Type 2 Diabetes
Current Awareness Bulletin
July 2019

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Title: Treatment patterns and associated factors in 14 668 people with type 2 diabetes initiating a second-line therapy: results from the global DISCOVER study programme.

Citation: Diabetes, obesity & metabolism; Jul 2019

Author(s): Nicolucci, Antonio; Charbonnel, Bernard; Gomes, Marilia B; Khunti, Kamlesh; Kosiborod, Mikhail; Shestakova, Marina V; Shimomura, Iichiro;Watada, Hirotaka;Chen, Hungta;Cid-Razufa, Javier; Fenici, Peter; Hammar, Niklas; Surmont, Filip; Tang, Fengming; Pocock, Stuart

Aims: Data on treatment patterns in people with type 2 diabetes are scarce in many countries. We report treatment data from DISCOVER (NCT02322762 and NCT02226822), a global, prospective, observational study programme of patients with type 2 diabetes initiating a second-line glucose-lowering therapy.

Materials and Methods: Data were collected using a standardized case report form. First- and second-line treatments were assessed in 14 668 patients from 37 countries across six regions. Among patients prescribed first-line metformin monotherapy, Firth logistic regression models were used to assess factors associated with second-line treatment choices.

Results: The most common first-line therapies were metformin monotherapy (57.9%), and combinations of metformin with a sulphonylurea (14.6%). The most common second-line therapies were combinations of metformin with other agents (72.2%), including dipeptidyl peptidase-4 (DPP-4) inhibitors (25.1%) or sulphonylureas (21.3%). Among patients prescribed first-line metformin monotherapy, the most common second-line therapies were combinations of metformin with a DPP-4 inhibitor (32.8%; across-region range [ARR]: 2.4-51.3%) or a sulphonylurea (30.0%; ARR: 18.3-63.6%); few patients received combinations of metformin with sodium-glucose co-transporter-2 inhibitors (6.7%; ARR: 0.0-10.8%) or glucagon-like peptide 1 receptor agonists (1.9%; ARR: 0.1-4.5%). Both clinical and non-medical factors were associated with choice of second-line therapy after metformin monotherapy.

Conclusions: Fewer patients than expected received metformin monotherapy at first line, and the use of newer therapies at second line was uncommon in some regions of the world. Patients' socio-economic status was associated with treatment patterns, suggesting that therapy choices are influenced by cost and access. This article is protected by copyright. All rights reserved.

Title: Diabetes Therapies for Dementia.

Citation: Current neurology and neuroscience reports; Jul 2019; vol. 19 (no. 8); p. 58

Author(s): Moran, Chris; Callisaya, Michele L; Srikanth, Velandai; Arvanitakis, Zoe

Purpose of Review: Type 2 diabetes (T2D) is a well-established risk factor for the development of dementia. Dementia and T2D share some underlying pathophysiology that has led to interest in the potential to repurpose drugs used in the management of T2D to benefit brain health. This review describes the scientific data available on the use of T2D medications for the risk reduction or management of dementia, in people with and without T2D.

Recent Findings: Results from basic laboratory research support the potential for commonly-used medications for T2D, including those with direct glucose-lowering properties, to have a beneficial effect on brain health. However, human studies have been mostly observational in nature and report conflicting results. Preliminary data suggest that intranasal insulin, metformin, and GLP-1 agonists show promise for dementia, but confirmatory evidence for their benefit in dementia is still lacking. Current evidence does not support the repurposing of T2D medications for dementia risk reduction or management. Research in the field of T2D and dementia is active, and further data are required before definitive conclusions can be drawn.
Title: Cost-effectiveness analysis of empagliflozin treatment in people with Type 2 diabetes and established cardiovascular disease in the EMPA-REG OUTCOME trial.

Citation: Diabetic medicine: a journal of the British Diabetic Association; Jul 2019
Author(s): Kansal, A; Reifsnider, O S; Proskorovsky, I; Zheng, Y; Pfarr, E; George, J T; Kandaswamy, P; Ruffolo, A

Aim: In the EMPA-REG OUTCOME trial, empagliflozin therapy reduced cardiovascular death by 38% compared with placebo when added to standard of care. Using the trial results, we created a discrete-event simulation model to assess lifetime health economic outcomes in people with Type 2 diabetes and established cardiovascular disease.

Methods: Time-dependent survival regression analysis was performed on data from EMPA-REG OUTCOME for 10 cardiovascular and renal events (e.g. stroke, heart failure hospitalization, macroalbuminuria, cardiovascular mortality) to capture event rates over time, and interaction between events. Model performance was assessed by comparing predicted and observed outcomes at 3 years. Costs in the United Kingdom (UK) and health utilities were obtained from published literature. Outcomes included cumulative event rates, life-years, costs and quality-adjusted life-years (QALYs).

Results: The model predicted an 18% relative increase (by 2.1 life-years) in survival for empagliflozin (14.0 life-years) vs. standard of care (11.9 life-years), attributable to direct treatment effect on cardiovascular mortality, and to indirect effect via reductions in other events. Participants treated with empagliflozin may experience improved quality of life (1.0 QALY) and higher costs (£3737/participant), yielding an incremental cost-effectiveness ratio (ICER) of £4083/QALY. Sensitivity analyses confirmed the robustness of these results to changes in input parameters.

Conclusions: Based on extrapolation of EMPA-REG OUTCOME trial data using a participant-level simulation model, empagliflozin in addition to standard of care is projected to be highly cost-effective using UK healthcare costs. The impact in other countries will vary due to differences in drug pricing and accrual of other costs. This article is protected by copyright. All rights reserved.

Title: Second-line Glucose-Lowering Therapy in Type 2 Diabetes Mellitus.

Citation: Current diabetes reports; Jul 2019; vol. 19 (no. 8); p. 54
Author(s): Shin, Jung-Im

Purpose of Review: There is consensus that metformin should be the first-line pharmacological therapy for type 2 diabetes. Although new evidence on effective treatments for type 2 diabetes is rapidly evolving, there is uncertainty regarding the optimal choice of second-line therapy. Our aim was to review the current major guidelines for second-line therapy in type 2 diabetes, along with findings from the recent cardiovascular outcome trials, focusing on two particularly promising classes of glucose-lowering drugs, sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP1 RAs).

Recent Findings: In the recent randomized controlled trials, two SGLT2 inhibitors (i.e., empagliflozin and canagliflozin) and two GLP1 RAs (i.e., liraglutide and albiglutide) reduced cardiovascular events in patients with type 2 diabetes, of whom most had established atherosclerotic cardiovascular disease. Some clinical guidelines have changed their recommendations for second-line therapy based on these findings. The first choice for a second-line therapy by the new American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) guidelines is SGLT2 inhibitors or GLP1 RAs for patients with atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease. For patients without these conditions, the ADA/EASD lists five options of noninsulin second-line therapy without a suggested hierarchy of use. On the other hand, the 2019 consensus statement from the American Association of Clinical Endocrinologists/American College of Endocrinology lists nine hierarchical options, with GLP1 RAs as the first recommended therapy, followed by SGLT2 inhibitors and dipeptidyl peptidase 4 (DPP4) inhibitors, and sulfonylurea as the last option. The American College of Physicians recommends four oral treatment options, which do not include GLP1 RAs. The International Diabetes Federation recommends sulfonylureas, DPP4
inhibitors, or SGLT2 inhibitors as preferred second-line drugs with GLP1 RAs as an alternative in obese patients. The World Health Organization strongly recommends sulfonylureas in low-resource settings. The National Institute for Health and Care Excellence in the UK recommends DPP4 inhibitors, thiazolidinediones, or sulfonylureas, with use of SGLT2 inhibitors only under special circumstances. Clinical guidelines for the choice of second-line therapy in type 2 diabetes are inconsistent. A comprehensive assessment of the risks and benefits of second-line therapy is needed to address knowledge gaps that underlie core clinical practice.

Title: Long-term efficacy and safety of combined insulin and GLP-1 therapy: evidence from the LEADER trial.

Citation: Diabetes, obesity & metabolism; Jul 2019

Author(s): Tack, Cees J; Jacob, Stephan; Desouza, Cyrus; Bain, Stephen C; Buse, John B; Nauck, Michael A; Petrie, John R; Poulter, Neil R; Pratley, Richard E; Stegmann, Helen Vanya B K; Bosch-Traberg, Heidrun; Startseva, Elena; Zinman, Bernard; LEADER Publication Committee on behalf of the LEADER Trial Investigators

Aims: Glucagon-like peptide-1 receptor agonist (GLP-1RA) and insulin combination therapy is an effective treatment option for type 2 diabetes, but long-term data are lacking. We assessed the long-term efficacy of the GLP-1RA liraglutide in subgroups by insulin use in the LEADER trial.

