What's New in Incretin based Therapies in 2025

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Nutrient –stimulated hormones and hormone based treatments

1. Gut hormones (GLP1, GIP, Glucagon, Amylin)
2. GLP1 agonists (Dulaglutide and Semaglutide)
3. Dual and triple agonists (Tirzepatide and others)
4. Monoclonal AB for treatment of obesity

Development of exenatide: an incretin mimetic (1980 and 90's)

- Synthetic version of salivary protein found in the Gila Gila monster[1]
- More than 50% overlap with human GLP-1[1]
  - Binds GLP-1 receptors on β-cells (*in vitro*)[2]
  - Resistant to DPP-IV inactivation[3]
    - Following injection, exenatide is measurable in plasma for up to 10 hours[4]

[1]**Eng J, et al. *J Biol Chem* 1992;267:7402–7405**; Adapted from [2]Nielsen LL, et al. *Regul Pept* 2004;117:77–88; [3]Drucker DJ. *Diabetes Care* 2003;26:2929–2940; [4]Calara F, et al. *Clin Ther* 2005;27:210–215.

Incretin Therapies: Effects Beyond Glycemic Control

Mudaliar S, Henry RR Eur J Intern Med. 2009 Jul; 20 Suppl 2: p 319-28 (Review)

The incretin hormones

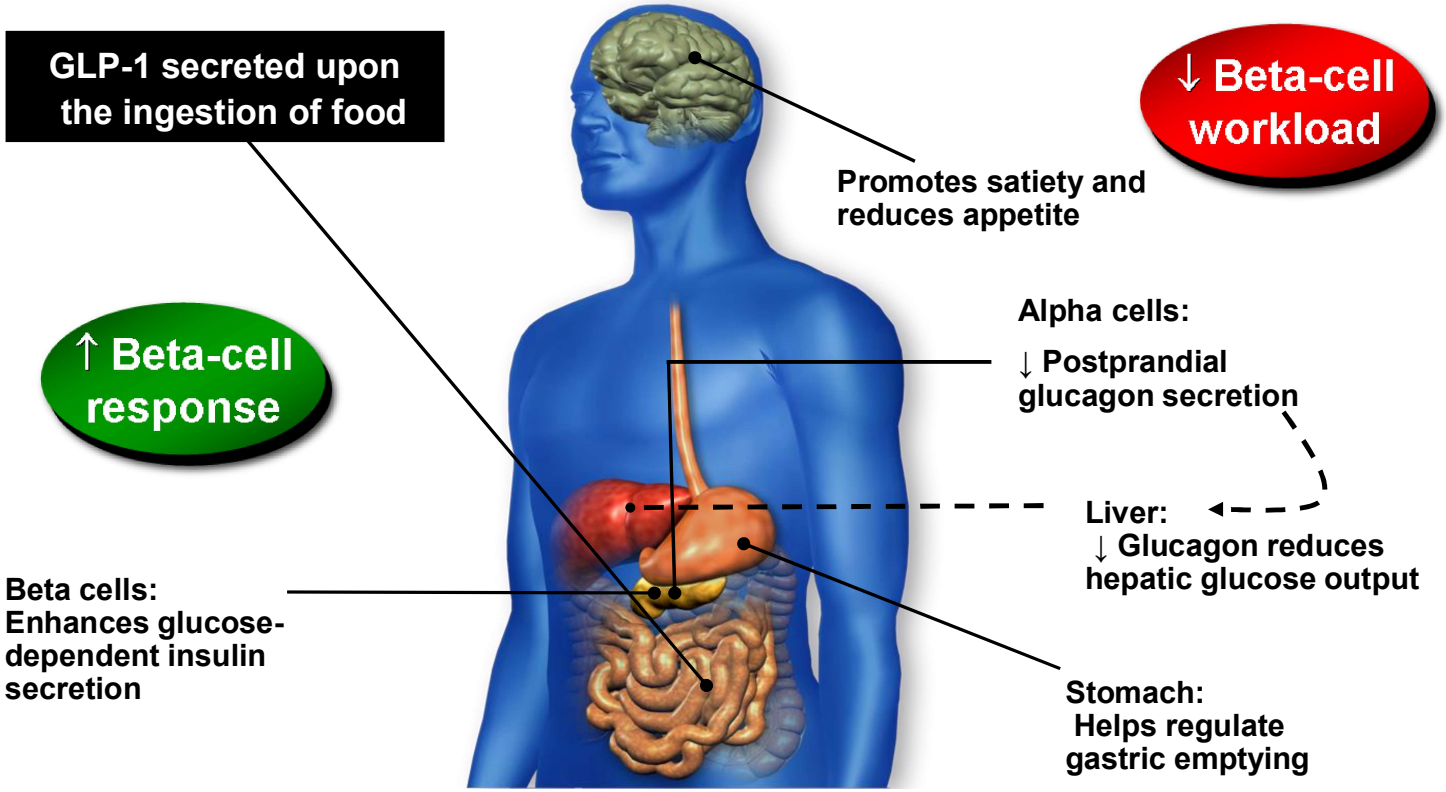
1. **glucagon-like peptide-1 (GLP-1)**
2. glucose-dependent insulinotropic polypeptide (GIP)

