Type 2 Diabetes
Current Awareness Bulletin
October 2019

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Title: Inequalities in glycemic control in childhood onset type 2 diabetes in England and Wales—A national population-based longitudinal study.

Citation: Pediatric Diabetes; Nov 2019; vol. 20 (no. 7); p. 821-831

Author(s): Khanolkar, Amal R.; Amin, Rakesh; Taylor-Robinson, David; Viner, Russell M.; Warner, Justin; Stephenson, Terence

Background: Not much is known about glycaemic-control trajectories in childhood-onset type 2 diabetes (T2D). We investigated characteristics of children and young people (CYP) with T2D and inequalities in glycemic control.

Methods: We studied 747 CYP with T2D, 95% diabetes cases in England/Wales]. Linear mixed-effects modeling was used to assess socioeconomic and ethnic differences in longitudinal glycated hemoglobin (HbA1c) trajectories during 4 years post-diagnosis (3326 HbA1c data points, mean 4.5 data points/subject). Self-identified ethnicity was grouped into six categories. Index of Multiple Deprivation (a small geographical area-level deprivation measure) was grouped into SES quintiles for analysis.

Results: Fifty-eight percent were non-White, 66% were female, and 41% were in the most disadvantaged SES quintile. Mean age and HbA1c at diagnosis were 13.4 years and 68 mmol/mol, respectively. Following an initial decrease between diagnosis and end of year 1 (−15.2 mmol/mol 95%CI, −19.2, −11.2), HbA1c trajectories increased between years 1 and 3 (10 mmol/mol, 7.6, 12.4), followed by slight gradual decrease subsequently (−1.6 mmol/mol, −2, −1.1). Compared to White CYP, Pakistani children had higher HbA1c at diagnosis (13.2 mmol/mol, 5.6-20.9). During follow-up, mixed-ethnicity and Pakistani CYP had poorer glycemic control. Compared to children in the most disadvantaged quintile, those in the most advantaged had lower HbA1c at diagnosis (−6.3 mmol, −12.6, −0.1). Differences by SES remained during follow-up. Mutual adjustment for SES and ethnicity did not substantially alter the above estimates.

Conclusions: About two-thirds of children with childhood-onset T2D were non-White, female adolescents, just under half of whom live in the most disadvantaged areas of England and Wales. Additionally, there are substantial socioeconomic and ethnic inequalities in diabetes control.

Title: Impact of Depression and Anxiety on Change to Physical Activity Following a Pragmatic Diabetes Prevention Program Within Primary Care: Pooled Analysis From Two Randomized Controlled Trials.

Citation: Diabetes Care; Oct 2019; vol. 42 (no. 10); p. 1847-1853

Author(s): Yates, Thomas; Gray, Laura J.; Henson, Joseph; Edwardson, Charlotte L.; Khunti, Kamlesh; Davies, Melanie J.

Objective: The impact of major affective disorders on the effectiveness of diabetes prevention programs at promoting health behaviors has not been established. We investigated whether depression modifies the effectiveness of two pragmatic diabetes prevention programs at promoting increased physical activity.

Research Design and Methods: This study pooled data from two cluster randomized controlled trials (Walking Away from Type 2 Diabetes and Let’s Prevent Type 2 Diabetes) that included individuals at high risk of type 2 diabetes who were recruited from primary care. The trials used very similar intervention methods to promote physical activity and had annual follow-up over a 36-month period. Depressive symptoms were measured by the Hospital Anxiety and Depression Scale, and physical activity was measured by a piezoelectric pedometer (Let’s Prevent Type 2 Diabetes) or an accelerometer (Walking Away from Type 2 Diabetes) and expressed as steps per day.

Results: This analysis included 1,163 individuals (571 control, 592 intervention) who had concurrent baseline and follow-up data for ambulatory activity, depression, and anxiety. The median depression score was 3 at baseline; 11% of individuals were classified as having mild to severe depression. Those with no depressive symptoms at baseline or during follow-up increased their ambulatory
activity by 592 steps per day (P < 0.001); this effect decayed by 88 steps per day (95% CI 21, 155) for every additional depressive symptom score at baseline, and each increase in the depressive symptom score between baseline and follow-up further attenuated the intervention effect by 99 steps per day (95% CI 2, 196).

Conclusions: Both depressive symptom burden at baseline and change in this burden are associated with a graded reduction in the effectiveness of diabetes prevention programs at increasing physical activity in primary care.

Title: Comparative Effectiveness of Metformin Dosage Uptitration Versus Adding Another Antihyperglycemic Medication on Glycemic Control in Type 2 Diabetes Patients Failing Initial Metformin Monotherapy: A Retrospective Cohort Study.

Citation: Population Health Management; Oct 2019; vol. 22 (no. 5); p. 457-463

Author(s): Mahabaleshwarkar, Rohan; Liu, Tsai-Ling; Mulder, Holly

Abstract: Metformin is recommended as first-line treatment for type 2 diabetes (T2D). A disadvantage of metformin is the possibility of gastrointestinal adverse effects in some patients. Many T2D patients are not able to achieve/maintain glycemic control from initial metformin treatment and receive treatment intensification by means of metformin dosage uptitration or addition of a T2D drug. This retrospective study evaluated the comparative effectiveness of these 2 treatment intensification strategies. The study cohort included T2D patients at a US integrated health care system who: were initiated on metformin monotherapy (MM) during January 2009 – September 2013; had an uncontrolled HbA1c (≥7%) after at least 90 days of MM; and received metformin dosage uptitration or an additional T2D medication within 6 months of the uncontrolled HbA1c reading. Statistical techniques included Kaplan-Meier curves and Cox proportional hazards regression. The study cohort included 1167 patients, 52.4% male and 65.1% white, with a mean age of 55.3 (±11.9) years. Of these, 49.1% received metformin dosage uptitration and 50.9% received an additional T2D medication. Metformin dosage uptitration was as effective as adding another T2D medication with the probability of not achieving glycemic control (P = 0.599) and rate of glycemic control (adjusted hazard ratio = 1.28, 95% confidence interval = 0.98 – 1.68) within 6 months of intensification not significantly different between the 2 groups. Metformin dosage uptitration could be a preferable initial intensification strategy in patients failing initial MM unless there is a concern for gastrointestinal adverse effects, in which case adding a T2D medication might be preferable.

Title: Impacts of nurse-led clinic and nurse-led prescription on hemoglobin A1c control in type 2 diabetes: A meta-analysis.

Citation: Medicine; Jun 2019; vol. 98 (no. 23)

Author(s): Wang, Qun; Shen, Yan; Chen, Yongmin; Li, Xiaohua; Zhan., Yiqiang

Background: To evaluate the impacts of nurse-led clinic and nurse-led prescription on hemoglobin A1c (HbA1c) control in type 2 diabetes.

Methods: We searched relevant publications in English and Chinese database and conducted meta-analysis by Stata 12.0. We divided the case groups of included studies into 2 categories according to the role of nurse: nurse-led clinic and nurse-led prescription. Nurse-led clinic was implemented on the basis of standard diabetes care provided by doctor, and control group also receive the standard diabetes care but without nurse-led clinic. The doctor mentioned above might work alone or in a health care team. Nurse-led prescription was prescribed by nurse independently and compared with that of doctor.

Results: The meta-analysis shown that, compared with the standard diabetes care, nurse-led clinic significantly decreases HbA1c level (standard mean difference [SMD] = -0.767; 95% confidence interval [CI]: -1.062, -0.471; P < .001). In subgroup analysis, nurse-led clinic also had positive impacts
on controlling HbA1c level, no matter in developed countries (SMD = -0.353; 95% CI: -0.6, -0.106; P = .005) or developing countries (SMD = -1.114; 95% CI: -1.498, -0.73; P < .001). Additionally, there was no significant difference between nurse-led prescription and doctor prescription in controlling HbA1c levels (SMD = -0.203; 95% CI: -0.434, 0.029; P = .086).

**Conclusion:** The nurse-led clinic had positive significance for HbA1c control. Meanwhile, the impact of nurse-led prescription on controlling HbA1c is comparable to that of doctor. It is valuable to provide nurse-led clinic on the basis of standard diabetes care provided by doctor to better control HbA1c, and nurse-led prescription should be provided when doctor-led service is limited.