Materials and Methods: LEADER assessed cardiovascular (CV) safety and efficacy of liraglutide (1.8 mg) vs placebo (plus standard of care therapy) in 9340 patients with type 2 diabetes and high risk for CV disease, for up to 5 years. We analyzed CV events, metabolic parameters and hypoglycemia post hoc in three subgroups by baseline insulin use (basal-only insulin, other insulin, or no insulin). Insulin was a non-random treatment allocation as part of standard of care therapy.

Results: At baseline, 5171 (55%) patients were not receiving insulin, 3159 (34%) were receiving basal only insulin and 1010 (11%) other insulins. Insulin users had a longer diabetes duration and slightly worse glycemic control (HbA1c ) than the no-insulin subgroup. Liraglutide reduced HbA1c and weight vs placebo in all three subgroups (P < 0.001), and severe hypoglycemia rate in the basal-only insulin subgroup. The need for insulin was less with liraglutide. CV risk reduction with liraglutide was similar to the main trial results in the basal-only and no-insulin subgroups.

Conclusions: In patients on insulin, liraglutide improved glycemic control, weight and need for insulin vs placebo, for at least 36 months with no increased risk of severe hypoglycemia, while maintaining CV safety/efficacy, supporting the combination of liraglutide and insulin for management of type 2 diabetes. This article is protected by copyright. All rights reserved.

Title: Sulfonylureas as Initial Treatment for Type 2 Diabetes and the Risk of Adverse Cardiovascular Events: A Population-based Cohort Study.

Citation: British journal of clinical pharmacology; Jul 2019

Author(s): Filion, Kristian B; Douros, Antonios; Azoulay, Laurent; Yin, Hui; Yu, Oriana H; Suissa, Samy

Aims: Sulfonylureas are recommended as second-line treatment in the management of type 2 diabetes. However, they are still commonly used also as first-line treatment instead of metformin. Given the controversial cardiovascular safety of sulfonylureas, we aimed to determine if their use as first-line treatment is associated with adverse cardiovascular events among patients with newly-treated type 2 diabetes compared with metformin.

Methods: We conducted a population-based cohort study of patients with newly-treated type 2 diabetes using the United Kingdom's Clinical Practice Research Datalink. Initiators of metformin and sulfonylurea monotherapy were matched on high-dimensional propensity score, and Cox proportional hazards models were used to compare the rate of cardiovascular events (myocardial infarction [MI], ischemic stroke, cardiovascular death, and all-cause mortality) with sulfonylureas versus metformin.
Our cohort included 94,750 patients initiating treatment for type 2 diabetes, 17,612 on a sulfonylurea and 77,138 on metformin. After matching, sulfonylurea monotherapy, compared with metformin monotherapy, was not associated with an increased risk of MI (HR: 1.04, 95% CI: 0.85 to 1.25) but was associated with increased risks of ischemic stroke (HR: 1.25, 95% CI: 1.002 to 1.56), cardiovascular death (HR: 1.25, 95% CI: 1.06 to 1.47), and all-cause mortality (HR: 1.60, 95% CI: 1.45 to 1.76). This represents an additional 2.0 ischemic strokes, 3.5 cardiovascular deaths, and 21.4 all-cause deaths per 1,000 patients per year with sulfonylureas.

Initiating treatment of type 2 diabetes with a sulfonylurea rather than metformin is associated with higher rates of ischemic stroke, cardiovascular death, and all-cause mortality.

Title: Metabolic Effects of Testosterone Therapy in Men with Type 2 Diabetes and Metabolic Syndrome.

Citation: Sexual medicine reviews; Jul 2019; vol. 7 (no. 3); p. 476-490

Author(s): Hackett, Geoffrey

Introduction: Up to 40% of men with type 2 diabetes (T2DM) and metabolic syndrome (MetS) have hypogonadotrophic hypogonadism (HH). Men with HH are at increased risk of cardiovascular (CV) and all-cause mortality, as well as of the development of incident T2DM. AIM To review the current literature on the metabolic effects of testosterone therapy (TTh) in men with T2DM and MetS.

Methods: We searched MEDLINE, Embase, and Cochrane Reviews for articles on T2DM, HH, testosterone deficiency, and CV and all-cause mortality published between May 2005 and July 2018, yielding 1817 articles, including 54 clinical trials and 32 randomized controlled trials (RCTs).

Main Outcome Measures: The main outcomes were glycemic control, insulin resistance, lipid profile, and metabolic markers associated with increased CV risk.

Results: RCTs of TTh suggest significant benefits for sexual function, quality of life, glycemic control, insulin sensitivity, anemia, bone density, and fat and lean muscle mass that might be expected to translate into reduced long-term morbidity and mortality. Several longitudinal and observational studies suggest long-term sustained improvements in metabolic parameters and a trend toward reduced CV and all-cause mortality, especially in men at increased CV risk, such as those with T2DM and MetS. The greatest benefit is seen in those men treated with TTh to target levels and for longer durations.

Conclusion: Meta-analyses of RCTs, rather than providing clarification, may have further confused the issue by including underpowered studies of inadequate duration, multiple therapy regimens, some obsolete or withdrawn, and built-in bias in terms of studies included or excluded from analysis.


Title: Treatment of type 2 diabetes by targeting interleukin-1: a meta-analysis of 2921 patients.

Citation: Seminars in immunopathology; Jul 2019; vol. 41 (no. 4); p. 413-425

Author(s): Kataria, Yachana; Ellervik, Christina; Mandrup-Poulsen, Thomas

Abstract: With obesity and type 2 diabetes prevalence steadily increasing and no effective means in sight to support the population in obtaining and maintaining stable weight loss, there is an imminent need for pharmacological therapy to treat and prevent type 2 diabetes. Current anti-diabetic treatment is symptomatic, and very few drugs have both a strong preclinical rationale and clinical proof-of-principle as therapies targeting pathogenic processes in type 2 diabetes. The emerging appreciation of low-grade inflammation as a significant cause of insulin resistance and beta cell failure warrants exploring anti-inflammatory compounds as drug candidates. Since recent studies have demonstrated considerable phenotypic heterogeneity in the type 2 diabetic syndrome, the concept of one drug fits all is naive, and biomarkers for the selection of type 2 diabetes subtypes for differentiated treatment based on genetic and pathogenic stratification are urgently needed. Biologics antagonizing the master
pro-inflammatory cytokine interleukin-1 is one of the few principles specifically targeting low-grade inflammation in type 2 diabetes. Although early phase II studies were encouraging, subsequent underpowered studies and phase III studies designed primarily with cardiovascular endpoints have discredited the potential of anti-interleukin-1 approaches to treat the subgroup of patients that may benefit from this treatment. In this meta-analysis of 2921 individuals from eight phase I-IV studies, we demonstrate a significant overall HbA1c-lowering effect of interleukin-1 antagonism. Meta-regression analyses demonstrated a significant correlation between baseline C-reactive protein and C-peptide, and HbA1c outcome. The identification of further biomarkers for future clinical trials to define the potential of anti-interleukin-1 therapies in type 2 diabetes is urgently needed.

Title: Improving pregnancy outcomes in women with diabetes mellitus: modern management.

Citation: Nature reviews. Endocrinology; Jul 2019; vol. 15 (no. 7); p. 406-416
Author(s): Ringholm, Lene; Damm, Peter; Mathiesen, Elisabeth R

Abstract: Women with pre-existing (type 1 or type 2) diabetes mellitus are at increased risk of pregnancy complications, such as congenital malformations, preeclampsia and preterm delivery, compared with women who do not have diabetes mellitus. Approximately half of pregnancies in women with pre-existing diabetes mellitus are complicated by fetal overgrowth, which results in infants who are overweight at birth and at risk of birth trauma and, later in life, the metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus. Strict glycaemic control with appropriate diet, use of insulin and, if necessary, antihypertensive treatment is the cornerstone of diabetes mellitus management to prevent pregnancy complications. New technology for managing diabetes mellitus is evolving and is changing the management of these conditions in pregnancy. For instance, in Europe, most women with pre-existing diabetes mellitus are treated with insulin analogues before and during pregnancy. Furthermore, many women are on insulin pumps during pregnancy, and the use of continuous glucose monitoring is becoming more frequent. In addition, smartphone application technology is a promising educational tool for pregnant women with diabetes mellitus and their caregivers. This Review covers how modern diabetes mellitus management with appropriate diet, insulin and antihypertensive treatment in patients with pre-existing diabetes mellitus can contribute to reducing the risk of pregnancy complications such as congenital malformations, fetal overgrowth, preeclampsia and preterm delivery.

Title: Management of ketosis-prone type 2 diabetes mellitus.

