were reported as part of postmarketing surveys, although none were seen during clinical trials.

Studies have found that pancreatitis is significantly more prevalent in people with diabetes, with the risk related to traditional risk factors for the disease, including alcohol intake, obesity, hypertriglyceridemia, gallstones, and the use of certain antihypertensive drugs. An evaluation of a claims-based database that contained more than 40,000 individuals who received either exenatide or sitagliptin, matched against an equal number of patients who received metformin or glyburide initiators, found a relative risk of 1.0 (95% CI, 0.6 to 1.7, exenatide; 95% CI, 0.5 to 2.0, sitagliptin), providing no evidence of a direct association between the drugs and pancreatitis [Dore DD et al. *Curr Med Res Opin* 2009].

Incretin Mimemics and C-Cell Abnormalities

Concern has also been raised about the drug liraglutide, after animal studies found a slightly higher risk of C-cell abnormalities and C-cell medullary thyroid carcinoma, a cancer that is very rare in humans. However, further studies found significant differences in C-cell response to GLP-1 receptor agonist stimulation compared with human C-cell response. Specifically, rat C-cells demonstrated far greater calcitonin release and adenylate cyclase activation than human cells, in which no immediate response was seen after GLP-1 receptor activation [Knudsen B et al. *Endocrinology* 2010]. No cases of medullary thyroid carcinoma have been reported in humans who have taken liraglutide, and it is unlikely that any direct association between this rare form of cancer and the GLP-1 receptor agonist will be found.

Incretin Mimetics and Cardiovascular Effects

Studies that have been conducted in dogs, rats, and pigs using exenatide and liraglutide have found far smaller areas of necrotic tissue following induced myocardial infarction (MI) on animals who received exenatide or liraglutide at the time of MI [Timmers L et al. *J Am Coll Cardiol* 2009; Sauve M et al. *Diabetes* 2008; Bose AK et al. *Diabetes* 2005].

Although large human studies are pending, a small pilot study, involving 5 patients with type 2 diabetes and 5 without who arrived in the emergency department with acute MI and low left ventricular ejection fraction, found that those who were randomized to a 72-hour infusion of a GLP-1 receptor agonist demonstrated significantly improved left ventricular ejection fraction, global wall motion score indexes, and regional wall motion score indexes compared with controls ($p<0.01$ for all) [Nikolaidis LA et al. *Circulation* 2004].

There is also some evidence that the DPP-4 inhibitors may significantly reduce cardiovascular events in patients with diabetes compared with sulfonylureas [Filozof C & Gautier JF. *Diabet Med* 2010; Ferrannini E et al. *Diabetes Obes Metab* 2009]. This conclusion, however, is based on small numbers of events in studies that aimed at demonstrating improved glycemic control. Larger trials are needed to better characterize the benefits and risks of incretin-based antidiabetic medications with regard to cardiovascular outcome.

The Future of Antidiabetic Drug Development: GPR40-Selective Agonist TAK-875

GPR40 is a G-protein-coupled receptor that is highly expressed in pancreatic β-cells and is involved in free fatty acid-induced insulin secretion. TAK-875 is a GPR40-selective agonist that improves glucose control in type 2 diabetic animal models by stimulating glucose-dependent insulin secretion. In a study that was presented by Hiroaki Yahiro, Takeda Pharmaceuticals, Osaka, Japan, researchers examined the effects of the compound on insulin and glucagon secretion and on intracellular calcium (Ca^{2+}) in pancreatic β- and α-cells from human and rat islets.

The islets were isolated through collagenase digestion. Radioimmunoassay was used to measure secreted insulin and glucagon. The human islets were derived from normal subjects aged 33 to 57 years.

In static incubation, TAK-875 augmented insulin secretion from rat and human islets at high (16 mmol/L) but not low (1 mmol/L) glucose.

An islet perfusion experiment was conducted to determine the glucose-dependent insulinotropic action of TAK-875. The compound enhanced both first- and second-phase insulin secretion at high glucose but had no effect at low glucose. It demonstrated comparable expression with a GLP-1 agonist and a sulfonylurea, enhancing glucose-dependent insulin secretion as much as GLP-1 in the static incubation experiment.

In both rat and human islets, TAK-875 had no effect on glucagon secretion, regardless of glucose dosing. Calcium measurements in intact rat and human islets showed that TAK-875 enhanced glucose-induced calcium in β-cells, while

α-cells demonstrated an oscillatory $[Ca^{2+}]_i$ response at low glucose that was suppressed by high glucose concentration. The addition of TAK-875 at high glucose did not affect α-cell oscillatory $[Ca^{2+}]_i$ in rat islets, while it augmented the inhibitory effect of glucose in human islets.