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**Title:** Metabolite Profiles of Incident Diabetes and Heterogeneity of Treatment Effect in the Diabetes Prevention Program.

**Citation:** Diabetes; Oct 2019

**Author(s):** Chen, Zsu-Zsu; Liu, Jinxi; Morningstar, Jordan; Heckman-Stoddard, Brandy M; Lee, Christine G; Dagogo-Jack, Samuel; Ferguson, Jane F; Hamman, Richard F; Knowler, William C; Mather, Kieren J; Perreault, Leigh; Florez, Jose C; Wang, Thomas J; Clish, Clary; Temprosa, Marinella; Gerszten, Robert E; and the Diabetes Prevention Program Research Group

**Abstract:** Novel biomarkers of type 2 diabetes (T2D) and response to preventative treatment in individuals with similar clinical risk may highlight metabolic pathways that are important in disease development. We profiled 331 metabolites in 2,015 baseline plasma samples from the Diabetes Prevention Program (DPP). Cox models were used to determine associations between metabolites and incident T2D, as well as whether associations differed by treatment group (i.e. lifestyle (ILS), metformin (MET), or placebo (PLA)) over an average of 3.2 years of follow up. We found 69 metabolites associated with incident T2D regardless of treatment randomization. In particular, cytosine was novel and associated with the lowest risk. In an exploratory analysis, 35 baseline metabolite associations with incident T2D differed across the treatment groups. Stratification by baseline levels of several of these metabolites, including specific phospholipids and adenosine monophosphate (AMP), modified the effect that ILS or MET had on diabetes development. Our findings highlight novel markers of diabetes risk and preventive treatment effect in individuals that are clinically at high risk and motivate further studies to validate these interactions.

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**Title:** Relationship between number of contacts between previous dropouts with type 2 diabetes and health care professionals on glycaemic control: A cohort study in public primary health care.

**Citation:** Primary care diabetes; Oct 2019; vol. 13 (no. 5); p. 468-473

**Author(s):** Kauppila, Timo; Eriksson, Johan G; Honkasalo, Mikko; Raina, Marko; Laine, Merja K

**Aim:** Previous study findings have shown that more frequent contacts with the diabetes care team predict better diabetes control. It is unknown whether this is true also for previous dropouts with type 2 diabetes (T2D). The aim of this study was to evaluate if those previous dropouts with T2D who succeeded to improve their glycaemic control had more frequent contacts with health care professionals in the public primary diabetes health care system than those dropouts who did not show improvement.

**Methods:** In this "real life" retrospective cohort study, we identified 115 dropouts with T2D who were contacted by trained diabetes nurses and who returned to a public T2D-care system. Those previous dropouts who had baseline haemoglobin A1c ≥53mmol/mol (7%) and had a reduction in HbA1c ≥6mmol/mol (0.5%) during the follow-up were compared with those with unsatisfactory change in HbA1c (baseline HbA1c≥53mmol/mol and change <6mmol/mol, or HbA1c<53mmol/mol at the baseline measurement but above that in the end of the study period) or with those who remained at good glycaemic control over the study period. Trained diabetes nurses collected quantitative data from the patient records about visits and contacts during the follow-up.
Results: Previous dropouts showing improvement had more visits to the diabetes nurse (p=0.003) and other nurses (p<0.001) than those with no improvement or those with satisfactory glycaemic control. Telephone calls not focusing on diabetes (p<0.001) were also more frequent among previous dropouts with improvement than among the others.

Conclusions: Especially previous dropouts with T2D who had poor glycaemic control, may benefit from more frequent contacts including visits and telephone calls. Recalling dropouts does not seem to lead to overuse of the T2D care-system by those recalled patients whose glycaemic control does not require special care.

Title: Disparities in glycaemic control, monitoring, and treatment of type 2 diabetes in England: A retrospective cohort analysis.

Citation: PLoS medicine; Oct 2019; vol. 16 (no. 10); p. e1002942

Author(s): Whyte, Martin B; Hinton, William; McGovern, Andrew; van Vlymen, Jeremy; Ferreira, Filipa; Calderara, Silvio; Mount, Julie; Munro, Neil; de Lusignan, Simon

Background: Disparities in type 2 diabetes (T2D) care provision and clinical outcomes have been reported in the last 2 decades in the UK. Since then, a number of initiatives have attempted to address this imbalance. The aim was to evaluate contemporary data as to whether disparities exist in glycaemic control, monitoring, and prescribing in people with T2D.

Methods and Findings: A T2D cohort was identified from the Royal College of General Practitioners Research and Surveillance Centre dataset: a nationally representative sample of 164 primary care practices (general practices) across England. Diabetes healthcare provision and glucose-lowering medication use between 1 January 2012 and 31 December 2016 were studied. Healthcare provision included annual HbA1c, renal function (estimated glomerular filtration rate [eGFR]), blood pressure (BP), retinopathy, and neuropathy testing. Variables potentially associated with disparity outcomes were assessed using mixed effects logistic and linear regression, adjusted for age, sex, ethnicity, and socioeconomic status (SES) using the Index of Multiple Deprivation (IMD), and nested using random effects within general practices. Ethnicity was defined using the Office for National Statistics ethnicity categories: White, Mixed, Asian, Black, and Other (including Arab people and other groups not classified elsewhere). From the primary care adult population (n = 1,238,909), we identified a cohort of 84,452 (5.29%) adults with T2D. The mean age of people with T2D in the included cohort at 31 December 2016 was 68.7 ± 12.6 years; 21,656 (43.9%) were female. The mean body mass index was 30.7 ± SD 6.4 kg/m2. The most deprived groups (IMD quintiles 1 and 2) showed poorer HbA1c than the least deprived (IMD quintile 5). People of Black ethnicity had worse HbA1c than those of White ethnicity. Asian individuals were less likely than White individuals to be prescribed insulin (odds ratio [OR] 0.86, 95% CI 0.79-0.95; p < 0.01), sodium-glucose cotransporter-2 (SGLT2) inhibitors (OR 0.68, 95% CI 0.58-0.79; p < 0.001), and glucagon-like peptide-1 (GLP-1) agonists (OR 0.37, 95% CI 0.31-0.44; p < 0.001). Black individuals were less likely than White individuals to be prescribed SGLT2 inhibitors (OR 0.50, 95% CI 0.39-0.65; p < 0.001) and GLP-1 agonists (OR 0.45, 95% CI 0.35-0.57; p < 0.001). Individuals in IMD quintile 5 were more likely than those in the other IMD quintiles to have annual testing for HbA1c, BP, eGFR, retinopathy, and neuropathy. Black individuals were less likely than White individuals to have annual testing for HbA1c (OR 0.89, 95% CI 0.79-0.99; p = 0.04) and retinopathy (OR 0.82, 95% CI 0.70-0.96; p = 0.011). Asian individuals were more likely than White individuals to have monitoring for HbA1c (OR 1.10, 95% CI 1.01-1.20; p = 0.023) and eGFR (OR 1.09, 95% CI 1.00-1.19; p = 0.048), but less likely for retinopathy (OR 0.88, 95% CI 0.79-0.97; p = 0.01) and neuropathy (OR 0.88, 95% CI 0.80-0.97; p = 0.01). The study is limited by the nature of being observational and defined using retrospectively collected data. Disparities in diabetes care may show regional variation, which was not part of this evaluation.

Conclusions: Our findings suggest that disparity in glycaemic control, diabetes-related monitoring, and prescription of newer therapies remains a challenge in diabetes care. Both SES and ethnicity were important determinants of inequality. Disparities in glycaemic control and other areas of care may lead to higher rates of complications and adverse outcomes for some groups.
Title: Risk of first stroke in patients with type 2 diabetes and the relation to glycaemic control: a nationwide observational study.

Citation: Diabetes, obesity & metabolism; Oct 2019

Author(s): Zabala, Alexander; Darsalia, Vladimer; Holzmann, Martin J; Franzén, Stefan; Svensson, Ann-Marie; Eliasson, Björn; Patrone, Cesare; Nyström, Thomas; Jonsson, Magnus

Aims: To compare stroke incidence between patients with type 2 diabetes (T2D) and a matched control group, and investigate whether glucose exposure in T2D patients can predict first-time stroke event and mortality.