Citation: Journal of the American Association of Nurse Practitioners; Jul 2019; vol. 31 (no. 7); p. 430-436
Author(s): Smolenski, Stefan; George, Nancy M

Abstract: Diabetic ketoacidosis (DKA) has largely been considered unique to type 1 diabetes because of the absolute lack of insulin production secondary to beta-cell dysfunction. However, a relatively new diabetes subtype known as ketosis-prone type 2 diabetes mellitus (DM) may also elicit diabetic ketoacidosis. Ketosis-prone type 2 DM shares a similar pathophysiology as type 2 DM, but presents initially with signs and symptoms consistent with type 1 DM. Patients with ketosis-prone type 2 DM often present with elevated glucose levels of 500-700 mg/dl, elevated ketone levels, and elevations in hemoglobin A1C. Unlike DKA seen in type 1 DM, they do not exhibit autoantibodies to beta cells. The similarity with type 1 DM exists in their impaired insulin secretion, which, when combined with extreme insulin resistance, will lead to ketoacidosis. Despite the initial clinical presentation that resembles type 1 DM, patients may not require lifelong insulin and achieve appropriate glycemic control with oral agents. Nurse practitioners must recognize the clinical picture of ketosis-prone type 2 DM and use a multifaceted approach, encouraging dietary changes, increased physical activity, and medication adherence to build the self-management skills of the patient and ultimately decrease the long-term disease burden.
Title: The prevalence of cardiovascular disease and antidiabetes treatment characteristics among a large type 2 diabetes population in the United States.

Citation: Endocrinology, diabetes & metabolism; Jul 2019; vol. 2 (no. 3); p. e00076

Author(s): Weng, Wayne; Tian, Ye; Kong, Sheldon X; Ganguly, Rahul; Hersloev, Malene; Brett, Jason; Hobbs, Todd

Objectives: The purpose of this study was to assess atherosclerotic cardiovascular disease (ASCVD) prevalence, antidiabetes medication usage and physician specialty encounters among individuals with type 2 diabetes mellitus (T2DM) in the United States during 2015.

Design: Retrospective, cross-sectional analysis. Patients Adults with T2DM in a large US administrative claims database. Patients were divided into ASCVD and non-ASCVD groups. Subgroup analyses were conducted for three age groups (18-44, 45-64 and 65+ years).

Results: Of 1,202,596 patients with T2DM, 45.2% had established ASCVD. About 40% of T2DM patients with ASCVD had visited a cardiologist during 2015, compared to 11% in the non-ASCVD group. The use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium-glucose co-transporter 2 inhibitors (SGLT-2is) was low overall (<12%), and even lower in the ASCVD group (<9%). The prevalence of ASCVD was 15%, 36% and 71% in the 18-44, 45-64 and 65+ year age groups, respectively. GLP-1RA and SGLT-2i use was ≤5% in the 65+ subgroup, regardless of ASCVD status.

Conclusions: These real-world data showed a high prevalence of ASCVD among T2DM patients, and confirmed, as a baseline assessment, low use of GLP-1RAs and SGLT-2is in these at-risk patients prior to the 2017 American Diabetes Association guidelines recommending use of agents with proven cardiovascular benefits.

Title: Hypoglycaemia and treatment patterns among insulin-treated patients with type 2 diabetes who switched to insulin glargine 300 units/mL versus other basal insulin in a real-world setting.

Citation: Endocrinology, diabetes & metabolism; Jul 2019; vol. 2 (no. 3); p. e00073

Author(s): Zhou, Fang L; Nicholls, Charlie; Xie, Lin; Wang, Yuexi; Vaidya, Neel; Meneghini, Luigi F

Introduction: Type 2 diabetes (T2D) is characterized by worsening pancreatic β-cell function often requiring treatment escalation with oral antidiabetic drugs (OADs), glucagon-like peptide-1 and eventually insulin. Although there is much evidence available on the initiation of basal insulins, fewer studies have investigated the effects of switching from one basal insulin to another. This study aims to evaluate treatment persistence and hypoglycaemia in adult patients with T2D on prior basal insulin who were switched to insulin glargine 300 units/mL (Gla-300) or other basal insulins in a real-world setting.

Materials and methods: This study is a retrospective cohort analysis of patient-level data extracted from the Optum® Clinformatics™ database between 1 October 2014 and 30 June 2016. Adult patients (≥18 years) with T2D who were being treated with basal insulin during the 6-month baseline period, who switched to either Gla-300 or other basal insulins, were followed up for ≥3 months after switching. Outcomes included treatment persistence, and incidence and number of hypoglycaemic events.

Results: Of the included patients, 1,204 switched to Gla-300 and 616 switched to other basal insulins. Adjusting for baseline confounders, patients who switched to Gla-300 were 34% less likely to discontinue their basal insulin than patients who switched to other basal insulins (hazard ratio [HR] 0.66; 95% confidence interval [CI] 0.54-0.81; P < 0.001). Patients who switched to Gla-300 were less likely to experience hypoglycaemia at 3-month follow-up (odds ratio [OR] 0.56, 95% CI 0.32-0.97; P = 0.039) and at 6-month follow-up (OR 0.58, 95% CI 0.38-0.87; P = 0.009) compared with patients who switched to other basal insulins.
**Conclusions:** Patients with T2D on prior basal insulin in a real-world setting who switched to Gla-300 were more persistent with their basal insulin and experienced less hypoglycaemia than patients who switched to other basal insulins.

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**Title:** Effect of Flash Glucose Monitoring Technology on Glycemic Control and Treatment Satisfaction in Patients With Type 2 Diabetes.

**Citation:** Diabetes care; Jul 2019; vol. 42 (no. 7); p. 1178-1184

**Author(s):** Yaron, Marianna; Roitman, Eytan; Aharon-Hananel, Genya; Landau, Zohar; Ganz, Tali; Yanuv, Ilan; Rozenberg, Aliza; Karp, Moshe; Ish-Shalom, Maya; Singer, Joelle; Wainstein, Julio; Raz, Itamar

**Objective:** To assess treatment satisfaction and the effectiveness of a flash glucose monitoring (FGM) system in patients with type 2 diabetes using insulin.

**Research Design And Methods:** A total of 101 patients with type 2 diabetes on multiple daily insulin injections (MDI) for at least 1 year were assigned randomly to the FGM intervention (n = 53) or the standard care (control) group (n = 48) and followed for 10 weeks. Both groups were instructed to adjust their insulin doses in face-to-face and telephone visits. Satisfaction with treatment, quality of life, comfort using FGM, HbA1c, and frequency of hypoglycemic events were evaluated.

**Results:** The intervention group found treatment significantly more flexible (P = 0.019) and would recommend it to their counterparts (P = 0.023). Satisfaction using the FGM system was high. The changes in HbA1c were -0.82% (9 mmol/mol) vs. -0.33% (3.6 mmol/mol) in the intervention and control group, respectively (P = 0.005); in nonprespecified post hoc analysis, 68.6% of the patients in the intervention group had their HbA1c reduced by ≥0.5% (5.5 mmol/mol) compared with 30.2% in the control group (P < 0.001), and 39.2% had their HbA1c reduced by ≥1.0% (10.9 mmol/mol) vs. 18.6% in the control group (P = 0.0023) without an increased frequency of hypoglycemia.

**Conclusions:** FGM tends to improve treatment satisfaction and may lead to amelioration of glycemic control in patients with type 2 diabetes on MDI without increasing the frequency of hypoglycemia.

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**Title:** Postprandial hypoglycemia after gastric bypass surgery: from pathogenesis to diagnosis and treatment.

**Citation:** Current opinion in clinical nutrition and metabolic care; Jul 2019; vol. 22 (no. 4); p. 295-302

**Author(s):** Honka, Henri; Salehi, Marzieh

**Purpose of Review:** The Roux-en-Y gastric bypass surgery (RYGB) improves glucose control in majority of patients with type 2 diabetes. However, a minority group of individuals develop a life-threatening complication of hyperinsulinemic hypoglycemia. The goal of this review is to identify underlying mechanisms by which RYGB cause hypoglycemia and describe pathogenesis-driven strategies to diagnose and treat this condition.

**Recent Findings:** Gastric bypass leads to higher and earlier peak levels of glucose and lower nadir glucose after eating along with larger insulin and glucagon-like peptide 1 (GLP-1) secretion, resetting the balance between glucose appearance and clearance after this procedure. These weight-loss independent glycemic effects of RYGB have been attributed to changes in ingested glucose appearance as a result of rapid nutrient emptying from stomach pouch to the intestine and increased glucose clearance as a result of prandial hyperinsulinemia. The exaggerated effect of RYGB on postmeal glucose metabolism is a syndrome of postprandial hyperinsulinemic hypoglycemia manifesting in a group of individuals several years after this surgery. Affected patients have larger systemic appearance of ingested glucose and greater postmeal secretion of insulin and GLP-1 compared to those with history of RYGB without symptomatic hypoglycemia. Current evidence supporting a multifactorial model of glucose dysregulation among patients with hypoglycemia will be highlighted in this review.
Summary: Hypoglycemia after RYGB is a life-threatening condition and likely represents the extreme glycemic phenotype of this procedure. Diagnosis is challenging and treatment options are limited.

