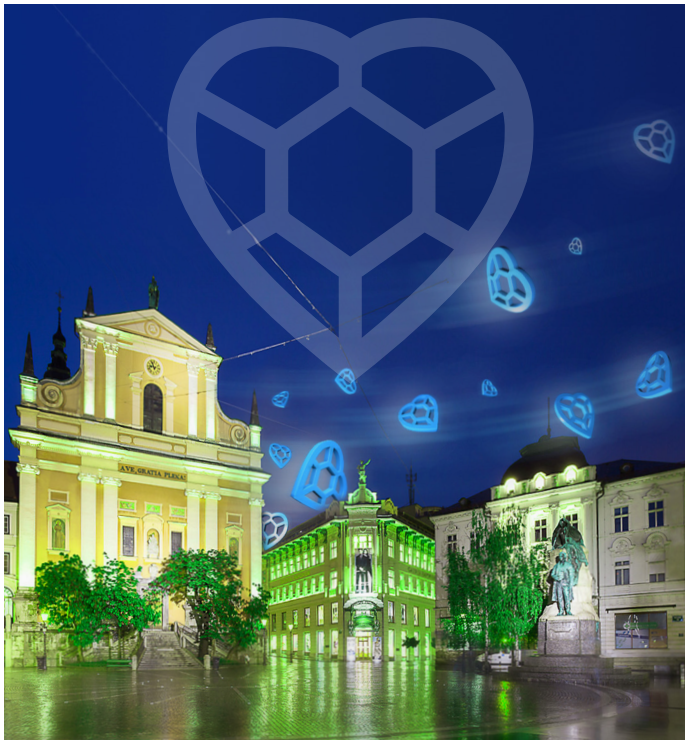
Meeting Impression

Satellite symposium during EuroPrevent 2018 Congress
May 3, 2018 – Ljubljana, Slovenia

Preventing Cardiovascular Disease in Patients with T2DM – How to apply novel outcome data with GLP-1RA to clinical practice

This educational program was held during Europrevent 2018 in Ljubljana, Slovenia. Richard Hobbs, Diederick Grobbee and Lars Rydén discussed the association between type 2 diabetes (T2DM) and cardiovascular disease (CVD) and stressed the importance of CV risk management in these patients in primary care. Traditional therapies to reduce CV risk and the need for novel approaches beyond glucose control to prevent CVD in T2DM patients were discussed. The presenters explained potential mechanisms of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and presented results from recent CV outcome trials in T2DM patients. Finally, practical implications of these insights on treatment and prevention strategies in T2DM patients with high CV risk were proposed.

TOPICS



The cardiovascular challenge for primary care in diabetes

Prof. Richard Hobbs, MD – *Oxford, UK*

Prof. Hobbs started his presentation by asking whether vascular disease prevention is especially important in diabetes patients. In general, preventing CVD is one of the most important challenges faced by healthcare. Data from the Global Burden of Disease project showed that ischemic heart disease (IHD) and stroke, the main clinical manifestations of vascular disease, are the most important causes of premature death and disability (1). Therefore, it is not surprising that risk factors for vascular disease are the most important issues for healthcare systems. Important to realize is that the high impact of vascular disease is similar world-wide; it is a global problem.

The risk of vascular disease is almost two-fold higher in diabetes patients compared to individuals without diabetes.

The significance of diabetes in relation to vascular risk can be explained, among other reasons, by the high prevalence of diabetes. Diabetes affects ~8% of the world population, resulting in high absolute patient numbers (2). The risk of vascular disease is almost two-fold higher in diabetes patients compared to individuals without diabetes (3).

Vascular disease is not a direct consequence of diabetes. It takes about a decade after diagnosis of diabetes before risk of coronary heart disease (CHD) reaches the CHD equivalent threshold (4). Needless to say, vascular disease is an important cause of death in diabetes patients and it results in significant loss of life; up to seven years of life are lost in an individual at the age of 50 years with diabetes, but no history of vascular disease, with an even greater impact in women (5).

Beyond glucose control, an important factor via which vascular risk can be modified is smoking. Obviously, it is very important for patients to prevent or stop smoking. On average, an individual will lose ten years of life by smoking, but the earlier one quits smoking, the more years lost can be regained. Worthwhile to notice is that it is never too late to stop; even if an individual stops smoking at 50 years, the number of years lost is reduced (6).