- peptide hormones produced by the gastrointestinal tract (L cells in the ileum and colon) in response to nutrient entry

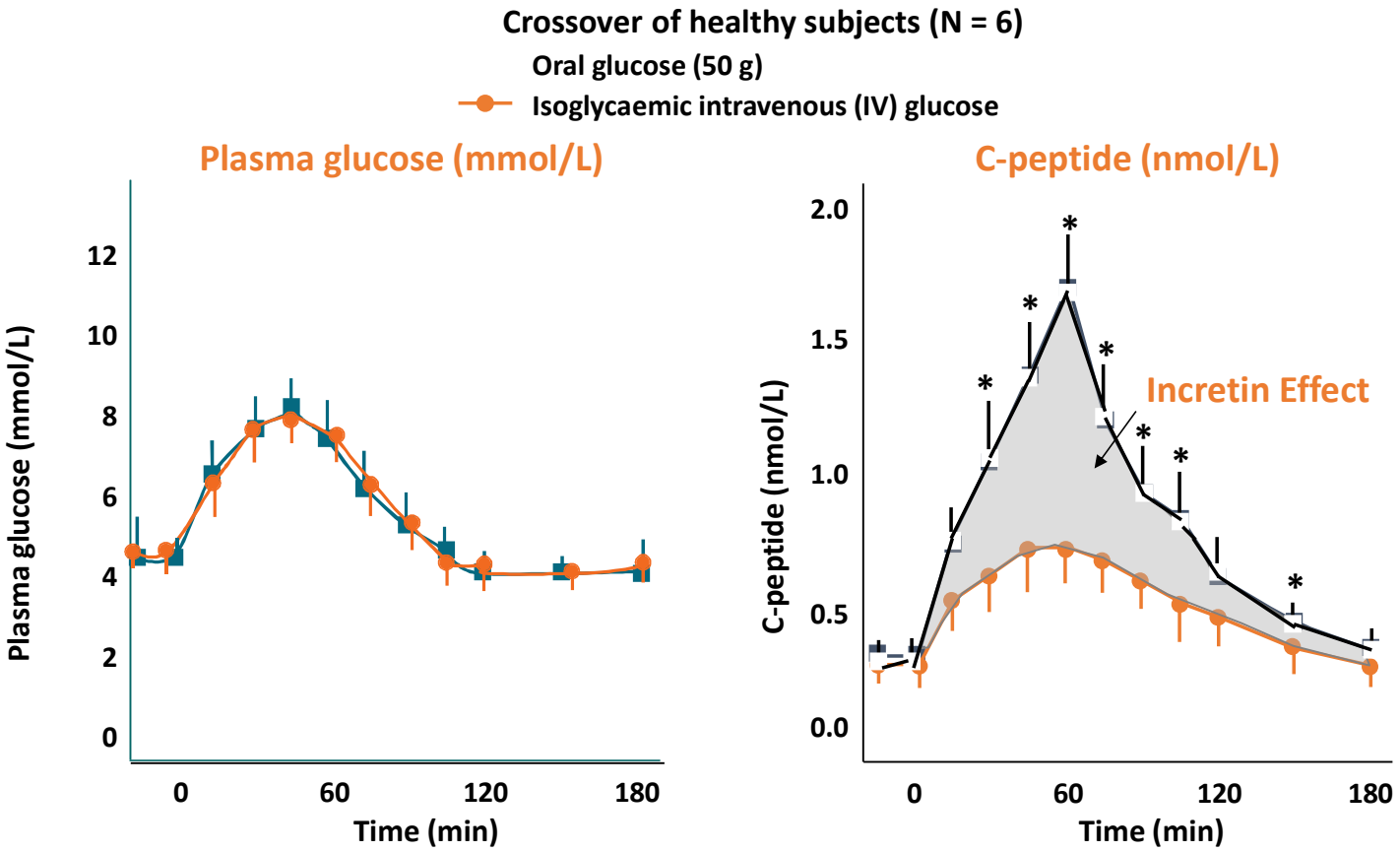
- **play a major role in glucose homeostasis**

1. stimulate insulin secretion
2. suppress glucagon secretion
3. inhibit gastric emptying
4. reduce appetite and food intake