Title: Team-Based Care to Improve Diabetes Management: A Community Guide Meta-analysis.

Citation: American journal of preventive medicine; Jul 2019; vol. 57 (no. 1); p. e17
Author(s): Levengood, Timothy W; Peng, Yinan; Xiong, Ka Zang; Song, Ziwei; Elder, Randy; Ali, Mohammed K; Chin, Marshall H; Allweiss, Pamela; Hunter, Christine M; Becenti, Alberta; Community Preventive Services Task Force

Context: Team-based care has been increasingly used to deliver care for patients with chronic conditions, but its effectiveness for managing diabetes has not been systematically assessed.

Evidence Acquisition: RCTs were identified from two sources: a high-quality, broader review comparing 11 quality improvement strategies for diabetes management (database inception to July 2010), and an updated search using the same search strategy (July 2010-October 2015).

Evidence Synthesis: Thirty-five studies were included in the current review; a majority focused on patients with Type 2 diabetes. Teams included patients, their primary care providers, and one or two additional healthcare professionals (most often nurses or pharmacists). Random effect meta-analysis showed that, compared with controls, team-based care was associated with greater reductions in blood glucose levels (-0.5% in HbA1c, 95% CI= -0.7, -0.3) and greater improvements in blood pressure and lipid levels. Interventions also increased the proportion of patients who reached target blood glucose, blood pressure, and lipid levels, based on American Diabetes Association guidelines available at the time. Data analysis was completed in 2016.

Conclusions: For patients with Type 2 diabetes, team-based care improves blood glucose, blood pressure, and lipid levels.

Title: Pharmacological treatment for Type 2 diabetes integrating findings from cardiovascular outcome trials: an expert consensus in the UK.

Citation: Diabetic medicine : a journal of the British Diabetic Association; Jun 2019
Author(s): Bain, S C; Bakhai, A; Evans, M; Green, A; Menown, I; Strain, W D

Abstract: In people with Type 2 diabetes, cardiovascular disease is a leading cause of morbidity and mortality. Thus, as well as controlling glucose, reducing the risk of cardiovascular events is a key goal. The results of cardiovascular outcome trials have led to updates for many national and international guidelines. England, Wales and Northern Ireland remain exceptions, with the most recent update to the National Institute for Health and Care Excellence (NICE) guidelines published in 2015. We reviewed current national and international guidelines and recommendations on the management of people with Type 2 diabetes. This article shares our consensus on clinical recommendations for the use of sodium-glucose co-transporter 2 inhibitors (SGLT-2) and glucagon-like peptide 1 receptor agonists (GLP-1RA) in people with Type 2 diabetes and established or at very high risk of cardiovascular disease in the UK. We also consider cost-effectiveness for these therapies. We recommend considering each person's cardiovascular risk and using diabetes therapies with proven cardiovascular benefits when appropriate to improve long-term outcomes and cost-effectiveness. This article is protected by copyright. All rights reserved.

Title: Initial injectable therapy in type 2 diabetes: key considerations when choosing between glucagon-like peptide 1 receptor agonists and insulin.

Citation: Metabolism: clinical and experimental; Jun 2019
Author(s): Alexopoulos, Anastasia-Stefania; Buse, John B
Abstract: Managing type 2 diabetes is complex and necessitates careful consideration of patient factors such as engagement in self-care, comorbidities and costs. Since type 2 diabetes is a progressive disease, many patients will require injectable agents, usually insulin. Recent ADA-EASD guidelines recommend glucagon-like peptide 1 receptor agonists (GLP-1 RAs) as first injectable therapy in most cases. The basis for this recommendation is the similar glycemic efficacy of GLP-1 RAs and insulin, but with GLP-1 RAs promoting weight loss instead of weight gain, at lower hypoglycemia risk, and with cardiovascular benefits in patients with pre-existing cardiovascular disease. GLP-1 RAs also reduce burden of glucose self-monitoring. However, tolerability and costs are important considerations, and notably, rates of drug discontinuation are often higher for GLP-1 RAs than basal insulin. To minimize risk of gastrointestinal symptoms patients should be started on lowest doses of GLP-1 RAs and up-titrated slowly. Overall healthcare costs may be lower with GLP-1 RAs compared to insulin. Though patient-level costs may still be prohibitive, GLP-1 RAs can replace 50-80 units of insulin daily and reduce costs associated with glucose self-monitoring. Decisions regarding initiating injectable therapy should be individualized. This review provides a framework to guide decision-making in the real-world setting.

Title: Efficacy and Safety of Esaxerenone (CS-3150) for the Treatment of Type 2 Diabetes with Microalbuminuria: A Randomized, Double-Blind, Placebo-Controlled, Phase II Trial.

Citation: Clinical journal of the American Society of Nephrology : CJASN; Jun 2019
Author(s): Ito, Sadayoshi; Shikata, Kenichi; Nangaku, Masaomi; Okuda, Yasuyuki; Sawanobori, Tomoko

Background and Objectives: The progression of kidney disease in some patients with type 2 diabetes mellitus may not be adequately suppressed by renin-angiotensin system inhibitors. Esaxerenone (CS-3150) is a nonsteroidal mineralocorticoid receptor blocker that has shown kidney protective effects in preclinical studies, and it is a potential add-on therapy to treat diabetic kidney disease. This phase 2 study evaluated the efficacy and safety of esaxerenone in Japanese patients with type 2 diabetes mellitus and microalbuminuria.

Design, Setting, Participants, & Measurements: This multicenter, randomized, double-blind, placebo-controlled trial enrolled 365 hypertensive or normotensive patients with type 2 diabetes mellitus and microalbuminuria (urinary albumin-to-creatinine ratio ≥45 to <300 mg/g creatinine) treated with renin-angiotensin system inhibitor who had eGFR≥30 ml/min per 1.73 m2. Participants were randomized to receive 0.625, 1.25, 2.5, or 5 mg/d esaxerenone or placebo for 12 weeks. The primary end point was the change in urinary albumin-to-creatinine ratio from baseline to week 12 (with last observation carried forward).

Results: Esaxerenone treatment at 1.25, 2.5, and 5 mg/d significantly reduced urinary albumin-to-creatinine ratio by the end of treatment (38%, 50%, and 56%, respectively) compared with placebo (7%; all P<0.001). The urinary albumin-to-creatinine ratio remission rate (defined as urinary albumin-to-creatinine ratio <30 mg/g creatinine at the end of treatment and ≥30% decrease from baseline) was 21% in the 2.5- and 5-mg/d groups versus 3% for placebo (both P<0.05). Adverse events occurred slightly more frequently with esaxerenone versus placebo, but the frequencies of drug-related adverse events and discontinuation rates were similar in the placebo and the 0.625-, 1.25-, and 2.5-mg/d groups. Drug-related adverse events and treatment discontinuations were marginally higher in the 5-mg/d group. The most common drug-related adverse event was hyperkalemia, which was dose proportional.

Conclusions: Adding esaxerenone at 1.25, 2.5, and 5 mg/d for 12 weeks to an ongoing renin-angiotensin system inhibitor significantly reduces urinary albumin-to-creatinine ratio in patients with type 2 diabetes mellitus and microalbuminuria.

Title: Cross-sectional study about the use of telemedicine for type 2 diabetes mellitus management in Spain: patient’s perspective. The EnREDa2 Study.

Citation: BMJ open; Jun 2019; vol. 9 (no. 6); p. e028467
Author(s): Rodríguez-Fortúnez, Patricia; Franch-Nadal, Josep; Fornos-Pérez, José A; Martínez-Martínez, Fernando; de Paz, Hector David; Orera-Peña, María Luisa

Objectives: The usefulness of telemedicine (TM) in type 2 diabetes mellitus (T2DM) has been discussed in recent years. The aim of this study is to describe patients’ perceptions about TM and to identify preferences on TM resources, in Spain.

Design: An observational, cross-sectional study was conducted using a structured questionnaire.

Participants: 1036 patients with T2DM accepted to participate in the study (response rate: 68%).

Results: Blood glucose values were recorded by 85.9% of the patients while data such as lifestyle habits were only recorded by 14.4% of the patients. Previous experience in TM was reported by 9.8% of the patients, out of which 70.5% were satisfied with its service and 73.5% considered that the use of TM had optimised their T2DM management. However, most of these patients noted aspects to be improved such as user-friendliness (81.4%), interaction with the medical team (78.4%) and time required for recording/transferring data (78.4%). Experienced patients had better perception about TM usefulness than naïve patients for all listed aspects (p<0.05). Among naïve patients, 38.2% expressed their willingness to participate in TM programmes, but only 4.7% were invited to do so. Patients considered that physicians’ (77.5%) and pharmacists’ (75.5%) encouragement can boost the use of TM.

