L Regier BSP, BA
www.RxFiles.ca Nov 2019 Revised Aug 2020

SC GLP1 Agonist Major RCT Results
Should we assume North Americans will benefit if the trial data suggests otherwise?
(Questions arising from the North American Subgroup Data)

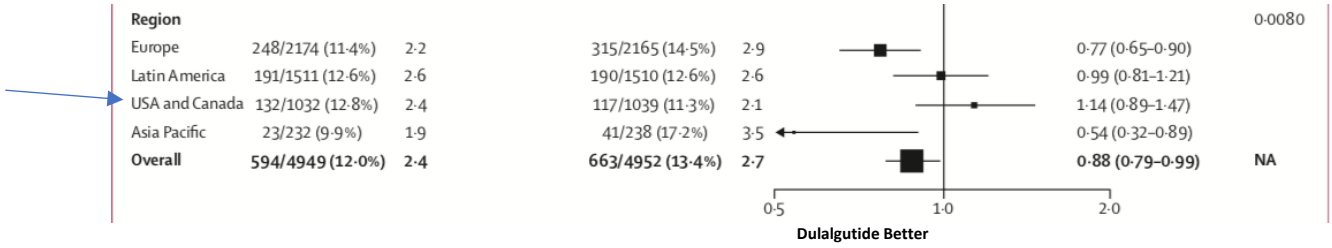
- Three SC GLP1 Agonists have shown CV outcome benefit in patients with CV disease, or high CV risk.
- It is reasonable to question whether the benefit applies North American patients. In the two largest & longest trials, the North American trial subgroup did not contribute at all to the 1° outcome benefit seen overall.[REWIND, LEADER] In the 3rd, smaller-shorter trial, the contribution was marginal. [SUSTAIN-6] What is different in the N. American context that that reduces the CV outcome benefits realized by patients in N. America relative to Europe and Asia?
- Technically, such subgroup results would be considered "hypothesis generating" warranting further exploration (e.g. conducting a trial specific to N. America). However, given the results, such a trial would be risky for the manufacturer. The signals for both dulaglutide and liraglutide are that MACE benefits would not be seen in a N. American population.
- **SUMMARY: The SC GLP1 Agonist trials have shown modest positive CV outcome benefits in high CV risk patients. However, it is possible that this benefit may not actually be realized in North American patients given the subgroup data. One may consider this additional uncertainty when deciding whether or not to use one of the SC GLP1 agents for a given patient. Future studies may want to include an *a priori* effect modification analysis of this subgroup to assess.**

From: GLP1 & SGLT2 - SUBSET of DIABETES AGENTS in T2DM: Outcomes Comparison Summary Table

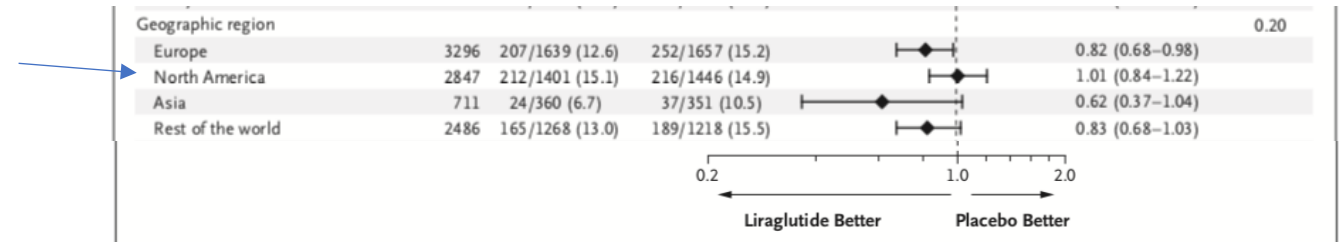
Drug Class	GLP1 Agonists		
Generic ⇨ BRAND	Dulaglutide SC TRULICITY (SC WEEKLY)	Liraglutide SC VICTOZA (SC DAILY)	Semaglutide SC OZEMPIC (SC WEEKLY)
Major trial(s) to support findings/Outcomes*	REWIND n=9901 / 5.4 yr	LEADER n=9340 / 3.8 yr Vs Pl (but ↑ insulin use)	SUSTAIN-6 n=3297 / 2 yr Vs Pl (but ↑ insulin use)
↓ Risk of Major CV - MACE	✓✓✓ ↓ MACE NNT=71/5.4yrs REWIND ? N. America - neutral HR: 1.14 (0.89-=1.47)	✓✓✓ ↓ MACE NNT=53/3.8yr LEADER ? N. America - neutral HR: 1.01 (0.84-1.22)	✓✓✓ ↓ MACE NNT=44/2yr SUSTAIN-6 ? N. America – marginal HR: 0.87 (0.57-1.34)

Excerpted from page 2 of the RxFiles Diabetes Color Outcomes Chart

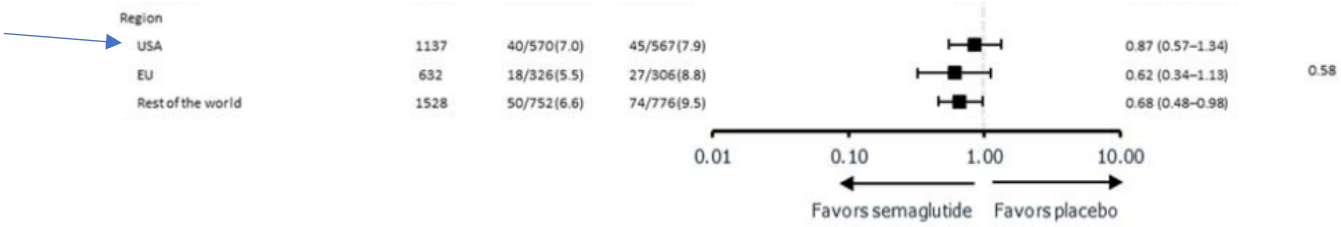
Dulaglutide SC *TRULICITY*: Primary Outcome "MACE" in the **REWIND** Trial – Regional Subgroups



Liraglutide SC *VICTOZA*: Primary Outcome "MACE" in the **LEADER** Trial – Regional Subgroups



Semaglutide SC *OZEMPIC*: Primary Outcome "MACE" in the **SUSTAIN-6** Trial – Regional Subgroups



Bibliography

Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al.; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (**REWIND**): a double-blind, randomised placebo-controlled trial. Lancet. 2019 Jul 13;394(10193):121-130.

Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutideand Cardiovascular Outcomes in Type 2 Diabetes. (**LEADER**) N Engl J Med. 2016 Jun 13. (Link to RxFiles trial summary)

Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al; **SUSTAIN-6** Investigators.. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10;375(19):1834-1844.

Schandelmaier S, Matthias B, Varadhan R, et al; Development of the Instrument to assess the Credibility of Effect Modification Analyses (ICEMAN) in randomized controlled trials and meta-analysesCMAJ 2020 August 10;192:E901-6. doi: 10.1503/cmaj.200077

RxFiles Diabetes Mini-book: Click here