factors. For patients with type II diabetes who have established ASCVD or have indicators of ASCVD glucagon-like peptide-1 (GLP-1) receptor agonists are one of two classes of medications that can be considered.[2] The mechanism of action for this class of medications includes increasing endogenous insulin secretion, delaying gastric emptying, and inhibiting glucagon production from the alpha cells of the pancreas.[3] GLP-1 receptor agonists have other benefits as well, such as weight loss, which is an important aspect of diabetes management that has been linked to more beneficial outcomes.[4] Dulaglutide is an approved GLP-1 receptor agonist that is available in both 0.75 mg and 1.5 mg and is administered weekly through the subcutaneous route.[1] Prior to this study, other research had been conducted that assessed other medications within the class and "suggested that GLP-1 receptor agonists might only reduce cardiovascular outcomes in people with previous cardiovascular disease."[1]

Primary Objective: To determine if once weekly dulaglutide reduces the incidence of cardiovascular events when added to patients with diabetes medication regimen.

Primary Efficacy Measure: Time to first occurrence of any component of the composite outcome including non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular or unknown causes.

Study Design: This was a randomized, multicenter, double-blind, placebo-controlled trial that took place at 371 sites located across 24 countries. Patients were screened and began a 3-week, single-blinded run-in period where they received placebo. Patients were able to remain on any medication for diabetes other than dipeptidyl peptidase-4 (DPP-4) inhibitors. This study ran from August 2011 to August 2018. An independent data monitoring committee reviewed accruing and unblinded data every 6 months. Investigators were instructed to promote healthy lifestyles and were free to manage glucose according to local guidelines including the addition of medications except for other GLP-1 receptor agonists or pramlintide.

Subjects: Randomization of patients produced groups that showed similarities in age, race, tobacco use, cardiovascular disease, cardiovascular events, and specific diabetes and cardiovascular elements such as duration, HbA_{1c}, medications, BMI, SrCr, eGFR, and cholesterol.

Inclusion Criteria:

- Men and women (50 or older) with established or new type II diabetes
- HbA_{1c} less than or equal to 9.5% on stable doses of up to two oral glucose-lowering agents (with or without basal insulin)
- BMI of at least 23 kg/m^2
- Patients 50 years old or older had to have vascular disease (a previous myocardial infarction, ischaemic stroke, revascularisation, hospital admission for unstable angina, or imaging evidence of myocardial ischaemia)
- Patients 55 years old or older had to have myocardial ischemia, coronary, carotid, or lower extremity artery stenosis exceeding 50%, left ventricular hypertrophy, eGFR less than 60 $mL/min/1.73m^2$, or albuminuria
- Patients 60 years old or older had to have at least two of the following: tobacco use, dyslipidemia, hypertension, or abdominal obesity

Exclusion Criteria:

- eGFR less than 15 $mL/min/1.73m^2$
- Cancer in the previous 5 years
- Severe hypoglycemia in the previous year
- Life expectancy less than year
- Coronary or cerebrovascular event within the previous 2 months
- Plans for revascularization
- Uncontrolled diabetes requiring immediate therapy
- Past history of pancreatitis

Study Period: This study occurred from August 2011 to August 2018 with a 3-week run-in where patients were instructed on how to inject the study medication. Patients that were completely adherent to the run-in injections were randomized in a 1:1 fashion to receive 1.5 mg of dulaglutide or the same volume of a masked placebo.

Monitoring: Patients in the study were seen at 2 weeks, 3 months, and 6 months, followed by every 3 months for medication dispensing and every 6 months for assessments such as cardiovascular events, adverse effects, vital signs, questionnaires, laboratory tests, and electrocardiograms. Unless patients withdrew consent all patients were followed until the end of the study.

Data Analysis: Analysis of an intent-to-treat population was performed with 4,949 patients assigned to dulaglutide and 4,952 patients assigned to placebo (9,901 total). Power was set at 90% with 9,600 people total needed to detect a hazard ratio of 0.82 or lower. Alpha was set at 0.05. Interim analysis was performed and alpha was adjusted to 0.046.