Conclusions: In Spain, nearly 10% of patients with T2DM have experience with TM and it is well accepted, especially one based on glucometers. Nevertheless, in order to promote TM use, easier and time-saving programmes for patient-physician interaction should be optimised.

Title: Comparison of the Effectiveness of Lifestyle Modification with Other Treatments on the Incidence of Type 2 Diabetes in People at High Risk: A Network Meta-Analysis.

Citation: Nutrients; Jun 2019; vol. 11 (no. 6)
Author(s): Yamaoka, Kazue; Nemoto, Asuka; Tango, Toshiro

Background: Many clinical trials have been conducted to verify the effects of interventions for prevention of type 2 diabetes (T2D) using different treatments and outcomes. The aim of this study was to compare the effectiveness of lifestyle modifications (LM) with other treatments in persons at high risk of T2D by a network meta-analysis (NMA).

Methods: Searches were performed of PUBMED up to January 2018 to identify randomized controlled trials. The odds ratio (OR) with onset of T2D at 1 year in the intervention group (LM, dietary, exercise, or medication) versus a control group (standard treatments or placebo) were the effect sizes. Frequentist and Bayesian NMAs were conducted.

Results: Forty-seven interventions and 12 treatments (20,113 participants) were used for the analyses. The OR in the LM was approximately 0.46 (95% CI: 0.33 to 0.61) times lower compared to the standard intervention by the Bayesian approach. The effects of LM compared to other treatments by indirect comparisons were not significant.

Conclusions: This meta-analysis further strengthened the evidence that LM reduces the onset of T2D compared to standard and placebo interventions and appears to be at least as effective as nine other treatments in preventing T2D.

Title: Type 2 diabetes treatment and outcomes worldwide: A short review of the DISCOVER study programme.

Citation: Diabetes, obesity & metabolism; Jun 2019
Author(s): Khunti, Kamlesh; Ji, Linong; Medina, Jesús; Surmont, Filip; Kosiborod, Mikhail

Abstract: The global burden of type 2 diabetes (T2D) is increasing, indicating an urgent need for improved disease prevention and management strategies. Contemporary, global, real-world data,
which are collected in a consistent way, on the characteristics, treatment and outcomes of people with T2D are lacking, particularly in low- and middle-income countries where disease burden is increasing most rapidly. The DISCOVER study programme (ClinicalTrials.gov identifiers: NCT02322762 and NCT02226822) is a global, prospective, 3-year programme of observational research, which has been designed to fill this knowledge gap. DISCOVER is being conducted in 38 countries across six continents, including several lower-middle- and upper-middle-income countries where patients have rarely or never been studied previously. A total of 15 992 people with T2D who had initiated a second-line glucose-lowering therapy have been recruited. Data being collected include information on demographics, clinical and treatment characteristics, socio-economic status, clinical outcomes, and patient-reported outcomes. Findings from DISCOVER will provide unique insights into current patterns of T2D care worldwide, which should contribute to informing clinical guidelines and health policy, and may help to improve patient care. This article is protected by copyright. All rights reserved.

Title: The New Era for Reno-Cardiovascular Treatment in Type 2 Diabetes.

Citation: Journal of clinical medicine; Jun 2019; vol. 8 (no. 6)

Author(s): García-Carro, Clara; Vergara, Ander; Agraz, Irene; Jacobs-Cachá, Conxita; Espinel, Eugenia; Seron, Daniel; Soler, María José

Abstract: Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease in the developed world. Until 2016, the only treatment that was clearly demonstrated to delay the DKD was the renin-angiotensin system blockade, either by angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. However, this strategy only partially covered the DKD progression. Thus, new strategies for reno-cardiovascular protection in type 2 diabetic patients are urgently needed. In the last few years, hypoglycaemic drugs, such as sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, demonstrated a cardioprotective effect, mainly in terms of decreasing hospitalization for heart failure and cardiovascular death in type 2 diabetic patients. In addition, these drugs also demonstrated a clear renoprotective effect by delaying DKD progression and decreasing albuminuria. Another hypoglycaemic drug class, dipeptidyl peptidase 4 inhibitors, has been approved for its use in patients with advanced chronic kidney disease, avoiding, in part, the need for insulinization in this group of DKD patients. Studies in diabetic and non-diabetic experimental models suggest that these drugs may exert their reno-cardiovascular protective effect by glucose and non-glucose dependent mechanisms. This review focuses on newly demonstrated strategies that have shown reno-cardiovascular benefits in type 2 diabetes and that may change diabetes management algorithms.

Title: Clinical benefits of switching to insulin degludec irrespective of previous basal insulin therapy in people with Type 1 or Type 2 diabetes: evidence from a European, multicentre, retrospective, non-interventional study (EU-TREAT).

Citation: Diabetic Medicine; Jul 2019; vol. 36 (no. 7); p. 868-877


Aims: To investigate whether the benefits of switching to insulin degludec observed in the European retrospective chart review study EU-TREAT were dependent on the previous basal insulin used.

Methods: People with Type 1 or Type 2 diabetes were switched to insulin degludec from other basal insulins ≥6 months before data collection. Participants were stratified into three groups based on their previous basal insulin: insulin glargine 100 units/ml (Type 1: n=888; Type 2: n=259); insulin detemir (Type 1: n=726; Type 2: n=415); and neutral protamine Hagedorn (Type 1: n=53; Type 2: n=95). Their glycaemic control and hypoglycaemia incidence at 6 and 12 months post-switch vs pre-switch was then evaluated.

Results: Significant HbA1c reductions were achieved in all previous basal insulin groups for participants with Type 1 diabetes [insulin glargine 100 units/ml: −2.08 mmol/mol (−0.19%); insulin
detemir: −2.40 mmol/mol (−0.22%)) and those with Type 2 diabetes [insulin glargine 100 units/ml: −5.90 mmol/mol (−0.54%); insulin detemir: −6.01 mmol/mol (−0.55%); neutral protamine Hagedorn: −2.73 mmol/mol (−0.25%)] at 6 months, except for the relatively small neutral protamine Hagedorn group in those with Type 1 diabetes [−1.75 mmol/mol (−0.16%)], where statistical significance was not reached. At 6 months in the Type 1 diabetes group, switching to insulin degludec from insulin glargine 100 units/ml resulted in significantly lower hypoglycaemia rates across all hypoglycaemia categories; for the insulin detemir group, this significance was also observed for severe and nocturnal non-severe hypoglycaemia, while the low number of people in the neutral protamine Hagedorn group resulted in nonsignificant reductions in hypoglycaemia rates. At 6 months in the people with Type 2 diabetes, switching to insulin degludec resulted in significantly lower rates of hypoglycaemia across all categories for all groups. Similar outcomes were observed at 12 months.

Conclusions: Switching to insulin degludec from other basal insulins can improve glycaemic control and/or reduce hypoglycaemia risk in people with diabetes (although there was a nonsignificant reduction in HbA1c and hypoglycaemia rates for the neutral protamine Hagedorn group in Type 1 diabetes) under routine care. What's new?: The EU-TREAT study previously demonstrated that switching to insulin degludec from other basal insulins improved glycaemic control and significantly lowered the risk of hypoglycaemia in people with Type 1 or Type 2 diabetes. In the present study, people from EU-TREAT were stratified into three groups, based on type of previous basal insulin used. Results showed that people who switched to insulin degludec from glargine U100 or detemir benefitted from improved glycaemic control and a lowered risk of hypoglycaemia at lower or similar insulin doses. This study indicates that insulin degludec can offer improved glycaemic control and reduced hypoglycaemia risk, irrespective of previous basal insulin therapy.