Material and Methods: Nationwide observational cohort study patients with T2D were linked in the Swedish National Diabetes Register and matched with five individual population-based control subjects. We calculated the crude incidence rates and 95% confidence intervals (CIs), and used Cox regression and multivariable hazard ratios (HR) to estimate the risk of stroke and mortality in relation to glycosylated haemoglobin A1c (HbA1c) levels.

Results: 406,271 patients with T2D (64.1±12.4 years/women 45.7%) and 2,008,640 control subjects (64.0±12.4 years/women 45.7%) were included. During a median follow-up of 7.3 years, 26,380 (6.5%) patients with T2D vs. 92,372 (4.4%) of control subjects were diagnosed with a stroke. The incidence rate was 10.88 events per 1,000 person-years vs. 7.03 events per 1,000 person-years (HR, 1.54; 95% CI, 1.52-1.56). In patients with T2D and after multivariable adjustments (HR, 95% CI) for stroke with HbA1c (mmol/mol) levels, 54-64 (HR, 1.27; 95% CI, 1.22-1.37), 65-75 (HR, 1.68, 1.60-1.76), 76-86 (HR, 1.89; 95% CI, 1.75-2.05) and >87 mmol/mol (HR, 2.14; 95% CI, 1.90-2.42), respectively, compared with the reference category of HbA1c ≤53 mmol/mol. There was a stepwise increased risk of death for every 10 mmol/mol categorical increment of HbA1c (HR, 1.71; 95% CI, 1.47-2.00) for the highest HbA1c category.

Conclusions: The increased risk of stroke and death is associated with poor glycaemic control in patients with T2D. This article is protected by copyright. All rights reserved.

Title: Evaluating Glycemic Control in Patients with Type 2 Diabetes Suboptimally Controlled on Basal Insulin: UK ATTAIN Real-World Study.

Citation: Diabetes therapy : research, treatment and education of diabetes and related disorders; Oct 2019; vol. 10 (no. 5); p. 1847-1858

Author(s): Jude, Edward B; Nixon, Mark; O'Leary, Caroline; Myland, Melissa; Gooch, Nick; Shaunik, Alka; Lew, Elisheva

Introduction: This retrospective, observational cohort study evaluated the effect of therapy intensification on change in glycated hemoglobin (HbA1c) at 6 and 12 months post intensification in patients with type 2 diabetes (T2D) suboptimally controlled on basal insulin (BI) (i.e., HbA1c ≥ 7.5% [≥ 58 mmol/mol]).

Methods: Patients with T2D with suboptimal glycemic control using BI were identified from The Health Improvement Network (THIN) database. Patients who underwent therapy intensification (intensifiers) within 12 months of index 1 (the date of the first incidence of suboptimally controlled HbA1c) were matched (1:1) to patients who did not intensify therapy (non-intensifiers). Index 2 was the date of therapy intensification for intensifiers, or a pseudo date for non-intensifiers that resulted in the same duration from index 1 to index 2 as their matched intensifier patient. Primary outcomes were HbA1c change and proportion of patients achieving the HbA1c target at 6 and 12 months post index 2.

Results: A total of 1342 patients (n = 646 intensifiers; n = 696 non-intensifiers) were included in the analysis. At post index 2, mean HbA1c change was substantially greater at 6 months for intensifiers
than for non-intensifiers (-0.81% vs. -0.35%), with no additional benefit at 12 months (-0.81% vs. -0.49%, respectively). Compared with non-intensifiers, a greater proportion of intensifiers achieved target HbA1c at 6 months (25.1% vs. 18.8%) and at 12 months (33.4% vs. 28.2%).

**Conclusions:** Many real-world patients with T2D suboptimally controlled with BI do not have their therapy intensified. The results of this study suggest that in this patient population, therapy intensification achieves significant reductions in HbA1c at 6 months post intensification, with little additional clinical benefit at 12 months. This suggests that, for patients who fail to achieve their glycemic targets at 6 months, since no meaningful additional clinical benefit is observed at 12 months when continuing the same therapy, further therapy intensification or change should be promptly considered.

**FUNDING** This study and the Rapid Service Fees were funded by Sanofi.

**Trial Registration:** 17THIN068.

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**Title:** Protective factors for diabetic retinopathy in Type 2 diabetes mellitus patients: Long duration of no less than 10 years

**Citation:** Journal of Diabetes and its Complications; Oct 2019; vol. 33 (no. 10)

**Author(s):** Liu, Yanli; Duan, Chunwen; Fang, Dejia; Liu, Yi; Xu, Hanchun; Zheng, Yarong; Xuan, Yaling; Wang, Lili; Lin, Ye; Su, Rui; An, Meixia

**Aim:** To study the factors protecting against diabetic retinopathy (DR) in patients with over a decade-long history of type 2 diabetes mellitus.

**Methods:** A total of 490 patients with type 2 diabetes mellitus lasting for ≥10 years were divided into DR and no diabetic retinopathy (no DR) groups. Their basic information was collected, including age, sex, and duration of diabetes mellitus, as well as pertinent laboratory data. Potential correlations between these factors and DR were evaluated using multivariate analysis.

**Results:** Overall, 208 patients met the diagnostic criteria for DR. Multivariate logistic regression was used to evaluate factors with P<0.10 after univariate analysis. Age, total bilirubin, and total cholesterol were found to be protective factors against DR. Presence of diabetic kidney disease and diabetic peripheral neuropathy, duration of diabetes mellitus, apolipoprotein B, blood urea nitrogen, and prothrombin time were found to be risk factors for DR.

**Conclusions:** We conclude that total cholesterol is a protective factor against DR. Specifically, it was confirmed that high levels of total cholesterol reduce the risk of DR. These findings may provide a basis for new diet and lifestyle guidelines for patients with diabetes mellitus.

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**Title:** Correction of hypomagnesemia by dapagliflozin in patients with type 2 diabetes: A post hoc analysis of 10 randomized, placebo-controlled trials

**Citation:** Journal of Diabetes and its Complications; Oct 2019; vol. 33 (no. 10)

**Author(s):** Toto, Robert D; Goldenberg, Ronald; Chertow, Glenn M; Cain, Valerie; Stefansson Bergur V Stefánsson; Sjostrom C David Sjöström; Sartipy, Peter

**Aims:** Hypomagnesemia (serum magnesium [Mg] <0.74 mmol/L [<1.8 mg/dL]) is commonly observed in patients with type 2 diabetes (T2D). This study investigated the effect of treatment with dapagliflozin 10 mg on Mg concentrations in patients with T2D.

**Methods:** In this post hoc analysis, we used pooled data from 10 placebo-controlled studies of dapagliflozin over 24 weeks of treatment in patients with T2D. We evaluated the change in Mg in patients receiving dapagliflozin vs. placebo overall, and in subgroups with baseline hypomagnesemia and normal/hypermagnesemia (≥0.74 mmol/L [≥1.8 mg/dL]). We determined the proportion of patients with baseline hypomagnesemia who achieved Mg ≥0.74 mmol/L (≥1.8 mg/dL).

**Results:** A total of 4398 patients with T2D were included. The mean change from baseline to week 24 in Mg was significantly larger with dapagliflozin vs. placebo; difference, 0.06 mmol/L (95%
confidence interval [CI]: 0.05, 0.06). The proportion of patients with Mg within the population reference range after 24 weeks of treatment was significantly higher with dapagliflozin vs. placebo; difference, 47.8% (95% CI: 41.4, 53.9). The proportion of patients displaying hypermagnesemia did not increase with dapagliflozin treatment.

**Conclusions:** Treatment with dapagliflozin 10 mg resulted in correction of Mg concentrations in patients with T2D and hypomagnesemia.

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**Title:** Considerations when using alpha-glucosidase inhibitors in the treatment of type 2 diabetes.

**Citation:** Expert opinion on pharmacotherapy; Oct 2019 ; p. 1-7

**Author(s):** Hedrington, Maka S; Davis, Stephen N

**Introduction:** Alpha-glucosidase inhibitors (AGIs) - oral antihyperglycemic drugs, inhibit upper gastrointestinal enzymes that break down complex carbohydrates into glucose. As a result, the absorption of glucose is delayed, postprandial glucose reduced, and glycemic control improved.

