IS IT TIME TO TRANSFORM OUR TREATMENT OF TYPE 2 DIABETES?

Summary of Presentations from the Bristol Myers Squibb/ AstraZeneca Alliance Symposium, European Association for the Study of Diabetes (EASD) 49th Annual Congress, Barcelona, Spain, 23rd September 2013.

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MEETING SUMMARY

This meeting comprised two sessions: the morning session centred around glucagon-like peptide-1 receptor (GLP-1R) agonists and SGLT-2 inhibitors, a new class of glucose-lowering compounds, while the afternoon session focused on new results of cardiovascular safety studies with diabetes medications, with special attention to the SAVOR-TIMI trial of saxagliptin.

Morning Session – Catalysts for Change?

How Can GLP-1 Receptor Agonists and SGLT-2 Inhibitors Help Us Reshape Individualised Diabetes Care?

Addressing the Type 2 Diabetes Pandemic: The Need for Transformational Thinking and Innovative Treatments

Professor Dídac Mauricio

Prof Mauricio began by highlighting the disease burden of type 2 diabetes (T2D) and indicated that previous predictions on prevalence of burden are far behind the reality of the situation. By 2030, there will be more than 500 million people around the world affected by T2D.[1,2] In recent years, diabetes has been estimated to account for 4–13% of national healthcare budgets in Europe,[3] with the estimated average yearly cost per patient at €2,834.[4]

The progressive nature of the disease also contributes to the burden; long-term complications develop that ultimately require additional treatment resources. Examples include macrovascular complications such as cardiovascular (CV) disease, and microvascular complications such as nephropathy, neuropathy and retinopathy.[5] Patients with T2D have a 2 to 4-fold higher risk of coronary heart disease than those without the condition, and 75–80% die due to CV events.[6]

Prof Mauricio discussed the benefit of early therapy in newly diagnosed T2D in reducing long-term complications. In the UK Prospective Diabetes Study (UKPDS), newly diagnosed patients were randomised to receive either conventional therapy (dietary restriction) or intensive therapy (sulphonylurea or insulin, or metformin if >120% ideal body weight). Early intensive intervention provided benefits not only for microvascular disease but also for myocardial infarction (MI).[7] The American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) now recommend early, patient-centred treatment in order to manage hyperglycaemia.[8]

Prof Mauricio presented recent European data concerning glycaemic control showing that conventional therapy is suboptimal, and patients receiving more complex treatments are less likely to achieve their target glycated haemoglobin (HbA1c).[9] He stressed that glycaemic control is not the only approach to consider when treating T2D; a multifactorial approach is essential, and comorbidities, efficacy, hypoglycaemia, weight, and cost have to be taken into account.

New Evidence from GLP-1 Receptor Agonist Studies: Their Role in Diabetes Care

Professor Michael Nauck

Prof Nauck started his presentation by giving an overview of the mechanism of action of GLP-1 receptor (GLP-1R) agonists. GLP-1 affects gastric motility and metabolism and reduces appetite; activation/stimulation of GLP-1Rs with GLP-1 agonists could provide a potential avenue for treatment of T2D. Endogenous GLP-1 has a short half-life (<2 minutes) due to degradation and inactivation by DPP-4, requiring GLP-1 analogues to have a longer half-life to be effective.[10] A number of GLP-1R agonists are available, which mainly differ in terms of their pharmacokinetic profile. Exenatide achieves peak plasma concentration 2 hours after injection, while liraglutide maintains high concentrations even after 24 hours.[11,12]

Prof Nauck presented results from the DURATION-1 study where long-acting once-weekly exenatide was more effective at lowering HbA1c and fasting glycaemia than the short-acting twice-daily formulation, but not at lowering body weight.[13] A comparison of the DPP-4 inhibitor sitagliptin and injectable GLP-1R agonist liraglutide showed that the injectable liraglutide was more potent in reducing glycaemia and body weight when compared to sitagliptin.[14]

Prof Nauck highlighted that the results of meta-analyses have shown that there is a higher likelihood of achieving target HbA1c levels with a GLP-1R agonist when compared to insulin, even more so when a longer-acting preparation is used, as was shown with exenatide once weekly in DURATION-3 study up to 3 years.[15] It was Prof Nauck's opinion that the short-acting GLP-1R agonists should be used in combination with long-acting insulin because they show a beneficial effect on postprandial glucose excursions.

