Diabetes Research Review™

Making Education Easy

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In this issue:

Abbreviations used in this issue:

BMI = body mass index; **CV** = cardiovascular; **DPP** = dipeptidyl peptidase; **GFR** = glomerular filtration rate; **GI** = gastrointestinal; **GLP** = glucagon-like peptide; **HbA_{1c}** = glycosylated haemoglobin; **HR** = hazard ratio; **OR** = odds ratio; **RCT** = randomised controlled trial; **RYGB** = Roux-en-Y gastric bypass; **SGLT** = sodium glucose cotransporter; **T2DM** = type 2 diabetes mellitus.

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Welcome to issue 114 of Diabetes Research Review.

This issue begins with long-term follow-up data from the VADT trial of intensive versus standard glucose-lowering therapy in patients with longstanding, poorly controlled T2DM (type 2 diabetes mellitus). We have also included the findings of the PIONEER 5 and 7 trials investigating oral semaglutide in T2DM; PIONEER 5 focused on patients with renal impairment, while PIONEER 7 looked at flexible dosing. Swedish researchers have reported that developing T2DM in midlife appears to increase the risk of developing cerebral infarction and cerebral artery occlusion but not intracerebral or subarachnoid haemorrhage later in life. The issue concludes with research suggesting no benefit on liver fat or metabolism by adding high doses of eplerenone to the background antidiabetic and antihypertensive therapy of patients with T2DM.

We always appreciate your input, so please send us any comments and feedback you have.

Kind Regards,

Dr Mathis Grossmann

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Intensive glucose control in patients with type 2 diabetes

Authors: Reaven PD et al., for the VADT Investigators

Summary: The full 15-year observational follow-up of a study of intensive versus standard glucose lowering in US military veterans with T2DM was reported; 1655 participants comprised the complete cohort with 1391 completing surveys. The separation of the HbA_{1c} level curves between the intensive- and the standard-therapy groups averaged 1.5 percentage points during the trial, but this had decreased to 0.2–0.3 percentage points 3 years after trial completion, and there was no significant difference between the two groups over 15 years of follow-up for the major CV event endpoint (HR 0.91 [95% CI 0.78–1.06]) or for death from any cause (1.02 [0.88–1.18]). While there was a reduced risk of major CV disease outcomes during an extended interval of separation of the HbA_{1c} level curves (HR 0.83 [95% CI 0.70–0.99]), this did not persist after HbA_{1c} levels equalised (1.26 [0.90–1.75]).

Comment: The original VADT RCT compared standard with intensive glucose lowering therapy in 1791 military veterans (baseline mean age 60 years, mostly men) with longstanding (11.5 years duration), poorly controlled T2DM (baseline HbA_{1c} level 9.4%). After 5.6 years, intensive glycaemic control (achieving an HbA_{1c} level of 6.9%) did not reduce CV events or mortality compared with standard therapy (achieving an HbA_{1c} level of 8.4%). A subsequent analysis after 10 years of follow-up, however, showed a lower incidence of CV events in the intensive therapy group. Because a 0.3% difference in HbA_{1c} level between groups persisted, a legacy effect could not be inferred. In this current 15-year follow-up, once the difference in HbA_{1c} level was no longer apparent, there was no continued CV benefit, arguing against a legacy effect. Likewise, there was no legacy effect in the similar studies ACCORD and ADVANCE. This is in contrast to older studies (UKPDS and DCCT), suggesting that in the current area of comprehensive risk factor control, older patients with advanced diabetes should not expect a CV legacy benefit. The findings emphasise the importance of smoking cessation, blood pressure control, antiplatelet and statin therapy, and consideration of newer agents (SLGT-2 inhibitors and GLP-1 receptor agonists) that may improve CV outcomes independent of glycaemic control.

Reference: N Engl J Med 2019;380:2215–24
Abstract

Effects of dapagliflozin on development and progression of kidney disease in patients with type 2 diabetes

Authors: Mosenzon O et al.