**Areas covered:** In this review, the authors describe the current recommendations on the use of the three major approved AGIs (acarbose, miglitol, voglibose). Efficacy and safety parameters together with ethnic considerations have been highlighted throughout the manuscript. The article also discusses potential diabetes prevention and cardiovascular effects of these medications. Expert opinion: The overall safety and efficacy of this class of drug appears to be high: AGIs do not increase the risk of hypoglycemia, do not cause weight gain; they also significantly improve postprandial hyperglycemia, have been associated with the reduction in risk factors for cardiovascular disease and may also delay the progression of prediabetes to T2DM. In general, we continue to believe that acarbose, miglitol, and voglibose should be used as third-line add on treatment options to other anti-hyperglycemic agents. However, this class can have earlier consideration in elderly and/or when metformin is contraindicated.

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**Title:** Combination therapy with SGLT-2 inhibitors and GLP-1 receptor agonists as complementary agents that address multi-organ defects in type 2 diabetes.

**Citation:** Postgraduate medicine; Oct 2019 ; p. 1-11

**Author(s):** Lajara, Rosemarie

**Abstract:** Type 2 diabetes (T2D) has a complex pathophysiology composed of multiple underlying defects that lead to impaired glucose homeostasis and the development of macrovascular and microvascular complications. Of the currently available glucose-lowering therapies, sodium-glucose cotransporter-2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) both provide effective glycemic control and have been shown to reduce cardiovascular (CV) events in patients with T2D and a high CV risk or established CV disease. Because these agents have complementary mechanisms of action, they are able to act on multiple defects of T2D when used in combination. This review discusses the rationale for and potential benefits of SGLT-2i plus GLP-1RA combination therapy in patients with T2D. A search of the PubMed database was conducted for studies and reviews describing the combined use of SGLT-2is and GLP-1RAs, with a specific focus on identifying clinical studies of combination therapy in patients with T2D. In clinical studies, glycated hemoglobin (A1c) was significantly reduced over 28-52 weeks with SGLT-2i plus GLP-1RA therapy versus the individual agents or baseline. Several CV risk factors, including body weight, blood pressure, and lipid parameters, were also improved. SGLT-2i plus GLP-1RA therapy was generally well tolerated, with a low risk of hypoglycemia and no unexpected findings. Taken together with results from large CV outcomes trials of SGLT-2is and GLP-1RAs, combination therapy with these agents potentially provides effective durable glycemic control and CV benefits due to their complementary actions on the defects of T2D.
Title: Thyroid Dysfunction and Type 2 Diabetes Mellitus: Screening Strategies and Implications for Management.

Citation: Diabetes therapy : research, treatment and education of diabetes and related disorders; Oct 2019
Author(s): Kalra, Sanjay; Aggarwal, Sameer; Khandelwal, Deepak

Abstract: Diabetes mellitus (DM) and thyroid dysfunction (TD) often tend to coexist in patients. Both hypothyroidism and hyperthyroidism are more common in type 2 diabetes mellitus (T2DM) patients than in their nondiabetic counterparts. Current guidelines are neither clear nor specific about the frequency of thyroid function monitoring in T2DM patients. Circulating thyroid hormones affect several different organs and cells, have a major impact on glucose, lipid, and protein metabolism, and can worsen glycaemic control in T2DM. Hyperthyroidism and thyrotoxicosis can worsen subclinical DM and cause hyperglycaemia in T2DM patients, increasing the risk of diabetic complications. T2DM reduces thyroid-stimulating hormone levels and impairs the conversion of thyroxine (T4) to triiodothyronine (T3) in the peripheral tissues. Poorly managed T2DM can lead to insulin resistance and hyperinsulinaemia, which causes thyroid tissue proliferation and increases nodule formation and goitre size. In addition, while metformin can be beneficial in both T2DM and TD patients, other antidiabetics such as sulfonylureas, pioglitazone, and thiazolidinediones can negatively impact TD. Antithyroid drugs such as methimazole can impair glycaemic control in T2DM patients. Thyrovigilance in T2DM patients and diabetovigilance in TD patients may therefore be necessary to facilitate individualized care and management. Funding: Abbott India Ltd.

Title: Optimizing Postprandial Glucose Management in Adults With Insulin-Requiring Diabetes: Report and Recommendations.

Citation Journal of the Endocrine Society; Oct 2019; vol. 3 (no. 10); p. 1942-1957
Author(s): Leahy, John Jack L; Aleppo, Grazia; Fonseca, Vivian A; Garg, Satish K; Hirsch, Irl B; McCall, Anthony L; McGill, Janet B; Polonsky, William H

Abstract: Faster-acting insulins, new noninsulin drug classes, more flexible insulin-delivery systems, and improved continuous glucose monitoring devices offer unprecedented opportunities to improve postprandial glucose (PPG) management and overall care for adults with insulin-treated diabetes. These developments led the Endocrine Society to convene a working panel of diabetes experts in December 2018 to assess the current state of PPG management, identify innovative ways to improve self-management and quality of life, and align best practices to current and emerging treatment and monitoring options. Drawing on current research and collective clinical experience, we considered the following issues for the ~200 million adults worldwide with type 1 and insulin-requiring type 2 diabetes: (i) the role of PPG management in reducing the risk of diabetes complications; (ii) barriers preventing effective PPG management; (iii) strategies to reduce PPG excursions and improve patient quality of life; and (iv) education and clinical tools to support endocrinologists in improving PPG management. We concluded that managing PPG to minimize or prevent diabetes-related complications will require elucidating fundamental questions about optimal ways to quantify and clinically assess the metabolic dysregulation and consequences of the abnormal postprandial state in diabetes and recommend research strategies to address these questions. We also identified practical strategies and tools that are already available to reduce barriers to effective PPG management, optimize use of new and emerging clinical tools, and improve patient self-management and quality of life.
Title: MANAGEMENT OF ENDOCRINE DISEASE: Are All GLP-1 Agonist Equal In The Treatment Of Type 2 Diabetes?

Citation: European journal of endocrinology; Oct 2019
Author(s): Nauck, Michael A; Meier, Juris J

Abstract: GLP-1, a peptide hormone secreted from the gut stimulating insulin and suppressing glucagon secretion was identified as a parent compound for novel treatments of diabetes, but was degraded (dipeptidyl peptidase-4) eliminated (mainly kidneys) too fast (half-life 1-2 min) to be useful as a therapeutic agent. GLP-1 receptor agonist have been used to treat patients with type 2 diabetes since 2007, when exenatide (twice daily) was approved in 2007. Compounds with longer duration of action (once daily, once weekly) and with increasingly better efficacy with respect to glycaemic control and body weight reduction have been developed, and in a recent ADA/EASD consensus statement were recommended as the first injectable diabetes therapy after failure of oral glucose-lowering medications. Most GLP-1 receptor agonists (lixisenatide q.d., liraglutide q.d., exenatide q.w., albiglutide q.w., albiglutide q.w., semaglutide q.w., all for subcutaneous injection, and the first oral preparation, oral semaglutide) have been examined in cardiovascular outcomes studies. Beyond proving their safety in vulnerable patients, most of whom had pre-existing heart disease, liraglutide, semaglutide, albiglutide, and dulaglutide reduced the time to first major adverse cardiovascular events (non-fatal myocardial infarction and stroke, cardiovascular death). Liraglutide, in addition, reduced cardiovascular and all-cause mortality. It is the purpose of the present review to describe clinically important differences, regarding pharmacokinetic behaviour, glucose-lowering potency, effectiveness of reducing body weight and controlling other cardiovascular risk factors, and of the influence of GLP-1 receptor agonist treatment on cardiovascular outcomes in patients either presenting with or without pre-existing cardiovascular disease (atherosclerotic, ischemic or congestive heart failure).

Title: Combination of GLP-1 receptor agonists and behavioural treatment in type 2 diabetes elicits synergistic effects on body weight: A retrospective cohort study.