These results demonstrate that TAK-875 potentiates glucose-dependent insulin secretion via direct stimulation of $[Ca^{2+}]_i$ in β-cells of both rat and human islets but has no effect on glucagon secretion or $[Ca^{2+}]_i$ in rat or human α-cells. This ability to affect insulin secretion without simultaneously increasing glucagon secretion may inhibit any hypoglycemic effects during use.

A Comparison of the OGTT and Measurement of HbA1C Using the ADA 2010 Recommendations

The American Diabetes Association (ADA) recently issued updated recommendations for the Standards of Medical Care for Diabetes [*Diabetes Care* 2010]. These recommendations include revised screening guidelines; revised diagnostic criteria for intermediate hyperglycemia (IH) and diabetes, both of which include suggested glucose values during oral glucose tolerance test (OGTT) and for HbA1C; and guidance on which patients should be considered for treatment with metformin (ie, those with both impaired fasting glucose and impaired glucose tolerance, or those with HbA1C ≥6%).

The new values for the diagnosis of diabetes are:

- HbA1C ≥6.5%, or
- Fasting glucose ≥126 mg/dL (7.0 mmol/L), or
- 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT, or
- Random plasma glucose ≥200 mg/dL (11.1 mmol/L) in patients with classic symptoms of hyperglycemia or hyperglycemic crisis

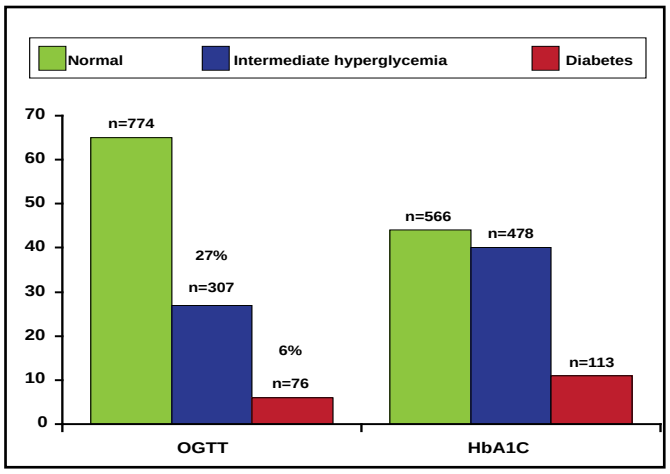
To diagnose individuals who are at high risk for diabetes, the values are:

- Fasting plasma glucose 100–125 mg/dL (5.6–6.9 mmol/L), or
- 2-hour glucose 75 g OGTT 140–200 mg/dL (7.8–11.0 mmol/L), or
- HbA1C between 5.7 and 6.4%

Emmaneul Cosson, MD, PhD, Paris-Nord University, Bondy, France, reported the results of a study that evaluated a diagnostic strategy using the new ADA OGTT and HbA1C criteria. The study included 1157 patients (962 women; body mass index 37.0 ± 7.2 kg/m^2; mean age 41.2 ± 13.5 years) who fulfilled the new ADA screening criteria but who had not been previously diagnosed with diabetes. All participants underwent an OGTT and measurement of HbA1C. Subjects were assessed for diabetes risk (using Findrisc and DESIR scores) and coronary risk (using UKPDS score).

Use of the HbA1C strategy resulted in more patients being diagnosed with either IH (41%) or diabetes (10%) compared with the OGTT (27% and 6%, IH and diabetes, respectively; Figure 1).

Figure 1. Patient Diagnosis: OGTT versus HbA1C.



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Based on the OGTT results, 11.2% of patients (n=130) would be eligible for treatment with metformin versus 22.0% (n=255) using the HbA1C strategy.

The sensitivity and specificity of HbA1C ≥6.5% for the diagnosis of diabetes according to the OGTT were 44.7% and 92.7%, respectively. In patients with HbA1C <6.5%, the sensitivity of HbA1C 5.7% to 6.4% for the diagnosis of IH was 57.9%, and the specificity was 59.3%. Diabetes risk score and UKPDS risk score were highest in patients with both an abnormal OGTT and HbA1C ≥5.7% (n=130).

The results of this study show that in a population that meets the new screening criteria, choosing the HbA1C strategy rather than the OGTT strategy leads to more individuals being diagnosed and more patients being treated with metformin, although the consistency of both diagnostic criteria is low (eg, 1/3 of patients with HbA1C ≥6.5% have a normal OGTT). The patients who have the highest *a priori* risk of diabetes and cardiovascular disease are those with an abnormal OGTT that is associated with HbA1C ≥5.7%.