HOSPITAL CHRONICLES 2020, 15(1): 31–32

DIABETES CORNER

Diabetes News / Recent Literature Review / Forth Quarter 2019

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Association of Metabolic Surgery With Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes and Obesity

In this observational retrospective study, 2287 patients with obesity (BMI ≥30) and type 2 diabetes who underwent metabolic surgery within the Cleveland Clinic Health System, were matched 1:5 to nonsurgical patients with diabetes and obesity.

The primary end point was the incident of extended major adverse cardiovascular events (MACE, composite of 6 outcomes), defined a first all-cause mortality, coronary artery events, cerebrovascular events, heart failure, nephropathy and atrial fibrillation. Secondary outcome included 3-component MACE (myocardial infarction, ischemic stroke and mortality). The median follow-up duration was 3.9 years. At the end of the study period, 385 (30.8%) patients in the surgical group and 3243 (44.7%) patients in the nonsurgical group experienced a primary end point (hazard ratio, HR 0.61, 95% CI, 0.55 – 0.69). All secondary putcomes showed significantly differences in favor of metabolic surgery. All-cause mortality occurred in 112 patients in the metabolic surgery group and 1111 patients in the nonsurgical group (HR = 0.59, 95%CI, 0.48-0.72). Metabolic surgery was also associated with a significant reduction of HbA1c (mean difference between groups 1.1%), and use of noninsulin diabetes medication, insulin antihypertensive medications and lipid lower therapies. In the 90 days after metabolic surgery, complications included bleeding requiring transfusion (n=68, 3.0%), pulmonary adverse events (n=58, 2.5%), venous thromboembolism (n=4, 0.2%), cardiac events (n=17, 0.7%), and renal failure requiring dialysis (n=4, 0.2%) (Aminlan A et al, *JAMA* 2019;322:1271-1282).

Comparative efficacy, safety, and cardiovascular outcomes with once-weekly subcutaneous semaglutide in the treatment of type 2 diabetes: Insights from the SUSTAIN 1–7 trials

Semaglutide has 94% amino acid sequence homology with native GLP-1 and is currently approved by the FDA and EMA for the treatment of type 2 diabetes.

The SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes) clinical trial program included 7 randomised control trials involving more than 8000 patients with type 2 diabetes. Comparators were placebo (SUSTAIN 1,5 and 6), sitagliptin (SUSTAIN 2), exenatide extended release (SUSTAIN 3), insulin glargine (SUSTAIN 4), and dulaglutide (SUSTAIN 7). Primary end points for SUSTAIN 1-5 and 7 were changes to HbA1c from baseline to the end of treatment. In SUSTAIN 6, which included patients at high risk of CV disease, primary end point was time to first occurrence of major adverse CV event (3-point MACE) compared to placebo as add-on therapy. Across SUSTAIN 1-5 and 7, mean HbA1c decreased by 1.2-1.5% vs 0.1-0.4% with placebo and 0.5-1.4% with sitagliptin, exenatide and insulin glargine. Across the SUSTAIN trials, semaglutide consistently demonstrated significantly greater body weight reduction vs. all comparators. In SUSTAIN 6, the primary outcome of CV death and non-fatal or strolled occurred in 108 pf 1648 patients in the semaglutide group vs. 146 of 1659 patients in the placebo group (HR 0.74, CI=0.58-0.95; p<0.001 for non-inferiority).

Overall, semaglutide demonstrated greater glycaemic efficacy combined with greater weight than comparator therapy. The safety profile was similar to other GLP-1RAs. In the SUSTAIN 6, semaglutide lowered the risk of adverse CV outcomes compared to placebo. (Aroda VR et al. *Diabetes Metabolis*m, 2019;45:409-418).

Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial

In this randomized, open-label 52-week trial, patients with type 2 diabetes uncontrolled on metformin were randomized 1:1 to once daily oral semaglutide 14 mg (n=412) or empagliflozin 25 mg (n=410) for 52 weeks with a further 5 weeks follow-up. The primary end point was change in HbA1c from baseline to week 52. The confirmatory secondary end point was change in body weight (kg) from baseline to week 52.

Oral semaglutide provided superior reduction in HbA1c vs. empagliflozin (-1.4% vs. -0.9%, p <0.0001). More patients achieved the predefined HbA1c targets of HbA1c <7% with oral semaglutide compared to empagliflozin without severe or symptomatic hypoglycemia. Fasting plasma glucose was equally reduced in both groups. At the end of the trial, a significantly greater reduction in body weight was achieved with oral semaglutide (-44.7 kg vs, -3.8 kg, p=0.0114). The overall number of adverse events were similar, and most events were mild to moderate (Rodbard H et al, *Diabetes Care* 2019;42:2272-2281).

Efficacy, Safety, and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients With Type 2 Diabetes: The PIONEER 8 Trial

Patients with type 2 diabetes uncontrolled on insulin (basal, basal-bolus, or premixed) with or without metformin were randomized to oral semaglutide 3 mg (n=148) 7 mg (n=182), or 14 mg (n=181) or to placebo (n=184) in a 52-week double-blind trial.