Blood pressure (BP) is another important risk factor of vascular disease and it is a very prevalent one. Trial results have shown that BP control results in large reduction of stroke, heart failure (HF) and myocardial infarction (MI) (7, 8). In general, effectiveness of BP control is similar in patients with diabetes and in individuals without diabetes. Interestingly, the effect of BP on some clinical outcomes, for example stroke, is even more favorable in patients with diabetes (9).

Control of LDL-c levels by statins is an another target of reducing vascular disease, which is very effective with a 16% reduction in CV events for each mmol/L reduction in LDL-c in patients with a history of CVD or in primary prevention (10), irrespective of diabetes status (11). Therefore, statin therapy is an important and effective strategy to reduce CV events in patients with diabetes, even though use of statins results in an increased risk of dysglycemia of ~9% (12). It is important to realize that patients who, end up developing diabetes as a consequence of statin initiation, still benefit from the same vascular risk reduction with statins as individuals without diabetes.

Adherence to therapy is an important factor that determines vascular risk, as patients who are non-adherent have a two-fold increased risk of vascular events compared to patients who adhere to therapy. Important to realize is that, even though patients adhere to their statin therapy, they may have a large residual risk (13). Therefore, there is a need for additional treatment to reduce vascular risk in patients with diabetes.

In the United States, elevated rates of obesity were followed by a similar increase in the rate of diabetes over time.

Glycemic control to reduce vascular risk has yielded much more disappointing effects. Until the appearance of sodium-glucose co-transporter 2 (SGLT2) inhibitors and GLP-1RAs, no large CV benefit had been observed with anti-diabetic agents. Intensive strategies with traditional glucose-lowering therapies have not shown benefit on clinical endpoints including mortality and macrovascular events (14). Lifestyle improvement has been demonstrated to prevent diabetes, but not to reduce vascular risk once diabetes has developed (15). The onset of diabetes could be delayed in ~50% of cases by a variety of lifestyle interventions (16) and is therefore an important strategy in patients with increased risk of diabetes.

Looking at the current trends in relation to primary care, the most important one is the increase in obesity. Data have shown that more than half of adults in the United Kingdom are either clinically overweight or obese. The obesity trend has increased over the last 20 years, culminating into nearly 25% of the population being obese. A close association between BMI and subsequent onset of diabetes was observed in the Nurses' Health Study with a 15 year follow-up (17). At a BMI >30 kg/m^2, the rate of diabetes incidents is increased, and this is observed world-wide. This was clearly demonstrated in the United States, where elevated rates of obesity were followed by a similar increase in the rate of diabetes over time. Obesity is a social as well as a medical problem and there are many interventions that need to be considered at a system level to stop the increase in weight in the population and reduce the impact on health.

Diabetes: How to reduce risk from a cardiovascular perspective?

Prof. Diederick Grobbee, MD – *Utrecht, The Netherlands*

When trying to understand the mechanisms responsible for the increased CV risk in T2DM patients, it becomes clear that this is a complex situation. It is known, however, that obesity plays a major role. Visceral adiposity is associated with inflammation, insulin resistance, dyslipidemia, and hypertension, which all contribute to vascular damage (18). These mechanisms provide entries for prevention strategies. Indeed, nowadays hyperglycemia, hypertension, dyslipidemia, and obesity are common and important modifiable risk factors in T2DM patients (19). There is a large body of evidence demonstrating that targeting these risk factors reduces CV risk. Anti-hypertensive treatment, control of LDL-c levels and anti-platelet therapy have been demonstrated to be beneficial (20).

Although it makes sense to think that reducing glucose modifies CV risk in T2DM patients, studies with traditional glucose-lowering drugs have not demonstrated large benefits.

Looking more specifically at the effect of anti-hypertensive therapy, even small reductions in BP can reduce CV risk in high-risk individuals. A study on the relationship between systolic BP (SBP) reductions and 5-year CV risk in different strata of patients, showed that the effect of large BP reductions in patients with low CV risk was similar to the benefit of small BP reductions in high-risk patients, including

T2DM patients (21). Large trials on statin therapy have demonstrated reduction of CV risk, with a larger benefit in diabetes patients compared with non-diabetes individuals (22).