Clinical Experience: How Can GLP-1 Receptor Agonists Improve Daily Life for Patients?

Professor Tina Vilsbøll

Prof Vilsbøll discussed the treatment options for diabetes available in her practice. When she first

decides on a treatment, she has to consider its efficacy with respect to change in HbA1c, change in body weight and risk of hypoglycaemia. Prof Vilsbøll noted that compared to sulphonylureas, thiazolidinedione and insulin, GLP-1R agonists have favourable efficacy outcomes since they reduce both HbA1c and body weight, with low hypoglycaemic risk.[8,16-18]

Prof Vilsbøll asked how GLP-1R agonists could improve daily life. She first looked at their effect on HbA1c, citing a meta-analysis performed in her lab that compared exenatide once-weekly, exenatide twice-daily and liraglutide to all the non-GLP-1R agonists given for more than 20 weeks in clinically-relevant doses. The GLP-1R agonists provided a sustained 0.6% difference HbA1c after 20 weeks.[19] GLP-1R agonists have also been shown to cause a reduced level of hypoglycaemia compared to insulin glargine, especially when on a non-sulphonylurea background,[17,20] and therefore may represent an improvement in treatment in this respect.

Patients with T2D have a 2 to 3-fold increase in risk of pancreatitis, and GLP-1R agonist therapies do not change this risk.[21-29] The European Medicines Association concluded that there are no new concerns for GLP-1 therapies based on the available evidence,[30] and Prof Vilsbøll was of the view that the side-effect profile is acceptable considering the sustained effect GLP-1R agonists have on glycaemic control, body weight, and hypoglycaemia.

An Innovative Treatment Target for Managing Type 2 Diabetes: Evidence from SGLT-2 Inhibitor Trials

Professor Samy Hadjadj

Prof Hadjadj started his presentation by introducing the sodium glucose co-transporter-2 (SGLT-2) inhibitors for the treatment of T2D. Currently, there are many of these drugs in clinical development, with the first-in-class dapagliflozin approved in the EU and canagliflozin approved in the USA.[31] SGLT-2 is expressed in the renal proximal tubule, and causes reabsorption of glucose back into the bloodstream. An SGLT-2 inhibitor such as dapagliflozin inhibits this reabsorption, leading to an increase in glucose excretion and caloric loss. This mechanism is specific to the kidney due to the localisation of SGLT-2 receptors.[32-35]

Prof Hadjadj presented data comparing dapagliflozin to current therapies. Dapagliflozin combined with metformin XR in drug naïve patients provided an even greater reduction up to 2% in HbA1c and body weight compared to metformin alone. In patients with background metformin therapy, these reductions were sustained well beyond the primary endpoint of 24 weeks; at 102 weeks patients treated with the combination therapy had a 0.78% reduction in HbA1c.[36,37] When dapagliflozin is used as part of triple-combination therapy it helps to reduce HbA1c and body weight in patients with T2D.[38] Other combinations of medications, such as empagliflozin in combination with metformin and sulphonylurea produce similar effects.[39]

Prof Hadjadj highlighted that SGLT-2 inhibitors have a low propensity to cause hypoglycaemia. Dapagliflozin in particular is no different to placebo in this respect.[40] Side-effects, such as genital and urinary tract infections, are manageable.[35,41,42] Professor Hadjadj noted that the incidence for bladder cancer was slightly raised in patients treated with dapagliflozin. He commented that this might be explained by a better opportunity to more efficiently diagnose bladder cancer, because the mechanism of action on urine outflow makes it easier to observe haematuria.[43] A meta-analysis for major adverse CV events showed no warning signal for dapagliflozin treatment.[44]

Clinical Experience with Dapagliflozin

Professor Peter Rossing

Prof Rossing outlined the current problems with diabetes disease progression and treatment. It has been shown that progressive loss of glycaemic control occurs in T2D patients, irrespective of treatment.[45] SGLT-2 inhibitors may provide some of the features that are necessary for obtaining good control of glucose and some of the other risk factors. SGLT-2 inhibitors act on glucose, body weight and blood pressure, and have a very low-risk of hypoglycaemia.[42] The SGLT-2 inhibitor dapagliflozin is indicated to improve glycaemic control as both a combination and monotherapy.[42]

Prof Rossing presented case studies. The first case was Anna, a 42-year-old female diagnosed with diabetes. After two years her HbA1c started to rise and her body weight increased. The patient was prescribed dapagliflozin, since she had normal

liver function, preserved renal function, and did not want to risk hypoglycaemia due to her active lifestyle. The patient responded very well to treatment and was happy with the results.