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins



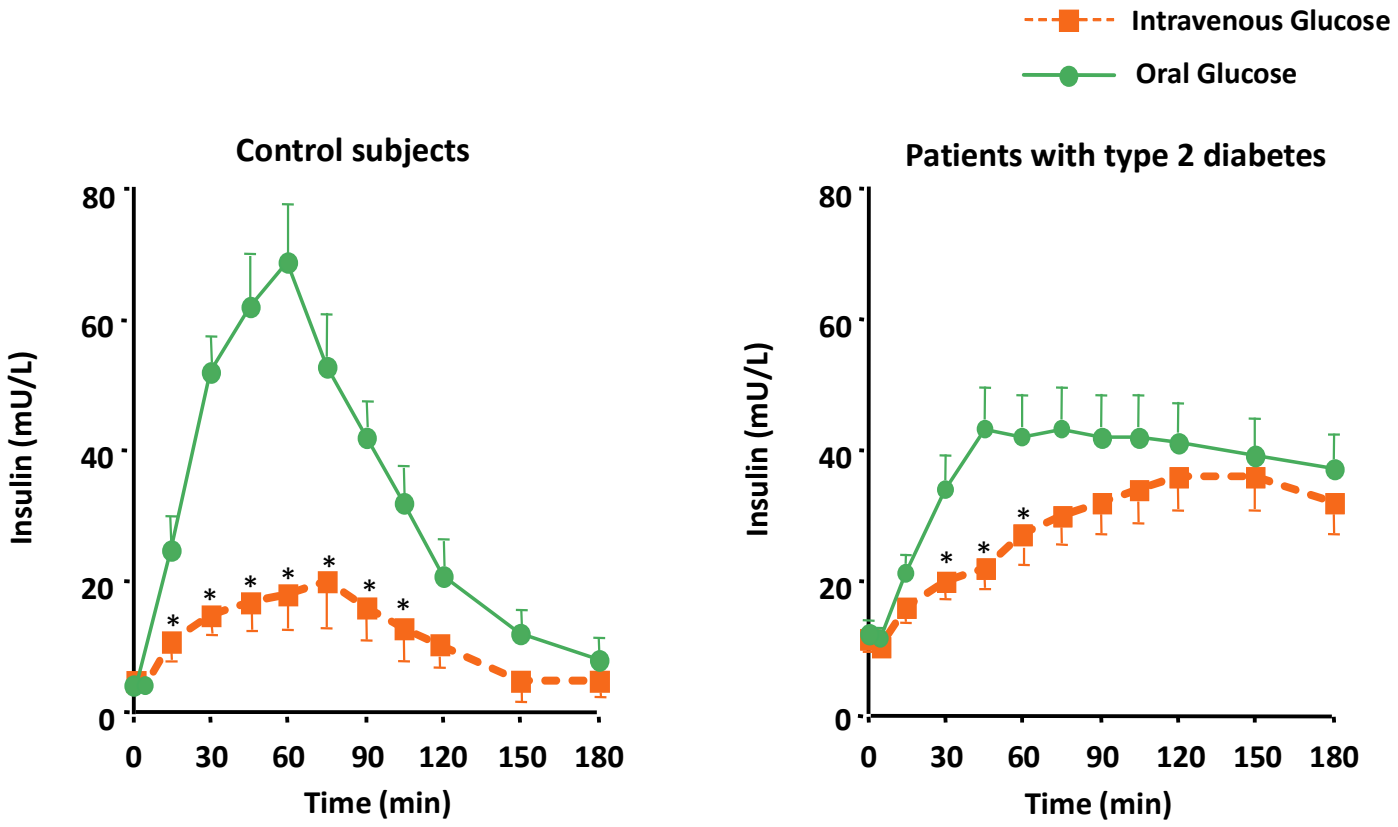
The incretin effect
β-cell response to oral vs IV glucose



Mean (SE); *$P \leq 0.05$

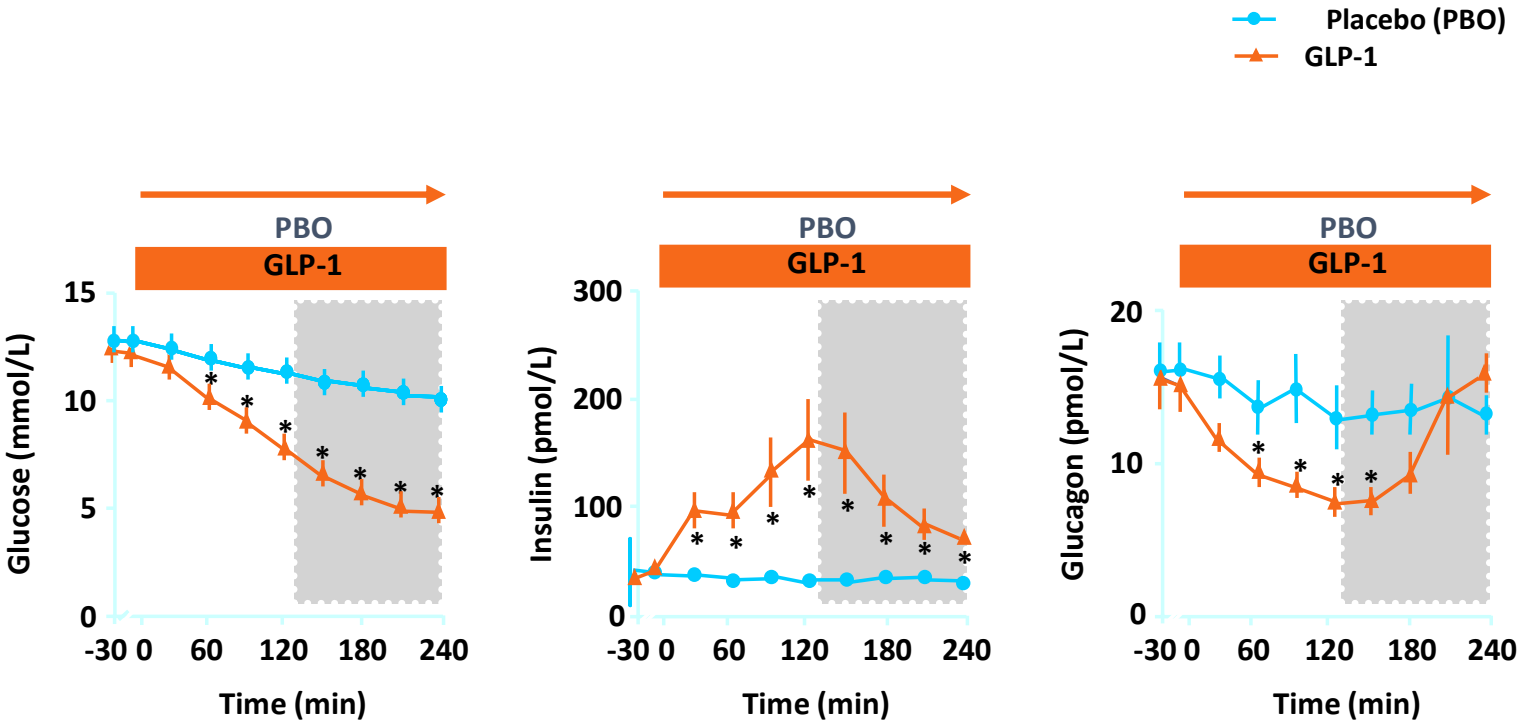
Data from Nauck MA, et al. *J Clin Endocrinol Metab* 1986;63:492–498. Plasma glucose values converted to mmol/L from mg/dL using conversion factor of 0.0555; C-peptide values converted to nmol/L from ng/mL using conversion factor 0.333.