**Title:** Management of hypoglycemia in older adults with type 2 diabetes.

**Citation:** Postgraduate Medicine; May 2019; vol. 131 (no. 4); p. 241-250

**Author(s):** Freeman, Jeffrey

**Abstract:** Treatment of older adults with type 2 diabetes (T2D) is complex because they represent a heterogeneous group with a broad range of comorbidities, functional abilities, socioeconomic status, and life expectancy. Older adults with T2D are at high risk of recurring hypoglycemia, a condition associated with marked morbidity and mortality, because their counter-regulatory mechanism to hypoglycemia is attenuated, and recurring hypoglycemic episodes can lead to hypoglycemia unawareness. In addition, polypharmacy, a result of multiple chronic comorbidities (including heart disease, stroke, and chronic kidney disease), can increase the risk of severe hypoglycemia, especially when patients are taking sulfonylureas or insulin. Often the signs of hypoglycemia are nonspecific (sweating, dizziness, confusion, visual disturbances) and are mistaken for neurological symptoms or dementia. Consequences of hypoglycemia include acute and long-term cognitive changes, cardiac arrhythmia and myocardial infarction, serious falls, frailty, and death, often resulting in hospitalization, which come at a high economic cost. The American Diabetes Association has recently added three new recommendations regarding hypoglycemia in the elderly, highlighting individualized pharmacotherapy with glucose-lowering agents with a low risk of hypoglycemia and proven cardiovascular safety, avoidance of overtreatment, and simplifying treatment regimens while maintaining HbA1c targets. Thus, glycemic goals can be relaxed in the older population as part of individualized care, and physicians must make treatment decisions that best serve their patients' circumstances. This article highlights the issues faced by older people with T2D, the risk factors for hypoglycemia in this population, and the challenges faced by health care providers regarding glycemic management in this patient group.

**Title:** Intensive Glucose Control in Patients with Type 2 Diabetes - 15-Year Follow-up.

**Citation:** New England Journal of Medicine; Jun 2019; vol. 380 (no. 23); p. 2215-2224

**Author(s):** Reaven, Peter D.; Emanuele, Nicholas V.; Wiitala, Wyndy L.; Bahn, Gideon D.; Reda, Domenic J.; McCarren, Madeline; Duckworth, William C.; Hayward, Rodney A.
**Background:** We previously reported that a median of 5.6 years of intensive as compared with standard glucose lowering in 1791 military veterans with type 2 diabetes resulted in a risk of major cardiovascular events that was significantly lower (by 17%) after a total of 10 years of combined intervention and observational follow-up. We now report the full 15-year follow-up.

**Methods:** We observationally followed enrolled participants (complete cohort) after the conclusion of the original clinical trial by using central databases to identify cardiovascular events, hospitalizations, and deaths. Participants were asked whether they would be willing to provide additional data by means of surveys and chart reviews (survey cohort). The prespecified primary outcome was a composite of major cardiovascular events, including nonfatal myocardial infarction, nonfatal stroke, new or worsening congestive heart failure, amputation for ischemic gangrene, and death from cardiovascular causes. Death from any cause was a prespecified secondary outcome.

**Results:** There were 1655 participants in the complete cohort and 1391 in the survey cohort. During the trial (which originally enrolled 1791 participants), the separation of the glycated hemoglobin curves between the intensive-therapy group (892 participants) and the standard-therapy group (899 participants) averaged 1.5 percentage points, and this difference declined to 0.2 to 0.3 percentage points by 3 years after the trial ended. Over a period of 15 years of follow-up (active treatment plus post-trial observation), the risks of major cardiovascular events or death were not lower in the intensive-therapy group than in the standard-therapy group (hazard ratio for primary outcome, 0.91; 95% confidence interval [CI], 0.78 to 1.06; P = 0.23; hazard ratio for death, 1.02; 95% CI, 0.88 to 1.18). The risk of major cardiovascular disease outcomes was reduced, however, during an extended interval of separation of the glycated hemoglobin curves (hazard ratio, 0.83; 95% CI, 0.70 to 0.99), but this benefit did not continue after equalization of the glycated hemoglobin levels (hazard ratio, 1.26; 95% CI, 0.90 to 1.75).

**Conclusions:** Participants with type 2 diabetes who had been randomly assigned to intensive glucose control for 5.6 years had a lower risk of cardiovascular events than those who received standard therapy only during the prolonged period in which the glycated hemoglobin curves were separated. There was no evidence of a legacy effect or a mortality benefit with intensive glucose control. (Funded by the VA Cooperative Studies Program; VADT ClinicalTrials.gov number, NCT00032487.)

**Title:** Efficacy and safety of linagliptin to improve glucose control in older people with type 2 diabetes on stable insulin therapy: A randomized trial.

**Citation:** Diabetes, obesity & metabolism; Jul 2019

**Author(s):** Ledesma, Gilbert; Umpierrez, Guillermo E; Morley, John E; Lewis-D’Agostino, Diane; Keller, Annett; Meinicke, Thomas; van der Walt, Sandra; von Eynatten, Maximilian

**Aims:** Intensification of glucose-lowering therapy in elderly patients with type 2 diabetes mellitus (T2DM) receiving insulin can be challenging due to the increased risk of hypoglycemia. We assessed the addition of linagliptin as an alternative to insulin up-titration in these individuals.

**Methods:** This phase 4, randomized, multicenter, double-blinded, placebo-controlled, 24-week study recruited individuals on stable insulin, with baseline glycated hemoglobin (HbA1c) 7.0-10.0%, age ≥60 years, and body mass index ≤45 kg/m2. HbA1c and fasting plasma glucose were measured at study visits, and participants assessed glycemic control with a self-monitoring blood glucose device. Adverse events (AEs) were reported during the study.

**Results:** 302 participants were randomized 1:1 to linagliptin 5 mg qd and placebo, with one third of patients from Japan. Study population age and HbA1c (baseline mean ± SD) were 72.4±5.4 years and 8.2±0.8%, respectively; ~80% of participants were ≥70 years. 80% had macrovascular complications, one third had a baseline estimated glomerular filtration rate 15 years. Linagliptin significantly improved glucose control at 24 weeks (HbA1c adjusted mean change versus placebo: -0.63%; p<0.0001), and the likelihood of achieving predefined HbA1c targets without hypoglycemia (HbA1c <8.0%: OR 2.02; p<0.05 and HbA1c <7.0%: OR 2.44; p<0.01). Linagliptin versus placebo was well tolerated, with similar incidences of AEs, including clinically important hypoglycemia (blood glucose <54 mg/dl) or severe hypoglycemia.
Conclusions: Addition of linagliptin improves glucose control without an excess of hypoglycemia in older patients with T2DM on stable insulin therapy. This article is protected by copyright. All rights reserved.

Title: Canagliflozin and Cardiovascular and Renal Outcomes in Type 2 Diabetes and Chronic Kidney Disease in Primary and Secondary Cardiovascular Prevention Groups: Results from the Randomized CREDENCE Trial.

Citation: Circulation; Jul 2019

Author(s): Mahaffey, Kenneth W; Jardine, Meg J; Bompoint, Severine; Cannon, Christopher P; Neal, Bruce; Heerspink, Hiddo J L; Charytan, David M; Edwards, Robert; Agarwal, Rajiv; Bakris, George; Bull, Scott; Capuano, George; de Zeeuw, Dick; Greene, Tom; Levin, Adeera; Pollock, Carol; Sun, Tao; Wheeler, David C; Yavin, Yshai; Zhang, Hong; Zinman, Bernard; Rosenthal, Norman; Brenner, Barry M; Perkovic, Vlado; CREDENCE study investigators

Background: Canagliflozin reduces the risk of kidney failure in patients with type 2 diabetes and chronic kidney disease, but effects on specific cardiovascular outcomes are uncertain, as are effects in people without prior cardiovascular disease (primary prevention).

Methods: In CREDENCE, 4401 participants with type 2 diabetes and chronic kidney disease were randomly assigned to canagliflozin or placebo on a background of optimized standard of care.

Results: Primary prevention participants (N=2181; 49.6%) were younger (61 vs 65 years), more often female (37% vs 31%), and had shorter diabetes duration (15 vs 16 years) compared to secondary prevention participants (N=2220; 50.4%). Canagliflozin reduced the risk of major cardiovascular events overall (hazard ratio [HR], 0.80; 95% confidence interval [CI] 0.67-0.95; P=0.01), with consistent reductions in both the primary (HR, 0.68; 95% CI, 0.49-0.94) and secondary (HR, 0.85; 95% CI, 0.69-1.06) prevention groups (P-interaction 0.25). Effects were also similar for the components of the composite including cardiovascular death (HR, 0.78; 95% CI, 0.61-1.00), nonfatal myocardial infarction (HR, 0.81; 95% CI, 0.59-1.10), and nonfatal stroke (HR, 0.80; 95% CI, 0.56-1.15). The risk of the primary composite renal outcome and the composite of cardiovascular death or hospitalization for heart failure were also consistently reduced in both the primary and secondary prevention groups (P-interaction >0.5 for each outcome).

Conclusions: Canagliflozin significantly reduced major cardiovascular events, as well as kidney failure, in patients with type 2 diabetes and chronic kidney disease, including in participants who did not have prior cardiovascular disease.

Clinical Trial Registration: URL: https://ClinicalTrials.gov Unique identifier: NCT02065791.

Title: 'We're all in the same boat': A qualitative study on how groups work in a diabetes prevention and management programme.