Summary: Patients with T2DM, established atherosclerotic CV disease or multiple risk factors, and creatinine clearance ≥60 mL/min were randomised to receive dapagliflozin 10mg or placebo once daily in the DECLARE-TIMI 58 trial. The trial included 8162, 7732 and 1265 participants with baseline estimated GFR values of ≥90, 60–90 and <60 mL/min/1.73m^2, respectively, of whom 6974 had established atherosclerotic CV disease and 10,186 had multiple risk factors. It was previously reported that compared with placebo, dapagliflozin was associated with significant reductions in the secondary cardiorenal and renal-specific composite outcomes. This analysis found that compared with placebo, dapagliflozin was associated with: i) a reduced risk of end-stage renal disease or renal death (HR 0.41 [95% CI 0.20–0.82]); ii) improvements in both the cardiorenal and renal-specific composite outcomes across prespecified subgroups, including those defined by baseline estimated GFR and the presence or absence of established atherosclerotic CV disease; and iii) a greater mean decrease in estimated GFR at 6 months postrandomisation.

Comment: This is a secondary analysis of the DECLARE CV outcome trial. Dapagliflozin demonstrated relatively robust effects on clinically important renal outcomes, including end-stage renal disease and renal death, in a large, diverse cohort of patients with T2DM with and without CV disease, most of whom had normal or only mildly reduced renal function at baseline. Together with other recent trials, such as EMPA-REG, CANVAS and CREDENCE, which showed renal efficacy for canagliflozin in patients with established chronic kidney disease, the results of these trials demonstrate that SLGT-2 inhibitors improve CV and renal outcomes across a wide range of patients with T2DM. In DECLARE-TIMI 58, renal benefits were independent of concurrent use of renin angiotensin blockade, probably because while renin angiotensin blockade leads to vasodilation of the efferent arteriole, SGLT-2 inhibitors reduce intraglomerular pressure by vasoconstriction of the afferent arteriole. This haemodynamic effect likely explains why the early estimated GFR decline (after 6 months) was greater in the dapagliflozin group compared with placebo, equalised at 2 years, and was less from the third year of the RCT onwards. While DECLARE-TIMI 58 had a relatively long duration, data on long-term outcomes of these agents are not yet available, including potential risks, such as diabetic ketoacidosis, fractures and lower-limb amputations. Moreover, other important questions, such as the lower limit of estimated GFR for initiating these agents (cardiorenal benefits may occur despite blunted glycaemic efficacy), their potential synergy with other new agents, such as GLP-1 receptor agonists, and their utility in nondiabetic kidney disease remain to be addressed. Overall, these results support a role for SGLT-2 inhibitors in both prevention and treatment of chronic kidney disease due to T2DM.

Reference: Lancet Diabetes Endocrinol; Published online June 10, 2019
Abstract

Independent commentary by Dr Mathis Grossmann, MD, PhD, FRACP, who is a physician-scientist trained in both basic biology and in clinical endocrinology/diabetes. He is Professor of Medicine at the Department of Medicine, University of Melbourne, Austin Health, Australia, and a Consultant Endocrinologist at Austin Health. His research focuses on the regulation of cardiometabolic and musculoskeletal health by androgens and oestrogens, at both the clinical and the molecular levels.

Efficacy and safety of oral semaglutide in patients with type 2 diabetes and moderate renal impairment (PIONEER 5)

Authors: Mosenzon O et al., for the PIONEER 5 Investigators

Summary: The double-blind, phase 3a PIONEER 5 trial randomised adults with T2DM and an estimated GFR of 30–59 mL/min/1.73m^2 on stable doses of metformin and/or a sulfonylurea or basal insulin with or without metformin for ≥90 days to receive oral semaglutide escalated to 14mg once daily (n=163) or placebo (n=161) for 26 weeks added to their background medication; the respective treatment completion rates for the two trial arms were 82% and 88%. Compared with placebo, oral semaglutide was associated with greater decreases in mean HbA_{1c} level at 26 weeks for two efficacy-related estimands, namely without consideration of treatment discontinuation or use of rescue medication and on treatment without use of rescue medication (–11 vs. –2 mmol/mol [–1.0% vs. –0.2%; p<0.0001] and –12 vs. –1 mmol/mol [–1.1% vs. –0.1%; p<0.0001]), respectively and bodyweight (–3.4 vs. –0.9kg and –3.7 vs. –1.1kg [p<0.0001 for both]). The respective adverse event rates in the semaglutide and sitagliptin arms were 74% and 65%, leading to discontinuation in 15% and 5%; GI events were more frequent in the semaglutide arm.

