

<b>DIABETES CORNER</b>
------------------------

**Diabetes News / Recent Literature Review / First Quarter 2018***Pinelopi Grigoropoulou, MD, PhD**Department of Internal Medicine and Diabetes Outpatient Department, General Hospital of Athens “ELPIS”***Metformin Treatment in Patients with Type 2 Diabetes and Chronic Kidney Disease Stages 3A, 3B, or 4**

The safety of metformin was examined in moderate and severe chronic kidney disease (CKD) (stages 3A/3B and 4, eGFR 59-45, 44-30, and <15 mL/min/1.72 m<sup>2</sup>, respectively). Three metformin doses were examined: 1,500mg (0.5g in the morning [qam]+ 1g in the evening [qpm]) in CKD3A, 1,000 mg (0.5g qam + 0.5g qpm) in CKD3B, and 500 mg (qam) in CKD 4. After 4 months on these regimens, patients displayed stable metformin concentrations that never exceeded the safe upper limit of 5.0 mg/L. Hyperlactatemia was absent, and HbA1c levels did not change. The study provided solid basis for the continuing metformin treatment in patients with moderate or severe CKD, supporting the recent guidelines on metformin treatment, providing that the dose is adjusted to the eGFR (Lalau JD et al, *Diabetes Care* 2018;43:547-553).

**How Does Empagliflozin Reduce Cardiovascular Mortality? Insights From a Mediation Analysis of the EMPA-REG OUTCOME Trial**

Empagliflozin was the first glucose-lowering agent to demonstrate a reduction in cardiovascular (CV) death in patients with type 2 diabetes and high CV risk. In the EMPA-REG OUTCOME trial, over a median observation time of 3.1 years, treatment with empagliflozin vs placebo in addition to standard care led to 14% reduction in the risk of CV death, nonfatal myocardial infarction, and nonfatal death. A small increase of hematocrit (and hemoglobin) appeared to be the variable with the largest impact on the reduction of CV death. Variables related to glycemia had smaller mediating effects. Changes on some traditional CV risk factors, including obesity, blood pressure, lipids, and renal function, made negligible contributions (Inzucchi S et al, *Diabetes Care* 2018;41:356-363).

**Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomised Clinical Trial**

In this phase 3a, open-label, parallel-group, randomized

controlled trial, 813 subjects with type 2 diabetes taking oral antidiabetic drugs were randomized (1:1) to semaglutide 1.0 mg or exenatide ER 2.0 mg for 56 weeks. Mean HbA1c was reduced by 1.5% with semaglutide vs 0.9% with exenatide ER (P<0.0001). Mean body weight was reduced by 5.6 kg with semaglutide vs 1.9 kg with exenatide ER (P<0.0001). Significantly more patients taking semaglutide achieved the goal of HbA1c <7.0%. Both treatments had similar safety profiles, yet gastrointestinal adverse effects were more common in semaglutide-treated participants (Ahmann A et al, *Diabetes Care* 2018;41:258-266).

**Standards of Medical Care in Diabetes - 2018**

The new 2018 recommendations include advances in cardiovascular disease risk management. Based upon the results of multiple cardiovascular outcome trials, it is recommended that in people with heart disease, after lifestyle management and metformin, a medication validated to improve heart health, such as liraglutide and/or empagliflozin should be included. Most adults with diabetes and hypertension should have a target blood pressure of <140/90 mmHg. Lower targets, such as 130/80, may be appropriate for some high-risk patients. Testing for prediabetes and type 2 diabetes should be considered in children and adolescents younger than 18 years who are overweight or obese and have one or more additional risk factors for diabetes. Health care providers need to be aware of the limitations regarding HbA1c test use and consider alternate diagnostic tests (fasting plasma glucose or oral glucose tolerance test) if there is a disagreement between A1c and blood glucose levels (*Diabetes Care* 2018;41 Suppl 1).