Citation: British journal of health psychology; Jul 2019

Author(s): Borek, Aleksandra J; Abraham, Charles; Greaves, Colin J; Tarrant, Mark; Garner, Nikki; Pascale, Melanie

Objectives: Although many health interventions are delivered in groups, it is unclear how group context can be best used to promote health-related behaviour change and what change processes are most helpful to participants. This study explored participants' experiences of attending type 2 diabetes prevention and management programme, and their perceptions of how group participation influenced changes in diet and physical activity.

Design: Qualitative.

Methods: Semi-structured telephone interviews were conducted with 20 participants (twelve men) from nine groups in the Norfolk Diabetes Prevention Study. Interviews were audio-recorded, transcribed verbatim, and analysed using thematic analysis in NVivo.

RESULTS Participants benefited from individual change processes, including information provision, structuring and prioritizing health
goals, action planning, self-monitoring, and receiving feedback. They also benefited from group processes, including having a common purpose, sharing experiences, making social comparisons, monitoring and accountability, and providing and receiving social support in the groups. Participants’ engagement with, and benefits from, the groups were enhanced when there was a supportive group context (i.e., group cohesion, homogeneous group composition, and a positive group atmosphere). Optimal facilitation to develop an appropriate group context and initiate effective change processes necessitated good facilitator interpersonal and professional skills, credibility and empathy, and effective group facilitation methods. Participants reported developing a sense of responsibility and making behaviour changes that resulted in improvements in health outcomes and weight loss.

Conclusions: This study highlights the role of individual and group processes in facilitating health-promoting behaviour change, and the importance of group context and optimal facilitation in promoting engagement with the programme. Statement of contribution What is already known on this subject? Many health interventions, including programmes to help prevent or manage diabetes and facilitate weight loss, are delivered in groups. Such group-based behaviour-change interventions are often effective in facilitating psychological and behaviour change. There is considerable research and theory on individual change processes and techniques, but less is known about which change processes and techniques facilitate behaviour change in group settings. What does this study add? This study contributes to our understanding of how participating in group-based health programmes may enhance or impede individual behaviour change. It identified individual (intrapersonal) and group (interpersonal, facilitated through group interaction) change processes that were valued by group participants. The findings also show how these change processes may be affected by the group context. A diagram summarizes the identified themes helping to understand interactions between these key processes occurring in groups. The study offers an insight into participants’ views on, and experiences of, attending a group-based diabetes prevention and management programme. Thus, it helps better understand how the intervention might have helped them (or not) and what processes may have influenced intervention outcomes. Key practical recommendations for designing and delivering group-based behaviour-change interventions are presented, which may be used to improve future group-based health interventions.

Title: Glycemic control and insulin treatment alter fracture risk in older men with type 2 diabetes mellitus.

Citation: Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research; Jul 2019

Author(s): Lee, Richard H; Sloane, Richard; Pieper, Carl; Lyles, Kenneth W; Adler, Robert A; Van Houtven, Courtney; LaFleur, Joanne; Colón-Emeric, Cathleen

Abstract: Diabetes mellitus among older men has been associated with increased bone mineral density, but paradoxically increased fracture risk. Given the interactions among medication treatment, glycemic control, and diabetes-associated comorbidities, the relative effects of each factor remains unclear. This retrospective study includes 652,901 male Veterans age ≥65 years with diabetes and baseline hemoglobin A1c (HbA1c) value. All subjects received primary care in the Veterans Health Administration (VHA) from 2000 to 2010. Administrative data included ICD9 diagnoses and pharmacy records, and was linked to Medicare fee-for-service data. Hazard ratios for any clinical fracture and hip fracture were calculated using competing risk hazards models, adjusted for fracture risk factors including age, race/ethnicity, BMI, alcohol and tobacco use, rheumatoid arthritis, corticosteroid use, as well as diabetes-related comorbidities including cardiovascular disease, chronic kidney disease, and peripheral neuropathy. HbA1c < 6.5% was associated with a higher risk of any clinical fracture [HR 1.08 (95%CI: 1.06-1.11)], compared to the reference HbA1c of 7.5-8.5%. Fracture risk was not increased among those with A1c ≥ 8.5%, nor among those with A1c 6.5-7.5%. Use of insulin was independently associated with greater risk of fracture (HR 1.10, 95% CI: 1.07-1.12). There was a significant interaction between insulin use and HbA1c level, (P < 0.001), such that those using insulin with HbA1c < 6.5% had HR 1.23 and those with HbA1c 6.5-7.5% had HR 1.15. Metformin use was associated with decreased fracture risk (HR 0.88, 95% CI: 0.87-0.90). We conclude that among older men with diabetes, those with HbA1c lower than 6.5% are at increased risk for any clinical and hip fracture. Insulin use is associated with higher fracture risk, especially among those with tight glycemic control. Our findings demonstrate the importance of the treatment regimen and avoiding
Title: Evaluating the impact of self-monitoring of blood glucose frequencies on glucose control in patients with type 2 diabetes who do not use insulin: A systematic review and meta-analysis.

Citation: International journal of clinical practice; Jul 2019; vol. 73 (no. 7); p. e13357

Author(s): Xu, Yingqi; Tan, David Hsien Yung; Lee, Joyce Yu-Chia

Aims: International diabetes guidelines have not established the frequencies of self-monitoring of blood glucose in patients with type 2 diabetes (T2D) who do not use insulin. The present study aimed to assess the impact of self-monitoring of blood glucose (SMBG) frequencies on the glucose control and other outcomes in non-insulin-treated patients with T2D.

Methods: A literature search was performed in four databases. Randomised controlled trials with ≥6-month follow-up duration that compared the impact of different frequencies of SMBG on glycated haemoglobin A1c (HbA1c) were included. Studies with abstract only or reported effects of SMBG as a secondary outcome were excluded.

Results: Of the 1557 studies identified, 12 RCTs with a total of 3350 patients were analysed. Overall, performing SMBG for 8 to 14 times per week was correlated with a better HbA1c control at 6 months (MD -0.46%, 95% CI -0.54 to -0.39) and 12 months (MD -0.20%, 95% CI -0.29 to -0.11). However, up to seven measurements of SMBG per week did not significantly affect glycaemic control. In addition, performing SMBG between 8 and 14 times per week was also associated with improved BMI (MD -0.46, 95% CI -0.84 to -0.08). When the results of SMBG were applied to adjust diabetes medication, a significant reduction in HbA1c levels was observed in the intervention arm compared to the control arm.

Conclusions: Eight to 14 measurements of SMBG per week were associated with an improved glycaemic control and a reduced BMI in patients with T2D not using insulin.

Title: Efficacy and safety of sodium-glucose cotransporter-2 inhibitors in type 2 diabetes mellitus with inadequate glycemic control on metformin: a meta-analysis.

Citation: Archives of endocrinology and metabolism; Jun 2019

Author(s): Jingfan, Zhang; Ling, Li; Cong, Liu; Ping, Li; Yu, Chen

Objectives: To provide a meta-analysis of the clinical efficacy and safety of sodium glucose co-transporter 2 inhibitors (SGLT2-i), as a combination treatment with metformin in type 2 diabetes mellitus (T2DM) patients with inadequate glycemic control with metformin alone.

Materials and Methods: We have searched randomized controlled trials (RCTs) in the database: MEDLINE, Embase and Cochrane Collaborative database. We used mean differences (MD) to assess the efficacy of glycemic and other clinical parameters, and risk ratios (RR) to evaluate the adverse events for safety endpoints. The heterogeneity was evaluated by I2.

Results: Finally 9 studies were included. SGLT2-i plus metformin had higher reduction level in HbA1C [MD = -0.50, 95% CI (-0.62, -0.38), p < 0.00001], FPG [MD = -1.12, 95%CI (-1.38, -0.87), p < 0.00001], body weight [MD = -1.72, 95% CI (-2.05, -1.39), p < 0.00001], SBP [MD = -4.44, 95% CI (-5.45, -3.43), p < 0.00001] and DBP [MD = -1.74, 95% CI (-2.40, -1.07), p < 0.00001] compared with metformin monotherapy. However, SGLT2-i plus metformin group had higher risk of genital infection [RR = 3.98, 95% CI (2.38, 6.67), p < 0.00001]. No significant difference was found in the risk of hypoglycemia, urinary tract infection or volume related adverse events.