Reference: Lancet Diabetes Endocrinol 2019;7:515–27
Abstract

Efficacy and safety of oral semaglutide with flexible dose adjustment versus sitagliptin in type 2 diabetes (PIONEER 7)

Authors: Pieber TR et al., for the PIONEER 7 investigators

Summary: The open-label phase 3a PIONEER 7 trial randomised adults with T2DM inadequately controlled on stable daily doses of 1–2 oral glucose-lowering drugs to receive oral semaglutide 3mg, 7mg or 14mg (n=253) or sitagliptin 100mg (n=251) once daily. Compared with sitagliptin, a greater proportion of semaglutide recipients achieved an HbA_{1c} level of <53 mmol/mol (<7%, primary endpoint) for the respective treatment estimands described in the previous (PIONEER 5) summary (58% vs. 25%; OR 4.40 [95% CI 2.89–6.70] and 63% vs. 28%; 5.54 [3.54–8.86]); semaglutide recipients also had a significantly greater decrease in mean bodyweight (treatment differences, –1.9kg and –2.9kg for the respective estimands [p<0.0001 for both]). The respective adverse event rates in the semaglutide and sitagliptin arms were 78% and 69%, with nausea affecting 21% of semaglutide recipients; there were two deaths in the sitagliptin arm.

Reference: Lancet Diabetes Endocrinol 2019;7:528–39
Abstract

Comment: PIONEER 5 and 7 are the latest in a series of clinical trials examining the effects of the first orally formulated GLP-1 receptor agonist semaglutide in patients with T2DM. PIONEER 1, 2 and 3 demonstrated glycaemic benefits compared with placebo, SGLT-2 inhibitor and DPP-4 inhibitor therapy, respectively, and PIONEER 4 reported noninferiority to the injectable GLP-1 receptor agonist liraglutide. PIONEER 6 showed that the CV risk profile of oral semaglutide was not inferior to that of placebo, but failed to demonstrate CV benefits previously reported with subcutaneous semaglutide (SUSTAIN-6), perhaps due to the lack of power because of a lower event rate in PIONEER 6 compared with SUSTAIN-6. The current PIONEER 5 study compared oral semaglutide with placebo in patients with chronic kidney disease (estimated GFR 30–59 mL/min/1.73m^2) and found a significant decrease in HbA_{1c} level, systolic blood pressure and bodyweight, and an overall low risk of hypoglycaemia. While renal protection has been reported in trials using injectable GLP-1 receptor agonists, the 26-week PIONEER 5 trial was likely too short to provide an answer on renal outcomes. Similar to other PIONEER RCTs, the most prominent adverse effects were GI (nausea, vomiting and diarrhoea), leading to discontinuation of treatment in 15% of the participants assigned to oral semaglutide compared with 5% in the placebo group.

Given the prominent GI intolerance, PIONEER 7 tested, in comparison with oral sitagliptin, whether an individualised flexible dosing schedule reduces the risk of premature oral semaglutide discontinuation and enables more patients to achieve their optimal dose. Similar to the findings reported in PIONEER 3, oral semaglutide achieved a greater reduction in HbA_{1c} level and bodyweight compared with DPP-4 inhibitor therapy. However, GI side effects and drug discontinuations occurred at comparable rates in PIONEER 7 and 3, suggesting that the flexible dosing approach did not achieve the goal of individually optimised dosing, nor reduced premature discontinuation. Most patients experienced adverse effects and discontinued oral semaglutide in the first 8 weeks while taking 3mg daily, suggesting an even lower starting dose might be necessary. Overall oral semaglutide, if approved, may be a useful future agent in patients who can tolerate it and wish to avoid injections. However, in contrast to the benefits reported for injectable GLP-1 receptor agonists or SLGT-2 inhibitors, CV and renal benefits for oral semaglutide have not yet been demonstrated.

Durability of insulin degludec plus liraglutide versus insulin glargine U100 as initial injectable therapy in type 2 diabetes (DUAL VIII)

Authors: Aroda VR et al.

Summary: Insulin-naive adults with T2DM (HbA_{1c} level 53–97 mmol/mol [7.0–11.0%]) and a BMI of ≥20 kg/m^2 on stable doses of oral antidiabetic drugs were randomised to receive subcutaneous insulin degludec 100 U/mL plus liraglutide 3.6 mg/mL (prefilled PDS290 pens; n=506) or insulin glargine 100 U/mL (prefilled Solostar pens; n=506) once daily added to existing therapy in this 104-week phase 3b trial; the respective trial completion rates were 96% and 95%. Compared with insulin glargine recipients, insulin degludec plus liraglutide recipients had a significantly longer median time until treatment intensification (>2 vs. ~1 year), with a significantly smaller proportion needing treatment intensification over 104 weeks (37% vs. 66%). There were no new or unexpected safety and tolerability concerns and there were no treatment-related deaths.