With regard to glycemic control, controversy exists on its effect on CV risk. Although it makes sense to think that reducing glucose modifies CV risk in T2DM patients, studies with traditional glucose-lowering drugs have not demonstrated large benefits. A pooled analysis of multiple observational studies showed that a fasting blood glucose of ~5.5 or 6% HbA1c resulted in a gradually increased risk of CHD (3). Hyperglycemia has therefore been considered an important risk factor for CV outcomes. A long history of several trials have examined the effect of lowering glucose on CV risk. The first study on glucose lowering was UKPDS, which included patients with newly diagnosed T2DM (23).

These patients had very high levels of fasting glucose, much higher than in current clinical practice. Later studies, such as ADVANCE (24) and ACCORD (25), included patients similar to those seen in clinical practice today and lower levels of HbA1c were targeted. Target HbA1c levels in ADVANCE were <6.5% and in ACCORD even <6.0%.

Results of the UKPDS study were slightly disappointing. Although there were clear benefits of lowering glucose on microvascular disease, such as microalbuminuria, retinopathy, and microvascular complications, no large benefit was observed for macrovascular disease, myocardial infarction (MI) and mortality (23). Similar findings were observed in the ADVANCE study 20 years later. In this study, patients were randomized to a regimen of tight glucose lowering or usual care. With a decrease of ~1% in HbA1c over time, no clear benefits were seen for macrovascular events, but there were small benefits for microvascular events, which could potentially be relevant (24). A long-term follow up of 10 subsequent years to examine the effects on mortality and CV mortality over time also showed no macrovascular benefits for the intensively treated group (26). With lower HbA1c target levels in ACCORD, a reduction in non-fatal MI was observed with intensive glucose lowering, but an increase in all-cause mortality (25). This left the investigators puzzled, as HbA1 levels were close to normal and no large CV benefit was observed, in contrast, harm was detected.

Altogether, the results of glucose lowering on all-cause mortality or CV mortality in large trials were disappointing (14) and in disagreement with the initial view that diabetes is a glucose problem and glucose lowering should therefore reduce CV risk. One of the explanations may be that these glucose-lowering drugs have side effects that counteract the benefits.

Treatment with empagliflozin resulted in not very impressive HbA1c decreases of 0.5% or even less, but still there was a clear benefit for 3-point MACE and all-cause mortality.

New drugs have been introduced in the past years, such as dipeptidyl peptidase-4 (DPP-4) inhibitors, SGLT2 inhibitors and GLP-1RAs. Results of first clinical trials evaluating these new classes are available and many more are to come. DPP-4 inhibitors and GLP-1RAs have the same mechanism of action, which is primarily stimulating insulin release. Early trials with DPP-4 inhibitors and GLP-1RAs have not been very impressive in terms of CV benefit (27). However, things then changed with the more recently published LEADER trial (28), which is discussed later in this document.

Studies evaluating SGLT2 inhibitors showed that treatment was associated with CV benefit. One of the suggested mechanisms of how SGLT2 inhibitors might lower CV risk in diabetes patients is by diuretic effects, resulting in removal of excess glucose from the body (29). The mechanisms of SGLT2 inhibitors still need further exploration, but besides small effects on glucose and HbA1c, there may be additional effects that cause CV risk reduction (30).

The EMPA-REG OUTCOME study evaluated the effect of two doses empagliflozin on CV outcome in high risk diabetes patients. Both doses showed the same effects, therefore most analyses have used pooled data. Treatment with empagliflozin resulted in not very impressive HbA1c decreases of ~0.5% or even less, but still there was a clear benefit for 3-point MACE, and all-cause mortality (31). These findings have gained a lot of interest and led to the perspective that these new drugs will reduce CV events in diabetes patients.