Conclusions: Although the risk of genital infection may increase, SGLT2-i plus metformin may provide an attractive treatment option to those T2DM patients who are unable to achieve glycemic control with metformin alone, based on its effects on glycemic control, reducing body weight and lowering blood pressure.
Title: Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial

Citation: The Lancet; Jul 2019; vol. 394 (no. 10193); p. 131

Author(s): Gerstein, Hertzel C; Colhoun, Helen M; Dagenais, Gilles R; Diaz, Rafael; Lakshmanan, Mark; Pais, Prem; Probstfield, Jeffrey; Botros, Fady T; Riddle, Matthew C; Rydén, Lars; et al

Background: Two glucagon-like peptide-1 (GLP-1) receptor agonists reduced renal outcomes in people with type 2 diabetes at risk for cardiovascular disease. We assessed the long-term effect of the GLP-1 receptor agonist dulaglutide on renal outcomes in an exploratory analysis of the REWIND trial of the effect of dulaglutide on cardiovascular disease.

Methods: REWIND was a multicentre, randomised, double-blind, placebo-controlled trial at 371 sites in 24 countries. Men and women aged at least 50 years with type 2 diabetes who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either weekly subcutaneous injection of dulaglutide (1·5 mg) or placebo and followed up at least every 6 months for outcomes. Urinary albumin-to-creatinine ratios (UACRs) and estimated glomerular filtration rates (eGFRs) were estimated from urine and serum values measured in local laboratories every 12 months. The primary outcome (first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes), secondary outcomes (including a composite microvascular outcome), and safety outcomes of this trial have been reported elsewhere. In this exploratory analysis, we investigate the renal component of the composite microvascular outcome, defined as the first occurrence of new macroalbuminuria (UACR >33·9 mg/mmol), a sustained decline in eGFR of 30% or more from baseline, or chronic renal replacement therapy. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01394952.

Findings: Between Aug 18, 2011, and Aug 14, 2013, 9901 participants were enrolled and randomly assigned to receive dulaglutide (n=4949) or placebo (n=4952). At baseline, 791 (7·9%) had macroalbuminuria and mean eGFR was 76·9 mL/min per 1·73 m² (SD 22·7). During a median follow-up of 5·4 years (IQR 5·1–5·9) comprising 51,820 person-years, the renal outcome developed in 848 (17·1%) participants at an incidence rate of 3·5 per 100 person-years in the dulaglutide group and in 970 (19·6%) participants at an incidence rate of 4·1 per 100 person-years in the placebo group (hazard ratio [HR] 0·85, 95% CI 0·77–0·93; p=0·0004). The clearest effect was for new macroalbuminuria (HR 0·77, 95% CI 0·68–0·87; p<0·0001), with HRs of 0·89 (0·78–1·01; p=0·066) for sustained decline in eGFR of 30% or more and 0·75 (0·39–1·44; p=0·39) for chronic renal replacement therapy. Interpretation Long-term use of dulaglutide was associated with reduced composite renal outcomes in people with type 2 diabetes.

Funding: Eli Lilly and Company.

Title: Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial

Citation: The Lancet; Jul 2019; vol. 394 (no. 10193); p. 121

Author(s): Gerstein, Hertzel C; Colhoun, Helen M; Dagenais, Gilles R; Diaz, Rafael; Lakshmanan, Mark; Pais, Prem; Probstfield, Jeffrey; Riesmeyer, Jeffrey S; Riddle, Matthew C; Rydén, Lars; et al

Background: Three different glucagon-like peptide-1 (GLP-1) receptor agonists reduce cardiovascular outcomes in people with type 2 diabetes at high cardiovascular risk with high glycated haemoglobin A1c (HbA1c) concentrations. We assessed the effect of the GLP-1 receptor agonist dulaglutide on major adverse cardiovascular events when added to the existing antihyperglycaemic regimens of individuals with type 2 diabetes with and without previous cardiovascular disease and a wide range of glycaemic control.

Methods: This multicentre, randomised, double-blind, placebo-controlled trial was done at 371 sites in 24 countries. Men and women aged at least 50 years with type 2 diabetes who had either a previous cardiovascular event or cardiovascular risk factors were randomly assigned (1:1) to either...
weekly subcutaneous injection of dulaglutide (1·5 mg) or placebo. Randomisation was done by a computer-generated random code with stratification by site. All investigators and participants were masked to treatment assignment. Participants were followed up at least every 6 months for incident cardiovascular and other serious clinical outcomes. The primary outcome was the first occurrence of the composite endpoint of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes (including unknown causes), which was assessed in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01394952.

Findings: Between Aug 18, 2011, and Aug 14, 2013, 9901 participants (mean age 66·2 years [SD 6·5], median HbA1c 7·2% [IQR 6·6–8·1], 4589 [46·3%] women) were enrolled and randomly assigned to receive dulaglutide (n=4949) or placebo (n=4952). During a median follow-up of 5·4 years (IQR 5·1–5·9), the primary composite outcome occurred in 594 (12·0%) participants at an incidence rate of 2·4 per 100 person-years in the dulaglutide group and in 663 (13·4%) participants at an incidence rate of 2·7 per 100 person-years in the placebo group (hazard ratio [HR] 0·88, 95% CI 0·79–0·99; p=0·026). All-cause mortality did not differ between groups (536 [10·8%] in the dulaglutide group vs 592 [12·0%] in the placebo group; HR 0·90, 95% CI 0·80–1·01; p=0·067). 2347 (47·4%) participants assigned to dulaglutide reported a gastrointestinal adverse event during follow-up compared with 1687 (34·1%) participants assigned to placebo (p<0·0001). Interpretation Dulaglutide could be considered for the management of glycaemic control in middle-aged and older people with type 2 diabetes with either previous cardiovascular disease or cardiovascular risk factors.

Funding: Eli Lilly and Company.

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Role of diet in type 2 diabetes incidence: umbrella review of meta-analyses of prospective observational studies

Author(s): Neuenschwander, Manuela; Ballon, Aurélie; Weber, Katharina S; Norat, Teresa; Aune, Dagfinn; Schwingshackl, Lukas; Schlesinger, Sabrina

Source: BMJ : British Medical Journal (Online); Jul 2019; vol. 366

Objective: To summarise the evidence of associations between dietary factors and incidence of type 2 diabetes and to evaluate the strength and validity of these associations.

Design: Umbrella review of systematic reviews with meta-analyses of prospective observational studies.

Data sources: PubMed, Web of Science, and Embase, searched up to August 2018.

Eligibility criteria: Systematic reviews with meta-analyses reporting summary risk estimates for the associations between incidence of type 2 diabetes and dietary behaviours or diet quality indices, food groups, foods, beverages, alcoholic beverages, macronutrients, and micronutrients.

Results: 53 publications were included, with 153 adjusted summary hazard ratios on dietary behaviours or diet quality indices (n=12), food groups and foods (n=56), beverages (n=10), alcoholic beverages (n=12), macronutrients (n=32), and micronutrients (n=31), regarding incidence of type 2 diabetes. Methodological quality was high for 75% (n=115) of meta-analyses, moderate for 23% (n=35), and low for 2% (n=3). Quality of evidence was rated high for an inverse association for type 2 diabetes incidence with increased intake of whole grains (for an increment of 30 g/day, adjusted summary hazard ratio 0.87 (95% confidence interval 0.82 to 0.93)) and cereal fibre (for an increment of 10 g/day, 0.75 (0.65 to 0.86)), as well as for moderate intake of total alcohol (for an intake of 12-24 g/day v no consumption, 0.75 (0.67 to 0.83)). Quality of evidence was also high for the association for increased incidence of type 2 diabetes with higher intake of red meat (for an increment of 100 g/day, 1.17 (1.08 to 1.26)), processed meat (for an increment of 50 g/day, 1.37 (1.22 to 1.54)), bacon (per two slices/day, 2.07 (1.40 to 3.05)), and sugar sweetened beverages (for an increase of one serving/day, 1.26 (1.11 to 1.43)).

Conclusions: Overall, the association between dietary factors and type 2 diabetes has been extensively studied, but few of the associations were graded as high quality of evidence. Further factors are likely to be important in type 2 diabetes prevention; thus, more well conducted research, with more detailed assessment of diet, is needed.

Systematic review registration

PROSPERO CRD: 42018088106.
Title: Trends in global prescribing of antidiabetic medicines in primary care: A systematic review of literature between 2000-2018

Citation: Primary Care Diabetes; 2019

Author(s): Ramzan S.; Timmins P.; Hasan S.S.; Babar Z.-U.-D.

Abstract: The aim of this review was to examine changes in the use of diabetes medicines prescribed to treat type 2 diabetes in the primary care setting. Five electronic databases were searched using strict inclusion/exclusion criteria. The quality of eligible studies was appraised using the Newcastle-Ottawa Scale. Findings show the trend has been away from using sulfonylurea and towards the use of metformin. The introduction of newer drugs has not shifted treatment outcomes and glycaemic control. It was not possible to determine how clinicians make choices about the medicines they prescribe for T2DM, or what influences those choices. Copyright © 2019 Primary Care Diabetes Europe

Sources Used: The following databases are used in the creation of this bulletin: BNI, CINAHL, EMBASE and Medline.

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