Citation: Endocrinology, diabetes & metabolism; Oct 2019; vol. 2 (no. 4); p. e00082
Author(s): Petroni, Maria Letizia; Montesi, Luca; Colosimo, Santo; Caletti, Maria Turchese; Mazzotti, Arianna; Marchesini, Giulio

Aims: Intensification of type 2 diabetes (T2DM) treatment with GLP-1 receptor agonists (GLP-1RAs) promotes weight loss. We aimed to determine the synergistic effect of behavioural programmes on body weight on top of GLP-1RA treatment.

Materials and methods: We retrospectively analysed the time course of 328 individuals with T2DM starting GLP-1RA treatment because of insufficient metabolic control. In 29, a structured programme of elementary nutritional counselling was also implemented (elementary nutritional education [ENE]-5 group sessions), whereas 53 entered a programme of cognitive-behavioural treatment (CBT-12 group sessions). Both programmes were completed within 6 months of switching to GLP-1RAs. Data of body weight and metabolic control were followed up to 2 years as part of regular follow-up. Weight loss targets (≥10% and ≥5%) and metabolic target (HbA1c < 7%) were analysed by Cox regression model in comparison with standard care (SC, N = 244).

Results: Body weight remarkably decreased following both behavioural programmes, with significant differences compared with SC at 2 years (CBT, 8.5 ± 5.9% vs 6.3 ± 6.9 in ENE and only 3.1 ± 5.7 in SC; P < 0.001 and P = 0.045 vs CBT and ENE, respectively). The 10% weight loss was achieved and maintained in approximately 30% of cases during follow-up, and an additional 35% of cases lost between 5% and 10%. Data were consistent between behavioural programmes, after adjustment for confounders, including initial body weight (logreg Mantel-Cox: ENE vs SC, P < 0.01; CBT vs SC, P < 0.001). No differences in metabolic control were detected between groups.

Conclusions: Initiation of GLP-1RA treatment provides an opportunity for addressing patients' needs of weight control. By producing initial weight loss, patients' motivation and self-efficacy are expected to increase and adherence to long-term lifestyle changes might be more easily attained.
Title: A 24-week, randomized, double-blind, active-controlled clinical trial comparing bexagliflozin with sitagliptin as an adjunct to metformin for the treatment of type 2 diabetes in adults.

Citation: Diabetes, obesity & metabolism; Oct 2019; vol. 21 (no. 10); p. 2248-2256

Author(s): Halvorsen, Yuan-Di; Lock, John P; Zhou, Wenjiong; Zhu, Fang; Freeman, Mason W

Aim: To compare the relative safety and effectiveness of bexagliflozin and sitagliptin as adjuncts to metformin for the treatment of adults with type 2 diabetes.

Methods: Participants (n = 386) were randomized to receive bexagliflozin (20 mg) or sitagliptin (100 mg) in addition to their existing doses of metformin. The primary endpoint was the non-inferiority of bexagliflozin to sitagliptin for change in HbA1c from baseline to week 24. Changes from baseline to week 24 in fasting plasma glucose (FPG), body mass (in subjects with baseline body mass index ≥25 kg m⁻²) and systolic blood pressure (SBP) were secondary endpoints.

Results: The mean change from baseline to week 24 in HbA₁c was -0.74 (95% CI -0.86%, -0.62%) in the bexagliflozin arm and -0.82% (95% CI -0.93%, -0.71%) in the sitagliptin arm, establishing non-inferiority. The changes from baseline FPG, body mass and SBP were -1.82 mmol L⁻¹, -3.35 kg and -4.23 mmHg in the bexagliflozin arm and -1.45 mmol L⁻¹, -0.81 kg and -1.90 mmHg in the sitagliptin arm, respectively. These differences were significant for the first two measures (one-sided P = 0.0123, P < 0.0001 and P = 0.0276, respectively.)

Conclusions: Bexagliflozin was non-inferior to sitagliptin and provided benefits over sitagliptin in FPG and body mass. Adverse event incidences in the two arms were similar.

Title: Risk of Fractures Associated with Dipeptidyl Peptidase-4 Inhibitor Treatment: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

Citation: Diabetes therapy : research, treatment and education of diabetes and related disorders; Oct 2019; vol. 10 (no. 5); p. 1879-1892

Author(s): Chen, Qing; Liu, Ting; Zhou, Haonan; Peng, Huawei; Yan, Caifeng

Introduction: More and more studies suggest that type 2 diabetes mellitus (T2DM) can lead to an increased fracture risk. Some previous clinical studies and experimental data have shown that some antidiabetic drugs can increase or decrease the incidence of fractures.

Methods: We searched Medline, Embase, Cochrane Library, and the ClinicalTrials.gov website (https://www.clinicaltrials.gov) for published or unpublished randomized controlled trials (RCTs) from inception through 2 December 2018 to compare the effects of dipeptidyl peptidase-4 (DDP-4) inhibitors with active control drugs or placebo in T2DM patients. All RCTs had a duration of at least 12 weeks, and the ultimate measure was whether a fracture occurs or not. We calculated odds ratios and their 95% confidence intervals by the fixed effect Mantel-Haenszel model. Publication bias was investigated firstly through visual observation of funnel plot asymmetry and then through Begg's test or Egger's test. The Cochrane bias risk tools were used to assess the quality of included studies.

Results: Eighty-seven eligible RCTs were included in this study. Of 93,772 participants, 49,270 patients received therapy and 44,502 were control patients. Five kinds of DDP-4 inhibitors were included: sitagliptin, saxagliptin, alogliptin, linagliptin and vildagliptin. There were 676 fractures in the DDP-4 inhibitor treatment group and 646 in the control group. The median average glycosylated hemoglobin level was 8.2%. DDP-4 inhibitor treatment did not seem to influence the fracture risk, no matter whether compared with placebo or active comparators in T2DM patients (Mantel-Haenszel odds ratio (MH-OR) = 1.01, 95% CI 0.90-1.12, P = 0.92). After three subgroup analyses which were defined by drug type, control regimen and duration, the results were still stable.
Conclusion: This systematic review and meta-analysis shows that DDP-4 inhibitors do not affect the fracture risk when compared with antidiabetic drugs or placebo in T2DM patients.

Title: Cardiorenal Protection: Potential of SGLT2 Inhibitors and GLP-1 Receptor Agonists in the Treatment of Type 2 Diabetes.

Citation: Diabetes therapy : research, treatment and education of diabetes and related disorders; Oct 2019; vol. 10 (no. 5); p. 1733-1752
Author(s): Nagahisa, Taichi; Saisho, Yoshifumi
Abstract: Recent large clinical trials on sodium-glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, with the aim of verifying cardiovascular safety, have revealed that these medications have a preventative advantage on adverse cardiovascular outcomes, including worsening of heart failure and deterioration of nephropathy, in patients with type 2 diabetes (T2D). These observed benefits do not seem to correlate with the glucose-lowering effect, and the underlying mechanism is being intensively investigated. Given the results from recent studies, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) recommend that patients with T2D and clinical cardiovascular disease (CVD) with inadequate glucose control despite treatment with metformin should receive an SGLT2 inhibitor or GLP-1 receptor agonist. In this review we summarize the results of recent cardiovascular outcome trials and discuss the potential clinical advantage of SGLT2 inhibitors and GLP-1 receptor agonists. We also present practical implications of these glucose-lowering agents for reducing the risk of adverse cardiovascular events and progressive renal comorbidity in patients with T2D and CVD.

Title: Heterogeneity of Treatment Effects From an Intensive Lifestyle Weight Loss Intervention on Cardiovascular Events in Patients With Type 2 Diabetes: Data From the Look AHEAD Trial.