The incretin effect is reduced in patients with type 2 diabetes



*$P \leq .05$ compared with respective value after oral load.
Nauck MA, et al. *Diabetologia* 1986;29:46–52.

GLP-1 effects are glucose-dependent in type 2 diabetes



Mean (SE); N = 10; **P* < 0.05.

Nauck MA, et al. *Diabetologia* 1993;36:741–744.

Different GLP1 agonists

Available in NZ

- Liraglutide 1.8 mg (for DM2)
- Liraglutide 3mg (for weight management)

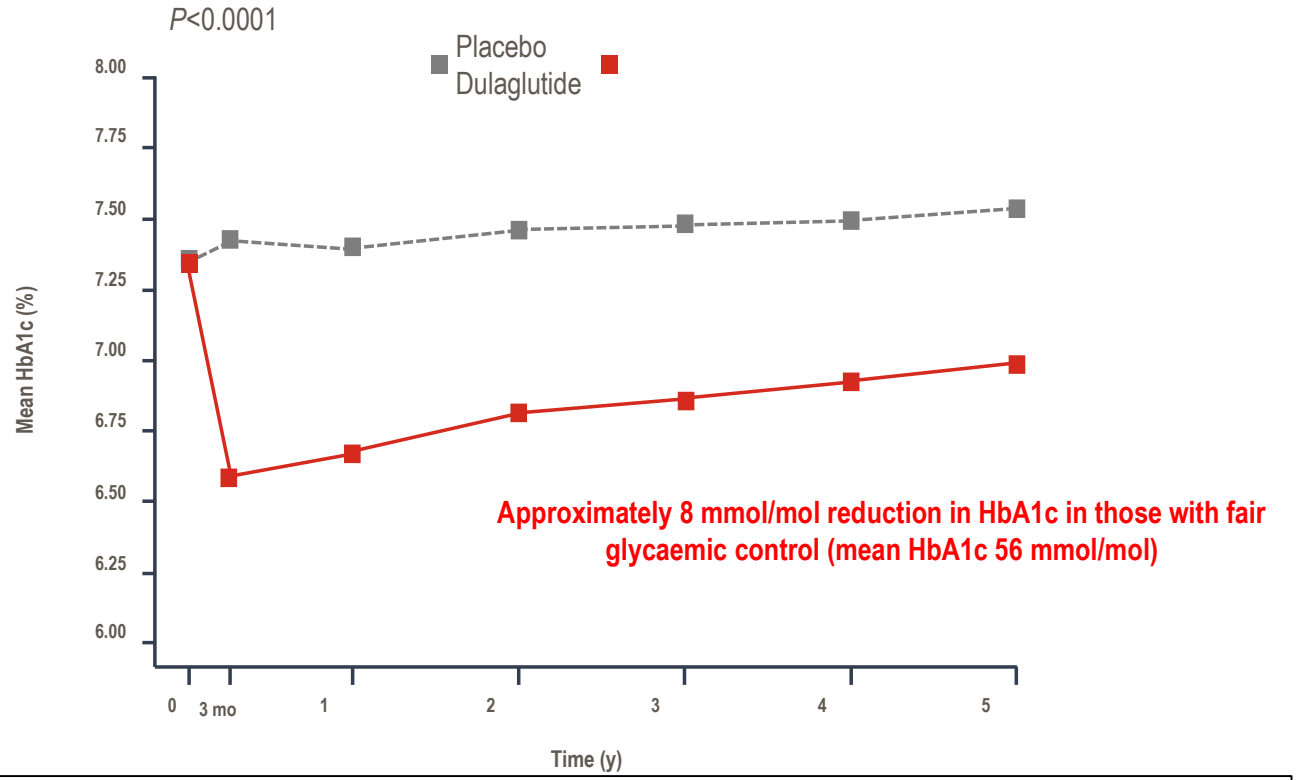
- **Dulaglutide (1x week)**

- **International**
- Exenatide bd
- Exenatide LAR (1x week)
- Liraglutide 1.8 mg
- Liraglutide 3mg (for weight management)
- Semaglutide s/c and **oral**
- Lixisenatide s/c
- Dulaglutide s/c
- Tircepatide (dual GLP1/GIP)

