There are about 371 million people with diabetes worldwide, of whom 50% are undiagnosed and these numbers will increase to about 552 million by 2030 worldwide. In Europe, where there are 55 million such patients, diabetes is rapidly increasing. For example, in Spain the Di@betes Study, which used a sophisticated cluster-sampling technique, examined some 5,072 participants across the country showed for the first time an extremely high prevalence of 13.8% among Spanish adults.

In 2010, diabetes cost the Spanish economy 5.45 billion euro and consumed 9% of the health budget. A total of 21,763 deaths per year were attributed to diabetes in Spain. This overall prevalence is set to increase to a total of 3.75 million diabetics by 2030.

In the USA, in 2012, the direct cost due to diabetes was US$471 billion.

Prof Jiten Vora, University of Liverpool, United Kingdom discussed the importance of basal insulin therapy. In managing this critically important issue, he said that today insulin therapy is often introduced too late in a patient’s care with initiation delayed until HbA1c is >9%. However current clinical guidelines recommend initiating insulin at HbA1c levels of ≤7.5%.

He stated that the ideal basal insulin should have the following characteristics:
1. Reproducible fasting glucose control
2. Long duration of action
3. Low hypoglycemic risk and flat action profile
4. Predictability
5. Flexibility and convenience

“Unfortunately NPH, glargine and detemir insulins do not match this ‘ideal’”, Prof Vora said.

As glucose variability increases, the risk of hypoglycemia increases at all levels of HbA1c; the highest risk being at the lowest HbA1c.

The flat dose-response, low variability in intra-patient response and flexible dosing of degludec was highlighted by Prof Vora as making it closer to the ideal profile of a basal insulin.

Dugledec’s clinical utility has been studied in more than 11,000 patients, including in type 2 diabetes patients, using basal only therapy plus other anti-diabetic agents, and as part of basal bolus therapy in both Type 1 and Type 2 diabetes patients.

Designing Degludec
This insulin molecule has been specifically designed to offer a flat profile with a long duration of action with low variability, Dr Peter Kurtzhals, Head of Diabetes Research, Novo Nordisk said. Degludec was designed by site-directed mutagenesis to produce an insulin with amino acid sequence identical to human insulin. At B29, a glutamic acid spacer is attached that bridges to a 16-carbon diacid. In solution, degludec exists as di-hexamers, and when injected into...
the sub-cutis, it forms multi-hexamer chains, creating a depot from which degludec is slowly released, allowing for a mean half-life of 25.4 hrs.  

Additionally, degludec does not interact with aspart insulin or liraglutide. Therefore, it can be safely combined with this insulin and oral antidiabetic agent. In fact, in combination with other insulins, degludec does not interfere with their effects, nor is its own activity altered. The binding of degludec to the insulin receptor is similar to human insulin and the metabolism route is the same with oxidation of the fatty acid side chain.

A new formulation which combines degludec with liraglutide known as IDegLira shows very promising results and will be available soon for once-a-day therapy for type 2 diabetic patients.

**Clinical profiles of new long-acting insulins and combination products**

Prof Thomas Pieber, Medical University of Graz, Austria showed that the half-life of degludec was 25.4 hours with a duration of action of 42 hours. After three days of degludec therapy, a steady state is reached with very little variability. Degludec also provided stable insulin levels in euglycaemic glucose clamp studies. As a result, the problem of missed doses is reduced and more flexible dosing is an option. In a comparative study with insulin glargine, there was significantly lower variability in control in patients receiving degludec.

Further studies show that in combination with insulin aspart both insulins maintained their own characteristics.

Meanwhile, the combination of degludec and liraglutide demonstrated good glycemic control, weight loss and minimal hypoglycemic risk.

**Improving efficacy without increasing hypoglycaemic risk**

Dr Athena Philis-Tsimikas, Vice-President of the Scripps Whittler Diabetes Institute, La Jolla, USA addressed the importance of hypoglycemia. She said insulin-induced hypoglycemia is second only to warfarin-induced adverse events as a cause for drug-related hospitalization, while oral anti-diabetic drugs rank fourth as a cause of hospitalization. Furthermore, 95% of all endocrine emergency room visits in patients >65 years are due to hypoglycemia.

Currently, hypoglycemia is commonly defined as glucose <3.1 mmol/l and this is the level at which most patients will have symptoms.

A study of 104 weeks of 1050 patients with degludec in type 2 diabetes however showed a 17% non-significant lowering of hypoglycemia as compared to glargine (1.52 episodes per patient year of exposure compared to 1.85 with glargine). Nocturnal hypoglycemia was reduced by 42% versus glargine (p<0.05).

In a two year study of patients with type 1 diabetes, there were no differences in total hypoglycaemic events after 104 weeks when patients were treated with degludec or glargine both in combination with insulin aspart, but nocturnal hypoglycaemia was reduced by 31% in degludec-treated patients versus the glargine group. A post-hoc analysis by Vora J et al presented as a poster at the current EASD meeting showed lower rates of hypoglycemia, both confirmed hypoglycemia and nocturnal hypoglycemia. Exercise-induced hypoglycaemia was similar with both degludec and glargine.

