Diabetes Management: Avoiding Combination Therapy of GLP-1 Receptor Agonists and DPP-4 Inhibitors

Diabetes Optimization

Combination therapy of GLP-1 receptor agonists and DPP-4 inhibitors has no additive effect on glycemic control and increases potential side effects and cost burden to patients. Treatment with DPP-4 inhibitors should not be utilized in combination with GLP-1 receptor agonists.[1,2]

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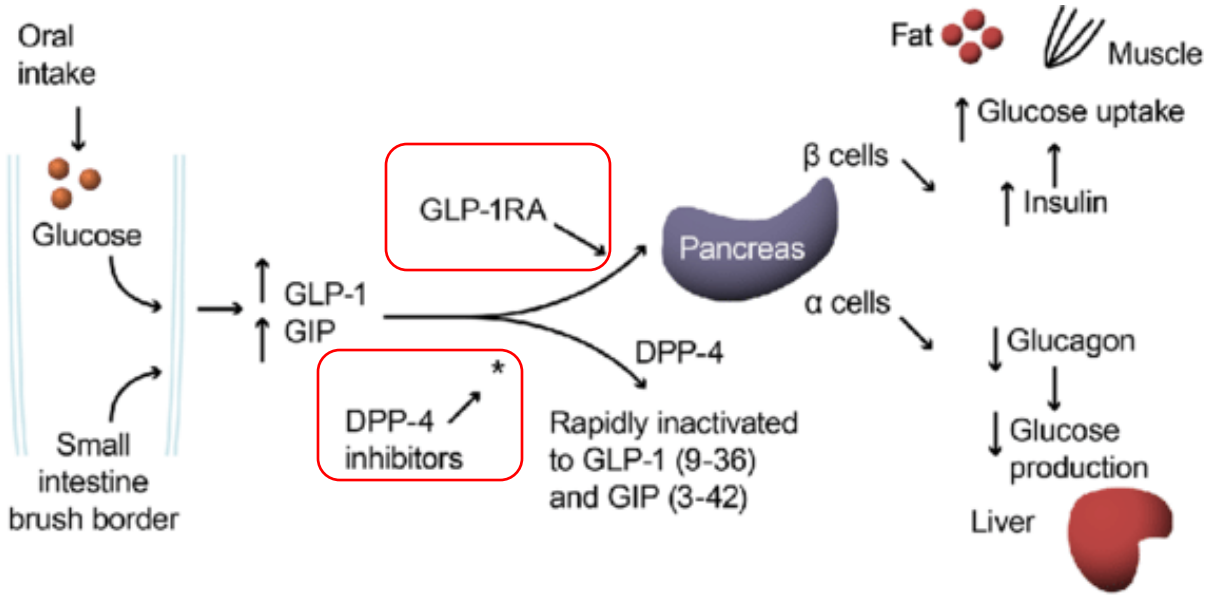
CLINICAL RATIONALE: WHY GUIDELINES DO NOT SUPPORT COMBINATION THERAPY

- American Diabetes Association recommends discontinuing DPP-4 inhibitors when GLP-1 agonists are initiated.[3]
- There are no additional glucose-lowering effects seen with combination therapy.[2]
- Combination of GLP-1 receptor agonists and DPP-4 inhibitors increases patient financial burden.[4]
- Combination therapy increases pill burden as well as the risk of side effects (gastrointestinal disturbance, pancreatitis, etc.).[5]

MECHANISM OF ACTION OF GLP-1 RECEPTOR AGONIST AND DPP-4 INHIBITOR[6, 7]



- In response to the presence of nutrients in the small intestines, incretin hormone GLP-1 and GIP are released.
- These hormones stimulate insulin and suppress glucagon. In patients with Type 2 Diabetes, an impaired response to GLP-1 and GIP contributes to elevated blood glucose.
- DPP-4 inhibitors block the breakdown of endogenous GLP-1 and GIP, to increase levels of active hormones.
- However, GLP-1 Receptor Agonists are *designed* to resist the activity of DPP-4 inhibitors, thus combination therapy yields no benefit.

COMPARISON OF GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS

	GLP-1 Receptor Agonists	DPP-4 Inhibitors
Place in Therapy	**First line therapy** for patients with ASCVD or high risk for ASCVD **First line therapy** for patients with CKD when SGLT-2 is not tolerated, or further glucose control is needed	Patients with contraindication to SGLT-2 and GLP-1 Previous trial and failure of SGLT-2 and GLP-1 Patients with no ASCVD heart failure, CKD or risk for ASCVD
Formulations	Injectable (once daily or weekly option) Oral	Oral
Impact on Renal Outcomes	**Benefit in CKD:** dulaglutide, liraglutide, semaglutide (SQ)	No benefit
Impact on Cardiovascular Outcomes	**Benefit in ASCVD:** dulaglutide, liraglutide, semaglutide (SQ)	Associated with **increased risk of heart failure** (saxagliptin and alogliptin)
Weight Loss Potential	Weight loss (intermediate to high)	Weight neutral
Blood Sugar Lowering Efficacy	High to very high	Intermediate
Cost	$$$	$$$

GLP-1 RECEPTOR AGONISTS AND DPP-4 INHIBITORS MEDICATIONS BY CLASS

GLP- 1 Receptor Agonists	DPP- 4 Inhibitors

Injectable
• Tirzapetide (**Mounjaro**®)
• Liraglutide (**Victoza**®)
• Lixisenatide (**Adlyxin**®)
• Dulaglutide (**Trulicity**®)
• Semaglutide (**Ozempic**®)
• Combination Medications Containing GLP-1 Agonists
  ○ Liraglutide + Insulin Degludec (**Xultophy**®)
  ○ Lixisenatide + Insulin Glargine (**Soliqua**®)
 	
Oral
• Semaglutide (**Rybelsus®)**
	Oral
	• Sitagliptin (**Januvia**®)
	• Linagliptin (**Tradjenta**®)
	• Saxagliptin (**Onglyza**®)
	• Alogliptin (**Nesina**®)
	• Combination Medications Containing DPP-4 Inhibitors*
	  ○ Alogliptin + Metformin (**Kazano**®)
	  ○ Alogliptin + Pioglitazone (**Osemi**®) Linagliptin + Metformin (**Jentadueto**®, **Jentadueto XR**®)
	  ○ Linagliptin + Empagliflozin (**Glyxambi**®)
	  ○ Saxagliptin + Metformin (**Kombiglyze XR®**)
	  ○ Saxagliptin + Dapagliflozin (**Qtern**®)
	  ○ Saxagliptin + Metformin + Dapagliflozin (**Qtermet XR**®)
	  ○ Sitagliptin + Metformin (**Janumet®**, **Janumet XR®**)
	*When patients discontinued combination therapy containing DPP-4 inhibitors, the other components from combination therapy should be evaluated and maintained if clinically appropriated.

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