Comment: DUAL VIII randomised middle-aged (mean age 57 years) obese (BMI 32 kg/m^2) patients (46% female) with a mean duration of T2DM of 10 years and poor glycaemic control (baseline HbA_{1c} level 8.5%), despite multiple oral agents (most commonly metformin, sulfonylureas and DPP-4 inhibitors, but not taking SGLT-2 inhibitors). It reported that fewer patients in the fixed-ratio insulin degludec plus liraglutide group achieved the primary outcome of need for treatment intensification compared with those in the basal insulin glargine group (37% vs. 66%) and the composite secondary outcome of HbA_{1c} level <7% without hypoglycaemia or weight gain. While encouraging, the study was limited by its open-label design, relatively short duration, and the failure to include a GLP-1 receptor agonist monotherapy arm. Such an arm would have been particularly relevant, given that current American and European diabetes guidelines recommend GLP-1 receptor agonists as first-line injectable therapy, due to their cardiorenal benefits. Whether combined insulin plus GLP-1 receptor agonist therapy (with a potentially lower GLP-1 receptor agonist dose) has similar benefits remains unknown. Further studies are required to compare the long-term benefits, risks, patient acceptability and cost effectiveness of GLP-1 receptor agonists compared with insulin therapy, either alone or in combination.

Reference: Lancet Diabetes Endocrinol; Published online June 9, 2019
Abstract

Adjunctive liraglutide treatment in patients with persistent or recurrent type 2 diabetes after metabolic surgery (GRAVITAS)

Authors: Miras AD et al.

Summary: Adults with T2DM with HbA_{1c} levels >48 mmol/mol (>6.5%) 1 year after RYGB (Roux-en-Y gastric bypass) or vertical sleeve gastrectomy were randomised to receive subcutaneous liraglutide 1.8mg (n=53) or placebo (n=27) once daily along with a reduced-calorie diet and increased physical activity; the study completion rate was 89%. Compared with placebo, liraglutide recipients had a significantly greater reduction in HbA_{1c} level at 26 weeks (adjusted difference, –13.3 mmol/mol [–1.22%; p=0.0001]); surgery type had no significant impact on outcome. The respective adverse event rates in the liraglutide and placebo arms were 45% and 41%, consisting mainly of GI events consistent with previous reports for liraglutide.

Comment: Depending on the surgical technique, 23–67% of patients with diabetes undergoing bariatric surgery remain in remission at 5 years after surgery. While weight loss is an important contributor, some studies suggest that the metabolic benefits of bariatric surgery may, at least in part, be weight loss-independent and contributed to by gut hormones such as GLP-1, leading to the new term 'metabolic surgery'. In GRAVITAS, a small (n=80) short-term (26-week) RCT in patients with persistent or recurrent T2DM who had undergone bariatric surgery at least 1 year previously, GLP-1 receptor agonist liraglutide treatment was associated with a 1.2% reduction in HbA_{1c} level and a 4.2kg reduction in bodyweight compared with placebo. The results are not entirely surprising and do not prove a pathogenetic role for GLP-1 signalling in diabetes relapse after metabolic surgery, given the study did not include an active comparator drug targeting a pathway not implicated in postsurgical diabetes relapse. Interestingly, the weight loss effect achieved with liraglutide was comparable with that reported with the use of minimally invasive surgical techniques commonly employed for weight regain after bariatric surgery. Whether the higher 3mg liraglutide dose (approved for obesity treatment) will be more effective remains unknown. While many pharmacological treatments for obesity are currently under development, it appears unlikely that these will replace metabolic surgery, at least in the foreseeable future. More research is clearly needed, given that, notwithstanding metabolic and potential CV benefits, bariatric surgery has been associated with potential adverse outcomes, such as increased risks of depression, hypoglycaemia and nutritional deficits.

Reference: Lancet Diabetes Endocrinol 2019;7:549–59
Abstract

Relationship of baseline HbA_{1c} and efficacy of current glucose lowering therapies

Authors: DeFronzo RA et al.