REWIND Trial

- Multinational study of **9901 patients** with T2D + either known CVD or ≥ risk factors randomized to:
  - Placebo (n = 4952)
  - Dulaglutide 1.5 mg weekly **(n = 4949)**
- Powered for 3-point MACE with median follow up **5.4 years**
- Baseline characteristics:
  - Mean age 66 years (57% male) with mean **BMI 32.3 kg/m^2**
  - 31.5% had had prior CVD
- Treatment was additional to standard management:
  - 82% on ACEi/ARB + 46% on β-blockers
  - 66% on statins
  - 54% on antiplatelet therapy

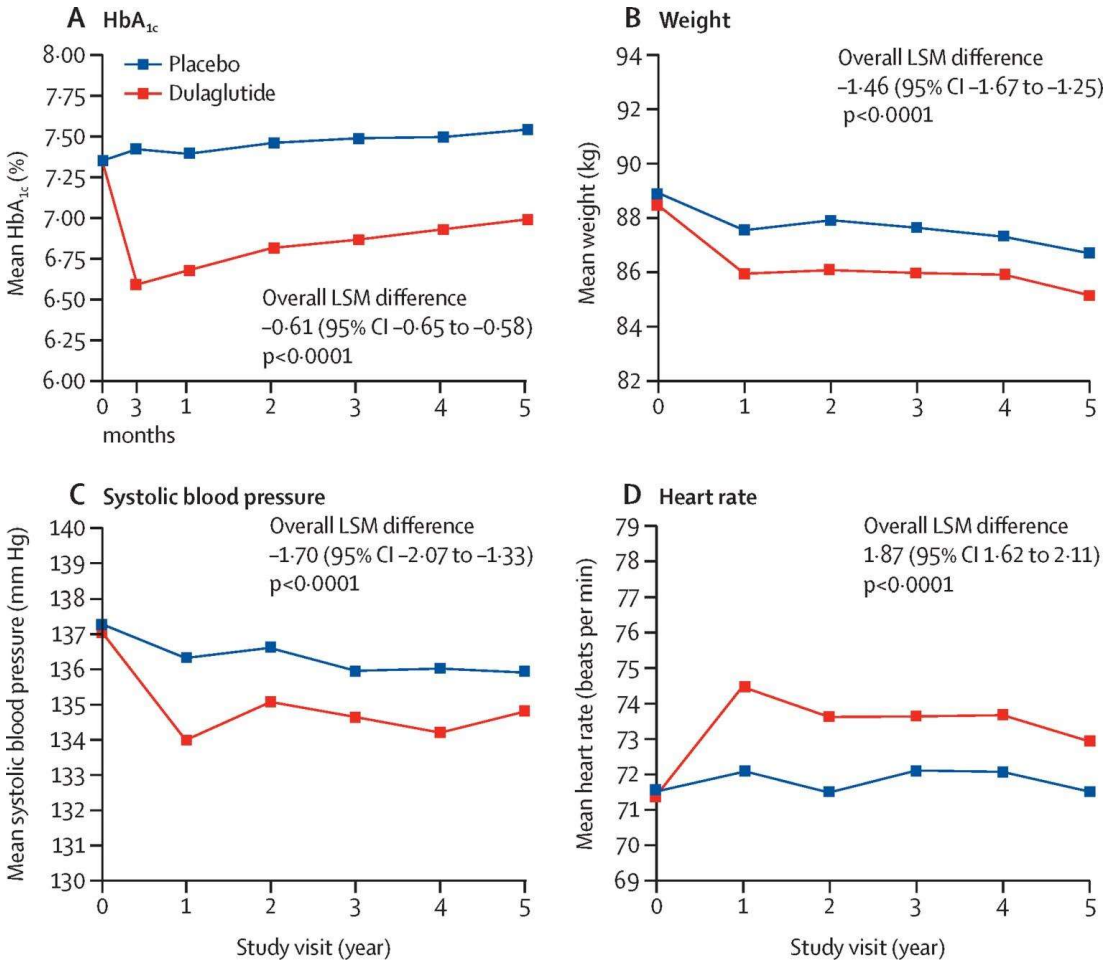
Reduction in HbA1c with dulaglutide



Associated with mean reductions in weight of 2 kg, SBP of 2 mmHg + LDLc 0.05 mmol/L (P all < 0.001)