The primary end point was change in HbA1c and confirmatory end point was change in body weight, from baseline to week 52.

Compared to placebo, HbA1c reductions were superior for all doses or oral semaglutide, with estimated difference of –0.5% (p <0.0001). The observed proportions of patients achieving HbA1c <7% and ≤6.5% were greater with semaglutide, without hypoglycemia. Changes from baseline in FPG and 7-point SMBG means were statistically greater with oral semaglutide than placebo. The body weight reductions were superior for all doses of oral semaglutide (-0.9 kg, - 2.0 kg, -3.3 kg for the 3-, 47-, and 14-mg doses, respectively). Gastrointestinal disorders occurred most frequently in the oral semaglutide group (Zinman B et al, *Diabetes Care* 219;42:2262-2271).

SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: a systematic review and meta-analysis

In this systematic review and meta-analysis of randomised, controlled, cardiovascular or kidney outcome trials of SGLT2 inhibitors (SGLT2i), the effects of this class medication on major kidney outcomes in people with type 2 diabetes was assessed. From 2085 records, four studies met the inclusion criteria, assessing three SGLT2 inhibitors: empagliflozin (EMPA-REG OUTCOME), canagliflozin (CANVAS Program and CREDENCE), and dapagliflozin (DECLARE-TIMI 58).

From a total of 38723 participants, 252 required dialysis or transplantation or died of kidney disease, 335 developed end-sage kidney disease, and 943 had acute kidney injury, SGLT2 inhibitors substantially reduced the risk of dialysis, transplantation, or death due to kidney disease (RR=0.67, 95% CI 0.52-0.86, p=0.0019). SGLT2i also reduced end-stage kidney disease (RR=0.65, p <0.0001), and acute kidney injury (RR=0.75, p <0.0001). These benefits were present across all eGFR subgroups, including for participants with a baseline eGFR=30-45 mL/min per 1.72 m² (Neuen B et al, *Lancet Diabetes Endocrinol* 2019;7:845-854).

Efficacy and safety of once-weekly semaglutide versus daily canagliflozin as add-on to metformin in patients with type 2 diabetes (SUSTAIN 8): a double-blind, phase 3b, randomised controlled trial

In this double-blind randomised controlled trial, patients with uncontrolled type diabetes (hbA1c= 7-10.5%) on stable daily metformin therapy, were assigned (1:1) to subcutaneous semaglutide 1.0 mg once weekly (n=394) or oral canagliflozin 300 mg once daily (n=394). The primary endpoint was change in HbA1c from baseline to week 52, and the confirmatory secondary endpoint was change in body weight.

Patients receiving semaglutide had significantly greater reductions in HbA1c (-0.49%, p<0.0001) and in body weight (-1.06 kg, p=0.0029). Gastrointestinal disorders, mainly nausea, were the most frequent adverse events with semaglutide, occurring in 47% of the semaglutide group; whereas infections, mainly urinary tract, occurred more often with canagliflozin (35% of the treated patients). Premature discontinuation due to adverse events was 10% (n=38) in the semaglutide and 5% (n=20) in the canagliflozin group (Lingvay I et al, *Lancet Diabetes Endocrinol* 2019;7:834-844).

Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

The meta-analysis summarizes the available evidence of the cardiovascular trials of GLP-1 receptor agonists, despite the differences in structure and duaration of acrions.

Of the 27 publications, seven trials with a total of 56004 participants were examined: ELIXA (lixisenatide), LEADER (liraglutide), SUSTAIN-6 (semaglutide), EXSCEL (exenatide), HARMONY (ablbiglutide), REWIND (dulaglutide), and PIONEER 6 (oral semaglutide). These trials were characterized by a wide variability in the inclusion criteria and the median follow-up period. The proportion of patients with established cardiovascular disease at baseline ranged from 100% in ELIXA and HARMONY to 31% in REWIND. Kidney function was similar across trials with median eGFR ranging from 75-80 mL/min per m². The estimated median follow-up was 3.2 years (1.3 in PIONEER to 5.4 in REWIND).

Overall, GLP-1RA significantly reduced MACE by 12% (HR=0.85, 95% CI 0.82- 0.94, p<0.001) with no statistically significant heterogeneity across the subgroups examined. HRs were 0.88 (95% CI 0.81-0.96, p=0.003) for death from cardiovascular causes, 0.84 (0.76-0.93, p<0.001) for fatal or non-fatal stroke and 0.91(0.84-1.00, p=0.0443) for fatal or non-fatal myocardial infarction. All-cause mortality was reduced by 12 % (p=0.001), hospitalization for heart failure by 9% (p=0.028) and kidney-related outcome by 17% (p<0.001), mainly due to the reduction of urinary albumin excretion. No increase in risk of severer hypoglycemia, pancreatic adverse effects or thyroid cancer was observed.

Overall, GLP-1 receptor agonists were characterized as cardioprotective drugs (Kristemsen S et al, *Lancet Diabetes Endocrinol* 2019;7:776-785).