Summary: This meta-analysis of 59 RCTs (n=8479) of glucose-lowering agents versus placebo or a comparator explored the relationship between baseline HbA_{1c} level and reported reductions. A significant association was detected between baseline HbA_{1c} level and absolute change in HbA_{1c} level (weighted R^2=0.35 [p<0.0001]), particularly in a subanalysis of eight metformin trials (weighted R^2=0.67 [p=0.0130]); excluding the metformin trials yielded a weighted R^2 value of 0.31 (p<0.0001). Subanalyses of clinical trials of glucose-lowering therapies predominantly targeting fasting or postprandial blood glucose levels produced respective weighted R^2 values of 0.27 and 0.42 (p≤0.005).

Comment: It is well known that using between-trial comparisons to judge the efficacy of different medical interventions has limited validity, due to between-trial differences in design and characteristics of the populations enrolled. Instead, head-to-head comparisons of different therapies in dedicated RCTs are required. This meta-analysis illustrates this point for antiglycaemic agents, identifying baseline glycaemic control as an important variable in determining their efficacy. While this is not a novel finding, this meta-analysis was conducted more rigorously and included a larger number of clinical trials than previous studies. The findings demonstrate, across ten classes of glucose lowering therapies, a stronger association, independent of therapy class, between higher baseline HbA_{1c} level and a greater reduction in HbA_{1c} level than reported previously. The authors concluded that 35% of the reduction of HbA_{1c} level is dependent on the baseline HbA_{1c} level. Therefore, baseline HbA_{1c} level is an important factor to consider when assessing the efficacy of contemporary glucose-lowering therapies, especially when assessing data from trials enrolling patients with relatively good baseline glycaemic control (HbA_{1c} level range 7.0–8.0%).

Reference: Diabet Med; Published online Aug 19, 2010
Abstract

Type 2 diabetes in midlife and risk of cerebrovascular disease in late life

Authors: Yang R et al.

Summary: The relationship between T2DM diagnosed between the ages of 40 and 59 years (midlife) and cerebrovascular disease in later life, along with the role of genetic and early-life familial environmental factors on this relationship, was explored using data from the Swedish Twin Registry in this prospective nested case-control study. The study population consisted of 33,086 twin individuals born before 1959 with no cerebrovascular disease documented prior to age 60 years, of whom 1248 (3.8%) were diagnosed with T2DM during midlife and 3121 (9.4%) developed cerebrovascular disease later in life. Generalised estimating equation models revealed increased odds of T2DM for cerebral infarction (adjusted OR 1.29 [95% CI 1.03–1.61]) and cerebral artery occlusion (2.03 [1.20–3.44]), but not subarachnoid haemorrhage (0.52 [0.12–2.21]) or intracerebral haemorrhage (0.78 [0.45–1.36]). A multi-adjusted conditional logistic regression model revealed no significant association between T2DM and cerebral infarction (OR 0.96 [95% CI 0.51–1.80]). There was no significant difference between ORs from generalised estimating equation models and co-twin control analyses of cerebrovascular disease-discordant twin pairs (p=0.780).

Comment: T2DM has been associated with an increased risk of cerebrovascular disease in many observational studies. In a previous meta-analysis of 100 prospective studies with almost 700,000 participants, the risk for incident ischaemic stroke was more than double in people with T2DM compared with those without diabetes (adjusted HR 2.27 [95% CI 1.95–2.65]). This population-based study of Swedish twins extends these observations to younger people, identifying midlife diabetes as a predictor of increased risk of ischaemic cerebral events in later life. While the study did not find any evidence that genetic and early life-familial factors modified this association, these findings are inconclusive due to the limited number of cerebral infarction-discordant twin pairs. Moreover, the study did not account for risk factors such as physical inactivity or hyperlipidaemia, and residual confounding remains possible. Although the authors' assertion that 'our study highlights the need to control T2DM in midlife for the prevention of cerebrovascular disease in late life' has not been tested in their work, it is intuitive that comprehensive CV risk factor control and optimisation of glycaemic control have clinical benefits in middle-aged people with T2DM, which may extend to the prevention of cerebrovascular events.

Reference: Diabetologia; Published online June 5, 2019
Abstract

Combined GLP-1, oxyntomodulin, and peptide YY improves body weight and glycemia in obesity and prediabetes/type 2 diabetes

Authors: Behary P et al.