John, a 55-year-old male, who was severely obese and a heavy smoker, did not drastically improve his lifestyle after diagnosis. After metformin administration he lost weight and had a large reduction in HbA1c, but like Anna this control waned after time. Treatment with DPP-4 inhibitors, GLP-1R agonists and insulin were not effective. Despite his slightly lowered GFR, the patient was prescribed dapagliflozin since other prescribing considerations such as liver function and infection history were normal. Dapagliflozin treatment led to a reduction in body weight and HbA1c.

Prof Rossing concluded that better treatment for glycaemia is needed. SGLT-2 inhibitors work in the kidneys and complement the action of metformin and other anti-diabetic drugs. Blocking SGLT-2 reduces blood glucose and has other beneficial effects on body weight and BP, with a low-risk of hypoglycaemia.

Afternoon Session – SAVOR Trial

How May the Largest DPP-4 Inhibitor CV Safety Study Influence Day-to-Day Clinical Practice?

From UKPDS to SAVOR: The Evolving Landscape of CV Outcomes Studies in Type 2 Diabetes

Professor Anthony Barnett

Prof Barnett presented the results of CV risk factor intervention trials from a glycaemia perspective. The UKPDS remains the first large-scale study of intensive versus conventional glucose control in T2D. In this study, over a mean of 10 years the difference in favour of tight control was 0.9% HbA1c, which was associated with a 25% risk reduction for microvascular complications.[45] After a further 10 years, patients from the UKPDS were followed-up; despite the fact that during the interim period there was no effort to maintain treatment and that HbA1c levels were the same between both groups, the intensively-treated patients had significantly improved health outcomes.

Prof Barnett then presented the PROactive study, the conclusions of which are still hotly debated. This study showed that oral pioglitazone reduced the composite endpoint of all-cause mortality, non-fatal MI and stroke in patients with T2D but with increased side-effects, particularly of heart failure.[46,47] Other confounding CV outcomes were also shown in the ACCORD and ADVANCE studies.[48,49] The VADT and ORIGIN study also showed similar results, that glycaemic control had a neutral effect on CV outcomes.[50,51]

Prof Barnett asked what we can conclude from these studies. His suggestion was that there is no one-for-all approach to glycaemic control, and that by increasing risk and rates of hypoglycaemia the benefits of tight glycaemic control may be negated. The current ADA and EASD Joint Position Statement, therefore, recommends an individualised approach to treatment targets.[8] As a result of causing more CV events, an increase in heart failure and MI risk, the thiazolidinedione rosiglitazone was withdrawn in the EU, and the EMA stated that 'a new glucose-lowering agent should preferably show a neutral or beneficial effect on parameters associated with CV risk'.[52-54]

Introducing the Latest CV Safety Studies in Type 2 Diabetes

Professor Edoardo Mannucci

Prof Mannucci started his presentation by discussing the case of rosiglitazone. In 2007, a meta-analysis of rosiglitazone studies suggested that its use could be associated with a relevant increase in the incidence of MI and also possibly CV mortality.[53] As a result of these findings, the Food and Drug

Administration (FDA) imposed new rules for the approval of newly-developed glucose-lowering agents; in particular, drugs must demonstrate CV safety, specifically by showing that they do not increase CV events by more than 30%.[55]

Since the FDA regulations only apply to drugs marketed after 2009, many older drugs that are currently used for treatment would not get approved if developed today. Only two current drugs have shown reliable data from large-scale CV outcome trials: pioglitazone and insulin were shown to be safe in the PROactive and ORIGIN trials, respectively.[46,51] There are a lack of good quality data for the CV safety of metformin, however a meta-analysis of all metformin trials showed that the drug is associated with a significant reduction in the incidence of major CV events,[56] and from this it can be concluded that under current FDA guidelines metformin would likely be approved. Similar results were shown for sulphonylureas and DPP-4 inhibitors.[29]

Prof Mannucci asked the audience about their experience with DDP-4 inhibitors; 10% of the audience's patients were receiving these drugs as secondary prevention after a major CV event. Prof Mannucci concluded by discussing the characteristics of the patients entered into these trials, specifically that those enrolled into large CV outcome trials are not representative of the general population. As such, when considering treatment options, the results of trials such as EXAMINE and SAVOR must be placed into context of the patient population.