**Flexibility and meeting patients’ needs**

Flexibility of dosing is an important benefit of degludec, Prof Luigi Meneghini, University of Miami, USA, said. A number of studies demonstrate that 20-50% of patients miss insulin doses adding to their risk of long term complications.

In the 26 week, Flex Type 2 Diabetes study, flexible dosing of degludec versus glargine fixed dose showed similar HbA1c levels despite variable dose intervals (8-40 hours) with degludec, while hypoglycemia rates were comparable.

Similarly, the Flex type 1 study included 493 patients and was extended after 26 weeks to 53 weeks in a subgroup of 329 patients in a free flexible regime of degludec versus glargine fixed dosing in basal bolus therapy using insulin aspart as the bolus insulin. There was no difference in HbA1c levels between the...
“Greater reductions in HbA₁c and weight with less hypoglycaemia in degludec plus liraglutide-treated patients.”

groups. Hypoglycaemic events were also similar, but nocturnal hypoglycaemia was reduced by 25% in the degludec-treated group.¹²

Synergies of complementary drugs
The importance of combination therapy was emphasized by Prof Stephen Bain, Swansea University, United Kingdom. He said that a recent 52 week study which added insulin detemir to patients treated with liraglutide and metformin showed sustained HbA₁c reduction with very low hypoglycaemia risk without weight gain.¹³

Another study compared liraglutide versus aspart insulin in 413 patients with type 2 diabetes patients already receiving degludec. Degludec plus aspart lowered HbA₁c 0.4% versus 0.7% in those receiving degludec plus liraglutide. In the liraglutide-degludec treated group, weight was reduced by 4 kg and there was 87% less hypoglycaemia in this group.

Insulin-Incretin combination therapy
Prof Stephen Gough, University of Oxford, UK presented data on Novo Nordisk’s new once-daily combination of degludec with liraglutide (IDegLira). A 26 week study in 1663 insulin-naïve type 2 diabetes patients compared IDegLira once a day and the single agents, degludec and liraglutide. In addition to background metformin, pioglitazone could also be added. IDegLira was shown to be superior to other treatment options with 1.9% HbA₁c lowering, an 0.7 kg weight loss and little hypoglycaemia. The mean dose used was 38iu degludec and 1.4 mg liraglutide in the IDegLira group with >80% achieving the target of less than 7% HbA₁c, and 70% achieving 6.5%. ¹⁴

Cardiovascular disease and Impaired renal function
The afternoon session focusing on cardiovascular and renal disease was chaired by Prof Eduard Montanya, University Hospital, Barcelona, who opened by reviewing the GLP-1 receptor agonists (GLP-RA) position in the ADA/EASD algorithm.

He noted the concern raised by the well-discussed Butler paper as well as the EMA and FDA combined statements that there is currently no proof that GLP-RA cause pancreatitis or pancreas cancer. The IDF/EASD/ADA have also stated that these drugs are currently safe. Two large studies are however ongoing to further investigate the safety of these agents and these studies are not funded by pharmaceutical companies.

Dr Steven Nissen, United States, discussed the history of cardiovascular trials reviewing the UGDP trial which showed increased mortality with tolbutamide.

He emphasised the importance of diabetic drugs not only lowering glucose but also showing cardiovascular safety and explained the recent introduction of pre- and post-approval studies for anti-diabetic agents with regard to cardiovascular safety.

Prof Jorge Plutsky, Brigham and Women’s Hospital, Boston, USA discussed the complexity of the pathogenesis of atherosclerosis and the concept of residual risk. He noted that oxidative stress and inflammation play a pivotal role in atherosclerosis and this is increased by both hyper- and hypoglycaemia. This seems to be countered by GLP-RA in laboratory studies. He then showed a rodent study supportive of a possible mechanism as to how GLP-1 causes natriuresis and smooth muscle relaxation and could have cardiovascular benefit. It seems that GLP-1 has benefit with regard to inflammation, endothelial function, blood pressure and lipids which could provide cardiovascular survival benefits.

Dr Thomas Engstrom, Denmark discussed the importance of limiting infarct size. Animal studies have shown that GLP-RA protects the myocardium against reperfusion injury and can limit infarct size. This was shown in mice and confirmed in pigs. It is possible that a small water conduction pore, referred to as the mitochondrial permeability transition pore, is blocked by these drugs. He also discussed the POSTCON2 study with exenatide which showed a 15-19% reduction in infarct size in humans. ¹⁵

Lixisenatide was also shown in animal studies to reduce infarct size and decrease myocardial fibrosis post-infarct.
It seems that GLP-RAs also increase the action of protein kinase A in the myocardium and this helps to protect the myocardium.

**Take Home Messages**

- Degludec is well-positioned to be the best basal insulin in the world.
- The degludec and liraglutide combination, known as IDegLira, is a further welcome development.
- IDegLira will give health practitioners and their patients the best of both worlds, as it seems to provide greater HbA1c lowering, better post-prandial control, lower hypo’s and no weight gain, all in a once-a-day injection.
- The importance of cardiovascular safety for all diabetic drugs cannot be over emphasized and the GLP-1 analogues’ provisional data looks promising.

**References:**