**Efficacy and safety of sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors as monotherapy or add-on to metformin in patients with type 2 diabetes mellitus: A systemic review and meta-analysis**

In this meta-analysis of randomized controlled trials, the efficacy and safety of dipeptidyl peptidase-4 inhibitors (DPP-4is) and sodium-glucose cotransporter-2 inhibitors (SGLT-2is) as

monotherapy or add-on to metformin were assessed in patients with type 2 diabetes. Combination therapy with metformin and DPP-4is led to a statistically significant decrease of HbA1c by -0.55% compared to metformin monotherapy. Similar results were seen with the SGLT-2is combination with metformin; combination therapy reduced HbA1c levels by 0.55%. Dual therapy with metformin and SGLT-2 also offers increased body weight loss by 1.82 kg ( $p < 0.0000$ .) as compared to metformin alone. More important, SGLT-2is were associated with a significantly stronger reduction in HbA1c and fasting plasma glucose than were DPP-4is. There was no difference in the risk for hypoglycemic events (Wang Z et al, *Diabetes Obes Metab* 2018;20:113-120).

#### **Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988-2014**

Using data from US National Health and Nutrition Examination Surveys (NHANES) between 1988 and 2014, the researchers examined the cardiovascular and renal burdens in adults with prediabetes over time and compared patterns with other glycemic status groups. This study analyzed data for 27,971 adults (over 19 years of age), excluding pregnancy. Individuals diagnosed with diabetes were more likely to receive blood pressure-lowering and cholesterol-lowering therapy compared with individuals with prediabetes. Adults diagnosed with prediabetes showed significantly higher renal and cardiovascular disease risk (Ali MK et al, *Lancet Diabetes Endocrinol.* 2018 May;6:392-403)

#### **Risk of Cardiovascular Disease and Death in Individuals with Prediabetes Defined by Different Criteria: The Whitehall II Study**

In this Whitehall II cohort study, 5,427 participants between the ages of 50-79 years with prediabetes were enrolled

and followed for mean of 11.5 years. The study compared the risk of fatal or nonfatal CVD or all-cause mortality in individuals with prediabetes identified by FPG, 2hPG or HbA1c. Prediabetes can be defined using HbA1c, fasting plasma glucose (FPG) or 2-hr plasma glucose (2hPG). According to World Health Organization (WHO) / International Expert Committee (IEC), prediabetes is defined as FPG 6.1–6.9 mmol/L and/or HbA1c 6.0–6.4%. According to the American Diabetes Association (ADA), prediabetes is defined as FPG 5.6–6.9 mmol/L and/or HbA1c 5.7–6.4%. Prediabetes defined by using the ADA criteria displayed lower risk of developing CVD or mortality than when prediabetes is defined using WHO/IEC criteria. HbA1c was more accurate in predicting CVD and mortality risk in individuals with prediabetes than FPG or 2hPG concentration (Vistisen D et al, *Diabetes Care* 2018;41:899-909).

#### **Dipeptidyl peptidase-4 inhibitors and incidence of inflammatory bowel disease among patients with type 2 diabetes: population based cohort study**

This cohort study assessed whether the use of dipeptidyl peptidase-4 inhibitors is related to the incidence of inflammatory bowel disease in patients with type 2 diabetes. Prolonged use of DPP-4 inhibitors in patients with type 2 diabetes is associated with an overall 75% increase in the risk of inflammatory bowel disease, more than a twofold increase in the risk of ulcerative colitis and no difference in the risk for Crohn's disease. Although the absolute risk is low, physicians should be aware of this possible association and perhaps refrain from prescribing dipeptidyl peptidase-4 inhibitors for people at high risk (that is, those with a family history of disease or with known autoimmune conditions). Moreover, patients presenting with persistent gastrointestinal symptoms, such as abdominal pain or diarrhea, should be closely monitored for worsening of symptoms (Abrahami DA et al, *BMJ* 2018;360;k872).