Data Analyzed	Type of Data	Statistical Test Used	Appropriate/Not Appropriate
Time to non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes or unknown cause	Survival	Kaplan-Meier estimates and Cox proportional hazards	Appropriate

Results: The addition of 1.5 mg dulaglutide was superior in reducing the risk of cardiovascular outcomes compared to placebo. This is shown by the upper bound of the 95% CI not crossing the absolute equivalency of 1 and p value less than alpha.

Primary Outcome	dulaglutide (n=4,949)		Placebo (n=4,952)		Hazard ratio (95% CI)	P value	NNT
	Number of patients (%)	Incidence rate (# events/100 person-years)	Number of patients (%)	Incidence rate (# events/100 person-years)			
Primary composite outcome	594 (12%)	2.35	663 (13.4%)	2.66	0.88 (0.79-0.99)	0.026	72
Non-fatal stroke	135 (2.7%)	0.52	175 (3.5%)	0.69	0.76 (0.61-0.95)	0.017	125
Renal outcomes	848 (17.1%)	3.47	970 (19.6%)	4.07	0.85 (0.77-0.93)	0.0004	40

*Non-fatal stroke was the biggest contributor to statistical significance as myocardial infarctions, fatal strokes, and deaths were not statistically significant. Similarly, renal outcomes were a big driver of composite microvascular outcomes. Patients assigned to dulaglutide also had a 0.61% lower Hb-A_{1c}.

Tolerability: Between both groups the rates of serious adverse events and were shown to be similar; however, more patients in the treatment group reported gastrointestinal side effects during follow up visits (47.4% vs 34.1%).

Author's Conclusion: Dulaglutide should be added to the medication regimen of patients with diabetes who have cardiovascular risk factors to reduce cardiovascular events.

Strengths:

- Power was set and met
- Treatment was appropriate and accepted
- Study period allowed adequate time for primary outcome to occur
- Inclusion and exclusion criteria were appropriate
- Blinding was present
- Randomization produced similar groups
- Biostatistical test was appropriate
- Primary outcome is standard and accepted
- Authors' conclusion supported by results

Limitations:

- Funded by Eli Lilly and Company who produce the medication
- Scientist employed by the funder helped create, implement, and analyze the trial
- Roughly 75% of each treatment group was white, this data may not be as applicable to all races
- It is not reported how many patients had previously been on a GLP-1 receptor agonist
- More than 25% of participants were no longer taking the study drug at the time of their last visit

Level of Evidence: Level I – interventional, placebo-controlled, randomized trial that met power with Minor Limitations

Recommendation: I recommend that dulaglutide be used in patients with type II diabetes who are 50 years old or older and would benefit from prevention of cardiovascular events based on previous cardiovascular history or risk factors. I believe that providers should titrate up to the study dose of 1.5 mg as tolerated.

- Efficacy
  - Dulaglutide was shown to be superior to placebo in reducing the risk of cardiovascular events
- Safety
  - The rates and types of adverse events were similar between dulaglutide and placebo
- Cost
  - According to LexiComp, the cost of one pen contain 1.5 mg dulaglutide is $253.31[5]
  - There is a manufacturer coupon available for Trulicity (dulaglutide), but not every patient is eligible[6]
- Special Considerations/Populations
  - Patients without insurance or insurance provided through the government (Medicare, Medicaid) may not be able to afford this medication
  - Per inclusion criteria only patients 50 or older were studied, so there is no data for patients under 50 with cardiovascular history
  - Future studies are needed before recommending for patients with hepatic dysfunction or severe renal failure

Grade of Recommendation: A

References:

1) Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet*. 2019;394(10193):121-130. doi:10.1016/S0140-6736(19)31149-3
2) American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care*. 2021;44(Suppl 1):S111-S124. doi:10.2337/dc21-S009
3) Collins L, Costello RA. Glucagon-like Peptide-1 Receptor Agonists. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; June 23, 2020.
4) American Diabetes Association. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: *Standards of Medical Care in Diabetes-2021*. *Diabetes Care*. 2021;44(Suppl 1):S53-S72. doi:10.2337/dc21-S005
5) Dulaglutide (Lexi-Drugs). Lexicomp. https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/5355165?cesid=2bI3kwqr1U7&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dtrulicity%26t%3Dname%26va%3Dtrulicity. Published June 5, 2021. Accessed June 9, 2021.
6) Save on Trulicity: Trulicity (dulaglutide) injection. Save on Trulicity | Trulicity (dulaglutide) injection. https://www.trulicity.com/saving-card-downloader?utm_source=google&utm_medium=ppc&campaign=8709076781&adgroup=87216946785&ad=497953849359&utm_keyword=kwd-305414032796&utm_id=go_cmp-8709076781_adg-87216946785_ad-497953849359_kwd-305414032796_dev-c_ext-_prd-_mca-_sig-CjwKCAjwqvyFBhB7EiwAER786Tm6fxJQCnX5DxtS1OBJIKKPXDIXFOVAhdBluqbHAd2wM7ngJPyyjRoCbV0QAvD_BwE&gclid=CjwKCAjwqvyFBhB7EiwAER786Tm6fxJQCnX5DxtS1OBJIKKPXDIXFOVAhdBluqbHAd2wM7ngJPyyjRoCbV0QAvD_BwE. Accessed June 9, 2021.

Ten Major Considerations

Article Title: Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

Level: **I** II III IV V **Limitations:** Major **or**

MAJOR CONSIDERATIONS *with justifications for each*	**Strength/Limitation Circle One**	
Power set/met? Set at **90%** Number patients needed **9600 patients total, 4800** per treatment group Population analyzed: **ITT** mITT PP **(circle one)** Number obtained: **9901 total (dulaglutide n=4949, placebo n=4952)** Other comments: **alpha = 0.05, 1067 unique primary endpoint events to show superiority, detectable HR – 0.82 between dulaglutide and placebo, 1200 primary outcomes ended the trial**	**S**	L

Dosage/treatment regimen appropriate? Dosage used: **1.5 mg SC every week** Within accepted dosage range, safe, proper interval, equivalent efficacy: **Yes** No **(circle one)** Please explain: **This dose is listed as one of the standard doses for type II DM therapy.** According to what source(s) **LexiComp**	S	L
Length of study appropriate to show effect? Length of treatment phase **7 years total.** Length of time required to show effect on drug: **T ½ = 5 days, time to peak is 24-72 hours**	S	L
Inclusion criteria adequate? **X** Adequate to result in a patient population appropriate for the study ___ Not adequate **(please explain)**	S	L
Exclusion criteria adequate? **X** Adequate for patient safety and needed to better show whether or not the effect seen was due to the study medication or any other medication that the patient might be on ___ Not adequate for patient safety and/or doesn't assist in showing whether or not the effect seen was due to the study medication or any other medication that the patient might be on **(please explain)**	S	L
Blinding present? **X** Mentioned **(please explain if details available) double-blinded, only members of an independent data monitoring committee and the statistician who supported them in reviewing the data had access to unblinded data.** ___ Not mentioned	S	L

Randomization resulted in similar groups? **X** Yes according to: **Table 1** ___ No **(please explain dissimilarities)**	S	L
Biostatistical tests appropriate for type of data analyzed? Primary end point or outcome measure: **First occurrence of any component of the composite outcome: non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes or unknown cause.** Type of data represented by above: ratio interval nominal ordinal **(circle one)** **Survival (time to event)** Statistical test used for primary end point or outcome measure: **Kaplan-meier estimates and cox proportional hazards**	S	L
Measurement (s) standard/validated/accepted practice? Primary end point or outcome measure: **First occurrence of any component of the composite outcome: non-fatal myocardial infarction, non-fatal stroke, and death from cardiovascular causes or unknown cause.** This primary endpoint or outcome measure is: **standard OR validated OR accepted** practice **(circle one or more)** NOTE: we would accept either or both of these.	S	L
Author's conclusions are supported by the results? Author's conclusion : **(abbreviated) Weekly injections of 1.5 mg dulaglutide reduced the risk of cardiovascular outcomes compared with placebo.** Results that support this conclusion: **HR 0.88 (0.79-0.99) does not cross AE-1. p=0.026 which is less than alpha.**	S	L