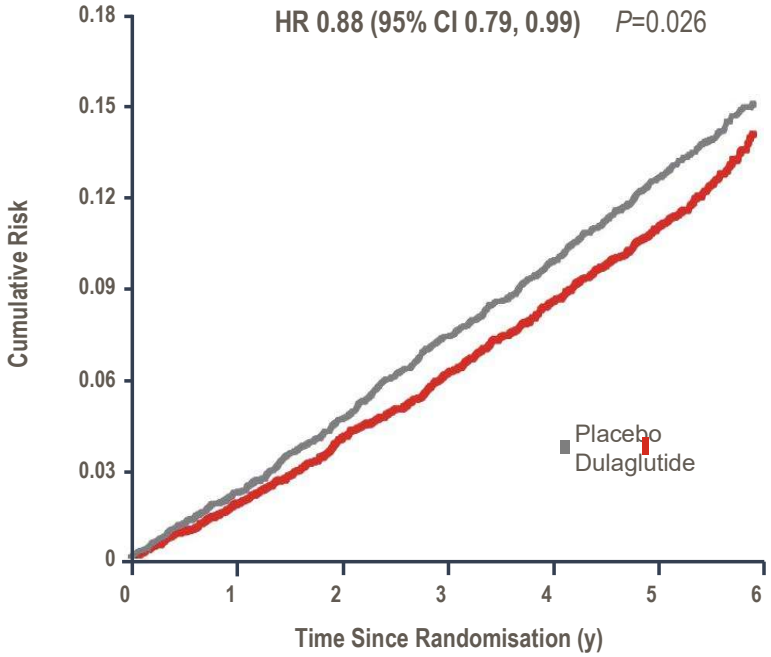
Adapted from Gernstein H *et al*. *Lancet* 2019; 394:121-130

Dulaglutide – REWIND trial



Gerstein et al 2019. Lancet

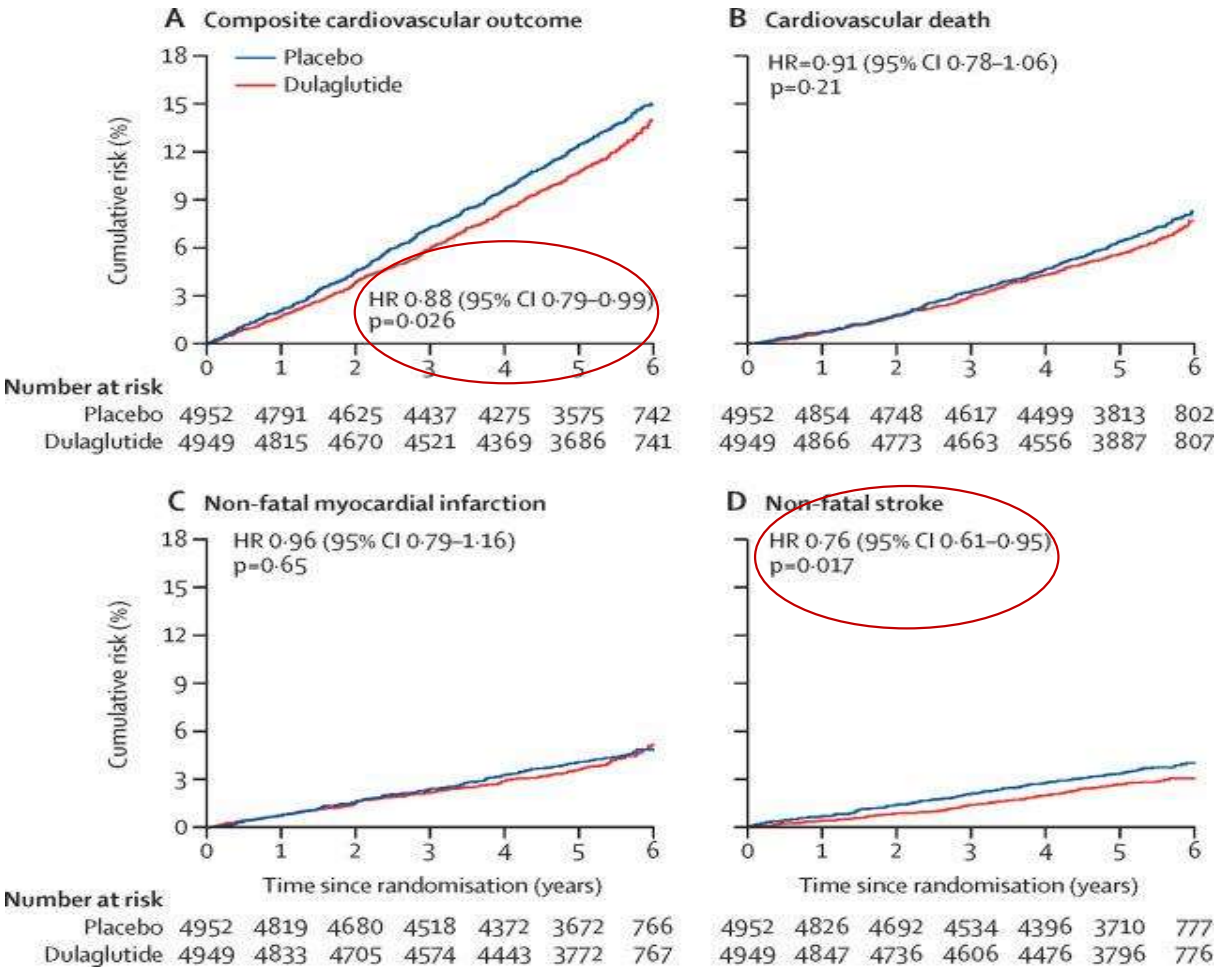
Reductions in CV death, non-fatal MI + stroke with dulaglutide