Practical management of cardiovascular risk: Lessons from latest diabetes trials

Prof. Lars Rydén, MD – *Stockholm, Sweden*

The two options to lower glucose based on incretins are DPP-4 inhibitors and GLP-1RAs. Effects of incretin-based glucose-lowering therapies are increased insulin secretion, decreased glucagon secretion, improved beta-cell mass in time and enhanced insulin sensitivity. Decreased gastric emptying and improved satiety are also effects of incretins, especially with GLP-1RAs (32). GLP-1RAs are administered by injections. These agents mimic the effect of natural GLP-1, which is released during eating.

GLP-1RAs reduce HbA1c by ~1% or more and result in weight loss of 2-3 kg. There is a low risk of hypoglycemia

when GLP-1RAs are used with metformin, and a reduced risk of hypoglycemia in combination with insulin.
The mechanisms of action of GLP-1RAs are broad. GLP-1RAs interfere with many organ systems and it is not known how exactly GLP-1RAs exert CV benefits. Many mechanistic studies are ongoing and to date, it has been suggested that the heart, kidney, vessels and intestines are all important targets of this drug class (33). There are two types of GLP-1RAs; short-acting and long-acting (34, 35). The short-acting is exendin-4 based and the long acting type exendin-4 based or a GLP-1 human analog.

Lixisenatide and exenatide are based on exendin-4, which was derived from the saliva of the lizard. First, lixisenatide was tested in ~6000 T2DM patients with a recent acute coronary syndrome (ACS) (36). They received lixisenatide or placebo on top of standard care, follow-up was ~2 years and the impact on CV mortality and morbidity was studied. There was no difference in HbA1c and 4-point MACE, a composite of CV death, non-fatal MI, stroke, and hospitalization for ACS between the two groups at the end of the study. Overall, there was no benefit for CV outcomes with lixisenatide.

Therapy with lixisenatide or exenatide was demonstrated to be safe, but the agents did not result in CV benefit.

Exenatide was evaluated in a study with almost 1500 T2DM patients with or without CVD (37). Three quarters of patients had CVD, while the remaining group were at high CV risk. Patients received either exenatide or placebo on top of standard, additional care. Follow-up was 3.2 years and the primary endpoint was a composite of CV mortality, non-fatal MI and non-fatal stroke. At the end of the study, a non-significant change in HbA1c and CV outcomes was observed with exenatide. These studies were designed to show non-inferiority and lixisenatide and exenatide were demonstrated to be safe, but they did not result in CV benefit.

Liraglutide and semaglutide are human analogs of GLP-1. Liraglutide was also tested in the LEADER trial in a non-inferiority design, including patients with a history of CVD or high CV risk (28). On top of standard care treatment, they received liraglutide or placebo. Liraglutide resulted in a 13% reduction of the primary endpoint 3-point MACE. This meant that there was a drug now that was not only safe, but which also reduced the number of CV events. A similar result was observed with semaglutide with a reduction in CV outcomes for the semaglutide group compared to placebo and also a reduction in HbA1c compared to the placebo group (7.3% vs 8.3%) (38).
The patients in the LEADER trial were ~64 years old and the majority was male, which is not surprising as more men than women suffer from CVD. The patients had a diabetes duration of ~13 years, had somewhat elevated HbA1c levels, were overweight or obese based on BMI, a well-controlled BP and 18% had a history of HF. The majority had a prior CV event. Background therapy was a combination of metformin, sulfonylurea, insulin or other glucose-lowering drugs. Other drugs, such as BP-lowering diuretics and lipid-lowering drugs, were also commonly used. Thus, these were well-treated patients, as is evident by the treatment goals set by the investigators: HbA1c ≤7.0, BP target 130/80 mmHg, LDL-c <1.8 mmol/L and treated with antiplatelet therapy after CV event.

Reduction in MACE with liraglutide was observed in all subgroups, and it seems as though there was a slightly increased benefit in younger patients and in those with CVD, although these data have to be interpreted with caution as it was a post-hoc analysis. The important message here is that the beneficial CV impact was consistent in all subgroups. Looking at the individual endpoints, a reduction was seen in total mortality and CV death with liraglutide, but not in non-fatal MI, non-fatal stroke, and HF hospitalization. In the past, incretins have been associated with an increase in HF, but there was no sign of harm with liraglutide. Co-treatment with insulin did not affect the CV benefit observed with liraglutide. There was also a reduction of microvascular events, a composite of renal and retinal outcomes, which was primarily driven by an improvement of 22% for renal function over time. An immediate decrease in HbA1c is observed after initiation with liraglutide and a small significant difference was seen compared to the placebo group at the end of the study, despite the fact that more glucose-lowering agents were added to the treatment regimen over time in the placebo group. Other effects of liraglutide were weight loss (2.3 kg), SBP reduction (1.2 mmHg), a small increase in HDL-c, a small decrease in LDL-c, and a small increase of 3 beats per min in heart rate (HR). It is known that GLP-1RAs can increase HR somewhat, but this small elevation of HR does not counteract the beneficial effects of liraglutide.

