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CARDIOVASCULAR AND RENAL PROTECTION WITH NOVEL ANTIDIABETIC AGENTS BEYOND BLOOD GLUCOSE LOWERING IN TYPE 2 DIABETES. NEWSLETTER FROM THE EUROPEAN SOCIETY HYPERTENSION WORKING GROUP ON OBESITY, DIABETES AND THE HIGH RISK PATIENT

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Introduction

Type 2 diabetes (T2D) is characterized by insulin resistance. In the progression of the disease functional failure of the pancreatic beta cells occurs. The prevalence of T2D has increased over the past few decades, as influenced by ageing populations and less healthy life style, with projections of an even greater burden growth over the coming decades. T2D has a strong genetic propensity that becomes overt when a patient is exposed to a typical Western lifestyle, gain weight and becomes obese. Weight loss prevent (or postpone) obese subjects with impaired glucose tolerance from developing T2D [(1)]. Obesity is the main aetiogical cause of T2D and the term 'diabesity' emphasize the coexistence of the two diseases [(2)] explaining the role of excess fat in the parallel increase of the two epidemics in western countries, that appear to be a "syndemic"[(3)]. Despite therapeutic advances demonstrating improved microvascular outcomes, cardiovascular deaths remain the leading cause of mortality in diabetic patients [(4)]. Intensive glucose control failed to reduce cardiovascular (CV) outcomes after a few years in previous clinical trials, despite improvement in microvascular complications. Excess risk among participants in the intensively treated group in the ACCORD population occurred above HbA1c 7% [(5,6)]. Current recommendations suggest metformin together with lifestyle management as the first-line approach for patients with T2D despite the lack of large clinical trials data on metformin. In the UKPDS study, metformin use [(7)] was associated with risk reductions for any diabetes-related endpoint, diabetes-related death and all-cause mortality in overweight patients. However the number of patients allocated to metformin was less than 10% of the randomized population (n=342) and early addition of metformin in sulphonylurea-treated patients was associated with an increased risk of diabetes-related death [(7)]. Furthermore, as the study was performed in the 1990´s the use of other drugs that can reduce cardiovascular risk, such as statins or inhibitors of the renin-angiotensin aldosterone system, was limited. The highly relevant field of CV disease prevention in patients with T2D has recently been enriched from placebo-controlled studies showing that both sodium-glucose cotransporter 2 (SGLT-2) inhibitors [(8-10)] and the glucagon-like peptide 1 (GLP-1) receptor agonists provided significant risk reductions of major cardiovascular events. [(11,12)] Clinical testing of these new agents and investigations into the mechanisms underlying their protective CV and renal properties triggered a major knowledge shift in the field and unraveled factors relevant to CV risk reduction in T2D beyond glycaemic control. As a consequence it has become apparent that CV disease specialists ought to play a key role in the clinical care of these patients because morbidity and mortality in T2D associated with macrovascular events.

Cardiovascular events reduction

I. Inhibitors of sodium–glucose cotransporter-2

SGLT-2 is a sodium-glucose cotransporter in the proximal tubule of the nephron responsible for the urinary glucose reabsorption. Inhibition of SGLT-2 results in glucosuria, thereby reducing blood glucose. The effects of empagliflozin in addition to standard care on cardiovascular morbidity and mortality in patients with T2D and established cardiovascular disease were studied in the EMPA-REG trial [(8)]. Patients received 10 mg or 25 mg of empagliflozin or placebo once daily. The primary composite outcome was the 3-point major adverse cardiac events (MACE)-death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Hazard ratio for the primary endpoint in the empagliflozin group (0.86; 95%CI: 0.74 to 0.99) was superior to placebo. In the empagliflozin group there was 38% relative risk reduction of death from cardiovascular causes, 35% relative risk reduction for hospitalization for heart failure and 32% relative risk reduction for death from any cause[(8)]. In patients with T2D at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events compared to placebo, when added to standard care [(13)], (Table 1).

In the CANVAS Program, participants with T2D and a history of symptomatic atherosclerotic cardiovascular disease (65.6%) or patients 50 years of age or older with high cardiovascular risk were randomly assigned to receive canagliflozin (100 or 300mg) or placebo [(9)]. The hazard ratio in the canagliflozin group for the 3-point MACE (0.86; 95%CI: 0.75 to 0.97) was superior to placebo. Renal outcomes were not statistically significant different between groups and adverse reactions were consistent with the previously reported risks associated with canagliflozin except for an increased risk of amputation [(9)], (Table 1).

In the recently published DECLARE–TIMI 58 trial [(10)] participants with T2D who had history of symptomatic atherosclerotic cardiovascular disease (40.6%), or men older than 55 and women older than 60 years of age with one or more traditional cardiovascular risk factors and creatinine clearance at screening higher than 60 ml per minute (93%), received either 10 mg of dapagliflozin or placebo. Dapagliflozin did not result in a lower rate of the 3-points MACE, but resulted in a lower rate of hospitalization for heart failure (hazard ratio, 95%CI: 0.73; 0.61 to 0.88) and a lower rate of renal events compared to the placebo group (0.76; 95%CI: 0.67 to 0.87) [(10)], (Table 1).

From these three large RCTs it is evident that SGLT-2 inhibition in general confers clinical benefit not only with regards to improved glycaemic control, but importantly in reducing risk for CV and renal events, and especially so in patients at very high cardiovascular risk. While a number of open questions remain to be addressed, SGLT-2 inhibitors are already being used a one of the first line drugs for glucose lowering, particularly in T2D patients with increased CV risk.