NNT = 18 for 5.4 years in established CVD
NNT = 60 for 5.4 years in subclinical vascular disease or ≥ 2 CVD risk factors

Adapted from Gernstein H *et al*. *Lancet* 2019; 394:121-130

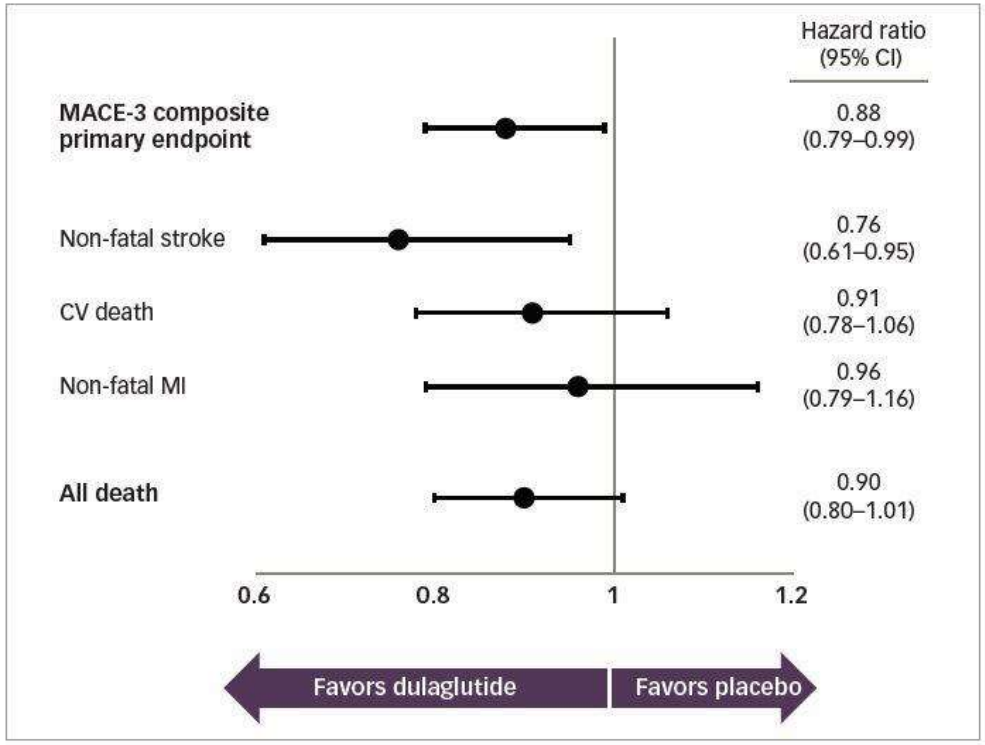
Dulaglutide – REWIND trial



Gerstein et al 2019. Lancet

Dulaglutide – REWIND trial

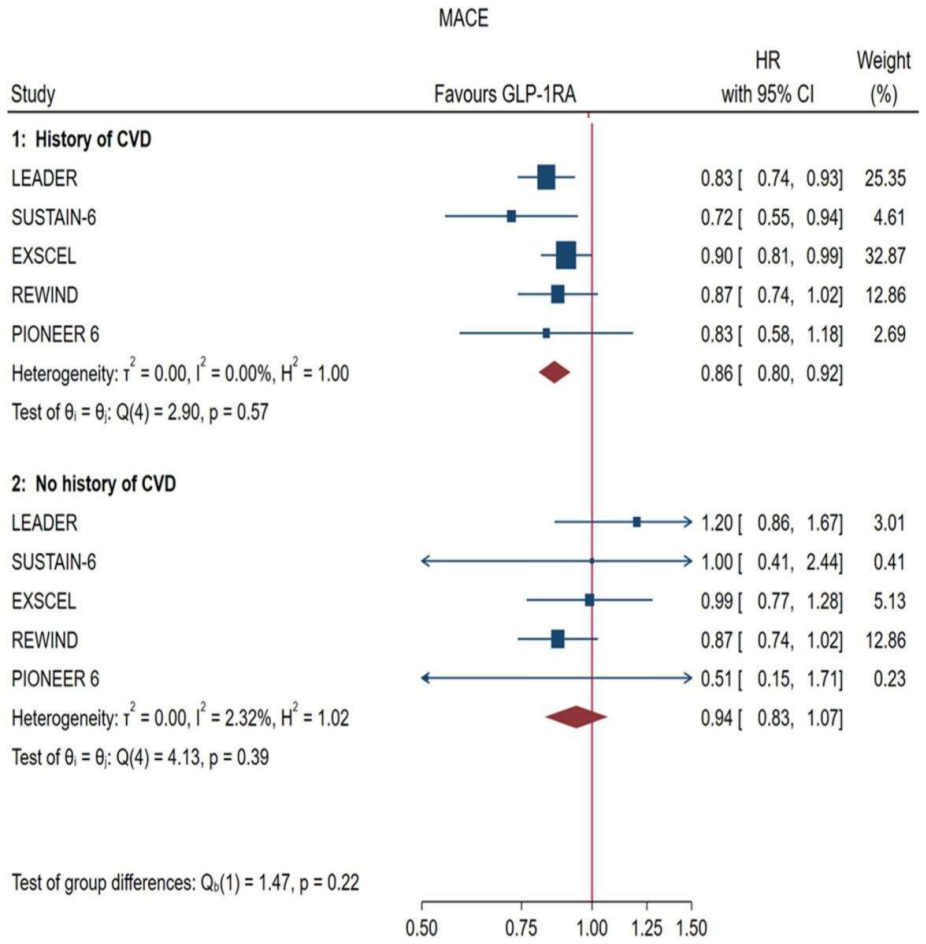
Figure 2: Individual cardiovascular outcomes of the REWIND trial



