# Incretin-based drugs: What do the data say?

Radcliffe Medical Education

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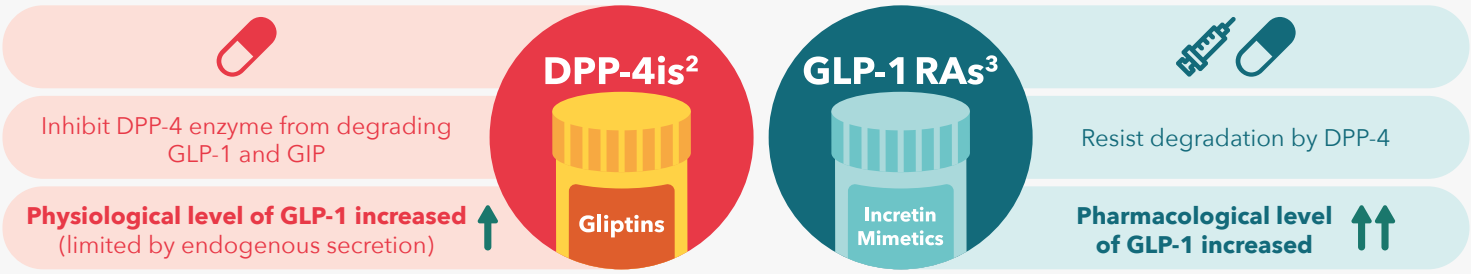
## Knowledge recap[1]

- The **incretin system** helps with releasing the GLP-1 hormone from the intestine. GLP-1 then stimulates the insulin secretion from the pancreas and exerts other health effects on several organs including the CV system
- While incretin hormones are severely reduced or absent in T2DM, the incretin-based therapies, **DPP-4is** and **GLP-1RAs**, prolong and mimic the actions of these hormones, hence play important roles in **T2DM** care [*for more info see pathophysiology module & downloadable asset*]
- **DPP-4is** and **GLP-1RAs** have different mechanisms of action – impacting $HbA_{1c}$ and weight loss benefits to a different extent:




Compared to DPP-4is, GLP-1 RAs result in

- **Larger $HbA_{1c}$ reduction**
- **Greater weight loss**

## Meta-data on efficacy and CV benefits of incretin-based therapy

**Meta-analysis of 27 RCTs**

Glycaemic lowering effect of **GLP-1RAs** ranged from **-0.7%** to **-1.7%** after 26 weeks[5]

**Meta-analysis of 19 RCTs**

As 2nd line treatment, **DPP-4is** were less efficacious than sulphonylureas, pioglitazone or **GLP-1 RAs** at reducing $HbA_{1c}$[6]

**Meta-analysis of 13 RCTs**

**GLP-1 RAs** significantly reduced $HbA_{1c}$ more than **DPP-4is** by **-0.41%** and significantly reduced weight over **DPP-4is** by **-2.15kg**[7]

**Meta-analysis of 8 CVOTs***

**GLP-1 RAs** reduced MACE by **14%**, CV death by **13%**, nonfatal stroke by **16%**, hospitalisation for HF by **10%**, all-cause mortality by **12%**[8]

* GLP-1 RAs included in the meta-analysis were lixisenatide, liraglutide, semaglutide, exenatide, albiglutide, dulaglutide, and efpeglenatide

## Takeaway points

**Both incretin-based therapies – DPP-4is and GLP-1RAs – have important roles in T2DM care[9]**

**"right medication, right person, right time"**

**GLP-1 RAs** have superior glycaemic control and additional weight loss and CV benefits compared to **DPP-4is**

**GLP-1 RAs** are prioritised to **DPP-4is** in international guidelines as 2nd line to metformin

- When established or high risk of CVD exist*
- When weight loss is required
- When hypoglycaemia needs to be avoided

Some **DPP-4is** have shown CV safety but none have shown CV benefit to date

**GLP-1 RAs** and **DPP-4is** both have low risk of hypoglycaemia (unless used with insulin or insulin or insulin secretagogues) and may be a good choice for elderly

* Liraglutide, semaglutide and dulaglutide haven been proven to reduce CV events in patients with DM and CVD, or who are at (very) high CV risk

**Abbreviations:** CV, cardiovascular; CVD, cardiovascular disease; CVOT, cardiovascular outcome trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; GIP, Gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; GLP-1 RA, glucagon-like peptide-1 receptor agonist; $HbA_{1c}$, Hemoglobin $A_{1c}$; HF, heart failure; MACE, major adverse cardiac events; RCT, randomised controlled trial

**References:** **1.** Nauck MA et al. *Diabetes Obes Metab*. 2018;1:5-21. **2.** Mari A et al. *J Clin Endocrinol Metab*. 2005;90:4888-94. **3.** Degn KB et al. *Diabetes*. 2004;53:1187-94. **4.** Pratley R et al. *Int J Clin Pract*. 2011;65:397-407. **5.** Nuhoho S et al. *Diabetes Ther*. 2019;10:2183-2199. **6.** Karagiannis T et al. BMJ. 2012;344: e1369. **7.** Tran S et al. *Diabetes, Obesity and Metabolism*. 2018;20(S1):68-76. **8.** Giugliano D et al. *Cardiovasc Diabetol*. 2021. 20:189. **9.** Gilbert MP et al. *Front Endocrinol* (Lausanne). 2020;11:178.