

## **Incretin based therapies: New cardiovascular data and development of novel molecules for the treatment of type 2 diabetes**

**Baptist Gallwitz**



**Prof. Dr. med., Internal Medicine,  
Deputy head of the Department  
for Endocrinology, Diabetes and  
Metabolism at the University of  
Tübingen, Past President of the  
German Diabetes Association,  
Germany**

Incretin based therapies were introduced for the treatment of type 2 diabetes in 2006 and comprise two classes of medications: the orally active DPP-4 inhibitors and the GLP-1 receptor agonists (GLP-1RA) as subcutaneous injectables. The incretin hormone GLP-1 stimulates insulin secretion and inhibits glucagon secretion in a dose dependent manner.

DPP-4 inhibitors elevate endogenous GLP-1 concentrations by retarding the enzymatic degradation of GLP-1. They are most widely used as add-on insulinotropic oral medication to metformin, when a metformin monotherapy is not sufficient. In contrast to sulfonylureas, DPP-4 inhibitors have no intrinsic hypoglycaemia risk and they are body weight neutral. In cardiovascular (cv) safety studies, they have shown non-inferiority regarding a combined MACE primary endpoint compared to classical standard therapy<sup>1-4</sup>. In the recent cv safety study CARMELINA with linagliptin, this DPP-4 inhibitor also demonstrated safety in a study cohort with a high percentage of patients with an impaired renal function with a mean baseline eGFR below 60 ml/min and macroalbuminuria (appr. 40% of patients enrolled)<sup>4</sup>.

GLP-1RA have pharmacological actions in addition to the stimulation of insulin secretion and the inhibition of glucagon secretion. They lower systolic blood pressure and allow body weight loss. The long acting injectable GLP-1RA albiglutide, dulaglutide, liraglutide and semaglutide have demonstrated superiority compared to standard therapy in cv safety studies regarding the primary MACE endpoint<sup>5-8</sup>.

These data have led to a change in the recommendations for the treatment of patients with type 2 diabetes. The above mentioned GLP-1RA should be used in patients with type 2 diabetes and pre-existing atherosclerotic cv disease as add on to metformin early on in order to reduce cv risk – independent of the HbA1c<sup>9,10</sup>. Likewise, GLP-1RA are now the injectables to be used primarily and before insulin therapy in the treatment of type 2 diabetes unless a severely deranged metabolic situation requires insulin or contraindications for GLP-1RA are present<sup>9,10</sup>.

Regarding novel developments in the field of incretin based therapies, an oral formulation of semaglutide using SNAC as an en-

hancer to locally neutralize the gastric pH and to allow absorption of the peptide semaglutide into the circulation is far advanced in clinical development and has been tested in phase III studies with the acronym PIONEER<sup>11</sup>.

Furthermore, dual- and triple incretin/glucagon agonists are in development, the dual GIP/GLP-1 agonist tirzepatide (compound LY3298176) is in the phase III clinical developmental programme demonstrating a stronger effect on HbA1c reduction and body weight reduction compared to dulaglutide<sup>12</sup>.

In summary, DPP-4 inhibitors are safe and efficacious oral antidiabetic agents especially for patients with impaired renal function and in therapeutic settings where hypoglycaemia and weight gain need to be avoided. GLP-1RA are recommended for patients with preexisting atherosclerotic cv disease. New developments like dual- or triple agonists as well as oral semaglutide may widen the spectrum of available effective antidiabetic treatment.

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