Summary of published SGLT-2 Inhibitor and GLP-1 analogue randomized outcomes trials with reduction in cardiovascular and renal endpoints					
Study	SGLT-2 Inhibitors			GLP-1 analogues	
	EMPA-REG (empagliflozin)	CANVAS (Canagliflozin)	DECLARE–TIMI 58 (Dapagliflozin)	LEADER (liraglutide)	SUSTAIN-6 (semaglutide 0.5 or 1.0 mg)
Patients enrolled	n=7,020	n=10,142	n= 17 160	n=9,340	n=3,297
Median duration of follow-up (years)	3.1	2.4	4.2	3.8	2.1
Weight reduction (kg)	~ 2	1.60 (1.70–1.51)	1.8 (1.7 -2.0)	2.3 (2.5 - 2.0)	2.87 (3.47–2.28 and 4.35 (4.94–3.75)
Baseline statin use (%)	77	75	75	72	73
Baseline prevalence of CV (%)Disease	100	65.6	40.6	81	72
Heart Failure (%)	11	14	10	18	24
Primary outcome (HR, 95% CI)	0.86 (0.74–0.99)	0.86 (0.75–0.97)	0.93 (0.84–1.03)	0.87 (0.78–0.97)	0.74 (0.58–0.95)
CV death (HR, 95% CI)	0.62 (0.49–0.77)	0.87 (0.72–1.06)	0.98 (0.82 -1.17)	0.78 (0.66–0.93)	0.98 (0.65–1.48)
Fatal or non-fatal MI (HR, 95% CI)	0.87 (0.70–1.09)	0.89 (0.73–1.09)	0.89 (0.77–1.01)	0.86 (0.73–1.00)	0.74 (0.51–1.08)

II. Glucagon-like peptide-1 receptor agonists

The cardiovascular effect of liraglutide, a GLP-1 analogue was studied in the LEADER Trial where T2D patients were assigned to receive liraglutide or placebo on top of their standard care treatment. Hazard ratio for the 3-point MACE in the liraglutide group was superior to placebo (0.87; 95%CI: 0.78 to 0.97). Liraglutide was associated with less all-cause and cardiovascular deaths, with no differences in nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure, but a lower rate of renal events (Table 1).

A second GLP-1 analogue with an extended half-life of approximately 1 week (semaglutide) was tested in the SUSTAIN-6 trial in T2D patients. Patients were assigned to receive semaglutide weekly or placebo on top of their standard care [12]. Hazard ratio for the 3-point MACE in the semaglutide group was superior to placebo (0.74; 95%CI: 0.58 to 0.95). Nonfatal myocardial infarction, nonfatal stroke and cardiovascular deaths were similar in the two groups. Rates of nephropathy were lower, but retinopathy complications were significantly higher in the semaglutide group. (Table 1).

Trials on cardiovascular outcomes in high-risk patients with type 2 diabetes with basal insulin-glargine [14], DPP-4 inhibitors [15-17] and thiazolidinediones [18], despite their beneficial effects on glycemic control, this did not translate into benefits for cardiovascular events or death. Pioglitazone reduced 3-points MACE, but increase heart failure complications [19].

Body weight and blood pressure reduction

A primary focus of T2D management is the prevention of additional weight gain and weight loss where possible. Awareness of the common effects of pharmacologic therapy on body weight, when selecting preferred treatment options for T2D patients who are usually obese, appears critical for the optimal management [20]. Unfortunately many of T2D treatments can induce undesirable weight gain, which could neutralize other possible cardiovascular benefits. Most of the traditional anti-diabetic drugs such as sulfonylureas (glyburide, glipizide, or glimepiride after the first year of treatment), glinides, thiazolidinediones (pioglitazone, rosiglitazone) and insulin (NPH, glargine, detemir, aspart, lispro) promote weight gain through various mechanisms [21]. Glucose-lowering agents, which are weight neutral (metformin, DPP-IV-inhibitors) or support weight loss (SGLT2-inhibitors and GLP1-analogs), should be the first choice for treatment of obese T2D patients [1,22]. In patients with T2D and hypertension, empagliflozin, canagliflozin and dapagliflozin reduced body weight and office SBP by 1 to 4 mm Hg versus placebo, irrespective of the use of other antihypertensive drugs [8-10]. Liraglutide and semaglutide also resulted in weight loss and lower SBP [11,12]. Preference for these drug classes in the context of T2D-associated hypertension should be considered.

Perspectives

CV disease is the leading cause of mortality in patients with diabetes. Recent studies in large cohorts of patients with T2D went beyond glucose control to CV risk reduction. CV specialists are playing a key role in the secondary prevention of CV disease in patients with T2D. Both SGLT-2 inhibitors and GLP-1 analogs promote weight loss and reduce SBP which are likely mechanisms to reduce total CV risk in obese T2D patients beyond glycaemic control. Thus, these agents may be useful in the glycemic control of T2D obese patients with uncontrolled or resistant hypertension, but further focused clinical trials are needed. Current evidence suggest that SGLT2 inhibitors [23] and GLP-1 analogs have positive results in the cardiovascular risk prevention, reducing hard end points in the secondary prevention trials, and have been associated with prevention of heart failure and renal disease in the primary prevention studies.

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