Key Findings from the SAVOR Study: The Effects of Saxagliptin

Professor Harald Darius

Prof Darius presented findings from the SAVOR study of the DPP-4 inhibitor saxagliptin, conducted in T2D patients with CV risk. The primary endpoint of the trial was namely CV death, non-fatal MI, and non-fatal ischaemic stroke. The study met this endpoint, meaning that CV risk increase could definitely be ruled out with a very high statistical power.[57] Saxagliptin was not shown to be superior to placebo in terms of efficacy.

The secondary endpoint, which included hospitalisations, came to a rate of 6.6% for saxagliptin and 6.5% for placebo, which again satisfied FDA requirements.[57] In terms of glycaemic control, Prof Darius noted that saxagliptin treatment led to a significant reduction in HbA1c compared to placebo: 7.5% versus 7.8% at year 2. The proportion of patients achieving a HbA1c of less than 7% was also increased in the treatment group. Fewer patients in the saxagliptin group required the addition or increase of any new anti-diabetic therapies, or initiation of insulin therapy for more than 3 months.[57,58]

Saxagliptin neither reduced nor increased the risk of the primary composite endpoint of CV death, MI, or ischaemic stroke in comparison to placebo, in patients with a very high CV risk. In addition, the saxagliptin group experienced an improved glycaemic control, an increased rate of hypoglycaemic events but not hospitalisation for hypoglycaemia, a higher rate of hospitalisation for heart failure, a reduced requirement for insulin or other diabetes medications, a favourable effect on microalbuminuria, and no increased risk of pancreatitis or pancreatic cancer.

The Potential Impact of SAVOR on Clinical Practice

Professor Chantal Mathieu

Prof Mathieu presented her views on the SAVOR trial. A major positive from the trial was that it met its primary safety endpoint, namely no increased risk of CV death, non-fatal MI, and non-fatal stroke. Thus, indicating there was no difference between the treatment and placebo groups (hazard ratio=1.0).[57,58] Another positive outcome was that the trial also met its secondary endpoint (composite primary endpoint plus hospitalisation for heart failure), and in Prof Mathieu's opinion this was an important result, and based on these data she would recommend saxagliptin as a safe drug to use in T2D treatment.

Prof Mathieu suggested that the 0.3% HbA1c difference observed between the treatment and placebo groups may diverge after additional time beyond the current 2-year measurement, since other studies only saw differences after several years of treatment. Prof Mathieu expressed a positive opinion about the safety profile of saxagliptin, in particular regarding pancreatitis and pancreatic cancer.

Prof Mathieu concluded that SAVOR provides an important set of data on the safety and efficacy of this DPP-4 inhibitor, and that the lack of increase in CV risk was a major finding. Stable glucose lowering and the lack of increase in pancreatitis and pancreatic cancer were also important findings. She ended her presentation by polling the audience on whether they were reassured about the use of DPP-4 inhibitors. Two-thirds of the audience were convinced by the data.

How Could We Transform Treatment in Type 2 Diabetes: Which Approach, When and for Whom?

A broader panel discussion then took place involving speakers from both sessions of the meeting. Discussion began by examining the evidence for metformin in the treatment of early stages of diabetes. Prof Mannucci stated that we cannot be sure that metformin is superior to other drugs, despite its effectiveness and safety, and that if another drug was developed that showed clear superiority it would replace metformin as first-line therapy.

The panel then discussed how recent trials such as SAVOR may change treatment strategies. Regarding the concept of treatment individualisation, Prof Barnett stressed that the whole package of treatment must be considered, not just pharmacotherapy. Adherence rates to therapy are very low, and as such, patient needs, lifestyle and attitude must be considered in addition to clinical factors. Prof Mathieu added that cost must be considered as part of this treatment package, since in her opinion sulphonylureas would not be used if they are more expensive.

One question asked whether the results of the SAVOR and EXAMINE trials could be used to generalise for the DPP-4 inhibitors and GLP-1R agonists. It was Prof Vilsbøll's opinion that it is unlikely we will get any surprises in patients having CV heart failure with DPP-4 inhibitor trials.

Prof Mauricio asked the panel for their opinion on the best method for treatment individualisation since phenotyping for patients is currently lacking. Prof Nauck concluded the panel discussion by suggesting that the best method of individualisation is to take into account all of a patient's characteristics, such as obesity and previous efforts at weight loss, since these will inform choices of medication.

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