Citation: Diabetes care; Oct 2019; vol. 42 (no. 10); p. 1988-1994
Author(s): de Vries, Tamar I; Dorresteijn, Jannick A N; van der Graaf, Yolanda; Visseren, Frank L J; Westerink, Jan
Objective: To explore the presence of heterogeneity of treatment effect (HTE) of an intensive lifestyle intervention on the occurrence of major cardiovascular events (MACE) in overweight or obese patients with type 2 diabetes, and to identify patient characteristics associated with individual treatment effect.
Research Design and Methods: In 4,901 participants from the Action for Health in Diabetes (Look AHEAD) trial, a penalized Cox regression model to predict treatment effect of intensive lifestyle intervention for the risk of MACE was derived, including all possible treatment-by-covariate interaction terms. The ability of the model to predict HTE was confirmed by calculating hazard ratios (HRs) and absolute risk change in quartiles of predicted treatment effect, and baseline patient characteristics were compared between quartiles.
Results: In quartile 1 of predicted treatment effect, with the highest predicted risk reduction, there was a significant treatment benefit of intensive lifestyle intervention (HR 0.64 [95% CI 0.49-0.83]), whereas there was no effect from treatment in quartiles 2 and 3 (HR 0.81 [95% CI 0.58-1.14] and 1.13 [95% CI 0.80-1.60], respectively) and a detrimental effect in quartile 4 (HR 1.37 [95% CI 1.09-1.73]). Several patient characteristics in demographics, medical history, physical examination, and laboratory values were associated with the level of treatment effect.
Conclusions: This post hoc analysis of the Look AHEAD trial showed that an intensive lifestyle intervention aimed at weight loss may reduce cardiovascular events in selected patients but may have a detrimental treatment effect in others.

Title: Risk of bone fracture associated with sodium-glucose cotransporter-2 inhibitor treatment: A meta-analysis of randomized controlled trials.
Aim: To evaluate the association between sodium-glucose cotransporter-2 (SGLT2) inhibitors and risk of bone fractures in patients with type 2 diabetes mellitus (T2DM).

Methods: A systematic literature search conducted of PubMed, Embase, the Cochrane Library and Web of Science from inception up to 31 August 2018 identified all eligible randomized controlled trials (RCTs). The following data were extracted from each study: first author; year of publication; sample size; patient characteristics; study design; intervention drug; control drug; follow-up durations; and incident bone-fracture events. A meta-analysis was performed using Review Manager 5.3 software to calculate odds ratios (ORs) and 95% confidence intervals (CI) for dichotomous variables.

Results: A total of 30 studies involving 23,372 patients with T2DM were included in our analysis. There were 387 incident bone-fracture cases (245 in the SGLT2 inhibitor group, 142 in the control group). Compared with patients who received placebo, those receiving SGLT2 inhibitor treatment had a pooled OR of bone fracture of 0.86 (95% CI: 0.70-1.06). Also, there was no evidence that individual SGLT2 inhibitors across different doses were associated with any increased risk of bone fracture. After stratification by follow-up duration, an SGLT2 inhibitor treatment period of ≤ 52 weeks appeared to have beneficial effects against bone fracture; however, when the treatment period exceeded 52 weeks, these beneficial effects for preventing bone fracture disappeared.

Conclusion: Our meta-analysis has indicated that SGLT2 inhibitors do not increase risk of bone fracture compared with placebo in patients with T2DM. However, these findings now need to be confirmed in well-designed RCT studies.
**Title:** Update on Cardiovascular Safety of Incretin-Based Therapy in Adults With Type 2 Diabetes Mellitus: A Meta-Analysis of Cardiovascular Outcome Trials.

**Citation:** Canadian journal of diabetes; Oct 2019; vol. 43 (no. 7); p. 538

**Author(s):** Alfayez, Osamah M; Almutairi, Abdulaali R; Aldosari, Ali; Al Yami, Majed S

**Objectives:** The authors of 2 large randomized trials have recently published their findings related to the effects of a glucagon-like peptide 1 receptor agonist (GLP-1RA) (the HARMONY trial) and a dipeptidyl peptidase 4 (DPP-4) inhibitor (the CARMELINA trial) on cardiovascular (CV) outcomes in patients with type 2 diabetes mellitus. In light of these new data, we conducted a systematic review and meta-analysis of GLP-1RAs and DPP-4 inhibitors in CV outcome trials to assess their CV safety in patients with type 2 diabetes.

**Methods:** We conducted a comprehensive literature search in the Embase and MEDLINE databases to identify trials involving GLP-1RAs and DPP-4 inhibitors with major CV-related outcomes reported, including major adverse CV events, CV death, myocardial infarction, stroke, death from any cause and hospitalization because of heart failure. A total of 9 CV outcome trials were included. Odds ratios and 95% confidence intervals were calculated based on the Mantel-Haenszel method.

**Results:** Relative to placebo, GLP-1RAs were associated with a statistically significant reduction in the odds of major adverse CV events (13%), CV death (12%), death from any cause (11%) and stroke (13%). DPP-4 inhibitors were comparable to placebo for all outcomes. Moreover, DPP-4 inhibitors were associated with a nonsignificant 5% increase in the odds of hospitalization from heart failure compared to placebo.

**Conclusions:** This meta-analysis demonstrated that GLP-1RAs were associated with a significant reduction in major adverse CV events, CV death, stroke and death from any cause, while DPP-4 inhibitors were comparable to placebo for all CV outcomes, including hospitalizations for heart failure.

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**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; Oct 2019; vol. 85 (no. 10); p. 2378-2389

**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 UK'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, ischaemic stroke, cardiovascular death, and all-cause mortality) with sulfonylureas vs metformin.

**Results:** 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 myocardial infarction (hazard ratio [HR]: 1.04, 95% confidence interval [CI]: 0.85-1.25) but was associated with increased risks of ischaemic stroke (HR: 1.25, 95% CI: 1.002-1.56), cardiovascular death (HR: 1.25, 95% CI: 1.06-1.47), and all-cause mortality (HR: 1.60, 95% CI: 1.45-1.76). This represents an additional 2.0 ischaemic strokes, 3.5 cardiovascular deaths, and 21.4 all-cause deaths per 1,000 patients per year with sulfonylureas.
**Conclusions:** Initiating treatment of type 2 diabetes with a sulfonylurea rather than metformin is associated with higher rates of ischaemic stroke, cardiovascular death, and all-cause mortality.

**Title:** Emerging glucose-lowering therapies: a guide for cardiologists.

**Citation:** Heart (British Cardiac Society); Sep 2019

**Author(s):** Gulsin, Gaurav S; Graham-Brown, Matthew P M; Davies, Melanie J; McCann, Gerry P

**Abstract:** In recent large-scale cardiovascular outcome trials, two new classes of glucose-lowering medications—sodium glucose cotransporter-2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP-1RAs)—demonstrated cardiovascular benefits in adults with type 2 diabetes mellitus (T2DM). These findings have prompted growing optimism among clinicians regarding the potential for these agents to reduce the burden of cardiovascular disease in people with T2DM. GLP-1RAs and SGLT2i are now advocated as second-line agents in European and US guidelines for management of both hyperglycaemia and for primary prevention of cardiovascular disease in people with T2DM. Given the high prevalence of T2DM in patients with cardiovascular disease, cardiologists will increasingly encounter these agents in routine clinical practice. In this review, we summarise evidence from cardiovascular outcome trials of GLP-1RAs and SGLT2i, give practical advice on prescribing and detail safety considerations associated with their use. We also highlight areas where further work is needed, giving details on active clinical trials. The review aims to familiarise cardiologists with these emerging treatments, which will be increasingly encountered in clinical practice, given the expanding representation of T2DM in patients with cardiovascular disease. Whether these drugs will be initiated by cardiologists remains to be determined.

**Title:** Type 2 Diabetes Mellitus and Menopausal Hormone Therapy: An Update.

**Citation:** Diabetes therapy: research, treatment and education of diabetes and related disorders; Sep 2019

**Author(s):** Paschou, Stavroula A; Papanas, Nikolaos

**Abstract:** During menopausal transition, various phenotypical and metabolic changes occur, affecting body weight, adipose tissue distribution and energy expenditure as well as insulin secretion and sensitivity. Taken together, these can predispose women to the development of type 2 diabetes mellitus (T2DM). Many women in midlife experience climacteric symptoms, including hot flashes and night sweats. Menopausal hormone therapy (MHT) is then indicated. MHT has a favourable effect on glucose homeostasis in both women without and with T2DM. T2DM was considered in the past as a cardiovascular disease (CVD) equivalent, which would suggest that women with T2DM should not receive MHT. This notion may still deter many clinicians from prescribing MHT to these patients. However, nowadays there is strong evidence to support an individualised approach after careful evaluation of CVD risk. In older women with T2DM (> 60 years old or > 10 years in menopause), MHT should not be initiated, because it may destabilise mature atherosclerotic plaques, resulting in thrombotic episodes. In obese women with T2DM or in women with moderate CVD risk, transdermal 17β-oestradiol could be used. This route of delivery presents beneficial effects regarding triglyceride concentrations and coagulation factors. In peri- or recently post-menopausal diabetic women with low risk for CVD, oral oestrogens can be used, since they exhibit stronger beneficial effects on glucose and lipid profiles. In any case, a progestogen with neutral effects on glucose metabolism should be used, such as natural progesterone, dydrogesterone or transdermal norethisterone. The goal is to maximise benefits and minimise adverse effects.