Summary: Obese patients with diabetes or prediabetes were randomised to receive infusions of a combination of GLP-1, oxyntomodulin and peptide YY (GOP; n=15) or saline (n=11) for 4 weeks, with 21 patients who had undergone RYGB and 22 who had followed a very low-calorie diet also used as unblinded comparators. The GOP infusions were well tolerated. Compared with the saline group, GOP recipients experienced a significantly greater mean reduction in bodyweight (–4.4 vs. –2.5kg [p=0.025]) and a significantly greater improvement in fructosamine level (–44.1 vs. –11.7 µmol/L [p=0.0026]). Compared with RYGB and a very low-calorie diet, GOP infusions were associated with superior glucose tolerance after a mixed-meal stimulus and reduced glycaemic variability, despite less weight loss.

Comment: While a substantial portion of the long-term metabolic benefits of bariatric surgery is dependent on the degree of weight loss, experimental studies have shown early improvements in insulin sensitivity and β-cell function prior to substantial weight loss. Postulated mechanisms include early postsurgical caloric restrictions and increased secretion of satiety-inducing gut hormones, including GLP-1, oxyntomodulin and peptide YY. This experimental study aimed to replicate the increased levels of gut hormones seen post-bariatric surgery by their subcutaneous infusion (GOP) in obese patients who had not undergone surgery. Over 4 weeks, weight loss was modestly greater in patients receiving GOP compared with placebo, a treatment effect of 1.9kg. Metabolic effects with GOP were somewhat greater than after RYGB or a very low-calorie diet, although comparisons were not blinded, nor were the interventions randomised. Additional limitations of this study include the small size, short duration and inability to examine the contribution of individual hormones to the overall effect. Larger double-blind studies have reported weight loss with GLP-1 agonist monotherapy or dual GLP-1/glucagon agonists. Whether combination multihormonal therapy provides synergistic benefits requires further evaluation. Larger long-term studies administering optimised combinations in a clinically feasible fashion will be necessary to evaluate whether such treatment could be a viable alternative to bariatric surgery.

Reference: Diabetes Care 2019;dc190449
Abstract

Effect of the mineralocorticoid receptor antagonist eplerenone on liver fat and metabolism in patients with type 2 diabetes

Authors: Johansen ML et al.

Summary: The MIRAD trial randomised 140 patients with T2DM at high risk of CV disease to receive either eplerenone target at doses of 200 and 100 mg/day for participants with estimated GFRs of ≥60 and 41–59 mL/min/1.73m^2, respectively, or placebo in a 1:1 ratio. Although there was no significant change in liver fat (primary outcome) in the eplerenone arm or in the placebo arm (+0.91% and –1.01%, respectively), the estimated absolute treatment difference of 1.92% was statistically significant (p=0.049); however, there was no beneficial impact of eplerenone on supporting secondary outcome parameters of metabolism. Incident hyperkalaemia (≥ 5.5 mmol/L) occurred in six eplerenone recipients and two placebo recipients (p=0.276).

Comment: Fatty liver is highly prevalent in patients with T2DM, and overlaps so closely with features of the metabolic syndrome that it may be considered its hepatic manifestation. Fatty liver augments insulin resistance, independently predicts diabetes-related complications, and increases the risk of progression to liver cirrhosis and hepatocellular carcinoma. Ample preclinical evidence has linked aldosterone signalling to adverse metabolic outcomes, including liver fat accumulation. In this RCT, the selective mineralocorticoid receptor antagonist eplerenone had no effect on liver fat, estimated by MRI, nor on secondary metabolic outcomes. A key limitation of the study was that less than 50% had fatty liver at baseline. Moreover, given the invasive nature of liver biopsy, a surrogate marker of liver fat was used. While rates of hyperkalaemia were low, at-risk patients (those with baseline estimated GFR <40 mL/min/173m^2 and/or serum potassium level >5.0 mmol/L) were excluded, and participants underwent frequent electrolyte monitoring. While the study is not definitive in excluding a benefit for eplerenone on liver fat and other metabolic outcomes, it illustrates the difficulty of translating preclinical evidence into clinical outcomes. The results suggest that future studies should instead focus on renal and CV effects of mineralocorticoid receptor blockade in patients with diabetes.

Reference: Diabetes Obes Metab; Published online June 10, 2019
Abstract

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