

Gliptins for Type 2 diabetes—should we be excited?

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After disappointment with the glitazones, have the gliptins, such as sitagliptin (Januvia®) and saxagliptin (Onglyza®), heralded a breakthrough in managing hyperglycaemia in people with Type 2 diabetes and its complications?

The incretin system

Incretins are intestinal hormones. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are key incretins. These stimulate insulin release in response to high blood glucose concentrations and inhibit glucagon secretion. As they are glucose dependent, the risk of hypoglycaemia is low.¹

The gliptins, such as sitagliptin, saxagliptin and vildagliptin are oral dipeptidyl peptidase-4 (DPP-4) inhibitors. They inhibit the breakdown of GLP-1 and GIP by inhibiting DPP-4, therefore increasing insulin release.¹ DPP-4 belongs to a family of ubiquitous, atypical serine proteases, with many physiological functions beyond incretin degradation, that are found in the central nervous system, lung, spleen, pancreas, surface macrophages and the adrenal gland.²

Blood glucose lowering

Haemoglobin A1c (HbA1c) reduction with gliptins is 6 to 11 mmol/mol, which is slightly less than metformin and similar to sulphonylureas and pioglitazone.³ There is no clear guide about when gliptins should be introduced. The potential to reduce HbA1c is similar, but at greater cost than with sulphonylureas. There has been inadequate time and usage to establish the rate of any uncommon or rare adverse effects.

Adverse effects

Compared to sulphonylureas, the gliptins have a reduced risk of hypoglycaemia and are weight neutral.³ Common adverse effects (1–10%) include dizziness, fatigue, headache, nausea, upper respiratory tract infections and urinary tract infections.

After post-marketing data by Singh et al.,⁴ a March 2013 FDA alert raised concerns about a twofold increased risk of pancreatitis and a possible increased risk of pancreatic cancer. These concerns have not been confirmed as yet.⁵ The SAVOR-TIMI-53⁶ and EXAMINE⁷ randomised controlled trials found no increased risk. Population cohort studies appear to suggest a reasonable risk-benefit ratio.⁸ Patients should be advised to report severe abdominal pain immediately.

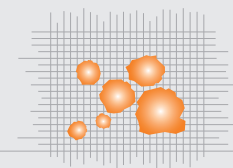
Cardiovascular effects

Although initial indications were that gliptins may have a positive effect on cardiovascular outcomes, recent randomised controlled trials have failed to confirm this.^{6,7,9} An approximate 0.7% absolute increased risk of hospitalisation due to heart failure suggests caution when using gliptins for people with heart failure.⁶

Precautions

Sitagliptin is renally excreted and the dose is halved (50 mg daily) for a creatinine clearance of 30 to 50 mL/min, and is one-quarter (25 mg daily) for a creatinine clearance less than 30 mL/min.

Saxagliptin is metabolised by the cytochrome P450 3A4 (CYP3A4) enzyme system and so diltiazem, ketoconazole and other potent



KEY POINTS

- HbA1c reduction for gliptins is no greater than for other antihyperglycaemics, and possibly a little less.
- Studies are generally less than two years and so long-term adverse effects are unclear.
- Pancreatitis and pancreatic cancer concerns are being investigated, though may be overstated.
- There are no apparent cardiovascular benefits, but there is a signal for increased hospitalisations due to heart failure.
- Gliptins *may* be useful therapy after metformin due to reduced risk of hypoglycaemia and weight gain compared to sulphonylureas, but are more expensive.

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CYP3A4 inhibitors, such as erythromycin, may increase the serum concentrations of saxagliptin. Phenytoin, carbamazepine and St John's Wort may reduce serum concentrations of saxagliptin.

Role in therapy

Metformin is still first-line therapy. The GRADE study is comparing sulphonylureas, insulin, gliptins and GLP-1 receptor agonists for use after metformin, but unfortunately results are unlikely to be available before 2019.¹⁰ Until then, we need confirmation that there is no increased risk of pancreatitis, and clarification around the risk of heart failure. There are no apparent benefits other than a moderate reduction in HbA1c and a reduced risk of weight gain and hypoglycaemia with gliptins compared to sulphonylureas—at a greater financial cost.

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