CI = confidence interval; CV = cardiovascular; MACE = major cardiovascular events; MI = myocardial infarction.
Reused with permission from The Lancet. *Source: Gerstein et al. 2019.*[10]

Gerstein et al 2019. Lancet

But clear class effect of GLP1RA on MI, stroke + CVD death



Data for potential role in primary prevention only for dulaglutide at present

LEADER = liraglutide

SUSTAIN-6 = semaglutide

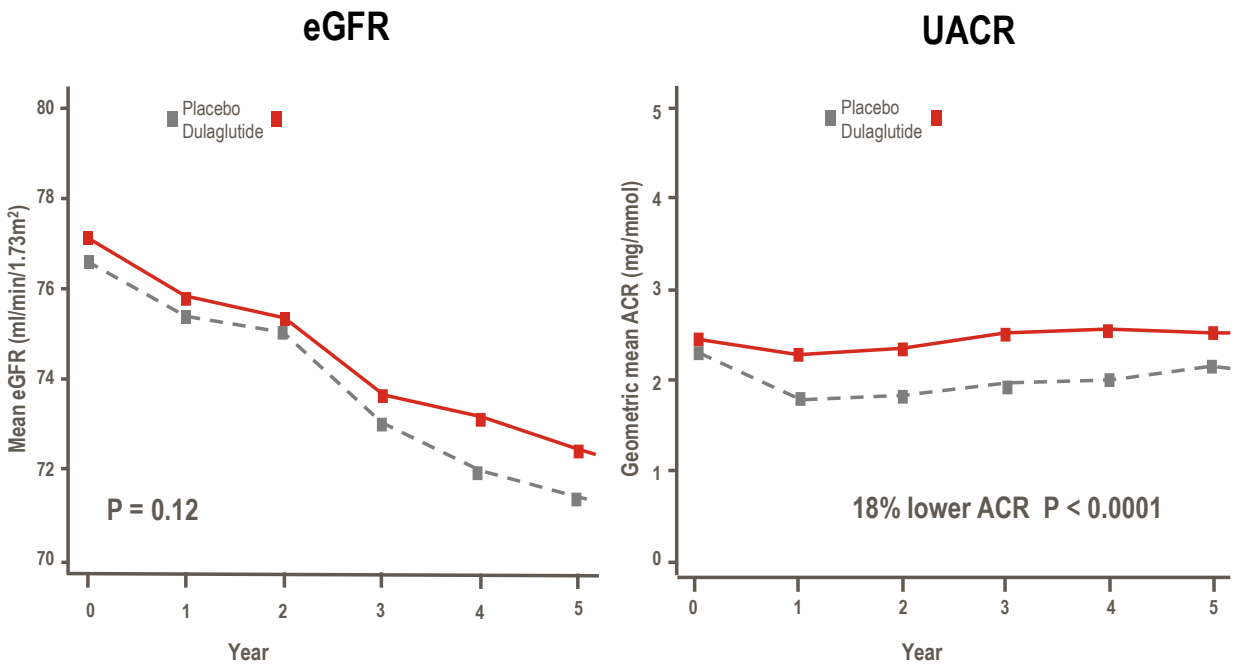
EXSCEL = exenatide

REWIND = dulaglutide

PIONEER-6 = semaglutide

Giugliano et al. Diabetes, Obesity + Metabolism. 2019; 21(11):2576

Effects of dulaglutide on diabetic renal disease



No evidence to date the improvements result in a significant reduction in RRT or renal death

Adapted from Gernstein H *et al*. *Lancet* 2019; 394:121-130

Precautions with use of dulaglutide

- No safety data so **not recommended** for use in:
  - Pregnancy/breast feeding
  - Children < 18 years of age
  - **eGFR < 15 mL/min**
  - Type 1 diabetes
- Due to risk of volume depletion be cautious in those > 75 years of age
  - Particularly those on diuretics, ACEi/ARBs + NSAIDs
- Due to risk of other potential adverse effects not recommended for use in:
  - Significant gastrointestinal disease – especially gastroparesis or **severe GORD**
  - Previous pancreatitis
  - History of medullary thyroid carcinoma or multiple endocrine neoplasia 2 (MEN2) syndrome