Considering that most benefit was observed for MI, stroke and need for revascularization, it is thought that semaglutide may result in reduced progression of atherosclerosis and/or stabilization of plaques.

Severe hypoglycemia was significantly less common in the liraglutide group compared to the placebo group and there was no difference in CV outcomes in patients with or without hypoglycemic episodes. Overall, the LEADER trial showed an absolute reduction of 1.9% in 3-point MACE, corresponding to a relative risk reduction of 13%, which was impressive considering that patients were already well-treated. CV death was reduced by 22% and all-cause mortality by 15%.

The patient group in the SUSTAIN-6 trial was similar to that in the LEADER, although 61% of patients in the SUSTAIN-6 trial had CVD compared to 81% in the LEADER trial. The SUSTAIN-6 trial was shorter in duration, but showed a clear significant impact on 3-point MACE, a composite of non-fatal MI, non-fatal stroke, and CV mortality. Considering that most benefit for individual endpoints was observed for MI, stroke and need for revascularization, it is thought that semaglutide may result in reduced progression of atherosclerosis and/or stabilization of plaques. Total mortality was not reduced by semaglutide, but CV mortality was. Glycemic control was more improved in the SUSTAIN-6 trial by semaglutide than by placebo in the LEADER trial and this was also observed for body weight, with a small dose effect.

A significant increase in retinopathy was observed in the semaglutide group in the SUSTAIN-6 trial and a non-significant increase with liraglutide in the LEADER trial. This has to be monitored in the future and more studies have to be done to examine the increased risk of retinopathy with GLP-1RAs. A possible explanation may be that a fast reduction in glucose may provoke already existing retinopathy.

Overall, treatment with semaglutide in the SUSTAIN-6 trail showed an absolute risk reduction in 3-point MACE of 2.3% and a relative risk reduction of 26%. This reduction was larger than that observed in the LEADER trial and achieved in a shorter period. CV mortality and all-cause mortality were not reduced, but perhaps this is due to the shorter duration of the trial. In time, less stroke and MI should lead to a reduction in mortality. A recent meta-analysis of all studies on GLP-1RAs showed there was no sign of hypoglycemia, pancreatitis and pancreatic cancer with the use of these agents (39).

There are several possible explanations for the differences in CV outcomes with GLP-1RAs. One of them is that the study populations in the trials were different. The ELIXA trial enrolled patients with T2DM and a recent ACS; these patients were perhaps more unstable than in other trials. Prior CVD was less evident in the ongoing REWIND trial (40) and in the EXSCEL trial (37) compared to other trials.

The impact on CV benefit seems to be greater in patients with established CVD. Therefore, the results of the REWIND study are highly anticipated. Differences in use of non-study medications and differences in glycemic control may also affect the observed CV benefits. And, exendin-4 based GLP-1RAs have not shown reduction in CV events, while long-acting human analogs that mimic natural GLP-1 did.

The results of the REWIND trial, enrolling less ill patients than in the other GLP-1RAs trials, will be presented in June 2019. Other results to come are those of the HARMONY trial and the PIONEER-6 trial. Also, already available drugs will be studied, for example an oral semaglutide is currently being evaluated. Furthermore, people with impaired glucose tolerance or obesity, not necessarily inflicted by diabetes, are of interest because GLP-1RAs can result in weight reduction and prevention of metabolic syndrome. The results of the trials have been translated into a substantial number of local and international guidelines. The American standardized medical care in diabetes recommends that patients with T2DM and established atherosclerotic CVD should receive an agent proven to reduce major adverse CV events and CV mortality (41).

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