**Title:** Insulin Therapy in Type 2 Diabetes.

**Citation:** American journal of therapeutics; Sep 2019
Author(s): Aschner, Pablo

Background: Since the discovery of insulin, it was the only drug available for the treatment of diabetes until the development of sulfonylureas and biguanides 50 years later. But even with the availability of oral glucose-lowering drugs, insulin supplementation was often needed to achieve good glucose control in type 2 diabetes. Insulin NPH became the basal insulin therapy of choice and adding NPH to metformin and/or sulfonylureas became the standard of care until basal insulin analogs were developed and new glucose-lowering drugs became available.

Areas of Uncertainty: The advantages in cost-benefit of insulin analogs and their combination with new glucose-lowering drugs are still a matter of debate. There is no general agreement on how to avoid inertia by prescribing insulin therapy in type 2 diabetes when really needed, as reflected by the diversity of recommendations in the current clinical practice guidelines.

DATA SOURCES When necessary for this review, a systematic search of the evidence was done in PubMed and Cochrane databases.

Therapeutic Advances: Adding new oral glucose-lowering drugs to insulin such as DPP-4 inhibitors lead to a modest HbA1c reduction without weight gain and no increase in hypoglycemia. When SGLT-2 inhibitors are added instead, there is a slightly higher HbA1c reduction, but with body weight and blood pressure reduction. The downside is the increase in genital tract infections. GLP-1 receptor agonists have become the best alternative when basal insulin fails, particularly using fixed ratio combinations. Rapid-acting insulins via the inhaled route may also become an alternative for insulin supplementation and/or intensification. "Smart insulins" are under investigation and may become available for clinical use in the near future.

Conclusions: Aggressive weight loss strategies together with the new glucose-lowering drugs which do not cause hypoglycemia nor weight gain should limit the number of patients with type 2 diabetes needing insulin. Nevertheless, because of therapeutic inertia and the progressive nature of the disease, many need at least a basal insulin supplementation and insulin analogs are the best choice as they become more affordable. Fixed ratio combinations with GLP1 receptor agonists are a good choice for intensification of insulin therapy.

Title: Population-based cross-sectional study of 11 645 Spanish nonagenarians with type 2 diabetes mellitus: cardiovascular profile, cardiovascular preventive therapies, achievement goals and sex differences.

Citation: BMJ open; Sep 2019; vol. 9 (no. 9); p. e030344

Author(s): Salinero-Fort, Miguel Angel; Mostaza-Prieto, Jose M; Lahoz-Rallo, Carlos; Vicente Díez, José Ignacio; Cárdenas-Valladolid, Juan

Objectives: To evaluate the risk profile, achievement of cardiometabolic goals, and frequency and optimal use of cardiovascular preventive therapies among nonagenarians with type 2 diabetes mellitus (T2DM). To investigate possible sex differences.

Design and Setting: A cross-sectional population study of 11 645 persons aged ≥90 years with T2DM living in Madrid (Spain). Sociodemographic, clinical and therapy profiles were collected through electronic records in primary care. We considered antihypertensive therapy and lipid-lowering therapy to be optimal when known patients with hypertension with albuminuria received renin-angiotensin system blockers and statins had been prescribed for overt cardiovascular disease.

Results: The prevalence of coronary artery disease was higher in males than in females (21.5% vs 12.6%, p<0.01), as was that of peripheral artery disease (8.5% vs 2.3%, p<0.01). However, the prevalence of cerebrovascular disease was similar in both sexes (16.5% vs 16%; p=0.44). Haemoglobin A1c was lower than 7% in 64.4% of cases, with female predominance in patients with known dementia (67.1% female vs 59.9% male; p<0.01). Antiplatelet therapy was significantly more frequent in males than in females (48.1% vs 44.3%; p<0.01), as were statins (43.2% vs 40.2%; p<0.01). Both in primary and in secondary prevention, rates for simultaneous achievement of the HbA1c, blood pressure, LDL-C goals were significantly lower among females (p<0.01). For each
criterion of optimal use of cardiovascular preventive therapies, adherence was significantly better in males than in females.

**Conclusion:** Our study showed that the risk of cerebrovascular disease was similar in both male and female Spanish nonagenarians. Adherence was poorer in females for all criteria of optimal use of cardiovascular preventive therapies. Our findings indicate that the known sex differences in younger patients with T2DM persist in patients aged ≥90 years. There is considerable room for improvement in standards of preventive care in nonagenarians with T2DM, especially in females.

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**Title:** The effectiveness of patient activation intervention on type 2 diabetes mellitus glycemic control and self-management behaviors: A systematic review of RCTs.

**Citation:** Primary care diabetes; Sep 2019

**Author(s):** Almutairi, Nasser; Hosseinzadeh, Hassan; Gopaldasani, Vinod

**Background:** Type 2 diabetes mellitus T2DM is a major health challenge and associated with several complications and mortality. Self-management behaviors SMBs such as healthy diet, physical activity, blood glucose self-monitoring, foot care and medication adherence are critical part of diabetic care. Empowered or activated patients, are more likely to practice better SMBs. However, the effectiveness of patient activation intervention on T2DM glycemic control and SMBs is not totally well understood.

**Aim:** To assess the effectiveness of patient activation intervention on T2DM glycemic control and SMBs.

**Method:** A systematic search was undertaken through five databases to find relevant studies published between 2004 and 2018. We included randomized controlled trials with sample size ≥120 and follow up period of ≥12 months and assess the effectiveness of patient activation intervention on T2DM glycemic control and SMBs. RESULTS 10 RCTs were identified for analysis. The total sample size is 3728 and the combined mean age is 57.3 years. The combined mean BMI is 31.2kg/m2 (obese). Seven intervention demonstrated a significant reduction in HbA1c, ranged from 0.36 to 0.80%. All interventions presented an improvement in at least one self-management behavior.

**Discussion and Conclusion:** Patient activation intervention showed a significant positive effect on T2DM glycemic control and SMBs, particularly physical activity, healthy diet, foot care and blood glucose self-monitoring. The effectiveness on SMBs was seen across different intervention strategies, modes of delivery, length of intervention, and number of providers. Better effectiveness on HbA1c was associated with poorly controlled participants, culturally tailored-intervention, and in-person sessions intervention combined with telephone calls follow up.

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**Title:** Treatment of heart failure with sodium glucose co-transporter-2 inhibitors in people with type 2 diabetes mellitus: current evidence and future directions.

**Citation:** Diabetic medicine : a journal of the British Diabetic Association; Sep 2019

**Author(s):** Sharma, A; Butler, J; Zieroth, S; Giannetti, N; Verma, S

**Abstract:** Diabetes is one the most common comorbidities among people with established heart failure. Interest in heart failure as an outcome among people with diabetes has emerged since it was shown that there was an association between increased risk of hospitalization for heart failure with use of thiazolidinediones and some dipeptidyl peptidase-4 inhibitors. Recently, sodium-glucose co-transporter-2 inhibitors were shown to lead to a reduction in the risk of cardiovascular death and hospitalization for heart failure in people with Type 2 diabetes mellitus and either cardiovascular risk factors or atherosclerotic cardiovascular disease. These findings appear to be consistent in people both with and without a baseline history of heart failure. Based on current evidence there are several clinical scenarios in which the use of sodium-glucose co-transporter-2 inhibitors would be justified for people with heart failure and atherosclerotic cardiovascular disease: (1) in people with a new diagnosis of Type 2 diabetes and for whom anti-hyperglycaemic management strategies are being
considered: (2) in people with sub-optimal glycaemic control, regardless of baseline antihyperglycaemic therapy; and (3) in people with symptomatic heart failure (or other high-risk features such as recent hospitalization for heart failure), if glycaemic control is optimized and the individual is on a sulfonylurea or dipeptidyl peptidase-4 inhibitor; here, it may be reasonable to consider substituting one of those therapies for a sodium-glucose co-transporter-2 inhibitor. There are now a number of ongoing trials evaluating the role of sodium-glucose co-transporter-2 inhibitors as therapy for people with established heart failure (with preserved or with reduced ejection fraction) and regardless of the presence of diabetes. These trials will provide the evidence for the safety and efficacy of sodium-glucose co-transporter-2 inhibitors among people with established heart failure.

Title: Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial.

Citation: Lancet (London, England); Sep 2019

Author(s): Matthews, David R; Paldánius, Páivi M; Proot, Pieter; Chiang, YannTong; Stumvoll, Michael; Del Prato, Stefano; VERIFY study group

Background: Early treatment intensification leading to sustained good glycaemic control is essential to delay diabetic complications. Although initial combination therapy has been suggested to offer more opportunities than a traditional stepwise approach, its validity remains to be determined.

Methods: Vildagliptin Efficacy in combination with metforMin For earY treatment of type 2 diabetes (VERIFY) was a randomised, double-blind, parallel-group study of newly diagnosed patients with type 2 diabetes conducted in 254 centres across 34 countries. The study consisted of a 2-week screening visit, a 3-week metformin-alone run-in period, and a 5-year treatment period, which was further split into study periods 1, 2, and 3. Patients aged 18-70 years were included if they had type 2 diabetes diagnosed within 2 years prior to enrolment, and centrally confirmed glycated haemoglobin A1c (HbA1c) of 48.5-58 mmol/mol (6.5-7.5%) and a body-mass index of 22-40 kg/m2. Patients were randomly assigned in a 1:1 ratio either to the early combination treatment group or to the initial metformin monotherapy group, with the help of an interactive response technology system and simple randomisation without stratification. Patients, investigators, clinical staff performing the assessments, and data analysts were masked to treatment allocation. In study period 1, patients received either the early combination treatment with metformin (stable daily dose of 1000 mg, 1500 mg, or 2000 mg) and vildagliptin 50 mg twice daily, or standard-of-care initial metformin monotherapy (stable daily dose of 1000 mg, 1500 mg, or 2000 mg) and placebo twice daily. If the initial treatment did not maintain HbA1c below 53 mmol/mol (7.0%), confirmed at two consecutive scheduled visits which were 13 weeks apart, patients in the metformin monotherapy group received vildagliptin 50 mg twice daily in place of the placebo and entered study period 2, during which all patients received the combination therapy. The primary efficacy endpoint was the time from randomisation to initial treatment failure, defined as HbA1c measurement of at least 53 mmol/mol (7.0%) at two consecutive scheduled visits, 13 weeks apart from randomisation through period 1. The full analysis set included patients who received at least one randomised study medication and had at least one post-randomisation efficacy parameter assessed. The safety analysis set included all patients who received at least one dose of randomised study medication. This study is registered with ClinicalTrials.gov, NCT01528254.

Findings: Trial enrolment began on March 30, 2012, and was completed on April 10, 2014. Of the 4524 participants screened, 2001 eligible participants were randomly assigned to either the early combination treatment group (n=998) or the initial metformin monotherapy group (n=1003). A total of 1598 (79.9%) patients completed the 5-year study: 811 (81.3%) in the early combination therapy group and 787 (78.5%) in the monotherapy group. The incidence of initial treatment failure during period 1 was 429 (43.6%) patients in the combination treatment group and 614 (62.1%) patients in the monotherapy group. The median observed time to treatment failure in the monotherapy group was 36.1 (IQR 15.3-not reached [NR]) months, while the median time to treatment failure time for those receiving early combination therapy could only be estimated to be beyond the study duration at 61.9 (29.9-NR) months. A significant reduction in the relative risk for time to initial treatment failure was observed in the early combination treatment group compared with the monotherapy group over the 5-
year study duration (hazard ratio 0.51 [95% CI 0.45-0.58]; p<0.0001). Both treatment approaches were safe and well tolerated, with no unexpected or new safety findings, and no deaths related to study treatment.

**Interpretation:** Early intervention with a combination therapy of vildagliptin plus metformin provides greater and durable long-term benefits compared with the current standard-of-care initial metformin monotherapy for patients with newly diagnosed type 2 diabetes. FUNDING Novartis.

**Title:** Switching to iGlarLixi Versus Continuing Daily or Weekly GLP-1 RA in Type 2 Diabetes Inadequately Controlled by GLP-1 RA and Oral Antihyperglycemic Therapy: The LixiLan-G Randomized Clinical Trial.

**Citation:** Diabetes care; Sep 2019

**Author(s):** Blonde, Lawrence; Rosenstock, Julio; Del Prato, Stefano; Henry, Robert; Shehadeh, Naim; Frias, Juan; Niemoeller, Elisabeth; Souhami, Elisabeth; Ji, Chen; Aroda, Vanita R

**Objective:** Fixed-ratio combinations of basal insulin plus glucagon-like peptide 1 receptor agonist (GLP-1 RA) allow concomitant administration of two proven complementary injectable therapies for type 2 diabetes. This study investigated switching to a titratable fixed-ratio combination of insulin glargine plus lixisenatide (iGlarLixi) in patients with type 2 diabetes receiving daily or weekly GLP-1 RA therapy.

**Research Design And Methods:** LixiLan-G, a randomized, open-label, 26-week trial, comparing switching to iGlarLixi versus continuing prior GLP-1 RA in patients with type 2 diabetes and HbA1c 7-9% (53-75 mmol/mol) taking maximum tolerated doses of a GLP-1 RA daily (60% on liraglutide once daily or exenatide twice daily) or weekly (40% on dulaglutide, exenatide extended release, or albiglutide) with metformin with or without pioglitazone and with or without sodium-glucose cotransporter 2 inhibitors. Adherence to randomized treatment was closely monitored throughout the study.

**Results:** iGlarLixi (n = 257) reduced HbA1c more than continued GLP-1 RA therapy (n = 257) from a baseline 7.8% (62 mmol/mol) in both to 6.7% (50 mmol/mol) and 7.4% (57 mmol/mol), respectively, at 26 weeks (least squares mean difference -0.6%; P < 0.0001). More iGlarLixi patients achieved HbA1c <7% (53 mmol/mol) (62% vs. 26%; P < 0.0001) and the composite of HbA1c <7% without documented symptomatic hypoglycemia (<54 mg/dL). Nausea and vomiting rates as well as numbers of documented symptomatic hypoglycemia events per patient-year were generally low but greater with iGlarLixi versus continued GLP-1 RA therapy.

**Conclusions:** Switching to iGlarLixi improves glucose control for patients with type 2 diabetes insufficiently controlled on a maximum tolerated dose of a GLP-1 RA plus oral antihyperglycemic agents.

**Title:** Management of type 2 diabetes: now and the future.

**Citation:** Clinical Medicine; Sep 2019; vol. 19 (no. 5); p. 403-405

**Author(s):** Edeghere, Simon; English, Patrick

**Abstract:** There are about 4.7 million people living with diabetes mellitus in the UK and 90% have type 2 diabetes mellitus (T2DM). This burden will only get worse as there are currently about 12.3 million more at risk of T2DM. Moreover, up to 30% of diagnosed patients already have eye, foot, kidney or nerve complications. This impacts the NHS considerably as it spends about £10 billion annually on diabetes (80% on complications alone). Atherosclerotic cardiovascular disease (ASCVD), the leading cause of death in diabetes, contributes significantly to this. Therefore, there is significant emphasis on the prevention of T2DM especially in at-risk groups with the setting up of initiatives like the Diabetes Prevention Programme. When prevention fails, it is essential to commence glucose-lowering agents to reduce the burden of disease, prevent associated complications and improve
quality of life. A patient-centred approach is required to ensure efficacy of treatment strategies and the presence of co-morbidities such as cardiovascular and renal disease should be considered.

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

Citation: Primary Care Diabetes; Oct 2019; vol. 13 (no. 5); p. 409-421
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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